Chronic Kidney Disease Associated With Environmental Toxins and Exposures

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People are exposed to various potentially toxic agents and conditions in their natural and occupational environments. These agents may be physical or chemical, may enter the human body through oral, inhalational, or transdermal routes, and may exert effects on all organ systems. Several well-known as well as lesser known associations exist between chronic kidney disease (CKD) and both environmental agents and conditions, such as heavy metals, industrial chemicals, elevated ambient temperatures, and infections. The effects of these agents may be modulated by genetic susceptibility and other comorbid conditions and may lead to the development of acute and CKD. In this article, we present environmental factors that are associated with CKD.

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Kidney disease is receiving increased global public health attention because of a significant increase in the prevalence of the disease, the enormous cost of treatment, and the appreciation of its role as a risk factor for cardiovascular disease.1 For every patient on dialysis in the United States, there are more than 200 with stage 3 or 4 chronic kidney disease (CKD), and almost 5000 with stage 1 or 2 disease.2 In the United States, the majority of these patients have diabetes and hypertension as a primary cause of their kidney disease. Although diabetes, hypertension, and other age and obesity-associated conditions are increasingly associated with CKD in developing nations, chronic glomerulonephritis and interstitial nephritis remain common causes of CKD in the developing world, in part reflecting the higher prevalence of bacterial, viral, and parasitic infections. In addition, environmental factors such as occupational exposures and nephrotoxins may be an underappreciated cause of CKD.

The establishment of a cause-and-effect link between an environmental factor and kidney disease requires exposure analysis. A potentially causal agent must have a plausible biologic association with kidney damage and has to be present in an endemic area in sufficient quantities to induce health damage. There must be a route of contamination for the offending agent to affect susceptible individuals. Finally, this agent should cause a similar pattern of kidney injury when present in disparate geographic regions.3 In the following review, we summarize toxins and environmental exposures that have been associated with CKD. Some of these exposures, such as industrial solvents, are more commonly associated with acute kidney injury (AKI) from accidental exposure, but as they have also been implicated as a cause of CKD, they are included in this review.

Heavy Metals

Among the common environmental toxins associated with CKD, heavy metals are the most widely known (Table 1). Exposure may occur at the workplace (eg, lead smelters), but industrial environmental contamination of groundwater is also recognized as an important source of exposure that may result in kidney disease in populations without direct occupational exposure.
Environmental sources of lead exposure include lead paint (pre-1977), water from lead pipes (common in homes built before 1986), contamination of food during processing, adulterated alcohol (moonshine), leaded gasoline (now phased out in most of the world), contamination of air, water, and soil from occupational sources of lead (lead smelters, garages and old mines), indoor firing ranges, cigarette smoke, occupational exposures (battery manufacturing, welders, use of lead solder).

Lead circulates in the blood, and can either be excreted by the kidneys or can deposit in the bone. The half-life of lead is approximately 35 days in the blood and 10 to 30 years in the bone. Accordingly, blood lead levels may denote both acute exposure and may also reflect equilibration with the bone pool, whereas bone stores reflect the cumulative or chronic exposure and account for 95% of total body lead burden. Body lead burden can be measured by x-ray fluorescence or by chelation tests and measurement of urinary lead excretion, although abnormal values for this test are uncertain.

Nephrotoxicity associated with lead may have acute and chronic manifestations. Acute toxicity causes direct proximal tubular injury, likely resulting from intranuclear, cytoplasmic, and mitochondrial inclusion bodies composed of a lead–protein complex; acute toxicity most commonly manifests with a Fanconi-type syndrome, including glucosuria, aminoaciduria, and phosphate wasting, potentially caused by mitochondrial dysfunction. Chronic lead
Exposure may result in hypertension, gout, and interstitial nephritis and fibrosis. Hypertension is likely multifactorial in nature with causes including disruptions in calcium-mediated cell signaling and effects on the renin-angiotensin-aldosterone system, whereas saturnine gout results from decreased clearance of uric acid in the setting of lead toxicity. The chronic nephrotoxicity of lead classically presents as decreased estimated glomerular filtration rate (eGFR), with minimal proteinuria and bland urine sediment. Prolonged exposures, even if low level, may result in CKD by causing interstitial nephritis, hypertension, and hyperuricemia.

Diagnosis is suspected in patients who present with the above symptoms and have a history of occupational or environmental exposure to lead. The prevalence of CKD attributable to lead exposure is very difficult to determine, given the unreliability of noninvasive tests to make this diagnosis and the confounding relationship of hypertension and lead with CKD. In the United States, blood lead levels are associated with higher serum creatinine in people with CKD; fortunately, blood lead levels are progressively declining there, likely reflecting extensive public health efforts that have resulted in removal of lead from fuels and paints.

Interestingly, one placebo-controlled study in individuals with creatinine levels consistent with stage 3-4 CKD suggested that chelation therapy with calcium disodium EDTA was associated with improved kidney outcomes in individuals with only moderately elevated blood lead levels, suggesting that even relatively low level lead exposure may be associated with ongoing kidney injury. Critically, this study has not yet been reproduced in other populations. Treatment of lead nephrotoxicity consists of minimizing exposure followed by chelation therapy, as indicated. Importantly, although EDTA chelation treatment reduces lead levels in soft tissues, it is not efficacious in reaching the bone lead deposits; thus, bone turnover may be a source of long-term lead exposure.

Cadmium

Environmental sources of cadmium toxicity include combustion of fuels and industrial and household waste, tobacco smoke, sewage, foods such as sea food, vegetables and cereals, residence in cadmium polluted areas, and Indian medicinal herbs. Cadmium is also a byproduct of mining and is used industrially in plating of steel, plastics, and nickel–cadmium batteries. The oral route is the primary route for environmental cadmium exposure in the nonsmoking general population. The best known example of environmental cadmium exposure is Itai-Itai disease, related to dietary exposure to cadmium from the contaminated waters of the Jinzu River in Japan. Affected individuals presented with anemia, severe bone pain and osteomalacia, and kidney toxicity including reduced kidney function and ultimately death attributable to kidney failure.

Cadmium has a long biological half-life, ranging from 7.4 to 16 years. It induces the synthesis of a protein called metallothionein by the liver, which acts as cadmium scavenger. Low metallothionein levels, iron deficiency, older age, female gender, smoking history, and place of residence (proximity to industrial cadmium sources) are risk factors for cadmium toxicity. Clinically, cadmium nephrotoxicity presents with features of proximal tubular dysfunction such as glucosuria, aminoaciduria, and low molecular weight proteinuria. These manifestations of toxicity may occur at much lower levels of urinary cadmium concentrations than those recognized as toxic by the World Health Organization. Other renal manifestations include hypercalcuria and renal stones. There is no specific treatment for cadmium nephrotoxicity, other than supportive care and removal from exposure.

Arsenic

Environmental sources of arsenic include groundwater, pesticides (by causing food contamination), seafood, folk or alternative remedies, and products used for wood preservation. High drinking water arsenic levels have been associated with increased mortality from CKD. Arsenic levels in serum and blood cells correlate with worsening kidney disease, with the development and progression of CKD attributed to arsenic-induced
oxidative stress. A recent retrospective study in Taiwan demonstrated a negative correlation between urinary arsenic level and eGFR, and a positive correlation between plasma lycopene (antioxidant) level and eGFR in the same patients. Currently, no specific recommendations exist for treatment of nephrotoxicity from arsenic.

**Mercury**

Environmental sources of mercury include contaminated water, fresh water fish from polluted waters and predatory ocean fish, fuel combustion, and whitening creams. There is conflicting evidence of nephrotoxicity secondary to dental amalgam. The most publicized mercury exposure occurred in the mid-1950s in Japan; known as Minamata disease, mercury poisoning occurred after contamination of the waters of the Minamata Bay of the Shiranui Sea from waste from a chemical factory. This waste contaminated the local food supply, predominantly comprised of locally caught fish. Although the clinical picture of Minamata disease was dominated by neurologic symptoms, low molecular weight proteinuria was reported. Since then, epidemics have also been reported in Iraq, Ghana, and Sweden from consumption of contaminated cereals treated with ethyl mercury as pesticide.

Mercury causes both tubular and glomerular damage. It is filtered by the glomerulus and reabsorbed in the proximal convoluted tubules, resulting in tubular toxicity with low molecular weight proteinuria and enzymuria. Mercury may also cause nephrotic syndrome, either because of membranous nephropathy or minimal change disease (described after use of whitening creams). Both organic and inorganic forms of mercury may cause toxicity, and the specific renal effects may be dependent on the chemical form and valence. Although chronically reduced GFR has not been reported in association with mercury toxicity, acute intoxication may result in acute tubular necrosis with the potential for residual interstitial nephritis. Because mercury-induced nephrotoxicity is generally reversible, treatment consists of preventing further exposure.

**Uranium**

Uranium, the heaviest of the naturally occurring elements, is a metal the biological effects of which were described in the published data in as early as the 1820s. Animal studies, as well as studies of occupationally exposed persons, have shown that the major health effect of uranium is chemical kidney toxicity, rather than a radiation hazard. Exposure to uranium is mainly oral, through groundwater and food, although dermal exposure has been reported for children playing in contaminated areas. Elevated levels have been found in uranium mining as well as in non-uranium-producing communities. In the latter case, the uranium has been introduced into drinking water, not through human activity, but through natural activity, such as volcanoes, wind, and streams. It can be found as dust in the air, and this dust can dissolve in water and settle on plants, and can be found in larger particles in soil.

Environmental uranium exposure from drinking water has been associated with glucosuria, microalbuminuria, beta 2 microglobulinuria, phosphaturia, and hypercalciuria. Studies in occupationally exposed populations have also reported aminoaciduria and low molecular weight proteinuria. An epidemiologic survey also reported statistically, but not clinically significant, higher serum creatinine levels in individuals residing in close proximity to a uranium processing plant in Ohio, compared with the general US population. Treatment involves removal from the source of exposure.

**Other Environmental Nephrotoxins**

Many occupational chemicals and substances other than metals are associated with kidney disease, mediated by either acute tubular necrosis or specific kidney lesions. Kidney failure caused by many of these toxins is often acute and becomes manifest in conjunction with hypotension, central nervous system symptoms such as seizures and altered consciousness, or gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. Examples include arsine gas, carbon tetrachloride, methylene chloride,
toluene,\textsuperscript{38} and trichloroethylene.\textsuperscript{39} When these toxic agents are used for industrial purposes, extensive precautions are generally taken to avoid exposure. However, accidental inhalation, cutaneous absorption, or ingestion can occur and can either be directly nephrotoxic or cause hemolysis and rhabdomyolysis with subsequent acute nephrotoxicity, although CKD is rarely reported.

There is evidence that exposure to occupational solvents may affect the progression of underlying kidney disease even if the primary lesion is unrelated to the exposure. The GN-PROGRESS cohort study evaluated 338 non–end-stage renal disease (ESRD) patients, with an initial biopsy for primary glomerulonephritis. Lifelong solvent exposures before and after diagnosis were assessed. Subjects were followed up for 5 years for progression to ESRD. A graded relationship was observed for membranous and for IgA nephropathy between increasing degree of exposure and development of ESRD. Patients with membranous nephropathy, for example, had an adjusted hazard ratio of 5.5 (1.3-23.9) for high exposure, versus low exposure to solvents in the development of ESRD.\textsuperscript{40}

**Aristolochic Acid, Balkan Endemic Nephropathy, and Chinese Herb Nephropathy**

In 1956, Tanchev\textsuperscript{41} first observed an unusual clustering of chronic tubulointerstitial renal disease in villages, families, and households in northwest Bulgaria. The disease was so focal that, within an affected town, there would be individual households experiencing the disease next to households that were not. In addition, there was no racial, ethnic, or religious predilection for the disease. Another feature of the disease is its long incubation period. Affected individuals must live in the area for 15 to 20 years. Therefore, it has neither been identified in children nor in adults who leave the area before reaching the age of 20 years. Finally, those with the disease were at a markedly increased risk of developing upper urinary tract tumors. This disease was initially called “endemic Vratza nephritis,” and was subsequently identified in Yugoslavia and discrete regions of Romania. Reflecting this wider geographic distribution, although still confined to the alluvial plains of the Danube Rivers, it was later renamed Balkan endemic nephropathy.\textsuperscript{42} Balkan endemic nephropathy is a tubulointerstitial nephropathy with a slow progression after an insidious presentation. Early clinical manifestations include low-grade tubular proteinuria without hypertension or edema.\textsuperscript{43} In addition to kidney failure, late manifestations may also include urothelial carcinomas; these are predominantly found in the upper urothelial tract, but may also affect the bladder.\textsuperscript{44}

The cause of Balkan endemic nephropathy remains subject to debate.\textsuperscript{45} One early hypothesis was contamination of food in endemic areas by ochratoxin A, a toxin produced by molds that belong to the Aspergillus or Penicillium fungal genera. Ochratoxin A causes mycotoxin-induced porcine nephropathy, a similar pathological entity to Balkan endemic nephropathy confined mainly to Northern Europe. In addition, subjects in endemic areas have been shown to have elevated blood levels of ochratoxin A. However, ochratoxin A is an unlikely cause as there is not a close correspondence between the geographic distribution of food contamination with ochratoxin A and Balkan endemic nephropathy, as well as a lack of definitive proof for formation of ochratoxin A-DNA adducts, pieces of DNA covalently bonded to ochratoxin A and a sign of chemical damage to the cell.\textsuperscript{46}

In 1993, an outbreak of kidney failure was identified among Belgian women who received a Chinese herbal medicine for weight loss at a clinic in Brussels.\textsuperscript{47} The toxic product was identified as aristolochic acid, produced from the seeds of *Aristolochia clematitis* (birthwort). The clinical manifestations of the disease in these women were remarkably similar to those seen in Balkan endemic nephropathy, with similar morphologic characteristics and the occurrence of uroepithelial tumors. The defining kidney lesion in these women was severe tubulointerstitial fibrosis with minimal glomerular injury and negative immunofluorescent staining, and the kidney survival rate at 2-years was only 17% in the original population.

In 1967, Kazantis had proposed that Balkan nephropathy was caused by the contamination...
of the baking flour in endemic areas by seeds of *A. clematitidis*, but this hypothesis had not garnered much attention.48 However, after the identification of Chinese herbal nephropathy, there was increasing interest in this toxin as a cause of Balkan nephropathy, with the subsequent identification of covalent aristolactam-DNA adducts in affected tissues of patients with the disease,46 and the finding of “signature” mutations known to be associated with aristolochic acid in tissue of patients affected by Balkan endemic nephropathy and urothelial tumors.45 Finally, a specific Balkan endemic nephropathy–associated locus was identified in 3q25 combined with instability of the long arm of chromosome 3. These genetic alterations may determine the susceptibility for the development of the disease in people exposed to aristolochic acid and relatives of patients with Balkan endemic nephropathy.49 To date, however, genome-wide scans have not been performed to identify single nucleotide polymorphisms associated with Balkan endemic nephropathy susceptibility.

Although it seems likely that contamination of flour with aristolochic acid is a likely cause of Balkan nephropathy, a final hypothesis that continues to be explored is the proximity of Pliocene age lignites, polycyclic aromatic hydrocarbons in water originating from Pliocene age coal beds, to the communities affected by Balkan endemic nephropathy. Weathering of the low-rank coals could lead to toxic substances leaking into groundwater and transported into the drinking water of the shallow farm wells. Settlements where inhabitants use the same limited number of wells have a greater incidence of Balkan endemic nephropathy. The presence of small concentrations of organic toxic materials is compatible with a low-level, chronic poisoning of Balkan endemic nephropathy patients. The lignite hypothesis can be used to develop a predictive model; an area of Serbia without prior Balkan endemic nephropathy was identified as an endemic area after characterizing that it lay close to a low-rank coal field.

**Endemic Infections as Causes of Kidney Disease**

Although human immunodeficiency virus and both hepatitis B and C are associated with significant kidney lesions, there are several other infectious etiologies of kidney disease that are related to specific environments (Table 2). Although these infections are more commonly associated with AKI, they have been implicated in the development of CKD, perhaps through the development of severe AKI, but also possibly from chronic exposure.

**Leptospirosis**

Leptospirosis, a spirochete, is exceedingly common in warm and humid climates. Infected animals shed organisms through urine, with human infection occurring through consumption of contaminated water or mucosal contact

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<th>Table 2. Geographical Distribution of Endemic Infections Causing Kidney Disease</th>
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<td><strong>Infectious Agent</strong></td>
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| Leptospirosis | South East Asia  
              | Central America  
              | Peru (Amazon basin)  
              | Hawaii |
| Hantavirus | Old World strains—China, Korea, Japan, Europe, Russia, Syria, Lebanon, Israel  
                 | New World strains—Central and South America, United States, particularly the Southeast and Southwest |
| Malaria | Africa (*P. falciparum*, *P. vivax*, *P. malariae* in sub Saharan Africa)  
              | Indian subcontinent and South East Asia (*P. vivax*, *P. falciparum*)  
              | China (*P. vivax*)  
              | Russia (*P. vivax*)  
              | South and Central America (*P. vivax*)  
              | Middle Eastern countries  
              | Philippine Archipelago (*P. ovale*)  
              | New Guinea (*P. falciparum*, *P. ovale*) |
| Leprosy | India, Bangladesh, Indonesia |
with contaminated water or soil. A broad spectrum of clinical syndromes is caused by leptospirosis, ranging from subclinical infection and self-limited anicteric febrile illness to fatal disease. Weil’s syndrome is the most severe form of infection, presenting as a febrile illness with hemorrhagic tendencies, hepatic dysfunction, and acute renal failure. Tubulointerstitial nephritis is the main cause of AKI. Polyuria and hypokalemia with an elevated urinary fractional excretion of potassium may be seen because of proximal tubule damage. Thrombocytopenia may be associated with severe endotoxin injury and may appear in association with acute renal failure. Kidney sonography typically reveals swollen, edematous kidneys that may indicate tubulointerstitial edema by the invasion of leptospira. Penicillin and tetracycline are the drugs of choice for treatment and may significantly improve morbidity and mortality from the infection. If left untreated, the infection can lead to a chronic carrier state in which leptospira localize to the kidney and remain viable in the tubules despite the presence of host immunity, although there is no evidence that leptospirosis can lead to CKD.

**Hantavirus**

There are more than 30 different strains of hantavirus that have coevolved with a specific rodent in specific geographic regions. Human infection occurs through inhalation of aerosolized rodent excrement. All Old World hantaviruses cause hemorrhagic fever with renal syndrome, a generalized infection with hantavirus nephropathy. All pathologic New World hantaviruses belong to a second lineage and cause hantavirus pulmonary syndrome, affecting primarily the lungs. Peripheral vascular injury with severely affected permeability is generalized with the kidneys as the primary target in hemorrhagic fever with renal syndrome. Hantavirus is present in the endothelial cells of the interstitial capillaries of the medulla, but rarely in tubular interstitial cells. Clinically patients present with fever, loin or abdominal pain, proteinuria, hematuria, and reduced glomerular filtration rate, although presentation and severity depends on the particular strain of hantavirus and may progress to CKD.

**Malaria**

There are 2 renal syndromes associated with malaria: (1) chronic, progressive glomerular lesions complicating quartan malaria because of *Plasmodium malariae*, and (2) AKI associated with falciparum malaria. Chronic malarial nephropathy typically affects children aged 4 to 8 and is a steroid resistant nephrotic syndrome. The pathologic lesion is mesangiocapillary glomerulonephritis with subendothelial immune complexes containing IgG, C3, and malarial antigens. The disease progresses to renal failure even after eradication of the infection. Acute malarial nephropathy is more frequent in nonimmune Europeans compared with residents of endemic areas. Most cases are oliguric and associated with additional manifestations of malarial infection. Jaundice, anemia, thrombocytopenia, and peripheral blood pooling are common with malaria-associated acute renal failure. Proteinuria is usually less than 1 g a day, and typically resolves with recovery of kidney function. Hyponatremia and severe hyperkalemia are common. Histopathologic evaluation reveals a variable mixture of acute tubular necrosis, interstitial nephritis, and glomerulonephritis.

**Leprosy**

Leprosy is a multisystem, granulomatous disease caused by *Mycobacterium leprae* that primarily involves the skin and peripheral nervous system. The typical clinical picture includes anesthetic skin lesions, peripheral neuropathy, and palpable enlargement of peripheral nerves. The disease remains prevalent in Asia, Africa, and Latin America, with over 5 million cases worldwide. The kidney is a target organ during the splanchnic localization of the disease with a broad spectrum of pathologies. Diffuse endocapillary proliferative, membranoproliferative, focal proliferative, membranous and crescentic glomerulonephritis, renal amyloidosis, and interstitial nephritis have all been associated with the infection. Duration of the disease has a significant correlation with renal involvement.

**Schistosomiasis**

Schistosomiasis is caused by a parasitic trematode worm that lives in the abdominal veins of
the host. The urogenital system is the primary target of Schistosoma haematobium and occasionally Schistosoma mansoni infestation, with the main initial lesion being pseudotubercles, polyps, and ulcers of the urinary bladder. When these lesions heal, they lead to a wide spectrum of bladder pathology including chronic cystitis, calcification, cystitis cystica, and villous squamous cell carcinoma. Several patterns of glomerular pathology have been described with schistosomiasis, including mesangio proliferative, exudative, membranoproliferative, and sclerosing glomerulonephritis and amyloidosis. Current evidence suggests that the pathogenesis of schistosomal glomerulopathy is triphasic. Mesangial deposition of antigens of different schistosomal species induces the initial glomerular injury usually manifesting as a mesangio proliferative lesion. Further progression into overt renal disease involves a multiplicity of agent and host factors. Finally, the disease may progress to ESRD.\[^{56}\]

### Exertion, Heat Stroke, and Recurrent AKI

In epidemiologic studies, it is apparent that AKI is a risk factor for development of CKD.\[^{57}\] The pathophysiology supporting this association was reviewed in depth by Venkatachalam and colleagues,\[^{58}\] where it is stressed that recovery from AKI is often not complete and is marked by residual structural damage, with interstitial fibrosis the most notable feature. This was elegantly demonstrated in a rat model by Nath and colleagues,\[^{59}\] where repeated exposure to a heme protein-instigated, oxidant-mediated kidney injury resulted in significant chronic tubulointerstitial disease, marked by interstitial cellular infiltration, tubular atrophy, tubular dilation, and tubular casts.

It is possible that similar repetitive kidney injury may occur in people subjected to severe working environments, particularly in developing nations where workplace protection laws are less prevalent and/or less stringent and in the setting of other nephrotoxins (eg, non-steroidal inflammatory drugs). Clinically, acute exertional rhabdomyolysis is described in populations who experience extremes of exertion, including Marine Corps recruits and Olympic athletes,\[^{60}\] although few individuals with single episodes of exertional rhabdomyolysis develop acute and chronic kidney failure.\[^{61}\] However, in theory, the long-term consequences of repeated episodes of exertional rhabdomyolysis on kidney function may be an unrecognized medical burden to worker populations in high heat environments, a setting in which a preponderance of kidney disease has been described. To date, the most extensive evaluation is of gold miners in South Dakota who had a standard incidence ratio of ESRD as high as 7.7 for workers with 10 years or more experience. Although the increased risk was attributed to silica exposure, extremes of heat may be an important factor.\[^{62}\] In addition, another report describes chronic interstitial nephritis as a consequence of heatstroke in South African gold miners.\[^{63}\]

### Nicaragua and Sri Lanka—Case Examples

An illustration of the environmental influences on kidney disease can be seen in the Central American country of Nicaragua, where an excess prevalence of CKD has been described in young, male agricultural workers, clustered in the northwestern regions of Leon and Chinandega.\[^{64}\] CKD is the leading cause of death among men in these regions, and, based on data from the Nicaragua Ministry of Health, the prevalence of CKD in this region appears far higher than that seen in other regions.

Although incompletely studied, pyuria, minimal or low-grade proteinuria, and small shrunken kidneys on imaging appear to characterize the CKD. Some observers also note a high prevalence of kidney stones, whereas the prevalence of diabetes mellitus and hypertension is insufficient to explain the prevalence of CKD. The predominance of cases among males and its occurrence among younger age groups also differ from the typical patterns seen in developed countries. Several unpublished studies have found associations between presence of CKD and pesticide exposure, dehydration, residence at lower altitude, heavy metal exposure, alcohol consumption
and smoking, whereas other potential associations include urinary tract infections, nonsteroidal anti-inflammatory use, and family history. The role of exposure to volcanic ash, heat, and infections such as malaria, Chagas disease, hantavirus, leptospirosis, and schistosomiasis have been suggested as possible causal or potentiating factors worth investigation.

A similar increase in the incidence of ESRD has occurred in males from rural farming communities in Sri Lanka. As in Nicaragua, pesticide use has been suggested as a possible cause. However, other than paraquat and diquat which cause AKI associated with intentional or accidental ingestion, agrichemicals and pesticides have had limited study as causes of CKD. In a study from Sri Lanka, acetylcholinesterase-inhibiting pesticides exposure has been associated with CKD. In a study from an unidentified Latin American country, agricultural workers with reported exposure to dibromochloropropane were more likely to have elevated serum creatinine levels, although exposure to the chemical was not clearly documented nor was it detectable in water samples from the work environment. Because of the short half-life in the environment and the possibility that remote exposure may lead to toxicity, establishing a link between agrichemical use and CKD will be difficult.

**Conclusion**

Environmental factors are an important cause of acute and CKD, especially in the developing world. It is important to note that most environmental renal disease is in fact multifactorial. As an example, only 2% to 5% of the residents in an endemic area for Balkan Endemic Nephropathy progress to the disease. Furthermore, even residents of nonendemic foci who are found to have this nephropathy belong to families with other individuals with the disease. This potential genetic link is strengthened by the observation that the proportion of sick offspring increases according to the number of parents affected, and the risk of developing the disease is much greater in first-degree compared with second-degree relatives. It is, therefore, highly likely that renal lesions associated with an environmental exposure will be superimposed on a certain genetic background to create the phenotype of the disease. Further evaluation of important genetic markers such as MYH9 will provide valuable insight into the intersection of environment and genetics.

**References**