

MPHP 441: Climate Change and Health

Heat Stress and Kidney Disease

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Objectives

- Part I: Understand how heat affects human health- heat stress and the cascade of heat related illness
- Part II: Describe the intersection of climate change, kidney health, and kidney disease
- Part III: Review other climate-related threats to kidney health
- Part IV: Think about the resources we use to treat kidney disease impacts our climate



2020 U.S. CLIMATE

COOLER THAN AVERAGE WARMER THAN AVERAGE



2020 U.S. CLIMATE

SEATTLE DROUGHT MODERATE SEVERE EXTREME EXCEPTIONAL



2020 GLOBAL CLIMATE

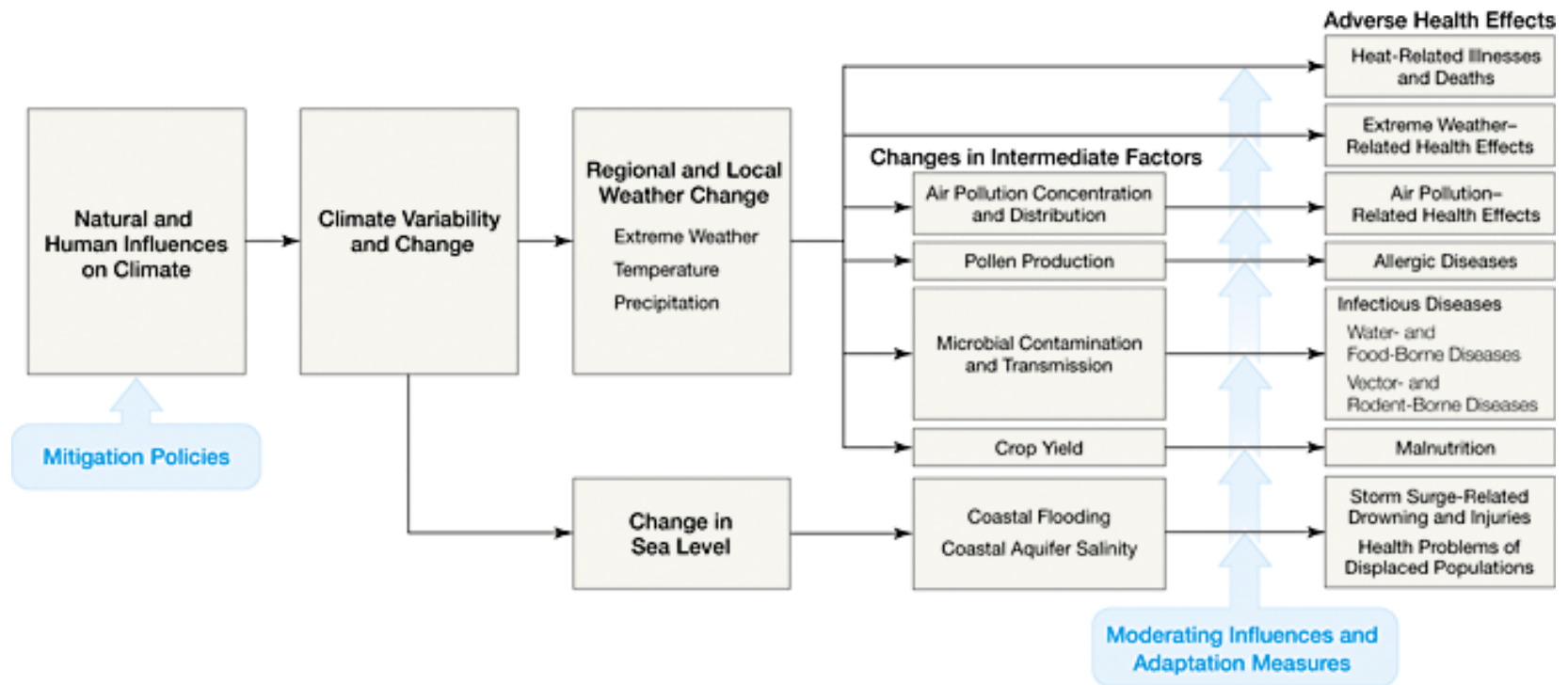
2ND HOTTEST YEAR ON RECORD

2020 GLOBAL TEMPERATURE ANOMALY
NASA GODDARD INSTITUTE FOR SPACE STUDIES

COOLER THAN AVERAGE WARMER THAN AVERAGE



Cascade of Illnesses Triggered by Climate Change



Mitigation Policies for Reduction of Greenhouse Gas Emissions

Energy Efficiency
Use of Renewable Energy Sources
Forest Preservation

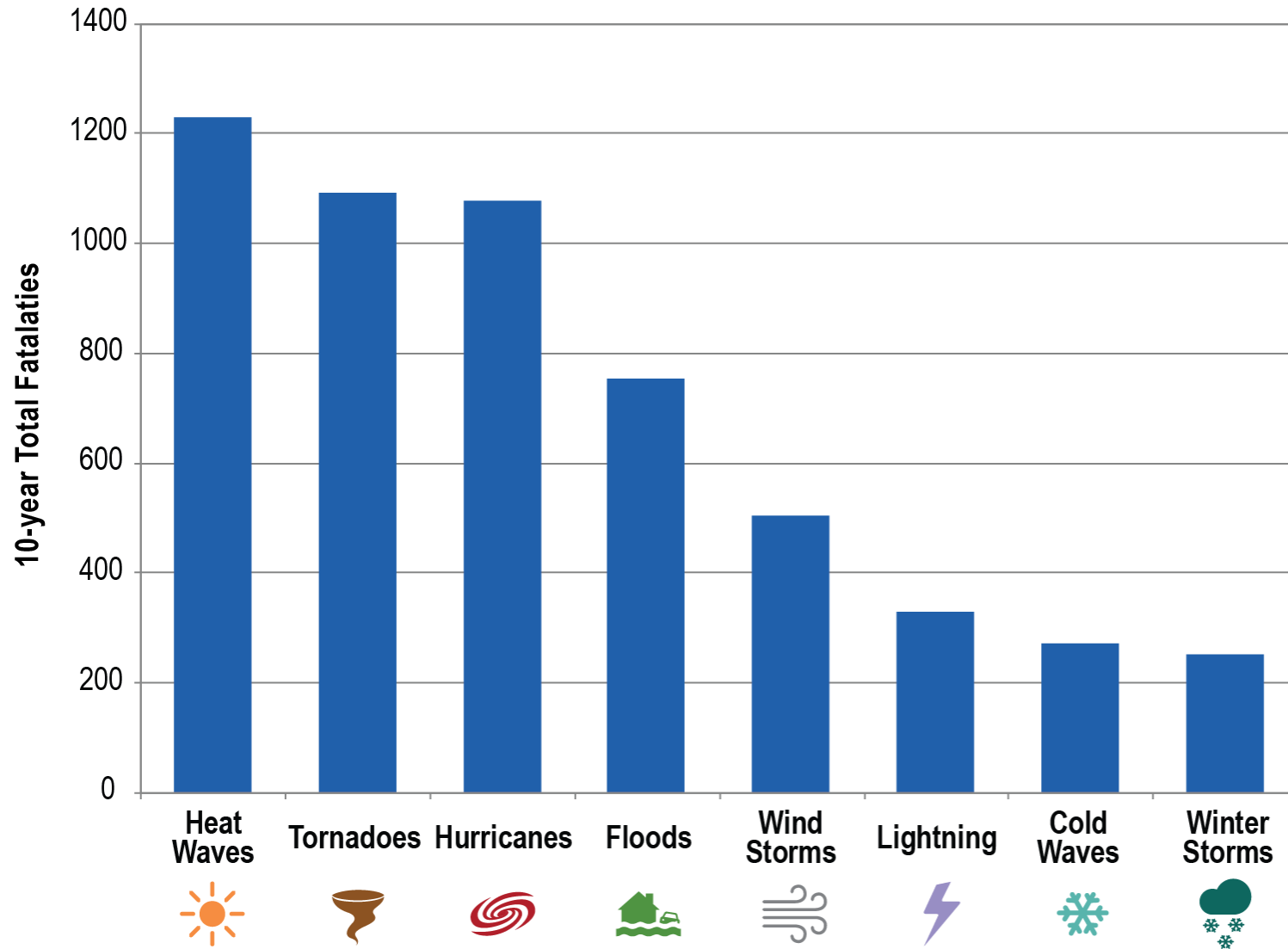
Moderating Influences

Population Density and Growth
Level of Technological Development
Standard of Living and Local Environmental Condition
Preexisting Health Status
Quality and Access to Health Care
Public Health Infrastructure

Adaptation Measures

Vaccination Programs
Disease Surveillance
Protective Technologies
Weather Forecasting and Warning Systems
Emergency Management and Disaster Preparedness
Public Health Education and Prevention
Legislation and Administration

Estimated Deaths and Billion Dollar Losses from Extreme Events in the U.S., 2004–2013



Billion Dollar Losses from Disasters (2004-2013)



\$392 Billion
Hurricanes



\$78 Billion
Heat Waves/Droughts



\$46 Billion
Tornadoes/Severe Storms



\$30 Billion
Flooding/Severe Storms

Climate Change & Kidney Disease: One piece of the puzzle

- Heat stress nephropathy
- CKDu
- Mesoamerican nephropathy
- Sri Lankan nephropathy
- Uddanam nephropathy



Wet-Bulb Globe Temperature Monitor in a Sugarcane Field in Guatemala during a Research Data Collection Day.

Characteristics of Affected Workers

Table 2: Risk factor prevalence in Salvadoran CKD patients (n = 46)

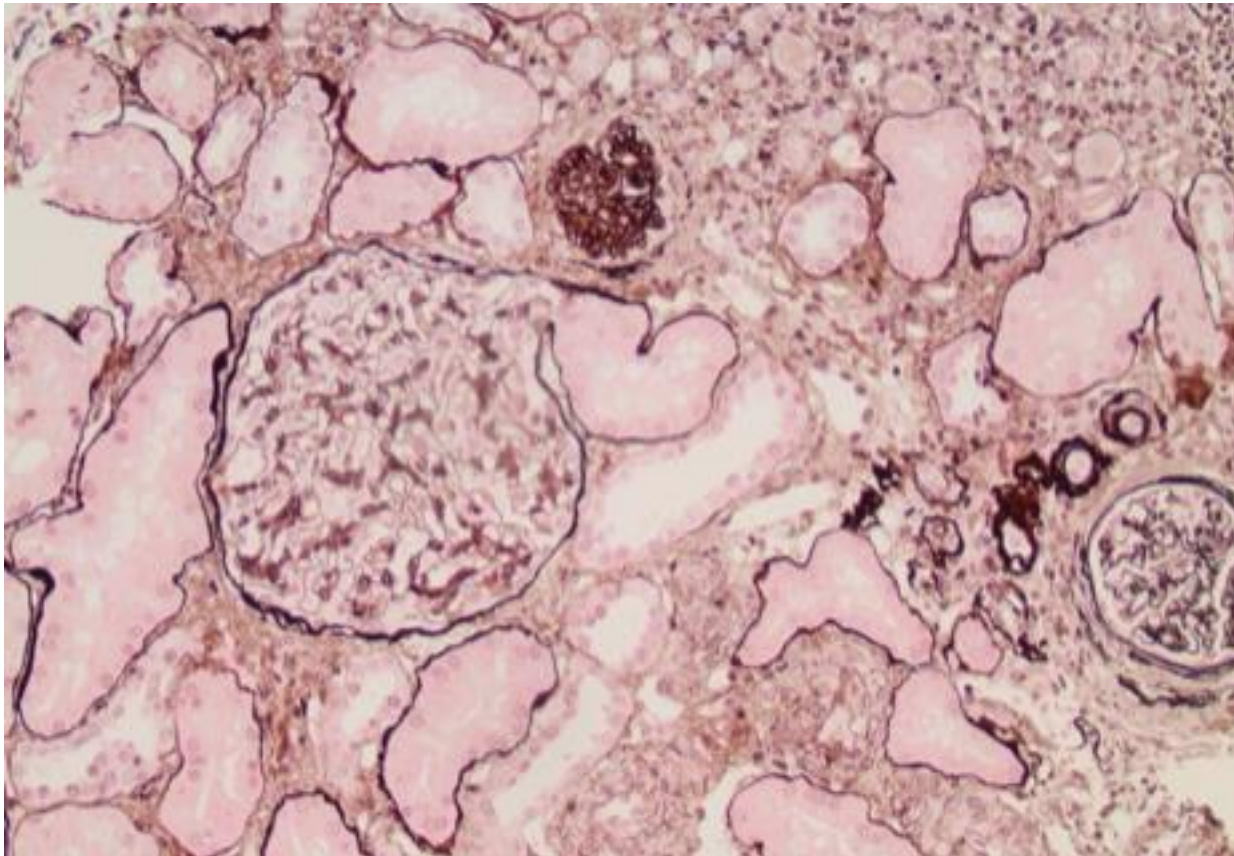
Variable	n	%
Contact with agrochemicals	44	95.7
Farmer	41	89.1
Male sex	38	78.3
Profuse sweating	35	76.1
CKD family history	20	43.5
Anemia	20	43.5
Malaria	20	43.5
NSAID use	19	41.3
Dyslipidemia	18	39.1
History of hypertension	17	36.9
Alcohol use	16	34.8
Smoker	11	23.9
Recurrent urinary tract infections	9	19.6
Nephrotoxic plant use	5	10.9
History of diabetes	2	4.3

CKD: chronic kidney disease

Table 3: Blood and urine electrolytes in Salvadoran CKD patients (n = 46)

Electrolyte	Blood						Urine			
	Normal		Low		High		Normal		High	
	n	%	n	%	n	%	n	%	n	%
Magnesium	38	78.3	9	19.6	1	2.2	0	0.0	48	100.0
Calcium	28	56.5	18	39.1	2	4.3	38	82.6	8	17.4
Potassium	31	67.4	14	30.4	1	2.2	35	76.1	11	23.9
Phosphorus	36	78.3	9	19.6	1	2.2	23	50.0	23	50.0
Sodium	24	52.2	22	47.8	0	0.0	25	54.3	21	45.7
Chlorine	34	73.9	12	26.1	0	0.0	45	97.8	1	2.2
Uric acid	40	87.0	0	0.0	6	13.0	46	100.0	0	0.0

Histology of a Patient with Mesoamerican Nephropathy



Johnson RJ, et al. N Engl J Med. 2019 May 9;380(19):1843-1852.

Location and Crop Type Matter

Prevalence of Elevated SCr

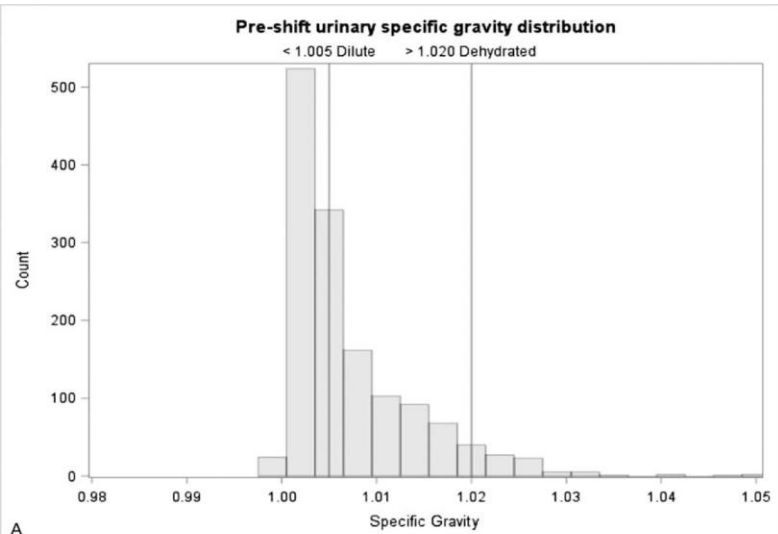
Region	Crop	Male	Female
Coastal Lowland			
	Sugarcane	37.0%	17.5%
	Cotton	29.4%	18.6%
Coastal Highland			
	Sugarcane	3.5%	0%
Coffee or subsistence		3.5%	0%

Males

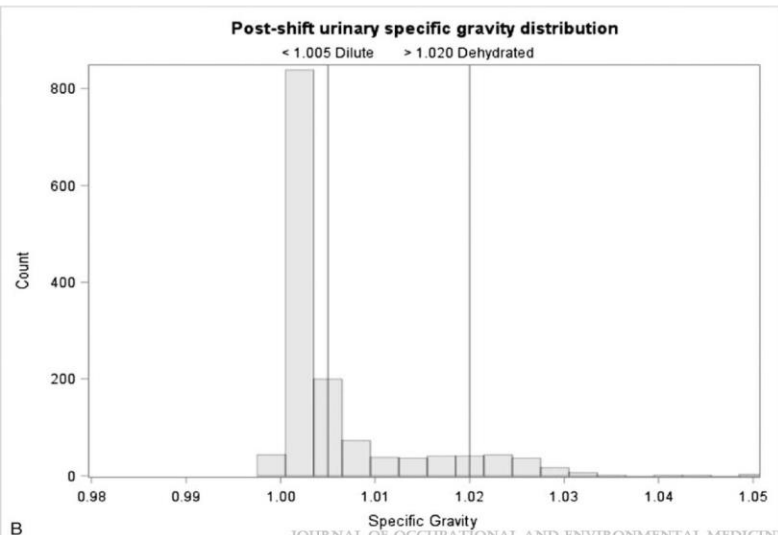
Females

Time working in coastal sugarcane or cotton (/10-y increase)		Males			Females	
Entire study population	—	3.5 (2.2-5.4)	3.1 (2.0-5.0)	—	2.4 (1.5-3.9)	2.3 (1.4-3.7)
Subpopulation of coastal communities	—	2.5 (1.6-4.1)	1.9 (1.2-3.3)	—	2.0 (1.3-3.2)	1.7 (1.0-2.9)

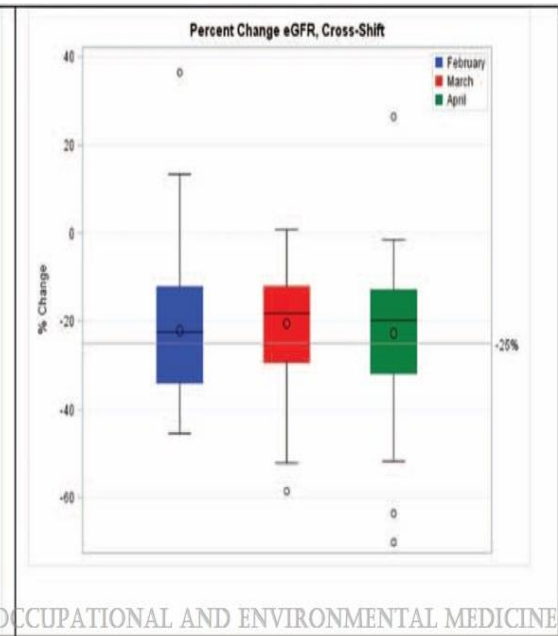
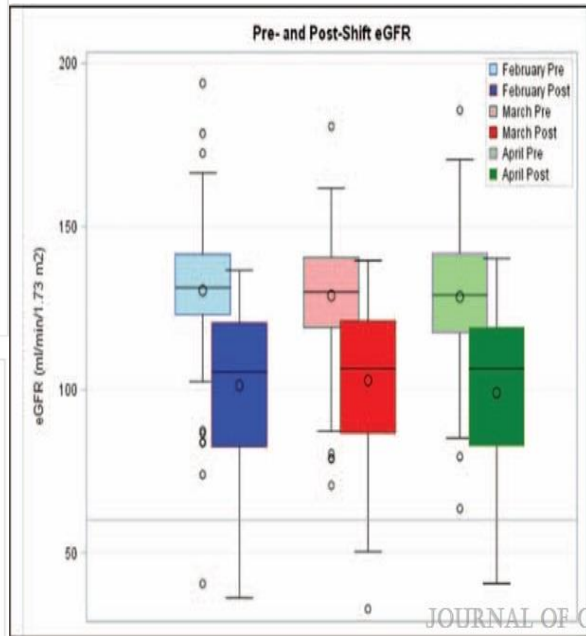
Mechanisms of Kidney Injury



A

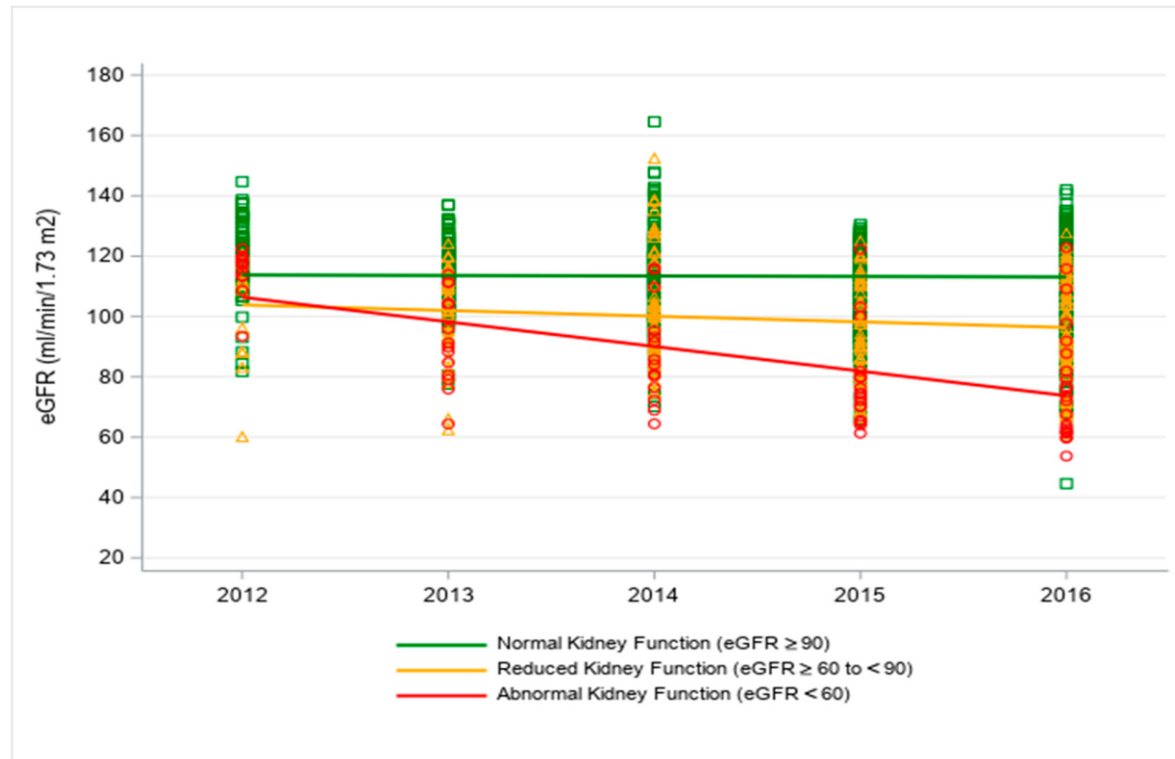


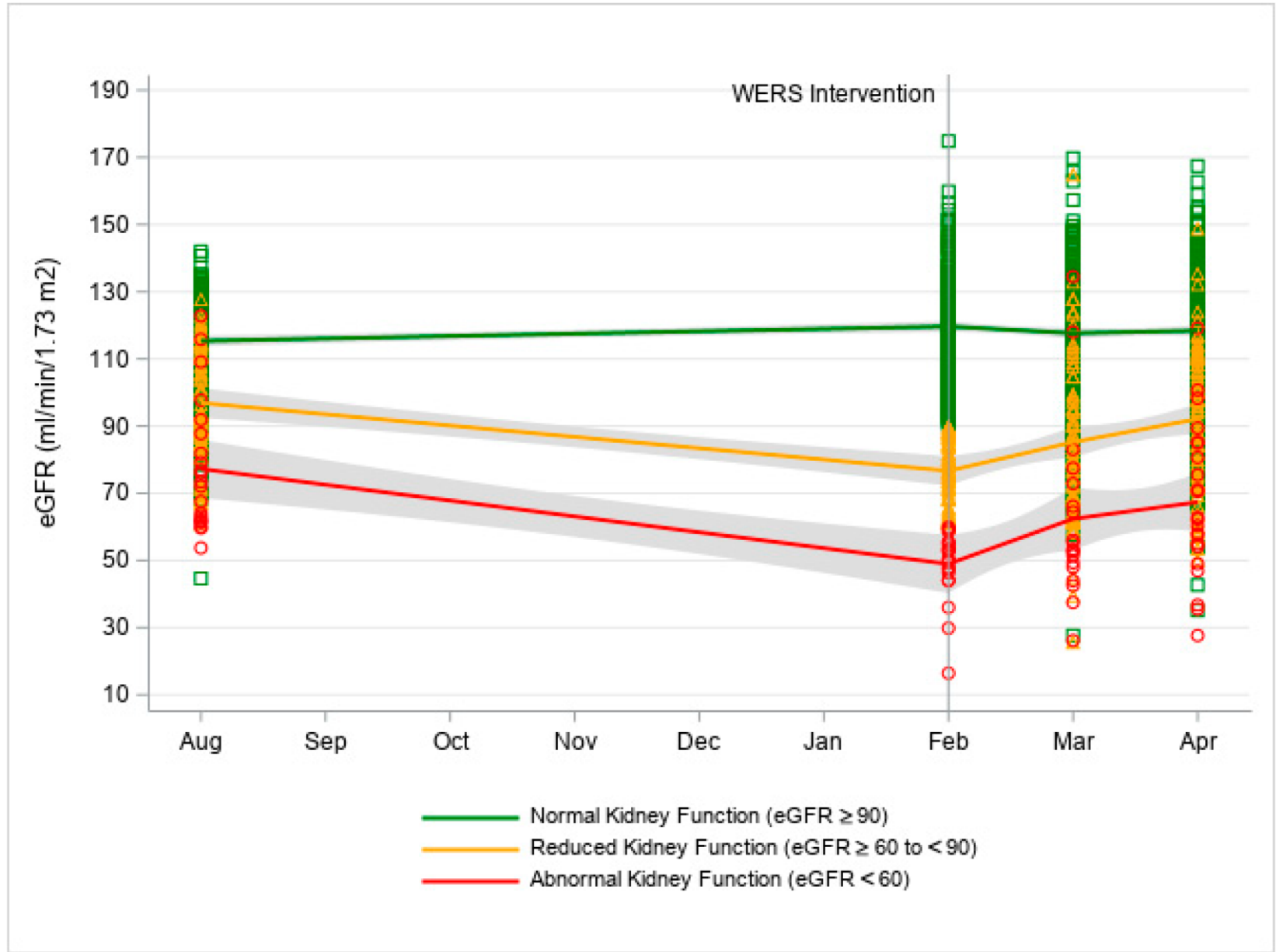
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JOURNAL OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Screening and Intervention to Slow Progression of Kidney Disease





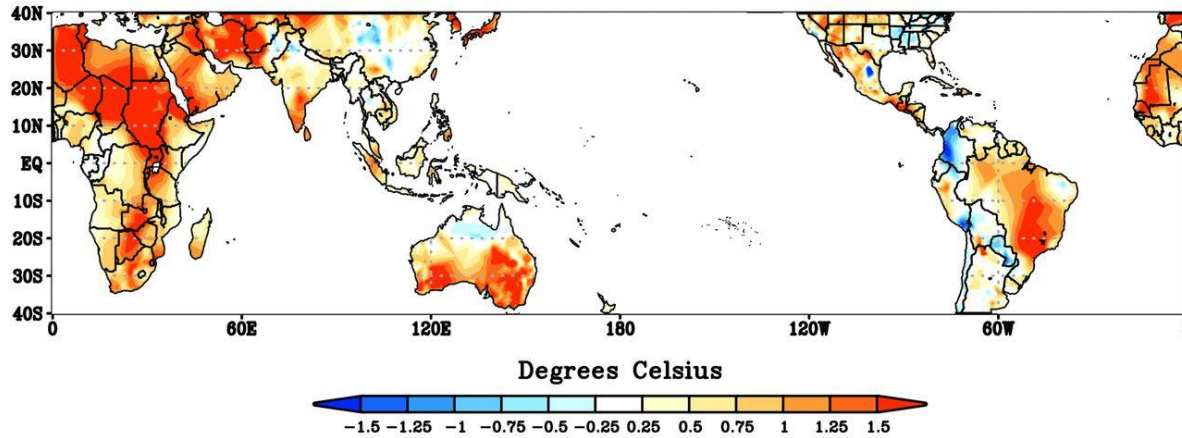
Clinical Implications



Krinsky and Levine. *Kidney International* (2014) 86, 221–223.

Kidney Disease Epidemics Occurring Elsewhere

Tmax Change 1945–2014



Average Tmax 1951–2010

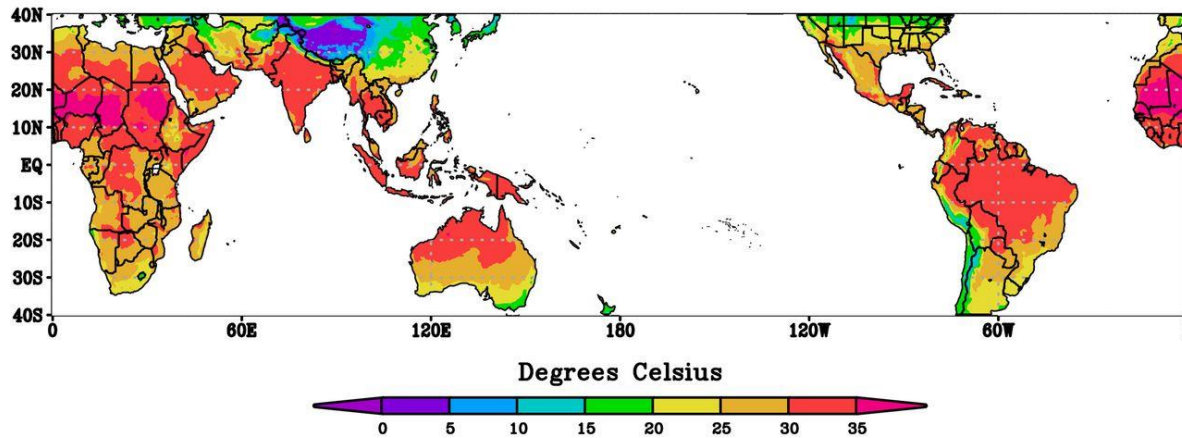
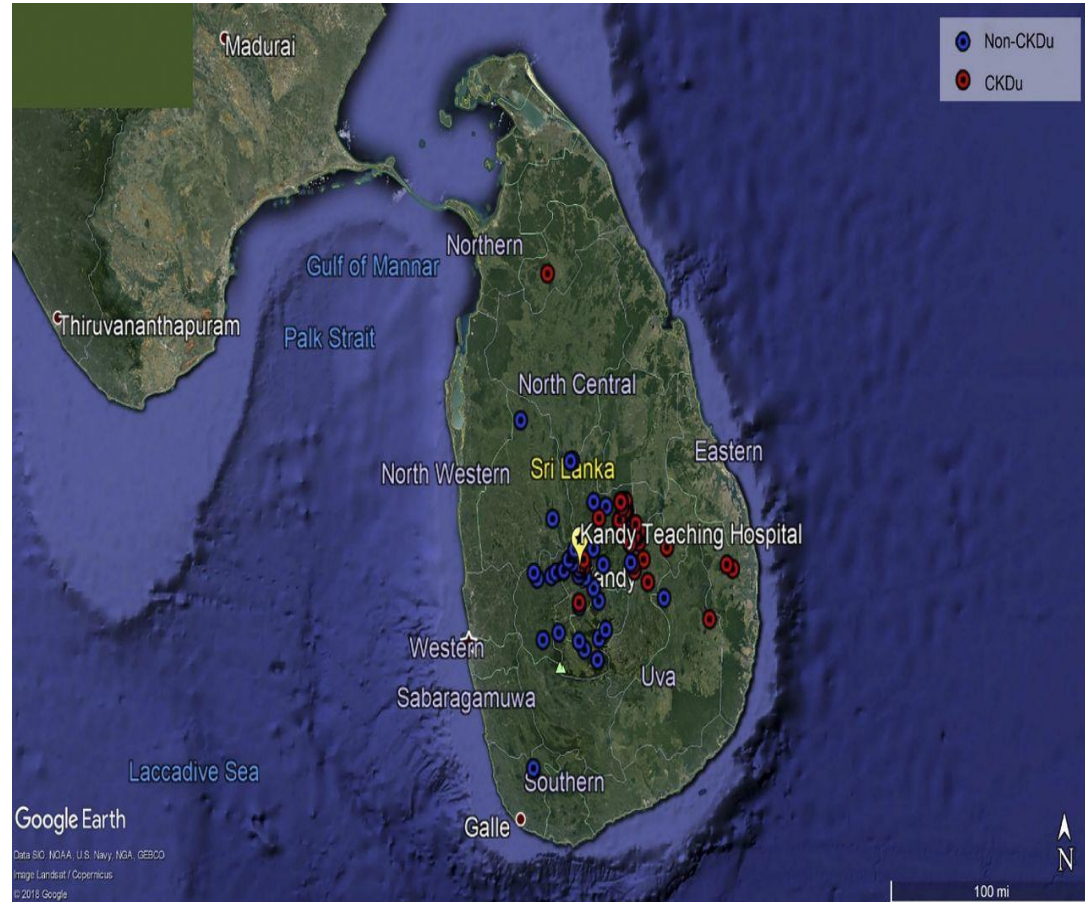


Table 1. Confirmed and suspected sites of heat stress-associated nephropathy (CKD)

Country	Region	Reference
Confirmed Sites		
Central America		
<i>Costa Rica</i>	Guanacaste	Wesseling <i>et al.</i> (39)
<i>El Salvador</i>	Bajo Lempa	Orantes <i>et al.</i> (45)
<i>Guatemala</i>	Southwest Region	Laux <i>et al.</i> (105)
<i>Nicaragua</i>	León and Chinandega	Torres <i>et al.</i> (36)
South Asia		
<i>India</i>	Andhra Pradesh	Reddy and Gunasekar (79), Abraham <i>et al.</i> (30)
<i>Sri Lanka</i>	North Central Region	Jayatilake <i>et al.</i> (72) Jayasumana <i>et al.</i> (106)
Possible Sites		
South Asia		
<i>India</i>	Goa, Odisha, and Maharashtra	Rajapurkar <i>et al.</i> (107)
<i>Thailand</i>	Northeast (Isan Region)	Sirirat Anutrakulchai (personal communication)
Middle East		
<i>Saudi Arabia</i>	Tabuk region	El Minshawy <i>et al.</i> (108)
Africa		
<i>Egypt</i>	El-Minia, Upper Egypt	El Minshawy <i>et al.</i> (96)
<i>Sudan</i>	Southern Sudan	Elamin <i>et al.</i> (109)
North America		
<i>Mexico</i>	Tierra Blanco, Veracruz	Mendoza-González <i>et al.</i> (90)
<i>United States</i>	California Central Valley	Moyce <i>et al.</i> (93)

Sri Lankan Nephropathy

- 1990s, rice paddies in rural region
- Men > Women
- Ages 40-50 yrs
- Asymptomatic rise in creatinine
- Electrolyte changes (hypoNa, K, Mg; hyperuricemia)



Shuchi Anand et al. CJASN 2019;14:224-232

Uddanam Nephropathy

- Noted in 1990s
- Coconut, cashew and rice farming
- Asymptomatic, bland urine
- Biopsy shows interstitial nephritis

#STOPCKDu team helping ensure that #dialysis patients in Andhra Pradesh continue to receive their life-saving treatment. Read full report from @gummidibalaji: bit.ly/2JwnWYY

#COVID19India #21DaysLockdown



7:58 AM · Apr 1, 2020 · Twitter Web App

Table 1. Demographic and Clinical Characteristics of Chronic Kidney Disease of Unknown Cause.*

Variable	Mesoamerican Nephropathy	Sri Lankan Nephropathy	Uddanam Nephropathy
Region	Pacific Coast, rural areas from Mexico to Panama	North Central Province	Central Indian states of Andhra Pradesh, Odisha, Chhattisgarh, Maharashtra
Demographic features	Age range, 20–50 yr Male:female ratio, $\geq 3:1$	Age range, 40–50 yr Male:female ratio, 1.3:1	Age range, 30–60 yr More common in men
Affected population	Sugarcane workers, cotton workers, corn farmers, construction workers, port workers, miners, fishing industry workers, shrimp farm workers, brick workers	Rice farmers	Cashew, rice, and coconut farmers
Hypothesized causes			
Heat exposure	Low-altitude areas with hot tropical climate, physical exertion, recurrent dehydration	Low-altitude areas with hot tropical climate	Coast and inland up to 60–70 m above sea level with hot tropical climate
Other	Toxic causes: pesticides, heavy metals, NSAIDs, tobacco use Infections: leptospirosis, hantavirus infection Gene–environment interactions	Cadmium, pesticides (glyphosate), hard water, high fluoride content in drinking water, arsenic, glyphosate chelation with metals, low water intake, malaria	Silica in groundwater, excessive use of painkillers, low water intake
Clinical findings			
Acute phase	Fever, elevated serum creatinine level, muscle and joint pain, leukocytosis, leukocyturia, hematuria	Fever, fatigue, dysuria, joint pain, elevated serum creatinine level	Not described so far
Chronic phase	Insidious presentation (elevated serum creatinine level), low-grade or no proteinuria, hypokalemia, hyponatremia, hypomagnesemia, frequent hyperuricemia, reduced kidney size on ultrasound	Insidious presentation (elevated serum creatinine level), low-grade or no proteinuria, hypokalemia, hyponatremia, hypomagnesemia, frequent hyperuricemia, reduced kidney size on ultrasound	Insidious presentation (elevated serum creatinine level), low-grade or no hypertension, low-grade or no proteinuria, microscopic hematuria (rare), reduced kidney size on ultrasound

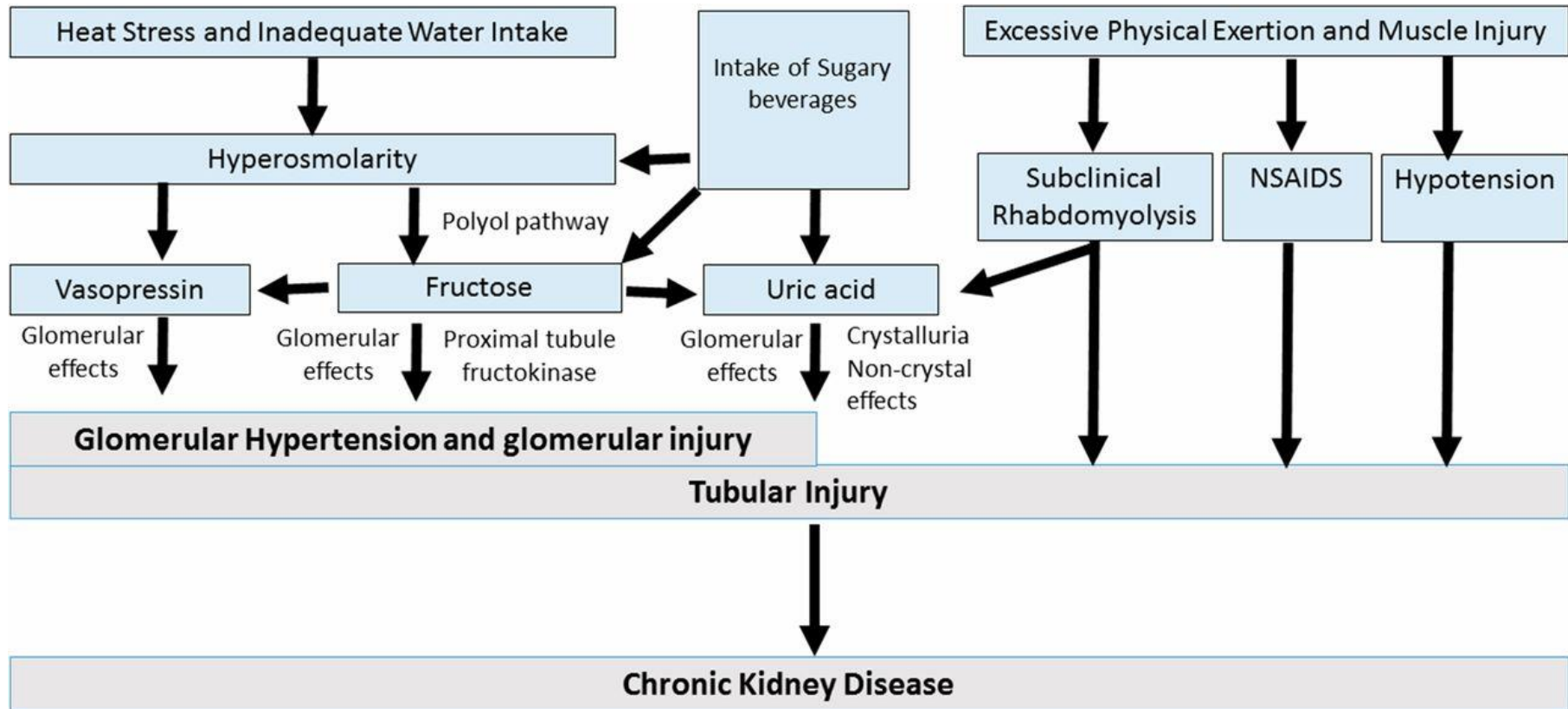
* NSAIDs denotes nonsteroidal antiinflammatory drugs.

Can It Be the Heat Alone?

Table 2. Hypothesized Occupational and Environmental Risk Factors for the Development or Progression of Chronic Kidney Disease (CKD).

Possible Cause	Potential Mechanisms	Positive Evidence	Negative Evidence
Heat and dehydration	Repeated intermittent injury from four processes: Heat stroke (elevated body temperature) with inflammatory response Dehydration leading to hyperosmolarity, mediated by vasopressin and polyol pathway Heat exposure and exertion, leading to repeated subclinical rhabdomyolysis Increased core temperature, leading to uricosuria or crystalluria	Heat and dehydration cause CKD in animals CKD occurs in hot regions, and symptoms of dehydration are common Acute kidney injury correlates with heat exposure and physical exertion Heat stroke may cause acute kidney injury with late chronic interstitial nephritis Hyperuricemia and urate crystalluria are common in sugarcane cutters	There is limited evidence that acute kidney injury during a work shift leads to CKD CKD has not been reported in some extremely hot regions of the world Many occupations associated with heat exposure have not been associated with an increased risk of CKD No studies have shown that preventing acute kidney injury with hydration reduces the risk of CKD Hyperuricemia is not required for CKD to develop
Pesticides: glyphosate, paraquat, 2,4-dichlorophenoxyacetic acid, atrazine, cypermethrin, organophosphates, carbamates	Uptake from urine into the proximal tubule of the kidney, with toxic effects	Pesticides are commonly used in agriculture, and some are known to be nephrotoxic; they can get into soil, crops, and groundwater The increase in Sri Lankan nephropathy in the 1990s corresponded with increasing mechanization and use of pesticides	Most studies show minimal levels of pesticides in the drinking water in affected regions No obvious signs of pesticide intoxication have been reported in association with CKD Pesticides comprise hundreds of active ingredients, and pesticide use is heterogeneous across regions and crops Besides glyphosate, no potential etiologic agent has been identified CKD has not been reported in many regions with extensive use of glyphosate or other pesticides
Heavy metals, minerals, and halides: arsenic, cadmium, lead, silica, fluoride, other (magnesium, mercury, nickel, uranium)	Uptake from urine into the proximal tubule of the kidney, with toxic effects	Many metals have known toxic effects on the kidney Silica levels are high in wells in areas affected by Uddanam nephropathy, and silica is also present in sugarcane soot and air particles; silica can cause chronic interstitial nephritis in animals	Most studies have not shown elevated concentrations of heavy metals or fluoride in groundwater; patients with CKD do not have silicosis of the lung
Infections: leptospirosis, hantavirus infection, vector-transmitted diseases (malaria, dengue)	Leptospirosis and hantavirus infection can cause acute kidney injury, leptospirosis can cause acute interstitial nephritis and fever, and malaria and dengue can cause acute kidney injury	Leptospirosis is common in rural agricultural workers, as are malaria and dengue; chronic infection from leptospirosis can lead to chronic interstitial nephritis	There is no evidence that leptospirosis or other infections are more common in patients with CKD than in those without CKD
Other: NSAIDs, tobacco smoking, sugared and phosphate-containing drinks (fructose and phosphate), alcohol (illegal alcohol), aristolochic acid, herbal remedies	Most of these are known risk factors for acute kidney disease or CKD	Some of these have been reported to be risk factors for Mesoamerican and Sri Lankan nephropathy (especially NSAIDs and tobacco)	Many persons in these regions in whom CKD develops do not have a history of NSAID or tobacco use

Metabolic Changes Contribute to Kidney Disease



Climate Related Threats to Kidney Health

- Air Pollution
- Heavy Metals
- Natural Disasters

Environmental Pollution and Kidney Disease

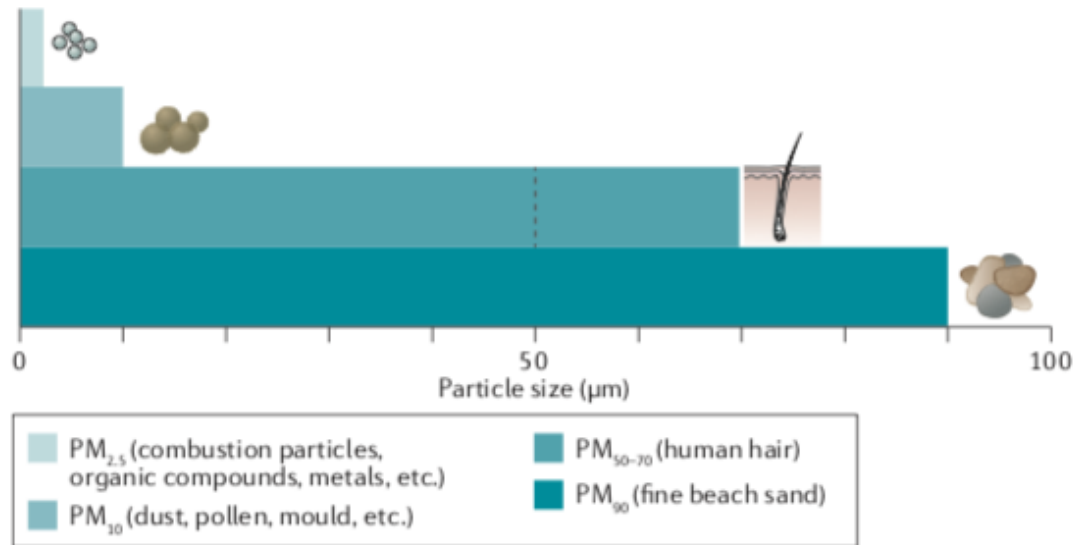


Figure 2 | **Size classification of particulate matter.** Particulate matter (PM) in airborne pollutants is classified based on the mean aerodynamic diameter of particles into PM₁₀ (<10 µm), PM_{2.5} (<2.5 µm) and ultrafine particles (<0.1 µm). The sizes of various biological entities are depicted for comparison.

Kidney Disease Can be Attributed to Air Pollution

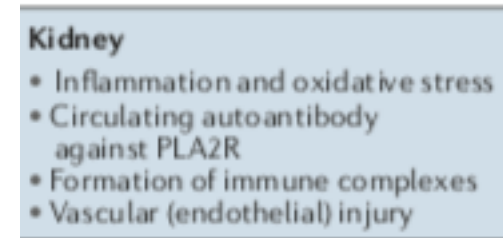
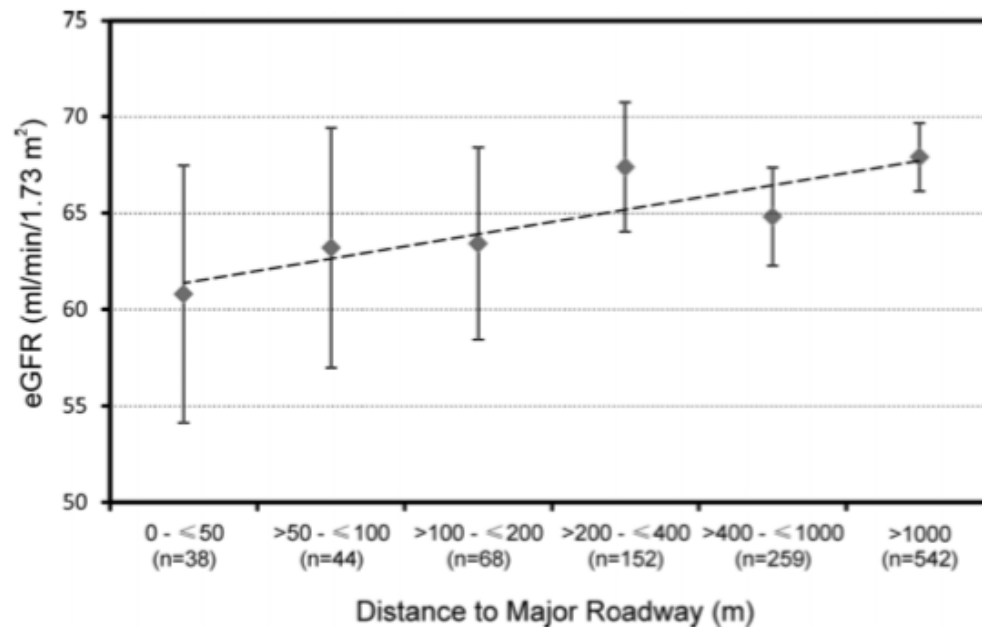
Table 1 Attributable burden of chronic kidney disease (ABD) associated with PM_{2.5} exposure globally and for the top 10 most populous countries

Country	PM _{2.5} (μg/m ³)	ABD (in 1000s)	ABD (per 100 000)	Age-standardised ABD (per 100 000)
Global	42.27	6950.51 (5061.53–8914.74)	94.29 (68.67–120.94)	101.39 (74.49–129.69)
China	57.2	766.73 (558.72–985.14)	55.42 (40.39–71.21)	48.98 (35.52–63.01)
India	72.6	1092.52 (791.38–1407.28)	83.30 (60.34–107.29)	108.21 (77.99–139.22)
US	8.3	163.49 (88.76–262.78)	50.53 (27.44–81.22)	35.44 (19.39–57.44)
Indonesia	15.0	76.81 (53.66–103.42)	29.81 (20.83–40.15)	37.38 (26.05–50.06)
Brazil	11.1	69.03 (45.11–99.44)	33.21 (21.70–47.84)	36.57 (23.68–52.72)
Pakistan	63.0	107.43 (78.85–137.04)	56.83 (41.71–72.49)	89.17 (64.66–114.14)
Nigeria	36.9	195.23 (141.44–250.95)	106.98 (77.51–137.52)	200.28 (145.24–261.20)
Bangladesh	87.0	136.17 (99.56–174.46)	84.60 (61.86–108.39)	121.08 (88.55–156.18)
Russia	15.8	170.89 (118.90–229.76)	115.38 (80.27–155.12)	82.87 (57.99–111.67)
Japan	13.1	134.56 (91.13–186.81)	104.88 (71.03–145.60)	44.79 (30.61–61.70)

PM_{2.5}, fine particulate matter <2.5μm.

Bowe B, Xie Y, Li T, et al. BMJ Open 2019;9:e022450. doi:10.1136/bmjopen-2018-022450

Epidemiological Evidence of Air Pollution and Kidney Disease

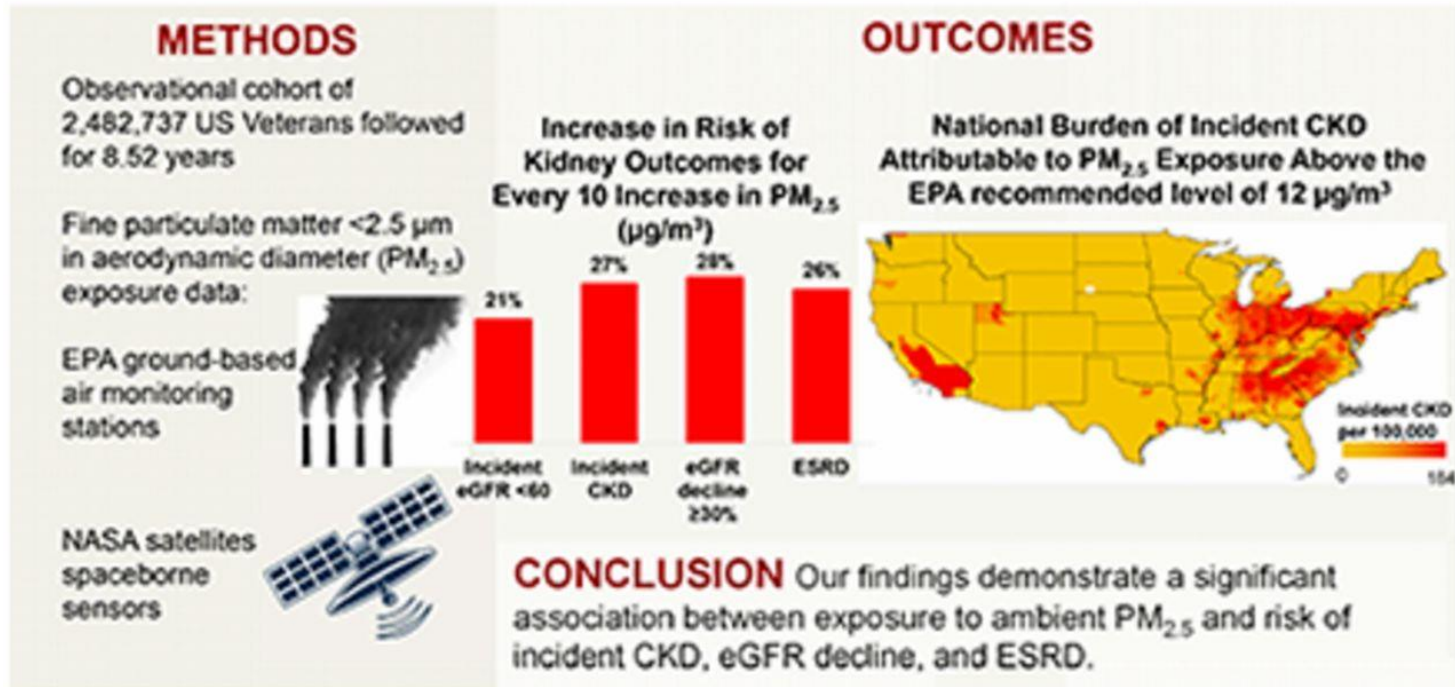


Xu X, et al. Nat Rev Nephrol. 2018 May;14(5):313-324

Figure 2 Adjusted mean estimated glomerular filtration rate (and 95% CIs) by distance to major roadway. Adjusted for age, sex, race, smoking status, diabetes, hypertension, heart failure, coronary artery disease, treatment with ACE inhibitor, median household income and percentage of residents without high school diploma.

Lue S, Wellenius GA, Wilker EH, et al. J Epidemiol Community Health 2013;67:629-634.

Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD



doi.org/10.1681/ASN.2017030253

JASN

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Benjamin Bowe et al. JASN 2018;29:218-230

JASN

Journal of the American Society of Nephrology

Heavy Metals and Kidney Disease

- Mining
- Industry
- Urban expansion
- Fertilizers



Table 1 | Effects of heavy metal pollution on the kidney

Metal	Source of exposure	Kidney injury	Mechanisms
Cadmium	Contaminated food (rice); cigarette smoke; industrial waste; occupational exposure (mining, production of batteries, plating of steel and plastic manufacturing)	Proximal tubular dysfunction (glucosuria, aminoaciduria and low-molecular-weight proteinuria) ^{83,84,131} ; reduced GFR	Oxidative stress ⁸⁵ ; impaired DNA repair ⁸⁶ ; reduced antioxidant ability; cellular apoptosis ⁸⁷
Lead	Contaminated food; petroleum; contaminated air, water and soil polluted with industrial waste; cigarette smoke; occupational exposure (mining, production of batteries, welding and lead soldering)	Proximal tubular dysfunction ¹¹⁰⁻¹¹³ ; interstitial fibrosis ¹³² ; tubular atrophy ¹³³ ; reduced GFR	Oxidative stress ¹³⁴ ; increased TGFβ expression and lipid oxidation ^{115,116} ; mitochondrial dysfunction ¹¹⁴ ; DNA fragmentation ¹³⁵
Mercury	Contaminated water; fish from polluted waters; fuel combustion; skin-whitening creams; mining	Secondary membranous nephropathy ¹³⁶ ; interstitial nephritis; acute tubular necrosis ¹³⁷ ; reduced GFR	DNA damage ^{90,91} ; mitochondrial dysfunction ¹³⁸ ; reduced enzymatic activity ¹³⁹
Arsenic	Occupational exposure (mining, wood preservatives, smelting metal ores and pesticides); contaminated seafood and water; specific medication	Tubular interstitial nephritis; acute tubular necrosis ¹⁴⁰ ; reduced GFR	Oxidative stress; reduced expression of RKIP ¹⁴¹ ; DNA methylation and histone acetylation ¹⁴² ; DNA oxidation; reduced antioxidant defences ¹⁴³

GFR, glomerular filtration rate; RKIP, RAF kinase inhibitor protein; TGFβ, transforming growth factor-β.

Xu X, Nie S, Ding H, Hou FF. Environmental pollution and kidney diseases. *Nat Rev Nephrol.* 2018 May;14(5):313-324

Heavy Metals and Kidney Health

- Itai-Itai disease from cadmium nephrotoxicity
- Anemia, severe bone pain, osteomalacia, and kidney failure



The [Jinzū River](#) in Toyama Japan, where cadmium-containing industrial waste was dumped. This began the spread of Itai-itai disease.

Kobayashi E, et al.. Environ Toxicol. 2009 Oct;24(5):421-8.

https://en.wikipedia.org/wiki/Itai-itai_disease

Dialysis



Climate Change and
Rising Temperatures



Increased
Number of
Extreme Heat
Days



Increased
Land Surface
Temperature



Increased
Number and
Severity of
Heat Waves



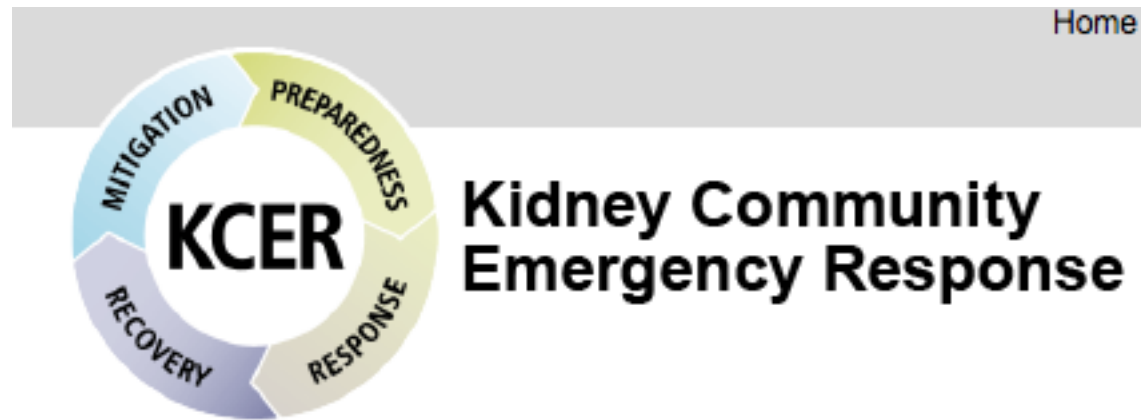
Natural Disasters



Heat Stress Nephropathy



Healthcare Delivery in Climate Change



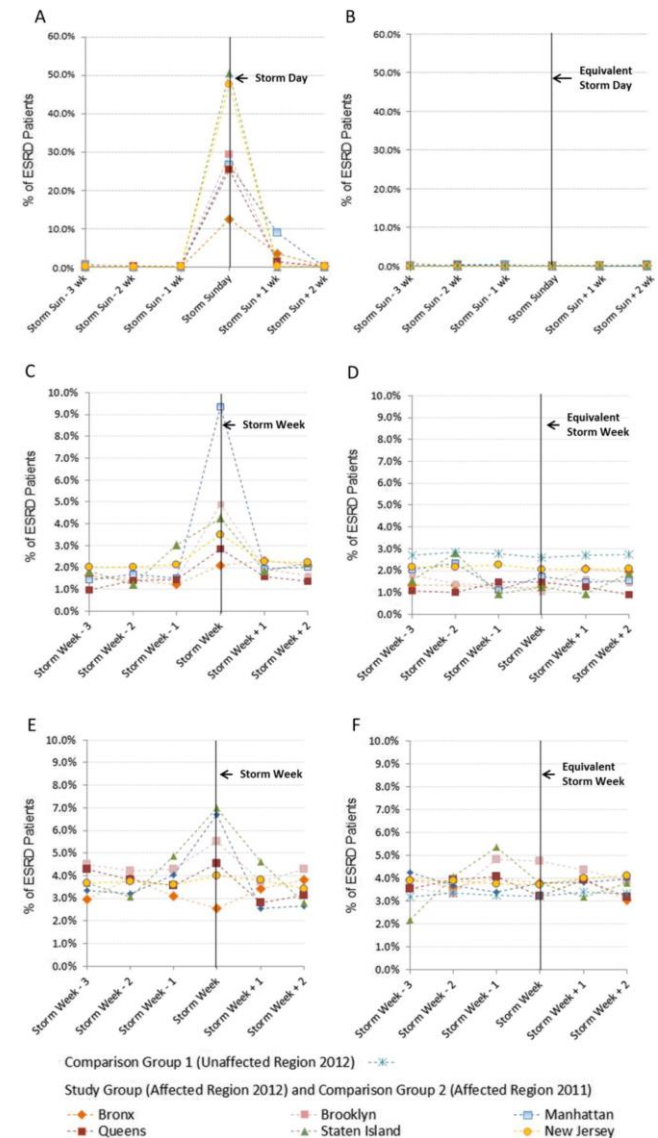
<https://www.kcercoalition.com/en/esrd-networks/>

Natural
Disasters

Impact of Hurricane Sandy on Dialysis Patients in the NE

- Identified 221 dialysis units affected by storm, representing approximately 15,000 dialysis patients
- 4.5% hospitalized (3.2-3.8%), 4.1% with ED visit (1.7-2.6%), 1.8% with 30-d mortality (1.5-1.6%)

Kelman J, et al. Am J Kidney Dis 2015;65(1):109-115.



Care for Dialysis Patients During and After Hurricane Maria



The facade of the shuttered Diagnosis and Treatment Center where dialysis patients once received treatments, in Vieques, Puerto Rico. Weeks after Hurricane Maria hit, health officials declared it contaminated and ordered that it be permanently (Carlos Giusti / AP)

<https://www.baltimoresun.com/photos/darkroom/bs-dk-puerto-rico-maria-ap-20180919-htmstory.html>

Kidney Disease Threatens Climate Health

- Resource utilization in dialysis– “Green Nephrology”
- WATER
- POWER
- SUPPLIES/WASTE



Dialysis

Water

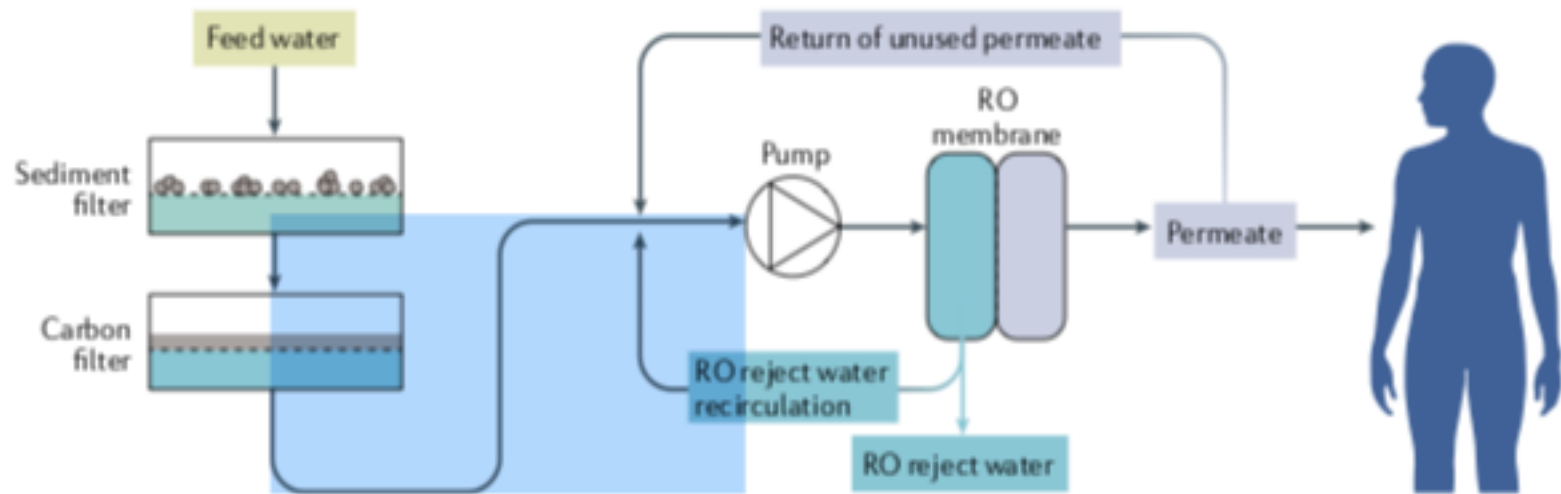


Fig. 3 | **Water treatment in haemodialysis.** Feed water is passed through a sediment filter to remove suspended solids and then a carbon filter to remove chlorine, chloramines and organic matter by absorption. The water is then pumped across a semi-permeable membrane that removes any remaining dissolved ions and salts via reverse osmosis (RO). This treatment produces water of a quality suitable for haemodialysis. The by-product is a similar volume of RO 'reject' water. Modern RO systems have the ability to recirculate a proportion of the reject water along with any unused permeate back to the inlet to be passed again through the RO membrane, thereby reducing water wastage.

Barracough KA, Agar JWM. Green nephrology. *Nat Rev Nephrol.* 2020 May;16(5):257-268.

Power/Waste

- Electricity use per dialysis treatment (at 2 Australian centers) was 12.0kWh- 19.6 kWh
- Ref: Australian household uses 18.7kWh per day
- 1.5-8 kg of waste per treatment reported. Less than 1/3 of the non-hazardous waste recyclable.
- Very large carbon footprint; difficult to estimate pharmaceutical carbon footprint

Table 1. Examples of Environmental Improvement Initiatives Undertaken and Benefits Obtained

	Measures	Costs and Benefits
Individual Dialysis Services		
Australia	Installation of HD RO reject water capture and reuse infrastructure in the hospital and home settings	Investment costs of ~AUD \$5,500 in the hospital setting and AUD \$1,500-\$2,000 in the home setting; savings of ~350 L of water per treatment ^a
Australia	Installation of a solar power system on a home HD unit	Investment cost of AUD \$16,219; 91% reduction in grid power consumption; 76.5% reduction in power costs; return on investment in 7-8 y
UK	Installation of RO reject water capture and reuse infrastructure in a new dialysis unit build	Investment cost of £2,500; annual savings of 4,492,000 L of water and £10,558 ^b
UK	Installation of baling machine to compact cardboard and plastic waste	Investment cost of £3,500 and annual running cost of £587; annual diversion of 1 ton of cardboard and 4.2 tons of plastic from landfill; annual savings of 8.665 tons of CO ₂ e and £4,150
UK	Improved recycling and diversion of waste from clinical to domestic waste streams across 6 HD units	Annual savings of 86 tons of CO ₂ e and £15,567
Italy	Emptying of residual fluid from receptacles before their disposal; staff training in best practice waste management	Up to 7 kg less hazardous waste generated and an average of €10 saved per HD treatment
Fresenius Medical Care (NephroCare)^c		
Electricity	Individualized meters for measuring per-dialysis treatment electricity consumption; upgrade to more energy-efficient lighting; progressive replacement of dialysis machines to more energy-efficient alternatives; installation of motion detectors and timers to automatically control lighting; reduced facility size ^d ; air conditioning programming; downsizing of administration offices; movement of a dialysis unit to a high environmental quality building	Reduction in electricity use from 23.11 to 16.26 kWh/session and savings of 92,400 tons of CO ₂ e over the 13-y study period
Water	Individualized meters for measuring per-dialysis treatment water consumption; progressive replacement of dialysis machines to more water-efficient alternatives; upgrades to water treatment systems	Reduction in water use from 801 to 382 L/session and savings of 17.5 tons of CO ₂ e over the 13-y study period
Care-related waste	Staff training in optimum waste management; caregiver training for waste sorting; regular audits	Reduction in waste from 1.77 to 1.11 kg/session and savings of 10,000 tons of CO ₂ e over the 13-y study period

Yau A, Agar JWM, Barraclough KA. Am J Kidney Dis. 2020 Nov 7:S0272-6386(20)31075-1.

Summary

- Climate change confers multiple adverse health effects in humans
- CKDu is an epidemic consequence of heat stress nephropathy manifesting in vulnerable populations throughout the globe
- There are many other climate-related threats to kidney health including air pollution and natural disasters
- Many opportunities and challenges exist to deal with these climate related health effects