Review Article

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Environmental Exposures and Kidney Disease

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Abstract

Accumulating evidence underscores the large role played by the environment in the health of communities and individuals. We review the currently known contribution of environmental exposures and pollutants on kidney disease and its associated morbidity. We review air pollutants, such as particulate matter; water pollutants, such as trace elements, per- and polyfluoroalkyl substances, and pesticides; and extreme weather events and natural disasters. We also discuss gaps in the evidence that presently relies heavily on observational studies and animal models, and propose using recently developed analytic methods to help bridge the gaps. With the expected increase in the intensity and frequency of many environmental exposures in the decades to come, an improved understanding of their potential effect on kidney disease is crucial to mitigate potential morbidity and mortality.

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Introduction

There is growing understanding of how the environment affects the health of individuals and communities. Exposure to human-made and naturally occurring toxins in the air, water, and soil can lead to accumulation in organs, and contribute to morbidity and mortality. Even transient events, such as extreme heat and natural disasters, may contribute to adverse health outcomes.

Patients with kidney disease may be especially susceptible to the effects of environmental exposures, given their innate frailty and high comorbidity burden. In this review, we discuss the potential contribution of environmental exposures to kidney disease and associated morbidity (Figure 1). We also discuss the current limitations in understanding and propose the use of recently developed analytic methods that may help to bridge some of these gaps. The intensity and frequency of many environmental exposures are expected to increase due to climate change while, at the same time, the global burden of chronic kidney disease (CKD) is rising for all countries, including those with limited resources (1).

Air

Particulate matter, an air pollutant that is a complex mixture of small particles and liquid droplets arising from the combustion of fossil fuels and biomass, has come into focus for its adverse effects (2,3). Particulate matter with an aero-diameter <2.5 μm ($PM_{2.5}$) can travel through the respiratory tract and enter the bloodstream after inhalation; its components include sulfates, nitrates, ammonium, hydrogen ions, carbon, volatile organic compounds, and trace metals. $PM_{2.5}$ is one of the six criteria pollutants regulated by the US Environmental Protection Agency (4).

Cell culture and animal studies demonstrated that both short-term (days) and long-term (months to years) exposure to $PM_{2.5}$ induces oxidative stress, inflammation, cell autophagy, and cell apoptosis (5–10), whereas studies in humans demonstrated acute thrombus formation and vascular dysfunction (11,12), which is postulated to eventually lead to clinical cardiovascular events and mortality. Mechanisms of injury specific to kidney disease are less clear. A recent study (13) of healthy volunteers demonstrated that inhaled inert gold nanoparticles, a model for $PM_{2.5}$, entering the bloodstream, are detected in the urine within minutes after exposure. The nanoparticle model suggests $PM_{2.5}$ can be filtered by the glomerulus and may thus lead to indirect and direct kidney tissue injury.

Epidemiologic data about $PM_{2.5}$ and kidney disease can be divided into two categories: (*1*) $PM_{2.5}$ as a risk factor for kidney disease and progression of CKD to end stage kidney disease (ESKD), and (2) $PM_{2.5}$ contributing to the morbidity and mortality of individuals with CKD, including ESKD.

A recent systematic review (14) identified 40 epidemiologic studies examining the association of $PM_{2.5}$ and adverse kidney function. Most of the studies (36 of 40) observed that $PM_{2.5}$ exposure was associated with adverse kidney function. The assessment of kidney function was clinically diverse, and included outcomes such as glomerular filtration rate (GFR), albuminuria, and glomerulonephritis. We point out some of the included studies to highlight the heterogeneity: (*1*) long-term $PM_{2.5}$ exposure was associated with the rise of a specific type of glomerular disease, membranous nephropathy, in an 11-year series of >71,000 native kidney biopsy specimens across China (15); (2) among nearly 1 million US veterans, $PM_{2.5}$ was associated with

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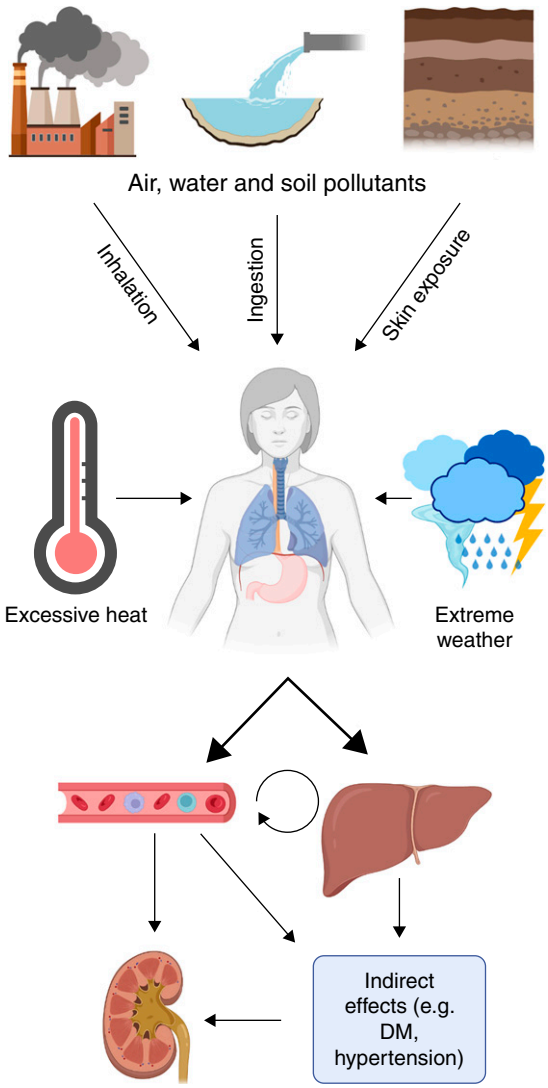

Figure 1. | Multiple routes of environmental exposures and their potential end-organ effects. Environmental exposures occur through a variety of routes that can directly and indirectly influence kidney health. Pollutants in the air, water, and soil may be ingested, inhaled, or absorbed through the skin. To varying degrees, these pollutants cross into the bloodstream, where they may travel to, and directly injure, the kidneys. Some compounds will first be absorbed *via* the gastrointestinal tract, undergoing first-pass metabolism in the liver before returning to the bloodstream. Some exposures may also indirectly contribute to kidney disease by causing conditions such as diabetes and hypertension—well-established risk factors for incident or progressive CKD. DM, diabetes mellitus.

incident CKD and the progression of CKD to ESKD (16); (3) among a community-dwelling cohort of middle-aged individuals, $PM_{2.5}$ was associated with both increased urine albumin and a decline in GFR (17); (4) modeling estimated 7 million incident cases of CKD annually are attributable to $PM_{2.5}$ worldwide (18); and (5) among a US national cohort of kidney transplant recipients, $PM_{2.5}$ was associated with increased risk of 1-year kidney rejection post-transplant, graft failure, and all-cause death (19).

Short-term $PM_{2.5}$ exposure during wildfires (20), and short- and long-term ambient $PM_{2.5}$, is associated with a 5% increased risk of all-cause and cardiovascular mortality among patients receiving maintenance hemodialysis (21–23). Short-term $PM_{2.5}$ exposure is also associated with an increased risk of hospital admissions and 30-day readmissions among these patients (24).

In addition, limited evidence suggests an association between tropospheric or ground-level ozone, which is formed by photochemical reactions between volatile organic compounds and nitrogen oxides in the atmosphere, and kidney disease (25,26).

Water

A range of heavy metals, perfluorinated compounds, pesticides, industrial hydrocarbons, and pathogens are common water contaminants. Human exposure to these agents occurs through drinking the water, consumption of animals (especially fish and mollusks) living in the water, or dermal/mucosal contact with the water.

Metals, including arsenic, cadmium, lead, mercury, and uranium, are among the most extensively studied waterborne nephrotoxins. Arsenic is a naturally occurring metalloid found in many parts of the world, especially in groundwater. Arsenic can also be introduced into water *via* mining and metal smelting (27). Worldwide, >200 million people are estimated to be chronically exposed to arsenic in drinking water at concentrations above the World Health Organization provisional guideline value of 10 μg/L (27,28). Epidemiologic studies linked high drinking water arsenic levels to increased CKD/ESKD incidence (29,30), progression (31), and mortality (32).

Cadmium is released into water, soil, and air *via* (*1*) mining and metal refining; (2) production and application of phosphate fertilizers; (3) burning of fossil fuels; and (4) waste incineration, disposal, and recycling (33). Although drinking water contributes only a small proportion of total cadmium exposure in the general population, it can be an important source of exposure for water in the vicinity of cadmium-emitting industries (33,34). Historically, a major outbreak of cadmium toxicity occurred in the Toyama Prefecture (Japan) after contamination of the Jinzu River basin from a zinc mine in 1912. Local inhabitants termed the resulting disease "itai-itai" or "ouch-ouch" disease because of severe, diffuse bone pain from vitamin D–resistant rickets with osteomalacia; other manifestations included proximal tubular dysfunction and hyperphosphaturia (35). Most studies of renal toxicity associated with cadmium have measured exposure *via* blood or urine levels and have linked exposure with several molecular markers of kidney injury and CKD (33,36,37).

The most common source of lead in drinking water is from leaching of plumbing materials, including lead service lines and residential pipes, lead solder, and certain fixtures (38). However, it can also result from runoff or dumping from lead smelters, lead battery production or recycling operations, and mining (38,39). In most countries, blood lead levels are decreasing, but continue to be of concern (40). Most studies investigating kidney effects related to lead exposure assessed exposure *via* blood lead levels; they identified associations with CKD incidence (41) and prevalence (42,43), and increased serum creatinine (44) or decreased eGFR (45,46). A recent study demonstrated that high lead levels were associated with a higher prevalence

of anemia among patients with ESKD (47). Overall, lead-induced kidney disease may be underdiagnosed or misdiagnosed as hypertensive kidney disease without accurate assessment of lead exposure from patient histories.

Globally, artisanal and small-scale gold mining and coal combustion are the primary sources of anthropogenic mercury emissions (48). General population exposure to mercury, primarily in the form of methylmercury, occurs mostly through consumption of fish, shellfish, and marine mammals from contaminated fresh- or seawater (48). Although chronic exposure to mercury has been shown to induce renal dysfunction, there is limited epidemiologic evidence of an association specifically between methylmercury and CKD (49). Methylmercury toxicity manifests primarily in neurologic changes (Minamata disease) (50) and less commonly in markers of kidney disease, such as proteinuria (51).

For the general population, drinking water is an important source of uranium exposure (52). Contamination of ground- and surface water arises largely from redistribution of uranium and uranium progeny through the natural erosion of rock and soil, although elevated levels can be found near mining operations. Epidemiologic studies have reported associations between uranium levels in drinking water and molecular markers of renal dysfunction, with stronger evidence from animal studies (52).

Per- and polyfluoroalkyl substances, known as PFAS, are a large family of manmade, persistent chemicals widely used in everyday products and widespread drinking water contaminants. PFAS are used in firefighting foam, food packaging, personal care products, nonstick cookware, carpet, upholstery, and many other applications. Two of these, perfluorooctanoic acid and perfluorooctane sulfonate, were manufactured and released into the environment for decades, but are no longer produced or used in the United States or most other industrialized countries (53). However, they and the PFAS that replaced them continue to be found in surface and groundwater sources. These legacy PFAS have been associated directly with increased risk of CKD in some (54–57), but not all (58–60), studies, and inversely with GFR in several studies (56,61,62). The exact nature of the association of PFAS and CKD is ambiguous because serum concentrations of PFAS may increase with decreased kidney function (63). PFAS exposure has also been linked to obesity, diabetes mellitus, hyperlipidemia, and cardiovascular conditions that are direct and indirect risk factors for kidney disease.

For the general population, the primary routes of exposure to trichloroethylene and tetrachloroethylene, used as industrial degreasers and in dry cleaning, are inhalation from ambient or indoor air and ingestion of contaminated drinking water (64,65). These chemicals have been shown to have nephrotoxic effects in epidemiologic and animal studies (64,65).

In addition to chemical pollutants often found in drinking water, biologic contaminants, including the bacteria *Leptospira* (66) and parasitic worms from the genus *Schistosoma* (67,68), have been implicated in the pathogenesis of CKD. Aristolochic acids, potent nephrotoxins produced by the *Aristolochia* plant, were first identified in relation to Balkan endemic nephropathy among individuals using *Aristolochia*-based herbal remedies (69). A recent study demonstrated the widespread presence and stability of aristolochic acids in groundwater in Serbia (69); however, the prevalence and levels of such groundwater contamination worldwide are unknown.

Exposure to pesticides occurs through several routes, including consumption of contaminated surface or well water. Most studies examining pesticides and CKD have been conducted among farmers or agricultural workers. They have assessed exposure *via* self-report in terms of applications, *i.e.*, either direct from handling of the pesticides or indirect from being in the vicinity of applications. Pesticides that have been linked to CKD/ESKD in one or more epidemiologic studies include the herbicides alachlor, atrazine, butylate, glyphosate, metolachlor, paraquat, and pendimethalin, and the insecticides methyl parathion and permethrin (70–75). The organochlorine insecticides hexachlorocyclohexane and endosulfan have also been associated with CKD (76,77). The herbicide dicamba has been associated with reduced eGFR (76), whereas the organochlorine insecticide dichlorodiphenyltrichloroethane (DDT) and its primary metabolite have been linked to insulin resistance and increased diabetes risk, which may indirectly impair renal function (78).

Extreme Weather Events and Natural Disasters

An extreme weather event is defined as "time and place in which weather, climate, or environmental conditions—such as temperature, precipitation, drought, or flooding—rank above a threshold value near the upper or lower ends of the range of historical measurements" (79). Natural disasters are weather conditions " … that have the potential to pose a significant threat to human health and safety, property, [and] critical infrastructure … " (80).

To date, the primary epidemiologic focus has been extreme heat, especially in the context of CKD of unknown etiology (CKDu) or CKD of nontraditional origin. CKDu/CKD of nontraditional origin occurs among individuals engaged in intense manual labor in hot environments. The described kidney injury is tubulointerstitial, associated with increased levels of urinary neutrophil gelatinase-associated lipocalin (NGAL) (81–83) and urinary IGF binding protein 7 in some studies (82), and renal biopsy specimens demonstrate acute tubular cell injury and chronic tubulointerstitial nephritis (84). An increase in urinary markers of kidney injury after physical work in the heat has been shown to be exacerbated by longer work durations (85) and the magnitude of hyperthermia and/or dehydration (82). The kidney injury may be exacerbated by the occurrence of muscle-damaging exercise (83) and/or the intake of sugar-sweetened beverages high in fructose (81) that are common in these workplaces (86) and associated with increased urinary neutrophil gelatinase-associated lipocalin. The National Institutes of Health has started a multicenter study of CKDu focused on hot-spot regions in Central America and India, with the intent of characterizing CKDu clinical features and identifying biomarkers for early disease, environmental exposures, and other risk factors.

A recent study demonstrated an association of extreme heat events, defined as temperature >95th percentile for the day and location over 30 years, and hospitalizations

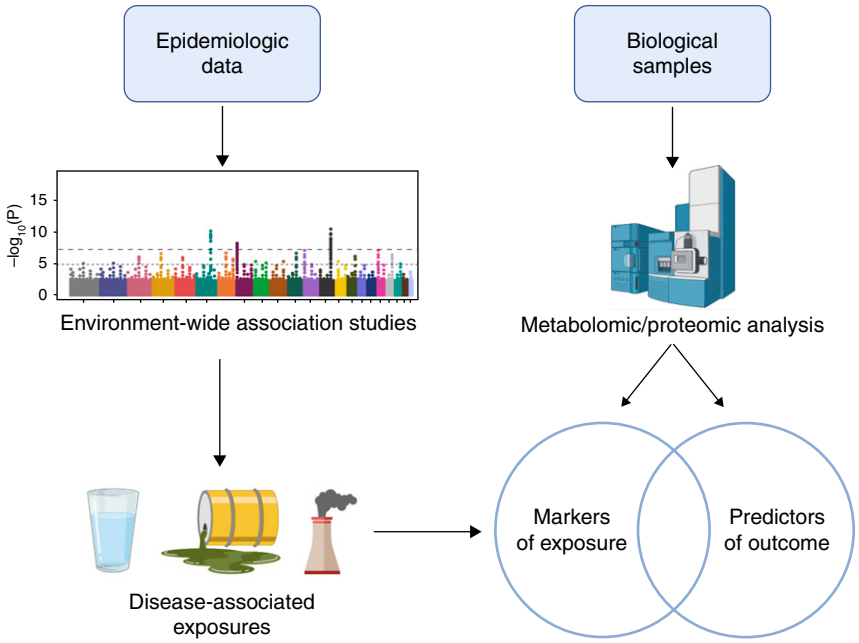

Figure 2. | **Integration of epidemiologic data with metabolomic/proteomic analyses to bridge the information gap.** Integrating large datasets from previously disparate fields, such as epidemiology and metabolomics, may be key to connecting environmental exposures to biologic outcomes. In the proposed framework, epidemiologic data contribute to epigenome-wide association studies (EWAS), which identify putative disease-associated exposures. Concurrently, metabolomic and proteomic studies can identify signals in biologic samples that are associated with exposure to pollutants, are predictors of outcome, or both. Exposures identified *via* EWAS can then be compared with these signals, and candidate compounds tested in preclinical models to confirm causality.

and mortality for patients receiving in-center hemodialysis in the northeastern United States (87).

A systematic review evaluated the effects of natural disasters on dialysis populations in the Americas, assessing 15 original research articles published in the English language from 2009 to 2019. They found that disasters have immediate, direct effects related to the ability to receive maintenance dialysis from loss of electricity and other infrastructure, such as water. Additionally, the disasters exacerbate depression and post-traumatic stress disorder in the long term (88). The effect of such extreme heat events and natural disasters (*e.g.*, hurricanes), is expected to increase in the coming years because of climate change.

Mind the Gap

The current literature on the potential role of environmental exposures in kidney disease has important limitations. First, national and international agencies have different accepted levels for pollutants, preventing the establishment of standard toxicity thresholds. Second, we rely either on cell and animal models or on epidemiologic studies—each with their respective challenges. Although *in vitro* and animal experiments can test highly specific exposures, quantify outcomes, and control conditions, they may not replicate the effects of exposures profiles (dose, duration) seen in the real world. For example, an individual's $PM_{2.5}$ exposure is influenced by both environmental and behavioral factors (*e.g.*, air filtration and duration of time outdoors) (89). Furthermore, an individual's potential effective exposure dose is governed by particle deposition, clearance, and retention within the respiratory tract and extrapulmonary tissues. In addition, interspecies differences in toxicant uptake, metabolism, and response may limit the utility of some animal models. Observational studies often generate and test hypotheses, but they cannot alone establish causation. Furthermore, existing banked specimens from established cohort studies have varying longitudinal follow-up, storage quality, and assay repeatability.

Advances in the "omic" technologies and new study designs may help address some of the limitations. Multiple omic approaches may offer a better picture of the different aspects related to the "exposome"—the measure of all exposures across a person's lifespan related to health (90). Genomics encompass the study of the DNA structure and its epigenetic regulation, and proteomics include the evaluation of gene products and protein post-translational modifications (91). Metabolomics measure intermediate metabolic chemical processes in biologic tissues and fluids (92). These omic assays have been applied in studies of patients with kidney disease and in healthy individuals (93) and, taken together, they can analyze the flow of biologic information from exposure to gene, protein, and function (and back).

New study designs include meeting-in-the-middle (MITM) (94) and environment-wide association studies. As an example, exposure to $PM_{2.5}$ is associated with epigenetic changes in DNA methylation (95,96), and exposure to PFAS is associated with plasma metabolites related to kidney injury (97). Alone, these findings are suggestive of associations between exposures and outcomes. MITM studies use advanced regression techniques and mediation analysis to find overlap between proteomic or metabolomic profiles resulting from exposure and those that are predictive of disease (94). This model is particularly useful in prospective cohorts with

Table 1. Summary of environmental pollutants and their potential effect on kidney disease

Pollutants	Source	Kidney Effect
Particulate matter <2.5 μm	Air	Associated with kidney function decline, and with CKD and ESKD morbidity/mortality
Ozone	Air	Limited association with CKD
Heavy metals		
Arsenic	Water, soil, diet	Associated with incident CKD and ESKD, and with CKD progression and mortality
Cadmium	Water, soil, air	Bone disease (itai-itai), proximal tubular dysfunction, AKI
Lead	Water, soil, air	Associated with incident and prevalent CKD, and with anemia of ESKD
Mercury	Seafood, air	Limited association with CKD
Uranium	Water	Associated with markers of kidney injury
Per- and polyfluoralkyl substances		
Perfluorooctanoic acid	Water, diet	Limited association with kidney disease
Perfluorooctane sulfonate	Water, diet	Limited association with kidney disease
Industrial degreasers		
Trichloroethylene Tetrachloroethylene	Air/water	Both cause nephrotoxicity in animal studies, limited association with CKD
Organisms and plants		
Leptospira	Water	Associated with CKD
Schistosoma	Water	Associated with CKD
Aristolochia	Water, diet	Chronic tubulointerstitial nephritis
Insecticides		
Methyl parathion, permethrin, hexachlorocyclohexane, endosulfan, dichlorodiphenyltrichloroethane	Water, diet, dermal contact	All associated with CKD, dichlorodiphenyltrichloroethane specifically associated with insulin resistance and increase risk for diabetes
Herbicides		
Alachlor, atrazine, butylate, glycophosate, metolachlor, paraquat, pendimethalin, dicamba	Water, diet, dermal contact	All associated with CKD
Heat	N/A	Associated with CKD of unknown cause, and with morbidity for patients with ESKD receiving dialysis
Natural disasters	N/A	Associated with increased morbidity for patients with ESKD receiving dialysis

N/A, not applicable.

longitudinal sample collection, such that biologic samples are available before disease onset. One such study examined the relationship between exposure to PFAS during pregnancy and fetal growth restriction (98), combining a metabolome-wide association study of PFAS exposure with a metabolome-wide association study of fetal growth to identify metabolites that were associated with both exposure and outcome. This study identified altered amino acid and lipid metabolism, linking exposure and outcome. Thus, incorporating the MITM approach can strengthen causal inference from these data.

Studies examining multiple exposures present an opportunity to expand the scope of MITM studies. These studies aim to identify environmental factors associated with the disease of interest that are examined individually or as combined exposures (99). Although few such studies are related to kidney disease, recent work in the National Health and Nutritional Examination Survey (NHANES) identified that blood cadmium, lead, and volatile organic compound exposures are associated with CKD (100). This study used biomarkers and additional studies, using survey or geospatial data, are needed to complement these findings.

By integrating multiple environmental exposures, MITM designs could help make connections from environmental exposure to intermediate markers, then to biologic effects, and finally to clinical outcomes in a stepwise fashion. Metabolome- and proteome-wide association studies of environ mental exposures can target metabolic pathways and identify biomarkers of exposure. These "exposure/early effect markers" can then be evaluated for their association with the outcome of interest (Figure 2). Although this type of study is ambitious, the infrastructure to perform it now exists. Multiple large cohorts (including participants with and without kidney disease) would lend themselves to such investigations, including NHANES, the Chronic Renal Insufficiency Study, the Atherosclerosis Risk in Communities study, and the Cure Glomerulopathy Network. Targets identified through these analyses could then be investigated in existing preclinical models to confirm their role in the pathogenesis of kidney disease. Such preclinical models already exist for exposures such as $PM_{2.5}$ and have helped to elucidate the mechanisms by which particulate matter may directly affect kidney function (101), illustrating how hypotheses generated by examining exposures in observational epidemiologic studies may be tested *in vivo*.

Finally, we acknowledge that the health effects from pollution and climate change are differentially distributed among communities in the United States and the world according to wealth/race/ethnicity (102), subjecting analyses to potential confounding and bias, and often limiting the ability to investigate associations in some subgroups. For example, distance to major roads, a proxy indicator for exposure to traffic-related air pollution and community wealth, are inversely associated with estimated GFR (103). Adequate attention to these issues and increased focus on vulnerable communities are needed to better understand the synergy of inequality and environmental exposures in the morbidity of kidney disease.

Summary and Future Directions

Current evidence suggests that environmental exposures may be important contributors to kidney disease morbidity and mortality (Table 1). Some concrete steps may help us bridge existing gaps: (*1*) regulatory agencies should adopt international consensus data on thresholds of toxicity for pollutants; (*2*) governments should consider funding an international repository of *in vitro*, animal, and human data on known environmental pollutants to facilitate pooling and mining of the data; and (*3*) researchers should integrate novel epidemiologic study designs with large biologic datasets with omics biomarkers. The ultimate goal is to inform individual-level action and public policies to potentially mitigate the risks from these environmental pollutants and reduce the burden of disease.

Disclosures

N. Franceschini reports serving on the editorial boards of *American Journal of Physiology–Renal Physiology* and *Contemporary Clinical Trials*; and serving in an advisory or leadership role as a convener for the National Heart, Lung, and Blood Institute TOPMed kidney working group, as vice-chair of the Women's Health Initiative Ancillary Committee, and on the Women's Health Initiative Publication and Presentation Committee. A.V. Kshirsagar reports having consultancy agreements with Alkahest, Rockwell, and Target RWE; serving on the editorial boards of *American Journal of Kidney Disease* and *Kidney Medicine*; and having royalties with UpToDate (as contributor). E.M. Zeitler reports receiving research funding, *via* spouse, from Dexcom, Novo Nordisk, Rhythm Pharmaceuticals, and VTV Therapeutics. All remaining authors have nothing to disclose.

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Author Contributions

A.V. Kshirsagar and E.M. Zeitler conceptualized the manuscript; A.V. Kshirsagar provided supervision and wrote the original draft; and all authors reviewed and edited the manuscript.

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