Section: Nephrology

Systematic Review

CHRONIC KIDNEY DISEASE OF UNDETERMINED AETIOLOGY (CKDu) - A SYSTEMATIC REVIEW

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Abstract

Background: Chronic Kidney Disease of Undetermined aetiology (CKDu) poses a significant public health challenge worldwide; however, its aetiology and risk factors are not yet fully understood. This systematic review aimed to synthesise current evidence on the epidemiology, risk factors, genotype associations, and management strategies for CKDu. **Material and Methods:** Following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, a systematic literature search was conducted on PubMed, Embase, and Scopus for peer-reviewed articles published from 2013 to 2024. Additional studies have been conducted using reference mining. The inclusion criteria encompassed original research articles in English, excluding reviews, expert opinions, and conference papers. Data extraction and synthesis were performed using a predesigned table with narrative synthesis owing to data heterogeneity, precluding meta-analysis. **Results:** Seven studies met the inclusion criteria, primarily conducted in India, with one from Sri Lanka comprising a cumulative sample size of 15,367 individuals. CKDu exhibited a male predominance, with variations in the male-to-female ratios across studies. Common risk factors include pesticide exposure, well water consumption, and a history of using abandoned wells. Genetic predisposition, particularly CYP1A1 polymorphisms, was significantly associated with CKDu risk. Biochemical analyses revealed distinctive biomarkers indicative of environmentally induced CKD. **Conclusion:** Seven studies met the inclusion criteria, primarily conducted in India, with one from Sri Lanka comprising a cumulative sample size of 15,367 individuals. CKDu exhibited a male predominance, with variations in the male-to-female ratios across studies. Common risk factors include pesticide exposure, well water consumption, and a history of using abandoned wells. Genetic predisposition, particularly CYP1A1 polymorphisms, was significantly associated with CKDu risk. Biochemical analyses revealed distinctive biomarkers indicative of environmentally induced CKD.

INTRODUCTION

Chronic kidney disease (CKD) is a major contributor to the illness and death rates of noncommunicable diseases (NCDs), making it a leading cause of death among all NCDs.[2] Chronic kidney disease (CKD) is characterised by a diminished glomerular filtration rate (GFR) below 60 ml/min and/or kidney damage, manifesting as structural or functional abnormalities other than GFR, persisting for more than 3 months.[3] Ageing, genetic predisposition, smoking, alcohol consumption, obesity, diabetes, and hypertension are recognised as the common causes and risk factors for CKD.[4] Interestingly, CKDs have been documented in various global regions, including Central America, Sri Lanka, and India, even in the absence of these established risk factors.[5-7] According to the 2012 Clinical Practice Guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO), these cases are termed chronic kidney disease of unknown aetiology (CKDu).[8] The potential determinants of CKDu include exposure to specific dietary patterns, environmental toxins, heat stress, and infections.

The definition of CKDu has been the subject of numerous discussions in recent years. For instance, many authors limit CKDu to a particular type of

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CKD frequently found in rural settings in non-diabetic individuals, accompanied by low-grade proteinuria and a rapid transition to end-stage kidney disease (ESKD). Many studies have attributed this to farming, cadmium exposure, heat exposure, lack of fresh water, and climate change.[9] Ochratoxin A (OTA), a mycotoxin found in numerous food items, was found to cause CKD at even low concentrations.[9,10] Some authors also link CKDu with snake bites and herbal use, frequently reported in South Asia and Central America. Additionally, air pollution, particularly particles with a diameter of <2.5 μm, has also been associated with CKD.[11,12] The definition also varies, depending on the region. Therefore, to avoid confusion, we restricted our definition by excluding the traditional risk factors of CKD, such as diabetes, hypertension, and HIV.

The atypical presentation of CKDu has become an epidemic in different regions of the world, which usually remains undiagnosed until its late stage.[13] Over the past few decades, parts of Central America, South Asia, Eastern Europe, and other countries, such as Sudan, Tunisia, Tanzania, and the El-Minia Governorate in Egypt, have reported similar disease patterns.[14] Furthermore, several studies have postulated the possible risk factors for CKDu. For instance, a cross-sectional survey in Nicaragua by Lebov et al. found that gender, age, residence, alcohol consumption, higher duration of working in agricultural lands, and comorbidities were positively associated with CKDu.[15] Another cross-sectional study conducted in Sri Lanka by Jayatilake et al. reported that exposure to heavy metals and pesticides is linked to CKDu.[14]

This systematic review aimed to consolidate information on the case definition, diagnostic criteria, and plausible determinants of CKDu across different geographical locations.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.

Literature search

We searched for peer-reviewed articles published between 2013 and 2024 using PubMed, Embase, and Scopus databases. Additional studies that investigated the risk factors for CKDu were explored by searching the references of the included articles. Three primary concepts were encapsulated in the search terms: CKDu, aetiology, and risk factors.

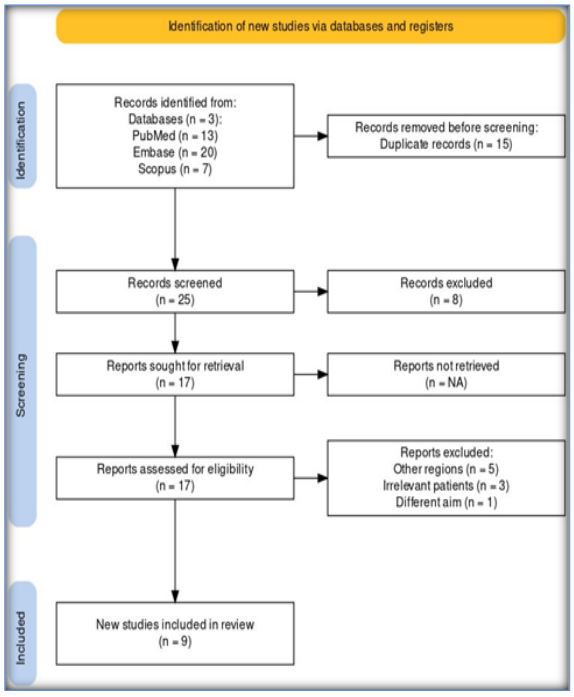
Inclusion/Exclusion Criteria

In our study, we included articles that reported original primary research, including both observational and experimental studies, published in English and peer-reviewed journals. We did not apply any specific exclusion criteria to the definition of CKDu; therefore, anyone diagnosed with CKDu by a doctor or hospital was included in our analysis. However, we excluded review articles, project reports, expert opinions, narrative reviews, commentaries, case reports, conference papers, and policy analyses. Additionally, studies that reported diabetes and hypertension as associated factors were excluded, as these factors are typically considered traditional causes of CKD.

Data Extraction and Synthesis

In a systematic and organised manner, two researchers gathered the necessary data from preselected sources using a predesigned table. The data extraction process was subsequently verified by a third researcher who cross-checked the information and corrected any errors through a collaborative review of the original publications. The extracted data were then entered into MS Excel, encompassing the following categories: study details (author(s), year of publication, and country), study setting, study design, sample size, participants, exposure(s), and CKDu prevalence, as well as the diagnostic tool used. Despite the initial plans to conduct a meta-analysis, insufficient data were available to combine the results. Consequently, the findings were summarised narratively, classifying the articles based on exposure or risk factor(s) of interest for CKDu.

PRISMA FLOW DIAGRAM



RESULTS

In this systematic review of chronic kidney disease of unknown aetiology (CKDu), a comprehensive analysis was conducted, incorporating data from a total of seven studies. These studies, spanning from 2013 to 2024, were primarily conducted in India, with one originating from Sri Lanka. The cumulative sample size across all the studies was

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15,367 individuals. Among these participants, there was a predominance of males, constituting approximately 67.3% of the total population, while females accounted for the remaining 32.7%. The male-to-female ratio varied across studies, ranging from 1.16 to 4.26, reflecting differing sex distributions within the investigated populations. Notably, the largest study by Hamilton et al,[16] significantly contributed to the cumulative sample size, encompassing 11,119 individuals recruited from community settings in India. Conversely, smaller-scale studies, such as those by Nayak-Rao et al,[17] with a sample size of 334 participants, provided valuable insights into CKDu within specific observational contexts.

Prevalence of CKD

Nayak et al. conducted a recent cross-sectional observational study in an Indian population of 334 patients. In a study conducted from October 2021 to July 2022, which included 334 patients diagnosed with chronic kidney disease (CKD), 70% of whom were male, CKD-U was identified as the leading cause of CKD in 154 (46.1%) patients, followed by diabetic nephropathy in 148 (44.3%). It should be noted that 80% of patients with CKD presented with advanced stages of the disease (stages 4 and 5). Additionally, approximately two-thirds of CKD patients reported a monthly family income of less than 10,000 Rs (equivalent to approximately 130 USD).[17]

CKDu exhibited a notably higher prevalence among agricultural workers compared to other causes of CKD, as well as among the uneducated population and those with lower-income brackets. Age and sex distributions did not differ significantly between the CKDu and non-CKDu groups.[21]

Hamilton et al. in his research cohort of 11,119 patients consisting of adult individuals aged 18 years and older, with 4696 males and 6423 females reported prevalence in 4 different regions which included.[16]

- In Haryana, the study included 3180 participants with a mean age of 38.93 years (SD = 12.01), with 1340 males and 1840 females. The site was located in the northern region, with an eGFR of 101.81 mL/min/1.73 m² and a CKDu prevalence of 1.4%. The heat index ranged from 25.27°C to 25.58°C, with an altitude of 206 to 247 meters. The majority of the land cover was cropland (61.5%). [16]
- Delhi had a similar sample size of 1798 participants with a comparable mean age of 38.93 years (SD = 11.14), including 819 males and 979 females. This northern site exhibited an eGFR of 110.23 mL/min/1.73 m² and a lower CKDu prevalence of 0.8%. The heat index varied from 23.95°C to 24.34°C, with an altitude ranging from 1 to 292 meters. Urban land cover dominated the study area (65.6%). [16]
- Tamil Nadu's sample comprised 3097 individuals with a slightly younger mean age of 36.87 years (SD = 10.85), with 1202 males and 1895 females. Located in the southern region, this site displayed an eGFR of 114.13 mL/min/1.73 m² and a low CKDu prevalence of 0.3%. The heat index ranged from 30.20°C to 30.31°C, with an altitude of 1–17 m. Croplands covered a smaller proportion (12.9%) than urban areas (87.1%).[16]
- Andhra Pradesh's sample included 3044 participants with a higher mean age of 43.15 years (SD = 10.69), comprising 1335 males and 1709 females. The site, situated in the south, exhibited an eGFR of 99.49 mL/min/1.73 m² and a relatively higher CKDu prevalence of 3.2%. The heat index varied from 25.80°C to 28.31°C, with an altitude ranging from 0 to 391 meters. Croplands accounted for the majority (65.0%) of the land cover in this area.[16]

The analysis conducted by Sidhu et al. performed the largest examination of cause-specific mortality in patients with advanced chronic kidney disease (CKD) and chronic coronary disease (CCD) within the Ischaemia-CKD cohort. Over 3 years, the cumulative all-cause mortality rate among Ischaemia-CKD participants reached 27.5%, with nearly half of these deaths attributable to definitively identified cardiovascular (CV) causes. The predictors of CV-related mortality included advanced age, reduced left ventricular ejection fraction (LVEF), and presence of diabetes. Conversely, older age and lower baseline systolic blood pressure emerged as predictors of non-CV-related mortality. Sudden cardiac death predominated among CV-related deaths, whereas infection-related mortality was the most common subtype among non-CV causes, irrespective of treatment assignment. Despite the elevated risk of CV mortality observed, their analysis found no incremental advantage associated with an invasive treatment strategy compared with an initial conservative approach.[22]

Prevalence of CKDu in Sri Lanka

Among the cohort of 125 individuals diagnosed with chronic kidney disease of undetermined aetiology (CKDu), a significantly higher proportion (n = 89, 71.2%) were male. Analysis of the mean ages revealed no statistically significant difference between male (45.51 ± 19.78 years) and female (47.45 ± 17.51 years) patients. The majority of the CKDu patients included in this study had education up to the ordinary level (n = 92, 73.6%) and were identified as farmers (n = 107, 85.6%). Only nine (7.2%) patients with CKDu reported a familial history of CKD-related deaths. Notably, among CKDu patients, a greater percentage of males (86, 96.6%) were identified as farmers than females (21, 58.3%). Controls comprised 180 healthy individuals who presented at the study site for CKDu screening, including 98 men (54.4%) and 82 women (45.6%).[19]

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The case-control study by Siddarth et al. reported no statistically significant difference was observed in age between the two groups (45.7 ± 7.2 years for controls vs. 46.0 ± 7.3 years for CKDu patients, p = 0.593). The sex distribution was equivalent in both groups, with a male-to-female ratio of 170 to 164 (p = 1.000). However, significant differences were observed in several other biochemical variables. CKDu patients exhibited significantly higher levels of serum creatinine (1.8 ± 0.4 mg/dL vs. 0.8 ± 0.2 mg/dL, p = 0.0001) and blood urea (100.7 ± 30.2 mg/dL vs. 24.6 ± 4.8 mg/dL, p = 0.0001) compared to healthy controls. Additionally, CKDu patients had markedly lower estimated glomerular filtration rates (eGFR) (47.07 ± 15.9 mL/min/1.73m² vs. 108.28 ± 14.5 mL/min/1.73m², p = 0.0001). Furthermore, CKDu patients exhibited elevated levels of total cholesterol (169.9 ± 18.2 mg/dL vs. 160 ± 8.14 mg/dL, p = 0.0001) and triglycerides (119.97 ± 16.8 mg/dL vs. 86.3 ± 6.9 mg/dL, p = 0.0001) compared to healthy controls. Urinary albumin excretion (UAE) over 24 h was substantially higher in patients with CKDu (700 ± 16 mg/24h) compared to in controls (20 ± 5 mg/24h, p = 0.0001). These findings underscore significant biochemical disparities between patients with CKDu and healthy individuals, highlighting the impact of the disease on renal function and lipid metabolism.[18]

Causes of CKD in patients

Diabetic nephropathy accounted for 21.7% of cases, hypertensive nephrosclerosis for 14.4%, chronic glomerulosclerosis for 7.5%, and cystic diseases for 0.8%. The predominant diagnostic category observed was chronic kidney disease of undetermined aetiology (CKDu), constituting 51.7% of cases with no discernible cause. The majority (56%) of the affected individuals hailed from Villupuram and Cuddalore districts in Tamil Nadu, with approximately half of the patients employed in farming or similar blue-collar occupations. Common crops cultivated by these individuals include rice paddies, sugarcane, and groundnut. Notably, a significant proportion (65.2%) of patients with CKD reported a monthly family income below US$77.[21]

Research has demonstrated that Several factors are significantly associated with chronic kidney disease of unknown aetiology (CKDu). These include being male (odds ratio [OR] 2.07, 95% confidence interval [CI] 1.27-3.36), engaging in farming-related activities (OR 3.12, 95% CI 1.74-5.61), applying pesticides (OR 3.31, 95% CI 2.04-5.36), applying fertilizers (OR 2.37, 95% CI 1.43-3.93), drinking well water (OR 4.82, 95% CI 2.27-10.24), and a history of drinking from recently abandoned wells (OR 6.93, 95% CI 3.87-12.40).[19]

In multivariate analysis, drinking well water (OR 2.52, 95% CI 1.12-5.70), a history of drinking from recently abandoned wells (OR 5.43, 95% CI 2.88-10.26), and glyphosate use (OR 5.12, 95% CI 2.33-11.26) were all significantly associated with the development of CKDu. However, we observed a significant difference in pesticide application (OR 2.34, 95% CI 0.97-5.57) among the groups, but with a smaller sample size; this difference may not have been statistically significant.[19]

A comprehensive biochemical analysis was conducted on blood samples from individuals affected and unaffected by chronic kidney disease of undetermined aetiology (CKDu), coupled with detailed hydrogeochemical investigations of groundwater in CKDu-affected and non-affected regions, specifically focusing on drinking water. The prevalence of trace geogenic elements, particularly silica, was notably elevated in the groundwater of the affected areas, prompting an assessment of its nephrotoxic potential through in vitro cytotoxicity assays using human kidney cell lines.[20]

Among CKDu-affected subjects, elevated levels of serum urea (52.85 mM), creatinine (941.5 μM), and uric acid (1384.5 μM) were consistently observed along with normal blood glucose levels (4.65 mM), collectively serving as distinct biomarkers indicative of environmentally induced CKD, specifically chronic tubulointerstitial nephritis. Furthermore, affected individuals exhibited elevated blood lead levels (1.48 μM), suggesting both direct nephrotoxic effects, leading to impaired blood clearance, and indirect nephrotoxic effects via disruption of calcium homeostasis, resulting in skeletal disorders, compounded by prolonged consumption of NSAIDs for pain alleviation, indirectly contributing to renal damage.[20]

The groundwater in the affected regions was acidic (pH 5.6), contributing to borderline lead (9.98 μg/L) and high silica (115.5 mg/L) contamination levels. Notably, the bioavailability of silica, a critical determinant of its nephrotoxicity, is heightened under acidic pH conditions and in the presence of a deficient composition of calcium and magnesium ions, as these cations are typically complexed with silica, reducing its bioavailability. Silica demonstrated renal proximal tubular cytotoxicity upon long-term exposure, comparable to the silica levels observed in affected-region groundwater, leading to apoptosis-mediated cell death, tubular atrophy, interstitial fibrosis, and irreversible renal damage, which are characteristic of CKD.[20]

Genotype analysis: CYP1A1

In the case-control study, 19.16% of cases carried the CYP1A12A CC genotype, compared to 13.17% in controls ($p < 0.05$). Similarly, the prevalence of CYP1A12C mutations was higher among cases (GG = 11.98%) than in controls (GG = 7.19%) ($p < 0.05$). Investigation of the association between CYP1A1 polymorphisms and chronic kidney disease of undetermined aetiology (CKDu) revealed that individuals carrying at least one mutant allele of CYP1A1*2A (TC, CC) and *2C (AG, GG) exhibited a 1.4-to-2-fold increased risk of CKDu compared to those with the wild-type homozygous genotype, namely TT (*2A) and AA (*2C).

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In this study, it was found that the *2A and *2C polymorphisms of the CYP1A1 gene were significantly associated with a 1.5-to-2.2-fold increased risk of chronic kidney disease of undetermined aetiology (CKDu) within the North Indian population.[18]

Risk factors stated by Hamilton et al.,

The analysis revealed substantial reductions in the effect estimates when transitioning from crude to minimally adjusted linear regression models, particularly concerning sex, proximity to cropland, and education. Further examination using stratified analyses revealed that age was the primary factor driving these alterations. Generally, male participants exhibited advanced age compared to females, coupled with diminished estimated glomerular filtration rate (eGFR). Additionally, a greater proportion of older individuals, characterised by lower eGFR values, resided close to cropland as opposed to urban areas. Regarding education, a positive association was noted between the number of school years and age, indicating that individuals with a more extensive education tended to be younger. These intricate dynamics elucidate the observed shifts in effect estimates after adjusting for age. Therefore, age emerged as a pivotal variable influencing the relationships between sex, proximity to cropland, education, and eGFR, shedding light on the nuanced interplay between demographic factors and renal function.[16]

The results obtained from the LMM analysis differed from those of the linear and logistic regression models. In terms of mean eGFR values, the southern Indian study sites in Tamil Nadu and Andhra Pradesh consistently ranked the lowest, whereas the northern urban sites in Delhi and Haryana ranked the highest. Similarly, proximity to cropland was found to have a negative correlation with eGFR, which is similar to the findings of the linear and logistic regression models.[16]

Management of CKDu

Conservative management was adopted for a quarter of the participants (24%), involving the administration of diuretics, antiemetics, oral hematinics, antihypertensives, and symptomatic measures, without resorting to renal replacement therapy. Renal replacement therapy was pursued by nearly one-fifth (19.6%) of participants. Among CKD patients with a glomerular filtration rate < 8 ml/min, 7% did not receive renal replacement therapy.

Table 1: Summary of study characteristics

Authors	Country	Year of Publication	Study setting	Design	Sample size	Male/Female
Siddarth et al.[18]	India	2013	Hospital	Case-control	235	178/57
Channa Jayasumana et al.[19]	Sri Lanka	2015	Hospital	Case-control	305	98/82
S Mascarenhas et al.[20]	India	2017	Community	Cohort	266	58/56
Hamilton SA et al.[16]	India	2021	Community	Case-control analysis	11,119	4696/6423
Parameswaran S et al.[21]	India	2023	Hospital	Prospective study	2424	1826/598
Sidhu MS et al.[22]	India	2023	Hospital	Cross-sectional	777	395/382
Nayak-Rao S et al.[17]	India	2024	Community	Observational, Cross-sectional study	334	233/101

DISCUSSION

Despite the growing global awareness of chronic kidney disease (CKD) and chronic kidney disease of undetermined aetiology (CKDu), many risk factors for these conditions remain elusive. Our review identified numerous potential risk factors for CKD that may vary by geographic region. However, the heterogeneity in reported associations with CKD hampers our ability to draw definitive conclusions regarding the aetiologies of CKDu. For example, in South Asia, studies have frequently explored family history, agrochemical use, and exposure to heavy metals, whereas investigations into altitude and temperature have been primarily conducted in Central America. Nevertheless, certain commonalities can be observed across the regions. Factors such as heavy metal exposure, heat stress, and dietary habits have consistently been reported in studies conducted across various geographic locations. Similarly, family history, temperature, altitude, dietary patterns, ochratoxin A exposure, herbal use, and snake bites emerged as frequent themes in both South Asian and Central American studies.

Key findings revealed a male predominance among CKDu patients, constituting approximately 67.3% of the total population, with variations in the male-to-female ratio observed across studies. Noteworthy contributions to the cumulative sample size were observed, particularly in the study by Hamilton et al,[16] encompassing 11,119 individuals recruited from community settings in India. Notable regional disparities in CKDu prevalence were highlighted, with higher prevalence rates noted among agricultural workers and individuals with lower educational and income levels. However, the age and sex distributions did not differ significantly between the CKDu and non-CKDu groups. The analysis further elucidated the association between

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CKDu and factors such as pesticide exposure, drinking well water, and history of using abandoned wells, emphasising the multifactorial aetiology of the disease.

Considering both the shared characteristics and distinct features observed in studies across various regions, it is apparent that the escalating burden of chronic kidney disease (CKD) may be influenced by factors that are both common and unique to specific geographic areas. Pathological exposure has the potential to affect disease outcomes through interactions with a multitude of factors, including emissions from sources, transport mechanisms, transformation processes, human contact patterns, bioavailability of contaminants, early manifestation of disease, and health impacts.[23] In low-income countries, rapid urbanisation has given rise to challenges such as inadequate sanitation, unplanned urban infrastructure, overcrowding, and environmental contamination. These environmental and social exposures could potentially exacerbate CKD prevalence by interacting with other urban-related risk factors, such as the high prevalence of both noncommunicable and communicable diseases.[24, 25]

Additionally, genotype analysis revealed significant associations between CYP1A1 polymorphisms and CKDu risk, with individuals carrying mutant alleles exhibiting a heightened predisposition to the disease. Biochemical analyses underscored distinctive biomarkers indicative of environmentally induced CKD, along with notable disparities in serum creatinine, blood urea, estimated glomerular filtration rates, total cholesterol, triglycerides, and urinary albumin excretion between CKDu patients and healthy controls.[18] Furthermore, the study by Sidhu et al. provided valuable insights into the cause-specific mortality among patients with advanced CKD and chronic coronary disease, elucidating predictors of cardiovascular and non-cardiovascular deaths, and highlighting the limited incremental benefit of invasive treatment strategies in reducing mortality rates.[22]

Genetic factors may contribute to the observed regional variability in CKDu epidemiology. Ethnic differences in genetics are known to significantly influence the prevalence and progression risk of CKD. In the United States, for instance, individuals of African descent carrying the APOL1 genotype exhibit higher CKD rates and faster disease progression, particularly when exposed to exacerbating factors such as diabetes and hypertension. Specific polymorphisms and single-nucleotide mutations have been linked to CKDu in certain endemic communities in India and Sri Lanka, as well as chromosomal aberrations associated with Balkan Endemic Nephropathy in the Balkan states. Therefore, further research is warranted to investigate the role of genetic predisposition in CKDu pathogenesis.[18,26,27]

Implications of these findings extend to public health policies and interventions aimed at mitigating the burden of CKDu, emphasizing the importance of targeted interventions addressing environmental exposures, genetic predispositions, and socioeconomic determinants. However, several limitations warrant consideration, including heterogeneity in study designs, populations, and outcome measures, precluding meta-analyses, and the potential for selection bias and confounding factors in individual studies.

CONCLUSION

In conclusion, this systematic review provides comprehensive insights into the epidemiology, risk factors, genotype associations, and management strategies for CKDu, elucidating its complex aetiology and highlighting the urgent need for multifaceted approaches to prevention and management. Further research is warranted to enhance our understanding of CKDu pathogenesis and inform evidence-based interventions aimed at reducing its global burden.

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