Reducing major risk factors for chronic kidney disease

Valerie A. Luyckx[1,2,18,19], Katherine R. Tuttle[3,18,19], Guillermo Garcia-Garcia[4], Mohammed Benghanem Gharbi[5], Hiddo J.L. Heerspink[6], David W. Johnson[7,8,9], Zhi-Hong Liu[10], Ziad A. Massy[11,12], Orson Moe[13], Robert G. Nelson[14], Laura Sola[15], David C. Wheeler[16] and Sarah L. White[17]

[1]*Institute of Biomedical Ethics and History of Medicine, University of Zurich, Zurich, Switzerland;* [2]*Klinik für Nephrologie, Universitätsspital, Zurich, Switzerland;* [3]*Providence Medical Research Center, Providence Health Care Kidney Research Institute, Nephrology Division and Institute for Translational Health Sciences, University of Washington, Spokane, Washington, USA;* [4]*Servicio de Nefrologia, Hospital Civil de Guadalajara Fray Antonio Alcalde, University of Guadalajara Health Sciences Center, Hospital 278, Guadalajara, Jalisco, Mexico;* [5]*Urinary Tract Diseases Department, Faculty of Medicine and Pharmacy of Casablanca, University Hassan II of Casablanca, Casablanca, Morocco;* [6]*Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [7]*Centre for Kidney Disease Research, University of Queensland at Princess Alexandra Hospital, Brisbane, Australia;* [8]*Translational Research Institute, Brisbane, Australia;* [9]*Metro South and Ipswich Nephrology and Transplant Services, Princess Alexandra Hospital, Brisbane, Australia;* [10]*National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China;* [11]*Division of Nephrology, Ambroise Paré Hospital, APHP, Boulogne Billancourt/Paris, France;* [12]*French National Institute of Health and Medical Research (INSERM) U1018, Team5, Centre for Research in Epidemiology and Population Health (CESP), Paris-Ile-de-France-West, Versailles-Saint-Quentin-en-Yvelines University, Villejuif, France;* [13]*Department of Internal Medicine and Charles and Jane Pak Center of Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas, USA;* [14]*National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona, USA;* [15]*Division Epidemiologia, Direccion General de Salud (DIGESA)-Ministerio Salud Publica, Montevideo, Uruguay;* [16]*Centre for Nephrology, Royal Free Hospital, University College London, London, UK; and* [17]*Charles Perkins Centre, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia*

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 the disease and are important *traditional* CKD risk factors; however, *nontraditional* CKD risk factors such as 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 the identification of CKD risk factors in the population, followed by the 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 CKD risk must be screened and treated early to prevent the onset of and delay the progression of the kidney disease. Systematically collected data should be analyzed at country, province, 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 into account all of these factors is therefore required to successfully tackle the global CKD epidemic.

Kidney International Supplements (2017) **7,** 71–87; http://dx.doi.org/10.1016/j.kisu.2017.07.003

KEYWORDS: acute kidney injury; chronic kidney disease; multi-sectoral approach; prevention; public health; risk factors

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, diabetes, hypertension, and obesity are *traditional* risk factors for CKD.[1] *Nontraditional* CKD risk factors such as 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 that is attributable to nontraditional risk factors is unknown and may even predominate in low- and middle-income countries (LMICs).

A broad approach to CKD prevention begins with the identification of the incidence, prevalence, and distribution of

Correspondence: *Valerie A. Luyckx, Klinik für Nephrologie, UniversitätsSpital Zürich, Rämistrasse 100, Zurich 8091, Switzerland. E-mail: valerie.luyckx@uzh.ch*

[18]Co-first authors followed by alphabetical listing of co-authors.

[19]GKHS Working Group Co-chairs.

risk factors, followed by the development of mitigation strategies. At-risk populations or individuals 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 expands on the recently published International Society of Nephrology (ISN) CKD roadmap,[4] which discusses the globally relevant major traditional and nontraditional risk CKD factors (outlined in Table 1), highlights gaps in knowledge, and recommends strategies to close these gaps and enhance CKD prevention.

Prioritization of CKD and detection and investigation of CKD hotspots

To understand whether CKD is a priority within a country, incidence and prevalence, as well as the contribution of various risk factors for 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, province, and district levels to identify local disparities and CKD hotspots. For example, the global burden of disease study has identified several hotspots in Central America where the prevalence of CKD is high and requires attention.[5–7] 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 is highly prevalent in men, primarily related to nontraditional risk factors.[7,8]

To illustrate the importance of subregional local analysis, in Nicaragua, increased CKD rates in male farmers aged <60 years were associated with pesticide exposure, dehydration, alcohol consumption, and exposure to heavy metals.[9] Costa Rica has reported a higher incidence of CKD among young sugarcane workers, with clinical and histological findings of chronic interstitial nephritis.[10] In El Salvador, a high prevalence of CKD (17%) was observed among male farmers exposed to toxic pollutants.[11,12] Studies in Sri Lanka reported an association between pesticide poisoning and pollutants, with repeated episodes of AKI and CKD.[13] In India and Pakistan, a large percentage of CKD cases are of undetermined etiology, potentially related to environmental factors.[14] Many knowledge gaps remain regarding these regional epidemics of CKD of unspecified cause.[5]

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

Action strategies. Including screening for kidney disease in established noncommunicable disease (NCD) risk factor surveys will add significant value to existing efforts to monitor the prevalence of NCD risk factor, likely at a lower cost than duplicating efforts with parallel CKD surveillance programs. Combining such survey data with global positioning technology will permit the identification of regional and local variations in CKD occurrence. For example, the World Health Organization (WHO) STEPwise approach to surveillance is an NCD household survey that was launched in 2002.[15] To date, 122 countries have participated.[16] Depending on the 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).[17] Advocacy efforts in Uruguay succeeded in including serum creatinine and urine protein measurements in the STEPwise approach to surveillance 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 checkups in the employed population. This program is raising CKD awareness and will permit tracking of prevention efforts.[18]

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 the rapid identification of geographic hotspots for CKD that require focused attention.[19] A task force supported by global experts should be setup 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 CKD of unspecified cause in Mesoamerica, organized by the Central American Program for Work, Environment, and Health.[20] Such efforts require a multi-sectoral approach with sustainable financing.[21]

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 to be integrally linked with CKD. Notably, CKD is an important risk amplifier within these conditions.[22] Across the world, 415 million adults have diabetes, 1.4 billion adults have hypertension, and 2.1 billion children and adults are overweight or obese.[23–25] The prevalence of CKD in adults with type 2 diabetes is approximately 25% to 40%, depending on population factors.[26–28] In the United States, the prevalence of CKD is approximately 30% among adults with hypertension and 17% among obese adults.[26] The size of the population at CKD risk is influenced by regional differences in demographics, different approaches to diagnosis and management, and 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 that links upstream factors such as poor diet, poverty, food insecurity, tobacco consumption, and other

Table 1 | Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy 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 (avoiding 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 UHC Access to diagnosis, reliable access to medication and lifestyle	37,42,43,59
Diabetes type 1	**Type 1:** About 5% of overall global prevalence	Viral exposure?	∼30% not known to vary by race-ethnicity	Glucose control, BP control, lifestyle factors (avoiding high dietary protein), ACEI, or ARB	Glucose targets, novel therapies for diabetic kidney disease	Glycemic control	Glycemic control, poor facilities for diagnosis and treatment	UHC Access to diagnosis Reliable access to medication and lifestyle	37
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%	BP control, ACEI, or ARB if high-level albuminuria, other medication types?	Albuminuria-based targets?	Obesity, dietary sodium	Obesity, dietary sodium, strokes also high Awareness, treatment, and control very low in LMIC	Policy development around food sodium content, tobacco, and alcohol Need to increase awareness, treatment, and control globally UHC Consider polypill strategy Awareness, access to diagnosis Reliable access to medication and lifestyle	23
Obesity (Risks may vary for childhood and adult obesity)	**Adult**: Overweight 2013: 36.9% men, 38.0% women Obesity 2014: 10.8% men,	Education, lifestyle, diet, exercise, weight management, stress reduction	Unknown proteinuria or macroalbuminuria present in 4%–10% obese patients In morbidly obese,	Diet, exercise, weight loss, bariatric surgery (HIC) ACEI or ARB for proteinuria	CKD risk optimal BMI and variance by race-ethnicity and age, safe and effective weight	Access to weight management programs	Access to weight management programs Social roots of obesity, namely poverty,	Policy development to regulate food content, food prices, urban planning	140,159–163

(*Continued on next page*)

Table 1 | Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies (Continued)

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
	14.9% women **Children**: In 2014, 41 million children aged <5 yr were overweight or obese (48% in Asia, 25% in Africa)		risk of GFR decline of ≥30% over 4 yr was 48.2 per 1000 person-yr Adolescent obesity associated with HR of 6.9 for all ESKD and HR of 19.4 for diabetic ESKD		management strategies, namely bariatric surgery		culture, access to nutritious food	to permit physical exercise 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 mo CKD risk variable, by medication	Early detection, urine screening for leukocytes, stop medications early	Burden of disease Which medication may increase CKD risk	Electronic alert systems, prescription data-sharing databases, package warnings	Reduce counterfeit drugs, regulate drug manufacturers to reduce adulterants	Awareness, prescription practices, marketing	64,71,72
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 of OTC and over-the-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 or fraudulent advertising UHC Awareness, collaboration with traditional healers, improve access to medical care or affordability of medication, encourage publication of case reports to build database	76,86,164
Kidney stones	Geographic variability Adults: 5%–9% Europe, 12% Canada, 13%–15% USA, 1%–5% East, 20% Saudi Arabia	Increase awareness of local risks, emphasize on the importance of hydration, certain infections	GFR tends to be reduced in stone formers vs. non–stone formers	Hydration, diet, recurrent stone prevention, early reversal of obstruction	Regional risks	High costs	Likely unrecognized important cause of CKD and infections	Access to clean water, reduce environmental or occupational risks Increase awareness of need for follow-up for CKD, CVD in stone formers	88,90,106

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, maintain 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	Preeclampsia, maternal malnutrition, poverty, war, poor antenatal care, pregnancy spacing, child marriage	Awareness, public health care measures, optimize maternal and child health, avoid childhood obesity UHC Document birth weights, prematurity in health care record Need for long-term follow-up of children at risk	112,114
Preeclampsia/ eclampsia	2%–5% globally Global prevalence 2013: 1.3 million	Optimize maternal health prepregnancy	RR HT–3.7 RR microalbuminuria 4–8 RR ESKD 4.7 RR kidney biopsy 3.3	Screen for BP and proteinuria and treat early	How to diagnose and prevent?	Prematurity, later CVD, ESKD	Prematurity, CVD, ESKD	Maternal health Access to antenatal care UHC Mothers require long-term follow-up for CKD and CVD	124,145,165,166
HIV	2013: 35 million worldwide, 24.7 million in sub-Saharan Africa	Education, use of 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, ongoing infection risk, ApoL1 genotype with African origin	Policies around needle sharing, prostitution UHC National policies for prevention education, access to ART, reduce gender and/or sexuality discrimination, empower women, surveillance of renal function on ART	134
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 Equity in access to vaccination.	145,146,149

(*Continued on next page*)

Table 1 | Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies (Continued)

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
								(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 of hepatitis C	Impact of treatment on disease burden	Reduce HCC, liver failure, kidney transplant. New medication is 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	145–147
Bacterial skin diseases	Global prevalence 2013: 5.8 million	Sanitation, early treatment	Acute PSGN 9 per 100,000 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 hematuria, proteinuria	144,145,167
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 care policies, neglected tropical diseases Clean water Consider screening school children for hematuria, proteinuria. Prompt access to diagnosis and treatment	132,145,148,168,169
Diarrheal illnesses	Global prevalence 2013: 4.24 million	Safe water, sanitation,	Important cause of AKI worldwide	Appropriate hydration,	Burden of CKD related to diarrhea-associated AKI.	Relatively low, diarrhea-associated HUS	High, important cause of childhood AKI	Public health care policies, sanitation,	145

		nutrition, vaccination		antibiotics when needed	Impact of vaccination on AKI/CKD		through volume depletion, sepsis, HUS	water education, infrastructure, vaccination Advocacy to chlorinate water, handwashing, improve water safety, equitable access to vaccination, education about oral rehydration therapy	
Malaria	Worldwide 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, 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 care policies, vector control, insecticide-treated nets, monitor medication resistance, combat counterfeit medication, introduce RDT Access to prevention, diagnosis, appropriate treatment	136–139,145
Tuberculosis	Worldwide 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 coinfection with HIV	Public health care policies on detection, supervision of therapy, GeneXpert, management of MDR, XDR, integration with HIV services Poverty, comorbid illness, nutrition, overcrowding, occupational exposure (mining), HIV infection	143,145

(*Continued on next page*)

Table 1 | Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies (Continued)

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
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 care policies, neglected tropical diseases Poverty, water quality, overcrowding	[137,170]
Environmental factors	Unknown risk factor prevalence for CKDu– likely association with environment (heat), occupation, poor fluid intake, coinfections, traditional remedies	Avoid occupational, climate, and 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	[5,139,171]
AKI	21% of hospital admissions (global data insufficient for accurate quantification)	Early risk identification, treat underlying cause early, avoid nephrotoxins	Adults: 25.8 per 100 person-yr (CKD), 8.6 per 100 person-yr (ESKD) Children: 3.1 per 100 person-yr (proteinuria), 0.9 per 100 person-yr (ESKD)	Early diagnosis and treatment of AKI	Actual risk of CKD after AKI in population, impact of interventions to reduce AKI on the prevalence CKD	Predominantly hospital acquired, older adults, multiple comorbidities	Predominantly community acquired, adults younger, few comorbidities	Increase awareness of risk of AKI and need for prompt treatment, require accessible methods to diagnose AKI, awareness of CCKD risk requiring long-term follow-up after severe AKI	[150,153,154]

ACEI, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CKDu, chronic kidney disease of uncertain etiology; CVD, cardiovascular disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; GDM, gestational diabetes mellitus; GFR, glomerular filtration rate; GN, glomerulonephritis; HAART, highly active antiretroviral therapy; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIC, high-income country; HT, hypertension; HUS, Hemolytic-uremic syndrome; HZ, hazard ratio; ITN, insecticide-treated nets; LBW, low birth weight; LIC, low-income country; LMIC, low- and middle-income countries; MDR, multi-drug resistance; NSAID, nonsteroidal antiinflammatory drug; OTC, over-the-counter; PEP, postexposure prophylaxis; PPI, proton pump inhibitor; PSGN, post-streptococcal glomerulonephritis; RDT, rapid diagnostic testing; RR, relative risk among those who experineced preeclampsia versus those who did not for the listed outcomes; 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.

lifestyle factors with the risk of developing CKD.[29–36] 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.[2,37–43]

Gaps. Epidemiological assessment, followed by prioritization of CKD risk factors according to their contribution to the local burden of the disease, is important to determine where public health care efforts should be focused on reducing the population burden of CKD. In addition, existing barriers to the implementation of locally relevant strategies for the 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 that are potentially affected by lifestyle modification campaigns.

Action strategies. Population-based studies are needed to determine the impact of diabetes, hypertension, and obesity prevention programs on the prevalence and incidence of CKD. Longitudinal studies are necessary to understand the impact of prevention programs on the rates of CKD and end-stage kidney disease (ESKD) and related comorbidities, including cardiovascular complications and infections. Studies are required to better understand appropriate risk-benefit thresholds (target hemoglobin A1c, BP, and 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 needs to be studied further.

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.[44] Public health care approaches with the greatest evidence of effectiveness in reducing NCD risk include economic incentives to lower the price 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.[45] Several countries have made efforts to reduce population consumption of sugary beverages, high-fat foods, and salt with the endorsement of the Panamerican Health Organization and WHO; however, more research is needed to understand which lifestyle interventions will have the greatest impact on CKD burden.[22,46,47]

An example of the importance of rigorous epidemiologic evidence required to inform policymaking and action is the ongoing debate on the utility of sodium reduction as a population measure to reduce BP and CVD.[48–53] Recent studies have demonstrated a J- or U-shaped relationship of sodium intake with BP and mortality.[54–56] The benefit of salt reduction is greater among hypertensive people, but definitive effects on kidney disease outcomes remain uncertain. Interventional studies have demonstrated that estimated glomerular filtration rate (eGFR) and albuminuria (proteinuria) increased with higher salt intake, and a recent study showed that reduction of sodium intake reduced albuminuria.[57] In the United Kingdom, voluntary food-manufacturing targets achieved a lower sodium intake of 15% between 2001 and 2011, which was associated with a decrease in mean BP (3 mm Hg) and 40% reduction in deaths owing to stroke and ischemic heart disease.[50,58] However, the respective role of sodium reduction versus other treatments for hypertension, dyslipidemia, and CVD are not clearly delineated.[50,58]

Implementing population-level approaches to reduce NCDs requires action across multiple sectors of the government and society, as well as a commitment of the governments. This is consistent with the Health in All policy strategies outlined by WHO, which emphasizes the importance of multi-sectoral engagement for the successful implementation of public health care policies.[44,46] At the level of health care departments, health care providers must have the necessary technology, tools, medicines, and services that are required for efficient assessment and control of risk factors. Community engagement and education are crucial to optimize success. Patients themselves are also a 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 care workers are being redefined through innovative strategies and technologies.[21] Ongoing monitoring and evaluation of policy implementation will permit a better understanding of barriers to and facilitators of CKD prevention. This is especially true of LMICs, where the major barriers are quality, price, and availability of drug treatments for diabetes and hypertension. Understanding how such barriers and facilitators vary by jurisdiction, health care system, race-ethnicity, age, sex, and socioeconomic status helps to inform the development of effective local strategies.

Systematic surveillance is recommended for the screening of diabetes, hypertension, and obesity using, for example, the STEPwise approach to surveillance survey model. Once individuals with these conditions are identified, they should be recognized as being at high risk for CKD and should be evaluated for eGFR and albuminuria. Clinical guidelines on BP, blood glucose, and weight and physical activity targets should be clear and easy to implement to optimize CKD risk factor management. Screening and early intervention when CKD is detected were shown to reduce ESKD and be cost-effective.[40,59–61]

Nephrotoxins as risk factors for AKI and CKD

Nephrotoxic agents can cause both AKI and CKD.[62] Nephrotoxin exposure is common in hospitalized patients and may account for up to 25% of AKI cases.[63–65] Common agents associated with AKI include nonsteroidal antiinflammatory drugs, antibiotics, iodinated contrast media, and chemotherapeutic drugs.[66,67] Clinician and patient education are important to reduce the risk of nephrotoxicity. Where electronic medical records exist, alerts to reduce the risk of nephrotoxic exposure and drug interactions can be activated.[68,69] Electronic medical records can simultaneously be used to monitor prescription practices, responsiveness to alerts and prompts, rates of AKI, and barriers to effective implementation.[70,71] In high-income countries, AKI typically develops during hospitalization and may impact long-term health. For example, CKD (urinary abnormalities, low eGFR, or hypertension) was found in 70% of children 6 months after nephrotoxin-induced AKI.[72]

The list of medications that can induce CKD is steadily expanding. The mechanisms range from interstitial inflammation to glomerular and tubular injury.[73–75] Strategies should be implemented to reduce nephrotoxin-induced AKI and CKD, as well as to emphasize the risks of medication overuse and dose adjustments for eGFR. Detection of medications that lead to CKD is challenging given the long lag time. As recently described for proton pump inhibitors, linkage between clinical and prescription databases can identify novel associations between CKD and medications, which enables ongoing surveillance.[73]

The use of culturally traditional and alternative remedies is common worldwide, reaching over 80% of the population in many regions.[76] 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.[77] In Europe and North America, the market for alternative remedies generates billions of dollars per year.[78] Remedy production is often unregulated, leading to high interproduct variability and underappreciated risk of kidney injury.[79] In LMICs, traditional remedies are often the only affordable means of health care. Given the large number of people worldwide using these remedies, toxicity cannot be universal but instead may relate to individual susceptibility, which remains underinvestigated.[76]

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 such as nonsteroidal antiinflammatory drugs with volume depletion. The magnitude of risk, which compounds are most toxic and under which circumstances, and how to best use these compounds safely if no alternatives exist remain unknown. In LMICs, traditional medicines are used for many reasons other than medical ones; therefore, a better understanding of the role that remedies play in people's lives is required.[80] Further studies are required to identify potentially toxic remedies, risk factors that may exacerbate nephrotoxicity, herb-medication interactions, and potentially beneficial compounds.[81–87]

Action strategies. In settings with electronic medical records, the use of medicines and alternative remedies should be captured. These databases will permit the monitoring of prescription practices to establish a true denominator of subjects who are at risk and to permit surveillance for determining associations with nephrotoxicity and potential exacerbating factors. Screening protocols should be developed to identify nephrotoxic effects of medications 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 the measurement of eGFR prior to the prescription of potentially nephrotoxic medications, with electronic warnings for medication interactions and risks. Shared pharmaceutical prescription databases will avoid repeat prescriptions or drug interaction potential. Research should continue to develop effective alternative agents with reduced nephrotoxicity.

To reduce the 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 the 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 on kidney disease, and learn about potentially beneficial remedies. The public and health care workers (HCWs) must be educated about nephrotoxicity and drug interactions relevant to herbal remedies and over-the-counter preparations.[87] Clinicians should be encouraged to ask about alternative remedy use. A global free web–based adverse event reporting site (across income settings) 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 the accuracy of advertising and health claims touted on the Internet and require efficacy data similar to that required for pharmaceuticals. Policies should enforce minimum standards of safety, manufacturing, labeling, and adverse event reporting on the alternative remedy industry.

Kidney stones and CKD risk

Kidney stone disease is now recognized as a chronic health condition that is associated with CKD and ESKD risks.[88–92] The association between kidney stones and CKD is partly explained by shared risk factors such as diabetes,[93–95] obesity,[96,97] hypertension,[94,97,98] metabolic syndrome,[99,100] and CVD.[101–103] However, kidney stones may also directly contribute to the development and progression of CKD via urinary tract obstruction and/or infection, nephrocalcinosis, and oxalate nephropathy.[88,104,105] The worldwide prevalence of kidney stones among adults is 5% to 9% and is apparently increasing, with variations between regions and countries.[106,107] 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).[90,97,105,107] Individuals who have experienced a single stone event are at an increased risk for a symptomatic stone recurrence (up to 50% within the first 5 years).[105] Therefore, prevention among these individuals is an important strategy to reduce further stone formation and CKD risks.[90] Higher fluid intake, avoidance of low dietary calcium and sweetened beverages and the reduction of dietary sodium and red meat intake reduce stone formation risk.[108–110]

Gaps. A 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 a better understanding of the impact of stone prevention strategies (lifestyle habits and medication) and treatments (e.g., lithotripsy and surgery) on the risks of new-onset and progressive CKD. Health care costs for kidney stone disease require further studies. The effectiveness and cost-effectiveness of prevention strategies across populations are unknown.

Action strategies. Tracking mechanisms and research should be developed to determine the relationships between kidney stones and the incidence, prevalence, progression, and complications of CKD in regional contexts. Environmental or occupational hotspots should be detected through surveillance. Understanding stone types and risk factors (e.g., genetics, infections, and diet) are important to inform local prevention strategies. Together with public health care strategies to reduce diabetes, hypertension, and obesity, surveillance activities should include impact on the rates of kidney stones and those of stone-related CKD to identify high-risk groups for targeted prevention and cost-effectiveness.[90] In areas with a high risk for stone formation, public and HCW education campaigns should increase awareness and emphasize simple prevention strategies (e.g., fluid intake and dietary modification). Where occupational exposure is detected as important, engagement with policy makers and employers is important to modify work conditions.[111]

Maternal, fetal, and childhood health as CKD risk factors

Low birth weight (LBW), small for gestational age, and preterm birth (PTB) impact the number of nephrons an individual starts life with and are increasingly being recognized as CKD risk factors.[112,113] In 2010, over 43 million babies in 139 LMICs were born too soon or too small, suggesting many children are born with a CKD risk.[114] 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.[112] Recent evidence also indicates high birth weight (especially an infant of a diabetic mother), in addition to LBW and PTB, to be a risk factor for obesity, hypertension, diabetes, and CKD.[115–119] Early onset of diabetes in offspring exposed to diabetes *in utero* in part explains the higher CKD risk in these individuals.[115,120] Childhood obesity is also an important risk amplifier for CKD after LBW, small for gestational age, or PTB.[121] Preterm babies are at an increased risk for AKI related to reduced nephron number, frequent nephrotoxin exposure, and comorbidities, which increase their subsequent CKD risk.[122,123] Not only the children of troubled pregnancies are at long-term risk of CKD, however. Women who develop pre-eclampsia/eclampsia have a higher life-time risk of hypertension, CKD, and CVD, and those who experience gestational diabetes mellitus have an increased risk for developing diabetes.[124–126] Preeclampsia occurs in 1% to 5% of pregnancies worldwide, and gestational diabetes mellitus occurs in around 2% to 6% of pregnancies in Europe, but in up to 25% in some LMICs.[125–127] Many individuals at a long-term CKD risk 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 the impact of 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 high birth weight on CKD risk has rarely been studied. Better methods to screen for and treat preeclampsia and its consequences require further studies.

Action strategies. The impact of fetal and early life development on the risk of adult NCDs is underappreciated. Monitoring the incidence of LBW, high birth weight, PTB, and fetal growth restriction is required to understand the burden with regard to the 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 LMICs.[114,128] Similarly, neonatal AKI should also be documented as a future CKD risk factor and should 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, gestational diabetes mellitus, and preeclampsia for mother and child. Both require early and ongoing education on healthy lifestyles and lifelong follow-up. Engagement with mothers, communities, traditional birth attendants, and HCW is important to encourage optimal feeding of LBW, high birth weight, small for gestational age, and preterm children to ensure healthy growth while avoiding obesity. Ensuring access to essential health care 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 and sustainable development goals, most countries have some form of data reporting or monitoring.[129] Policies should not focus only on maternal health during pregnancy and at delivery but should also include access to family planning, equity, and education for women, reduction of poverty, and access to better nutrition. Monitoring 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.[130] Such programs should be utilized to improve documentation of birth circumstances, maternal preeclampsia, or gestational diabetes mellitus, thereby identifying individuals who require long-term follow-up and to initiate lifestyle education peripartum. In LMICs, engagement with traditional birth attendants is important to build trust and educate them to detect and refer problem cases. Women with preeclampsia should undergo long-term follow-up to determine the impact of interventions to reduce long-term CVD and CKD risks.

Infections as CKD risk factors

CKD and AKI are considered as NCDs, but infections are an important cause of both conditions, especially in LMICs. Infections are also a common cause of AKI worldwide.[64,131,132] The three diseases, namely HIV, malaria, and tuberculosis (TB), that received much attention under the millennium development goals can cause CKD. In 2015, 36.7 million people were living with HIV.[133] The risk of HIV nephropathy (HIVAN) varies from <10% to almost 50% in Africa.[134] HIVAN is a well-recognized form of CKD that can be prevented and treated with access to effective antiretroviral therapy.[134,135] However, the impact of antiretroviral therapy on kidney disease is not straightforward. Although antiretroviral therapy 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.[134] Antiretroviral therapy does not reduce the incidence and/or rate of progression of non-HIVAN forms of CKD.[134] Kidney disease prevention in HIV infection is also affected by comorbidities such as diabetes and viral hepatitis and therefore requires additional management and health screening programs.[134,135] In 2015, 241 million cases of malaria were reported worldwide. AKI secondary to malaria occurs in up to 40% of adults with severe infection.[136] Although kidney function typically recovers in survivors, severe AKI may eventually lead to CKD.[136–138] A Sri Lankan study also reported an association of malaria with CKD of unknown cause.[139] Malaria-associated AKI can be prevented by widespread vector control, use of insecticide-treated bed nets, and access to rapid diagnosis and treatment.[136] In 2014, 9.6 million people became infected with TB.[140,141] Genitourinary TB may be a cause of CKD through miliary involvement or urinary obstruction and may occur in 27% of cases with extrapulmonary TB.[142,143] 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. CKD risk among adults with impetigo is high, strongly supporting proactive prevention and early treatment of skin infections as a possible means to reduce CKD risk.[144] The worldwide prevalence of hepatitis B (HBV) was 331 million people in 2013 and that of hepatitis C was 148 million.[145] The global risk of HBV-associated CKD is likely to be under 10%, whereas the risk of hepatitis C-associated CKD is likely to be higher.[146,147] HBV- and hepatitis C-associated CKD may be unrecognized contributors to chronic glomerulonephritis, which is a leading cause of ESKD in LMICs. Other infections such as leptospirosis and schistosomiasis are neglected tropical diseases associated with CKD.[137,148] Given the direct associations among 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 care interventions could reduce the CKD burden needs to be further studied. 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 the 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.[149] 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 care 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 associated with infections to support prompt diagnosis, institution of i.v. fluids and antibiotics, and avoidance of nonsteroidal antiinflammatory drugs and other nephrotoxins. Governments should suppress the use of counterfeit drugs, which contribute to increasing disease severity and risk of AKI in infections.

AKI as a CKD risk factor

Worldwide, approximately 20% of patients admitted to hospitals develop AKI.[150] This statistic is largely derived from high-income countries where the majority of AKI is hospital acquired. The true AKI incidence in LMICs is less well known but is likely at least as high.[150,151] Worldwide, it is estimated that 2 million people die of AKI annually.[152] The number of AKI survivors is unknown, and a considerable proportion will develop CKD.[153–155]

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

Action strategies. Regionally adapted strategies should be promoted to avoid AKI. Given that most AKI cases in high-income countries are hospital acquired, efforts to reduce AKI incidence should focus on increasing awareness among clinicians and encouraging proactive patient management. Strategies may include electronic medical record alerts for AKI risk and medication prescriptions.[68,69,156] In LMICs, the majority of AKI cases are community acquired, suggesting that prevention should start before hospital admission. Strategies include implementation of public health care measures to reduce the 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 health care and medication. Education campaigns should be conducted in communities and among HCWs to increase awareness of AKI risk, avoid nephrotoxins, and seek health care promptly.[157] Once patients present to a hospital, guidelines and facilities should be available to institute an appropriate therapy. Long-term follow-up of patients with AKI is required to determine the true burden of subsequent CKD and potential risk modifiers.

Conclusions

Morbidity and mortality owing to CKD are increasing worldwide, and CKD is progressively being recognized as an important contributor to the global burden of the disease.[1,8] Major contributors to the CKD burden are the growing frequencies of diabetes, hypertension, and obesity, which are well-established traditional risk factors for CKD. Public health care policies directed to address many lifestyle factors that contribute to these conditions are expected to positively impact CKD risk. 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 nontraditional 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 nontraditional risk factors may predominate in LMICs. The impact of reducing nontraditional CKD risk factors requires further studies. Mitigation of nontraditional CKD risk factors will require advocacy efforts to support policy development, implementation of strategies to reduce disparities, improve access to essential health care and maternal and child health, reduce environmental exposures, prevent AKI, better understand traditional remedy use, and prevent infections.[2,3,158] Race-ethnicity, genetics, sex, socioeconomic status, and geography likely modify the impact of CKD risk factors. Effective coordination within health care systems, and importantly in the era of the sustainable development goals, 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.

DISCLOSURE

KRT declared consulting fees from Eli Lily and Company, Boehringer Ingelheim, and Gilead and grant support from National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Patient-Centered Outcomes Research Institute, and Health Sciences and Services Administration of Washington State. GGG declared consulting fees from Pisa Farmaceutica. MBG declared lecture fees from Amgen, B. Braun, Leo Pharma, Novartis, Novo-Nordisk, Promopharm, Roche, Sanofi, Servier, Sophadial, and Sothema. HJLH declared consulting fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck; lecture fees from AstraZeneca; and grant support from Boehringer Ingelheim. DWJ declared consulting fees from AstraZeneca; lecture fees from Baxter Healthcare, Fresenius, and Medical Care; and support from Baxter Extramural and Clinical Evidence Council grants. ZAM declared lecture fees from Amgen and Genzyme; grant support from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Genzyme (a Sanofi Company), Eli Lilly and Company, and Otsuka; as well as government research grant support for the CKD REIN PROJECT and additional support for clinical and experimental works from AMGEN, Bayer, Merck Sharp and Dohme, and Genzyme. OM declared consulting fees from Allena and Adelyx; grant support from National Institutes of Health, American Heart Association, and Department of Defense; and is named as a coinventor of effervescent calcium magnesium citrate and synthetic antiKlotho antibodies. DCW declared consulting fees from Amgen, Boehringer Ingelheim, Akebia, Union Chimique Belge Celltech, Bristol-Myers Squibb, Vifor Fresenius, Otsuka, Janssen, Alberta Innovates Health Solutions, AstraZeneca, and Bio Nano; lecture fees from Fresenius, Amgen, Janssen, ZS Pharma, and Vifor Fresenius; and grant support from British Heart Foundation, Healthcare Quality Improvement Partnership, Kidney Research UK, National Institute for Health Research, and Australian National Health & Medical Research Council. All the other authors declared no competing interests.

Publication of this article was supported by the International Society of Nephrology.

ACKNOWLEDGMENTS

The manuscript emerged as an individual product of the Global Kidney Health Summit held in Vancouver, Canada in July 2016. Support of the summit was made possible through unrestricted grants from various organizations in addition to the International Society of Nephrology. These include (in alphabetical order) AbbVie Inc, Akebia Therapeutics Inc., Amgen, AstraZeneca LP, Boehringer Ingelheim-Lilly, Danone Nutricia Research, Janssen Canada, Merck Global, and Regulus Therapeutics Inc.

REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1459–1544.
2. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int*. 2011;80:1258–1270.
3. Garcia-Garcia G, Jha V, World Kidney Day Steering Committee. CKD in disadvantaged populations. *Kidney Int*. 2015;87:251–253.
4. Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy [e-pub ahead of print]. *Lancet*. http://dx.doi.org/10.1016/S0140-6736(17)30788-2. Accessed May 1, 2017.

5. Lunyera J, Mohottige D, Von Isenburg M, et al. CKD of uncertain etiology: a systematic review. *Clin J Am Soc Nephrol*. 2016;11:379–385.
6. Garcia-Trabanino R, Jarquin E, Wesseling C, et al. Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador–A cross-shift study of workers at risk of Mesoamerican nephropathy. *Environ Res*. 2015;142:746–755.
7. Institute for Health Metrics and Evaluation [IHME]. GBD Data Visualisations. 2015. Available at: http://www.healthdata.org/gbd/data-visualizations. Accessed December 16, 2016.
8. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1603–1658.
9. Raines N, Gonzalez M, Wyatt C, et al. Risk factors for reduced glomerular filtration rate in a Nicaraguan community affected by Mesoamerican nephropathy. *MEDICC Rev*. 2014;16:16–22.
10. Cerdas M. Chronic kidney disease in Costa Rica. *Kidney Int Suppl*. 2005;(97):S31–S33.
11. Orantes CM, Herrera R, Almaguer M, et al. Epidemiology of chronic kidney disease in adults of Salvadoran agricultural communities. *MEDICC Rev*. 2014;16:23–30.
12. Quinteros E, Ribo A, Mejia R, et al. Heavy metals and pesticide exposure from agricultural activities and former agrochemical factory in a Salvadoran rural community. *Environ Sci Pollut Res Int*. 2017;24:1662–1676.
13. Wanigasuriya K. Update on uncertain etiology of chronic kidney disease in Sri Lanka's north-central dry zone. *MEDICC Rev*. 2014;16:61–65.
14. Jha V. Current status of end-stage renal disease care in India and Pakistan. *Kidney Int Suppl*. 2013;3:157–160.
15. World Health Organization. STEPwise approach to surveillance (STEPS) 2002. Available at: http://www.who.int/chp/steps/en/. Accessed December 12, 2016.
16. Riley L, Guthold R, Cowan M, et al. The World Health Organization STEPwise approach to noncommunicable disease risk-factor surveillance: methods, challenges, and opportunities. *Am J Public Health*. 2016;106:74–78.
17. PAHO/WHO. PAHO/WHO Stepwise Approach to Chronic Non Communicable Diseases Risk-Factor Surveillance. Available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=1923%3A2009-stepwise-approach&catid=1384%3Asurveillance&Itemid=1670&lang=en. Accessed August 20, 2016.
18. Rios Bruno P, Schwedt E, Solá Schnir L, et al. Importance of preventive medical examination for early diagnosis of renal disease in Uruguay - The National Renal Health Program. *Arch Med Interna*. 2015;37:114–121.
19. Komenda P, Rigatto C, Tangri N. Screening strategies for unrecognized CKD. *Clin J Am Soc Nephrol*. 2016;11:925–927.
20. Wegman D, Crowe J, Hogstedt C, et al. Mesoamerican nephropathy: report from the Second International Research Workshop on MeN. Available at: https://www.researchgate.net/publication/312526028_Mesoamerican_nephropathy_Report_from_the_second_international_research_workshop_on_MeN. Accessed December 12, 2016.
21. Hung DY, Rundall TG, Tallia AF, et al. Rethinking prevention in primary care: applying the chronic care model to address health risk behaviors. *Milbank Q*. 2007;85:69–91.
22. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. 2013. Available at: http://www.who.int/nmh/events/ncd_action_plan/en/. Accessed August 20, 2016.
23. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–450.
24. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781.
25. International Diabetes Federation. IDF Diabetes Atlas, 7th ed. 2015. Available at: http://www.diabetesatlas.org/. Accessed December 12, 2016.
26. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*. 2016;67(suppl 1):Svii. S1–305.
27. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;63:225–232.
28. White S, Chadban S. Diabetic kidney disease in Australia: current burden and future projections. *Nephrology (Carlton)*. 2014;19:450–458.
29. Ghosh-Dastidar B, Cohen D, Hunter G, et al. Distance to store, food prices, and obesity in urban food deserts. *Am J Prev Med*. 2014;47:587–595.
30. Gutierrez OM. Contextual poverty, nutrition, and chronic kidney disease. *Adv Chronic Kidney Dis*. 2015;22:31–38.
31. Rebholz CM, Anderson CA, Grams ME, et al. Relationship of the American Heart Association's impact goals (life's simple 7) with risk of chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) Cohort Study. *J Am Heart Assoc*. 2016;5:e003192.
32. Freudenberg N. Healthy-food procurement: using the public plate to reduce food insecurity and diet-related diseases. *Lancet Diabetes Endocrinol*. 2016;4:383–384.
33. Crews DC, Kuczmarski MF, Grubbs V, et al. Effect of food insecurity on chronic kidney disease in lower-income Americans. *Am J Nephrol*. 2014;39:27–35.
34. Crews DC, Kuczmarski MF, Miller ER 3rd, et al. Dietary habits, poverty, and chronic kidney disease in an urban population. *J Ren Nutr*. 2015;25:103–110.
35. Suarez JJ, Isakova T, Anderson CA, et al. Food access, chronic kidney disease, and hypertension in the U.S. *Am J Prev Med*. 2015;49:912–920.
36. Manuel DG, Perez R, Sanmartin C, et al. Measuring burden of unhealthy behaviours using a multivariable predictive approach: life expectancy lost in canada attributable to smoking, alcohol, physical inactivity, and diet. *PLoS Med*. 2016;13:e1002082.
37. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Am J Kidney Dis*. 2014;64:510–533.
38. Stenvinkel P, Zoccali C, Ikizler TA. Obesity in CKD–what should nephrologists know? *J Am Soc Nephrol*. 2013;24:1727–1736.
39. Jun M, Hemmelgarn BR. Strategies for BP control in developing countries and effects on kidney function. *Clin J Am Soc Nephrol*. 2016;11:932–934.
40. Jafar TH, Allen JC, Jehan I, et al. Health education and general practitioner training in hypertension management: long-term effects on kidney function. *Clin J Am Soc Nephrol*. 2016;11:1044–1053.
41. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520.
42. Accord Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. *Diabetes Care*. 2016;39:701–708.
43. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014;371:1392–1406.
44. World Health Organization. Health in all policies: Helsinki statement. Framework for country action. 2014. Available at: http://apps.who.int/iris/bitstream/10665/112636/1/9789241506908_eng.pdf?ua=1. Accessed August 31, 2016.
45. Mozaffarian D, Afshin A, Benowitz NL, et al. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1514–1563.
46. PAHO/WHO. Pan American Health Organization. Regional consultation: priorities for cardiovascular health in the Americas. Key messages for policymakers. 2011. Available at: http://www1.paho.org/priorities/pdf-en/book.pdf. Accessed August 20, 2016.
47. Frieden TR. Sodium reduction–saving lives by putting choice into consumers' hands. *JAMA*. 2016;316:579–580.
48. World Health Organization. Prevention of Cardiovascular Disease. Guidelines for assessment and management of cardiovascular risk. 2007. Available at: http://apps.who.int/iris/bitstream/10665/43685/1/9789241547178_eng.pdf. Accessed December 16, 2016.
49. Institute of Medicine [IOM]. Sodium Intake in Populations: Assessment of Evidence. 2013. Available at: http://www.nap.edu/catalog/18311/sodium-intake-in-populations-assessment-of-evidence. Accessed August 20, 2016.
50. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk–measurement matters. *N Engl J Med*. 2016;375:580–586.
51. Cappuccio FP, Graudal N. Pro: Reducing salt intake at population level: is it really a public health priority? *Nephrol Dial Transplant*. 2016;31:1392–1396.
52. Graudal N, Cappuccio FP. Con: Reducing salt intake at the population level: is it really a public health priority? *Nephrol Dial Transplant*. 2016;31:1398–1403.

53. He FJ, MacGregor GA. Hypertension: salt: flawed research should not divert actions to reduce intake. *Nat Rev Nephrol*. 2016;12: 514–515.
54. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet*. 2016;388:465–475.
55. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med*. 2014;371:601–611.
56. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612–623.
57. Keyzer CA, van Breda GF, Vervloet MG, et al. Effects of vitamin D receptor activation and dietary sodium restriction on residual albuminuria in CKD: the ViRTUE-CKD trial. *J Am Soc Nephrol*. 2017;28: 1296–1305.
58. He FJ, Pombo-Rodrigues S, Macgregor GA. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. *BMJ Open*. 2014;4:e004549.
59. Narayan KM, Echouffo-Tcheugui JB, Mohan V, Ali MK. Global prevention and control of type 2 diabetes will require paradigm shifts in policies within and among countries. *Health Aff (Millwood)*. 2012;31:84–92.
60. Peprah E, Lopez-Class M, Shero S, et al. A global perspective on using implementation research to address hypertension-associated target organ damage. *Ethn Dis*. 2016;26:395–398.
61. Brouwer ED, Watkins D, Olson Z, et al. Provider costs for prevention and treatment of cardiovascular and related conditions in low- and middle-income countries: a systematic review. *BMC Public Health*. 2015;15:1183.
62. Mehta RL, Awdishu L, Davenport A, et al. Phenotype standardization for drug-induced kidney disease. *Kidney Int*. 2015;88:226–234.
63. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. *Crit Care Med*. 2008;36(suppl 4):S216–S223.
64. Mehta RL, Burdmann EA, Cerda J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. *Lancet*. 2016;387:2017–2025.
65. Rhone ET, Carmody JB, Swanson JR, Charlton JR. Nephrotoxic medication exposure in very low birth weight infants. *J Matern Fetal Neonatal Med*. 2014;27:1485–1490.
66. Perazella MA, Izzedine H. New drug toxicities in the onco-nephrology world. *Kidney Int*. 2015;87:909–917.
67. Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. *Pediatrics*. 2013;132:e756–e767.
68. Kashani K, Herasevich V. Utilities of electronic medical records to improve quality of care for acute kidney injury: past, present, future. *Nephron*. 2015;131:92–96.
69. Perazella MA, Wilson FP. Acute kidney injury: preventing acute kidney injury through nephrotoxin management. *Nat Rev Nephrol*. 2016;12: 511–512.
70. McCoy AB, Waitman LR, Gadd CS, et al. A computerized provider order entry intervention for medication safety during acute kidney injury: a quality improvement report. *Am J Kidney Dis*. 2010;56:832–841.
71. Goldstein SL, Mottes T, Simpson K, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. *Kidney Int*. 2016;90:212–221.
72. Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. *J Pediatr*. 2014;165:522–557.e2.
73. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med*. 2016;176:238–246.
74. Moledina DG, Perazella MA. Proton pump inhibitors and CKD. *J Am Soc Nephrol*. 2016;27:2926–2928.
75. Radhakrishnan J, Perazella MA. Drug-induced glomerular disease: attention required! *Clin J Am Soc Nephrol*. 2015;10:1287–1290.
76. Luyckx VA. Nephrotoxicity of alternative medicine practice. *Adv Chronic Kidney Dis*. 2012;19:129–141.
77. Luyckx VA, Naicker S. Acute kidney injury associated with the use of traditional medicines. *Nat Clin Pract Nephrol*. 2008;4:664–671.
78. Frass M, Strassl RP, Friehs H, et al. Use and acceptance of complementary and alternative medicine among the general population and medical personnel: a systematic review. *Ochsner J*. 2012;12:45–56.
79. De Smet PA. Herbal medicine in Europe–relaxing regulatory standards. *N Engl J Med*. 2005;352:1176–1178.
80. Stanifer JW, Patel UD, Karia F, et al. The determinants of traditional medicine use in Northern Tanzania: a mixed-methods study. *PloS One*. 2015;10:e0122638.
81. Hsieh CF, Huang SL, Chen CL, et al. Non-aristolochic acid prescribed Chinese herbal medicines and the risk of mortality in patients with chronic kidney disease: results from a population-based follow-up study. *BMJ Open*. 2014;4:e004033.
82. Lin MY, Chiu YW, Chang JS, et al. Association of prescribed Chinese herbal medicine use with risk of end-stage renal disease in patients with chronic kidney disease. *Kidney Int*. 2015;88:1365–1373.
83. Hu YW. Chinese herbal medicine use and risk of end-stage renal disease in patients with chronic kidney disease: is there an immortal time bias? *Kidney Int*. 2016;90:227–228.
84. Chen T, Zhan L, Fan Z, et al. Efficacy of Chinese herbal medicine as an adjunctive therapy on in-hospital mortality in patients with acute kidney injury: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2016;2016:7592705.
85. Colombo D, Lunardon L, Bellia G. Cyclosporine and herbal supplement interactions. *J Toxicol*. 2014;2014:145325.
86. Lai MN, Lai JN, Chen PC, et al. Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: a population-based case-control study. *Am J Kidney Dis*. 2010;55:507–518.
87. Shaw D, Graeme L, Pierre D, et al. Pharmacovigilance of herbal medicine. *J Ethnopharmacol*. 2012;140:513–518.
88. Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. *Curr Opin Nephrol Hypertens*. 2013;22:390–396.
89. Rule AD, Bergstralh EJ, Melton LJ 3rd, et al. Kidney stones and the risk for chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:804–811.
90. Scales CD Jr, Tasian GE, Schwaderer AL, et al. Urinary stone disease: advancing knowledge, patient care, and population health. *Clin J Am Soc Nephrol*. 2016;11:1305–1312.
91. Shoag J, Halpern J, Goldfarb DS, Eisner BH. Risk of chronic and end stage kidney disease in patients with nephrolithiasis. *J Urol*. 2014;192: 1440–1445.
92. El-Zoghby ZM, Lieske JC, Foley RN, et al. Urolithiasis and the risk of ESRD. *Clin J Am Soc Nephrol*. 2012;7:1409–1415.
93. Daudon M, Jungers P. Diabetes and nephrolithiasis. *Curr Diab Rep*. 2007;7:443–448.
94. Lieske JC, de la Vega LS, Gettman MT, et al. Diabetes mellitus and the risk of urinary tract stones: a population-based case-control study. *Am J Kidney Dis*. 2006;48:897–904.
95. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int*. 2005;68:1230–1235.
96. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA*. 2005;293:455–462.
97. Obligado SH, Goldfarb DS. The association of nephrolithiasis with hypertension and obesity: a review. *Am J Hypertens*. 2008;21:257–264.
98. Strazzullo P, Barba G, Vuotto P, et al. Past history of nephrolithiasis and incidence of hypertension in men: a reappraisal based on the results of the Olivetti Prospective Heart Study. *Nephrol Dial Transplant*. 2001;16: 2232–2235.
99. West B, Luke A, Durazo-Arvizu RA, et al. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988-1994. *Am J Kidney Dis*. 2008;51: 741–747.
100. Jeong IG, Kang T, Bang JK, et al. Association between metabolic syndrome and the presence of kidney stones in a screened population. *Am J Kidney Dis*. 2011;58:383–388.
101. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and cardiovascular events: a cohort study. *Clin J Am Soc Nephrol*. 2014;9: 506–512.
102. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. *JAMA*. 2013;310:408–415.
103. Rule AD, Roger VL, Melton LJ 3rd, et al. Kidney stones associate with increased risk for myocardial infarction. *J Am Soc Nephrol*. 2010;21: 1641–1644.
104. Moe OW. Kidney stones: pathophysiology and medical management. *Lancet*. 2006;367:333–344.
105. Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. *Nat Rev Dis Primers*. 2016;2:16008.
106. Lopez M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. *Pediatr Nephrol*. 2010;25:49–59.

107. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol*. 2010;12:e86–e96.
108. Cheungpasitporn W, Rossetti S, Friend K, et al. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. *J Nephrol*. 2016;29:211–219.
109. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med*. 2002;346:77–84.
110. Prezioso D, Strazzullo P, Lotti T, et al. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU Working Group. *Arch Ital Urol Androl*. 2015;87:105–120.
111. Lotan Y, Antonelli J, Jimenez IB, et al. The kidney stone and increased water intake trial in steel workers: results from a pilot study. *Urolithiasis*. 2017;45:177–183.
112. Luyckx VA, Brenner BM. Birth weight, malnutrition and kidney-associated outcomes–a global concern. *Nat Rev Nephrol*. 2015;11:135–149.
113. White SL, Perkovic V, Cass A, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis*. 2009;54:248–261.
114. Lee ACC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health*. 2013;1:e26–e36.
115. Pavkov ME, Hanson RL, Knowler WC, et al. Effect of intrauterine diabetes exposure on the incidence of end-stage renal disease in young adults with type 2 diabetes. *Diabetes Care*. 2010;33:2396–2398.
116. de Jong F, Monuteaux MC, van Elburg RM, et al. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension*. 2012;59:226–234.
117. Mu M, Wang SF, Sheng J, et al. Birth weight and subsequent blood pressure: a meta-analysis. *Arch Cardiovasc Dis*. 2012;105:99–113.
118. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA*. 2008;300:2886–2897.
119. Cnattingius S, Villamor E, Lagerros YT, et al. High birth weight and obesity-a vicious circle across generations. *Int J Obes (Lond)*. 2012;36:1320–1324.
120. Pavkov ME, Bennett PH, Knowler WC, et al. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA*. 2006;296:421–426.
121. Abitbol CL, Rodriguez MM. The long-term renal and cardiovascular consequences of prematurity. *Nat Rev Nephrol*. 2012;8:265–274.
122. Selewski DT, Charlton JR, Jetton JG, et al. Neonatal acute kidney injury. *Pediatrics*. 2015;136:e463–e473.
123. Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis*. 2012;59:523–530.
124. Vikse BE. Pre-eclampsia and the risk of kidney disease. *Lancet*. 2013;382:104–106.
125. Paauw ND, Luijken K, Franx A, et al. Long-term renal and cardiovascular risk after preeclampsia: towards screening and prevention. *Clin Sci (Lond)*. 2016;130:239–246.
126. Damm P, Houshmand-Oeregaard A, Kelstrup L, et al. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia*. 2016;59:1396–1399.
127. Kanguru L, Bezawada N, Hussein J, Bell J. The burden of diabetes mellitus during pregnancy in low- and middle-income countries: a systematic review. *Glob Health Action*. 2014;7:23987.
128. World Health Organisation. Global nutrition targets 2025: low birth weight policy brief (WHO/NMH/NHD/14.5). 2014. Available at: http://www.who.int/nutrition/publications/globaltargets2025_policybrief_lbw/en/. Accessed August 20, 2016.
129. Nations U. Sustainable Development Goals. 2015. Available at: http://www.un.org/sustainabledevelopment/news/communications-material/. Accessed December 16, 2016.
130. Hodgins S, Tielsch J, Rankin K, et al. A new look at care in pregnancy: simple, effective interventions for neglected populations. *PloS One*. 2016;11:e0160562.
131. Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. *Lancet*. 2013;382:170–179.
132. Kayange NM, Smart LR, Tallman JE, et al. Kidney disease among children in sub-Saharan Africa: systematic review. *Pediatr Res*. 2015;77:272–281.
133. UNAIDS. Global AIDS update 2016. 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf. Accessed September 1, 2016.
134. Rosenberg AZ, Naicker S, Winkler CA, Kopp JB. HIV-associated nephropathies: epidemiology, pathology, mechanisms and treatment. *Nat Rev Nephrol*. 2015;11:150–160.
135. Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59:e96–e138.
136. White NJ, Pukrittayakamee S, Hien TT, et al. Malaria. *Lancet*. 2014;383:723–735.
137. Jha V, Prasad N. CKD and infectious diseases in Asia Pacific: challenges and opportunities. *Am J Kidney Dis*. 2016;68:148–160.
138. Ehrich JH, Eke FU. Malaria-induced renal damage: facts and myths. *Pediatr Nephrol*. 2007;22:626–637.
139. Siriwardhana EA, Perera PA, Sivakanesan R, et al. Dehydration and malaria augment the risk of developing chronic kidney disease in Sri Lanka. *Indian J Nephrol*. 2015;25:146–151.
140. GBD 2013 Risk Factors Collaborators, Forouzanfar MH, Alexander L, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:2287–2323.
141. World Health Organization. Global Tuberculosis Report 2015. 2015. Available at: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1. Accessed September 1, 2016.
142. Daher Ede F, da Silva GB Jr, Barros EJ. Renal tuberculosis in the modern era. *Am J Trop Med Hyg*. 2013;88:54–64.
143. de Oliveira JL, da Silva Junior GB, Daher Ede F. Tuberculosis-associated chronic kidney disease. *Am J Trop Med Hyg*. 2011;84:843–844.
144. Hoy WE, White AV, Dowling A, et al. Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. *Kidney Int*. 2012;81(10):1026–1032.
145. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:743–800.
146. Gupta A, Quigg RJ. Glomerular diseases associated with hepatitis B and C. *Adv Chronic Kidney Dis*. 2015;22:343–351.
147. Azmi AN, Tan SS, Mohamed R. Hepatitis C and kidney disease: an overview and approach to management. *World J Hepatol*. 2015;7:78–92.
148. Barsoum RS, Esmat G, El-Baz T. Human schistosomiasis: clinical perspective: review. *J Adv Res*. 2013;4:433–444.
149. Liao MT, Chang MH, Lin FG, et al. Universal hepatitis B vaccination reduces childhood hepatitis B virus-associated membranous nephropathy. *Pediatrics*. 2011;128:e600–e604.
150. Mehta RL, Cerda J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet*. 2015;385:2616–2643.
151. Cerda J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nat Clin Pract Nephrol*. 2008;4:138–153.
152. Li PK, Burdmann EA, Mehta RL. World Kidney Day 2013: acute kidney injury-global health alert. *Am J Kidney Dis*. 2013;61:359–363.
153. Greenberg JH, Coca S, Parikh CR. Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review. *BMC Nephrol*. 2014;15:184.
154. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*. 2012;81:442–448.
155. Pannu N, James M, Hemmelgarn B, Klarenbach S. Alberta Kidney Disease Network. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin J Am Soc Nephrol*. 2013;8:194–202.
156. Lewington AJ, Cerda J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int*. 2013;84:457–467.
157. Evans R, Rudd P, Hemmila U, et al. Deficiencies in education and experience in the management of acute kidney injury in Malawian healthcare workers. *Malawi Med J*. 2015;27:101–103.

158. Garcia-Garcia G. Poverty: the common denominator of CKD's global threat. *MEDICC Rev*. 2014;16:83.
159. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016;387:1377–1396.
160. Chang AR, Chen Y, Still C, et al. Bariatric surgery is associated with improvement in kidney outcomes. *Kidney Int*. 2016;90:164–171.
161. D'Agati VD, Chagnac A, de Vries AP, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. *Nat Rev Nephrol*. 2016;12:453–471.
162. Abaci O, Harmankaya O, Kocas B, et al. Long-term follow-up of patients at high risk for nephropathy after contrast exposure. *Angiology*. 2015;66:514–518.
163. World Health Organization. Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity. 2016. Available at: http://apps.who.int/iris/bitstream/10665/206549/1/9789241565332_eng.pdf?ua=1. Accessed December 1, 2016.
164. Olowu WA, Niang A, Osafo C, et al. Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review. *Lancet Glob Health*. 2016;4:e242–e250.
165. Skjaerven R, Wilcox AJ, Klungsoyr K, et al. Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study. *BMJ*. 2012;345:e7677.
166. Abalos E, Cuesta C, Carroli G, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*. 2014;121(suppl 1):14–24.
167. Rodriguez-Iturbe B, Haas M. Post-streptococcal glomerulonephritis. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. Oklahoma City, OK: University of Oklahoma Health Sciences Center; 2016. Available at: https://www.ncbi.nlm.nih.gov/books/NBK333429/. Accessed December 15, 2016.
168. Barsoum RS. Urinary schistosomiasis: review. *J Adv Res*. 2013;4:453–459.
169. Barsoum RS. End-stage renal disease in North Africa. *Kidney Int Suppl*. 2003;83:S111–S114.
170. Costa F, Hagan JE, Calcagno J, et al. Global morbidity and mortality of leptospirosis: a systematic review. *PLoS Negl Trop Dis*. 2015;9:e0003898.
171. Wesseling C, Aragon A, Gonzalez M, et al. Kidney function in sugarcane cutters in Nicaragua - a longitudinal study of workers at risk of Mesoamerican nephropathy. *Environ Res*. 2016;147:125–132.