Preventing chronic kidney disease and maintaining kidney health: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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To date, the primary focus of chronic kidney disease (CKD) care has been on managing disease progression, complications, and kidney failure. In contrast, maintaining kidney health and preventing CKD have received limited attention, despite their potential to save millions of lives, reduce health care costs, and lessen environmental burdens. The cardiovascular-kidney-metabolic (CKM) concept frames CKD as part of a complex, high-risk syndrome requiring global risk assessment and multifactorial intervention. CKD incidence along with CKM risk factors may be reduced by a healthy diet, physical activity, and a supportive environment. However, risk for CKD does extend beyond the cardiovascular-metabolic component, and residual risk persists despite healthy lifestyles and treatment of risk factors. *Post hoc* analyses of clinical trials suggest pharmacological interventions, such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, may help to prevent or regress CKD in individuals with type 2 diabetes or obesity. Clinical trials are needed to validate these findings in broader high-risk populations. Personalized strategies to improve kidney health should include CKD risk prediction via targeted testing, genetic or biomarker assessments, shared decision-making, cost considerations, selection of therapeutics, and the potential for adverse effects. The overall goals of CKD prevention should prioritize a lifespan approach to risk evaluation along with safe, efficacious, and accessible interventions to maintain kidney health.

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The primary focus of care for chronic kidney disease (CKD) has been managing progression, complications, and kidney failure after the development of CKD.[1] Maintaining or restoring kidney health has received scant

attention within nephrology or the broader medical community.[1,2] However, promoting kidney health and preventing CKD could save millions of lives and markedly reduce health care costs.

Globally, >800 million individuals live with CKD,[3,4] and >2 million die each year, with one-half of these deaths occurring due to lack of access to kidney replacement therapy (KRT) in the form of dialysis or transplantation.[5–7] The cost of KRT is extraordinarily high,[8] consuming up to 3% of health care budgets in high-income countries (HICs).[5] Approximately 40% of HICs and 70% of low- and middle-income countries (LMICs) do not provide insurance coverage for KRT, resulting in high out-of-pocket costs that can preclude adequate access to lifesaving care.[6,9] Additionally, dialysis, especially hemodialysis, has an unsustainable environmental impact.[10]

The global age-standardized mortality rate of CKD is increasing,[7] and CKD is predicted to be the fifth leading cause of death globally by 2040.[11] Both public health surveillance of CKD and global public health strategies to maintain kidney health are urgently needed.[12] Efforts to address the CKD epidemic require interventions to maintain kidney health because current approaches that only address established CKD are not effectively curbing kidney failure or related conditions[13] such as cardiovascular disease (CVD),[14,15] cancer,[14,16–25] and infection.[18] Indeed, the majority of individuals die from CKD complications before reaching kidney failure.

In December of 2023, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference to assess the state of knowledge related to CKD prevention across the lifespan. At the conference, international experts from multiple health care and scientific disciplines as well as individuals living with kidney disease focused on the evidence regarding primary prevention, considering lifestyle and pharmacologic approaches to prevent CKD onset. The potential for arresting CKD progression or inducing regression was also discussed.

THE CASE FOR KIDNEY HEALTH

In 2023, noncommunicable diseases (NCD), defined by the World Health Organization as CVD, diabetes, cancer, respiratory disease, and mental illness, accounted for 74% of global deaths, with CVD being responsible for 44% of all NCD deaths.[19,20] CKD is a major driver for CVD. The clustering of risk factors including high blood pressure, elevated blood glucose, dyslipidemia, and obesity plays a causal role in the development of life-threatening CVD and CKD.[21,22] The cardiovascular-kidney-metabolic (CKM) health concept emphasizes the importance of recognizing this multifaceted syndrome and the need for comprehensive risk assessment and multifactorial management to maintain health.[14] However, risk for CKD extends beyond a cardiovascular-metabolic component.

Features common to NCD are chronicity and long disease duration, where individuals who develop NCD at a young age are particularly vulnerable to adverse outcomes over time, including premature mortality. The accrual of multiple risk factors and complications accelerates vascular aging and also results in early loss of structure and function in multiple organs.[23] Resulting outcomes include premature morbidity and mortality, frequent hospitalizations, and health care expenditures, as well as reduced societal productivity, negative environmental impact, and poor quality of life.[24–26]

The classification of CKD is risk-based.[1,27,28] In the absence of other markers of kidney damage, CKD is diagnosed based on estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) threshold values[1,27] that associate with increased risks of adverse outcomes. However, the threshold values—eGFR 60 ml/min per 1.73 m^2 and UACR 30 mg/g (3 mg/mmol)—are not normal values in healthy individuals. Data from an analysis of a large Canadian administrative database[29] supports a negative health impact of mildly reduced eGFR in young adults (≤39 yr), highlighting the importance of preserving kidney function at eGFR >90 ml/min per 1.73 m^2 and UACR <30 mg/g (3 mg/mmol). By the time CKD is diagnosed, subclinical kidney injury may have increased UACR >6-fold and diminished the functioning kidney mass by one-half, thus exhausting the kidney's reserve capacity in response to various stressors. This subclinical phase has been termed "the blind spot" in CKD development (Figure 1)[30,31] and represents an opportunity for preventive intervention. Recognition of high risk for CKD during a subclinical stage may allow earlier and more successful interventions, as in recognizing prediabetes prior to development of overt diabetes.[28,32] The term pre-CKD has been proposed as a concept, although use of the term will require a consensus and a definition.[28,32]

IDENTIFYING AND STRATIFYING INDIVIDUALS FOR CKD PREVENTION

Biological, environmental, and individual lifestyle factors affect kidney health. Given the diversity of individual phenotypes, risk factors, and health histories, trajectories and outcomes across the lifespan are heterogeneous (Figure 2).[33]

Risk factors

Risk factors for incident CKD include advanced age, lifestyle factors, metabolic disorders, hypertension, acute kidney injury, inflammatory conditions, low nephron number, and environmental, genetic, and geographical factors, among others (Table 1).[34–54] Metabolic disorders such as obesity, type 2 diabetes mellitus (T2DM), and hypertension account for the majority of CKD cases worldwide.[3] Programs that address metabolic risks of CKD should consider the relevant social determinants of health and address lifestyle factors. Individuals who lack access to adequate housing, good education, healthy food and water supplies, and safe places for physical activity are at risk for obesity, T2DM, and hypertension.[55] Adverse childhood experiences have been correlated with unhealthy behaviors during adolescence and adulthood[56–58] and increased incidence of diabetes[59] and hypertension.[60]

Infections remain a major threat for kidney health, especially in LMICs.[3] Kidneys are highly susceptible to damage from environmental toxins such as heavy metals, pesticides, and unsafe drinking water.[41,61–64] Prolonged exposure to high

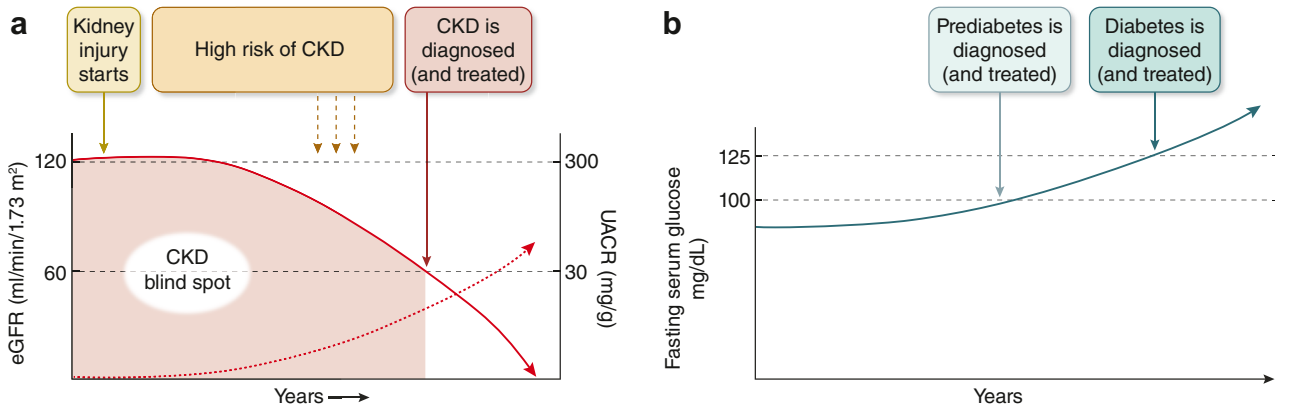

Figure 1 | The blind spot issue was addressed for diabetes by creating the concept of prediabetes. The current diagnostic criteria for chronic kidney disease (CKD) may identify CKD only after years or decades from the initiation of kidney injury, delaying specific therapy for CKD. (**a**) The CKD blind spot refers to the years or decades in which kidney function is not evaluated, monitored, or managed therapeutically. Defining and naming this preclinical condition that refers to high risk of CKD may facilitate understanding and uptake of the concept by diverse health care workers and specialties, akin to the coining of the term *prediabetes*. However, the precise biomarker(s) and cutoffs used to define such a condition have yet to be determined. (**b**) The existence of the prediabetes concept allows diagnosis of a treatable condition years before diabetes develops, enabling primary prevention. Panel (**a**) was adapted from Sanchez-Niño *et al.*[30] Diabetes and prediabetes diagnosis criteria of the American Diabetes Association.[28] eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

heat, especially when combined with inadequate access to water, is associated with kidney injury,[36] making environmental change a critical factor in kidney health. Low nephron endowment at birth, which heightens the lifetime risk of CKD, associates with low birth weight for gestational age, prematurity, adverse intrauterine exposure (e.g., preeclampsia, high levels of maternal blood glucose and blood pressure, and xenobiotics exposure[65,66]), low socioeconomic status, poor nutrition, and childhood illness.[67–69] Nephron number also decreases as a result of aging, nephrectomy, acute kidney injury, and use of nephrotoxic medications. CKD hotspots with endemic CKD of unknown etiology may result from combinations of genetic risk, high temperatures, or exposure to environmental toxins.[34–36,38–44,53,63,64,70,71] These interactions highlight the complex and multifaceted contributors to kidney health disparities in vulnerable populations.

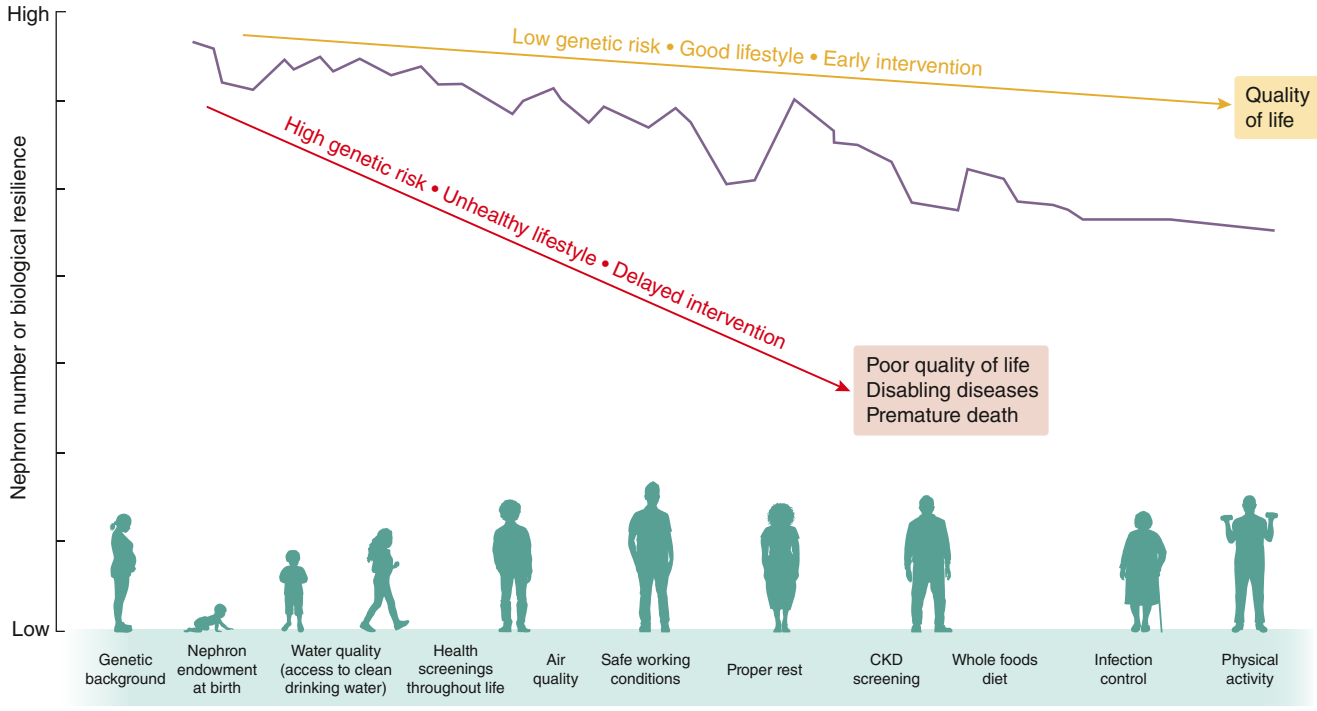

Figure 2 | A conceptual framework summarizing the trends for kidney health during the life course. Adapted from Xie *et al.*[33] CKD, chronic kidney disease.

Table 1 | Risk factors for CKD[1]

Domain	Example conditions
Older age or frailty	Increasing prevalence of metabolic risk factors and hypertension and other insults that impact on decreasing number of nephrons
Nutrition and physical activity level	High intake of salt,[45] red meat and processed foods,[46] sugar-sweetened beverages,[47] and foods with a high glycemic index.[48] Low levels of physical activity among older adults.[49–52]
Metabolic risk factors and hypertension	Hypertension, prediabetes and type 1 or 2 diabetes mellitus, overweight and obesity, cardiovascular disease, adverse intrauterine and childhood experiences (metabolic imprinting, epigenetic factors), and social determinants of health
Inflammatory or infectious disease	Systemic lupus erythematosus, rheumatoid arthritis, HIV, hepatitis B and C, COVID-19, malaria, schistosomiasis, dysentery
Environment, nephrotoxins, iatrogenic	Air and water pollution, increasing drinking water salinity, use of platinum-based chemotherapy, abdominal radiation, cadmium, lead, mercury, polycyclic hydrocarbons, fluoride, microplastics, other nephrotoxic medication (nonsteroidal anti-inflammatory drugs, proton pump inhibitors, long-term lithium use, calcineurin inhibitors), phytotoxin aristolochic acid in Balkan nephropathy[53,54]
Reduced nephron number and structural urinary tract disease	Pregnancy and birth (prematurity, intrauterine growth retardation, preeclampsia/eclampsia, gestational diabetes, prenatal exposures [e.g., drugs, xenobiotics]), nephrectomy or kidney agenesis, CAKUT, previous AKI or AKD, recurrent kidney stones
Genetic and family history of kidney disease	CKD in families (a high genetic risk score), monogenic kidney diseases such as polycystic kidney disease and Alport syndrome, and common genetic variants such as *APOL1* kidney disease
Geographical	Undetermined etiology, such as among agricultural workers in Central America,[34–36] Mexico,[34,35,37–41] Sri Lanka,[42,43] and India[44]
Multifactorial (including social)	Ethnic minorities

AKD, acute kidney disease; AKI, acute kidney injury; *APOL1*, *apolipoprotein L1*; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus.

Screening and case finding

While CKD testing in high-risk groups has become more common during the past decade, the majority of persons with CKD remain unaware of their disease and lack information on how to improve kidney health.[14,72–78] The concept of CKD screening may be expanded beyond identification of existing CKD to also include identifying people at high risk of CKD who may benefit from preventive interventions, analogous to the approach of identifying hypercholesterolemia to address primary CVD prevention.[79] Identification of CKD can be done via screening the general population regardless of known risk, or case finding, referring to testing individuals with known risk factors,[80] such as annual CKD testing in persons with diabetes.[81]

To develop optimal testing strategies, populations at risk should first be identified and characterized with local or regional CKD prevalence studies.[80] Communities could utilize data from local lab databases to examine distributions of eGFR values and determine the frequency of low eGFR by gender (sociocultural factors), sex (biological attributes), age, race, ethnicity, and social determinants of health.[82] For example, Aguascalientes, Mexico, has the highest prevalence globally of advanced CKD in residents aged 20–40 years, 2.3-fold higher than the country with the second-highest prevalence, the United States.[40,83] CKD testing may also be considered in young people with risk factors for low nephron number,[84] because in these groups CKD preventive measures could have substantial impact across the lifespan. Targeted testing that suggests presence of CKD should be followed by confirmational testing.

The benefits of case finding and screening extend beyond prevention of kidney failure to identifying individuals with other CKM conditions, for whom interventions can reduce associated adverse health outcomes such as CVD and mortality.[85–87] Additional research is needed to determine optimal strategies for CKD testing, including duration and frequency, as well as clinical effectiveness and cost-effectiveness (Table 2[88]). In high-resource settings, the cost-effectiveness of screening for CKD appears to result from prevention of kidney failure, CVD events, and hospitalizatons.[79,89]

The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD recommends CKD case finding in high-risk groups including persons with diabetes, hypertension, CVD, or family history of CKD.[1] Other guidelines have expanded the recommendation to all people over 60 years (https://kidney.org.au/health-professionals/ckd-management-handbook).[90] The American Heart Association has called for annual testing for CKD in persons aged ≥21 years with CKM stage 2, defined as presence of 1 or more metabolic risk factors (serum triglycerides ≥135 mg/dl [1.53 mmol/l], hypertension, metabolic syndrome, or diabetes). The European Society for Cardiology recommends assessing eGFR and UACR to estimate CVD risk within a framework that also includes blood pressure, cholesterol, and glycemia (diabetes).[91,92]

Tools to identify CKD risk

Most of the point-of-care prediction formulas or tools identifying individuals at risk for CKD onset or progression include eGFR and UACR.[93–96] Risk equations that include age, gender (sociocultural factors) or sex (biological attributes), race or ethnicity, eGFR, history of CVD, history of smoking, hypertension, body mass index, albuminuria,

Table 2 | Research recommendations for implementing a lifespan approach to kidney health

Domain	Priority research strategies
Screening, diagnosis, and prognosis	• Establish prediction models for onset of CKD and apply analytical tool or artificial intelligence to EMR systems, registers, or databases of cohorts. • Link different environmental, sociodemographic, and health data to examine their inter-relations and independent associations (e.g., temperature, pollution) on onset of CKD with age- and sex (biological attributes)-specific analysis. • Evaluate biomarkers (e.g., tubular, glomerular, endocrine) and imaging to predict onset and progression of kidney disease and its modulation by treatment. • Develop risk scores and risks in relation to genetic abnormalities discovered along with the use of biomarkers (other than albuminuria). • Evaluate the additional predictive value and inter-relations of social determinants of health and explore their lifetime effects on kidney health in addition to known risk factors. • Identify lifespan risk factors and their associations with CKM health in children and young adults (<40 yr). • Investigate the role of genetic (including polygenic risk scores) and environmental factors and their interactions in personalized interventions. • Evaluate the impact of sleep, shift work, and stress management on development or progression of CKD. • Evaluate the effectiveness of multicondition screening approaches and dynamic testing for kidney functional reserve (e.g., imaging, biomarkers). • Identify strategies that optimize CKD screening in populations with high prevalence of CKD risk factors. • Determine whether case finding or screening, or a combination of case finding with screening, is clinically effective, as well as cost effective, for CKD. • Conduct comprehensive population-based studies using standardized screening protocols for timely detection and identification of risk of CKD. • Explore the effectiveness of digital health platforms and mobile applications in promoting awareness and self-monitoring in at-risk individuals. • Evaluate the feasibility, cost-effectiveness, and scalability of integrating new technologies and approaches into routine clinical practice. • Determine whether CKD prediction models improve outcomes through more targeted screening or treatment. • Outline the optimal time frame for CKD risk prediction (e.g., 5-, 10-, or 30-yr risk)[88] to maximize treatment. • Examine whether non-CKD outcomes should be predicted in conjunction with CKD (e.g., hospitalization for heart failure or mortality). • Establish international research consortia to share data and findings to advance a global perspective on CKD detection and prevention to promote kidney health.
Management	• Test various nonpharmacologic and drug interventions in different CKD populations, (e.g., persons with diabetes, hypertension, cardiovascular disease, family history, or obesity, etc.). • Employ clinical trials or registries to assess effectiveness of specific interventions and/or care models to prevent CKD. • Identify the optimal diet, including carbohydrate/protein split, to minimize metabolic disease and CKD risk. • Determine optimal protein and protein type to minimize CKD risk and optimize health. • Identify optimal weight management strategies to promote kidney health. • Determine the optimal water intake to prevent CKD in various environmental settings and high-risk occupations. • Develop community strategies to monitor water quality and safety to promote kidney health.
Health care systems	• Contextualize (e.g., country, region, setting, population) and model the clinical and cost effectiveness for maintaining kidney health. • Assess optimal means to utilize local resources (e.g., nonphysician health care workers). • Determine whether regular surveillance by UACR and eGFR testing reduce risk of CKD. • Determine whether prevention strategies for AKI may prevent CKD.

AKI, acute kidney injury; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; UACR, urinary albumin-to-creatinine ratio.

triglyceride levels, use of diabetes medications, and glycated hemoglobin predict declining eGFR with sensitivity and specificity of 0.7–0.8.[93,96–99] Associated online calculators can be found at http://ckdpcrisk.org/ckdrisk (risk of eGFR <60 ml/min per 1.73 m^2) and at http://ckdpcrisk.org/gfrdecline40 (risk of 40% reduction in eGFR). While equations may be used to identify individuals for early intervention, they do not capture all lifespan factors predisposing to CKD. Other biomarkers could theoretically provide additional information on kidney health, especially in patients with UACR <30 mg/g (3 mg/mmol), but currently tubular biomarkers or urine peptidomics remain untested for clinical use.[100–103] Ongoing research is evaluating tools for identifying individuals at risk for CKD who have unknown eGFR and UACR results, such as the prediction formula used by the National Kidney Foundation (NKF) campaign "Take a Minute for Your Kidneys."[104] This quiz aims to identify individuals with elevated risk of developing CKD through use of information on demographics, comorbidities (obesity, diabetes, hypertension), and family history of kidney disease. Individuals predicted to be at risk for CKD are recommended for testing.

Polygenic contributions to CKD have been observed in large-scale genome-wide association studies.[105] In multiethnic consortia, polygenic risk scores show good performance in discriminating individuals at high risk of developing CKD (Table 3).[105–107] However, most of these studies have been cross-sectional, with participants predominantly from

Table 3 | Risk of incident CKD

Condition	Fold increase in risk of incident CKD
Type 2 diabetes mellitus[106,107]	3 to 5[a]
GWAS polygenic risk scores (top 1% of population)[105]	
European ancestry	4
African ancestry	3
Latinx ancestry	6
Asian ancestry	8

CKD, chronic kidney disease; GFR, glomerular filtration rate; GWAS, genome-wide association studies.
[a]Estimated from Risk of Decline in Kidney Function, 3 Year Probability of 40% decline in GFR at https://ckdpcrisk.org/gfrdecline40/ by testing different scenarios with or without diabetes mellitus: for example, diabetes = no, age = 20 yr, gender = male, estimated GFR = 85 ml/min per 1.73 m^2, urinary albumin-to-creatinine ratio = 10 mg/g (1 mg/mmol), systolic blood pressure = 130 mm Hg, antihypertensive medication use = no, heart failure = no, congenital heart disease = no, atrial fibrillation = no, body mass index = 25 kg/m^2, current smoker. Same characteristics for diabetes = yes, plus: diabetes mellitus medication = insulin use, hemoglobin A_{1c} = 9%.

high-income European countries. Various biomarkers have been associated with progression of CKD.[105,108–112] However, there is considerable heterogeneity in their discriminative performance with few, if any, being validated in prospective or interventional studies to confirm their clinical utility.[113–115]

Research is needed to determine whether inclusion of family history of kidney disease and lifespan events that affect nephron number would improve performance of risk prediction tools. Formulas to identify individuals at risk for CKD may also achieve better accuracy through incorporating contextual factors such as occupation and environmental exposures. In low-resource settings, the benefits or drawbacks of implementing formulas to identify persons at risk for CKD have not been evaluated. In adequately resourced settings, risk prediction tools may hold value for patients and families by helping them make informed decisions about care needs and by providing support after CKD testing. However, many persons who undergo risk evaluation may not directly benefit, and some may be burdened or harmed by anxiety or additional testing.[80] Therefore, for CKD screening or case finding to be beneficial, health systems must provide appropriate care to support kidney health and overall well-being.[80] Research is needed to determine how to optimize use of risk prediction tools in routine clinical practice and in clinical trials of CKD prevention.[116]

INTERVENTIONS FOR CKD PREVENTION AND REGRESSION

Lifestyle interventions

Physical inactivity and unhealthy dietary patterns, including high intakes of sodium, red meat, processed and high-glycemic index foods, and sugar-sweetened beverages (Table 1), are associated with incident CKD.[45–52] Given the benefits for NCDs, a healthy lifestyle is recommended for all people, irrespective of the risk or presence of CKD.[117] However, how lifestyle modification may prevent incident CKD independent of improved risk factors is unclear.[118–120] Dietary factors are particularly relevant to populations undergoing rapid acculturation that results in a high prevalence of obesity.[121–126] Increased water intake is often recommended to promote kidney health, but the amount of water intake needed remains uncertain and is dependent on water losses and other fluid intake. Research has not demonstrated that higher water intake reduces CKD progression,[127–129] but high fluid intake mitigates kidney stone disease, a risk factor for CKD.[130] Individuals living and working in hot environments are encouraged to drink water to prevent dehydration, volume depletion, and kidney injury. Clinical trial data suggest that physical activity may reduce the risk of incident CKD[119,120,131] as well as risks of T2DM[132–134] and diabetes complications.[135] In a *post hoc* analysis of the Look AHEAD (Action for Health in Diabetes) trial,[120] which examined the effects of intensive lifestyle modification versus support and education alone in participants with T2DM and obesity, a difference in weight loss of 3% (8.6% vs. 6%) demonstrated a 31% reduction in incident very high-risk CKD (KDIGO category) that was at least partly attributable to lower blood pressure, glucose, and body weight.

Medical interventions

Pharmaceutical. Drug therapies that regress CKD to lower risk categories can be disease-specific, for example, immunosuppressants for glomerulonephritis,[136] or nonspecific, meaning those that modify common pathways of kidney injury, such as with sodium-glucose cotransporters-2 inhibitors (SGLT2i),[137–140] nonsteroidal mineralocorticoid receptor antagonists (nsMRA),[141–144] and glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RA).[145,146] Treatment of CKD with newer agents (SGLT2i, nsMRA, GLP-1RA) is extensively discussed in the KDIGO 2024 CKD Guideline.[1] For GLP-1RA, the recently completed Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial showed significantly reduced risks of kidney, cardiovascular, and all-cause death outcomes with weekly semaglutide in persons with T2DM and CKD.[86,147]

Data from cardiovascular outcomes trials (CVOTs) indicate that SGLT2i and GLP-1RA may prevent or regress CKD.[148] Prior to these CVOTs, there was scant evidence to support CKD prevention using medication used to treat hypertension and diabetes, which are 2 key CKD risk factors. While blood pressure targets have been recommended in clinical practice guidelines to minimize CKD progression, clinical trials of antihypertensive medications were generally not designed to assess their impact on incident CKD. In the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), which included patients with hypertension, T2DM, and UACR <30 mg/g (3 mg/mmol), there was an approximately 50% risk reduction for new-onset microalbuminuria (overnight albumin excretion or ≥ 20 mcg/min at 2 consecutive visits) in the comparison between the angiotensin-converting enzyme inhibitor trandolapril and placebo.[149]

Intensive glycemic control reduces the development of diabetes complications.[150,151] However, among 5 key complications, kidney failure saw the smallest relative decline between 1990 and 2010.[152] Since then, declines in diabetes

complications have slowed in younger individuals,[153] while rates of kidney failure have increased in the White population of the United States.[154] Notably, prevention of CKD has not been observed with the glucose-lowering agents metformin, sulfonylureas, insulin, or dipeptidyl peptidase-4 inhbitors.[150,155,156]

CKD prevention by SGLT2i was initially observed in analyses of CVOTs among participants with T2DM: CANagliflozin cardioVascular Assessment Study (CANVAS), Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG Outcome), and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI-58) (Figure 3).[87,157–162] Collectively, the trials enrolled 20,156 participants with no CKD (eGFR ≥60 ml/min per 1.73 m^2 and UACR <30 mg/g [3 mg/mmol]). The observed hazard ratio (HR) for reduced kidney function outcomes in participants without CKD was aligned with that observed for participants with CKD and in CKD trials (Figure 3a), but participants without CKD on SGLT2i had the lowest residual risks (Figure 3b), and SGLT2i treatment reduced the eGFR slope to nearly 0 ml/min per 1.73 m^2 per year, below the expected age-associated value (−1 ml/min per 1.73 m^2 per year), which was observed in the placebo group (Figure 3c; Supplementary Table S1).[157–159] In subsets with elevated albuminuria at baseline, eGFR decline slowed and albuminuria remitted on empagliflozin treatment, with sustained reductions of 22%–29% after treatment withdrawal for a median of 34–35 days.[157] Treatment of participants without CKD was also associated with decreased risk of all-cause mortality.[161] Similar kidney protection was observed among DECLARE-TIMI-58 participants without CKD at baseline.[158]

GLP-1RA and the dual incretin GLP-1/glucose-dependent insulinotropic polypeptide receptor agonist (tirzepatide) were originally developed for treatment of hyperglycemia and obesity.[163–168] Trials of glycemic lowering with these agents found reductions in kidney disease events as major secondary outcomes. GLP-1RA (e.g., liraglutide, semaglutide, lixisenatide, dulaglutide) and tirzepatide reduced albuminuria and slowed eGFR decline in patients with T2DM, most of whom did not have CKD at baseline.[145,169–173] In studies of people with obesity, with or without T2DM, semaglutide also reduced albuminuria and increased the number who remitted from albuminuria categories A2 or A3 to lower levels including A1.[174]

Meta-analyses of the GLP-1RA studied in CVOTs also found lower risk of a composite kidney disease outcome (A3 albuminuria, serum creatinine doubling, ≥40% eGFR decline, kidney failure, death due to kidney disease), with a HR of 0.77 (95% confidence interval [CI]: 0.79–0.87) in participants with T2DM.[175] The Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial, a CVOT of subcutaneous semaglutide 2.4 mg weekly versus placebo in persons with overweight or obesity and without diabetes, has since reported comparable results with a HR of 0.78 (95% CI: 0.63–0.96) for a similar composite outcome (A3 albuminuria, ≥50% eGFR decline, eGFR <15 ml/min per 1.73 m^2, dialysis or transplant, death due to kidney disease).[176] As only 21% in SELECT had eGFR <60 ml/min per 1.73 m^2 or UACR ≥30 mg/g (3 mg/mmol) at baseline, these data support the concept that CKD can be prevented. In A Study of Tirzepatide (LY3298176) versus Insulin Glargine in Participants with Type 2 Diabetes (CVOT SURPASS-4), the rate of eGFR decline was significantly slower with tirzepatide, and albuminuria onset or progression was not seen across strata of eGFR and albuminuria, including those without CKD at baseline.[5] In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), participants with T2DM were more likely to remit to a lower KDIGO risk category (HR: 1.69; 95% CI: 1.32–2.16) and less likely to progress to a higher risk category (HR: 0.71; 95% CI: 0.59–0.86) by weekly semaglutide relative to placebo.[177] Notably, one-half of the SUSTAIN-6 population had low KDIGO risk at baseline (eGFR >60 ml/min per 1.73 m^2 and UACR <30 mg/g [3 mg/mmol]), again making the case for CKD prevention or regression by a GLP-1RA. In a mediation analysis of kidney disease outcomes (A3 albuminuria, doubling of serum creatinine, eGFR <45 ml/min per 1.73 m^2, kidney failure) from CVOTs of liraglutide and semaglutide, lower glycemia or blood pressure only moderately mediated (10%–25%) these benefits, pointing to direct actions on the kidney by GLP-1RA.[178] Recent real-world clinical practice data support randomized controlled trial findings on CKD prevention by SGLT2i and GLP-1RA in people with diabetes in the primary care setting.[179]

In sum, *post hoc* analyses of clinical trials of SGLT2i and GLP-1RA provide evidence that it is possible to prevent CKD onset, or induce remission, in the context of T2DM or obesity. For finerenone and anti-inflammatory therapies, data examining CKD prevention are limited but are of interest given the potential benefits (Table 4).[143,144,180–184]

Nonpharmaceutical. Weight reduction following bariatric surgery can lead to reduced albuminuria and improved kidney function, highlighting the importance of weight control in kidney protection.[185–187] Despite the efficacy of several surgical procedures for managing resistant hypertension (renal denervation, carotid baroreflex stimulation), currently evidence is lacking for these procedures to prevent CKD onset.

IMPLEMENTING A LIFESPAN APPROACH TO KIDNEY HEALTH

The aim of a lifespan approach is to sustain ongoing health throughout life by disease prevention, detection, and intervention, as well as health promotion and accessibility to care. Stakeholders include patients, patient advocacy groups, health policymakers, health plan administrators, and health care professionals and societies. Optimal screening or early detection approaches (Figures 4 and 5) should be followed by interventions that prevent CKD development and possibly slow or reverse CKD progression.

Stakeholders benefit from education about the cost and consequences of CKD, and therefore messages on

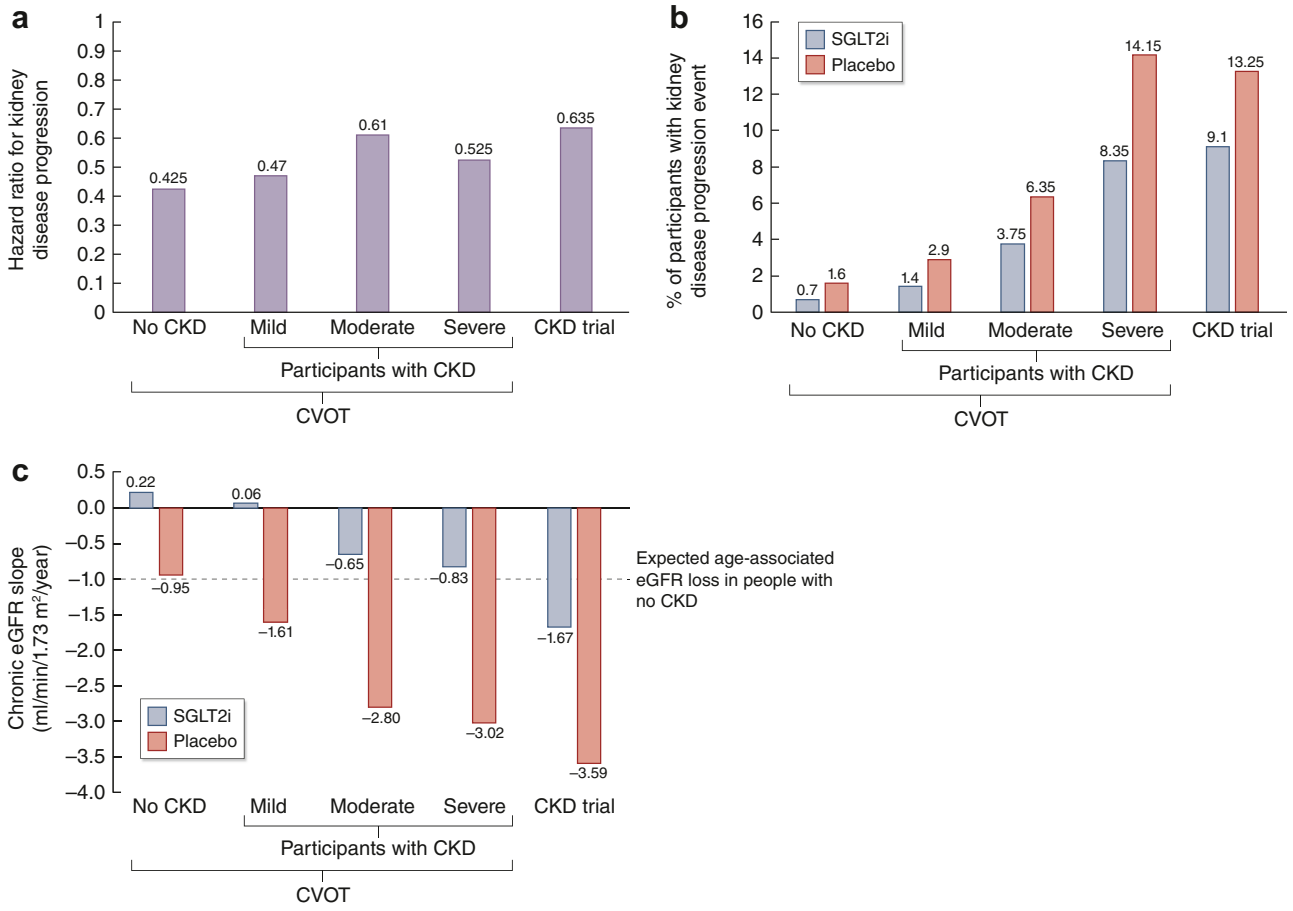

Figure 3 | Despite large reductions in relative risk of kidney events, the absolute residual risk remains high in patients with chronic kidney disease (CKD) treated with current kidney-protective therapy. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are examples where *post hoc* analyses have described participants in cardiovascular outcomes trials (CVOTs) at high risk of CKD (type 2 diabetes mellitus [T2DM] plus high cardiovascular disease risk) but with no CKD, as defined by estimated glomerular filtration rate (eGFR) >60 ml/min per 1.73 m^2 and urinary albumin-to-creatinine ratio < 30 mg/g (3 mg/mmol). (**a**) Mean hazard ratios for kidney disease progression for dapagliflozin and empagliflozin CVOTs in T2DM plus high cardiovascular disease risk (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 [DECLARE-TIMI 58] and Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG Outcome]) and in CKD trials (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD] and Study of Heart and Kidney Protection with Empagliflozin [EMPA-KIDNEY]). Relative risk reduction is observed across all categories tested for a CKD progression endpoint (kidney failure, kidney death, or persistent reduction in eGFR). Note that DAPA-CKD and EMPA-KIDNEY enrolled patients with and without T2DM and other inclusion/exclusion criteria may differ across trials. Results obtained in CANagliflozin cardioVascular Assessment Study (CANVAS) (CVOT in T2DM plus high cardiovascular disease risk) and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) (CKD T2DM) testing canagliflozin were aligned with those for dapagliflozin and empagliflozin but percentage of patients with events were not reported for Kidney Disease: Improving Global Outcomes (KDIGO) risk categories. Available results for CANVAS and KDIGO risk categories, expressed as events per 100 patient-years, are shown in Supplementary Table S1. (**b**) Residual risk expressed as percentage of participants with kidney disease progression events is shown in blue for participants on SGLT2i in trials from panel (**a**). For comparison, percentage of participants with events while taking placebo are shown in red. The proportion with CKD progression is nearly 9-fold higher when therapy is started with severe CKD rather than treating to prevent CKD (14.15% vs. 1.6%). (**c**) Median chronic eGFR slopes for canagliflozin, dapagliflozin, and empagliflozin CVOTs (T2DM plus high cardiovascular disease risk: CANVAS, DECLARE-TIMI 58, and EMPA-REG Outcome) and for CKD trials (CREDENCE, DAPA-CKD, and EMPA-KIDNEY). Note that for the duration of the trials, the median eGFR slopes across trials for participants with no CKD or mild CKD were neutral. The expected age-associated eGFR loss of −1 ml/min per 1.73 m^2 in people with no CKD is indicated. Note that this was the eGFR slope observed in participants on placebo with no CKD. Data are from Neuen *et al.*,[159] Perkovic *et al.*,[160] Mosenzon *et al.*,[158] Heerspink *et al.*,[87] Levin *et al.*,[161] and Herrington *et al.*[162] Mild, moderate, and severe CKD is based on European Society of Cardiology terminology for KDIGO risk categories of moderate, high, and very high risk. The reason for using this simplified nomenclature is that it may facilitate implementation by non-nephrologists. The number (percentage) of participants with no CKD was 5876 (58%) in CANVAS, 10,958 (64%) in DECLARE-TIMI 58, and 3322 (48%) in EMPA-REG Outcome for a total of 20,156 participants with no CKD among the 3 trials.

kidney health need to be decluttered and simplified for patients and communities. In health care settings, mentality should move away from being organ focused. Within nephrology, consideration should broaden beyond kidney function to encompass holistic health and well-being.

Although guideline-recommended care can be difficult to implement, coordinated care involving multidisciplinary health

Table 4 | nsMRA and anti-inflammatory therapy for prevention or remission of CKD

Drug	Placebo-controlled trial	Population	Nature of analysis	Outcome	Comment
Finerenone (nsMRA)[143,144,184]	FIDELIO and FIGARO	T2DM with albuminuric CKD	Primary/secondary endpoint	HR for combined kidney outcome of reduced eGFR[a]: 0.82; 95% CI: 0.73–0.93	KDIGO 2024 CKD guideline[1] recommended to treat CKD in T2DM when UACR > 30 mg/g (3 mg/mmol)
Low-dose methotrexate (immunosuppressant)[180]	Cardiovascular Inflammation Reduction Trial	Atherosclerotic CVD and diabetes or metabolic syndrome, eGFR >40 ml/min per 1.73 m^2	Secondary analysis	Less eGFR decline over a median follow-up time of nearly 2 yr irrespective of baseline kidney function	No UACR data
Baricitinib (Janus kinase 1/2 inhibitor)[181,182]	Phase 2	T2DM with albuminuric CKD	Primary endpoint	Reduced UACR at 6 mo, and this was sustained after a 4-wk washout period	

CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FIDELIO, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial; FIGARO, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.
[a]Kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes.

professionals is possible, even in resource-challenged areas. In a systematic review of care models in LMICs, large-scale programs supporting primary care or allied health workers achieved effectiveness in slowing eGFR decline.[188] Addressing patient concerns over data privacy, shifting focus toward practical approaches (e.g., routine screening among families of dialysis patients), and adopting common language for patient communications could all be used to improve delivery of care. Government-sponsored implementation of a system-wide program for diabetes risk assessment, education, and management program led to improved control of multiple CKD and CVD risk factors[189,190] and a 54% reduction in the incidence of diabetes-related kidney failure and all-cause death in indigenous populations in the United States.[154,191–195]

Measurements for implementation

Process measures have some advantages over outcome measures, such as ease of measurement and clearer attribution. In

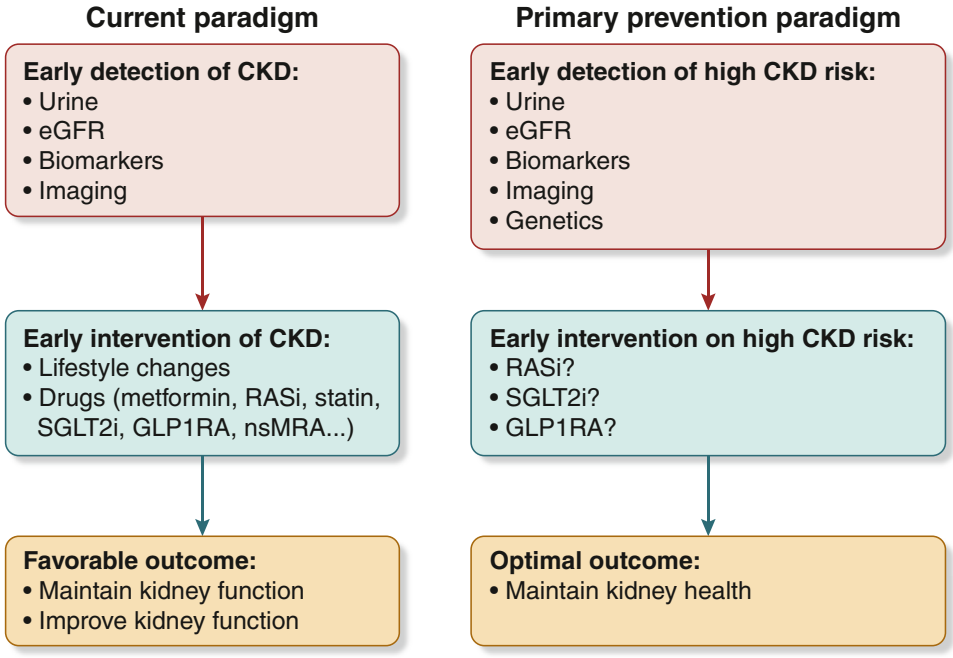

Figure 4 | Shifting the paradigm from treatment to prevention of kidney disease. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide 1 receptor agonists; nsMRA, non-steroidal mineralocorticoid receptor antagonists; RASi, renin-angiotensin system inhibitors; SGLT2i, sodium-glucose cotransporters-2 inhibitors.

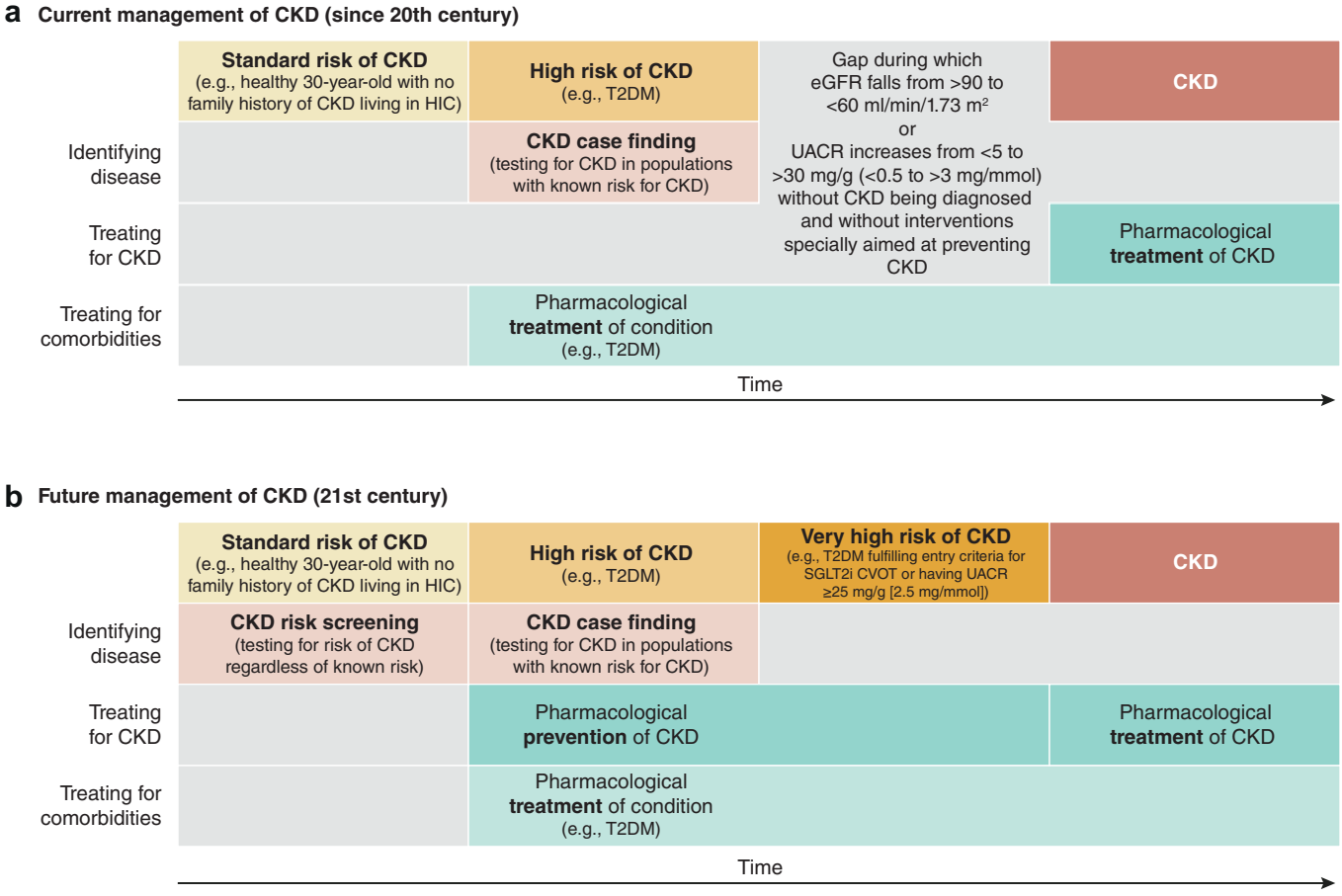

Figure 5 | Incorporation of strategies to assess actionable risk of incident chronic kidney disease (CKD) into the overall management of CKD burden with the aim of preserving kidney health. (**a**) Conditions that are risk factors for CKD, such as type 2 diabetes mellitus (T2DM) or hypertension, are treated, but even in patients with high risk of CKD, treatment is not specifically tailored to prevent progression of kidney disease until after CKD has developed. (**b**) Future management of CKD calls for a novel actionable category of very high risk of incident CKD that mirrors concepts from other noncommunicable diseases (NCDs). The interventions aligned to a diagnosis of very high risk of CKD would be pharmacological, as in both examples from other NCDs, as well as a healthy lifestyle. CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; HICs, high-income countries; UACR, urinary albumin-to-creatinine ratio.

implementing process measures, it is important to ensure that risk factors are queried deliberately. Examples include querying for use of pesticides in agricultural communities with a high prevalence of CKD. Health systems can consider shifting from organ-specific measures to creating standard health metrics around chronic conditions with related multiorgan pathophysiology as exemplified by the CKM syndrome concept.[23]

Cost-effectiveness

The identification of a large number of individuals with or at risk for CKD could be overwhelming to health care systems and their payers.[196,197] Cost-effectiveness could be routinely incorporated into clinical guidelines to help guide optimal decisions. Community engagement efforts should highlight the value of a lifespan approach to CKD prevention, with real-life examples emphasizing quality of life and reduced health care costs. Information on value-for-money, practicality, and improvement in health equity can aid policymakers and health care administrators. Benefits relating to public health, environmental impact, and financial sustainability are important to policymakers. Employers have interest in reducing workforce sick days and lowering health plan expenditures.

Primary prevention programs

Successful primary prevention programs have proactive, condition-appropriate protocols. Risk scores have been shown to identify individuals for testing and quantify health risks among those without established conditions. In low-resource settings, task shifting to allied health workers with technology support can improve uptake and quality of care. A randomized controlled trial of this approach among high-risk individuals in Malang, Indonesia, showed greater use of preventive CVD medication and lower blood pressure levels.[198] Clinical decision support systems involving recommendations for proactive laboratory testing may prompt physicians to more reliably order assessments based on clinical guidelines.[199]

Multisectoral collaborations for closing care gaps

The Lancet Commission Report on Diabetes[200] proposed the use of data to drive actions including the establishment of

Table 5 | Preventing CKD: lessons from diabetes

Preventive tactics	CKD: KDIGO[1]	DM: ADA[2]
Make definitions available	Risk-based definition based on thresholds for laboratory values	Risk-based definition based on thresholds for laboratory values
Include a chapter on prevention in major guidelines	No	Yes
Provide prevention guidance that includes lifestyle changes	NA	Yes
Provide prevention guidance that includes medication	NA	Yes: metformin to prevent DM
Define a precondition stage	No	Prediabetes
Ensure the precondition stage is actionable	NA	Yes: metformin to prevent DM
Emphasize prevention of other NCD in major guidelines	Yes: CVD	Yes: CVD (not CKD)

ADA, American Diabetes Association; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; NCD, noncommunicable diseases.
NA indicates that this statement does not apply because prevention is not addressed by major guidelines, such as the KDIGO 2024 CKD guideline,[1(pS135)] which specifies that "prevention and screening for CKD should be conducted mostly by health care professionals in primary care and in other specialties, such as endocrinology, cardiology, and oncology rather than restricted to nephrologists." The guideline "strongly supports efforts aimed at the early detection and treatment of CKD among people at high risk for CKD, including those with hypertension, diabetes, and CVD."

registers with linkage to electronic medical record (EMR) systems. Databases used for quality assurance, benchmarking, and analysis could be built by regularly evaluating and monitoring a common clinical data set including patient history and measures of health, including blood and urine biomarkers, especially if qualitative or descriptive responses can be digitalized and incorporated in the EMR system.[21] Accessing personalized data can empower self-management, aid in triaging care, enhance patient–provider communication, and inform shared decision-making. Many NCDs, including CKD, share common risk factors and outcomes.[19,201,202] Linkage of registered data to population surveys and health care administrative databases may reveal disease causes and outcomes as well as the clinical effectiveness and cost-effectiveness of interventions.[19,200] From a research perspective, creation of these registers increases the efficiency of recruitment of family-based cohorts with or at risk of CKD with accompanying biobanks and databases.

SUMMARY AND CONCLUSIONS

Given the growing global threats to kidney health and the known benefits of kidney protective strategies and therapies, the current era holds an opportunity to broaden focus from managing existing CKD to maintaining kidney health. Based on a large body of evidence, the consensus of meeting participants centered on a lifespan approach that takes into consideration physical, mental, and social determinants of health. Beyond healthy lifestyle and treatment of risk factors, therapeutics such as SGLT2i and GLP-1RA may prevent or regress CKD. To achieve goals for optimal, cost-effective means for implementing CKD prevention, the nephrology and primary care communities must ambitiously advocate for system-level change focused on kidney risk profiling and appropriate testing (including both eGFR and UACR). Future kidney guidelines may consider recommendations for screening to identify individuals at high risk of CKD, similar to the approach used in diabetes (Table 5).[1,2] Additionally, measures of overall well-being can expand relevant kidney health outcomes. Societal perspectives should be considered in messaging the imperatives for CKD prevention to broad public health audiences. Endorsements from authoritative bodies such as the World Health Organization add legitimacy to health-related messages. Application of logic models can be used to enhance understanding of interdependent systems for implementation efforts.[203,204] Collaborations among primary care and specialist health care professionals, health systems, payers, and policymakers are needed to align goals.

APPENDIX

Other Conference Participants

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DISCLAIMER

The findings and conclusions are those of the authors and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention (CDC).

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

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