**Supplementary Table 1.** Search strategies used for online databases

The following databases were searched:

* PubMed
* Scopus
* Web of Science
* Cochrane Library

The search strategy was to combine searches of:

|  |  |
| --- | --- |
| Probiotic | (Probiotics) OR (probiotic\*) OR ("cultured milk products") OR (yogurt) OR ("milk product") OR (kefir) OR (“dairy product”) OR (Bifidobacterium) OR (Bifido\*) OR (Bacteroides) OR (Bacteroid\*) OR (Lactobacillus) OR (Lactobacil\*) OR (Lactobacillaceae) OR (Pediococcus) OR (“Fermented Foods and Beverages”) OR (“Fermented milk”) OR (Nissle) OR (“Fermented Foods”) OR (Streptococ\*) OR (Saccharomyces) OR (Saccharomy) OR (Enterococcus) OR (Lactobacillales) OR (“Lactic acid bacteria”) OR (“Bacillus mesentericus”) OR (“Escherichia coli”) OR (acidophilus) OR (microorganism∗) OR (buttermilk) OR (lassi) OR (doogh) OR (dough) OR (dahi) OR (amasi) OR (filmjolk) OR (chal) OR (VSL#3) OR (Synbiotic\*) OR (Symbiotic\*) |
| Population | (Diabetes) OR (“Diabetes Mellitus”) OR (hyperglycemia) OR (diabet\*) |
| Study design | Randomized OR random OR "Random allocation" OR "Random assignment" OR Intervention OR "Clinical trial" OR "Randomized controlled trial" OR trial OR Placebo OR "Double-blind" OR "Single-blind" OR "Random Allocation" OR "Randomised clinical trial") |

“Probiotic, “population”, and “study design” related terms

**Supplementary Table 2**. References for excluded studies

|  |
| --- |
| **Wrong population (n=4)**  1**-**Mazloomi M, Tanideh N, Rezainzadeh A. The effects soymilk fremented with bifidobacterium lactis and containing omega-3 on haematological, oxidative stress, anti-oxidant and inflammatory parameters in type 2 diabetic rats. Iranian Journal of Diabetes and Metabolism. 2015;14(6):379-89.  2- Kushugulova A, Benberin V, Karabayeva R, Saduakhasova S, Kozhakhmetov S, Shakhabayeva G, et al. Randomized Clinical Trial: Efficacy of a New Synbiotic in Adults with Metabolic Syndrome. Cent Asian J Glob Health. 2013;2(Suppl)  3- Parastouei K, Saeidipoor S, Sepandi M, Abbaszadeh S, Taghdir M. Effects of synbiotic supplementation on the components of metabolic syndrome in military personnel: a double-blind randomised controlled trial. BMJ Mil Health.  4- Simon MC, Strassburger K, Nowotny B, Kolb H, Nowotny P, Burkart V, et al. Intake of Lactobacillus reuteri improves incretin and insulin secretion in glucose-tolerant humans: a proof of concept. Diabetes Care. 2015;38(10):1827-34. |
| **Wrong intervention (n=16)**  1- Asemi Z, Alizadeh SA, Ahmad K, Goli M, Esmaillzadeh A. Effects of beta-carotene fortified synbiotic food on metabolic control of patients with type 2 diabetes mellitus: A double-blind randomized cross-over controlled clinical trial. Clinical Nutrition. 2016;35(4):819-25  2- Kobyliak N, Abenavoli L, Falalyeyeva T, Kovalchuk O, Kyriienko D, Komisarenko I. Metabolic benefits of probiotic combination with absorbent smectite in type 2 diabetes patients: a randomised controlled trial. Rev Recent Clin Trials. 1574-8871. 2020.  3- Kobyliak N, Abenavoli L, Falalyeyeva T, Mykhalchyshyn G, Boccuto L, Kononenko L, et al. Beneficial effects of probiotic combination with omega fatty acids in NAFLD: A randomized clinical study. Minerva Medica. 2018;109(6):418-28 %9 Article %! Beneficial effects of probiotic combination with omega fatty acids in NAFLD: A randomized clinical study.  4- Kobyliak N, Abenavoli L, Mykhalchyshyn G, Falalyeyeva T, Tsyryuk O, Kononenko L, et al. Probiotics and smectite absorbent gel formulation reduce liver stiffness, transaminase and cytokine levels in NAFLD associated with type 2 diabetes: a randomized clinical study. Clinical Diabetology. 2019;8(4):205-14  5- Kobyliak N, Falalyeyeva T, Mykhalchyshyn G, Molochek N, Savchuk O, Kyriienko D, et al. Probiotic and omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance, improves glycemia and obesity parameters in individuals with type 2 diabetes: A randomised controlled trial. Obesity Medicine. 2020  6- Raygan F, Ostadmohammadi V, Asemi Z. The effects of probiotic and selenium co-supplementation on mental health parameters and metabolic profiles in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. Clinical Nutrition. 2019;38(4):1594-8  7- Król E, Krejpcio Z, Byks H, Bogdański P, Pupek-Musialik D. Effects of chromium brewer's yeast supplementation on body mass, blood carbohydrates, and lipids and minerals in type 2 diabetic patients. Biol Trace Elem Res. 2011;143(2):726-37.  8- Król E, Krejpcio Z, Byks H, Bogdański P, Pupek-Musialik D. Effects of chromium brewer's yeast supplementation on body mass, blood carbohydrates, and lipids and minerals in type 2 diabetic patients. Biol Trace Elem Res. 2011;143(2):726-37  9- Lang R, Wang X-H, Li A-F, Liang Y, Zhu B-C, Shi B, et al. Effects of Jian Pi Qu Shi Formula on intestinal bacterial flora in patients with idiopathic membranous nephropathy: A prospective randomized controlled trial. Chronic Diseases and Translational Medicine. 2020;6(2):124-33.  10- Urita Y, Noda T, Watanabe D, Iwashita S, Hamada K, Sugimoto M. Effects of a soybean nutrition bar on the postprandial blood glucose and lipid levels in patients with diabetes mellitus. Int J Food Sci Nutr. 2012;63(8):921-9  11- Birkeland E, Gharagozlian S, Birkeland KI, Valeur J, Mage I, Rud I, et al. Prebiotic effect of inulin-type fructans on faecal microbiota and short-chain fatty acids in type 2 diabetes: a randomised controlled trial. European Journal of Nutrition. 2020;59(7):3325-38.  12- Canfora EE, van der Beek CM, Hermes GDA, Goossens GH, Jocken JWE, Holst JJ, et al. Supplementation of Diet with Galacto-oligosaccharides Increases Bifidobacteria, but Not Insulin Sensitivity, in Obese Prediabetic Individuals. Gastroenterology. 2017;153(1):87-97.  13- Dehghan P, Farhangi MA, Tavakoli F, Allasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: A randomized placebo-controlled Trial. Complementary Therapies in Medicine. 2016; 24:96-102.  14- Gonai M, Shigehisa A, Kigawa I, Kurasaki K, Chonan O, Matsuki T, et al. Galacto-oligosaccharides ameliorate dysbiotic Bifidobacteriaceae decline in Japanese patients with type 2 diabetes. Beneficial Microbes. 2017;8(5):705-16 %! Galacto-oligosaccharides ameliorate dysbiotic Bifidobacteriaceae decline in Japanese patients with type 2 diabetes %@ 1876-2883.  15- Jafari T, Faghihimani E, Feizi A, Iraj B, Javanmard SH, Esmaillzadeh A, et al. Effects of vitamin D-fortified low-fat yogurt on glycemic status, anthropometric indexes, inflammation, and bone turnover in diabetic postmenopausal women: A randomised controlled clinical trial. Clinical Nutrition. 2016;35(1):67-76.  16- Pino JL, Mujica V, Arredondo M. Effect of dietary supplementation with oat β-glucan for 3 months in subjects with type 2 diabetes: A randomized, double-blind, controlled clinical trial. Journal of Functional Foods. 2021;77. |
| **Wrong outcome (n= 51)**  1- Abbasi B, Mirlohi M, Daniali M, Ghiasvand R. Effects of probiotic soy milk on lipid panel in type 2 diabetic patients with nephropathy: A double-blind randomized clinical trial. Progress in Nutrition. 2018; 20:70-8.  2- Andreasen AS, Larsen N, Pedersen-Skovsgaard T, Berg RM, Møller K, Svendsen KD, et al. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr. 2010;104(12):1831-8.  3- Bahijiri SM, Mira SA, Mufti AM, Ajabnoor MA. The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes. Saudi Med J. 2000;21(9):831-7.  4- Bayat A, Azizi-Soleiman F, Heidari-Beni M, Feizi A, Iraj B, Ghiasvand R, et al. Effect of Cucurbita ficifolia and Probiotic Yogurt Consumption on Blood Glucose, Lipid Profile, and Inflammatory Marker in Type 2 Diabetes. International Journal of Preventive Medicine. 2016;7.  5- Bazyar H, Maghsoumi-Norouzabad L, Yarahmadi M, Gholinezhad H, Moradi L, Salehi P, et al. The Impacts of Synbiotic Supplementation on Periodontal Indices and Biomarkers of Oxidative Stress in Type 2 Diabetes Mellitus Patients with Chronic Periodontitis Under Non-Surgical Periodontal Therapy. A Double-Blind, Placebo-Controlled Trial. Diabetes Metabolic Syndrome and Obesity-Targets and Therapy. 2020; 13:19-29.  6- Dalal S, Nicolle L, Marrs CF, Zhang L, Harding G, Foxman B. Long-term Escherichia coli asymptomatic bacteriuria among women with diabetes mellitus. Clin Infect Dis. 2009;49(4):491-7 %7  7- Ebrahimi ZS, Nasli-Esfahani E, Nadjarzade A, Mozaffari-khosravi H. Effect of symbiotic supplementation on glycemic control, lipid profiles and microalbuminuria in patients with non-obese type 2 diabetes: a randomized, double-blind, clinical trial. Journal of Diabetes and Metabolic Disorders. 2017;16.  8- Ejtahed HS, Mohtadi Nia J, Homayouni Rad A, Niafar M, Asghari Jafarabadi M, Mofid V. The effects of probiotic and conventional yoghurt on diabetes markers and insulin resistance in type 2 diabetic patients: A randomized controlled clinical trial. Iranian Journal of Endocrinology and Metabolism. 2011;13(1):112.  9- Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition. 2012;28(5):539-43.  10- Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V, et al. Effect of probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis on lipid profile in individuals with type 2 diabetes mellitus. Journal of Dairy Science. 2011;94(7):3288-94.  11- Farrokhian A, Raygan F, Soltani A, Tajabadi-Ebrahimi M, Esfahani MS, Karami AA, et al. The Effects of Synbiotic Supplementation on Carotid Intima-Media Thickness, Biomarkers of Inflammation, and Oxidative Stress in People with Overweight, Diabetes, and Coronary Heart Disease: a Randomized, Double-Blind, Placebo-Controlled Trial. Probiotics and Antimicrobial Proteins. 2019;11(1):133-42.  12- Feizollahzadeh S, Ghiasvand R, Rezaei A, Khanahmad H, Sadeghi A, Hariri M. Effect of Probiotic Soy Milk on Serum Levels of Adiponectin, Inflammatory Mediators, Lipid Profile, and Fasting Blood Glucose Among Patients with Type II Diabetes Mellitus. Probiotics and Antimicrobial Proteins. 2017;9(1):41-7.  13- Ghafouri A, Zarrati M, Shidfar F, Heydari I, Shoormasti RS, Eslami O. Effect of synbiotic bread containing lactic acid on glycemic indicators, biomarkers of antioxidant status and inflammation in patients with type 2 diabetes: a randomized controlled trial. Diabetology & Metabolic Syndrome. 2019;11.  14- Horvath A, Leber B, Feldbacher N, Tripolt N, Rainer F, Blesl A, et al. Effects of a multispecies synbiotic on glucose metabolism, lipid marker, gut microbiome composition, gut permeability, and quality of life in diabesity: a randomized, double-blind, placebo-controlled pilot study. European Journal of Nutrition. 2020;59(7):2969-83.  15- Hove KD, Brons C, Faerch K, Lund SS, Rossing P, Vaag A. Effects of 12 weeks of treatment with fermented milk on blood pressure, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: a randomised double-blind placebo-controlled study. European Journal of Endocrinology. 2015;172.  16- Hsieh MC, Tsai WH, Jheng YP, Su SL, Wang SY, Lin CC, et al. The beneficial effects of Lactobacillus reuteri ADR-1 or ADR-3 consumption on type 2 diabetes mellitus: a randomized, double-blinded, placebo-controlled trial. Scientific Reports. 2018;8.  17- Judiono J, Hadisaputro S, Indranila KS, Cahyono B, Suzery M, Widiastuti Y, et al. Effects of clear kefir on biomolecular aspects of glycemic status of type 2 diabetes mellitus (T2DM) patients in bandung, west Java [Study on human blood glucose, c peptide and insulin]. Functional Foods in Health and Disease. 2014;4(8):340-8.  18- Kassaian N, Feizi A, Aminorroaya A, Amini M. Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial. Diabetes Metab Syndr. 2019;13(5):2991-6.  19- Kassaian N, Feizi A, Aminorroaya A, Ebrahimi MT, Norouzi A, Amini M. Effects of probiotics and synbiotic on lipid profiles in adults at risk of type 2 diabetes: A double-blind randomized controlled clinical trial. Functional Foods in Health and Disease. 2019(7):494-507.  20- Kassaian N, Feizi A, Rostami S, Aminorroaya A, Yaran M, Amini M. The effects of 6 mo of supplementation with probiotics and synbiotics on gut microbiota in the adults with prediabetes: A double blind randomized clinical trial. Nutrition. 2020;79-80.  21- Khalili L, Alipour B, Jafarabadi MA, Hassanalilou T, Abbasi MM, Faraji I. Probiotic assisted weight management as a main factor for glycemic control in patients with type 2 diabetes: a randomized controlled trial. Diabetology & Metabolic Syndrome. 2019;11.  22- Khosravi-Boroujeni H, Rostami A, Ravanshad S, Esmaillzadeh A. Favorable effects on metabolic risk factors with daily brewer's yeast in type 2 diabetic patients with hypercholesterolemia: a semi-experimental study. J Diabetes. 2012;4(2):153-8.  23- Kobyliak N, Falalyeyeva T, Mykhalchyshyn G, Kyriienko D, Komissarenko I. Effect of alive probiotic on insulin resistance in type 2 diabetes patients: Randomized clinical trial. Diabetes & Metabolic Syndrome-Clinical Research & Reviews. 2018;12(5):617-24.  24- Kooshki AA, Tofighiyan T, Rakhshani MH. Effects of Synbiotics on Inflammatory Markers in Patients With Type 2 Diabetes Mellitus. Glob J Health Sci. 2015;7(7 Spec No):1-5.  25- Kooshki AA, Tofighiyan T, Rakhshani MH. Effects of synbiotics on inflammatory markers in patients with type 2 diabetes mellitus. Global journal of health science. 2015;7(7):1.  26- Madempudi RS, Ahire JJ, Neelamraju J, Tripathi A, Nanal S. Efficacy of UB0316, a multi-strain probiotic formulation in patients with type 2 diabetes mellitus: A double blind, randomized, placebo-controlled study. Plos One. 2019;14.  27- Mahboobi S, Iraj B, Maghsoudi Z, Feizi A, Ghiasvand R, Askari G, et al. The effects of probiotic supplementation on markers of blood lipids, and blood pressure in patients with prediabetes: a randomized clinical trial. Int J Prev Med. 2014;5(10):1239-46.  28- Mazloom Z, Yousefinejad A, Dabbaghmanesh MH. Effect of probiotics on lipid profile, glycemic control, insulin action, oxidative stress, and inflammatory markers in patients with type 2 diabetes: a clinical trial. Iran J Med Sci. 2013;38(1):38-43.  29- Mazruei Arani N, Emam-Djomeh Z, Tavakolipour H, Sharafati-Chaleshtori R, Soleimani A, Asemi Z. The Effects of Probiotic Honey Consumption on Metabolic Status in Patients with Diabetic Nephropathy: a Randomized, Double-Blind, Controlled Trial. Probiotics Antimicrob Proteins. 2019;11(4):1195-201.  30- Miraghajani M, Zaghian N, Mirlohi M, Feizi A, Ghiasvand R. The Impact of Probiotic Soy Milk Consumption on Oxidative Stress Among Type 2 Diabetic Kidney Disease Patients: A Randomized Controlled Clinical Trial. Journal of Renal Nutrition. 2017;27(5):317-24.  31- Mirmiranpour H, Huseini HF, Derakhshanian H, Khodaii Z, Tavakoli-Far B. Effects of probiotic, cinnamon, and synbiotic supplementation on glycemic control and antioxidant status in people with type 2 diabetes; a randomized, double-blind, placebo-controlled study. Journal of Diabetes and Metabolic Disorders. 2020;19(1):53-60.  32- Mohamadshahi M, Veissi M, Haidari F, Shahbazian H, Kaydani GA, Mohammadi F. Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes. Bioimpacts. 2014;4(2):83-8.  33- Mohseni S, Bayani M, Bahmani F, Tajabadi-Ebrahimi M, Bayani MA, Jafari P, et al. The beneficial effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Diabetes-Metabolism Research and Reviews. 2018;34.  34- Moroti C, Magri LFS, Costa MD, Cavallini DCU, Sivieri K. Effect of the consumption of a new symbiotic shake on glycemia and cholesterol levels in elderly people with type 2 diabetes mellitus. Lipids in Health and Disease. 2012;11.  35- Naito E, Yoshida Y, Kunihiro S, Makino K, Kasahara K, Kounoshi Y, et al. Effect of Lactobacillus casei strain Shirota-fermented milk on metabolic abnormalities in obese prediabetic Japanese men: a randomised, double-blind, placebo-controlled trial. Biosci Microbiota Food Health. 2018;37(1):9-18.  36- Perraudeau F, McMurdie P, Bullard J, Cheng A, Cutcliffe C, Deo A, et al. Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double blind, randomized placebo-controlled trial of a novel probiotic formulation. Bmj Open Diabetes Research & Care. 2020;8.  37- Raygan F, Rezavandi Z, Bahmani F, Ostadmohammadi V, Mansournia MA, Tajabadi-Ebrahimi M, et al. The effects of probiotic supplementation on metabolic status in type 2 diabetic patients with coronary heart disease IRCT2017082733941N5 IRCT. Diabetology and Metabolic Syndrome. 2018;10  38- Razmpoosh E, Javadi A, Ejtahed HS, Mirmiran P, Javadi M, Yousefinejad A. The effect of probiotic supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A randomized placebo-controlled trial. Diabetes & Metabolic Syndrome-Clinical Research & Reviews. 2019;13(1):175-82.  39- Rezaei M, Sanagoo A, Jouybari L, Behnampoo N, Kavosi A. The effect of probiotic yogurt on blood glucose and cardiovascular biomarkers in patients with type II diabetes: A randomized controlled trial. Evidence Based Care Journal. 2017;6(4):26-35.  40- Sabatini S, Lauritano D, Candotto V, Silvestre FJ, Nardi GM. ORAL PROBIOTICS IN THE MANAGEMENT OF GINGIVITIS IN DIABETIC PATIENTS: A DOUBLE BLINDED RANDOMIZED CONTROLLED STUDY. Journal of Biological Regulators and Homeostatic Agents. 2017;31(2):197-202.  41- Sabico S, Al-Mashharawi A, Al-Daghri NM, Wani K, Amer OE, Hussain DS, et al. Effects of a 6-month multi-strain probiotics supplementation in endotoxemic, inflammatory and cardiometabolic status of T2DM patients: A randomized, double-blind, placebo-controlled trial. Clin Nutr. 2019;38(4):1561-9.  42- Sabico S, Al-Mashharawi A, Al-Daghri NM, Yakout S, Alnaami AM, Alokail MS, et al. Effects of a multi-strain probiotic supplement for 12 weeks in circulating endotoxin levels and cardiometabolic profiles of medication naive T2DM patients: a randomized clinical trial. Journal of Translational Medicine. 2017;15.  43- Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, et al. Consumption of Synbiotic Bread Decreases Triacylglycerol and VLDL Levels While Increasing HDL Levels in Serum from Patients with Type-2 Diabetes. Lipids. 2014;49(7):695-701.  44- Soleimani A, Motamedzadeh A, Mojarrad MZ, Bahmani F, Amirani E, Ostadmohammadi V, et al. The Effects of Synbiotic Supplementation on Metabolic Status in Diabetic Patients Undergoing Hemodialysis: a Randomized, Double-Blinded, Placebo-Controlled Trial. Probiotics and Antimicrobial Proteins. 2019;11(4):1248-56.  45- Tajabadi-Ebrahimi M, Sharifi N, Farrokhian A, Raygan F, Karamali F, Razzaghi R, et al. A Randomized Controlled Clinical Trial Investigating the Effect of Synbiotic Administration on Markers of Insulin Metabolism and Lipid Profiles in Overweight Type 2 Diabetic Patients with Coronary Heart Disease. Exp Clin Endocrinol Diabetes. 2017;125(1):21-7.  46- Tajadadi-Ebrahimi M, Bahmani F, Shakeri H, Hadaegh H, Hijijafari M, Abedi F, et al. Effects of Daily Consumption of Synbiotic Bread on Insulin Metabolism and Serum High-Sensitivity C-Reactive Protein among Diabetic Patients: A Double-Blind, Randomized, Controlled Clinical Trial. Annals of Nutrition and Metabolism. 2014;65(1):34-41.  47- Tazakori Z, Zare M, Jafarabadi MA. Probiotic yogurt effect on macronutrients ingredients, blood glucose and lipid profile in type 2 diabetes. Journal of the Pakistan Medical Association. 2017;67(7):1123.  48- Tonucci LB, dos Santos KMO, de Oliveira LL, Ribeiro SMR, Martino HSD. Clinical application of probiotics in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study. Clinical Nutrition. 2017;36(1):85-92.  49- Toshimitsu T, Gotou A, Sashihara T, Hachimura S, Shioya N, Suzuki S, et al. Effects of 12-Week Ingestion of Yogurt Containing Lactobacillus plantarum OLL2712 on Glucose Metabolism and Chronic Inflammation in Prediabetic Adults: A Randomized Placebo-Controlled Trial. Nutrients. 2020;12.  50- Venkataraman R, Jose P, Jose J. Impact of probiotics on health-related quality of life in Type II diabetes mellitus: A randomized single-blind, placebo-controlled study. Journal of Natural Science, Biology and Medicine. 2019;10(1):2-7.  51- Zhang YF, Gu YY, Ren HH, Wang SJ, Zhong HZ, Zhao XJ, et al. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study). Nature Communications. 2020;11. |
| **Without control group (n= 2)**  1- Alihosseini N, Moahboob SA, Farrin N, Mobasseri M, Taghizadeh A, Ostadrahimi AR. EFFECT OF PROBIOTIC FERMENTED MILK (KEFIR) ON SERUM LEVEL OF INSULIN AND HOMOCYSTEINE IN TYPE 2 DIABETES PATIENTS. Acta Endocrinologica-Bucharest. 2017;13(4):431-6.  2- Ostadrahimi A, Taghizadeh A, Mobasseri M, Farrin N, Payahoo L, Beyramalipoor Gheshlaghi Z, et al. Effect of probiotic fermented milk (kefir) on glycemic control and lipid profile in type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. Iran J Public Health. 2015;44(2):228-37. |
| **Insufficient data (n=1)**  1- Ahmadian F, Ejtahed HS, Javadi M, Razmpoosh E, Mirmiran P, Azizi F. The effects of probiotic supplementation on glycemic control, insulin resistance and inflammatory biomarkers of type 2 diabetic patients. Iranian Journal of Endocrinology and Metabolism. 2017;19(2):72-83 |
| **Repeated reports (n= 6)**  1- Asemi Z, Aarabi MH, Hajijafari M, Alizadeh SA, Razzaghi R, Mazoochi M, et al. Effects of Synbiotic Food Consumption on Serum Minerals, Liver Enzymes, and Blood Pressure in Patients with Type 2 Diabetes: A Double-blind Randomized Cross-over Controlled Clinical Trial. International Journal of Preventive Medicine. 2017;8.  2- Hariri M, Salehi R, Feizi A, Mirlohi M, Ghiasvand R, Habibi N. A randomized, double-blind, placebo-controlled, clinical trial on probiotic soy milk and soy milk: effects on epigenetics and oxidative stress in patients with type II diabetes. Genes and Nutrition. 2015;10.  3- Hariri M, Salehi R, Feizi A, Mirlohi M, Kamali S, Ghiasvand R. The effect of probiotic soy milk and soy milk on anthropometric measures and blood pressure in patients with type II diabetes mellitus: A randomized double-blind clinical trial. Arya Atherosclerosis. 2015; 11:74-80.  4- Kassaian N, Feizi A, Aminorroaya A, Jafari P, Ebrahimi MT, Amini M. The effects of probiotics and synbiotic supplementation on glucose and insulin metabolism in adults with prediabetes: a double-blind randomized clinical trial. Acta Diabetol. 2018;55(10):1019-28.  5- Miraghajani M, Zaghian N, Dehkohneh A, Mirlohi M, Ghiasvand R. Probiotic Soy Milk Consumption and Renal Function Among Type 2 Diabetic Patients with Nephropathy: a Randomized Controlled Clinical Trial. Probiotics and Antimicrobial Proteins. 2019;11(1):124-32.  6- Mohamadshahi M, Veissi M, Haidari F, Javid AZ, Mohammadi F, Shirbeigi E. Effects of probiotic yogurt consumption on lipid profile in type 2 diabetic patients: A randomized controlled clinical trial. Journal of Research in Medical Sciences. 2014;19(6):531-6. |
| **Without full-text (n= 3)**  1- Mykhal'chyshyn HP, Bodnar PM, Kobyliak NM. [Effect of probiotics on proinflammatory cytokines level in patients with type 2 diabetes and nonalcoholic fatty liver disease]. Likars'ka sprava / Ministerstvo okhorony zdorov'ia Ukraïny. 2013(2):56-62.  2- Yuan T, Zhao W, Cao Y, Li Q, Yao M, Hao X, et al. Effect of bifidobacterium tetragenous viable bacteria tablets on blood glucose level in patients with type 2 diabetes mellitus. Chinese Journal of Clinical Nutrition. 2017;25(4):205-13.  3- Yuan T, Zhao WG, Cao Y, Li Q, Yao MX, Hao XX, et al. [An efficacy and safety study of bifidobacterium tetragenous viable bacteria tablets in the treatment of constipation in patients with type 2 diabetes mellitus]. Zhonghua Nei Ke Za Zhi. 2018;57(4):252 |

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| **First author, year** | **Sequence generation** | **Allocation concealment** | **Blinding of participants** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Selective reporting** | **Funding** | **Overall** |
| Abbasi, 2017 | U | U | L | L | L | L | L | Fair |
| Abbasi, 2018 | L | L | L | L | L | L | L | Good |
| Arani, 2018 | L | L | L | L | L | L | L | Good |
| Asemi, 2013 | L | L | L | L | L | L | L | Good |
| Asemi, 2014 | L | L | L | L | L | L | L | Good |
| Asemi, 2015 | L | L | L | L | L | L | L | Good |
| Asemi, 2017 | L | L | L | L | L | L | L | Good |
| Bahmani, 2015 | L | L | L | L | L | L | L | Good |
| Ebrahimi, 2017 | L | L | L | L | L | L | L | Good |
| Firouzi, 2015 | L | L | L | L | L | L | L | Good |
| Kobyliak, 2018 | L | L | L | L | L | L | L | Good |
| Mafi, 2018 | L | L | L | L | L | L | L | Good |
| Miraghajani, 2017 | L | L | L | L | L | L | L | Good |
| Mobini, 2017 | U | U | L | L | L | L | L | Fair |
| Soleimani, 2017 | L | L | L | L | L | L | L | Good |

**Supplementary Table 3**. Study quality and risk of bias assessment using the Cochrane Collaboration’s tool

**Supplementary Table 4**. GRADE assessment of confidence in estimates of effect in randomized trials

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| **Outcome** | **Participants (studies)** | | **Risk of bias1** | **Inconsistency2** | **Indirectness3** | **Imprecision4** | **Publication bias5** | **Certainty of evidence6** |
| ALP (U/L) | | 310 (4) | Not Serious7 | Serious8 (I2=63.3) | Serious9 | Serious10 | NA11 | Very Low12 |
| ALT (U/L) | | 397 (6) | Not Serious13 | Serious14 (I2=58.1) | Serious15 | Serious16 | NA17 | Very Low18 |
| AST (U/L) | | 397 (6) | Not Serious19 | Not Serious(I2=43.7) | Serious20 | Serious21 | NA22 | Low23 |
| Bilirubin (mg/dl) | | 256 (3) | Not Serious24 | Serious25 (I2=93.1) | Serious26 | Serious27 | NA28 | Very Low29 |
| BUN (mg/dl) | | 386 (5) | Not Serious30 | Not Serious(I2=36.1) | Serious31 | Serious32 | NA33 | Low34 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | | 426 (6) | Not Serious35 | Serious36 (I2=87.7) | Serious37 | Serious38 | NA39 | Very Low40 |
| GFR (mL/min/1.73m2) | | 236 (3) | Not Serious41 | Serious42 (I2=90.7) | Serious43 | Serious44 | NA45 | Very Low46 |
| Microalbuminuria (Alb/Cr (mg/gr) | | 139 (3) | Serious47 | Serious48 (I2=80.9) | Not Serious | Serious49 | NA50 | Very Low51 |
| [Alkaline Phosphatase;](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase;](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; Blood urea nitrogen; Glomerular filtration rate](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) | | | | | | | | |

1. Cochrane tool was used to assess trial quality across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Trials were considered good quality if all domains were low RoB; low quality if more than one domain was high RoB, and unclear quality if two or more domains were unclear RoB. We downgraded one level (Serious) if 50% to 75% of RCTs were at high RoB and two levels (very serious) if more than 75% of RCTs were high ROB
2. We downgraded one level for inconsistency when I2 ≥50%. Where I2>50%, and the sensitivity analysis did not explain the source of heterogeneity. The I2 was ≤ 50% inconsistency considered as Not serious limitation.
3. We downgraded one level for indirectness if more than 50% included trials have been conducted in the same geographical location.
4. We downgraded one level for imprecision if the number of participants was less than 400. We also downgraded one level if point estimate was smaller than 5% baseline value (6.9 U/L for ALT, 4.6 U/L for AST, 25.87 U/l for ALP, 4.82 mg/dl for BUN, 0.5 mg/dl for bilirubin and [creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0), 0.5 mL/min/1.73m2 for GFR, and 0.5 (Alb/Cr (mg/gr)) for microalbuminuria, or point estimate surpassed smaller than 5% baseline value, but 95%CI overlapped with it.
5. We assessed for potential publication bias when ≥10 trials were available. We downgraded if there was evidence of bias with Egger's test (P<0.05) or there was evidence of asymmetry in the funnel plot.
6. Data from RCTs begin with a grade of “HIGH”. Downgraded for high RoB, inconsistency, indirectness, imprecision and Publication bias.
7. Less than 50% of trials (1 of 4) were at low quality. Not downgraded.
8. I2=63.3, P heterogeneity=0.043. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
9. Approximately more than half of trials (3 of 4) were conducted in Iran that limited the generalizability of the findings. Downgraded.
10. The number of participants was less than <400. Downgraded.
11. Publication bias test was not assessed because n<10.
12. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
13. Less than 50% of trials (2 of 6) were at low quality. Not downgraded.
14. I2=58.1, P heterogeneity=0.036. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
15. Approximately the half of trials (3 of 6) were conducted in Iran that limited the generalizability of the findings. Downgraded.
16. The number of participants was less than <400. Downgraded.
17. Publication bias test was not assessed because n<10.
18. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
19. Less than 50% of trials (2 of 6) were at low quality. Not downgraded.
20. Approximately the half of trials (3 of 6) were conducted in Iran that limited the generalizability of the findings. Downgraded.
21. The number of participants was less than <400. Downgraded.
22. Publication bias test was not assessed because n<10.
23. Data from RCTs begin with a grade of “HIGH”. Downgraded for indirectness and imprecision.
24. Less than 50% of trials (1 of 3) were at low quality. Not downgraded.
25. I2=93.1, P heterogeneity<0.001. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
26. Approximately more than half of trials (2 of 3) were conducted in Iran that limited the generalizability of the findings. Downgraded.
27. The number of participants was less than <400. Downgraded.
28. Publication bias test was not assessed because n<10.
29. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
30. All of included trials were at high quality. Not downgraded.
31. Approximately more than half of trials (4 of 5) were conducted in Iran that limited the generalizability of the findings. Downgraded.
32. The number of participants was less than <400. Downgraded.
33. Publication bias test was not assessed because n<10.
34. Data from RCTs begin with a grade of “HIGH”. Downgraded for indirectness and imprecision.
35. Less than 50% of trials (2 of 6) were at low quality. Not downgraded.
36. I2=87.7, P heterogeneity<0.001. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
37. The most of trials (5 of 6) were conducted in Iran that limited the generalizability of the findings. Downgraded.
38. More than 400 participants were available. The point estimate was smaller than 5% baseline weight (WMD= -0.10 mg/dl). Downgraded.
39. Publication bias test was not assessed because n<10.
40. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
41. Less than 50% of trials (1 of 3) were at low quality. Not downgraded.
42. I2=90.7, P heterogeneity<0.001. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
43. The most of trials (2 of 3) were conducted in Iran that limited the generalizability of the findings. Downgraded.
44. The number of participants was less than <400. Downgraded.
45. Publication bias test was not assessed because n<10.
46. Data from RCTs begin with a grade of “HIGH”. Downgraded for inconsistency, indirectness and imprecision.
47. Approximately more than half of trials (2 of 3) were at low quality. Main trial limitation was lack of random sequence generation, allocation concealment. Downgraded.
48. I2=80.9, P heterogeneity=0.005. The sensitivity analysis did not explain the source of heterogeneity. Downgraded.
49. The number of participants was less than <400. Downgraded.
50. Publication bias test was not assessed because n<10.
51. Data from RCTs begin with a grade of “HIGH”. Downgraded for ROB, inconsistency and imprecision.

**Supplementary Table 5.** Meta-analysis showing the effect of probiotics/synbiotics supplementation on liver and renal biomarkers (all analyses were conducted using random effects model)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Participants (Studies)** | **Meta- analysis** | | **Heterogeneity** | | |
| WMD (95% CI) | *P* effect | Q statistic | P within group | I2 % |
| **Liver biomarkers** | | | | | | |
| ALP (U/L) | 310 (4) | 7.26 (-3.39, 17.91) | 0.182 | 8.17 | 0.043 | 63.3 |
| ALT (U/L) | 397 (6) | -0.76 (-4.12, 2.58) | 0.653 | 11.82 | 0.037 | 57.7 |
| AST (U/L) | 397 (6) | -0.91 (-3.05, 1.22) | 0.40 | 6.95 | 0.224 | 28.1 |
| Bilirubin (mg/dl) | 256 (3) | -0.04 (-0.16, 0.08) | 0.529 | 14.45 | 0.001 | 86.2 |
| **Renal biomarkers** | | | | | | |
| BUN (mg/dl) | 386 (5) | -0.87 (-1.91, 0.18) | 0.104 | 6.29 | 0.180 | 36.1 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 426 (6) | -0.10 (-0.20, -0.00) | 0.010 | 40.61 | <0.001 | 87.7 |
| GFR (mL/min/1.73m2) | 236 (3) | 4.55 (-0.94, 10.05) | 0.104 | 21.42 | <0.001 | 90.7 |
| Microalbuminuria (Alb/Cr (mg/gr)) | 139 (3) | -10.36 (-22.87, 2.16) | 0.105 | 10.46 | 0.005 | 80.9 |
| ALP, [Alkaline Phosphatase; ALT,](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase; AST,](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; BUN, Blood urea nitrogen; GFR, Glomerular filtration rate](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) | | | | | | |

**Supplementary Table 6.** Meta-analysis showing the effect of probiotics/synbiotics supplementation on liver and renal biomarkers across subgroups (all analyses were conducted using random effects model)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Participants (Studies)** | **Meta- analysis** | | **Heterogeneity** | | |
| WMD (95% CI) | *P* effect | Q statistic | P within group | I2 % |
| **Duration of the intervention (week)** | | | | | | |
| ***Less than 12 weeks*** | | | | | | |
| ALP (U/L) | 310 (4) | 7.441 (-2.870, 17.752) | 0.15 | 7.75 | 0.05 | 62.4 |
| ALT (U/L) | 368 (5) | -0.875 (-4.568, 2.819) | 0.64 | 11.35 | 0.02 | 64.7 |
| AST (U/L) | 368 (5) | 0.186 (-2.585, 2.957) | 0.89 | 8.11 | 0.08 | 50.7 |
| Bilirubin (mg/dl) | 256 (3) | -0.041 (-0.168, 0.086) | 0.53 | 14.6 | 0.001 | 86.3 |
| BUN (mg/dl) | 206 (2) | -0.374 (-1.466, 0.718) | 0.5 | 1.7 | 0.19 | 41.3 |
| Creatinine (mg/dl) | 246 (3) | -0.028 (-0.125, 0.069) | 0.57 | 23.38 | <0.001 | 91.4 |
| ***12 weeks and more*** | | | | | | |
| ALP (U/L) | 136 (1) | 0.640 (-5.045, 6.325) | 0.82 | 0.0 | - | - |
| ALT (U/L) | 165 (2) | -0.756 (-4.922, 3.410) | 0.72 | 0.59 | 0.44 | 0.0 |
| AST (U/L) | 165 (2) | -0.440 (-5.398, 4.518) | 0.86 | 2.53 | 0.11 | 60.5 |
| Bilirubin (mg/dl) | 136 (1) | 0.030 (-0.023, 0.083) | 0.26 | 0.0 | - | - |
| BUN (mg/dl) | 316 (4) | -1.215 (-1.933, -0.496) | 0.001 | 2.88 | 0.41 | 0.0 |
| Creatinine (mg/dl) | 316 (4) | -0.168 (-0.397, 0.062) | 0.15 | 23.21 | <0.001 | 87.1 |
| **Renal complications** |  |  |  |  |  |  |
| ***Yes*** |  |  |  |  |  |  |
| BUN (mg/dl) | 180 (3) | -1.634 (-4.040, 0.771) | 0.18 | 2.87 | 0.23 | 30.4 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 220 (4) | -0.209 (-0.322, -0.096) | <0.001 | 5.6 | 0.13 | 46.7 |
| ***No*** |  |  |  |  |  |  |
| BUN (mg/dl) | 206 (2) | -0.540 (-2.120, 1.040) | 0.5 | 3.21 | 0.07 | 68.9 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl) | 206 (2) | 0.014 (-0.017, 0.046) | 0.36 | 0.1 | 0.75 | 0.0 |
| ALP, [Alkaline Phosphatase; ALT,](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase; AST,](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; BUN, Blood urea nitrogen](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) | | | | | | |

**Supplementary Table 7**. Sensitivity analysis showing the effect of probiotics/synbiotics supplementation on liver and renal biomarkers in patients with diabetes (all analyses were conducted using random effects model)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Participants (Studies)** | **Meta- analysis** | | **Heterogeneity** | | |
| WMD (95% CI) | *P* effect | Q statistic | P within group | I2 % |
| **Excluding studies supplemented synbiotic** | | | | | | |
| ALP (U/L)1 | 248 (3) | 1.35 (3.94, 6.64) | 0.61 | 1.61 | 0.44 | 0.0 |
| ALT (U/L)1 | 335 (5) | -2.003 (-4.61, 0.6) | 0.13 | 4.81 | 0.3 | 16.9 |
| AST (U/L)1 | 335 (5) | 1.13 (-2.48, 4.74) | 0.54 | 8.82 | 0.06 | 54.6 |
| BUN (mg/dl)2 | 316 (4) | -1.21 (-1.93, -0.49) | 0.001 | 2.88 | 0.41 | 0.0 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl)2 | 356 (5) | -0.15 (-0.28, -0.015) | 0.03 | 32.99 | <0.001 | 87.9 |
| **Excluding studies recruited mix population of type 1 and type diabetic patients** | | | | | | |
| BUN (mg/dl)3 | 266 (3) | -0.65 (-1.62, 0.32) | 0.18 | 3.29 | 0.19 | 39.3 |
| [Creatinine](https://www.google.com/search?sxsrf=ALeKk02mJV1vbX9L_pYjqYJNy7bYl7JXEQ:1616002789612&q=creatinine&spell=1&sa=X&ved=2ahUKEwiK9uvB77fvAhWxgVwKHaARDNoQkeECKAB6BAgXEC0) (mg/dl)3 | 306 (4) | -0.05 (-0.14, 0.03) | 0.25 | 23.44 | <0.001 | 87.2 |
| **Excluding studies recruited diabetic patients with liver complications** | | | | | | |
| ALT (U/L)4 | 339 (5) | -0.911 (-5.232, 3.410) | 0.67 | 11.75 | 0.01 | 0.66 |
| AST (U/L)4 | 339 (5) | -0.440 (-2.660, 1.781) | 0.69 | 5.39 | 0.25 | 25.8 |
| ALP, [Alkaline Phosphatase; ALT,](https://labtestsonline.org/tests/alkaline-phosphatase-alp) [Alanine Aminotransferase; AST,](https://labtestsonline.org/tests/alanine-aminotransferase-alt) [Aspartate Aminotransferase; BUN, Blood urea nitrogen](https://labtestsonline.org/tests/aspartate-aminotransferase-ast) | | | | | | |

1. The studies by Bahmani etal and Asemi (2017) etal were excluded from analysis.
2. The study by Ebrahimi etal was excluded from analysis.
3. The studies by Soleimani etal and Mafi etal were excluded from analysis
4. The study by Kobyliak etal was excluded from analysis.