



# The effect of probiotics on lipid profile & anthropometric indices in diabetic nephropathy; a systematic review and meta-analysis of clinical trials

Amir Reza Moravejolahkami<sup>1</sup> · Mohammad Ali Hojjati Kermani<sup>2</sup> · Zakiyeh Balouch Zehi<sup>3</sup> · Seyed Mohammad Sadegh Mirenayat<sup>4</sup> · Marjan Mansourian<sup>5</sup>

Received: 1 December 2020 / Accepted: 7 February 2021 / Published online: 23 February 2021  
© Springer Nature Switzerland AG 2021

## Abstract

**Purpose** Recent trials have demonstrated the possible improvements in lipid profile & anthropometric indices after probiotics supplementation. We aimed to reanalyze the related literature to explore the efficacy of probiotics in Diabetic Nephropathy (DN) patients.

**Methods** PubMed, Embase, Web of science, google scholar, Scopus, and Cochrane Library databases were systematically searched to find the related data on diabetic nephropathy population. All Randomized controlled trials (RCTs) that investigated the effect of probiotics on serum lipid markers (High-Density Lipoprotein [HDL], Triglyceride, Total Cholesterol, TC-to-HDL ratio, Low-Density Lipoprotein, Very Low-Density Lipoprotein) and anthropometric indices (Body Weight, Body Mass Index, waist-to-hip ratio) were included (PROSPERO No.CRD42020186189). Meta-analysis was performed using the random-effect model.

**Results** Of 156 studies, seven were eligible for inclusion. Lipid biomarkers had a marginal reduction (except for HDL; WMD = 2.59 mg/dl; 95% CI = -0.28, 5.47;  $P = 0.077$ ); whereas anthropometric indices increased in a non-significant manner.

**Conclusion** There is limited evidence to support the efficacy of probiotics for the modulation of lipid profile and anthropometric indices in DN patients.

**Keywords** Probiotics · Lipoproteins · Body weights and measures · Diabetic nephropathies · Meta-analysis · Systematic review

## Introduction

Diabetic Nephropathy (DN; also called Diabetic kidney disease) occurs in approximately 30% of diabetic people as the

leading cause of End-Stage Renal Disease (ESRD) [1]. Researchers have shown that Individuals with DN represent a particularly high-risk group for adverse Cardiovascular Disease (CVD) [2]. Dyslipidemia, defined by the presence

---

This study has not been duplicate publication or submission elsewhere.

✉ Amir Reza Moravejolahkami  
a.moravej@mail.mui.ac.ir; amimohs@gmail.com

✉ Marjan Mansourian  
j\_mansourian@hlth.mui.ac.ir

Mohammad Ali Hojjati Kermani  
Imhojjati@gmail.com

Zakiyeh Balouch Zehi  
zakiyebz@gmail.com

Seyed Mohammad Sadegh Mirenayat  
Sadegh.mir1374@gmail.com

<sup>1</sup> Department of Clinical Nutrition, School of Nutrition & Food Science, Isfahan University of Medical Sciences, P.O. Box 81746-73461, Hezar-Jerib Ave, Isfahan, Iran

<sup>2</sup> Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup> Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>4</sup> Department of Community Nutrition, School of Nutrition & Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>5</sup> Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Science, P.O. Box 81746-73461, Hezar-Jerib Ave, Isfahan, Iran

of one or more abnormal serum lipid concentrations (Total Cholesterol [3], Triglyceride [TG], Low-Density Lipoprotein [LDL], and High-Density Lipoprotein [HDL]) and obesity (especially abdominal obesity), are of the main risk factors of DN and CVD [4–6]. Therefore, it is urgent to develop therapeutic strategies for DN and its comorbidities such as dyslipidemia and obesity; probiotic supplementation has high potential for achieving this goal [7–9].

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. *Lactobacillus (L) spp.*, *Bifidobacterium (B) spp.*, *Streptococcus spp.*, *Enterococcus spp.*, and *Saccharomyces boulardii* are the most common administered strains for supplementation [10, 11]. Human clinical studies using various probiotics have yielded inconsistent results. A randomized trial reported that probiotics supplementation improves glycaemic control and anthropometric indices in adults with Type 2 Diabetes (T2D) [12]. Furthermore, probiotics supplement consisted of 7 viable strains *Lactobacillus*, *Bifidobacterium* and *Streptococcus* significantly reduced HDL without any significant effect on TC, TG and anthropometric measurements [13]. Results of two recent meta-analyses showed that supplementation with probiotics improves the metabolic variables such as TC, TG and HDL in T2D patients [14, 15]. In contrast, Two meta-analyses did not find any significant effect of probiotics on lipid profile [16, 17].

The effect of probiotic strains on Body Weight (BW) has also been investigated. Certain *Lactobacillus* species, such as *L. fermentum*, *L. ingluviei* and *L. acidophilus* induces weight gain, while supplementation with *L. gasseri* and *L. plantarum* resulted in weight loss in animal and human studies [18]. In practice, the limited number of studies in this regard have shown controversial results.

Recently, a systematic review by Vlachou et al. [19] indicated that probiotic supplementation has beneficial impact on systemic inflammation, oxidative stress and renal biomarkers in subjects with DN, although the authors did not discuss the possible effects on lipid profile and anthropometric measurements. Although several studies have reported the beneficial effect of probiotics in patients with T2D, a lot of their results were marginally significant and inconclusive. Therefore, the present study was planned to collect and reanalyze the available information and reach a conclusion on the effectiveness of probiotics on lipid profile and anthropometric indices in DN patients.

## Materials & methods

### Protocol registration

The review protocol has been published in the International Prospective Register of Systematic Reviews ([www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO)) (Registration ID. CRD42020186189; submission date: July 05, 2020; last update date: November 30, 2020) and developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [20]. PRISMA checklist of the meta-analysis was presented in S1 Appendix.

### Search strategy

The electronic search for the current systematic review and meta-analysis was performed on material published through May 10, 2020. The included databases were Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Cochrane Database of Systematic Reviews, Google Scholar, PubMed, ScienceDirect, ISI Web of Science, and Scopus. One author searched the above electronic database. The gray literature including conference abstracts, presentations, proceedings; regulatory data; unpublished trial data; government publications; reports (such as white papers, working papers, internal documentation); dissertations/theses; patents; and policies & procedures were not entered.

Two authors independently searched the aforementioned databases to identify RCTs, using the following MeSH and text keywords: (“Diabetic Nephropathy” OR “Diabetic kidney disease” OR “DKD”) AND (“High-Density Lipoprotein” OR “HDL” OR “Triglyceride” OR “TG” OR “Total Cholesterol” OR “TC” OR “TC-to-HDL ratio” OR “Low-Density Lipoprotein” OR “LDL” OR “Very Low-Density Lipoprotein” OR “VLDL” OR “Body Weight” OR “Body Mass Index” OR “BMI” OR “waist-to-hip ratio” OR “WHR”) AND (“Synbiotics” OR “Probiotics” OR “Prebiotics” OR “Probiotic”) AND (“Intervention Studies” OR “intervention” OR “controlled trial” OR “randomized” OR “randomised” OR “random” OR “randomly” OR “placebo” OR “assignment” OR “randomized controlled trial” OR “trial” OR “Clinical Trial” OR “RCT”). Also, all references of previous relevant meta-analyses, systematic reviews, and selected RCTs were manually reviewed to find any additional trials that had not been confined via online database searches.

### Study selection criteria

We included trials with English language and the following characteristics: (1) Type of study: RCT with either parallel or cross-over design, and at least two arms; (2) Participants: limited to DN patients aged  $\geq 18$  years and disease duration between 2 and 20 years; (3) Intervention: probiotic-contained food products or supplements, compared with placebo for more than two weeks; and (4) Outcomes: assessed blood parameters of lipid profiles (HDL, TG, TC, TC-to-HDL ratio,

LDL, VLDL), and anthropometric indices (Body Weight [BW], BMI, Waist-to-Hip Ratio [WHR]).

We excluded trials that reported: (1) studies without clear inclusion and exclusion criteria; (2) outcomes that had not been clearly stated; (3) uncontrolled studies; and (4) preclinical studies with animal models.

The relevance of articles and abstracts for inclusion was judged by two independent authors. Then, one reviewer independently evaluated the full text of potentially relevant non-duplicated articles. Any disagreement between investigators was resolved by the third reviewer.

## Data extraction

Two reviewers independently extracted data. Any discrepancies were resolved by a third author. The following details were extracted and tabulated: study first author publication year & country, study design and duration, samples' characteristics such as gender, disease duration, mean BMI and age; composition, and dose of probiotics/placebo and outcome indicators. Corresponding authors of included studies, in which published data had some ambiguous results, were contacted to respond to the related questions.

## Risk of bias (quality) assessment

The included studies were evaluated for bias by using the Cochrane Risk-Of-Bias (RoB) tool (version 5.0) [21]. Each included study was evaluated for the following biases: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participant and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. The reviewers' judgment was classified as "Low risk," "High risk" or "Unclear risk" of bias.

## Statistical analysis

Using STATA software version 14 (Stata Corp LP, College Station, TX, USA), statistical analysis was done. Data from RCTs were analyzed using mean difference with standard deviation (SD). Moreover, the random-effects model was used to compute Weighted Mean Differences (WMDs) with 95% confidence intervals (CIs) for all selected markers. The conversion of median/interquartile range (IQR) (or 95% Confidence Interval [CI]) to the mean  $\pm$  SD values was performed according to Hozo et al. [22] method. In some states where only the standard error of the mean (SEM) was available, the following formula was used to calculate SD [23]:

$$SD = SEM \times \text{square root of } n(n; \text{the number of subjects})$$

Therefore, the mean changes (difference of values before and after the intervention) and SD were used to pool effect sizes. Results were visualized using forest plots. The potential for publication bias was measured through the Egger weighted regression method. A *P* value of 0.05 was considered to be statistically significant.

## Results

### Literature search

The study inclusion process was illustrated in Fig. 1. In total, 156 records were identified in a combined search of electronic databases; of the 131 unduplicated papers, 124 were excluded because they were animal studies ( $n = 44$ ), not relevant to the topic ( $n = 42$ ), review articles ( $n = 5$ ), irrelevant outcomes ( $n = 3$ ), non-diabetic nephropathy population ( $n = 18$ ), or insufficient data ( $n = 12$ ). Finally, six eligible articles with publication range of 2017–2019 were entered in the data synthesis (300 participants) [24–29] (Table 1). Miraghajani et al. [30] study did not enter into quantitative analysis, because the measured variables in Miraghajani et al. study (2017) were different from the other included trials. Therefore, it was just systematically reviewed.

### Study characteristics

The characteristics of seven studies were summarized in Table 1. A total of 340 participants (170 as intervention group/ 170 as controls) were included. The mean age of participants ranged from 55 to 60 years old with a mean disease duration of 8–18 years for all trials. Mean baseline BMI was under 30 kg/m<sup>2</sup>, representing an overweight state. Three papers did not report sexuality [26, 27, 30], however, others were conducted on both sexes [24, 25, 28, 29].

All studies were performed in Iran, had parallel design, and were related to nephropathy secondary to T2D. The study duration varied between 8 and 12 weeks.

In four papers, probiotics were administrated with soy milk [24, 25, 28, 30]. One study used probiotic honey [26], and other trials prescribed probiotics capsules [27, 29]. *Lactobacillus plantarum* A7 [24, 25, 28, 30], *L. acidophilus* [27, 29], *Bifidobacterium bifidum* [27, 29], *L. reuteri* [27], *L. fermentum* [27], *L. casei* [29], and *Bacillus coagulans* T4 [26] were considered for intervention. Besides, the daily dose of probiotics ranged from  $2.5 \times 10^9$  to  $8 \times 10^9$  CFU.

### Risk of bias (quality) assessment

Risk of bias was low in the following domains: selection bias (random sequence generation and allocation

**Table 1** Characteristic of randomized controlled trials that included for analysis; effects of probiotics on clinical manifestations of Diabetic Nephropathy

First author (publication year)	Country	Analyzed Sample size In/Co Male/Female	Target population	Disease duration M (SD)	BMI at base (M)	Age (M)	Study design	Intervention, Dose	Control, Dose	Probiotic content and numbers	Investigated markers
Abbasi (2018)	Iran	20/20 19/21	Diabetic Nephropathy	7.8 (3.5)	26.6	55.2	R, DB, PC Parallel 8 wks	Probiotics soy milk 200 ml QD	soy milk 200 ml QD	<i>Lactobacillus plantarum</i> A7 2×10 <sup>7</sup> CFU/ml Totally 4×10 <sup>9</sup> CFU	TG, TC, LDL-C, HDL-C, non HDL-C, Serum creatinine, Serum phosphorus, Serum genistein, eGFR
Abbasi (2017)	Iran	20/20 19/21	Diabetic Nephropathy	7.8 (3.5)	26.6	55.2	R, DB, PC Parallel 8 wks	Probiotics soy milk 200 ml QD	soy milk 200 ml QD	<i>lactobacillus plantarum</i> A7 2×10 <sup>7</sup> CFU/ml Totally 4×10 <sup>9</sup> CFU	Body Weight, BMI, WHR, IL-18, Serum sialic acid, Serum creatinine, Serum genistein, eGFR, Urinary albumin/creatinine ratio
Mafi (2018)	Iran	30/30 NR	Diabetic Nephropathy	18.1 (5.4)	25.8	59.9	R, DB, PC Parallel 12 wks	Probiotic capsule QD	Placebo capsule (contained only starch) QD	<i>Lactobacillus acidophilus</i> strain ZT-L1, <i>Bifidobacterium bifidum</i> strain ZT-B1, <i>Lactobacillus reuteri</i> strain ZT-Lre, and <i>Lactobacillus fermentum</i> strain ZT-L3 (each 2×10 <sup>9</sup> CFU/g) Totally 8×10 <sup>9</sup> CFU per capsule	Body Weight, BMI, TAC, MDA, hs-CRP, FPG, Insulin, GSH, HOMA-IR, NO, QUICKI, TC, TG, LDL-C, HDL-C, VLDL-C, Hb A1C, TC/HDL ratio, AGEs, BUN, Serum creatinine, GFR, Urine protein, gene expression (IL-1, TNF-α, TGF-β, PPAR-γ and LDLR)
Miraghajani (2019)	Iran	20/20 19/21	Diabetic Nephropathy	7.8 (3.5)	26.6	55.2	R, DB, PC Parallel 8 wks	Probiotics soy milk 200 ml QD	soy milk 200 ml QD	<i>Lactobacillus plantarum</i> A7 (KC353240, LA7) 2×10 <sup>7</sup> CFU/ml Totally 4×10 <sup>9</sup> CFU	Calorie, Protein, Fat, Carbohydrate, Fiber, Calcium, Magnesium, Potassium, NGAL, sTNFR1, Cys-C, PGRN, Weight, WHR, BMI
Soleimani (2017)	Iran	30/30 40/20	Diabetic Hemodialysis	18.1 (5.4)	26.2	56.7	R, DB, PC Parallel 12 wks	Probiotic capsule QD	Placebo capsule (contained only starch) QD	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , and <i>Bifidobacterium bifidum</i> (each 2×10 <sup>9</sup> CFU/g) Totally 6×10 <sup>9</sup> CFU per capsule	Body Weight, BMI, MET, TAC, MDA, hs-CRP, FPG, Insulin, GSH, HOMA-IR, HOMA-B, NO, QUICKI, TC, TG, LDL-C, HDL-C, VLDL-C, Hb A1C, TC/HDL ratio, BUN, Serum creatinine, GFR, SGA score, Albumin, TIBC, Na, K
Arani (2019)	Iran	30/30 NR	Diabetic Nephropathy	18.1 (5.4)	26.2	56.7	R, DB, PC Parallel 12 wks	Probiotic honey 25 g QD	Control honey 25 g QD	<i>Bacillus coagulans</i> T4 (IBRC-N10791) (10 <sup>8</sup> CFU/g) Totally 2.5×10 <sup>9</sup> CFU	Body Weight, BMI, TAC, MDA, hs-CRP, FPG, Insulin, GSH, HOMA-IR, NO, QUICKI, TC, TG, LDL-C, HDL-C, VLDL-C, TC/HDL ratio, BUN, Serum creatinine

**Table 1** (continued)

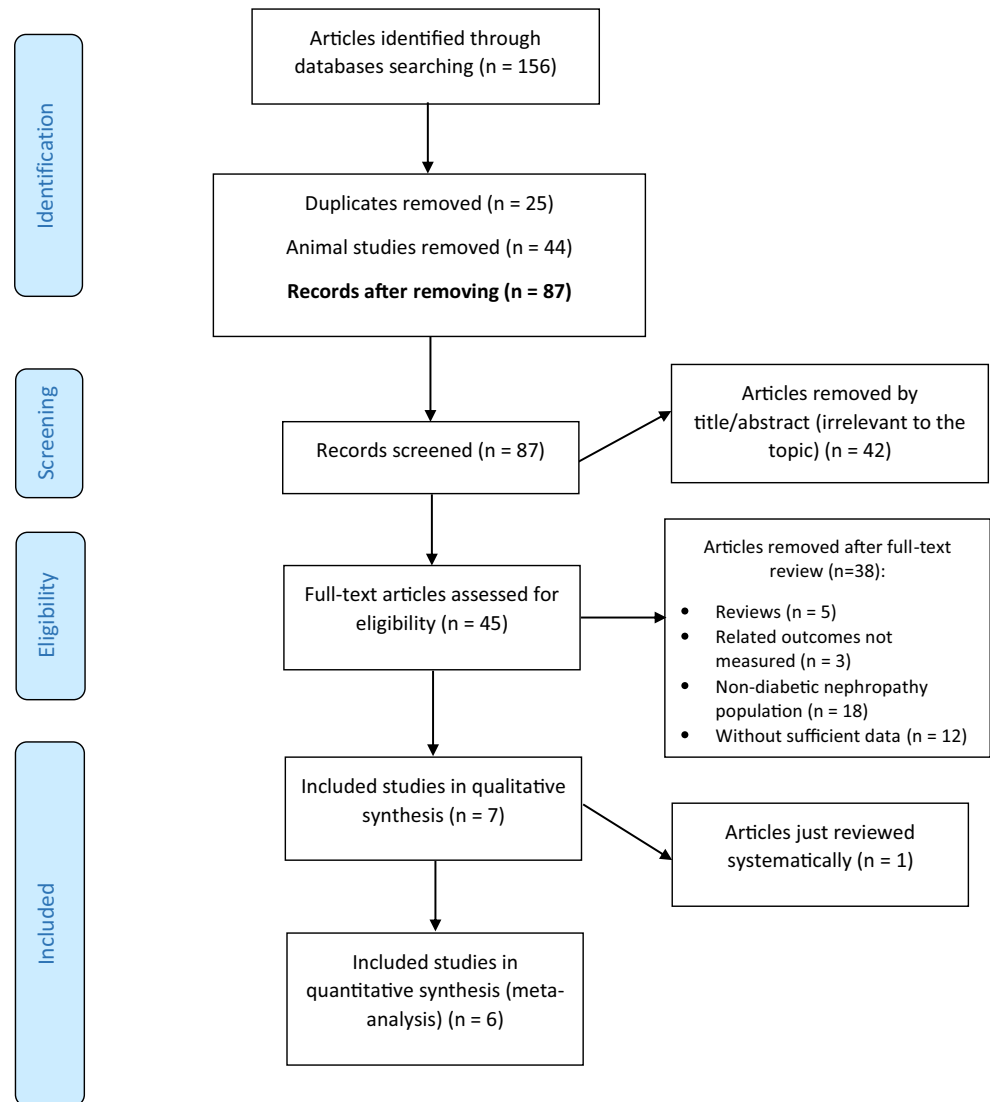
First author (publication year)	Country	Analyzed Sample size In/Co Male/Female	Target population	Disease duration M (SD)	BMI at base (M)	Age (M)	Study design Duration	Intervention, Dose	Control, Dose	Probiotic content and numbers	Investigated markers
Miraghajani (2017) <sup>†</sup>	Iran	20/20 NR	Diabetic kidney disease	7.8 (3.5)	26.6	55.2	R, DB, PC Parallel 8 wks	Probiotics soy milk 200 ml QD	soy milk 200 ml QD	<i>Lactobacillus plantarum</i> A7 (KC355240, LA7) 2 × 10 <sup>7</sup> CFU/ml Totally 4 × 10 <sup>9</sup> CFU	Calorie, Protein, Fat, Carbohydrate, Fiber, Cholesterol, MUFA, PUFA, Saturated fatty acid, Selenium, Vitamin E, and C, MDA, TAC, GSH, 8-iso-PGF2a, Oxidized glutathione, Glutathione peroxidase, Glutathione reductase

<sup>†</sup>One selected study was just systematically reviewed and not included in analysis due to irrelevant outcome markers

Functional abbreviations: In, intervention group; Co, control group; M, mean; SD, standard deviation; QD, once a day; CFU, colony forming unit; RDBPC, randomized double blind placebo control trial; wks, weeks; NR, not reported

Study outcome abbreviations: hs-CRP, high sensitive C-reactive protein; MDA, malondialdehyde; TAC, total antioxidant capacity; IL interleukin; FPG, fasting plasma glucose; GHQ, general health questionnaire; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; HOMA-B, homeostasis model of assessment estimated B cell function; NO, nitric oxide; QUICKI, quantitative insulin sensitivity check index; TG, Triglycerides; TC, Total cholesterol; LDL, low density lipoprotein; VLDL, very low density lipoprotein; HDL, high density lipoprotein; TG, triacylglycerol; AGEs, advanced glycation end products; GFR, glomerular filtration rate; BUN, blood urea nitrogen; LDLR, low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; HbA1c, hemoglobin A1c; NGAL, neutrophil gelatinase-associated lipocalin; sTNFR1, soluble tumor necrosis factor receptor 1; PGRN, Progranulin; Cys-C, cystatin C; METs, metabolic equivalents; SGA, subjective global assessment; TIBC, total iron binding capacity; Na, sodium; K, potassium; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; 8-iso-PGF2a, 8-iso-prostaglandin F2a

**Fig. 1** Flow diagram of the included and excluded studies



concealment, five and four studies, respectively), performance bias (three studies), detection bias (five studies), attrition bias (one study), and reporting bias (four studies).

Two studies seemed to be at a high risk of attrition bias (through high loss to follow-up and no explanation of how data were addressed), and in overall state, two were rated as having a high risk of bias. However, Soleimani et al. [29] and Arani et al. [26] had a low overall risk.

Unclear risk of bias was recognized for selection bias (random sequence generation and allocation concealment, two and three studies, respectively), performance bias (four studies), detection bias (two studies), attrition bias (four studies), and reporting bias (three studies). Overall, two studies had unclear risk of bias. More details were presented in Fig. 2.

## Results of meta-analysis for serum lipid profiles

### The effects of probiotics on HDL

The efficacy of probiotics on HDL was reported by four studies with 220 participants (intervention, 110; control, 110) [25–27, 29]. No significant improvement was observed in patients who received treatment (WMD = 2.59 mg/dL; 95% CI = -0.28, 5.47,  $P = 0.077$ ) with no between-study heterogeneity ( $I^2 = 50.8\%$ ,  $P = 0.107$ ) (Fig. 3a).

### The effects of probiotics on TG

In the pooled analysis of four studies with 220 participants (intervention, 110; control, 110) [25–27, 29], effect of probiotics on serum TG level (WMD = -9.05 mg/dL; 95%

**Fig. 2** Risk of bias summary across the included studies

		Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Overall risk of bias		
1	Abbasi et al (2018)	?	?	+	+	-	+	-	+	Low risk
2	Abbasi et al (2017)	?	+	+	+	-	+	-	?	Some concerns
3	Mafi et al (2018)	+	?	?	+	?	?	!	-	High risk
4	Miraghajani et al (2019)	+	?	?	?	?	+	!		
5	Soleimani et al (2017)	+	+	+	+	+	+	+		
6	Arani et al (2019)	+	+	?	+	?	?	+		
7	Miraghajani et al (2017)	+	+	?	?	?	?	!		

CI = -26.08, 7.99,  $P = 0.298$ ) was not statistically significant with no study heterogeneity ( $I^2 = 21.8\%$ ;  $P = 0.280$ ) (Fig. 3b).

**The effects of probiotics on TC**

There was no significant effect of probiotics on TC (WMD = -7.17 mg/dL; 95% CI = -15.30, 0.96,  $P = 0.084$ ) after analyzing four studies with 220 participants (intervention, 110; control, 110) [25–27, 29] with no heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.759$ ) (Fig. 3c).

**The effects of probiotics on TC-to-HDL ratio**

The pooled estimate did not demonstrate any significant reduction in TC-to-HDL ratio as a result of probiotics intervention in 220 DN patients (WMD = -0.63; 95% CI = -1.39, 0.14,  $P = 0.107$ ) [25–27, 29] (Fig. 3d). Results showed a significant heterogeneity ( $I^2 = 64.5\%$ ,  $P = 0.038$ ).

**The effects of probiotics on LDL**

Four clinical trials examined the effect of probiotics on LDL (total subjects = 220; intervention, 110; control, 110) [25–27, 29]. In the pooled analysis of selected studies, a marginal non-significant reduction was observed (WMD = -6.77 mg/dL; 95% CI = -13.87, 0.33,  $P = 0.062$ ) without any study heterogeneity ( $I^2 = 0.0\%$ ,  $P = 0.875$ ) (Fig. 3e).

**The effects of probiotics on VLDL**

Probiotics supplementation could not decrease serum VLDL levels in overall results of the three clinical trials (subjects = 180; intervention, 90; control, 90) (WMD = -2.08 mg/dL; 95% CI = -6.66, 2.50,  $P = 0.374$ ;  $I^2 = 47.1\%$ ,  $P = 0.151$ ) [26, 27, 29].

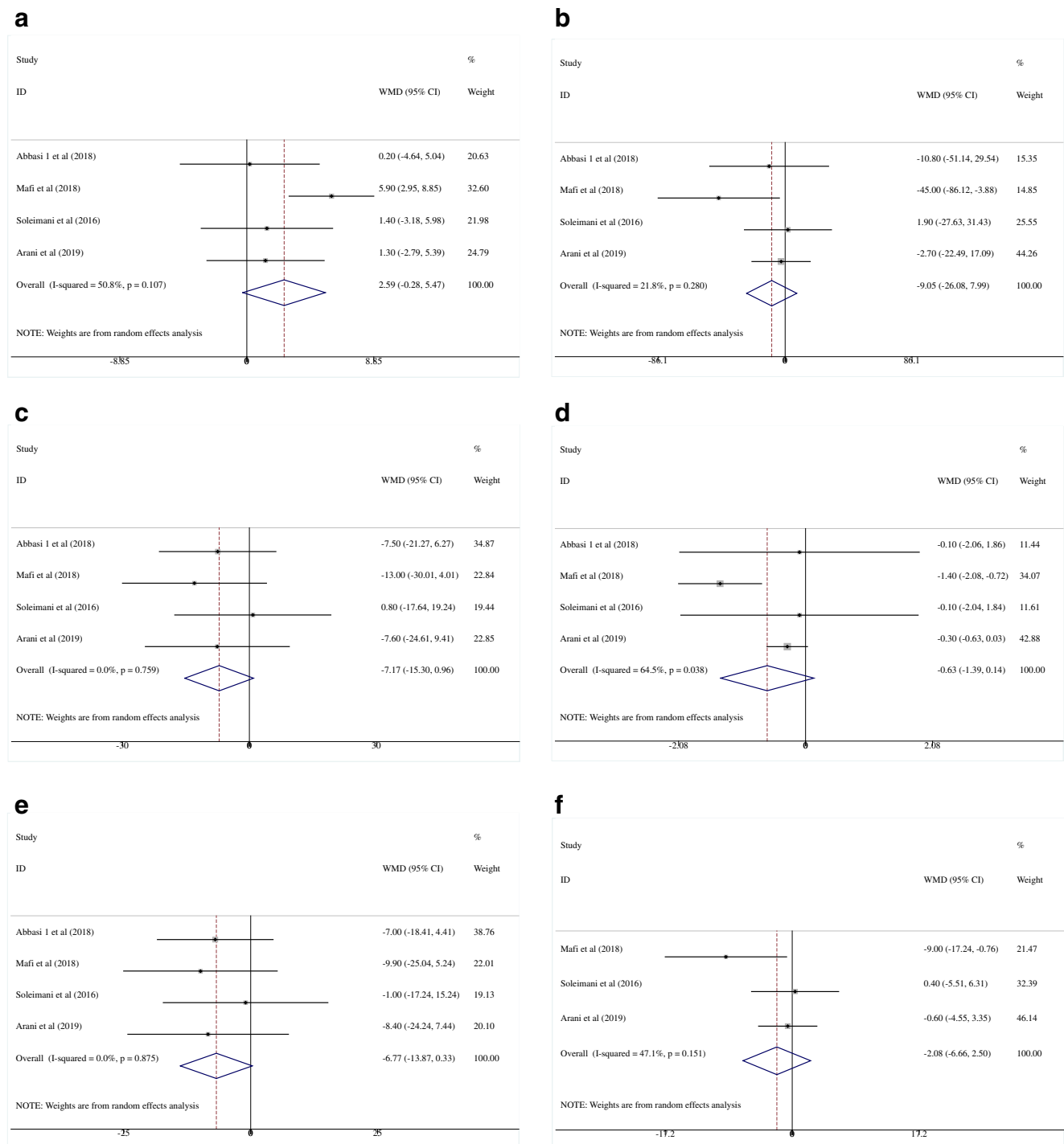
**Results of meta-analysis for anthropometric indices**

**The effects of probiotics on BW**

Five RCTs [24, 26–29] investigated the impact of probiotics administration on BW (subjects = 260; intervention, 130; control, 130). Overall, probiotics could not make significant reduction in BW (WMD = 0.22 kg; 95% CI = -2.28, 2.72,  $P = 0.864$ ) (Fig. 4a). No heterogeneity was recognized ( $I^2 = 0.0\%$ ,  $P = 0.999$ ).

**The effects of probiotics on BMI**

Results of the meta-analysis indicated that probiotics could not significantly improve BMI levels (WMD = 0.12 kg/m<sup>2</sup>; 95% CI = -0.77, 1.02;  $P = 0.784$ ). After evaluation of five studies with 260 participants (intervention, 130; control, 130) [24, 26–29], no heterogeneity was seen ( $I^2 = 0.0\%$ ,  $P = 0.999$ ) (Fig. 4b).



**Fig. 3** Forest plot of randomized controlled trials investigating the effect of probiotics on serum lipid profile “HDL (a), TG (b), TC (c), TC-to-HDL ratio (d), LDL (e), and VLDL (f)” in Diabetic Nephropathy patients. The area of each square is proportional to the inverse of the variance of

the WMD. Horizontal lines represent 95% CIs. HDL, high-density lipoprotein; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein

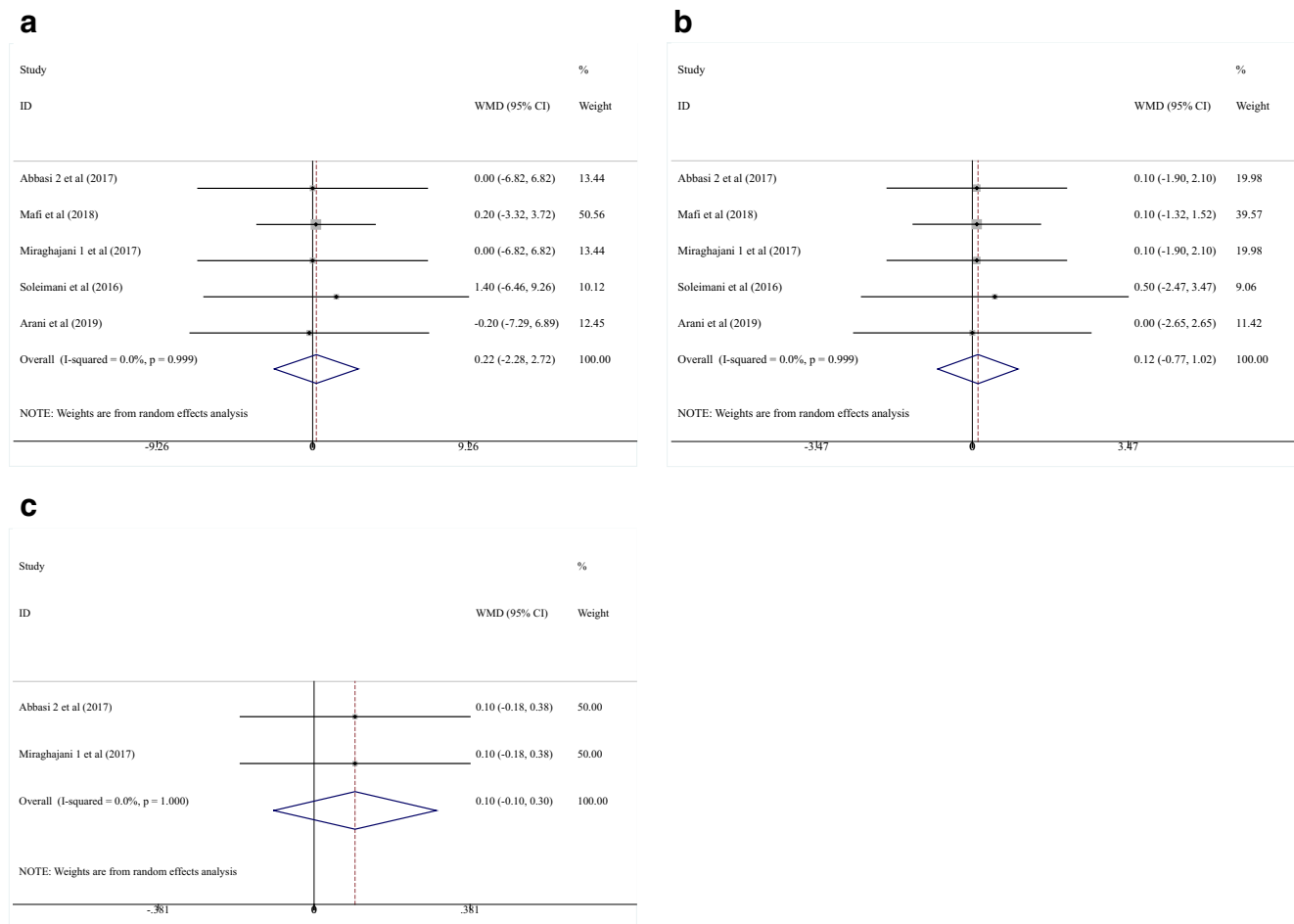
### The effects of probiotics on WHR

Of the two RCTs investigating the impact of probiotics vs. placebo on WHR in 80 patients (intervention, 40; control, 40), no one reported significant favorable effects [24, 28].

### Sensitivity analysis and publication bias

Sensitivity analysis showed that the effect of probiotics on the level of selected markers was not significant except for TC-to-





**Fig. 4** Forest plot of randomized controlled trials investigating the effect of probiotics on anthropometric indices “Body Weight (a), BMI (b), and WHR (c)” in Diabetic Nephropathy patients. The area of each square is

proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CIs. BMI, body mass index; WHR, waist-to-hip ratio

HDL ratio (WMD = -0.29; 95% CI, -0.61- 0.03; conducted by Mafi et al. [27]).

Moreover, there was no evidence of publication bias (assessed by Egger’s test) for studies examining the probiotics on HDL ( $P = 0.056$ ), TG ( $P = 0.337$ ), TC ( $P = 0.684$ ), TC-to-HDL ( $P = 0.803$ ), LDL ( $P = 0.795$ ), VLDL ( $P = 0.464$ ), BW ( $P = 0.767$ ), and BMI ( $P = 0.424$ ).

## Discussion

The present study systematically reviewed and quantitatively synthesized six RCTs to evaluate the effects of probiotics on lipid profile and anthropometric measurements among patients with DN. The pooled analysis showed that supplementation with probiotics did not significantly affect the selected biomarkers.

To date, there were no studies performing point-to-point comparison in DN patients for clarification and these findings should be interpreted with caution. One meta-analysis has

shown the effects of probiotics on other clinical markers. Jia et al. [31] included eight studies with 261 Chronic Kidney Disease (CKD) patients (stage 3 to 5)- with and without dialysis - and found a decrease of P-Cresyl Sulfate (PCS) and an increase of IL-6 in the probiotics group. In addition, no significant changes were obtained for serum Cr, BUN, and C-reactive protein (CRP) ( $P = 0.55$ ). Thongprayoon et al. [3] also reported that there were no significant differences in serum Cr and GFR after probiotic therapy (Five RCTs with 161 CKD patients had been enrolled).

Based on our knowledge, this study is the first meta-analysis investigated the potential effects of microbial therapy on lipid profile and anthropometric indices in DN patients. Recently, a meta-analysis was also conducted by AbdelQadir et al. [32] in T2D and DN patients. They included three trials to evaluate the effect of probiotics on lipid profile and anthropometric indices (BW, BMI). Similar to our results, the overall effect size for lipid profile (except for LDL) were not significant. Unlike AbdelQadir et al. meta-analysis, we did

not find any significant results for BMI, perhaps due to the inclusion of five studies in the analysis.

Resent meta-analysis on T2D patients showed that probiotics significantly decreased the serum level of TC (SMD = -0.57 mg/dL, 95% CI = -0.92 to 0.21), TG (SMD = -0.66 mg/dL, 95% CI = -0.93 to 0.39) and LDL (SMD = -0.40 mg/dL, 95% CI = -0.79 to 0.01) compared with the placebo group. Apart from this, probiotics could significantly improve HDL concentration (SMD = 0.38 mg/dL, 95% CI = 0.03 to 0.73) (11). Kocsis et al. (26) also showed a significant effect of probiotics on reducing TC (-10.06 mg/dL, 95% CI = -15.94 to -4.18;  $P = 0.001$ ) and TG (-17.18 mg/dL, 95% CI = -26.17 to -8.19;  $P < 0.001$ ) in T2D subjects. However, similar to our results, they did not observe a significant effect on BMI or LDL levels. Another similarity was found by Yao et al. [17]; they did not detect any significant changes for lipid profile after pooled analysis; 12 studies with 684 T2D patients were included.

Anthropometric measurements did not positively change in the current meta-analysis, however, Koutnikova et al. [33] reported positive results in overweight but not obese subjects. Probiotics - mostly *bifidobacteria* (*Bifidobacterium breve*, *B. longum*), *Streptococcus salivarius subsp. thermophilus* and *lactobacilli* (*L. acidophilus*, *L. casei*, *L. delbrueckii* - induced improvements in BW (WMD = -0.94 kg, 95% CI = -1.17 to -0.70;  $P < 0.05$ ), BMI (WMD = -0.55 kg/m<sup>2</sup>, 95% CI = -0.86 to -0.23;  $P < 0.05$ ), waist circumference (WMD = -1.31 cm, 95% CI = -1.79 to -0.83;  $P < 0.05$ ), body fat mass (WMD = -0.96 kg, 95% CI = -1.21 to -0.71;  $P < 0.05$ ) and visceral adipose tissue mass (WMD = -6.30 cm<sup>2</sup>, 95% CI = -9.05 to -3.56;  $P < 0.05$ ).

Although we were unable to show the anti-dyslipidemic and BW-modulatory effects of probiotics in DN patients, some mechanisms were defined to describe these positive effects. It seems that careful targeting of Toll-Like Receptor 2 (TLR2), TLR4, and NOD-Like Receptor & Pysin Domain-Containing Protein 3 (NLRP3) signaling pathways can be beneficial for the treatment of T2D and DN [34]. Probiotics may reduce TLR4 activation which may explain their beneficial impact on serum lipid profile [35, 36]. TLR4 is a transmembrane protein which is capable to produce inflammatory cytokines [37]. In recent reports, probiotics were also considered as cholesterol-lowering agents [38].

We attempted to determine whether the observed heterogeneity in our outcomes was due to the differences in the study/disease duration, baseline BMI or in the dose of probiotics used. However, according to our subgroup analyses high heterogeneity still remained unknown.

## Limitations

There are substantial limitations in our study. The number of analyzed studies was small and the included trials

had been performed in small sample sizes. Many of the analyzed studies used probiotic mixtures or food-based probiotic products (e.g. dairy products, honey); the food-supplement interactions might decrease the consistency of results. Usual dietary intakes were not assessed in terms of possible prebiotics and probiotics consumption through the normal dietary patterns of participants. The most probiotic interventions were limited to one strain in our data, for example *L. plantarum* A7 was administered in four included RCTs [24, 25, 28, 30]. Therefore, our evidence is not applicable to all probiotic strains.

The included studies had follow-up periods ranging from 8 to 12 weeks, which were relatively short-term. The current meta-analysis was performed in age group between 50 and 60 years, so it is unclear how probiotics affect lipid profile and anthropometric measurements in children. The most important limitation was the heterogeneity between studies, which might stem from the intra-individual strain differences, duration of intervention, optimal dose of the probiotics, and genotype of individuals, among other factors. The responses to probiotic administration may also have been influenced by a number of within-study factors, such as antibiotic use [39] and corticosteroid therapy [40].

The subgroup analysis also had some limitations. The restricted number of included studies resulted in the tiny subgroups, which suggested that the evidence was not generalizable.

## Strengths

We performed an exclusive investigation for DN; this is the main strength of the current study. The prevalence of DN is now growing worldwide and the treatments are very limited, hence the probiotics-related studies can allow clinicians to use these compounds as adjunct therapy.

## Conclusion

Our meta-analysis did not find any beneficial effect of probiotics on lipid profile and anthropometric measurements; however, there were marginal improvements in some lipid markers such as TC ( $P = 0.084$ ), LDL ( $P = 0.062$ ) and HDL ( $P = 0.077$ ). Subgroup analyses also failed to show any significant subset across the selected confounders (study duration, disease duration, probiotics dose, baseline BMI). More trials are needed to characterize specific alterations of the intestinal microbiota in diabetic nephropathy and to assess possible effects of

probiotic, prebiotic, and synbiotic treatments in this setting. The authors suggest researchers to conduct more special interventions (single strains of probiotics; prebiotics alone; synbiotics) in DN patients.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s40200-021-00765-8>.

**Acknowledgements** This research was supported by Isfahan University of Medical Sciences, Isfahan, Iran.

PROSPERO Registration ID. CRD42020186189.

**Authors' contributions (CRediT author statement)** Amir Reza Moravejolahkami: Conceptualization, Investigation, Methodology, Software, Validation, Formal analysis, Writing - Original Draft.

Mohammad Ali Hojjati Kermani: Visualization, Project administration, Writing - Review & Editing.

Zakiyeh Balouch Zehi: Data Curation, Resources, Writing - Review & Editing.

Seyed Mohammad Sadegh Mirenayat: Writing - Review & Editing. Marjan Mansourian: Supervision, Funding acquisition.

## Declaration

**Conflict of interest** The authors declare that they have no conflict of interest to the publication of this article.

## References

- Kikuchi K, Saigusa D, Kanemitsu Y, Matsumoto Y, Thanai P, Suzuki N, et al. Gut microbiome-derived phenyl sulfate contributes to albuminuria in diabetic kidney disease. *Nat Commun*. 2019;10(1):1–17.
- Morimoto K, Matsui M, Samejima K, Kanki T, Nishimoto M, Tanabe K, et al. Renal arteriolar hyalinosis, not intimal thickening in large arteries, is associated with cardiovascular events in people with biopsy-proven diabetic nephropathy. *Diabet Med*. 2020;37:2143–52.
- Thongprayoon C, Hatch ST, Kaewput W, Sharma K, Ungprasert P, Wijampreecha K, et al. The effects of probiotics on renal function and uremic toxins in patients with chronic kidney disease; a meta-analysis of randomized controlled trials. *Journal of Nephrology*. 2018;7(3).
- Maric C, Hall JE. Obesity, metabolic syndrome and diabetic nephropathy. *Diabetes and the Kidney*. 2011;170: Karger Publishers;: 28–35.
- Sabapathy V, Stremaska ME, Mohammad S, Corey RL, Sharma PR, Sharma R. Novel immunomodulatory cytokine regulates inflammation, diabetes, and obesity to protect from diabetic nephropathy. *Front Pharmacol*. 2019;10:572.
- Russo G, Piscitelli P, Giandalia A, Viazzi F, Pontremoli R, Fioretto P, et al. Atherogenic dyslipidemia and diabetic nephropathy. *Journal of Nephrology*. 2020:1–8.
- Fang B, Zhang M, Dong L, Zhou X, Ren F, Ge S. Probiotic camel milk powder improves glycemic control, dyslipidemia, adipose tissue and skeletal muscle function in T2DM patients: a randomized trial. 2020.
- Asad F, Anwar H, Yassine HM, Ullah MI, Kamran Z, Sohail MU. White button mushroom, *agaricus bisporus* (Agaricomycetes), and a probiotics mixture supplementation correct dyslipidemia without influencing the colon microbiome profile in hypercholesterolemic rats. *International Journal of Medicinal Mushrooms*. 2020;22(3).
- López-Moreno A, Suárez A, Avanzi C, Monteoliva-Sánchez M, Aguilera M. Probiotic strains and intervention Total doses for modulating obesity-related microbiota Dysbiosis: a systematic review and meta-analysis. *Nutrients*. 2020;12(7):1921.
- Bahreini-Esfahani N, Moravejolahkami AR. Can synbiotic dietary pattern predict Lactobacillales strains in breast Milk? *Breastfeeding Medicine*. 2020.
- Moravejolahkami A, Chitsaz A. Mediterranean-style diet co-supplemented with synbiotics improved quality of life, fatigue and disease activity in five secondary progressive multiple sclerosis patients. *Ann Med & Surg Case Rep: AMSCR*. 2019;2019(02).
- Khalili L, Alipour B, Jafarabadi MA, Hassanilou 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(1):5.
- Razmpoosh E, Javadi A, Ejtahed HS, Mirmiran P, Javadi M, Yousefinejad A. The effect of probiotic supplementation on glyce-mic 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.
- Bock PM, Telo GH, Ramalho R, Sbaraini M, Leivas G, Martins AF, et al. The effect of probiotics, prebiotics or synbiotics on metabolic outcomes in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia*. 2020:1–16.
- Kocsis T, Molnár B, Németh D, Hegyi P, Szakács Z, Bálint A, et al. Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials. *Sci Rep*. 2020;10(1):1–14.
- Kasińska MA, Drzewoski J. Effectiveness of probiotics in type 2 diabetes: a meta-analysis. *Pol Arch Med Wewn*. 2015;125(11): 803–13.
- Yao K, Zeng L, He Q, Wang W, Lei J, Zou X. Effect of probiotics on glucose and lipid metabolism in type 2 diabetes mellitus: a meta-analysis of 12 randomized controlled trials. *Medical science monitor: international medical journal of experimental and clinical research*. 2017;23:3044–53.
- Million M, Angelakis E, Paul M, Armougoum F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. *Microb Pathog*. 2012;53(2): 100–8.
- Vlachou E, Ntikoudi A, Govina O, Lavdaniti M, Kotsalas N, Tsartsalis A, et al. Effects of probiotics on diabetic nephropathy: a systematic review. *Curr Clin Pharmacol*. 2020;15:234–42.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of internal medicine*. 2009;151(4):W-65–94.
- Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*. 2019;366.
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(1):13.
- Peng W, Mao P, Liu L, Chen K, Zhong Y, Xia W, et al. Effect of carnosine supplementation on lipid profile, fasting blood glucose, HbA1C and insulin resistance: a systematic review and meta-analysis of long-term randomized controlled trials. *Complementary Therapies in Medicine*. 2019;102241.
- Abbasi B, Ghiasvand R, Mirlohi M. Kidney function improvement by soy milk containing Lactobacillus plantarum A7 in type 2 diabetic patients with nephropathy: a double-blinded randomized controlled trial. *Iran J Kidney Dis*. 2017;11(1):36–43.

25. Abbasi B, Mirlohi M, Daniali M, Ghiasvand R. Effects of probiotic soymilk on lipid panel in type 2 diabetic patients with nephropathy: a double-blind randomized clinical trial. *Prog Nutr*. 2018;20:70–8.
26. Arani NM, 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 and antimicrobial proteins*. 2019;11(4):1195–201.
27. Mafi A, Namazi G, Soleimani A, Bahmani F, Aghadavod E, Asemi Z. Metabolic and genetic response to probiotics supplementation in patients with diabetic nephropathy: a randomized, double-blind, placebo-controlled trial. *Food Funct*. 2018;9(9):4763–70.
28. Miraghajani M, Zaghian N, 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.
29. Soleimani A, Mojarrad MZ, Bahmani F, Taghizadeh M, Ramezani M, Tajabadi-Ebrahimi M, et al. Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects. *Kidney Int*. 2017;91(2):435–42.
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. *J Ren Nutr*. 2017;27(5):317–24.
31. Jia L, Jia Q, Yang J, Jia R, Zhang H. Efficacy of probiotics supplementation on chronic kidney disease: a systematic review and meta-analysis. *Kidney Blood Press Res*. 2018;43(5):1623–35.
32. AbdelQadir YH, Hamdallah A, Sibaey EA, Hussein AS, Abdelaziz M, AbdelAzim A, et al. Efficacy of probiotic supplementation in patients with diabetic nephropathy: a systematic review and meta-analysis. *Clinical Nutrition ESPEN*. 2020;40:57–67.
33. Koutnikova H, Genser B, Monteiro-Sepulveda M, Faurie J-M, Rizkalla S, Schrezenmeir J, et al. Impact of bacterial probiotics on obesity, diabetes and non-alcoholic fatty liver disease related variables: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2019;9(3):e017995.
34. Wada J, Makino H. Innate immunity in diabetes and diabetic nephropathy. *Nat Rev Nephrol*. 2016;12(1):13–26.
35. Mohammed SK, Magdy YM, El-Waseef DA, Nabih ES, Hamouda MA, El-kharashi OA. Modulation of hippocampal TLR4/BDNF signal pathway using probiotics is a step closer towards treating cognitive impairment in NASH model. *Physiol Behav*. 2020;214:112762.
36. Ahmed LA, Salem MB, El-Din SHS, El-Lakkany NM, Ahmed HO, Nasr SM, et al. Gut microbiota modulation as a promising therapy with metformin in rats with non-alcoholic steatohepatitis: role of LPS/TLR4 and autophagy pathways. *Eur J Pharmacol*. 2020;887:173461.
37. Tuoheti A, Gu X, Cheng X, Zhang H. Silencing Nrf2 attenuates chronic suppurative otitis media by inhibiting pro-inflammatory cytokine secretion through up-regulating TLR4. *Innate Immunity*. 2020;1753425920933661.
38. Bhat B, Bajaj BK. Multifarious cholesterol lowering potential of lactic acid bacteria equipped with desired probiotic functional attributes. *3 Biotech*. 2020;10:1–16.
39. Bäckhed F, Fraser CM, Ringel Y, Sanders ME, Sartor RB, Sherman PM, et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. *Cell Host Microbe*. 2012;12(5):611–22.
40. Kaur L, Gordon M, Baines PA, Iheozor-Ejiofor Z, Sinopoulou V, Akobeng AK. Probiotics for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2020;3.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.