KI REPORTS
KIReports.org

Kidney Diseases in Agricultural Communities: A Case Against Heat-Stress Nephropathy

Chula Herath[1], Channa Jayasumana[2], P. Mangala C.S. De Silva[3], P.H. Chaminda De Silva[4], Sisira Siribaddana[2] and Marc E. De Broe[5]

[1]Department of Nephrology, Sri Jayewardenepura General Hospital, Sri Lanka; [2]Department of Pharmacology, Faculty of Medicine, Rajarata University of Sri Lanka, Saliyapura, Sri Lanka; [3]Department of Zoology, University of Ruhuna, Matara, Sri Lanka; [4]Department of Meteorology of Sri Lanka, Colombo, Sri Lanka; and [5]Laboratory of Pathophysiology, University of Antwerp, Wilrijk, Belgium

The beginning of the 21st century has seen the emergence of a new chronic tubulo-interstitial kidney disease of uncertain cause among agricultural communities in Central America and Sri Lanka. Despite many similarities in demography, presentation, clinical features, and renal histopathology in affected individuals in these regions, a toxic etiology has been considered mainly in Sri Lanka, whereas the predominant hypothesis in Central America has been that recurrent acute kidney injury (AKI) caused by heat stress leads to chronic kidney disease (CKD). This is termed the *heat stress/dehydration hypothesis*. This review attempts to demonstrate that there is sparse evidence for the occurrence of significant AKI among manual workers who are at high risk, and that there is little substantial evidence that an elevation of serum creatinine < 0.3 mg/dl in previously healthy people will lead to CKD even with recurrent episodes. It is also proposed that the extent of global warming over the last half-century was not sufficient to have caused a drastic change in the effects of heat stress on renal function in manual workers. Comparable chronic tubulo-interstitial kidney disease is not seen in workers exposed to heat in most tropical regions, although the disease is seen in individuals not exposed to heat stress in the affected regions. The proposed pathogenic mechanisms of heat stress causing CKD have not yet been proved in humans or demonstrated in workers at risk. It is believed that claims of a *global warming nephropathy* in relation to this disease may be premature and without convincing evidence.

Kidney Int Rep (2018) **3,** 271–280; https://doi.org/10.1016/j.ekir.2017.10.006
KEYWORDS: chronic interstitial nephritis in agricultural communities; CKDu in Sri Lanka; heat-stress nephropathy

In the last decade of the 20th century, clinicians in Central America (CA) and Sri Lanka (SL) were struck by the unusually high number of patients with chronic kidney disease (CKD) in their rural agricultural communities, predominantly among sugarcane workers in CA and paddy farmers in SL.[1,2] The traditional causes of CKD such as diabetes and hypertension were not implicated. This clinical setting was named *Mesoamerican nephropathy* (MEN) in CA and *chronic kidney disease of unknown etiology* (CKDu) in SL. Recently, a more appropriate term, chronic interstitial nephritis in agricultural communities (CINAC), has been used to identify both.[3,4] Proteinuria was not prominent, and hypertension was a late manifestation. Ultrasound showed small kidneys, and renal biopsies demonstrated a chronic tubulo-interstitial nephropathy.[5,6] Recently, analogous regional epidemics of CKD have been suspected in Andhra Pradesh in India[7] and in Egypt.[8] Interregional comparisons have been described more comprehensively elsewhere.[3,9,10]

Existing literature suggests multiple etiological factors, but a systematic search failed to provide a consensus on a main causative agent.[9,10] Environmental pollution due to heavy metals[11,12] and agrochemicals,[12] excess fluoride in water,[13] sodium/calcium imbalance in water,[13] and genetic factors[14] have been implicated in SL. Conversely, it has been proposed that the heat stress/dehydration hypothesis is the likely explanation for causation of MEN and other similar epidemics of CINAC elsewhere.[15,16] Severe dehydration with heavy work in excessive heat leads to a cascade of events. In addition to the prerenal acute kidney injury (AKI) due to volume depletion, dehydration causes hyperosmolarity, which activates aldose reductase in the proximal tubule,

Correspondence: Marc E. De Broe, Laboratory of Pathophysiology, University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Belgium. E-mail: marc.debroe@uantwerpen.be
Received 26 August 2017; revised 7 October 2017; accepted 16 October 2017; published online 23 October 2017

converting glucose to fructose that is metabolized by fructokinase, leading to release of oxidants that cause local tubular injury. Hyperosmolarity also increases vasopressin, which accelerates progression of CKD. Hyperuricemia and rhabdomyolysis, the other detrimental results of dehydration, contribute to progression of chronic tubulo-interstitial disease. Several recent publications have supported the heat stress/dehydration hypothesis, endorsing the view that it is the main drive or the necessary cause of CINAC.[15] Some authors have claimed this to be a *global-warming nephropathy* and the first epidemic due to global warming.[15,17] We believe that this claim is too premature. In recently published *pro* and *con* arguments on the heat stress hypothesis, the moderator was of the view that there is not enough evidence to show cyclical dehydration as the *sole relevant cause* to explain the epidemic.[18] At least 1 study, a spatial distribution analysis from El Salvador, presented data that indicates that high temperatures do not appear to strongly influence the occurrence of MEN after adjustment for area under cultivation for specific crops.[19] Our attempt in this review is a detailed *con* argument, and our line of reasoning is based on the chain of evidence pointing to heat stress and recurrent dehydration as the main drive for CINAC (Table 1), in which each link is scrutinized to ascertain its veracity and/or probability. Although we believe that cyclical dehydration is likely to be a contributory factor in making underlying CKD progress faster, our contention is against dehydration as the primary drive or the necessary cause of these epidemics.

Recurrent Acute Kidney Injury is Demonstrable in Workers Under Their Work Conditions

Five studies have focused on biochemical changes in Mesoamerican sugarcane workers in their work environment. Some were cross-shift studies of single-day variations of renal function before and after a day's work,[20–22] and others were cross-harvest changes across the whole harvest period.[20,22–24] All 3 cross-shift studies

Table 1. Chain of evidence: Conditions to be fulfilled for the heat stress theory to be valid

1. Recurrent acute kidney injury is demonstrable in workers under their work conditions
2. Recurrent acute prerenal injury can lead to CKD
3. The temperature in the region before the epidemic was not adequate to cause the same effect
4. Comparable chronic tubulo-interstitial kidney disease is seen in people who work in hot environments elsewhere in the world
5. CINAC is not seen in those not in the manual work force in the same community and those who do not develop recurrent severe dehydration
6. Sustained elevations of vasopressin, recurrent hyperuricemia, and high fructokinase activity caused by dehydration contribute to progression of CKD, and these phenomena are demonstrated in agricultural workers under heat stress

CINAC, chronic interstitial nephritis in agricultural communities; CKD, chronic kidney disease.

demonstrated an increase in serum creatinine after a heavy workday: a mean increase of serum creatinine of 0.21 mg/dl in Brazil,[20] 0.12 mg/dl in El Salvador,[21] and 0.12 mg/dl in Nicaragua.[22] In Brazil, 5 of 28 workers (17%) had a creatinine rise of 0.3 mg/dl or more at the end of a workday, defined by the Acute Kidney Injury Network (AKIN) as stage 1 AKI.[25] There were no significant cross-harvest changes in serum creatinine in the Brazilian study. In the Nicaraguan cross-harvest study,[23] which compared the field workers with non−field workers, field workers had a mean decline of eGFR of 6.9 ml/min more than the non−field workers over the harvest period of 4 to 6 months.

Although the cross-shift studies of serum creatinine demonstrate some degree of prerenal AKI, mostly not fulfilling AKIN stage 1 (pre−AKIN stage 1), it is uncertain whether the cross-harvest decline in eGFR represents an AKI or CKD. This does not fall into the category of *acute kidney disease* as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines requiring a decline in GFR of 35% or more within 3 months.[26] Chronicity too has not been demonstrated by 2 measurements 3 months apart. A recent representative, randomized, adult population study from Morocco found that single measurements of eGFR led to both over- and underdiagnosis of CKD by up to 40%.[27] Normal daily biological variations and factitious elevations should also be considered, especially as KDIGO criteria require only a small change (0.3 mg/dl) to diagnose AKI. Random variations in serum creatinine may be a significant contributor to AKI diagnosis in the absence of a true reduction in GFR.[28] A cooked meat meal can cause an elevation in serum creatinine even up to 52%.[29] Heavy muscular exertion and low-grade muscle injury are known to cause a significant increase in serum creatinine.[30] In the cross-shift study from Brazil, there was a noteworthy increase in serum creatinine kinase in the workers.

Therefore, data from field studies do not give a clear idea about the actual changes in renal function in the workers during field work. Single-day, cross-shift assessments show some evidence of acute prerenal dysfunction (less than AKIN stage 1) in some workers, likely caused by dehydration, but across-the-harvest changes in renal biomarkers do not incriminate dehydration as the main cause. An environmental toxin can be expected to produce the same effect on biomarkers.

Recurrent Acute Prerenal Injury Can Lead to CKD

Traditional descriptions of AKI emphasize its total reversibility with no critical long-term sequelae, a view which has been challenged by the long-term follow-up studies of patients with AKI discharged from

hospitals.[31,32] There is currently little doubt that even mild in-hospital AKI events with full recovery might lead to the development of CKD.[33] The pathophysiology of such an AKI−CKD continuum has been discussed comprehensively.[34,35]

It is crucial to recognize that most published follow-up studies of AKI, which have revealed CKD as a long-term sequel, are retrospective, from databases of hospitalized AKI patients who mostly have been elderly with multiple comorbidities such as diabetes, hypertension, CKD, heart disease, liver disease, and malignancies, many in an intensive care unit setting with sepsis a common accompaniment. It has even been suggested that AKI may be an epiphenomenon of a chronic disease rather than the cause of CKD.[36] AKI may not be causal but may identify individuals who fail their renal *stress test* based on their limited renal reserve[37] and therefore can be considered a risk marker for underlying systemic illness rather than a risk factor *per se*.[35] Even patients labeled as having *mild AKI* in the follow-up studies have had at least a 0.3-mg/dl elevation of serum creatinine during initial hospitalization with AKI (AKIN stage 1). In comparison, workers in CA and SL have been previously healthy, younger individuals, with no other comorbidities,[1,2] who possibly develop community-acquired, recurrent, acute, prerenal dysfunction at a *pre−AKIN stage 1*, caused by dehydration. None of the above follow-up studies on AKI sequelae have included *pre−AKIN stage 1* patients in their long-term follow-up (they are probably absorbed into the *no AKI* groups at initial hospitalization). In the cross-shift study from Brazil,[20] some workers had some degree of acute renal dysfunction, but there was no reported higher prevalence of CKD among the field workers in Brazil,[20] giving us an intimation that in some areas with conditions similar to those in Mesoamerica, recurrent AKI has not led to CKD. It is recognized that acute hepato-renal syndrome and acute cardio-renal syndrome are examples of *prerenal failure* leading to CKD—namely, chronic hepato-renal and chronic cardio-renal syndromes respectively[38]—but these are protracted forms of prerenal dysfunction often satisfying AKIN criteria, unlike the reversible *pre−AKIN stage 1* AKI seen with dehydration. Hence, CKD as a sequel of recurrent *pre−AKIN stage 1* acute renal dysfunction, caused by dehydration, could only be a conjecture at present, with brittle support from current evidence.

Two recent studies, 1 each from SL and CA, have described similar groups of patients in CINAC-prevalent areas presenting for hospital admission with fever, fatigue, backache, and AKI.[39,40] Renal biopsies showed acute interstitial nephritis and tubulitis on a background of chronic tubulo-interstitial disease. There was no acute tubular necrosis consistent with dehydration due to heat stress.

Most animal studies on the AKI−CKD continuum are those with severe AKI caused by direct repetitive ischemic or toxic insults resulting in significant elevations of serum creatinine.[41] These models are not comparable to the hypothesized AKI caused by dehydration in Mesoamerican workers. One animal model,[42] claimed to be a suitable comparison, needs more critical evaluation. Wild-type and fructokinase-deficient mice were subjected to recurrent heat-induced dehydration daily for 5 weeks. One group of each genotype had free access to water throughout the day, and the other group was hydrated at night only. Wild-type mice that received delayed hydration developed tubular injury, high serum creatinine, and, later, fibrosis. Fructokinase-knockout mice with delayed hydration were protected from renal injury. The mice were kept at a temperature of 39.5°C (2.5°C above their core temperature) and the delayed-hydrated mice were not given any water at all during the daytime. They also lost 15% of their body weight during this time, indicating severe dehydration. Effects of heat stress are greater at an ambient temperature surpassing the core temperature.[43] Mesoamerican workers work in temperatures less than the normal body temperature of 37°C most of the time[21,23] and have free access to water during the day (in 1 study, an average of 3.3 L per 4 working hours).[21] Field studies show a mean loss of weight of about 0.2 kg by the end of the working day,[21] less than 1% of body weight. The above-mentioned animal study was designed to demonstrate that lack of fructokinase is protective against dehydration-induced renal injury, but is not an appropriate animal model to illustrate that heat-stress/dehydration is the main cause of CINAC.

Validating and establishing reference levels for newer biomarkers such as cystatin C, neutrophil gelatinase−associated lipocalin, interleukin-18 (IL-18), and kidney injury molecule−1 (KIM-1), some of which are likely to have the ability to diagnose prerenal dysfunction,[44] and the less well-known biomarkers such as insulin-like growth factor−binding protein (IGFBP), which possibly could predict renal recovery,[45] would be useful tools in demonstrating the AKI−CKD continuum in agricultural workers.

The Temperature or the Workload Before the CKD Epidemic Was Not Adequate to Cause the Same Effect

When we look at the epidemics of CINAC reported since the early 21st century, one may ask *Why now, and not then?* The first published reports of CINAC appeared in early 21st century, but physicians in the regions noticed this phenomenon at least in the mid-

1990s. If we accept heat stress/dehydration as the main drive for the disease, it should be assumed that the temperature before the 1960s was not adequate to cause the same effect. When there are many references to global warming as the underlying issue,[15,17] we ought to take a look at the temporal trend of global warming and its effect on occupational kidney health.

Catastrophic effects of global warming have been highlighted frequently in the scientific literature as well as in the mass media. It should be emphasized that this was a century-scale event, at least in the last century, although there is evidence that it will be felt more acutely in the coming decades. An increase in mean temperature up to 7°C within this century alone is a possibility in the absence of strong measures of mitigation.[43] However, when we consider causation of the CKDu epidemic, we have to look at past events rather than future projections, especially the latter half of the 20th century, to see if the warming during that era brought about an extent of dehydration that had not been seen before.

The rise in mean global surface temperature over the 20th century has been about 0.8°C.[46,47] (Figure 1). The rise in mean temperature from 1960 to 1990 has been about 0.4°C. It is unlikely that an approximate warming of 0.4°C has made such a devastating difference to the kidneys of the affected agricultural workers. This small increase in temperature does not explain the degree and the rapidity of the epidemic.[48] It is often argued, perhaps rightly, that the extremes of weather resulting from global warming have more dire consequences to health than the increase in mean temperature alone. However, these extreme weather events are not daily occurrences. Data from a regional climate change workshop held in Guatemala in 2004 demonstrates extremes of temperature in CA and northern South America over the 1961 to 2003 period. Figure 2 shows the percentage of extremely warm days, and it

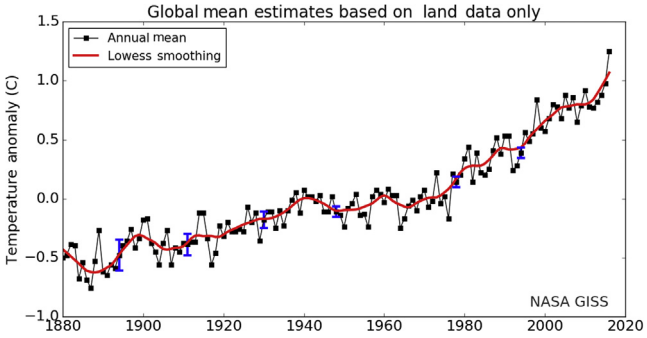

Figure 1. Global annual mean surface air temperature change, based on land data only.[46,47] NASA GISS, National Aeronautics and Space Administration Goddard Institute for Space Studies. Adapted from GISTEMP Team, 2016. GISS Surface Temperature Analysis (GISTEMP). NASA Goddard Institute for Space Studies. Available at: http://data.giss.nasa.gov/gistemp/. Accessed September 13, 2016.

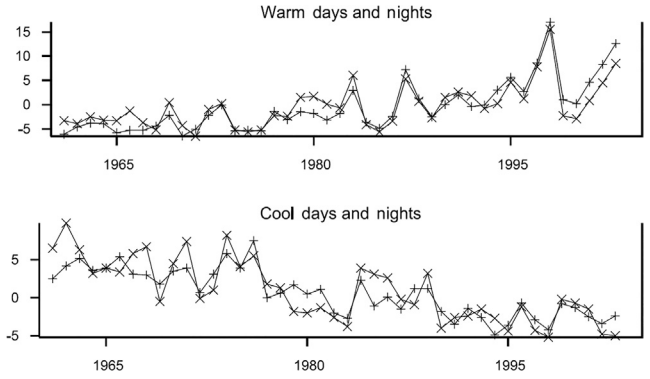

Figure 2. Regional annual anomalies: Central and Northern South America.[49] (Top) Regional annual anomalies (% of days) for TX90p (plus signs) and TN90p (crosses). (Bottom) Regional annual anomalies (% of days) for TX10p (plus signs) and TN10p (crosses). TN, minimum daily temperature; TN10p (cool nights), percentage of days when TN < 10th percentile % days; TN90p (warm nights), percentage of days when TN > 90th percentile % days; TX, maximum daily temperature; TX10p (cool days), percentage of days when TX < 10th percentile % days; TX90p (warm days), percentage of days when TX > 90th percentile % days.

is apparent that in the mid-1980s there were 2 years with 5% unusually warm days in each, and in the late 1990s a single year with a higher peak of 15% extremely warm days.[49] Extreme warm days in all the other years had been less than 5%. It is questionable whether these numbers of unusually warm days can make a difference to the magnitude of dehydration over the long term, compared to an earlier period, for example before 1960.

Sri Lanka is divided into 4 zones on its climatic variability: namely, the Wet Zone, Dry Zone, Intermediate Zone, and Arid Zone. Figure 3a shows the distribution of CINAC in SL, which shows its low prevalence even in the Arid Zone, where the temperature is highest. Figure 3c shows the temperature variation (maximum and minimum temperature) in 3 selected locations in the Dry Zone of Sri Lanka. Figure 3c1, c2, and c3 respectively represent Anuradhapura, where CINAC has been highly prevalent since 1993, and Hambanthota and Pottuvil, where CINAC is of low prevalence or is seen as sporadic cases. All 3 locations are at similar altitudes and experience similar environmental conditions throughout the year, and temperature profiles do not vary within the locations with no extreme fluctuations. Figure 3b indicates the *mosaic* pattern of distribution of CINAC in the highly CINAC-prevalent division of Medawachchiya, where hot spots are clearly shown with adjacent areas of low or zero prevalence. These comparable temperature profiles and the pronounced mosaic pattern of CINAC occurrence raises the question that if the heat stress/dehydration hypothesis is correct, why the prevalence of CINAC across the Dry Zone is not more homogeneous.

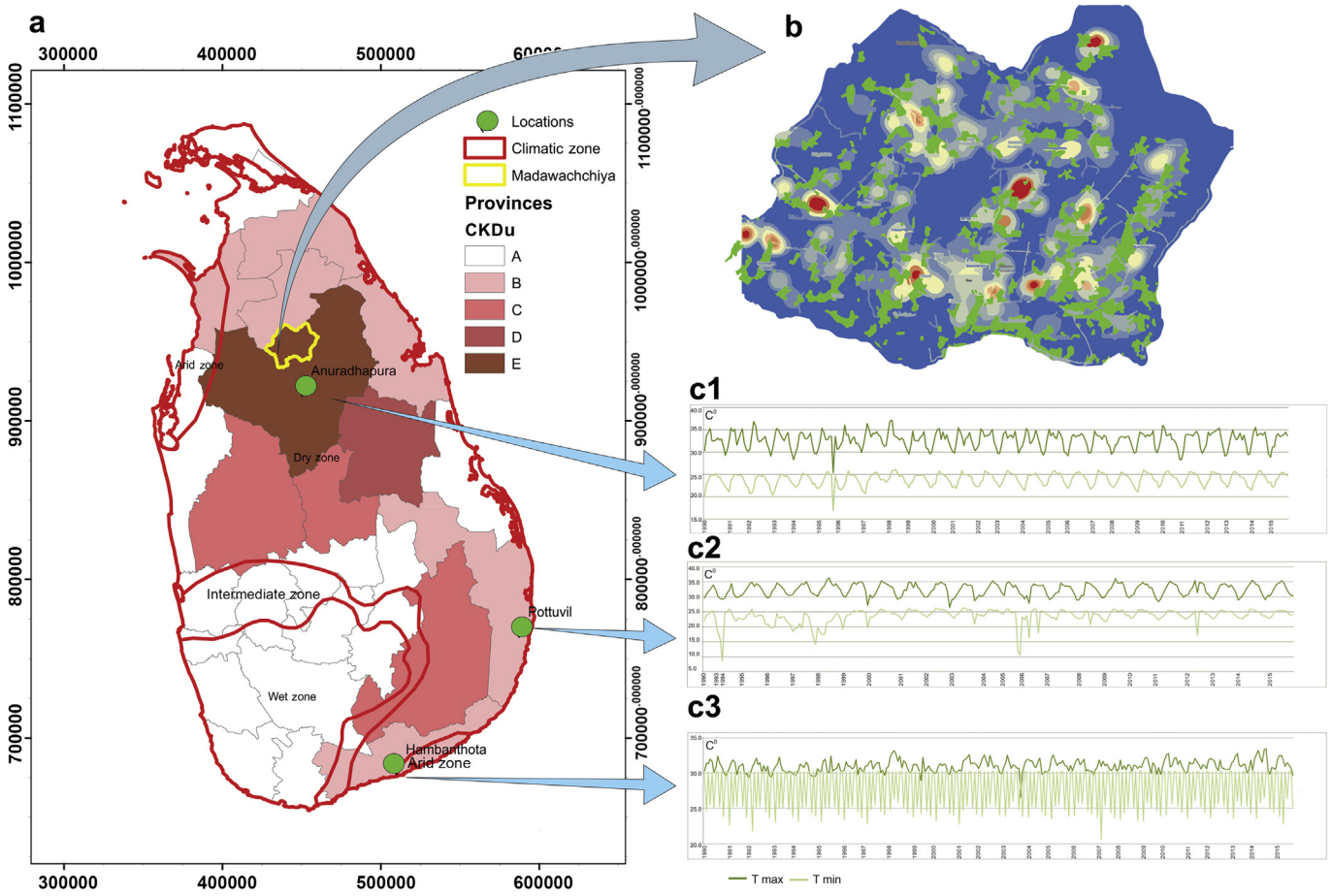

Figure 3. (a) Climatic zones of Sri Lanka based mainly on temperature and annual rain fall. Provinces with a high prevalence of chronic interstitial nephritis in agricultural communities (CINAC) are shown in darker color, whereas areas with a lower prevalence are shown in lighter colors. CKDu, chronic kidney disease of unknown etiology. (A) No CINAC. (B) Sporadic cases in some divisions. (C) Moderate prevalence in some divisions. (D) High prevalence in some divisions. (E) Very high prevalence in all divisions. (b) Mosaic pattern of distribution of CINAC in Medawachchiya DS, Anuradhapura District in Sri Lanka. Red indicates high prevalence; blue areas indicate low prevalence; green indicates paddy fields. (By courtesy of Dr. Asanga Venura Ranasinghe, Renal Diseases Prevention & Research Unit, Ministry of Health, Sri Lanka.) (c) Temperature variation (maximum and minimum) during 1990 to 2015 in 3 selected locations (c1, Anuradhapura; c2, Hambanthota; c3, Pottuvil) in the Dry Zone of Sri Lanka. Source: The Meteorology Department, Colombo, Sri Lanka.

Comparable Chronic Tubulo-interstitial Kidney Disease Is Seen in People Who Work in Hot Environments Elsewhere in the World

In addition to CA and SL, only the Uddanam area in South India has a biopsy-confirmed epidemic of CINAC.[50] There are other regions reported as having epidemics of CINAC: El Minia Governorate of Egypt; India (Goa, Maharashtra, and Odisha); Northeastern Thailand; the Tabuk region in Saudi Arabia; Southern Sudan; Mexico (Tierra Blanco); and the California Central Valley in the United States.[15] These are all hot regions, and this article attempts to link heat stress/dehydration as the cause.[15] There are no published reports from Goa, Odisha, and Maharashtra in India to date. In a population screening in Thailand, the prevalence of CKD in the northeastern region (one of the hottest areas) was found to be only 1.9% higher than the national prevalence.[51] There is no published evidence that areas of higher prevalence have an excess of CINAC. In above-mentioned areas, the clinical characteristics and pathology have not been studied in detail, with little published data to make any solid inferences. It is worth stressing the difference between CINAC (seen in CA and SL) and CKD of unknown etiology, encountered more or less in all renal databases. The number of undiagnosed cases of CKD is higher in developing countries because of poor access to diagnostic facilities and late referral for nephrology care. The high percentage of CKD of unknown etiology does not imply that they are due to CINAC. Many of them may be due to end-stage chronic glomerulonephritis, chronic pyelonephritis, and vascular disease.

It is worth repeating the classical dictum in epidemiology that correlation, no matter how strong, does not imply causation. It is known that the prevalence of CKD is higher among disadvantaged populations,[52] and these societies do mainly live in the *hotspots* of the world. Poor socio-economic conditions, genetics, maternal undernutrition, low birth weight, and exposure to

environmental pollutants may be contributing factors. In the late 1980s, Tiwi Islanders of Australia had the highest described rates of CKD in the world.[53] The temperatures in this region often go above 36°C. CKD in Tiwi Islanders would have been mistaken for a heat-stress nephropathy if Hoy had not found their genetic susceptibility, low nephron number, and glomerulomegaly.[53] An excess of CKD has not been reported among sugarcane workers in Brazil, India, Thailand, Pakistan, Mexico, Colombia, Cuba, Indonesia, or the Philippines, some areas of which are hotter than CA. In the highlands of CA, where CINAC prevalence is low, the temperature often reaches levels considered *very high to extreme risk* by US Occupational Safety and Health Administration (OSHA), according to 1 cross-shift study from El Salvador.[21] A closer analysis of the temperature recordings and the working hours from this study shows that the workers in high altitudes work for longer hours than those at the coast, often until noon, and the temperatures cross the *extreme risk* zone before 10 AM, yet they are protected from CKD. Some nonagricultural workers, such as miners, fishermen, and construction workers, have been shown to have MEN in Nicaragua,[54] albeit in small numbers. CKD was diagnosed with a single measure of serum creatinine, and diabetes was not excluded with blood glucose measurements. These workers live in the same agricultural communities, so an environmental toxin could be expected to have the same effect if it is water or food borne. Similar CKD is not reported among workers in other *hot jobs* in nonagricultural communities: for example, in iron foundries, brick-firing plants, glass factories, boiler rooms, bakeries, chemical plants, mining sites, steam tunnels, and oil wells. Millions of devout Muslims all over the world undergo voluntary dehydration 14 hours daily for 1 month each year for Ramadan fasting. Some studies have described acute abnormalities in renal function following Ramadan fasting.[55] No increase in CKD has been described in this community. It would be intriguing to check the renal function of sugarcane workers in Islamic countries such as Pakistan and Indonesia.

In SL, introduction of a 2-wheel tractor was a major change in agricultural practice in the early 1980s that significantly reduced the workload for farmers, with a concomitant reduction of the risk for heat stress.[3] The heat stress hypothesis cannot explain the mosaic pattern of geographical distribution of CINAC, as shown in Medwachchiya, 1 of the highest CINAC-prevalent areas in SL (Figure 3b). Some villages adjacent to CINAC-prevalent villages do not have the disease.[56] The Northern Province of Sri Lanka, where environmental conditions are harsher than in the endemic North Central Province (NCP), does not have a higher prevalence. It is often claimed that this is due to underreporting as a result of the Sri Lankan Civil War. However, it is 8 years since the war ended, and a high prevalence still has not been reported, despite health services having been returned to normal and taking into account the heightened awareness about CINAC among doctors. It is noteworthy that from the 1980s onward, this province had no access to most agrochemicals and fertilizers, as it was feared that these could be used for incendiary devices by the terrorist groups.[3] Three other districts, namely, Puttalam, Batticaloa, and Ampara, with conditions similar to those of the North Central Province, have had no reports of excess CKD. In 1 study from Sri Lanka,[57] geographic information system (GIS) and global positioning system (GPS) mapping showed a low prevalence of CKD in communities consuming water from natural springs. In the village of Girandurukotte, the disease is reported only among the villagers on the left bank of the Mahaweli River, supplied by 2 reservoirs, whereas individuals who live on the right bank, supplied by natural springs, are not affected. Even within affected villages, areas in the lowest altitudes (but similar temperatures) are affected more. It could be hypothesized that the effects of water-borne agrochemicals used/abused by farmers would be felt *downstream* of rivers and reservoirs more, which could explain the higher prevalence in lowlands.

We believe that the absence of the diagnosis of CINAC in the majority of agricultural communities in tropical countries is a stronger argument against the heat stress hypothesis than the supportive argument indicated by the high CINAC prevalence in a few tropical regions. It could also be argued that CKD is not reported in some groups at high risk for heat stress because no one has looked for it. However, even in disadvantaged communities, if the prevalence is high in a region, doctors working in those areas usually notice an excess of cases in hospitals and the local, modestly equipped clinics. In fact, that is how Mesoamerican and Sri Lankan epidemics were first noticed. Active surveys or statistics from a renal registry have not played the slightest role in the initial phase of the discovery of CINAC throughout world.

CINAC Is Not Seen in Individuals Who Are Not in the Manual Work Force in the Same Community and in Those Who Do Not Develop Recurrent Severe Dehydration

If the heat stress/dehydration theory is true, CINAC should be seen mainly in manual workers who work hard in the hot temperatures. Adolescents and women not exposed to the oppressive working conditions could not be expected to develop the effects of severe

dehydration, including recurrent AKI. Most cohort studies show that in CA, men have a higher prevalence of CKDu, but the prevalence among women is higher than is seen in international CKD studies.[58] In Sri Lanka, where women rarely work in the fields, 1 study showed a women-to-men ratio of 1:1.3.[59] Conversely, in the large U.S. Agricultural Health Study, there was an association between pesticide exposure and end-stage renal disease,[60] which was observed even among wives of pesticide applicators.[61] In a Boston University investigation of CKDu in western Nicaragua,[62] 200 adolescents were checked for signs of tubular injury by assessment of urinary biomarkers. Biomarkers of tubular damage, particularly neutrophil gelatinase-associated lipocalin and N-acetyl-glucosaminidase (lysosomal marker), showed higher concentrations in those schools and regions within Nicaragua that were defined *a priori* as having increased CKD risk. This suggests that there may be early kidney damage present in adolescents in Nicaragua, and that the damage is occurring in the proximal tubules, which is consistent with CINAC. These results indicate that CINAC occurs in individuals not exposed to the harsh working conditions of the sugarcane plantations or paddy fields.

Sustained Elevations of Vasopressin, Recurrent Hyperuricemia, and Fructokinase Activity Caused by Dehydration Contribute to Progression of CINAC, and These Phenomena Are Observed in Agricultural Workers Under Heat Stress

Evidence from animal experiments suggests that vasopressin may contribute to progression of CKD.[63] However, most human studies that suggest vasopressin may be involved in CKD progression are those showing an association rather than a direct effect of the hormone.[64] No studies of vasopressin or co-peptin levels in agricultural workers have been published to date. The role of vasopressin in AKI caused by dehydration is unclear, but it is worth noting that in an experiment with dehydration in mice,[42] the fructokinase-knockout mice did not get AKI or CKD although vasopressin was not blocked. Hyperuricemia can cause glomerular damage and interstitial fibrosis in normal rats and can accelerate progression of interstitial fibrosis in individuals with CKD.[65] At present, there are no definite data as to whether hyperuricemia is causal, compensatory, coincidental, or only an epiphenomenon in CKD.[66] Hyperuricemia and hyperuricosuria with uric acid crystalluria are seen in about 50% of patients with CINAC in CA,[67,68] suggesting that uric acid may play a contributing but not an essential role.[48] Hyperuricemia also may be a feature with chronic exposure to pesticides such as dioxins and other environmental toxins.[69] High fructokinase levels or their effect on kidney injury have not been demonstrated in humans under heat stress or dehydration. Hyperosmolarity is the main stimulus responsible for increased fructokinase and vasopressin, according to the heat stress/dehydration hypothesis, but blood hyperosmolarity was not demonstrated in sugarcane workers in 1 cross-shift study from CA.[21]

In conclusion, we do not believe that there is adequate evidence for heat stress and dehydration initiating and maintaining a major global epidemic of CKD as its main drive. We have shown the tenuous evidence for the hypothesis that recurrent acute prerenal dysfunction in field workers is an adequate initiating mechanism for progression to CKD. Moreover, the pathophysiological mechanisms postulated to trigger chronic interstitial fibrosis following recurrent dehydration still have not been proved in humans. The correlation of the presence of CINAC with hot environments is weak in comparison to the lack of CINAC in many such comparable environments. We have also cast an element of doubt on the speculation that the scale of global warming over the last few decades was sufficient to cause a catastrophic global effect on occupational kidney health. It is known that dehydration worsens most kidney diseases—CKD, urolithiasis, urinary tract infections, and most forms of AKI—but evidence is insufficient for cyclical dehydration as the essential cause for CINAC on a global scale. We believe this to be an important contributory factor to the progression of CINAC, and consider prevention of dehydration in manual workers with commendable programs such as the *water, rest and shade* program in El Salvador as vital imperatives in improving global kidney health.

CINAC was discovered in agricultural communities and is still seen in such communities; hence agriculture seem to have had an inextricable link to the disease, at least up to now. Even if some of the affected individuals are not agricultural workers, the vast majority live in communities with high agricultural activity.[70] The only specific *signature* of this chronic interstitial nephritis is its link to agriculture. Biopsy findings of predominantly interstitial disease associated with glomerulosclerosis, in the absence of overt proteinuria and progressive shrinking of kidneys, with mild or no hypertension, makes it more likely that it is a toxic nephropathy. For example, Balkan nephropathy, which is pathologically and epidemiologically similar to CINAC, was considered a CKDu until recently. The epidemic of Chinese herbs nephropathy in Europe provided a key to its possible etiology as aristolochic acid. However, aristolochic acid is unlikely as a causative agent for CINAC, as the signature

urothelial malignancies seen in aristolochic acid nephropathy are not a feature.[71] Other putative toxic agents include the following: agrochemicals such as organochlorines,[72] organophosphates,[73] and glyphosate[74,75]; heavy metals such as cadmium, mercury, arsenic, and lead[2,76,77]; and fluorides found in high concentrations in water in epidemic areas in SL.[78] The role of exposure to toxins such as agrochemical residues and heavy metals has not been systematically addressed, especially the possibility of long-term low-dose exposure. A recent epidemiological review found scarce evidence of a link between agrochemicals and regional CKDu epidemics in existing studies, but acknowledges that most studies have been weak to very weak in design.[79] An infective etiology with an agent such as Leptospira[80] or Hantavirus[81] in the light of reports of *acute CKDu* from both SL and CA has to be considered in the differential diagnosis.[39,40]

If further research proves heat stress/dehydration to be the necessary cause, it would be fortunate for the affected regions, as prevention would be straightforward and easier. Nevertheless, we believe that premature claims of a *global-warming nephropathy* can be detrimental to the efforts of the search for other possible etiological factors; in case 1 or more environmental toxin is the main cause, research on these agents would be stalled, as such premature claims can induce a sense of complacency in the scientific community.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Trabanino RG, Aguilar R, Silva CR, et al. End-stage renal disease among patients in a referral hospital in El Salvador. *Rev Panam Salud Publica*. 2002;12:202–206.
2. Jayatilake N, Mendis S, Maheepala P, et al. Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. *BMC Nephrol*. 2013;14:180.
3. Jayasumana C, Orantes C, Herrera R, et al. Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. *Nephrol Dial Transplant*. 2017;32:234–241.
4. De Broe ME, D'Haese PC, Navarro CMO, Elseviers MM. Chronic tubulointerstitial nephritis. In: Firth JD, Cox TM, Conlon CC eds. *Oxford Textbook of Medicine*. 6th ed. Oxford, UK: Oxford University Press; in press.
5. Wijetunge S, Ratnatunga NV, Abeysekera DT, et al. Retrospective analysis of renal histology in asymptomatic patients with probable chronic kidney disease of unknown aetiology in Sri Lanka. *Ceylon Med J*. 2013;58:142–147.
6. Lopez-Marin L, Chavez Y, Garcia XA, et al. Histopathology of chronic kidney disease of unknown etiology in Salvadoran agricultural communities. *MEDICC Rev*. 2014;16:49–54.
7. Reddy DV, Gunasekar A. Chronic kidney disease in two coastal districts of Andhra Pradesh, India: role of drinking water. *Environ Geochem Health*. 2013;35:439–454.
8. Kamel E, El-Minshawy O. Environmental factors incriminated in the development of end stage renal disease in El-Minia Governorate, Upper Egypt. *Int J Nephrol Urol*. 2010;2:431–437.
9. Weaver VM, Fadrowski JJ, Jaar BG. Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy? *BMC Nephrol*. 2015;16:145.
10. Lunyera J, Mohottige D, Von Isenburg M, et al. CKD of uncertain etiology: a systematic review. *Clin J Am Soc Nephrol*. 2016;11:379–385.
11. Bandara JM, Wijewardena HV, Liyanege J, et al. Chronic renal failure in Sri Lanka caused by elevated dietary cadmium: Trojan horse of the green revolution. *Toxicol Lett*. 2010;198:33–39.
12. Jayasumana C, Gunatilake S, Senanayake P. Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka? *Int J Environ Res Public Health*. 2014;11:2125–2147.
13. Chandrajith R, Dissanayake CB, Ariyarathna T, et al. Dose-dependent Na and Ca in fluoride-rich drinking water—another major cause of chronic renal failure in tropical arid regions. *Sci Total Environ*. 2011;409:671–675.
14. Nanayakkara S, Senevirathna ST, Abeysekera T, et al. An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central Region of Sri Lanka. *J Occup Health*. 2014;56:28–38.
15. Glaser J, Lemery J, Rajagopalan B, et al. Climate change and the emergent epidemic of CKD from heat stress in rural communities: the case for heat stress nephropathy. *Clin J Am Soc Nephrol*. 2016;11:1472–1483.
16. Roncal-Jimenez C, Lanaspa MA, Jensen T, et al. Mechanisms by which dehydration may lead to chronic kidney disease. *Ann Nutr Metab*. 2015;66(suppl 3):10–13.
17. Roncal-Jimenez CA, García-Trabanino R, Wesseling C, Johnson RJ. Mesoamerican nephropathy or global warming nephropathy? *Blood Purif*. 2016;41:135–138.
18. Zoccali C. Causal mechanism and component causes in Mesoamerican-Sri Lankan nephropathy: the moderator's view. *Nephrol Dial Transplant*. 2017;32:607–610.
19. VanDervort DR, Lopez DL, Orantes CM, Rodriguez DS. Spatial distribution of unspecified chronic kidney disease in El Salvador by crop area cultivated and ambient temperature. *MEDICC Rev*. 2014;16:31–38.
20. Paula Santos U, Zanetta DM, Terra-Filho M, Burdmann EA. Burnt sugarcane harvesting is associated with acute renal dysfunction. *Kidney Int*. 2015;87:792–799.
21. García-Trabanino R, Jarquín E, Wesseling C, et al. Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador—a cross-shift study of workers at risk of Mesoamerican nephropathy. *Environ Res*. 2015;142:746–155.
22. Wesseling C, Aragón A, González M, et al. Kidney function in sugarcane cutters in Nicaragua—a longitudinal study of workers at risk of Mesoamerican nephropathy. *Environ Res*. 2016;147:125–132.

23. Laws RL, Brooks DR, Amador JJ, et al. Changes in kidney function among Nicaraguan sugarcane workers. *Int J Occup Environ Health*. 2015;21:241–250.
24. Laws RL, Brooks DR, Amador JJ, et al. Biomarkers of kidney injury among Nicaraguan sugarcane workers. *Am J Kidney Dis*. 2016;67:209–217.
25. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
26. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2: 1–138.
27. Benghanem Gharbi M, Elseviers M, Zamd M, et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney Int*. 2016;89:1363–1371.
28. Lin J, Fernandez H, Shashaty MG, et al. False-positive rate of AKI using consensus creatinine-based criteria. *Clin J Am Soc Nephrol*. 2015;10:1723–1731.
29. Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. *Br J Clin Pharmacol*. 1983;15:227–230.
30. Warburton DE, Welsh RC, Haykowsky MJ, et al. Biochemical changes as a result of prolonged strenuous exercise. *Br J Sports Med*. 2002;36:301–303.
31. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*. 2009;20:223–228.
32. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*. 2012;81:442–448.
33. Newsome BB, Warnock DG, McClellan WM, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med*. 2008;168:609–616.
34. Yang L, Humphreys BD, Bonventre JV. Pathophysiology of acute kidney injury to chronic kidney disease: maladaptive repair. *Contrib Nephrol*. 2011;174:149–155.
35. Bedford M, Farmer C, Levin A, et al. Acute kidney injury and CKD: chicken or egg? *Am J Kidney Dis*. 2012;59:485–491.
36. Liaño F, Tenorio MT, Rodríguez-Mendiola N, Ponte B. Acute kidney injury as a risk factor for chronic kidney diseases in disadvantaged populations. *Clin Nephrol*. 2010;74(suppl 1): S89–S94.
37. Bydash JR, Ishani A. Acute kidney injury and chronic kidney disease: a work in progress. *Clin J Am Soc Nephrol*. 2011;6: 2555–2557.
38. Slack A, Yeoman A, Wendon J. Renal dysfunction in chronic liver disease. *Crit Care*. 2010;14:214.
39. Badurdeen Z, Nanayakkara N, Ratnatunga NV, et al. Chronic kidney disease of uncertain etiology in Sri Lanka is a possible sequel of interstitial nephritis. *Clin Nephrol*. 2016;86(suppl 1): 106–109.
40. Fischer RS, Mandayam S, Chavarria D, et al. An evidence-based clinical case definition of acute Mesoamerican nephropathy. *Am J Trop Med Hyg*. 2017;97:1247–1256. https://doi.org/10.4269/ajtmh.17-0260.
41. Nath KA, Croatt AJ, Haggard JJ, Grande JP. Renal response to repetitive exposure to heme proteins: chronic injury induced by an acute insult. *Kidney Int*. 2000;57:2423–2433.
42. Roncal Jimenez CA, Ishimoto T, Lanaspa MA, et al. Fructo-kinase activity mediates dehydration-induced renal injury. *Kidney Int*. 2014;86:294–302.
43. Sherwood SC, Huber M. An adaptability limit to climate change due to heat stress. *Proc Natl Acad Sci U S A*. 2010;25(107):9552–9555.
44. Nejat M, Pickering JW, Devarajan P, et al. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. *Kidney Int*. 2012;81:1254–1262.
45. Endre ZH. Recovery from acute kidney injury: the role of biomarkers. *Nephron Clin Pract*. 2014;127:101–105.
46. GISTEMP Team, 2016. GISS Surface Temperature Analysis (GISTEMP). NASA Goddard Institute for Space Studies. Available at: http://data.giss.nasa.gov/gistemp/. Accessed September 13, 2016.
47. Hansen J, Ruedy R, Sato M, Lo K. Global surface temperature change. *Rev Geophys*. 2010;48:RG4004.
48. Campese VM. Con: Mesoamerican nephropathy: is the problem dehydration or rehydration? *Nephrol Dial Transplant*. 2017;32:603–606.
49. Aguilar E, Peterson TC, Ramirez Obando P, et al. Changes in precipitation and temperature extremes in Central America and northern South America, 1961–2003. *J Geophys Res*. 2005;110:D23107.
50. Abraham G, Varughese S, Thandavan T, et al. Chronic kidney disease hotspots in developing countries in South Asia. *Clin Kidney J*. 2016;9:135–141.
51. Ong-Ajyooth L, Vareesangthip K, Khonputsa P, Aekplakorn W. Prevalence of chronic kidney disease in Thai adults: a national health survey. *BMC Nephrol*. 2009;10:35.
52. Garcia-Garcia G, Jha V. Chronic kidney disease (CKD) in disadvantaged populations. *Clin Kidney J*. 2015;8:3–6.
53. Hoy WE. Kidney disease in Aboriginal Australians: a perspective from the Northern Territory. *Clin Kidney J*. 2014;7:524–530.
54. Torres C, Aragón A, González M, et al. Decreased kidney function of unknown cause in Nicaragua: a community-based survey. *Am J Kidney Dis*. 2010;55:485–496.
55. Trabelsi K, el Abed K, Trepanowski JF, et al. Effects of Ramadan fasting on biochemical and anthropometric parameters in physically active men. *Asian J Sports Med*. 2011;2:134–144.
56. Chandrajith R, Nanayakkara S, Itai K, et al. Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. *Environ Geochem Health*. 2011;33:267–278.
57. Jayasekara JM, Dissanayake DM, Adhikari SB, Bandara P. Geographical distribution of chronic kidney disease of unknown origin in North Central Region of Sri Lanka. *Ceylon Med J*. 2013;58:6–10.
58. Almaguer M, Herrera R, Orantes CM. Chronic kidney disease of unknown etiology in agricultural communities. *MEDICC Rev*. 2014;16:9–15.
59. Senevirathna L, Abeysekera T, Nanayakkara S, et al. Risk factors associated with disease progression and mortality in

chronic kidney disease of uncertain etiology: a cohort study in Medawachchiya, Sri Lanka. *Environ Health Prev Med*. 2012;17:191–198.

60. Lebov JF, Engel LS, Richardson D, et al. Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the Agricultural Health Study. *Occup Environ Med*. 2016;73:3–12.
61. Lebov JF, Engel LS, Richardson D, et al. Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the Agricultural Health Study. *Environ Res*. 2015;143:198–210.
62. Ramírez-Rubio, Amador JJ, Kaufman JS, et al. Urine biomarkers of kidney injury among adolescents in Nicaragua, a region affected by an epidemic of chronic kidney disease of unknown aetiology. *Nephrol Dial Transplant*. 2016;31:424–432.
63. Bankir L, Bouby N, Ritz E. Vasopressin: a novel target for the prevention and retardation of kidney disease? *Nat Rev Nephrol*. 2013;9:223–239.
64. Clark WF, Sontrop JM, Macnab JJ, et al. Urine volume and change in estimated GFR in a community-based cohort study. *Clin J Am Soc Nephrol*. 2011;6:2634–2641.
65. Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002;13:2888–2897.
66. Dousdampanis P, Trigka K, Musso CG, Fourtounas C. Hyperuricemia and chronic kidney disease: an enigma yet to be solved. *Ren Fail*. 2014;36:1351–1359.
67. Kupferman J, Amador JJ, Lynch KE, et al. Characterization of Mesoamerican nephropathy in a kidney failure hotspot in Nicaragua. *Am J Kidney Dis*. 2016;68:716–725.
68. Roncal-Jimenez C, García-Trabanino R, Barregard L, et al. Heat stress nephropathy from exercise-induced uric acid crystalluria: a perspective on Mesoamerican nephropathy. *Am J Kidney Dis*. 2016;67:20–30.
69. Kataria A, Trasande L, Trachtman H. The effects of environmental chemicals on renal function. *Nat Rev Nephrol*. 2015;11:610–625.
70. Pan American Health Organization (PAHO). Epidemic of chronic kidney disease in agricultural communities in Central America. Case definitions, methodological basis and approaches for public health surveillance. Washington, DC: PAHO; 2017. Available at: http://iris.paho.org/xmlui/handle/123456789/34132. Accessed September 5, 2017.
71. De Broe ME. Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy. *Kidney Int*. 2012;81:513–515.
72. Siddharth M, Datta SK, Bansal S, et al. Study on organochlorine pesticide levels in chronic kidney disease patients: association with estimated glomerular filtration rate and oxidative stress. *J Biochem Mol Toxicol*. 2012;26:241–247.
73. Peiris-John RJ, Wanigasuriya JK, Wickremasinghe AR, et al. Exposure to acetylcholinesterase-inhibiting pesticides and chronic renal failure. *Ceylon Med J*. 2006;51:42–43.
74. Jayasumana C, Paranagama P, Agampodi S, et al. Drinking well water and occupational exposure to herbicides is associated with chronic kidney disease in Padavi-Sripura, Sri Lanka. *Environ Health*. 2015;14:6.
75. Jayasumana C, Gunatilake S, Siribaddana S. Simultaneous exposure to multiple heavy metals and glyphosate may contribute to Sri Lankan agricultural nephropathy. *BMC Nephrol*. 2015;16:103.
76. Soderland P, Lovekar S, Weiner DE, et al. Chronic kidney disease associated with environmental toxins and exposures. *Adv Chronic Kidney Dis*. 2010;17:254–264.
77. Meharg AA, Norton G, Deacon C, et al. Variation in rice cadmium related to human exposure. *Environ Sci Technol*. 2013;47:5613–5618.
78. Wasana HM, Aluthpatabendi D, Kularatne WM, et al. Drinking water quality and chronic kidney disease of unknown etiology (CKDu): synergic effects of fluoride, cadmium and hardness of water. *Environ Geochem Health*. 2016;38:157–168.
79. Valcke M, Levasseur ME, Soares da Silva A, Wesseling C. Pesticide exposures and chronic kidney disease of unknown etiology: an epidemiologic review. *Environ Health*. 2017;16:49.
80. Yang CW. Leptospirosis renal disease: emerging culprit of chronic kidney disease unknown etiology. *Nephron*. https://doi.org/10.1159/000480691
81. Gamage CD, Yoshimatsu K, Sarathkumara YD, et al. Serological evidence of hantavirus infection in Girandurukotte, an area endemic for chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka. *Int J Infect Dis*. 2017;57:77–78.