Assessing the impact of screening, early identification and intervention programmes for chronic kidney disease: protocol for a scoping review

Ikechi G Okpechi, Fergus J Caskey, Abduzhappar Gaipov, Elliot K Tannor, Laura N Hamonic, Gloria Ashuntantang, Jo-Ann Donner, Ana Figueiredo, Reiko Inagi, Magdalena Madero, Charu Malik, Monica Moorthy, Roberto Pecoits-Filho, Vladimir Tesar, Adeera Levin, Vivekanand Jha

ABSTRACT

Introduction Chronic kidney disease (CKD) is a major threat to public health, especially in low-income and lower-middle income countries, where resources for treating patients with advanced CKD are scarce. Although early CKD identification and intervention hold promise for reducing the burden of CKD and risk factors, it remains unclear if an uniform strategy can be applicable across all income groups. The aim of this scoping review is to synthesise available evidence on early CKD identification programmes in all world regions and income groups. The study will also identify efforts that have been made to use interventions and implementation of early identification programmes for CKD across countries and income groups.

Methods and analysis This review will be guided by the methodological framework for conducting scoping studies developed by Arksey and O’Malley. Empirical (Medline, Embase, Cochrane Library, CINAHL, ISI Web of Science and PsycINFO) and grey literature references will be searched to identify studies on CKD screening, early identification and interventions across all populations. Two reviewers will independently screen references in consecutive stages of title/abstract screening and then full-text screening. We will use a general descriptive overview, tabular summaries and content analysis on extracted data.

Ethics and dissemination The findings from our planned scoping review will enable us to identify items in early identification programmes that can be used in developing screening toolkits for CKD. We will disseminate our findings using traditional approaches that include open-access peer-reviewed publication, scientific presentations and a white paper (call to action) report. Ethical approval will not be required for this scoping review as the data will be extracted from already published studies.

INTRODUCTION

Worldwide, the burden of chronic kidney disease (CKD) continues to rise. This is evidenced by its climb in ranking of global causes of death from 17th in 1990 to 12th in 2017 when the global prevalence of CKD was 697.5 million with an estimated 1.2 million deaths. More recently, the WHO ranked CKD as the 10th most common cause of death. It is currently the third fastest-growing cause of death and, according to projections, will become the fifth most common cause of years of life lost, rising from 16th in 2016. Even more alarmingly, although increase in CKD is occurring globally, most of this growth is projected to be in low-income and lower-middle income countries (LLMICs) and among disadvantaged and indigenous communities in high-income countries (HICs) where access to care is significantly limited.

Although cost, workforce, leadership and organisation of care represent major barriers to accessing kidney care in LMICs, the impact of cost of care and excessive out-of-pocket payment systems affect the people...
directly and are more devastating. While governments pay for dialysis in HICs, patients in LLMICs often have to partly or fully cover the cost of treatment out-of-pocket. One study has estimated that the annual cost of providing haemodialysis (HD) in Kenya, Nigeria and Senegal to be (International dollar) Int$1·7 billion, Int$3·5 billion and Int$450 million, respectively, equivalent to 15·2%, 55·8% and 35·8% of the total domestic government health expenditure of those countries.6 The annual cost of HD in Nepal is about US$2500, far higher than the minimum wage.11 Moreover, CKD, even in early stages, massively increases the risk of development of cardiovascular disease (CVD).12 13 In addition, other modalities of kidney replacement therapies (KRT—that is, peritoneal dialysis (PD) and kidney transplantation (KT)) are unavailable in many LLMICs. Compared with HICs, PD and KT availability was very low in low-income countries: 0·9 per million population (pmp) versus 53·0 pmp14 and 23% countries versus 89% countries, respectively.4

The massive cost of KRT suggests the need to prioritise preventive strategies to delay kidney failure, rather than expand dialysis services.6 This requires implementation of efficient and cost-effective screening and early detection and treatment programmes to delay progression of kidney disease.15–17 A few studies have shown that this is indeed possible. Out of 20 811 individuals screened for CKD in Nepal,18 4471 were found to have hypertension, diabetes, proteinuria or impaired kidney function. After 3 years of treatment with low-cost antihypertensive medications, antidiabetic medications or angiotensin converting enzyme-inhibitors (ACE-i), 63% of dipstick positive proteinuria had decreased to normal and 48% of those with mildly to moderately impaired kidney function at baseline had stabilised or improved, highlighting the impact of early disease detection for reducing or halting CKD progression and cardiovascular morbidity and mortality in such settings.18

Screening and early identification programmes are also used in HICs to assess disease burden and institute measures to improve kidney health, prevent dialysis and improve cardiovascular outcomes.10–22 However, these measures have sometimes been criticised as ineffective as they show no overall benefits23 or are not cost-effective.24

The concept of prevention being better than cure is not new—but preventive measures are more effective if directed at those identified to be in danger of harm. Intuitively, screening and early CKD detection should lead to better outcomes as patients and their care givers are able to apply measures to retard progression and improve outcomes; however, this has not always been the case and has prompted the age-old nephrology debate ‘To Screen or not to Screen?’26–27 In many instances, attempts to determine CKD prevalence, increase awareness and determine cardiovascular risk through screening or early detection programmes have not been coupled with follow-up actions.28 The futility and possible harms of screening for CKD without availability of treatment have been pointed out.29 Other programmes have included interventions, for example, referral to nephrology30–32 or commencing specific therapies33 34 when CKD or risk factors were detected. Despite these, various questions persist regarding the usefulness and methodology of CKD screening programmes (table 1).15 26 29 35 36 As these questions linger, there remains limited evidence to guide choices and decisions about screening, which continues to be based on available local and regional resources as well as the cultural acceptability of modality of screening. An initial approach with risk scores and questionnaires to identify high-risk individuals appears to be potentially useful for large-scale screening. However, available models for risk prediction and CKD progression are largely based on European or North American populations and often require measuring biomarkers. This is a major inconvenience in many LLMICs, where laboratory testing is not readily available.15

These persistent questions led to a controversies conference on ‘early identification and interventions in CKD’ organised by Kidney Disease Improving Global Outcomes

### Table 1 Persisting questions on usefulness and methodology of CKD screening programmes

| Questions related to the usefulness of CKD screening | Questions related to the methodology of CKD screening |
|------------------------------------------------------|-----------------------------------------------------|
| ► Should CKD screening be used in an asymptomatic population with or without CKD risk factors such as hypertension or diabetes? | ► Are single measurements sufficient for detecting CKD? |
| ► Are there unique risk factors in some populations we do not know about? | ► Does population screening with serum creatinine and urine protein testing lead to improved outcomes without undue harm? |
| ► Should therapies be initiated in those with mildly impaired eGFR or microalbuminuria? | ► Should screening be conducted in younger age groups without CKD risk factors? |
| ► Does earlier treatment improve the prognosis? | ► What threshold of dipsticks positive proteinuria should be considered relevant for screening? |
| ► Are CKD screening programmes cost-effective? | ► Who should manage screening and subsequent treatment? |
| ► Do the potential harms of CKD screening outweigh the benefits? | ► What tests should be selected for CKD screening? |
| ► What is the yield of the screening service? | ► How valid and repeatable is the screening test? |
| ► What are the implications of CKD screening for public health policy? |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
(KDIGO) after which a consensus emerged that CKD screening coupled with risk stratification and treatment should be implemented in primary or community care settings for high-risk persons. Major nephrology groups and regional bodies of nephrology have also developed guidelines for CKD screening tailored to their population with differences arising around who to test (general public vs those at risk), recommended tests to use (urine protein vs serum creatinine vs cystatin C assays) and frequency of testing (once annually vs more than once annually). As most of the recommendations are largely based on evidence from observational studies (there are no randomised controlled studies assessing the benefits or harms of screening), selective approaches have been used in making recommendations for screening in different income groups and populations, including CKD hotspots.

Due to the weak and observational nature of the evidence base, guidelines that have made recommendations have tended not to be readily accepted, based on the degree of uncertainty and the magnitude of impact of kidney disease on public health. In 2012, the report of a systematic review on CKD screening and monitoring conducted for the US Preventive Services Task Force and the American College of Physicians did not recommend CKD screening in asymptomatic adults without risk factors as no direct evidence was found that such screening improved outcomes. The American Society of Nephrology countered this with a strong recommendation to continue regular screening for kidney disease, regardless of an individual’s risk factors.

Lack of awareness of CKD is still perceived as a significant challenge to tackling the public health problems of CKD, particularly in LLMIC, where most individuals with CKD remain undetected until they have progressed to kidney failure. Population wide studies in high-risk individuals have reported high prevalence and low awareness of CKD. In Mexico, of 1519 participants of a CKD screening programme, only 1% of those with CKD were aware, despite 71% having visited a physician in the preceding year. However, recent data from participants with CKD in the REasons for Geographic And Racial Differences in Stroke study, a national, longitudinal, population-based cohort did not show an association between awareness of CKD with odds of subsequent changes in health behaviours, CKD management indicators or changes in estimated glomerular filtration rate (eGFR) and urine albumin–creatinine ratio. The study concluded that clinician education needs to be coupled with interventions to increase popular awareness of CKD for optimal impact on health behaviours and chronic disease management indicators.

As these controversies continue and given the large body of literature on screening, early identification programmes and interventions in CKD, we have designed a scoping review to identify, describe and assess CKD early identification/screening/awareness programmes worldwide. Our aim is to synthesise available evidence on early CKD identification programmes in all world regions and income groups and to use the strengths and weaknesses of such programmes into developing a toolkit that can be used by nephrologists across all income groups for early identification and intervention programmes in CKD.

METHODS AND ANALYSIS

Approach

We will be guided by the methodological framework for conducting scoping studies developed by Arksey and O’Malley in 2005. This framework has been further enhanced by work done by others including the JBI International Committee. The framework includes five steps (with an optional sixth step): (1) identifying the research question; (2) identifying the relevant studies; (3) study selection; (4) charting the data and (5) reporting the results and (6) consultation (optional). We will also use best practices for conducting and reporting systematic reviews (ie, Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols and Scoping Reviews for reporting our findings.

Stage 1. Identifying the research question

We used a comprehensive approach that included screening methods, target population and interventions used in framing our research question: ‘What efforts have been made to establish CKD early detection/screening/awareness programmes?’ Using key themes in the conclusions from KDIGO and to be able to fully answer the main study question, other questions will need to be addressed, including:

1. What populations have been screened for CKD and what risk stratification has been included in screening?
2. What measurement methods have been used to screen for CKD?
3. What secondary preventive interventions have been used in those identified with CKD?
4. What efforts have been made to implement or integrate CKD screening programmes into health system?

We believe that answering these questions will enable us to identify all potential components required to launch and sustain a CKD screening or early detection programme.

Stage 2. Identifying the relevant studies

Development of the search strategy will aim at getting a comprehensive review of the existing evidence base. We will identify studies through a detailed search (from inception) of the following bibliographic databases: Medline (Ovid), Embase (Ovid), Cochrane Library, CINAHL, ISI Web of Science and PsycINFO. We will also search grey literature (including ProQuest Dissertations & Theses Global and Conference Proceedings Citation Index (Clarivate Analytics)) using recommended resources in consultation with our medical librarian (LH). However, we will specifically hand search for information (eg, policy documents or position papers) on guidelines for CKD early identification/screening for countries and regions.
that will be represented in our study. We have developed the search strategy to be used in Medline (box 1) and will adapt this strategy for other databases. The search strategy includes subject headings, related terms and key words necessary for the research question. We will use Boolean logic and operators (ie, ‘AND’, ‘OR’, ‘NOT’) to combine and refine search terms. Given the complexities associated with implementing CKD early identification programmes, and that post-programme implementation policies may not have been included in primary publications, we will search for secondary publications and documents where necessary, contact authors of selected studies to ascertain if such programmes became health policy.

**Stage 3. Study selection**

We will include studies that report the results of CKD screening. We will group the studies based on the World Bank country income groups and type of screening. Two reviewers (ET and AG) will independently screen all identified citations for potential inclusion. When agreement on a citation cannot be reached between the two reviewers, a third reviewer (MMA) will be consulted for reconciliation. The review process will first involve screening of the titles and abstracts and then a detailed review of all selected full texts to ascertain eligibility for inclusion (figure 1). An article will be included if it meets the following criteria:

- Population: studies that provided results of CKD screening (with or without an intervention) carried out in any adult (≥18 years) population. For studies in the same population with multiple years of publications, the result of the latest study will be used, and studies conducted across multiple countries will be reported as ‘multinational’ with the list of participating countries provided.
- Intervention: CKD screening, or CKD early detection programmes or CKD awareness programmes.
- Comparator: standard of care (if applicable).
- Outcomes: CKD early identification programmes/studies reporting at least one of the following: CKD detection rate (with or without risk factor detection rate), methods used for screening, people who carried out the screening, interventions used (eg, proportion referred to nephrology clinics, proportion that started treatment, etc), cost-effectiveness of the programme and CKD screening policies implemented.
- Study design: all screening study designs that reported at least one of the outcomes.
- Limits: all databases will be searched from inception with no language restrictions.

The following studies will be excluded:

- Screening studies in children.
- Screening studies for acute kidney injury, urological diseases (eg, prostate cancer awareness programmes) or CKD risk factors (eg, hypertension and diabetes), if no attempt was made to specifically screen for CKD.
- Organ donor screening or awareness programmes.
- Review articles, editorials, commentaries, letters to the editor and guidelines and recommendations on CKD screening.

**Stage 4. Data extraction**

Results of the search will be collated in a Microsoft Excel spreadsheet. We will follow recommended data charting methods to capture relevant details for included studies (table 2). The data items collected will follow four themes: (1) population screened and screening methods used (eg, duration of screening, country of study, type of programme: ‘national’ or ‘other’, screening type: mass screening (with or without an intervention) carried out in any adult (≥18 years) population. For studies in the same population with multiple years of publications, the result of the latest study will be used, and studies conducted across multiple countries will be reported as ‘multinational’ with the list of participating countries provided.

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eGFR, etc), (3) interventions used in those identified with CKD (eg, referral to nephrology or specialist care, initiation of specific treatment (lifestyle measures, ACE-I, attempts to follow-up patients offered interventions, etc) and (4) health systems and economic factors associated with screening (eg, implementation programmes, cost-effectiveness, etc). All extracted data will be reviewed for accuracy and completeness.

Stage 5. Collating, summarising and reporting of the results
We will follow recommendations to extend the scoping review process by adding thematic analysis. Hence, extracted data will be analysed qualitatively using both deductive (preidentified themes) and inductive (new identified themes) approaches. Primary analysis of data will be based on four themes identified by KDIGO: (1) population screened, (2) diagnostic characteristics of tests for kidney disease used, (3) treatments (interventions) used to reduce the risk of CKD progression and cardiovascular disease and (4) implementation strategies for early CKD identification programmes. These approaches will enable us to answer the broad research question and allow us to expand our response with new findings that were not previously included. Although specific data (eg, CKD detection rate) will be collected, such data will not be pooled for further analysis. Textual data from included papers will be coded individually using simple ‘yes’ or ‘no’ responses and other broad-based coding scheme by (EKT) and (AG) to look for common themes across papers. We will present overall results using percentages of ‘yes’ responses.

Stage 6. Consultation exercise
Consultation is an optional part of conducting a scoping review, however, where necessary, we will contact primary authors, regional nephrology leaders or Departments/Ministries of Health for policy documents on implementation of CKD screening programmes. Consultation will be necessary after selecting studies to be included and only if we are unable to identify online policy documents on early CKD identification for countries represented in selected studies. This process will be facilitated by members of the International Society of Nephrology (ISN) Regional Board (https://www.theisn.org/about-isn/governance/regional-boards/) for countries represented in selected studies.

Patient and public involvement
Patients and the public will not be involved in this scoping review; however, the ISN is seeking to establish a globally representative patient advisory group. It would be appropriate for such a group to make input into subsequent,
more specific research questions that are generated from studies identified in this scoping review.

**DISCUSSION, ETHICS AND DISSEMINATION**

The findings from our planned scoping review will enable us to identify items in screening and early identification programmes that can be used in developing screening toolkits for CKD. The results will also enable us to understand what is feasible and the capacity of countries in different income groups for conducting and sustaining screening programmes. Various reviews and recommendations have suggested using different screening approaches in LLMICs, given the lack of capacity to integrate identified CKD cases into the broader health system and the general lack of capacity to measure the quality of care in existing CKD cases.29 37 Thus, based on our results, this scoping review will be able to suggest components for consideration for inclusion in screening toolkits for countries in different income groups, though these are likely to need testing for effectiveness. Furthermore, we anticipate that this scoping review will likely lead to more specific questions (eg, how sensitive and specific are urine dipsticks findings for screening?) that require detailed interrogation through systematic reviews or randomised controlled study designs. A potential limitation of this scoping review could be our inability to access policy documents backing the implementation/integration strategies of early identification programmes to health systems, particularly in LLMICs. We hope that by contacting nephrology leaders and experts in those regions, we will be able to obtain information on the availability of such policy documents. Finally, ethical approval will not be needed for this study as data used will be extracted from already published studies. Our dissemination strategy will use traditional approaches, including open-access peer-reviewed publication(s), scientific presentations and a report.

**Author affiliations**

1Division of Nephrology and Hypertension, University of Cape Town, Cape Town, South Africa
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