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PLEASE CITE THE PUBLISHED VERSION

<https://doi.org/10.1053/j.jrn.2019.07.006>

PUBLISHER

Elsevier

VERSION

AM (Accepted Manuscript)

PUBLISHER STATEMENT

This paper was accepted for publication in the journal Journal of Renal Nutrition and the definitive published version is available at <https://doi.org/10.1053/j.jrn.2019.07.006>.

LICENCE

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REPOSITORY RECORD

March, Daniel S., A.W. Jones, Nicolette Bishop, and James O. Burton. 2019. "The Efficacy of Prebiotic, Probiotic and Synbiotic Supplementation in Modulating Gut-derived Circulatory Particles Associated with Cardiovascular Disease in Individuals Receiving Dialysis: A Systematic Review and Meta-analysis of Randomized Controlled Trials". Loughborough University. <https://hdl.handle.net/2134/38307>.

The efficacy of oral prebiotic, probiotic and synbiotic supplementation in modulating gut derived circulatory toxic particles associated with cardiovascular disease in individuals receiving dialysis: a systematic review and meta-analysis of randomised controlled trials

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Word Count: 3,701

Short Title: Supplementation in individuals receiving dialysis

Acknowledgements

This work falls under the portfolio of research conducted within the NIHR Leicester Biomedical Research Centre. Approval has been obtained from all authors prior to submission.

Authors' Contributions

DSM and JOB developed the review topic. DSM and AWJ designed and developed the topic protocol. DSM and AWJ coordinated the review process. DSM and AWJ conducted the trial searches, screened the search results, assessed the trials for quality, extracted the data and analysed the data. DSM, AWJ, JOB and NCB prepared the manuscript. All authors reviewed final manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Abstract

Background: There is accumulating evidence that modification of the microbiota through prebiotic, probiotic or synbiotic supplementation in individuals with end-stage renal disease receiving dialysis may be efficacious in reducing circulating levels of toxic metabolites. This systematic review and meta-analyses provides an up to date synthesis on the effects of supplementation on circulating levels of toxic metabolites, markers of uremia and inflammation, blood lipids and other clinical outcomes. **Methods:** Seventeen databases were searched, supplemented with internet and hand searching. Randomised controlled trials of adult end stage renal-disease individuals receiving either haemodialysis or peritoneal dialysis were eligible. Trials were restricted to those which had administered a prebiotic, probiotic or synbiotic as an oral supplement. Primary outcomes were measures of circulating endotoxin, indoxyl-sulphate and p-cresyl sulphate. **Results:** Twenty-one trials were eligible (1152 randomised participants) of which 16 trials were considered to have a high risk of bias. The number of trials available for meta-analysis varied for each primary outcome. Synthesised data indicated that supplementation significantly reduced circulating levels of endotoxin (standardised mean difference -0.61, 95% confidence interval -1.03 to -0.20, $P=0.004$, $I^2=0\%$), indoxyl-sulphate (-0.34, -0.64 to -0.04, $P=0.02$, $I^2=0\%$) and p-cresyl sulphate (-0.34, -0.61 to -0.07, $P=0.01$, $I^2=0\%$). For secondary outcomes supplementation significantly reduced gastrointestinal symptoms (-0.54, -1.02 to -0.07, $P=0.02$, $I^2=0\%$). **Conclusions:** Supplementation reduces toxic metabolites associated with cardiovascular disease and mortality in individuals receiving dialysis. However, the majority of trials included were low in quality.

Key words: prebiotic, probiotic, synbiotic, microbiota, end-stage renal disease, systematic-review, meta-analysis

26 **Introduction**

27 Individuals with end- stage renal disease (ESRD) have a significantly increased risk of
28 cardiovascular disease (CVD) ¹, and unsurprisingly this is the leading cause of death in this
29 population ². The risk factors contributing to the excessive rates of CVD in ESRD individuals
30 receiving either haemodialysis or peritoneal dialysis (PD) are not explained by traditional risk
31 factors such as hypertension and diabetes ³. This is believed to be as a result of the different
32 pathophysiological processes that drive CVD in this population. Therefore, targeting the non-
33 traditional risk factors (such as systemic inflammation ⁴) that are specific to chronic kidney
34 disease (CKD) may be more efficacious in lowering risk in this population.

35 There is accumulating evidence that dialysis results in a number of unique factors that can
36 alter both the microbiota and the integrity of the intestinal barrier ⁵. This results in an increase
37 of circulatory toxic metabolites (such as endotoxin, indoxyl-sulphate and p-cresyl-sulphate)
38 associated with systemic inflammation, CVD risk and mortality ^{6, 7}. There is some evidence
39 that attempting to modify the microbiota through supplementation of prebiotics, probiotics or
40 synbiotics may prove efficacious in improving outcomes in the ESRD population ⁵. To date,
41 there have been some systematic reviews and meta-analyses that have synthesised data
42 investigating the effect of prebiotic, probiotic and synbiotic interventions on circulating toxic
43 metabolites and inflammation (although not circulating endotoxin) in this population ⁸⁻¹².
44 However these reviews are limited by the fact that they have pooled randomised and non-
45 randomised trials together ¹¹, not performed a meta-analysis ⁸, or pooled individuals with
46 CKD receiving and not receiving dialysis ^{9, 10}. Lastly and most notably there has been a
47 number of recent experimental investigations in the area ¹³⁻²⁰. Therefore, the primary aim of
48 this systematic review is to provide an up-to date assessment of the efficacy and safety of

prebiotic, probiotic and synbiotic oral supplementation in reducing circulating endotoxin, indoxyl-sulphate and p-cresyl sulphate in ESRD individuals receiving haemodialysis and PD.

Methods

Protocol Registration

Methods of analysis and inclusion criteria were specified in advance and documented in a protocol that was registered on PROSPERO (International Prospective Register of Systematic Reviews; www.crd.york.ac.uk/PROSPERO/) with identifier CRD42018097032.

Settings and Trial Population

Participants

Participants with ESRD over the age of 18 years who are receiving either prevalent (for at least 3 months) haemodialysis or PD.

Intervention

Any prebiotic, probiotic or synbiotic oral supplement.

Comparison

Any concurrent control group who is receiving a placebo or not receiving an intervention aimed to modulate the gut microbiota.

Outcome

Primary outcome measures included circulatory endotoxin, indoxyl-sulphate and p-cresyl sulphate. Secondary outcome measures included any other gut derived biomarker (associated with cardiovascular risk), circulatory biomarkers of inflammation (e.g. interleukins (IL), C-reactive protein (CRP), tumour necrosis factor alpha (TNF- α)), circulatory markers associated with uremia (blood urea nitrogen, creatinine, potassium), circulating blood lipids

(triglyceride, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol) and clinical outcomes (adverse events, gastrointestinal symptoms and cardiovascular events).

Trial Design

Trials included in this review had to have adhered to the following trial designs: parallel-group randomised controlled trials (allocation at individual or cluster level or using a quasi-randomised method) or crossover randomised controlled trials.

Search Strategy

Searches were conducted to identify any relevant completed or ongoing systematic reviews using the following sources: Cochrane Database of Systematic Reviews, PROSPERO, the National Health Service Centre for Reviews and Dissemination: Database of Abstracts of Reviews of Effects (DARE). The following bibliographic databases were searched for completed and ongoing trials: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, Current Controlled Trials, UK Clinical Trials Gateway, WHO International Clinical Trials Registry Platform, the National Health Service Centre for Reviews and Dissemination: Health Technology Assessment (HTA). British Library (ETHOS), DART Europe E theses, OpenGrey, The New York Academy of Medicine and ProQuest Dissertations and Theses, and Conference Proceedings Citation Index (Web of Science™ Core Collection) were searched for obtaining non-published data. All databases were searched from inception to April 2019 and no limits on language was set. Database searches were supplemented with internet searches (e.g. Google Scholar), forward and backward citation tracking of included trials, and contact with experts and research groups. An example of a full search strategy for the MEDLINE database is presented in Supplementary Table 1. Search results were compiled using EndNote (Clarivate Analytics,

Philadelphia, PA, USA). Duplicate citations were removed, and titles and abstracts screened independently by two reviewers (DSM and AWJ) against the inclusion criteria. Full-text articles of trials not excluded based on title or abstract were retrieved and assessed by two reviewers (DSM and AWJ). **Conference abstracts were included and authors were contacted in order to obtain full trial details and data.**

Selection Criteria, Data extraction and Quality Appraisal

We developed, tested and refined a structured data collection form based on the Cochrane Data Extraction Template for interventions. For each included trial, two reviewers (DSM and AWJ) extracted information on trial methods, participants, intervention/comparator and outcomes, which were cross-checked for accuracy. Two reviewers (DSM and AWJ) independently assessed the risk of bias for each trial using the Cochrane Risk of Bias Tool across five domains²¹. Each domain was classified as adequate, unclear, or inadequate, with risk of bias for each trial to be classified using the following criteria: (a) low risk of bias (all criteria are deemed adequate), (b) moderate risk of bias (one criterion graded as inadequate or two graded as unclear), and (c) high risk of bias (more than one criterion is deemed inadequate, or more than two graded unclear).

Analytical Approach

Where means and standard deviation of outcome measures were neither reported or not available from trial authors^{17, 18, 22, 23}, they were estimated from medians and interquartile ranges^{24, 25}. A meta-analysis was performed for trials that reported the same outcome measures using a generic inverse variance random-effects method via Review Manager version 5.3²⁶. Primary and secondary measures of efficacy were treated as continuous data and interpreted as standardised mean differences. Data pertaining to adverse events were narratively synthesised. Analysis was based upon final (post-intervention) values only, with the exception of circulating

blood lipids (triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol) which were based on a change from baseline score²¹ as a result of considerable baseline imbalances between groups. One trial (two reports)^{13, 14} had two intervention and one placebo group, therefore the placebo group was halved to avoid double counting²¹. In trials²⁰ where outcome data was only presented in graphical format, and authors could not be contacted, data was extracted using WebPlotDigitizer Version 4.2²⁷. Statistical heterogeneity was assessed by the I^2 value. Data were not pooled if $I^2 > 40\%$ (this is the threshold to which heterogeneity is considered unimportant²¹). **Subgroup analysis on the primary outcomes only (endotoxin, indoxyl-sulphate and p-cresyl-sulphate) for type of trial (individual, cluster or crossover randomised controlled trial), and intervention type (prebiotic, probiotic or synbiotic administration) was planned.** To test the robustness of findings in primary outcome measures, pre-specified sensitivity analysis removed trials categorised as medium or high risk of bias using the Cochrane Risk of Bias Tool.

Results

Characteristics of Included Trials

Figure 1 provides a flow diagram of trial selection. Twenty-one trials, available as twenty-four reports were eligible (1152 randomised participants) for the review (see Table 1). Three conference abstracts were included²⁸⁻³⁰ with data for gastrointestinal symptoms provided by the authors from one of these trials³⁰. Intervention duration ranged from 2-24 weeks. All trials included adult participants with ESRD, with eighteen^{13-20, 23, 28-39} involving participants receiving haemodialysis, and three trials including participants receiving PD^{22, 40, 41} (Table 1). Seven trials tested prebiotics^{18, 30, 31, 35, 37, 40, 41} seven trials tested probiotics^{15, 17, 22, 29, 33, 34, 36, 39}, while six trials tested synbiotics^{16, 19, 20, 23, 28, 32, 38}, and one trial^{13, 14} tested both probiotics

and synbiotics. Eighteen trials were parallel-group randomised controlled trials, while three were randomised controlled crossover trials (Table 1).

Risk of Bias

Risk of bias summaries are provided in Figure 2. The three included conference abstracts²⁸⁻³⁰ were not included in the risk of bias assessment due to insufficient published detail on trial methodology. All trials with the exception of two^{16, 36} were rated as either moderate or high risk of bias. Consequently our pre-specified sensitivity analysis was not possible.

Primary Outcomes

Synthesised data from two trials^{14, 22} (104 participants) indicated that probiotic and synbiotic supplementation significantly reduced circulating levels of endotoxin (standardised mean difference, -0.61, 95% confidence interval -1.03 to -0.20, $P=0.004$, $I^2=0\%$) (Figure 3). A significant reduction in endotoxin (-0.53, -0.98 to -0.09, $P=0.02$, $I^2=0\%$) was still observed for probiotic data only^{14, 22}. For indoxyl-sulphate, data for synthesis was unavailable from three trials due to insufficient reporting^{28, 29, 33}. Therefore, four randomised controlled trials^{18, 20, 35, 39} (175 participants) including prebiotic^{18, 35}, probiotic³⁹ and synbiotic²⁰ supplementation were meta-analysed and indicated a significant reduction (-0.34, -0.64 to -0.04, $P=0.02$, $I^2=0\%$) (Figure 4). Prebiotic trials only (^{18, 35}, 84 participants) showed a non-significant reduction (-0.17, -0.60 to 0.26, $P=0.44$, $I^2=0\%$). Six trials^{15, 18, 20, 33, 35, 39} reported measurement of p-cresyl sulphate (indirectly quantified as p-cresol in two trials^{15, 37}). Five randomised controlled trials (217 participants) (prebiotic^{18, 35}, probiotic^{15, 39} and synbiotic²⁰ supplementation) included for meta-analyses indicated a significant reduction in circulating p-cresyl sulphate (-0.34, -0.61 to -0.07, $P=0.01$, $I^2=0\%$) (Figure 5). A significant reduction was seen with probiotic data (^{15, 39}, 75 participants) (-0.55, -1.01 to -0.09, $P=0.02$, $I^2=0\%$) but not prebiotic (^{18, 35}, 84 participants) (-0.21, -0.64 to 0.22, $P=0.34$, $I^2=0\%$).

Secondary Outcomes

Other circulating gut derived toxic metabolites

One trial reported data for circulating trimethylamine n-oxide ¹⁷. Probiotic supplementation resulted in a non-significant increase (0.19, -0.67 to 1.05, $P=0.67$).

Circulating markers of inflammation

Fourteen trials (15 records) reported measurement of CRP ^{14, 16-19, 23, 28, 29, 33-39}. Data from four trials could not be included in a meta-analysis as a result of insufficient reporting ^{28, 29, 33, 38}. Substantial heterogeneity ($I^2=69\%$) was present among the remaining ten trials (502 participants) ^{14, 16, 18, 19, 23, 34-37, 39}, therefore a meta-analysis was deemed inappropriate. Independently, four trials reported no significant change in CRP following supplementation ^{18, 34, 35, 39} whereas significant reductions following prebiotic ³⁷, probiotic ³⁶, and synbiotic supplementation ^{14, 16, 19, 23} were reported in six trials. Six trials reported data for IL-6 ^{14, 22, 23, 37-39}, however there was considerable statistical heterogeneity ($I^2=84\%$) between trials. Four trials reported no change in IL-6 ^{22, 23, 38, 39}, two further trials reported significant reductions following prebiotic ³⁷ and synbiotic ¹⁴ supplementation. No significant changes for IL-5, IL-10, IL-17 ^{22, 38}, or IL-8 ³⁷ were reported. Four trials ^{22, 23, 37, 38} reported data for TNF- α , but there was substantial statistical heterogeneity between trials $I^2=82\%$ with data for synthesis ^{22, 23, 37}. No trial independently reported any significant change in TNF- α .

Circulatory markers associated with uremia

Ten trials reported measurement of blood urea nitrogen ^{18, 22, 23, 28, 29, 31, 33, 35, 36, 40}. Two further trials ^{20, 39} reported urea, data from one ³⁹ was able to be converted to blood urea nitrogen ⁴². Data was unavailable for three trials ^{28, 29, 33} due to insufficient reporting. A randomised controlled crossover trial reported no-significant effect of prebiotic on blood urea nitrogen ⁴⁰. There was substantial heterogeneity ($I^2=64\%$) between the remaining seven trials ^{18, 22, 23, 31, 35,}

^{36, 39} therefore a meta-analysis was deemed inappropriate. None of these trials reported any significant change in circulating blood urea nitrogen. For creatinine, four trials did not report data ^{20, 28, 29, 33}, and a further trial reported no effect following probiotic supplementation ⁴⁰. Data from the five remaining trials ^{18, 22, 23, 36, 39} was heterogeneous ($I^2=47\%$), only one trial ¹⁸ reported any significant changes following supplementation. Three trials did not report data for potassium ^{20, 28, 29}. A randomised controlled crossover trial reported no difference in potassium following probiotic supplementation ⁴⁰. Synthesised data for six trials (244 participants) ^{15, 23, 31, 36, 39, 41}, indicated that prebiotic, probiotic and synbiotic supplementation resulted in a non-significant increase in potassium (0.13, -0.14 to 0.39, $P=0.35$, $I^2=6\%$) (Supplementary Figure 1).

Circulating lipids

One trial ²³ was excluded from the circulating blood lipid analysis as a result of differences in participant numbers reported for baseline and final data. This trial reported no between group significant changes for any circulating lipid ²³. A further trial ²⁹ reported significant reductions in triglyceride, total cholesterol and LDL cholesterol following probiotic supplementation, however could not be included in the analysis due to insufficient reporting. A further randomised controlled crossover trial reported no effect of probiotic supplementation on circulating lipids ⁴⁰. Data from six trials ^{16, 18, 19, 31, 36, 37} (346 participants) indicated that supplementation resulted in no effect on circulating triglyceride (-0.01, -0.22 to 0.20, $P=0.93$, $I^2=0\%$) (Supplementary Figure 2). Five trials ^{16, 18, 19, 36, 37} (293 participants) provided HDL cholesterol data for a meta-analysis and indicated a minimal increase (0.08, -0.15 to 0.31, $P=0.49$, $I^2=0\%$) (Supplementary Figure 3). There was considerable statistical heterogeneity ($I^2=57\%$) between six trials measuring total cholesterol ^{16, 18, 19, 31, 36, 37} and the four remaining trials ^{16, 19, 36, 37} that measured LDL cholesterol ($I^2=81\%$), therefore data was not meta-analysed.

Clinical Outcomes

Ten trials did not report adverse events^{15, 20, 28-32, 34, 37, 38, 41}. Eight trials found no adverse events after prebiotic³⁵ probiotic^{17, 22, 36}, or synbiotic supplementation^{16, 19, 23} or both^{13, 14}. A further trial³³ reported one adverse event which was not related to the trial protocol, and the withdrawal of two patients (7% of trial sample) as a result of nausea and vomiting following probiotic supplementation. For prebiotic supplementation one trial reported minor adverse events following the first few days of supplementation⁴⁰, and a further trial reported one adverse event in the intervention group, which included epigastric pain and vomiting, therefore the participant was withdrawn¹⁸. A trial reported sixteen incidences of gastrointestinal symptoms (diarrhea and constipation were the most common) that required intervention in five participants³¹. Three randomised controlled trials^{18, 35, 36} reported no change in gastrointestinal symptoms following prebiotic^{18, 35}, and probiotic³⁶ supplementation. Two randomised controlled crossover trials reported a significant increase in frequency of defecation over 30 days, and mild flatulence and abdominal discomfort which disappeared after a dose reduction⁴⁰, and flatulence over 4-weeks³⁰ following prebiotic supplementation. Three trials (four reports) investigated the effect of probiotic^{13, 14}, and synbiotic^{13, 14, 23, 32} supplementation on gastrointestinal symptoms using the Gastrointestinal Symptom Rating Scale. Data from one trial²³ (which reported a significant reduction in symptoms following 2-months of supplementation) could not be synthesised due to insufficient reporting. The remaining trials^{13, 14, 32} (83 participants) indicated a significant reduction in Gastrointestinal Symptom Rating Scale Total Score (-0.54, -1.02 to -0.07, $P=0.02$, $I^2=0\%$) (Supplementary Figure 4). One trial reported no cardiovascular events in either the placebo or probiotic groups over a six-month supplementation period²².

Discussion

This systematic review and meta-analysis assessed the evidence for prebiotic, probiotic and symbiotic supplementation in individuals receiving dialysis. The main findings of this review

were that supplementation reduces levels of endotoxin, indoxyl-sulphate, p-cresyl sulphate and has favourable effects on gastrointestinal symptoms. The majority of trials included in the review were considered to be at high risk of bias (primarily due to lack of allocation concealment and blinding of outcome assessment).

Five recent systematic reviews have attempted to establish the efficacy of prebiotic, probiotic and synbiotic supplementation on individuals with CKD receiving and not receiving dialysis⁸⁻¹². In contrast to the findings of the present work a recent review reported no significant effect of supplementation on indoxyl-sulphate or p-cresyl sulphate⁹. The discrepancy between the results could be explained by the omission of three recent trials^{15, 18, 20} in the previous review⁹. This review found a significant reduction in gastrointestinal symptoms (measured using the Gastrointestinal Symptom Rating Scale) following supplementation, which is in agreement with the synthesised results of another review¹¹. A previous review found a significant reduction in blood urea nitrogen (reported as urea) following prebiotic supplementation in individuals with non-dialysis dependent CKD⁹, however in concordance with the present results they found no effect following supplementation on levels in dialysis dependent individuals⁹. Despite a number of recent trials assessing the effect of prebiotics, probiotics and synbiotics on blood lipids^{16, 18, 19} this work and another recent review⁹ found no effect of supplementation.

In contrast to recent reviews for this topic, the current review focussed solely on randomised controlled trials in participants with ESRD receiving dialysis. This patient population has a number of unique factors that may disrupt the microbiota and intestinal barrier⁵, therefore interventions that target the microbiota may have different effects compared to other populations (e.g. individuals with CKD not receiving dialysis). This review is also strengthened by the inclusion of a number of recent investigations in the area¹³⁻²⁰. Moreover, we have reported the effects of supplementation on circulating toxic metabolites (endotoxin,

indoxyl-sulphate and p-cresyl sulphate) that have been associated with hard endpoints such as cardiovascular events and all-cause mortality⁴³⁻⁴⁵ in this population.

It is important, however, to highlight that most of the included trials within this review were small and underpowered to detect true differences, with only five of the included trials reporting any *a priori* sample size calculation^{15, 16, 18, 20, 36, 38}. Despite the inclusion of twenty-one trials in the review, **there was only a small number included in the meta-analyses for the primary outcomes of endotoxin, indoxyl-sulphate and p-cresyl sulphate (two, four and five trials respectively).** In addition, data for CRP, IL-6, TNF- α , blood urea nitrogen, creatinine, total cholesterol and LDL cholesterol were not synthesised as a result of significant statistical heterogeneity, indicating clinical or methodological diversity (or both) between trials. Whilst antibiotic consumption immediately prior to enrolling in many of the trials was stated as an exclusion criteria, only three trials^{19, 34, 35} actively recorded consumption during the supplementation period. Lastly eleven included trials (thirteen reports) measured adverse events (^{13, 14, 16-19, 22, 23, 33, 35, 36, 39, 40}). The majority reported that supplementation was not associated with adverse events, although they provided limited information around how events were monitored, and many of the included trials are likely underpowered to assess this outcome. Future trials should implement better recording of adverse events to inform safety.

The finding that supplementation reduces circulating levels of endotoxin, indoxyl sulphate and p-cresyl sulphate has clinical importance. Endotoxin is contained within the outer cell wall of complex lipopolysaccharides⁴⁶, and can translocate across the intestinal barrier into the central circulation, initiating an inflammatory response⁴⁷. Indoxyl-sulphate and p-cresyl sulphate are uraemic toxins and are primarily produced from intestinal anaerobic bacteria, it has previously been demonstrated that individuals with ESRD have an expansion of this family of bacteria⁴⁸, moreover p-cresyl sulphate is poorly removed by the HD process⁴⁹. Levels of both endotoxin and p-cresyl sulphate have both been associated with cardiovascular

events and all-cause mortality in this population ⁴³⁻⁴⁵, although it is worthy of note that the precise nature of this relationship is unclear. Interestingly, the effect of prebiotic supplementation alone on indoxyl-sulphate and p-cresyl sulphate was not significant, this may be explained by the different mechanisms of effect compared to probiotics ⁵⁰. A reduction in gastrointestinal symptoms observed in this review has importance as there has been shown to be a high prevalence of gastrointestinal symptoms (measured using the Gastrointestinal Symptom Rating Scale) in individuals with ESRD, and such symptoms are negatively associated with psychological well-being ⁵¹. Only one of the included trials recorded cardiovascular events ²², none were reported for the duration of the trial. Assessing the relationship between prebiotic, probiotic and synbiotic supplementation and cardiovascular events may not be pragmatic as large sample sizes and long follow-up will be required. Therefore, the assessment of surrogate markers of cardiovascular risk (such as endotoxin and p-cresyl sulphate) may be more feasible, although exactly how these markers interact with hard end-points is currently not clear.

Practical Application

There is evidence that supplementation with prebiotics, probiotics and synbiotics in individuals receiving dialysis may reduce circulating levels of toxic metabolites associated with cardiovascular disease and mortality. Furthermore, this review demonstrated favourable effects on gastrointestinal symptoms with no apparent safety concerns. However, the majority of included evidence was considered to have a high risk of bias. Further high quality trials (including sample size calculation, robust random sequence generation, allocation concealment and blinding of trial personnel, participants and outcome assessment), and adequate reporting of these investigations may be appropriate.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1. Characteristics of included trials

Trial	Type of trial	Participants	Haemodialysis or Peritoneal Dialysis.	Sample Size (<i>n</i> randomised)	Dialysis Vintage	Type of Intervention (Prebiotic, Probiotic, Synbiotic)	Strain of Prebiotic/Probiotic/Synbiotic	Type of Comparison	Intervention (method of delivery, dose, frequency, duration)	Compliance
Birute et al., 2017 (conference abstract)	Randomised controlled crossover trial.	(Participants analysed). Age (mean $\pm$ SD): 55 $\pm$ 10 years. Sex: 50% Male.	Haemodialysis.	<i>n</i> =12.	Not reported.	Prebiotic	Inulin	Maltodextrin.	2 x 4 weeks of supplementation separated by a 4 week washout period.	Not reported.
Borges et al., 2018a & 2018b	Randomised controlled trial.	(Participants analysed). Age (mean $\pm$ SD): Intervention: 53.6 $\pm$ 11 years. Placebo:	Haemodialysis.	Intervention: <i>n</i> =23. Placebo: <i>n</i> =23.	Intervention (mean (95% CI)): 60 (38.2-105) months. Placebo: 36.5	Probiotic	90 billion colony-forming units (CFU) per day. Including the following strains: Streptococcus thermophilus, Lactobacillus acidophilus, and Bifidobacteria longum.	The placebo was composed of wheat germ.	The dosage was 3 capsules of probiotic or placebo per day for 3 months.	Adherence was high with 82% of patients (placebo and probiotics) consuming more than

		50.3 ± 8.5 years. Sex: Intervention: n=11 Males, n=5 Females. Placebo: n=10 Males. n=7 Females.			(24.2-72) months.					80% of the capsules.
Cockram et al., 1998	Randomised controlled trial.	(Participants randomised). Age (mean ± SEM): Intervention: 46 ± 2 years. Placebo: 53±3 years. Sex: Intervention: 59% Males. Placebo: 54% Males.	Haemodialysis.	Intervention: n=26. Placebo: n=27.	Intervention ((mean (range)): 7 (2-26) years. Placebo: 8 (1-18) years.	Prebiotic	Fructooligosaccharides and B-carotene-containing product.	"Standard" medical nutritional formulations.	14 days. "Was consumed as a sole source of nutrition". Liquid formula. "Orally administered".	Not reported.

Cruz-Mora et al., 2014	Randomised controlled trial.	(Participants randomised). Age (mean $\pm$ SD): Intervention: 46 ± 2 years. Placebo: 53 ± 3 years. Sex: Intervention: 50% Males. Placebo: 59% Males.	Haemodialysis.	Intervention: $n=18$. Placebo: $n=10$.	Intervention (mean $\pm$ SD): 5.7 ± 3.2 years. Placebo: 4.1 ± 2.2 years.	Synbiotic	The symbiotic gel (Nutrihealth) contained a mix of probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum), for total as probiotic of 2.0×10^{12} CFU; 2.31 g of a prebiotic fiber (inulin); 1.5 g of omega 3 fatty acids (eicosapentaenoic and docosahexaenoic acid) and vitamins (complex B, folic acid, ascorbic acid, and vitamin E).	The placebo was a gel without prebiotic fiber, probiotics, omega 3 fatty acids, and vitamins. It had identical color, size, and flavor to the intervention product (symbiotic gel).	2 months.	Not reported.
Eidi et al., 2018	Randomised controlled trial.	(Participants analysed). Age (mean $\pm$ SD): Intervention: 57.05 ± 13.95 years. Placebo: 59.67 ± 15.04 years.	Haemodialysis.	Intervention: $n=30$. Placebo: $n=30$.	Intervention ((median (25%-75% percentile))): 18 (11-48) months. Placebo: 24 (6-54) months.	Probiotic	One capsule contained 1.6×10^7 CFU of Lactobacillus Rhamnosus.	One placebo capsule per day of Infant formula after meal for 28 days.	28 days. One capsule after meal.	Not reported.

Sex:
Intervention: *n*=15
Males.
Placebo:
n=17
Males.

Haghighat et al., 2018 & 2019.	Randomised controlled trial.	(Participants analysed). Age (mean $\pm$ SD): Intervention: 46.21 $\pm$ 11 years, Probiotic: 48.04 $\pm$ 10 years. Placebo: 45.47 $\pm$ 10 years. Sex: Intervention: Probiotic: <i>n</i> =12 Males. Synbiotic: <i>n</i> =12 Males.	Haemodialysis.	Intervention: Probiotic: <i>n</i> =25. Synbiotic: <i>n</i> =25. Placebo: <i>n</i> =25.	Intervention: Probiotic: 6-23 months: <i>n</i> =5, 24-59 months: <i>n</i> =5, 60-120 months: <i>n</i> =13 months. Synbiotic: 6-23 months: <i>n</i> =5, 24-59 months: <i>n</i> =8, 60-120 months: <i>n</i> =10: Placebo: 6-23	Probiotic & Synbiotic	Probiotic: Lactobacillus acidophilus T16 (IBRC-M10785), Bifidobacterium bifidum BIA 6, Bifidobacterium lactis BIA-6, and Bifidobacterium longum LAF-5 (2.7×10^7 CFU/g each) in sachets. Synbiotic: same probiotic and 15 g of prebiotics, including three fiber types: 5 g of fructooligosaccharides, 5 g of galactooligosaccharides, and 5 g of inulin.	The placebo powder was comparable in colour, texture, and taste to the synbiotics and probiotics, but contained only maltodextrin.	The supplements were prescribed for 12 weeks as 5 g of powder to be dissolved in water four times a day with meals.	The compliance of all patients was > 90%.
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		Placebo <i>n</i> =10 Males.			months: <i>n</i> = 4. 24-59 months: <i>n</i> = 4, 60- 120 months: <i>n</i> =11.					
Khosroshahi et al., 2019	Randomised controlled trial.	(Participants randomised). Age: Intervention (mean $\pm$ SD): 53.17 $\pm$ 10.15 years. Placebo: 57.90 $\pm$ 13.34 years. Sex: Intervention: <i>n</i> =14 Males. Placebo <i>n</i> =15 Males.	Haemodialysis.	Intervention: <i>n</i> =25. Placebo: <i>n</i> =25.	Intervention (mean $\pm$ SD): 5.12 $\pm$ 1.25 years. Placebo: 4.78 $\pm$ 1.75 years.	Prebiotic	HAM-RS2 (60% pure) was purchased from Ingredion ANZ Pty Ltd., Lane Cove, NSW, and Australia. The crackers had the same rectangular shape, weight (60 g) and calories, which contained 20 g or 25 g of 60% resistant starch (amylose) in HAM-RS2 enriched crackers. We administered crackers with 20 g resistant starch (RS) for the first 4 weeks and then 25 g for the second 4 weeks.	20 g or 25 g of waxy corn starch as the placebo that ingested during hemodialysis and at home between main meals. The control patient received crackers with the same shape, weight and calorie, which prepared with waxy	The treatment group took supplements for 8 weeks.	Not reported.

								corn starch without using high amylose.		
Kooskhi et al., 2019	Randomised controlled trial.	(Participants analysed). Age (mean $\pm$ SD): Intervention: 62.92 $\pm$ 16.80 years. Placebo: 62.83 $\pm$ 16.62 years. Sex: Intervention: $n=10$ Males. Placebo: $n=11$ Males.	Haemodialysis.	Intervention: $n=25$. Placebo: $n=25$.	Intervention (mean $\pm$ SD): 35 $\pm$ 12 months. Placebo: 33 $\pm$ 15 months.	Synbiotic	Each synbiotic tablet contained 100 mg of Lactol probiotic, which contains Lactobacillus coagulans and fructo-oligosaccharides.	The placebo tablet contained farina.	Subjects in the synbiotic group received synbiotic supplement capsules daily for 8 weeks.	Compliance was more than 90%.
Lopes et al., 2018 & 2019	Randomised controlled trial.	(Participants analysed). Age (mean $\pm$ SD): Intervention: 63.17 $\pm$ 11.16 years.	Haemodialysis.	Intervention: $n=50$. Placebo: $n=49$.	Intervention ((median (25%-75% percentile)): 34 (15.5- 34) months. Placebo:	Synbiotic	Synbiotic group – (100 mL of probiotic dairy drink and 40 g of extruded sorghum flakes). The dairy drinks used in the study were pasteurized milk, used in the control group (CG) and pasteurized	(100 mL of pasteurized milk and 40 g of extruded corn flakes).	7 weeks. During the hemodialysis, two food kits were given to patients, one which was consumed in the third	Not reported.

		Placebo: 63.03 ± 10.77 years. Sex: Intervention: <i>n</i> =17 Males. Placebo: <i>n</i> =21 Males.			31 (14- 71.5) months.		milk with addition of the probiotic bacterium Bifidobacterium longum BL-G301 (Granotec do Brasil S.A.), used in the synbiotic group (SG).		hour of hemodialysis and another who was consumed on the interdialytic day at home.	
Mady et al., 2018 (conference abstract)	Randomised controlled trial.	Not reported.	Haemodialysis.	<i>n</i> =92.	Not reported.	Probiotic	Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus casai, Bifidobacterium brevis, Bifidobacterium longum in a dose of 10 billion CFU/10 gm for each strain.	Not reported.	6 weeks.	Not reported.
Meksawan et al., 2016	Randomised controlled crossover trial.	(Participants analysed). Age (mean ± SD): 71.2 ± 6.5 years. Sex: <i>n</i> =5 Males and <i>n</i> =4 Females.	Peritoneal dialysis.	<i>n</i> =13.	(mean ± SD) 17.8 ± 3.2 months.	Prebiotic	Fructo-oligosaccharides.	Sucrose.	Each subject was given either FOS (20 g/d) or placebo (sucrose) for 30 days, followed by a 14-day washout period. Then the subjects were	Subjects appropriately consumed both FOS and placebo, as compliance was higher than 95%.

									switched to receive the other experimental substance for another 30-day period. 20 g/d. Prepared in a 10 g sachet consumed after breakfast and dinner.	
Natarajan et al., 2017	Randomised controlled crossover trial.	(Participants analysed). Age (mean (range)): 54 (29-79) years. Sex: 27% Males.	Haemodialysis.	<i>n</i> =28.	Not reported.	Probiotic	30 billion CFU of <i>S. thermophilus</i> KB 19, <i>L. acidophilus</i> KB 27, and <i>B. longum</i> KB 31. Orally administered, strain specific probiotic formulation (Renadyl, Kibow Biotech, Inc., Newtown Square, PA).	1:1 blend of cream of-wheat and psyllium husk.	2 months. 2 capsules thrice daily with meals.	No major issues were encountered with regard to patient adherence to the treatment regimen. Average adherence amounted to 92.5%, with a standard deviation of 13.7%.

Shariaty et al., 2017	Randomised controlled trial.	(Participants analysed). Age: Intervention (mean $\pm$ SD): 54.17 $\pm$ 13.60 years. Placebo: 61.50 $\pm$ 8.68 years. Sex: $n=20$ Males.	Haemodialysis.	$n=36$.	6-12 months: $n=9$. 13-25 months: $n=8$. 26-38 months: $n=8$. Up to 38 months: $n=11$.	Probiotic	1. <i>L. acidophilus</i> (3×10^{10} CFU/g) 2. <i>Lactobacillus casei</i> (3×10^9 CFU/g) 3. <i>Lactobacillus rhamnosus</i> (7×10^9 CFU/g) 4. <i>Lactobacillus bulgaricus</i> (5×10^8 CFU/g) 5. <i>Bifidobacterium breve</i> (2×10^{10} CFU/g) 6. <i>Bifidobacterium longum</i> (1×10^9 CFU/g) 7. <i>S. thermophilus</i> (3×10^8 CFU/g).	500 mg daily oral dose of a placebo that was similar to the probiotic supplements and contained starch.	The intervention group received a 500 mg daily oral dose of probiotics for 12 weeks.	Five patients in the fiber group decreased consumption to one sachet per day for 3–5 weeks due to flatulence or loose stools. One patient did not complete study (missed supplements).
Sirich et al., 2014	Randomised controlled trial.	(Participants analysed). Age: Intervention (mean $\pm$ SD): 54 $\pm$ 14 years. Placebo: 58 $\pm$ 13 years. Sex:	Haemodialysis.	Intervention $n=28$. Placebo $n=28$.	Intervention ((median (25%-75% percentile)): 5 (2-6) years. Placebo: 3 (2-6) years.	Prebiotic	15 g of high-amylose corn starch (Hi-maize 260), composed of approximately 40% digestible starch and 60% resistant starch.	Control sachets contained 15 g of waxy corn starch (AMIOCA), a high-amylopectin starch that is almost	Patients were instructed to mix the supplements in either liquid or food. They took the supplements for 6 weeks, consuming one sachet	Five patients in the fiber group decreased consumption to one sachet per day for 3–5 weeks due to flatulence

		Intervention: <i>n</i> = 11 Males. Placebo: <i>n</i> =13 Males.						entirely digestible.	daily for the first week followed by two sachets daily for the remainder of the study.	or loose stools. One patient did not complete study (missed supplements).
Soleimani et al., 2017	Randomised controlled trial.	(Participants analysed). Age: Intervention (mean ± SD): 59.4 ± 16.0 years. Placebo: 54.0 ± 16.0 years. Sex: Intervention: <i>n</i> =20 Males. Placebo: <i>n</i> =20 Males.	Haemodialysis.	Intervention: <i>n</i> =30. Placebo: <i>n</i> =30.	Intervention (mean ± SD): 3.6 ± 1.1 years. Placebo: 3.5±1.1 years.	Probiotic	<i>L. acidophilus</i> , <i>L. casei</i> , and <i>B. bifidum</i> (2 x 10 ⁹ CFU/g each).	Not reported.	One capsule a day for 12 weeks.	On average, the rate of compliance in our study was high, such that >90% of probiotic and placebo capsules were consumed throughout the study in both groups.

Soleiman i et al., 2018	Randomi sed controlle d trial.	(Participa nts analysed). Age: Interventi on (mean ± SD): 62.8 ± 12.7 years. Placebo: 62.8 ± 14.8 years. Sex: Interventi on: <i>n</i> =21 Males. Placebo: <i>n</i> =21 Males.	Haemodial ysis.	Interventi on: <i>n</i> =30. Placebo: <i>n</i> =30.	Interventi on (mean ± SD): 3.6 ± 1.1 years. Placebo: 3.9 ± 1.2 years.	Synbiotic	Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum (2 × 10 ⁹ CFU/day each) plus 0.8 g/day of inulin.	One capsule a day of corn starch.	One capsule a day for 12 weeks.	The complianc e rate was high, since more than 90% of placebo and synbiotic capsules were taken by study participant s during the course of the interventio n in both groups.
Soliman et al., 2018 (conferen ce abstract)	Randomi sed controlle d trial.	Not reported.	Haemodial ysis.	<i>n</i> =80.	Not reported.	Synbiotic	Synbiotic (prebiotic 15 gm lactulose/day), (the probiotics include 5 bacterial strains; Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus casai, Bifidobacterium brevis, Bifidobacterium	Not reported.	6 weeks.	Not reported.

							longum in a dose of 10 billion CFU/10 gm).			
Sutton et al., 2014	Randomised controlled trial.	(Participants analysed). Age: Intervention (mean $\pm$ SD): 67.2 $\pm$ 9.9 years. Placebo: 69.8 $\pm$ 10.3 years.	Peritoneal dialysis.	$n=41$.	Not reported.	Prebiotic	High fibre supplement.	The placebo was a polysaccharide (food grade starch amylopectin), which had the same appearance as the fibre supplement.	Subjects in this group were asked to increase their dietary fibre for a four-week period using a dietary fibre supplement. Introduction of the supplement was in 2-g increments to avoid bloating, flatulence and abdominal discomfort up to the recommended dose of 12 g per day.	Not reported.
Viramontes-Horner et al., 2015	Randomised controlled trial.	(Participants analysed). Age: Intervention (mean $\pm$ SD):	Haemodialysis.	Intervention: $n=22$. Placebo: $n=20$.	Intervention (mean $\pm$ SD): 4.6 $\pm$ 2.1 years. Placebo:	Synbiotic	Probiotics (Lactobacillus acidophilus NCFM and Bifidobacterium lactis Bi-07) for a total of 11 x 10 ⁶ CFU; 2.31 g of a prebiotic fiber	The placebo had identical color, size, and flavor to the	2 months. Participants of both groups consumed 1 gel/day in fasting.	To evaluate the treatment adherence, there was a monthly

		40.6 ± 17.1 years. Placebo: 39.0 ± 16.0 years. Sex: Intervention: <i>n</i> =16 Males. Placebo: <i>n</i> =16 Males.		5.5 ± 3.4 years.		(inulin); 1.5 g of omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids); and vitamins (complex B, folic acid, ascorbic acid, and vitamin E).	interventional product.		count of the empty package.	
Wang et al., 2015	Randomised controlled trial.	(Participants analysed). Age: Intervention ((median (25%-75% percentile))): 51 (39-57) years. Placebo 53.5 (43 to 59) years. Sex: Intervention: <i>n</i> =10	Peritoneal dialysis.	Intervention: <i>n</i> =23. Placebo: <i>n</i> =24.	Intervention ((median (25%-75% percentile))): 36 (12-60) months. Placebo: 46.5 (24-72) months.	Probiotic	109 CFU B. bifidum A218, 109 CFU B. catenulatum A302, 109 CFU B. longum A101, and 109 CFU L. plantarum A87 (ProMD, with a total of 4×10 ⁹ CFU/day.	The placebo group received similar capsules containing maltodextrin for the same duration.	One capsule before bedtime daily for six months.	Two patients in the probiotics group and five patients in the placebo group dropped out of the study because of noncompliance.

		Males. Placebo: <i>n</i> =8 Males.								
Xie et al., 2015	Randomi sed controlle d trial.	(Participa nts randomis ed). Interventi on (mean ± SD): Group A: 53.7 ± 14.2 years, Group B: 51.7 ± 15.2 years. Placebo: 53.1 ± 13.2 years. Sex: Interventi on: Group A: <i>n</i> =24 Males. Group B: <i>n</i> =18 Males. Placebo: <i>n</i> =26	Haemodial ysis.	Interventi on: Group A: <i>n</i> =41, Group B: <i>n</i> =39. Placebo: <i>n</i> =44.	Interventi on (mean ± SD): Group A: 22.7 ± 6.5 months, Group B: 22.9 ± 7.1 months. Control: 22.2 ± 7.2 months.	Prebiotic	Water soluble fiber fermentable rate > 75%).	Starch	During nutritional intervention period (which was 6 weeks), patients maintained their regular diets and add either 10 grams fiber (Group A), 20 grams fiber (Group B) or pla-cebo starch (Control group) to their staple food rice.	Not reported.

Males.

Identification

Records identified through database searching
(n = 3692)

Additional records identified through other sources
(n = 8)

Records after duplicates removed
(n = 3190)

Screening

Records screened
(n = 3190)

Records excluded
(n = 3134)

Eligibility

Full-text articles assessed for eligibility
(n = 56)

Full-text articles excluded, with reasons*
(n = 35)

- CKD patients not receiving dialysis (n=20)
- Not a relevant intervention (n=2)
- No concurrent control group (n=13)
- No relevant outcomes (n=2)
- Not a randomised study (n=11)

Included

Trials included in qualitative synthesis
(n = 21)

Trials included in quantitative synthesis (meta-analysis)
(n = 6)

Figure 1. Prisma flow diagram of trial selection. * some trials excluded for multiple reasons.

	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)	Other bias
Borges et al., 2018a & 2018b	?	+	+	+	-	+	+
Cockram et al., 1998	?	?	-	?	?	+	+
Cruz-Mora et al., 2014	?	?	?	?	+	+	-
Eidi et al., 2018	?	?	?	?	-	-	+
Haghighat et al., 2018 & 2019	+	?	+	+	+	+	+
Khosroshahi et al., 2019	?	?	+	?	+	-	+
Kooshki et al., 2019	?	?	?	?	+	+	+
Lopes et al., 2018 & 2019	?	?	-	?	-	-	+
Meksawan et al., 2016	?	?	?	?	-	+	+
Natarajan et al., 2017	?	?	?	?	-	-	-
Shariaty et al., 2017	?	?	+	?	+	+	+
Sirich et al., 2014	+	?	-	?	-	-	+
Soleimani et al., 2017	+	+	+	+	+	+	+
Soleimani et al., 2018	+	+	+	+	+	+	+
Sutton et al., 2014	?	?	+	?	-	+	+
Viramontes-Horner et al., 2015	?	?	?	?	+	+	+
Wang et al., 2015	+	+	+	+	+	-	+
Xie et al., 2015	?	?	?	?	?	?	+

Figure 2. Risk of bias for included trials (assessed using the Cochrane Risk of Bias tool). Unclear risk of bias: ?. Low risk of bias +. High risk of bias -.

Figure 3. Effect of probiotic and synbiotic supplementation on endotoxin (EU/mL) in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.

Figure 4. Effect of prebiotic, probiotic and synbiotic supplementation on indoxyl sulphate (mg/L) in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.

Figure 5. Effect of prebiotic, probiotic and synbiotic supplementation on p-cresyl sulphate (mg/L) in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.

Supplementary Table 1: Full search strategy for the MEDLINE database

	Search term	Field
1	Kidney Failure, Chronic	MH (explode)
2	Renal Dialysis	MH explode
3	Haemodialysis Or hemodialysis	TX
4	Peritoneal dialysis	TX
5	Dialysis	TX
6	ESRD	TX
7	kidney disease N2 end-stage OR end stage OR chronic	TX
8	renal disease N2 end-stage OR end stage OR chronic	TX
9	kidney failure N2 end-stage OR end stage OR chronic	TX
10	Renal replacement therapy	TX
11	renal failure N2 end-stage OR end stage OR chronic	TX
12	CKD	TX
13	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	
14	Probiotics	MH (explode)
15	Prebiotics	MH (explode)
16	Synbiotics	MH
17	Lactobacillus	MH (explode)
18	Bifidobacterium	MH (explode)
19	Lactobacill	TX
20	Bifido	TX
21	Streptococcus	TX
22	Saccharomyces	TX
23	Clostridium	TX
24	Enterococcus faecium	TX
25	inulin	TX
26	oligosaccharides	TX
27	lactulose	TX
28	Probiotics	TX
29	Pro-biotics	TX
30	Prebiotics	TX
31	Pre-biotics	TX
32	Synbiotics	TX
33	Syn-biotics	TX
34	14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 32 OR 33	
35	Clinical trial	MH (explode)
36	Randomised Controlled Trials as Topic	MH (explode)
37	Random allocation	MH
38	Double-blind method	MH
39	Single-blind method	MH
40	randomised OR randomized	TI, AB
41	trial	TI, AB
42	group	TI, AB
43	allocated N2 random*	TI, AB
44	placebo	TI, AB
45	35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44	TI,AB
46	13 AND 34 AND 45	TI,AB

Supplementary Figure 1. Effect of prebiotic, probiotic and synbiotic supplementation on potassium (mg/dL) in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.

Supplementary Figure 2. Effect of prebiotic, probiotic and synbiotic supplementation on triglyceride (mg/dL) in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.

Supplementary Figure 3. Effect of prebiotic, probiotic and synbiotic supplementation on HDL cholesterol (mg/dL) in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.

Supplementary Figure 4. Effect of probiotic and synbiotic supplementation on Gastrointestinal Symptom Rating Scale Total Score in dialysis patients. Data are expressed as standardised mean difference and 95% confidence interval.