Supplementary Materials

Prisma Checklist.			
Section and Topic	**Item #**	**Checklist item**	**Location where item is reported**
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4, Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4, 15
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Table 2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4-5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4-5, Figure 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA

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Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4-5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4-5, Fig 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2, Table S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	NA
	23b	Discuss any limitations of the evidence included in the review.	15-16
	23c	Discuss any limitations of the review processes used.	15-16
	23d	Discuss implications of the results for practice, policy, and future research.	15-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	19

Prisma Checklist.			
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Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplemental Table 1. Longitudinal studies of kidney injury biomarkers in CKDu.

	Country	Biomarker(s)	Length of Follow Up	No. of Kidney Biomarker Assessments	Study Outcome(s)
Hansson, et al. *Occup Environ Med,* 2022	Nicaragua	Urinary KIM-1 Urinary MCP-1 Urinary Calbindin Urinary GST-π Urinary Clusterin Urinary IL-18	6 months	2 (pre-harvest and post-harvest)	Change in SCr Change in biomarker concentration
Wesseling, et al. *Envi Res*, 2016	Nicaragua	Urinary KIM-1 Urinary NGAL Urinary Hsp72	2.3 months	3 (harvest day 1, harvest day 6, and 9 weeks into harvest)	Change in SCr Change in biomarker concentration Change in serum electrolytes and serum uric acid
Laws, et al. *AJKD*, 2016	Nicaragua	Urinary NGAL Urinary IL-18 Urinary NAG	4-6 months	2 (pre-harvest and late harvest)	Change in eGFR Change in UACR Change in biomarker concentration
Gonzalez-Quiroz, et al. *J Am Soc Nephrol*, 2018†	Nicaragua	Urinary NGAL	2.5 years	5 (baseline and every six months)	eGFR trajectory (rate of decline)
Gonzalez-Quiroz, et al. *BMC Nephrol*, 2019†	Nicaragua	Urinary NGAL	2.5 years	5 (baseline and every six months)	eGFR trajectory (rate of decline)
Butler-Dawson, et al. *J Expo Sci Environ Epidemiol*, 2022‡	Guatemala	Urinary NGAL	8 months	2 (baseline and two months later)	Change in eGFR Association between NGAL, eGFR, and urinary metal concentration

† These two manuscripts describe the same study population, with differing analyses.

‡ This study selected a subset of patients for longitudinal analysis.

Abbreviations: CKDu, chronic kidney disease of uncertain etiology; eGFR, estimated glomerular filtration rate; GST-π, glutathione-S-transferase pi; Hsp72, heat shock protein 72; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant factor 1; NAG, N-acetyl-beta-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine; UACR, urinary albumin-to-creatinine ratio.

Supplemental Table 2. Urinary Biomarker Concentrations		
	NGAL (ng/mg)	**KIM-1 (ng/g)**
Adult Populations		
Abdul, et al. *Int J Environ Res Public Health,* 2021 ‡	2.1	3.1
De Silva, et al. *PLOS Negl Trop Dis*, 2016 †	0.4	460
Ekanayake, et al. *Int J Environ Res Public Health*, 2022 ‡	5.2	1600
Fernando, et al. *KIR*, 2019 ‡	0.01	0.07
Wijkstrom, et al. *PLOS One*, 2018 *	0.00005	1100
Wanigasuriya, et al. *Ceylon Med J*, 2017 ‡		533.4
Kulasooriya, et al. *Int J Envi Res Public Health,* 2021 *	0.42	
Hansson, et al. *Occup Environ Med,* 2022 ‡		6300
Wesseling, et al. *Envi Res*, 2016 ‡	8.0	3.95
Laws, et al. *AJKD*, 2016	10.0	
Petropoulos, et al. *Kidney360,* 2020 †	10.4	
Gonzalez-Quiroz, et al. *BMC Nephrol*, 2019 ‡	0.05	
Butler-Dawson, et al. *J Expo Sci Environ Epidemiol*, 2022 * ‡	4.3	
Diaz de Leon-Martinez, et al. *Envi Sci Pollut Res Int*, 2019 * ‡	6.8	185
Pediatric Populations		
De Silva, et al. *Children*, 2021 ‡	3.1	100
Gunasekara, et al. *Sci Rep*, 2022 ‡	3.2	200
Gunasekara, et al. *Ped Neph,* 2023 ‡	232	3.5
Ramirez-Rubio, et al. *NDT*, 2016 ‡	13.3	
Leibler, et al. *Ped Neph*, 2021 ‡	9.0	812.6
Cardenas-Gonzalez, et al. *Environ Res*, 2016 †	83.4	518.8

Values expressed as mean, geometric mean(†), or median(‡) for the overall study population, including all subgroups of exposure and baseline kidney function. Among studies for which no overall, summary biomarker concentration was provided, a weighted mean or median was calculated (weighted for the number of participants in each clinical phenotype, observational group, or exposure category). Due to inconsistencies in reporting measures of variability across studies (or missing measures of variability), variability is not reported in this table. Blanks indicate that the biomarker was not studied.

* These studies report non-normalized biomarker concentrations. To facilitate comparisons to normalized values, the values are shown in units of ng/L for KIM-1 or ng/ml for NGAL. This is because approximate urine output is 1L/day and approximate urine creatinine excretion is 1g/day; therefore the units ng/g and ng/L (or ng/mg and ng/ml) are roughly comparable within an order of magnitude.

Web of Science Search (2/13/2023)

((((ALL=(CKDu)) OR ALL=("Mesoamerican nephropathy")) OR ALL=("CKD of unknown etiology")) AND (ALL=(biomarker) OR ALL=(urin*) OR ALL=(plasma)))

CKD Biomarkers and Multi-Omics Platforms Not Yet Studied in CKDu

The CKD biomarker literature includes multiple candidate kidney biomarkers that have not been studied in CKDu to date. The following is a brief overview of biomarkers that may be considered in future CKDu studies based on relevant biology and promising associations in the CKD literature.

Urinary Uromodulin

Uromodulin (UMOD) is a protein expressed by tubular epithelial cells in the thick ascending limb of the loop of Henle and is the most abundant protein expressed in the kidney and excreted in the urine in healthy individuals. UMOD regulates salt homeostasis by modulating NKCC2, prevents urinary infections, and inhibits stone formation. Investigators have consistently identified *UMOD* in genome-wide association studies of kidney function and hypertension.[S1] Rare variant mutations in UMOD cause autosomal dominant tubulointerstitial kidney disease (ADTKD),[S2,S3] which shares histopathological features with CKDu.[S4] Epidemiologic studies have shown that lower urinary UMOD concentration is associated with tubulointerstitial lesion severity, [S5] incident CKD,[S6] and eGFR decline[S5–7] and that higher serum UMOD is associated with lower risk of progression to ESKD.[S8,9]

Urinary Epidermal growth factor

Epidermal growth factor (EGF) is produced by nearly every tissue type and stimulates cell growth and differentiation. In the kidney, EGF acts as a renal tubular trophic factor and is hypothesized to mediate tubular repair. EGF was identified in a kidney biopsy transcriptomic study in which candidate genes and proteins were prioritized by correlation with eGFR, kidney specificity of transcript and protein expression, and relevant biology.[S10] EGF emerged as the top candidate, and in clinical studies lower urinary EGF was associated with more severe interstitial fibrosis and

tubular atrophy in patients with primarily glomerular diseases.[S10] Low urinary EGF has also been studied in clinical cohorts of traditional CKD and AKI as a biomarker of kidney disease progression, rapid eGFR decline, and incident CKD.[S11–17]

Plasma soluble tumor necrosis factor receptors

Soluble tumor necrosis factor receptor-1 (sTNFR-1) and sTNFR-2 serve as inflammatory markers in the systemic circulation, where they participate in TNF signaling pathways. In the bound form, TNFR-1 is expressed by nearly all cell types, whereas TNFR-2 is expressed by hematopoietic, immunologic, and endothelial cells.[S18, S19] Higher levels of circulating sTNFR-1 were associated with increased interstitial fibrosis, tubular atrophy, mesangial expansion, and glomerular inflammation in patients undergoing clinically indicated kidney biopsy.[S20] Both sTNFR-1 and sTNFR-2 have been studied in several prospective cohorts in the traditional CKD literature[S20–25] and are associated with adverse kidney outcomes in a recent meta-analysis.[S26]

Plasma KIM-1

Although mostly studied in urine, KIM-1 may also enter the circulation after release into the interstitium by injured tubular cells that have lost their polarity or detached from the basement membrane.[S27] Plasma KIM-1 has been studied in several prospective cohorts in the traditional CKD literature.[S23, S25, S28–30] A recent meta-analysis of these studies showed a strong association between plasma KIM-1 and a pooled kidney outcome of incident CKD, CKD progression, or incident ESKD.[S26]

Proteomics and Metabolomics

Another promising area of kidney research beyond traditional biomarkers is in the fields of proteomics and metabolomics.[S31–33] These techniques are increasingly used in investigations

of CKD to facilitate a deeper understanding of molecular patterns of disease, as well as risk for eGFR decline.[S34–40] Combining metabolomic analyses with genomics and proteome-wide association studies may advance causal inference in CKD.[S41, S42] Integrated or multi-"omics" strategies may be particularly relevant to improving risk stratification and disease phenotyping in CKDu, where little is known about the underlying pathophysiology in early stages of the disease.[S43] Omics data may also provide insight into molecular pathways that are potential therapeutic targets for treatment of CKDu.[S33]

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