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Fermented dairy products, probiotic supplementation and cardiometabolic diseases: a systematic review and meta-analysis

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Abbreviations

B: *Bifidobacterium*
BF: Body fat
BFM: Body fat mass
BW: Body weight
CFU: Colony forming units
CI: Confidence interval
CLA: Conjugated linoleic acid
CMD: Cardiometabolic disease
CRP: C-reactive protein
FDFs: Fermented dairy foods
GLP-1: Glucagon-like peptide-1
Hba1C: Glycosylated hemoglobin
HDL: High density lipoprotein
HOMA-IR: Homeostatic model assessment
HR: Hazard Ratio
ITT: Intention-to-Treat
L: *Lactobacillus*
LDL: Low density lipoprotein
MeSH: Medical subject headings
OR: Odds Ratio
PCS: Prospective cohort studies
PICOS: Population, Intervention, Comparison, Outcomes and Study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT: Randomized controlled trial
RR: Relative Risk
SCFA: Subcutaneous fat area
SD: Standard deviation
SE: Standard error
T2D: Type 2 diabetes
VAF: Visceral fat area
WC: Waist circumference
WMD: Weight mean difference

Summary (30 words maximum): Fermented milk and yogurt consumption are associated with reduced cardiometabolic disease risk. Furthermore, probiotic supplementation could be considered beneficial for lowering lipid levels, reducing anthropometry and contributing to T2D management.

Abstract

Fermented dairy foods (FDFs) and probiotics are promising tools for the prevention and management of cardiometabolic diseases (CMDs), respectively. The relationship 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, coronary 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 of lipid biomarkers than when added into capsules/powder in hypercholesterolemic subjects, and probiotic supplementation by capsules/powder produced a greater reduction of 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 levels and reducing anthropometric parameters. Additionally, probiotic capsule/powder supplementation could contribute to T2D management and reduce anthropometric

88 parameters. However, these results should be interpreted with caution due to the heterogeneity of
89 the studies and the different probiotic strains used in the studies.

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

92 **1. Introduction**

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

99 A new strategy could include the use of probiotics, live microorganisms that confer a health
00 benefit to the host when administered in adequate amounts(5). Probiotics can be provided as
01 supplements or may be present in fermented dairy products, particularly yogurt, cheese and
02 fermented milk. However, for a food to be considered probiotic, the microorganisms administered
03 must be present at concentrations higher than 10^8-10^9 colony forming units (CFU)/mL^{-1}, show
04 tolerance to acidic environments and bile and confer a health benefit(6,7). Notably, similarities
05 and differences can be observed when consuming fermented dairy products and probiotic
06 supplements. In general, fermented dairy products contain live microorganisms(7,8), such as
07 *Lactobacillus* bacteria; although not all of these products can be considered probiotics, and we can
08 only speculate on this issue. Fermented dairy products are foods with variable composition that
09 are eaten in the context of a dietary pattern and are one of the most common and traditional ways
10 to consume probiotics among people in most cultures(9,10). Additionally, fermented dairy
11 products and their relationship with disease or/and 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* (L), particularly *L. plantarum* and *L. gasseri* and *Bifidobacterium* (*B*), 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) in RCTs. 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 relationships 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 were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, was to evaluate the relationship 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.

2. 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.

2.1 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 (**Supplemental Table 1).**

2.2 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 August 12, 2019 (the complete search strategy is illustrated in **Supplemental Table 2**).

2.3 Study selection

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

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

66 2.4 Data collection and extraction

67 The literature search results were uploaded to www.covidence.org, a software program that
68 facilitates screening. First, the titles of all the studies identified from the database search were
69 screened. Second, the abstracts of the relevant titles were screened for the selection of potentially
70 eligible studies. Third, the full-text articles that met the inclusion criteria were screened.

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

76 The data extracted from the RCTs included the first author, year of publication, study design,
77 study duration, sex and age range of the subjects, number of subjects in the intervention and
78 placebo groups, intention-to-treat (ITT), details of the intervention (including probiotic strain) and
79 control groups, and significant and nonsignificant results for BW, body mass index (BMI), waist
80 circumference (WC), body fat mass (BFM), fat mass % (BF), visceral fat area (VAF),
81 subcutaneous fat area (SCFA), fasting insulin, homeostatic model assessment (HOMA-IR),

glycosylated hemoglobin (Hba1C), fasting glucose, plasma C-reactive protein (CRP), total cholesterol, low-density lipoprotein cholesterol (LDL-cholesterol), high-density lipoprotein cholesterol (HDL-cholesterol) and triglycerides.

2.5 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 (J.C. and L.P-P.), and any disagreement between these authors regarding the risk of bias in a study was resolved through discussion with a third author (L.C-P.).

2.6 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.

2.7 Statistical analyses

The systematic review and meta-analysis were performed using RevMan 5.3, and STATA 12.0 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 differentiate into various types)) based on the consumption level 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 standard deviations (SDs), standard errors (SEs) or 95% confidence intervals, were used to calculate the mean difference with 95% CIs between the intervention and control groups. Specifically, the difference 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 PCSs 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 a RCT, the corresponding author was contacted by email 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.

3. Results

3.1. Study selection

Of the 7,926 articles identified in the databases (PubMed=2,151, SCOPUS=4,781, and Cochrane Plus=994) and the 3 articles identified from a review of the references of the retrieved articles, 3,433 were excluded for being duplicated studies, and 5,269 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 a one meta-analysis and 37 RCTs in the other meta-analysis (see **Figure 1**).

3.2. 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**, **3, 4, 5, 6, 7, 8, and 9**.

In the 20 PCSs analyzed, the subjects (men and women) were between 20 and 90 years of age and presented one of the following outcomes: risk for obesity, T2D, metabolic syndrome, CV mortality risk, stroke or CHD. The sample size ranged from 1,868 to 409,885 subjects, and the follow-up duration ranged from 2 to 30 years. 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 years old and presented at least one 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 days to 24 weeks, and the probiotic doses ranged from 1×10^4 to 27×10^{10} CFU/day. The probiotic strains studied were: *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 two studies utilized a different control product [i.e., vegetal cream capsules(20) or magnesium stearate capsules(21)] for

54 the control group and administered probiotic capsules to the intervention group. The dairy
55 matrices studied were yogurt, fermented milk, kefir, cheese and milk.

56 3.3. Quality and risk of bias of the included studies

57 A risk of bias assessment was performed for the individual PCSs during the systematic review
58 (**Supplemental Figure 1)**. All of the included PCSs (*n*=20) clearly stated the research question,
59 measured the exposure of interest prior to the outcome, correctly described the exposure and
60 outcome measures and statistically adjusted for all potential confounding variables. In 19 PCSs,
61 the study population was clearly specified, the subjects selected were from a similar population,
62 the timeframe was sufficient, the exposure assessed was more than once over time, and different
63 levels of the exposure were examined. The participation rate of eligible subjects was at least 50%
64 in 17 PCSs. Finally, only 8 PCSs correctly described that the loss of follow-up after baseline was
65 20% or less. The blinding of the outcome assessor was described in only 4 PCSs, and the sample
66 size justification was not provided in any study.

67 In the systematic review of RCTs, the risk of bias within the individual studies was assessed
68 (**Supplemental Figure 2)**. All 52 included RCTs were randomized, and 6 RCT did not correctly
69 describe the method used for randomization. The allocation concealment of the included articles
70 was not properly described in 14 studies, and allocation concealment was not performed in 3
71 RCT. Blinding of both participants and personnel was performed correctly in 46 RCT, but only 17
72 RCT correctly blinded the outcome assessment. Complete outcome data were not correctly
73 described in 11 RCT and were selectively reported in 22 RCT, likely because these were
74 preregistered in a clinical trial registry. In addition, the authors of some of the included RCT
75 reported conflicts of interest (*n*=7).

76 3.4. Meta-analysis of PCSs

77 **Table 2** shows a summary of the individual information extracted from each PCSs included in the
78 systematic review that evaluated the relationship of fermented dairy intake with risk for CMD
79 (CV mortality, stroke, CHD, T2D, obesity, and MetS) (*n*=20).

80 Fermented dairy intake and risk for stroke, CHD and CV mortality

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

85 The meta-analysis of 4 PCSs(25–28) evaluating the relationships between of yogurt intake and
86 stroke, CHD and CV mortality risk development did not show significant results (**Supplemental**
87 **Figure 3-A**).

88 Fermented dairy intake and T2D risk

89 The meta-analysis of 7 PCSs(28–34) evaluating the relationship of yogurt intake with T2D risk
90 development resulted in a significant 27% reduction in T2D risk development [RR (95% CI); 0.73
91 (0.70, 0.76)], and the heterogeneity between PCSs was moderate (P=0.070, I^2=57.6%; **Figure**
92 **2B**).
93 The meta-analysis of 3 PCSs(28,31,35) that evaluated the relationship of cheese intake with T2D
94 risk development resulted in a significant 24% increase in T2D risk development [RR (95% CI);
95 1.24 (1.03, 1.49)], and the heterogeneity between PCSs was low (P=0.787, I^2=0.0%; **Figure 2-C**).

96 The meta-analysis of 3 PCSs(28,31,36) evaluating the relationship between total fermented dairy
97 intake and T2D risk development did not show significant results (**Supplemental Figure 3-B**).

98 Fermented dairy intake and metabolic syndrome risk

The meta-analysis of 3 PCSs(37–39) that evaluated the relationship 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 2-D**).

3.5. 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, **Table 3, 4, 5 and 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 at least one 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(40–45) 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 3-A**). The probiotic strain that showed a significant reduction in BMI was *L. gasseri* SBT2055(44,45), and the heterogeneity between the RCTs was moderate (P=0.042, I^2=56.7%; **Figure 3-A**).

The meta-analysis results of the 6 RCTs(41–46) 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 3-B**). The probiotic strain that showed significant reduction in WC was *L. gasseri* SBT2055(44,45), 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(40,42–45) 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 3-C**). The probiotic strain that presented significant reduction in BF was *L. gasseri* SBT2055(44,45), and the heterogeneity between the RCTs was moderate (P=0.015, I^2=67.5%; **Figure 3-C**). 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(40–44,46–48) did not show significant results (**Supplemental Figure 4-A**). Regarding BFM, the authors did not have sufficient RCTs to perform meta-analysis.

<u>Effects of probiotic supplementation into a dairy matrix on diabetic parameters in T2D subjects</u>

Our meta-analysis of the 6 RCTs(40,42,46,48–50) 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 3-D**). The probiotic strains that revealed significant reduction in fasting glucose were *L. helveticus* Cardi04(46), a combination of *L. acidophilus* La5 and *B. lactis* BB12(49), and a combination of *L. casei*, *L. acidophilus* and *B. lactis*(48). In addition, the heterogeneity between the RCTs was observed to be moderate (P=0.058, I^2=53.1%; **Figure 3-D**).

The meta-analysis of 6 RCTs(40,42,46,48–50) that evaluated fasting insulin, Hba1C and plasma CRP did not show significant results (**Supplemental Figures 4-B, 4-C** and **4-D**).

<u>Effects of probiotic supplementation into a dairy matrix on lipid profiles in hypercholesterolemic subjects</u>

46 The meta-analysis of the 4 RCTs(40,42,51,52) evaluating the effect of probiotic supplementation
47 added into a dairy matrix on total cholesterol changes showed a significant reduction [WMD
48 (95% CI); -0.46 (-0.73, -0.19) mmol/L] (**Figure 4-A**). The probiotic strains that yielded
49 significant reductions in total cholesterol concentrations were *L. casei* 01(52) and *L. casei* Shirota
50 YIT9029(40), and the heterogeneity between the RCTs was low (P=0.696, I^2=0.0%; **Figure 4-A**).

51 The meta-analysis of the 4 RCTs(40,42,51,52) that evaluated the effect of probiotic
52 supplementation added into a dairy matrix on LDL-cholesterol changes, exposed a significant
53 reduction [WMD (95% CI); -0.50 (-0.77, -0.22) mmol/L] (**Figure 4-B**). The probiotic strains that
54 showed significant LDL-cholesterol reduction were *L. casei* 01(52) and *L. casei* Shirota
55 YIT9029(40), and the heterogeneity between RCTs was low (P=0.829, I^2=0.0%; **Figure 4-B**).

56 Our meta-analysis of the 4 RCTs(40,42,51,52) evaluating the effect of probiotic supplementation
57 added into a dairy matrix on HDL-cholesterol changes demonstrated a significant increase [WMD
58 (95% CI); 0.26 (0.01, 0.52) mmol/L] (**Figure 4-C**). The probiotic strains that revealed significant
59 increases in HDL-cholesterol were *L. casei* 01(52) and a combination of *L. acidophilus* La-5 and
60 B. *lactis* BB-12(42), and the heterogeneity between the RCTs was moderate (P=0.007, I^2=56.3%;
61 **Figure 4-C**).

62 The meta-analysis of the 3 RCTs(40,42,52) that evaluated the effect of probiotic supplementation
63 added into a dairy matrix on triglyceride changes showed a significant reduction [WMD (95%
64 CI); -0.46 (-0.75, -0.14) mmol/L] (**Figure 4-D**). The probiotic strain that showed significant
65 reduction in triglyceride concentrations was *L. casei* 01(52), and the heterogeneity between the
66 RCTs was low (P=0.505, I^2=0.0%; **Figure 4-D**).

67 3.6. Meta-analysis of RCTs with a capsule/powder matrix on CMD

68 **Figures 5, 6** and **7** show the forest plot of RCTs with capsule/powder matrix with significant
69 CMD results. Additionally, **Table 7, 8, and 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 at least one 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(20,53–61) 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 5-A**). The probiotic strains that showed significant BW reduction were *L. casei*(56), *L. gasseri*(57) and a combination of *L. curvatus* and *L. plantarum*(58). The heterogeneity between the RCTs was moderate (*P*=0.002, I^2=66.4%; **Figure 5-A**), 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(20,55,64,65,56–63) 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 5-B**). The probiotic strains that showed significant BMI reduction were *L. casei*(56), *L. gasseri*(57), *Pediococcus pentosaceus LP28*(65) and a combination of *L. curvatus* and *L. plantarum*(58). In addition, the heterogeneity between theRCTs was moderate (P=0.076, I^2=36.7%; **Figure 5-B**).

The meta-analysis results of the 9 RCTs(54–59,62,63,65) evaluating the effect of probiotic intake in capsule/powder form on WC changes showed a significant reduction in WC [WMD (95% CI); -0.37 (0.52, -0.21) cm] (**Figure 5-C**). The probiotic strains that revealed significant WC reduction were *L. casei*(56), Ecologic Barrier®(63), Danisco®(59), *Pediococcus pentosaceus LP28*(65) and *L. gasseri*(57). The heterogeneity between the RCTs was moderate (*P*=0.015, I^2=53.0%; **Figure**

5-C), 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(20,59,61–63,65) 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 5-D**). The probiotic strains that showed significant reduction in BFM were *Pediococcus pentosaceus LP28*(65) and *B. breve*(61), and the heterogeneity between the RCTs was moderate (P=0.016, I^2=59.3%; **Figure 5-D**).

The meta-analysis of the 3 RCTs(58,62,63) evaluating the effect of probiotic intake in capsule/powder form on VAF changes revealed a significant reduction in VAF [WMD (95% CI); -0.42 (-0.63, -0.21) kg] (**Figure 6-A**). The probiotic strains that showed significant reduction in VAF were a combination of *L. curvatus* and *L. plantarum*(58), and the heterogeneity between the RCTs was high (P<0.001, I^2=85.6%; **Figure 6-A**).

Our meta-analysis of the 3 RCTs(58,62,63) 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 6-B**). The probiotic strain that showed significant reduction in SCFA was a combination of *L. curvatus* and *L. plantarum*(58), and the heterogeneity between the RCTs was high (P<0.001, I^2=95.3%; **Figure 6-B**). 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(58,61–63,65) 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(21,53,55,56,60,66–69) 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 6-C**). The probiotic strains that showed fasting glucose reduction were *L. casei*(56), a combination of *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *L. breve*, *L. longum* and *S. thermophilus*(66) or a combination of *B. bifidum, L. casei* and *L. acidophilus*(67). In addition, the heterogeneity between the RCTs was observed to be moderate (P=0.093, I^2=36.9%; **Figure 6-C**).

The meta-analysis of the 8 RCTs(21,53,56,60,66–69) 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 6-D**). The probiotic strains that revealed significant HOMA-IR reduction were Ecologic Barrier®(53), a combination of *L. acidophilus*, *B. lactis*, *B. bifidum* and *B. longum*(68), a combination of *B. bifidum*, *L. casei* and *L. acidophilus*(67) and a combination of *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum* and *B. infantis*(60). In addition, and the he heterogeneity between the RCTs was found to be moderate (P=0.041, I^2=50.3%; **Figure 6-D**).

The meta-analysis of the 5 RCTs(55,56,60,68,69) 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 7-A**). The probiotic strains that showed significant reduction in HbA1c were *L. reuteri* ADR-1(69), *L. reuteri* ADR-3(69) and a combination of *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum* and *B. infantis*(60). In addition, the heterogeneity between the RCTs was found to be moderate (P=0.186, I^2=33.3%; **Figure 7-A**).

Our meta-analysis of the 9 RCTs(21,53,55,56,60,66–69) 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 7-B**). The probiotic strains that yielded significant reduction in fasting insulin were *L. casei*(56), a combination of *B. bifidum*, *L. casei* and *L. acidophilus*(67) and a combination of *L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. longum* and *B. infantis*(60). The heterogeneity between the RCTs was observed to be moderate (P=0.005,

I^2=61.7%; **Figure 7-B**), 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(21,60,67,69) did not show significant results (**Supplemental Figure 6-A**).

Effects of probiotic supplementation with capsule/powder on lipid profile in hypercholesterolemic subjects

The meta-analysis of the 5 RCTs(70–74) 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 7-C**). The probiotic strains that yielded significant results were *L. plantarum*(71), *L. reuteri*(74) and a combination of *L. acidophilus* and *L. bifidum*(73). The heterogeneity between the RCTs was high (P<0.001, I^2=88.1%; **Figure 7-C**), 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(70–74) 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 7-D**). The probiotic strains that showed significant results were *L. plantarum*(71), *L. reuteri*(74) and a combination of *L. acidophilus* and *L. bifidum*(73). The heterogeneity between the studies was high (P<0.001, I^2=82.8%; **Figure 7-D**), 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(70–74) did not show significant results (**Supplemental Figure 6-B**).

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

67 **4. Discussion**

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

78 The reduced risk for stroke, CHD and CV mortality associated to fermented milk in the meta-
79 analysis of PCSs are in concordance with a systematic review of observational studies that also
80 showed a favorable association between fermented milk consumption and stroke risk (12).
81 Moreover, the finding of our meta-analysis that yogurt consumption associated with a reduced risk
82 for T2D risk development in the general population is in agreement with previous results described
83 in various narrative reviews that explained the possible mechanisms involved(75–77). In addition,
84 our meta-analysis of PCSs showed that yogurt intake is associated with a reduced risk of metabolic
85 syndrome development in the general population. In agreement with these results, another
86 systematic review of PCSs, published in 2016, suggested a reduction in the risk for metabolic
87 syndrome development with yogurt consumption(78). Nevertheless, the meta-analyses of 3 PCSs
88 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 (79). 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 levels were significantly reduced by the consumption of probiotic concentrations of 3.7×10^6 and 1×10^{11} CFU for at least 4 weeks in T2D subjects. In addition, the probiotic strains L. *helveticus* Cardi04(46), a combination of *L. acidophilus* La5 and *B. lactis* BB12(49), and a combination of *L. casei*, *L. acidophilus* and *B. lactis*(48) 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*(56), Ecologic® Barrier(53), a combination of *B. bifidum*, *L. casei* and *acidophilus*(67), a combination of *B. bifidum, B. longum, B. infantis*, *L. casei*, *L. acidophilus*, and *L. lactis*(60) at a concentration of 1×10^8 to 6×10^{10} CFU for minimum treatment duration of 8 weeks. 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(80) also observed a significant decrease in fasting glucose in T2D subjects who consumed probiotics in different forms, such as yogurt, capsules or bread for at least 8 weeks. In addition, another meta-analysis showed a reduction in serum CRP levels by consuming probiotics, whereas our analysis did not show significant results(81). Notably, all RCT probiotic interventions were performed with a mix of probiotics, except 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 appear to be the most effective with *L. acidophilus* with *B. lactis* BB12(49) and *L. gasseri* SBT2055(44,45) at a concentration of 1×10^7 to 1×10^{11} CFU and when consumed for

at least 12 weeks. In comparison, probiotic supplementation with capsules/powder also produces a reduction in anthropometric parameters in obese subjects with the consumption of *L. casei*(56), *P. pentosaceus* LP28(65), *L. gasseri* BNR17(57) and a combination of *L. curvatus* and *L. plantarum* at a probiotic concentration of 1×10^8 to 1×10^{11} CFU for at least 8 weeks. In agreement with these results, a previous meta-analyses of 15 RCTs showed in a significantly larger reduction in body weight, BMI and fat percentage(14). Moreover, it has become evident that a 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, 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 but 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(82–84). 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(40), *L. casei*(52) and a combination of *L. acidophilus* and *B. lactis* BB12(42) appeared to be the most effective probiotic strains when used at an amount of 3.7×10^6 to 1×10^{11} CFU during a least 28 days 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*(71), *L. reuteri*(74) and a combination of *L. acidophilus* and *L. bifidum*(73) at a concentration of 2.9×10^9 to 1×10^{10} CFU during at least 6 weeks of intervention. In accordance with our results, other meta-analysis

performed (85) showed a significant reduction in total cholesterol and LDL-cholesterol in individuals with hypercholesterolemia after *L. acidophilus* supplementation for at least 8 weeks.

Notably, the significant reduction in serum total cholesterol (reduction of 1.4 to 11.87%) and LDL-cholesterol (reduction of 2.20 to 22.5%) levels 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 to 10% decrease caused by garlic intake at a dose of 6 g/day (depending on the percentage of allicin)(86,87).

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, result in better cholesterol reduction than without probiotics consumption (88). 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 levels of glucagon-like peptide-1 (GLP-1)(89), and though stimulation of the production of short-chain fatty acids, which promotes the secretion of GLP-1 in obese subjects(90). GLP-1 impairment may contribute to an increase in appetite and faster gastric emptying, which often accompany obesity(91). In obesity, the decrease in VAF obtained through the use of probiotics could involve the production of specific molecules that interfere with certain metabolites, such as conjugated linoleic acid (CLA) (92). With respect to lipid profile modulation, probiotic intake could increase short-chain fatty acid production in the gut (93,94), which would induce a decrease in the synthesis of hepatic cholesterol and promote a redistribution of cholesterol from the blood to the

liver(95). Moreover, probiotics are considered generally safe, but as Cicero et al.(86) and Sahebkar et al.(93) 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 they constitute the first simultaneous evaluation of PCSs investigating the relationship between fermented dairy intake and risk for CMD and RCTs investigating the effects of probiotic supplementation added into a dairy matrix on the reduction in CMD parameters and compare 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, CHD and CV mortality" and "regular fermented dairy intake and risk for obesity" because there are not sufficient articles (at least 3 PCSs) to perform meta-analyses.

In summary, in PCSs, fermented milk consumption is associated with reduced cardiovascular risk, while yogurt intake is associated with a reduced risk for T2D and metabolic syndrome development, thus reducing the risk of a pandemic increase in CV disease, T2D and metabolic syndrome in 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 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 being due to the fat composition? Or there is another reason? Secondly, because results lead 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 the type of probiotic supplementation (into a dairy matrix or powder/capsules) have 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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All authors have read and approved the final manuscript.

Author contributions

J.C., R.M.V., and A.P. designed the search strategy. J.C. obtained the studies identified in database searches for inclusion in the review. J.C and L.P.-P. evaluated the quality of the studies, and L.C.-P. validated and discussed any discrepancies. The results of the studies were entered by J.C. J.C. drafted the manuscript, and L.P-P., L.C.-P., E.L., A.P., R.M.V., and R.S. reviewed the final content of the manuscript, prior to submission and provided feedback. All authors have read and approved the final version of the manuscript.

Figure Legends

Figure 1. PRISMA flowchart of the systematic review and meta-analysis.

Figure 2. Forest plot of meta-analysis of observational studies that assess the relationship between fermented dairy intake and cardiometabolic diseases. A: Fermented milk intake and risk for stroke, CHD and cardiovascular mortality (P<0.001); B: yogurt intake and risk for type 2 diabetes development (P<0.001); C: cheese intake and risk for type 2 diabetes development (P=0.023); D: yogurt intake and risk for metabolic syndrome development (P<0.001). CHD, coronary heart disease; CV, cardiovascular; RR, relative risk, CI, confidence interval.

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: Body mass index changes (P<0.001); B: waist circumference changes (P<0.001); C: body fat changes (P<0.001); D: fasting glucose changes (P<0.001). BMI, body mass index; WC, waist circumference; BF, body fat; RR, relative risk; CI, confidence interval.

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: triglyceride changes (P=0.004).

LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; RR, relative risk; CI, confidence interval.

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: Body weight changes (P=0.002); B: body mass index changes (P<0.001); C: waist circumference changes (P<0.001); D: body fat mass changes (P=0.001); BW, body weight; BMI, body mass index; WC, waist circumference; BFM, body fat mass; RR, relative risk; CI, confidence interval.

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: visceral fat area changes (P<0.001); B: subcutaneous fat area changes (P=0.001); C: Fasting glucose changes (P=0.001); D: HOMA-IR changes (P=0.001). CI, confidence interval; HOMA-IR, homeostatic model assessment index; SCFA: subcutaneous fat area; VAF, visceral fat area; RR, relative risk.

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). CI, confidence interval; HbA1c: glycated hemoglobin; LDL, low-density lipoprotein; RR, relative risk.

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Table 1. PICOS criteria for inclusion and exclusion of studies

Criteria	Inclusion and exclusion criteria of observational studies	Inclusion and exclusion criteria of clinical trials
Population	Adult subjects (>18 years old) of all sexes and races with cardiovascular risk factors (obesity, diabetes mellitus type 2, hypercholesterolemia or metabolic syndrome) or cardiovascular disease were eligible for inclusion	Adult subjects of all sexes and races with 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, 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 in 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 product were eligible for inclusion.
Outcomes	Studies that measured the incidence of CHD, stroke, cardiovascular mortality, obesity, T2D or metabolic syndrome development are 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. Non-randomized clinical trials, systematic reviews and meta-analysis were excluded.
Meta-analysis	At least three studies for each parameter	At least three studies for each parameter, and the same type or study (RCTs).

Abbreviations: BMI, body mass index; BW, body weight; CHD, coronary heart disease; CRP, c-reactive protein; CVD, cardiovascular disease; GD, gastrointestinal disorders; Hba1C, glycosylated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment index; LDL-c, low-density lipoprotein cholesterol; SCFA, subcutaneous fat area; T2D, type 2 diabetes; VFA, visceral fat area; WC, waist circumference.

Table 2. Summary of the individual information extracted from each included prospective cohort study evaluating the relationship of fermented dairy intake with risk for CMD (CV mortality, stroke, CHD, T2D, obesity, and MetS) (*N*=20).

Author, year	Study, country	Design	Follow up (years)	N total	N Cases	Age (years range)	Measurement	Adjusted variables	Outcome	Dairy exposures analyzed	Dairy products subgroups	Comparison	OR, RR or HR (95% CI)
1. CV mortality, stroke and CHD (*n*=8)													
Key et al. (2019)(94)	EPIC Cohort, 10 countries*	PC	12,6	409,885	7,198	41-70	24-hour 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 (150g/d) vs Q1 (0g/d)	[HR: 0.90 (0.84-0.97)]
Johansson et al. (2019)(23)	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 T2DM, screening project, quintiles of red meat, wholegrain, fruit and vegetables and energy.	Myocardial infarction	FM	Total FM	M Q4 VS no consumption	[HR: 0.92 (0.82, 1.03)]
										FM	Total FM	W Q4 VS no consumption	[HR: 1.00 (0.84, 1.18)]
									Stroke	FM	Total FM	M Q4 VS no consumption	[HR:0.91 (0.79, 1.05)]
										FM	Total FM	W Q4 VS no consumption	[HR:0.87 (0.75, 1.03)]
Dehghan et al. (2018)(25)	PURE study, from 21 countries**	PC	9,1	136,384	7,828	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	>244g/d vs 0 g/d	[HR: 0.82 (0.72-0.93)]
Farvid et al. (2016)(26)	Golestan study, Iran	PC	8	42,402	1,467	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 (207g/d) vs Q1 (23g/d)	[HR: 0.84 (0.70-1.00)]
Goldbohm et al. (2011)(24)	Netherlands Cohort study, The Netherlands	PC	10	120,852	16,135	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 (53g/d) vs Q1 (0g/d)	[RR: 0.93 (0.88-0.98)]
										FM	Whole-fat FM	W Q2 (53g/d) vs Q1 (0g/d)	[RR: 0.93 (0.87-1.00)]
										FM	Low-fat FM	M Q3 (146g/d) vs Q1 (0g/d)	[RR: 0.97 (0.93-1.03)]
										FM	Low-fat FM	W Q3 (192g/d) vs Q1 (0g/d)	[RR: 1.02 (0.95-1.09)]
Praagman et al. (2014)(27)	Rotterdam Study, Netherlands	PC	13.3	4,235	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	>100g/d vs <50g/d	[HR: 1.08 (0.87-1.34)]
										Yogurt	Total Yogurt	>100g/d vs <50g/d	[HR: 1.10 (0.90-1.34)]
										Cheese	Total Cheese	>40 g/d vs <20g/d	[HR: 0.96 (0.75-1.22)]
								Age, gender, total energy intake, BMI, smoking, education level, alcohol, vegetables, fruit, meat, bread, fish coffee, and tea intake.	CHD	FD	Buttermilk, yogurt, curd, cheese	>100g/d vs <50g/d	[HR: 1.01 (0.82-1.24)]
										Yogurt	Total Yogurt	>100g/d vs <50g/d	[HR: 1.11 (0.91-1.35)]
										Cheese	Total Cheese	>40 g/d vs <20g/d	[HR: 1.01 (0.79-1.30)]
Soedamah-Muthu et al. (2013)(28)	Whitehall II study, UK	PC	10	4,526	323	35-55	Validated FFQ	Age, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity and family history of CHD/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea and total energy intake	CHD	Yogurt	Total Yogurt	T3 (117g/d) vs T1 (0g/d)	[HR: 1.23 (0.93-1.63)]
										Cheese	Total cheese	T3 (31g/d) vs (6g/d)	[HR: 0.82 (0.61-1.09)]
										FD	Total yogurt and cheese	T3 (105g/d) vs (17g/d)	[HR: 0.97 (0.73-1.28)]
Sonestedt et al. (2011)(22)	MDC study, Sweden	PC	12	26,445	2,520	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 (55g/d) vs Q1 (0g/d)	[HR: 0.87 (0.77-0.97)]
2. T2D risk (*n*=9)													
Jeon et al. (2019)(29)	Korean Genome and Epidemiology Study, Korea	PC	7,3	10,030	1,173	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 T2DM, use of antihypertensive medication, use of dietary supplements, intakes of vegetables, fruits, red meat, processed meat, soft drinks, coffee, and tea	T2DM	Yogurt	Total Yogurt	625g/week vs 0 g/week	[HR: 0.73 (0.61-0.88)]
Hruby et al. (2017)(30)	FHS Offspring, EEUU	PC	12	2,809	902	45-63	FFQ-126 item	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	277g/d vs 0g/d	[HR: 1.24 (0.67-2.29)]

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; EEUU, United States; EPIC, European Prospective Investigation into Cancer and Nutrition; FD, fermented dairy; FFQ, food frequency questionari; FHS, Framingham Heart Study; FM, fermented milk; g/d, grams per day; g/week, grams per week; HR, hazard ratio; M, men; MDC, Malmö Diet Cancer; MetS, metabolic syndrome; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; OR, odds ratio; PC, prospective cohort; Pure study, Prospective Urban Rural Epidemiology; Q, quartil; RR, risk ratio; SBP, systolic blood pressure; SFFQ, semiquantitative food frequency questionnaire; T, tercil; T2D, type 2 diabetes; VIP, Västerbotten Intervention Programme; vs, versus; W, women.

*Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, United Kingdom **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 2. Continued.

Author, year	Study, country	Design	Follow up (year)	N total	Cases	Age (years mean)	Measurement	Adjusted variables	Outcome	Dairy exposures analyzed	Dairy products subgroups	Comparison	OR, RR or HR (95% CI)
Díaz-López et al. (31)	PREDIMED study, Spain	PC	2.5-5.7	3,454	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 (120g/d) vs T1 (3g/d)	[HR: 0.61 (0.43-0.85)]
											Whole-fat yogurt	T3 (45g/d) vs T1 (0g/d)	[HR: 0.64 (0.46-0.89)]
											Total yogurt	T3 (128g/d) vs T1 (13g/d)	[HR: 0.53 (0.37-0.75)]
										Cheese	Total cheese	T3 (40g/d) vs T1 (11g/d)	[HR: 1.31 (0.94-1.83)]
										FD	Total yogurt and cheese	T3 (167g/d) vs T1 (39g/d)	[HR: 0.63 (0.45-0.87)]
Ericson et al. (36)	Malmö Diet and Cancer cohort study, Sweden	PC	14	26,930	2860	45–74	Validated FFQ-168-item	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	480g/d vs 0g/d	[HR: 1.06 (0.95, 1.18)]
											High fat yogurt, sour milk and cheese	792g/d vs 66g/d	[HR: 0.89 (0.79, 1.01)]
Chen et al. (32)	HPFS, EEUU	PC	24	51,529	3,364	40-75	131-item FFQ	Age, BMI and other lifestyle and dietary risk factors, total dairy consumption.	T2D	Yogurt	Total yogurt	Q4 (732g/week) vs Q1 (61g/week)	[RR: 0.95 (0.84-1.08)]
	NHS I, EEUU	PC	30	121,700	7,841	30-55	61-131 item FFQ	Age, BMI and other lifestyle and dietary risk factors, total dairy consumption.	T2D	Yogurt	Total yogurt	Q4 (708g/week) vs Q1 (0g/week)	[RR: 0.84 (0.76-0.91)]
	NHS II, EEUU	PC	16	116,671	3,951	25-42	131-item FFQ	Age, BMI) and other lifestyle and dietary risk factors, total dairy consumption.	T2D	Yogurt	Total yogurt	Q4 (659g/week) vs Q1 (0g/week)	[RR: 0.90 (0.81-1.00)]
Soedamah-Muthu et al. (28)	Whitehall II study, UK	PC	10	4,526	273	35-55	Validated FFQ	Age, ethnicity, employment grade, smoking, alcohol intake, BMI, physical activity and family history of CHD/hypertension, fruit and vegetables, bread, meat, fish, coffee, tea and total energy intake.	T2D	Yogurt	Total Yogurt	T3 (117g/d) vs T1 (0g/d)	[HR: 1.04 (0.77-1.42)]
										Cheese	Total cheese	T3 (31g/d) vs (6g/d)	[HR: 1.20 (0.88-1.64)]
										FD	Total yogurt and cheese	T3 (105g/d) vs (17g/d)	[HR: 1.17 (0.87-1.58)]
Struijk et al. (35)	Inter99 study, Denmark	PC	5	5,953	214	30-60	Validated FFQ-198 item	Age, gender, intervention group, diabetes family history, education level, physical activity smoking, alcohol intake, wholegrain cereal, meat, fish, coffee, tea, fruit, vegetables, energy intake, change in diet from baseline to 5-year follow-up, waist circumference.	T2D	FM	Total FM	150g/d vs 0g/d	[OR: 0.88 (0.69-1.11)]
										Cheese	Total cheese	20g/d vs 0g/d	[OR: 0.97 (0.82-1.15)]
Grantham et al. (33)	AusDiab, Australia	PC	5	5,582	209	>25	Validated FFQ-121 item	Age, sex, energy intake, family history of diabetes, education level, physical activity, smoking status, TAG, HDL-cholesterol, SBP, waist circumference and hip circumference.	T2D	Yogurt	Total Yogurt	T3 (>380g/d) vs T1 (<240g/d)	[HR: 1.14 (0.78, 1.67)]
Margolis et al. (34)	Women's Health Initiative, EEUU	PC	8	82,076	3,946	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	>500g/week vs <250g/month	[HR: 0.46 (0.31, 0.68)]
3. Obesity risk (*n*=1)													
Martinez-Gonzalez et al. (95)	SUN project, Spain	PC	6.6	8,516	1,860	26-48	Validated FFQ-136 item	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	>889g/week vs 0-250g/week	[HR: 0.84 (0.61-1.15)]
											Whole-fat yogurt	>889g/week vs 0-250g/week	[HR: 0.62 (0.47-0.82)]
											Total Yogurt	>889g/week vs 0-250g/week	[HR: 0.80 (0.68-0.94)]
4. MetS risk (*n*=3)													
Kim et al. (37)	KoGES, Korea	PC	4	5,510	2,103	40-69	Validated FFQ-103 item	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	≥85g/d vs ≤21g/d	[HR: 0.68 (0.58-0.79)]
Babio et al. (38)	PREDIMED study, Spain	PC	2-7	1,868	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 (124g/d) vs T1 (1g/d)	[HR: 0.73 (0.62-0.86)]
											Whole-fat yogurt	T3 (46g/d) vs T1 (0g/d)	[HR: 0.78 (0.66-0.92)]
											Total yogurt	T3 (127g/d) vs T1 (7g/d)	[HR: 0.77 (0.65-0.91)]
Sayón-Orea et al. (39)	SUN project, Spain	PC	6	8,063	306	20-90	Validated FFQ-136 item	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	≥875g/week vs 0-250g/week	[OR: 0.63 (0.39-1.02)]
											Whole-fat yogurt	≥875g/week vs 0-250g/week	[OR: 0.98 (0.68-1.41)]
											Total Yogurt	≥875g/week vs 0-250g/week	[OR: 0.84 (0.60-1.18)]

Abbreviations: AusDiab, Australian Diabetes Obesity and Lifestyle Study; BMI, *body mass index*; CI, confidence interval; DBP, diastolic blood pressure; EEUU, United States; FD, fermented dairy; FFQ, *food frequency questionnaire*; FM, fermented milk; g/d, grams per day; g/week, grams per week; HDL, high density lipoprotein; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; InterAct, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage *Trial;* KoGES, The Korean Genome and Epidemiology Study**;** MetS, *Metabolic Syndrome*; NHS, Nurses' Health Study; OR, odds ratio; PC, *prospective cohort*; PREDIMED, Prevención con Dieta Mediterránea; Q, quartile; SBP, systolic blood pressure; SFFQ, semi-quantitative food frequency questionnaire; SUN, seguimiento universidad de Navarra; T, tercil; T2D, *Type 2 diabetes*; TG, triglycerides; Vs, versus.

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)(*N*=24)

Author, year	Study design Duration (Country)	Gender, age (years)	n (I./ PL)	ITT	Intervention (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	Significant results						
								BW (kg)	BMI (kg/m2)	WC (cm)	BFM (Kg)	BF (%)	VAF (cm²)	SCFA (cm²)
Added to yogurt matrix														
Zarrati et al. (96)	R, DB, PC 8 weeks (Iran)	M and W, 20 to 50	60 (30/30)	Yes	Yogurt with *L. acidophilus* La5, *B.* 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. (41)	R, SB, CT, PC 12 weeks (Iran)	W, 18 to 50	89 (44/45)	Yes	Low-fat yogurt with *L. acidophilus* and *B. lactis* BB12. (1 x 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. (97)	R, DB, CT, PC 8 weeks (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. (42)	R, DB, CT, PC 8 weeks (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. (43)	R, DB, CT, PC 8 weeks (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. (82)	R, DB, CT, PC 8 weeks (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. I2. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12.	Regular yogurt with LCD	End vs BL (I1/I2)	↓4.23/ *P*>0.05	↓1.55/ *P*>0.05	↓2.78/ *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. (98)	R, DB, PC, CO 4,3 weeks (Canada)	M and W, 18 to 60	56 (28/28)	No	I1. Yogurt with *L. amylovorus.* (1.39 x 10^9) I2. Yogurt with *L. Fermentum.* (1.08 x 10^9)	PL yogurt	End vs BL (I1/I2)	*P*>0.05	-	-	↓1.40/↓1.00	-	-	-
							Between interv.	*P*>0.05	-	-	*P*>0.05	-	-	-
Zarrati et al. (83)	R, DB, CT, PC 8 weeks (Iran)	M and W, 20 to 50	75 (25/25/25)	Yes	I1. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12 (3x10^8) with LCD. I2. Yogurt with *L. acidophilus* LA5, *L. casei* DN001, *B. lactis* BB12. (3x10^8)	Regular yogurt with LCD	End vs BL (I1/I2)	↓4.23/ *P*>0.05	↓1.55/ *P*>0.05/	↓2.78/ *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. (40)	R, DB, PC, PG 8 weeks (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. (47)	R, DB, PC, MC 12 weeks (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. (46)	R, DB, PC 12 weeks (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. (45)	R, DB, PG, MC, PC 12 weeks (Japan)	M and W, 35 to 60	210 (69/71/70)	No	I1. FM with *L. gasseri* SBT2055. (200 x 10^7) I2. FM with *L. gasseri* SBT2055. (200 x 10^6)	PL FM	End vs BL (I1/I2)	-	↓0.30/↓0.40	↓1.30/↓1.10	↓0.60/↓0.50	↓0.50*P*>0.05	↓8.50%/8.2%	↓2.60%/*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. (44)	R, DB, PC, MC 12 weeks (Japan)	M and W, 33 to 63	87 (43/44)	No	FM with *L. gasseri* SBT2055. (10 x 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. (99)	R, DB, PC 12 weeks (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. (48)	R, DB, PC 8 weeks (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. (84)	R, DB, PC, PG 3 weeks (Russia)	M and W, 30 to 69	40 (25/15)	No	Cheese with *L. plantarum* TENSIA (1 x 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	-	-	-

Abbreviations: Admin, administration; B, bifidobacterium; BF, body fat, BFM, body fat mass; BL, baseline; BMI, body mass index, BW, body weight; CFU/day, colony formin units per day; CG; control group; CMD, cardiometabolic disease; CO, crossover; CT, controlled trial; DB, double blind, FM, fermented milk, I, intervention; IG, intervention group; ITT, intention-to-treat; L, Lactobacillus; LCD, low calorie diet; MC, multi-center; PG, parallel, group; M, men; n.d. , no data; PC, placebo-controlled; PL, placebo; Prob, probiotic; R, randomized; S, streptococcus; SB, single blind; SCFA, subcutaneous fat area; T2D, type 2 diabetes, VAF, visceral fat area; W, women; WC, waist circumference.

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 non-significant was shown P>0.05. (-) mean that the study does not evaluate this parameter.

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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 (*N*=7)

Author, year	Study design Duration (Country)	Gender, age (years)	*n* (I./ PL)	ITT	Intervention (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	Significant results				
								F. insulin (µIU/mL)	HOMA-IR	Hba1C (%)	F. glucose (mmol/L)	Plasma CRP (mg/l)
Added to yogurt matrix												
Rezaei et al. (49)	R, DB, PC 4 weeks (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. (43)	R, DB, CT, PC 8 weeks (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. (100)	R, DB, CT, PC 6 weeks (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. (40)	R, DB, PC, PG 8 weeks (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. (50)	R, DB, PC, PG 6 weeks (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. (46)	R, DB, PC 12 weeks (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. (48)	R, DB, PC 8 weeks (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	-

Abbreviations: Admin, administration; B, bifidobacterium; CFU/day, colony formin units per day; CG; control group; CMD, cardiometabolic disease; CRP, C-reactive protein; CT, controlled trial; DB, double blind; F, fasting; FM, fermented milk, I, intervention; IG, intervention group; Hba1C, glycosylated hemoglobin; HOMA-IR, Homeostatic model assessment index; ITT, intention-to-treat; L, Lactobacillus; PG, parallel, group; M, men; n.d., no data; PC, placebo-controlled; PL, placebo; Prob, probiotic; R, randomized; T2D, type 2 diabetes, VAF, visceral fat area; W, women; WC.
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 non-significant was shown P>0.05. (-) mean that the study does not evaluate this parameter.

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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 (*N*=5)

Author, year	Study design Duration (Country)	Gender, age (years)	*n* (I./ PL)	ITT	Intervention (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	Total cholesterol (mmol/L)	LDL-cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	Triglycerides (mmol/L)
Added to yogurt matrix											
Nishiyama et al. (51)	R, DB, CT, PC 8 weeks (Japan)	W, 23 to 66	76 (37/39)	No	Yogurt with L. *lactis* 11/19-B1 and BB-12. (nd.)	PL yogurt	End vs BL (IG) Between interv.	↓0.3 *P*>0.05	↓0.25 *P*>0.05	*P*>0.05 *P*>0.05	
Ivey et al. (101)	R, DB, CT, PC 6 weeks (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 x 10^9) I2. Yogurt with *L. acidophilus* La5, *B. lactis* BB12 (3 x 10^9) + PL capsules I3. Milk + Capsules with *L. acidophilus* La5, *B. lactis* BB12 (3x10^9)	Milk + PL capsules	End vs BL (I1/I2/I3) Between interv. (I1 vs I3)	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05
Mohamadshahi et al.(42)	R, DB, CT, PC 8 weeks (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) Between interv.	↓0.67 *P*>0.05	↓0.79 -0.61	*P*>0.05 +0.89	*P*>0.05 *P*>0.05
Added to FD matrix											
Sperry et al. (52)	R, DB, PC, PG 28 days (Brazil)	W, 35 to 72	30 (15/15)	No	Cheese with *L. casei* 01. (1x 10^8)	PL cheese	End vs BL (IG) Between interv.	↓0.32 +0.09	↓0.28 -0.12	↑0.14 +0.1	↓0.13 -0.05
Naito et al. (40)	R, DB, PC, PG 8 weeks (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) Between interv.	*P*>0.05 -7.5	*P*>0.05 -↓6.0	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05

Abbreviations: *B, Bifidobacterium*; BL, baseline; CFU/day, colony forming units per day; CG, control group; CT, controlled trial; DB, double-blind; HDL, high density lipoprotein; IG, intervention group; ITT, Intention-to-treat; L, *Lactobacillus;* LDL, low density lipoprotein; M, men; PC, placebo-controlled; PG, parallel-group; PL, placebo; prob, probiotic; R, randomized; W, women.

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 non-significant was shown *P*>0.05. (-) mean that the study does not evaluate this parameter.

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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 (*N*=2)

Author, year	Study design Duration (Country	Gender, age (years)	*n* (I./ PL)	ITT	Intervention (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	WC (cm)	Triglycerides (mg/dL)	Total cholesterol (mmol/L)	LDL-cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	F. glucose (mmol/L
Added to yogurt matrix													
Rezazadeh et al.	R, DB, PC, PG	M and W,	44 (22/22)	No	Yogurt with *L. acidophilus* La5 (6.45×10^6) and *B. lactis* BB12. (4.94×10^6)	PL yogurt	End vs BL (IG)	-	-	-	-	-	↓4.81
(102)	8 weeks (Iran)	20 to 65					Between interv.	-	-	-	-	-	-3.80
Added to milk matrix													
Bernini et al.	R	M and W,	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
(103)	45 days (Brazil)	18 to 60					Between interv.	*P*>0.05	*P*>0.05	-0.55	-0.40	*P*>0.05	*P*>0.05

Abbreviations: *B, Bifidobacterium*; BL, baseline; CFU/day, colony forming units per day; CG, control group; CT, controlled trial; DB, double-blind; HDL, high density lipoprotein; IG, intervention group; ITT, Intention-to-treat; L*, Lactobacillus;* LDL, low density lipoprotein; M, men; PC, placebo-controlled; PG, parallel-group; PL, placebo; prob, probiotic; R, randomized; W, women.

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 non-significant was shown *P*>0.05. (-) mean that the study does not evaluate this parameter.

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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 (*N*=17)

Author, year	Study design Duration (Country)	Gender, age (years)	*n* (I./ PL)	ITT	Intervention (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	Significant results BW (kg)	BMI (kg/m2)	WC (cm)	BFM (Kg)	BF (%)	VAF (cm²)	SCFA (cm²)
Khalili et al. (56)	R, DB, PC, PG, 8 weeks (Iran)	M and W, 60 to 50	40 (20/20)	No	Capsules with L. *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. (104)	R, DB, PC 12 weeks (Korea)	M and W, 20 to 75	90 (30/30/30)	No	I1. Capsules with L. *gasseri* BNR17. (10^9) I2. Capsules with L. *gasseri* BNR17. (10^{10})	PL powder	End vs BL(IG)	*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. (55)	R, DB, PC, PG 8 weeks (Ukraine)	M and W, 18 to 75	53 (31/22)	No	Powder with 14 probiotic strains of *L.* + *Lactococcus*($6×10^{10}$), B. ($1×10^{10}$), 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. (105)	R, DB, PC, PG 12 weeks (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. (62)	R, DB, PC, PG 12 weeks (Spain)	M and W, >18	126 (42/44/40)	Yes	I1. Capsules with B. *animalis subsp. lactis* CECT 8145.($1 X 10^{10}$) I2. Heat-killed B. *animalis subsp. lactis* CECT 8145. ($1 X 10^{10}$)	PL powder	End vs BL(I1/I2)		↓0.34/ *P*>0.05	↓1.74/↓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. (63)	R, DB, PC, PG 12 week (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.($1 × 10^{10}$) I2. Powder of Ecologic® Barrier. ($2,5 x 10^9$)	PL powder	End vs BL(I1/I2)	-	*P*>0.05	-0.54/-1.06	-0.22/-0.62	*P*>0.05/-0.54	*P*>0.05/-0.58/ *P*>0.05	-0.83/-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. (59)	R, DB, PC, PG 8 weeks (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. ($2 x 10^{10}$)	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	-	-	-
Mahadzir et al. (54)	R, DB, CT, PG 4 weeks (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.* ($60x10^9$)	PL powder	End vs BL(IG)	*P*>0.05	-	*P*>0.05	-	-	-	-
							Between interv.	*P*>0.05	-	*P*>0.05	-	-	-	-
Mobini et al. (106)	R, DB, PC, PG 12 weeks (Sweden)	M and W, 50 to 75	44 (14/15/15)	No	I1. Powder of *L. reuteri* DS17938. ($1x10^{10}$) I2. *L. reuteri* DS17938. ($1x10^8$)	PL powder	End vs BL(I1/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. (64)	R, DB, PC 12 weeks (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. (60)	R, DB, PG, PC 12 weeks (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. I2. Same I1 powder only in women.	PL powder	End vs BL(I1/I2)	*P*>0.05	*P*>0.05	*P*>0.05/↓2.00	-	-	-	-
							Between interv.	*P*>0.05	*P*>0.05	*P*>0.05	-	-	-	-
Higashikawa et al. (65)	R, DB, PC, PG 12 weeks (Japan)	M and W, 20 to 70	62 (21/21/20)	Yes	I1. Powder of *P. pentosaceus* LP28 living. I2. Powder of *P. pentosaceus* LP28 heat-killed. ($1 x 10^{11}$)	PL powder	End vs BL(I1/I2)	-	*P*>0.05	*P*>0.05/↓1.83	*P*>0.05/ ↓1.77	↓0.51/ ↓ 1.03	-	-
							Between interv. (I2 vs CG)	-	*P*>0.05	-2.84	-1.17	-1.11	-	-
Jung et al.(58)	R, DB, PC 12 weeks (Korea)	M and W, 20 to 65	95 (49/46)	No	Powder of *L. curvatus* HY7601 and *L. plantarum* KY1032. ($5 x 10^9$)	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 weeks (Korea)	M and W, 25 to 65	37 (18/19)	No	Capsules of *L.* JBD301. ($1 x 10^9$)	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.(61)	R, DB, PG, PC 12 weeks (Japan)	M and W, 40 to 69	44 (19/25)	No	Capsules of *B. breve* B-3. ($5 x 10^{10}$)	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.(57)	R, DB, PC 12 weeks (Korea)	M and W, 19 to 60	62 (29/23)	Yes	Capsules of *L. gasseri* BNR17. ($1 x 10^{10}$)	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. (107)	R, DB, PC 12 weeks (Spain)	M and W, 39 to 59	28 (14/14)	No	Tablet of *L. bulgaricus, S. thermophiles.* ($5 x 10^8$)	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	-	-	-

Abbreviations: *B, Bifidobacterium*; BL, baseline; BMI, body mass index; BW, body weight; BF, body fat; BFM, body fat mass; CG, control; CT, controlled trial; DB, double-blind; I, intervention IG, intervention group; ITT, Intention-to-treat; L*, Lactobacillus;* M, men; n.d.; *P, Pediococcus;* prob, PC, placebo-controlled; PG, parallel-group; probiotic; PL, placebo; R, randomized; *S, Streptococcus*; SCFA, subcutaneous fat area; VAF, visceral fat area; W, women; WC, waist circumference.

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 non-significant was shown *P*>0.05. (-) mean that the study does not evaluate this parameter.

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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 (*N*=11)

Author, year	Study design Duration (Country)	Gender, age (years)	*N* (I./PL)	ITT	Intervention (CFU/day) (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	Significant results F. insulin (µIU/mL)	HOMA-IR	Hba1C (%)	F. glucose (mmol/L)	Plasma CRP (mg/L)
Razmpoosh et al. (66)	R, DB, PC, PG 6 weeks (Iran)	M and W, 30 to 75	68 (34/34)	No	Capsules with *L. acidophilus* (2x10^9), *L. casei* (7X10^9), *L. rhamnosus* (1.5x109*), L. bulgaricus* (2x10^8*), B.breve* (3x10^{10}), *B. longum* (7x10^9), *S. thermophiles.* (1.5x$10^{9)}$	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. (53)	R, DB, PC, PG 24 weeks (Saudi Arabia)	M and W, 30 to 60	96 (48/48)	Yes	Powder with Ecologic®Barrier. (2.5x10^9)	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.(68)	R, DB, PC, PG 24 weeks (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. (56)	R, DB, PC, PG 8 weeks (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. (55)	R, DB, PC, PG 8 weeks (Ukraine)	M and W, 18 to 75	53 (31/22)	No	Powder with 14 alive probiotic strains of L. + *Lactococcus* (6×10^{10}), B. (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. (69)	R, DB, PC, PG 9 weeks (Taiwan)	M and W, 25 to 70	74 (25/25/24)	No	I1. Capsules with L*. reuteri* ADR-1. (4 × 10^9) I2. Capsules with Heat-killed L*. reuteri* ADR-3. (2 × 10^{10})	PL powder	End vs BL(I1/I2)	-	-	-	-	-
							Between interv. (I1 vs CG)	*P*>0.05	*P*>0.05	*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	*P*>0.05
Raygan et al. (67)	R, DB, PC, PG 12 weeks (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. (106)	R, DB, PC, PG 12 weeks (Sweden)	M and W, 50 to 75	44 (14/15/15)	No	Powder with *L. reuteri* DS17938. (1 x 10^8)	PL powder	End vs BL(IG)	-	-	*P*>0.05	-	*P*>0.05
							Between interv.	-	-	*P*>0.05	-	*P*>0.05
Sabico et al. (64)	R, DB, PC 12 weeks (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. (60)	R, DB, PG, PC 12 weeks (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 weeks (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	-	-	-

Abbreviations: B, *Bifidobacterium*; BL, baseline; CFU/day, colony forming units per day; CG, control group; CRP, C-reactive protein; CT, controlled trial; d, day; DB, double-blind; F, fasting; g, grams; Hba1C, glycosylated hemoglobin; HOMA-IR, Homeostatic model assessment index; ITT, Intention-to-treat; IG, intervention group; L*, Lactobacillus*; LDL, low density lipoprotein; M, men; mL, milliliters; mmol/L, milimol per liter; n.d., no data; PC, placebo-controlled; PG, parallel-group; PL, placebo; prob, probiotic; S, *Streptococcus*; R, randomized; W, women.
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 non-significant was shown *P*>0.05. (-) mean that the study does not evaluate this parameter.

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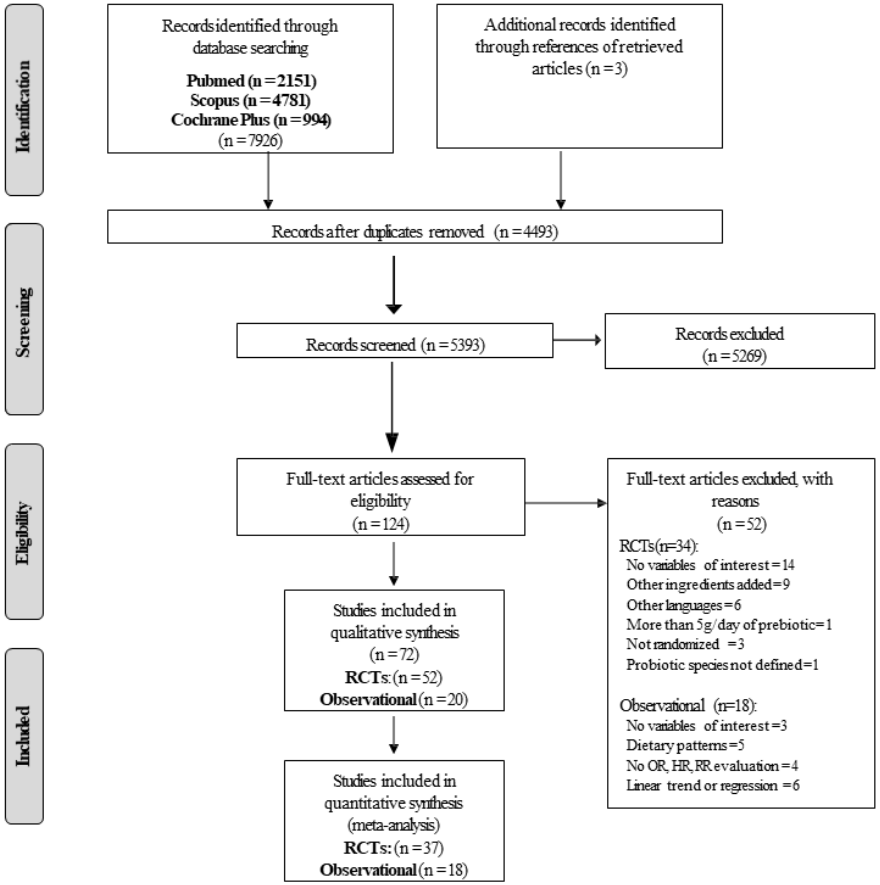
Table 9. Summary of the individual information extracted from each included randomized clinical trial evaluating the effectiveness of probiotics in powder or capsules on CMD in subjects with hypercholesterolemia (*N*=5)

Author, year	Study design Duration (Country)	Gender, age (years)	*N* (I./PL)	ITT	Intervention (CFU/day) (IG) (Type of admin. – Probiotic strain – CFU/day)	Control group (CG)	Compared to	Significant results Total cholesterol (mmol/L)	LDL-cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	Triglycerides (mmol/L)
Culpepper et al. (70)	R, DB, PC, CO 18 weeks (EEUU)	M and W, 18 to 65	114	No	*I1.Capsules of Bacillus subtilis R0179. (5x10^9)* *I2. L. plantarum HA-119. (5x10^9)* *I3. B. animalis subsp. lactis B94. (5x10^9)*	PL powder	End vs BL(I1/I2/I3) Between interv.	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
Brahe et al. (72)	R, PG, PC 6 weeks (Denmark)	Menopausal W, 40 to 70	53 (18/19/16)	No	Powder with *L. paracasei* spp. *paracasei F1.* (9.4 x 10^{10})	PL powder	End vs BL(IG) Between interv.	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05
Fuentes et al. (71)	R, DB, PC, PG 16 weeks (Spain)	M and W, 18 to 65	60 (30/30)	No	Capsules with *L. plantarum* CECT7527, CECT7528, CECT7529. (1 x 10^{10})	PL capsules	End vs BL(IG) Between interv.	↓0.7 -0.45	↓0.53 -0.28	↑0.07 +0.06	↓0.87 -0.70
Rerksuppaphol et al. (73)	R, DB, CT, PC 6 weeks (Thailand)	M and W, 40 to 58	64 (31/33)	No	Capsules with *L. acidophilus (*3 x 10^9*), L. bifidum. (*3 x 10^9*)*	PL capsules	End vs BL(IG) Between interv.	↓0.64 -1.20	*P*>0.05 -0.70	*P*>0.05 -0.08	*P*>0.05 *P*>0.05
Jones et al. (74)	R, DB, PC, PG, MC 13 weeks (Czech Republic)	M and W, 20 to 75	127 (66/61)	No	Capsules with *L. reuteri* NCIMB 30242. (2.9 X 10^9)	PL capsules	End vs BL(IG) Between interv.	*P*>0.05 -0.58	*P*>0.05 -0.51	*P*>0.05 *P*>0.05	*P*>0.05 *P*>0.05

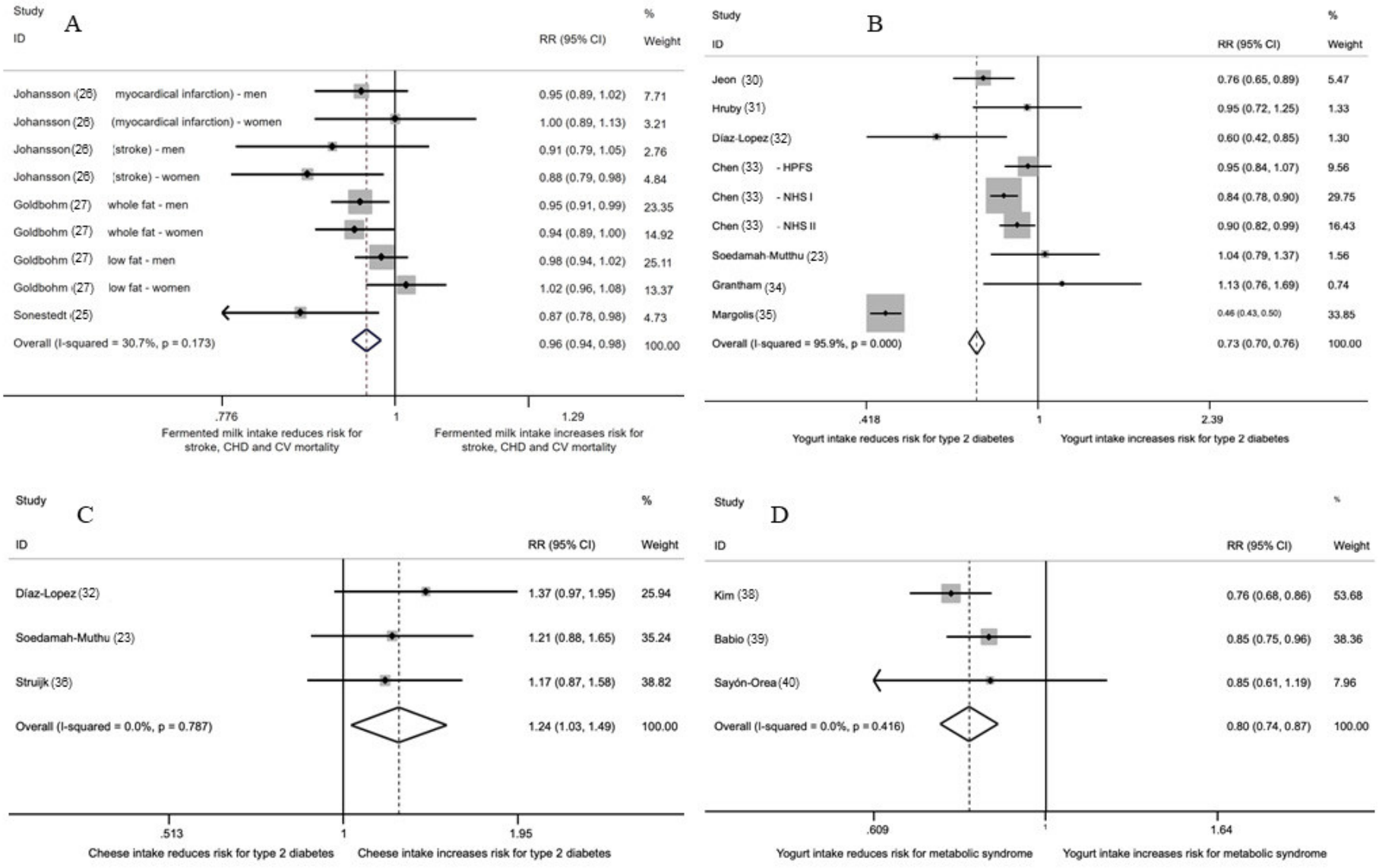
Abbreviations: B, *Bifidobacterium*; BL, baseline; CFU/day, colony forming units per day; CG, control group; CO, cross-over; CRP, C-reactive protein; CT, controlled trial; d, day; DB, double-blind; Hba1C, glycosylated hemoglobin; HOMA-IR, Homeostatic model assessment index; ITT, Intention-to-treat; IG, intervention group; L, *Lactobacillus*; M, men; MC, multicenter; mL, milliliters; mmol/L, milimol per liter; n.d., no data; PC, placebo-controlled; PG, parallel-group; PL, placebo; prob, probiotic; R, randomized; W, women

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 non-significant was shown *P*>0.05. (-) mean that the study does not evaluate this parameter.

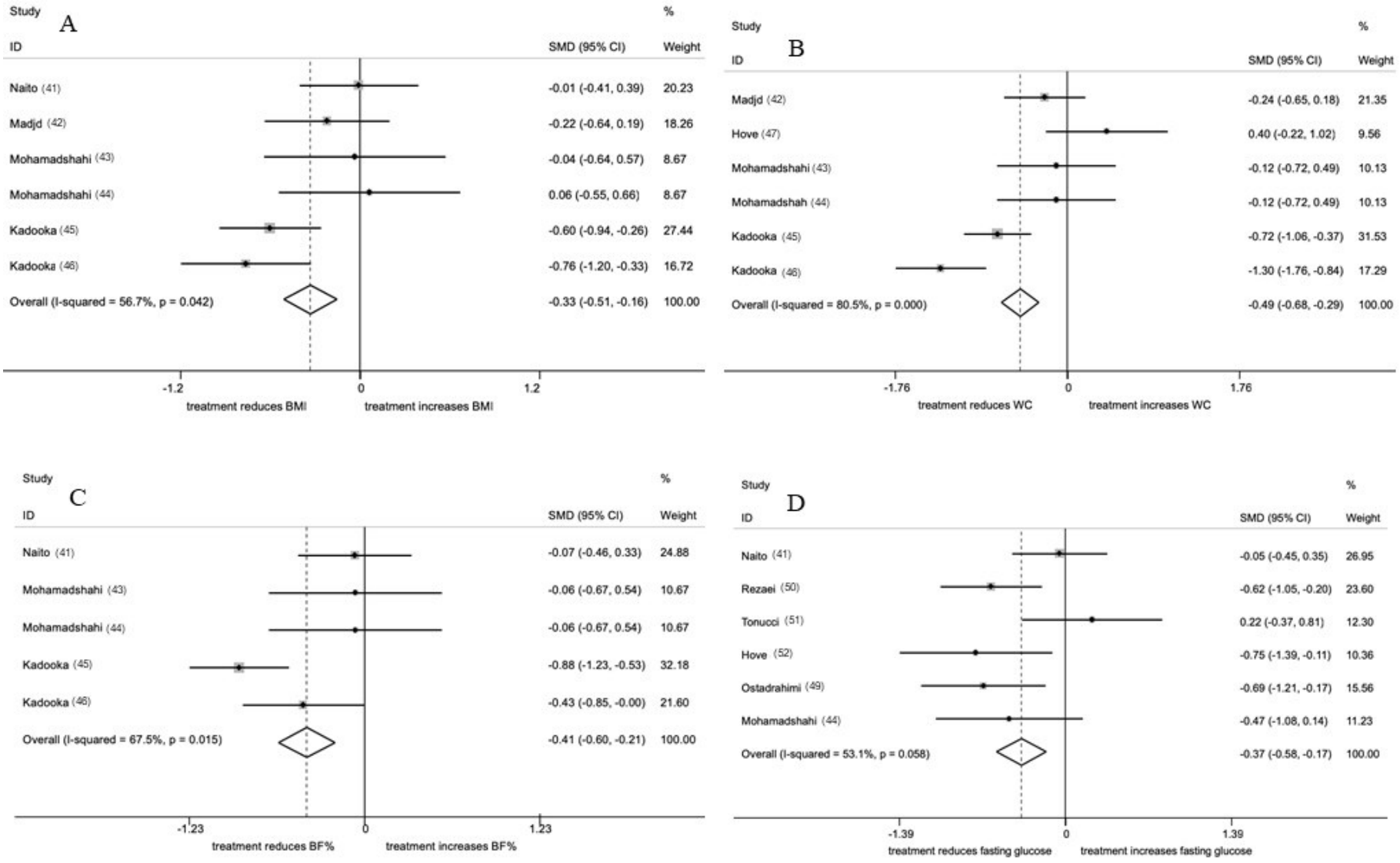
1097


Identification
Screening
Eligibility
Included
Records identified through database searching
Pubmed (n = 2151)
Scopus (n = 4781)
Cochrane Plus (n = 994)
(n = 7926)
Additional records identified through references of retrieved articles (n = 3)
Records after duplicates removed (n = 4493)
Records screened (n = 5393)
Records excluded (n = 5269)
Full-text articles assessed for eligibility (n = 124)
Full-text articles excluded, with reasons (n = 52)
RCTs(n=34):
No variables of interest = 14
Other ingredients added = 9
Other languages = 6
More than 5g/day of prebiotic = 1
Not randomized = 3
Probiotic species not defined = 1
Observational (n=18):
No variables of interest = 3
Dietary patterns = 5
No OR, HR, RR evaluation = 4
Linear trend or regression = 6
Studies included in qualitative synthesis (n = 72)
RCTs: (n = 52)
Observational (n = 20)
Studies included in quantitative synthesis (meta-analysis)
RCTs: (n = 37)
Observational (n = 18)

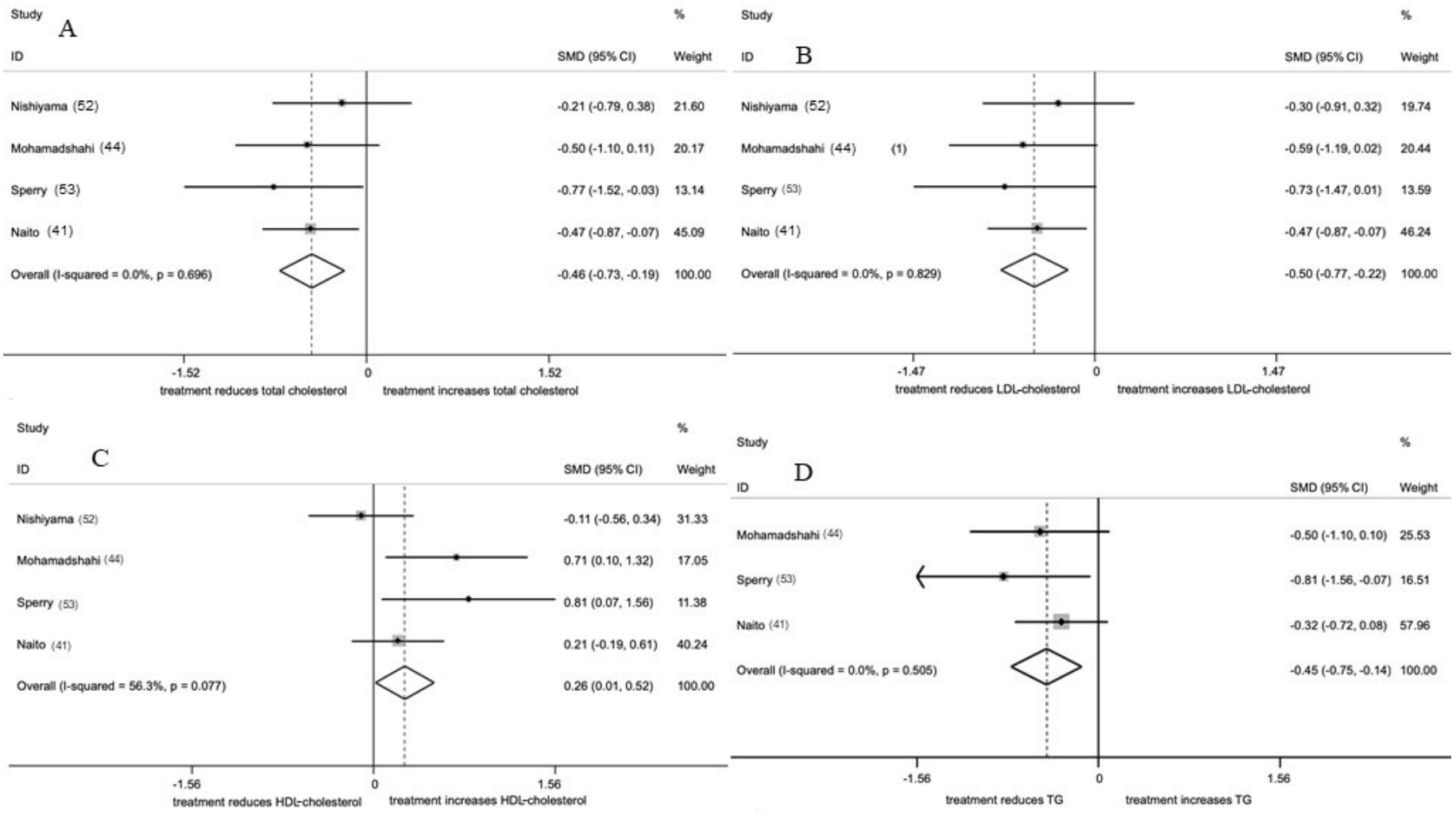
1098


A
Study
ID
RR (95% CI)
%
Weight
Johansson (26) myocardical infarction) - men
0.95 (0.89, 1.02)
7.71
Johansson (26) (myocardical infarction) - women
1.00 (0.89, 1.13)
3.21
Johansson (26) (stroke) - men
0.91 (0.79, 1.05)
2.76
Johansson (26) (stroke) - women
0.88 (0.79, 0.98)
4.84
Goldbohm (27) whole fat - men
0.95 (0.91, 0.99)
23.35
Goldbohm (27) whole fat - women
0.94 (0.89, 1.00)
14.92
Goldbohm (27) low fat - men
0.98 (0.94, 1.02)
25.11
Goldbohm (27) low fat - women
1.02 (0.96, 1.08)
13.37
Sonestedt (25)
0.87 (0.78, 0.98)
4.73
Overall (I-squared = 30.7%, p = 0.173)
0.96 (0.94, 0.98)
100.00
.776
1
1.29
Fermented milk intake reduces risk for stroke, CHD and CV mortality
Fermented milk intake increases risk for stroke, CHD and CV mortality
B
Study
ID
RR (95% CI)
%
Weight
Jeon (30)
0.76 (0.65, 0.89)
5.47
Hruby (31)
0.95 (0.72, 1.25)
1.33
Díaz-Lopez (32)
0.60 (0.42, 0.85)
1.30
Chen (33) - HPFS
0.95 (0.84, 1.07)
9.56
Chen (33) - NHS I
0.84 (0.78, 0.90)
29.75
Chen (33) - NHS II
0.90 (0.82, 0.99)
16.43
Soedamah-Mutthu (23)
1.04 (0.79, 1.37)
1.56
Grantham (34)
1.13 (0.76, 1.69)
0.74
Margolis (35)
0.46 (0.43, 0.50)
33.85
Overall (I-squared = 95.9%, p = 0.000)
0.73 (0.70, 0.76)
100.00
.418
1
2.39
Yogurt intake reduces risk for type 2 diabetes
Yogurt intake increases risk for type 2 diabetes
C
Study
ID
RR (95% CI)
%
Weight
Díaz-Lopez (32)
1.37 (0.97, 1.95)
25.94
Soedamah-Muthu (23)
1.21 (0.88, 1.65)
35.24
Struijk (36)
1.17 (0.87, 1.58)
38.82
Overall (I-squared = 0.0%, p = 0.787)
1.24 (1.03, 1.49)
100.00
.513
1
1.95
Cheese intake reduces risk for type 2 diabetes
Cheese intake increases risk for type 2 diabetes
D
Study
ID
RR (95% CI)
%
Weight
Kim (38)
0.76 (0.68, 0.86)
53.68
Babio (39)
0.85 (0.75, 0.96)
38.36
Sayón-Orea (40)
0.85 (0.61, 1.19)
7.96
Overall (I-squared = 0.0%, p = 0.416)
0.80 (0.74, 0.87)
100.00
.609
1
1.64
Yogurt intake reduces risk for metabolic syndrome
Yogurt intake increases risk for metabolic syndrome

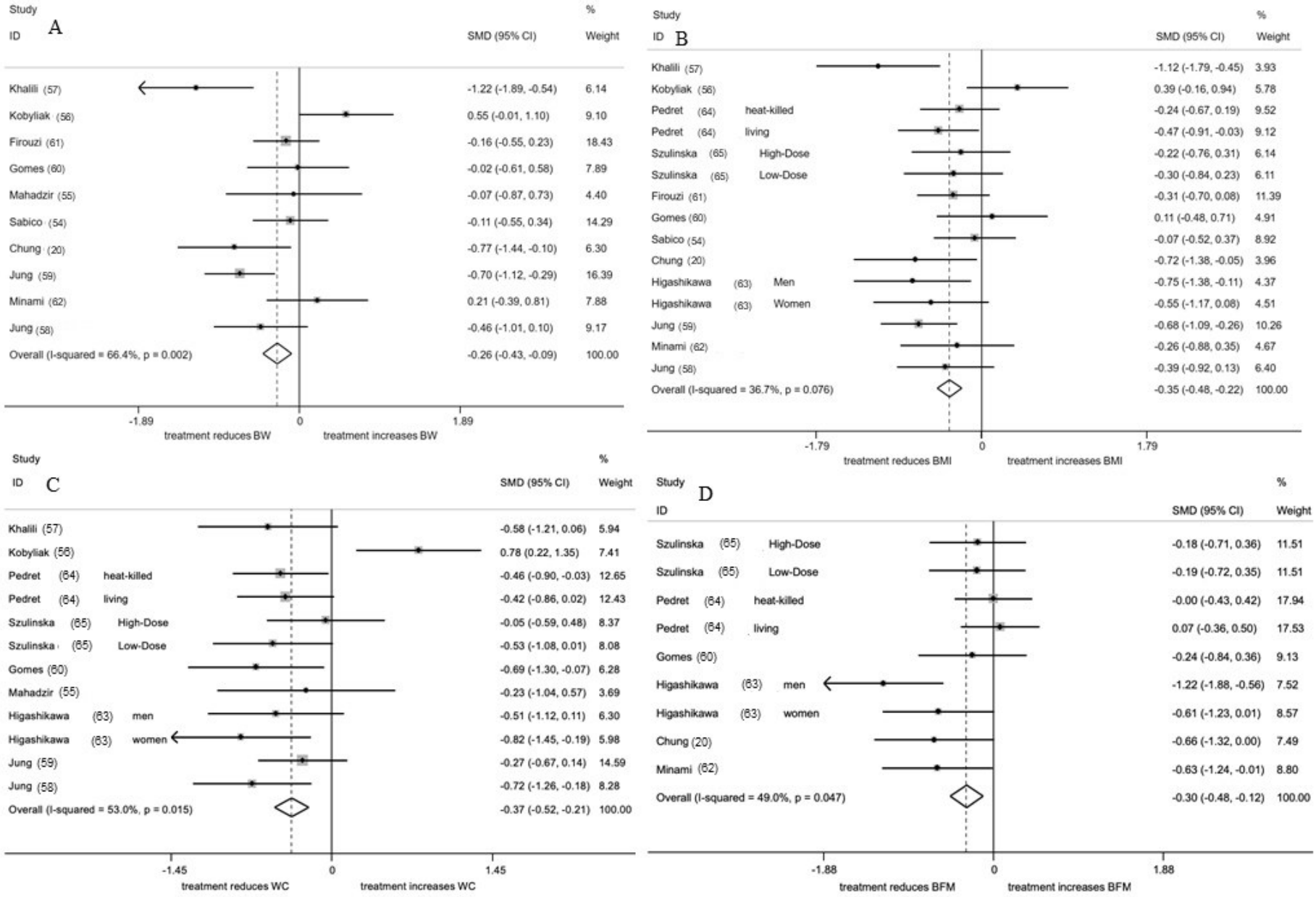
1099


A
Study
ID
SMD (95% CI)
%
Weight
Naito (41)
-0.01 (-0.41, 0.39)
20.23
Madjd (42)
-0.22 (-0.64, 0.19)
18.26
Mohamadshahi (43)
-0.04 (-0.64, 0.57)
8.67
Mohamadshahi (44)
0.06 (-0.55, 0.66)
8.67
Kadooka (45)
-0.60 (-0.94, -0.26)
27.44
Kadooka (46)
-0.76 (-1.20, -0.33)
16.72
Overall (I-squared = 56.7%, p = 0.042)
-0.33 (-0.51, -0.16)
100.00
-1.2
0
1.2
treatment reduces BMI
treatment increases BMI
B
Study
ID
SMD (95% CI)
%
Weight
Madjd (42)
-0.24 (-0.65, 0.18)
21.35
Hove (47)
0.40 (-0.22, 1.02)
9.56
Mohamadshahi (43)
-0.12 (-0.72, 0.49)
10.13
Mohamadshah (44)
-0.12 (-0.72, 0.49)
10.13
Kadooka (45)
-0.72 (-1.06, -0.37)
31.53
Kadooka (46)
-1.30 (-1.76, -0.84)
17.29
Overall (I-squared = 80.5%, p = 0.000)
-0.49 (-0.68, -0.29)
100.00
-1.76
0
1.76
treatment reduces WC
treatment increases WC
C
Study
ID
SMD (95% CI)
%
Weight
Naito (41)
-0.07 (-0.46, 0.33)
24.88
Mohamadshahi (43)
-0.06 (-0.67, 0.54)
10.67
Mohamadshahi (44)
-0.06 (-0.67, 0.54)
10.67
Kadooka (45)
-0.88 (-1.23, -0.53)
32.18
Kadooka (46)
-0.43 (-0.85, -0.00)
21.60
Overall (I-squared = 67.5%, p = 0.015)
-0.41 (-0.60, -0.21)
100.00
-1.23
0
1.23
treatment reduces BF%
treatment increases BF%
D
Study
ID
SMD (95% CI)
%
Weight
Naito (41)
-0.05 (-0.45, 0.35)
26.95
Rezaei (50)
-0.62 (-1.05, -0.20)
23.60
Tonucci (51)
0.22 (-0.37, 0.81)
12.30
Hove (52)
-0.75 (-1.39, -0.11)
10.36
Ostadrahimi (49)
-0.69 (-1.21, -0.17)
15.56
Mohamadshahi (44)
-0.47 (-1.08, 0.14)
11.23
Overall (I-squared = 53.1%, p = 0.058)
-0.37 (-0.58, -0.17)
100.00
-1.39
0
1.39
treatment reduces fasting glucose
treatment increases fasting glucose

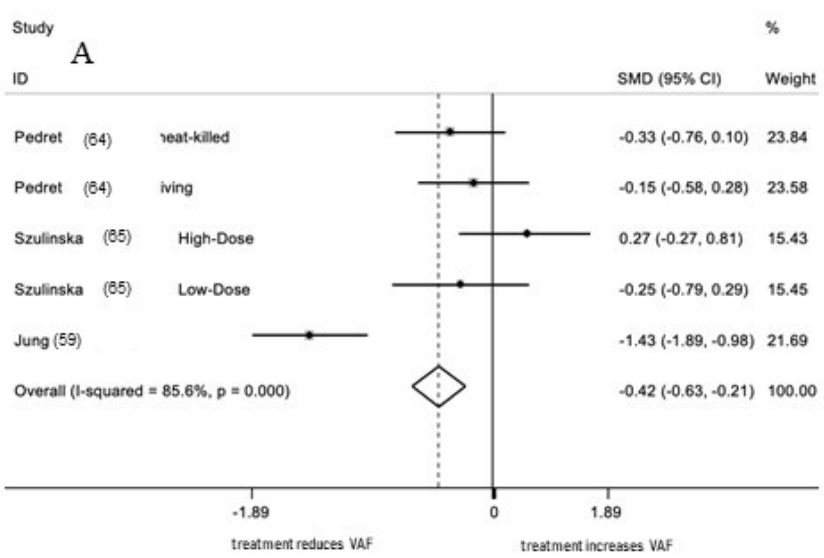
1100

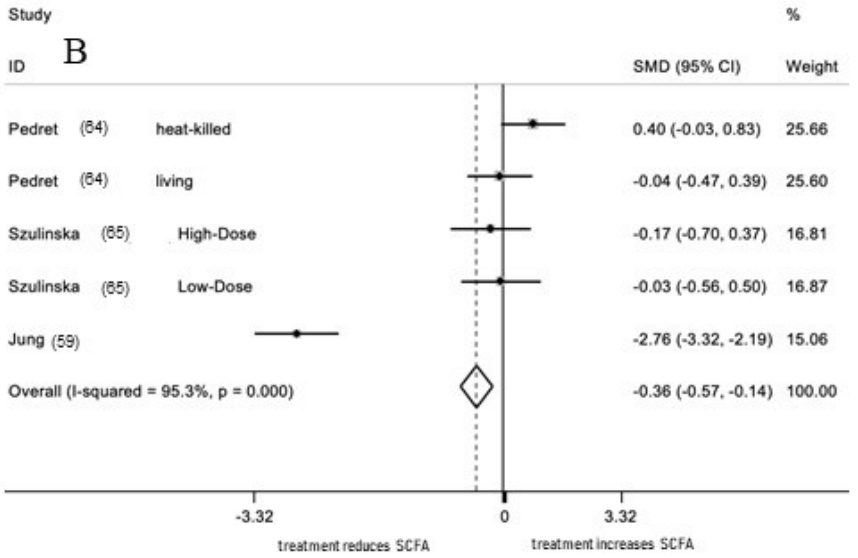

A
Study
ID
SMD (95% CI)
%
Weight
Nishiyama (52)
-0.21 (-0.79, 0.38)
21.60
Mohamadshahi (44)
-0.50 (-1.10, 0.11)
20.17
Sperry (53)
-0.77 (-1.52, -0.03)
13.14
Naito (41)
-0.47 (-0.87, -0.07)
45.09
Overall (I-squared = 0.0%, p = 0.696)
-0.46 (-0.73, -0.19)
100.00
-1.52
0
1.52
treatment reduces total cholesterol
treatment increases total cholesterol
B
Study
ID
SMD (95% CI)
%
Weight
Nishiyama (52)
-0.30 (-0.91, 0.32)
19.74
Mohamadshahi (44)
(1)
-0.59 (-1.19, 0.02)
20.44
Sperry (53)
-0.73 (-1.47, 0.01)
13.59
Naito (41)
-0.47 (-0.87, -0.07)
46.24
Overall (I-squared = 0.0%, p = 0.829)
-0.50 (-0.77, -0.22)
100.00
-1.47
0
1.47
treatment reduces LDL-cholesterol
treatment increases LDL-cholesterol
C
Study
ID
SMD (95% CI)
%
Weight
Nishiyama (52)
-0.11 (-0.56, 0.34)
31.33
Mohamadshahi (44)
0.71 (0.10, 1.32)
17.05
Sperry (53)
0.81 (0.07, 1.56)
11.38
Naito (41)
0.21 (-0.19, 0.61)
40.24
Overall (I-squared = 56.3%, p = 0.077)
0.26 (0.01, 0.52)
100.00
-1.56
0
1.56
treatment reduces HDL-cholesterol
treatment increases HDL-cholesterol
D
Study
ID
SMD (95% CI)
%
Weight
Mohamadshahi (44)
-0.50 (-1.10, 0.10)
25.53
Sperry (53)
-0.81 (-1.56, -0.07)
16.51
Naito (41)
-0.32 (-0.72, 0.08)
57.96
Overall (I-squared = 0.0%, p = 0.505)
-0.45 (-0.75, -0.14)
100.00
-1.56
0
1.56
treatment reduces TG
treatment increases TG

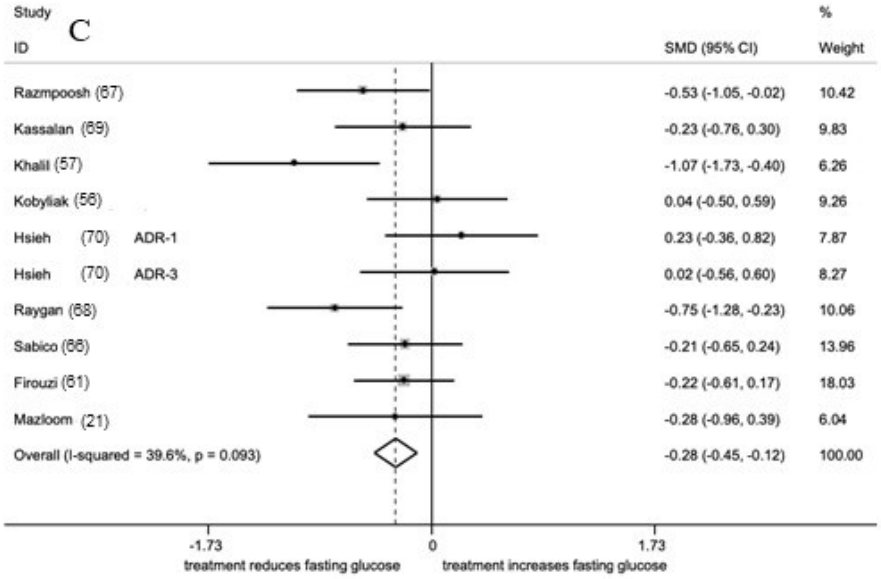
1101

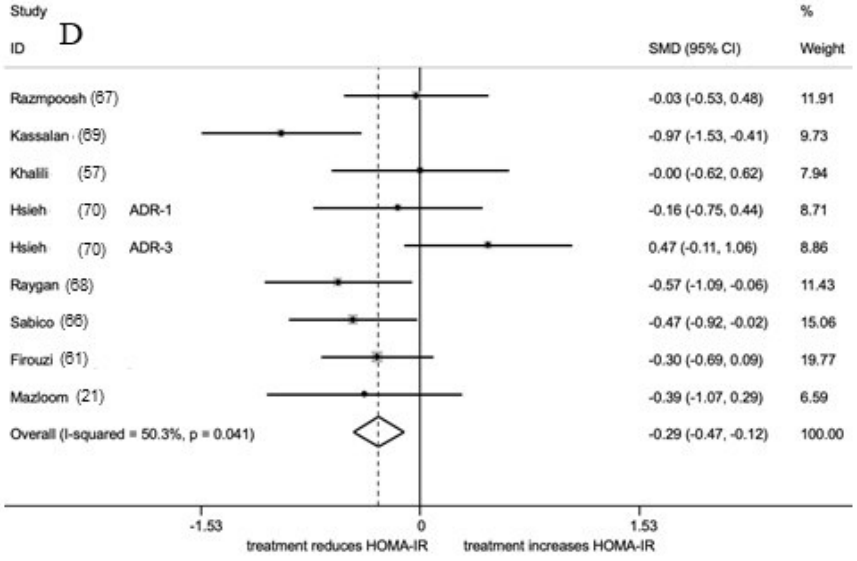

A
Study
ID
SMD (95% CI)
%
Weight
Khalili (57) -1.22 (-1.89, -0.54) 6.14
Kobyliak (56) 0.55 (-0.01, 1.10) 9.10
Firouzi (61) -0.16 (-0.55, 0.23) 18.43
Gomes (60) -0.02 (-0.61, 0.58) 7.89
Mahadzir (55) -0.07 (-0.87, 0.73) 4.40
Sabico (54) -0.11 (-0.55, 0.34) 14.29
Chung (20) -0.77 (-1.44, -0.10) 6.30
Jung (59) -0.70 (-1.12, -0.29) 16.39
Minami (62) 0.21 (-0.39, 0.81) 7.88
Jung (58) -0.46 (-1.01, 0.10) 9.17
Overall (I-squared = 66.4%, p = 0.002) -0.26 (-0.43, -0.09) 100.00
-1.89
0
1.89
treatment reduces BW
treatment increases BW
B
Study
ID
SMD (95% CI)
%
Weight
Khalili (57) -1.12 (-1.79, -0.45) 3.93
Kobyliak (56) 0.39 (-0.16, 0.94) 5.78
Pedret (64) heat-killed -0.24 (-0.67, 0.19) 9.52
Pedret (64) living -0.47 (-0.91, -0.03) 9.12
Szulinska (65) High-Dose -0.22 (-0.76, 0.31) 6.14
Szulinska (65) Low-Dose -0.30 (-0.84, 0.23) 6.11
Firouzi (61) -0.31 (-0.70, 0.08) 11.39
Gomes (60) 0.11 (-0.48, 0.71) 4.91
Sabico (54) -0.07 (-0.52, 0.37) 8.92
Chung (20) -0.72 (-1.38, -0.05) 3.96
Higashikawa (63) Men -0.75 (-1.38, -0.11) 4.37
Higashikawa (63) Women -0.55 (-1.17, 0.08) 4.51
Jung (59) -0.68 (-1.09, -0.26) 10.26
Minami (62) -0.26 (-0.88, 0.35) 4.67
Jung (58) -0.39 (-0.92, 0.13) 6.40
Overall (I-squared = 36.7%, p = 0.076) -0.35 (-0.48, -0.22) 100.00
-1.79
0
1.79
treatment reduces BMI
treatment increases BMI
C
Study
ID
SMD (95% CI)
%
Weight
Khalili (57) -0.58 (-1.21, 0.06) 5.94
Kobyliak (56) 0.78 (0.22, 1.35) 7.41
Pedret (64) heat-killed -0.46 (-0.90, -0.03) 12.65
Pedret (64) living -0.42 (-0.86, 0.02) 12.43
Szulinska (65) High-Dose -0.05 (-0.59, 0.48) 8.37
Szulinska (65) Low-Dose -0.53 (-1.08, 0.01) 8.08
Gomes (60) -0.69 (-1.30, -0.07) 6.28
Mahadzir (55) -0.23 (-1.04, 0.57) 3.69
Higashikawa (63) men -0.51 (-1.12, 0.11) 6.30
Higashikawa (63) women -0.82 (-1.45, -0.19) 5.98
Jung (59) -0.27 (-0.67, 0.14) 14.59
Jung (58) -0.72 (-1.26, -0.18) 8.28
Overall (I-squared = 53.0%, p = 0.015) -0.37 (-0.52, -0.21) 100.00
-1.45
0
1.45
treatment reduces WC
treatment increases WC
D
Study
ID
SMD (95% CI)
%
Weight
Szulinska (65) High-Dose -0.18 (-0.71, 0.36) 11.51
Szulinska (65) Low-Dose -0.19 (-0.72, 0.35) 11.51
Pedret (64) heat-killed -0.00 (-0.43, 0.42) 17.94
Pedret (64) living 0.07 (-0.36, 0.50) 17.53
Gomes (60) -0.24 (-0.84, 0.36) 9.13
Higashikawa (63) men -1.22 (-1.88, -0.56) 7.52
Higashikawa (63) women -0.61 (-1.23, 0.01) 8.57
Chung (20) -0.66 (-1.32, 0.00) 7.49
Minami (62) -0.63 (-1.24, -0.01) 8.80
Overall (I-squared = 49.0%, p = 0.047) -0.30 (-0.48, -0.12) 100.00
-1.88
0
1.88
treatment reduces BFM
treatment increases BFM

1102

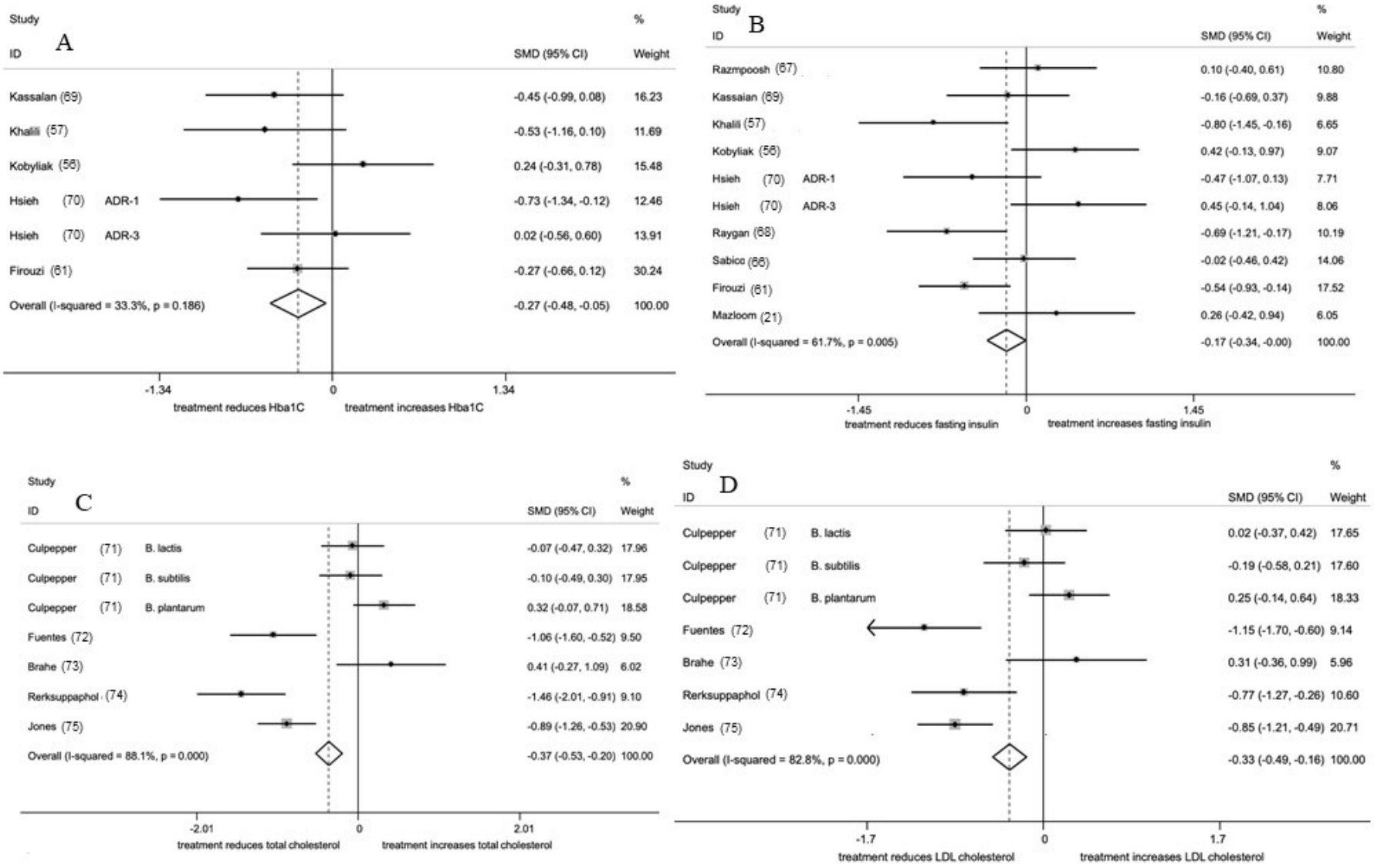

A
Study
ID
%
SMD (95% CI)
Weight
Pedret (64) heat-killed -0.33 (-0.76, 0.10) 23.84
Pedret (64) living -0.15 (-0.58, 0.28) 23.58
Szulinska (65) High-Dose 0.27 (-0.27, 0.81) 15.43
Szulinska (65) Low-Dose -0.25 (-0.79, 0.29) 15.45
Jung (59) -1.43 (-1.89, -0.98) 21.69
Overall (I-squared = 85.6%, p = 0.000) -0.42 (-0.63, -0.21) 100.00
-1.89
0
1.89
treatment reduces VAF
treatment increases VAF


B
Study
ID
%
SMD (95% CI)
Weight
Pedret (64) heat-killed 0.40 (-0.03, 0.83) 25.66
Pedret (64) living -0.04 (-0.47, 0.39) 25.60
Szulinska (65) High-Dose -0.17 (-0.70, 0.37) 16.81
Szulinska (65) Low-Dose -0.03 (-0.56, 0.50) 16.87
Jung (59) -2.76 (-3.32, -2.19) 15.06
Overall (I-squared = 95.3%, p = 0.000) -0.36 (-0.57, -0.14) 100.00
-3.32
0
3.32
treatment reduces SCFA
treatment increases SCFA


C
Study
ID
%
SMD (95% CI)
Weight
Razmpoosh (67) -0.53 (-1.05, -0.02) 10.42
Kassalan (69) -0.23 (-0.76, 0.30) 9.83
Khalili (57) -1.07 (-1.73, -0.40) 6.26
Kobyliak (56) 0.04 (-0.50, 0.59) 9.26
Hsieh (70) ADR-1 0.23 (-0.36, 0.82) 7.87
Hsieh (70) ADR-3 0.02 (-0.56, 0.60) 8.27
Raygan (68) -0.75 (-1.28, -0.23) 10.06
Sabico (66) -0.21 (-0.65, 0.24) 13.96
Firouzi (61) -0.22 (-0.61, 0.17) 18.03
Mazloom (21) -0.28 (-0.96, 0.39) 6.04
Overall (I-squared = 39.6%, p = 0.093) -0.28 (-0.45, -0.12) 100.00
-1.73
0
1.73
treatment reduces fasting glucose
treatment increases fasting glucose


D
Study
ID
%
SMD (95% CI)
Weight
Razmpoosh (67) -0.03 (-0.53, 0.48) 11.91
Kassalan (69) -0.97 (-1.53, -0.41) 9.73
Khalili (57) -0.00 (-0.62, 0.62) 7.94
Hsieh (70) ADR-1 -0.16 (-0.75, 0.44) 8.71
Hsieh (70) ADR-3 0.47 (-0.11, 1.06) 8.86
Raygan (68) -0.57 (-1.09, -0.06) 11.43
Sabico (66) -0.47 (-0.92, -0.02) 15.06
Firouzi (61) -0.30 (-0.69, 0.09) 19.77
Mazloom (21) -0.39 (-1.07, 0.29) 6.59
Overall (I-squared = 50.3%, p = 0.041) -0.29 (-0.47, -0.12) 100.00
-1.53
0
1.53
treatment reduces HOMA-IR
treatment increases HOMA-IR

1103


A
Study
ID
SMD (95% CI)
%
Weight
Kassalan (69) -0.45 (-0.99, 0.08) 16.23
Khalili (57) -0.53 (-1.16, 0.10) 11.69
Kobyliak (56) 0.24 (-0.31, 0.78) 15.48
Hsieh (70) ADR-1 -0.73 (-1.34, -0.12) 12.46
Hsieh (70) ADR-3 0.02 (-0.56, 0.60) 13.91
Firouzi (61) -0.27 (-0.66, 0.12) 30.24
Overall (I-squared = 33.3%, p = 0.186) -0.27 (-0.48, -0.05) 100.00
-1.34
0
1.34
treatment reduces Hba1C
treatment increases Hba1C
B
Study
ID
SMD (95% CI)
%
Weight
Razmpoosh (67) 0.10 (-0.40, 0.61) 10.80
Kassaian (69) -0.16 (-0.69, 0.37) 9.88
Khalili (57) -0.80 (-1.45, -0.16) 6.65
Kobyliak (56) 0.42 (-0.13, 0.97) 9.07
Hsieh (70) ADR-1 -0.47 (-1.07, 0.13) 7.71
Hsieh (70) ADR-3 0.45 (-0.14, 1.04) 8.06
Raygan (68) -0.69 (-1.21, -0.17) 10.19
Sabico (66) -0.02 (-0.46, 0.42) 14.06
Firouzi (61) -0.54 (-0.93, -0.14) 17.52
Mazloom (21) 0.26 (-0.42, 0.94) 6.05
Overall (I-squared = 61.7%, p = 0.005) -0.17 (-0.34, -0.00) 100.00
-1.45
0
1.45
treatment reduces fasting insulin
treatment increases fasting insulin
C
Study
ID
SMD (95% CI)
%
Weight
Culpepper (71) B. lactis -0.07 (-0.47, 0.32) 17.96
Culpepper (71) B. subtilis -0.10 (-0.49, 0.30) 17.95
Culpepper (71) B. plantarum 0.32 (-0.07, 0.71) 18.58
Fuentes (72) -1.06 (-1.60, -0.52) 9.50
Brahe (73) 0.41 (-0.27, 1.09) 6.02
Rerksuppaphol (74) -1.46 (-2.01, -0.91) 9.10
Jones (75) -0.89 (-1.26, -0.53) 20.90
Overall (I-squared = 88.1%, p = 0.000) -0.37 (-0.53, -0.20) 100.00
-2.01
0
2.01
treatment reduces total cholesterol
treatment increases total cholesterol
D
Study
ID
SMD (95% CI)
%
Weight
Culpepper (71) B. lactis 0.02 (-0.37, 0.42) 17.65
Culpepper (71) B. subtilis -0.19 (-0.58, 0.21) 17.60
Culpepper (71) B. plantarum 0.25 (-0.14, 0.64) 18.33
Fuentes (72) -1.15 (-1.70, -0.60) 9.14
Brahe (73) 0.31 (-0.36, 0.99) 5.96
Rerksuppaphol (74) -0.77 (-1.27, -0.26) 10.60
Jones (75) -0.85 (-1.21, -0.49) 20.71
Overall (I-squared = 82.8%, p = 0.000) -0.33 (-0.49, -0.16) 100.00
-1.7
0
1.7
treatment reduces LDL cholesterol
treatment increases LDL cholesterol

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