

FACTOR ASSOCIATED OF CHRONIC KIDNEY DISEASE OF UNCERTAIN ETIOLOGY:A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: Recent interest in chronic kidney disease of non-traditional causes, also named as chronic kidney disease of unknown etiology (CKDu) has identified both individual and environmental/occupational risk factors.

The aim: The aim of this study to show factor associated of chronic kidney disease of uncertain etiology.

Methods: By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Sciencedirect were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: the results of our search get 91 articles, whereas the results of our search on SagePub get 1976 articles, on Sciencedirect 14.279 articles. Records remove before screening are 5676, so we get 10670 articles for screening. We included five research that met the criteria.

Conclusion: Different multifactorial etiologies like chronic exposure to dehydration, heat stress, agrochemicals, heavy metals, intake of fructose-rich drinks, frequent use of self-prescribed non-steroidal anti-inflammatory drugs (NSAIDS), lower income and genetics were proposed in its development.

Keyword: Chronic kidney disease, unknow, etiology, risk factor.

INTRODUCTION

Many previous studies have indicated that the etiologies of chronic kidney disease (CKD) include primary kidney damage (chronic glomerular nephritis, nephrotic syndrome, polycystic kidney disease); secondary renal damage (hypertension, diabetes, Henoch-Schonlein purpura nephritis (HSPN); lupus nephritis, urinary tract infections, gouty nephropathy); and others (kidney stones, pyelonephritis, tumors). However, there are still a high proportion of CKD patients without the above etiologies, whose condition is named chronic kidney disease of unknown etiologies (CKDu).¹

A growing number of geographically diverse regions have reported widespread incidence and prevalence of chronic kidney disease of uncertain or unknown etiology (CKDu) not attributed to traditional risk factors. CKDu, which is also called Mesoamerican Nephropathy (MeN) in Latin America, is characterized as asymptomatic until late stages and is not linked with common causes of chronic kidney disease including diabetes, hypertension, snake bite, glomerulonephritis, or urological diseases. As such, it is commonly referred to as a diagnosis of exclusion, and epidemics in geographically disparate regions are often regarded as separate instances with unclear or potentially no links between them.²

The global burden of chronic kidney disease (CKD) has risen, and chronic kidney disease of unknown etiology (CKDu) contributes considerably to the national burden of CKD. It is characterized by irreversible, slowly advancing disease, and symptoms often appear in the late stages of the disease. It is a serious, novel cause of kidney failure and leads to premature deaths. Many hypotheses have emerged; however, the etiology of CKDu continues to be elusive and debatable and it is claimed that the etiology is multifactorial, encompassing environmental, genetic, occupational, and social factors. The dominant histopathological feature is chronic tubulointerstitial nephritis. It predominantly affects individuals with low socio-economic status, of working age, largely without chronic comorbidities, who perform strenuous labor in extreme conditions in various tropical areas of the world.³

Epidemiological studies conducted in HICs have found some known traditional risk factors for the progression of kidney disease, such as ageing, obesity, hypertension, and diabetes. Non-traditional risk factors (such as environmental, occupational, and infectious diseases), disproportionately higher in LMICs, remain unexplored. Hence, kidney diseases without identifiable traditional risk factors are termed CKD of unknown etiology (CKDu). However, this definition is not generally agreed upon either. 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 CKD frequently found in rural settings in non-diabetic people, accompanied by low-grade proteinuria, and a rapid transition to end-stage kidney disease (ESKD).^{4,5}

The atypical presentation of CKDu has become epidemic in different regions of the world, which usually remains undiagnosed until its late stage. 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 reported a similar disease pattern. However, the exact cause remains unidentified to date. Subsequently, a similar endemic was also reported, such as Balkan endemic nephropathy, Mesoamerican nephropathy, and Chinese herb nephropathy, which were named after the area of origin.⁴

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

CRITERIA FOR ELIGIBILITY

For the purpose of this literature review, we compare and contrast factor associated of chronic kidney disease of uncertain etiology. It is possible to accomplish this by researching or investigating factor associated of chronic kidney disease of uncertain etiology. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about factor associated of chronic kidney disease of uncertain etiology. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

SEARCH STRATEGY

We used "factor associated of chronic kidney disease of uncertain etiology." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciondirect databases by inputting the words: ("Chronic kidney disease"[MeSH Subheading] OR "kidney disese"[All Fields] OR "Prevalence" [All Fields])

AND ("Risk factor"[All Fields] OR " Etiology "[All Fields]) AND ("Mechanism"[All Fields]) OR ("Pathophysiology" [All Fields])) used in searching the literature.

DATA RETRIEVAL

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

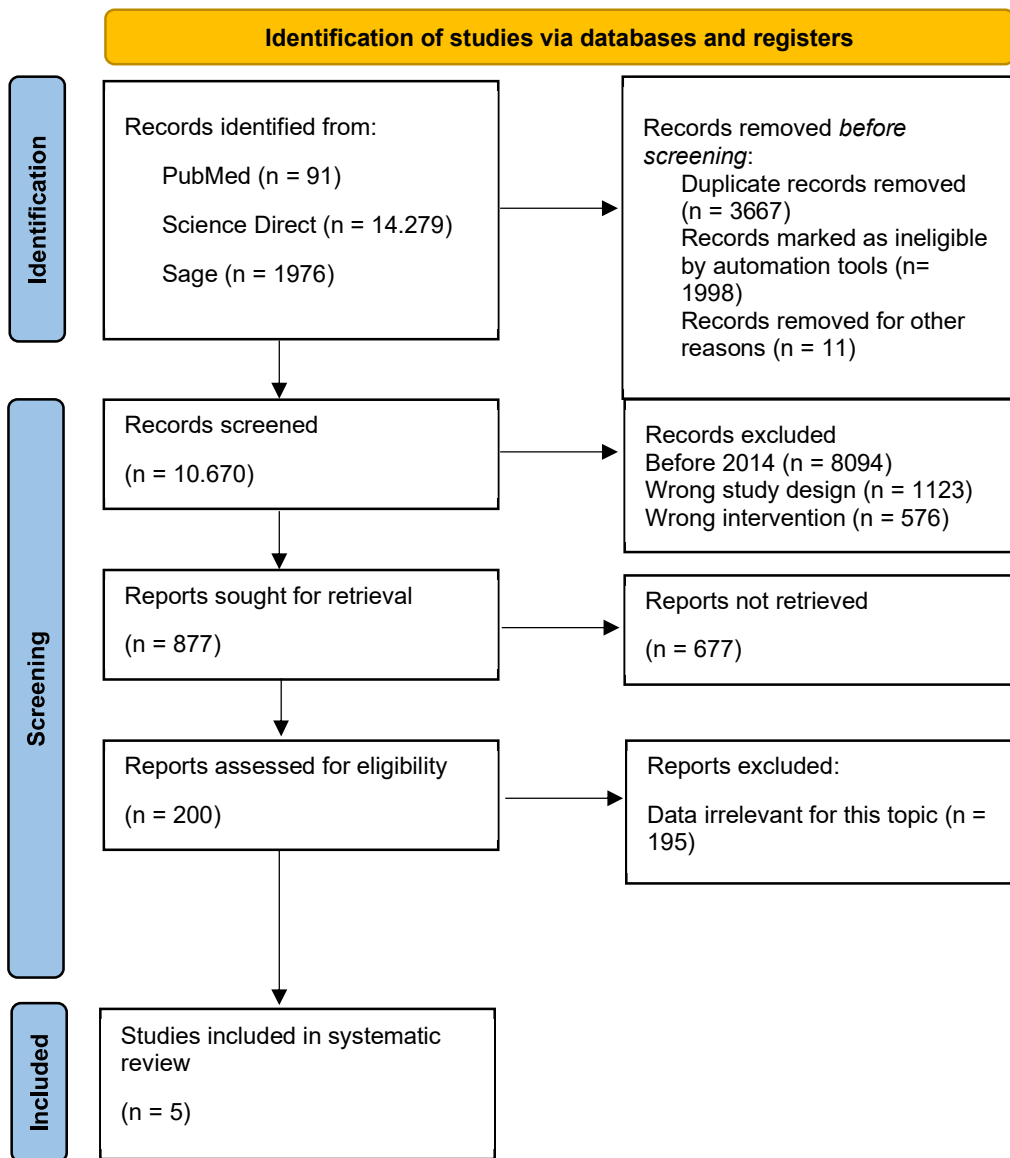


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

QUALITY ASSESSMENT AND DATA SYNTHESIS

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting

papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

From the PubMed database, the results of our search get 91 articles, whereas the results of our search on SagePub get 1976 articles, on Sciencedirect 14.279 articles. Records remove before screening are 5676, so we get 10670 articles for screening. We included five research that met the criteria.

Study by Hewavitharana, P et al in 2023 showed in a cohort of persons with CKDu living in Sri Lanka’s central province, the overall decline of kidney function was slow. A modest and similar proportion of both men and women experienced significant kidney function decline. We observed mild hypernatremia in this cohort, and associations with specific residence locale and source of water among men with kidney function decline. These need further study. Future research could build on our observed [disease progression](#) variation within endemic areas to interrogate environmental differences within these subregions, and therefore, narrow potential candidate causes of CKDu.⁶

Aekplakorn, W et al in 2021 found although the prevalence of CKDu in Thailand was low overall, there remained areas with higher risk. Our study may be a model for higher-middle income country, where despite overall economic and healthcare improvement, much work needs to be done to increase the awareness and reduce the risk for CKDu in underserved regions. Although there were some differences, risk factors for CKDu were generally similar to older subjects with decreased GFR without traditional causes. Unlike other countries, Thai women had an increased risk of CKDu. Future studies are necessary to identify causes of CKDu in high-risk groups in Thailand.⁷

Table 1. The literature include in this study

| Author | Origin | Method | Sample Size | Result |
|--|-----------|--|-------------|--|
| Hewavitharana, P et al., 2023 ⁶ | Sri Lanka | We initiated the Kidney Progression Project (KiPP) to prospectively follow 292 persons with Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate (eGFR) 20 to 60 ml/min per 1.73 m ² living in a CKDu | 40000 | Median eGFR at enrollment was 28 ml/min among 71 women; 30 ml/min among 221 men; 91% to 99% had trace or no proteinuria during follow-up. At enrollment, median serum sodium, uric acid, and potassium were 143 mmol/l, 6.3 mg/dl, 4.5 meq/l, respectively among women; and 143 mmol/l, 6.9 mg/dl, 4.3 meq/l among men. Mean slope of eGFR decline was -0.5 (SD 4.9) ml/min/yr. In exploratory analyses, men with greater years of education and those living in northern region of the study area experienced lower likelihood of disease progression (hazard ratios [HR] 0.87 [0.77–0.98] per additional year and 0.33 [0.12–0.89] for northern versus other subregions, respectively). There was a suggestion that men drinking well water had higher likelihood and men living further away from reservoirs had lower likelihood of >30% decline in eGFR (HR 2.07 [0.95–4.49] for drinking well water versus not, and HR 0.58 [0.32–1.05] per kilometer distance, respectively). |
| Aekplakorn, W et al., 2021 ⁷ | Thailand | We determined the prevalence and risk factors for CKDu using data from a cross-sectional, | 18118 | The associations between risk factors and CKDu or elderly subjects with eGFR < 60 without traditional causes were assessed by multivariable logistic regression. Of 17,329 |

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|--|-----------|---|-----|--|
| | | nationally representative survey of the adult population of Thailand. | | <p>subjects, the prevalence were: eGFR < 60, 5.3%; CKDu1 0.78%; CKDu2, 0.75%. CKDu differed by 4.3-folds between regions. Women, farmers/laborers, older age, gout, painkillers, rural area, and stones were independent risk factors for CKDu. Women, age, rural, gout, painkillers were significant risk factors for both CKDu and elderly subjects. These data collected using standardized methodology showed that the prevalence of CKDu in Thailand was low overall, although some regions had higher risk. Unlike other countries, Thai women had a two-fold higher risk of CKDu.</p> |
| Fitria, L et al., 2020⁸ | Indonesia | The study design was cross-sectional. | 354 | <p>From SCr level and proteinuria, we categorized the farmers into five stages of CKD; then we distinguished CKDu from CKD if the farmers had stage 1–4 of CKD but without diabetes, hypertension and other traditional causes. Data were analyzed with multivariate logistic regression to get prevalence odd ratios of CKDu and its relationship with environmental and occupational factors, adjusted with other risk factors of CKDu. The overall prevalence of CKD was 24.9% and CKDu was 18.6%. For the environmental factors, farm location (high altitude versus low altitude location) was associated with CKDu (Prevalence Odds Ratio (POR): 2.0; 95% CI: 1.2–3.5). For the occupational factors, although not significant, the risk of CKDu increased with the longer use of insecticide and with the more frequent of insecticide use. We suggested that there was a need to conduct future research to investigate more on the association of those environmental and occupational factors with CKDu.</p> |
| Hettiarachchi, Thilini W et al., 2021⁹ | Sri Lanka | This observational study was based on records of | 379 | <p>CKD-u cases (379) were included in analyses based on the adequacy of variables. Mean age was 53 years, male-to-female ratio of 2.5:1, and</p> |

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|--|-------|---|-------|---|
| | | CKD-u cohort from 2005-14 at Girandurukotte, an endemic area for CKD-u in Uva Province, Sri Lanka. | | smoking were significant risk factors ($P < 0.10$) for CKD-u progression. Males had 2.3 times hazard for CKD-u survival than females, and males who smoked had 2.57 times risk of CKD-u progression than nonsmoking males. Faster eGFR decline rate of $>5 \text{ mL/min/1.73 m}^2/\text{year}$ have been identified in 25% of the sample ($n = 100$); this group is significantly younger than the slower progression group (mean age 46 years) and was at an early stage at the time of presentation (mean eGFR 76.02). CKD-u progression was not equal in all patients but faster in young people who presented at earlier stages. Continuous exposure to environmental risk factors may influence the rate of progression. Females have higher CKD-u survival rates than males. Tobacco smoking was associated with a lower survival of CKD-u but could be a proxy indicative of other exposures. |
| Gordo, CO et al., 2019¹⁰ | India | Secondary data analysis of three population-based cross-sectional studies conducted between 2010 and 2014 | 12500 | The mean eGFR was $105.0 \pm 17.8 \text{ mL/min per } 1.73 \text{ m}^2$. The prevalence of eGFR < 60 was 1.6% (95% CI=1.4 to 1.7), but this figure varied markedly between areas, being highest in rural areas of Southern Indian (4.8% (3.8 to 5.8)). In Northern India, older age was the only risk factor associated with lower mean eGFR and eGFR < 60 (regression coefficient (95% CI)=-0.94 (0.97 to 0.91); OR (95% CI)=1.10 (1.08 to 1.11)). In Southern India, risk factors for lower mean eGFR and eGFR < 60 , respectively, were residence in a rural area (-7.78 (-8.69 to -6.86); 4.95 (2.61 to 9.39)), older age (-0.90 (-0.93 to -0.86); 1.06 (1.04 to 1.08)) and less education (-0.94 (-1.32 to -0.56); 0.67 (0.50 to 0.90) for each 5 years at school). |

Study by Fitria, L et al in 2020 showed farmers in higher altitude/ lower WBGT locations were at higher risk for CKDu compared to farmers in lower altitude/ higher WBGT locations. However, once the type of farming was included (degree of mechanization) the findings become more explainable, that farmers who applied less mechanized type of farming, the risk for having CKDu was higher in the high altitude/ low WBGT locations compared to the lower altitude/ higher WBGT

locations. There was a statistically insignificant increase in the risk of CKDu with the longer lifetime duration of insecticide use and the more frequent use of insecticides, after controlling for other covariates including farm location.⁸

Hettiarachchi, Thilini W et al in 2021 found data reveal that females have higher CKD-u survival rates than males. Smoking was a significant risk factor for survival of CKD-u. Patients with more progressive disease were significantly younger and presented at an earlier stage. Findings further conclude that the progression of the disease is not equal in all patients, with three distinct categories based on the rate of eGFR decline, possibly due to different exposure levels to causative factors.⁹

Study by Gordo, CO et al in 2019 showed reduced eGFR, consistent with the definition of CKDu, is common in rural settings of Southern India (Vishakhapatnam district). This results support the hypothesis that the epidemic of CKDu, initially described in agricultural communities of Central America and Sri Lanka, may be common in other rural communities of tropical/subtropical countries. This has important implications for global health, since it indicates that CKDu may have a substantial public health burden globally that has been previously unrecognized. Population-based studies in other tropical/subtropical countries are required to assess the global patterns of burden of disease from CKDu.¹⁰

DISCUSSION

Chronic kidney disease (CKD) is a progressively degenerative condition characterized by the gradual deterioration of renal function, representing a significant and pressing global health issue. CKD affects about 10% of the general population worldwide. Yet, when interpreted in absolute figures, the profound scale of individuals affected by various stages of CKD amounts to 850 million, with a substantial 85% concentrated in low- to middle-income countries. Almost innumerable determinants contribute to the development and progression of chronic kidney disease, including age, hypertension, genetic factors, diabetes, obesity, proteinuria, dyslipidemia, and environmental factors such as dietary salt intake. Notably, recent research has identified pollution as an additional risk factor. More recently, an escalating body of evidence underscores the implications of climate change and pollution as emergent detrimental factors to overall public health, particularly concerning kidney diseases. The list of risk factors for the progression is even more complex, and many of them are intimately interrelated. To start with ascertaining the causes of the CKD epidemics, a deep analysis of the population's composition is imperative, mainly with stratification by age.^{11,12}

The global prevalence of chronic kidney disease (CKD) is approximately 9.1%–13.4%, and is a major source of morbidity and mortality. As the twelfth leading cause of worldwide mortality, deaths due to CKD or due to CKD-attributable cardiovascular disease are estimated at 1.2 million and 1.4 million, respectively. International data show that, while the age-standardized mortality for other chronic diseases (i.e. cardiovascular disease, cancer, chronic obstructive pulmonary disease) has declined over the past two decades, a similar reduction in age-standardized deaths has not been observed for CKD.¹³

Understanding genetic and environmental factors influencing kidney function in healthy and diseased conditions and the interaction between genetic susceptibility factors and the environment can provide important insights into renal physiology and pathophysiology. It can reveal previously unknown or unexpected mechanisms, and consequently, research of genetic and environmental factors associated with chronic kidney disease (CKD) has the potential to identify novel therapeutic or preventive targets.¹⁴

We found consistent evidence for the adverse effect of agrochemicals on chronic kidney disease, and in some studies, an association with end-stage renal failure (see the Supplementary Materials). In our meta-analysis, which included 13 studies from different regional areas, the overall effect was positive, and became significant when cross-sectional studies were removed. It is important to stress that high quality studies found significant associations for specific agrochemicals and in regions not declared as “endemic”. These cohort studies not only involved men and women working as applicators and/or mixers of agrochemicals, but also women married to applicators, both of whom live in the same agricultural environment. Among married women who directly applied pesticides, and among women who did not but whose husbands directly applied specific pesticides, the effect observed was positive and also showed a significant biological gradient over time.¹⁵

KD is a major public health problem engendered by various modifiable and non-modifiable risk factors spanning across cardiovascular, endocrine, lifestyle, and genetic/environmental domains. Understanding the major determinants of CKD and the clinical phenotype of high-risk populations are essential for prevention, improved detection, and earlier implementation of interventions that mitigate progression. With the emergence of new pharmacotherapies, diagnostic tools, and public health initiatives that are directing greater attention towards CKD in the global health agenda, further efforts are needed to improve access to these evidence-based interventions across high-risk groups and vulnerable populations.¹³

Few studies have reported on urinary findings in CKDu patients. However, in described clinical presentations, typical patients present with a bland urine sediment and minimal proteinuria. Recent studies have measured levels of kidney early biological effect markers in urine. The results are consistent with proximal tubular damage and may be useful in future work to identify CKDu at earlier stages and to determine etiology. Information on renal pathology has also been very limited to date. The two studies reporting biopsy results from patients with CKDu in El Salvador both found interstitial

fibrosis with varying degrees of tubular atrophy, essentially proportional to stage of CKD. Both series also reported non-specific glomerular damage. Whether this is secondary to a primary tubulointerstitial process or represents a primary glomerular disease or could be due to recurrent ischemia of the glomerular capillaries, such as from dehydration or concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), remains unknown.¹⁶

CONCLUSION

Different multifactorial etiologies like chronic exposure to dehydration, heat stress, agrochemicals, heavy metals, intake of fructose-rich drinks, frequent use of self-prescribed non-steroidal anti-inflammatory drugs (NSAIDS), lower income and genetics were proposed in its development.

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