REVIEW

Fermented Dairy Products, Probiotic Supplementation, and Cardiometabolic Diseases: A Systematic Review and Meta-analysis

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ABSTRACT

Fermented dairy foods (FDFs) and probiotics are promising tools for the prevention and management of cardiometabolic diseases (CMDs), respectively. The relation between the regular consumption of FDFs and CMD risk factors was assessed by prospective cohort studies (PCSs), and the effect of probiotic supplementation added into a dairy matrix on CMD parameters was evaluated by randomized controlled trials (RCTs). Moreover, the effects of probiotic supplementation added into a dairy matrix were compared with those administered in capsule/powder form. Twenty PCSs and 52 RCTs met the inclusion criteria for the systematic review and meta-analysis. In PCSs, fermented milk was associated with a 4% reduction in risk of stroke, ischemic heart disease, and cardiovascular mortality [RR (95% CI); 0.96 (0.94, 0.98)]; yogurt intake was associated with a risk reduction of 27% [RR (95% CI); 0.73 (0.70, 0.76)] for type 2 diabetes (T2D) and 20% [RR (95% CI); 0.80 (0.74, 0.87)] for metabolic syndrome development. In RCTs, probiotic supplementation added into dairy matrices produced a greater reduction in lipid biomarkers than when added into capsules/powder in hypercholesterolemic subjects, and probiotic supplementation by capsules/powder produced a greater reduction in T2D biomarkers than when added into dairy matrices in diabetic subjects. Both treatments (dairy matrix and capsules/powder) resulted in a significant reduction in anthropometric parameters in obese subjects. In summary, fermented milk consumption is associated with reduced cardiovascular risk, while yogurt intake is associated with a reduced risk of T2D and metabolic syndrome development in the general population. Furthermore, probiotic supplementation added into dairy matrices could be considered beneficial for lowering lipid concentrations and reducing anthropometric parameters. Additionally, probiotic capsule/powder supplementation could contribute to T2D management and reduce anthropometric parameters. However, these results should be interpreted with caution due to the heterogeneity of the studies and the different probiotic strains used in the studies. This trial is registered with PROSPERO (CRD42018091791) and the protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018091791. *Adv Nutr* 2020;11:834–863.

Keywords: probiotics, fermented dairy, cardiometabolic disease, obesity, hypercholesterolemia, type 2 diabetes

Introduction

Cardiometabolic diseases (CMDs) are a group of chronic diseases that include obesity, dyslipidemia, type 2 diabetes (T2D), hypertension, and metabolic syndrome that promote cardiovascular (CV) disease (1), the leading cause of death throughout the world (2–4). Most of the identified risk factors for CMDs can be modified by healthy lifestyle recommendations (2). Despite attempts at lifestyle interventions, CMDs remain a major problem, and new strategies are needed to address the reduction or/and prevention of CMD.

A new strategy could include the use of probiotics, live microorganisms that confer a health benefit to the host when administered in adequate amounts (5). Probiotics can be provided as supplements or may be present in fermented dairy products, particularly yogurt, cheese, and fermented milk. However, for a food to be considered probiotic, the microorganisms administered must be present at concentrations $>10^8$–10^9 CFU/mL, show tolerance to acidic environments and bile, and confer a health benefit (6, 7). Notably, similarities and differences can be observed when consuming fermented dairy products and probiotic supplements. In general, fermented dairy products contain live microorganisms (7, 8), such as *Lactobacillus* bacteria, although not all of these products can be considered probiotics, and we can only speculate on this issue. Fermented dairy

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products are foods with variable composition that are eaten in the context of a dietary pattern and are one of the most common and traditional ways to consume probiotics among people in most cultures (9, 10). Additionally, fermented dairy products and their relation with disease and/or health have been evaluated in various observational studies (11, 12). In fact, yogurt (consumed daily/weekly) is the primary fermented dairy product that has been widely investigated in prospective cohort studies (PCSs), and although the results have shown a favorable association between the fat content of yogurt and CMD (12), the impact of the presence of probiotics in this fermented dairy product cannot be assessed.

In contrast, probiotic supplements contain controlled quantities of probiotics, and their effects are usually tested in randomized controlled trials (RCTs). Supplementation with different probiotic genera, such as *Lactobacillus*, particularly *L. plantarum* and *L. gasseri* and *Bifidobacterium*, has been demonstrated to reduce visceral fat mass and body weight (BW) (13, 14), and *L. casei* has been shown to improve glucose homeostasis in RCTs. Some RCT studies have systematically reviewed the existing evidence describing the effects of probiotic supplementation on different CMDs, such as obesity (15), dyslipidemia, and T2D (16, 17). However, the effects of probiotics on each CMD have not been simultaneously evaluated or discussed.

To the best of our knowledge, no previous systematic review and meta-analysis has provided a wide and integrative vision of the role of probiotics by examining relations between the consumption of fermented dairy foods and CMD risk factors by PCSs with the effectiveness of specific probiotic supplementation added in a dairy product (into a dairy matrix) on obesity, T2D, and hypercholesterolemia reduction with RCTs.

Therefore, the objective of the current systematic review and meta-analysis, which was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, was to evaluate the relation between regular consumption (daily/weekly) of fermented dairy products and different risks of CMDs by PCSs and to assess the effectiveness of probiotic supplementation into a dairy matrix on different CMD parameters by RCTs. Moreover, our study compared the effects of probiotics supplementation into a dairy matrix with those administered in capsule/powder form (not eaten with other foods). Our results will be able to provide new nutritional perspectives on the management of CMDs.

Methods

This systematic review and meta-analysis was designed following the general principles published in the PRISMA statement (18). The study has been registered with PROSPERO (CRD42018091791), and the protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018091791.

Eligibility criteria

PCSs and RCTs were eligible for inclusion in this systematic review. The Population, Intervention, Comparison, Outcomes and Study design (PICOS) criteria used to define the inclusion and exclusion criteria for the systematic review and meta-analysis are listed in **Table 1**. The changes to the original protocol registered along with the reasons for the changes are assessed are shown in **Supplemental Table 1**.

Information sources and search strategy

A literature search using medical subject headings (MeSH) was performed in cooperation with health science librarians, and multiple databases were examined, including the PubMed (www.ncbi.nlm.nih.gov/pubmed), SCOPUS (www.scopus.com), and Cochrane Plus (www.bibliotecacochrane.com) databases. The analysis of electronic databases was complemented by a search for trial protocols in ClinicalTrials.gov. Additional studies were identified through a review of the references of the retrieved articles. The database searches were conducted from 2010 to 12 August, 2019 (the complete search strategy is illustrated in **Supplemental Table 2**).

Study selection

The literature search was restricted to studies written in the English language and studies that included only adult subjects. The included articles were published from 2010 to 12 August, 2019.

To ensure an accurate assessment of the eligibility of the included articles, the titles and abstracts of the studies identified using the search strategy and those identified from additional sources were screened independently by 2 of the authors (JC and LP-P). The full texts of the potentially eligible studies were then retrieved, and their eligibility was independently assessed by the same 2 authors. Any disagreement between the authors regarding the eligibility of a study was resolved through discussion with a third author (LC-P).

Data collection and extraction

The literature search results were uploaded to www.covidence.org, a software program that facilitates screening. First, the titles of all the studies identified from the database search were screened. Second, the abstracts of the relevant titles were screened for the selection of potentially eligible

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Address correspondence to AP (e-mail: anna.pedret@eurecat.org) or RS (e-mail: rosa.rosa@urv.cat).
Abbreviations used: BF, body fat; BFM, body fat mass; BW, body weight; IHD, ischemic heart disease; CMD, cardiometabolic disease; CRP, C-reactive protein; CV, cardiovascular; FDF, fermented dairy food; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; PCS, prospective cohort study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial; SCFA, subcutaneous fat area; T2D, type 2 diabetes; VFA, visceral fat area; WC, waist circumference; WMD, weighted mean difference.

TABLE 1 PICOS criteria for inclusion and exclusion of studies[1]

Criteria	Inclusion and exclusion criteria of observational studies	Inclusion and exclusion criteria of clinical trials
Population	Adult subjects (>18 y old) of all sexes and races with cardiovascular risk factors (obesity, T2D, hypercholesterolemia or metabolic syndrome) or cardiovascular disease were eligible for inclusion	Adult subjects of all sexes and races who were overweight or obese, or were diagnosed with T2D, hypercholesterolemia, or metabolic syndrome were eligible for inclusion. Subjects with GD, bariatric surgery, rheumatoid arthritis, or polycystic ovarian syndrome, and pregnant women or infants were excluded.
Intervention or exposure	Studies that evaluated the effect of fermented dairy consumption were eligible for inclusion. Studies that evaluated the effect of whole dietary pattern were excluded.	Studies with probiotic supplementation (all probiotic genera, administered through powder or capsules forms or added to a dairy matrix) were eligible for inclusion. Studies that do not specify probiotic species were excluded.
Comparison	Studies that compared individuals in highest category of fermented dairy consumption compared with individuals in lowest category of fermented dairy consumption were eligible for inclusion.	Studies with placebo products were eligible for inclusion.
Outcomes	Studies that measured the incidence of IHD, stroke, cardiovascular mortality, obesity, T2D, or metabolic syndrome development were eligible for inclusion.	Studies that measured: BW, BMI, WC, body fat, body fat mass, VFA and/or SCFA in obese subjects; fasting insulin, HOMA-IR, HbA1c, fasting glucose, and/or plasma CRP in T2D subjects; total cholesterol, LDL-c, HDL-c, and/or triglycerides in hypercholesterolemic subjects; WC, total cholesterol, LDL-c, HDL-c, triglycerides, and/or fasting glucose in metabolic syndrome subjects were eligible for inclusion.
Study design	Prospective cohort studies were considered for inclusion. Systematic reviews and meta-analyses were excluded.	Randomized clinical trials were considered for inclusion. Nonrandomized clinical trials, systematic reviews, and meta-analysis were excluded.
Meta-analysis	At least 3 studies for each parameter	At least 3 studies for each parameter, and the same type or study (RCTs).

[1] BW, body weight; IHD, ischemic heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; GD, gastrointestinal disorders; HbA1c, glycosylated hemoglobin; HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; PICOS, Population, Intervention, Comparison, Outcomes and Study design; RCT, randomized controlled trial; SCFA, subcutaneous fat area; T2D, type 2 diabetes; VFA, visceral fat area; WC, waist circumference.

studies. Third, the full-text articles that met the inclusion criteria were screened.

The data extracted from PCSs included the first author, year of publication, country in which the study was conducted, study design, follow-up duration, number of subjects, age range of the subjects, exposure assessment, adjusted variables, outcome, dairy exposures analyzed, dairy product subgroups, comparison (e.g., high vs low or no consumption), and the specific relative risk estimates (OR, RR, or HR).

The data extracted from the RCTs included the first author, year of publication, study design, study duration, sex and age range of the subjects, number of subjects in the intervention and placebo groups, intention-to-treat, details of the intervention (including probiotic strain) and control groups, and significant and nonsignificant results for BW, BMI, waist circumference (WC), body fat mass (BFM), fat mass percentage (BF), visceral fat area (VFA), subcutaneous fat area (SCFA), fasting insulin, HOMA-IR, glycosylated hemoglobin (HbA1c), fasting glucose, plasma C-reactive protein (CRP), total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Study quality and risk of bias within individual studies

For assessments of the quality and possible risk of bias of each observational study, we used the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Moreover, for each RCT, we collected information for quality assessment using the RevMan 5.3 program, a Cochrane Collaboration tool. Specifically, the following criteria were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Two authors evaluated the risk of bias in each RCT (JC and LP-P), and any disagreement between these authors regarding the risk of bias in a study was resolved through discussion with a third author (LC-P).

Meta-regression and subgroup analyses

We performed a meta-regression (random-effects) to evaluate between-group heterogeneity and assess the association between the significant estimated effect sizes with potential confounders, which included the method of probiotic administration, duration of intervention, and different risk of bias evaluated.

Statistical analyses

The systematic review and meta-analysis were performed using RevMan 5.3, and STATA 12.0 (StataCorp) was also used for the meta-analysis. In the analysis of the PCSs, the study-specific dose–response risk was estimated for each category of fermented dairy [yogurt, cheese, fermented milk, and total fermented dairy (when dairy content was not differentiated into various types)] based on the consumption amount of each category. In the analysis of the RCTs, the changes in the mean values from the endpoint to initial (baseline) values, as well as the corresponding SDs, SEs, or 95% CIs, were used to calculate the mean difference with 95% CIs between the intervention and control groups. Specifically, the differences between the intervention and control groups were calculated by obtaining the differences between the endpoint value after an intervention and the baseline value. In the PCS meta-analysis, the HRs and ORs of the included articles were considered approximations of RRs. The results of the meta-analysis performed using random-effects inverse-variance weights were compared with those obtained using fixed-effects inverse-variance weights through sensitivity analyses, and the results from the primary multivariable model that included most confounders were used. The results of the meta-analysis of RCTs are expressed as weighted mean differences (WMDs) that are defined as the difference between the start and finish values. If the SD or SE values were not specified in the original article describing an RCT, the corresponding author was contacted by e-mail and asked to provide the missing information (n = 7), and if the corresponding author did not provide this information, the RCT was not included in the meta-analysis (n = 7). In the meta-analysis, the between-study heterogeneity was assessed using the Cochran's Q and I^2 statistics, and I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively (19). We excluded the RCT studies that included interventions with low-calorie diets from the meta-analysis.

Results

Study selection

Of the 7926 articles identified in the databases (PubMed = 2151, SCOPUS = 4781, and Cochrane Plus = 994) and the 3 articles identified from a review of the references of the retrieved articles, 3433 were excluded for being duplicated studies, and 5269 were excluded for not meeting the eligibility criteria. Ultimately, 72 studies (20 PCSs and 52 RCTs) were included in the systematic review, with 18 PCSs in 1 meta-analysis and 37 RCTs in the other meta-analysis (see **Figure 1**).

Study characteristics

The characteristics of the 72 studies, 20 PCSs and 52 RCTs (24 RCTs of probiotic supplementation added in dairy products and 28 RCTs probiotic supplementation in powder or capsules), included in the systematic review are presented in **Tables 2–9**.

In the 20 PCSs analyzed, the subjects (men and women) were between 20 and 90 y of age and presented one of the following outcomes: risk of obesity, T2D, metabolic syndrome, CV mortality risk, stroke, or ischemic heart disease (IHD). The sample size ranged from 1868 to 409,885 subjects, and the follow-up duration ranged from 2 to 30 y. The study populations originated from Europe, the United States, and Asia, and the food exposures analyzed in these studies were yogurt, cheese, fermented milk, and total fermented dairy.

In the 52 RCTs analyzed, the subjects (men and women) were between 18 and 75 y old and presented at $\geq$1 of the following CMDs: obesity/overweight, T2D, hypercholesterolemia, and metabolic syndrome. The sample size was between 24 and 210 subjects, the intervention period ranged from 45 d to 24 wk, and the probiotic doses ranged from 1×10^4 to 27×10^{10} CFU/d. The probiotic strains studied were as follows: *L. acidophilus*, *L. amylovorus*, *L. bravis*, *L. bulgaricus*, *L. casei*, *L. curvatus*, *L. fermentum*, *L. gasseri*, *L. helveticus*, *L. lactis*, *L. paracasei*, *L. plantarum*, *L. rhamnosus*, *L. reuteri*, *L. salivarius*, *B. lactis*, *B. breve*, *B. bifidum*, *B. longum*, *B. infantis*, *Pediococcus pentosaceus*, and *Streptococcus thermophilus*. The populations investigated in the studies originated from Europe (n = 10), Asia (n = 35), Oceania (n = 1), and North (n = 2) and South (n = 4) America. Additionally, in most of the studies, the product used for the intervention was the same as the control product but without the probiotic, whereas 2 studies utilized a different control product [i.e., vegetal cream capsules (20) or magnesium stearate capsules (21)] for the control group and administered probiotic capsules to the intervention group. The dairy matrices studied were yogurt, fermented milk, kefir, cheese, and milk.

Quality and risk of bias of the included studies

A risk-of-bias assessment was performed for the individual PCSs during the systematic review (**Supplemental Figure 1**). All of the included PCSs (n = 20) clearly stated the research question, measured the exposure of interest prior to the outcome, correctly described the exposure and outcome measures, and statistically adjusted for all potential confounding variables. In 19 PCSs, the study population was clearly specified, the subjects selected were from a similar population, the timeframe was sufficient, the exposure assessed was more than once over time, and different levels of the exposure were examined. The participation rate of eligible subjects was $\geq$50% in 17 PCSs. Finally, only 8 PCSs correctly described that the loss of follow-up after baseline was $\leq$20%. The blinding of the outcome assessor was described in only 4 PCSs, and the sample size justification was not provided in any study.

In the systematic review of RCTs, the risk of bias within the individual studies was assessed (**Supplemental Figure 2**). All 52 included RCTs were randomized, and 6 RCTs did

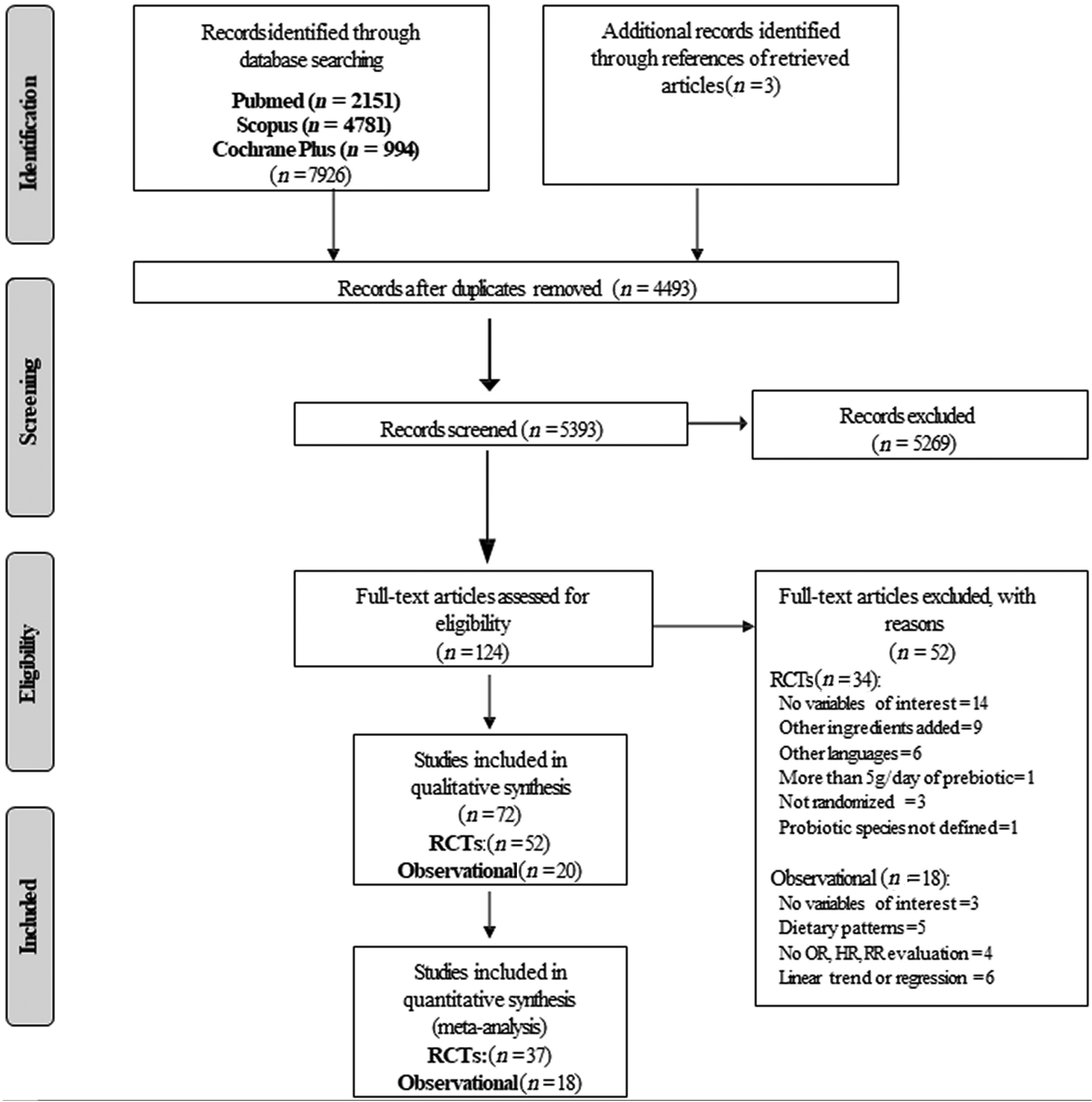

FIGURE 1 PRISMA flowchart of the systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial.

not correctly describe the method used for randomization. The allocation concealment of the included articles was not properly described in 14 studies, and allocation concealment was not performed in 3 RCTs. Blinding of both participants and personnel was performed correctly in 46 RCTs, but only 17 RCTs correctly blinded the outcome assessment. Complete outcome data were not correctly described in 11 RCTs and were selectively reported in 22 RCTs, likely because these were preregistered in a clinical trial registry. In addition, the authors of some of the included RCTs reported conflicts of interest ($n = 7$).

Meta-analysis of PCSs

Table 2 shows a summary of the individual information extracted from each PCS included in the systematic review that evaluated the relation of fermented dairy intake with risk of CMD (CV mortality, stroke, IHD, T2D, obesity, and metabolic syndrome) ($n = 20$).

Fermented dairy intake and risk of stroke, IHD, and CV mortality.

The meta-analysis of 3 PCSs (22–24) that evaluated the relation of fermented milk intake with stroke, IHD, and CV mortality risk development in PCSs resulted in a significant 4% reduction in risk of stroke, IHD, and CV mortality development [RR (95% CI); 0.96 (0.94, 0.98)], and the heterogeneity between PCSs was high ($P < 0.001$, $I^2 = 95.9\%$; **Figure 2**A).

The meta-analysis of 4 PCSs (25–28) evaluating the relations between yogurt intake and stroke, IHD, and CV

TABLE 2 Summary of the individual information extracted from each included prospective cohort study evaluating the relation of fermented dairy intake with risk for CMD (CV mortality, stroke, IHD, T2D, obesity, and MetS)[1]

Study (year) (ref)	Study, country	Design	Follow-up, y	Total n	Cases, n	Age range, y	Measurement	Adjusted variables	Outcome	Dairy exposures analyzed	Dairy products subgroups	Comparison	OR, RR, or HR (95% CI)
1. CV mortality, stroke, and IHD ($n = 8$)													
Key et al. (2019) (29)	EPIC cohort, 10 countries[2]	PC	12.6	409,885	7198	41–70	24-h recalls	Age, smoking status, and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidemia, Cambridge physical activity index, employment status, level of education completed, BMI, current alcohol consumption, observed intakes of energy, fruit and vegetables combined, sugars and fiber from cereals, and stratified by sex and EPIC center	CV mortality	Yogurt	Total yogurt	Q5 (150 g/d) vs Q1 (0 g/d)	[HR: 0.90 (0.84–0.97)]
Johansson et al. (2019) (22)	VIP and MONICA, Sweden	PC	14.2	120,061	11,641	40–60	FFQ	Dairy product categories, sex, age, screening year, BMI, education, physical activity, smoking, family history of CV disease or T2D, screening project, quintiles of red meat, whole-grain, fruit and vegetables and energy	Myocardial infarction	FM	Total FM	M: Q4 vs no consumption	[HR: 0.92 (0.82, 1.03)]
												W: Q4 vs no consumtion	[HR: 1.00 (0.84, 1.18)]
									Stroke	FM	Total FM	M: Q4 vs no consumption	[HR:0.91 (0.79, 1.05)]
												W: Q4 vs no consumption	[HR:0.87 (0.75, 1.03)]
Dehghan et al. (2018) (25)	PURE study, from 21 countries[3]	PC	9.1	136,384	7828	35–70	Validated FFQ	Age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of CV, family history of cancer, and quintiles of fruit, vegetable, red meat, starchy foods intake, and energy	CV disease	Yogurt	Total yogurt	>244 g/d vs 0 g/d	[HR: 0.82 (0.72–0.93)]
Farvid et al. (2016) (26)	Golestan study, Iran	PC	8	42,402	1467	36–85	Validated FFQ, 116 items	Age, gender, BMI, physical activity, ethnicity, education, marital status, residency, smoking, opium use, alcohol, SBP, family history of cancer, wealth score, medication use, energy intake	CV mortality	Yogurt	Total yogurt	Q5 (207 g/d) vs Q1 (23 g/d)	[HR: 0.84 (0.70–1.00)]
Goldbohm et al. (2011) (23)	Netherlands Cohort study, Netherlands	PC	10	120,852	16,136	55–69	Validated FFQ, 150 items	Age, education, smoking, physical activity, BMI, multivitamin use, alcohol, energy, energy-adjusted mono- and polyunsaturated fat intakes, and vegetable and fruit consumption	CV mortality	FM	Whole-fat FM	M: Q2 (53 g/d) vs Q1 (0 g/d)	[RR: 0.93 (0.88–0.98)]
												W: Q2 (53 g/d) vs Q1 (0 g/d)	[RR: 0.93 (0.87–1.00)]
											Low-fat FM	M: Q3 (146 g/d) vs Q1 (0 g/d)	[RR: 0.97 (0.93–1.03)]
												W: Q3 (192 g/d) vs Q1 (0 g/d)	[RR: 1.02 (0.95–1.09)]
Praagman et al. (2014) (27)	Rotterdam Study, Netherlands	PC	13.3	4235	564	>55	SFFQ, 170 items	Age, gender, total energy intake, BMI, smoking, education level, alcohol, vegetables, fruit, meat, bread, fish coffee, and tea intake	Stroke	FD	Buttermilk, yogurt, curd, cheese	>100 g/d vs <50 g/d	[HR: 1.08 (0.87–1.34)]
										Yogurt	Total yogurt	>100 g/d vs <50 g/d	[HR: 1.10 (0.90–1.34)]
										Cheese	Total cheese	>40 g/d vs <20 g/d	[HR: 0.96 (0.75–1.22)]

(*Continued*)

TABLE 2 (*Continued*)

Study (year) (ref)	Study, country	Design	Follow-up, y	Total *n*	Cases, *n*	Age range, y	Measurement	Adjusted variables	Outcome	Dairy exposures analyzed	Dairy products subgroups	Comparison	OR, RR, or HR (95% CI)
								Age, gender, total energy intake, BMI, smoking, education level, alcohol, vegetables, fruit, meat, bread, fish coffee, and tea intake	IHD	FD	Buttermilk, yogurt, curd, cheese	>100 g/d vs <50 g/d	[HR: 1.01 (0.82–1.24)]
										Yogurt	Total yogurt	>100 g/d vs <50 g/d	[HR: 1.11 (0.91–1.35)]
										Cheese	Total cheese	>40 g/d vs <20 g/d	[HR: 1.01 (0.79–1.30)]
Soedamah-Muthu et al. (2013) (28)	Whitehall II study, UK	PC	10	4526	323	35–55	Validated FFQ	Age, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity and family history of IHD/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea and total energy intake	IHD	Yogurt	Total yogurt	T3 (117 g/d) vs T1 (0 g/d)	[HR: 1.23 (0.93–1.63)]
										Cheese	Total cheese	T3 (31 g/d) vs (6 g/d)	[HR: 0.82 (0.61–1.09)]
										FD	Total yogurt and cheese	T3 (105 g/d) vs (17 g/d)	[HR: 0.97 (0.73–1.28)]
Sonestedt et al. (2011) (24)	MDC study, Sweden	PC	12	26,445	2520	44–74	FFQ, 168 item	Age, gender, season, method, energy intake, BMI, smoking, alcohol consumption, physical activity, education, intakes of vegetables, fruit, berries, fish shellfish, meat, coffee, whole grains	CV disease	FM	Total FM	Q4 (55 g/d) vs Q1 (0 g/d)	[HR: 0.87 (0.77–0.97)]
2. T2D risk ($n = 9$)													
Jeon et al. (2019) (30)	KoGES, Korea	PC	7.3	10,030	1173	40–69	SFFQ	Age, sex, BMI, residential area, education level, household income, physical activity, alcohol consumption, and smoking status, history of hypertension, family history of T2D, use of antihypertensive medication, use of dietary supplements, intakes of vegetables, fruits, red meat, processed meat, soft drinks, coffee, and tea	T2D	Yogurt	Total yogurt	625 g/wk vs 0 g/wk	[HR: 0.73 (0.61–0.88)]
Hruby et al. (2017) (31)	FHS Offspring, USA	PC	12	2809	902	45–63	FFQ, 126 items	Age, gender, energy intake, history of diabetes, smoking, dyslipidemia, hypertension or treatment, intake of coffee, nuts, fruits, vegetables, meats, alcohol, and fish, glycemic index, low-fat, high-fat dairy intake, BMI, weight change follow-up	T2D	Yogurt	Total yogurt	277 g/d vs 0 g/d	[HR: 1.24 (0.67–2.29)]
Díaz-López et al. (32)	PREDIMED study, Spain	PC	2.5–5.7	3454	270	55–80	Validated FFQ, 137 items	Age, gender, BMI, intervention group, physical activity, educational level, smoking, hypertension, antihypertensive use, fasting glucose, HDL, and TG concentrations	T2D	Yogurt	Low-fat yogurt	T3 (120 g/d) vs T1 (3 g/d)	[HR: 0.61 (0.43–0.85)]
											Whole-fat yogurt	T3 (45 g/d) vs T1 (0 g/d)	[HR: 0.64 (0.46–0.89)]
											Total yogurt	T3 (128 g/d) vs T1 (13 g/d)	[HR: 0.53 (0.37–0.75)]
										Cheese	Total cheese	T3 (40 g/d) vs T1 (11 g/d)	[HR: 1.31 (0.94–1.83)]
										FD	Total yogurt and cheese	T3 (167 g/d) vs T1 (39 g/d)	[HR: 0.63 (0.45–0.87)]

(*Continued*)

TABLE 2 (*Continued*)

Study (year) (ref)	Study, country	Design	Follow-up, y	Total *n*	Cases, *n*	Age range, y	Measurement	Adjusted variables	Outcome	Dairy exposures analyzed	Dairy products subgroups	Comparison	OR, RR, or HR (95% CI)
Ericson et al. (33)	Malmö Diet and Cancer cohort study, Sweden	PC	14	26,930	2860	45–74	Validated FFQ, 168 items	Age, sex, method version, season, total energy intake, physical activity, smoking, alcohol intake, and education, BMI	T2D	FD	Low- fat yogurt, sour milk, and cheese	480 g/d vs 0 g/d	[HR: 1.06 (0.95, 1.18)]
											High-fat yogurt, sour milk, and cheese	792 g/d vs 66 g/d	[HR: 0.89 (0.79, 1.01)]
Chen et al. (34)	HPFS, USA	PC	24	51,529	3364	40–75	131-item FFQ	Age, BMI and other lifestyle and dietary risk factors, total dairy consumption	T2D	Yogurt	Total yogurt	Q4 (732 g/wk) vs Q1 (61 g/wk)	[RR: 0.95 (0.84–1.08)]
	NHS I, USA	PC	30	121,700	7841	30–55	61–131 item FFQ	Age, BMI and other lifestyle and dietary risk factors, total dairy consumption	T2D	Yogurt	Total yogurt	Q4 (708 g/wk) vs Q1 (0 g/wk)	[RR: 0.84 (0.76–0.91)]
	NHS II, USA	PC	16	116,671	3951	25–42	131-item FFQ	Age, BMI, and other lifestyle and dietary risk factors, total dairy consumption	T2D	Yogurt	Total yogurt	Q4 (659 g/wk) vs Q1 (0 g/wk)	[RR: 0.90 (0.81–1.00)]
Soedamah-Muthu et al. (28)	Whitehall II study, UK	PC	10	4526	273	35–55	Validated FFQ	Age, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity and family history of IHD/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea and total energy intake	T2D	Yogurt	Total yogurt	T3 (117 g/d) vs T1 (0 g/d)	[HR: 1.04 (0.77–1.42)]
										Cheese	Total Cheese	T3 (31 g/d) vs (6 g/d)	[HR: 1.20 (0.88–1.64)]
										FD	Total yogurt and cheese	T3 (105 g/d) vs (17 g/d)	[HR: 1.17 (0.87–1.58)]
Struijk et al. (35)	Inter99 study, Denmark	PC	5	5953	214	30–60	Validated FFQ, 198 items	Age, gender, intervention group, diabetes family history, education level, physical activity smoking, alcohol intake, whole-grain cereal, meat, fish, coffee, tea, fruit, vegetables, energy intake, change in diet from baseline to 5-y follow-up, waist circumference	T2D	FM	Total FM	150 g/d vs 0 g/d	[OR: 0.88 (0.69–1.11)]
										Cheese	Total cheese	20 g/d vs 0 g/d	[OR: 0.97 (0.82–1.15)]
Grantham et al. (36)	AusDiab, Australia	PC	5	5582	209	>25	Validated FFQ, 121 items	Age, sex, energy intake, family history of diabetes, education level, physical activity, smoking status, TG, HDL cholesterol, SBP, waist circumference and hip circumference	T2D	Yogurt	Total yogurt	T3 (>380 g/d) vs T1 (<240 g/d)	[HR: 1.14 (0.78, 1.67)]
Margolis et al. (37)	Women's Health Initiative, USA	PC	8	82,076	3946	50–79	Validated SFFQ	Age, race/ethnicity, total energy intake, income, education, smoking, alcohol intake, family history of diabetes, use of postmenopausal hormone therapy, SBP, DBP, BMI, physical activity, an interaction term between quintiles of yogurt intake and time	T2D	Yogurt	Total yogurt	>500 g/wk vs <250 g/mo	[HR: 0.46 (0.31, 0.68)]

(*Continued*)

TABLE 2 (*Continued*)

Study (year) (ref)	Study, country	Design	Follow-up, y	Total *n*	Cases, *n*	Age range, y	Measurement	Adjusted variables	Outcome	Dairy exposures analyzed	Dairy products subgroups	Comparison	OR, RR, or HR (95% CI)
3. Obesity risk ($n = 1$)													
Martinez-Gonzalez et al. (38)	SUN project, Spain	PC	6.6	8516	1860	26–48	Validated FFQ, 136 items	Age, gender, physical activity, hours of TV watching, hours spent sitting down, smoking, snacking between meals, following a special diet, total energy intake, adherence to the Mediterranean diet, marital status, years of education, baseline BMI	Obesity	Yogurt	Low-fat yogurt	>889 g/wk vs 0–250 g/wk	[HR: 0.84 (0.61–1.15)]
											Whole-fat yogurt	>889 g/wk vs 0–250 g/wk	[HR: 0.62 (0.47–0.82)]
											Total yogurt	>889 g/wk vs 0–250 g/wk	[HR: 0.80 (0.68–0.94)]
4. MetS risk ($n = 3$)													
Kim et al. (39)	KoGES, Korea	PC	4	5510	2103	40–69	Validated FFQ, 103 items	Age, gender, BMI, residential location, educational level, household income, smoking, alcohol intake, physical activity, nutrient intakes (energy and energy-adjusted Ca, fiber)	MetS	Yogurt	Total yogurt	≥85 g/d vs ≤ 21 g/d	[HR: 0.68 (0.58–0.79)]
Babio et al. (40)	PREDIMED study, Spain	PC	2–7	1868	930	55–80	Validated FFQ, 137 items	Age, gender, intervention group, physical activity, BMI, smoking and former, hypoglycemic, hypolipemic, antihypertensive or insulin treatment, mean consumption during follow-up: vegetables, fruit, legumes, cereals, fish, red meat, cookies, olive oil nuts, alcohol, MetS at baseline	MetS	Yogurt	Low-fat yogurt	T3 (124 g/d) vs T1 (1 g/d)	[HR: 0.73 (0.62–0.86)]
											Whole-fat yogurt	T3 (46 g/d) vs T1 (0 g/d)	[HR: 0.78 (0.66–0.92)]
											Total yogurt	T3 (127 g/d) vs T1 (7 g/d)	[HR: 0.77 (0.65–0.91)]
Sayón-Orea et al. (41)	SUN project, Spain	PC	6	8063	306	20–90	Validated FFQ, 136 items	Age, gender, baseline weight, total energy, alcohol intake, soft drinks, red meat, French fries, fast food, Mediterranean diet, physical activity, sedentary behavior, hours sitting, smoking, snacking between meals, following special diet	MetS	Yogurt	Low-fat yogurt	≥875 g/wk vs 0–250 g/wk	[OR: 0.63 (0.39–1.02)]
											Whole-fat yogurt	≥875 g/wk vs 0–250 g/wk	[OR: 0.98 (0.68–1.41)]
											Total yogurt	≥875 g/wk vs 0–250 g/wk	[OR: 0.84 (0.60–1.18)]

[1] $n = 20$. AusDiab, Australian Diabetes Obesity and Lifestyle Study; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; EPIC, European Prospective Investigation into Cancer and Nutrition; FD, fermented dairy; FFQ, food-frequency questionnaire; FHS, Framingham Heart Study; FM, fermented milk; HPFS, Health Professionals Follow-Up Study; IHD, ischemic heart disease; InterAct, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; KoGES, Korean Genome and Epidemiology Study; M, men; MDC, Malmö Diet Cancer; MetS, metabolic syndrome; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; NHS, Nurses' Health Study; PC, prospective cohort; PREDIMED, Prevención con Dieta Mediterránea; Pure study, Prospective Urban Rural Epidemiology; Q, quartile; ref, reference; SBP, systolic blood pressure; SFFQ, semiquantitative food-frequency questionnaire; SUN, Seguimiento Universidad de Navarra; T, tertile; T2D, type 2 diabetes; TG, triglycerides; VIP, Västerbotten Intervention Program; W, women.
[2] Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, United Kingdom.
[3] Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, occupied Palestinian territory, Pakistan, Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe.

TABLE 3 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in dairy products on CMD in subjects with different CMDs (obesity, T2D, hypercholesterolemia, and metabolic syndrome)[1]

Study (ref)	Study design, duration (country)	Gender, age (y)	n (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results: BW (kg)	BMI (kg/m^2)	WC (cm)	BFM (kg)	BF (%)	VFA (cm^2)	SCFA (cm^2)
Added to yogurt matrix														
Zarrati et al. (42)	R, DB, PC, 8 wk (Iran)	M and W, 20 to 50	60 (30/30)	Yes	Yogurt with *Lactobacillus acidophilus* La5, *Bifidobacterium* BB12, and *L.* DN001 (10^8) with LCD	PL yogurt with LCD	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	−0.63	—	—
Madjd et al. (43)	R, SB, CT, PC, 12 wk (Iran)	W, 18 to 50	89 (44/45)	Yes	Low-fat yogurt with *L. acidophilus* and *B. lactis* BB12 (1×10^7)	PL low-fat yogurt	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
Nabavi et al. (44)	R, DB, CT, PC, 8 wk (Iran)	M and W, 23 to 63	72 (36/36)	No	Yogurt with *B. lactis* Bb12 (3.85×10^6), *L. acidophilus* La5 (4.42×10^6)	PL yogurt	End vs BL (IG)	↓2.74	↓1.02	↓1.69	—	—	—	—
							Between interv.	−2.49	−0.91	$P > 0.05$	—	—	—	—
Mohamadshahi et al. (45)	R, DB, CT, PC, 8 wk (Iran)	M and W, ≈51	42 (21/21)	No	Yogurt with *L. acidophilus* La-5, *B. lactis* BB-12 (3.7×10^6)	PL yogurt	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—
Mohamadshahi et al. (46)	R, DB, CT, PC, 8 wk (Iran)	M and W, 42 to 56	42 (21/21)	No	Yogurt with *L. acidophilus* La-5, *B. lactis* BB-12 (3.7×10^6)	PL yogurt	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—
Zarrati et al. (47)	R, DB, CT, PC, 8 wk (Iran)	M and W, 20 to 50	75 (25/25/25)	No	I1. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12 with LCD	Regular yogurt with LCD	End vs BL (I1)	↓4.23	↓1.55	↓2.78	—	—	—	—
					I2. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12	Regular yogurt with LCD	End vs BL (I2)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
							Between interv. (I1 vs I2)	−4.27	−1.55	−2.78	—	—	—	—
							Between interv. (I2 vs CG)	4.91	1.9	2.0	—	—	—	—
Omar et al. (48)	R, DB, PC, CO; 4, 3 wk (Canada)	M and W, 18 to 60	56 (28/28)	No	I1. Yogurt with *L. amylovorus.* (1.39×10^9)	PL yogurt	End vs BL (I1)	$P > 0.05$	—	—	↓1.40	—	—	—
					I2. Yogurt with *L. Fermentum.* (1.08×10^9)		End vs BL (I2)	$P > 0.05$	—	—	↓1.00	—	—	—
							Between interv.	$P > 0.05$	—	—	$P > 0.05$	—	—	—

(*Continued*)

TABLE 3 (*Continued*)

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results						
								BW (kg)	BMI (kg/m^2)	WC (cm)	BFM (kg)	BF (%)	VFA (cm^2)	SCFA (cm^2)
Zarrati et al. (49)	R, DB, CT, PC, 8 wk (Iran)	M and W, 20 to 50	75 (25/25/25)	Yes	I1. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12 (3 × 10^8) with LCD	Regular yogurt with LCD	End vs BL (I1)	↓4.23	↓1.55	↓2.78	—	—	—	—
					I2. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12 (3 × 10^8)		End vs BL (I2)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
							Between interv. (I1 vs I2)	−4.27	−1.55	−2.78	—	—	—	—
							Between interv. (I2 vs CG)	4.91	1.9	2.0	—	—	—	—
Added to FD matrix														
Naito et al. (50)	R, DB, PC, PG, 8 wk (Japan)	M and W, 20 to 64	100 (50/50)	No	FM with *L. casei* Shirota YIT 9029 (>1.0 × 10^{11})	PL non-FM	End vs BL (IG)	↑0.6	↑0.2	—	—	↑0.8	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	—	$P > 0.05$	—	—
Takahashi et al. (51)	R, DB, PC, MC, 12 wk (Japan)	M and W, 20 to 65	137 (69/68)	No	FM with *B. lactis* GCL2505 (8 × 10^{10})	PL FM	End vs BL (IG)	$P > 0.05$	$P > 0.05$	—	—	—	↓5.1	$P > 0.05$
							Between interv.	$P > 0.05$	$P > 0.05$	—	—	—	−6.60	$P > 0.05$
Hove et al. (52)	R, DB, PC, 12 wk (Denmark)	M, 40 to 70	41 (23/18)	No	FM with *L. helveticus* Cardi04 (n.d)	PL FM	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
Kadooka et al. (53)	R, DB, PG, MC, PC, 12 wk (Japan)	M and W, 35 to 60	210 (69/71/70)	No	I1. FM with *L. gasseri* SBT2055 (200 × 10^7)	PL FM	End vs BL (I1)	—	↓0.30	↓1.30	↓0.60	↓0.50	↓8.50%	↓2.60%
					I2. FM with *L. gasseri* SBT2055. (200 × 10^6)		End vs BL (I2)	—	↓0.40	↓1.10	↓0.50	$P > 0.05$	8.2%	$P > 0.05$
							Between interv. (I1 vs CG)	—	$P > 0.05$	−1.20	−1.10	−1.10	−7.80	$P > 0.05$
							Between interv. (I2 vs CG)	—	$P > 0.05$	−1.00	−1.00	$P > 0.05$	−7.50	$P > 0.05$
Kadooka et al. (54)	R, DB, PC, MC, 12 wk (Japan)	M and W, 33 to 63	87 (43/44)	No	FM with *L. gasseri* SBT2055 (10 × 10^{10})	PL FM	End vs BL (IG)	↓1.10	↓0.40	↓1.70	↓0.80	↓0.05	↓5.80	↓7.40
							Between interv.	−1.40	−0.50	−1.70	−1.10	−0,7	−7.20	−6.10
Nakamura et al. (55)	R, DB, PC, 12 wk (Japan)	M and W, >19	197 (98/99)	No	Shake with *L. amylovorus* CP1563 (n.d.)	PL shake	End vs BL (IG)	—	$P > 0.05$	—	—	↓0.40	↓0.40	—
							Between interv.	—	$P > 0.05$	—	—	$P > 0.05$	$P > 0.05$	—
Ostadrahimi et al. (56)	R, DB, PC, 8 wk (Iran)	M and W, 35 to 65	60 (30/30)	No	Kefir with *L. casei*, *L. acidophilus*, *B. lactis* (n.d.)	Dough	End vs BL (IG)	$P > 0.05$	—	—	—	—	—	—
							Between interv.	$P > 0.05$	—	—	—	—	—	—
Sharafedtinov et al. (57)	R, DB, PC, PG, 3 wk (Russia)	M and W, 30 to 69	40 (25/15)	No	Cheese with *L. plantarum* TENSIA (1 × 10^4) + LCD	PL cheese with LCD	End vs BL (IG)	↓5.70	↓2.00	—	$P > 0.05$	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—	—

[1] $n = 24$. The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of the intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant $P > 0.05$ was shown . Admin, administration; BF, body fat, BFM, body fat mass; BL, baseline; BW, body weight; CG, control group; CMD, cardiometabolic disease; CO, crossover; CT, controlled trial; DB, double-blind, FM, fermented milk, I, intervention; IG, intervention group; interv, internvention; ITT, intention-to-treat; LCD, low-calorie diet; MC, multicenter; M, men; n.d., no data; PC, placebo-controlled; PG, parallel, group; PL, placebo; R, randomized; SB, single-blind; SCFA, subcutaneous fat area; T2D, type 2 diabetes, VFA, visceral fat area; W, women; WC, waist circumference; —, indicates that the study does not evaluate this parameter.

TABLE 4 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in dairy products on CMD in subjects with T2D[1]

Author, year	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results: Fasting insulin (μIU/mL)	HOMA-IR	HbA1c (%)	Fasting glucose (mmol/L)	Plasma CRP (mg/L)
Added to yogurt matrix												
Rezaei et al. (58)	R, DB, PC, 4 wk (Iran)	M and W, 35 to 69	90 (45/45)	No	Yogurt with *L. acidophilus* La5, *B. lactis* BB12 (n.d.)	PL yogurt	End vs BL (IG)	—	—	↓0.40	↓0.89	$P > 0.05$
							Between interv.	—	—	−0.60	−1.23	−0.34
Mohamadshahi et al. (46)	R, DB, CT, PC, 8 wk (Iran)	M and W, 42 to 56	42 (21/21)	No	Yogurt with *L. acidophilus* La-5, *B. lactis* BB-12 (3.7×10^6)	PL yogurt	End vs BL(IG)	—	—	↓1.15	$P > 0.05$	$P > 0.05$
							Between interv.	—	—	−0.91	$P > 0.05$	$P > 0.05$
Ejtahed et al. (59)	R, DB, CT, PC, 6 wk (Denmark)	M and W, 30 to 60	60 (30/30)	No	Yogurt with *L. acidophilus* La5 (7.23×10^6), *B. lactis* BB12. (6.04×10^6)	PL yogurt	End vs BL (IG)	$P > 0.05$	—	$P > 0.05$	↓0.70	—
							Between interv.	$P > 0.05$	—	−0.42	−0.88	—
Added to FD matrix												
Naito et al. (50)	R, DB, PC, PG, 8 wk (Japan)	M and W, 20 to 64	100 (50/50)	No	FM with *L. casei* Shirota YIT 9029. ($>1.0 \times 10^{11}$)	PL non-FM	End vs BL (IG)	$P > 0.05$	$P > 0.05$	↓0.05	$P > 0.05$	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	—
Tonucci et al. (60)	R, DB, PC, PG, 6 wk (Brazil)	M and W, 35 to 60	45 (23/22)	No	FM with *L. acidophilus* La-5, *B. animalis* subsp. *lactis* BB-12 (2×10^9)	PL FM	End vs BL(IG)	$P > 0.05$	$P > 0.05$	↓0.67	$P > 0.05$	—
							Between interv.	$P > 0.05$	$P > 0.05$	−0.98	$P > 0.05$	—
Hove et al. (52)	R, DB, PC, 12 wk (Denmark)	M, 40 to 70	41 (23/18)	No	FM with *L. helveticus* Cardi04 (n.d.)	PL FM	End vs BL(IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	−0.90	$P > 0.05$
Ostadrahimi et al. (56)	R, DB, PC, 8 wk (Iran)	M and W, 35 to 65	60 (30/30)	No	Kefir with *L. casei*, *L. acidophilus*, *B. lactis* (n.d.)	Dough	End vs BL(IG)	—	—	↓1.21	↓1.24	—
							Between interv.	—	—	$P > 0.05$	−1.17	—

[1] $n = 7$. The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant was shown, $P > 0.05$. Admin, administration; BL, baseline; CG; control group; CMD, cardiometabolic disease; CRP, C-reactive protein; CT, controlled trial; DB, double-blind; FM, fermented milk; HbA1c, glycosylated hemoglobin; I, intervention; IG, intervention group; ITT, intention-to-treat; M, men; n.d., no data; PC, placebo-controlled; PG, parallel, group; PL, placebo; R, randomized; T2D, type 2 diabetes; W, women; —, indicates that the study does not evaluate this parameter.

TABLE 5 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in dairy products on CMD in subjects with hypercholesterolemia[1]

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Total cholesterol (mmol/L)	LDL cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Triglycerides (mmol/L)
Added to yogurt matrix											
Nishiyama et al. (61)	R, DB, CT, PC, 8 wk (Japan)	W, 23 to 66	76 (37/39)	No	Yogurt with L. *lactis* 11/19-B1 and BB-12 (n.d.)	PL yogurt	End vs BL (IG)	↓0.3	↓0.25	$P > 0.05$	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—
Ivey et al. (62)	R, DB, CT, PC, 6 wk (Australia)	M and W, ≥55	156 (40/37) (39/40)	No	I1. Yogurt with *L. acidophilus* La5, *B. lactis* BB12 + Capsules with *L. acidophilus* La5, *B. lactis* BB12 (3×10^9)	Milk + PL capsules	End vs BL (I1)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
					I2. Yogurt with *L. acidophilus* La5, *B. lactis* BB12 (3×10^9) + PL capsules	Milk + PL capsules	End vs BL (I2)	$P > 0.05$	$P > 0.05$	$P > 0.05$	P > 0.05
					I3. Milk + Capsules with *L. acidophilus* La5, *B. lactis* BB12 (3×10^9)	Milk + PL capsules	End vs BL (I3)	$P > 0.05$	$P > 0.05$	$P > 0.05$	P > 0.05
							Between interv. (I1 vs I3)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Mohamadshahi et al. (45)	R, DB, CT, PC, 8 wk (Iran)	M and W, ≈51	42 (21/21)	No	Yogurt with *L. acidophilus* La-5, *B. lactis* BB-12 (3.7×10^6)	PL yogurt	End vs BL (IG)	↓0.67	↓0.79	$P > 0.05$	$P > 0.05$
							Between interv. $P > 0.05$	$P > 0.05$	-0.61	+0.89	$P > 0.05$
Added to FD matrix											
Sperry et al. (63)	R, DB, PC, PG, 28 d (Brazil)	W, 35 to 72	30 (15/15)	No	Cheese with *L. casei* 01 (1×10^8)	PL cheese	End vs BL (IG)	↓0.32	↓0.28	↑0.14	↓0.13
							Between interv.	+0.09	−0.12	+0.1	−0.05
Naito et al. (50)	R, DB, PC, PG, 8 wk (Japan)	M and W, 20 to 64	100 (50/50)	No	FM with *L. casei* Shirota YIT 9029. ($>1.0 \times 10^{11}$)	PL non-FM	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	−7.5	−6.0	$P > 0.05$	$P > 0.05$

[1] $n = 5$. The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant a $P > 0.05$ was shown. Admin., administration; BL, baseline; CG, control group; CMD, cardiometabolic disease; CT, controlled trial; DB, double-blind; FD, fermented dairy; FM, fermented milk; IG, intervention group; ITT, intention-to-treat; M, men; n.d., no data; PC, placebo-controlled; PG, parallel-group; PL, placebo; R, randomized; ref, reference; W, women; —, indicates that the study does not evaluate this parameter.

TABLE 6 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in dairy products on CMD in subjects with metabolic syndrome[1]

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	WC (cm)	Triglycerides (mg/dL)	Total cholesterol (mmol/L)	LDL cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Fasting glucose (mmol/L)
Added to yogurt matrix													
Rezazadeh et al. (64)	R, DB, PC, PG, 8 wk (Iran)	M and W, 20 to 65	44 (22/22)	No	Yogurt with *Lactobacillus acidophilus* La5 (6.45 × 10^6) and *Bifidobacterium lactis* BB12 (4.94 × 10^6)	PL yogurt	End vs BL (IG)	—	—	—	—	—	↓4.81
							Between interv.	—	—	—	—	—	−3.80
Added to milk matrix													
Bernini et al. (65)	R, 45 d (Brazil)	M and W, 18 to 60	54 (26/25)	No	Milk with *B. lactis* subsp. nov. HN019 (3.4 × 10^8)	Untreated	End vs BL (IG)	$P > 0.05$	$P > 0.05$	↓0.39	↓0.45	$P > 0.05$	$P > 0.05$
							Between interv.	$P > 0.05$	$P > 0.05$	−0.55	−0.40	$P > 0.05$	$P > 0.05$

[1] $n = 2$. The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant was shown, $P > 0.05$. admin., administration; BL, baseline; CG, control group; CMD, cardiometabolic disease; DB, double-blind; IG, intervention group; ITT, intention-to-treat; M, men; PC, placebo-controlled; PG, parallel-group; PL, placebo; R, randomized; ref, reference; W, women; —, indicates that the study does not evaluate this parameter.

mortality risk development did not show significant results (**Supplemental Figure3**A).

Fermented dairy intake and T2D risk.
The meta-analysis of 7 PCSs (28, 30–32, 34, 36, 37) evaluating the relation of yogurt intake with T2D risk development resulted in a significant 27% reduction in T2D risk development [RR (95% CI); 0.73 (0.70, 0.76)], and the heterogeneity between PCSs was moderate ($P = 0.070$, $I^2 = 57.6\%$; Figure 2B).

The meta-analysis of 3 PCSs (28, 32, 35) that evaluated the relation of cheese intake with T2D risk development resulted in a significant 24% increase in T2D risk development [RR (95% CI); 1.24 (1.03, 1.49)], and the heterogeneity between PCSs was low ($P = 0.787$, $I^2 = 0.0\%$; Figure 2C).

The meta-analysis of 3 PCSs (28, 32, 33) evaluating the relation between total fermented dairy intake and T2D risk development did not show significant results (Supplemental Figure 3B).

Fermented dairy intake and metabolic syndrome risk.
The meta-analysis of 3 PCSs (39–41) that evaluated the relation of yogurt intake with metabolic syndrome risk development resulted in a significant 20% reduction in metabolic syndrome risk development [RR (95% CI); 0.80 (0.74, 0.87)], and the heterogeneity between PCSs was low ($P = 0.416$, $I^2 = 0.0\%$; Figure 2D).

Meta-analysis of RCTs with dairy matrix on CMDs

Figures 3 and **4** show the forest plot of RCTs of probiotic supplementation added into a dairy matrix with significant CMD results. Additionally, Tables 3–6 show a summary of the individual information extracted from each RCT included in the systematic review that evaluated the effectiveness of probiotic supplementation added into a dairy matrix on CMDs in subjects with ≥1 CMD (obesity, T2D, hypercholesterolemia, and metabolic syndrome) ($n = 24$). The complete information obtained from each study is shown in **Supplemental Table 3.**

Effects of probiotic supplementation into a dairy matrix on anthropometric parameters in overweight/obese subjects.
The results of the meta-analysis of the 6 RCTs (43, 45, 46, 50, 53, 54) that evaluated the effect of probiotic intake added into a dairy matrix on BMI changes revealed a significant reduction in BMI [WMD (95% CI); −0.33 (−0.51, −0.16) kg/m^2] (Figure 3A). The probiotic strain that showed a significant reduction in BMI was *L. gasseri* SBT2055 (53, 54), and the heterogeneity between the RCTs was moderate ($P = 0.042$, $I^2 = 56.7\%$; Figure 3A).

The meta-analysis results of the 6 RCTs (43, 45, 46, 52–54) that evaluated the effect of probiotic supplementation added into a dairy matrix on WC changes showed a significant reduction in WC [WMD (95% CI); −0.49 (−0.68, −0.29) cm] (Figure 3B). The probiotic strain that showed a significant reduction in WC was *L. gasseri* SBT2055 (53, 54),

TABLE 7 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in powder or capsules on CMD in subjects with obesity[1]

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results						
								BW (kg)	BMI (kg/m^2)	WC (cm)	BFM (kg)	BF (%)	VFA (cm^2)	SCFA (cm^2)
Khalili et al. (66)	R, DB, PC, PG, 8 wk (Iran)	M and W, 60 to 50	40 (20/20)	No	Capsules with *Lactobacillus casei* (10^8)	PL powder	End vs BL (IG)	↓1.20	↓0.485	↓2.15	—	—	—	—
							Between interv.	−1.52	−0.84	−1.77	—	—	—	—
Kim et al. (67)	R, DB, PC, 12 wk (Korea)	M and W, 20 to 75	90 (30/30/30)	No	I1. Capsules with *L. gasseri* BNR17 (10^9)	PL powder	End vs BL (I1)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
					I2. Capsules with *L. gasseri* BNR17 (10^{10})	PL powder	End vs BL (I2)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
							Between interv. (I1 vs CG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	$P > 0.05$	—
							Between interv. (I2 vs CG)	−4.4	$P > 0.05$	$P > 0.05$	—	—	−21.6	—
Kobyliak et al. (68)	R, DB, PC, PG, 8 wk (Ukraine)	M and W, 18 to 75	53 (31/22)	No	Powder with 14 probiotic strains of *Lactobacillus* + *Lactococcus* (6×10^{10}), *Bifidobacterium* (1×10^{10}), *Propionibacterium* (3×10^{10}), *Acetobacter* (1×10)	PL powder	End vs BL (IG)	↑0.94	↑0.26	↑0.75	—	—	—	—
							Between interv.	+0.79	$P > 0.05$	+0.62	—	—	—	—
Minami et al. (69)	R, DB, PC, PG, 12 wk (Japan)	M and W, 20 to 64	80 (40/40)	No	Capsules with *B. breve* B-3 (2×10^{10})	PL powder	End vs BL (IG)	—	$P > 0.05$	↓1.0	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	—	$P > 0.05$	$P > 0.05$	−0.6	−0.7	$P > 0.05$	$P > 0.05$
Pedret et al. (70)	R, DB, PC, PG, 12 wk (Spain)	M and W, >18	126 (42/44/40)	Yes	I1. Capsules with *B. animalis subsp. lactis* CECT 8145 (1×10^{10})	PL powder	End vs BL (I1)	—	↓0.34	↓1.74	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
					I2. Heat-killed *B. animalis subsp. lactis* CECT 8145 (1×10^{10})	PL powder	End vs BL (I2)	—	$P > 0.05$	↓1.88	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv. (I1 vs CG)	—	−0.43	−1.88	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv. (I2 vs CG)	—	$P > 0.05$	−1.66	$P > 0.05$	$P > 0.05$	−7.01	$P > 0.05$
Szulinska et al. (71)	R, DB, PC, PG, 12 wk (Poland)	W, 45 to 70	81 (27/27/27)	No	I1: Powder of Ecologic® Barrier: *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. bravis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and W58 (1×10^{10})	PL powder	End vs BL (I1)	—	$P > 0.05$	−0.54	−0.22	$P > 0.05$	$P > 0.05$	−0.83
					I2. Powder of Ecologic® Barrier (2.5×10^9)	PL powder	End vs BL (I2)	—	$P > 0.05$	↓1.06	↓0.62	↓0.54	↓0.58	↓0.99
							Between interv. (I1 vs CG)	—	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Gomes et al. (72)	R, DB, PC, PG, 8 wk (Brazil)	W, 20 to 59	43 (21/22)	No	Powder of Danisco®: *L. acidophilus* LA-14, *L. casei* LC-11, *L. lactis* LL-23, *B. bifidum* BB-06, *B. lactis* BL-4 (2×10^{10})	PL powder	End vs BL (IG)	↓0.98	↓0.45	↓5.14	↓1.34	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	−1.81	$P > 0.05$	—	—	—

(*Continued*)

TABLE 7 (*Continued*)

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results: BW (kg)	BMI (kg/m^2)	WC (cm)	BFM (kg)	BF (%)	VFA (cm^2)	SCFA (cm^2)
Mahadzir et al. (73)	R, DB, CT, PG, 4 wk (Malaysia)	M and W, 18 to 50	24 (12/12)	No	Powder of *L. acidophilus, L. casei, L. lactis, B.bifidum, B. longum, B. infantis* (60 × 10^9)	PL powder	End vs BL (IG)	$P > 0.05$	—	$P > 0.05$	—	—	—	—
							Between interv.	$P > 0.05$	—	$P > 0.05$	—	—	—	—
Mobini et al. (74)	R, DB, PC, PG, 12 wk (Sweden)	M and W, 50 to 75	44 (14/15/15)	No	I1. Powder of *L. reuteri* DS17938 (1 × 10^{10})	PL powder	End vs BL (I1)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—
					I2. *L. reuteri* DS17938 (1 × 10^8)	PL powder	End vs BL (I2)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—
Sabico et al. (75)	R, DB, PC, 12 wk (Saudi Arabia)	M and W, 30 to 60	61 (31/30)	Yes	Powder of Ecologic® Barrier (2.5 × 10^9)	PL powder	End vs BL (IG)	$P > 0.05$	$P > 0.05$	—	—	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	—	—	—	—
Firouzi et al. (76)	R, DB, PG, PC, 12 wk (Malaysia)	M and W, 30 to 70	136 (68/68)	Yes	I1. Powder of *L. acidophilus, L. casei, L. lactis, B. bifidum, B. longum, B. infantis.* (6 × 10^{10}) only in men	PL powder	End vs BL (I1)	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
					I2. Same I1 powder only in women	PL powder	End vs BL (I2)	$P > 0.05$	$P > 0.05$	↓2.00	—	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	—	—	—
Higashikawa et al. (77)	R, DB, PC, PG, 12 wk (Japan)	M and W, 20 to 70	62 (21/21/20)	Yes	I1. Powder of *Pediococcus pentosaceus* LP28, living	PL powder	End vs BL (I1)	—	$P > 0.05$	$P > 0.05$	$P > 0.05$	↓0.51	—	—
					I2. Powder of *P. pentosaceus* LP28, heat-killed (1 × 10^{11})	PL powder	End vs BL (I2)	—	$P > 0.05$	↓1.83	↓1.77	↓ 1.03		
							Between interv. (I2 vs CG)	—	$P > 0.05$	−2.84	−1.17	−1.11	—	—
Jung et al. (78)	R, DB, PC, 12 wk (Korea)	M and W, 20 to 65	95 (49/46)	No	Powder of *L. curvatus* HY7601 and *L. plantarum* KY1032 (5 × 10^9)	PL powder	End vs BL (IG)	↓0.65	↓0.24	↓0.50	—	—	$P > 0.05$	↓3.60
							Between interv.	−1.0	−0.3	$P > 0.05$	—	—	$P > 0.05$	−8.10
Chung et al. (20)	R, DB, PC, 12 wk (Korea)	M and W, 25 to 65	37 (18/19)	No	Capsules of *Lactobacillus* JBD301 (1 × 10^9)	Vegetable cream capsule	End vs BL (IG)	↑0.31	↑0.32	—	$P > 0.05$	—	—	—
							Between interv.	−1.46	−1.33	—	$P > 0.05$	—	—	—
Minami et al. (79)	R, DB, PG, PC, 12 wk (Japan)	M and W, 40 to 69	44 (19/25)	No	Capsules of *B. breve* B-3 (5 × 10^{10})	PL capsules	End vs BL (IG	↑0.20	$P > 0.05$	—	↓0.70	↓1.00	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	↓0.1	$P > 0.05$	—	—
Jung et al. (80)	R, DB, PC, 12 wk (Korea)	M and W, 19 to 60	62 (29/23)	Yes	Capsules of *L. gasseri* BNR17 (1 × 10^{10})	PL capsules	End vs BL (IG)	$P > 0.05$	↓0.60	↓2.00	—	$P > 0.05$	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—
Aller et al. (81)	R, DB, PC, 12 wk (Spain)	M and W, 39 to 59	28 (14/14)	No	Tablet of *L. bulgaricus, Streptococcus thermophiles* (5 × 10^8)	PL tablet	End vs BL (IG)	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—	—	—

[1] $n = 17$. The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant was shown, $P > 0.05$. admin., administration; BF, body fat; BFM, body fat mass; BL, baseline; BW, body weight; CG, control group; CMD, cardiometabolic disease; CT, controlled trial; DB, double-blind; I, intervention IG, intervention group; ITT, intention-to-treat; M, men; PC, placebo-controlled; PG, parallel-group; PL, placebo; R, randomized; ref, reference; SCFA, subcutaneous fat area; VFA, visceral fat area; W, women; WC, waist circumference; —, indicates that the study does not evaluate this parameter.

TABLE 8 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in powder or capsules on CMD in subjects with T2D[1]

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (CFU/d) (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results: Fasting insulin (μIU/mL)	HOMA-IR	HbA1c (%)	Fasting glucose (mmol/L)	Plasma CRP (mg/L)
Razmpoosh et al. (82)	R, DB, PC, PG, 6 wk (Iran)	M and W, 30 to 75	68 (34/34)	No	Capsules with *Lactobacillus acidophilus* (2×10^9), *L. casei* (7×10^9), *L. rhamnosus* (1.5 × 109), *L. bulgaricus* (2×10^8), *Bifidobacterium breve* (3×10^{10}), *B. longum* (7×10^9), *Streptococcus thermophiles* (1.5×10^9)	PL capsules	End vs BL (IG)	$P > 0.05$	$P > 0.05$	—	↓17.8	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	$P > 0.05$	—
Sabico et al. (83)	R, DB, PC, PG, 24 wk (Saudi Arabia)	M and W, 30 to 60	96 (48/48)	Yes	Powder with Ecologic®Barrier. (2.5×10^9)	PL powder	End vs BL (IG)	↓3.8	↓3.4	—	↓4.5	↓2.9
							Between interv.	$P > 0.05$	−0.34	—	$P > 0.05$	$P > 0.05$
Kassaian et al. (84)	R, DB, PC, PG, 24 wk (Iran)	M and W, 35 to 75	120 (40/40/40)	No	Freeze-dried powder with *L. acidophilus*, *B. lactis*, *B. bifidum*, and *B. longum*. (1×10^9)	PL powder	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	↓6.49	—
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	—
Khalili et al. (66)	R, DB, PC, PG, 8 wk (Iran)	M and W, 30 to 50	40 (20/20)	No	Capsules with *L. casei.* (10^8)	PL powder	End vs BL (IG)	↓2.33	↓29.72	$P > 0.05$	↓28.35	—
							Between interv.	−3.12	−32.31	$P > 0.05$	−28.32	—
Kobyliak et al. (68)	R, DB, PC, PG, 8 wk (Ukraine)	M and W, 18 to 75	53 (31/22)	No	Powder with 14 alive probiotic strains of *Lactobacillus* + *Lactococcus* (6×10^{10}), *Bifidobacterium* (1×10^{10}), Propionibacterium (3×10^{10}), Acetobacter (1×10) genera	PL powder	End vs BL (IG)	$P > 0.05$	—	$P > 0.05$	$P > 0.05$	—
							Between interv.	$P > 0.05$	—	$P > 0.05$	$P > 0.05$	—
Hsieh et al. (85)	R, DB, PC, PG, 9 wk (Taiwan)	M and W, 25 to 70	74 (25/25/24)	No	I1. Capsules with L. *reuteri* ADR-1 (4×10^9)	PL powder	End vs BL (I2)	—	—	—	—	—
					I2. Capsules with Heat-killed *L. reuteri* ADR-3 (2×10^{10})	PL powder	End vs BL (I2)	—	—	—	—	—
							Between interv. (I1 vs CG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv. (I2 vs CG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Raygan et al. (86)	R, DB, PC, PG, 12 wk (Iran)	M and W, 40 to 85	60 (30/30)	No	Capsules with *B. bifidum* (2×10^9), *L. casei* (2×10^9), *L. acidophilus* (2×10^9)	PL capsules	End vs BL (IG)	—	—	—	—	—
							Between interv.	−2.09	−0.50	—	−20.02	−0.88
Mobini et al. (74)	R, DB, PC, PG, 12 wk (Sweden)	M and W, 50 to 75	44 (14/15/15)	No	Powder with *L. reuteri* DS17938. (1×10^8)	PL powder	End vs BL (IG)	—	—	$P > 0.05$	—	$P > 0.05$
							Between interv.	—	—	$P > 0.05$	—	$P > 0.05$

(*Continued*)

TABLE 8 (*Continued*)

Study (ref)	Study design, duration (country)	Gender, age (y)	*n* (I/PL)	ITT	Intervention (CFU/d) (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results				
								Fasting insulin (μIU/mL)	HOMA-IR	HbA1c (%)	Fasting glucose (mmol/L)	Plasma CRP (mg/L)
Sabico et al. (75)	R, DB, PC, 12 wk (Saudi Arabia)	M and W, 30 to 60	61 (31/30)	Yes	Powder with Ecologic® Barrier. (2.5×10^9)	PL powder	End vs BL (IG)	↓3.00	↓3.20	—	↓3.20	—
							Between interv.	$P > 0.05.$	$P > 0.05$	—	$P > 0.05$	—
Firouzi et al. (76)	R, DB, PG, PC, 12 wk (Malaysia)	M and W, 30 to 70	136 (68/68)	Yes	Powder with *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum*, *B. infantis*. (6×10^{10})	PL powder	End vs BL (IG)	↓2.90	$P > 0.05$	↓0.14	$P > 0.05$	$P > 0.05$
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Mazloom et al. (21)	R, SB, 6 wk (Iran)	M and W, 25 to 65	34 (16/18)	No	Capsules with *L. acidophilus*, *L. bulgaricus*, *L. bifidum*, *L. casei*. (n.d.)	Magnesium stearate	End vs BL (IG)	$P > 0.05$	$P > 0.05$	—	—	—
							Between interv.	$P > 0.05$	$P > 0.05$	—	—	—

[1] $n = 11$. The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant was shown, $P > 0.05$. admin., administration; BL, baseline; CG, control group; CMD, cardiometabolic disease; CRP, C-reactive protein; CT, controlled trial; DB, double-blind; HbA1c, glycosylated hemoglobin; ITT, intention-to-treat; IG, intervention group; M, men; n.d., no data; PC, placebo-controlled; PG, parallel-group; PL, placebo; R, randomized; ref, reference; T2D, type 2 diabetes; W, women; —, indicates that the study does not evaluate this parameter.

and the heterogeneity between the RCTs was high ($P < 0.001$, $I^2 = 80.5\%$; Figure 3-B), and the covariate "number of probiotic" (single or multiple probiotic) and "duration of intervention" explained 92.9% and 76.3% of the between-study heterogeneity, respectively (**Supplemental Table 4**).

The meta-analysis of the 5 RCTs (45, 46, 50, 53, 54) evaluating the effect of probiotic supplementation added into a dairy matrix on BF changes revealed a significant reduction in BF [WMD (95% CI); −0.41% (−0.60%, −0.21%)] (Figure 3C). The probiotic strain that presented a significant reduction in BF was *L. gasseri* SBT2055 (53, 54), and the heterogeneity between the RCTs was moderate ($P = 0.015$, $I^2 = 67.5\%$; Figure 3C). The covariate "duration of intervention" explained 86.5% of the between-study heterogeneity (Supplemental Table 4).

With respect to BW changes, our meta-analysis of 7 RCTs (43, 45, 46, 50–52, 54, 56) did not show significant results (**Supplemental Figure 4**A). Regarding BFM, the authors did not have sufficient RCTs to perform meta-analysis.

Effects of probiotic supplementation into a dairy matrix on diabetic parameters in T2D subjects.

Our meta-analysis of the 6 RCTs (45, 50, 52, 56, 58, 60) that evaluated the effect of probiotic supplementation added into a dairy matrix on fasting glucose changes displayed a significant reduction [WMD (95% CI); −0.37 (−0.58, −0.17) mmol/L] (Figure 3D). The probiotic strains that revealed a significant reduction in fasting glucose were *L. helveticus* Cardi04 (52), a combination of *L. acidophilus* La5 and *B. lactis* BB12 (58), and a combination of *L. casei*, *L. acidophilus* , and *B. lactis* (56). In addition, the heterogeneity between the RCTs was observed to be moderate ($P = 0.058$, $I^2 = 53.1\%$; Figure 3D).

The meta-analysis of 6 RCTs (45, 50, 52, 56, 58, 60) that evaluated fasting insulin, HbA1c, and plasma CRP did not show significant results (Supplemental Figure 4B–D).

Effects of probiotic supplementation into a dairy matrix on lipid profiles in hypercholesterolemic subjects.

The meta-analysis of the 4 RCTs (45, 50, 61, 63) evaluating the effect of probiotic supplementation added into a dairy matrix on total cholesterol changes showed a significant reduction [WMD (95% CI); −0.46 (−0.73, −0.19) mmol/L] (Figure 4A). The probiotic strains that yielded significant reductions in total cholesterol concentrations were *L. casei* 01 (63) and *L. casei* Shirota YIT9029 (50), and the heterogeneity between the RCTs was low ($P = 0.696$, $I^2 = 0.0\%$; Figure 4A).

The meta-analysis of the 4 RCTs (45, 50, 61, 63) that evaluated the effect of probiotic supplementation added into a dairy matrix on LDL-cholesterol changes exposed a significant reduction [WMD (95% CI); −0.50 (−0.77, −0.22) mmol/L] (Figure 4B). The probiotic strains that showed a significant LDL-cholesterol reduction were *L. casei* 01 (63) and *L. casei* Shirota YIT9029 (50), and the heterogeneity between RCTs was low ($P = 0.829$, $I^2 = 0.0\%$; Figure 4B).

TABLE 9 Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in powder or capsules on CMD in subjects with hypercholesterolemia[1]

Study (ref)	Study design, duration (country)	Gender, age (years)	*n* (I/PL)	ITT	Intervention (CFU/d) (IG) (type of admin.—probiotic strain—CFU/d)	Control group	Compared with	Significant results: Total cholesterol (mmol/L)	Significant results: LDL cholesterol (mmol/L)	Significant results: HDL cholesterol (mmol/L)	Significant results: Triglycerides (mmol/L)
Culpepper et al. (87)	R, DB, PC, CO, 18 wk (USA)	M and W, 18 to 65	114	No	I1. Capsules of *Bacillus subtilis* R0179 (5×10^9)	PL powder	End vs BL (I1)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
					I2. *Lactobacillus plantarum* HA-119 (5×10^9)	PL powder	End vs BL (I2)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
					I3. *Bifidobacterium animalis subsp. lactis* B94 (5×10^9)	PL powder	End vs BL (I3)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Brahe et al. (88)	R, PG, PC, 6 wk (Denmark)	Menopausal W, 40 to 70	53 (18/19/16)	No	Powder with *L. paracasei* spp. *paracasei* F1 (9.4×10^{10})	PL powder	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
Fuentes et al. (89)	R, DB, PC, PG, 16 wk (Spain)	M and W, 18 to 65	60 (30/30)	No	Capsules with *L. plantarum* CECT7527, CECT7528, CECT7529 (1×10^{10})	PL capsules	End vs BL (IG)	↓0.7	↓0.53	↑0.07	↓0.87
							Between interv.	−0.45	−0.28	+0.06	−0.70
Rerksuppaphol et al. (90)	R, DB, CT, PC, 6 wk (Thailand)	M and W, 40 to 58	64 (31/33)	No	Capsules with *L. acidophilus* (3×10^9), *L. bifidum* (3×10^9)	PL capsules	End vs BL (IG)	↓0.64	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	−1.20	−0.70	−0.08	$P > 0.05$
Jones et al. (91)	R, DB, PC, PG, MC, 13 wk (Czech Republic)	M and W, 20 to 75	127 (66/61)	No	Capsules with *L. reuteri* NCIMB 30,242 (2.9×10^9)	PL capsules	End vs BL (IG)	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
							Between interv.	−0.58	−0.51	$P > 0.05$	$P > 0.05$

[1] $n = 5$, The difference between interventions was calculated by performing subtraction of the difference between end and baseline of each intervention. (End vs BL) indicated the difference between end and baseline of intervention group. If the result was statistically significant, the difference was shown; if the result was statistically nonsignificant was shown, $P > 0.05$. admin., administration; BL, baseline; CG, control group; CMD, cardiometabolic disease; CO, crossover; CT, controlled trial; DB, double-blind; ITT, intention-to-treat; IG, intervention group; M, men; MC, multicenter; n.d., no data; PC, placebo-controlled; PG, parallel-group; PL, placebo; R, randomized; ref, reference; W, women.

Our meta-analysis of the 4 RCTs (45, 50, 61, 63) evaluating the effect of probiotic supplementation added into a dairy matrix on HDL-cholesterol changes demonstrated a significant increase [WMD (95% CI); 0.26 (0.01, 0.52) mmol/L] (Figure 4C). The probiotic strains that revealed significant increases in HDL cholesterol were *L. casei* 01 (63) and a combination of *L. acidophilus* La-5 and *B. lactis* BB-12 (45), and the heterogeneity between the RCTs was moderate ($P = 0.007$, $I^2 = 56.3\%$; Figure 4C).

The meta-analysis of the 3 RCTs (45, 50, 63) that evaluated the effect of probiotic supplementation added into a dairy matrix on triglyceride changes showed a significant reduction [WMD (95% CI); −0.46 (−0.75, −0.14) mmol/L] (Figure 4D). The probiotic strain that showed a significant reduction in triglyceride concentrations was *L. casei* 01 (63), and the heterogeneity between the RCTs was low ($P = 0.505$, $I^2 = 0.0\%$; Figure 4D).

Meta-analysis of RCTs with a capsule/powder matrix on CMD

Figures 5–7 show the forest plots of RCTs with capsule/powder matrix with significant CMD results. Additionally, Tables 7–9 present a summary of the individual information extracted from each RCT included in the systematic review that evaluated the effectiveness of probiotic supplementation as capsules or powder on CMDs in subjects with ≥1 CMD (obesity, T2D, hypercholesterolemia, and metabolic syndrome) ($n = 28$). The complete information obtained from each study is shown in **Supplemental Table 5.**

Effects of probiotic supplementation with capsules/powder on anthropometric parameters in overweight/obese subjects.

The results of the meta-analysis of the 10 RCTs (20, 66, 68, 72, 73, 76, 78–80, 83) that evaluated the effect of probiotic intake in capsule/powder form on BW changes revealed a significant reduction in BW [WMD (95% CI); −0.26 (−0.43, −0.09) kg] (Figure 5A). The probiotic strains that showed significant BW reduction were *L. casei* (66), *L. gasseri* (80), and a combination of *L. curvatus* and *L. plantarum* (78). The heterogeneity between the RCTs was moderate ($P = 0.002$, $I^2 = 66.4\%$; Figure 5A), and the covariate "number of probiotic" (single or multiple probiotic) explained 84% of the between-study heterogeneity (**Supplemental Table 6**).

The results of the meta-analysis of the 12 RCTs (20, 66, 68, 70–72, 75–80) that evaluated the effect of probiotic intake in capsule/powder form on BMI changes revealed a significant reduction in BMI [WMD (95% CI); −0.35 (−0.48, −0.22) kg/m^2] (Figure 5B). The probiotic strains that showed a significant BMI reduction were *L. casei* (66), *L. gasseri* (80), *Pediococcus pentosaceus* LP28 (77), and a combination of *L. curvatus* and *L. plantarum* (78). In addition, the heterogeneity between the RCTs was moderate ($P = 0.076$, $I^2 = 36.7\%$; Figure 5B).

The meta-analysis results of the 9 RCTs (66, 68, 70–73, 77, 78, 80) evaluating the effect of probiotic intake in

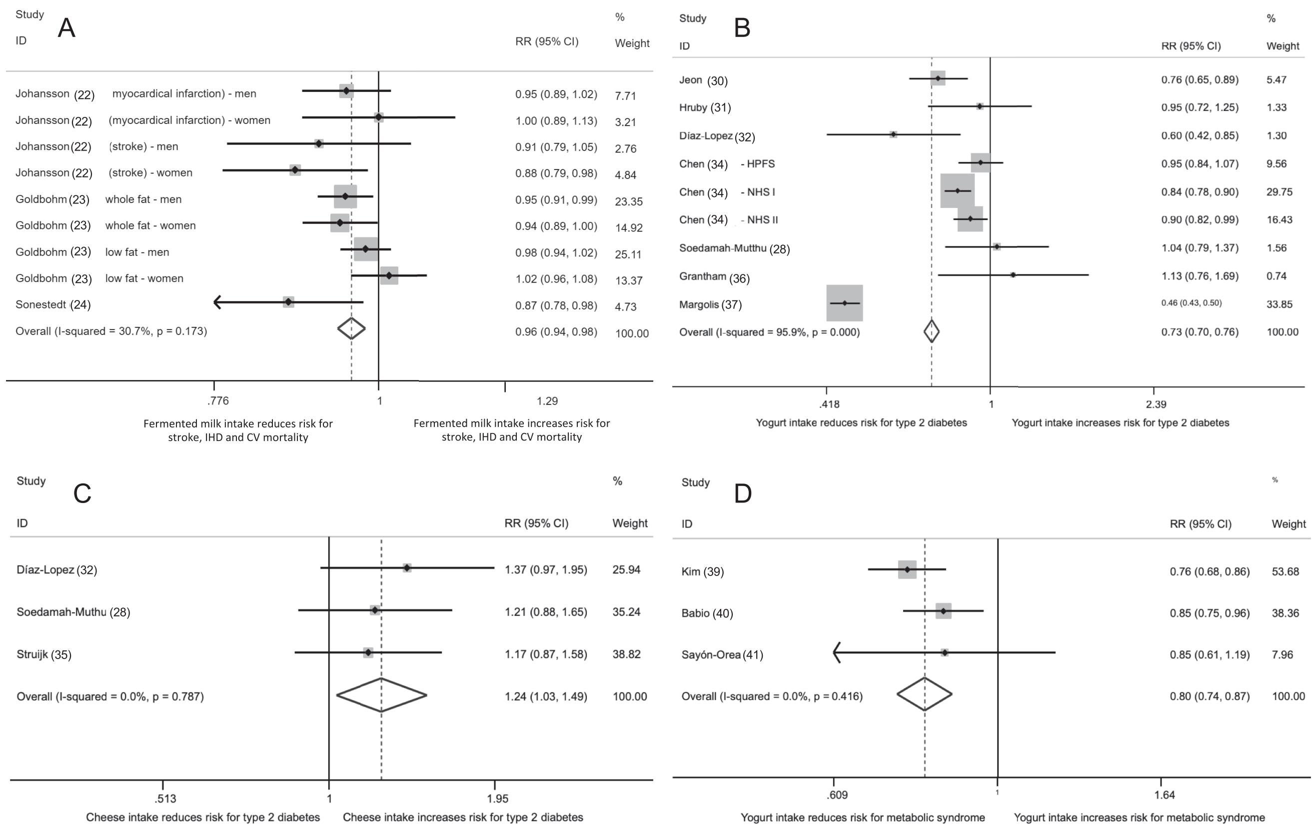

FIGURE 2 Forest plot of meta-analysis of observational studies that assess the relation between fermented dairy intake and cardiometabolic diseases. A: Fermented milk intake and risk of stroke, IHD, and CV mortality ($P < 0.001$). B: Yogurt intake and risk of type 2 diabetes development ($P < 0.001$). C: Cheese intake and risk of type 2 diabetes development ($P = 0.023$). D: Yogurt intake and risk of metabolic syndrome development ($P < 0.001$). IHD, ischemic heart disease; CV, cardiovascular.

capsule/powder form on WC changes showed a significant reduction in WC [WMD (95% CI); −0.37 (0.52, −0.21) cm] (Figure 5C). The probiotic strains that revealed a significant WC reduction were *L. casei* (66), Ecologic Barrier® (Winclove Probiotics, Amsterdam, The Netherlands)(71), Danisco® (72), *Pediococcus pentosaceus* LP28 (77), and *L. gasseri* (80). The heterogeneity between the RCTs was moderate ($P = 0.015$, $I^2 = 53.0\%$; Figure 5C), and the covariate "number of probiotic" (single or multiple probiotic) explained 83.1% of the between-study heterogeneity (Supplemental Table 6).

The meta-analysis of the 5 RCTs (20, 70–72, 77, 79) that evaluated the effect of probiotic intake in capsule/powder form on BFM changes revealed a significant reduction in BFM [WMD (95% CI); −0.30 (−0.48, −0.12) kg] (Figure 5D). The probiotic strains that showed significant reduction in BFM were *Pediococcus pentosaceus* LP28 (77) and *B. breve* (79), and the heterogeneity between the RCTs was moderate ($P = 0.016$, $I^2 = 59.3\%$; Figure 5D).

The meta-analysis of the 3 RCTs (70, 71, 78) evaluating the effect of probiotic intake in capsule/powder form on VFA changes revealed a significant reduction in VFA [WMD (95% CI); −0.42 (−0.63, −0.21) kg] (Figure 6A). The probiotic strains that showed significant reduction in VFA were a combination of *L. curvatus* and *L. plantarum* (78), and the heterogeneity between the RCTs was high ($P < 0.001$, $I^2 = 85.6\%$; Figure 6A).

Our meta-analysis of the 3 RCTs (70, 71, 78) that evaluated the effect of probiotic intake in capsule/powder form on SCFA changes revealed a significant reduction in SCFA [WMD (95% CI); −0.36 (−0.57, −0.14) kg] (Figure 6B). The probiotic strain that showed a significant reduction in SCFA was a combination of *L. curvatus* and *L. plantarum* (78), and the heterogeneity between the RCTs was high ($P < 0.001$, $I^2 = 95.3\%$; Figure 6B). The covariate "number of probiotic" (single or multiple probiotic) explained 90.4% of the between-study heterogeneity (Supplemental Table 6).

With respect to BF changes, our meta-analysis of 5 RCTs (70, 71, 77–79) did not show significant results (**Supplemental Figure 5**).

Effects of probiotic supplementation with capsule/powder on diabetic parameters in T2D subjects.

The results of the meta-analysis of the 9 RCTs (21, 66, 68, 76, 82–86) evaluating the effect of probiotic intake in capsule/powder form displayed a significant fasting glucose reduction [WMD (95% CI); −0.28 (−0.45, −0.12) mmol/L] (Figure 6C). The probiotic strains that showed fasting glucose

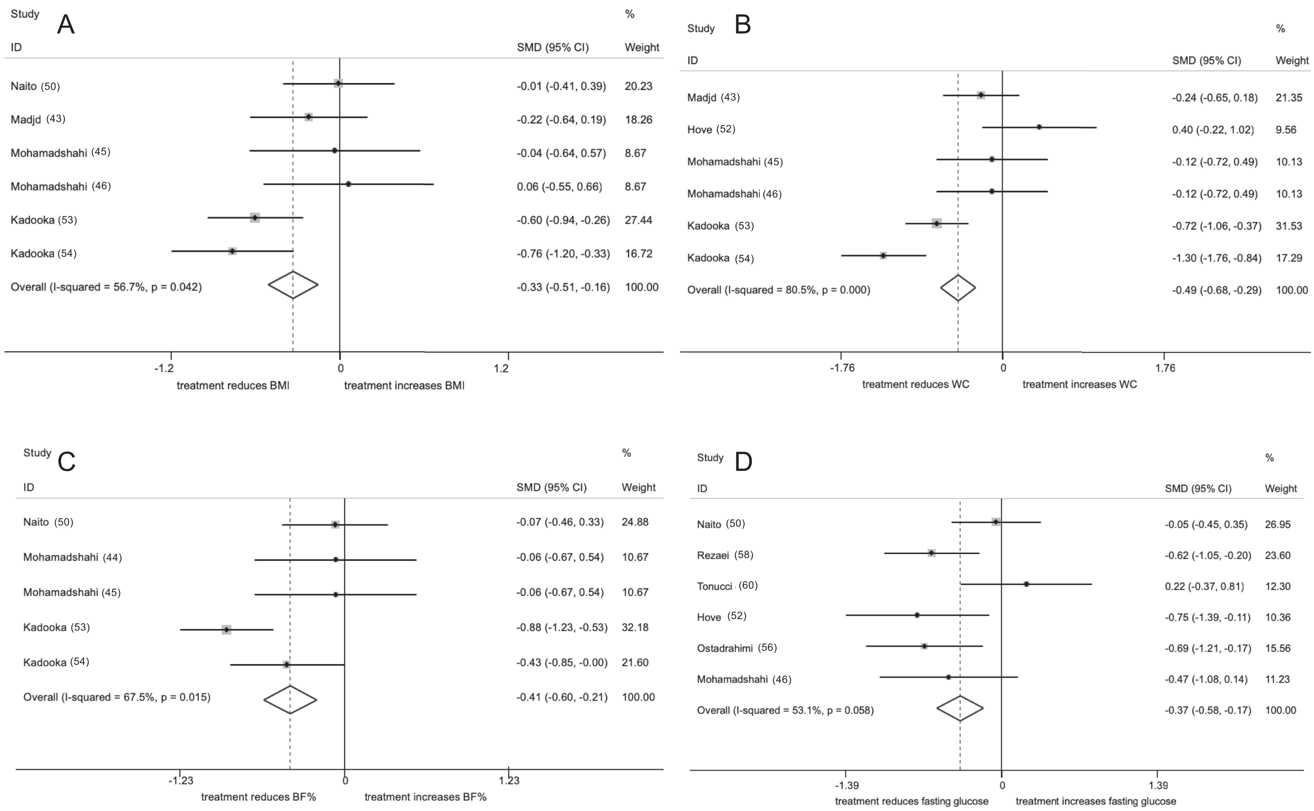

FIGURE 3 Forest plot of meta-analysis of randomized controlled trials that assess the effect of probiotic supplementation into a dairy matrix and anthropometric parameters on overweight and obese subjects and on diabetic biomarkers in subjects with type 2 diabetes. A: BMI changes ($P < 0.001$). B: WC changes ($P < 0.001$). C: BF changes ($P < 0.001$). D: Fasting glucose changes ($P < 0.001$). BF, body fat; SMD, standard mean difference; WC, waist circumference.

reduction were *L. casei* (66); a combination of *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *L. breve*, *L. longum*, and *S. thermophilus* (82); or a combination of *B. bifidum, L. casei*, and *L. acidophilus* (86). In addition, the heterogeneity between the RCTs was observed to be moderate ($P = 0.093$, $I^2 = 36.9\%$; Figure 6C).

The meta-analysis of the 8 RCTs (21, 66, 76, 82–86) that evaluated the effect of probiotic intake in capsule/powder form on HOMA-IR changes displayed a significant reduction [WMD (95% CI); −0.29 (−0.47, −0.12)] (Figure 6D). The probiotic strains that revealed significant HOMA-IR reduction were Ecologic Barrier® (83); a combination of *L. acidophilus*, *B. lactis*, *B. bifidum*, and *B. longum* (84); a combination of *B. bifidum*, *L. casei*, and *L. acidophilus* (84); and a combination of *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum*, and *B. infantis* (76). In addition, and the heterogeneity between the RCTs was found to be moderate ($P = 0.041$, $I^2 = 50.3\%$; Figure 6D).

The meta-analysis of the 5 RCTs (66, 68, 76, 84, 85) evaluating the effect of probiotic intake in capsule/powder form on HbA1c changes displayed a significant reduction [WMD (95% CI); −0.27 (−0.48, −0.05) %] (Figure 7A). The probiotic strains that showed significant reduction in HbA1c were *L. reuteri* ADR-1 (85), *L. reuteri* ADR-3 (85), and a combination of *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum*, and *B. infantis* (76). In addition, the heterogeneity between the RCTs was found to be moderate ($P = 0.186$, $I^2 = 33.3\%$; Figure 7A).

Our meta-analysis of the 9 RCTs (21, 66, 68, 76, 82–86) that evaluated the effect of probiotic intake in capsule/powder form on fasting insulin changes displayed a significant reduction [WMD (95% CI); −0.17 (−0.34, −0.00) mmol/L] (Figure 7B). The probiotic strains that yielded significant reduction in fasting insulin were *L. casei* (66); a combination of *B. bifidum*, *L. casei*, and *L. acidophilus* (86); and a combination of *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum*, and *B. infantis* (76). The heterogeneity between the RCTs was observed to be moderate ($P = 0.005$, $I^2 = 61.7\%$; Figure 7B), and the covariates "number of probiotic" (single or multiple probiotic) and "duration of intervention" explained 80.3% and 79.3% of the between-study heterogeneity, respectively (Supplemental Table 6).

The meta-analysis of plasma CRP in 4 RCTs (21, 76, 85, 86) did not show significant results (**Supplemental Figure 6**A).

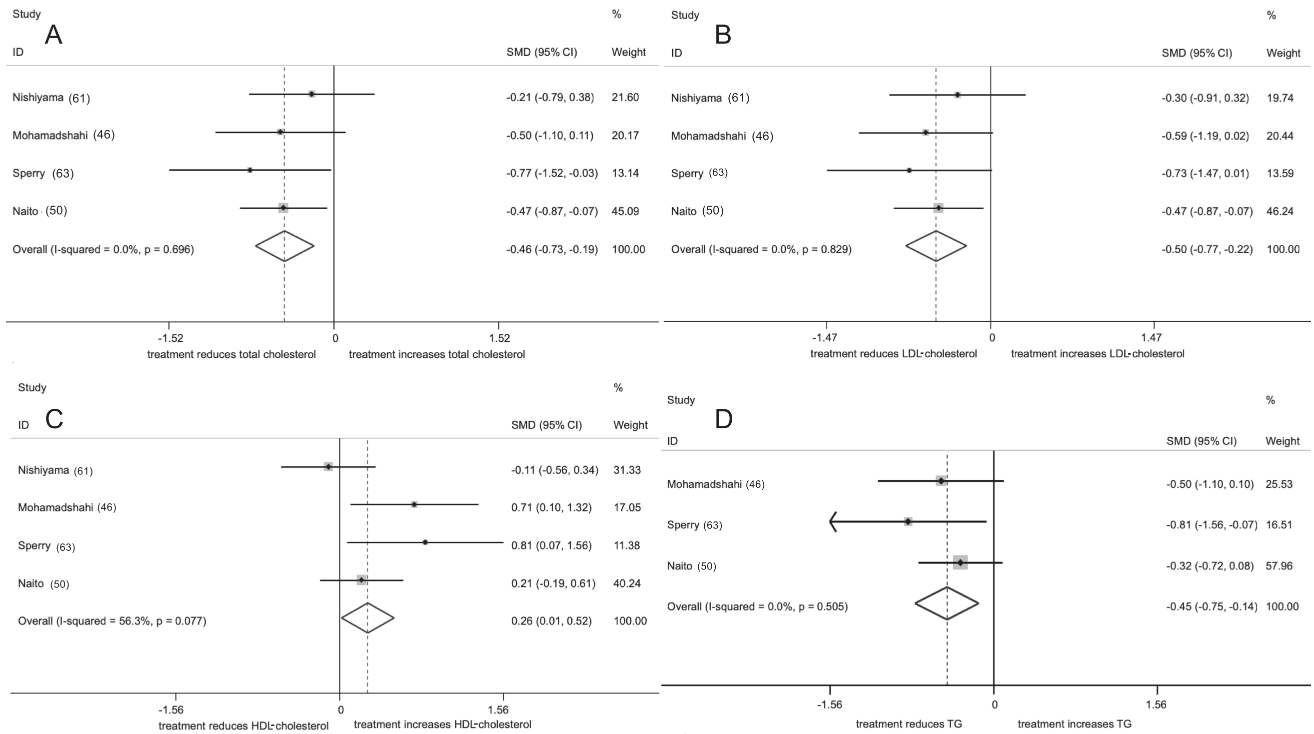

FIGURE 4 Forest plot of meta-analysis of randomized controlled trials that assess the effect of probiotic supplementation into a dairy matrix and on lipid biomarkers in hypercholesterolemic subjects. A: Total cholesterol changes ($P < 0.001$). B: LDL-cholesterol changes ($P < 0.001$). C: HDL-cholesterol changes ($P = 0.040$); D: TG changes ($P = 0.004$). SMD, standard mean difference; TG, triglyceride.

Effects of probiotic supplementation with capsule/powder on lipid profile in hypercholesterolemic subjects.
The meta-analysis of the 5 RCTs (87–91) evaluating the effect of probiotic intake in capsule/powder form on total cholesterol changes showed a significant reduction [WMD (95% CI); −0.37 (−0.53, −0.20) mmol/L] (Figure 7C). The probiotic strains that yielded significant results were *L. plantarum* (89), *L. reuteri*, (91) and a combination of *L. acidophilus* and *L. bifidum* (90). The heterogeneity between the RCTs was high ($P < 0.001$, $I^2 = 88.1\%$; Figure 7C), and the covariate "number of probiotic" (single or multiple probiotic) explained 97.5% of the between-study heterogeneity (Supplemental Table 6).

The meta-analysis of the 5 RCTs (87–91) that evaluated the effect of probiotic intake in capsule/powder form on LDL-cholesterol changes exposed a significant reduction [WMD (95% CI); −0.33 (−0.49, −0.16) mmol/L] (Figure 7D). The probiotic strains that showed significant results were *L. plantarum* (89), *L. reuteri* (91), and a combination of *L. acidophilus* and *L. bifidum* (90). The heterogeneity between the studies was high ($P < 0.001$, $I^2 = 82.8\%$; Figure 7D), and the covariate "number of probiotic" (single or multiple probiotic) explained 96% of the between-study heterogeneity (Supplemental Table 6).

The meta-analysis of HDL cholesterol in 5 RCTs (87–91) did not show significant results (Supplemental Figure 6B).

Supplemental Table 7 shows the levels of evidence provided by the RCTs, supporting the results obtained in the systematic review and meta-analysis on the consumption of probiotics and CMD.

Discussion

The results of our meta-analysis of PCSs showed that the consumption of fermented milk was associated with a reduced risk of stroke, IHD, and CV mortality events and that yogurt consumption was associated with a reduced risk of development of T2D and metabolic syndrome. Furthermore, the results of our meta-analysis of RCTs studying the effects of probiotic supplementation added into a dairy matrix and into capsules/powder form showed a reduction in various anthropometric parameters in obese and overweight subjects. Additionally, an improvement in the lipid profile in hypercholesterolemic subjects with probiotic supplementation added into a dairy matrix and a reduction in fasting glucose in T2D subjects with probiotic supplementation added into a dairy matrix and supplementation with capsules/powder form showed significant results for more diabetes biomarkers.

The reduced risks of stroke, IHD, and CV mortality associated with fermented milk in the meta-analysis of PCSs are in concordance with a systematic review of observational studies that also showed a favorable association between fermented milk consumption and stroke risk (12). Moreover, the finding of our meta-analysis that yogurt consumption was associated with a reduced risk of T2D risk development in the general population is in agreement with previous

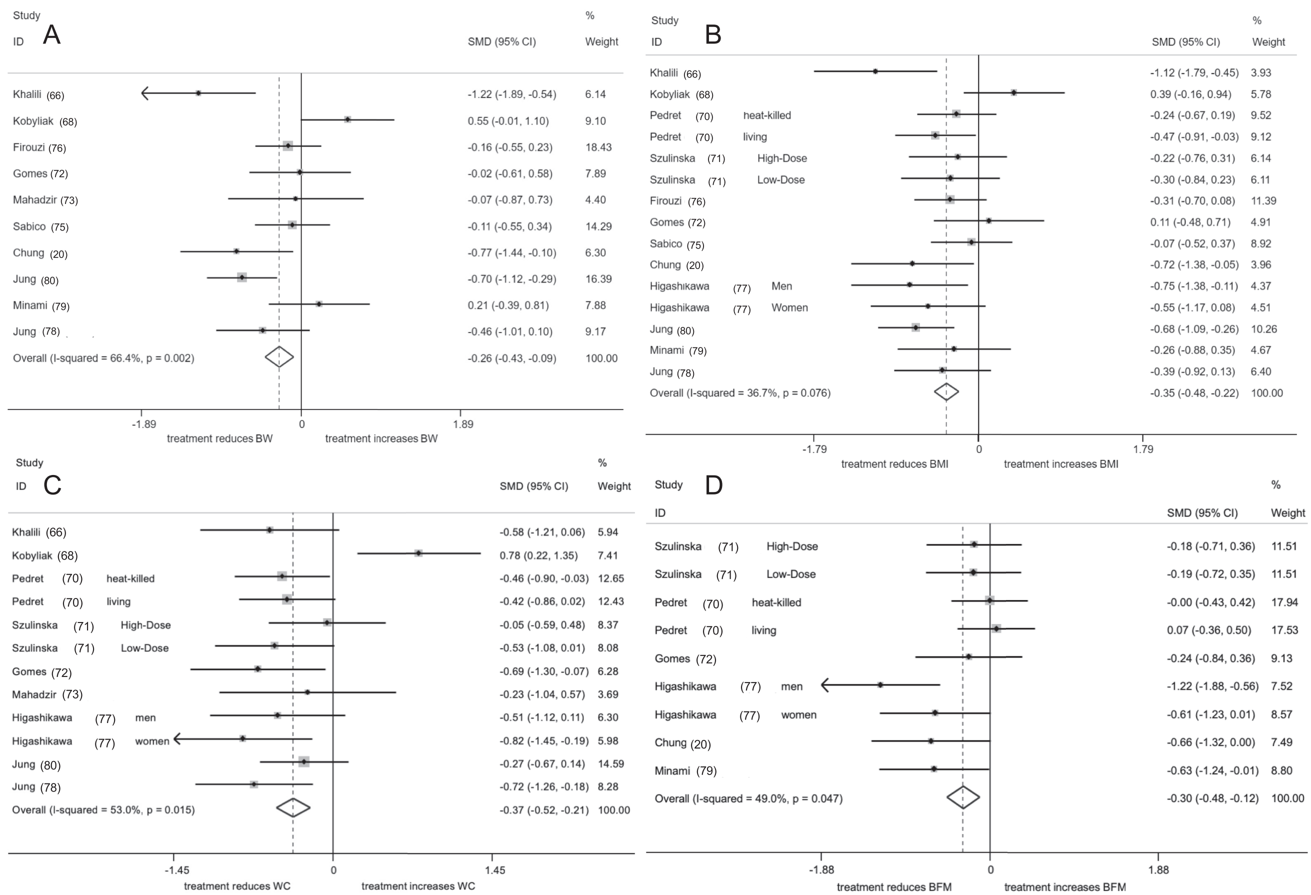

FIGURE 5 Forest plot of meta-analysis of randomized controlled trials that assess the effect of probiotic supplementation with capsules/powder on anthropometric parameters in overweight and obese subjects. A: BW changes ($P = 0.002$). B: BMI changes ($P < 0.001$). C: WC changes ($P < 0.001$). D: BFM changes ($P = 0.001$). BFM, body fat mass; BW, body weight; SMD, standard mean difference; WC, waist circumference.

results described in various narrative reviews that explained the possible mechanisms involved (92–94). In addition, our meta-analysis of PCSs showed that yogurt intake is associated with a reduced risk of metabolic syndrome development in the general population. In agreement with these results, another systematic review of PCSs, published in 2016, suggested a reduction in the risk of metabolic syndrome development with yogurt consumption (95). Nevertheless, the meta-analyses of 3 PCSs showed that cheese consumption resulted in an increase of 24% in T2D risk development. Similarly, in another meta-analysis of 2 PCSs, cheese intake was associated with a 5% higher T2D risk (96). However, these meta-analysis results should be interpreted with caution due to the heterogeneity of the PCSs.

Our meta-analysis of RCTs verified the effectiveness of probiotic supplementation added into a dairy matrix in that only fasting glucose concentrations were significantly reduced by the consumption of probiotic concentrations of 3.7×10^6 and 1×10^{11} CFU for ≥4 wk in T2D subjects. In addition, the probiotic strains *L. helveticus* Cardi04 (52), a combination of *L. acidophilus* La5 and *B. lactis* BB12 (58), and a combination of *L. casei*, *L. acidophilus*, and *B. lactis* (56) appear to be the most effective probiotic strains. In comparison, probiotic supplementation with capsules/powder produced a reduction in all diabetic biomarkers analyzed in T2D subjects when consuming *L. casei* (66); Ecologic® Barrier (83); a combination of *B. bifidum*, *L. casei*, and *L. acidophilus* (86); *and* a combination of *B. bifidum, B. longum, B. infantis*, *L. casei*, *L. acidophilus*, and *L. lactis* (76) at a concentration of 1×10^8 to 6×10^{10} CFU for minimum treatment duration of 8 wk. In the meta-analysis, capsules and powder form of probiotic supplementation appear to be more effective than probiotic supplementation added into a dairy matrix to reduce more diabetic biomarkers in subjects with T2D. In accordance with our RCT meta-analysis results, a previous meta-analysis (97) also observed a significant decrease in fasting glucose in T2D subjects who consumed probiotics in different forms, such as yogurt, capsules, or bread, for ≥8 wk. In addition, another meta-analysis showed a reduction in serum CRP concentrations by consuming probiotics, whereas our analysis did not show significant

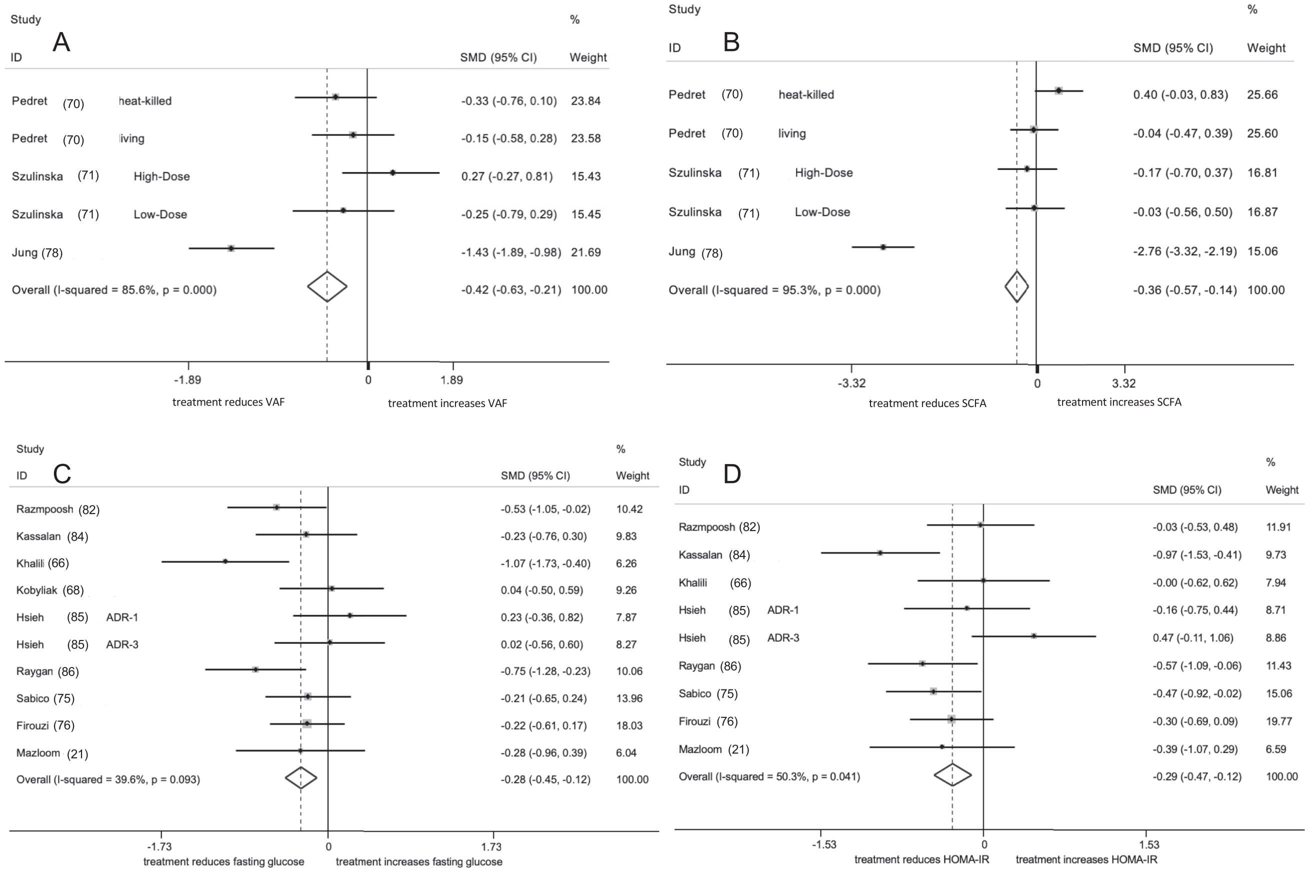

FIGURE 6 Forest plot of meta-analysis of randomized controlled trials that assess the effect of probiotic supplementation with capsules/powder on anthropometric parameters in overweight and obese subjects or in type 2 diabetes biomarkers. A: VFA changes ($P < 0.001$). B: SCFA changes ($P = 0.001$). C: Fasting glucose changes ($P = 0.001$). D: HOMA-IR changes ($P = 0.001$). SCFA, subcutaneous fat area; SMD, standard mean difference; VFA, visceral fat area.

results (98). Notably, all RCT probiotic interventions were performed with a mix of probiotics, except for one; for this reason, the authors cannot assess whether a single probiotic is more effective than a mix of probiotics on reducing T2D biomarkers.

The reduction in anthropometric biomarkers in obese subjects by probiotic supplementation added into a dairy matrix appears to be the most effective with *L. acidophilus* with *B. lactis* BB12 (58) and *L. gasseri* SBT2055 (53, 54) at a concentration of 1×10^7 to 1×10^{11} CFU and when consumed for ≥12 wk. In comparison, probiotic supplementation with capsules/powder also produces a reduction in anthropometric parameters in obese subjects with the consumption of *L. casei* (66), *P. pentosaceus* LP28 (77), *L. gasseri* BNR17 (80), and a combination of *L. curvatus* and *L. plantarum* at a probiotic concentration of 1×10^8 to 1×10^{11} CFU for ≥8 wk. In agreement with these results, a previous meta-analysis of 15 RCTs showed a significantly larger reduction in BW, BMI, and fat percentage (14). Moreover, it has become evident that an RCT intervention with a single probiotic strain is more effective than a combination of probiotics, whereas no specific matrix (dairy or capsules/powder) was more effective than the other for a reduction in anthropometric parameters in overweight/obese subjects. Importantly, although a small but significant reduction in all anthropometric parameters was observed, whether the clinical relevance of probiotic supplements, when added into a dairy matrix or taken in capsules/powder form, can add to the effectiveness of other measures and/or treatments for obesity remains to be determined.

Importantly, the combination of probiotic intake with a low-calorie diet was a more effective treatment for reducing anthropometric parameters than probiotics or diet alone (47, 49, 57). Thus, the synergistic effect of probiotic intake with a low-calorie diet could represent a new strategy for treating obesity and can improve the results obtained with the currently recommended lifestyle treatments. The effects of probiotic supplementation added into a dairy matrix showed reductions in all lipid biomarkers evaluated in hypercholesterolemic subjects. *L. casei* Shirota YIT9029 (50), *L. casei* (63), and a combination of *L. acidophilus* and *B. lactis* BB12 (45) appeared to be the most effective probiotic strains when used at an amount of 3.7×10^6 to 1×10^{11} CFU during

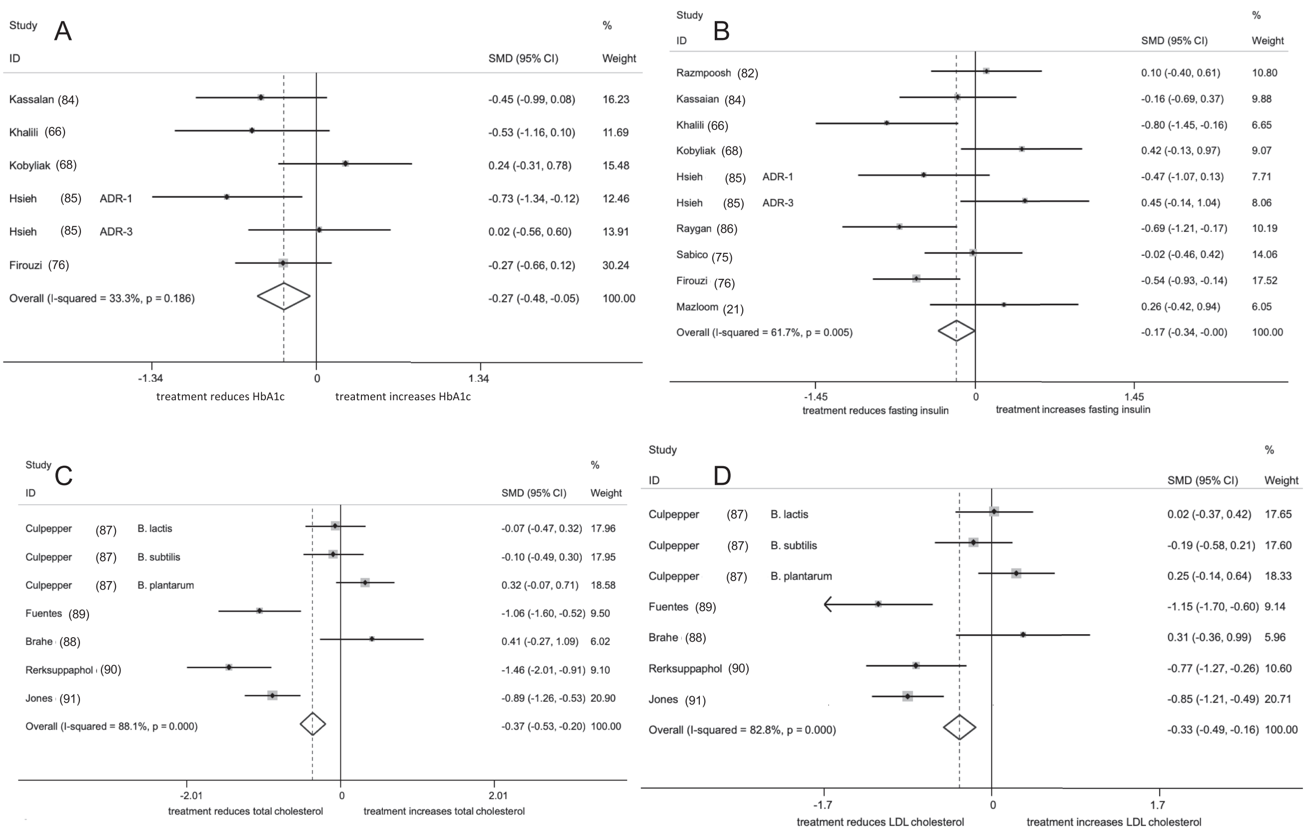

FIGURE 7 Forest plot of meta-analysis of randomized controlled trials that assess the effect of probiotic supplementation with capsules/powder on diabetic biomarkers in subjects with type 2 diabetes and lipid biomarkers in hypercholesterolemic subjects. A: HbA1c changes ($P = 0.015$). B: Fasting insulin changes ($P = 0.044$). C: Total cholesterol changes ($P < 0.001$). D: LDL-cholesterol changes ($P < 0.001$). HbA1c, glycated hemoglobin; SMD, standard mean difference.

≥28 d of intervention. The effectiveness of probiotic supplementation with capsules/powder produced a low reduction, while only total cholesterol and LDL cholesterol showed a significant reduction with the consumption of probiotic strains *L. plantarum* (89), *L. reuteri* (91), and a combination of *L. acidophilus* and *L. bifidum* (90) at a concentration of 2.9×10^9 to 1×10^{10} CFU during ≥6 wk of intervention. In accordance with our results, another meta-analysis (99) showed a significant reduction in total cholesterol and LDL cholesterol in individuals with hypercholesterolemia after *L. acidophilus* supplementation for ≥8 wk.

Notably, the significant reductions in serum total cholesterol (reduction of 1.4% to 11.87%) and LDL-cholesterol (reduction of 2.20% to 22.5%) concentrations induced by probiotic supplementation added into a dairy matrix observed in this study are similar to an observed 8–12% decrease in LDL cholesterol caused by 2 g of plant sterols and stanols or the 5–10% decrease caused by garlic intake at a dose of 6 g/d (depending on the percentage of allicin) (100, 101).

Furthermore, the administration of probiotic strains provided in dairy matrices in combination with the recommended treatments to reduce hypercholesterolemia, such as a low-saturated-fat diet, results in better cholesterol reduction than without probiotic consumption (102). Moreover, it has become evident that probiotic supplementation into a dairy matrix appears to be more effective than supplementation with capsules or powder for the reduction in lipid biomarkers in hypercholesterolemic subjects, and both specific treatments (a single probiotic or a combination) appear to have similar effectiveness.

In T2D subjects, the proposed mechanism through which probiotics can influence glucose metabolism can occur through modulation of the gut microbiome, which increases the concentrations of glucagon-like peptide-1 (GLP-1) (103), and through stimulation of the production of short-chain fatty acids, which promote the secretion of GLP-1 in obese subjects (104). GLP-1 impairment may contribute to an increase in appetite and faster gastric emptying, which often accompany obesity (105). In obesity, the decrease in VFA obtained through the use of probiotics could involve the production of specific molecules that interfere with certain metabolites, such as c12-conjugated linoleic acid (106). With respect to lipid profile modulation, probiotic intake could increase short-chain fatty acid production in the gut (29, 107), which would induce a decrease in the synthesis of hepatic cholesterol and promote a redistribution of cholesterol from the blood to the liver (38). Moreover, probiotics are considered generally safe, but as Cicero et al. (100) and Sahebkar et al. (107) described, with interventional study data, we do not have enough data to describe the safety of each probiotic.

Our systematic review and meta-analysis have several strengths and limitations. The most important strength of this systematic review and meta-analysis is that it constitutes the first simultaneous evaluation of PCSs investigating the relation between fermented dairy intake and risk of CMD and RCTs investigating the effects of probiotic supplementation added into a dairy matrix on the reduction in CMD parameters and compares their effects with probiotic supplementation with capsules/powder. As limitations, we have the inclusion of studies with different intervention durations, monitoring approaches, supplementation methods, and product doses administered and the high heterogeneity of the populations. Another limitation is that, after removing the PCSs in which the authors did not specify that cheeses were fermented foods, other potential risks of bias exist because we cannot confirm that all fermented dairy foods consumed in the included PCSs contain probiotics. Thus, the association between fermented dairy intake and benefits on CMD can only be speculated. Moreover, hypertension, another major CMD, was not investigated because of the small number of related studies that were identified. Finally, the authors have not reported information in the results section regarding "regular fermented dairy intake and risk for stroke, IHD and CV mortality" and "regular fermented dairy intake and risk for obesity" because there were not sufficient articles ($\geq$3 PCSs) to perform meta-analyses.

In summary, in PCSs, fermented milk consumption is associated with reduced CV risk, while yogurt intake is associated with a reduced risk of T2D and metabolic syndrome development, thus reducing the risk of a pandemic increase in CV disease, T2D, and metabolic syndrome in the general population. Moreover, in RCTs, probiotic supplementation added into a dairy matrix could be indicated for the reduction of lipids and anthropometric parameters. Additionally, probiotic capsule/powder supplementation could contribute to T2D management and reduce anthropometric parameters. Thus, for subjects with CMD, the addition of probiotics to recommended traditional therapies can lead to new perspectives regarding the management of CMDs, whereas the appropriate probiotic strain type, dose, and treatment duration period remain to be determined. However, the results should be interpreted with caution due to the high heterogeneity of the studies and the different probiotic strains used in the studies.

Perspectives

After this systematic review and meta-analyses there are a few questions that can be considered for future investigations. First, it is not clear why yogurt consumption had a different association with CMD risk than cheese consumption. Are yogurt probiotic strains better than cheese? Is the observed difference due to the fat composition? Or there is another reason? Second, because results led us to specific strains for which few studies are available, it may be interesting in the future to compare the effects with specific strains by RCT to supply information and increase the number of studies that have evaluated the same probiotic strain. Ultimately, in the present work, the authors have evaluated if one type of probiotic supplementation (into a dairy matrix or powder/capsules) has more effects than the other without considering the dose, and more studies are needed to confirm the dose efficacy of each supplementation.

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