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Heterogeneity in diagnostic criteria for chronic kidney disease of undetermined etiology (CKDu): a systematic review of the literature

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Abstract

Background Chronic kidney disease (CKD) of undetermined etiology (CKDu) is an important public health problem. It is a diagnosis of exclusion and the diagnostic approach varies widely across geographies. We aimed to systematically examine criteria used to diagnose CKDu in published literature.

Method PubMed, Medline, Embase, and Web of Science were searched systematically for published studies and conference abstracts pertaining to CKDu using relevant search terms. Systematic reviews/meta-analyses and reviews were screened to identify additional studies. Findings are presented in tables and figures and discussed critically.

Results 60 studies were identified which mention the definition used to diagnose CKDu. A combination of pre-specified estimated glomerular filtration rate (eGFR) and proteinuria/albuminuria cut-offs was used as diagnostic criteria in only 18 studies (30%), while another 11 studies (18.3%) relied solely on proteinuria/albuminuria cut-offs. Nineteen studies classified all CKD patients without any identifiable cause as CKDu irrespective of level of proteinuria/albuminuria. 18 studies excluded patients with significant proteinuria/albuminuria, although cut-offs used for exclusion varied. Limited studies mention the criteria used to exclude diabetes($n=22$) and hypertension($n=23$) related kidney disease, the two most common causes of CKD with wide variability.

Conclusions There is considerable variability in diagnostic criteria used to define CKDu in epidemiologic studies, especially in excluding proteinuria and other causes of kidney disease. Such heterogeneity may cause misclassification and erroneous estimation of disease burden making comparisons between studies difficult.

Clinical trial number Not applicable.

Keywords Chronic Kidney Disease of unknown etiology (CKDu), Diagnostic criteria, eGFR, Proteinuria, Albuminuria, Hypertension

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Introduction

CKD is an often-neglected facet of chronic non-communicable diseases, though it causes significant disability, mortality and loss of productivity [1]. The estimated worldwide prevalence of CKD was 9.1% in the Global Burden of Disease, Injuries, and Risk Factors Study (GBD) resulting in 1.2 million deaths and 35.8 million disability adjusted life years (DALYs) in 2017 [2]. Awareness about the disease is lacking in the community as well as among the general medical/allied healthcare fraternity. Though diabetes and hypertension remain the most common causes of CKD, chronic kidney disease of undetermined etiology (CKDu) has emerged as an important entity in last two decades especially in low-middle income countries (LMICs) in certain regions.

CKDu was first observed in El Salvador in 2002 in a large agricultural community where none of the conventional risk factors could be identified in 67% cases [3]. Though it is now reported worldwide, there is an unusually high prevalence in Central America, Sri Lanka and southern and eastern parts of India where the climate is hot and humid [4–24].

Conventionally CKDu is a diagnosis of exclusion which should be considered only when all attributable causes of kidney disease have been ruled out after thorough diagnostic work-up. A kidney biopsy should be done if feasible since CKDu is now widely recognized as a tubule-interstitial disease. Most epidemiologic studies have defined CKDu based on clinical and laboratory investigations requiring absence of diabetes, significant hypertension, proteinuria and other urinary abnormalities, structural abnormalities in kidneys and any other identifiable cause of kidney disease. Unfortunately, there is wide variability in how these parameters have been defined and extent of diagnostic work-up done to exclude other causes.

Given these challenges, outlining the variability in how CKDu is defined across studies is crucial for interpreting their findings accurately and informing effective health policy and planning. Previous reviews have mainly focussed on epidemiology, pathology and potential risk factors [17–20] of CKDu or have been restricted to specific regions [21, 22]. The heterogeneity in diagnostic criteria of CKDu has not been well studied. We systematically reviewed existing literature to examine CKDu definitions and shortcomings and benefits of the criteria used [25, 26].

Method

A systematic approach was used to review available studies related to CKDu to explore how they have diagnosed or defined this entity. The study was not registered in Prospero as it is a literature review of diagnostic criteria and does not examine any intervention.

Databases

PubMed, Medline, Embase, and Web of Science were search for peer reviewed published studies and abstracts from conference proceedings about CKDu. The rationale for selecting each database is provided in supplementary Table 1.

Search concepts and keywords

CKDu is chronic kidney disease of undetermined etiology. There is significant heterogeneity in terminology used to describe CKDu in the literature and this was addressed by the key concepts and key words selected. The two key concepts identified pertaining to the research question were "chronic kidney disease" and "undetermined etiology". So, the keywords or key phrases considered were "chronic kidney disease", "undetermined" and "etiology and their synonyms. However, using too many synonyms for each keyword led to an excessive output of irrelevant publications. So, it was decided to use the phrase "undetermined etiology" and the alternatives instead of "undetermined" and "etiology" as separate keywords which produced a reasonable output of relevant papers across all databases. Since CKDu is a widely accepted abbreviation for "chronic kidney disease of undetermined etiology" it was included as a key term along with alternative key terms including "heat stress nephropathy" and "Mesoamerican nephropathy" which has been used to describe this entity in Central America. The concepts and keywords as well the synonyms/alternate terms used are provided in supplementary Table 2.

Search strategy

MeSH terms and subject heading were used for "chronic kidney disease" as permitted in each database. Keyword search was also done for all the concepts. Boolean operators ("AND" and "OR") were used to combine the key concepts for the search. To maintain the uniformity of the search strategy across all databases, proximity search technique was not used as it is not allowed in PubMed.

Eligibility criteria

Inclusion criteria: [1]Studies pertaining to CKDu [2] Studies from January to 2002 to September 2022 [3] Human Studies [4] Published in English language.

Exclusion criteria: [1] Criteria used for diagnosing CKDu not described in the study [2] Editorials, letters, notes, case reports, comments, erratum or corrections, book chapters, news items and retracted publications were filtered and excluded as permitted in each database [3]. Duplicate studies based on same dataset [4]. Inability to access the full text of the article from any source.

Limits

The keyword search was limited to "title and abstract" to refine the search and avoid irrelevant output. The limits or filters used to distil the search were based on the inclusion and exclusion criteria described subsequently. The limits were literature published in English language due to logistic constraints and time i.e., inclusion of publications from 2002 till 2022 since this entity was first reported in 2002 from El Salvador. Only human studies were included. Editorials, letters, notes, case reports, comments, erratum or corrections, book chapters, news items and retracted publications were filtered and excluded as permitted in each database. Though systematic reviews, reviews and meta-analyses were not included, they were not filtered at this stage as they were subsequently used for additional search for relevant articles. The detailed search strategy for each database is provided in supplementary Table 3.

Additional search

Snowballing technique was used to supplement the search by reviewing references cited by the initial papers identified. References included in systematic reviews/meta-analyses and other reviews were also utilized to capture additional studies.

Study selection

Search output from each database was imported to Mendeley. Publications were included for final review according to PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analysis) guidelines [27]. Duplicate studies were removed by manual review and by using the "check for duplicates" function in Mendeley. In the first step the studies were screened based on the title and abstract. Then full text of the studies selected in the first step were screened to determine eligibility based on inclusion and exclusion criteria described above.

Data extraction

Information extracted from the studies identified were entered in a Microsoft Excel sheet. The information collected from each study were year of publication, authors, study design, country of study, participants, criteria used for diagnosis of CKDu used has been mentioned or not and if yes, then details of criteria used.

Study appraisal

The Quality Assessment Tool of National Institute of Health (NIH) for Observational Cohort/Cross-Sectional Studies and case-control studies was used for appraisal [28]. The Observational Cohort/Cross-Sectional Studies assessment tool has 14 questions and the case-control studies assessment tool has 12 questions which have to be answered as yes, no or CD[cannot determine) or NA (not available) or NR (not recorded)]. The details of the questions in each tool are provided in supplementary Table 4.

Sine NIH does not provide a scoring system we scored the studies based on the number of positive("yes") responses to the questions, as Good (≥ 8 = "yes" for cross-sectional/cohort studies and ≥ 7 = "yes" for case-control studies), fair (5–7 = "yes" for cross-sectional/cohort studies and 4–6 = "yes" for case-control studies) and poor (≤ 4 = "yes" for cross-sectional/cohort studies and ≤ 3 = "yes" for case-control studies).

Ethical considerations

The project was reviewed at the London School of Hygiene and Tropical Medicine through the Combined Academic, Risk assessment and Ethics (CARE) process and being a literature review, was assessed by the Research Governance & Integrity Office as not requiring ethical approval as all data are in the public domain.

Results

Overview of studies

4099 studies were identified from four databases. As shown in Fig. 1, once duplicates were removed, title and abstracts were reviewed and references of other review articles and meta-analyses were screened. 110 studies [4–7, 9–11, 13, 15, 16, 24, 29–127] were identified of which 9 were conference abstracts. Only 60 of 110 studies mentioned how CKDu was diagnosed and they were included in the final review.

If we look at the geographic distribution of studies (Table 1), they were predominantly from regions in Asia (43, 71.7%) and Central America (11,18.3%) known to harbour hotspots of CKDu.

Quality appraisal

There were 42 cross-sectional,14 case-control, 1 ecological and 3 cohort studies.

The Quality Assessment Tool of National Institute of Health (NIH) for Observational Cohort/Cross-Sectional Studies and case-control studies were used for appraising the studies [28]. Quality appraisal was done for 54 of 60 studies (supplementary Table 4), after excluding one ecological study (the tool is not applicable) and five conference abstracts (complete information required for appraisal not available).

Out of 54 studies, methodology was graded as good quality only in 5 while the rest were of fair [31] or of poor [17] quality. None of the cohort studies had a poor score (Table 2).

Diagnostic criteria of CKDu

Sixty studies were included as they mentioned specific definition used for diagnosis of CKDu. Since CKDu is a

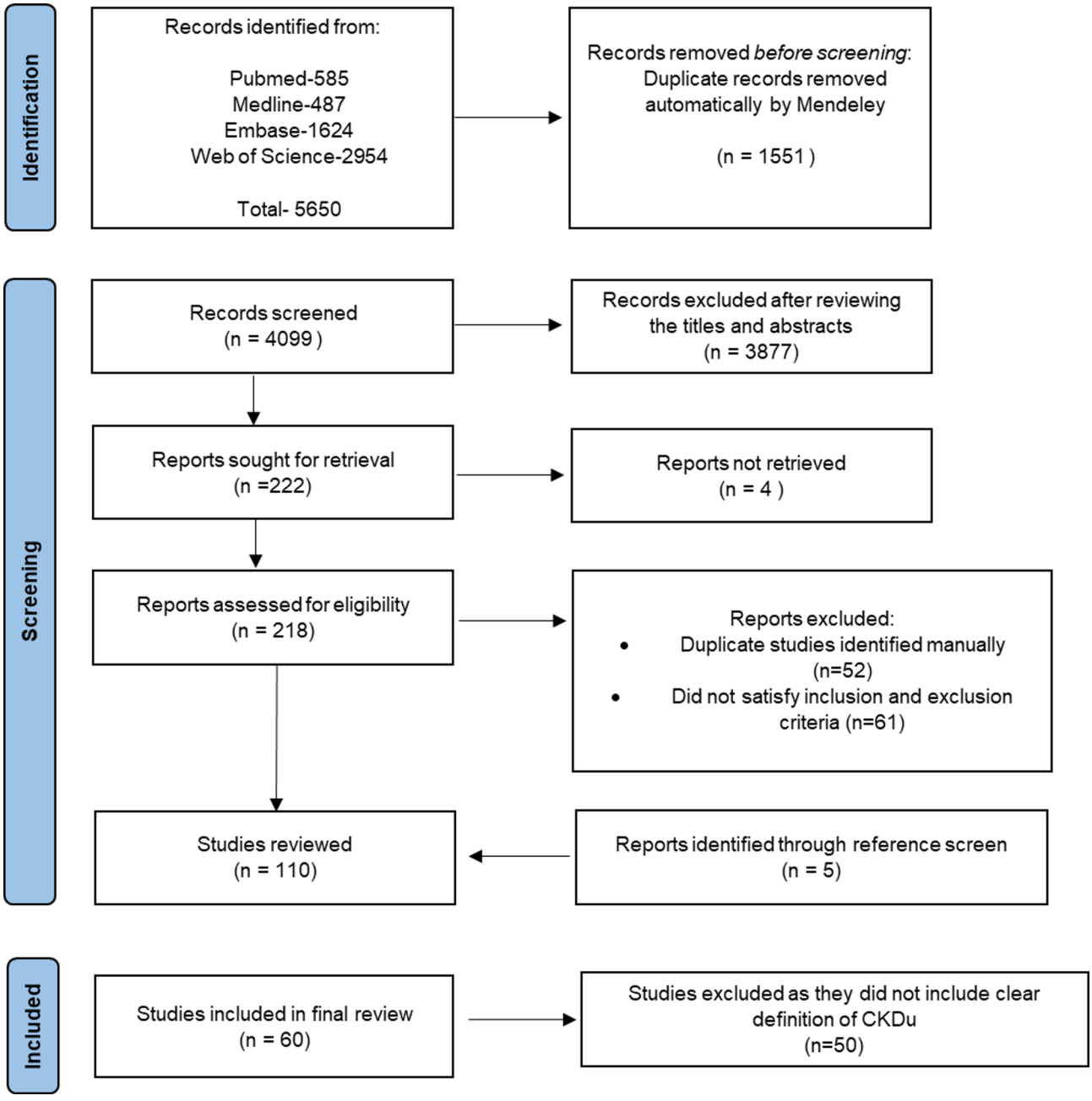

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses diagram showing the literature search* [28]. *(modified to include articles obtained through reference screen)

Table 1 Geographic distribution of studies

Continent	Studies(*n*, %)
Asia	43, 72%
South America	01, 1.7%
North America	11,18.3%
• Central America	02,3.3%
• Others	
Africa	3, 5%
Total	60, 100%

Table 2 Quality of included studies*

Study quality	Total	Cross-sectional studies	Cohort studies	Case control studies
Good	5	4	0	1
Fair	32	21	3	8
Poor	17	12	0	5

* As per quality assessment tools of National Institute of Health [28]

diagnosis of exclusion, the diagnostic criteria should have two components [1], to identify presence/absence of kidney disease and the [2] to confirm CKDu status, i.e. to rule out other causes of kidney disease and/or perform a kidney biopsy when feasible. The overview of each study is provided in supplementary Table 5.

Presence/absence of kidney disease

18(30.0%) studies used a combination of estimated glomerular filtration rate (eGFR) with proteinuria/albuminuria and 11(18.3%) studies used only proteinuria/albuminuria with varying thresholds, to define presence/absence of kidney disease (Table 3). Isolated eGFR (9,15.0%) or serum creatinine (6,10.0%) cut-offs were less commonly used. Eight (13.3%) followed the KDOQI/KDIGO CKD classification [128] without discussing specific exclusion criteria. 23(38.3%) studies used a single measurement of serum creatinine/urine analysis to diagnose CKDu, 20(33.3%) studies repeated the investigations at-least twice (with variable time intervals) to confirm chronicity while the number of measurements was not clarified in 17 studies. Overall, 37 studies provided specific criteria for proteinuria/albuminuria (Table 4).

Excluding other causes and/or confirming CKDu with biopsy

Nineteen studies defined a patient without an identifiable cause of kidney disease as CKDu irrespective of degree of proteinuria/albuminuria. Eighteen studies excluded patients with significant proteinuria though the cut-off used for exclusion varied widely. Four included only patients with no or minimal proteinuria (dipstick proteinuria ≤ 1 + or urine albumin creatinine ration < 30 mg/g). Ten studies considered 24-hour urinary protein of which 4 used urinary protein < 1 g/day, 4 used < 3 g/day and 2 used < 1.5–2 g/day as the inclusion criteria to define CKDu. Two studies required urine albumin creatinine ratio to be less than 300 mg/g urine creatinine. Studies which exclude heavy proteinuria/albuminuria to diagnose CKDu report lower prevalence of CKDu [15, 31, 32, 62, 70, 83] compared to those which include cases with any level of proteinuria [37, 48, 60, 112] (supplementary Table 6).

Although all studies stated that known causes of CKD had been excluded, only 21 (35%) provided specific information on the investigations performed and/or the alternative causes ruled out prior to diagnosing CKDu [16, 38, 40, 41, 43, 45–49, 59, 73, 74, 76, 83, 85, 96, 101, 102, 123].

Sixteen studies had kidney biopsy as part of the diagnostic work-up of which 4 (6.7%) required a kidney biopsy demonstrating tubulointerstitial disease as essential criteria for diagnosing CKDu irrespective of serum creatinine, eGFR and urinary findings.

Criteria used to rule out other causes of CKD mainly focus on excluding kidney disease due to diabetes and hypertension (Table 5). However, only 23(38.3%) studies provided definite criteria for elimination hypertension associated CKD and only 22(36.7%) studies specified the diagnostic definition for diabetes.

Five studies excluded elderly patients [31, 32, 38, 59, 62]. Nine studies excluded patients with past history of snake bite, 8 being from Sri Lanka [11, 24, 47, 49, 59, 94, 101, 102] and one from India [123]. Three studies [73, 85, 123] excluded cases with HIV infection.

Discussion

We reviewed 60 studies for the definition of CKDu. 38.3% studies diagnosed CKDu based on a single measurement of kidney function. This can cause misclassification of acute kidney injury (AKI) as CKD. There was significant variability in the cut-off level used to exclude "proteinuria" and the methods used for proteinuria/albuminuria estimation. Definitions which permit higher levels of proteinuria are more likely to overestimate the CKDu burden due to misclassification especially in the absence of kidney biopsy. Substantial variability was also observed in criteria used for excluding diabetes, hypertension and other causes of kidney disease. Use of self-reported history to rule out diabetes and hypertension may cause information bias. There may be reverse causality since hypertension can be secondary to long standing undiagnosed CKD. A single recording of blood pressure to define hypertension may overestimate its prevalence. Using the number of anti-hypertensive drugs prescribed to estimate severity can cause recall bias. Use of kidney biopsy was also inconsistent across studies. The heterogeneity in diagnostic criteria for CKDu was evident even in studies within a single region which makes comparisons of reported disease burden challenging.

The variability in diagnostic criteria have made it difficult to compare findings in CKDu research, highlighting the need for more standardized definitions to better understand the disease and its global impact. Diagnostic criteria have been developed by regional and global scientific organizations including the International Society of Nephrology (ISN), Pan American Health Organization (PAHO) and the World Health Organization (WHO) [26, 129–133]. Though CKDu is now recognized as a tubulointerstitial disease with no/low grade proteinuria [129, 133], there is a debate on whether it is a specific entity or phenotypic manifestation of diverse exposures in different populations [26, 129]. Consequently, establishing a single uniform definition of CKDu may not be feasible, given the varying research objectives (e.g., population-based surveillance versus hospital-based cohort or case-control studies) and logistic constraints. To address these issues, definitions [130, 133] have classified CKDu cases

Table 3 Criteria used for diagnosing presence/absence of CKD

No	Main criteria	Studies (*n*, %)	Strength and limitations
1	Specific serum creatinine cut-off	**6** (10.0%) Ref [47,48,52, 53,83,98]	• Routine investigation, widely available and inexpensive • Serum creatinine varies with age, sex and population. An absolute cut-off that is the same for men and women will fail to diagnose to women with early CKD • In certain regions like sub-Saharan Africa, creatinine does not work well to detect significant kidney disease as shown by the ARK study. • It is an invasive test and requires more resources • Using serum creatinine as sole criteria can underestimate prevalence of CKD as it may be normal in the initial stages despite decreased GFR • Using serum creatinine without any cut-off for proteinuria may lead to misclassification especially in regions where other etiologies like diabetes and glomerular diseases are commonly prevalent. This is especially likely if kidney biopsy is not feasible and diagnostic workup for ruling out other cause of CKD is not complete
2	Pre-specified eGFR cut-off	9 (15.0%) Ref [31,57,61,64,74,80,92,96,115]	• Enables earlier detection of CKDu as compared to serum creatinine if the eGFR equation used has been validated in the study population • Using eGFR only without any cut-off for proteinuria may lead to overestimation as discussed above • Most of the hotspots of CKDu are clustered in Central America and South Asia. The equations routinely used to calculate eGFR have not been validated in these populations and may overestimate the GFR
3	Proteinuria/Albuminuria cut-off	**11**(18.3%) Ref [10,11,24,44,46,49,56,95,97,102,103]	• May yield false positive as well as false negative results as it is affected by factors like dehydration, exercise, urinary tract infection, hematuria. • If presence of albuminuria is an essential criterion, those with early CKDu and mild tubulointerstitial disease having no/minimal albuiminuria will be missed • If all CKD cases without any identifiable cause are included irrespective of level of proteinuria, patients with other diseases (e.g. glomerular or hypertensive kidney disease) may be misdiagnosed as CKDu especially if kidney biopsy is not feasible
4	eGFR + Proteinuria/ Albuminuria cut-off	19 (31.7%) Ref [15,16,32,33,38,39,42,63,71,76,77,84,113,116,120,121,122,124,126]	• Though most comprehensive and widely used criteria, it is limited by the lack of validation of the equations used to calculate eGFR in South Asian populations • The accuracy of this criteria would also depend on proteinuria/albuminuria cut-off used as exclusion criteria since as per the DEGREE protocol definition patients with CKDu should have no albuminuria
5	Serum creatinine + eGFR + Proteinuria/ Albuminuria cut-off	**3** (5%) Ref [13,105,106]	• Does not provide any additional advantage over method 4 and so seldom used

Table 3 (continued)

No	Main criteria	Studies (*n*, %)	Strength and limitations
6	KDOQI/KDIGO** criteria for CKD	**8**(13.3%) Ref [35,41,43,50,51,60,73,86]	• Standard and widely accepted method of diagnosing and classifying CKD. • KDIGO classifies patients with eGFR > 60 ml/min/1.73m2 as CKD only if albuminuria is present. Patients with early CKDu(eGFR > 60 ml/min/1.73m2 with no albuminuria) may be missed in screening studies • If all patients of CKD without a known cause are included irrespective of degree of proteinuria, it may overestimate CKDu by misclassifying patients with other kidney diseases if diagnostic workup is not complete and/or kidney biopsy is not done
	Biopsy based-tubule-interstitial disease (Original CKD screening criteria not specified)	**3**(5.0%) Ref [93,110,117]	• Cases may be missed if biopsy is not feasible e.g. advanced kidney disease, contracted kidney, lack of patient consent.
8	ICD-10	**1***(1.7%) Ref [75]	• May underestimate the overall CKD burden compared to laboratory investigations if reporting is not consistent. Accuracy of CKDu diagnosis would depend on investigations done to rule out other causes of CKD-measurement bias
9	Total	60	

eGFR: estimated glomerular filtration rate, ** KDOQI-*Kidney Disease Outcomes Quality initiative/KDIGO-Kidney Disease Improving Global Outcomes*, * *Undiagnosed chronic kidney disease/end stage renal disease as per ICD 10 classification*

Table 4 Proteinuria/Albuminuria definitions used($n = 37$)

	Studies (*n*, %)
Patients with CKD without any identifiable cause labeled as CKDu irrespective of degree of proteinuria which was defined as:	19*(51.35%)
• Dipstick proteinuria ≥ 1	11
• Albumin creatinine ratio > 30 mg/g	8 *Ref [10,11,38,43,44,48,49,52,57,61,83,11,24,64,86,95,102,120,126]
Only patients with low grade proteinuria/albuminuria considered to be CKDu if no other cause identified:	18**(48.65%)
• Dipstick proteinuria ≤ 1+	2
• Dipstick proteinuria ≤ 2+	2
• 24-hour urinary protein ≤ 1 g/day	4
• 24-hour urinary protein < 1.5–2 g/day	2
• 24-hour urinary protein < 3 g/day	4
• Albumin creatinine ratio < 300 mg/g	2
• Albumin creatinine ratio < 30 mg/g	2 **Ref [13,15,16,32,33,39,42,53,71,76,77,85,97,105,106,121,122,124]

as "suspected" (for initial disease surveillance) and probable/confirmed (with more stringent requirements for verification). However, there is some discordance, with older definitions allowing inclusion of patients with higher level of proteinuria (130 – 32) while newer definitions require absent or minimal proteinuria/albuminuria [25, 129, 133].

Labelling patients with higher levels of proteinuria as CKDu especially without a kidney biopsy may lead to misclassification of potentially treatable diseases like IgA nephropathy with long term risk of kidney failure and overestimate the CKDu burden. This should be avoided particularly in community-based screening studies where detailed diagnostic workup and kidney biopsy are not feasible. Conversely, the degree of proteinuria varies with age and CKDu patients with advanced disease may have worsening proteinuria due to secondary glomerulosclerosis. Estimation of albumin creatinine ratio or 24-hour urinary protein is resource intensive compared to a urine dipstick test which maybe more cost-effective for screening [25, 133].

Excluding patients with diabetes, hypertension and advanced age may underestimate the disease burden. Non-traditional causes like obesity associated CKD (e.g. life-time overweight) may be mis-labelled as CKDu [134]. Some diagnostic uncertainty is also expected if kidney biopsy is an essential criterion for confirmation of CKDu [13] particularly in patients with advanced disease and in resource limited settings. Comprehensive work-up for exclusion of all known causes of CKD is also resource intensive and may not always be feasible in LMICs where CKDu is predominantly reported. Restricting the diagnosis to populations in certain geographies or certain occupations [129, 130] can prevent identification of new clusters of CKDu.

Table 5 Exclusion criteria used for diabetes and hypertension

Hypertension (*n* = 60)						
Criteria used	Any hypertension (No definite criteria)	Self-reported history of treatment for hypertension or BP ≥ 140/90 mm Hg	Chronic and/or severe hypertension	Requiring > 2 anti-hypertensive drugs to maintain BP < 140/90 mm Hg OR untreated Hypertension with BP > 160/100 mm Hg	BP > 140/90 mm Hg or requiring > 1 anti-hypertensive drug	Duration of hypertension > 5 years or requiring > 2 drugs to maintain BP < 140/90 mm Hg OR untreated BP > 160/100 mm Hg
Studies (n)	37(61.7%)	7(11.7%) Ref [15,33,38,42,84,97,116]	6(10%) Ref [10*,13*,14,47,48,60]	7(11.7%) Ref [11,35,39,44,50,103,124]	2(3.3%) Ref [105,106]	1(1.7%) Ref (16)
Diabetes (*n* = 60)						
Criteria used	Any diabetes (No definite criteria)	Self-reported history of treatment or FBS > 126 mg/dl	Self-reported history of treatment or HbA1C ≥ 6.5%	Self-reported history of treatment or RBS > 200 mg/dl	Self-reported history of treatment or RBS > 200 mg/dl or FBS > 126 mg/dl	Self-reported history of treatment or FBS > 126 mg/dl or HbA1C ≥ 6.5%
Studies (n)	38(63.3%)	7(11.7%) Ref [16,32,33,84,105,106,116]	9(15.0%) Ref [11,24,35,39,41,44,47,50,103]	4(6.7%) Ref [10,38,42,97]	1(1.7%) Ref [13]	1(1.7%) Ref [15]

*These studies had evaluated for hypertension related target organ damage to exclude long standing and severe hypertension

Considering these complexities, the definition of CKDu should be more nuanced and stratified according to the research goals and clinical scope. Proteinuria and hypertension should be strictly excluded as required by the DEGREE protocol [25] in community-based screening studies to avoid overestimation of the disease. More liberal definitions for hypertension and proteinuria maybe considered especially in those with advanced disease in hospital settings. However, this should incorporate a well-defined diagnostic algorithm to exclude other causes of CKD highlighting the need for a kidney biopsy for confirmation. A single measurement for kidney function may suffice for screening, but repeat testing after 3 months should be reinforced for cohort and case-control studies, hospital-based protocols and for further patient management. eGFR should be interpreted cautiously in South Asian populations in whom the equations have not been validated which may lead to differential bias when comparing with other ethnic populations. Relying solely on serum creatinine without estimating GFR to define CKD may underestimate disease prevalence.

Using the NIH quality assessment tool (supplementary Table 4), only 10% of the evaluated studies were deemed "good" while a substantial 30% were of "poor" quality. A common methodological limitation observed across many studies (supplementary Table 5) was the lack of clearly defined inclusion and exclusion criteria describing the study population. This reduces the internal validity, and highlights the inconsistencies in CKDu definitions which undermine the generalizability of study findings. The resulting significant variability in estimates of disease incidence and prevalence further hampers international and regional comparisons of the disease burden.

Accurate definition of CKDu is essential to design high quality studies and precisely estimate the disease burden, plan resource allocation for health interventions as well as research funding and improve overall management of kidney diseases. It is important to recognize that every patient for whom we are unable to identify the underlying cause of CKD is not a case of CKDu. This is especially crucial in resource limited economies from where CKDu is widely reported. In LMICs with limited healthcare access, incorrect diagnosis increases the patients' socioeconomic burden further fostering health inequity.

The recent multi-regional international cohort study using the DEGREE protocol has been a significant progress in addressing this lacuna [135]. It should be applied in large-scale population screening studies in the future to ensure standardized and accurate assessment of the disease burden across populations and regions and facilitate international comparisons.

Our literature review has certain limitations. Some studies may have been missed since we initially did a "title and abstract" search though this would be mitigated to some extent by additional review of the references of all articles identified in the initial search. Limiting the search to literature published only in English language may have resulted in an incomplete retrieval of data especially since significant work on CKDu has been published from Central America. We may have also missed unpublished data in grey literature.

Despite these limitations, this is a comprehensive review of global literature. Four major databases were searched and a large number of articles were screened. Attempt was made to ensure inclusion of most relevant work done in recent years by including conference abstracts.

Conclusion

There is wide variability in CKDu definitions across studies. This can impact patient outcomes through diagnostic misclassification, hinder the comparability of disease burden across studies, and potentially influence the allocation of resources for public health interventions. Developing standardized diagnostic criteria for CKDu—accounting for population differences, disease severity, and both research and clinical contexts—will enhance the comparability of evidence and may improve informed clinical decision-making.There should be consistency in criteria for excluding proteinuria/albuminuria and hypertension across similar studies as these are the main causes of misclassification. The definition of CKDu should be updated regularly informed by the changing research landscape.

Abbreviations

CKDu Chronic Kidney Disease of unknown etiology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04258-1.

Supplementary Material 1

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Not applicable.

Author contributions

SB developed the protocol, did the analysis and wrote the manuscript, LP was involved in developing the protocol, the analysis and writing the manuscript, DN was involved in writing the manuscript. All authors reviewed the final manuscript.

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Data availability

This is a systematic review of previously published studies that are already available in the public domain.

Declarations

Ethics approval and consent to participate

The project was reviewed at the London School of Hygiene and Tropical Medicine through the Combined Academic, Risk assessment and Ethics (CARE) process and being a literature review, was assessed by the Research Governance & Integrity Office as not requiring ethical approval as all data are in the public domain. Consent to participate is not applicable as this is review of previously published studies and does not involve collection and analysis of individual patient data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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