The gut microbiota profile of adults with kidney disease: A systematic review of the literature

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Abstract
Background
There is mounting evidence that individuals with kidney disease have an abnormal gut microbiota composition. No studies to date have summarised the evidence to categorise how the gut microbiota profile of individuals with kidney disease may differ from healthy controls. Synthesis of this evidence is important to inform future clinical trials. This systematic review aims to characterise differences of the gut microbiota composition in adults with kidney disease, as well as to describe the functional capacity of the gut microbiota and reporting of diet as a confounder in these studies.

Methods
Included studies were those that investigated the gut microbial community in adults with any type of kidney disease and compared this to the profile of healthy controls. Six scientific databases (CINHAL, Medline, PubMed, Scopus, Web of Science, Cochrane Library) as well as selected grey literature sources were searched up until August 2018. Quality assessment was undertaken independently by three authors. The system of evidence level criteria was employed to quantitatively evaluate the alteration of microbiota by strictly considering the number, methodological quality and consistency of the findings. Additional findings relating to altered functions of the gut microbiota, dietary intakes and dietary methodologies used were qualitatively summarised.

Results
Sixteen articles, reporting 15 studies met the eligibility criteria and included a total of 540 adults with kidney disease and 1117 healthy controls. Compared to healthy controls, individuals with kidney disease had increased abundances of Enterobacteriaceae, and decreased abundances of Coprococcus and Prevotella. Adults with kidney stones also had an altered microbial composition with variations to Bacteroides, Lachnospiraceae NK4A136
group, Ruminiclostridium 5 group, Dorea, Enterobacter, Christensenellaceae and its genus
Christensenellaceae R7 group. Altered microbial functions in adults with kidney disease
were reported, particularly in the context of metabolic pathways relating to urea and
uremic toxin generation. Only three of the 16 articles accounted for diet, and of these
studies only two used a valid dietary assessment method.

Conclusions

The gut microbiota profile of adults with kidney disease differs from healthy controls.
Future study designs should include adequate reporting of important confounders such as
dietary intakes to assist with interpretation of findings.

Background

The link between the gut microbiome and human diseases continues to emerge in recent
literature and has become a focus for global scientific endeavours to mitigate kidney
disease development and progression [1-4]. The human microbiome is a complex
ecosystem comprising of all the genetic material inside the trillions of micro-organisms
that live within and on us—bacteria, archaea, eukaryotes and viruses—which are
collectively known as the microbiota [2, 5]. Advancements in microbial characterisation
methods have facilitated our understanding of the complex mechanistic links between the
microbiome and disease. There are numerous methods to categorise gut microbial
composition and measure diversity. For instance, some methods are based on sequence
divergences of the small subunit ribosomal RNA (16S rRNA) [6, 7], which provide helpful
insights into the diversity of the gut microbiota and qualitative and quantitative
information based on what microbes are present. Examples of this technique include
fluorescence in situ hybridization (FISH), DNA microarrays, and next-generation
sequencing of the 16S rRNA gene or its amplicons [7]. Another type of analysis is
metagenomic or shotgun sequencing, which randomly sequences all extracted DNA in a given sample to provide a comprehensive view of the abundance of specific genes (microbiome). This enables researchers to reconstruct metabolic pathways associated with those genes as well as describe the taxonomic composition [6-8].

Typically, these microbes have a harmonious relationship with their host [9] and contribute to several functional activities including micronutrient and immune homeostasis, energy metabolism, and host defences against pathogens [2, 10, 11]. However, in individuals with kidney disease, evidence suggests that a microbial imbalance (dysbiosis) is present leading to an increase in harmful nephrovascular uremic toxins [12-15]. The retention of these uremic toxins, particularly p-cresyl sulfate (PCS), phenylacetylglutamine (PAG), indoxyl sulfate (IS) and trimethylamine N-oxide (TMAO) are associated with adverse complications, which negatively impact on the quality of life for individuals living with kidney disease. These complications include accelerated disease progression [16, 17], increased risk of cardiovascular-related mortality [17-19] and common symptoms such as constipation and cognitive decline [20]. Currently, the only known mechanism for reducing uremic toxins in kidney disease is dialysis. Yet, existing evidence indicates that only the free fraction of the protein-bound toxins PCS and IS can diffuse across the dialysis membrane, resulting in limited capacity for removal [21]. Therefore, development of novel strategies (other than dialysis) to reduce the production of major uremic toxins, particularly in the earlier stages of chronic kidney disease is warranted.

Diet forms a critical component in the overall medical strategy for kidney disease and plays a fundamental role in determining the composition and functional activity of the human gut microbiota [22], with implications for uremic toxin formation [15, 21, 23-25].
Therefore, dietary interventions and targeted nutritional therapies offer a potential approach to mitigate uremic toxin and microbiota-associated diseases. Investigations into how the gut microbiota differ in relation to disease and lifestyle factors such as diet, will not only enhance our understandings of the contribution these microbes have in host biology, but also understandings of the complex exchange between diet and disease. The differences in the composition of the gut microbiota in kidney disease populations compared to healthy controls remains unclear due to the lack of a quantitative overview of existing evidence. Investigation into how the microbial signatures of adults with kidney disease may deviate from healthy controls is essential to inform future trials. Hence, this review aims to systematically characterise the gut microbial composition in adults with kidney disease compared to healthy controls and gain a better understanding of the functional capacity of the microbiota and reporting of diet as a confounder in these studies.

Methods

Protocol

The systematic literature review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[26] and registered at PROSPERO (no. CRD42018109173).

Article Selection

Studies that compared the gut microbiota of adults with kidney disease to healthy controls were included.

The inclusion criteria were as follows:

original research reporting primary data of adults with kidney disease diagnosis using definite criteria: kidney stones, any stage chronic kidney disease (CKD), glomerulonephritis, nephrotic syndrome, IgA nephropathy (IgAN) polycystic kidney disease, Allport syndrome, Fabry disease and those receiving renal replacement therapies (haemodialysis, peritoneal dialysis or kidney transplant); studies reporting on the microbial community from stool or intestinal biopsy samples;
full text articles available in English.

Studies for exclusion were:

animal or in-vitro studies, case reports, abstracts, editorials, expert opinion, letters, guidelines, protocols, seminars, reports, books or book chapters.
study populations which included children or individuals with haemolytic uremic syndrome, acute kidney injury, urinary tract infection, renal cancer, Kidney-Yin Deficiency Syndrome or stones in other sites, such as the ureter or urethra.

Search strategy and study selection

Six scientific databases including CINHAL, Medline, PubMed, Scopus, Web of Science and Cochrane Library as well as grey literature sources: Trove, the National Kidney Foundation Website, Google Scholar, Google.com.au, National Institute for Clinical Excellence (NICE) and TRIP Medical Database, were searched. Reference lists of manuscripts were also scanned to discover additional relevant articles. A research librarian was consulted to refine search terms. The final search strategy for all databases can be found in Item 1 of this manuscript’s supplementary materials. All citations were imported by one member of the research team in Endnote (Endnote X8, Thomson Reuters, 2016) for review.

Two reviewers [JS, RI] independently screened the titles, abstracts and full text for inclusion in this review. Discrepancies were resolved by consensus or adjudication by other members of the research team [KC, KL]. At the stage of full text review, the decision to restrict articles to only those that included at least one of the following methods was made: Metagenomic sequencing (shotgun sequencing), 16S ribosomal RNA (rRNA) gene sequencing, quantitative real-time polymerase chain reaction (qPCR) sequencing, DNA microarray or FISH techniques. These methods are culture-independent methods that enable phylogenetic identification and quantification, which will help to provide novel insights into the composition, diversity and potentially the functional capacity of the microbiota.

Summary measures

The overall microbiota structure (α-diversity and β-diversity) and differences in the
abundance of microbes at specific taxonomic levels (phylum, order, class, family, genus, OTU) were the primary outcomes of this paper. The secondary outcomes were descriptions of the real or predicted functional capacity of the microbiota and details on the dietary assessment methods used in each study.

*Data extraction and quality assessment*

Relevant data in all eligible studies were extracted into an excel spreadsheet by one investigator and 25% of the input was cross-checked by another member of the research team. Only statistically significant results ($p \leq 0.05$) that reported compositional differences of the gut microbiota between groups of interest (kidney disease versus controls) at each taxonomic level were imported into excel. Additional information was also extracted: country of study, demographics (age, gender, and ethnicity), sample collection and storage methods, description of antibiotic and medication use, type of taxonomic database used, and microbial characterisation method, diversity metrics, dietary methods.

To assess the quality of studies, three independent reviewers [JS, KL, ASN] used the Newcastle-Ottawa Scale (NOS) [27]. Appraisal items in the NOS tool were grouped into three categories: the selection of the study groups; the comparability of the groups; and the ascertainment of the exposure (the collection and assessment of samples for microbial communities) as the outcome of interest [27]. Overall, studies which scored 7 or above using the NOS tool was considered to be of ‘good quality’, while studies rating less than 7 were deemed ‘poor quality’.

*Data synthesis*

Due to the heterogeneity of study methods as well as the absence of raw sequencings and/or meta-data of included articles to re-analyse results for a meta-analysis, a
quantitative assessment of the microbial composition was performed. The quantitative approach utilised the system of evidence level criteria (Table 1), a ranking-based system as documented elsewhere. This approach considered the number and methodological quality of studies, as well as the consistency of reported findings across studies. Study findings were deemed highly consistent and graded as ‘strong evidence’ when 75% or more of the studies that reported a particular bacteria were in agreement, whereby the same trend in microbial alteration (increased or decreased) relative to healthy controls was found in at least two high quality studies as determined by the NOS quality score. Results based on the alterations of the microbial composition were pooled and separated into cohorts with kidney disease and kidney stones.

Results

Summary of included studies

The literature search yielded 4155 articles of which 137 full-text articles were evaluated. Two articles obtained through the search strategy were unable to be located in both national and international libraries and therefore excluded from the final analysis. A final 16 articles, reporting 15 studies met the eligibility criteria. All 15 studies were cross-sectional and included a total of 540 adults with kidney disease or kidney stones and 1117 healthy controls (Figure 1, Table 2). Only different results of the two papers from the same study were extracted to avoid duplication.

Of the 16 articles, only four groups of kidney disease were reported. These were dominated by studies of non-dialysis dependent adults with kidney disease (Table 2, n=7), including a study that exclusively investigated an IgAN cohort; followed by four studies investigating adults with kidney stones. One study exclusively investigated adults undertaking haemodialysis (HD); and another included individuals
undertaking peritoneal dialysis (PD) [47]. Two additional studies included mixed kidney disease populations within their sample [48, 49].

There were no studies that included a control group and exclusively investigated or separated results for cohorts diagnosed with glomerulonephritis, nephrotic syndrome, polycystic kidney disease, Allport syndrome, Fabry disease or kidney transplant recipients. Overall, studies were predominately published from China (n=6/18), followed by the United States of America (n=3/18) and Italy (n=2/18). The age of adults with kidney disease or kidney stones reportedly ranged from 25-71 years and the portion of males ranged from 22-100%.

All eligible studies used stools samples for gut microbiota analysis. Eleven studies used frozen stool samples for their analysis, where storage temperatures ranged from -20°C to -80°C. Others reported samples were processed within 24 hours of receipt [35] or kept on ice and processed within one hour of defecation [47]. The remaining two studies failed to provide sufficient details regarding the storage and processing methods utilised [33, 34, 39].

Two articles assessed the gut microbiota using only qPCR [40, 47]. Fourteen studies assessed gut microbiota via high-throughput molecular approaches: Illumina platforms (MiSeq, NextSeq, HiSeq), Iron Torrent PGM system or bTEFAP using 454 FLX sequencer, DNA microarray analysis performed using PhyloChip, while a further two papers did not report the sequencing platform used. Among these studies, three employed multiple microbial characterisation techniques in addition to 16S rRNA sequencing, including: shotgun sequencing [43]; qPCR [38]; as well as qPCR, DGGE fingerprinting and frc-gene amplicon sequencing [46].
**Risk of bias and heterogeneity**

Using the Newcastle-Ottawa Scale, of the 16 final articles, seven were considered of good quality with a score of 7 or above (Table 3). There were multiple sources of heterogeneity among studies, including: the collection of samples (self-sampled and temperature of storage), DNA extraction method, primer used for PCR, variable region of the 16S rRNA gene and sequencing platform used. Furthermore, some methods employed also lacked the ability to evaluate the whole microbial community such as qPCR, which can only detect selected microbes.

Other sources of heterogeneity among studies included age, gender, ethnicity and the classification or recruitment of healthy controls. The age structure of cohorts did vary; although, there were some overlap across studies including a mean sample population age between 42-65 years. In terms of gender and ethnicity, one study only recruited males [46] and three of the four studies that reported ethnicity recruited one ethnic group: Han Nationality Chinese [38, 45] or Caucasian [42]. Details relating to the recruitment of control groups were often missing or differed across studies, with some studies reporting that their controls were hospital staff. Furthermore, the classification of ‘healthy controls’, timing of antibiotic usage prior to study participation, reporting of medications and other co-existing conditions was not consistent across studies and more often poorly defined.

**Altered Microbiota**

**Microbial diversity and richness**

Alpha (α) diversity is the measure of the number (richness) and distribution (evenness) of taxa within a sample [50]. Ten studies included in this review compared α-diversity between groups, of which four reported that α-diversity was significantly reduced in kidney disease or kidney stones compared to controls (Table 2). In contrast, two other
studies reported a significant increase in α-diversity (observed species/OTUs) was observed in EKSD (p<0.05) and HD participants (p=0.044) [39, 49].

Beta (β) diversity, a measure of the diversity that represents the similarity or difference in microbial composition between sites or different samples [50], was evaluated in seven studies (Bray-Curtis, weighted and unweighted UniFrac distance metrics). Four studies reported compositional differences in the overall microbial communities between controls and kidney disease cohorts, of which three studies [41, 43, 48] reported a statistically significant p-value (Table 2).

Microbiota profile of patients with kidney disease compared to healthy controls

Adults with kidney disease

Figure 2 characterises the differences in the gut microbiota profile of individuals with kidney disease compared to those of healthy controls. There is strong evidence that individuals with kidney disease in general have increased abundance of Enterobacteriaceae [34, 41, 48], and decreased abundance of the Coprococcus [38, 41, 48] and Prevotella [38, 41, 48].

Nine other taxa were identified as being of reduced abundance compared to healthy controls, based on the moderate evidence criteria: Firmicutes [41, 49], Alcaligenaceae [34, 38, 41], Prevotellaceae [34, 38, 41, 42], Prevotella [38, 41, 48], Dorea [38, 41], Roseburia [38, 40, 41] and species Fecalibacterium prausnitzii [38, 40, 48]. In contrast, Proteobacteria [41, 49], Enterobacter [35, 39, 48], Streptococcus [35, 48] were present in an increased abundance. Bacterial families Alcaligenaceae and Prevotellaceae, and genera Coprococcus, Dorea, Prevotella, Roseburia remained depleted in non-dialysing adults compared to healthy
controls based on moderate evidence, when separating out results from cohorts who received dialysis therapy.

The population of an additional 64 microbial taxa were altered based on weak evidence (data not shown), 22 of which increased, while the remaining 42 decreased relative to controls (Table S1, supplementary material).

Adults undertaking dialysis

Across studies when separating results from cohorts who did not receive dialysis therapy, no taxa satisfied the criteria for strong evidence in individuals receiving dialysis. However, Enterobacteriaceae was observed in higher abundances in adults receiving dialysis therapy compared to healthy controls based on criteria for moderate evidence. Differences in the microbial profile were evident according to dialysis type. Findings of Stadlbauer et al.[48] who compared individuals receiving PD and HD with healthy controls, found that individuals undertaking PD dialysis had reduced abundances of Comamonadaceae and Campylobacteraceae and increased abundances of Ruminococcaceae and Corpococcus. In contrast, microbial families Comamonadaceae and Campylobacteraceae were enriched, while Fecalbacterium prausnizii, Roseburia intestinalis and Clostridium nexile were depleted in HD participants when compared to healthy controls. Paraprevotella was reported to be in decreased abundances in both PD and HD dialysis groups.

Adults with kidney stones

Based on strong evidence criteria, six taxa were observed to be altered in adults with kidney stones. Within the phylum Firmicutes, Lachnospiraceae NK4A136 group[43, 45], Ruminiclostridium 5 group[43, 45], Dorea[43, 45], Christensenellaceae[43, 45] and its genus Christensenellaceae R7 group[43, 45], as well as genus Enterobacter[43, 45], which is part of
the Proteobacteria phyla were all significantly reduced compared to healthy controls (Figure 3). In contrast, *Bacteroides*[^43, 44] were present in an increased abundance in cohorts with kidney stones.

Three other taxa including *Bidifidobacterium*[^45, 46] and *Faecalibacterium*[^43, 46] were all found to be significantly reduced based on moderate evidence in kidney stone participants (Figure 3). The population of an additional 84 microbial taxa were altered in kidney stone populations compared to healthy controls based on weak evidence (data not shown; Table S2 in supplementary material), of which 31 microbes increased and 53 taxa decreased comparatively.

**Altered genetic functions of the microbiota**

Functional capacities of the microbial community were investigated with respect to known metabolic pathways in the one study that undertook shotgun sequencing in a subset of their sample (n=10 participants)[^43]. However, the functional capacity of the gut microbiota was predicted in a further four studies using the bioinformatics software platform PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) [^41, 45, 46, 48]. Among these five studies, four[^41, 43, 46, 48] reported that the functional capacity of the gut microbiota in individuals with kidney disease and kidney stones were substantially different than healthy controls.

In kidney disease (stage 4-5), using PICRUSt, functional genes relating to trimethylamine metabolism were enriched (K07811, K07821, and K03532), while functional genes relevant to choline, betaine and L-carnitine metabolism (K07271, K01004, K00499, K00130 and K00540) were found significantly depleted when compared to healthy controls[^41].

In adults undergoing dialysis (HD and PD), analysis using PICRUSt revealed four
discriminative functional pathways of the microbiota relevant to the renin-angiotensin system, glycosphingolipid biosynthesis, isoflavonoid biosynthesis and vasopressin regulated water reabsorption [48]. However, the authors[48] did not report if these functional pathways were upregulated or downregulated compared to the control group.

In adults with kidney stones, shotgun sequencing analysis revealed that functional genes involved in oxalate degradation, such as formyl-CoA transferase and oxalyl-CoA decarboxylase, were significantly reduced compared to healthy controls[43]. The highest representation of these genes were detected in some Archaea and Bacteria, either with known (Oxalobacter formigenes) or previously unknown oxalate-degrading properties (Escherichia coli, Eggerthella spp, Roseburia hominis, Bacteroides massiliensis, Clostridium citroniae)[43]. Similarly in a study of Suryavanshi et al[46], the application of DGGE fingerprinting and targeted metagenomic analysis of the frc-gene confirmed that in addition to Oxalobacter formigenes, several gut inhabitants possessed the ability to metabolise oxalate. However, their findings through the application of PICRUSt differed to the shotgun sequencing results observed by Ticinesi et al[43] in that genes involved in oxalate degradation were enriched in their kidney stone cohort[46]: formate dehydrogenase (K08349), oxalate/formate antiporter (K08177), formyl-CoA transferase (K07749), oxalyl-CoA decarboxylase (K01577) and oxalate decarboxylase (K01569)[46]. In contrast, Tang et al[45] found no significant difference in these pathways (oxalate degradation) between groups. Other predicted functional activities of the gut microbiota relevant to energy metabolism, glycan synthesis, metabolism of co-factors and vitamins were down regulated, while lipid metabolism, carbohydrate metabolism and xenobiotic degradation metabolism were upregulated in adults with kidney stones [46].
Wong et al\(^{[34]}\) employed a different approach to the above methods. This research group adopted the Kyoto Encyclopedia of Genes and Genomes (KEGG) database to search for corresponding functional genes and enzymes of interest alongside the list of bacterial families differing in relative abundance between participants receiving HD and healthy controls. In the HD group, 12 of the 19 microbial families that were of greatest abundance were urase-possessing families, while an additional five families possessed the uricase gene (\textit{Cellulomonadaceae, Dermabacteraceae, Micrococcaceae, Polyangiaceae, Xanthomonadaceae}). Three bacterial families contained the tryptophanase gene (\textit{Clostridiaceae, Enterobacteriaceae, and Verrucomicrobiaceae}) and four were capable of delaminating tyrosine into p-cresol, a precursor of PCS\(^{[34]}\). Furthermore, two of three bacterial families that were less abundant in participants receiving HD\(^{[34]}\), \textit{Lactobacillaceae} and \textit{Prevotellaceae}, were those families that contained butyrate-producing functions, such as members that possessed phosphotransbutyrylase\(^{[34]}\) and the butyrate kinase gene.

**Dietary intakes and methodologies**

Three of the 16 articles (18.75\%) reported assessment of dietary intake, of which two used the 131-item European Prospective Investigation of Cancer and Nutrition (EPIC) Food Frequency Questionnaire (FFQ)\(^{[37, 43]}\). However, among the two studies, only one employed a trained research nutritionist to administer the FFQ\(^{[43]}\).

Barrios et al\(^{[51]}\) generated dietary scores from the FFQ results through principal component analysis\(^{[37]}\). These dietary scores were then considered as covariates in the
analysis of the gut microbiota. In the second study, Ticinesi et al.\textsuperscript{[43]} assessed total energy (kcal), macronutrient (protein, carbohydrates, fats in grams), dietary fiber (grams), alcohol (grams) and micronutrient consumption (grams) between groups (adults with kidney stones and healthy controls). They found no significant differences between these measures, with the exception of dietary calcium\textsuperscript{[43]}. Only dietary calcium intakes along with other outcomes such as BMI, age, sex, urinary volume were adjusted as covariates. The third study presented macronutrient percentage consumption for carbohydrates, proteins and fats between groups, but details relaying their methods used for data collection or if the dietary data was considered in the analysis were missing\textsuperscript{[35]}. The two articles that considered diet in their analysis\textsuperscript{[37, 43]}, concluded that dietary factors did not seem to be involved in the kidney disease- or nephrolithiasis-associated abnormalities of gut microbiota composition.

Other papers reported to assess nutritional status through anthropometric measures such as weight and skinfold tests\textsuperscript{[36]} or provided participants with dietary restrictions without detailing the specific nutrition prescription, counselling methods and compliance approaches used\textsuperscript{[33, 34]}.

Discussion

To the best of our knowledge, this is the first systematic review to quantitatively summarise the composition of the gut microbiota profile in adults with kidney disease compared to controls. There is some consistent evidence that the gut microbial composition is altered in specific ways relative to controls. However, more research in this area is required to establish the role that these microbes have in kidney disease physiology and importantly, the clinical relevance in disease management. The findings
from this review have highlighted an important gap in the current evidence-base regarding a lack of reporting to control for the potential confounding effects of dietary intakes. Furthermore, future studies also need to employ more sophisticated microbial characterisation methods appropriate for functional annotation, use of multi-omic technology such as metabolomics, and investigate the gut microbiota in larger sample sizes and in different kidney disease cohorts.

Bacterial diversity is often promoted as an indicator for the ecosystem state, because of its relationships with productivity, functionality, resilience and role in the mediating pro- and anti-inflammatory immune responses \[^{52, 53}\]. Lower bacterial diversity has been observed in a range of other clinical conditions including inflammatory bowel disease (IBD), obesity, type 1 and 2 diabetes and coeliac disease \[^{54, 55}\]. However, differences in the diversity of microbial communities between cohorts with kidney disease and healthy controls remained inconclusive in this review. The overall change in the microbial community structure as evaluated via β-diversity distance metrics was reported in four studies. However, conflicting results were found for α-diversity measures. Four studies agreed that α-diversity significantly reduced in kidney disease or kidney stones compared to healthy controls. In contrast, two studies reported an increase in microbial richness, both of which investigated adults with end stage kidney disease \[^{39, 49}\]. It was inferred that the increase of microbial richness may reflect the proliferation of certain bacterial species \[^{39, 49}\]. While the specific bacterial species that did preliterate was not reported among these studies, overgrowth of microbes with pathogenic potential (pathobiont) has been observed along with increases in intestinal concentrations of uremic toxins\[^{56}\] associated with the progression of kidney disease, leading to the loss and of the breach in
the epithelial barrier\textsuperscript{[56]}. Changes at the phylum level with the elevation of Proteobacteria and decrease of Firmicutes was found in participants with kidney disease. Previously studies have reported this enrichment of Proteobacteria is indicative of an unstable microbial structure\textsuperscript{[57]} and has been correlated to diseases of inflammatory phenotype\textsuperscript{[57]} such as cardiovascular disease and Inflammatory bowel disease\textsuperscript{[58]}. Lipopolysaccharides (LPS) constitute the outer membranes of most Gram-negative bacteria\textsuperscript{[59]} and members of Proteobacteria have been reported as potent LPS producers\textsuperscript{[60]}. A connection between low-grade inflammation, sustained by LPS, and the development of metabolic disorders is well established, including evidence that indicates subclinical endotoxemia is a potential cause for inflammation in patients with CKD\textsuperscript{[56]}. Further, a mechanistic exploration in male C57BL/6 mice showed that endotoxemia resulted in the activation of mTOR signalling in macrophages, leading to progressive kidney inflammatory injuries and subsequent fibrosis\textsuperscript{[61]}. The elevated abundance of \textit{Enterobacteriaceae} \textsuperscript{[34, 41, 48]}, \textit{Enterobacter}, \textit{Streptococcus} and depletion of \textit{Coprococcus}\textsuperscript{[38, 41, 48]}, \textit{Prevotella}\textsuperscript{[38, 41, 48]} \textit{Alcaligenaceae}, \textit{Prevotellaceae}, \textit{Dorea}, \textit{Roseburia} and \textit{Faecalibacterium Prausnitzii} were reported in participants with kidney disease. Increased presences of \textit{Enterobacteriaceae}, \textit{Enterobacter} and \textit{Streptococcus} have been responsible for a range of human infections\textsuperscript{[62, 63]}. Further, members of the \textit{Enterobacteriaceae} family have been similarly detected in greater abundances in inflammatory bowel disease and thought to potentially contribute to disease pathogenesis\textsuperscript{[64]}, however the mechanism is yet to be confirmed. Specific to kidney disease, \textit{Enterobacteriaceae} was reported to be among the families that contain
the typtophanase gene and functional capacity to transform tyrosine into p-cresol, a precursor of PCS\textsuperscript{[34]}. In another study, Streptococcus along with Clostridium, Klebsiella and Pseudomonas were reportedly associated with serum TMAO production \textsuperscript{[35]}, while elevated abundances of Enterobacter along with Bacteroides, Fusobacterium, Escherichia and Klebsiella all positively correlated with Cystatin C and serum creatinine\textsuperscript{[38]}. Thus, the elevated abundance of bacterial members from Enterobacteriaceae, Enterobacter and Streptococcus deserves continued attention in future studies.

Overall, members of bacterial families Ruminococcaceae and Lachnospiraceae were consistently reported to be in reduced abundances among kidney disease cohorts when compared to controls (Figure 2). Findings of Barrios et al \textsuperscript{[37]} suggested that Ruminococcaceae and Lachnospiraceae may be protective in individuals kidney disease given that these bacterial families were associated with lower circulating levels of indoxyl-sulfate, p-cresyl-sulfate, phenylacetylglutamine and better renal function (eGFR)\textsuperscript{[37]}. Further the depletion of known commensal bacteria that typically reflect a ‘healthy’ gastrointestinal flora\textsuperscript{[11, 65]} was also consistently reported in cohorts with kidney disease, especially Prevotella, Coprococcus, Roseburia \textsuperscript{[38]} and Fecalibacterium prausnitzii\textsuperscript{[40]}, which have been found to positively associate with eGFR. In addition, higher abundances of Roseburia species, Fecalibacterium prausnitzii, Clostridium Coccoides, and Prevotella have been shown to negatively correlate with Cystatin C levels \textsuperscript{[38]}.

The predictive biological functions of microbial communities observed in individuals with kidney disease offers insightful clues for future research. Genes relevant to choline, betaine, and L-carnitine metabolism were found to be downregulated\textsuperscript{[41]}, possibly
resulting in the production of redundant trimethylamine (TMA) in the intestinal tract, a precursor of TMAO. Further, majority of microbial families (12/19) that were found enriched in a cohort of participants receiving haemodialysis possessed the urease gene, while five out of 19 microbial families possessed uricase gene[34]. Collectively, these findings support the notion that the gut microbiome may play a role in the production of ammonia from urea, and formation of uremic toxin TMAO via the reduced decomposition of its precursor TMA. Additionally, commensal microbes of Roseburia, Coprococcus and Facalibacterium prausnitzii are well known to produce short chain fatty acid (SCFA) [55, 66, 67]. This capacity is important physiologically as SCFAs provide energy for growth and proliferation of colonocytes [68], protect the colonic epithelium from damage by reactive oxygen species and immune-modulating prostaglandins [68] and assist in processes that reduce luminal pH associated with the inhibition of pathogenic microorganisms [69]. This evidence is supported by findings of a reduction in bacterial families that possessed the butyrate-kinase gene and phosphotransbutyrylase needed to produce butyrate, a four carbon SCFA[34], among adults undertaking HD when compared to healthy controls. Although kidney stones are not commonly identified as the primary cause of kidney disease, they are associated with an increased risk [70, 71]. Lachnospiraceae NK4A136 group, Ruminiclostridium 5 group, Dorea, Christensenellaceae and its genus Christensenellaceae R7 group were consistently reported across studies to be in reduced abundances among adults with kidney stones compared to healthy controls. As previously discussed, bacterial family Christensenellaceae may be potentially protective in kidney disease, with an increased abundance being associated with better renal function and reduced serum uremic toxin levels [37]. However, further investigation regarding the role
of this bacterial family specifically in adults with kidney stones is warranted. Elevated urinary oxalate is amongst the most common causes of kidney stone formation \(^{[72]}\), and it has been suggested that the existence of oxalate-degrading bacteria is critical in the reduction of stone formation \(^{[73, 74]}\). Discrepancies existed across studies in this review in relation to the up-regulation or down-regulation of microbial genes involved in oxalate degradation. Previous studies have largely focused on linking the absence of gut inhabitants like *Oxalobacter formigenes* with urinary oxalate excretion and risk of kidney stone formation\(^{[75-77]}\). However, through the employment of high-throughput genomic technology, findings of this review did agree that several microbes possessed functional oxalate-degrading properties, challenging the concept that the gut-nephrolithiasis-axis is merely limited to *Oxalobacter formigenes*. Furthermore, unlike *Oxalobacter formigenes*, other bacterial groups were consistently identified as being altered in adults with kidney stones compared to healthy controls. These findings will undoubtedly incite future research to uncover the relationship between oxalate degradation as well as other mechanistic functions of these altered bacterial groups in the broader biological context of kidney stones.

Modulation of the microbiome provides an exciting potential therapeutic target for preventing or personalising treatment in kidney disease. Despite hypotheses that postulate deleterious effects of certain diets and nutrients on the gastrointestinal microbiota and uremic toxin generation\(^{[14, 23, 25, 78]}\), few studies have explored this in adults with kidney disease. Only three studies considered diet in their study design \(^{[37, 43, 76]}\), of which, only two provided adequate details of the methodology used and considered the dietary outcomes as co-variates in their analysis of the microbiota. Other, limitations
existed within the included studies as noted by Barrios et al.\textsuperscript{[37]} who reported that information relating to dietary assessment and antibiotic use was only available for 11% of their sample, making interpretation of the results difficult. To date, the majority of the published studies have focused largely on the effect of nutritional supplements such as prebiotics and probiotics to improve gut health and symptoms in individuals with kidney disease. Unfortunately these types of therapies add further to the pill burden for this patient group\textsuperscript{[79]}, and have produced inconsistent results in either case\textsuperscript{[80-83]}. Clinical trials that explore the effects of dietary components, such as dietary fiber in other clinical conditions are emerging\textsuperscript{[84]}. However, few studies have examined the effect of dietary patterns on the gut microbiome in kidney disease. Because nutrients are not consumed in isolation, exploring the impact of whole foods and overall dietary patterns on the gut microbiota offers a more superior and rigorous methodological approach. Furthermore, the addition of other sophisticated multi-omic technologies such as metabolomics \textsuperscript{[85, 86]} may also be warranted to provide a more comprehensive exploration of the metabolic interactions between the microbiome and diet in the context of kidney disease.

Our study has several limitations. Overall, the evaluation of results relating to alterations in the gut microbiota was difficult to evaluate largely due to heterogeneity based on methodologies used and reporting of results. This made conducting a meta-analysis not possible. Majority of cited studies had small sample sizes and background information relating to diet, comorbidities, medications and other lifestyle factors (such as smoking status, alcohol consumption and physical activity), were poorly accounted for and this may have influenced the results. The strength of this review is reflected in its design to highlight the current state of evidence in the area of the gut microbiota and kidney
disease, and hopefully serve to unify methods and improve study design needed to produce complementary findings and progress this field of research.

Conclusions

The gut microbiota profile of adults with kidney disease or kidney stones was consistently reported to be substantially different to healthy individuals. Evidence for altered genetic functions of the gut microbiota in adults with kidney disease and disorders, suggests a potential role of the gut microbiota in modulating host metabolism, particularly in the context of uremic toxin generation, although greater investigation is required. Future research aiming to transform our understanding of the interactions between the microbiota and nutrition is needed, underpinned by validated dietary data collection methods and analytical techniques. Studies with high statistical power, comparable and reproducible methods, as well as the utilisation of more sophisticated multi-omic technologies such as metagenomics and metabolomics, are required to map functional capabilities and more clearly elucidate the role of the microbiota in kidney health.

Abbreviations

CKD: Chronic kidney disease
DGGE: Denaturing gradient gel electrophoresis
EPIC: European Prospective Investigation of Cancer and Nutrition
ESKD: End stage kidney disease
FFQ: Food Frequency Questionnaire
FISH: Fluorescence in situ hybridization
HD: Haemodialysis
IBD: Inflammatory bowel disease
IgAN: Immunoglobulin A nephropathy
IS: Indoxyl sulfate
KEGG: Kyoto Encyclopedia of Genes and Genomes
LPS: Lipopolysaccharides
NOS: Newcastle-Ottawa Scale
PAG: Phenylacetylglutamine
PCR: Polymerase chain reaction
PCS: P-cresyl sulfate
PD: Peritoneal Dialysis
PICRUSt: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
qPCR: Quantitative polymerase chain reaction
rRNA: ribosomal RNA
SCFA: Short chain fatty acid
TMA: Trimethylamine
TMAO: Trimethylamine N-oxide

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and materials
The datasets supporting the conclusions of this article are included within the article and/or its additional files. Please refer to the manuscript's additional files for the following
supplementary information:
Final search strategy for all databases can be found in Item 1
Datasets presenting the reported direction of microbial alteration in adults with kidney disease can be found in Table S1
Datasets presenting the reported direction of microbial alteration in adults with kidney stones can be found in Table S2

**Competing interests**
The authors declare that they have no competing interests.

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**Authors’ contributions**
Research idea and study design: KL, JS; data acquisition: JS, RI; data analysis/interpretation: JS, KL, KC, ASN; supervision or mentorship: KL, KC, ASN. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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**Additional files**
Additional file 1- Item 1: Complete database search strategy; Table S1: Dataset for kidney diseases; Table S2: Dataset for kidney stones.

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Tables

Table 1. The system of evidence level criteria

| Grading     | Criterion                                                                 |
|-------------|---------------------------------------------------------------------------|
| Strong      | Consistent findings (≥75%) in at least 2 high-quality studies              |
| Moderate    | Consistent findings in one high-quality study and at least one low-quality study |
| Weak        | Findings of one high-quality study or consistent findings (≥75%) in at least 3 or more low-quality studies |
| Inconclusive| Inconsistent findings, or consistent findings (≥75%) reported in less than 3 low-quality studies |

Table 2. Characteristics of included studies
| Country       | Ethnicity | Age       | Gender | Sample Preparation | Storage Conditions | Exclusion Criteria |
|--------------|-----------|-----------|--------|--------------------|--------------------|-------------------|
| Ticinesi, 2018 | Italy     | N=52 recurrent idiopathic calcium stones 48±11yrs, 60% male | Ethnicity not reported | N=48 47±13yrs 58% male | Self-sampled; Stored at -22°C; Processed ≤2 weeks of receipt | Excluded if taken in prior 30 days |
| Stern, 2016   | USA       | N=23; all stone types included 53.7 ± 15.4yrs; 22% male 13% African American, 35% Hispanic, 52% Caucasian | | N=6 53.5±16.0 yrs, 67% male 50% African American, 50% Caucasian | Self-sampled; Flash frozen with dry ice & stored -80°C | Excluded if taken in prior 2 weeks |
| Tang, 2018    | China     | N=13; stone types not reported. 52.25±7.25yrs; 38% male 100% Chinese | | N=13 55.81±5.79yrs 38% male, 100% Chinese | Self-sampled; Immediately frozen & Stored -80°C (DNA samples stored at -20°C) | Excluded if taken in prior 3 months |
| Suryavanshi, 2016 | India   | N=24 recurrent calcium oxalate stones. 25-50yrs; 100% male | Ethnicity not reported | N=15 22-52yrs; 100% male | Self-sampled; Stored -80°C | Excluded if taken in prior 3 months |
| Study                          | Country | N | CKD Stages | eGFR (Mean ± SD) | Age (Mean ± SD) | Gender (Male %) | Ethnicity | Sample Handling | Inclusion/Exclusion Criteria |
|-------------------------------|---------|---|------------|------------------|----------------|-----------------|-----------|----------------|-----------------------------|
| De Angelis 2014[42]           | Italy   | 32 | 4-5        | 76±15            | 41±10          | 69% males       | 100% Caucasian | Self-sampled; Stored -80°C  | Excluded if take in prior 3 months |
| Subgroups:                    |         |    |            |                  |                |                 |           |                |                             |
| n=16 Non-progressors          |         |    |            |                  |                |                 |           |                |                             |
| eGFR: 30±18                   |         |    |            |                  |                |                 |           |                |                             |
| 45±6yrs; 63% males            |         |    |            |                  |                |                 |           |                |                             |
| n=16 Progressors              |         |    |            |                  |                |                 |           |                |                             |
| eGFR: 43±8yrs; 60% male       |         |    |            |                  |                |                 |           |                |                             |
| 100% Caucasian                |         |    |            |                  |                |                 |           |                |                             |
| Al-Obaide 2017[35]            | USA     | 20 | 4-5        | 16.54 ± 3.01     | 64.4± 2.3yrs   | Ethnicity and gender not reported |         | Self-sampled; Processed ≤24hrs of receipt | Excluded if take in prior 3 months |
| Barrios 2015[37]              | UK      | 62 | 6 ≤60      | eGFR ≤60         | Age/ gender/ ethnicity not reported for sub-sample |         |         | Self-sample; Refrigerated up to 2 days; Stored at -80°C | Data on antibiotics was available for on 11% of the subjects |
| Jiang 2016[40]                | China   | 65 | 1-5        | 55.61 ± 52.55    | 43.45 ± 16.90yrs ; 65% male, Ethnicity not reported |         |         | Self-sampled; Stored at -80°C | Excluded if take in prior 4 weeks |
| Xu 2017[41]                   | China   | 32 | 4-5        | eGFR not reported | 53.34 ±       |                  |           | Self-sampled; Stored at -40°C | Excluded if take in prior month |
| N=16                          |         |    |            |                  |                |                 |           |                |                             |
| eGFR: 96±67                   |         |    |            |                  |                |                 |           |                |                             |
| 43±8yrs; 60% male             |         |    |            |                  |                |                 |           |                |                             |
| 100% Caucasian                |         |    |            |                  |                |                 |           |                |                             |
| Study            | Country | Participants | EGF  | Age  | Gender | Ethnicity | Storage Method | Exclusion Criteria |
|------------------|---------|--------------|------|------|--------|-----------|----------------|-------------------|
| Wang 2012[39]    | China   | N=30         | end  | stage| CKD    | N=10      | Not reported   | Excluded if taken in prior 3 weeks. |
|                  |         |              | stage|      |        |            |                |                   |
|                  |         |              |      |      |        | eGFR: n.r. |                |                   |
|                  |         |              |      |      |        | 54yrs(37-71yrs); |                |                   |
|                  |         |              |      |      |        | 53% male, |                |                   |
|                  |         |              |      |      |        | Ethnicity |                |                   |
|                  |         |              |      |      |        | not reported |                |                   |
| Jiang 2017[38]   | China   | N=52         | stage| 5    | CKD    | N=60      | Self-sampled; Stored at -80°C | Excluded if taken in prior 4 weeks. |
|                  |         |              |      |      |        |            |                |                   |
|                  |         |              |      |      |        | eGFR: 6.86±2.87 |                |                   |
|                  |         |              |      |      |        | 51.58±18.33yrs; |                |                   |
|                  |         |              |      |      |        | 56% male |                |                   |
|                  |         |              |      |      |        | 100% Han |                |                   |
|                  |         |              |      |      |        | nationally |                |                   |
|                  |         |              |      |      |        | Chinese   |                |                   |
| Vaziri 2013[33]  & Wong 2014[34] | USA     | N=24        |      |      |        | N=12      | Not reported   | Excluded if taken in prior 3 months. |
|                  |         |              |      |      |        |            |                |                   |
|                  |         |              |      |      |        | 57±14 yrs; 25% |                |                   |
|                  |         |              |      |      |        | male      |                |                   |
|                  |         |              |      |      |        | Dialysis vintage: |                |                   |
|                  |         |              |      |      |        | ≥3 months, Kt/V |                |                   |
|                  |         |              |      |      |        | =1.5±0.3 |                |                   |
|                  |         |              |      |      |        | Ethnicity not reported |                |                   |
| Renal replacement therapy: peritoneal dialysis | | | |
|---|---|---|---|
| Wang 2012[48] | Taiwan | N=29 | 53.7±11.7yrs; 33% male Dialysis vintage: 49.7±35.4 months. Kt/V and ethnicity not reported |
| | | N=41 | 58.2±12.8yrs 37% male Ethnicity not reported |
| | | Self-sampled; Immediately put on ice; Processed ≤1hr of defecation | Excluded if take in prior 30 day: |

| Mixed kidney disease cohorts | | | |
|---|---|---|---|
| Shi 2014[50] | China | N=52 | HD group: n = 22; Dialysis vintage: 6-40 months, Kt/V not reported. CKD group: n = 30 Age/gender / ethnicity not reported |
| | | N=10 | Age/gender / ethnicity not reported |
| | | Samples immersed in 90% alcohol and stored at -20°C | Excluded if take in prior 3 week: |

| | Austria | N= 30 | 61yrs (54-71); 67% male Dialysis vintage: 25 (15-74) months |
| | | n=15 PD 64yrs (54-69); 80% male Dialysis vintage: 70 (40-197) months. Kt/V and ethnicity not reported |
| | | N=21 | 58yrs (53-62) 43% male Ethnicity not reported. |
| | | Self-sampled; Stored at -80°C | Not reported |

Legend: ESKD= End-stage kidney disease; HD= Haemodialysis, PD= Peritoneal Dialysis; KS= Kidney Stones; HC= Healthy controls; OTU= Operational Taxonomic Unit; Wt=Weight, Ht=Height, WC=Waist Circumference, KS= Kidney stones, T2DM= Type 2 Diabetes mellitus, PPI- Protein pump inhibitors, ESA= Erythropoiesis-stimulating agents, ACEi = Angiotensin-converting-enzyme inhibitor, ARBs = Angiotensin II Receptor Blockers, OHA= Oral Hypoglycaemic Agents; ↓= decreased; ↑= increased.

Table 3. Quality assessment of included articles (n=16)
| Reference | Sampling (4 points) | Confounders controlled (2 points) | Exposure (3 points) | Total rating (9 points) |
|-----------|---------------------|-----------------------------------|---------------------|-------------------------|
| [39]      | + - - -              | --                                | +++                 | 4                       |
| [33, 34]  | + - - -              | + -                               | +++                 | 5                       |
| [50]      | +++--                | --                                | +++                 | 5                       |
| [38, 40, 42, 46] | +++--              | ++                                | +++                 | 6                       |
| [35]      | ++ - -               | + -                               | +++                 | 6                       |
| [37, 41, 44, 45, 48, 49] | +++--          | ++                                | +++                 | 7                       |
| [43]      | +++++                | ++                                | +++                 | 8                       |

Legend: ‘+’ Quality criterion satisfied; ‘-’ Quality criterion not satisfied or insufficient information to adjudicate as satisfied. Studies with a quality score of 7 or above were considered of good quality.

Figures
Figure 1

PRISMA flow diagram.
| Bacteria                                      | Taxa      | Reference        | Decreased | Increased |
|----------------------------------------------|-----------|------------------|-----------|-----------|
| Bacteroidetes | Bacteroidia | Bacteroidales | Family    | [34,38,41,42] |
| Bacteroidetes | Bacteroidia | Bacteroidales | Genus     | [38,41,48]  |
| Firmicutes                                    | Phylum    | [41,49]          |           |           |
| Firmicutes | Bacilli | Lactobacillales | Streptococcaceae | Streptococcus | Genus     | [55,68]  |
| Firmicutes | Clostridiales | Lachnospiraceae | Coprococcus | Genus     | [38, 41,48]  |
| Firmicutes | Clostridiales | Lachnospiraceae | Dorea     | Genus     | [38,41]     |
| Firmicutes | Clostridiales | Lachnospiraceae | Roseburia | Genus     | [38,49,41]  |
| Firmicutes | Clostridiales | Ruminococcaceae | Faecalibacterium | Faecalibacterium Prausnitzii | Species | [38,40,48] |
| Proteobacteria                                | Phylum    | [41,49]          |           |           |
| Proteobacteria | Gammaproteobacteria | Entero bacteriales | Entorobacteriaceae | Family | [34,41,48]  |
| Proteobacteria | Betaproteobacteria | Zetaproteobacteria | Azoaligenaceae | Family | [54,28,41]  |
| Proteobacteria | Gammaproteobacteria | Enterobacteriales | Enterobacteriaceae | Enterobacter | Genus     | [35,39,48] |

**Legend:** Bolded taxa represents the bacteria reported to change in studies; Bacteria not bolded are there for reference only and organised according to detailed taxonomy to illustrate the commonalities of taxonomic distribution of altered microbes.

**Figure 2**

Altered bacteria based on strong/moderate level of evidence for adults with kidney disease compared to healthy controls.
**Supplementary Files**

This is a list of supplementary files associated with the primary manuscript. Click to download.

**SUPPLEMENTARY MATERIAL.docx**