Title: The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: Report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset

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Running title: i3C Report on Population-level Detection of CKDu

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1. INTRODUCTION

There is an epidemic of chronic kidney disease (CKD) clustering in rural communities, predominantly in a number of low-and-middle income countries[1]. Tens of thousands of working-aged adults are estimated to have died from the disease in Central America[2] with similar numbers in Sri Lanka[3]. Similar diseases have been reported elsewhere, e.g. rural regions or communities in India, North and West Africa. Those affected do not have common risk factors or underlying conditions that lead to CKD, e.g. diabetes, immune-mediated glomerulonephritis or structural renal disease. In instances where histopathology is available, the predominant feature is tubular atrophy and interstitial fibrosis. Although it is currently unclear whether there is a unified underlying cause, these conditions have been collectively termed CKD of unknown cause ("CKDu"). Other terms used include CKD of non-traditional Cause, Mesoamerican Nephropathy, Chronic Intestinal Nephritis in Agricultural Communities and Kidney Disease of Unknown Cause in Agricultural Laborers but we have chosen CKDu as the most agnostic terminology.

The current clinical and research landscape in CKDu consists of multiple similar, but non-concordant approaches to individual-level diagnosis and detection at the population-level[4]. In combination with the ongoing lack of treatment or prevention strategies the heterogeneity in identification of CKDu is a significant obstacle to combating the disease.

A uniform approach to detecting CKDu on a population-level would allow comparisons between studies and regions, providing valuable data for healthcare agencies and a basis for understanding key risk factors for disease. However even when "gold-standard" diagnostic investigations are available, no single approach will capture CKDu with complete certainty, and, depending on the reasons for evaluation, clinicians or researchers may accept differing levels of uncertainty. Nonetheless a uniform approach enables comparability and allows the international nephrology community to speak with a single voice in attempts to advocate for research, prevention and treatment resources.

To this end the International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology (i3C) created a workgroup to guide a common approach to the detection of CKDu. This work shares many goals, and aims to be complementary to, the recent Resolution on Chronic Kidney Disease[5] from the Pan American Health Organization. We list different study populations that might be of interest alongside kidney-specific and other measures that could be used to determine the burden of disease. Finally, we

recommend a number of elements for a 'minimum dataset' endorsed by the i3C, for use in studies aimed at quantifying and comparing disease burden.

Key to this work is the recognition that there is currently no consensus on the case definition(s) for CKDu, and existing definitions may be refined in future. Therefore the aim should be to obtain key information that can be used in a variety of definitions of CKDu now and going forward. Hence this approach is designed to estimate the extent of ESRD or impaired kidney function in a specific region of interest, and then determine the proportion of that estimate attributable to the "CKDu" as later defined.

We selectively focus on detection, rather than surveillance, as an initial step to building consensus approaches. Although the methodologies described could be part of wider surveillance efforts, systems required for continual monitoring, real-time data interpretation and reporting are not discussed. Furthermore we also recognize diagnosis of CKDu in individuals can be challenging, particularly in resource-constrained settings; potential strategies are discussed further in the Supplementary Material.

We have divided detection efforts into:
(i) *Passive detection* based on routine data collected for clinical or administrative purposes, and,
(ii) *Active detection* undertaken specifically for the purposes of determining disease prevalence (based on prospective epidemiological studies or extant datasets for the study of non-communicable diseases in general).

Recommended approaches and the minimum dataset are highlighted in the tables.

2. PASSIVE DETECTION.

Death certification, and end-stage renal disease (ESRD) registries are potential data sources (Table 1) that can help identify regions as "hot spots" of kidney disease. Indeed, such approaches have been a key first step in recognizing existing CKDu epidemics [6]. Two issues arise when using routine data:

1. Scarce and poor-quality routine data collection in many of the potentially affected regions. The World Health Organization (WHO) and Institute for Health Metrics and Evaluation have published global estimates on cause-specific deaths included those attributed to kidney disease[7]. The methodology underlying WHO estimates of cause-specific mortality is available elsewhere however data-quality, including that based on verbal autopsy-based diagnosis of CKD[8], from almost all regions likely to be impacted by CKDu is suboptimal (Figure 1).

2. Difficulty differentiating whether recorded kidney disease is due to the CKDu. Misattribution of cause, a major challenge worldwide but particularly in settings where biopsies are not routinely obtained, could lead to misclassification as CKDu where a biopsy would have provided a diagnosis (e.g. IgA Nephropathy).

Additionally, CKDu is unlikely to be recorded specifically in death registries so underlying knowledge of diabetes, (and ideally rates of CKD attributed to diabetes) are key to generate useful estimates (as diabetes is the commonest cause of ESRD). Dialysis and transplant registries usually record cause-specific diagnoses albeit subject to misclassification as well; however terminology may vary and in most low-resource settings, registries capture only a small fraction of patients reaching ESRD.

3. ACTIVE DETECTION

Active detection of CKDu will involve the systematic survey of populations to detect disease. This may involve new studies focused on CKDu or the use of existing datasets or plans for non-communicable disease surveillance, where minimum requirements are met. Indeed, there may be significant gains to be made in terms of rapid acquisition of prevalence data by accessing or modifying existing studies/processes (e.g. WHO STEPS instruments or USAID Demographic and Health Surveys).

Populations and study design

The possible populations and study approaches to active detection are outlined in Table 1. A critical feature of the reporting of all efforts is a description of the geographical area along with both the source population and the study responders so that conclusions about the representativeness of the study sample be drawn. These summary response rate data should be stratified by sex and age with adequate granularity to detect response bias (e.g. 10-year age bands).

Numerator (determined by measures of kidney dysfunction)

As alluded to in the introduction our aim is not to presuppose a definition of CKDu, but to provide a framework for the collection of data that will allow detection of CKD in a reproducible manner, to which a number of

definitions of CKDu to be applied (e.g. using different thresholds of kidney function or presence or absence of proteinuria or comorbidity). Importantly The Kidney Disease Improving Global Outcomes collaboration provides internationally accepted criteria for the clinical identification of CKD. Given the asymptomatic nature and other attributes of CKDu population-based detection methods for this disease need to be based on measures of kidney function (estimated glomerular filtration rate, eGFR). Although the KDIGO definition of CKD requires two-measurements of eGFR the multiplicative increase in resources required to re-contact participants after a prolonged period means that, in common with a large body of CKD-epidemiology, the i3C workgroup recommends accepting initial detection efforts based on a single eGFR estimate only. Furthermore, definitions of CKD use a threshold of GFR, however to allow maximum flexibility i3C advocates collection and reporting of the entire distribution of GFR values along with numbers below a particular (CKD) threshold. The different methods to quantify renal dysfunction are outlined in Table 2.

Other important data items

Key associations of CKDu at a population level are the absence of heavy proteinuria, and other causes of, or risk factors for, CKD and the socio-demographic characteristics of those that are affected. Therefore, information on these variables are needed to produce informative prevalence estimates (Table 2). The recommendations have been kept to a ***minimum*** to ensure minimal resource implications and allow the use of extant datasets.

4. APPLICATION OF SUGGESTED APPROACH

There is an urgent need for data that are comparable regionally and internationally, and the aim of a minimum data set(s) is/are to obtain the key information that can be used to define CKDu currently and in future (see supplementary material for an example). Such a dataset is contingent upon an international agreement to collect uniform data but it is **presumed and expected that researchers, agencies and service providers should collect additional data to meet their own specific needs.**

Active or passive approaches may be more or less appropriate for these different aims including:

1. Alerting health services/communities/researchers to a possible problem of CKDu,
2. Estimating scope and scale of CKDu within populations
3. Determining secular trends in CKDu
4. Insight into disease etiology

Therefore, it may be appropriate to apply two (or more) approaches in any single region. A protocol using a similar minimum dataset to undertake population-level detection has recently been published and is already being used in a number of settings in South Asia, Latin America and Sub-Saharan Africa[9].

5. SUMMARY

A uniform approach to detecting CKDu on a population-level allows the understanding key risk factors for disease, provides valuable data for healthcare agencies and establishes a basis for comparisons between regions and research studies. This document elaborates the methodology to detect CKDu via passive or active detection and suggests criteria for minimum data set. Such a common approach would allow the international nephrology community to speak with a single voice in attempts to advocate for research, prevention and treatment resources for CKD in general, and for CKDu in specific areas.

Disclosures: All authors declare no conflicts of interest.

6. FIGURE LEGEND

Figure 1. Map showing data-quality of cause-of-death by WHO member state as assessed by the 2016 Global Health Estimates project. Data from http://www.who.int/healthinfo/global_burden_disease/en/. WHO advises data from countries labeled in green (high completeness and quality) can be used for time or country comparisons whereas data from countries labeled yellow (moderate quality issues) or orange (severe quality issues) should only be used with caution. Estimates of cause-of death from countries labeled red (unavailable or unusable) should not be used for comparisons or policy purposes. Note: The impact of the availability of treatment for ESRD in a region may impact on estimates of the burden of chronic kidney disease (of any cause) from death registries as patients receiving renal replacement therapy may have a non-kidney related primary cause of death recorded and ESRD only recorded as a contributory cause (or not at all) .

Table 1 Detection approaches – populations and study design

Data source	Numerator or outcome	Population (Denominator)	Steps to yield comparability & greater specificity	Example referent source	Advantages	Disadvantages	Other potentially useful measures if available
Passive Detection Approaches							
Mortality registry	**Deaths attributable to kidney disease#**	**National or regional mortality**	**Age-standardize*** **Subtract deaths attributable to diabetic kidney disease, or if not available, adjust for age-standardized diabetes prevalence^** **Include only CKD not AKI**	**High-income countries mortality registries**	**A high-level, resource efficient approach to identify hot spots**	**Sometimes difficult to disaggregate to regional or state level** **Data are non-specific and not be able to differentiate CKDu from high rates of cause-specific kidney disease (e.g., IgA nephropathy).**	**Cause of ESRD or cause of kidney disease leading to death** **Data on the proportion of (non-CKD) deaths of unknown cause should also be reported as a quality indicator**
Dialysis and transplant registry	**Prevalent or incident numbers of patients with ESRD of unknown cause**	**Prevalent or incident ESRD population**	**Age standardize*** **Only include those with 'unknown' cause if registry provides these data**	**USRDS, ERA-EDTA, ANZDATA**	**A high-level, resource efficient approach to identify hot spots** **May also able to give a regional or state-level estimate if data are available.**	**Not available, or not representative of entire burden of (untreated) ESRD, in many low- and middle-income countries** **Attribution of kidney disease cause may be incorrect (or both known causes and CKDu may coexist)**	**Occupation of persons with ESRD** **Family history of persons with ESRD**
Active Detection Approaches							
Population-based study	**Kidney function measures (see Table 2)**	**Random (or stratified random) sample or whole population of Geographically defined community (aged>18)†**	**Strategies to achieve high response rates across entire population**	**NHANES**	**Representative of true population prevalence of disease**	**Fieldwork can be challenging and response variable** **Requires new or existing census data**	**See Table 2**
Clinic or camp based study	Kidney function measures	Self-presenting or volunteer community population		KEEP, ISN KDC	Convenient to implement	Not representative and prone to major issues in interpretation due to selection bias	
Workplace	Kidney function measures	Random sample, whole population		Appropriate comparator populations may be challenging to identify (i.e., similar demographics)	Can be easier to capture participants than community based studies	Unlikely to be representative of whole community so may be misleading with regard to population prevalence and risk factors. Investigators need to be sensitive to differing incentives between employees and employers to taking part	

Suggested approaches highlighted in bold with grey background. We propose, that to the extent feasible, the data should be disaggregated to regional (in addition to national) levels and presented by age- and sex-strata so localized clustering can be identified.

*To referent World population as recommended by WHO http://www.who.int/healthinfo/paper31.pdf?ua=1

The latest WHO and IHME Global burden of disease estimates include age-specific kidney disease attributable death estimates (but see text)

^These data are available on a national level at least via the IDF for many countries; the WHO also provides estimates for age-specific deaths due to diabetic kidney disease

†Reporting of response rates stratified by age- and sex- are essential. These summary response rate data should be stratified by sex and age with adequate granularity to detect response bias (e.g. 10-year age bands).

Table 2 Active detection –Outcome measures and other data items

Data item	Method	Rationale / Advantages / Disadvantages	Recommended by i3C for minimum data set
		Outcome Measure	
Kidney Function	**eGFR from creatinine SINGLE MEASURE* (CKD-EPI formula)†**	**Serum creatinine measures available in most countries IDMS referenced methods critical to allow comparison between centres Population specific non-renal sources of creatinine will bias estimates‡**	**Yes, if IDMS referenced measures**
	eGFR from creatinine REPEAT MEASURE#	As above Reduces misclassification of AKI as CKD, aligns with KDIGO clinical guideline Requires recontact of all those with abnormal results after > 3 months.	Yes, if resources allow but not as part of a minimum dataset
	eGFR from cystatin C	Cystatin C based eGFR may be less dependent on non-renal factors Impact of ethnicity on equations used to calculate the eGFR using cystatin C are unknown No widely used method for standardization across laboratories yet Expensive	Not yet but may become the international standard Biobanking samples may be advised
	Measured GFR	Likely overcomes the ethnicity dependent bias in eGFR Not dependent on non-renal sources of analyte Invasive Expensive	No
		Other data items	
Proteinuria	**Urinalysis**	**No or low-level proteinuria typical for CKDu Urinalysis cheap but affected by urinary concentration**	**Yes, or ACR**
	Albumin/creatinine ratio (ACR)	**More expensive than urinalysis but quantitative**	**Yes, or urinalysis**
	Protein/creatinine ratio	Less specific than ACR	No
Age	**Self-report**	**Rates of CKD and CKDu are age- dependent**	**Yes**
Sex	**Self-report**	**Rates of CKD and CKDu are sex- dependent**	**Yes**
Ethnicity / racial group	**Self-report**	**Rates of CKD and CKDu are ethnicity dependent Can be difficult to capture and may be sensitive in some popualtions**	**Yes**
Occupation	**Self-report**	**CKDu has been mainly described in agricultural communities/workers. Occupational history can be very difficult to capture in many populations unless using detailed questionnaires**	**Yes, although it is acknowledged that international comparisons of occupational categories are likely to be difficult**
Education and income	**Self-report**	**Many studies demonstrate an association between social deprivation and CKDu Reasonably simple to capture using questionnaires.**	**Yes, can be reported as primary/secondary education and/or quartiles/quintiles of income**
Address or geolocation	**Self-report or cluster level data**	**CKDu has generally been described in rural populations and at low-altitudes**	**Yes, can be captured at individual or population level.**
Climate data	**Regional routine data (e.g. average daytime and nighttime temperatures)**	**CKDu has been described in tropical regions**	**Yes**
Diabetes	**Self-report of diagnosis or medication**	**Although diabetes might co-exist with CKDu the high prevalence of diabetic nephropathy means most estimates of CKDu have excluded those with diabetes^**	**Yes, discriminate type 1 (insulin dependent at diagnosis) from type 2 if possible**
	Glycosuria		No, except if performing urinalysis
	Fasting glucose or HbA1c		Only If resources allow
Hypertension	**Self-report of diagnosis or medication**	**Severe hypertension appears atypical in CKDu and may indicate alternative causes of CKD**	**Yes**
	Direct measurement		**Yes (using calibrated devices and trained personnel).**
Nephrotoxic drugs and traditional remedies	Self-report	Drugs may cause CKD (or CKDu)	If resources allow, recognising that international comparisons are likely to be difficult
Infections	Self-report	Likely to differ by population Many of those affected will be undiagnosed	No
Snake bite	Self-report	Important cause of kidney injury	If resources allow where relevant
History or cause of CKD	Self-report	Many of those with CKD are unaware, or even if aware may not know the cause	No
Family history of CKD	Self-report	Family history of CKD has been described in CKDu	If resources allow as prone to misclassification
Water source/ intake	Self-report	Participants may have multiple water sources	If resources allow, recognising that simple assessments are likely to be prone to misclassification

Agrichemical exposure	Self-report	Difficult to capture	If resources allow, recognising that simple assessments are likely to be prone to misclassification
Haematuria	Urinalysis	May help exclude other forms of CKD e.g. Schistosomiasis	Only if performing urinalysis for protein
Imaging	Ultrasound	Smooth small kidneys; operator dependent expensive and difficult at scale	No

Suggested minimum dataset highlighted in bold with grey background.

*We acknowledge that comparing GFR between populations internationally is problematic as the normal distribution of this variable has not been established in many of the groups/regions and furthermore the implications for health of a particular GFR is also unknown in many populations. These issues are felt to be beyond the remit of the i3C and require substantial global efforts to address but are nonetheless accepted. Beyond this issue, the GFR is generally estimated from serum markers (the eGFR) and existing GFR estimating equations have not been validated in many of the relevant populations. This is a particular issue when comparing eGFR distributions internationally as this will lead to ethnicity-specific differential bias. Validated eGFR equations in all relevant populations are unlikely to be available in the short term so this is again accepted as a limitation of the proposed collaborative approach. Furthermore although the i3C suggest estimates of the prevalence of impaired eGFR for the purposes of regional or international comparisons can be based on a single eGFR measurement only this does not detract from the responsibility to refer those with an abnormal finding (e.g. elevated creatinine, hypertension, protein/glycosuria) at initial survey to local health services for further assessment.

†CKD-EPI equation although not validated in many populations of interest has been shown to be more precise in the normal and near-normal GFR range that will be predominant in prevalence studies.

[#] It is also recognized that investigators with resources may want to perform repeat measures in participants with abnormal results after an interval >3 months to reduce misclassification of episodes of acute kidney injury as CKD.

‡Measures such as self-report of meat intake/vegetarianism and estimates of body composition e.g. DEXA or bioelectrical impedance measurements may be useful in adjusting for the impact of non-renal sources of creatinine when comparing eGFR distributions between populations. Similarly, sampling should ideally occur in the morning, i.e. prior to large meals or physical work.

^Note that CKDu can be seen in patients with diabetes, so although an individual with diabetes might be excluded from population estimates of prevalence a clinical diagnosis of CKDu may still be appropriate (see Supplemental Material)

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