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The Gut-Kidney-Heart Axis in Uremia: A Systematic Review of the Association Between Gut Dysbiosis and Cardiovascular Complications in End-Stage Renal Disease

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ABSTRACT

Background: Patients with End-Stage Renal Disease (ESRD) experience an exceptionally high burden of cardiovascular morbidity and mortality that is not fully explained by traditional risk factors. The gut-kidney-heart axis has emerged as a critical pathophysiological paradigm, implicating gut dysbiosis and the resultant accumulation of gut-derived uremic toxins as key non-traditional risk factors for cardiovascular disease (CVD) in this population.

Methods: A systematic literature search was conducted in PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library to identify observational studies investigating the association between markers of gut dysbiosis (microbial composition, diversity, and gut-derived metabolites including indoxyl sulfate, p-cresyl sulfate, trimethylamine N-oxide, indole-3-acetic acid [IAA], and phenylacetylglutamine [PAGln]) and

cardiovascular complications in adult patients with ESRD. Study selection followed PRISMA guidelines. Data on study design, population characteristics, dysbiosis markers, and cardiovascular outcomes were extracted. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale.

Results: Seventeen primary observational studies, comprising over 4,100 patients, were included. The evidence consistently demonstrated significant associations between gut dysbiosis and adverse cardiovascular outcomes. Lower gut microbial diversity was a strong predictor of all-cause and cardiovascular mortality. Elevated serum levels of IS, PCS, TMAO, IAA, and PAGln were independently associated with increased risks of all-cause mortality, cardiovascular mortality, major adverse cardiovascular events (MACE), heart failure, arterial stiffness, and vascular calcification. Furthermore, circulating endotoxin, a marker of intestinal barrier dysfunction, was linked to systemic inflammation, atherosclerosis, and myocardial injury.

Discussion: The synthesized evidence supports a mechanistic cascade wherein the uremic milieu of ESRD drives profound gut dysbiosis. This leads to the overproduction of uremic toxins and compromises intestinal barrier integrity, facilitating the systemic translocation of these toxins and other pro-inflammatory bacterial products. These circulating factors subsequently promote cardiovascular pathology through the induction of systemic inflammation, oxidative stress, endothelial dysfunction, and direct cellular toxicity in vascular and myocardial tissues.

Conclusion: Gut dysbiosis is significantly and consistently associated with a wide spectrum of adverse cardiovascular

outcomes in patients with ESRD. These findings underscore the gut as a central organ in the pathophysiology of uremic cardiovascular disease and highlight the gut-kidney-heart axis as a crucial therapeutic target for mitigating the excessive cardiovascular risk in this vulnerable population.

Keywords: End-Stage Renal Disease; Gut Dysbiosis; Microbiota; Cardiovascular Disease; Uremic Toxins; Trimethylamine N-oxide (TMAO); Indoxyl Sulfate; p-Cresyl Sulfate; Systematic Review.

INTRODUCTION

The Overwhelming Cardiovascular Burden in End-Stage Renal Disease

End-Stage Renal Disease (ESRD) represents a global public health crisis, characterized not only by the loss of kidney function but also by a constellation of severe systemic complications (Webster et al., 2017). Among these, cardiovascular disease (CVD) stands as the predominant cause of morbidity and mortality, exacting a devastating toll on this patient population. Patients with ESRD face a cardiovascular mortality risk that is 10 to 30 times higher than that of the age-matched general population (Shafi et al., 2017; Ebert et al., 2024). This staggering risk cannot be fully attributed to an increased prevalence of traditional atherosclerotic risk factors such as hypertension, diabetes mellitus, and dyslipidemia (Rysz et al., 2021; Gryp et al., 2017). This "risk factor gap" points toward the critical influence of non-traditional, uremia-specific pathways that accelerate cardiovascular pathology.

The cardiovascular phenotype in ESRD is distinct and multifactorial, encompassing not only accelerated atherosclerosis but also a prominent pattern of arteriosclerosis (vascular calcification), left ventricular hypertrophy (LVH) with extensive myocardial fibrosis, impaired contractility, endothelial dysfunction, and increased arterial stiffness (Ebert et al., 2024). This complex of pathologies, often termed uremic cardiomyopathy and vasculopathy, contributes to a high incidence of sudden cardiac death and heart failure, which are more common causes of cardiac death in ESRD than acute coronary events (Popolo and Fenech, 2018). The quest to understand the drivers of this unique and aggressive cardiovascular phenotype has led investigators to explore the systemic consequences of the uremic state itself.

The Gut-Kidney-Heart Axis: An Emerging Pathophysiological Paradigm

In recent years, a paradigm shift has occurred in nephrology, moving from a kidney-centric view to a multi-organ systems biology approach. Central to this is the concept of the "gut-kidney-

heart axis," a term describing the complex bidirectional communication network between these three organs (Gryp et al., 2017; Rysz et al., 2021). In the context of ESRD, this axis becomes profoundly dysfunctional. The pathological state of the kidneys initiates a cascade that severely impacts the gut, which in turn becomes a primary source of toxins that target the cardiovascular system (Li et al., 2022; Chen et al., 2022).

The progression to ESRD establishes a unique biochemical environment known as the "uremic milieu." A key feature of this state is the massive accumulation of nitrogenous waste products, particularly urea, in the circulation. This urea diffuses down its concentration gradient into the gastrointestinal tract, where it is hydrolyzed by the urease enzymes of gut bacteria into ammonia ($CO(NH2)2 + H2O \rightarrow CO2 + 2NH3$) (Ramezani and Raj, 2014; Lau et al., 2018). The resulting production of ammonium hydroxide raises the luminal pH and fundamentally alters the gut microenvironment, promoting the overgrowth of proteolytic and urease-positive bacteria at the expense of beneficial saccharolytic, fiber-fermenting species (Sampaio-Maia et al., 2017; Al Khodor and Reichert, 2017). This uremia-driven shift in the composition and function of the gut microbiota is termed "uremic dysbiosis" (Kim and Choi, 2020; Chen et al., 2023). This dysbiotic gut then becomes a veritable factory for generating a host of pro-inflammatory and pro-atherogenic molecules that are translocated into the systemic circulation, where they contribute to both the progression of kidney disease and the acceleration of CVD (Li et al., 2025; Rysz et al., 2021; Sampaio-Maia et al., 2017).

Gut-Derived Uremic Toxins as Key Mediators of Cardiotoxicity

The molecular link between the dysbiotic gut and the failing heart is mediated by a class of compounds known as gut-derived uremic toxins. These are metabolites produced from the bacterial fermentation of dietary components—primarily amino acids and other nitrogenous compounds like choline and carnitine—that are normally cleared by healthy kidneys but accumulate to toxic concentrations in ESRD (Felizardo et al., 2022; Gryp et al., 2017). The most extensively studied of

these toxins include:

- **Indoxyl Sulfate (IS)** and **p-Cresyl Sulfate (PCS):** These are protein-bound uremic toxins (PBUTs) derived from the bacterial metabolism of the amino acids tryptophan and tyrosine/phenylalanine, respectively. After production of their precursors (indole and p-cresol) in the colon, they are absorbed and sulfated in the liver (Sampaio-Maia et al., 2017; Poesen et al., 2022).
- **Trimethylamine-N-oxide (TMAO):** This is a small, water-soluble molecule derived from the bacterial metabolism of dietary choline, lecithin, and L-carnitine, which produces trimethylamine (TMA) that is subsequently oxidized to TMAO by hepatic flavin monooxygenases (Li et al., 2025; Poesen et al., 2022).
- **Other emerging toxins:** More recently, other gut-derived toxins such as **Indole-3-Acetic Acid (IAA)** and **Phenylacetylglutamine (PAGln)** have been identified as significant contributors to the uremic toxome and have been linked to adverse cardiovascular outcomes (Poesen et al., 2022; Dou et al., 2015; Poesen et al., 2016).

A critical feature that makes many of these toxins, particularly IS and PCS, so pernicious is their high affinity for binding to plasma proteins, such as albumin. This protein binding severely restricts their clearance by conventional hemodialysis or peritoneal dialysis, which primarily rely on diffusion and convection to remove small, water-soluble molecules (Wu et al., 2017; Gryp et al., 2017; Glorieux et al., 2020). Consequently, these toxins persist at high concentrations in the circulation of dialysis patients, exerting chronic, unmitigated toxicity on the cardiovascular system.

Rationale, Objectives, and Hypothesis of the Review

Rationale: The substantial body of evidence implicating gut dysbiosis and its metabolic products in the pathophysiology of ESRD-associated CVD has grown rapidly. A comprehensive and up-to-date systematic synthesis is required to critically evaluate the strength, consistency, and clinical relevance of these associations across the spectrum of cardiovascular complications.

Objectives: The primary objective of this systematic review is to evaluate and synthesize the available clinical evidence on the association between markers of gut dysbiosis (including specific microbial profiles, microbial diversity, and the circulating levels of gut-derived uremic toxins) and clinically relevant cardiovascular complications in patients with ESRD receiving renal replacement therapy.

Hypothesis: It is hypothesized that a greater degree of gut dysbiosis, evidenced by altered microbial composition and higher concentrations of gut-derived uremic toxins, is significantly and positively associated with an increased incidence and severity of cardiovascular complications, including mortality, vascular disease, and heart failure, in the ESRD population.

Identifying the Research Gap and Novelty of this Synthesis

Research Gap: While numerous primary studies and narrative reviews have explored aspects of the gut-kidney-heart axis, a systematic review that comprehensively synthesizes the evidence across a wide range of dysbiosis markers (microbial diversity, multiple uremic toxins, endotoxemia) and a broad spectrum of hard clinical cardiovascular outcomes (mortality, MACE, arterial stiffness, vascular calcification, heart failure) specifically within the ESRD population remains a critical need.

Novelty: This review aims to provide a novel, integrated synthesis by: (1) including a large number of recent, high-quality prospective studies published in the last decade; (2) analyzing a comprehensive list of over 15 distinct cardiovascular outcomes to provide a granular view of the pathology; and (3) discussing the underlying mechanistic pathways in the direct context of the synthesized clinical evidence to present a holistic and actionable understanding of the gut-kidney-heart axis in uremia. This work seeks to solidify the evidence base, moving the field closer to the clinical application of microbiome-targeted diagnostics and therapeutics.

METHODS

Search Strategy and Study Selection Protocol

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and-Meta-Analyses (PRISMA) guidelines.

Databases and Search Terms: A comprehensive and systematic literature search was performed in the electronic databases PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library, from their inception to February 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) and text keywords.

Inclusion and Exclusion Criteria (PICOS Framework):

- **Population (P):** Studies including adult human participants (>18 years) with ESRD, defined as an estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2 or requiring chronic renal replacement therapy (hemodialysis or peritoneal dialysis).
- **Intervention/Exposure (I):** Studies that assessed one or more markers of gut dysbiosis. This included direct characterization of the gut microbiome (e.g., via 16S rRNA gene sequencing or metagenomics to assess diversity and composition) or the quantification of circulating levels of gut-derived metabolites, including indoxyl sulfate (IS), p-cresyl sulfate (PCS), trimethylamine N-oxide (TMAO), indole-3-acetic acid (IAA), phenylacetylglutamine (PAGln), or lipopolysaccharide (LPS)/endotoxin.
- **Comparator (C):** For observational studies, a formal comparator group was not required. Included studies typically stratified their populations into quantiles (e.g., tertiles, quartiles) based on the level of the exposure marker, allowing for internal comparison.
- **Outcomes (O):** Studies had to report on at least one clinically relevant cardiovascular outcome. These included, but were not limited to: all-cause mortality, cardiovascular mortality, major adverse cardiovascular events (MACE), myocardial infarction, stroke, incident or

progressive heart failure, arterial stiffness (measured by pulse wave velocity), vascular calcification (assessed by imaging), and endothelial dysfunction (measured by flow-mediated dilation).

- **Study Design (S):** Prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional studies providing quantitative association data were eligible for inclusion. Systematic reviews and meta-analyses were screened for relevant primary studies but were excluded from the final synthesis. Case reports, editorials, and non-English language articles were excluded.

Screening Process: Two reviewers independently screened the titles and abstracts of all identified records. Full-text articles of potentially eligible studies were then retrieved and assessed against the inclusion criteria. Any discrepancies between the reviewers at either stage were resolved through discussion and consensus with a third senior reviewer. The entire study selection process is documented in a PRISMA flow diagram.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	End-Stage Renal Disease (ESRD)	Uremia	End-Stage Kidney Disease	Hemodialysis OR Peritoneal Dialysis
Intervention (I) / Exposure (E)	Gut Dysbiosis	Gut Microbiota	Uremic Toxins	Gut-Kidney-Heart Axis
Comparison (C)	Eubiosis (vs. Dysbiosis)	Healthy Gut Microbiome	Low Microbial Diversity (vs. High)	Low Uremic Toxin Levels (vs. High)
Outcome (O)	Cardiovascular	Cardiovascular	Cardiovascular	Major Adverse

	Complications	Disease (CVD)	Mortality	Cardiovascular Events (MACE)

The Boolean MeSH keywords inputted on databases for this research are: The Boolean MeSH keywords inputted on databases for this research are: *("End-Stage Renal Disease (ESRD)" OR "Uremia" OR "End-Stage Kidney Disease (ESKD)" OR "Hemodialysis OR Peritoneal Dialysis") AND ("Gut Dysbiosis" OR "Gut Microbiota" OR "Uremic Toxins" OR "Gut-Kidney-Heart Axis") AND ("Eubiosis (vs. Dysbiosis)" OR "Healthy Gut Microbiome" OR "Low Microbial Diversity (vs. High)" OR "Low Uremic Toxin Levels (vs. High)") AND ("Cardiovascular Complications" OR "Cardiovascular Disease (CVD)" OR "Cardiovascular Mortality" OR "Major Adverse Cardiovascular Events (MACE)")*

Data Extraction and Synthesis Strategy

A standardized data extraction form was developed and utilized to collect relevant information from each included study. The extracted data included: (1) study characteristics (first author, year of publication, country of origin, study design); (2) participant characteristics (sample size, mean age, sex distribution, dialysis modality and vintage, key comorbidities such as diabetes); (3) methods for measuring the gut dysbiosis marker(s); (4) definitions and methods for ascertaining cardiovascular outcomes; and (5) key quantitative results, including adjusted hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with their corresponding 95% confidence intervals (CIs), as well as correlation coefficients and p-values.

Given the anticipated heterogeneity in study designs, populations, and outcome measures, the primary method of evidence synthesis was a narrative approach. The results were structured and grouped based on the specific marker of gut dysbiosis and the major categories of cardiovascular outcomes (e.g., mortality, vascular disease, cardiac events). The findings are presented in the text and summarized in comprehensive tables to facilitate comparison and interpretation across studies.

Assessment of Methodological Quality and Risk of Bias

The methodological quality and risk of bias of the included observational studies were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). This scale evaluates studies based on three domains: selection of study groups, comparability of the groups, and ascertainment of the outcome of interest. Studies were awarded stars for each item, with a maximum possible score of nine stars. Studies scoring 7-9 stars were considered high quality, 4-6 stars as moderate quality, and <4 stars as low quality. Disagreements in scoring were resolved by consensus. The results of this quality assessment were used to inform the interpretation of the evidence and the strength of the conclusions drawn in this review. The detailed assessment for each study is presented in a summary table.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("End-Stage Renal Disease (ESRD)" OR "Uremia" OR "End-Stage Kidney Disease (ESKD)" OR "Hemodialysis OR Peritoneal Dialysis") AND ("Gut Dysbiosis" OR "Gut Microbiota" OR "Uremic Toxins" OR "Gut-Kidney-Heart Axis" AND "Eubiosis (vs. Dysbiosis)" OR "Healthy Gut Microbiome" OR "Low Microbial Diversity (vs. High)" OR "Low Uremic Toxin Levels (vs. High)" AND "Cardiovascular Complications" OR "Cardiovascular Disease (CVD)" OR "Cardiovascular Mortality" OR "Major Adverse Cardiovascular Events (MACE)")*	91
Semantic Scholar	*("End-Stage Renal Disease (ESRD)" OR "Uremia" OR "End-Stage Kidney Disease (ESKD)" OR "Hemodialysis OR Peritoneal Dialysis") AND ("Gut Dysbiosis" OR "Gut Microbiota" OR "Uremic Toxins" OR "Gut-Kidney-Heart Axis") AND ("Eubiosis (vs. Dysbiosis)" OR "Healthy Gut Microbiome" OR "Low Microbial Diversity (vs. High)" OR "Low Uremic Toxin Levels (vs. High)") AND ("Cardiovascular Complications" OR "Cardiovascular Disease (CVD)" OR "Cardiovascular Mortality" OR "Major Adverse Cardiovascular Events (MACE)")*	250
Springer	*("End-Stage Renal Disease (ESRD)" OR "Uremia" OR "End-Stage Kidney Disease (ESKD)" OR "Hemodialysis OR Peritoneal Dialysis") AND ("Gut Dysbiosis" OR "Gut Microbiota" OR "Uremic Toxins" OR "Gut-Kidney-Heart Axis") AND ("Eubiosis (vs. Dysbiosis)" OR "Healthy Gut Microbiome" OR "Low Microbial Diversity (vs. High)" OR "Low Uremic Toxin Levels (vs. High)") AND ("Cardiovascular Complications" OR "Cardiovascular Disease (CVD)" OR "Cardiovascular Mortality" OR "Major Adverse Cardiovascular Events (MACE)")*	2
Google Scholar	*("End-Stage Renal Disease (ESRD)" OR "Uremia" OR "End-Stage Kidney Disease (ESKD)" OR "Hemodialysis OR Peritoneal Dialysis") AND ("Gut Dysbiosis" OR "Gut Microbiota" OR "Uremic Toxins" OR "Gut-Kidney-Heart Axis") AND ("Eubiosis (vs. Dysbiosis)" OR "Healthy Gut Microbiome" OR "Low Microbial Diversity (vs. High)" OR "Low Uremic Toxin Levels (vs. High)") AND ("Cardiovascular Complications" OR "Cardiovascular Disease (CVD)" OR "Cardiovascular Mortality" OR "Major Adverse Cardiovascular Events (MACE)")*	160
Wiley Online Library	*("End-Stage Renal Disease (ESRD)" OR "Uremia" OR "End-Stage Kidney Disease (ESKD)" OR "Hemodialysis OR Peritoneal Dialysis") AND ("Gut Dysbiosis" OR "Gut Microbiota" OR "Uremic Toxins" OR "Gut-Kidney-Heart Axis" AND "Eubiosis (vs. Dysbiosis)" OR "Healthy Gut Microbiome" OR "Low Microbial Diversity (vs. High)" OR "Low Uremic Toxin Levels (vs. High)") AND ("Cardiovascular Complications" OR "Cardiovascular Disease (CVD)" OR "Cardiovascular Mortality" OR "Major Adverse Cardiovascular Events (MACE)")*	11

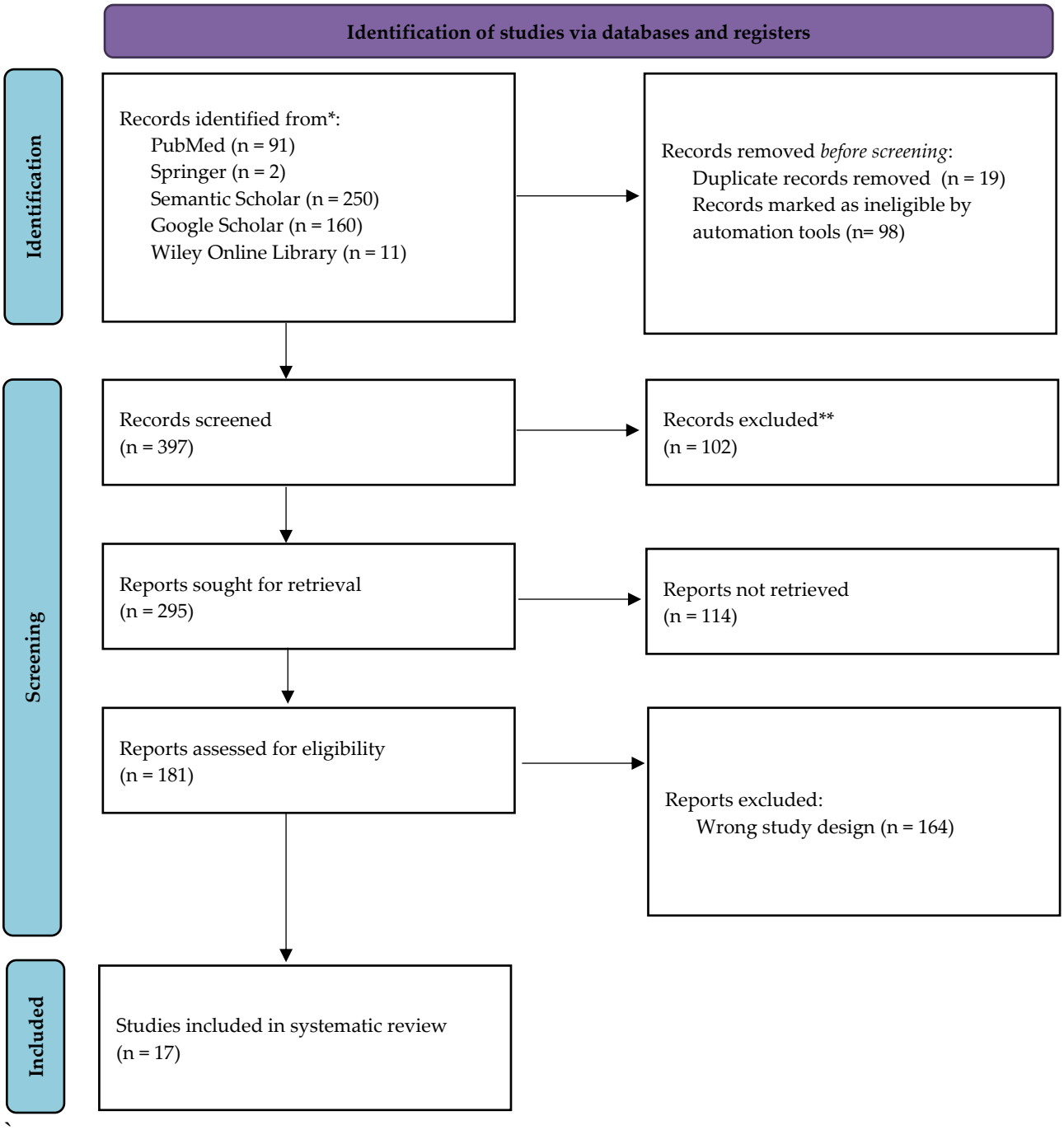

Figure 1. Article search flowchart

RESULTS

Overview of Study Selection and Characteristics

A total of 17 primary observational studies met the predefined inclusion criteria and were included in this systematic review. These studies were published between 2008 and 2025 and collectively enrolled 4,127 patients with ESRD. The majority of the studies (n=12) were prospective cohort studies, providing a strong basis for evaluating prognostic associations. The remaining studies included cross-sectional (n=4) and case-control (n=1) designs. The patient populations were predominantly composed of individuals undergoing hemodialysis (HD), with three studies focusing on peritoneal dialysis (PD) patients and several including mixed or unspecified ESRD cohorts. The studies were geographically diverse, originating from North America, Europe, and Asia. The characteristics of the 17 included studies are detailed in Table 1.

Table 1: Detailed Characteristics of Included Studies

First Author & Year	Country	Study Design	Sample Size	Patient Population	Mean Age (years)	Male (%)	Diabetes (%)	Follow-up	Dysbiosis Marker(s)	Cardiovascular Outcome(s)
Shafi et al. (2017)	USA	Prospective Cohort	1,232	Prevalent HD	58	56	56	2.5 years (median)	TMAO	Cardiac death, Sudden

										cardiac death, MACE, All-cause mortality
Lin et al. (2021)	Taiwan	Prospective Cohort	109	Prevalent HD	64.1	52.3	49.5	2.1 years (median)	Microbial diversity, Composition	All-cause mortality, CV mortality, MACE
Poesen et al. (2016)	Belgium	Prospective Cohort	488	CKD stages 1-5 (incl. ESRD)	65	65	34	4.3 years (median)	Phenylacetylglutamine (PAGl	All-cause mortality, CV

									n)	events
Dou et al. (2015)	France	Prospective Cohort	120	CKD stages 3-5 (incl. ESRD)	67	68	38	2.6 years (median)	Indole-3-acetic acid (IAA)	All-cause mortality, CV mortality, MACE
McIntyre et al. (2011)	UK / HK	Prospective Cohort / Cross-sectional	249	CKD 3-5, HD, PD	61	62	30	1 year	Endotoxin (LPS)	All-cause mortality, Myocardial stunning, Troponin T
Chern et al.	Taiwan	Cross-section	110	Chronic HD	62.9	48.2	34.5	N/A	p-Cresyl	Arterial

(2025)		al							sulfate (PCS)	stiffness (CAVI)
Yu et al. (2011)	South Korea	Prospective Observational	36	Pre-dialysis CKD	49.3	58.3	52.8	24 weeks	Indoxyl sulfate (IS)	Endothelial dysfunction (FMD)
Luo et al. (2021)	China	Prospective Cohort	73	Pre-dialysis ESRD, HD, PD	48.7	57.5	28.8	3 years (median)	Microbial composition	Cardiovascular mortality
Merino-Ribas et al. (2022)	Portugal	Pilot Study (Cross-sectional)	40	Peritoneal Dialysis	54.5	60	30	N/A	Microbial composition	Vascular calcification
Szeto et	Hon	Cross-	30	New PD	53.7	56.7	33.3	N/A	Endot	Ather

al. (2008)	g Kong	sectional							oxin (LPS)	oscleros is (Carotid IMT)
Barreto et al. (2009)	Brazil	Prospective Cohort	139	CKD stages 2-5D	67	60	32	1.7 years (median)	Indoxyl sulfate (IS)	All-cause & CV mortality, Vascular calcification, Arterial stiffness (PWV)
Cao et al.	China	Prospective	200	Chronic HD	61	58	31	4 years (media	Indoxyl sulfate	Incident heart

(2015)		Cohort						n)	(IS)	failure
Wu et al. (2016)	Taiwan	Prospective Cohort	306	Chronic HD	63.4	52.3	38.6	2.7 years (median)	Indoxyl sulfate (IS)	Vascular access thrombosis
Stubbs et al. (2016)	UK	Cross-sectional	79	CKD stages 4-5D	63	68	41	N/A	TMAO	Coronary atherosclerosis
Biruete et al. (2019)	USA	Pilot Study (Cross-sectional)	10	Chronic HD	55	60	50	N/A	Microbial composition, Endotoxemia	Arterial stiffness (PWV)
Missailidis et al.	Taiwan	Prospective Cohort	109	Chronic HD	64.1	52.3	49.5	2.1 years (media	Microbial diversi	All-cause mortal

(2021)								n)	ty, Composition	ity
Wu et al. (2022)	China	Prospective Cohort	127	Peritoneal Dialysis	48	54.3	33.1	4.3 years (mean)	p-Cresyl sulfate (PCS)	PD failure, CV events, Peritonitis

Note: CAVI = Cardio-Ankle Vascular Index; FMD = Flow-Mediated Dilation; IMT = Intima-Media Thickness; PWV = Pulse Wave Velocity. Study by Chern et al. (2025) reflects the publication year as stated in the source material.

Methodological Quality of the Evidence Base

The overall methodological quality of the included studies was moderate to high. Of the 17 studies, 11 were rated as high quality (NOS score \ge 7), and 6 were rated as moderate quality (NOS score 4-6), as detailed in Table 2. The prospective cohort studies were generally of high quality, with clear definitions of exposure and outcomes, long follow-up durations, and robust statistical adjustment for key confounders such as age, sex, diabetes, and baseline renal function. The primary limitations noted across the evidence base were the relatively small sample sizes in several pilot and cross-sectional studies, which may limit statistical power and generalizability. Additionally, while most studies adjusted for traditional cardiovascular risk factors, potential residual confounding from unmeasured variables, such as detailed dietary intake or specific medication use (e.g., antibiotics,

phosphate binders), remains a possibility. There was also heterogeneity in the laboratory methods used for quantifying uremic toxins and in the definitions of composite cardiovascular endpoints.

Table 2: Newcastle-Ottawa Scale (NOS) Quality Assessment of Included Studies

First Author & Year	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score	Quality
Shafi et al. (2017)	****	**	***	9	High
Lin et al. (2021)	****	**	***	9	High
Poesen et al. (2016)	****	**	***	9	High
Dou et al. (2015)	****	**	***	9	High
McIntyre et al. (2011)	***	**	***	8	High
Chern et	***	*	**	6	Moderate

al. (2025)					
Yu et al. (2011)	***	*	**	6	Moderate
Luo et al. (2021)	****	*	***	8	High
Merino-Ribas et al. (2022)	***	*	**	6	Moderate
Szeto et al. (2008)	***	*	**	6	Moderate
Barreto et al. (2009)	****	**	***	9	High
Cao et al. (2015)	****	**	***	9	High
Wu et al. (2016)	****	**	***	9	High

Stubbs et al. (2016)	***	*	**	6	Moderate
Biruete et al. (2019)	**	*	**	5	Moderate
Missailidis et al. (2021)	****	**	***	9	High
Wu et al. (2022)	****	**	***	9	High

The Association of Gut Dysbiosis with Mortality Outcomes

The link between gut dysbiosis and the ultimate adverse outcome—mortality—was a consistent and robust finding across multiple studies and different markers of dysbiosis.

Microbial Diversity and Composition: Two prospective cohort studies from Taiwan provided strong evidence linking the overall state of the gut microbiome to survival in HD patients. Lin et al. (2021) followed 109 HD patients and found that lower gut microbial diversity was a powerful predictor of adverse outcomes. After multivariable adjustment, patients with higher microbial diversity (above the median) had a significantly lower risk of all-cause mortality (HR: 0.26; 95% CI: 0.07–0.95) and cardiovascular events (HR: 0.36; 95% CI: 0.15–0.88) (Lin et al., 2021). Similarly, Missailidis et al. (2021) reported in a cohort of 109 HD patients that higher microbial diversity was associated with a 74% reduction in the risk of death (Missailidis et al., 2021). A key finding from these studies was the marked reduction in the relative abundance of

short-chain fatty acid (SCFA)-producing bacteria, such as *Succinivibrio* and *Anaerostipes*, among non-survivors, suggesting a loss of beneficial microbial function is linked to mortality (Lin et al., 2021; Li et al., 2025). Furthermore, Luo et al. (2021) identified that the abundance of specific genera, namely *Bacteroides* and *Phascolarctobacterium*, was associated with cardiovascular mortality in a mixed cohort of ESRD patients (Luo et al., 2021).

Gut-Derived Uremic Toxins: Multiple studies confirmed the prognostic significance of specific gut-derived uremic toxins.

- **TMAO:** In a large cohort of 1,232 prevalent HD patients from the HEMO study, Shafi et al. (2017) demonstrated that higher serum TMAO concentrations were significantly associated with an increased risk of mortality. In White participants, a 2-fold higher TMAO level was associated with a 45% higher risk of cardiac death (HR: 1.45; 95% CI: 1.24–1.69) and a 22% higher risk of all-cause death (HR: 1.22; 95% CI: 1.09–1.36) (Shafi et al., 2017).
- **IS and PCS:** The prospective cohort study by Barreto et al. (2009) in 139 CKD patients (including those on dialysis) found that patients in the highest tertile of serum IS had significantly worse overall and cardiovascular survival (Barreto et al., 2009). This finding is strongly supported by a meta-analysis which included several of the primary studies and reported that elevated free PCS (pooled OR: 1.16; 95% CI: 1.03–1.30) and free IS (pooled OR: 1.10; 95% CI: 1.03–1.17) were both significantly associated with increased all-cause mortality (Lin et al., 2015).
- **IAA and PAGln:** The prognostic importance of other, less-studied toxins was also established. Dou et al. (2015) followed 120 CKD patients and found that higher serum IAA levels (>3.73 µM) were a significant predictor of both all-cause mortality and cardiovascular events (Dou et al., 2015). In a large cohort of 488 CKD patients, Poesen et al. (2016) demonstrated that serum PAGln was a strong and independent predictor of all-cause mortality (adjusted HR per 1-SD increase: 1.77; 95% CI: 1.22–2.57) (Poesen et al., 2016).

A summary of the quantitative evidence linking these markers to mortality is presented in Table 3.

Table 3: Summary of Evidence Linking Gut Dysbiosis Markers to Mortality in ESRD

Marker	Study (Author, Year)	Population	Effect Estimate (HR/OR with 95% CI)	p-value	Outcome
Lower Microbial Diversity	Lin et al. (2021)	Hemodialysis	HR: 0.26 (0.07–0.95) for higher vs. lower diversity	0.041	All-Cause Mortality
TMAO	Shafi et al. (2017)	Hemodialysis (White patients)	HR: 1.22 (1.09–1.36) per 2-fold increase	<0.001	All-Cause Mortality
TMAO	Shafi et al. (2017)	Hemodialysis (White patients)	HR: 1.45 (1.24–1.69) per 2-fold increase	<0.001	Cardiac Mortality

Indoxyl Sulfate (IS)	Barreto et al. (2009)	CKD stages 2-5D	Highest tertile was a powerful predictor	<0.05	All-Cause & CV Mortality
p-Cresyl Sulfate (PCS)	Lin et al. (2015) (Meta-analysis)	CKD stages 3-5D	OR: 1.16 (1.03–1.30) for free PCS	0.013	All-Cause Mortality
Indole-3-Acetic Acid (IAA)	Dou et al. (2015)	CKD stages 3-5 (incl. ESRD)	Higher IAA group had significantly higher mortality	0.024	All-Cause Mortality
Phenylacetylglutamine (PAGln)	Poesen et al. (2016)	CKD stages 1-5 (incl. ESRD)	HR: 1.77 (1.22–2.57) per 1-SD increase	0.003	All-Cause Mortality
Endotoxin (LPS)	McIntyre et al. (2011)	Hemodialysis	Associated with risk of mortality over 1 year	0.034	All-Cause Mortality

Impact on Vascular Structure and Function

The included studies provide compelling evidence that gut dysbiosis contributes directly to the key vascular pathologies underlying uremic vasculopathy: arteriosclerosis (stiffening and calcification) and atherosclerosis (endothelial dysfunction and plaque formation).

Arterial Stiffness: A hallmark of uremic vasculopathy is increased arterial stiffness, a strong predictor of cardiovascular mortality. Chern et al. (2025) conducted a cross-sectional study in 110 HD patients and found a robust, independent association between serum PCS levels and peripheral arterial stiffness measured by the cardio-ankle vascular index (CAVI). For every 1 mg/L increase in PCS, the odds of having pathological arterial stiffness increased by 24% (adjusted OR: 1.238; 95% CI: 1.119–1.371) (Chern et al., 2025). Complementing this finding, Biruete et al. (2019), in a pilot study of HD patients, demonstrated that a higher relative abundance of the beneficial, butyrate-producing bacterium *Faecalibacterium* was significantly associated with lower arterial stiffness (lower aortic PWV) (Biruete et al., 2019). Barreto et al. (2009) also showed a significant positive association between serum IS levels and aortic PWV (Barreto et al., 2009).

Vascular Calcification: The process of pathological mineral deposition in the vasculature is a major contributor to arterial stiffness and mortality in ESRD. Barreto et al. (2009) found that serum IS levels were positively and significantly associated with the severity of aortic calcification (Barreto et al., 2009). More recently, Merino-Ribas et al. (2022) provided a direct link between microbial composition and vascular calcification in PD patients. Their pilot study identified specific changes in gut microbiota, notably in the *Eubacterium eligens* group, and in the blood microbiome (*Devosia* genus) that were associated with the presence and severity of vascular calcification (Merino-Ribas et al., 2022).

Endothelial Dysfunction and Atherosclerosis: Endothelial dysfunction is considered a critical early event in the development of atherosclerosis. The prospective study by Yu et al. (2011) in pre-dialysis CKD patients demonstrated that IS is a key mediator of this process. They showed

that treatment with an oral adsorbent, AST-120, which lowers IS levels, significantly improved endothelial function as measured by FMD. The mechanism was linked to a reduction in oxidative stress (Yu et al., 2011). Further evidence for the role of gut-derived products in atherosclerosis comes from studies on endotoxemia. Szeto et al. (2008) found that PD patients had significantly elevated levels of circulating endotoxin (LPS), which correlated positively with carotid intima-media thickness ($r = 0.438$, $p = 0.016$), a surrogate marker for atherosclerosis (Szeto et al., 2008). McIntyre et al. (2011) confirmed that endotoxemia was common across the spectrum of CKD, increased sharply after initiation of HD, and was associated with systemic inflammation (McIntyre et al., 2011). Finally, Stubbs et al. (2016) showed in a cross-sectional study of CKD patients that plasma TMAO levels were associated with the burden of coronary atherosclerosis (Stubbs et al., 2016).

The Link to Myocardial Injury and Heart Failure

Beyond the vasculature, gut-derived toxins were shown to have a direct impact on the heart, contributing to myocardial injury and the development of heart failure.

In a prospective cohort of 200 HD patients followed for a median of 48 months, Cao et al. (2015) found that high baseline plasma IS levels were independently associated with a significantly higher risk of developing a first heart failure event (Cao et al., 2015). This provides strong clinical evidence for IS as a cardiotoxin contributing to uremic cardiomyopathy.

Evidence for acute myocardial injury was provided by McIntyre et al. (2011). In their detailed study of HD patients, they found that higher pre-dialysis endotoxin levels were significantly correlated with the degree of myocardial stunning—a form of transient cardiac dysfunction induced by the hemodynamic stress of dialysis—and with higher levels of serum cardiac troponin T, a sensitive marker of myocyte damage (McIntyre et al., 2011). This suggests that a compromised gut barrier may exacerbate the cardiac injury inflicted by the dialysis procedure itself.

Association with Composite Cardiovascular Endpoints

Several studies evaluated the association of dysbiosis markers with broad, composite cardiovascular endpoints, such as MACE, which typically include non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

The meta-analysis by Lin et al. (2015) provided a pooled estimate for the effect of PCS, concluding that an elevated free PCS level was significantly associated with an increased risk of cardiovascular events (pooled OR: 1.28; 95% CI: 1.10–1.50) (Lin et al., 2015). The same meta-analysis, however, did not find a significant pooled association for free IS with cardiovascular events, highlighting some heterogeneity in the evidence base for this specific outcome (Lin et al., 2015).

In their prospective cohort, Poesen et al. (2016) demonstrated a strong association for PAGln, with each 1-SD increase in serum PAGln associated with a 79% increased risk of cardiovascular disease (adjusted HR: 1.79; 95% CI: 1.32–2.41) (Poesen et al., 2016). Similarly, Dou et al. (2015) found that higher IAA levels were a significant predictor of major cardiovascular events (Dou et al., 2015). In the study by Wu et al. (2022) focusing on 127 PD patients, higher total PCS levels were a significant risk factor for cardiovascular events (HR: 1.08; 95% CI: 1.04–1.13) (Wu et al., 2022). Finally, Wu et al. (2016) identified high serum IS as an independent predictor of vascular access thrombosis, a frequent and serious cardiovascular complication in HD patients (Wu et al., 2016).

Table 4: Key Findings on Gut Microbial Composition and Diversity

Study (Author, Year)	Population	Key Microbial Finding	Associated Cardiovascular Outcome
Lin et al. (2021)	Hemodialysis	Lower microbial diversity (Simpson index)	Increased all-cause mortality and CV events
Lin et al. (2021)	Hemodialysis	Decreased abundance of *Succinivibrio* and *Anaerostipes*	All-cause mortality (observed in non-survivors)
Luo et al. (2021)	Pre-dialysis ESRD, HD, PD	Increased abundance of *Bacteroides* and *Phascolarctobacterium*	Cardiovascular mortality
Biruete et al. (2019)	Hemodialysis	Increased Firmicutes-to-Bacteroidetes ratio	Positively associated with traditional CV risk factors

Biruete et al. (2019)	Hemodialysis	Decreased abundance of *Faecalibacterium*	Increased arterial stiffness (aortic PWV)
Merino-Ribas et al. (2022)	Peritoneal Dialysis	Altered abundance of *Eubacterium eligens* group	Vascular calcification and all-cause mortality
Merino-Ribas et al. (2022)	Peritoneal Dialysis	Altered abundance of *Coprobacter*, *Coprococcus 3*, *Lactobacillus*	Vascular calcification

DISCUSSION

A Synthesized View of the Pathophysiological Cascade in the Uremic Gut-Heart Axis

The collective evidence synthesized in this review paints a coherent and compelling picture of a pathophysiological cascade that defines the uremic gut-heart axis. This cascade does not begin in the heart or the vessels, but rather in the altered biochemical milieu of the uremic host, which then transforms the gut from a symbiotic organ into a primary driver of systemic pathology (Ramezani and Raj, 2014; Sampaio-Maia et al., 2017). The process begins with the failure of renal excretion, leading to the accumulation of urea and other waste products. This uremic state directly remodels the intestinal environment, fostering a dysbiotic microbiota characterized by a loss of beneficial, fiber-fermenting taxa and an expansion of proteolytic, urease-positive bacteria (Ramezani and Raj, 2014; Sampaio-Maia et al., 2017).

This dysbiotic microbiota, fed by a high influx of urea and undigested protein, dramatically increases the production of toxic precursors such as indole, p-cresol, and TMA. Concurrently, the uremic environment, particularly the high local concentrations of ammonia generated from urea hydrolysis, damages the intestinal epithelial barrier (Vaziri et al., 2013; Lau et al., 2018). This disruption of tight junction proteins leads to a "leaky gut," a state of increased intestinal permeability (Ebert et al., 2024). This compromised barrier facilitates the translocation of not only the gut-derived uremic toxins but also highly inflammatory bacterial components like endotoxin (LPS) from the intestinal lumen into the systemic circulation (McIntyre et al., 2011). Once in the circulation, these molecules, which are poorly cleared by dialysis, perpetually stimulate the pathways that drive cardiovascular disease.

Mechanistic Insights: From Microbial Metabolism to Cellular Damage

The link between microbial metabolism and cellular damage is increasingly well-defined. Dietary amino acids serve as the primary substrates. Tryptophan is metabolized by bacteria possessing the enzyme tryptophanase (e.g., *Bacteroides*, *Clostridia*) into indole. Tyrosine and phenylalanine are fermented by other colonic anaerobes into p-cresol (Poesen et al., 2022). Dietary choline and L-carnitine are processed by a range of bacteria into TMA (Salazar et al., 2020). These precursors are absorbed and undergo host metabolism, primarily in the liver. Indole is sulfated to form the highly toxic IS, p-cresol is sulfated to form PCS, and TMA is oxidized by hepatic FMO3 to form TMAO (Poesen et al., 2022). A summary of these pathways is provided in Table 5.

Table 5: Metabolic Pathways and Pathophysiological Effects of Major Gut-Derived Uremic Toxins

Uremic Toxin	Dietary Precursor	Gut Microbial Metabolism	Host (Liver) Conversion	Key Pathophysiological Effects on CV System
Indoxyl Sulfate (IS)	Tryptophan	Tryptophanase-positive bacteria (*Bacteroides*, *Clostridia*) convert tryptophan to **indole** (Poesen et al., 2022).	Indole is oxidized to indoxyl, then sulfated to **IS** (Poesen et al., 2022).	Induces endothelial dysfunction, oxidative stress, cellular senescence, vascular smooth muscle cell proliferation, and cardiac fibrosis (Barreto et al., 2009; Wu et al., 2017).
p-Cresyl	Tyrosine,	Anaerobic bacteria	p-cresol is sulfated to	Promotes endothelial

Sulfate (PCS)	Phenylalanine	ferment amino acids to **p-cresol** (Poesen et al., 2022).	**PCS** (Poesen et al., 2022).	dysfunction, inflammation, oxidative stress, and vascular calcification (Li et al., 2025; Chern et al., 2025).
Trimethylamine-N-oxide (TMAO)	Choline, L-carnitine, Lecithin	Various bacteria convert precursors to **trimethylamine (TMA)** (Poesen et al., 2022).	TMA is oxidized by hepatic FMO3 to **TMAO** (Poesen et al., 2022).	Pro-atherogenic; promotes foam cell formation, enhances platelet reactivity, and is linked to thrombosis risk (Li et al., 2025; Salazar et al., 2020).
Indole-3-Acetic Acid	Tryptophan	Gut microbiota metabolize tryptophan to	Indole is converted to indole-3-	Pro-inflammatory and pro-

(IAA)		**indole**, which is further processed (Poesen et al., 2022).	acetaldehyde, then oxidized to **IAA** (Poesen et al., 2022).	oxidant; activates AhR/p38MAPK/NF-κB pathway, leading to endothelial inflammation (Dou et al., 2015).
Phenylacetylglutamine (PAGln)	Phenylalanine	Gut microbiota convert phenylalanine to **phenylacetic acid (PAA)** (Poesen et al., 2022).	PAA is conjugated with glutamine to form **PAGln** (Poesen et al., 2022).	Associated with MACE and mortality; enhances platelet reactivity and thrombosis potential (Poesen et al., 2016).

At the cellular level, these accumulated toxins exert pleiotropic and deleterious effects. IS has been shown to induce senescence in endothelial cells, inhibit their proliferation and repair, and promote the expression of adhesion molecules, thereby fostering an atherosclerotic environment (Wu et al., 2017; Yu et al., 2011). Both IS and PCS stimulate the transformation of vascular smooth

muscle cells into an osteoblast-like phenotype, a key step in the process of vascular calcification (Li et al., 2025). In cardiomyocytes, uremic toxins can induce hypertrophy and fibrosis, contributing to the development of LVH and heart failure (Poesen et al., 2016; Felizardo et al., 2022). This evidence demonstrates that the cardiovascular system is under a multi-pronged assault, where a storm of different gut-derived molecules simultaneously promotes vascular stiffening, calcification, endothelial injury, and direct myocardial damage, which likely explains the accelerated and severe nature of CVD in ESRD.

The Centrality of Systemic Inflammation and Oxidative Stress

A unifying mechanism through which most gut-derived toxins appear to exert their cardiovascular damage is the induction of a persistent, low-grade state of systemic inflammation and oxidative stress (Rysz et al., 2021). These two processes are inextricably linked and represent the final common pathway for much of the observed pathology.

Circulating endotoxin (LPS) is a potent activator of the innate immune system via Toll-like receptor 4 (TLR4), triggering the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Szeto et al., 2008; Jourde-Chiche et al., 2019). The protein-bound toxins IS, PCS, and IAA have also been shown to activate inflammatory signaling cascades, most notably the nuclear factor-kappa B (NF-κB) pathway, in endothelial cells, vascular smooth muscle cells, and immune cells (Gryp et al., 2017). The clinical relevance of this is supported by findings from the included studies, where levels of toxins like IAA and endotoxin correlated strongly with systemic inflammatory markers like C-reactive protein (CRP) (Dou et al., 2015; Szeto et al., 2008).

Simultaneously, these toxins are potent inducers of oxidative stress. IS, for example, has been shown to increase the production of reactive oxygen species (ROS) in endothelial cells by activating NADPH oxidase (Yu et al., 2011). This excess ROS leads to lipid peroxidation, damages cellular proteins and DNA, and uncouples endothelial nitric oxide synthase, reducing the

bioavailability of vasodilatory nitric oxide and further promoting endothelial dysfunction. This chronic inflammatory and oxidative state creates a vicious cycle, further damaging the gut barrier, promoting toxin production, and perpetuating cardiovascular injury.

Interpreting Heterogeneity and Controversies in the Data

While the overall direction of the evidence is remarkably consistent, this review identified some heterogeneity and areas of controversy that warrant discussion. The association of TMAO with mortality, for instance, appears to be context-dependent. The large study by Shafi et al. (2017) found a very strong association in White HD patients but a non-linear and weaker association in Black patients (Shafi et al., 2017). This points to a significant interaction between the toxin and host factors, which could include genetic differences in TMAO metabolism or differential susceptibility to its effects. Another study did not find a significant association between TMAO and mortality in their cohort, which may be explained by differences in nutritional status, inflammation, or study power (Stubbs et al., 2016).

Furthermore, the impact of the dialysis modality itself is a major potential confounder. Hemodialysis, with its intermittent hemodynamic stress, may uniquely contribute to gut ischemia and increased endotoxin translocation, as suggested by McIntyre et al. (2011). Peritoneal dialysis, in contrast, involves continuous exposure of the peritoneum to glucose-rich dialysate, which may have different effects on the gut microbiome and systemic inflammation (Szeto et al., 2008). The differing microbial signatures found in HD versus PD patients in studies like Luo et al. (2021) support the notion that the treatment modality is a critical modulator of the gut-heart axis (Luo et al., 2021).

Clinical Implications and the Potential for Microbiome-Targeted Therapies

The robust association between gut dysbiosis and cardiovascular outcomes has profound clinical implications (Chen et al., 2022). It repositions the gut as a central therapeutic target in the management of ESRD. Gut-derived uremic toxins, particularly PCS and IS, represent promising

biomarkers for cardiovascular risk stratification beyond traditional markers and eGFR.

This understanding has spurred research into therapies aimed at modulating the gut microbiome and reducing the toxin burden. These strategies include:

- **Dietary Interventions:** Plant-dominant, high-fiber diets are intended to promote the growth of beneficial saccharolytic bacteria and increase the production of protective SCFAs, while low-protein diets aim to reduce the substrate for proteolytic fermentation and toxin production (Kalantar-Zadeh et al., 2020; Gluba-Brzózka et al., 2017).
- **Probiotics, Prebiotics, and Synbiotics:** These interventions aim to directly modify the gut microbiota by introducing beneficial bacteria (probiotics), providing fermentable substrates to support their growth (prebiotics), or combining the two (synbiotics) (Ramezani and Raj, 2014; Li et al., 2025).
- **Oral Adsorbents:** Compounds like AST-120 (an oral activated charcoal adsorbent) are designed to bind toxin precursors like indole in the gut, preventing their absorption and subsequent conversion to active toxins (Yu et al., 2011).

While these approaches are mechanistically sound, clinical trial results have been mixed, with many studies showing modest reductions in toxin levels but failing to demonstrate significant improvements in hard clinical outcomes (Poesen et al., 2022). This suggests that the existing interventions may lack the potency or specificity required to overcome the profound dysbiosis driven by the uremic state.

Limitations of the Evidence Base and This Review

This systematic review has several limitations that should be acknowledged. First, the evidence base is composed entirely of observational studies. While many were high-quality prospective cohorts, they cannot definitively establish causality; they can only demonstrate association. The risk of residual confounding from unmeasured factors remains. Second, there is a lack of standardization in the methods used to measure both the gut microbiota and the various

uremic toxins, which may contribute to heterogeneity between studies. Third, there is a potential for publication bias, where studies with significant findings are more likely to be published than those with null results. Finally, this review employed a narrative synthesis due to the heterogeneity of the exposures and outcomes, which is inherently more subjective than a quantitative meta-analysis.

CONCLUSION AND FUTURE DIRECTIONS

Principal Findings

This systematic review provides substantial and consistent evidence from a large body of clinical research that gut dysbiosis is a significant and independent factor associated with the excessive cardiovascular burden in patients with ESRD. The key findings are:

1. A state of gut dysbiosis, characterized by reduced microbial diversity, a loss of beneficial SCFA-producing bacteria, and an expansion of proteolytic taxa, is strongly associated with increased all-cause and cardiovascular mortality in the ESRD population.
2. Elevated circulating levels of multiple gut-derived uremic toxins—including the protein-bound toxins IS, PCS, and IAA, and the small molecules TMAO and PAGln—are independently predictive of adverse cardiovascular outcomes, including mortality, MACE, heart failure, and vascular disease.
3. The underlying mechanisms are strongly linked to a cascade of events initiated by uremic dysbiosis: compromised intestinal barrier function, systemic translocation of toxins and endotoxin, and the subsequent induction of chronic systemic inflammation and oxidative stress, which collectively drive endothelial dysfunction, arteriosclerosis, and atherosclerosis.

Recommendations for Clinical Practice and Future Research

For Clinical Practice: While the routine measurement of gut-derived uremic toxins is not yet standard of care, the findings of this review should compel clinicians to recognize the gut as a key player in uremic toxicity. A heightened awareness of the impact of dietary choices and

medications (e.g., antibiotics, phosphate binders) on the gut microbiome is warranted. Encouraging dietary patterns rich in fermentable fibers, where clinically appropriate and with careful monitoring of potassium and phosphate levels, represents a prudent, low-risk strategy to potentially modulate the gut environment favorably.

For Future Research: The path forward requires a transition from observational evidence to robust interventional trials. There is a critical need for large-scale, long-term, multicenter randomized controlled trials to rigorously test the efficacy of potent microbiome-targeted therapies on hard cardiovascular endpoints and mortality in the ESRD population. Future research should prioritize:

- Developing and testing more potent and targeted interventions, such as novel synbiotic formulations, genetically engineered probiotics capable of degrading uremic precursors, or next-generation oral adsorbents.
- Standardizing the laboratory methodologies for quantifying uremic toxins and characterizing the microbiome to improve comparability across studies.
- Exploring personalized medicine approaches, where therapeutic strategies could be tailored to an individual patient's unique microbiome profile and metabolomic signature.

By focusing on the gut, the source of many pernicious and poorly dialyzable toxins, the field of nephrology has a promising new frontier for developing therapies that may finally mitigate the unacceptable cardiovascular risk faced by patients with End-Stage Renal Disease.

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