Prebiotic, Probiotic, and Synbiotic Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-analysis

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Objective

Gut dysbiosis has been implicated in the pathogenesis of chronic kidney disease (CKD). Restoring gut microbiota with prebiotic, probiotic and synbiotic supplementation has emerged as a potential therapeutic intervention, but has not been systematically evaluated in the CKD population.

Design

Systematic review

Method

A structured search of Medline, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials and the International Clinical Trials Register Search Portal was conducted for articles published since inception until July 2017. Included studies were randomised controlled trials investigating the effects of pre-, pro- and/or synbiotic supplementation (>1 week) on uraemic toxins, microbiota profile, clinical and patient-centred outcomes in adults and children with CKD.

Results

Sixteen studies investigating 645 adults met the inclusion criteria; five investigated prebiotics, six probiotics and five synbiotics. The quality of the studies (GRADE) ranged from moderate to very low. Pre-, pro- and synbiotic supplementation may have led to little or no

difference in serum urea (9 studies, 345 participants: MD -0.30mmol/L, 95%CI -2.20 to 1.61, P=0.76, I^2=53%), indoxyl sulphate (4 studies, 144 participants: MD -0.02mg/dL, 95%CI -0.09 to 0.05, P=0.61, I^2=0%) and p-cresyl sulphate (4 studies, 144 participants: MD -0.13mg/dL, 95% CI -0.41 to 0.15, P=0.35, I^2=0%). Prebiotic supplementation may have slightly reduced serum urea concentration (4 studies, 105 participants: MD -2.23mmol/L, 95%CI -3.83 to -0.64, P=0.006, I^2=11). Of the two studies investigating microbiota changes, synbiotic interventions significantly increased *Bifidobacterium.* Supplement effects on clinical outcomes were uncertain.

Conclusions:

There is limited evidence to support the use of pre- pro- and/or synbiotics in CKD management.

Key words (5): Chronic Kidney Disease, Gut dysbiosis, Prebiotic, Probiotic, Synbiotic, Microbiota

Introduction

Chronic kidney disease (CKD) is a major health burden worldwide. (1) The prevalence of CKD is steadily increasing (2) and individuals with CKD have a significantly increased risk of cardiovascular disease (CVD) (3), which is only partially explained by the traditional risk factors of older age, obesity, tobacco use, diabetes mellitus, hypertension and dyslipidaemia. (4)

Over the last decade, there has been a growing body of evidence linking gut dysbiosis and intestinal wall permeability to progressive kidney failure and cardiovascular risk (5, 6) via systemic inflammation and production of uraemic toxins, including indoxyl sulphate (IS), p-cresyl sulphate (PCS) and trimethylamine N-oxide (TMAO). (7-9) The imbalance of gut micro-organisms in patients with CKD may be therapeutically modifiable. For example, pre-, pro- and synbiotics may competitively decrease the relative population of protein-fermenting intestinal flora and consequently reduce the production of uraemic toxins. This is achieved by altering the carbohydrate-to-protein ratio and augmenting short-chain fatty-acid production. This low-cost therapy therefore represents an appealing therapeutic strategy.

To date, the results from individual studies investigating the effects of pre-, pro- and/or synbiotic supplementation within the CKD population have produced conflicting results. (10-12) Furthermore, there has been no prior systematic review of the effects of pre-, pro- and/or synbiotic supplementation on kidney function, uraemic toxin production, microbiota composition and patient-level outcomes exclusively within the CKD population. Therefore, the aim of this review was to systematically evaluate randomised controlled trials assessing

the effectiveness of pre-, pro- and/or synbiotic supplementation on clinical and patient-centred outcomes in CKD.

Materials and Methods

This review was conducted according to PRISMA reporting guidelines following a pre-specified protocol (PROSPERO CRD42017075771) (13).

Criteria for considering studies

Studies were included in the review if they met all of the following criteria: 1) randomised controlled trial (RCT) including crossover, cluster or quasi-RCT designs; 2) in participants with CKD as defined by the Kidney Disease Outcome Quality Initiative (K/DOQI) Guidelines (14); and, 3) interventions that included supplementation with pre-, pro- or synbiotics for a duration of at least one week. Studies were excluded if they were utilising high dose prebiotics for purgation, populations with altered gastrointestinal function and those where nutrition was provided enterally.

The primary outcome was change in kidney function (eGFR, serum creatinine) and kidney damage (proteinuria, albuminuria). Secondary outcomes included uraemic toxins (urea, free and protein bound concentrations of serum indoxyl sulphate [IS] and *p*-cresyl sulphate [PCS], trimethylamine N-oxide [TMAO] phenylacetylglutamine [PAG]), microbiota composition, change in clinical markers (fasting blood glucose, HbA1c, weight, waist circumference), markers of cardiovascular risk (left ventricular mass index, diastolic function, blood pressure, blood lipid profile), infections including antibiotic use, clinical outcomes (hospitalisations, cardiovascular events, progression to end-stage kidney disease

[ESKD], mortality, adverse events) and patient centred outcomes (colonic transit time, faecal characteristics, gastrointestinal tolerance, health related quality of life and treatment adherence).

Search methods

A comprehensive search was conducted using MEDLINE, CINAHL, Embase and Cochrane from inception until 2017 utilising a combination of MeSH and free text terms relevant to the review in consultation with an experienced systematic review search librarian. MESH search terms are outlined in the pre-specified protocol (PROSPERO CRD42017075771). Searches of the International Clinical Trials Register and clinicaltrials.gov were undertaken to identify any ongoing trials. Additionally, manual searches were performed to retrieve relevant studies through citation searches of conference abstracts, theses and biographies of relevant published articles.

Data Collection

Articles were screened independently by two review authors (CM, CIR), with disagreements resolved by consensus or discussion with a third reviewer (KLC). Data extraction from included studies comprised of intervention details, study design, duration, sample size, attrition and participant characteristics. Mean, standard deviations (SD), standard error (SE) or 95% confidence intervals (CI) for all pre-specified primary and secondary outcome data that were reported at baseline and follow-up were extracted for data analysis. The units of measurement for uraemic toxins were converted to mg/dL using molecular weights from the Human Metabolome Database. (15) Corresponding authors were contacted for information that was not published, including missing numerical data of outcome measures.

Assessment of Study and Evidence Quality

Risk of bias was assessed by two review authors (CM, CR) independently using Cochrane methodology (16) The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach for grading the evidence was applied for each outcome category (17) and assessed independently by two review authors (CM, CR). Disagreements in risk of bias and GRADE classification were managed by consensus and discussion with a third reviewer (KC).

Statistical Analysis

The overall treatment effects for primary and secondary outcomes were calculated as the differences between the intervention and comparison groups' change scores from baseline to the end of follow-up. If the change from baseline score was not available, the end of intervention value was extracted with the assumption that no significant differences were observed at baseline between intervention and comparison groups.

Quantitative analysis was undertaken for adequately reported outcomes by pooling data into Revman (Review Manager 5, version 5.3, The Cochrane Collaboration) for meta-analysis through DerSimonian-Laird random-effects model. (16) Heterogeneity between studies was assessed using the I^2 statistic and was considered substantial if the I^2 statistic was $\geq$50%. Publication bias was investigated using funnel plots and Egger's test.

Results

Characteristics of Included Studies

The search identified 586 citations after removal of duplicates (Figure 1). Sixteen studies were included in the review, with a total sample size of 645 participants (individual studies ranging from nine to 124 participants) and intervention durations ranging from two to 24 weeks. All included studies involved adult participants with chronic kidney disease (CKD) with seven studies involving non-dialysis patients (7, 9, 18-23), eight studies involving patients undergoing haemodialysis for ESKD (8, 24-29) and one study involving participants undergoing peritoneal dialysis (30). Five trialled prebiotics (7, 8, 18, 23, 29), six trialled probiotics (21, 22, 24, 26, 27, 30) and five trialled synbiotics (9, 19, 20, 25, 28). (Table 1) Pre-, pro- and synbiotic formulations are outlined in Table 1. Additional information was provided by three of the nine contacted authors. (7, 9, 19)

Risk of Bias

Risk of bias was low in the following domains; detection bias (13 studies) (7-9, 18-22, 24-26, 28, 30), attrition bias (9 studies) (7, 9, 18, 20, 21, 23, 26-28), performance bias (7 studies) (7, 9, 19, 20, 24, 28, 30), selection bias (random sequence generation (5 studies) (8, 9, 20, 27, 30), allocation concealment (6 studies) (7, 9, 20, 24, 27, 30)), and reporting bias (4 studies) (7-9, 27). Five studies were rated as having a high risk of attrition bias (through high loss to follow-up and no explanation of how data were addressed) (8, 22, 24, 29, 30), four studies were rated as having a high risk of performance bias (no blinding or blinding may have been broken) (8, 18, 23, 29), while three were rated as having a high risk of reporting bias (a number of outcome measures were not reported in the results) (21, 22, 26). Bias related to control of dietary intake was low in four studies (9, 23, 28, 29), while four studies were rated as having an unclear risk of bias related to dietary advice and assessment of dietary compliance (7, 18, 27, 30). The eight studies which did not provide dietary advice nor assess

dietary intake were rated as having a high risk of bias related to potential dietary confounders. (8, 19-22, 24-26) Three studies were determined as having other risks of bias relating to the absence of a wash-out period in crossover trials and possible or undeclared conflicts of interest. (18, 21, 22) (Figure 4)

Change in kidney function and damage

Nutrition supplementation probably made little or no difference to kidney function, measured by eGFR (3 studies, 132 participants: MD 0.34mL/min/1.73m^2, 95%CI -2.20 to 2.89, P=0.79, I^2=0%; moderate certainty evidence) (Supplementary Figure 1). (7, 9, 19) Two studies reported that nutrition supplementation had no impact on serum creatinine (sCr). (18, 19)

Kidney damage was reported in one study, with a significant increase in albuminuria (38mg/24hr, 95% CI, 1 to 295mg/24hr, P=0.03) noted after synbiotic therapy. (9) The effect of nutrition supplementation on proteinuria was not reported as an outcome measure in any included study.

Uraemic toxins

Nutrition supplementation may have led to little or no difference to serum urea (9 studies, 345 participants: MD -0.30mmol/L, 95%CI -2.20 to 1.61, P=0.76, I^2=53%; low certainty evidence) (7, 8, 18, 19, 23, 24, 27, 28, 30) (Supplementary Figure 2), serum IS (4 studies, 144 participants: MD -0.02mg/dL, 95%CI -0.09 to 0.05, P=0.61, I^2=0%; moderate certainty evidence) (7-9, 24) and serum PCS (4 studies, 144 participants: MD -0.13mg/dL, 95% CI -0.41

to 0.15, P=0.35, I^2=0%; moderate certainty evidence) (7-9, 24) (Supplementary Figures 3 and 4).

Sensitivity analyses were conducted to determine the effects that the type of nutrition supplementation, CKD stage and duration of intervention had on serum urea levels. Prebiotics may have slightly reduced serum urea concentrations (4 studies, 105 participants: MD -2.23mmol/L, 95%CI -3.83 to -0.64, P=0.006, I^2=11%) (7, 8, 18, 23) though not probiotics (3 studies, 132 participants: MD 2.30mmol/L, 95%CI -0.25 to 4.85, P=0.08, I^2=0%) (24, 27, 30) nor synbiotics (2 studies, 108 participants, MD 0.62mmol/L, 95%CI -2.70 to 3.95, P=0.71, I^2=9%) (19, 28) (Figure 2). A small but statistically significant reduction was observed in serum urea concentration in non-dialysis patients (4 studies, 131 participants: MD -2.12mmol/L, 95%CI -3.86 to -0.37, P=0.02, I^2=17%) (7, 18, 19, 23) but not in dialysis patients (5 studies, 214 participants: MD 1.36mmol/L, 95%CI -0.76 to 3.48, P=0.21, I^2=14%) (8, 24, 27, 28, 30) (Figure 3). There was no subgroup difference by intervention duration.

Sensitivity analyses demonstrated no subgroup differences by type of nutrition supplementation, CKD stage or intervention duration for both IS and PCS.

One study reported the impact of nutrition supplementation on serum TMAO concentrations and found prebiotic supplementation resulted in a significant decrease in TMAO (-0.237μmol/L, P=0.04). (7)

The impact of nutrition supplementation on serum PAG was reported in one study. (7) Prebiotic supplementation had no significant effect on serum PAG (0.080μmol/L P=0.41).

Microbiota composition

Two studies investigated the effect of nutrition supplementation on microbiota composition, both were synbiotic studies. (9, 25) Intervention duration ranged from six to eight weeks, with 18 to 31 participants. Synbiotic formulation differed between the two studies (Table 1). Both studies noted significant increases in *Bifidobacterium* (3.2% P=0.003 (9) and 4.2 ± 0.88 $\log_{10}$ cells/g to 5.5 ± 1.72 $\log_{10}$ cells/g P=0.034 (25)) with one study also finding a significant increase in *Lachnospiraceae* (2.1% P=0.01), a non-significant increase in *Lactobacillus* (0.7% P=0.36) and a significant decrease in *Ruminococcaceae* (4.3% P=0.01). (9)

Clinical markers

Few studies reported on change in clinical markers with pre-, pro- and/or synbiotic supplementation. Blood glucose levels were reported in two studies (7, 27) and weight in seven studies (7, 18, 19, 23, 27-29), while waist circumference was not reported in any included studies. It was uncertain whether pre- or probiotic supplementation improved blood glucose levels as the certainty of this evidence was very low (2 studies, 100 participants: MD -8.19md/dL, 95%CI -32.45 to 16.07, P=0.51, I^2=80%) (7, 27) (Supplementary Figure 5). Heterogeneity was not able to be explained through sensitivity analyses. Compared to placebo, pre-, pro- and/or synbiotic supplementation may have had little or no impact on weight (7 studies, 357 participants: MD 0.40kg, 95%CI -0.95 to 1.74, P=0.56, I^2=0%; low certainty evidence) (7, 18, 19, 23, 27-29) (Supplementary Figure 6).

Cardiovascular risk

Few studies reported on the effect of pre-, pro- and/or synbiotic supplementation on cardiovascular risk. Blood lipids were reported in three studies. (27-29) It was uncertain whether nutrition supplementation improved total cholesterol (3 studies, 226 participants: MD -6.23mg/dL, 95%CI -25.86 to 13.41, P=0.53, I^2=76%), LDL cholesterol (3 studies, 226 participants: MD -5.50mg/dL, 95%CI -15.54 to 4.54, P=0.28, I^2=83%) or triglyceride levels (3 studies, 226 participants: MD -1.57mg/dL, 95%CI -22.56 to 19.42, P=0.88, I^2=0%) as the certainty of this evidence was very low. (Supplementary Figures 7, 8 and 9) Heterogeneity was not able to be explained through sensitivity analyses. Left ventricular mass index, diastolic function and blood pressure were not reported in any included studies.

Infections

None of the included studies reported an infection as an adverse event. One study reported on antibiotic use throughout the intervention. (9) Patients who did not receive antibiotics during the study had marked reductions in IS (-5μmol/L, 95%CI -8 to -1μmol/L, P=0.03) and PCS (-25μmol/L, 95%CI -38 to -12μmol/L, P=0.001) compared to those who received antibiotics. Antibiotic use preceding baseline visit was an exclusion criterion in six of the 16 studies. (7-9, 19, 27, 30)

Adverse events

Three studies provided data on adverse events. (9, 21, 26) One study reported initial hospitalisation for six patients; three during washout, two during placebo and one during synbiotic periods. (9) Two studies each had one patient die of a myocardial infarct during the study period, both of which were deemed unrelated to the study intervention. (21, 26) None of the included studies reported on progression to ESKD as an outcome measure.

Patient-centred outcomes

Faecal characteristics were reported in four of the included studies. (7, 18, 20, 23) Two studies utilised the Bristol Stool Scale to measure stool consistency, with both reporting no effect after prebiotic and synbiotic supplementation. (7, 20) Stool frequency was reported in two studies with no effect after synbiotic supplementation (P=0.92)(7) or prebiotic supplementation (P=0.48) (18). Younes et al (23) noted an increase in stool weight after prebiotic supplementation ($P<0.05$).

Gastrointestinal tolerance was investigated using a variety of measures: Gastrointestinal Symptom Rating Scale (GSRS) (9, 25), other patient-reported questionnaires (7, 20, 28) and through patient interviews (8, 18, 22, 27). No significant change in GSRS scores were noted after synbiotic supplementation (P=0.168 (9) and P=0.72 (25)). An increase in flatulence was reported in two prebiotic interventions (7, 18), while improvements in bloating ($P\leq0.05$) and constipation ($P\leq0.05$) were noted after synbiotic supplementation. (28)

Colonic transit time was not reported in any of the included studies.

A variety of measures were utilised to assess adherence to treatment, with pill count the most common. (8, 9, 24, 26-28) Overall adherence to nutrition supplementation was high, ranging from 82% to 97%. (7, 9, 24, 26, 27)

Health related quality of life (QoL) was assessed using a range of tools (SF-36 (9, 26), Kidney Disease Quality of Life Short Form-36 (KDQoL-36) (8) and utilising a 10-point scale (21, 22)).

No significant change to quality of life was found in three studies (8, 9, 26), while one study found 85% (P>0.05) of participants had a perceived higher quality of life during the intervention period (22).

Discussion

This systematic review assessed the effectiveness of pre-, pro- and/or synbiotic supplementation in adults with CKD. In mostly low certainty evidence, pooled results indicated that nutrition supplementation may have had little or no effect on eGFR, serum creatinine, serum urea, serum IS, serum PCS, blood glucose levels, weight, total cholesterol, LDL cholesterol, HDL cholesterol or triglyceride levels. Prebiotic supplementation may have slightly reduced serum urea concentrations (-2.23mmol/L P=0.006), although there was no appreciable effect with probiotic or synbiotic supplementation. Additionally, there may have been a positive benefit with all three types of nutrition supplementation (pre-, pro- and synbiotics) on serum urea concentrations (-2.12mmol/L P=0.02) in non-dialysis dependent CKD, however not to those who were dialysis dependent.

The reduction in serum urea with prebiotic supplementation is supported by the results of an earlier systematic review which found that dietary fibre intake was associated with significant reductions in serum urea (MD −1.76mmol/L (95% CI, −3.00, −0.51), P<0.01) in CKD. (31) Reducing serum urea concentrations in CKD may be of importance as the diffusion of urea into the gut lumen favours the growth of intestinal bacteria that express urease as well as those that produce uraemic toxins. Increased urease expression promotes the degradation of urea leading to the erosion of the epithelial barrier, thereby promoting systemic inflammation. (32, 33) The low certainty of effect of pre-, pro- and synbiotic

supplementation on the uraemic toxins, IS and PCS, reflects the conflicting findings found in individual studies with increases, decreases and neutral effects reported in the literature. (10-12) Study design was likely an important limiting factor underpinning the disparate findings, given the short intervention durations (4 - 12 weeks), small participant numbers (31-40) and variable product formulations in these studies.

Microbiota composition was investigated in two studies, with synbiotic supplementation leading to higher abundances of *Bifidobacterium* (9, 25) and *Lachnospiraceae* (9) and a decrease in *Ruminococcaceae* (9). Although the significant change in microbiota composition is encouraging, it is important to note that product formulation and dosage differed between the two studies and only one study considered the potential modifying effects of participants' baseline microbiota profiles (9). Moreover, both studies utilised faecal samples as a surrogate for gut microbiota composition, even though this may not have accurately reflected the colonic mucosal microbiota. (34)

Pre- pro- and synbiotic supplementation appeared to be well-tolerated with few gastrointestinal side-effects. In conjunction with a high rate of patient adherence, few adverse events and no decrease in health-related quality of life, this preliminary, low certainty evidence suggested that pre-, pro- and synbiotic supplementation may be safe, well-tolerated and acceptable forms of supplementation within the CKD population.

To our knowledge, this is the first systematic review investigating the effects of pre-, pro- and/or synbiotic supplementation on clinical and patient-centred outcomes in the CKD population. The strengths of this study included its robust design and comprehensive search

strategy. However, it is acknowledged that this study had some limitations. Only a limited number of studies reported the primary outcome of kidney function and damage. The wide variability in product formulations further limited comparisons between interventions and measured outcomes. Moreover, some studies possibly provided inadequate amounts of product and/or an insufficient duration of treatment (2 to 24 weeks) to elicit a therapeutic response. (35) The prebiotic studies evaluated used dosages ranging from 10 - 50g/day, while the synbiotic studies used significantly lower dosages of prebiotic (2.3 – 15g/day). A prebiotic dose of >5g/day has previously been shown to influence microbiota diversity, while a threshold dose of 15-20g/day may be required to reduce uraemic toxin concentrations. (36) The included probiotic studies contained an array of strains and dosages. In other chronic diseases, the therapeutic response to probiotics has been strain specific (37), indicating that a specific mix of bacterial genera and dosages may be required for the CKD population. The responses to pre-, pro- and synbiotic supplementation may also have been influenced by a number of within-study factors, such as antibiotic use (38), wash-out periods (39) and dietary intake (40, 41). Antibiotic use throughout the intervention period was only documented in one study. (9) A number of studies either did not describe or did not include a wash-out period (18, 21-23), potentially confounding the results. Few studies included in this review controlled for potential dietary confounders. Finally, when applying the GRADE assessment, most studies were rated as “moderate” to “very low” quality thereby reducing confidence that the observed effect size was representative of the true effect.

Practical Applications

At this time, there is limited evidence to support the use of pre-, pro- and synbiotic supplementation in CKD. However, the observed reduction in serum urea in non-dialysis dependent CKD patients is promising. Due to the small number of available studies it is premature to conclude whether one type of nutrition supplementation is superior to another at this time. Further well-designed interventions are required to establish the most appropriate supplementation formulation and its influence on patient-level outcomes.

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Legends to Tables

Table 1: Characteristics of included prebiotic, probiotic and synbiotic interventions in CKD

Table 2: Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of pre- pro- and synbiotic supplementation compared to placebo in patients with chronic kidney disease

Tables

Table 1: Characteristics of included prebiotic, probiotic and synbiotic interventions in CKD

Author, year	Study Design	Participants	Intervention	Time	Primary Outcome Measure	Potential Confounders		
						Assessed Diet	Washout Period	Compliance
Bliss, 1996	Single-blind, crossover RCT	n=16 (63% male) Non-dialysis	Prebiotic: 50g gum arabic	1 wk	Stool weight, bacterial mass, faecal N, urinary N	No	No	No
Younes, 2006	Crossover RCT	n=9 (67% male) Non-dialysis	Prebiotic: 40g Fermentable CHO	2 wks	Faecal N and stool weight, urinary N	No	Yes	Yes
Sirich, 2014	Single-blind RCT	n=40 (60% male) Haemodialysis	Prebiotic: 30g Hi-maize 260	6 wks	Free and total plasma IS and PCS	No	NA	Yes
Xie, 2015	RCT	n=124 (55% male) Haemodialysis	Prebiotic: 10g or 20g soluble dietary fibre	6 wks	Lipid profile, oxidative and inflammatory status	Yes	NA	No
Poesen, 2016	Double-blind Crossover RCT	n=40 (70% male) CKD Stage: 3b, 4	Prebiotic: 20g arabinoxylan oligosaccharides (AXOS)	4 wks	TMAO, PCS, PCG, IS, PAG, urea	Yes	Yes	Yes
Ranganathan, 2009 (pilot)	Double-blind, crossover RCT	n=13 (69% male) CKD Stage: 3, 4	Probiotic: $9x10^{10}$ CFU/day (Kibow Biotics®: *S.thermophilus* KB19, *L.acidophilus* KB27, and *B.longum* KB31)	3 mths	BUN, uric acid, serum creatinine or CRP Gut microbiota	No	No	No
Ranganathan, 2010 (pilot)	Double-blind, Crossover RCT	n=46 (67% male) CKD Stage: 3, 4	Probiotic: $9x10^{10}$ CFU/day (Kibow Biotics)	3 mths	BUN, serum creatinine, uric acid QoL	No	No	No
Natarajan, 2014	Double-blind, Crossover RCT	n=22 (27% male) Haemodialysis	Probiotic: $18x10^{10}$ CFU/day (Renadyl®: *S.thermophilus* KB19, *L.acidophilus* KB27, and *B.longum* KB31)	2 mths	Indoxyl glucuronide, IS, PCS, IAA, hippuric acid Quality of life	No	Yes	Yes
Wang, 2015	Double-blind, RCT	n=39 (46% male) Peritoneal Dialysis	Probiotic: $4x10^{9}$ CFU/day (*B.bifidum* A218, *B.catenulatum* A302, *B.longum* A101, *L.platarum* A87)	6 mths	Endotoxin	No	NA	Yes
Soleimani, 2016	Double-blind, RCT	n=60 (67% male) Diabetic Haemodialysis	Probiotic: 6 x 10^{9} CFU/day (*L.acidophilus*, *L.casei*, and *B.bifidum*)	3 mths	Glucose homeostasis	Yes	NA	Yes
Borges, 2016	Double-blind, RCT	n=33 (64% male) Haemodialysis	Probiotic: 90 x 10^{9} CFU/day (*S. thermophilus, L.acidophilus, B.longum*)	3 mths	Serum urea, CRP, IL-6, IS, PCS, IAA faecal bacterial profile	No	NA	Yes
Cruz-Mora, 2014	Double-blind, RCT	n=18 (83% male) Haemodialysis	Synbiotic (Nutrihealth®): - Prebiotic: 2.3g/day (Inulin) - Probiotic: $2x10^{12}$ CFU/day (*L. acidophilus* & *B. bifidum)*	2 mths	Gut microbiota	No	NA	No
Guida, 2014	Double-blind, RCT	n=30 (87% male) CKD Stage: 3, 4	Synbiotic (Probinul neutro®) - Prebiotic: 6.6g/day (inulin) - Probiotic: $5,7x10^{10}$ CFU/day (*L.plantarum*, *L.casei subsp. Rhamnosus, L.gasseri*, *B.infantis,*	1 mth	Plasma p-cresol	Yes	NA	No

Author, year	Study Design	Participants	Intervention	Time	Primary Outcome Measure	Potential Confounders		
						Assessed Diet	Washout Period	Compliance
			B.longum, *L.acidophilus*, *L.salivarius, L.sporogenes, S.thermophilus)*					
Viramontes-Horner, 2015	Double-blind, RCT	n=35 (91% male) Haemodialysis	Synbiotic (Nutrihealth®): - Prebiotic: 2.3g/day (inulin) - Probiotic: $11x10^6$ CFU/day (*L.acidophilus* NCFM and *B. lactis* Bi-07) - plus: omega-3 and vitamins	2 moths	GI symptoms	Yes	NA	No
Dehghani, 2016	Double-blind, RCT	n=66 (76% male) CKD Stage: 3, 4	Synbiotic (Familact®) - Prebiotic (FOS) - Probiotic: (*L. casei, L. acidophilus, L. bulgarigus, L.rhamnosus, B. breve, B. longum, S. thermophilus)*	6 wks	BUN, serum creatinine, uric acid, CrCl, eGFR	No	NA	No
Rossi, 2016	Double-blind, Crossover RCT	n=21 (62%) CKD Stage: 4, 5 non-dialysed	Synbiotic: - Prebiotic: 15g/day (Inulin, FOS & GOS) - Probiotic: 9×10^{10} CFU/day (9 strains from *Lactobacillus*, *Bifidobacteria,* and *Streptococcus* genera)	6 wks	Serum IS	Yes	Yes	Yes

BUN: blood urea nitrogen; CFU: Colony forming unit; CHO: carbohydrate; CRP: c-reactive protein; FOS: fructooligosaccharide; GFR: glomerular filtration rate; GI: gastrointestinal symptoms; GOS: galactooligosaccharide; HDL-C: high density lipoprotein cholesterol; IAA: Indole 3-acetic acid; IL: interleukin; IS: indoxyl sulfate; LDL-C: low density lipoprotein cholesterol; N: nitrogen NCFM: North Carolina Food Microbiology; PCS: p-cresyl sulfate; PAG: phenylacetylglutamine; PCG: *p*-cresyl glucuronide; TC: total cholesterol; TG: triglycerides; TMAO: trimethylamine N-oxide; TNF-α: tumour necrosis factor α

Table 2: Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of pre- pro- and synbiotic supplementation compared to placebo in patients with chronic kidney disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			**Relative (95% CI)**	**Absolute (95% CI)**		
Urea (follow up: range 4 weeks to 24 weeks; assessed with: mmol/L)												
9	randomised trials	serious [a,b,c,d]	not serious	not serious	serious [e]	none	203	200	-	MD **0.3 lower** (2.2 lower to 1.61 higher)	⊕⊕◯◯ LOW	NOT IMPORTANT
p-cresyl sulphate (follow up: range 4 weeks to 24 weeks; assessed with: mg/dl)												
4	randomised trials	serious [d]	not serious	not serious	serious [e]	none	97	98	-	MD **0.13 lower** (0.41 lower to 0.15 higher)	⊕⊕◯◯ LOW	NOT IMPORTANT
Indoxyl Sulphate (follow up: range 4 weeks to 24 weeks; assessed with: mg/dl)												
4	randomised trials	serious [d]	not serious	not serious	serious [f]	none	97	98	-	MD **0.02 lower** (0.09 lower to 0.05 higher)	⊕⊕◯◯ LOW	NOT IMPORTANT
eGFR (follow up: range 4 weeks to 6 weeks; assessed with: mL/min/1.73m2)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomised trials	not serious	not serious	not serious	serious [e]	none	92	96	-	MD **0.34 higher** (2.2 lower to 2.89 higher)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Weight (follow up: range 4 weeks to 24 weeks; assessed with: kg)												
7	randomised trials	serious [a,b,c,g]	not serious	not serious	serious [e]	none	226	233	-	MD **0.4 higher** (0.95 lower to 1.74 higher)	⨁⨁◯◯ LOW	NOT IMPORTANT
Blood Glucose (follow up: range 4 weeks to 12 weeks; assessed with: mg/dl)												
2	randomised trials	not serious	serious [h]	not serious	serious [e]	publication bias strongly suspected [i]	70	70	-	MD **0.33 lower** (7.17 lower to 6.5 higher)	⨁◯◯◯ VERY LOW	NOT IMPORTANT
Triglycerides (follow up: range 6 weeks to 12 weeks; assessed with: mg/dl)												
3	randomised trials	serious [a,b,c,g]	not serious	not serious	serious [e]	publication bias strongly suspected [i]	130	133	-	MD **1.57 lower** (22.56 lower to 19.42 higher)	⨁◯◯◯ VERY LOW	NOT IMPORTANT
Cholesterol (follow up: range 6 weeks to 12 weeks; assessed with: mg/dl)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomised trials	serious [a,b,c,g]	serious [h]	not serious	serious [e]	none	130	133	-	MD **4.88 lower** (14.43 lower to 4.68 higher)	⊕◯◯◯ VERY LOW	NOT IMPORTANT
LDL Cholesterol (follow up: range 6 weeks to 12 weeks; assessed with: mg/dl)												
3	randomised trials	serious [a,b,c,g]	serious [h]	not serious	serious [e]	none	130	133	-	MD **11.76 lower** (15.15 lower to 8.36 lower)	⊕◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **MD:** Mean difference **a.** Insufficient information about sequence generation **b.** Insufficient information about allocation concealment **c.** Selective reporting likely **d.** A number of included studies did not control for dietary changes nor assess participants dietary intake **e.** Small participant numbers and wide CI suggests both benefit and no benefit **f.** Small participant numbers **g.** Blinding was not adequate **h.** Significant heterogeneity I^2>50% **i.** Publication bias suspected

Legends to Figures

Figure 1: Study selection for pre- pro- and synbiotic literature review in CKD

Figure 2: Effects of pre- pro- and synbiotic supplementation on serum urea (mmol/L) in patients with CKD.

Figure 3: Effects of pre- pro- and synbiotic supplementation on serum urea (mmol/L), by CKD stage.

Figure 4: Risk of bias summary across the included studies. Unclear risk of bias: "?", Low risk of bias: "+", High risk of bias: "-"

Figures

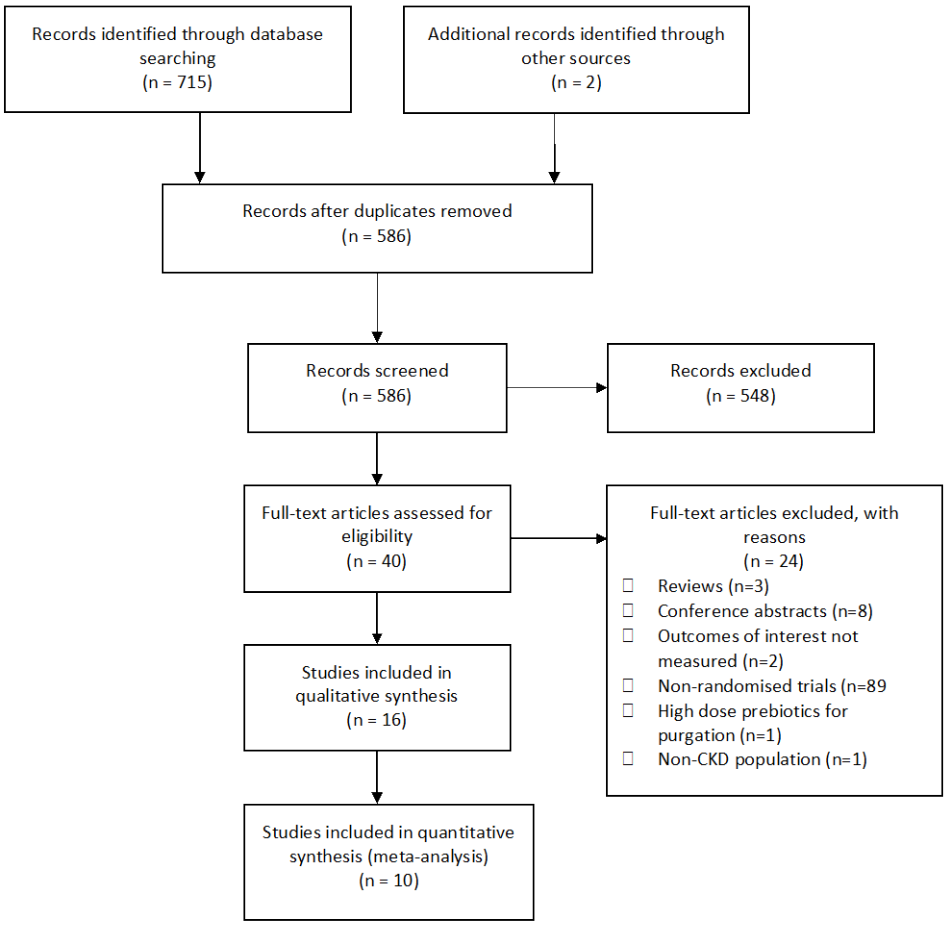


Figure 1: Flow chart describing pre- pro- and synbiotic study selection

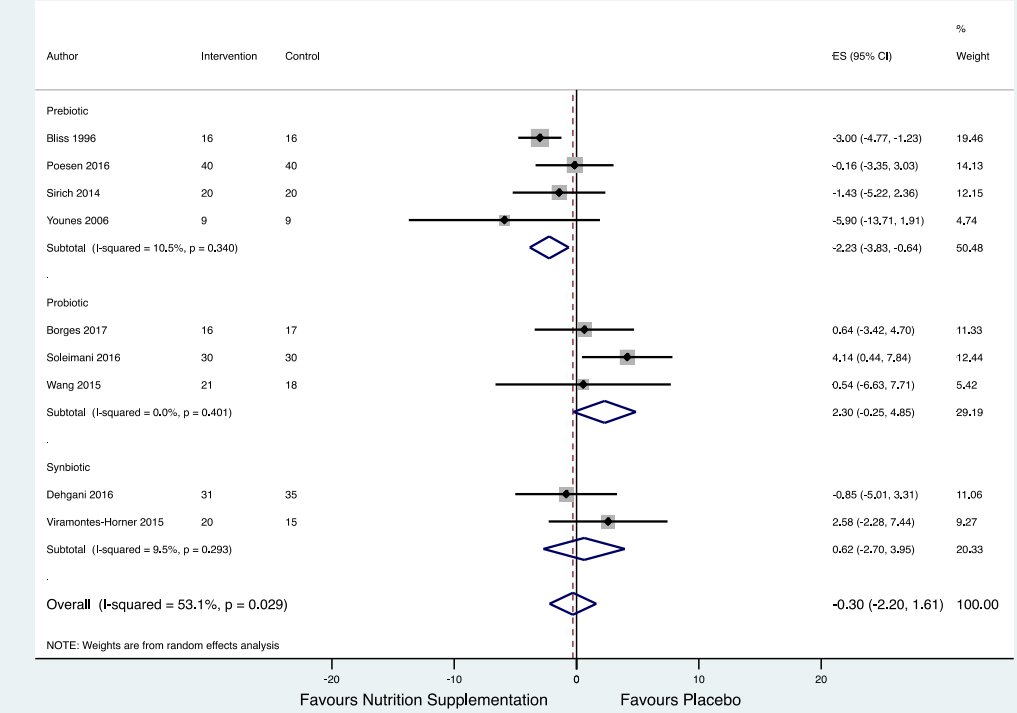


Figure 2: Effects of pre- pro- and synbiotic supplementation on serum urea (mmol/L) in patients with CKD. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.

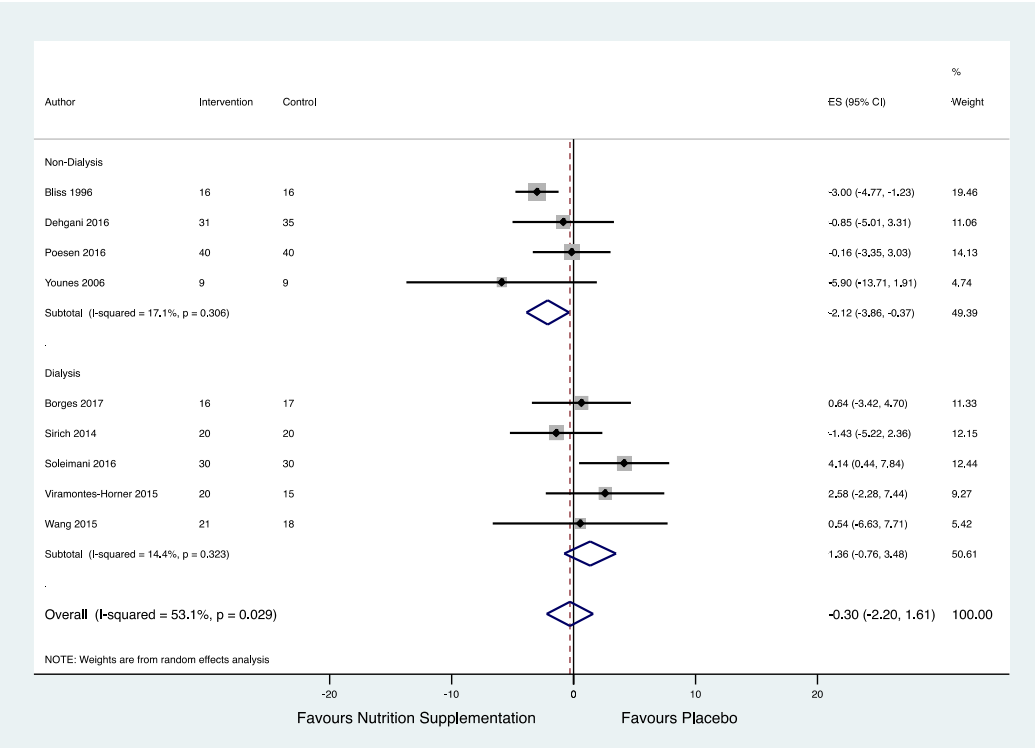


Figure 3: Effects of pre- pro- and synbiotic supplementation on serum urea (mmol/L), by CKD stage. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.

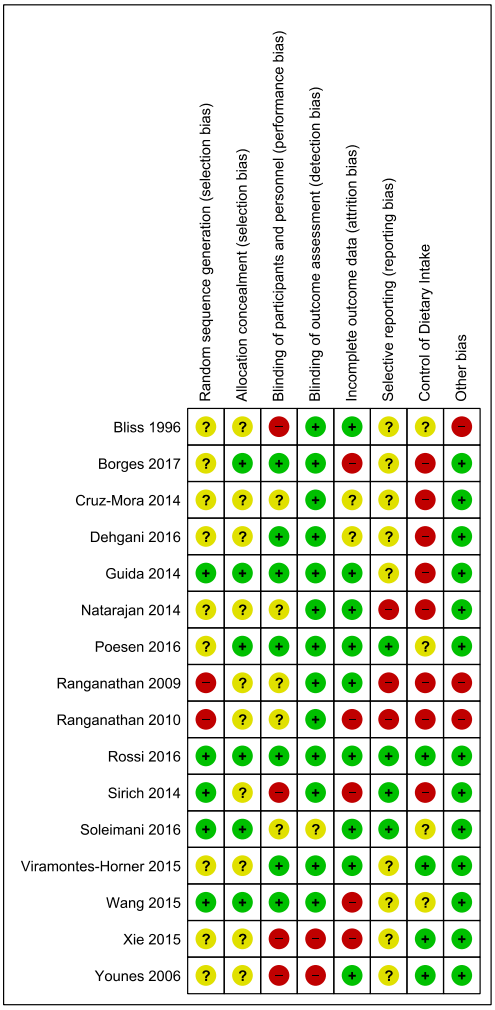


Figure 4: Risk of bias summary across the included studies. Unclear risk of bias: "?", Low risk of bias: "+", High risk of bias: "-"

Legends to Supplementary Figures

*Supplementary Figure 1: Effects of pre-, pro- and synbiotic therapy on eGFR(*mL/min/1.73m^2*) in the CKD population.*

*Supplementary Figure 2: Effects of pre-, pro- and synbiotic therapy on serum urea concentrations (*mmol/L*) in the CKD population.*

Supplementary Figure 3: Effects of pre-, pro- and synbiotic therapy on serum IS (mg/dL) in the CKD population.

Supplementary Figure 4: Effects of pre-, pro- and synbiotic therapy on serum PCS (mg/dL) in the CKD population.

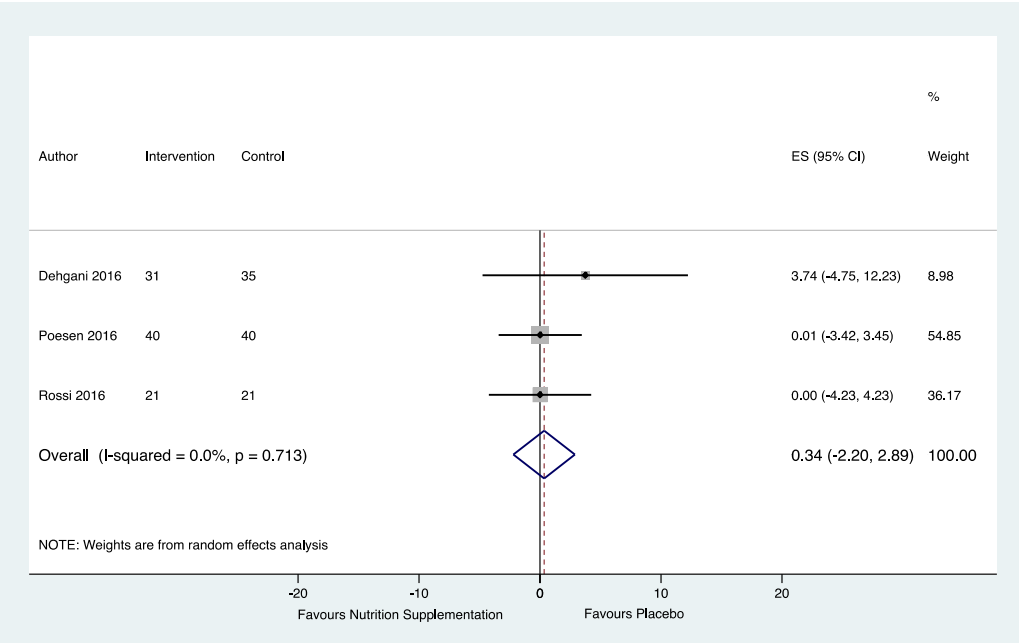
*Supplementary Figure 5: Effects of pre-, pro- and synbiotic therapy on BGL (*mg/dL*) in the CKD population.*

*Supplementary Figure 6: Effects of pre-, pro- and synbiotic therapy on weight (*kg*) in the CKD population.*

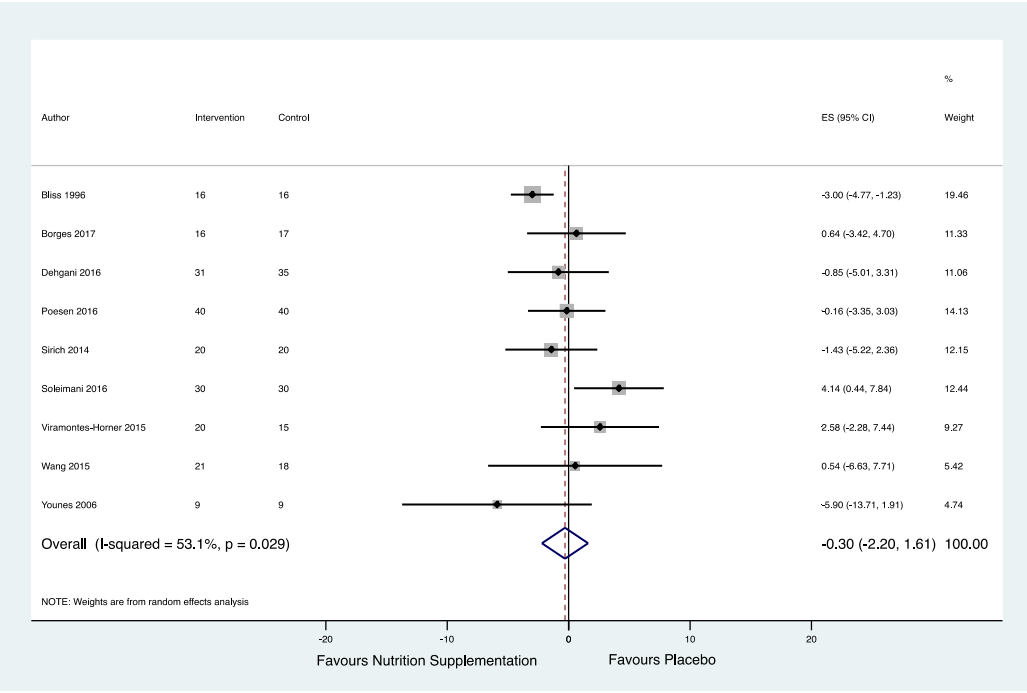
*Supplementary Figure 7: Effects of pre-, pro- and synbiotic therapy on total cholesterol levels (*mg/dL*) in the CKD population.*

*Supplementary Figure 8: Effects of pre-, pro- and synbiotic therapy on LDL cholesterol levels (*mg/dL*) in the CKD population.*

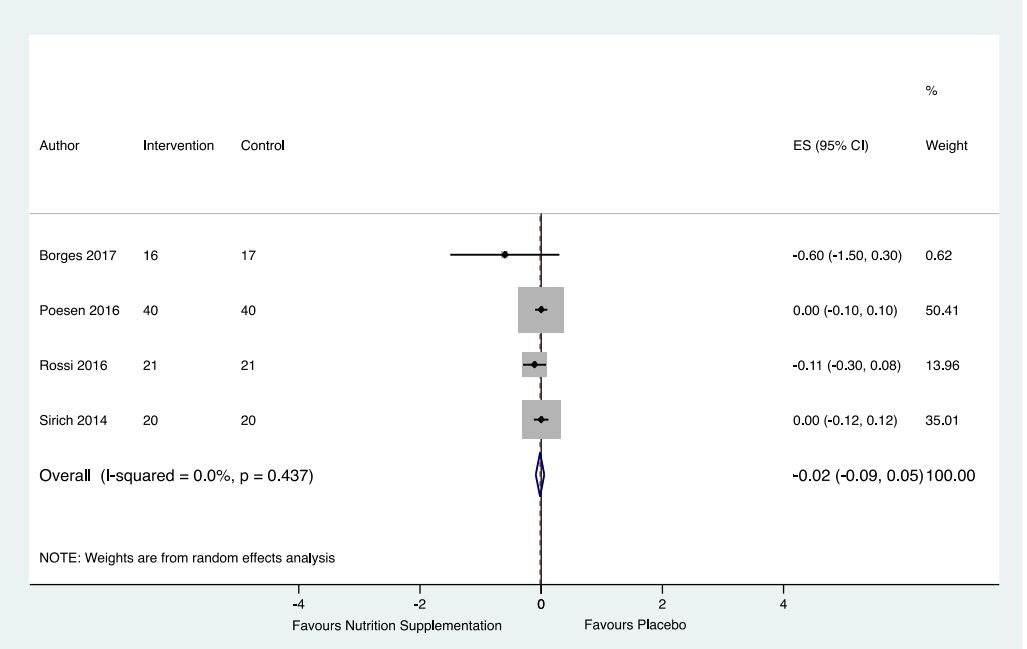
*Supplementary Figure 9: Effects of pre-, pro- and synbiotic therapy on triglyceride levels (*mg/dL*) in the CKD population.*



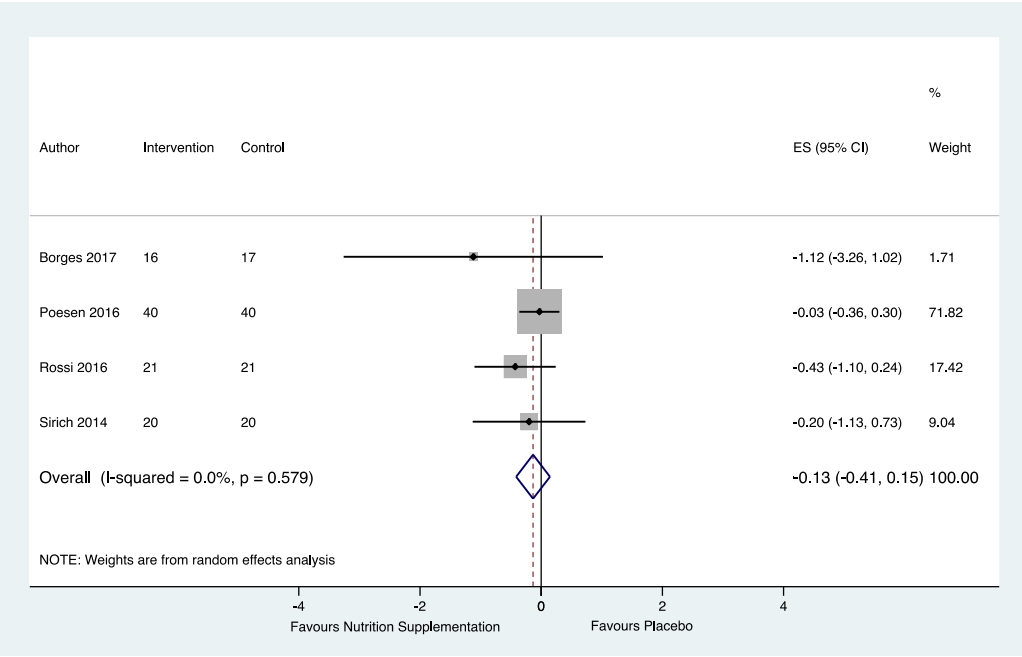
*Supplementary Figure 1: Effects of pre-, pro- and synbiotic therapy on eGFR(*mL/min/1.73m^2*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*



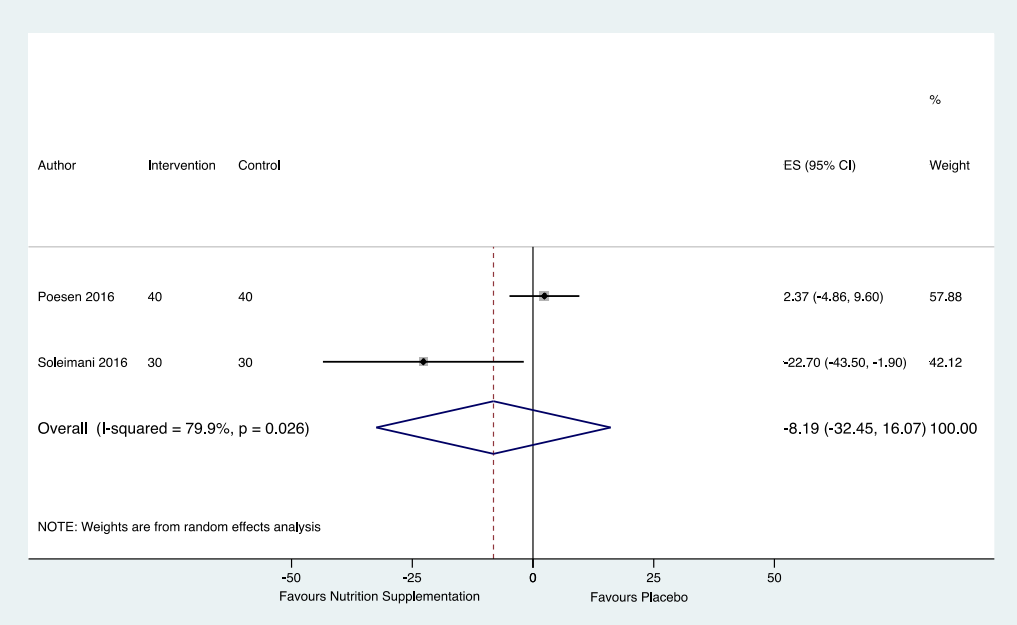
*Supplementary Figure 2: Effects of pre-, pro- and synbiotic therapy on serum urea concentrations (*mmol/L*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*



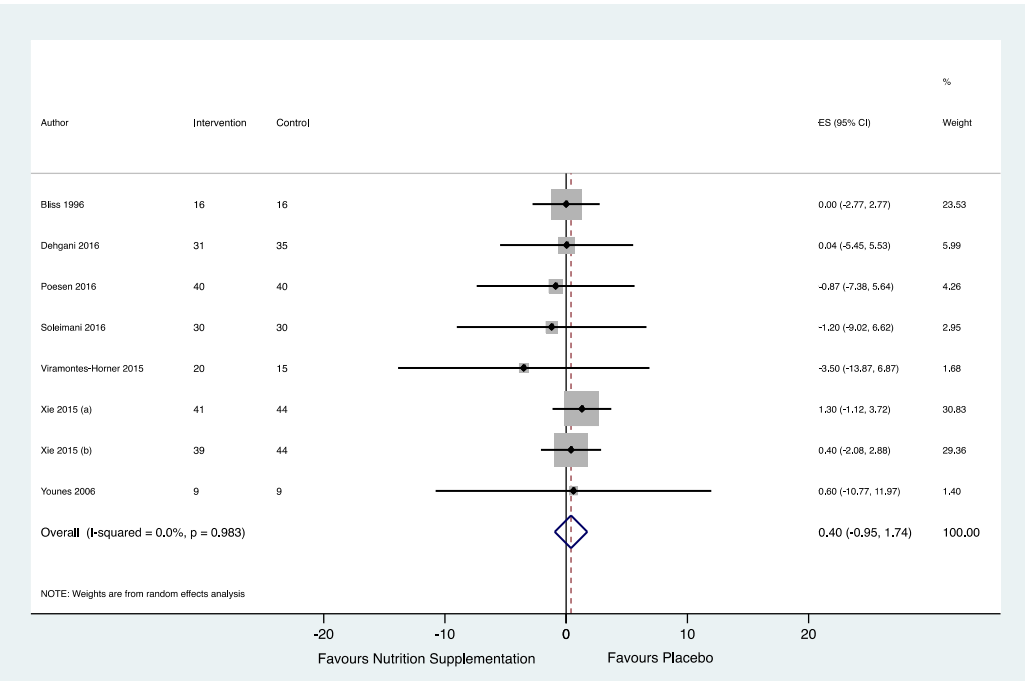
Supplementary Figure 3: Effects of pre-, pro- and synbiotic therapy on serum IS (mg/dL) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.



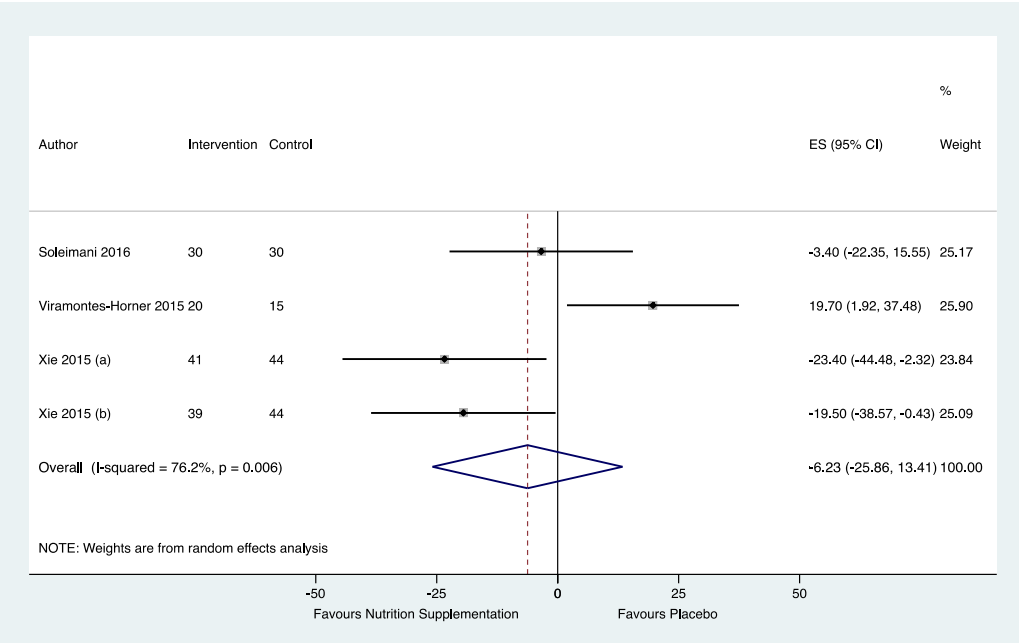
Supplementary Figure 4: Effects of pre-, pro- and synbiotic therapy on serum PCS (mg/dL) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.



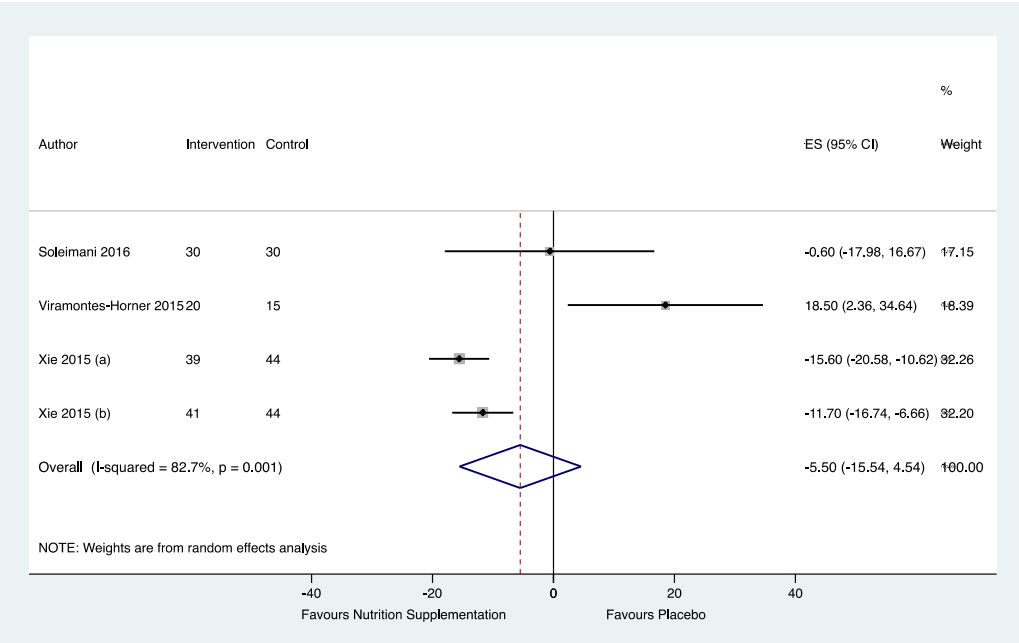
*Supplementary Figure 5: Effects of pre-, pro- and synbiotic therapy on BGL (*mg/dL*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*



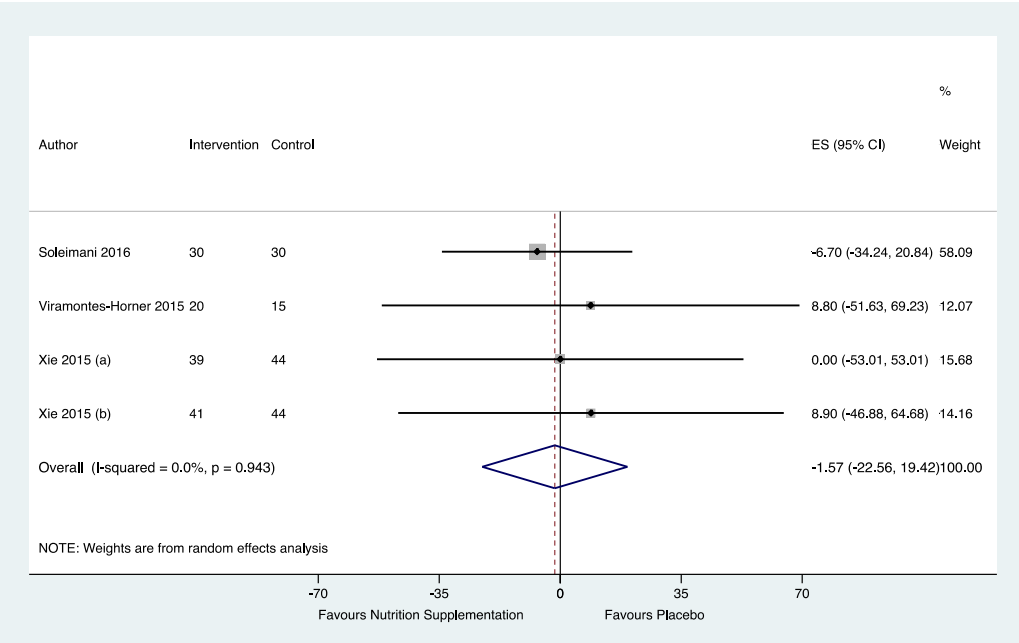
*Supplementary Figure 6: Effects of pre-, pro- and synbiotic therapy on weight (*kg*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*



*Supplementary Figure 7: Effects of pre-, pro- and synbiotic therapy on total cholesterol levels (*mg/dL*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*



*Supplementary Figure 8: Effects of pre-, pro- and synbiotic therapy on LDL cholesterol levels (*mg/dL*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*



*Supplementary Figure 9: Effects of pre-, pro- and synbiotic therapy on triglyceride levels (*mg/dL*) in the CKD population. The means and SDs of changes from baseline are reported for trials. Effects of trials are presented as weights (percentages) and mean differences (95%CIs). IV, inverse variance.*