Reducing Major Risk Factors for Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is a global public health concern and a key determinant of poor health outcomes. While the burden of CKD is reasonably well defined in developed countries, increasing evidence indicates that the CKD burden may be even greater in developing countries. Diabetes, hypertension, and obesity are major contributors to the global burden of disease and are important *traditional* risk factors for CKD; however *non-traditional* CKD risk factors, including nephrotoxin exposure, kidney stones, fetal and maternal factors, infections, environmental factors and acute kidney injury are also increasingly being recognized as major threats to global kidney health. A broad approach to CKD prevention begins with identification of CKD risk factors in the population, followed by development of appropriate mitigation strategies. Effective prevention policies rely on an accurate understanding of the incidence and prevalence of CKD in a given setting, as well as the distribution and burden of risk factors. Populations or individuals at risk for CKD must be screened and treated early to prevent onset and delay progression of kidney disease. Systematically collected data should be analyzed at country, provincial, and district levels to identify regional disparities and CKD "hotspots" and develop targeted prevention strategies. Race/ethnicity, genetics, sex, socioeconomic status, and geography are likely modifiers of CKD risk. A comprehensive, informed approach to prevention that takes account of all of these factors is therefore required to successfully tackle the global CKD epidemic.

Key words: prevention - risk factors - chronic kidney disease – acute kidney injury – public health – multi-sectoral approach

Introduction

Chronic kidney disease (CKD) is increasingly recognized as a global public health concern and an important contributor to morbidity and mortality.[1] While the burden of CKD is reasonably well defined in developed countries, increasing evidence indicates that the CKD burden may be even greater in developing countries.[1,2] Of the major contributors to the global burden of disease (GBD), diabetes, hypertension, and obesity, are *traditional* risk factors for CKD.[1] *Non-traditional* CKD risk factors, including nephrotoxins (e.g. prescription medicines and alternative remedies), kidney stones, fetal and maternal exposures, infections, environmental exposures, and acute kidney injury (AKI) are also being increasingly recognized as major threats to kidney health:.[3] The burden of CKD attributable to non-traditional risk factors is unknown and may even predominate in low and middle-income countries (LMIC).

A broad approach to CKD prevention begins with identification of the incidence, prevalence and distribution of risk factors followed by development of mitigation strategies. Populations or individuals at-risk for CKD must be screened and treated early to prevent onset and delay progression. Reducing CKD risk is also highly dependent on addressing the fact that it is both a consequence of and a contributor to socioeconomic disparities. This review discusses the globally-relevant major traditional and non-traditional risk CKD factors, highlights gaps in knowledge, and recommends strategies to close these gaps and enhance CKD prevention. Environmental risk factors are discussed elsewhere in this issue.

Prioritization of CKD and detecting and investigating CKD hotspots

To understand whether CKD is a priority within a country, incidence and prevalence, as well as the contribution of various risk factors to the burden of disease should be determined. Systematic and reliable data collection is required. It is important that such data are analyzed at region, country, provincial, and district levels to identify local disparities and CKD "hotspots". For example, the GBD Study, has identified several hotspots in Central America where CKD prevalence is high and requires attention.[4-6] These include Mexico, where women have one of the highest disability-adjusted life year rates for CKD (related to obesity, diabetes and hypertension), as well as pockets in Nicaragua, Guatemala and El Salvador where CKD of unspecified cause (CKDu) is highly prevalent in men, primarily related to non-traditional risk factors.[6,7]

To illustrate the importance of sub-regional local analysis, in Nicaragua, increased CKD rates in male farmers aged <60 years of age are associated with pesticide exposure, dehydration, alcohol consumption and exposure to heavy metals.[8] Costa Rica has reported a higher incidence of CKD among young sugar-cane workers, with clinical and histological findings of chronic interstitial nephritis.[9] In El Salvador, a high prevalence of CKD (17%) was observed among male farmers exposed to toxic pollutants.[10,11]. Studies in Sri Lanka reported an association between pesticide poisoning and pollutants with repeated episodes of AKI and CKD.[12] In India and Pakistan, a large percentage of CKD cases are of undetermined etiology potentially related to environmental factors.[13] Many knowledge gaps remain regarding these regional CKDu epidemics.[4]

Gaps: There are no reliable statistics about prevalence of CKD in most of the developing world. Improving and expanding local data collection, processing and research infrastructure is recommended to ensure better understanding of the burden and regional distribution of specific CKD risk factors.

Action strategies: Including screening for kidney disease in established non-communicable disease (NCD) risk factor surveys would add significant value to existing efforts to monitor NCD risk-factor prevalence, likely at lower cost than duplicating efforts with parallel CKD surveillance programs. Combining such survey data with global positioning technology would permit identification of regional and local variations in CKD occurrence. For example, the World Health Organization (WHO) STEPwise approach to surveillance (STEPS) is an NCD household survey launched in 2002.[14] To date, 122 countries have participated.[15] Depending on local resources, the survey collects behavioral risk factors (Step 1), physical measurements including blood pressure (BP), height and weight (Step 2) and biochemical parameters (blood glucose and lipids, Step 3).[16] Advocacy efforts in Uruguay succeeded in gaining inclusion of serum creatinine and urine protein measurements in the STEPS Survey in 2006. This effort captured the attention of policy makers and resulted in a policy mandating kidney disease screening in individuals with hypertension or diabetes at regular health check-ups in the employed population. This program is raising CKD awareness and will permit tracking of prevention efforts.[17]

Importantly, surveillance or outreach activities must include vulnerable groups and ensure equitable representation of the population. Monitoring activities should integrate national data at regional and local levels with data obtained in research and screening activities to optimize efficiency, facilitate

surveillance, and permit rapid identification of geographic "hotspots" for CKD that require focused attention.[18] A task force supported by global experts should be set-up to investigate hotspots rapidly. Investigations should include standardized data on social, structural, and clinical risk factors, clinical course, and potential interventions. A guideline-based approach should be disseminated and adapted in regions experiencing CKD hotspots. An example is the international study group on CKDu in Mesoamerica, organized by the Central American Program for Work, Environment and Health.[19] Such efforts require a multi-sectoral approach with sustainable financing.[20]

Tackling CKD risk factors: diabetes, hypertension and obesity

The WHO Global Action Plan for the prevention and control of NCDs does not include CKD among the four priority NCDs. However, diabetes, hypertension and cardiovascular disease (CVD) are acknowledged as integrally linked with CKD. Notably, CKD is an important risk amplifier within these conditions.[21] Across the world, 415 million adults are living with diabetes, 1.4 billion adults have hypertension, and 2.1 billion children and adults are overweight or obese.[22-24] The prevalence of CKD in adults with type 2 diabetes is approximately 25-40%, depending on population factors.[25-27] In the United States, the prevalence of CKD is approximately 30% among adults with hypertension, and 17% among obese adults.[25] The size of the population at-risk of CKD is influenced by regional differences in demographics, different approaches to diagnosis and management, and the effectiveness of local interventions to address lifestyle-related risks. Reduction of lifestyle-related risks is a cornerstone of mitigating the public health impact of diabetes, hypertension, and obesity. There is clear evidence linking upstream factors such as poor diet, poverty, food insecurity, tobacco consumption and other lifestyle factors with risk of developing CKD.[28-35] Conversely, interventions to manage hypertension and promote weight loss are associated with reduced risks of developing CKD and better outcomes among those living with CKD.[2,36-42]

Gaps: Epidemiological assessment, followed by prioritization of CKD risk factors according to their contribution to the local burden of disease, is important to determine where public health efforts should be focused to reduce the population burden of CKD. In addition, existing barriers to implementation of locally-relevant strategies for prevention and management of diabetes, hypertension and obesity must be identified. Barriers may include resistance to change in the communities themselves or push-back from industry and others potentially impacted by for lifestyle modification campaigns.

Action strategies: Population-based studies are needed to determine the impact of diabetes, hypertension, and obesity prevention programs on CKD prevalence and incidence. Longitudinal studies are necessary to understand the impact of prevention programs on rates of CKD and end-stage kidney disease (ESKD) and related comorbidities including cardiovascular complications and infections. Studies are required to better understand the appropriate risk-benefit thresholds (target hemoglobin A1c, BP, weight) for CKD prevention and management, and to understand interactions between race/ethnicity, genetics, socioeconomic status, and geography as modifiers of CKD risk and progression. The impact of tobacco consumption on CKD requires further study.

Strategies to reduce CKD risk attributable to diabetes, hypertension and obesity will be most effectively implemented as part of a broad approach to NCD prevention. Interventions to reduce lifestyle related NCD risk factors are most successful when implemented at both patient and community levels, supported by legislation and regulation.[43] Public health approaches with the greatest evidence of effectiveness in reducing NCD risk include economic incentives to lower prices of healthy food, taxation on unhealthy food, education and physical activity programs in schools, food advertising restrictions and standards, providing more recreation spaces and facilities, sustained media campaigns for smoking cessation, cigarette packet warnings, restrictions on tobacco advertising, higher taxes on tobacco and restrictions on smoking in public areas and workplaces.[44] Several countries have made efforts to reduce population consumption of sugary beverages, high fat foods, and salt with the endorsement of Panamerican Health Organization and the WHO, however more research is needed to understand what lifestyle interventions will have the greatest impact on the CKD burden.[21,45,46]

An example of the importance of rigorous epidemiologic evidence required to inform policymaking and action, is the on-going debate on the utility of sodium reduction as a population measure to reduce BP and CVD.[47-52] Recent studies have demonstrated a J- or U-shaped relationship of sodium intake with BP and mortality.[53-55] The benefit of salt reduction is greater among hypertensive people, but definitive effects on kidney disease outcomes remains uncertain. Interventional studies have demonstrated that estimated glomerular filtration rate (eGFR) and albuminuria (proteinuria) increase with higher salt intake, and a recent study showed that reduction of sodium intake reduced albuminuria.[56] In the United Kingdom, voluntary food manufacturing targets achieved a lower sodium intake of 15% between the years 2001 and 2011 that was associated with a decrease in mean BP (3 mmHg) and 40% reduction in deaths from stroke and ischemic heart disease.[49,57] However, the respective role of sodium reduction

versus other treatments for hypertension, dyslipidemia, and CVD are not clearly delineated.[49,57]

Implementing population-level approaches to reduce NCDs requires action across multiple sectors of government and society, as well as commitment of governments. This is consistent with the "Health in All" policies strategy outlined by the WHO, which emphasizes the importance of multi-sectoral engagement to the successful implementation of public health policies.[43,45] At the level of health departments, healthcare care providers must have the necessary technology, tools, medicines and services required for efficient assessment and control of risk factors. Community engagement and education are crucial to optimize success. Patients themselves are also key to NCD prevention. In the Chronic Care Model, patient self-care takes on great importance, while the roles and responsibilities of physicians, nurses, and community health workers are being redefined through innovative strategies and technologies.[20] Ongoing monitoring and evaluation of policy implementation will permit better understanding of barriers to and facilitators of CKD prevention. This is especially true of LMIC, where major barriers are quality, price and availability of drug treatments for diabetes and hypertension. Understanding how such barriers and facilitators vary by jurisdiction, health system, race/ethnicity, age, sex, and socioeconomic status help to inform development of effective local strategies.

Systematic surveillance is recommended to screening for diabetes, hypertension and obesity, using the STEPS survey model for example. Once individuals with these conditions are identified, they should be recognized as being at high-risk of CKD and have eGFR and albuminuria measured. Clinical guidelines on blood pressure, blood glucose, weight and physical activity targets should be clear and easily implementable to optimize CKD risk-factor management. Screening and early intervention when CKD is detected have been shown to reduce ESKD and be cost-effective.[39,58-60]

Nephrotoxins as risk factors for AKI and CKD

Nephrotoxic agents can cause both AKI and CKD.[61] Nephrotoxin exposure is common in hospitalized patients and may account for up to 25% of AKI.[62-64] Common agents associated with AKI include non-steroidal anti-inflammatory drugs (NSAIDS), antibiotics, iodinated contrast media, and chemotherapeutic drugs.[65,66] Clinician and patient education are important to reduce risk of nephrotoxicity. Where electronic medical records (EMR) exist, alerts to reduce risk of nephrotoxic exposure and drug interactions can be activated.[67,68] EMR can simultaneously be used to monitor prescription practices, responsiveness to alerts and prompts, rates of AKI, and barriers to effective

implementation.[69,70] In high-income countries, AKI typically develops during hospitalization and may impact long-term health. For example, evidence of CKD (urinary abnormalities, low eGFR, or hypertension) was found in 70% of children 6 months after nephrotoxin-induced AKI.[71]

The list of medications that can induce CKD is steadily expanding. The mechanisms range from interstitial inflammation to glomerular and tubular injury.[72-74] Strategies should be implemented to reduce nephrotoxin-induced AKI and CKD, as well as emphasizing risks of medication over-use and dose-adjustments for eGFR. Detection of medications that lead to CKD is challenging given the long time dimension. As recently described for proton pump inhibitors, linkage of clinical and prescription databases can identify novel links between CKD and medication that enables ongoing surveillance.[72]

Use of culturally-traditional and alternative remedies is common worldwide, reaching over 80% of the population in many regions.[75] The rates of associated AKI and CKD are unknown, although up to 30% of AKI in sub-Saharan Africa may be related to traditional remedy use.[76] In Europe and North America, the market for alternative remedies generates billions of dollars per year.[77] Remedy production is often unregulated leading to high inter-product variability and underappreciated risk of kidney injury.[78] In LMIC, traditional remedies are often the only affordable means of healthcare. Given the large numbers of people worldwide using theses remedies, toxicity cannot be universal, but instead may relate to individual susceptibility which remains under-investigated.[75]

Gaps: The true risk of nephrotoxicity of commonly used medications or remedies is uncertain given the unknown denominators of use. Some medications are known to be nephrotoxic, especially in particular circumstances e.g. NSAIDS with volume depletion. The magnitude of risk, which compounds are most toxic and under which circumstances, and how best to use these compounds safely if no alternative exists remain unknown. In LMIC traditional medicines are used for many reasons other than medical, therefore better understanding is required of the role remedies play in people's lives.[79] Further studies are required to identify potentially toxic remedies, risk factors that may exacerbate nephrotoxicity, herb-medication interactions and potentially beneficial compounds.[80-86]

Action strategies: In settings with EMR, use of medicines and alternative remedies should be captured. These databases would permit monitoring of prescription practices to establish a true denominator of subjects "at risk" and permit surveillance to determine associations with nephrotoxicity and potential

exacerbating factors. Screening protocols should be developed to identify nephrotoxic effects of medication to improve consistency in case/compound identification and comparability of outcomes. When nephrotoxicity is suspected, attempts should be made to analyze culprit remedies and detailed case reports should be published. Education of health care practitioners is important to foster regular prescription reviews. Guidelines should emphasize measurement of eGFR prior to prescription of potentially nephrotoxic medication with electronic warnings for medication interactions and risks. Shared pharmaceutical prescription databases would avoid repeat prescriptions or drug interaction potential. Research should continue to develop effective alternative agents with reduced nephrotoxicity.

To reduce use of nephrotoxic remedies, it is important to ensure that individuals have access to essential medical care and medication. Where alternative remedy use is widespread, strategies should be identified to minimize exposure to nephrotoxins. Such approaches should be customized based on region, economic realities, and community perspectives to improve safety without alienating groups or challenging fundamental beliefs. Engagement with traditional healers is crucial to foster collaboration, educate about kidney disease, and to learn about potentially beneficial remedies. The public and healthcare workers (HCW) must be educated about nephrotoxicity and drug interactions relevant to herbal remedies and over-the-counter preparations.[86] Clinicians should be encouraged to ask about alternative remedy use. A global free web-based adverse event reporting (across income settings) site should be developed to gather data and study associations of remedy use with rates of CKD.

Given easy access to alternative remedies, governments should develop policies about accuracy of advertising and health claims touted on the Internet and require efficacy data similar to that required of pharmaceuticals. Policies should enforce minimum standards of safety, manufacture, labeling and adverse event reporting on the alternative remedy industry.

Kidney stones and risk of CKD

Kidney stone disease is now recognized as a chronic health condition that is associated with risks of CKD and ESKD.[87-91] The association between kidney stones and CKD is partly explained by shared risk factors, such as diabetes[92-94], obesity[95,96], hypertension[93,96,97], metabolic syndrome[98,99] and CVD[100-102]. However, kidney stones may also directly contribute to CKD development and progression via urinary tract obstruction and/or infection, nephrocalcinosis, and oxalate nephropathy.[87,103,104] The worldwide prevalence of kidney stones among adults is 5-9% and apparently increasing, with variation between

regions and countries.[105,106] The rising global rate of kidney stones may be contributing to the overall CKD burden related to dietary factors, obesity, global warming, and environmental and occupational exposures (e.g. high ambient temperatures, contact with zinc or cadmium).[89,96,104,106] Individuals who have experienced a single stone event are at increased risk for a symptomatic stone recurrence (up to 50% within the first 5 years).[104] Therefore, prevention among these individuals is an important strategy to reduce further stone and CKD risks.[89] Higher fluid intake, avoidance of low dietary calcium and sweetened beverages, and reduction of dietary sodium and red meat intake reduce stone risk.[107-109]

Gaps: Better understanding of regional risk for kidney stones is important to prioritize stone prevention and reduce CKD risk. The regional impact of climate change on kidney stones is unknown. Long-term surveillance should permit better understanding of the impact of stone prevention strategies (lifestyle habits and medication) and treatments (e.g. lithotripsy, surgery) on risks of new-onset and progressive CKD. Healthcare costs for kidney stone disease require further study. The effectiveness and cost-effectiveness of prevention strategies across populations are unknown.

Action strategies: Tracking mechanisms and research should be developed to determine relationships between kidney stones and CKD incidence, prevalence, progression and complications in regional contexts. Environmental or occupational "hot spots" should be detected through surveillance. Understanding stone types and risk factors (e.g. genetics, infections, diet) are important to inform local prevention strategies. In concert with public health strategies to reduce diabetes, hypertension and obesity, surveillance activities should include impact on rates of kidney stones and of stone-related CKD to identify high-risk groups for targeted prevention and cost-effectiveness.[89] In high stone-risk areas, public and HCW education campaigns should increase awareness and simple prevention strategies (e.g. fluid intake, dietary modification). Where occupational exposure is detected as important, engagement with policy makers and employers is important to modify work conditions.[110]

Maternal, fetal and childhood health as risk factors for CKD

Low birth weight (LBW), small for gestational age (SGA), and preterm birth (PTB) impact the number of nephrons an individual starts life with, and are increasingly being recognized as CKD risk factors.[111,112] In 2010, over 43 million babies in 139 LMIC were born too soon or too small, suggesting many children are born at-risk of CKD.[113] Developmental programming for CKD results from many structural, environmental, social and physical factors that impact maternal and fetal health throughout pregnancy

as well as the child's nutrition and growth.[111] Recent evidence also points to high birth weight (HBW, especially an infant of a diabetic mother), in addition to LBW and PTB, to be a risk factor for obesity, hypertension, diabetes and CKD.[114-118] Early onset of diabetes in offspring associated with intrauterine diabetes exposure is partly responsible for the earlier development of CKD and ESKD in the offspring.[114,119] Childhood obesity is also an important risk amplifier for CKD after LBW, SGA or PTB.[120] Preterm babies are at increased risk of AKI related to reduced nephron number, frequent nephrotoxin exposure and co-morbidities which increase their risk of subsequent CKD.[121,122] Not only the children of troubled pregnancies are at long-term risk of CKD however. Women who developed pre-eclampsia/eclampsia have a higher life-time risk of hypertension, CKD and CVD and those who experienced gestational diabetes (GDM) have an increased risk of developing diabetes.[123-125] Pre-eclampsia occurs in 1-5% of pregnancies worldwide and GDM occurs in around 2-6% of pregnancies in Europe but in up to 25% in some LMIC.[124-126] Many individuals at long-term risk of CKD can be identified early, in prenatal clinics and delivery rooms.

Gaps: The contribution of maternal and fetal risk factors to the CKD burden is unknown. *In vivo* counting of nephron number is not yet possible and poses an obstacle to further understanding developmental programming in the kidney. Variability of nephron number between racial and ethnic groups and geographic locations is largely unknown. Tracking fetal size by fundal height, ultrasound and doppler velocimetry can detect intrauterine growth restriction, but the impact of interventions during pregnancy or soon after birth on CKD risk is unknown. Similarly, the impact of PTB on CKD requires longitudinal studies. The impact of HBW on CKD risk has rarely been studied. Better methods to screen for and treat pre-eclampsia and consequences require further study.

Action strategies: The impact of fetal and early life development on risk of adult NCDs is underappreciated. Monitoring the incidence of LBW, HBW, PTB and fetal growth restriction is required to understand the burden by region and to raise awareness of potential long-term risks. Identification of regional and demographic disparities in birth weights or PTB within countries requires specific interventions or intensification of prevention efforts. Babies must be weighed at birth or soon thereafter, and the birth weight and gestational age should be documented in an enduring health record, which is often not done in LMIC.[113,127] Similarly neonatal AKI should also be documented as a risk factor for future CKD and trigger follow-up. Education of the public, HCW and traditional birth attendants is required to raise awareness of the long-term risks of LBW, growth restriction, PTB, GDM

and pre-eclampsia for mother and child. Both require early and ongoing education about healthy lifestyles and lifelong follow-up. Engagement with mothers, communities, traditional birth attendants and HCW is important to encourage optimal feeding of LBW, HBW, SGA and preterm children to ensure healthy growth while avoiding obesity. Ensuring access to essential healthcare and medications is crucial to optimize child and maternal health.

Given the attention focused on improvements in maternal and child health initiated by the Millennium Development Goals (MDG) and Sustainable Development Goals (SDG), most countries have some form of data reporting or monitoring.[128] Policies should not focus only on maternal health during pregnancy and at delivery, but include access to family planning, equity and education for women, reduction of poverty and access to better nutrition. Monitoring of women throughout pregnancy is important to detect and manage problems early. Innovative programs have improved prenatal clinic visits and deliveries attended by skilled birth attendants.[129] Such programs should be utilized to improve documentation of birth circumstances, maternal pre-eclampsia or GDM, thereby identifying individuals requiring long-term follow up and to initiate life-style education peri-partum. In LMIC engagement with traditional birth attendants is important to build trust and educate them to detect and refer problem cases. Women with pre-eclampsia should be followed long-term to determine the impact of interventions to reduce their long-term CVD and CKD risks.

Infections as risk factors for CKD

CKD and AKI are considered NCDs, but infections are an important cause of both conditions, especially in LMIC. Infections are also a common cause of AKI worldwide.[63,130,131] The three diseases that received much attention under the MDGs, HIV, malaria and tuberculosis (TB), all can cause CKD. In 2015, 36.7 million people were living with HIV.[132] The risk of HIV nephropathy (HIVAN) varies from under 10% percent to almost 50% in Africa.[133] HIVAN is a well-recognized form of CKD that can be prevented and treated with access to effective antiretroviral therapy (ART).[133,134] However, the impact of ART on kidney disease is not straightforward. Although ART reduces the incidence and rate of HIVAN progression to ESKD, it also reduces the competing risk of death, therefore the prevalence of HIVAN-ESKD tends to increase in treated populations.[133] ART does not reduce the incidence/rate of progression of non-HIVAN forms of CKD.[133] Kidney disease prevention in HIV infection is also impacted by comorbidities such as diabetes and viral hepatitis and, therefore, requires additional management and health screening programs.[133,134] In 2015, 241 million cases of malaria were reported worldwide. AKI secondary to malaria

occurs in up to 40% of adults with severe infection.[135] Although kidney function typically recovers in survivors, severe AKI may eventually lead to CKD.[135-137] A Sri-Lankan study also reported an association of malaria with risk of CKDu.[138] Malaria-associated AKI can be prevented by widespread vector control, use of insecticide-treated bed nets and access to rapid diagnosis and treatment.[135] In 2014, 9.6 million people became infected with TB.[139,140] Genitourinary TB may be a cause of CKD through miliary involvement or urinary obstruction and may occur in 27% of cases of extra-pulmonary TB.[141,142] HIV and TB infections frequently coexist, therefore the combined kidney risk, exacerbated by medication toxicities and interactions may be higher.

Many infections other than HIV, malaria, and TB increase CKD risk. Impetigo is frequent in adults and children living in disadvantaged conditions. The risk of CKD among adults with impetigo is high, strongly supporting proactive prevention and early treatment of skin infections as a possible means to reduce CKD risk.[143] The worldwide prevalence of hepatitis B (HBV) was 331 million people in 2013 and that of hepatitis C (HCV) was 148 million.[144] The global risk of HBV-associated CKD is likely under 10%, whereas the risk of HCV-associated CKD is likely higher.[145,146] HBV- and HCV-associated CKD may be unrecognized contributors to "chronic glomerulonephritis" which is a leading cause of ESKD in LMIC. Other infections, such as leptospirosis and schistosomiasis are neglected tropical diseases associated with CKD.[136,147] Given the direct associations between infections, AKI, and CKD, it is likely that strategies to prevent infection will reduce the global CKD burden.

Gaps: The magnitude of regional CKD burden related to specific infections is unknown. How increasing the effectiveness and reach of public health interventions could reduce the CKD burden requires study. The impact of the successful treatment of malaria on the incidence of malaria-associated AKI should be tracked as fewer people may develop endemic immunity and may be more susceptible to severe disease.

Action strategies: Many guidelines mention CKD as a risk factor for infections, but few recognize CKD as a complication. A survey of existing guidelines is necessary to gauge current level of awareness and intervention for infection as a CKD risk factor. HBV vaccination, for example, successfully reduced the incidence of childhood HBV-associated membranous nephropathy.[148] Efforts should be made to ensure access to vaccinations to reduce infection-associated risks of AKI and CKD. Short- and long-term surveillance for kidney disease in regions where these vaccines are implemented should be conducted

to determine the impact. Where the CKD burden associated with a specific infection is high, research is required to develop locally effective and sustainable methods to prevent and treat these infections. Such strategies require partnerships with local policy makers, public health practitioners, governmental organizations and communities to raise awareness and develop implementation strategies. HCWs and communities should be educated about the risks of AKI and CKD with infections to support prompt diagnosis, institution of intravenous fluids and antibiotics, and avoidance of NSAIDS and other nephrotoxins. Governments should suppress use of counterfeit drugs, which contribute to increasing disease severity and increase risk of AKI in infections.

AKI as a risk factor for CKD

Worldwide approximately 20% of patients admitted to hospitals develop AKI.[149] This statistic is largely derived from high-income countries where the majority of AKI is hospital-acquired. The true AKI incidence in LMIC is less well known but is likely at least as high.[149,150] Worldwide it is estimated that 2 million people die of AKI annually.[151] The number of AKI survivors is unknown and a considerable proportion will develop CKD.[152-154]

Gaps: The actual risk of CKD after AKI is not known. Risk modifiers and the long-term impact of AKI prevention on the CKD burden are unknown.

Action strategies: Regionally-adapted strategies should be promoted to avoid AKI. Given that most AKI in high-income countries is hospital-acquired, efforts to reduce AKI incidence should focused on increasing awareness among clinicians and encouraging proactive patient management. Strategies may include EMR alerts for AKI risk and medication prescribing.[67,68,155] In LMIC, the majority of AKI is community-acquired suggesting that prevention should start before hospital admission. Strategies include implementation of public health measures to reduce risk of infections and use of nephrotoxins; ensure access to clean water; reduce poverty, accidents and trauma; improve maternal health; and provide access to essential healthcare and medication. Education campaigns should be conducted in communities and among HCWs to increase awareness of AKI risk, avoid nephrotoxins and seek healthcare promptly.[156] Once patients present to a hospital, guidelines and facilities should be available to institute appropriate therapy. Long-term follow up of patients with AKI is required to determine true burden of subsequent CKD and potential risk modifiers.

Conclusions

Morbidity and mortality from CKD are increasing worldwide, and CKD is progressively being recognized as an important contributor to the global burden of disease.[1,7] Major contributors to the CKD burden are the growing frequencies of diabetes, hypertension and obesity, well-established traditional risk factors for CKD. Public health policies directed towards addressing many life-style factors that contribute to these conditions would be expected to positively impact the risk of CKD. Systematic screening for CKD in at-risk individuals is required for timely intervention when needed and to understand the impact of such policies on CKD incidence. The contribution of non-traditional CKD risk factors, including nephrotoxin exposure, kidney stones, fetal and maternal factors, infections, environmental factors and AKI, to the global CKD burden is unknown. Moreover, many non-traditional risk-factors may predominate in LMIC. The impact of reducing non-traditional CKD risk factors requires study. Mitigation of non-traditional CKD risk factors will require advocacy efforts to support policy development, implementation of strategies to reduce disparities, improve access to essential healthcare and maternal and child health, reduce environmental exposures, prevent AKI, better understand traditional remedy use, and prevent infections.[2,3,157] Race/ethnicity, genetics, sex, socioeconomic status, and geography likely modify the impact of CKD risk factors. Effective coordination within health systems, and importantly in the era of the SDGs, a broad multi-sectoral approach are required to identify and tackle achievable goals to reduce CKD risk factors, and thereby, the global burden of CKD.

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Table 1: Global relevance of major risk factors for CKD and suggested mitigation strategies

Risk factor	Global prevalence	Primary prevention	Projected risk for CKD	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevance for LIC	Advocacy required	Refs
Diabetes Type 2	**All diabetes** 387 million with largest concentrations in Western Pacific (138 million) and Southeast Asia (75 million) **Type 2:** About 95 % of overall global prevalence	Education, Lifestyle Diet Exercise Weight management	*~40 % overall and >50 % in most non-white populations*	Glucose control BP control, Lifestyle factors (avoidance of high dietary protein), ACEI or ARB	Glucose targets Best medications Need for novel therapies for diabetic kidney disease	Obesity DM GDM	Increasing obesity and DM, GDM Poor facilities for diagnosis and treatment	Policy development around food content and prices of healthy food, urban planning to increase walking opportunities, tobacco Universal health care Access to diagnosis Reliable access to medication, lifestyle	36,41,42,58
Diabetes Type 1	***Type 1:*** *About 5 % of overall global prevalence*	*Viral exposures?*	*~30 %* *Not known to vary by race/ethnicity*	Glucose control BP control Lifestyle factors (avoidance of high dietary protein), ACEI or ARB	Glucose targets Novel therapies for diabetic kidney disease	Glycemic control	Glycemic control Poor facilities for diagnosis and treatment	Universal health care Access to diagnosis Reliable access to medication, lifestyle	36
Hypertension	2010: 31% of adults globally (28·5% in HIC, 31·5% LMIC) 1·39 billion people (349 million in HIC, 1·04 billion in LMIC)	Education Lifestyle Diet Exercise Weight management Smoking Stress reduction	~10 %	Blood pressure control ACEI or ARB if high-level albuminuria Other medication types?	BP targets Albuminuria-based?	Obesity Dietary sodium	Obesity, dietary sodium Strokes also high Awareness, Rx and control v low in LMIC	Policy development around food sodium content, tobacco, alcohol Need to increase awareness, treatment and control globally Universal health care Consider Polypill strategy Awareness, access to diagnosis Reliable access to medication, lifestyle	22
Obesity (Risks may vary for childhood and adult	**Adult**: Overweight 2013: 36·9% men, 38·0%	Education Lifestyle Diet Exercise	Unknown Proteinuria or macroalbuminuria present in 4-10%	Diet Exercise Weight loss Bariatric	Risk of CKD Optimal BMI and variance by race/ethnicity	Access to weight management programs	Access to weight management programs	Policy development to regulate food content, food prices, urban planning to permit physical exercise	139,158-162

Risk factor	Global prevalence	Primary prevention	Projected risk for CKD	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevance for LIC	Advocacy required	Refs
obesity)	women. Obesity 2014: 10·8% men, 14·9% women **Children**: In 2014 41 million children < age 5 years were overweight or obese (48% in Asia, 25% in Africa)	Weight management Stress reduction	obese patients In morbidly obese risk of GFR decline ≥ 30% over 4 years was 48·2 per 1000 person years Adolescent obesity associated with HR of 6·9 for all ESKD and a HR of 19·4 for diabetic ESRD	surgery (HIC) ACEI/ARB for proteinuria	and age Safe and effective weight management strategies, e.g. bariatric surgery		Social roots of obesity – poverty, culture, access to nutritious food	Access to better diet Education, physical activity education	
Medications (Antibiotics, NSAIDS, PPI, counterfeit drugs, contrast media)	AKI: 24% globally related to nephrotoxins (29% HIC, 22% UMIC, 23% LLMIC) CKD: Unknown	Improve awareness Prescription flagging Stop unnecessary prescriptions	70% of children with nephrotoxin-induced AKI had CKD at 6 months CKD risk variable, by medication	Early detection Urine screening for leukocytes, Stop medications early	Burden of disease Which medication may increase risk for CKD	Electronic alert systems Prescription data sharing databases Package warnings	Reduce counterfeit drugs Regulate drug manufacture to reduce adulterants	Awareness Prescription practices Marketing	63,70,71
Traditional/ alternative remedies	Frequent use globally, > 80% in LMIC	Improve awareness Improve access to alternatives (UHC)	35% of AKI in Africa Unknown contribution to CKD Increased risk of ESKD with consumption of some remedies	Stop medication, hydration	Burden of disease Toxic compounds	Huge market OTC and over internet Need regulation of the industry	Engage with communities to understand reasons for use, barriers to western medicine etc.	Policies to regulate manufacture and sale of alternative remedies, Limit unfounded/fraudulent advertising Universal health care Awareness, collaboration with traditional healers, improve access to medical care/affordability of medication Encourage publication of case reports to build database	75,85,163
Kidney stones	Geographic variability Adults: 5-9% Europe, 12% Canada, 13-	Increase awareness of local risks Emphasize importance of	GFR tends to be reduced in stone formers vs. controls	Hydration, diet, recurrent stone prevention,	Regional risks	High costs	Likely unrecognized important cause of CKD and infections	Access to clean water, reduce environmental/occupation-al risks Increase awareness of need for follow up for CKD, CVD in stone	87,89,105

Risk factor	Global prevalence	Primary prevention	Projected risk for CKD	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevance for LIC	Advocacy required	Refs
	15% USA, 1-5% East, 20% Saudi Arabia	hydration, certain infections		early reversal of obstruction				formers	
Low birth weight/SGA/ prematurity	Globally: LBW 15%, Preterm 10% In LMIC *2010 13·7 million babies preterm* *2010 43·3 million babies LBW/SGA*	Avoid obesity Healthy lifestyle	70% increased risk	Screen for BP and proteinuria Treat early	Would reduction impact future risk?	Increased maternal age, Assisted reproduction, Maternal chronic illness	Pre-eclampsia Maternal malnutrition, Poverty War Poor antenatal care Pregnancy spacing Child marriage	Awareness, public health measures, optimize maternal and child health, avoid childhood obesity Universal health care Document birth weights, prematurity in health record Need for low term follow up of children at risk	111,113
Pre-eclampsia/ eclampsia	2-5% globally Global prevalence 2013: 1.3 Million	Optimize maternal health pre-pregnancy	RR HT – 3·7 RR microalbuminuria 4-8 RR ESKD 4·7 RR kidney biopsy 3·3	Screen for BP and proteinuria treat early	How to diagnose and prevent?	Prematurity, later CVD, ESKD	Prematurity, CVD, ESKD	Maternal health Access to ante-natal care Universal health care Mothers require long term follow up for CKD and CVD	123,144,164,165
HIV	2013: 35 million world-wide, 24·7 million in sub-Saharan Africa	Education Condoms	Africa: 6·0-48.5%, Europe 3·5 – 18%, Hong Kong 18%, Brazil 1·1-5·6%, India 27%, Iran 20%	PEP, HAART	Impact of HAART on all forms of renal disease, other kidney diseases in HIV-infected individuals	Competing risks of mortality	Poverty, suboptimal access to ART, On-going infection risk ApoL1 genotype with African-origin	Policies around needle sharing, prostitution Universal health care National policies for prevention education, Access to ART, reduce gender/sexuality discrimination, empower women Surveillance of renal function on ART	133
Hepatitis B	Global prevalence 2013: 331·0 million	Education Reduce scarification Vaccination	Hepatitis B associated GN: 3% France, 3% China	Treatment Hepatitis B	Impact of routine vaccination on CKD burden	Reduce HCC Liver failure Transplant	High prevalence	Policies around needle sharing, vaccination Advocacy for sexual health, drug abuse	144,145,148

Risk factor	Global prevalence	Primary prevention	Projected risk for CKD	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevance for LIC	Advocacy required	Refs
								Equity in access to vaccination. (Vaccination reduced Membranous nephropathy among Taiwanese children) Equity in access to antiviral therapy	
Hepatitis C	Global prevalence 2013: 147·8 million	Education	Global : 10-16% Glomerular lesions in 54·8% HCV positive subjects at autopsy	Treatment Hepatitis C	Impact of treatment on disease burden	Reduce HCC Liver failure Kidney transplant. New medication very costly	Lower prevalence Unlikely to gain access to expensive therapies	Policies around needle sharing Advocacy against drug abuse Lobby for access to therapy in HIC and LMIC	144-146
Bacterial skin diseases	Global prevalence 2013: 5·8 million	Sanitation Early treatment	Acute PSGN 9 per 100000 in LMIC Higher frequency or CKD after post-streptococcal GN, worse in adults	Early detection of renal involvement Treatment and follow up	Contribution to CKD burden in LIC unknown	Likely low	Likely high	Policies to improve child nutrition, school feeding schemes Poverty, overcrowding Scabies prevention and early treatment Consider screening school children for haematuria, proteinuria	143,144,166
Schistosomiasis	Global prevalence 2013: 290·6 million	Safe water Education	Obstruction (urinary) 2-62%, chronic glomerulonephritis (hepatosplenic) in 15%	Prompt treatment Screening for obstruction	Obstruction usually not severe, renal function preserved. Regional contribution to ESKD may be 3 - 7% (Egypt)	Low	High regional	Public health policies, Neglected Tropical Diseases Clean water Consider screening school children for haematuria, proteinuria Prompt access to diagnosis and treatment	131,144,147,167,168
Diarrhoeal illnesses	Global prevalence 2013: 4·24 million	Safe water Sanitation Nutrition Vaccination	Important cause of AKI worldwide	Appropriate hydration, antibiotics when needed	Burden of CKD related to diarrhoea-associated AKI Impact of vaccination on AKI/CKD	Relatively low, diarrhoea-associated HUS	High, important cause of childhood AKI through volume depletion, sepsis, HUS	Public health policies, sanitation, water education, infrastructure, vaccination Advocacy to chlorinate water Handwashing Improve water safety Equitable access to vaccination	144

Risk factor	Global prevalence	Primary prevention	Projected risk for CKD	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevance for LIC	Advocacy required	Refs
								Education about oral rehydration therapy	
Malaria	World-wide prevalence 2013: 351 million	Use of ITNs Vector control Prompt treatment with correct drugs	AKI <1 % to > 50% in adults with severe falciparum malaria. CKD not often reported among survivors	Early screening and diagnosis and management	Contribution to CKD burden regionally unknown, possible differences among those living in endemic areas or not? May be associated with CKDu	Low	High regional	Public health policies vector control, insecticide treated nets, monitor medication resistance, combat counterfeit medication, introduce RDT Access to prevention, diagnosis, appropriate treatment	135-138,144
Tuberculosis	World-wide prevalence 2013: 12·1 million	Healthy diet, reduce poverty, reduce HIV	Genitourinary 27% of extrapulmonary TB (obstruction, parenchymal infection, interstitial nephritis)	Prompt diagnosis and full treatment	Low	Low, higher in immigrant, prison, indigenous, immune suppressed populations	High, regional. Often co-infection with HIV	Public health policies about detection, supervision of therapy, GeneXpert, management of MDR, XDR, integration with HIV services Poverty, comorbid illness, nutrition, overcrowding, occupational exposure (mining), HIV infection	142,144
Leptospirosis	Global incidence 1·03 million	Use of ITNs, vector control, prompt treatment	AKI (Weil's disease) 10-60%	Early diagnosis	Contribution to burden of CKD unknown	Little	High, regional	Public health policies, Neglected Tropical Diseases Poverty, water quality, overcrowding	136,169
Environmental factors	? risk factor prevalence for CKDu - likely association with environment (heat), occupation, poor fluid intake, co-infections, traditional	Avoid occupation, climate, environmental hazards	Prevalence 13-26% in high risk populations	Hydration Avoid nephrotoxins	Causes and pathophysiology unknown	Low	CKDu major problem in multiple LMIC	Policies around working conditions, environmental contamination	4,138,170

Risk factor	Global prevalence	Primary prevention	Projected risk for CKD	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevance for LIC	Advocacy required	Refs
	remedies								
AKI	21% of hospital admissions (global data insufficient for accurate quantitation)	Early risk identification Treat underlying cause early Avoid nephrotoxins	Adults: 25·8 per 100 person years (CKD), 8·6 per 100 person years (ESKD) Children: 3·1 per 100 person years (proteinuria), 0·9 per 100 person years (ESKD)	Early diagnosis and treatment of AKI	Actual risk of CKD after AKI in population, impact of interventions to reduce AKI on CKD prevalence	Predominantly hospital acquired, older adults, multiple co-morbidities	Predominantly community acquired, adults younger, few co-morbidities	Increase awareness of risk of AKI and need for prompt treatment Require accessible methods to diagnose AKI Awareness of risk of CKD requiring long term follow up after severe AKI	149,152,153

Abbreviations: ACEI – angiotensin converting enzyme inhibitor; AKI – acute kidney injury; ARB – angiotensin receptor blocker; ART – anti-retroviral therapy; BMI – body mass index; BP –blood pressure; CKD – chronic kidney disease; CKDu – chronic kidney disease of uncertain aetiology; CVD – cardiovascular disease; DM – diabetes mellitus; GDM – gestational diabetes mellitus; GFR – glomerular filtration rate; GN – glomerulonephritis; ESKD – end stage kidney disease; HAART – highly active anti-retroviral therapy; HIC – high income country; HIV – human immunodeficiency virus; HCV – hepatitis C Virus; ITN – insecticide-treated nets; LBW – low birth weight; LMIC – low middle income country; MDR – multi-drug resistance; NSAID – non-steroidal anti-inflammatory drug; OTC – over the counter; PEP – post-exposure prophylaxis; PPI – proton pump inhibitor; PSGN – post-streptococcal glomerulonephritis; Rx – treatment; SDG=Sustainable Development Goal; SGA – small for gestational age; TB – tuberculosis; UHC - Universal Health Care; UMIC – upper middle income country; XDR – extensive drug resistance.