International prevalence patterns of low eGFR in adults aged 18-60 without traditional risk factors from a population-based cross-sectional disadvantaged populations eGFR epidemiology (DEGREE) study

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The disadvantaged populations eGFR (estimated glomerular filtration rate) epidemiology (DEGREE) study was designed to gain insight into the burden of chronic kidney disease (CKD) of undetermined cause (CKDu) using standard protocols to estimate the general-population prevalence of low eGFR internationally. Therefore, we estimated the age-standardized prevalence of eGFR under 60 ml/min per 1.73m^2 in adults aged 18-60, excluding participants with commonly known causes of CKD; an ACR (albumin/creatinine ratio) over 300 mg/g or equivalent, or self-reported or measured (HT) hypertension or (DM) diabetes mellitus, stratified by sex and location. We included population-representative surveys conducted around the world that were either designed to estimate CKDu burden or were re-analyses of large surveys. There

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were 60,964 participants from 43 areas across 14 countries, with data collected 2007- 2023. The highest prevalence was seen in rural men in Uddanam, India (14%) and Northwest Nicaragua (14%). Prevalence above 5% was generally only observed in rural men, with exceptions for rural women in Ecuador (6%) and parts of Uddanam (6%−8%), and for urban men in Leon, Nicaragua (7%). Outside of Central America and South Asia, prevalence was below 2%. Our observations represent the first attempts to estimate the prevalence of eGFR under 60 without commonly known causes of CKD around the world, as an estimate of CKDu burden, and provide a starting point for global monitoring. It is not yet clear what drives the differences, but available evidence supports a high general-population burden of CKDu in multiple areas within Central America and South Asia, although the possibility that unidentified clusters of disease may exist elsewhere cannot be excluded.

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Lay Summary

In recent decades, there have been reports of epidemics of chronic kidney disease (CKD) killing young men in Central America and South Asia. These cases do not involve the commonly known causes of CKD, such as diabetes, so they are known as CKD of unknown cause (CKDu). To understand the size and extent of the problem around the world, we included data from studies that measured kidney function from 43 areas across 14 countries (60,964 people). We calculated the prevalence of poor kidney function in working-age men and women in urban and rural areas, in those without indicators of the commonly known causes of CKD. The most affected groups were rural men in Uddanam, India (14%), and Northwest Nicaragua (14%). Low prevalence (<2%) was seen in included areas outside of Central America and South Asia. These findings are important to direct future research, give clues to the possible causes of CKDu, and as a starting point for global monitoring.

Globally, chronic kidney disease (CKD) is most commonly associated with diabetes, hypertension, other cardiovascular diseases, glomerulonephritis, genetic or congenital abnormalities, or urological diseases. However, there is an increasing recognition of forms of progressive CKD that are not associated with these known risk factors, and that are mostly affecting the working-age populations in low- and middle-income countries).[1,2] This clinical syndrome has been termed CKD of undetermined cause (CKDu); other names used include CKD of nontraditional cause, Mesoamerican nephropathy, Uddanam nephropathy, and chronic interstitial nephritis of agricultural communities. Over the past few decades, clusters of CKDu have been reported in Central America,[3] Mexico,[4] India,[5] and Sri Lanka.[6] Other reports have suggested that similar patterns may be occurring in other regions of the world, but it is only recently that efforts have increased to undertake comparable population surveys in working-age populations elsewhere in low- and middle-income countries.

Perhaps the most clearly established risk factor/epidemiologic association in both Central America and South Asia is that CKDu is more common among men engaged in manual labor in hot climates, particularly in agricultural communities.[7] In Central America, CKDu occurs frequently in sugar cane workers but also in other occupational groups, including other agricultural workers, fishermen, miners, and brick kiln and construction workers[8]; it also occurs, albeit at a lower frequency, in women, most of whom have not reported working in agriculture. In common with historical endemic kidney diseases, such as Balkan nephropathy,[9] the absence of substantial albuminuria or hematuria, alongside geographical clustering, supports a primarily tubular-interstitial disease, and potentially a causal role for environmental exposure(s). Many specific potential causes related to agriculture have been suggested for CKDu. Heat/dehydration, pesticides, and heavy metals are the main hypotheses proposed for Central America, whereas in South Asia the emphasis has been on the possible roles of water contamination by metals and/or pesticides.[10–12]

In the past, international comparisons have played a key role in identifying possible causes of chronic disease.[13] For example, many of the discoveries on the causes of cancer (e.g., human papilloma virus and cervical cancer) have their origins, directly or indirectly, in the systematic international comparisons of cancer incidence conducted in the 1950s and 1960s. Hypotheses generated from these studies were investigated in more depth in further studies.[14] A more recent example is the International Study of Asthma and Allergies in Childhood, a standardized protocol to estimate the prevalence of asthma internationally,[15,16] which has now evolved into the Global Asthma Network.[17,18] This has led to a greater understanding of the possible causes of asthma globally, as well as the creation of a large international network of researchers.

We have proposed a similar approach involving a simple and practical protocol to describe distributions of kidney function, using the estimated glomerular filtration rate (eGFR), in disadvantaged communities globally: the disadvantaged populations eGFR epidemiology (DEGREE) study. The DEGREE protocol was explicitly developed for general population-based surveys.[19] It was noted that the same method could be used in other contexts (e.g., workforce surveys), but the current article focuses on population surveys.

As the causes of CKDu are unknown, diagnosis is often made by exclusion of known causes of kidney disease. The DEGREE protocol uses pragmatic criteria (absence of diabetes,

hypertension, or heavy proteinuria) to estimate the prevalence of low eGFR unrelated to known causes of kidney disease (with the latter features being common in most forms of glomerular diseases). This enables standardized comparisons across multiple centers and is intended to identify population patterns, rather than diagnose CKDu in individuals.

We here report the first findings from the DEGREE study, involving 60,964 participants with complete data from 19 studies across 43 areas in 14 countries, with date of data collection varying by study between 2007 and 2023 (Table 1). These are primarily in low- and middle-income countries, plus 1 study in rural Italy, another in Chile, and publicly available data from England and the United States as reference points for comparison.

METHODS

The DEGREE collaboration aims to gain insight into the burden of CKDu by using standard protocols to estimate the prevalence of low eGFR in population-representative surveys; the detailed rationale and methods have previously been published.[19] Here, we use the term CKDu to describe the endemic kidney disease of unknown cause occurring at epidemic levels in geographic clusters (i.e., the disease[s] also termed Mesoamerican nephropathy, Uddanam nephropathy, or chronic interstitial nephritis in agricultural communities) rather than all forms of CKD without a diagnosis. Defining CKDu is challenging, both at the individual level and for epidemiologic studies, as there is no gold standard diagnostic test, and diagnosis currently relies on the exclusion of known causes of kidney disease, with only a small number of cases fully documented as tubulointerstitial disease with a kidney biopsy. For these international comparisons of general population prevalence, we have used a pragmatic definition of an eGFR <60 ml/min per 1.73 m^2 in the absence of diabetes, hypertension, and heavy proteinuria in the working-age population as a surrogate indicator of CKDu burden.

Another important consideration when conducting international comparisons of eGFR is analytical variability in laboratory assays. In this analysis, all studies used standardized isotopic dilution mass spectrometry referenced creatinine measurements, which should minimize this problem, although interlaboratory and time-dependent variations are still present.[36] Note that we do not have written confirmation for Nicaragua 1, but this was conducted in a Ministry of Health laboratory where isotopic dilution mass spectrometry references were being used at that time. Similar quality control methods are not widely used for cystatin C determination. For our studies, the cystatin C measurements for India, Malawi, and Peru were all standardized to a central reference laboratory, but the cystatin C data from Kenya were not standardized.

There were 11 studies formally registered with DEGREE that agreed to conduct population surveys using the DEGREE protocol. Of these, 10 provided data for this analysis. In addition, we identified 11 other studies, using methods compatible with the DEGREE protocol, that had already been conducted in areas with reported high CKDu prevalence or in settings with proposed CKDu risk factors. The organizers of these other studies were therefore invited to contribute their data to the joint analyses, of whom 7 responded positively and provided data. The studies varied both in the size of the sample and the size of the source population, from focused surveys of specific communities to regional or national surveillance projects (details in Table 1). However, all surveyed the general population of the relevant area (most using either simple random sampling or multistage cluster random sampling; see Supplementary Table S1). Of the 17 collaborating studies, 7 provided us with their data in tabular form, whereas 10 provided us with individual-level data sets to create the relevant tables (see Supplementary Table S1). Additionally, publicly available data from health surveys in England[22] and the United States[35] were obtained to provide reference data from high-income countries. Thus, a total of 19 studies were involved in the current analysis, each reporting data from ≥ 1 separately sampled areas.

Populations vary in their age distribution, and to make our country comparisons fair, the main outcome was the age-standardized prevalence of eGFR <60 ml/min per 1.73 m^2 (using the World Health Organization global standard population[37]) in those without hypertension, diabetes, and heavy proteinuria (eGFR $<60_{[\text{absent HT, DM, high ACR}]}$), for working-age adults, stratified by rural-urban classification (except the United States, where this was not available) and biological sex (referred to as sex throughout this article). The age-standardization method is described in Supplementary Text S1.

We also calculated the overall prevalence of eGFR <60 ml/min per 1.73 m^2 without excluding the population with hypertension, diabetes, or heavy proteinuria (eGFR $<60_{[\text{no exclusions}]}$), for comparison. Confidence intervals were calculated for all standardized prevalence estimates.

Except where indicated in Supplementary Table S1, eGFR was calculated using the creatinine-based CKD Epidemiology Collaboration 2009 equation[38] but without race adjustment; heavy proteinuria was defined by an albumin-to-creatinine ratio (ACR) of >300 mg/g or $\geq$++ when studies used dipstick urinalysis; diabetes was determined by self-report or hemoglobin A1c $\geq 6.5\%$; and hypertension was determined by self-report, treatment, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg.

To better understand any selection bias impacting the prevalence estimates, we compared the prevalence of eGFR $<60_{[\text{no exclusions}]}$ in the whole available sample with those with complete data for hypertension, diabetes, and proteinuria (before making any exclusions).

Similar analyses were completed using secondary outcomes with a cutoff of 90 ml/min per 1.73 m^2(eGFR $<90_{[\text{no exclusions}]}$ and eGFR $<90_{[\text{absent HT, DM, high ACR}]}$) to help understand the distribution of low to moderate kidney function and whether the patterns follow or differ to that of low eGFR.

The main analysis used eGFR calculated from serum creatinine, but in a subset, data were available to calculate eGFR using serum cystatin C. Within this subset, we

Table 1 | Characteristics of study areas and samples

Country	Study type	Rationale	Area name	Urban, %[a]	Climate	Survey dates	Survey season	Source population	Overall response rate, %	Sample information[b]		
										n	Male, %	Age, yr, median (IQR)
Chile	Reuse of population survey[20]	Proposed risk factors	Molina	69	Mediterranean	Oct 2022–Nov 2023	All year	45,976	92	476	41	53 (48–57)
Ecuador	CKD focused study[21]	DEGREE registered	Miguelillo, Manabi Province	0	Tropical	Jul 2021–Sep 2021	Dry	14,164	61	754	41	39 (28–49)
England	HSE 2016: reuse of population survey[22]	Reference	England	83	Temperate	2016	All year	56,000,000	59	2135	42	44 (34–52)
Guatemala	CKD focused study[23]	DEGREE registered	Tecpán, Chimaltenango	0	Temperate Highland Tropical	Jun 2018–Oct 2019	All year	85,000	58	336	34	34 (24–47)
			San Antonio Suchitepéquez	0	Tropical wet	Jun 2018–Oct 2019	All year	52,000	69	318	34	33 (25–45)
India	1. CARRS: reuse of population survey[24]	DEGREE registered	Chennai	100	Tropical	Oct 2010–Nov 2011	All year	4,680,000	92	5366	43	39 (31–47)
			Delhi	100	Semiarid	Oct 2010–Nov 2011	All year	16,300,000	96	3564	49	42 (35–50)
	2. ICMR-IHD: reuse of population survey[25]	DEGREE registered	Delhi	100	Semiarid	Aug 2011–Jan 2012	Rainy, autumn, winter	16,300,000	NR	1888	44	41 (35–48)
			Faridabad	0	Semiarid	Aug 2011–Jan 2012	Rainy, autumn, winter	90,000	NR	1413	45	42 (36–49)
	3. UDAY: reuse of population survey[26]	DEGREE registered	Sonipat	50	Semiarid	Jul 2014–Dec 2014	Rainy, autumn, winter	203,000	90[c]	4126	44	44 (37–51)
			Vizag	50	Tropical	Jul 2014–Dec 2014	Rainy, autumn, winter	275,000		4209	44	43 (35–50)
	4. Uddanam: CKD focused study[27]	Reported high CKDu area	Kanchili	0	Hot tropical	Jun 2018–Dec 2019	Summer, winter	66,657	85[c]	317	47	43 (35–51)
			Kaviti	0	Hot tropical	Jun 2018–Dec 2019	Summer, winter	75,974		212	48	43 (35–51)
			Mandasa	0	Hot tropical	Jun 2018–Dec 2019	Summer, winter	82,699		200	48	42 (33–50)
			Palasa	0	Hot tropical	Jun 2018–Dec 2019	Summer, winter	97,551		362	51	44 (36–51)
			Sompeta	0	Hot tropical	Jun 2018–Dec 2019	Summer, winter	78,908		443	46	42 (33–51)
			V_kothuru	0	Hot tropical	Jun 2018–Dec 2019	Summer, winter	73,212		531	47	44 (35–52)
	5. Prakasam: CKD focused study[d]	DEGREE registered	Kanigiri	0	Hot tropical	Dec 2021–Feb 2022	Winter	1780	84	1052	40	39 (30–49)

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Table 1 | (Continued) **Characteristics of study areas and samples**

Country	Study type	Rationale	Area name	Urban, %[a]	Climate	Survey dates	Survey season	Source population	Overall response rate, %	Sample information[b]		
										n	Male, %	Age, yr, median (IQR)
Italy	CKD focused study[28]	Reported high CKD area	Barga	0	Temperate	Jun 2021–Mar 2022	Summer, autumn, winter	9574	92[e] (or 50[f])	301	43	47 (33–54)
Kenya	CKD focused study[29]	DEGREE registered	Muhoroni East	100	Subtropical	Jul 2020–Nov 2020	Dry	3740	85	260	53	34 (26–43)
			Owaga	0	Subtropical	Jul 2020–Nov 2020	Dry	3769	87	242	47	36 (26–46)
			Tonde	0	Subtropical	Jul 2020–Nov 2020	Dry	3045	98	233	49	36 (28–45)
Malawi	CKD focused study[30]	DEGREE registered	Southern Karonga District	0	Subtropical	Jan 2018–Aug 2018	Dry, rainy	40,000	66	646	42	33 (24–41)
			Lilongwe	100	Subtropical	Jan 2018–Aug 2018	Dry, rainy	66,000	37	312	31	28 (22–38)
Nepal	Reuse of population survey[31]	Proposed risk factors	Nepal	67	Subtropical to arctic	2016–2018	All year	29,000,000	92	8 916	37	41 (33–50)
Nicaragua	1. CKD focused study[3]	Reported high CKDu area	Chinandega (banana/ sugarcane)	0	Tropical	Jul 2007–Oct 2007	Rainy	384	86	331	47	34 (26–44)
			Chinandega (service)	0	Tropical	Jul 2007–Oct 2007	Rainy	177	79	140	36	32 (25–43)
			Leon (coffee)	0	Tropical	Jul 2007–Oct 2007	Rainy	92	84	77	52	36 (27–46)
			Leon (fishing)	0	Tropical	Jul 2007–Oct 2007	Rainy	216	77	166	46	32 (25–44)
			Leon (mining)	0	Tropical	Jul 2007–Oct 2007	Rainy	445	86	382	41	33 (26–43)
	2. CKD focused study[32]	Reported high CKDu area	Leon municipality	70	Tropical	Jun 2014–Sep 2014	Rainy	204,000	97	1672	39	37 (28–48)
Peru	CKD focused study[33]	DEGREE registered	Tumbes	94	Arid and subtropical	Nov 2017–May 2018	Spring, summer, autumn	224,863	83	1238	43	39 (30–49)
Sri Lanka	Anuradhapura District: CKD focused study[6]	DEGREE registered	Halambagaswewa, Rambewa	0	Tropical	Mar 2017–May 2017	Dry	1188	90	739	33	41 (33–49)
			Lolugaswewa, Medawachchiya	0	Tropical	Mar 2017–May 2017	Dry	1262	86	790	28	41 (34–50)
			Pothana, Mihintale	0	Tropical	Mar 2017–May 2017	Dry	1391	88	691	28	41 (33–51)

(*Continued on following page*)

Table 1 | (Continued) **Characteristics of study areas and samples**

Country	Study type	Rationale	Area name	Urban, %[a]	Climate	Survey dates	Survey season	Source population	Overall response rate, %	Sample information[b]		
										n	Male, %	Age, yr, median (IQR)
			Puhudivula, Medawachchiya	0	Tropical	Mar 2017–May 2017	Dry	1362	91	798	28	41 (32–50)
			Sangilikandarawa, Rambewa	0	Tropical	Mar 2017–May 2017	Dry	1228	90	818	33	41 (33–50)
Thailand	Reuse of population survey[34]	Proposed risk factors	Bangkok	100	Tropical	Nov 2013–Aug 2014	Cool, hot, rainy	6,969,010[g]	81	1604	24	48 (40–55)
			Central	46	Tropical	Nov 2013–Aug 2014	Cool, hot, rainy	14,424,785[g]	92	2752	41	46 (35–54)
			North	35	Tropical	Nov 2013–Aug 2014	Cool, hot, rainy	8,638,732[g]	83	2447	45	47 (37–54)
			North East	29	Tropical	Nov 2013–Aug 2014	Cool, hot, rainy	13,445,305[g]	80	2315	46	46 (36–53)
			South	34	Tropical	Nov 2013–Aug 2014	Cool, hot, rainy	6,442,937[g]	73	2019	42	44 (34–53)
USA	NHANES 2017–2018: reuse of population survey[35]	Reference	USA	83	All types	2017–2018	All year	320,842,721	49	3373	47	39 (30–49)

CARRS, Centre for cArdiometabolic Risk Reduction in South-Asia; CKD, chronic kidney disease; CKDu, chronic kidney disease of unknown cause; DEGREE, disadvantaged populations eGFR [estimated glomerular filtration rate] epidemiology; HSE, Health Survey England; ICMR-IHD, Indian Council of Medical Research International Health Division; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; NR, not reported; UDAY, dawn in Sanskrit.

[a]Proportion of the source population of the area living in an urban environment.

[b]Includes ages 18–60 years with complete data available.

[c]Overall response rate not area specific.

[d]Personal written communication with Professor Prabhdeep Kaur (kprabhdeep@gmail.com), July 20, 2023.

[e]Denominator includes refusal/incomplete surveys but excludes mailing failures.

[f]Denominator includes mailing failures.

[g]Population aged >20 years.

compared the results from the original creatinine-based equation with the CKD Epidemiology Collaboration 2012 cystatin C only equation and combined creatinine and cystatin C equation.[39] We also calculated the Lin concordance correlation coefficient on the individual eGFR data to compare the different measurements.

Prevalence estimates of the main outcome (eGFR $<60_{[\text{absent HT, DM, high ACR}]}$) were plotted on international maps, categorized into low (<2%), moderate (2%–5%), and high (>5%), to enable visualization of geographical differences.

Finally, we undertook some sensitivity and other supplementary analyses as follows:

(i) Where individual-level data were available, we ran a sensitivity analysis using age-dependent cutoffs of eGFR from a 2020 article by Jonsson.[40]

(ii) We ran another sensitivity analysis to consider different eGFR equations using serum creatinine, including CKD Epidemiology Collaboration 2021 and CKD Modification of Diet in Renal Disease, where it was possible to calculate.

(iii) We looked for any associations between the main prevalence outcome and study/sample characteristics, including response rate, the proportion of men in the sample, and date of the study.

Data were analyzed using Stata version 17,[41] and maps were created using the free open-source QGIS software.[42]

RESULTS

The characteristics of the 19 studies and 43 areas, including study rationale, response rates, and the size of representative populations, are shown in Table 1 (with location maps in Supplementary Figure S1). Most studies were in tropical regions and low- and middle-income countries. The studies were undertaken at different times, ranging from 2007 in Leon and Chinandega, Nicaragua, to 2023 in Molina, Chile. The proportion of men in each sample varied from 24%–53% with a median of 43%. The median age varied from 28 years (interquartile range, 22–38 years) in Lilongwe, Malawi, to 53 (interquartile range, 48–57) years in Molina, Chile. Stratifying by sex and using age standardization mitigates these differences to allow for valid comparisons.

Response rates were mainly high (>75% and up to 98%), with the exceptions of the high-income reference data sets (England, 59%; and United States, 49%) and the Ecuador (61%), Guatemala (58% and 69%), and Malawi (66% and 37%) studies plus 1 area of Thailand (South, 73%).

Overall, 2015 (3.2%) participants were missing data on hypertension, diabetes, or proteinuria, used in the exclusions, leaving a total sample size of 60,964. The study with the most missing data on these factors was Nepal, where 874 participants (8.9%) had missing data. For all areas considered, estimates of the prevalence of eGFR <60 ml/min per 1.73 m^2 in the total sample were similar to those in the sample with complete data (Supplementary Table S2).

There were 22,255 (36.5%) participants identified as having ≥1 conditions of hypertension, diabetes, and heavy proteinuria, leaving a sample size of 38,709 for the restricted analyses. The proportion of participants with these conditions varied greatly by area, ranging from ≈16% in 2 Kenyan areas to >50% in 4 areas of India. Some of this difference could be explained by the age structure of the samples (as this is before age standardization; Tables 1 and 2).

The age-standardized prevalence estimates of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ stratified by area, sex, and rural-urban classification are shown in Table 2 and Figures 1–4, with a comparison between men and women in Figure 5. For men, standardized prevalence estimates of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ were highest in rural areas of Uddanam, India (up to 13.7%; 95% confidence interval, 4.8%–22.6%) and areas in northwest Nicaragua (up to 13.6%; 95% confidence interval, 6.3%–20.9%). Of the other areas considered, prevalence in rural males was low (<2%) in Nepal and some other areas of India and in all areas outside of Central America and South Asia, including Kenya, Peru, Chile, Malawi, and Thailand. High prevalence (>5%) in men was generally only seen in rural areas, but there was 1 high prevalence urban area in Leon, Nicaragua, and moderate prevalence in Lilongwe, Malawi. There was 1 low prevalence (<2%) rural area in Nicaragua that was included because residents mainly worked in the service sector. As expected, the prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ was low in the United States, England, and Italy.

For women, the prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ was generally low, except rural women had an 8.0% (95% confidence interval, 2.0%–14.1%) prevalence in 1 area of Uddanam and 6.0% (95% confidence interval, 2.2%–9.7%) in Ecuador. There was a moderately high prevalence (2%–5%) in women in Malawi and urban women in Nepal (Table 2 and Figures 1 and 2).

Standardized prevalence of eGFR $<60_{[\text{no exclusions}]}$ was generally higher than the standardized prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ as expected, but followed a similar pattern, being highest in rural Uddanam, India (men up to 18.4%, women up to 11.0%) and rural men in Nicaragua (up to 19.0%; Table 2).

When considering low-moderate eGFR values (eGFR $<90_{[\text{absent HT, DM, high ACR}]}$), there was great variability of prevalence and much higher prevalences in some areas, even those without a high prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$, such as England (Supplementary Table S3).

Concordance between eGFR measurements in individuals calculated using creatinine alone compared with cystatin C alone and both creatinine and cystatin C can be seen in Supplementary Table S4. The standardized prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ using cystatin C was substantially higher in Sonipat and Vizag, India, compared with using creatinine in both men and women (from 12.1%–21.3% vs. 0.0%–6.7%). The equation using both creatinine and cystatin also gave higher prevalence but at a much closer level (0.4%–10.1%). In 2 areas of Kenya, there was 0.0% prevalence with the creatinine equation and the creatinine-cystatin equation, but prevalences of 10.4% and 14.3% in

Table 2 | Age-standardized prevalence of eGFR <60 ml/min per 1.73 m^2 by sex, for ages 18–60 years

			Sample with complete data				Sample of people without hypertension, diabetes, or heavy proteinuria			
			Men		Women		Men		Women	
Center	Area	Rural/urban	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]
Chile[b]	Molina	Rural	39	0.0 (N/A)	17	0.0 (N/A)	16	0.0 (N/A)	6	0.0 (N/A)
		Urban	156	0.0 (N/A)	264	1.6 (0.1–3.1)	66	0.0 (N/A)	137	0.5 (0–1.6)
Ecuador	Miguelillo	Rural	312	2.2 (0.7–3.8)	442	6.4 (4.3–8.5)	180	1.2 (0–2.8)	235	6.0 (2.2–9.7)
England	All	Rural	161	0.4 (0–1.0)	223	2.2 (0.8–3.7)	98	0.0 (N/A)	169	1.8 (0.4–3.2)
		Urban	744	0.5 (0.1, 0.9)	1007	1.0 (0.6, 1.5)	515	0.1 (0, 0.4)	759	0.8 (0.3, 1.4)
Guatemala	San Antonio Suchitepequez	Rural	115	3.1 (0–6.3)	221	0.9 (0–2.2)	86	3.0 (0–7.0)	171	0.0 (N/A)
	Tecpan	Rural	109	0.9 (0–2.6)	209	0.0 (N/A)	83	0.0 (N/A)	152	0.0 (N/A)
India 1 (CARRS)	Chennai	Urban	2333	0.9 (0.5–1.3)	3033	0.6 (0.3–0.9)	1161	0.5 (0.0–0.9)	1915	0.2 (0–0.5)
	Delhi	Urban	1733	1.0 (0.6–1.5)	1831	1.2 (0.8–1.6)	770	0.6 (0.1–1.1)	935	0.6 (0.0–1.1)
India 2 (ICMR)	Delhi	Urban	837	1.2 (0.6–1.9)	1051	2.3 (1.5–3.1)	399	0.6 (0–1.3)	571	1.8 (0.6–3.0)
	Faridabad	Rural	629	1.6 (0.8–2.4)	784	1.6 (0.9–2.4)	380	1.9 (0.8–3.1)	520	1.5 (0.5–2.5)
India 3 (UDAY)	Sonipat	Rural	768	0.6 (0.2–1.1)	1136	0.6 (0.2–1.0)	530	0.4 (0.0–0.8)	847	0.5 (0.1–0.9)
		Urban	1038	0.9 (0.4–1.3)	1184	0.6 (0.2–0.9)	586	0.6 (0.1–1.1)	768	0.3 (0–0.6)
	Vizag	Rural	934	6.7 (2.9–10.4)	1242	3.1 (2.2–4.1)	696	6.5 (1.9–11.0)	933	2.6 (1.5–3.7)
		Urban	903	1.2 (0.6–1.8)	1130	0.7 (0.3–1.1)	469	0.4 (0–1.1)	692	0.5 (0–1.1)
India 4 (Uddanam)	Kanchili	Rural	148	4.8 (1.1–8.6)	169	7.2 (3.2–11.3)	71	6.9 (1.0–12.9)	83	1.1 (0–3.2)
	Kaviti	Rural	102	12.2 (7.7–16.7)	110	8.0 (3.5–12.4)	52	6.7 (1.3–12.2)	65	8.0 (2.0–14.1)
	Mandasa	Rural	95	18.4 (10.7–26.1)	105	10.6 (6.0–15.1)	57	13.7 (4.8–22.6)	54	5.6 (0.4–10.7)
	Palasa	Rural	186	11.2 (5.9–16.5)	176	11.0 (6.1–15.9)	84	6.8 (0.1–13.4)	81	4.6 (0.5–8.7)
	Sompeta	Rural	202	9.2 (4.9–13.4)	241	2.7 (0.9–4.5)	99	8.2 (2.2–14.3)	127	5.8 (1.1–10.6)
	V_kothuru	Rural	250	5.3 (3.0–7.5)	281	4.9 (2.9–7.0)	101	2.1 (0–4.8)	121	7.5 (3.2–11.9)
India 5 (Prakasam)	Kanigiri	Rural	420	5.3 (3.4–7.2)	632	3.4 (2.0–4.7)	221	2.5 (0.3–4.6)	432	1.9 (0.7–3.1)
Italy	Barga	Rural	128	0.9 (0–2.3)	173	0.7 (0–1.7)	73	1.2 (0–3.5)	149	0.0 (N/A)
Kenya	Muhoroni East	Urban	138	0.0 (N/A)	122	0.9 (0–2.7)	113	0.0 (N/A)	104	0.0 (N/A)
	Owaga	Rural	113	0.0 (N/A)	129	2.2 (0–4.8)	88	0.0 (N/A)	98	2.4 (0–5.8)
	Tonde	Rural	114	0.0 (N/A)	119	0.0 (N/A)	94	0.0 (N/A)	100	0.0 (N/A)
Malawi	Karonga	Rural	271	3.0 (0.7–5.4)	375	3.0 (1.0–5.1)	214	1.4 (0–3.5)	309	2.8 (0.3–5.3)
	Lilongwe	Urban	96	2.2 (0–6.2)	216	4.9 (1.4–8.4)	74	3.1 (0–8.6)	159	4.0 (0.7–7.2)
Nepal	All	Rural	1690	0.9 (0.6–1.3)	2790	2.1 (1.6–2.6)	1002	0.5 (0.1–1.0)	1981	1.7 (1.1–2.3)
		Urban	1602	0.8 (0.4–1.1)	2834	3.0 (2.4–3.6)	822	0.3 (0.0–0.7)	1777	2.6 (1.9–3.4)
Nicaragua 1	Chinandega (banana/sugarcane)	Rural	155	19.0 (12.5–25.5)	176	3.5 (0.6–6.4)	104	13.6 (6.3–20.9)	111	0.0 (N/A)
	Chinandega (service)	Rural	50	0.0 (N/A)	90	0.0 (N/A)	34	0.0 (N/A)	58	0.0 (N/A)
	Leon (coffee)	Rural	40	6.3 (0–14.4)	37	0.0 (N/A)	30	8.6 (0–19.1)	26	0.0 (N/A)

(*Continued on following page*)

Table 2 | (Continued) **Age-standardized prevalence of eGFR <60 ml/min per 1.73 m^2 by sex, for ages 18–60 years**

			Sample with complete data				Sample of people without hypertension, diabetes, or heavy proteinuria			
			Men		Women		Men		Women	
Center	Area	Rural/urban	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]	n	eGFR <60 ml/min per 1.73 m^2, % (95% CI)[a]
	Leon (fishing)	Rural	76	10.2 (3.2–17.3)	90	2.1 (0–5.9)	55	6.4 (0–13.0)	73	0.0 (N/A)
	Leon (mining/subsistence farming)	Rural	158	16.2 (10.4, 22.0)	224	4.8 (1.7, 7.9)	106	12.1 (4.5, 19.6)	144	2.6 (0, 6.6)
Nicaragua 2	Leon municipalities	Rural	247	15.3 (10.9–19.7)	329	3.1 (1.2–5.0)	145	9.4 (4.4–14.3)	211	2.5 (0–5.4)
		Urban	400	10.0 (7.2–12.7)	696	3.6 (2.3–4.8)	256	6.6 (3.0–10.1)	436	2.4 (1.0–3.9)
Peru	Tumbes	Rural	278	0.5 (0–1.3)	344	0.3 (0–0.9)	210	0.0 (N/A)	285	0.6 (0–1.7)
		Urban	257	0.5 (0–1.2)	359	0.5 (0–1.1)	186	0.0 (N/A)	305	0.0 (N/A)
Sri Lanka	Halambagaswewa	Rural	242	8.3 (5.5–11.0)	497	3.8 (2.2–5.3)	136	3.9 (1.1–6.8)	336	1.3 (0.1–2.6)
	Lolugaswewa	Rural	221	5.8 (3.5–8.1)	569	4.5 (3.1–5.9)	138	7.7 (3.9–11.5)	372	2.6 (1.0–4.2)
	Pothana	Rural	194	5.0 (2.6–7.3)	497	1.7 (0.7–2.6)	115	0.7 (0–1.9)	330	0.7 (0–1.6)
	Puhudivula	Rural	222	7.7 (5.2–10.2)	576	3.6 (2.3–5.0)	112	7.6 (3.8–11.3)	378	1.4 (0.2–2.6)
	Sangilikandarawa	Rural	270	6.1 (3.8–8.4)	548	2.9 (1.6–4.3)	157	3.1 (0.6–5.6)	346	2.4 (0.8–3.9)
Thailand	Bangkok	Urban	381	1.1 (0.1–2.2)	1223	0.7 (0.0–1.3)	233	1.2 (0–2.7)	943	0.5 (0–1.1)
	Central	Rural	606	0.9 (0.3–1.4)	795	1.1 (0.4–1.9)	424	0.2 (0–0.4)	576	1.0 (0.1–1.8)
		Urban	519	0.6 (0.1–1.1)	832	0.4 (0.1–0.7)	336	0.0 (N/A)	587	0.2 (0–0.5)
	North	Rural	668	1.1 (0.6–1.7)	730	1.0 (0.1–1.8)	407	0.4 (0–0.9)	498	0.5 (0–1.3)
		Urban	445	1.1 (0–2.3)	604	1.0 (0.4–1.6)	267	0.7 (0–1.9)	409	0.3 (0–0.7)
	North East	Rural	577	1.3 (0.5–2.1)	637	0.8 (0.3–1.3)	428	0.6 (0.1–1.2)	479	0.3 (0–0.7)
		Urban	492	0.7 (0–1.4)	609	0.6 (0.2–1.0)	351	0.2 (0–0.5)	450	0.1 (0–0.4)
	South	Rural	549	0.5 (0.1–1.0)	678	0.2 (0–0.5)	366	0.2 (0–0.6)	493	0.2 (0–0.5)
		Urban	303	0.7 (0.0–1.4)	489	1.1 (0.3–2.0)	193	1.1 (0–2.4)	356	0.7 (0–1.4)
USA	All	All	1586	2.1 (1.4–2.8)	1787	1.3 (0.8–1.8)	925	0.6 (0.1–1.0)	1143	0.7 (0.2–1.2)

CARRS, Centre for cArdiometabolic Risk Reduction in South-Asia; CI, confidence interval using normal approximation; eGFR, creatinine-based estimated glomerular filtration rate; ICMR, Indian Council of Medical Research; N/A, no confidence interval available because estimate is 0; UDAY, dawn in Sanskrit.

[a]Age-standardized prevalence using World Health Organization global population age weights.

[b]Only 41–60 years included.

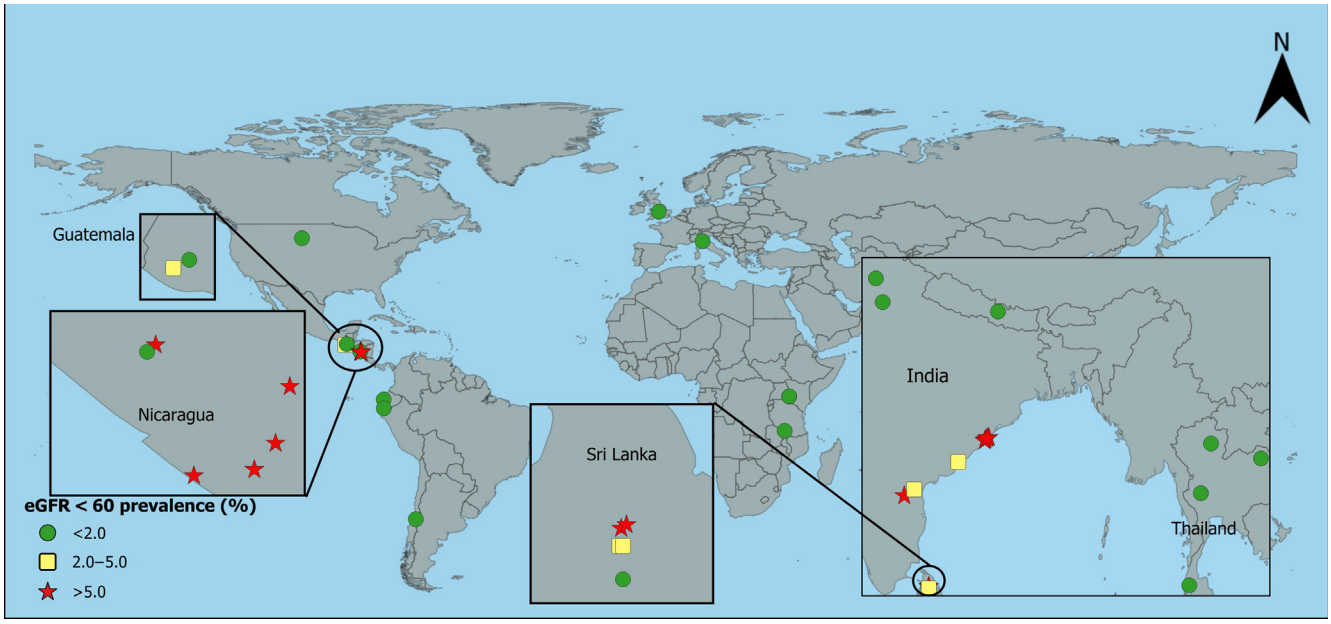

Figure 1 | Age-standardized prevalence of creatinine-based estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 in rural[a] men without hypertension, diabetes, or heavy proteinuria. [a]USA includes rural and urban together.

women and 3.6% and 0.0% in men using cystatin alone, although numbers with cystatin C measures were small. Estimates of the prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ did not differ substantially by measure in Peru, and were lower in Malawi and England when using cystatin C. Similar patterns were seen for eGFR $<60_{[\text{no exclusions}]}$ (Table 3 and Supplementary Table S5).

Results from the sensitivity analyses can be found in Supplementary Text S2.

DISCUSSION

Our findings are consistent with, and build upon, previous evidence, suggesting a high general population burden of impaired kidney function in the absence of traditional risk factors in areas of Central America and South Asia (Sri Lanka and South India). Applying the same definition to reference populations from high-income countries, as expected, demonstrated a low prevalence. A key strength of the approach used is that it only depends on eGFR and is

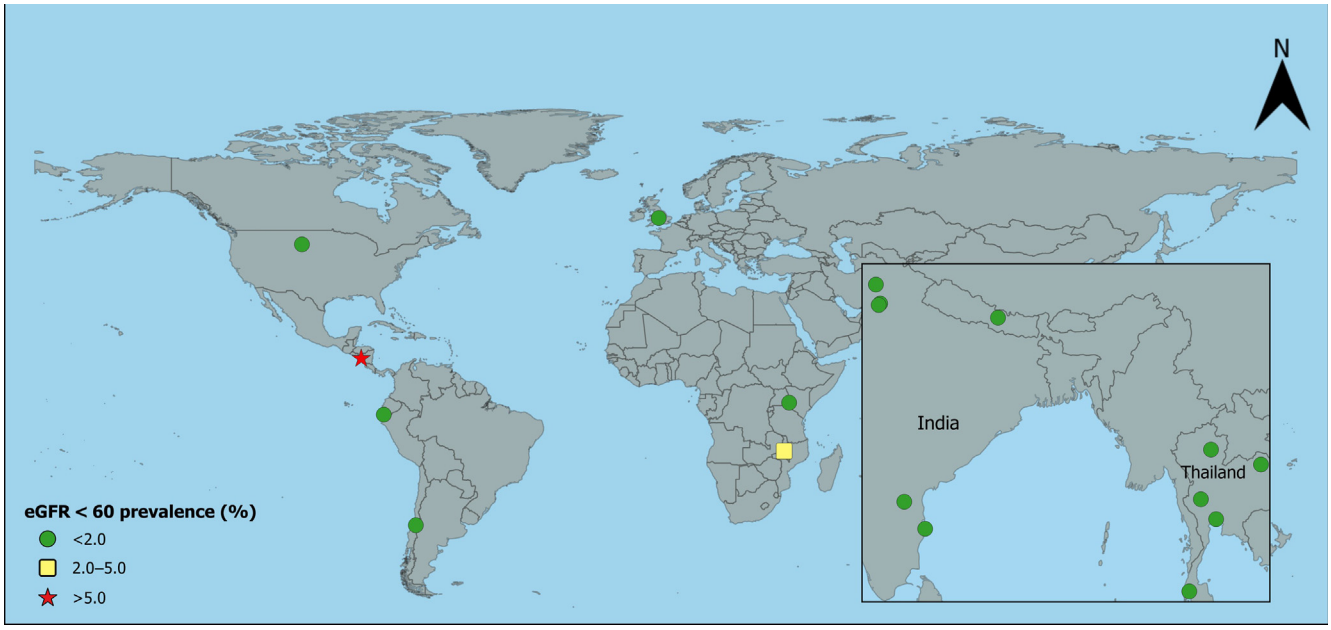

Figure 2 | Age-standardized prevalence of creatinine-based estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 in urban[a] men without hypertension, diabetes, or heavy proteinuria. [a]USA includes rural and urban together.

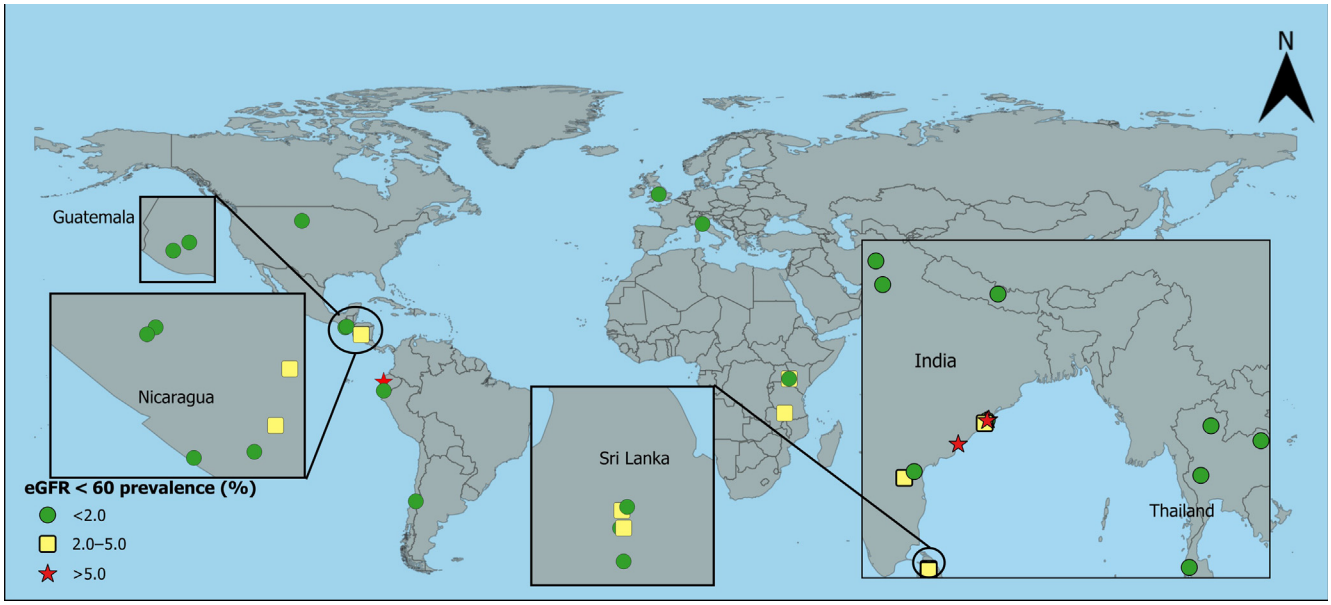

Figure 3 | Age-standardized prevalence of creatinine-based estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 in rural[a] women without hypertension, diabetes, or heavy proteinuria. [a]USA includes rural and urban together.

independent of the presence or absence of a kidney disease diagnosis. This is of critical importance as such diagnoses are highly dependent on access to nephrology care, which is extremely limited in many CKDu affected regions, making comparisons that rely on "absence of diagnosis" across regions almost impossible to interpret.

Summary of findings and comparisons to existing literature

In India, studies with a range of sizes of source populations (from thousands to millions) and conducted both with the specific aim of quantifying CKDu prevalence and as part of non-CKDu focused noncommunicable disease surveillance surveys demonstrated similar patterns. That is of a high general population burden of disease in areas of rural coastal Uddanam, but not in urban areas of South India or urban or rural areas in northern India. Interestingly, in the rural coastal areas of Uddanam, where women may also work in the agricultural sector, the prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ in women approached or exceeded that in men in some study sites (Figure 5). In the Anuradhapura district of Sri Lanka, we observed a high prevalence among men in 2 of 5 rural communities (with

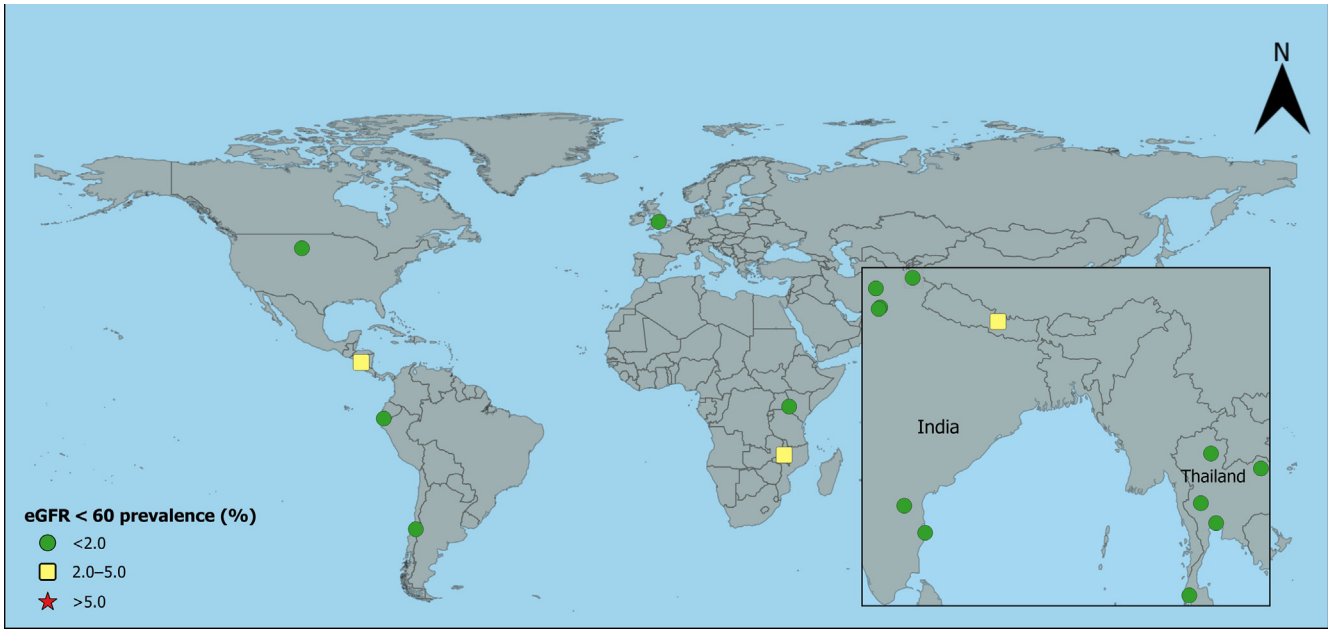

Figure 4 | Age-standardized prevalence of creatinine-based estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 in urban[a] women without hypertension, diabetes, or heavy proteinuria. [a]USA includes rural and urban together.

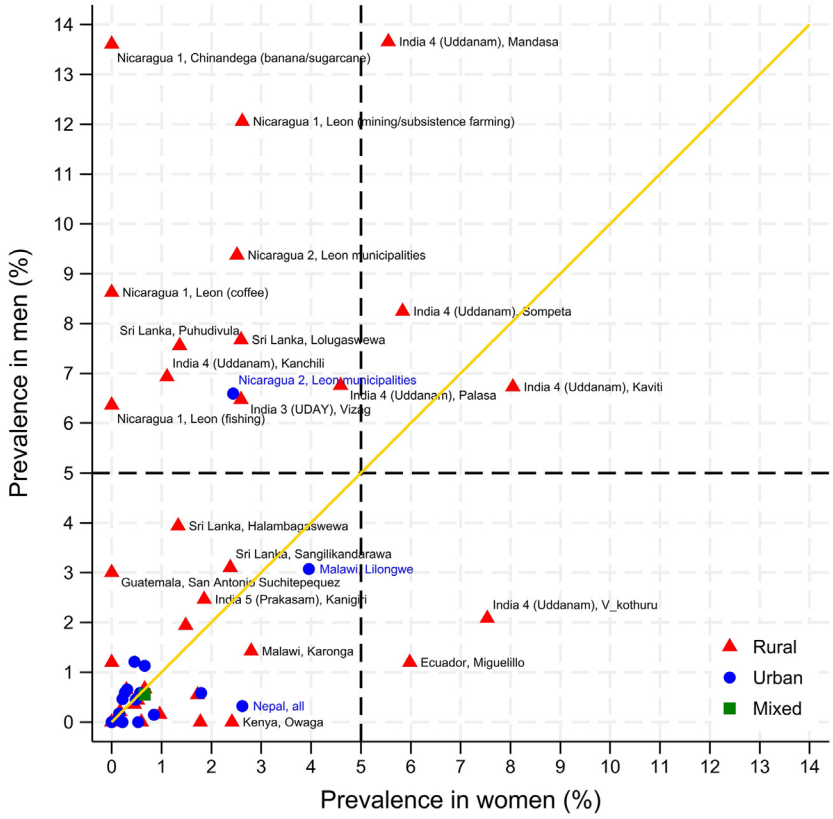

Figure 5 | Age-standardized prevalence of estimated glomerular filtration rate <60 ml/min per 1.73 m^2 by sex in population without hypertension, diabetes, or heavy proteinuria.

moderate prevalence in another 2) with small source populations. However, these communities were specifically selected on the basis of clinical data on CKDu burden; thus, it is impossible to make generalizations as to the burden of disease across the wider district.

In northwest Nicaragua, similar to India, data from both a study with a small source population (of thousands) focused on reported high CKDu communities, and a non-CKDu focused noncommunicable disease surveillance survey with a larger source population (hundreds of thousands) demonstrated similar patterns with a high prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ in men. Unusually, there was also a high prevalence of this outcome in the urban population in the latter study, although it is possible that those living in this urban area may still work in agricultural settings. Unfortunately, we were unable to include data from a national survey conducted in El-Salvador (source populations of millions), but this study used similar definitions and reported a prevalence well above reference levels among rural males.[43] The single study in Guatemala also showed moderate levels of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ in males living in the lowland population sample but low levels in the high-altitude sample.

Many of the studies were conducted using the DEGREE protocol specifically to explore whether there was a burden of CKDu in areas with similar profiles to those seen in areas reported to be affected by a high disease burden. However, the prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ in rural males was low in Tumbes, Peru (Pacific Coast Latin America, subtropical climate, agricultural), Manabi Province, Ecuador (Pacific Coast Latin America, tropical, agricultural), Karonga District, Malawi (subtropical, agricultural), and Muhoroni Sub-County, Kenya (subtropical, agricultural [specifically sugarcane]). Interestingly, we did identify high prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ among women in Ecuador, and moderately high among urban males and both urban and rural women in Malawi, patterns that are not considered typical of CKDu in Central America and South Asia. The relevance of these latter findings remains unclear.

The Thailand study was a reanalysis of a national population survey with a large source population (millions). Subpopulations with a higher prevalence of individuals meeting the case definition (i.e., localized "hot spots") may be obscured in the larger sampling frames. However, (i) the prevalence of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ is lower than that in the high-income reference populations; and (ii) the source populations of the individual regions in the Thai study are comparable to other large population surveys (included and not included[43] in this analysis). This suggests that the general population burden of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ is several fold lower in rural regions of Thailand than in the areas most impacted by CKDu in Central America or India. Another population-based study conducted in northeastern Thailand (not included in this analysis) reported rates of eGFR <60 ml/min per 1.73 m^2 of ~10% (without

Table 3 | Age-standardized[a] prevalence rates of creatinine- and cystatin C–based eGFR <60 ml/min per 1.73 m^2 in people without hypertension, diabetes, or heavy proteinuria, by sex, for ages 18–60 years with both creatinine and cystatin C measurements available

			Men				Women		
Center	Area	Rural/urban	n	CKD-EPI 2009_{creat}, % (95% CI)	CKD-EPI 2012_{cys}, % (95% CI)	CKD-EPI $2012_{creat-cys}$, % (95% CI)	n	CKD-EPI 2009_{creat}, % (95% CI)	CKD-EPI 2012_{cys}, % (95% CI)	CKD-EPI $2012_{creat-cys}$, % (95% CI)
England	All	Rural	98	0.0 (N/A)[b]	0.5 (0–1.4)	[c]	169	1.8 (0.4–3.2)[b]	0.3 (0–0.8)	[c]
		Urban	515	0.1 (0–0.4)[b]	0.8 (0.1–1.4)	[c]	759	0.8 (0.3–1.4)[b]	0.4 (0–0.7)	[c]
India 3 (UDAY)	Sonipat	Rural	177	0.3 (0–0.9)	14.3 (10.5–18.0)	1.7 (0.2–3.2)	253	0.0 (N/A)	12.9 (7.3–18.4)	0.6 (0–1.3)
		Urban	199	0.0 (N/A)	14.1 (10.4–17.8)	2.5 (0.7–4.3)	273	0.0 (N/A)	14.1 (10.6–17.6)	2.8 (0.8–4.8)
	Vizag	Rural	269	6.7 (0–15.2)	21.3 (9.9–32.6)	10.1 (1.5–18.8)	325	2.8 (1.2–4.5)	12.1 (8.7–15.5)	4.8 (2.7–7.0)
		Urban	152	0.0 (N/A)	12.5 (3.2–21.9)	0.4 (0–1.2)	244	0.0 (N/A)	12.8 (8.1–17.5)	2.1 (0.1–4.1)
Kenya	Muhoroni East	Urban	4	0.0 (N/A)	0.0 (N/A)	0.0 (N/A)	9	0.0 (N/A)	0.0 (N/A)	0.0 (N/A)
	Owaga	Rural	37	0.0 (N/A)	3.6 (0–10.0)	0.0 (N/A)	43	0.0 (N/A)	10.4 (4.8–16.0)	0.0 (N/A)
	Tonde	Rural	19	0.0 (N/A)	0.0 (N/A)	0.0 (N/A)	29	0.0 (N/A)	14.3 (3.7–24.9)	0.0 (N/A)
Malawi	Karonga	Rural	214	1.4 (0–3.5)	1.1 (0–2.6)	1.8 (0–4.0)	309	2.8 (0.3–5.3)	1.6 (0–3.8)	2.3 (0–4.7)
	Lilongwe	Urban	74	3.1 (0–8.6)	0.7 (0–2.1)	0.0 (N/A)	159	4.0 (0.7–7.2)	0.0 (N/A)	0.7 (0–2.1)
Peru	Tumbes	Rural	210	0.0 (N/A)	1.7 (0.1–3.3)	0.0 (N/A)	284	0.6 (0–1.7)	0.9 (0–2.0)	0.0 (N/A)
		Urban	186	0.0 (N/A)	1.5 (0–3.2)	0.0 (N/A)	304	0.0 (N/A)	1.4 (0.1–2.7)	0.0 (N/A)

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; creat, creatinine-based equation; creat-cys, creatinine and cystatin C–based equation; cys, cystatin C–based equation; eGFR, estimated glomerular filtration rate; N/A, no confidence interval available because estimate is 0; UDAY, dawn in Sanskrit.

[a]Age-standardized prevalence using World Health Organization global population age weights.

[b]Includes race adjustment.

[c]Not available as eGFR values supplied and exact age not available.

excluding diabetes, hypertension, or heavy proteinuria),[44] but this was almost entirely driven by participants aged >60 years, and estimates in the working age population were completely consistent with those reported in the analysis included in the current study. The aggregated data from Nepal were derived from a large source population, and as reports of possible CKDu are mainly focused on returning migrant workers in this country,[45] it would likely not be possible to detect a high burden of eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ in this group using our approach.

Limitations

When drawing conclusions about CKDu burden, the above findings must be considered in the context of limitations of our approach. The pragmatic definition we have used will of course be prone to misclassification in both directions. For example, the definition we used will lead to the inclusion of a range of nonproteinuric (and moderately proteinuric, non-hypertensive) chronic kidney diseases of both known (e.g., due to congenital abnormalities, granulomatous, or drug-induced chronic interstitial nephritides) and unknown (but non-CKDu) causes. Furthermore, the absence of confirmatory eGFR measures means a proportion of cases reflect those with acute, rather than chronic, kidney injury. Conversely, some true cases of CKDu were probably excluded, particularly where the disease coexists with diabetes or hypertension (although this would only have biased the prevalence estimates if the prevalence of CKDu was markedly different in people with these conditions than in those without), or in advanced disease where proteinuria is well described. Given this potential for misclassification, a low disease burden will not be observable using our definitions. Nonetheless, a high general population prevalence of eGFR $<60_{[\text{absent HT,DM,high ACR}]}$ clearly identifies regions known to be hotspots of CKDu.

The rationale and scale of the studies included in this analysis varied substantially. Some studies were part of large country-wide noncommunicable disease surveys, some were specific to kidney disease but covering smaller areas with typical CKDu population characteristics but without previous reports of a high burden of disease, and others were targeted at specific areas chosen on the expectation that the prevalence was high or low. However, all studies were population representative, and although response rates varied, this did not appear to be related to the prevalence of the outcome (Supplementary Table S8).

Similarly, working age men tended to be underrepresented in most studies. However, this will not affect the prevalence estimates for this group (i.e., the proportion with low eGFR in the working age men who actually participated), unless specific high-risk subgroups (e.g., men in occupations with high prevalence) are underrepresented or overrepresented.

Another important limitation is that the CKD Epidemiology Collaboration equation has been reported to substantially overestimate eGFR around the 60 ml/min per 1.73 m^2 threshold in Indian[46] and sub-Saharan African[47] populations, and the validity of the equation is unknown in other groups, such as indigenous Americans. We were able to use cystatin C–based equations, which have been shown to be more precise,[48] to address this issue in several studies included in this analysis. This subanalysis demonstrated an increased proportion meeting the outcome across all regions in the Indian study, although relative patterns of prevalence were preserved. This confirms the challenges surrounding using GFR estimating equations in the Indian population but does not alter the conclusions around the areas most affected by CKDu. This subanalysis also demonstrated increases in prevalence of the outcome in the Kenyan study, particularly in women, although numbers with cystatin C testing were small, preventing firm conclusions. The cystatin C analysis did not change the major conclusions in the Malawi or Peru studies.

It is important to highlight that although we report substantial variability in age-standardized eGFR $<60_{[\text{absent HT, DM, high ACR}]}$, we only aim to describe international patterns in the general population. We identified substantial variability eGFR $<60_{[\text{absent HT, DM, high ACR}]}$ even between areas within high prevalence regions, and in both Central America[11,49] and South Asia[50] there is evidence supporting an even higher prevalence of CKDu in specific high-risk (i.e., occupational) groups. Therefore, there might be an important burden of CKDu in similar groups located in regions where we have not identified evidence of a high general population prevalence of disease. Only adequately powered, targeted studies in these high-risk populations can address this, and specific studies are therefore needed. Furthermore, other than sex and urban-rural residence, we have not explored any ecological or individual-level risk factors for eGFR $<60_{[\text{absent HT, DM, high ACR}]}$.

Finally, this study was descriptive and intended to identify areas with high burden of disease. It was not intended to identify the causes of CKDu or to explain the observed international patterns. Factors that may affect the international patterns may include differences in exposure to potential risk factors for CKDu (leading hypotheses as to the primary cause of CKDu include occupational heat stress, metal[loid] exposure [particularly in water], and pesticide and particulate matter exposure[1]), differences in the degree of misclassification (e.g., the proportion of non-CKDu causes of low $\text{eGFR}_{[\text{absent HT, DM, high ACR}]}$) between studies, as well as differences in methods across the included studies. The patterns we have identified clearly require further research.

Conclusion

The study findings provide useful estimates of population patterns of low eGFR and are of considerable interest. Taken alongside published evidence, the observations from large surveys and smaller studies support a high general-population burden of CKDu in Central America and Uddanam, India; however, there is no evidence for a similar population burden of disease from large surveys in other parts of India or in Thailand. There is also evidence from smaller surveys for a substantial burden of disease, in particular communities in the Anuradhapura district of Sri Lanka, again supporting published evidence. Several other regions surveyed, that have

superficially similar characteristics to affected areas (i.e., hot, low-income, agricultural settings), did not demonstrate a prevalence of low eGFR consistent with a high general population burden of CKDu.

APPENDIX

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DISCLOSURE

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DATA STATEMENT

Data from the reference data sets can be found in the public domain: National Health and Nutrition Examination Survey at https://www.cdc.gov/nchs/nhanes/index.htm and Health Survey England at https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=2000021.

Data for the other included studies may be available by contacting the authors of the respective study papers.

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AUTHOR CONTRIBUTIONS

NP and BC conceived and designed the study; NP, BC, KJ, JG, DNi, VJ, AS, and RC-R wrote the study protocol; PJC, DP, VJ, PK, SM, RRT, AB, PR, MHH, ACC, MD, AP, AB-O, CO-G, PC, NG, TR, SCW, SS, CK, MG-Q, SC, AA, and DNa collected and contributed data; CER and SR were responsible for data cleaning and management; CER and MN analyzed and visualized the data; CER, NP, and BC wrote the first draft of the manuscript; all other authors contributed to revisions of the manuscript. Remaining members of the DEGREE Study Group (listed in the Appendix) also contributed to the planning and conduct of the study and to the revisions of the article.

Supplementary material is available online at www.kidney-international.org.

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