Commented Summary report on available and published reports on Mesoamerican Nephropathy (MeN), Chronic Kidney Disease of unknown Cause (CKDu), CKDnT, and CINAC.

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Table of content

Innehåll

Introduction

This is a text that has been developed and updated for several years. I have compiled this text to keep myself, and hopefully help some other interested, at the edge of what is known and published about Mesoamerican Nephropathy (MeN), often referred to as CKDu, and sometimes also called CKDnT or CINAC. My background in short. I am clinical consultant in Renal Medicine the Karolinska University Hospital, professor in Nephrology at Karolinska Institutet. Previously I had a position as professor in Occupational and Environmental Medicine in Stockholm, Sweden. I have been involved in research on health effects from pesticides and later epidemiological and clinical studies on MeN/CKDu in Central America and elsewhere for more than thirty years.

Publications are presented in chronological order, i.e., the year when presented/published. Review papers are cited at the end of each calendar year, when appropriate. Most of the cited reports have been read thoroughly and I have subsequently made a short summary of each publication. Often – but not always – based on the abstract. Specific comments are given. In the beginning a bulleted list of key reports and findings is presented.

A great number of review papers on CKDu and MeN has now been published. These are cited here. Many of the reviews are extensive, but unfortunately often poor in analysing and evaluating. An interested reader will understand that there is a kidney health problem (MeN/CKDu) in some countries/regions but get the impression that we hardly know anything about its causes. This is however not my impression after compiling and critically evaluating all that has been published. When reading trough this chronological presentation, in my eyes, 'the fog of uncertainty clears, and the contours of evidence and facts become clear'.

I have attempted to make this presentation as comprehensive as possible. Everything that has been published is in! Information about pertinent papers that are not, but may well be cited, is appreciated. After the chronological presentation, from 2002 to 2023, I have also included a few pages with citations of other reports that may be pertinent for the understanding of MeN/CKU and is cause and prevention; *Some aspects on using p-creatinine and/or cystatin to estimate the glomerular filtration rate (GFR), Could metals or silica be the culprit for CKDu?, Herbal medication, traditional medicines, and CKD, Air pollution, with fine particulate matter, and CKD, Ambient temperature, mortality and CKD, and Prevalence of CKD in relation to age in 'normal' population*. The total number of cited references now is 372.

Key reports and findings on MeN and CKDu

- 2000–5 The first reports on a chronic kidney disease (CKD) epidemic in Central America were published. A new type of CKD was described as 'not associated with diabetes, hypertension, primary glomerular diseases or obstructive uropathy' affecting agricultural workers. Later this type of CKD was named Mesoamerican Nephropathy (MeN) or chronic kidney disease of unknown cause (CKDu) [1-3].
- 2007-9 a similar type of CKD is also seen among farmers in certain areas of Sri Lanka[4, 5].
- 2010-11 Three large cross-sectional studies from Nicaragua revealed a high prevalence (10-18%) of CKD with an eGFR<60 ml/min per 1.73 m^2 among men engaged in farming and agricultural work, and exposed to heat during heavy workload, e.g., sugarcane cutting. Few had proteinuria or hypertension [6-8]
- 2011-12 Twenty-six patients with CKD and proteinuria in Sri Lanka underwent renal biopsy, findings were indicative of tubulointerstitial disease [9]. Another 57 renal biopsies in Central of Sri Lanka showed frequent global sclerosis, ischemic-type obsolescence, and wrinkled and collapsed glomerular tufts were suggestive of ischemia of glomeruli [10].
- 2012 In a cross-sectional study in five populations of El Salvador dose-effect and dose-response relation was shown between intensity and duration of heat exposure on the one hand and prevalence of CKD on the other [11].
- 2012 The first international workshop on MeN/CKDu concludes that repeated episodes with dehydration with loss electrolytes and minerals with attending acute kidney injury AKI was the leading hypothesis and pathway to cause the epidemic of CKDu in Central America. Alternative hypothesis and cofactors were also considered needing further attention were NSAID use, inorganic arsenic, and infection from leptospirosis. Pesticides, hard water, and urinary tract infections were considered unlikely causes [12] [13] [14].
- 2013 The first detailed clinical and pathological characterization of Mesoamerican Nephropathy (MeN). Eight cases from El Salvador showed signs of chronic glomerular ischemia in combination with tubular atrophy and interstitial fibrosis, but only mild vascular lesions. The findings suggest that excessive and repeated losses of salts due to excessive sweating may be involved in the pathogenies [15].
- 2014 Additional studies show high rates of CKD in villages of El Salvador and Nicaragua. Male gender and lifetime hours cutting sugarcane during the dry season, are major risk factors for CKD[16]. Individuals with MeN/CKDu often display metabolic alkalosis, hyponatremia, hypocalcaemia, hypokalemia, and hypomagnesemia [17, 18].
- 2015 job-specific differences in renal tests over a 6-month sugarcane harvest season in Nicaraguan sugarcane workers revealed that those considered to be exposed to 'heat stress' lost more of their renal function (eGFR) compared to workers not exposed to 'heat stress'[19].
- 2014-16 Daily, as well as harvest seasonal, increase in p-creatinine, indicative of acute kidney injury as well as more long-term renal effects were reported from, Brazilian and Nicaraguan workers engaged in sugar cane harvest [20, 21].
- 2014-16 Incidence of and mortality in CKD was reported to much higher in MeN/CKDu endemic areas along the Pacific coast 2015 in Costa Rica, El Salvador, Guatemala, and Nicaragua [22, 23].
- 2016 -22 Interventions to reduce symptoms and signs of dehydration and to reduce kidney function damage from hard labour among sugarcane workers work in El Salvador and Nicaragua by implementation a water, rest, shade (WRS) and efficiency intervention program was shown to have favourable effects on renal function and health [24-28]. Less loss of GFR during the harvest season and fewer events if acute kidney injury.
- 2017 Renal biopsies from eleven patients with suspected acute kidney injury from MeN (elevated serum creatinine, leukocyturia, and leucocytosis and/or neutrophilia) in Nicaragua showed tubulointerstitial nephritis, with varying degrees of inflammation and chronicity [29].
- 2018 a renal biopsy study on CKDu cases from Sri Lanka, selected and examined in a similar way as previously done in Central America, show many similarities in the biochemical and morphological profile of the CKDu endemics in Central America and Sri Lanka, but there

were differences, such as a more mixed morphology, more interstitial inflammation, and vascular changes in Sri Lankan patients [30].

- 2018 -19 Signs of AKI and short-term decrease in GFR are seen in sugarcane workers in Nicaragua and Guatemala. Individuals that experience acute kidney injury (AKI) more often develop CKD [31] [32].
- Follow-up studies, up to 8 years, of patients diagnosed with MeN/CKU up show that about one third may progress rather rapidly to more severe kidney failure, but most remain relatively stable if exposure has ceased[33].
- 2019 It was suggested populations whose distant history included out-of-Africa migrations, such as that of most inhabitants along the Pacific coast of Mesoamerica, may have lost resistance to heat stress or equatorial pathogens. Thereby more prone than other populations to develop CKD from heat exposure [34].
- 2020 Early signs of AKI could in an experimental setting be precipitated by physical work in the heat and lack of active rehydration[35].
- 2020 Renal pathology findings from patients with MeN/CKDu was discussed and one group of investigators claims that the findings are typical of some sort of renal toxicity from ‘agrocrochemicals’ [36] but this is not supported by any epidemiology and is challenged by others[37].
- 2014-22 An increasing number of reviews are being published about of CKDu in agricultural communities of El Salvador, Nicaragua, Costa Rica, Sri Lanka, Egypt, and India. Apart from agricultural work and heat exposure many other potential causative exposures and conditions are now suggested, usually without providing any evidence, agrochemical exposure, the herbicide glyphosate, homemade alcohol, water hardness, arsenic in drinking water, exposure to metals such as cadmium and lead, use of drugs, mould toxins, viral infections, and family history of chronic kidney disease. According to many of the review authors there is no strong evidence for a single cause, but multiple environmental, occupational, and social factors are probably involved.
- Many specific studies, most of the from Sri Lanka either, suggest or refute, a wide range of proposed environmental exposers that may cause CKDu. Many of them in some way related to the variable drinking water quality in this country. Hard evidence, however, is lacking.
- Cross-sectional studies of populations in many different countries indicate that CKDu endemic hotspots may occur at some areas/countries but not in others. A remarkable, and alarmingly, high prevalence of CKD has been reported from one area in India [38].
- 2022 Erik Hansson, in a thesis report [39] based on five publications, present clinical and epidemiological evidence that excessive heat strain from high internal heat production and external heat load is a main cause of the Mesoamerican epidemic of CKDu.

Year of publication

2002

Trabanino RG, et al 2002 [1]is the first publications on the CKDu epidemic in Central America. A hospital study of 205 new dialysis patients 1999–2000 in **El Salvador**. For 135 of these, the cause kidney failure was unknown; it was not associated with diabetes, hypertension, primary glomerular diseases or obstructive uropathy. Patients were predominantly men (87%) had average age of 51 where 63% had worked in agriculture and 73% had been exposed to agrochemicals. The authors suggested exposure to such toxic chemicals as a possible causal factor. However already in 2000 Dr Zelaya, a company doctor in Nicaragua, reported an epidemiologic study of more than 900 workers that compared sugar cane workers with high S-creatinine to healthy controls and concluded that strenuous physical work in high environmental temperatures without proper hydration leads to repeated "heat fatigue syndrome" and subsequently to CKD [40] cited by [3].

2005

Gracia-Trabanino et al 2005 examined 291 men from the coastlands of **El Salvador** and found a high prevalence of previously undiagnosed chronic kidney disease (CKD) (13%) having a mean creatinine of 2.6 mg/dl. It was noted that only one third (38%) of the patients with CKD had diabetes or hypertension, while the remaining did not appear to have a clear cause for CKD. Farm living, pesticides exposure and alcohol consumption were found to be very common but was not associated to proteinuria [2].

2006

Cuadra et al 2006 at a conference on Work and health in Central America, in Leon Nicaragua summarizes information available on CKD in **Central America**. Only limited data were available on incidence of CKD at that time, and cross-sectional results from population health screening programmes or results from occupational health examinations largely missing. However, data on mortality from chronic kidney disease in Nicaragua showed an increase from 1992 to 2002 from 4 to 10 per 100,000 inhabitants and year and remarkable differences between different regions with rates up to 35 per 100,000 inhabitants and year in Leon and Chinandega close to the pacific. It was concluded at this meeting those serious problems with chronic kidney disease exist in the area and that research on incidence, prevalence and risk factors for CKD should urgently be examined [41].

2007

Wanigasuriya et al 2007 reported that chronic renal failure (CRF) is emerging as a major health problem in **Sri Lanka**. To examine risk factors 183 patients with CKD of unknown aetiology were recruited randomly from among patients at Anuradhapura Hospital (n = 136 males and n = 47 females). Patients with a serum creatinine concentration greater than 2 mg/dl with no obvious underlying cause were considered as cases. A control group of 200 subjects (n = 139 males and n = 61 females) in the age group 36—67 years, at the same hospital were selected as controls. Most of the patients were farmers or were actively involved in farming activities (86 and 62% of males and females, respectively). Among the males, being a farmer, having used pesticides, drinking water from the well in the field, having a family history of renal dysfunction, taking Ayurvedic treatment (Hindu traditional medicine) and a history of snake bite were more common among patients with CRF compared with controls. Although initial analysis indicated that being a farmer and use of pesticides were associated with CRF, in the multivariate model, exposure to pesticides did not impact on the development of CRF [4].

2008

Ochratoxin A (OA) is a naturally occurring mycotoxin with nephrotoxic properties that can contaminate plant food products. OA concentrations were assessed in commonly consumed food items in the North Central Province of **Sri Lanka**, where chronic kidney disease is diagnosed at epidemic proportions. Ninety-eight randomly selected food samples were analysed. The levels of OA found in

these food commodities were below the recommended statutory maximum limit and are unlikely to be a potential risk factor for nephropathy in the North Central Province of Sri Lanka[42].

2009

Athuraliya et al 2009 in a letter to Ceylon Medical Journal that CKD of unknown aetiology was common in certain areas of Central **Sri Lanka.** It was noted to affect young males, from low socio-economic, paddy farming communities. Mild proteinuria (<1 gram/24 hours) and bilateral echogenic small kidneys were typical findings. Urine examination did not show evidence of high inflammatory activity and hypertension was not a common feature [5].

2010

Torres et al 2010 gave the first cross-sectional report published in an international scientific journal and revealed that an increased prevalence of CKD in certain areas of the Mesoamerica's. In a survey more than 1300 persons from five villages of North-western **Nicaragua** were invited to take part in a health examination. 1,096 persons participated and provided blood and urine for analysis: a mining/subsistence farming, a banana/sugarcane, a fishing, a service and a coffee village type. In the mining/subsidence farming and in the fishing village the prevalence of elevated p-creatinine (>1.2 mg/dl) was high among men, 26% and 22% respectively, whereas it was intermediate (13%) in the fishing village and low in the service and coffee village. The pattern was similar for women, but at a lower level. An analysis of the prevalence of eGFR<60 ml/min per 1.73 m^2 as calculated using the MDRD formula showed a similar pattern. Proteinuria, measured by paper strip, was recorded in about one third of those with eGFR<60 ml/min per 1.73 m^2. It was noted the high CKD prevalent villages were located close the coast and at a low altitude and it was suggested that heavy workload in a hot climate leading to repeated dehydration may be one explanation [6].

Sanoff et al 2010 also report from north-western **Nicaragua**. Blood samples were obtained from 997 individuals and eGFR calculated from (using the MDRD formula) from analysis of plasma creatinine. 12.4% were identified as having an eGFR<60 ml/min per 1.73 m^2. In a case- control approach various exposure and demographic factors were compared with those having an eGFR>60 ml/min per 1.73 m^2. In a multivariable analysis age, male gender, low body mass, agricultural field work, several other types of occupations but not exposure to pesticides. Reported consumption of 'lija' which a type of locally brewed liquor and increasing amounts water consumed daily also comprised risk factors. It was suggested that high consumption of lija and/or contaminated water may cause CKD. However it is evident that high consumption of water, and fluids, may also be a proxy for heat exposure [7].

2011

O'Donnell et al 2011 report from a cross-sectional study in Quezalguaque, a municipality in County of Leon at the pacific coast in **Nicaragua**. 771 participated in a health exam including measurements of serum creatinine and eGFR was calculated from the MDRD formula. The prevalence of lowered eGFR (eGFR<60 ml/min per 1.73 m^2, CKD stage 3 to 5) was overall high (12.7%) but increased markedly with age and was almost twice as high in men compared with women. In men aged 57 or older the prevalence of CKD stage 3, and 4 to 5 was 26% and 26% respectively (>3 53%). Figure 1, from this publication, present the prevalence of lowered eGFR in different age-groups of examined men in Leon compared to NHANES figures from the US population. Prevalence of CKD were much lower in different age groups in the US. Most of the 'cases' with low eGFR (<60 ml/min per 1.73 m^2) did not display proteinuria (52%) or 'trace' (20%) and as assessed by a paper strip indicator. 21% was classified as >1+ on the paper strip indicator. There were no associations with well-known risk factors for CKD such as hypertension or diabetes [8].

Athuraliya et al 2011 provide more specific information on individuals with CKD in **Sri Lanka**. Screening for proteinuria was done in three areas: Medawachchiya, Yatinuwara and Hambantota. Altogether 6,153 were screened and 264 were found to have proteinuria. The prevalence of diabetes and long-standing hypertension were strikingly lower among the patients from Medawachchiya when compared with those from the other two study sites and the percentage of patients with CKD of uncertain aetiology was considerably higher (84%) in this area. Further examination of the patients with proteinuria from Medawachchiya revealed that 65% of the men and 54% of the women had an eGFR<60 ml/min per 1.73 m^2. The proteinuria in most of the cases were of relatively low degree and

few had hypertension. 26 of 109 patients from Medawachchiya with proteinuria underwent a renal biopsy. The light microscopic findings were indicative of tubulointerstitial disease, whereas the immunofluorescence tests for immune-mediated kidney injury, IgG, IgM, IgA, and Complement 3, were negative. A toxic aetiology was hypothesized, affecting vulnerable groups of people in Medawachchiya which is a relatively poor farming area where people are more prone to become exposed chronic dehydration and environmental pollutants than other populations of Sri Lanka [9].

Orantes et al 2011 describe CKD and associated risk factors in the Bajo Lempa region of **El Salvador**. 775 persons (343 men) were examined. eGFR was calculated form serum creatinine using the MDRD formula. The prevalence of eGFR<60 ml/min per 1.73 m^2 was 17% in men and 4% in women. Aetiology was neither diabetes, obesity, nor hypertension but considered to be 'unknown' in most of the cases. However, there were clear associations with agricultural work [43].

Overview/review/discussion paper

At World Congress of Nephrology 2011 in Vancouver, organized by the International Society of Nephrology (ISN) and the Canadian Society of Nephrology (CSN), Professor Correa-Rotter in a talk draw attention to the recently reported occurrence of lowered renal function among sugar cane workers in Central America. The name **Mesoamerican Nephropathy** was suggested due to similarities with another infamous kidney disease, Balkan Nephropathy, affecting inhabitants living along to the Danube River in southern Europe. For decades the cause of the Balkan Nephropathy was elusive but eventually it has convincingly been shown that Balkan Nephropathy is associated with the consumption of food containing aristolochic acid (AA) and the CKD is now better termed aristolochic acid nephropathy (AAN) [44]. As also people living elsewhere may develop AAN after food, or tea, containing (AA) [45].

Chandrajith et al 2011 from **Sri Lanka** reported a high prevalence of CKD of unknown cause in certain areas of the country, the north central dry zone. It was suggested that genetic predisposition and some or several environmental factors are involved in the pathogenesis [46].

2012

Nanayakkara et al in 2012 give a detailed presentation on the morphological changes seen in 57 renal biopsies obtained patients with CKD of unknown aetiology examined at Anuradhapura General Hospital in Central of **Sri Lanka**. Frequent global sclerosis, ischemic-type obsolescence, and wrinkled and collapsed glomerular tufts were suggestive of ischemia of glomeruli. Glomerular enlargement was observed in 21 renal biopsy specimens (37%), being the second most common lesion in glomeruli. Typical FSGS lesions was observed in two specimens with non-nephrotic range of proteinuria.

In contrast to the frequently observed sclerotic lesions, no specimen showed endocapillary, extracapillary, or mesangial cell proliferation typical chronic glomerulonephritis and diabetic glomerulosclerosis. Tubulointerstitial lesions were also seen with interstitial fibrosis being the most prominent observation and less of mononuclear cell interstitial inflammation. Arteriolar hyaline thickening score and fibrous intimal thickening was mild to moderate. This study concludes that tubulointerstitial damage is the major pathological lesion in CKDu in Sri Lanka, albeit the morphological changes that are described emphasize the glomerular lesions. It was suggested that exposure(s) to an environmental pathogen(s) should be systematically investigated to elucidate CKD of unknown cause in Central Sri Lanka [10].

Peraza et al 2012. Performed a cross-sectional study in five populations of **El Salvador**; Two sugarcane production communities close to the coast from where a high prevalence of CKD had been noted, and three additional villages from where there was no previous information on CKD. Altogether 664 persons were examined with measurements of blood pressure, serum creatinine and urinary paper test strips. Occupational exposure and some basic information of lifestyle and medical history were also obtained. It was possible to divide the examined population to five groups: rural coastal sugarcane, semirural coastal sugarcane, high-altitude sugarcane, coffee and urban. Significant differences in the prevalence of lowered eGFR, or elevated s-creatinine, was observed. Men in the two coastal sugarcane communities often displayed elevated s-creatinine (>1.2 mg/dl). The prevalence of

eGFR<60 ml/min per 1.73 m^2 among men was 19% and 18%, whereas the prevalence of low eGFR in the high-altitude sugarcane, coffee and urban population was below 2%. In a multivariate logistic regression analysis residence coastal community having a hot climate came out as the strongest predictor; 3.1 (CI 2.0-5.0) for each 10-year period. The prevalence of elevated s-creatinine increased with increasing number of years of work in the coastal sugarcane or cotton plantations. In spite of a high occurrence of lowered eGFR few had proteinuria; 3% of the men with eGFR >60 ml/min per 1.73 m^2 and 14% of those with eGFR below this level. The overall conclusion from this study was that long-term exposure to heat in connection hard physical work comprises a major risk factor for developing CKD in the area [11].

Laux et al 2012 conducted a cross-sectional study on the renal function in 267 (147 women) individuals aged 20 to 60 in a coffee-growing village in north-central **Nicaragua**, located 1000 meters above the sea level where the climate is less hot as compared areas close to the pacific coast. eGFR was calculated from plasma creatinine and, in contrast, to farming villages at the pacific coast less than 1% (0.7%) had an eGFR < 60 ml/min per 1.73m^2. Macroalbuminuria, as assessed by a paper indicator test strip, was seen in 5% of the men and 2% of women. It was noted that 92% of the men reported 'high levels of working with pesticides'. This report thus provide support for the notion that heat exposure rather than pesticides are involved in the causative pathway of CKDu (or MeN) [47].

Senevirathna et al 2012 examined risk factors associated with mortality in 143 patients with chronic kidney disease of uncertain aetiology **Sri Lanka**. Eight out of 45 patients (18% aged under 65 and with eGFR below 60 ml/min per 1.73m^2 in 2003) had died within two years. Out of nine aged over 65 having an eGFR < 60 ml/min per 1.73m^2 three (33%) had died. High blood pressure was a risk factor for disease progression and death in this cohort [48].

Overview/review/discussion paper.

Brooks et al in in an editorial in AJKD called attention to epidemic of CKD in Central America and mentioned that it 'results in many thousands of deaths' by refereeing to national statistics in Nicaragua and El Salvador. Points out occupational heat strain as one putative cause [49].

Funakoshi et al EHP 2012. Cross-sectional examination of prevalence of CKD in reaction to reported intake of alcohol (drinks/day) in 9,196 Japanese men (mean age 58). Negative associations were observed between reported alcohol consumption and prevalence of CKD III or higher [50].

2013

Jayasumana et al [51] analysed the arsenic concentration in urine from clinically diagnosed CKDu patients (n=125) and non-CKDu persons (n=180) in **Sri Lanka**. 68% of CKDu patients and 28% of the controls had urine arsenic levels above 21 µg/g creatinine and it was suggested that arsenic exposure from agrochemicals might be involved in the pathogenies of CKDu. However, albeit inorganic arsenic is severely toxic and may cause several types of systemic toxicity kidney has rarely been reported [52]. [53]inorganic arsenic) is complicated by the fact that organic forms of non-toxic arsenic is common in several forms of seafood (such as shrimps and shellfish). Consumption of certain types of common seafood may thus increase the urinary excretion of arsenic considerably. To differentiate between exposures to inorganic, or organic 'non-toxic' arsenic speciation of arsenic in urine is needed, and this was not done in this study, merely total arsenic was measured. Possibly the type of food varied between CKDu patient and controls.

Ramirez-Rubio (2013) and a team from Boston University School of Public Health made a semi-structured interview with 10 physicians and 9 pharmacists in North-western **Nicaragua** which has a high prevalence of chronic kidney disease (CKD) of unknown cause. The interviews were performed 2010. Health professionals perceived CKD as a serious and increasing problem in the region, primarily affecting young men working as manual labourers. All interviewees regarded occupational and environmental exposure to sun and heat, and dehydration as critical factors associated with the occurrence of CKD. These factors were also considered to play a role in the occurrence of a set of symptoms referred to locally as "chistata," characterized by painful urination and often accompanied by "kidney" and/or back pain. The health professionals indicated that reluctance among workers to

hydrate might be influenced by perceptions of water contamination. Symptoms often were treated with self-medication using non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and antibiotics. Albeit the diagnosis of urinary tract infection was sometimes set and treated with antibiotics this diagnose was usually not based on microbial culture. Likewise, the incidence renal stones were not considered be unusually high or frequently diagnosed. Despite the media attention given to the potential role of agrochemicals in causing CKD, physicians and pharmacists were much more likely to cite exposure to heat, physical work and dehydration as key factors responsible for the CKD development [54].

Severe heat exposure during sugarcane harvesting in Costa Rica has been documented. Non-participatory observation and Wet Bulb Globe Temperatures (WBGT) measurements were carried out during two typical working weeks in 2012 and 2011 in Guanacaste, in north-western **Costa Rica**. Sugarcane in this area is typically burnt the night before harvesting, and these ads to the ambient heat exposure. Already at 7:15, after a little more than one hour work, the OSHA threshold of 26.0 degrees WBGT was reached after 4 hours 30.0 degrees was often reached at which level no more than 15 minutes per hour is recommended to avoid health risks. However, the sugarcane cutters typically kept on for several more hours (until noon) to get there needed income which typically is based on the amount (weight) of the cut [55].

The first detailed clinical and pathological characterization of what has been named Mesoamerican Nephropathy (MeN) was published 2013[15]. Eight male patients with CKD of unknown cause and clinically suspected MeN were examined in **El Salvador**. All had been working on plantations. Renal morphology examined with light microscopy, immunofluorescence and electron microscopy. A similar morphological pattern was seen in all 8 biopsy specimens, with extensive glomerulosclerosis (29%-78%) and signs of chronic glomerular ischemia in combination with tubular atrophy and interstitial fibrosis, but only mild vascular lesions. Electron microscopy indicates podocytic injury. Biochemical workup showed reduced estimated glomerular filtration rate (27-79 mL/min/1.73 m^2 with the CKD-EPI equation, low-grade albuminuria, and increased levels of tubular injury biomarkers. Hypokalemia was found in 6 of 8 patients. This observation (low potassium) in combination with glomerular changes indicative of ischemia suggested that perturbations in the renin angiotensin system due to excessive and repeated losses of salts due to excessive sweating may be involved in the pathogenies [15].

Overview/review/discussion papers

Wesseling et al 2013 in American Journal of Public Health call for action and further research based on the conference in Costa Rica in December 2012. Emphasize that the most affected group are sugarcane cutters, exposed to extreme ambient heat during hard physical work. Repeated episodes with dehydration with loss electrolytes and minerals with attending AKI was the leading hypothesis and pathway to cause the epidemic of CKDu in Central America. Alternative hypothesis and cofactors were also considered needing further attention; NSAID use, inorganic arsenic, and infection from leptospirosis. Based on available evidence at the time of the meeting (December 2012) pesticides, hard water and urinary tract infections were considered unlikely causes. At the workshop it was also pointed out that heat stress-associated CKD possible is not an isolated Mesoamerican problem and that are suggestive evidence that it also occurring in Sri Lanka [56].

Lewington et al (2013) in KI try to raise the awareness that acute kidney injury (AKI) is a major global health problem resulting in millions of deaths per year on a global basis. If not prevented, or treated, properly a large proportion of the incident AKI may progress to CKD and ESRD. Proper hydration, and rehydration, and avoidance of nephrotoxic drugs are key elements for prevention [57].

2014

Rosa-Diez et al 2014 present data on the prevalence of renal replacement therapy (RRT) in twenty **Latin America** countries. The overall prevalence of RRT is rapidly increasing and was 660 per million in 2011. El Salvador and Nicaragua, which have areas with many cases of CKD from MeN, have the lowest RRT rates; 28 and 11 per million. These low prevalence figures are most probably due

to insufficient allocation of resources as there was an almost linear and highly significant correlation between each country's gross national income and prevalence of RRT [58].

In 2014 two medical students, Krinsky and Levine in KI, gave a personal presentation of the CKD epidemic in **Nicaragua**: Chronic kidney disease of unknown origin (CKDu), also known as Mesoamerican Nephropathy or Mesoamerican endemic Nephropathy. La Isla Foundation from the nickname for 'La Isla de Viduas' or the Island of Widows. Site information from the area reporting that 'at least 3000 people in Chinandega (a region in north-western Nicaragua with population of around 150,000) alone has the disease. Present the almost unsurmountable difficulties to provide peritoneal dialysis to patients with end stage renal disease due to poverty, insufficient training and medical support and in particular poor hygienic facilities at the homes of affected individuals [59].

Raines et al 2014 report from one of the most affected townships in **Nicaragua**; community near the town of Chichigalpa. Participants were recruited using door-to-door canvassing in May–June 2012. All eligible household members were invited to a single study visit at a central location for interview on medical history and various environmental and occupational exposures and physical and biochemical measures which included urine paper strip and analysis of serum creatinine and calculation of eGFR using the CKD-EPI formula. 424 people (166 men) participated. Mean age was 32 for men and 35 for women. Prevalence of eGFR <60 mL/min/1.73 m^2 was 42% among men 9.8% in women. Among participants with GFR <60 mL/min/1.73 m2, 44% had proteinuria ≥30mg/dL and only 7 participants (9%) had proteinuria ≥300 mg/dL. A subset of the participants formed the base for a case-control analysis to assess risk factors for reduced GFR, with cases defined as individuals with a single GFR calculation <60 mL/min/1.73 m^2 and controls defined by an eGFR >90 mL/min/1.73 m^2. Hypertension was more prevalent among cases than controls although overall prevalence of hypertension was only 8.6%. Prevalence of HbA1c >6.5% was 3.7% in case group and 3.2% in control group (p = 0.88. NSAID use was common (>70% in both cases and controls and there was no significant difference between cases and controls (p = 0.44). Aside from age and male sex, the strongest independent association observed was between reduced GFR and lifetime hours cutting sugarcane, particularly during the dry season. In models adjusted for total hours cutting sugarcane during the dry season, a history of high 'bolis' consumption, a sugary rehydration packet (OR 1.39, 95% CI 0.99–1.95) and inhaling pesticides (OR 2.61, 95% CI 0.99–6.90) were close to significant [16].

VanDervort et al (2014) in an exploratory ecological study in **El Salvador** analysed unspecified CKD (unCKD) and non-diabetic ESRD (ndESRD) hospital admissions. 16,384 and 8,342 respectively in 242 municipalities. Admission rates for CKD was calculated and related to environmental factors and type of production in these municipalities. The areas of highest unspecified CKD admission rates were in the south-western municipalities of La Paz Department. This area is the region of highest ambient temperatures (33–36 ºC) in El Salvador. Percent area of sugarcane cultivation produced the greatest bivariate regressions. However, when models where made more complex multivariate and sophisticated association with heat become less evident [60].

Orantes et al 2014 report from a population screening study in **El Salvador**. 2388 individuals in three agricultural communities were examined: Bajo Lempa, Guayapa Abajo and Las Brisas (976 men). The prevalence of CKD was (eGFR <60 mL/min/1.73 m^2) was high in all three villages, 6.8% in woman and 17% in men and increased with age. At age >60 57% of men and 28% of women had eGFR below 60 mL/min/1.73 m^2. Few displayed proteinuria. As in other cross-sectional studies neither hypertension nor diabetes or obesity was particularly high in these communities, but the prevalence lowered eGFR was twice as common among in kidney function male agricultural works compared to non-agricultural workers. Contact with of agrochemicals was common among men and reported by 54 of the men and 15% of women. Use of NSAIDs was overall common and similar in both sexes (84% in men and women. The others were not able to pinpoint any specific type of exposure that could explain the high prevalence of CKD in the examined populations but that 'poor working conditions, and contact with agrochemicals' are involved [17].

Herrera el al 2014 present clinical characteristics from 46 participants in the **El Salvador** screening programme reported by Orantes et al (2014) who were aged between 18-59 and had an eGFR<60

mL/min/1.73 m^2. Overall, the patients characterized by poverty were the leading social determinant observed. Risk factor Prevalence of various conditions and exposures where as follows; exposure to agrochemicals (95.7%), agricultural work (78%), male sex (78%), profuse sweating during work (76.3%), malaria (44%), NSAID use (41%), hypertension (37%), diabetes (4%). General symptoms included: arthralgia (54.3%), asthenia (52%), cramps (46%), and fainting (30%). Renal symptoms included: nycturia (65%), and dysuria (39.1%). Markers of renal damage where often abnormal in this group of selected patients with low eGFR; macroalbuminuria (80%), elevated β2 microglobulin (78%), and NGAL (26%). These data are however somewhat difficult to interpret as only 26 individuals were reported to have macroalbuminuria in the screening report and cut-of levels for β2 microglobulin and NGAL are not given. Analysis of plasma showed that metabolic alkalosis (46%), hyponatremia (48%), hypocalcaemia (39%), hypokalemia (30%), and hypomagnesemia (20%) was common in this group [18].

López-Marín et al 2014 performed renal biopsies of the patient's characterized by Herrea et al 2014 in **El Salvador**. The main findings were interstitial fibrosis and tubular atrophy with or without inflammatory monocyte infiltration. In addition, generalized glomerulosclerosis, increased glomerular size, collapse of some glomerular tufts, and lesions of extraglomerular blood vessels (such as intimal proliferation and thickening and vacuolization of the tunica media) were observed. Overall these observations are well compatible with those presented by Wijkström et al (2013) albeit the authors of this report conclude that the renal biopsies are more consistent with tubulointerstitial nephritis accompanied by glomerular damage and concluded that toxic environmental or other occupational exposures, chronic ischemia from dehydration, or nephrotoxic medications, are all compatible with the histopathological findings [61].

Vela et al 2014 present another descriptive cross-sectional study from two **El Salvador**an farming communities; Dimas Rodríguez (El Paisnal municipality) and El Jícaro (San Agustín municipality) facing the Pacific with an alarming high prevalence of CKD: A total of 223 persons of both sexes were studied. Overall prevalence of chronic kidney disease was 16.1% (men 10.9%; women 21%). It noteworthy that CKD was more common in women than in men in this study. Most of the examined reported agrochemical occupation and contacts with agrochemicals [62].

Ordunez et al (2014) presents data on the age standardized mortality rate due to chronic kidney disease in **Nicaragua** and **El Salvador** compared to other countries in the region. The age standardized mortality rate due to chronic kidney diseases (coded as N18 (CKD-N18) by the 2010 International Classification of Diseases) was notably higher for men and women in Nicaragua and El Salvador compared to other countries in the region, and rapidly increasing. In men aged 50-54 the mortality rate in CKD in Nicaragua and El Salvador 2000-2009 was about 110/100,000 population compared to less than 40/100,000 population in countries such as Panama, Cuba, and Costa Rica. Lack of dialysis facilities in Nicaragua and El Salvador can hardly explain these remarkable differences in CKD mortality: The data really confirms that a fatal endemic of CKD was present in these two countries [22].

The incidence prevalence distribution of pediatric chronic kidney disease (CKD) in **Guatemala** has been presented [63]. Overall, the prevalence of CKD in children appeared low but this may well be due to poor access to diagnosis. Worth to note is that ESRD was much more common along the Pacific coast, the same side of the land as where CKDu/MeN are most prevalent among adults.

Paula Santos et al 2014 examined 28 healthy non-African **Brazilian** workers engaged in sugar cane harvesting during 2009[20]. Blood and urine samples were collected before starting harvest, and before and after a workday in the last month of the harvesting season. Although there was no systematic change in p-creatinine at start of work the harvesting season and a morning sample later, p-creatinine at the end the workday (taken at the end of the harvest season) had increased in all men (average 21 umol/l), and eGFR dropped on average about 20 ml/min per 1.73 m^2 and five of the 28 examined men (18%) displayed acute kidney injury as was diagnosed by the p-creatinine increase. During the harvesting season the men worked from 7 to 16 hours, six days a week cutting in the order of 10 tons of burnt sugarcane per day in a high ambient temperature. Several of the workers experienced frequent cramps during the cutting season and measurement of urine osmolarity (average

890 mOsm/l) revealed that significant dehydration occurred during the cutting. White blood cells also increased significantly during the heavy work, and there were significant positive correlations between p-creatinine on the one hand and changes in haematocrit, or serum albumin, on the other [20]. In context of rapidly increasing p-creatinine after a workday seen at the end of the harvest is worth noting that GFR need to drop rather dramatically to result in an increase of the p-creatinine concentration of 20 umol/l within 8 hours (50%!).

CKD mortality in **Costa Rica** has examined to explore if there were the relationships with altitude, climate and sugarcane production [64] [23]. SMRs for CKD deaths (1970-2012) among population aged 20 or more were computed for 7 provinces and 81 counties over 4 time periods. Excess CKD mortality occurs primarily in Guanacaste lowlands and was already present 4 decades ago. During 1970-2012, age-adjusted mortality rates in the Guanacaste province increased among men from 4.4 to 38.5 per 100,000 vs. 3.6-8.4 in the rest of Costa Rica, and among women from 2.3 to 10.7 per 100,000 vs. 2.6-5.0 in the rest of Costa Rica. A significant moderate excess mortality was observed among men in Guanacaste already in the mid-1970s, steeply increasing thereafter; a similar female excess mortality appeared a decade later, remaining stable. The increasing rates among Guanacaste men in hot, dry lowland counties with sugarcane was consistent with an occupational component.

42 male patients with confirmed CKDu were interviewed about how they used pesticides in three communities of Bajo Lempa region, **El Salvador** [65]**.** Interviewed did not use appropriate personal protective equipment; hazardous pesticides were often misused, 95% of interviewed mixed different types of pesticides and 63% dumped empty pesticide containers in the fields.
There was inadequate legislation and a poor law enforcement to prevent the misuse of pesticides in El Salvador at the time of this report. Very similar results were also reported later [66] but also included some environmental measurements of cadmium and arsenic.

In the North Central Region (NCR) of **Sri Lanka** the aetiology of chronic kidney disease of unknown cause (CKDu) was examined in a social-environmental-and-genetic epidemiology study [67]. 311 case-series patients and 504 controls were recruited. Of the 504 control candidates, 218 (43%) were eliminated because of the presence of hypertension, proteinuria, high HbA1c, high serum creatinine or high alpha-1 microglobulin in urine. None of 18 metals measured in urine, including Cd, As and Pb, showed significantly higher concentrations in cases compared with controls. Arsenic (As) speciation results showed that 75-80% of total urinary As was in the form of arsenobetaine, which is non-toxic to humans. None of the metal concentrations in drinking water samples exceeded guideline values. A genome-wide association study (GWAS) yielded a genome-wide significant association with CKDu for a single nucleotide polymorphism (SNP; rs6066043; p=5.23 x 10(-9) in quantitative trait locus analysis; p=3.73 x 10(-9) in dichotomous analysis) in SLC13A3 (sodium-dependent dicarboxylate transporter member 3). Genetic susceptibility, but not exposure to metals, was identified as the major risk factor for CKDu.

Animal model

Roncal Jimenez et al 2014 in an **animal model** have elucidated a possible mechanism for heat and dehydration induced nephrotoxicity involving activation of renal fructokinase. Wild-type and fructokinase deficient mice were subjected to recurrent heat-induced dehydration. This was achieved by placing mice in heated chambers for a total of 3.5 h per day, for 5 days per week, for a total of 5 weeks. The first major finding was that the mice that were severely dehydrated (losing on average 15% of their body weight), during the day and had delayed rehydration activated the aldose reductase pathway in their kidneys, and this was associated with the development of renal injury, as noted by an increase in urinary neutrophil gelatinase-associated lipocalin (NGAL), an increase in serum creatinine, proximal tubular injury by biopsy, an increase in renal MCP-1 and macrophage infiltration, and early renal fibrosis. This was associated with activation of the polyol pathway, with increased renal cortical sorbitol and fructose levels. Mice that were exposed to the same heat but who hydrated during the day were protected. Interestingly mice lacking fructokinase were protected from renal injury despite similar degrees of dehydration. These experimental studies may have practical consequences also on the type of rehydration that is provided and recommended. Many of the sugar cane cutters hydrate

themselves with fructose-rich juices or beverages that might compound the problem with dehydration as the acute renal injury might be potentiated by fructose provided in the drinks [68].

Overview/review/discussion papers

At the first international MeN meeting it was concluded. 'There is an epidemic of chronic kidney disease of unknown aetiology (CKDu) in several parts of Mesoamerica. This public health problem is of such magnitude and severity that urgent, exhaustive, and collaborative actions must be put into place to elucidate the cause(s), act on available information to prevent further disease and find permanent solutions for prevention and mitigation'.

The consensus of the workshop was that 'the strongest causal hypothesis for the epidemic is repeated episodes of heat stress and dehydration during heavy work in hot climates. Co-factors to consider interacting with heat stress or influencing the progression of CKDu, include excess use of nonsteroidal anti-inflammatory drugs (NSAIDs) and fructose consumption in rehydration fluids. Contributing factors for the epidemic could include inorganic arsenic, leptospirosis, pesticides, or hard water. Interventions to reduce heat stress and improve hydration with controlled trials are recommended.' [13].

Correa-Rotter et al (2014) provide a more in depth presentation from the first international MeN meeting in Costa Rica, present epidemiologic studies on CKD in Central America and discuss pros and cons for a number of suggested causative factors including; Aristolochic Acid and Mycotoxins, Heavy Metals, Agrochemicals, Leptospirosis and Other Infectious Causes, Alcohol Drinks Containing Toxins, Nonsteroidal Agents and Other Nephrotoxic Drugs, Recurrent Dehydration/Volume Depletion, Fructose, Hypokalemia and Hyperuricemia, and Social Determinants[14]. Heat stress, dehydration end volume depletion was the only potential causes given 'high priority' and activation of the fructokinase pathway was suggested as a potential mechanism for dehydration associated CKD. The use of nephrotoxic medications was considered a possible cofactor, in particular the concomitant use of NSAID and heat dehydration. Other exposures were given low or medium priority. Prevention and treatment were also touched upon. The best-known prevention is possibly to provide adequate hydration and limit exposure of workers to heat. Working in the early morning hours before the temperature gets excessive may be of benefit. Increased drinking of water is recommended to minimize the effects of excessive sweating, and avoidance of NSAIDs is highly recommended. Providing appropriate sources of hydration and sanitation and allowing for reasonable working shifts accompanied by periods of rest and provision of shade are all recommended strategies for prevention. Rehydration interventions should be adequately studied for effectiveness by means of field trials. Even if pesticides eventually are found not to cause CKD, there is no doubt that any potential hazards associated with their use should be minimized, and sustainable nontoxic pest control methods should be encouraged [14].

Wernerson et al 2014 present an update on different forms of endemic nephropathies and point out that in addition to epidemiologic studies which focus on the prevalence of nephropathy in different areas and its association with different risk factors careful clinical studies, case reports and renal biopsies, are needed to fully understand and unravel the possible mechanism [69].

Robey 2014; in an editorial in KI suggest that, based on animal experiments, fructokinase deficiency and fructose metabolism may be promoting a dehydration-induced acute kidney injury to CKD [70].

Jayasumana et al 2014 in a review paper on the possible cause(s) of the ongoing epidemic of CKD affecting the population of several rice paddy farming areas of **Sri Lanka** suggest that the culprit is the used herbicide: glyphosate. This is the most used pesticide in Sri Lanka, highly water soluble, chelating and may form complexes with metals and other constituents of hard water. Consumption of hard water has previously been related to a high incidence of CKDu in Sri Lanka. However, the evidence presented are, yet, mainly circumstantial [71].

Almaguer et al 2014 provide a review of chronic kidney disease of unknown aetiology in agricultural communities globally, by reviewing published findings from El Salvador, Nicaragua, Costa Rica, Sri Lanka, Egypt, and India. Summarizes that associations were reported with agricultural work, agrochemical exposure, dehydration, hypertension, homemade alcohol use and family history of

chronic kidney disease. According to the authors there is no strong evidence for a single cause, and multiple environmental, occupational and social factors are probably involved [72].

In review paper on CKD hotspots around the world [73] Mesoamerican nephropathy is mentioned along with Balkan nephropathy, Chinese herb nephropathy and the high prevalence of CKD in the Australian Aboriginal population.

Another review [74] on the chronic kidney disease epidemic affecting Central American farming communities summarizes the two main causal hypotheses (heat stress and agrochemicals) and draw attention to the consequences of dichotomous reasoning concerning causality and warns of potential conflicts of interest and their role in "manufacturing doubt." Likewise Ordunez [22]in a Viewpoint editorial in PLOS suggest that misuse of pesticides has a major influence on the rapidly increasing mortality of CKD in two Central American countries; Nicaragua and El Salvador.

Wanigasuriya 2014 in a review update what is known about a new form of chronic kidney disease that has emerged over the past two decades in the northcentral dry zone of **Sri Lanka**. 16 manuscripts published in peer reviewed journals and three peer-reviewed abstracts were included in the review. Disease prevalence was 5.1%–16.9% with more severe disease seen in men than in women. Lack of distinctive criteria for CKDu diagnosis was a problem in interpreting the various study results. Almost all studies seem to be based on screening for proteinuria rather that a low eGFR. This makes comparisons with the cross-sectional studies is Central America difficult as many of the individuals in the Mesoamerican studies with lowered eGFR do not display proteinuria. However, as in Mesoamerica, in Sri Lanka no association was found with conventional risk factors for CKD. Patients with mild to moderate stages of disease were asymptomatic or had nonspecific symptoms; urinary sediments were bland; 24-hour urine protein excretion was <1 g; and ultrasound demonstrated bilateral small kidneys. Interstitial fibrosis was the main pathological feature on renal biopsy. Heterogeneity of definitions and methodologies in the studies examined limit the possibility of conclusions regarding possible cause(s). The author suggests that aetiology of CKDu in north-central Sri Lanka is multifactorial, involving one or more environmental agents and possibly genetic predisposition in vulnerable populations [75].

2015

Laws et al (2015) investigated changes and job-specific differences in renal tests over a 6-month sugarcane harvest season in 284 **Nicaraguan** sugarcane workers performing seven distinct tasks as: cane cutters- (n=51), seeders (n=36), seed cutters (n=19), agrochemical applicators (n=29), irrigators (n=49), drivers (n=41) and factory workers (n=59). eGFR (CKD-EPI equation) varied by job and decreased during the harvest in all groups considered to be exposed to ‘heat stress’ groups and significantly so in seed cutters (-4.5 ml/min/1.73 m^2) and irrigators (-4.9 ml/min/1.73 m^2) but was not seen in drivers and factory workers not exposed to ‘heat stress’. The number of years employed at the company was negatively associated with eGFR. Fewer than 5% of workers had albumin-to-creatinine ratio (ACR) >30 mg/g [19]. As the differences between groups and changes in serum creatinine over time are relatively small (from –7% to +9%) the interpretation may be confounded by variations in diet and/or intrinsic muscle composition which may be influenced by a physically demanding work, such as cane cutting. Another circumstance is that workers with elevated creatinine already at the start of the season where not hired. Nevertheless, this report indicate that workers exposed to severe heat strain lose renal function!

Orantes Navarro et al (2015) in a cross-sectional study 2009 - 2011 examined 1,412 women aged ≥ 18 years in three disadvantaged populations of **El Salvador**: Bajo Lempa (Usulután Department), Guayapa Abajo (Ahuachapán Department), and Las Brisas (San Miguel Department). eGFR was calculated from the CKD-EPI formula. Prevalence of CKD (eGFR < 60 ml/min/1.73 m^2) was 13.9%. 5.7% had microalbuminuria (30 - 300 mg/L) and 0.8% macroalbuminuria (> 300 mg/L). Information of various risk factors were reported and 31% reported contact with agrochemicals. The study confirms that CKDu is a major health problem in poor populations of El Salvador, and among women. Unfortunately, exposure to heat and water and salt depletion was not reported [76].

Herrera Valdés R et al 2015 undertook a thorough exam, including renal biopsies from 10 of the screened women. Nine of them had U-albumin exceeding 0.3 g/mol creatinine and 7 of the eGFR > 60 ml/min/1.73 m^2. Histopathological findings were rather non-specific and included interstitial fibrosis and glomerulomegaly. Due to the selection of the examined patients (from a large screening programme) and the high prevalence of albuminuria and a relatively high eGFR in most of the examined woman the results are not really comparable with other case series of CKDu or MeN [77].

Heat stress and workload associated with sugarcane cutting was examined in 45 sugarcane cutters in **El Salvador** during the 2015 harvest [78]. Sugarcane cutters worked on average for 7:30 hours. In the field, Outdoor Wet Bulb Globe Temperatures (WBGT) averaged 32.1°C. The cardiac strain of sugarcane cutting was like that associated with competitive exercise and higher than that typically associated with self-paced hard work. It should be noted that sugarcane cutters maintain this work intensity daily throughout the harvest (~6 months). (95% confidence interval [CI]: 33.0°C to 31.1°C).

Crowe et al (2015) examined the frequency of heat-related health effects among harvesters in **Costa Rica** (n = 106) exposed to occupational heat stress compared to non-harvesters (n = 63). Heat and dehydration symptoms (headache, tachycardia, muscle cramps, fever, nausea, difficulty breathing, dizziness, swelling of hands/feet, and dysuria) were experienced at least once per week significantly more frequently among harvesters. Percentages of workers reporting heat and dehydration symptoms increased in accordance with increasing heat exposure categories [79].

Laux et al (2015) analysed enrolment rates in RRT **Guatemala** and found the rates were significantly higher in the southwest compared to the rest of the country and concluded that the elevated incidence had a similar geographic distribution as Nicaragua and El Salvador (higher in the high temperature and sugar cane growing regions), and that it is likely that the CKD epidemic extends throughout the Mesoamerican region [80].

Lebov et al (2015) conducted a cross-sectional study of 2275 residents in Leon, **Nicaragua**. CKD (eGFR<60 ml/min/1.73 m^2) prevalence was 9.1%; twice as high for males (13.8%) than females (5.8%). Older age, rural zone, lower education level, and self-reported high blood pressure, more years of agricultural work, lija (unregulated alcohol) consumption, and higher levels of daily water consumption were significantly associated, and dose-response related with CKD. Adjusted odds ratio for low eGFR increased from 1.3, 1.7, 2.6 and 2.9 with increasing five years of work in agriculture and likewise decreasing educational level. This study provides additional support for an environmental and/or occupational cause of MeN [81].

Further support dehydration and loss of minerals being the major cause of MeN have been presented from **El Salvador**. Sugarcane cutters (N=189, aged 18–49 years, 168 of them male) from three regions in El Salvador were examined before and after shift. Cross-shift changes in markers of dehydration and renal function were examined and associations with temperature, work time, region, and fluid intake were assessed. Pre-shift glomerular filtration rate was estimated (eGFR). Pre-shift serum uric acid levels were remarkably high and pre-shift eGFR was reduced (<60 mL/min) in 23 male workers (14%). The mean worktime was 4 (1.4–11) hours. Mean workday temperature was 34–36 °C before noon, and 39–42°C at noon. The mean liquid intake during work was 0.8 L per hour. The mean urine specific gravity, urine osmolality and creatinine increased, and urinary pH decreased. Serum creatinine, uric acid and urea nitrogen increased, while chloride and potassium decreased. The changes are consistent with recurrent dehydration from strenuous work in a hot and humid environment and a pathophysiology including decreased renal blood flow, high demands on tubular reabsorption, and increased levels of uric acid [82].

Wijetunge et al (2015) in a retrospective study of 251 renal biopsies from **Sri Lanka**. The predominant feature of stage I disease was mild and moderate interstitial fibrosis; most did not have interstitial inflammation. The typical stage II disease had moderate interstitial fibrosis with or without mild interstitial inflammation. Stage III disease had moderate and severe interstitial fibrosis, moderate interstitial inflammation, tubular atrophy and some glomerulosclerosis. Stage IV disease typically had severe interstitial fibrosis and inflammation, tubular atrophy and glomerulosclerosis [83].

In a cross-sectional epidemiological study Jayasumana et al (2015) compered anamnestic information from 107 patient with CKDu to that of 180 healthy controls in Trincomalee district of Sri Lanka. The

proportion of patients that were men, drank well water, had history of drinking water from an abandoned well, and had sprayed glyphosate was higher in patients than in healthy controls. Water analysis higher amount of hardness, electrical conductivity and glyphosate in the CKDu endemic areas where both patients and their healthy controls lived. As this is not a proper case-control study no generalizing suggestions or conclusions can be made but hypothesize generation [84].

Lebov et al (2015) evaluated the association between exposure to 39 specific pesticides and end-stage renal disease (ESRD) incidence in a cohort study of licensed pesticide applicators in **Iowa and North Carolina**. 320 ESRD cases were diagnosed among 55,580 male licensed pesticide applicators. Participants provided information on use of pesticides via self-administered questionnaires. Cox proportional hazards models, adjusted for age and state, were used to estimate associations between ESRD. A great number (<100!) statistical associations were examined, and a few showed statistical significance. Positive exposure-response trends were observed for the herbicides alachlor, atrazine, metolachlor, paraquat, and pendimethalin, and the insecticide permethrin. More than one medical visit due to pesticide use (HR=2.13; 95% CI 1.17 to 3.89) and hospitalisation due to pesticide use (HR=3.05; 95% CI 1.67 to 5.58) were also significantly associated with ESRD [85].

Overview/review/discussion papers***:*** Elinder et al (2015) in a review summarizes what has been published up to the mid 2015 on Mesoamerican Nephropathy (MeN) and a similar type of CKD in Sri Lanka. An epidemic of CKD affecting agricultural workers in the Mesoamerica. At an early stage the kidney disease is characterized by a lowered glomerular filtration rate (GFR) but no, or limited, albuminuria. It mainly affects men that have been working for years with hard physical work in hot climate prone to repeated episodes of dehydration and, as result of this, repeated subclinical acute kidney injuries. Cofactors for the development of the disease, such as consumption of NSAID and large amount of fructose rich fluids, and genetic predisposition possibly exist. Severe and terminal CDK may develop. Thousands of inhabitants along the Pacific coast possibly are affected. Histopathological examination of renal biopsies shows glomerular and interstitial changes that are compatible with repeated episodes of ischemia. Reports from Sri Lanka indicate that agricultural workers in certain areas of the island may develop CKD of a similar type [86].

Another review text on MeN, which is updated regularly and available on line, appear in UpToDate since 2015 [87] [88].

Measurement of arsenic, cadmium, and lead in biological media from populations with CKD of unknown cause in **Central America** has not shown potentially toxic levels of these metals, rather levels are in the normal range. Likewise, the concentration of a series of potentially nephrotoxic metals, including arsenic, cadmium, lead and lithium has been measured in drinking water and urine from patients with CKDu, and individuals without CKDu in CKD endemic and non-endemic areas of **Sri Lanka**. Overall, the concentrations were low in water as well as in urine and there was nothing indicating a causative association between exposure to metals and CKDu [89].

Likewise, Wimalawansa (2015) in a review from **Sri Lanka** concludes that available data do not support any so far postulated agents, chemicals, heavy metals, fluoride, salinity/ionicity, or individual agrochemical components, such as phosphate or glyphosate, as causative factors for the CKD epidemic in parts of Sri Lanka. A combination of these factors (or an unknown toxin) together with harmful behaviour and chronic dehydration may cause this disease [90].

Lunyera et al (2015) provides an overview of epidemics of CKD of uncertain etiology (CKDu) are emerging around the world, searched PubMed, Embase, Scopus and Web of Science databases to identify published studies on CKDu. 1607 articles, of which 26 met inclusion criteria. Eighteen (69%) were conducted in known CKDu-endemic countries: Sri Lanka (38%), Nicaragua (19%), and El Salvador (12%). The other studies were from India, Japan, Australia, Mexico, Sweden, Tunisia, Tanzania, and the United States. Heavy metals, heat stress, and dietary exposures were reported across all geographic regions. In south Asia, family history, agrochemical use, and heavy metal exposures were reported most frequently, whereas altitude and temperature were reported only in studies from Central America. Across all regions, CKDu was most frequently associated with a family history of CKDu, agricultural occupation, men, middle age, snake bite, and heavy metal exposure [91].

Weaver et al (2015) in an overview emphasises that CKDu appears to have a complex and possibly multifactorial cause, but exposure to metals such as cadmium, lead and arsenic do not appear to have a major role [92].

Murray el al 2015 [93] suggested that Mesoamerican nephropathy might have an infectious etiology in the Chichigalpa area, in Chinandega, Nicaragua. In this 'hot spot' area interviewed patients had often experienced fever, nausea and vomiting, arthralgia, myalgia, headache, neck and back pain, weakness, and paresthesia at the onset of acute kidney disease. Rodents, particularly of Sigmodon species, in are common in the sugarcane fields where most of the patients have been working. It was hypothesized that infectious pathogens are being shed through the urine and feces of these rodents, infecting agricultural workers in sugar cane plantations. But no evidence for this theory was presented.

2016

Regional variations in prevalence the prevalence of chronic kidney disease (CKD) in **Costa Rica** have been analysed and reported 2019 [94]. A cohort comprised of 2657 adults born before 1946 in Costa Rica was chosen through a sampling algorithm to represent the national population of Costa Ricans >60 years of age. Participants answered questionnaire data and completed laboratory testing. The primary outcome of this study was CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. The overall estimated prevalence of CKD for older Costa Ricans was 20% (95% CI 18.5-21.9%). In multivariable logistic regression, older age (adjusted odds ratio [aOR] 1.08 per year, was independently associated with CKD. For every 200 m above sea level of residence, subjects' odds of CKD increased 26% (OR 1.26). There was large regional variation in adjusted CKD prevalence, highest in Limon (40%) and Guanacaste (36%) provinces. Regional and altitude effects remained robust after adjustment for socio-economic status. These provinces also display a higher mortality rate in CKD, have a high proportion of immigrants from other Central American countries, including Nicaragua, and are engaged in agricultural activities; the main crops in Guanacaste are sugar cane and rice, whereas in Limon, bananas and other fruits are predominant.

Bodin and co-workers (2016) examined an intervention modelled on OSHA's Water-Rest-Shade programme (WRS) during sugarcane cutting in **El Salvador**. Health data (anthropometric, blood, urine, questionnaires) were collected pre-harvest, pre-intervention, mid-intervention and at the end of harvest. Self-reported water consumption increased 25% after the intervention. Symptoms associated with heat stress and with dehydration decreased. At the same time the individual daily cut cane production increased. A WRS intervention is feasible in sugarcane fields and appears to markedly reduce the impact of the heat stress conditions for the workforce. With proper attention to work practices, production can be maintained with less impact on worker health [24].

Laux et al (2016) document the prevalence of non-traditional causes (CKDnt) among 242 hemodialysis patients in southwestern **Guatemala**. The prevalence of CKDnT appeared to be lower than in El Salvador. Nevertheless 242 total patients (including 171 non-diabetics) enrolled in hemodialysis in southwestern Guatemala, 45 (18.6% of total patients and 26.3% of non-diabetics) lacked traditional CKD risk factors [95]. While agricultural work history was common, only travel time greater than 30 minutes and age were significantly associated with CKD in the absence of traditional risk factors.

A descriptive epidemiologic study on children (<18 years) in three agricultural regions with known high prevalence of chronic kidney disease of uncertain etiology: Bajo Lempa, Guayapa Abajo and Las Brisas**, El Salvador** has been reported [96]. Prevalence of microalbuminura was 4%; 4.3% in girls and 3.8% in boys. eGFR, based on the Schwartz formula was higher than anticipated and the prevalence of abnormally low eGFR was only 0.1%.

Kupferman et al (2016) performed a cross-sectional family-based study among 266 members of 24 families with high chronic kidney disease (CKD) burdens in a MeN hotspot in North-western **Nicaragua**. Hyperuricemia was common among patients with MeN. The results suggest that rather

than being solely a consequence of CKD, hyperuricemia may play a role in MeN pathogenesis, a hypothesis that deserves further study [97].

Roncal-Jamines et al (2016) argue that MeN may be a uric acid disorder. Individuals at risk for developing the disease are primarily male workers exposed to heat stress and physical exertion that predisposes to recurrent water and volume depletion, often accompanied by urinary concentration and acidification. Uric acid is generated during heat stress, in part consequent to nucleotide release from muscles. They hypothesize that working in the sugarcane fields may result in cyclic uricosuria in which uric acid concentrations exceed solubility, leading to the formation of dihydrate urate crystals and local injury. Consistent with this hypothesis, they present pilot data documenting the common presence of urate crystals in the urine of sugarcane workers from **El Salvador.** High end-of-workday urinary uric acid concentrations were common in a pilot study, particularly if urine pH was corrected to 7. Hyperuricemia may induce glomerular hypertension, whereas the increased urinary uric acid may directly injure renal tubules. Thus, MeN may result from exercise and heat stress associated with dehydration-induced hyperuricemia and uricosuria. Increased hydration with water and salt, urinary alkalinization, reduction in sugary beverage intake, and inhibitors of uric acid synthesis should be tested for disease prevention [98].

Wesseling et al (2016) performed a cross-sectional study in Chinandega and Leon municipalities, a MeN hotspot on the **Nicaraguan** Pacific coast. 194 male workers aged 17-39 years: 86 sugarcane cutters, 56 construction workers, 52 small-scale farmers. Sugarcane cutters were more exposed to heat and consumed more fluid on workdays and had less obesity, lower blood sugar, lower blood pressure and a better lipid profile. Reduced eGFR occurred in 16%, 9% and 2% of sugarcane cutters, construction workers and farmers, respectively. Sugarcane cutters also more often had proteinuria and blood and leucocytes in the urine. Workers with eGFR <80 mL/min/1.73 m^2 reported a higher intake of water and lower intake of sugary beverages. Serum uric acid levels related strongly and inversely to eGFR levels [99].

Wesseling et al (2016) the same year present an important study on kidney function changes among male sugarcane cutters in **Nicaragua** during the harvest period. A group of male sugarcane cutters in Nicaragua (N=29, aged 17-38 at start of harvest, and then at end of harvest 5 months later. The pre-shift renal function (eGFR) decreased significantly during 9 weeks of work in the cane cutters (9%, or 10 mL/min and mean urinary neutrophil gelatinase-associated lipocalin (NGAL) increased (four times). The longitudinal decrease in eGFR tended to be associated with the cross-shift increase in serum creatinine [21].

Badurdeen et al (2016) present the clinicopathological profile of a group of patients presenting with acute symptoms and renal dysfunction from CKDu endemic regions in **Sri Lanka** was studied. Patients' mean age, occupation, and sex ratio were 44 (9) years, 57 farmers, and male/female 55/4, respectively. Mean serum creatinine at biopsy was 143.8 (47.9) umol/L. Elevated inflammatory markers and active urine sediment were reported. Histology was compatible with an interstitial nephritis with a mixture of acute and chronic tubulointerstitial lesions and glomerular scarring. In the natural course of an acute episode of CKDu, serum creatinine and histological activity were reduced while histological chronicity increased [100].

De Silva et al (2016) measured p-creatinine, albuminuria and two tubular protein markers; kidney injury molecule (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) in male farmers from 4 regions in **Sri Lanka**; Matara and Nuwara Eliya (farming locations with no CKDu prevalence) and two CKDu emerging locations from Hambantota District in Southern Sri Lanka. The average urinary KIM-1 and NGAL was significantly higher in CKDu areas, but the association between the urinary excretion of these proteins and eGFR was poor and it is, as yet, not known if measurements of tubular enzymes can be used to diagnose, or assess, CKDu in Sri Lanka [101].

Dare et al (2016) investigated changes in adult renal failure mortality and its key risk factors in **India**. Age-standardised renal death rates were highest in the southern and eastern states, particularly among adults aged 45-69 years in 2010-13. Diabetes, hypertension, and cardiovascular disease were all significantly associated with increased renal failure deaths, with diabetes the strongest predictor-odds ratio (OR) vs control 9.2 (95% CI 6.7-12.7) in 2001-03, rising to 15.1 (12.6-18.1) in 2010-13. In the

2010-13 study population, the diabetes to non-diabetes OR was twice as large in adults born in the 1970s (25.5, 95% CI 17.6-37.1) as in those individuals born during or before the 1950s (11.7, 9.1-14.9). Renal failure is a growing cause of premature death in India. Poorly treated diabetes is the most probable reason for this increase [102].

In the 1990s, reports of endemic nephropathy started trickling in from the **Indian** state of Andhra Pradesh around a coastal belt referred to as the Uddanam region [103]. The region is a subtropical low-altitude terrain known for coconut and cashew plantations. Despite a lack of official statistics, the media reports that claim nearly 34,000 cases and 4,500 deaths have occurred in the last decade.

Garcia-Trabanino et al (2016) report on chronic kidney disease in the Bajo Lempa region, an impoverished rural coastal region of **El Salvador** affected by Mesoamerican nephropathy. The average annual ESRD incidence rate: 1410 per million population. Two-thirds did not report diabetes or hypertension. Few received RRT. Patient mortality is high even with RRT. Most patients are male (9:1). Social determinants influenced the high mortality [104].

Roncal-Jimenez et al (2016) exposed rats to heat stress and recurrent dehydration. This induced functional changes (albuminuria, elevated urinary NGAL), glomerular changes (mesangiolysis, matrix expansion) and tubulointerstitial changes (fibrosis, inflammation). Addition of injection of desmopressin exacerbated the injury. Both heat stress and/or desmopressin were also associated with activation of the polyol pathway in the renal cortex, likely due to increased interstitial osmolarity [105].

Moyce et al (2016) investigated the cumulative incidence of acute kidney injury (AKI) over one work shift among agricultural workers in **California**. Serum creatinine was measured both before and after a work shift. In 295 agricultural workers, AKI after a summer work shift was detected in 35 participants (12%) [106].

Overview/review/discussion papers

Roncal-Jimenez et al (2016) in a review concludes that an epidemic of chronic kidney disease (CKD) of unknown cause has emerged along the Pacific Coast of Central America. An epidemic of CKD has led to the death of more than 20,000 lives in Central America. The disease primarily affects men working manually outdoors, and the major group affected is sugarcane workers. The disease presents with an asymptomatic rise in serum creatinine that progresses to end-stage renal disease over several years. Recent studies suggest that it is driven by recurrent dehydration in the hot climate. The epidemic is postulated to be increasing because of global warming. The epidemic of CKD in Mesoamerica may be due to chronic recurrent dehydration because of global warming and working conditions. This entity may be one of the first major diseases attributed to climate change and the greenhouse effect [107].

Glaser and more than 20 colleagues (2016) discussed climate change that has led to increases in the frequency and severity of heat waves (extreme heat events) and that one of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to acute mortality from exacerbations of pre-existing chronic disease and that inadequate hydration can lead to CKD that is distinct from that caused by diabetes, hypertension, or GN. Epidemics of CKD consistent with heat stress nephropathy are now occurring across the world [108].

Debate; 'Should we consider renaming 'Mesoamerican Nephropathy' as Nephropathy of Unknown Cause in Agricultural Labourers (NUCAL)?'[109].

Jayasumana et al (2016) [110] suggest the name chronic interstitial nephritis in agricultural communities (CINAC). CINAC patients live and work in poor agricultural communities located in CINAC endemic areas with a hot tropical climate, and are exposed to toxic agrochemicals through work, by ingestion of contaminated food and water, or by inhalation. The disease is characterized by low or absent proteinuria, small kidneys with irregular contours in CKD stages 3-4 presenting tubulo-interstitial lesions and glomerulosclerosis at renal biopsy. Two different primary triggers have been proposed: one related to toxic exposures in the agricultural communities, the other related to heat stress with repeated episodes of dehydration heath stress and dehydration. Existing evidence supports

occupational and environmental toxins as the primary trigger according to the authors. The heat stress and dehydration hypothesis cannot explain why the incidence of CINAC went up along with increasing mechanization of paddy farming in the 1990s; the non-existence of CINAC in hotter northern **Sri Lanka**. This indicates that heat stress and dehydration may be a contributory or even a necessary risk factor, but which is not able to cause CINAC by itself. This interpretation and conclusion however have been criticized [111], and attempts to change the globally accepted term, CKDu, to KDUCAL, NUCAL, or CINAC are inappropriate according to Wimalawansa et al [112]

Lozier at al (2016) propose a **case-definition** and a new name for CKDu; **chronic kidney disease of non-traditional cause CKDnT** [113]. CKDnT is suggested to be defined as a person age < 60 years with CKD, without type 1 diabetes mellitus, hypertensive diseases, and other well-known causes of CKD. A probable case of CKDnT is defined as a suspect case with the same findings confirmed three or more months later.

The concept of case-definition, which is very useful in surveillance programs, has been further developed [114]. In short, this proposal includes:

1) Estimated glomerular filtration rate (eGFR) <60 ml/ min/1.73 m^2.
2) and/or Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased eGFR: non-nephrotic proteinuria (albuminuria >30 and <3 000 mg/24 hours,) and/or urinary sediment abnormalities as markers of kidney damage (i.e., microscopic hematuria with abnormal erythrocytes morphology, or red blood cell casts, granular casts, or oval cells) and/or renal tubular disorders (i.e., renal tubular acidosis, nephrogenic diabetes insipidus, renal potassium wasting, other).
3) Age: 2 to 59 years.
4) Ultrasonography of the urinary tract demonstrating the presence of two morphologically symmetrical kidneys (eventually diminished in size), without urinary tract obstruction or renal polycystic disease.

Suggested exclusion criteria are:

1) Diabetes neuropathy) or history (current or previous) of nephrotic proteinuria.
2) Hypertension: BP (≥160/100).
3) Urologic pathology.
4) Primary glomerulopathy confirmed by renal biopsy or suspected due to presence of nephrotic-range proteinuria.
5) Hematologic disease.
6) Genetic and/or hereditary-familial renal disease.
7) Autoimmune.
8) Repeated exposure to X-ray contrast media and/or administration of phospho-soda solutions, as preparation for colonoscopy.

It is also recommended that in each case, record the following: 1) Residing or having resided for at least six months in an agricultural production area of Central America and 2) Working or having worked for at least six months in agricultural activities in Central America.

While appreciating the value and importance of this attempt, the suggested criteria become rather broad and will include many cases of undiagnosed kidney diseases of various types. At least if these criteria are used outside the high prevalence areas of MeN/CKDu/CKDnT. For example, many types of primary or secondary GN with non-nephrotic proteinuria that have not underwent diagnostic renal biopsy and different types of interstitial nephritis caused by infections and/or drugs, such as lithium would be included as CKDnT. In fact – using these wide criteria a good number of CKDnT cases would be found in e.g., Sweden in northern Europe.

One of the first reviews on CKDu in **Sri Lanka** was presented this year [115] and summarized that that there is a problem with CKDu in some district of Sri Lanka, but 'pinpointing a definite cause for CKDu is challenging. It is plausible that CKDu is multifactorial. No specific guidelines or recommendations exist for treatment'.

2017

Wijkstrom et al (2017) studied kidney biopsies from 19 male sugarcane workers with suspected MeN in **Nicaragua**[116]. Participants had a mean eGFR creatinine of 57 (range, 33-96) mL/min/1.73m^2. 47% had low plasma sodium and 21% had low plasma potassium levels. 16 kidney biopsies were representative and showed glomerulosclerosis (mean, 38%), glomerular hypertrophy, and signs of chronic glomerular ischemia. Mild to moderate tubulointerstitial damage and mostly mild vascular changes were seen. The study confirms the renal morphology of MeN: chronic glomerular and tubulointerstitial damage with glomerulosclerosis and chronic glomerular ischemia. Follow-up urine and blood samples from both biopsy studies were collected to investigate the natural history.

In the follow up-study, median duration of follow-up was 13 (range, 13-27) months. Mean change in eGFRcr was -4.4 (range, -27.7 to 10.2) mL/min/1.73m^2 per year [116].

In 2017 a group of clinicians and researchers described clinical and morphological findings in agricultural workers, mostly sugarcane, which may be the acute phase of Mesoamerican nephropathy (MeN) in **Nicaragua**. Over a 1-year period, physicians identified 247 mostly young (median 29 years), male (89.5%) patients with acutely elevated creatinine. This comprised 1.6% of the total workforce of about 15,000. Almost all patients presented to the hospital because of acute symptoms of illness such as nausea (59.4%), back pain (57.9%), fever (54.6%), vomiting (50.4%), headache (47.3%), and muscle weakness (45.0%) were common. Blood test revealed that leucocytosis (81%), and neutrophilia (86%) was common. Mean serum creatinine was 2.0 +/- 0.6 mg/dL. In urine almost, all patients displayed leukocyturia (98%), haematuria was also common (82%) and 34% had albuminuria exceeding 0.3g/L. Bacteriuria was not seen. Patients were given supportive treatment with fluids intravenously but only 2% were prescribed antibiotics. Symptoms, clinical-, blood- and urine findings are well compatible with an acute inflammation and interstitial nephritis. In a follow-up CKD was later recorded in 8.5% of patients [29].

Largely the same group of investigators have also reported from examination of renal biopsies of 11 patients with suspected acute MeN in this **Nicaragua**n population [31], where the inclusion criteria was elevated serum creatinine, leucocyturia, and leucocytosis and/or neutrophilia. The renal biopsy showed tubulointerstitial nephritis, with varying degrees of inflammation and chronicity. Interstitial cellular infiltrates (predominantly T lymphocytes and monocytes), mostly in the corticomedullary junction; neutrophilic accumulation in the tubular lumens was prominent whereas the glomeruli were largely preserved albeit a few mild ischemic changes were observed. The acute components of tubulointerstitial nephritis were acute tubular cell injury, interstitial oedema, and early fibrosis. Chronic tubulointerstitial nephritis included severe tubular atrophy, thickened tubular basement membrane, and interstitial fibrosis.

The morphological findings in this renal biopsy study [31] differ from that of Wijkström et al 2015 and 2017 from MeN patients in El Salvador and Nicaragua respectively [15] [111] where interstitial inflammation was not prominent and glomerular changes observed. The case-mix is however very different; in the study of patients with acute MeN by [29] included leucocyturia, and leucocytosis and/or neutrophilia i.e. displaying acute evidence of ongoing acute inflammation and renal disease whereas Wijkstrom et al[15] [111] patients with established CKD taken, without signs of acute inflammation that were not currently working or exposed. Nevertheless, the results by [31] suggest that the chronic glomerular changes seen in typical cases of MeN may indeed by proceeded by acute interstitial inflammation. An observation that possible also have bearings on the proposed pathogenic process underlying chronic MeN. The acute interstitial inflammation suggests that dehydration and loss of electrolytes from heat stress is not the sole, perhaps not even the major cause, of acute MeN. However, heat stress may well contribute to the development of chronic CKD from MeN.

In an intervention study Wegman et al (2017) tried to reduce kidney function damage from hard labour among sugarcane workers work in **El Salvador** by implementation a water, rest, shade (WRS) and efficiency intervention program. Cross-shift eGFR decrease was present in both groups; -10.5 mL/min/1.73m^2 [95% confidence interval (95% CI) -11.8- -9.1], but smaller for the intervention group after receiving the program. Decreased eGFR over the 5-month harvest was smaller in the intervention group -3.4 mL/min/1.73m^2 (95% CI -5.5- -1.3) than in the reference -5.3 (95% CI -7.9 to -2.7) [25].

From **Sri Lanka** a higher-than-expected rate of seropositivity to hanta virus in both CKDu patients and healthy in disease endemic compared to non-endemic areas of Sri Lanka has reported [117]. A subsequent report indicated that the residents in this area were in fact frequently infected with a virus similar to hanta; *Thailand orthohantavirus* or an antigenically related virus[118].

Overview/review/discussion papers

In a review paper al Orantes-Navarro (2017) points out that there has been an increase in what is considered as a form chronic interstitial nephritis in agricultural communities (CINAC) in certain countries which is not associated with traditional risk factors. This disease has become an important public health problem and is observed in several countries in Central America and Asia. The presence of toxicological, occupational, and environmental risk factors within these communities suggests a multifactorial aetiology for CINAC. This may include exposure to agrochemicals, a contaminated environment, repeated episodes of dehydration with heat stress, and an underlying genetic predisposition [119].

Madero et al 2017 [120]in the journal *Current Opinion in Nephrolology and Hypertension* gave a review on Mesoamerican nephropathy (MeN) and concluded that the evidence supports the assumption that recurrent cycles of heat stress, dehydration, and strenuous work may cause this type if CKD.

An epidemiologic review on the importance of pesticide exposures for the development of chronic kidney disease of unknown aetiology was presented by Valcke et al 2017[121]. A systematic review was performed of the 21 analytical studies identified, seven were categorized as with low, ten with medium and four with relatively high explanation value. Thirteen (62%) studies reported one or more positive associations, but four had a low explanation value and three presented equivocal results. The main limitations of both positive and negative studies were unspecific and unquantified exposure measurement ('pesticides'), the cross-sectional nature of most studies, confounding and selection bias. No study investigated interactions between pesticides and other concomitant exposures in agricultural occupations, in particular heat stress and dehydration. It was concluded that existing studies provide scarce evidence for an association between pesticides and regional CKDu epidemics, but a role of nephrotoxic agrochemicals cannot be conclusively discarded.

In yet another review paper Johnson (2017) discussed that CKDu, or as is called in Central America, Mesoamerican Nephropathy, is now recognized in Central America, Mexico, India and Sri Lanka, and there is also some evidence that similar epidemics may be occurring in the USA, Thailand and elsewhere. A common denominator for each location is manually working outside in extremely hot environments. And that while some of the epidemics have been recognized by better reporting, the most important reasons are increasing heat extremes (heat waves) coupled with hydration with sugary or, less commonly, alcoholic beverages [122], while Zoccateli argued cyclic dehydration hypothesis alone could hardly explain the epidemics outside Mesoamerica [123] and Campese (2017) [124] suggest that the disease may be largely due to rehydration with large amounts of contaminated water.

A systematic literature search of epidemiological studies of CKDu in **Central America** has been reported by Gonzalez-Quiroz et al (2017) [125]. Twenty-five epidemiological studies were included in the analysis of risk factors for CKDu. Increased prevalence odds ratio (POR) for CKDu were found males versus female gender 2.42 (95% CI 1.76–3.08), family history of CKD 1.84 (95% CI 1.37–2.30), high water intake (versus low) 1.61 (95% CI 1.01–2.21) and living at low altitude (versus highland) 2.09 (95% CI 1.00–3.17). However, there were no significant associations between CKDu and pesticide exposure (versus no) 1.17 (95% CI 0.87–1.46), alcohol consumption (versus no) 1.34

(95% CI 0.84–1.84), non-steroidal anti-inflammatory drugs (versus no) 0.99 (95% CI 0.60–1.39) and heat stress (versus no) 1.52 (95% CI 0.91 – 3.95).

Nerbass et al (2017) [126] provide an in-depth review to examine the known effects of occupational heat stress on the kidney and concluded the extreme occupational heat stress combined with chronic dehydration may contribute to the development of CKD and ultimately kidney failure. Rising global temperatures, coupled with decreasing access to clean drinking water, may exacerbate the effects of heat exposure in both outdoor and indoor workers who are exposed to chronic heat stress and recurrent dehydration.

In the next issue of the same journal Herath et al [127] argue against the "heat stress/dehydration hypothesis" and also the proposal that global warming over the last half-century has been sufficient to have caused a drastic change in renal function in manual workers in hot climates.

2018

Wijkstrom et al 2018 [30] conducted a renal biopsy study in **Sri Lanka** to compare clinical and morphological findings in patients with CKDu in this country with the MeN morphology from Central America. Eleven patients with CKDu using similar inclusion and exclusion criteria as previous MeN studies were recruited. Participants were between 27-61 years of age and had a mean eGFR of 38+/-14 ml/min/1.73m^2. Main findings in the biopsies were chronic glomerular and tubulointerstitial damage with glomerulosclerosis (8-75%), glomerular hypertrophy and mild to moderate tubulointerstitial changes. The morphology was more heterogeneous and interstitial inflammation and vascular changes were more common compared to previous studies of MeN. In two patients the biopsies showed morphological signs of acute pyelonephritis, but urine cultures were negative. Electrolyte disturbances with low levels of serum sodium, potassium, and/or magnesium were common. In the urine, only four patients displayed albuminuria, but many patients exhibited elevated alpha-1-microglobulin and magnesium levels. There are many similarities in the biochemical and morphological profile of the CKDu endemics in Central America and Sri Lanka, but there were differences, such as a more mixed morphology, more interstitial inflammation, and vascular changes in Sri Lankan patients.

From **Nicaragua** [128] in 2018 comes a report on the risk of acute injury in sugarcane workers. 326 sugarcane workers with normal serum creatinine and no history of CKD working in a high prevalence area of CKD/MeN in Nicaragua were examined at the end of the harvest season. 34(10%) of 326 tested displayed a Scr level increase ≥ 1.3 mg/dL (corresponds to a p-creatinine of > 115 umol/l). Elevated Scr (called Acute Kidney Injury (AKI) in the report) was more common among cane cutters. Follow-up of 29 and 24 of those with elevated Scr after 6 and 12 months showed that average Scr went down (increased eGFR) from 1.64 mg/dl to 1.25 and 1.27. However, 7(24%) of the 29 before harvest season healthy men that was tested at least once displayed evidence eGFR < 60 ml/min 6-12 months after the harvest season. Taken at their face these data suggest that roughly 2-3% of employed healthy men may develop CKD after a harvest season.

From **Guatemala** (2018) at has been reported that sugarcane cutters with lowered renal function, eGFR< 60 ml/min, 2% of a total workforce of 4095 tested, had lower productivity than those with eGFR > 60 ml/min and this was seen at high Wet Bulb Globe Temperatures (WBGT) from 30 up to 34C [129]. A large proportion of the hired men left work during the half-year of cane harvesting, and those with impaired renal function were prone to this; 42 versus 25% of men hired.

In a similar follow-up study of the kidney function over the 6-month harvest period of 330 sugarcane cutters was done in **Guatemala** [130]. Albeit a decline in kidney function across the harvest was observed in 36% of the participants the average eGFR for the whole group did not change and only 3% had eGFR <60 ml/min. The drop in eGFR noted for one third of the examined group may well an effect of random variation as similar sized group displayed increased eGFR. This is however not the conclusion of the authors who conclude that both occupational and behavioural factors play significant roles in declines in kidney function.

In another report from **Guatemala** Cross-shift changes in kidney function of sugarcane workers was examined [131]. 105 healthy sugarcane workers were followed. Pre-harvest clinical data as well as

daily environmental, clinical, and productivity data for each worker was assessed. Post-shift p-creatinine levels were significantly higher than pre-shift values (eGFR dropped on average 25%) but there was no evidence of eGFR (pre- or post-shift) to decrease over the three months observation period. It can theoretically be shown that also a rather dramatic decrease in the GFR will not be evident in plasma until at least 8 hours has passed A 50% drop in GFR increase p-creatinine with only produce an increase in p-creatinine of about 20 umol/l after 8 h. Principles, and rather sophisticated theoretical and mathematical background, for interpreting p-creatinine when GFR is rapidly changing has been presented [132].

Gonzalez-Quiroz and collaborators have reported remarkable results from a 2-year community-based prospective cohort study of kidney function in a young rural population 520 young adults (286 males and 234 females) in the 9 different communities of Northwest **Nicaragua** severely affected by CKD [133]. After exclusion of individuals with known, or self-reported, kidney disease 350 agreed to participate. The natural history of, and factors associated with, loss of kidney function was examined every 6 months a 2-year period. eGFR was assessed by p-creatinine and cystatin C. Among men 81% remained stable, 9.5% experienced rapid decline in eGFR of -18.2 ml/min per 1.73 m^2 per year), and 9.5% that had a baseline dysfunction (58 ml/min per 1.73 m^2) experienced an average drop in eGFR of -3.8 ml/min per 1.73 m^2 per year. Among women: 96.6% remained stable and 3.4% experienced rapid decline. Among men, outdoor and agricultural work and lack of shade availability during work breaks, reported at baseline, were associated with rapid decline. Urinary NGAL concentrations were higher in men with low kidney function at baseline and among those that experienced rapid drop in eGFR[134].

In a logistic model to predict prediction rapid eGFR decline however U-NAGL alone was not able to predict individuals with rapidly declining eGFR[135].

Another important follow-up study of the kidney function was published from an area in the Pacific lowland of **Nicaragua** with an established high prevalence of CKD/MeN in 2018 [32]. From February 2015 to May 2017, 586 previously overall healthy agricultural workers (median age 28 years, 90% male) presented with symptoms and signs of acute MeN was followed. The majority had a normal baseline creatinine, but leukocyturia (98.8%) and peripheral leukocytosis (80.7%) were common. Within 6 months 8.4% individuals with acute MeN progressed to some level of CKD and 5.5% to eGFR < 60 ml/min. The strongest predictors of CKD progression were anemia and paresthesias at presentation, while leukocytosis was associated with renal recovery. High blood uric acid, low p-sodium (< 135 mmol/l) and low p-magnesium was much more common among those that progressed to CKD.

A group of researchers from Pan American Health organization (PAHO) [136] present Chronic kidney disease mortality trends in **selected Central America countries,** 1997-2013 and clues to cause of the CKD epidemic, now renamed from CKDnT to of chronic interstitial nephritis of agricultural communities (CINAC). It is shown (see figure) that the age adjusted mortality rate in chronic kidney disease (ICD CKD-N18) among males is markedly higher in El Salvador and Nicaragua as compared to USA,

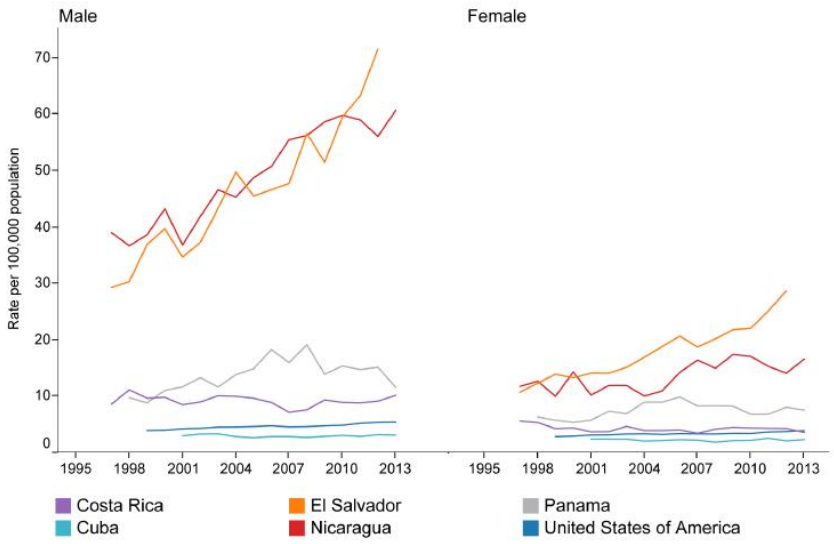


Figure 1 Chronic kidney disease age-standardised mortality rate trends in all ages population, by sex and selected Central American country, 1995–2013.

Panama, Costa Rica and Cuba, and furthermore that the rates are rapidly increasing. Based on temporal associations and increasing rates of CKD mortality in parallel to the rapidly and unsafe use agrochemicals that has been reported from Central America [137]. One major problem in the interpretation of these data on mortality in CKD in different countries is the uptake in renal replacement therapy (RRT) of patients with end stage renal disease (ESRD) in the different countries. If a CKD patient enters RRT they rarely die from CKD but from complications of EDRD such as CVD and infections and will then not be recorded as death from CKD. The uptake rate in RRT the country in the figure varies much, depending on resources available for health care and RRT. In the US, the uptake in RRT at age 45-64 is close to 60 per 100,000 inhabitants. There are also substantial differences in incidence of starting RRT between different socioeconomic groups. The incidence of RRT is much higher for non-whites and native Americans. Thus, the striking differences in CVD displayed in the figure most likely is influenced by differences in uptake rate in RRT.

Experimental work: A hypothesis that the CKD may be caused by recurrent heat stress and dehydration, and potentially by hyperuricemia has been tested in a mice model [138]. In the experiment, it was tested whether treatment with allopurinol (a xanthine oxidase inhibitor that reduces serum urate) provides renal protection against recurrent heat stress and dehydration. Eight-week-old mice were subjected to recurrent heat stress (39.5 degrees C for 30 min, 7 times daily, for 5 wk) with or without allopurinol treatment and were compared with control animals with or without allopurinol treatment. Allopurinol provided significant protection and improved renal function in the heat-stressed mice.
In another, similar experiment it was tested if rehydration with fructose may induce worse kidney injury in mice than rehydration with equal amounts of water [139]. Compared to control animals, there was a progressive worsening of renal injury (inflammation and fibrosis) with fructose alone, heat stress alone, and heat stress with fructose rehydration. The combination of heat stress with rehydration with fructose was associated with increased intrarenal expression of the inflammasome markers, NLRP3 and IL-18, compared to heat stress alone. The study suggest that heat stress may activate intrarenal inflammasomes leading to inflammation and renal injury and provide evidence that rehydration with fructose may accelerate the renal injury and inflammatory response.

Overview/review/discussion papers

A literature review on Sugarcane cutting work, risks, and health effects was provided in 2018 [140]. The inclusion criteria were articles published between January 1997 and June 2017, which evaluated working conditions and health effects on sugarcane cutters. From the 89 articles found, 52 met the selection criteria and were evaluated. It was concluded that manual cutting of sugarcane, especially of burned sugarcane, exposes workers to various risks, with different health impacts. Risk reduction for exposure to pollution and thermal and physical overload is required as a measure to preserve the health of the worker.

Pedro Ordunez in the scientific journal Kidney International [141] summarizes a 54-page document from the Pan American Health organisation (PAHO) on diagnosing and surveillance of CKDnT [141]. This PAHO document presents a background to the CKD epidemic epidemic, including its epidemiology and updated mortality estimates. The paper present case definitions of CKDnT developed for the purposes of CKDnt surveillance. A multideterminant model of causation is suggested [141].

Ordunez and associated researchers have in several reviews and overview papers suggested that exposure to agrochemicals and pesticides have an important role in the CKD, if not the sole cause most likely contributing to the epidemic [142] [136]. The name chronic interstitial nephritis of agricultural communities (CINAC) rather than MeN or CKDu has been suggested [127, 136]. But this proposal has not been generally accepted but criticised by others [111] [143] as ‘there is no convincing scientific data to support that CKDu is caused by agrochemicals or is confined to agricultural workers’. The association between CKD and agrochemicals/pesticides is mainly circumstantial and there are limited epidemiological or toxicological evidence to support this. Elinder at al [86]in a

review wrote 'Although pesticides can be responsible for both acute and occasionally chronic health effects [144], they are rarely nephrotoxic unless associated with a serious systemic intoxication with multiorgan damage [145]. A parallel might be made; 'If a crook happens to pass the scene of a crime, he is not necessary the culprit!'

Marc E. De Broe and associates [127] in a review paper argue fiercely against Heat-Stress Nephropathy. The authors appreciate the emergence of a new chronic tubulo-interstitial kidney disease of uncertain cause among agricultural communities in Central America and Sri Lanka but claims 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 stated that the 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.

In June 2018, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Environmental Health Sciences sponsored a workshop to identify research gaps in an increasingly common form of chronic kidney disease in agricultural communities. Discussion was focused on selected topics, including identifying and mitigating barriers to research in CKDu, creating a case definition, and defining common data elements. All hypotheses regarding etiology were entertained, and meeting participants discussed potential research strategies, choices in study design, and novel tools that may prove useful in this disease [146].

This year (2018) an interesting review paper, which up till August 2021, had escaped my attention was published [147] suggesting that Leptospirosis infection could be the culprit of CKDu, or at least be an important contributor. Leptospirosis is a prevalent zoonosis affecting millions worldwide. Often in regions that coincide with chronic kidney disease (CKD) hotspots. Acute leptospirosis induces multiple organ dysfunction including acute kidney injury and may predispose to CKD and end-stage renal disease, if not treated timely. Asymptomatic infection may carry the bacteria in the kidney and CKD progresses insidiously. Kidney pathology shows a chronic tubulointerstitial disease. A few papers report increased anti-leptospira seropositivity in populations where CKDu is common.

However hard evidence showing that leptospirosis is causing, or contributing to CKDu/MeN is missing, and the renal biopsy studies on CKDu/MeN patients that has been published have not shown for leptospirosis infection typical findings.

2019

A high a prevalence of CKD has also reported from Uddanam in Western **India** [148]. 2210 individuals (age >18 years) living in a rural area were examined. CKD with eGFR <60 ml/min per 1.73 m^2 was seen in 14%, of these less than 20% had proteinuria. Major risk factors, such as diabetes, long-standing hypertension, and significant proteinuria, were absent in most (73%) of patients with CKD, which is then compatible with CKDu. It was concluded that CKDu is a 'true public health threat in Uddanam'.

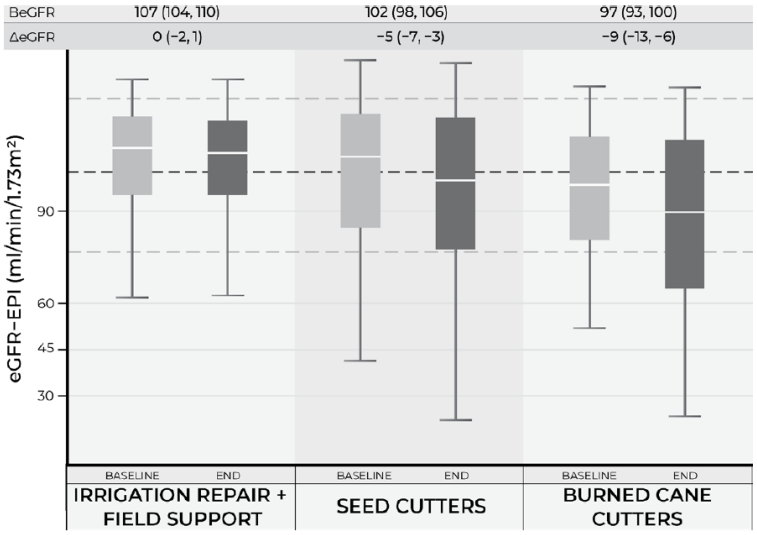
In another **Indian** report prevalence of lowered eGFR in different Indian populations; Urban and rural areas of Northern India (states of Delhi and Haryana) and Southern India (states of Tamil Nadu and Andhra Pradesh) was compared [149]. 12 500 individuals without diabetes, hypertension or heavy proteinuria were examined between 2010 and 2014. The prevalence overall prevalence of eGFR <60 ml/min per 1.73 m^2 was 1.6%, but this figure varied markedly between areas, being highest in rural areas of Southern Indian (4.8%). In Southern India, risk factors for eGFR <60, were residence in a rural area, older age and less education. Among individuals aged less than 49 the prevalence ratio of eGFR below 60 ml/min per 1.73 m^2 was 5 to 6 times for rural versus urban residents. It is suggested that the CKDu epidemic is not confined to Central America and Sri Lanka.

In a third report from the same research group and cohort of sugarcane workers in **Guatemala** [150] Butler-Dawson et al (2019) attempts to examine cumulative incidence of acute kidney injury (AKI) and if it can be prevented. AKI was defined as an increase in serum creatinine of 26.5 umol/L or 50% or more from the pre-shift value. The prevalence of dehydration post-shift (> 1.020 specific gravity) was 11% in February 9% in March, and 6% in April. Cumulative incidence of AKI was 53% in February 54% in March, and 51% in April. AKI was associated with increasing post-shift specific gravity, a dehydration marker, (OR 1.24, 95% CI 1.02-1.52) and with lower electrolyte solution intake (OR 0.94, 95% CI 0.89-0.99). A short term (post-shift) increases in p-creatinine may indicate changes in the muscle- and protein metabolism, as well as an effect on the GFR. It can theoretically be shown that also a rather dramatic decrease in the GFR will not be evident in plasma until at least 8 hours has passed. This has to do with the half-time of creatinine in plasma and body fluids which, in the case of a normal GFR, is around 8 h. A 50% drop in GFR increase p-creatinine with only produce an increase in p-creatinine of about 20 umol/l after 8 h. Such a severe change on the real GFR (and not the estimated) would hardly be totally reversible. Therefore, it seems strange that no long-term changes in the GFR are seen i.e. in the beginning verses the end of the harvest season. It is also worth noting that acute symptoms from heat exposure seem to be uncommon in this Guatemalan cohort (a few percent) compared to what has been reported from e.g., Costa Rica [79].

A cross-sectional cohort study of heat exposed brick-makers in **Nicaragua** indicate that also other occupational groups than agricultural workers may present with CKD [151]. Prevalence and risk factors for CKD was examined among brickmaking workers in La Paz Centro, Nicaragua. Male and female workers (n = 224) employed by artisanal brickmaking facilities in La Paz Centro, Nicaragua was examined. CKD was defined as estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m^2. The CKD prevalence was 12.1% (n = 27), all cases were male, 8 had stage 5 CKD (eGFR < 15mL/min/1.73m^2), and 22% were younger than 35 years. Predictors of CKD, using logistic regression analysis, was oven work and lack of education. Albeit exposure assessment was crude these results are consistent with the hypothesis that occupational heat exposure is a risk factor for kidney disease in Nicaragua.

An important report on environmental exposures associate with declining kidney function in a population at risk of Mesoamerican nephropathy in **Nicaragua** has been published [152]. A nested case–control study using biosamples from a rural, community-based follow-up study of 350 young adults from Northwest Nicaragua at risk of MeN was conducted. The aim was to find possible associations between urinary concentrations of metals, pesticides and mycotoxins from samples collected in the first 6 months and decline in kidney function over a two-year period. Twelve metals and metalloids (aluminium, total arsenic, cadmium, chromium, cobalt, copper, lead, manganese, mercury, selenium, silicon and strontium) were analysed by inductively coupled plasma-mass spectrometry. Twelve pesticides or their metabolites (2,4-dichlorophenoxyacetic acid, 3-phenoxybenzoic acid, 4-fluoro-3-phenoxybenzoic acid, chloro-3,3,3-trifluoro-1-propen-1-yl-2,2-dimethylcyclopropanecarboxylic acid, cis/trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, ethylenethiourea, glyphosate, 4-chloro-2-methylphenoxy acetic acid, 3-hydroxy-pyrimetanil, 5-hydroxytiabendazole, hydroxy-tebuconazole and 3,5,6-trichloro-2-pyridinol) and two mycotoxins (ochratoxin A (OTA) and citrinin (CIT)) were analysed by liquid chromatography coupled-mass spectrometry. Elevated levels of aluminium and total arsenic as well as metabolites of several pesticides were detected across the population, but no differences were identified between the declining and stable groups in the levels of metals or pesticides tested. OTA and CIT were below the limit of detection. It was concluded that tested metals, metalloids, pesticides and mycotoxins were not associated with loss of kidney function in participants at-risk of MeN. One comment regarding ‘elevated levels of aluminium and total arsenic’ is that aluminium in biological samples is almost always contaminated and virtually impossible to get rid of if not special precautions are taken, and that arsenic in urine needs to be speciated to be evaluated [153].

A well-conducted land-mark study on the relationship between workload and incidence of kidney injury in a fieldworker cohort with different levels of physically demanding work over a sugarcane harvest in **Nicaragua** was published in October 2019 [26]. The results provide evidence of dose-effect as well as dose-response relations between high-heat and high workload exposure and kidney injury.



Biological and questionnaire data were collected before (n=545) and at the end (n=427) of harvest among field support staff (low workload), drip irrigation workers (moderate), seed cutters (high) and burned sugarcane cutters (very high). Dropouts were contacted (87%) and reported the reason for leaving work. Cross-harvest incident kidney injury (IKI) was defined as serum creatinine increase >0.30 mg/dL or >/=1.5 times the baseline value, or among dropouts reporting kidney injury leading to leaving work. Mean cross-harvest estimated glomerular filtration rate change was significantly associated with workload, increasing from 0 mL/min/1.73 m^2 in the low-moderate category to -5 mL/min/1.73 m^2 in the high and -9 mL/min/1.73 m^2 in the very high workload group. A similar pattern occurred with IKI, where low-moderate workload had 2% compared with 27% in the very high workload category. A healthy worker selection effect was detected, with 32% of dropouts reporting kidney injury. Fever and C reactive protein elevation were associated with kidney injury. Very few workers reported pesticide use during harvest. The figure (next to text) present renal function (eGFR) by job and time of testing. BeGFR denotes mean (95% CI) baseline eGFR. ΔeGFR denotes mean (95% CI) cross-harvest change in eGFR. Dropouts are not included in this figure. If they had been able to include the difference in eGFR between the three work-load groups would be even more pronounced.

Factory workers in **Brazil** exposed to heat stress (wet bulb globe temperature >/=28.9) and not exposed to heat have been examined [154]. Clinical and biochemical markers of hydration and kidney function were evaluated before and after a single 8.5 h work shift (lunch time not included. This was more of a feasibility study as only 14 heat-exposed, and 17 controls were examined. Workers exposed to heat stress had a greater decline in estimated glomerular filtration rate, as assessed from p-creatinine measurements, compared to controls over the work.

From **El Salvador** [155] results from a large prevalence study on CKD is presented. Both interviews and measurements, including serum and urine laboratory tests, were completed for 4817 participants. The overall prevalence of chronic kidney disease (eGFR < 60 mL/min/1.73m^2 was high; 12.8% (men 18.0%; women 8.7%). Prevalence of chronic kidney disease from nontraditional causes was 3.9% (men 6.1%; women 2.2%). CKD was relatively common also at age 41-60 (8%) and more often seen among farmers and rural dwellers.

In depth interview with ten patients with CKD/MeN in **El Salvador** illustrates how difficult it is for patients to comply with CKD prevention programs due to social unrest and gang violence [156]. In a review report based on previous cross-sectional studies in El Salvador [155] CKD is prevalent and a major health problem in agricultural communities. The general prevalence of CKD (eGFR <60 ml/min) El Salvador was 12.8% (men 18.0%; women 8.7%). Of the chronically ill kidney patients, 13.1% were between 20 and 40 years of age. Nontraditional risk factors for CKD includes, high levels of sugary drink consumption (81.0%), insufficient hydration (65.9%) and high levels of exposure to agrochemicals in the work environment (12.6%). Chronic kidney disease from nontraditional (CKDu) comprise one third of all CKD in El Salvador.

Reports on CKDu have also been published from **Mexico** [157, 158]. A high prevalence of CKDu was among the inhabitants of Poncitlan, a very poor municipality. The prevalence of CKD and proteinuria was higher in adults compared to those from other municipalities (CKD: 20 vs. 10%, and proteinuria: 36 vs. 11%), The prevalence of proteinuria in children was also higher (44 vs. 5%). However, the prevalence of diabetes mellitus and obesity were lower in Poncitlan than elsewhere.

The prevalence and risk factors for impaired kidney function was examined in the district of Anuradhapura, **Sri Lanka** was examined in a cross-sectional population-representative survey [159]. A total of 4803 participants (88.7%) took part in the study and 202 (6.0%; 95% CI 5.2–6.8) had a low eGFR in the absence of hypertension, diabetes and heavy proteinuria and hence met the criteria for proxy CKDu. The proportion of males (11.2%; 95% CI 9.2–13.1) were triple than the females (3.7%; 95% CI 2.9–4.5). Advancing age and history of CKD among parents or siblings were risk factors for low GFR among both males and females while smoking was found to be a risk factor among males. Full time farming for ≥10 yrs gave a non-significant OR of 2.1 in men. The reported prevalence's of CKDu lower than in the 'hot spots' of Mesoamerica but much higher than in non CKDu endemic areas or the US or Europe. It was concluded that the etiology of CKDu in Sri Lanka remains unclear and there is a need for longitudinal studies to describe the natural history and better characterize risk factors for this disease in Sri Lanka. The incidence, prevalence and trends of Chronic Kidney Disease and Chronic Kidney Disease of uncertain aetiology (CKDu) in the North Central Province of Sri Lanka has been analysed [160]. The identification of cases, population at risk and time, all crucial to the calculation of prevalence and incidence was hard understand from the paper but it was nevertheless concluded that the incidence of CKD/CKDu increased up to 2016 with a slight decrease in 2017. The most vulnerable age group was 40 to 60 years. That there is a male preponderance and that farmers are at higher risk.

Agricultural workers in four villages (n=261) in North Central Province, **Sri Lanka** completed an evaluation of heat stress using a questioner, including a heat stress/dehydration index based on the frequency of 16 symptoms [161]. 41 participants that reported diabetes or chronic kidney disease scored higher on the heat stress-dehydration index than 216 agricultural workers without diabetes or CKD. However, it was not possible to analyze blood or urine samples and the results are based on interviews only.

In a macro-epidemiological study from Sri Lanka self-reported household prevalence of chronic kidney disease was related to groundwater as the primary source of drinking or cooking water for at least five years between years 1999 and 2018 [162]. Across the ten most-CKD-affected districts in **Sri Lanka**, about 15% of households had at least one resident individual affected by CKD in the ten years between 2009 and 2018. Ninety-eight percent of all household's used groundwater was their primary source of drinking or cooking water for at least five of the years between 1999 and 2018. A related paper examined whether there are systematic differences in the historical behaviours of households that are affected and unaffected by chronic kidney disease (CKD) in Sri Lanka pertaining to their water source choices, water treatment practices, and agrochemical use [163]. It is seen in this report that the source of household water has changed much since 2012 and the use of RO-cleaning has increased considerably. However, the small systematic differences in the historical patterns of water sources and treatments used by CKD affected and non-affected households suggest that the sources of water and the treatment practices themselves may not be the sole risk factors in developing CKD.

A cross sectional survey has been conducted in North Central Province of **Sri Lanka [160]**. The objective of this study was to describe the incidence, prevalence, and trend of CKD/CKDu in North Central Province of Sri Lanka. There were 30,566 CKD/CKDu patients in the North Central Province. Definitions of CKD and CKDu is not evident from text nor how incidence and prevalence has been calculated. The 5 year survival rate was 71%, Farmers were the most affected varying from 65-71% in different districts. A clustering of CKD cases was seen in certain areas and villages.

A high seroprevalence, indicating previous or current infection, with Thailand orthohantavirus (THAIV) or THAIV-related orthohantavirus (TRHV) has been seen among patients with chronic kidney disease of unknown etiology in Girandurukotte, **Sri Lanka** [164]. This infection may be transmitted by rodents. 116 rodents were captured, and seroprevalences were examined; 19.6% (22/112) of the rats possessed antibodies against THAIV. This study reveals that black rats and lesser bandicoot rats belonging to Sri Lankan endemic lineages are possible reservoirs for THAIV or TRHV.

In a cross-sectional study of positive hantavirus seroprevalence in patients with and without kidney disease from two geographically areas of **Sri Lanka**, was compared [165]. Fifty kidney disease patients and 270 community controls from Kandy and 104 kidney disease patients and 242 community controls from Girandurukotte were examined. Seropositivity's were 50% and 17.4% in kidney patients and controls, respectively, in Girandurukotte, and they were 18% and 7% in Kandy. The odds (OR) of exposure to hantaviruses in kidney patients were 3.7 in Girandurukotte and 2.6 in Kandy. As controls were recruited from the community and cases with CKDu from the hospitals this comparison in prevalence is however confounded.

A well-conducted study on the role of hantavirus and/or leptospirosis infection in **Central America** provide no support for this hypothesis. In a **Nicaraguan** mining community with CKDu serum from 112 cases, 176 controls and 32 indeterminant was analyzed for antibodies to Leptospira and hantavirus. Eighty-three (26%) of all participants (n=320) were seropositive for at least one tested strain of Leptospira. No evidence of a causal link between leptospirosis or hantavirus and CKDu was found [166].

In **Sri Lanka** an attempt has been made to use urinary biomarkers for Diagnosis of CKDu [167]. Eight renal urinary markers; neutrophil gelatinase-associated lipocalin (NGAL), Kidney Injury Molecule-1 (KIM1), cystatin C (CST3), beta 2 microglobulin (B2M), osteopontin (OPN), alpha 1 microglobulin (A1M), tissue inhibitor of metalloproteinase 1 (TIMP1), and retinol binding protein 4 (RBP4) were examined in five study groups comprising subjects from CKDu, endemic CKD, nonendemic CKD, and endemic healthy and nonendemic healthy controls. A 3-marker signature panel comprising A1M, KIM1, and RBP4 was identified to represent the best minimum marker combination for differentiating all CKD categories, including CKDu, from healthy controls with an overall sensitivity of 0.867 and specificity 0.765. Interestingly initial elevation of one of these proteins in urine, U- A1M, in connection with acute kidney injury (AKI) has in a large prospective study [168], the SPRINT trial in the USA, been associated with a somewhat elevated risk to get AKI again.

An early intervention study in **Sri Lanka**, aimed at decreasing CKD progression, was published 2018[169]. 26 CKD patients attending the renal care unit of Medawachchiya were divided in two groups, one group (n=12) was provided certified bottled water for a period 18 whereas a control group (n=12) continued to use their usual drinking water. In the group provided bottled water average s-creatinine increased less, from 159 to 202 umol/l compared with the group that used their common drinking water, where s-creatinine increased from 183 to 286 umol/l. Unfortunately, eGFR was not calculated or compered, and the examined groups are small.

Experimental work

An **experimental study** that may great importance for the understanding of MeN and CKDu [170]. In an animal model (mice) the influence of core body temperature to kidney injury was explored. Wild type mice were exposed heat (39.5 degrees C, 30 min, 2 times daily) with or without the mitochondrial uncoupling agent, 2,4-dinitrophenol (DNP) for 10 days. Core temperature, renal function, proteinuria, renal histological and biochemical analyses were performed. DNP increased the body core temperature in response to heat by 1 degree C (42 versus 41) This mild increase in temperature correlated with worsening albuminuria, renal tubular injury and interstitial infiltration of monocyte/macrophages. The tubular injury was marked in the outer medulla. The observations are consistent with the hypothesis that clinical and subclinical heat stroke may play a role in Mesoamerican Nephropathy. This may be one explanation as to why MeN mainly affect populations on the Pacific side of Mesoamerica but has not been reported from the Atlantic side. There is evidence that Native Americans who entered the Americans via the Bering Strait in general have higher resting metabolic rates due to mitochondrial mutations that increased mitochondrial uncoupling, that likely provided a survival advantage by increasing their core temperature in the cold Arctic environment [171]. Today most Hispanic Americans in Central America have some Native American Indian genes, which might be associated with higher core temperatures. A comparison of resting metabolic rate (RMR), respiratory quotient (RQ) and body temperature between adults of African and. The adjusted RMR and RQ of South Africans was significantly lower compared to those of European (northern) descent. To make it short,

individuals with Native American Indian, or more northern European, genes are less capable to cope with work hard in a hot climate as they get more overheated than individuals with genes from Africa. And thereby, according to this experimental study, more prone to get AKI which may develop into CKDu. Variations in the prevalence of genes that are related to heat susceptibility possibly vary between populations with different decent.

Overview/review/discussion papers

Yet another non-critical review suggesting a role of heavy metals such as cadmium and lead for the endemic of CKDu in **Sri Lanka** was published but provides no new or pertinent information [172]. Another review suggests that 'Glyphosate's synergistic health effects in combination with exposure to other pollutants, paraquat, and physical labour in the ubiquitous high temperatures of lowland tropical regions, could result in renal damage consistent with CKDu in **Sri Lanka** [173] but provide no hard data or evidence to support this suggestion.
Another review paper on CKDu/CINAC, its possible causes and prevention in **Sri Lanka** is presented by Jayasumana [174]. CKDu/CINAC is considered the most significant public health issue in the paddy farming areas with more than 70,000 estimated patients and many deaths. Certain natural and man-made toxins, heat stress with repeated volume and salt depletion, infections such as hantavirus and leptospirosis, and a genetic origin have been proposed and investigated as possible aetiologies, and an association between CINAC and herbicides is discussed.

In **India**, an increased prevalence of CKDu has been observed in Andhra Pradesh, Odisha, Goa, and Maharashtra[175]. Although no single causative factor has been proved, several have been proposed: water-borne agrochemicals, silica, chemical flavors in betel nuts, and pesticides. The renal biopsy findings have been like those seen in Sri Lanka and Mesoamerican nephropathy, predominant findings have been tubular atrophy and interstitial fibrosis with little or no involvement of the glomerular and vascular compartments. Because most of the affected communities belong to the lower socioeconomic group including farmers, a multipronged approach is required for addressing this CKDu epidemic with an emphasis on awareness, prevention, screening, surveillance, provision of renal replacement therapy, increased government spending on health care, and systematic research.

In a review of entitled; *Chronic Kidney Disease of Unknown Etiology: Hotspots in **India and Other Asian Countries*** [175] it is underlined that most of the affected communities belong to the lower socioeconomic group including farmers, and that a multi-professional approach is required for addressing this CKDu epidemic with an emphasis on awareness, prevention, screening, surveillance, provision of renal replacement therapy, increased government spending on health care, and systematic research.

In a review paper from **El Salvador** the severity of the CKDu problem is once again pointed out, albeit CKDu is given the acronym CKDnt [176]. It is pointed out that rural population are most affected. Agrochemicals are most suspected, mainly as pesticides are used a lot and an unsafe way.

In a review paper on hotspots of chronic kidney disease of unknown etiology (CKDu) [177], of which the Mesoamerican nephropathy in Central America is the most conspicuous example, attention is directed to **Tierra Blanca,** a rural region **in Mexico**, have shown that the prevalence of probable CKD is high (25%) among the population, of which almost half of the identified cases had no known risk factor (such as diabetes or hypertension).

In early 2019 researchers at the Pan American Health Organization (PAHO) and other South American institutions presented a systematic review of the most frequent exposures suspected to be possible causes of CKDnT[178]. Four systematic reviews and 61 primary studies from many different countries, among these China, Taiwan, and Tanzania i.e., outside the typically CKD endemic areas, were included. Results of the meta-analysis reached significance for working in agriculture, and when cross-sectional studies were excluded, agrochemical exposure also became significant. Why cross-sectional studies in this review should be excluded, was not explained. Exposure to heat-stress, not

very precisely defined, was not significantly associate with an increased risk. Albeit this review is systematic it seems to use of very crude assessments of possible pertinent exposures and appear to be too much of 'mixing apples and oranges' to allow any conclusions on likely and less likely causes/contributors of CKDnT.

With support from the International Society of Nephrology, a multidisciplinary group of nephrologists, epidemiologists, and occupational health and environmental scientists formed a group to identify a coherent approach to studying CKDu/MEN. Table 1, below, provide recommendations for studies focused on investigating cause(s) [179].

Table 1 | i3C Recommendations to strengthen investigations of CKDu/MEN cause(s)

1. Pursue longitudinal studies and make provisions for biorepositories
2. Bolster capacity for kidney biopsies, diagnosis, and investigation of pathogenesis
3. Create an open access database of ongoing studies to enhance collaboration and transparency
4. Partner with participants and community leaders in study design and ensure return of study results to participants
5. Build long-term relationships between international and local researchers that emphasize fairness, trust, and shared commitment

CKDu/MEN, chronic kidney disease of unknown etiology/Mesoamerican nephropathy; i3c, International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology.

In short debating comment entitled 'Let's take the heat out of the CKDu debate: more evidence is needed' Pearce and Caplin argue that the commonly favored 'Heat stress and dehydration' theory cannot really explain the CKDu epidemic but do not provide any plausible alternatives [180].

To improve research and reporting on CKDu a standardised protocol for cohort studies in high-risk communities has been suggested[181] [182]; A generic cohort protocol which provides information to establish a prospective population-based cohort study in low-income settings with a high prevalence of CKDu is suggested. This involves a baseline survey that included key elements from the DEGREE survey (e.g., using the previously published DEGREE methodology) of a population-representative sample, and subsequent follow-up visits in young adults (without a pre-existing diagnosis of CKD (eGFR<60 mL/min/1.73m^2), proteinuria or risk factors for CKD at baseline) over several years. The DEGREE protocol makes it possible to undertake comparisons internationally, by mandating a population-representative sample and standardised collection of information on sociodemographic factors, occupational and environmental exposures, body composition and kidney function.
From **India** it is now reported this protocol (Disadvantaged Populations eGFR Epidemiology Study [DEGREE]) protocol will be used to identify and characterize occurrence of CKD in the Uddanam region including CKDu, and to determine the age-specific incidence and natural history of CKD in the region [183].

Back-ground information on the on average eGFR and prevalence of lowered eGFR and albuminuria in different age-categories in **Sri Lanka** has recently been provided [184]. The study sample included 7768 apparently healthy people aging 18 to 93 years and females.

An excellent review on '**Chronic Kidney Disease of Unknown Cause in Agricultural Communities'** was published in May 2019 [34]. It points out that chronic kidney disease is occurring in several regions of the world, affecting manual workers in hot, agricultural communities. One possible mechanism that has been proposed for the development of Mesoamerican nephropathy is the uptake of toxins in the tubules, resulting in direct toxicity. Another proposed mechanism is heat exposure leading to dehydration and volume depletion or an increase in core temperature, which may cause kidney injury directly through tissue dysfunction or indirectly through hyperosmolarity or rhabdomyolysis. In addition, heat-associated dehydration may also cause kidney injury by amplifying the renal effects of toxins or toxicants. It has also been proposed that infectious agents may be

involved in the pathogenesis of Mesoamerican nephropathy, although this hypothesis remains unproven. For all mechanisms, genetic factors could be important. It is concluded that causes remain unclear and may involve a complex interplay of environmental exposures, infections, genetic factors, and heat. In the Preventive measures should include measures to ensure safe drinking water, adequate hydration, rest, and shade for workers at risk, as well as to reduce exposure to toxins.

In another review paper [185] Ricardo Correa-Rotter, the researcher who initially named Mesoamerican Nephropathy for CKDu occurring in the Mesoamerica's, and Ramon Garcıa-Trabanino, provides a valuable information about epidemiology and possible causes but also on prevention and treatment. It is concluded that the best prevention is the limitation of heat exposure, provision of adequate hydration, and rest in shaded areas at proper intervals. In addition to proper hydration practices, improved sanitation, banning of potentially harmful agrochemicals, and limiting exposure to those that are in use by using proper protective equipment is advocated. Avoidance of nonsteroidal anti-inflammatory drugs is recommended. Poverty and social margination are critical factors that need to be addressed.

Rick Johnson, one of the most actively publishing major researcher in the field off CKDu, together with colleagues 2019 published another review which focuses on how a worldwide increase in temperature has resulted in a marked increase in heat waves (heat extremes) and carries a markedly increased risk for morbidity and mortality [186]. Recurrent heat and dehydration can result in chronic kidney disease (CKD) in animals and theoretically plays a role in epidemics of CKD developing in hot regions of the world where workers are exposed to extreme heat. Given the rise in world temperatures, there is a major need to better understand how heat stress can induce kidney disease, how best to provide adequate hydration, and ways to reduce the negative effects of chronic heat exposure.

In a commentary in NEJM in august 2019[187] conclude that there is increasing evidence that heat exposure can cause daily subclinical acute kidney injury (ischemia, temperature-induced oxidative stress, and decreasing intracellular energy stores), which may cumulatively impair kidney function and result in CKD either directly or by exacerbating renal insults caused by other environmental exposures — or both. The combined effect of increasing heat extremes and water shortages is creating a new era of climate-health crises, are arising CKDu as one of many heat-sensitive illnesses that will be unmasked and accelerated by climate change.

An important paper published 2019 discuss **genetic and developmental factors** in CKDu hotspots [188]. Well-documented areas of MeN occur primarily on the Pacific coast of Central America with admixed populations that of Native American and European ancestry, with lesser African contribution. Conversely, populations on the Caribbean coast of Central America tend to have much more African ancestry, and there are few, if any, convincing reports of MeN in these populations. It is speculated that populations whose distant history included out-of-Africa migrations may have lost resistance to heat stress or equatorial pathogens. The migration to the Americas by early (Native) Americans that included millennia near or above the Arctic Circle may have increased evolutionary pressure for heat conservation and decreased resistance to pathogens. The ancestors of populations that developed MeN may carry genetic variants adapted for the very different climates their ancestors traversed. Also, from Sri Lanka and southern India there are some suggestions inherited increased susceptibility for CKD. However, the plausibility of these conjectures can be confirmed only by identification of specific genetic variants associated with CKD discovered in rigorous and methodologically sound genetic studies.

In a paper from **Sri Lanka** [189] an unusual approach is taken to elucidate the cause/causes of CKDu in some areas of the country. Two types of data were collected for this study, qualitative data from key informant interviews and abstracts of 33 peer-reviewed research articles during the past decade. A total of 35 key informants were recruited, mainly from communities in the northern dry zone region where a higher number of CKDu patients have been reported. The interview transcripts were examined using a range of techniques including content, thematic and semantic network analyses. The findings

of the research articles were explored through a word cloud analysis. The study indicates that CKDu seems to be influenced by multifactorial ecohydrological changes linked to anthropogenic stressors such as inefficient use of fertilisers and weedicides in agriculture. The key informants indicated grave concerns on the flow on effects of poor surface and groundwater quality in the region on health, livelihood, and well-being of communities. The study concludes that there is a need for more in-depth research to better understand how the surface and groundwater quality influence CKDu and other health conditions in the region. Another paper from **Sri Lanka** [190] presents dynamic models incorporating exposures from pesticides and heavy metals, drinking hard water with high levels of fluoride, poverty, low birth weight, micronutrient deficiencies and heat stress to model the epidemic, understand the impacts of different factors, predict potential populations at risk, and formulate multi-pronged prevention strategies that target leverage points of the system. Unfortunately, however, nothing about the aetiology or cause of CKDu becomes clear from this paper.

Kidney progression project (KiPP): a longitudinal cohort study of progression in chronic kidney disease of unknown etiology in **Sri Lanka** has been launched [191]. This project seeks to ascertain factors associated with the rapidity of kidney disease progression in one of Sri Lanka's CKDu endemic areas. A sample of 296 male and female residents aged 21 to 65 with moderate CKD, as measured by their serum creatinine level, and a clinical diagnosis of CKDu are followed using quarterly serum testing to track the rate of progression. Forthcoming reports are much awaited!

2020

According to Chapman et al occupational heat stress increases the risk of acute kidney injury (AKI) and kidney disease [35]. Thirteen healthy adults (3 females, 23+/-2 years) exercised for two hours in a 39.7+/-0.6 degrees C, 32+/-3% relative humidity environmental chamber. In a four arm trials, all subjects received: water to remain euhydrated (Water), continuous upper body cooling (Cooling), a combination of both (Water + Cooling), or no intervention (Control). The magnitude of hyperthermia (increased core temperature of 1.9+/-0.3 degrees C, and dehydration (percent loss of body mass of -2.4+/-0.5%, were greatest in Control. There were greater increases in the urinary biomarkers of AKI in the Control trial: albumin (increase of 13+/-11 microg/mL, P</=0.05 compared to other trials), neutrophil gelatinase-associated lipocalin (NGAL) (increase of 16+/-14 ng/d. The differences in urine biomarkers between the most heat exposed exercise period and the others however became much less pronounced and mostly insignificant when urine biomarkers were normalized for urinary concentration/content of osmolarity/creatinine. Nevertheless, these findings indicate that the risk of AKI is highest with greater magnitudes of hyperthermia and dehydration during physical work in the heat.

From **Sri Lanka** a descriptive study presents the health-related quality of life (HRQOL) and the associated factors among CKD/CKDu patients in a rural district affected by CKDu [192].

Associations between BMI and the estimated glomerular filtration rate (eGFR) was investigated in people with CKDu in the Polonnaruwa district of **Sri Lanka**, which has one of the highest densities of patients with CKDu[193]. Comparisons was made with unaffected age-matched control groups in disease-endemic areas. The study was comprised of 242 individuals: 139 with CKDu (eGFR of less than 60 mL/min/1.73 m^2) and 103 without. The group with the highest number of people affected with CKDu had lower BMI compared to those with normal eGFR. The majority were male farmers. Those who consumed water from household dug wells had significantly lower eGFR. A linear regression analysis revealed a significant positive association between lower eGFR and lower BMI ($p < 0.001$). It was hypothesised that a low BMI increase susceptibility to develop CKDu. An alternative idea is that CKDu lower BMI.

The association of past hantavirus infection and leptospirosis with the occurrence of CKDu has been examined once again in **Sri Lanka**. A cohort (n = 179) of known CKDu patients living in high-CKDu prevalent areas of Anuradhapura district was compared with a group of 49 healthy, sex-matched

younger relatives of CKDu patients (control-1) and another 48 healthy, age, and sex-matched individuals living in low-CKDu prevalent area (control-2) of the same district where same life style and climate conditions prevail [194]. Fifty out of 179 (27.9%) CKDu patients, 16/49 (32.7%) of control-1 and 7/48 (14.6%) of control-2 were found positive for IgG antibodies to Puumala, Hantaan or both strains of hantaviruses. Hantavirus IgG sero-prevalence of healthy individuals living in low-CKDu prevalent area was significantly lower compared to CKDu patients and healthy younger relatives living in high-CKDu prevalent areas ($p = 0.03$). IgG seroprevalence to hantaviruses was not significantly different in CKDu patients and healthy younger relatives living in high-CKDu prevalent areas indicating past hantavirus infection has no association with the occurrence of CKDu or possibly, younger relatives may develop CKDu in subsequent years. Seroprevalence to leptospirosis showed no significant difference between CKDu patients and healthy controls.

A research report from **Sri Lanka** focus on various microbial pathogens in drinking water as a potential causal or contributing factors to CKDu [195]. The chemical composition and total microbial content of 30 domestic household wells in the Medawachchiya District, where CKDu is prevalent, was tested. While the chemical composition in the tested wells mostly lies within standard drinking water limits, except for high levels of fluoride (F), magnesium (Mg), sodium (Na), chloride (Cl) and calcium (Ca) in some samples, cyanotoxin-producing Microcystis, was often found in the drinking water.

An attempt to quantify chronic exposure to cadmium, lead and arsenic through food in people living in an area in **Sri Lanka**, where prevalence of (CKDu) is high has been made [196]. First a dietary survey was carried out in the subjects to estimate the type and quantity of typical food items to estimate an average consumption. Secondly cadmium, lead and arsenic the various identified food items were determined. Assuming the major route of intake is food and based on the quantity and type of food items consumed, a 60 kg man is exposed to average doses of 84 µg cadmium, 924 µg lead, and 180 µg arsenic per week. Cadmium and lead is somewhat high but not in the amounts that may be considered to cause any kidney effects [52] [53, 197]. In another Sri Lankan report [198] hydrochemical and isotopic samples collected from groundwater wells in selected CKDu endemic areas in Sri Lanka was examined. Results obtained do not provide evidence of polluting heavy metals in groundwater but identifies elevated concentrations of silica.

A lot of attention has been given to the possibility of metal exposure as a cause of CKDu in **Sri Lanka.** In an autopsy study the metal concentration in bone and kidney was analysed from 14 cases with CKDu and 33 controls [199]. The variations were large, and few significant differences were seen. Nevertheless, farfetched conclusions were made regarding the possible role of lead, calcium, and fluoride.

Comparisons have also been made on various aspects of water quality in CKDu endemic areas versus not endemic areas In **Sri Lanka**. In a recent report [200] measured heavy metals (Cd, As, Pb, and V) and organic pesticides (e.g., glyphosate) in the drinking water from different sources and wells in Sri Lanka. have been hypothesized to play a role in childhood onset and progression of this disease. Zebrafish, *Danio rerio*, a toxicology model, was used to examine kidney developmental effects of exposure to environmentally derived samples from CKDu endemic and non-endemic regions and Cd, As, V, Pb, and glyphosate as individual compounds and in mixtures. Drinking water was contaminated with various organic chemicals and heavy metals, but at levels were considered safe for drinking. In another study water samples were obtained from patients diagnosed with CKDu [201]. Serum creatinine levels of the CKDu patients were significantly and negatively correlated with phosphate while positively correlated with total dissolved solids (TDS) and arsenic content of the drinking water. Findings, as I see it, impossible to interpretate.

A previously unrecognized endemic area of CKDu among the underprivileged population engaged in agricultural labour in coastal southeaster India in the states of Tamil Nadu and Puducherry in **India**. A total of 2,424 patients kidney disease were analysed; the median age was 52 years and 75.3% were male. Seventy-five percent had advanced CKD. CKDu was the most common (51.7%) etiologic category. A clustering of cases of CKDu was noted in specific districts using a geographic information

system software. Screening of 447 people in an outreach program at a village located in an area identified to have clustering of CKDu showed a CKD prevalence of 19% [202].

A remarkable achievement and attempt to assess and improve kidney health and working conditions related to heat stress was among sugarcane harvest workers in Chichigalpa, **Nicaragua** was published in May 2020[27]. Based on experiences and observations on the working conditions and renal effect in field studies workers during the 2017-2018 harvest recommendations that enhanced rest and improved access to hydration and shade were given before the 2018-2019 harvest, involving 719 irrigation repair workers, seed cutters and burned cane cutters. Serum creatinine (SCr) was measured before and at end-harvest, and cross-harvest changes in estimated glomerular filtration rate (eGFR) and incident kidney injury (IKI, ie, SCr increase by >/=0.30 mg/dL or >/=1.5 times the baseline value) were compared between harvest 2017-2018 and harvest 2018-2019 for three jobs with different physical workloads using regression modelling. In burned cane cutters, mean cross-harvest eGFR decreased with 9/min/1.73 m^2 during the first harvest, and significantly less (4 ml/min/1.73 m^2) after the preventive intervention. IKI was 70% (95% CI 90% to 50%) lower during the second harvest. No such improvements were seen among seed cutters groups with less successful intervention implementation. These results support further efforts to prevent kidney injury among sugarcane workers, and other heat-stressed workers, by improving access to water, rest, and shade.

In a nested case-control study using urine samples from a rural, community-based follow-up study of 350 young adults from Northwest **Nicaragua** the associations between deteriorating eGFR was related to the urinary concentrations of metals, pesticides and mycotoxins [203]. Urine samples collected at baseline (pre-sugarcane harvest) and the first 6-month follow-up (post-sugarcane harvest) visit were tested. Twelve metals and metalloids (aluminium, total arsenic, cadmium, chromium, cobalt, copper, lead, manganese, mercury, selenium, silica, and strontium) were analysed by inductively coupled plasma-mass spectrometry. Twelve pesticides or their metabolites (2,4-dichlorophenoxyacetic acid, 3-phenoxybenzoic acid, 4-fluoro-3-phenoxybenzoic acid, chloro-3,3,3-trifluoro-1-propen-1-yl-2,2-dimethylcyclopropanecarboxylic acid, cis/trans 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, ethylenethiourea, glyphosate, 4-chloro-2-methylphenoxy acetic acid, 3-hydroxy-pyrimetanil, 5-hydroxytiabendazole, hydroxy-tebuconazole and 3,5,6-trichloro-2-pyridinol) and two mycotoxins (ochratoxin A (OTA) and citrinin (CIT)) were analysed by liquid chromatography coupled-mass spectrometry. Elevated levels of aluminium and total arsenic as well as metabolites of several pesticides were detected across the population. No differences were identified between the declining and stable groups in the levels of metals or pesticides tested. OTA and CIT were below the limit of detection. It was concluded that the tested metals, metalloids, pesticides, and mycotoxins were not associated with loss of kidney function in participants at-risk of MeN. About the overall (in cases as well as controls) elevated levels of aluminium, manganese and silica it is worth to consider the great risk of contamination when sampling urine. Special vials and cleaning techniques are required to get non contaminated samples.

Prevalence and risk factors for CKD in the general population of southwestern **Nicaragua** have been examined and reported [204]. Participants were recruited from 32 communities and enrolled 1242 of 1397 adults (89%) living in 533 households (median age 41 years; 43% male). Overall prevalence of CKD (eGFR<60 ml/min per 1.73 m^2) in 53 of 1227 (4.3%) evaluable participants. In multivariable testing, risk factors for prevalent CKD included age, self-reported history of hypertension, diabetes, or current or past work in the sugarcane industry (OR 2.9; 95% CI, 1.4 to 6.3).

In an unusual approach 15 trace elements, including heavy metals was analysed in toenail clippings from renal case-patients (n = 18) and healthy controls (n = 36) in a MeN high-risk region of **Nicaragua** [205]. Nickel (Ni) concentrations were significantly higher in toenails from cases and Ni concentrations in toenails correlated positively with serum creatinine levels (p = 0.001) and negatively with eGFR. To assess exposure metals by measurements in toenails however very difficult, not to say

impossible. Nickel, and other metals, may be released from utensils used for sampling. Strict control must be kept avoiding contamination from instruments. Analytical accuracy should be thoroughly assessed by using certified external quality control samples [153]. The wide variation in reported values, from 0.05 to 51.24 Ni mg/kg suggest that contamination is a problem. Reported nickel concentrations in blood and urine from other investigators are 100-1000 times lower. Next, nickel has carcinogenic properties and is allergic but has few nephrotoxic effects [206]. Thus, the statement that 'this study provides new compelling evidence that Ni, even at low doses, is associated with increased risk of renal injury…' [205]is farfetched to say the least. In the chapter dealing with Nickel in the recently (2012) published two volume book Handbook on the Toxicology of Metals nothing is mentioned about renal effects or toxicity from nickel [207].

In **Guatemala** longitudinal trends in renal function (eGFR) among sugarcane harvesters have been investigated [208]. Of 181 new workers, median age 19 years, 39 (22%) were identified as having non-stable kidney function with an annual age-adjusted decline of estimated glomerular filtration rate (eGFR) of -1.0 ml/min per 1.73 m^2 (95% CI: -3.4, 1.3) whereas the rest (n=142) remained stable in eGFR. Follow-up was up to 4 years but was one year for most of the examined workers. Low eGFR, mild hypertension and having a local home of residence prior to employment in sugarcane were associated with non-stable eGFR. That elevated blood pressure and low eGFR comprise risk factors is anticipated in any follow-up of GFR. To what extent excessive heat exposure comprise an additional risk for attaining lowered eGFR cannot be assessed in this study, as individuals with low eGFR was not hired and thus not examined. Previous studies from Guatemala indicate that heat exposure is less severe in Guatemala compered to e.g. Nicaragua [131].

In another report from **Guatemala** an attempt is made to forecast cross-harvest eGFR decline among sugarcane workers [209]. Daily changes in creatinine over six consecutive days in 103 Guatemalan sugarcane harvesters was examined in the beginning and followed-up at the end of the harvest season in 2018. Twenty-nine percent (n = 30) of the 103 workers experienced repeated severe fluctuations in creatinine across shift. Workers who experience repeat severe daily fluctuations in creatinine, on average, experienced a greater reduction in kidney function at the end of the season; eGFR of workers in the severe group on average decreased eGFR 20% across season compared to 11% decline for those in the moderate group. These findings support the concept that repeated AKI during harvest with excessive heat strain at work increase the risk for MeN/CKDu.

In a third report from **Guatemala** by the same group investigators [210] retrospectively examine sugarcane workers who develop abnormal kidney function (AKF) (eGFR, <60 mL/min per 1.73 m^2), workers with reduced kidney function (RKF) (eGFR 60-89), and workers who maintained normal kidney function (NKF). Between 2012 and 2016, eGFR declined at a rate of 0.18 mL/min per 1.73 m^2 per year for the NKF group (95% CI: -0.7, 0.3), 2.0 per year for the RKF group (95% CI: 1.0, 3.0) and 7.5 per year for the AKF group (95% CI: 6.0, 9.0). All study groups stabilized or improved their trajectory of eGFR decline when a 'water, electrolytes, rest, and shade' (WERS) intervention was implemented. It was concluded that early detection of rapid kidney function decline combined with appropriate interventions hold promise for stopping or slowing progression of renal insufficiency among these workers.

A publication from 2020, that has previously escaped my attention, describes how electrolyte and fluid supplementation improved certain health variables in 46 **Guatemalan** sugarcane cutters, performing heavy work under hot climatic conditions [211]. During week 1 (baseline) with no intervention, each worker was provided with the standard 2.5 L of electrolyte solution per day week 2, the provided electrolyte solution amount was 5L per day, followed by an increase to 10L per day during week 3. The electrolyte solution, based on the World Health Organization (WHO) recommended oral rehydration formula, consisted of 2.6 g NaCl, 2 g KCl, 13.5 g carbohydrates (glucose), and 40 kcal,

per liter. Average serum creatine kinase (CK), an indicator of muscle breakdown, decreased from 753 U/l at baseline to 561 and 311 U/L when much more of the electrolyte solution was used.

Another paper from **Guatemala** suggest that copeptin could be a potential prognostic biomarker for CKDu[212]. In a longitudinal study of 105 workers in Guatemala relationships between hydration indices, plasma copeptin concentrations, and kidney function markers at 3 times during the 6-month harvest was examined. Copeptin concentrations were negatively associated with eGFR. As workers improved their hydration (measured by increases in fluid balance), copeptin concentrations were reduced, and this reduction was associated with an improvement in kidney function.

In an editorial comment in *Pediatric Nephrology* [213]a study from [214] in the same issue of Paediatric Nephrology is cited. 210 youths aged 7–17 years residing predominantly in a CKDu endemic region of **Nicaragua** was examined. Urinary concentrations of biomarkers of kidney injury such as neutrophil gelatinase-associated lipocalin (uNGAL), kidney injury molecule1 (uKIM-1), interleukin-18 (uIL-18), monocyte chemoattractant protein 1 (MCP-1) and chitinase-3-like protein 1 (YKL-40), as well as urine and serum creatinine and eGFR was estimated. Median uNGAL, uIL-18 and uKIM-1 concentrations in their study population exceeded healthy reference values, indicating renal injury. The authors conclude that children between 7 and 17 years of age who live in a MeN-endemic agricultural region are at high risk of subclinical kidney injury prior to occupational exposures. There are some concerns regarding the interpretation of this study. It is a cross-sectional study where eGFR, calculated from creatinine using the 'bedside Schwartz equation', a method that hast not been validated in the examined population. The biomarker concentration in urine expressed as unit/L divided by creatinine/L, giving biomarker unit/g creatine. This is done to decrease variation in concentration related to the concentration of the urine under the assumption that there is a constant daily excretion of creatinine per day, or 24h. This may be reasonable for adults but is not correct for children as the creatine excretion in urine is much influenced by sex, muscle mass and diet. And therefore girls, who excrete less creatinine in urine, appear to have much higher concentrations of biomarkers in urine. Then to relate prevalence 'top quartile biomarkers in urine' is questionable.

A case-control study of risk factors for CKD has been reported in a Cuban Medical journal from **El Salvador** [215]. 4,817 adults ≥20 years old in a national sample of the population were interviewed regarding a great number of exposure variables including self-reported exposure to agrochemicals. Answers from individuals with CKD (n=519) was compared to those without. Increased odds ratio (OR) of CKD and CKDnT was observed for several types of exposure to agrochemicals. However, as exposure assessment were crude and did not include exposure to heat and/or history of dehydration, nothing can really be deducted from this report.

Nonspecific symptoms of urinary tract infections are commonly diagnosed among men in **Nicaragua**, who often receive antibiotics and nonsteroidal anti-inflammatory drugs for urinary symptoms. Two-hundred-and-fifty-one male Nicaraguan sugarcane workers were followed over one harvest including urine dipstick parameters, kidney injury biomarkers, and eGFR [216]. A questionnaire about urinary symptoms, health-related behaviours, and medication history was used. Cane cutters reported higher proportions of urinary-related symptoms compared with agrichemical applicators, irrigators, and seeders/reseeders. Proteinuria was uncommon, whereas dipstick leukocyte esterase was relatively common, especially among cane cutters, seed cutters, and seeders/reseeders. In general, workers who reported urinary-related symptoms had higher mean kidney injury biomarker levels at late harvest. However, none of the workers had positive urine cultures, including those reporting urinary symptoms and/or with positive leukocyte esterase results.

In a cross-sectional study chronic kidney disease of unknown etiology (CKDu) in agricultural population in male rice farmers in **Indonesia**; have been examined [217]. The study included 354 healthy male farmers in two rice agriculture areas, Karawang and Bogor, in West Java with different altitudes (low altitude and high-altitude location). Ambient temperature and humidity in both study

locations was measured. The overall prevalence of CKD, as defined in this report, was 24.9% and CKDu was 18.6%. For the environmental factors, farm location (high altitude versus low altitude location) was associated with CKDu, being higher in the less hot area, 23.8%, versus 14.0% in the less hot. The average measured temperature and humidity in the past year from weather stations show an average heat index of 22 degrees C in Bogor and an average heat index of 32 degrees C in Karawang [218]. That CKDu is more common in the less warm area is contrary to what may have been anticipated as a high prevalence of CKDu has, as a rule, been associated with working had outdoor in high temperatures. However, in this report, the definition of CKDu was wide and if the commonly used cut off eGFR< 60 ml/min is used the prevalence of CKD was low; 2.7% and 4.2% in Karawang (low altitude, comparably hot) and Bogor (high altitude, less hot), respectively. The results from Java are therefore not comparable with what has been reported elsewhere[219].

A cross-sectional study CKDu on the prevalence of lowered eGFR in **Malawi** has been reported [220]. Adults > 18 years (n = 821) without diabetes, hypertension, and proteinuria was examined. The mean eGFR was 117.1 +/- 16.0 ml/min per 1.73m^2 and the mean participant age was 33.5 years. The prevalence of eGFR< 60 was low; 0.2% and the prevalence of eGFR< 90 likewise; 5%. Age and BMI were associated with reduced eGFR< 90. No increased risk of eGFR < 90 was observed for rural participants. It is concluded that reduced kidney function consistent with the definition of CKDu is not common in the areas of Malawi sampled, compared to that observed in other tropical or sub-tropical countries in Central America and South Asia. Data on exposure to heat and/or agrichemicals is mot presented nor discussed in relation to reduced eGFR, albeit occurring at a low rate.

An important measure to prevent CKDu possibly is decrease occupational heat exposure, i.e. cooling, A systematic review is to examine cooling intervention research in outdoor occupations, evaluate the effectiveness of such interventions, and offer recommendations has been made [221]. A systematic search yielded a total of 1042 articles, of which 21 met the inclusion criteria. The studies focused on multiple types of cooling interventions cooling gear (vest, bandanas, cooling shirts, or head-cooling gel pack), enhanced heat dissipation clothing, forearm or lower body immersion in cold water, water dousing, ingestion of a crushed ice slush drink, electrolyte liquid hydration, and modified Occupational Safety and Health Administration recommendations of drinking water and resting in the shade. Current evidence indicates that using multiple cooling gears along with rest cycles may be the most effective method to reduce heat-related illness.

In the rural farming community, Padaviya in the Anuradhapura district, of the North Central province of **Sri Lanka** healthy farmers, without CKD, were whether they were dehydrated [222]. Plasma and urine osmolarity were recorded upon waking up in the morning and evening during the non-farming and farming seasons. Farmers were often dehydrated according to the plasma osmolarity especially in the mornings, irrespective of whether they were farming or not. As by Both plasma and urine osmolarity and specific gravity indicated that approximately 40% of the farmers demonstrated acute dehydration at the end of the day due to farming activity.

Renal histopathology:

Vervaet and collaborators [36] have presented a report where they argue that the epidemic of chronic kidney disease of unknown cause (CKDu), or Mesoamerican Nephropathy (MeN), that occur in agricultural communities, is explained by toxins that produce a specific type of tubulo-interstititial nephritis. Already in 2017 [110] it was suggested that this kidney disease (CKDu/MeN) should be named chronic interstitial nephritis in agricultural communities (CINAC) and was caused by exposure to agrichemicals rather than, as considered as most likely by many researchers in the field, that repeated dehydration from hard physical work in hot environment, causing loss of water and minerals, have an important role in the pathogenesis.

To support their previous hypothesis results from a thorough examination, including electron microscopy, of renal biopsies from 34 cases of CINAC from four countries (**Sri Lanka, El Salvador,**

India and France) have been presented and compared to biopsies obtained from non CINAC cases [36]. It is not clear how these CINAC patients were selected. Reference is given four different papers but specific details from how the CINAC cases were identified and selected are meagre. It is noteworthy that 4 cases of CINAC are from France albeit CKDu, has not been reported from Europe. The CINAC cases seems to be defined by morphological observation rather than history and results from clinical and biochemical examinations. This contrasts with several other case series [15] [111] [30]. Periodic Acid Schiff (PAS) staining of renal biopsy sections demonstrated accumulation of proximal tubular cell cytoplasmic granules, varying extents of tubular atrophy, tubulointerstitial fibrosis, inflamed fibrosis, glomerulosclerosis, glomerulomegaly, and vascular hyalinosis/sclerosis. Jones staining revealed accumulations of silver positive light brown to black cytoplasmic granules in cortical tubular cells. These granules, optimally observed at magnifications >400x, varied in size from finely granular to prominent (> 1/3 of nuclear size), with discrete borders and were round to irregular/dysmorphic in shape. Tubular profiles ranged from unaffected to heavily involved, and affected tubular cells had few to several dozen granules observed on 2-4 μm sections. As a comparison several reference and control renal biopsies were examined: 22 cases of drug exposure and toxic nephropathies, 19 patients on calcineurin inhibitor treatment, 16 patients with 'proteinuric nephropathies', 6 cases of 'Sri Lankan glomerulopathies', and another 10 biopsies from 'healthy controls. CINAC alike findings, were observed almost all patients on calcineurin inhibitor treatment, 7 out of 15 with interstitial nephritis and 9 out of 11 patients exposed to Lithium, Lomustine or Clomiphene.

The observation of proximal tubular cell cytoplasmic granules in cases with CKDu/CINAC is interesting and worth exploring when attempting to elucidate the cause of CKDu. Letters to the Editor of Kidney International, the journal where this pathology paper was published, however emphasize that the reported lysosomal manifestations are nonspecific and preliminary to tie to exposure to agrochemicals [223] [224]. Herath [225]on the other hand argue that continuing to use the term CKDu (chronic kidney disease of unknown cause) is detrimental.

Since the publication by Vervaet and collaborators [36] the team of investigators that have published three of the previous renal pathology studies on MeN/CKDu have examined proximal tubular cell (PTC) cytoplasmic granules in renal biopsies from healthy controls (kidney donors), patients with focal segmental glomerulosclerosis, allergic interstitial nephritis, IgA nephropathy, and thin basement membrane disease [37]. Controls, as well as patients, displayed very similar lysosomal phenotype in PTCs as Vervaet et al reported in what they regard as CINAC patients and conclude the is unlikely that a calcineurin-inhibitor (CNI) toxicity pathway is causing CINAC since patients rarely display hallmark signs of CNI-toxicity (isometric vacuolization and arteriolar hyalinization). These lysosomal changes are not specific for toxicity, a link to a CNI-toxicity pathway is not evident, and a connection to pesticides even more questionable [223].
In order to suggest causality from exposure to agrochemicals it is necessary to present not only what kind of agrochemical(s) that may elicit these changes, that the CINAC cases have been exposed to a dose of the pinpointed substance (s) to such an extent that renal tubular toxicity can be anticipated, and that dose-effect and dose-response relationships can be demonstrated in epidemiological studies [226]. Indeed, such relationships, between heat exposure and lowered eGFR or CKD, have been reported from several epidemiological studies relating strenuous work in heat to CKD but not, as yet, for any agrochemical. To summarize; the morphological observations seen in tubules from renal biopsies of CKDu patients are noteworthy and worth exploring but cannot, detect or exclude any specific cause.

An interesting case report has come from **China**[227]; a 40-year-old man admitted to a Peking Medical College Hospital because acute kidney injury (AKI) from acute tubular necrosis (ATN) considered to be caused by long-distance running almost every and a desire of not drinking water during or within one hour after the exercise. CKD developed 1 year later. A second renal biopsy showed characteristics of ischemic renal disease but there was no evidence of vascular disease. The patient had been taking part in long-distance running without drinking adequate water for years, which

would have markedly decreased his renal blood flow. Thus, this patient may have developed chronic dehydration-associated kidney disease sharing the similar aetiology of MeN.

An increased frequency of CKD has been found in **Nepalese migrant workers**, almost three quarters working in Gulf countries where heat exposure is common and working conditions poor [228]. In most cases the ethology of CKD is unknown. Although long working hours and lack of medical care may be the contributing factors, more detailed studies are needed to investigate the causes of increased frequency of CKD in Nepalese migrant workers.

Experimental work

Using zebrafish, as toxicology and kidney disease model, exposure to (i) environmentally derived samples from **Sri Lanka** CKDu endemic and non-endemic regions water and (ii) Cd, As, V, Pb, and glyphosate as individual compounds and in mixtures toxicity was examined [200]. It was found that drinking water is contaminated with various organic chemicals including nephrotoxic compounds as well as heavy metals, but at levels considered safe for drinking. However, histological studies and gene expression analyses examining markers of kidney development and kidney injury showed novel effects on kidney development and the mitochondrial function.

Overview/review/discussion papers

Several of the first, and principal, MeN/CKDu investigators published a review and evaluation of all published epidemiological reports from Central America [3]. It was concluded that there is not yet consensus on the aetiology. Anecdotal evidence from the 1990s pointed to work in sugarcane; pesticides and heat stress were suspected. CKDnt was reported in sugarcane and other high-intensity agriculture, and in non-agricultural occupations with heavy manual labour in hot environments, but not among subsistence farmers. Recent studies with stronger designs have shown cross-shift changes in kidney function and hydration biomarkers and cross-harvest kidney function declines related to heat and workload. The implementation of a water-rest-shade intervention mid-harvest in El Salvador appeared to halt declining kidney function among cane cutters. In Nicaragua a water-rest-shade program appeared useful to prevent kidney damage among cane workers with low-moderate workload but not among cutters with heaviest workload. Studies on pesticides and infectious risk factors have been largely negative. Non-occupational risk factors do not explain the observed epidemiologic patterns. It is concluded in this review that work is the main driver of the CKDnt epidemic in Mesoamerica, with occupational heat stress being the single uniting factor shown to lead to kidney dysfunction in affected populations. Sugarcane cutters with extreme heat stress could be viewed as a sentinel occupational population. Occupational heat stress prevention is critical, even more so in view of climate change.

In a review paper in Nutrients [229] the possible pathophysiological mechanisms by which heat stress may induce kidney inflammation and eventually CKD in sugarcane workers is discussed.
Inflammation biomarkers and fever is associated with acute kidney injury (AKI) among sugarcane cutters. Signs of inflammation in kidney biopsies and serum do not necessarily indicate that an infection or toxin/precipitant rather than heat is the cause of injury, as heat-induced kidney injury could also be expected to be mediated by inflammation.
Due to strenuous physical activity in heat with concomitant sugar consumption, kidneys of sugarcane cutters are potentially exposed to pro-inflammatory stimuli including hypoxia, fructose, uric acid, as well as circulating endotoxins and cytokines (Figure, above). The frequency with which a prolonged exposure to heat and exercise occurs is one potentially crucial difference between the settings in which AKI has been noted in athletes and sugarcane cutters. Sugarcane cutters repeat the same activity for six or sometimes even seven days a week for five–six consecutive months, meaning the possibilities for recuperative rest are more limited than for athletes. Pushing kidneys to the physiological limits daily, causing high tubular reabsorption demand while reducing blood flow, and repeating pro-inflammatory stimuli such as uric acid, fructose, hypoxia, cytokines, and/or endotoxins may contribute to fibrotic changes rather than successful healing.

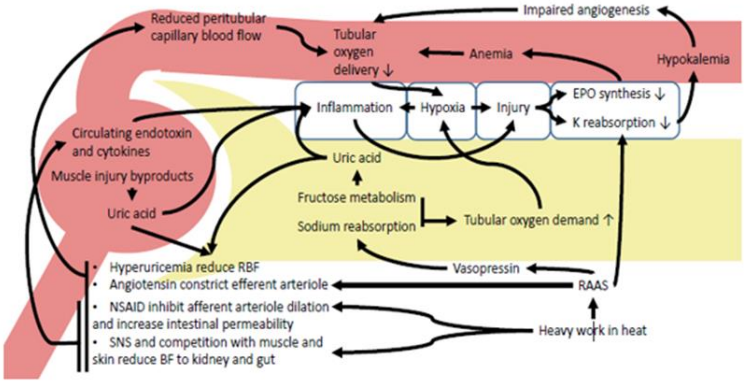


Figure 1. Schematic summary of potential pro-inflammatory stimuli in the sugarcane worker nephron. Red = blood vessels. Yellow = tubular lumen. White boxes = tubulointersitial cells. RBF = renal blood flow. NSAID = non-steroidal anti-inflammatory drug. SNS = sympathetic nervous system. BF = blood flow. RAAS = renin–angiotensin–aldosterone system. EPO = erythropoietin. Heavy work in heat leads to loss of volume and electrolytes triggering RAAS activation and vasopressin release, reducing renal blood flow, as well as increasing sodium absorption and potassium excretion. Heavy exercise and work decreases renal and gut blood flow through direct competition over the cardiac output and through sympathetic neural pathways. NSAID used to treat musculoskeletal pain from heavy work inhibits afferent arteriolar dilation, further decreasing renal blood flow, while also increasing intestinal permeability. Increased gut permeability enables endotoxins to enter the blood stream and trigger cytokine release systemically and in the tubuli, activating an inflammatory response. This inflammatory response in the tubuli can be further promoted by muscle cell breakdown products such as uric acid and tubular fructose metabolism, which also lead to uric acid production. Inflammation and relative hypoxia in the tubuli cause tubular cell injury, leading to further loss of potassium and decreased EPO synthesis, which in turn further impair tubular oxygen delivery.

In an editorial for CJASN in 2020 Kaufman [230] broadly discuss environmental risk factors for CKD. Agrochemical exposure as a cause of CKD is mentioned but no hard evidence on any specific exposure nor type pf renal effect elicited is available.

In an interesting and enlightening discussion paper [231] aspects of community-based participatory research and anti-colonial research is described using the currently ingoing occupational epidemiology study of CKDu in Mesoamerica conducted by the Boston University (BU) CKD Research Group since 2009. The research includes investigators from numerous countries in the global North and South and funding from the US government and corporations. The ability of researchers to navigate potentially conflicting interests with industry and workers, and establish trust within and outside the scientific community, is essential for sustained engagement in longitudinal studies. Trust is about human relationships. It takes time and effort to build and is essential for creating equitable, empowering research relationships. One understands that the author of this paper, a member of the BU team, consider the BU-Mesoamerican collaboration as overall well-balanced and successful.

A scientific debate on' *Is an environmental nephrotoxin the primary cause of CKDu (Mesoamerican nephropathy)?*' is presented in new scientific journal Kidney360, published by the American Society of Nephrology (ASN). Strong epidemiological evidence of occupational heat stress underlying the CKDu epidemic in Mesoamerica is presented by Dr Catharina Wesseling who is the most prominent and cited researcher in this research field, whereas it is concluded the evidence for pesticides, as well as other suggested agents or combinations, as the cause of CKDu is weak [232]. Professor de Broe,

who is a world-famous renal toxicologist together Dr Verveat, on the other hand argue against heat exposure as the cause of MeN/CKDu [233]. This is based mostly on lack of associations between heat exposure and occurrence of CKDu in Sri Lanka and the observations made in renal biopsies from CKDu cases (which they prefer to name Chronic interstitial nephritis in agricultural communities (CINAC). These biopsies, which have been obtained from several different countries, are considered to display typical features of toxicity. However, no specific substance or agent has been pinpointed. Dr Magdalena Madero, the moderator of this scientific debate concluded that, 'We agree that those affected by CKDu do not have traditional risk factors or underlying conditions that lead to CKD such as older age, diabetes mellitus, hypertension, glomerulonephritis or structural kidney disease, and that CKD is more frequent and has poorer outcomes among populations or communities considered 'disadvantaged' in both the developed and developing world [234]'.

Is CKDu/MeN caused by similar risk factors in different geographical regions? In order to resolve this critical question a comparative literature review was conducted to evaluate the CKDu research design for peer-reviewed articles published from 2015 to 2019 has been made [235]. In Asia and Latin America, 82 and 65 articles were identified in total, respectively, with 55 field studies in Asia versus 34 in Latin America. It was found that in Asia, research was focused on drinking water (34), heavy metals (20), and agrochemical product usage (19). Whereas in Latin America, research focused mostly on heat stress/dehydration (36) and agrochemical product usage (18). Using a harmonized approach to evaluate potential CKDu environmental risk factors across regions would yield improved understanding of the risk factors associated with CKDu and how they may vary across affected regions. Thus, the question if CKDu/MeN is an identical/very similar disease in different parts of the world, is as yet, unresolved.

A review entitled Mesoamerican Nephropathy (MeN): What we know so far [236] provides not only a good review of what we know but also some suggestions for prevention and treatment.

Other reviews '*The unresolved epidemic of chronic kidney disease of uncertain origin (CKDu) around the world: A review and new insights'*[237], '*Purposeful Review to Identify Risk Factors, Epidemiology, Clinical Features, Treatment and Prevention of Chronic Kidney Disease of Unknown Etiology*'[238], '*A Review of Chronic Kidney Disease of Unknown Etiology in Sri Lanka, 2001-2015*'[239], and '*The Utility of Novel Renal Biomarkers in Assessment of Chronic Kidney Disease of Unknown Etiology (CKDu): A Review*'[240] are interesting but do not really provide any novel interpretation nor evaluation of what has been made available in other reports. It is suggested that early diagnosis and treatment of CKDu is important but do not provide any specific evidence for this, albeit it is possibly reasonable. A fifth review '*Progression of potential etiologies of the chronic kidney disease of unknown etiology in Sri Lanka*'[241]adds nothing.

2021

Results from a clinical examination and 12 cases with CKD from in a poor agricultural community in a village of the central **Indian state** of Chhattisgarh has been presented [242]. Renal biopsies were performed in two. The clinical characteristics was like CKDu described elsewhere. Hypokalemia, hypomagnesemia, normophosphatemia/hypophosphatemia and hyperuricemia, was often seen. Kidney biopsy showed glomerulosclerosis, interstitial fibrosis, tubular atrophy, chronic vasculopathy, periglomerular fibrosis, and ischemic changes. Immunostaining was uniformly negative.

Associations of tungsten (W) in urine and the development of CKD has been reported from a rural agricultural community in **southern Colorado, USA**[243]. Urine was obtained from 1659 subjects from the San Luis Valley Diabetes Study, a prospective cohort study. Urine samples were analysed for 17 different trace metals, 20 including tungsten, arsenic, and cadmium Associations between urine tungsten (W) and time-to-CKD was assessed. Elevated urine W was strongly associated with

decreased time-to-CKD, even after controlling for hypertension and diabetes. As close to twenty metals were analysed there is a clear risk for spurious and random statistical association, increased U-W may be an indicator of an early renal effect rather than cause, and there was no prior mechanistic idea. Therefore, the hypothesis concerning exposure to tungsten and long-term renal toxicity, and cause of CKDu, in this report should be considered as suggestive, to say the most.

Kidney function was assessed by analysis of U-albumine and p-creatinine in farming communities in **Southwestern Nigeria** where the use of agrochemicals is widespread [244]. 438 farmers, males (46%), were studied. The mean microalbuminuria was 30.2 +/-11.7 mg/dl and a large proportion of the farmers had CKD stage 2 (42%) and CKD stage 3 (38%). There were positive associations between type of farming, use of hexachlorocyclohexane, and eGFR. These remarkable and worrying results concerning a high prevalence of CKD in areas of Nigeria need to be examined further and confirmed.

Highly interesting data on the prevalence of CKD has recently been published from **Peru**[245]. A cross-sectional study was conducted following the Disadvantaged Populations eGFR Epidemiology (DEGREE) protocol among adults in the Tumbes region of Peru. The area is located at sea level with an arid subtropical climate, average annual temperature of 25 oC. eGFR was estimated using the CKD-EPI equation. Environmental conditions related to CKDu (i.e., work in agriculture or sugarcane, water source, heat intolerance, and pesticide exposure) were evaluated, in addition to traditional risk factors for CKD (i.e., smoking, heavy drinking, physical activity, hypertension, type 2 diabetes mellitus, urolithiasis, among others). Of 1514 included in the study, mean age 45, only 26 cases (1.7%) had an eGFR < 60 mL/min. When those with hypertension and type-2 diabetes or heavy proteinuria were excluded, the estimate fell to 0.9%. The findings are particularly interesting because it has been conducted in a setting with high frequency of environmental exposures that previously has been associated with CKDu. Exposures to agrochemicals and heavy metal are frequent in the region, and nearly 60 and 90% of the rural male dwellers reported previous pesticide exposure and having worked in agriculture, respectively. However, few individuals reported work in sugarcane.
The difference in exposure to severe heat strain in this Peru population, as compared to that of sugar cane workers in the Mesoamerica's, may be critical for explaining the marked difference in prevalence of CKDu.

In **Guatemala,** a population survey of CKD prevalence, and risk factors, on two rural agricultural municipalities; Tecpán and San Antonio has been reported. Sugar cane working was much more common (44%) in San Antonio compared to Tecpán (10%) but otherwise the villages appear rather similar. 807 individuals were enrolled and estimated 4.0% had CKD, (eGFR) less than 60 ml/min per 1.73 m^2. Overall diabetes or hypertension were the important factors associated with risk for CKD and also underweight (body mass index [BMI] <18.5). Unadjusted OR for sugarcane work was 10.2 and for 'lives in hot climate' 2.8 but when multivariable adjustments were made the significance disappeared, but a significant interaction existed between poverty and history of sugar cane agriculture was associated with increased odds of CKD in individuals with higher poverty levels [246]. Exposure assessment in this valuable study was not very detailed but nevertheless it agrees with what has been reported from many others in Central America; that CKD is not uncommon and affects poor agricultural workers with heat exposure in the sugarcane production.

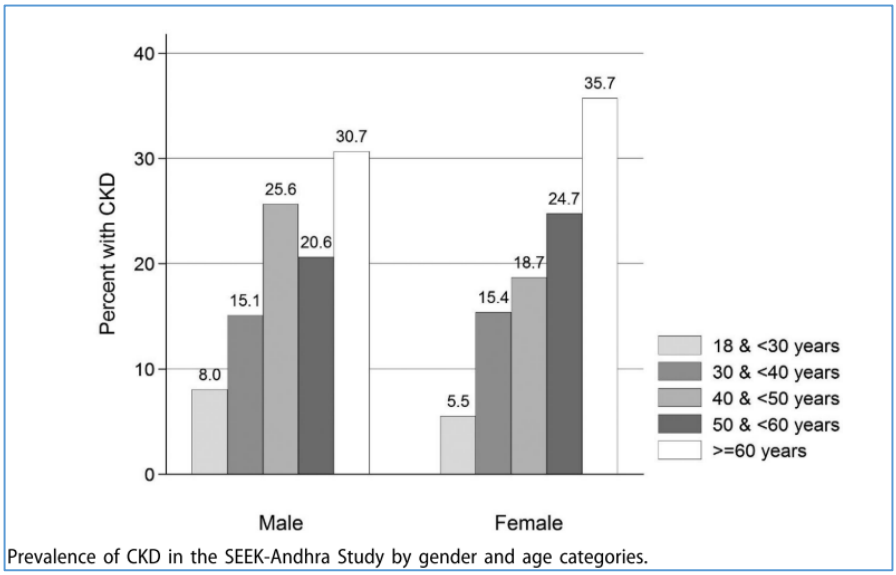
Mortality rates from CKDu appear to have increased dramatically since the 1970s. Heat exposure has, been suggested as possible causative, and/or contributing factor. To explore a possible association between heat and CKDu in Nicaragua data were collected at a weather station at a **Nicaraguan** sugar company where large numbers of workers have been affected by CKDu[247]. Comparisons with weather stations across Nicaragua demonstrate that this company is in one of the consistently hottest regions of the country. Trends in maximum and minimum temperatures during harvest months between 1973 and 2014 as well as in the number of days during the harvest season for which the maximum temperature surpassed 35 ◦C. Monthly averages of the daily maximum temperatures between 1996 and 2014 were also compared. The monthly average daily maximum temperature during the harvest season increased by 0.7 ◦C per decade between 1973 and 1990. The number of days per harvest season with a maximum temperature over 35 ◦C increased by approximately five days per year

between 1974 and 1990, from 32 days to 114 days. Between 1991 and 2013, the number of harvest days with a maximum temperature over 35 ◦C decreased by two days per year, and the monthly average daily maximum temperature decreased by 0.3 ◦C per decade. It is important to recognize that CKD is an insidious disease that is diagnosed late. It is therefore difficult to infer when in time previous excessive heat exposure may be anticipated to result in increased prevalence, morbidity and mortality in CKD. Nevertheless, it gives some hope for a more favourable development of the CKDu epidemic in this area if ambient temperatures are decreasing. But – on a global basis –evidence is showing that the average global temperature is rising.

The spatial distribution of CKDnt in Mesoamerica in relation to demographic, crop and climate data has been examined [248]. CKD mortality or hospital admissions data was available for five countries: **Mexico, Guatemala, El Salvador, Nicaragua, and Costa Rica**. There were regions within each of the five countries with elevated CKD burden. Municipalities in hot areas and much sugarcane cultivation had higher CKD burden, both compared to equally hot municipalities with lower intensity of sugarcane cultivation and to less hot areas with equally intense sugarcane cultivation. The finding of higher CKD burden in hot regions with intense sugarcane cultivation all five countries agree with studies identifying heavy physical labour in heat as a key CKDnt risk factor.

Recently it has been reported from **Taiwan** that the prevalence of a diagnosis CKDu is more common among farmers [249]. Data from a Community-based screening programme from 2005 to 2014 in Taiwan's largest rice-farming county. The study population included farmers and non-farmers aged 15-60 years. CKDu was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 at age under 60 years without hypertension, diabetes, proteinuria, haematuria or using Chinese herbal medicine. The prevalence of CKDu was 2.3% in the farmers and 0.9% in the non-farmers. The adjusted prevalence OR (POR) of CKDu in farmers compared with non-farmers was 1.45 (1.10-1.90). Dehydration (blood urea nitrogen-to-creatinine ratio >20) was found in 22% of the farmers and 14% of the non-farmers.

A remarkable, and alarmingly, high prevalence of CKD has been reported from **India** [38]. 1201 subjects from in the villages of Srikakulam district in Andhra Pradesh were examined. CKD was defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 using the CKD-EPI equation. Data for 1184 individuals was obtained, with a mean age of 45, where 44% were males. Overall prevalence of CKD was 32.2%. Working as a farmer had 20% more prevalence of CKD compared to non-farmers in a fully adjusted model. If confirmed the data on age related prevalence of CKD in Andhra Pradesh presented in this report (see figure to the right) are alarming showing age stratified prevalence of CKD in males and females surpassing the most severe hotspots of CKD in Central America, see e.g.[11]. A paper from Taiwan, above [249], report prevalence of CKDu of 2.3% in the farmers!



Prevalence of CKD in the SEEK-Andhra Study by gender and age categories.

In another report from **India**, from the Cuttack district of Odisha, comprising of 236 villages having total population of 172,119. Prevalence of CKD varied between villages and in a few (n=4) soared at 5

to 7%. Kidney biopsies were performed in six patients. All biopsies were suggestive of chronic interstitial nephritis with significant interstitial fibrosis and tubular atrophy [250].

Another paper summarizes the current state of knowledge around CKDu in **India**[251]. CKDu is reported from most regions in India; however, it is interpreted differently from the phenotype described from Central America and Sri Lanka. The differences include lack of a clear demographic or occupation group, older age of affected participants, and presence of mild hypertension and low-grade proteinuria. It is concluded that more data are needed to support the existence of a unique CKDu phenotype in India.

In a **Sri Lankan** paper the significance of *Mg-hardness and fluoride* in drinking water on CKDu was examined [252]. A total of 60 groundwater samples, 30 each, were collected from CKDu-prevalent locations and control locations where there are no CKDu cases reported. Water hardness, alkali (Na(+)+K(+)) and alkaline earth cations (Mg(2+), Ca(2+), Sr(2+), Ba(2+)) were relatively higher in drinking water sources used by CKDu patients, compared to the well waters used by healthy individuals. However nephrotoxic trace elements such as As, Cd, and Pb were found to be comparable in both types of wells and were well below the WHO permissible levels. In another Sri Lankan study potentially, nephrotoxic metals were analysed in rice obtained from 32 patients with 'acute interstitial nephritis without any known reason' [253]. Average Cd, As, and Pb was 0.18, 0.055, and 0.135 mg/kg, with ranges of 0.020-1.06, 0.012-0.222, and 0.003-0.744 mg/kg (on dry weight basis), respectively, well below the recommendations of FAO and WHO.

In another **Sri Lankan** study an attempt was made to assess hazardous exposures to metals by inductively coupled plasma mass spectrometry in areas with CKDu using duplicated diet sampling [254]. Sixty-two individuals participated. It is reported that Pb in rice, As and Pb in vegetables, and Cd in fish exceeded the recommended daily limits. As cadmium in fish, as in other meats, is always low, and no analytical quality assurance is presented, it is to be suspected that the analytical results presented are dubious. No human biological monitoring data are provided to support the findings.

Among sugarcane workers, cane cutters appear at greatest risk of MeN. One of the main proposed causal hypotheses has focused on the potential physical challenges faced by cane cutters, including strenuous physical exertion in extreme heat such that volume depletion in conjunction with other factors, such as muscle injury, results in recurrent episodes of subclinical kidney injury that eventually manifest with clinically apparent CKD. Using employment and medical data for male workers at a **Nicaraguan** sugarcane company, months of active work was classified as either work as a cane cutter or other sugarcane job and occurrence of dysuria, heat events and muscle events was determined [255]. Among 242 workers with 7257 active work months, 19.5% of person-months were as a cane cutter. There were 160, 21, and 16 episodes of dysuria, heat events, and muscle events, respectively. Compared with work months in other jobs, cane cutting was associated with an elevated odd (2.4) of experiencing dysuria. The number of heat and muscle events by cane cutter and other job were limited. It was concluded that working as a cane cutter, compared with other jobs in the sugarcane industry, was associated with increased dysuria, supporting the hypothesis that cane cutters are at increased risk of events suspected of inducing or presaging clinically evident kidney injury.

Urine specimens from 471 residents, aged 3 months to 89 years, in 4 rural agricultural communities in **Nicaragua** were examined [256]. The prevalence of leukocyturia was comparably high, increased with age and differed by community, ranging from 8.4% in San Marcos to 35.0% in Dulce Nombre de Jesus, which is in a agricultural area considered hyperendemic for MeN. Urine cultures were not taken. The high prevalence of leukocyturia could, according to the authors, support environmental exposures causing inflammation leading to reduced kidney function.

107 sugarcane workers in a thermally stressful environment were examined in **Guatemala** during a typical workweek [257]. Data were collected before and after work shifts on 6 uninterrupted days coinciding with the 6-day work week and the first day of next 6-day work week (day 8) after 1 rest

day. High wet bulb globe temperature and diastolic blood pressure were associated with increases in plasma creatinine across the shift indicating kidney strain. Consumption of water from chlorinated dormitory tanks and increasing number of rest breaks on the other hand were found to be protective against increases in creatinine. Also from Guatemala, the same group of investigators [258], measured cotinine levels in urine to assess smoking habits in agricultural workers, and noticed that self-reported smoking prevalence was much lower (12%) than indicated by biomonitoring (34%).

A Research letter to *KI Reports* presents how individual laboratory findings (including p-creatinine and creatine kinase) varies among sugarcane harvesters during a working week. 6% of the 103 workers had evidence of volume depletion. No specific lab findings were reported among these [259].

Body composition, the occurrence of anaemia, and kidney function has been examined in **Guatemalan** 203 male sugarcane workers [260]. Eleven percent of workers were at the level of essential body fat (2-5%). Anaemia was present among 13% of workers, 70% of which were normochromic normocytic. Anaemia was more common among those with lower BMI and fat free mass. The prevalence of elevated HbA1c was 21%. Twelve percent of workers had reduced kidney function with an eGFR < 90 mL/min/1.73 m^2, the eGFR was lower for those with anaemia than those without. It is suggested that anaemia, as well as undernutrition, have a role in the development of CKDu and interventions to improve nutrition for workers in low-resource settings should be considered.

The prevalence of decreased kidney function and risk factors CKDu was examined in three communities within the Tierra Blanca region, **Mexico** [261]. A cross-sectional study collected sociodemographic, occupational, medical and biometric data from 616 men and women aged 20-60 years. Kidney function was assessed by standardized serum creatinine and estimated glomerular filtration rate (eGFR). For 579 participants analysed the age- and sex-adjusted prevalence of low eGFR (<60 mL/min/1.73 m^2) was 3.5%. Agriculture was the occupation associated with the highest adjusted prevalence of low eGFR (8.8%). Working in agriculture was independently associated with more than a 5-fold risk of having low eGFR, after adjustment for age, sex, diabetes, hypertension, body mass index. It was concluded that 'The most outstanding risk factors in patients with CKDu in these regions are thought to be heat stress, cycles of repeated dehydration and extreme labour …'. Interestingly, but hard to understand, is a commentary in the journal where this report was published [262]states 'CINAC (suggested alternative name for CKDu, or MeN) which could be linked to exposure to toxic products such as herbicides (glyphosate and its metabolites being one potential culprit), heavy metals, infections or high altitude, all of them in the context of intense heat, although this may not be always the case since patients have been identified in regions with a temperate climate'

The renal function in migrant and seasonal farm workers, in the Northwest of **Mexico**, a semi-arid region with a growing agricultural industry was longitudinally assessed in relation to pesticide exposure, heat stress and dehydration [263]. 101 migrant and seasonal farm workers were enrolled, 50 worked in an organic certified area and 51 in a conventional area. 50 office workers served as a reference group. Urine and blood samples were collected from all workers in addition to demographic, behavioural, and occupational characteristics. The physiological strain index (PSI) was used to estimate workers' heat strain. Sampling was conducted at pre-harvest (March) and late in the harvest (July). A significant decrease in kidney function in the migrant and seasonal farm workers was seen compared to office workers. By the late harvest, one worker developed kidney disease, two suffered a kidney injury, and 14 were at risk of a kidney injury. eGFR decreased significantly from pre-harvest (125 mL/min/1.73 m^2) to late harvest (109 mL/min/1.73 m^2) ($p < 0.001$), while no significant change was observed in office workers. The eGFR dropped more in those who worked in the conventional field vs the organic field. Dehydration was associated with the decrease of eGFR. Decline in eGFR by job category (conventional/organic MSFWs and office workers) was related to an increase in heat

strain. As working in organic fields, where pesticides are not used, pesticide exposure should be considered in combination with heat stress and dehydration.

Two interesting publications from a CKD hotspot in **Mexico**, *Aguascalientes***,** has been published an original article [264]and an editorial comment [265]. Aguascalientes is a small state located at high altitudes in central Mexico, with a dry climate characterized by stable yearlong temperatures (average 19 °C) an environment, quite different from that of typical MeN affected areas elsewhere in Central America which is hot and humid. The incidence of initiating Renal Replacement Therapy (RRT) in 2019 was 336 per million inhabitants and year, which is not so remarkable, but the average age of 46 years is low. There was a bimodal distribution of the age at which RRT was initiated. The first and the most significant peaks are between the ages of 20 and 40 years and are usually the result of CKD of unknown cause (73%). Of patients in RRT glomerulopathy was an uncommon diagnose, whereas the cause was unknown in most of the RRT patients. Since 2012, 395 patients in the region had undergone diagnostic renal biopsy. This is group of biopsied patients is different from those in RRT as they do not have end stage renal disease necessitating RRT. In the biopsied group different types of glomerulopathy's were dominating and particularly in age span 1 to 30 years focal segmental glomerulosclerosis (FSGS) was remarkable common. In the commentary [265]it is suggested that the finding of many cases with FSGS in a high prevalence area of CKD in Mexico may give a clue to the cause om CKDu. It is speculated that large production and consumption of guava may have a role – but no evidence is provided.

Inflammation biomarkers of and signs of dehydration was examined in thirty-two agricultural workers in Homestead, **Florida, USA**, a large agricultural community in July-August 2017[266]. Urine specific gravity and kidney function were measured before and after work shifts on three subsequent days, and heat index, core body temperature, and heart rate were monitored during the work shifts. A participant was considered to have AKI if the pre- to post-shift change in serum creatinine was > 0.3 mg/dL or > 1.5 times the pre-shift value. AKI, as defined above, was seen in 15 of the workers. Participants with AKI had higher urine specific gravity at baseline. Reduced levels of uromodulin and sodium in urine and increased levels of interleukin-6 and C-reactive protein in serum were indicative of dehydration at baseline, and that dehydration, high body mass index, reduced urine uromodulin, and increased serum interleukin-6, C-reactive protein, and lipopolysaccharide-binding protein at baseline were predictive of acute kidney injury on subsequent workdays.

The prevalence and the risk of CVD in patients diagnosed with CKDu in **Sri Lanka** has examined [267]. A detailed medical history, blood pressure, electrocardiogram (resting and six minutes vigorous walking), echocardiograms, appropriate laboratory parameters and medical record reviews was considered for 119 patients with CKDu. In contrast to most other patients with CKDu, 97% of the CKDu patients were at low risk (<10%) for experiencing a cardiovascular event within the next 10 years. According to the authors CKDu patients are likely to survive long enough to reach end-stage kidney disease.

Also from **Sri Lanka**, reference values in children (10-18 years, n=909) for commonly used biomarkers of renal injury e.g., kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) are provided [268].

Additional work form **Sri Lanka** lend some support for virus infection have a role in the development of CKDu in this country. 116 small mammals were captured in CKDu endemic regions. Seven animals (five out of 11 Mus booduga and two out of 99 Rattus rattus) were PCR-positive for Thailand orthohantavirus (THAIV). According to phylogenetic analyses and whole-genome comparisons Mus-borne sequences belonged to a THAIV lineage, suggesting a novel orthohantavirus species. This genetic evidence indicates the presence of two THAIV-related viruses circulating in this CKDu endemic area, suggesting a basis for further investigations to identify the infectious virus in patients with CKDu and the CKDu induction mechanism of these viruses.

Heat stress symptoms and urine markers of chronic kidney disease (CKDu) have been investigated in **Sri Lanka** [269]. Totally 475 villagers were examined. In the endemic region, 293 were agricultural workers and 67 were not working primarily in agriculture. In the non-endemic region, 76 were agricultural workers. 218 were assessed for neutrophil gelatinase-associated lipocalin (NGAL). A heat stress index was highest among agricultural workers in the endemic region, intermediate in non-agricultural workers in the endemic region, and lowest among agricultural workers in the non-endemic region. Heat stress symptoms and NGAL values were higher among agricultural workers in endemic CKDu regions.

A survey of the prevalence CKD, and CKDu, in **Thailand** using data from a cross-sectional, nationally representative of the adult population provide enables interesting comparisons with populations more affected by the CKDu epidemic [270]. The prevalence of decreased GFR (< 60 ml/min, estimated from s-creatinine) without diabetes, hypertension, or severe proteinuria (here defined as CKDu2) was less than 1%, and higher in woman (.9%) compared to men (.6%). These prevalence estimates of CKDu are much lower than in CKDu effected regions.

A review [271] summarizes the *geographical distribution of CKDu* and its probable geochemical, behavioural, sociological, and environmental risk factors based on research related to hydrogeochemical influences on CKDu in **Sri Lanka**. More than 98% of CKDu patients have consumed groundwater as their primary water source in daily life which, according to the authors, indicate that groundwater is responsible for the disease. Apart from the hydrogeochemical factors, mycotoxins, cyanotoxins, use of some herbal medicines, dehydration, and exposure to agrochemicals which were alleged as risk factors. Sociological factors, including poverty, living habits and anthropogenic activities, may also provoke the emergence of CKDu. Therefore, the authors conclude, the interaction of geo-socio environmental risk factors should be sociologically and scientifically considered to prevent the prevalence of CKDu. In contrast to the ideas in this (above) report, another paper [272], also from Sri Lanka, after analysing total of 102 rice soil samples from main climatic zones viz. wet and dry zones including CKDu hotspots did not find any toxic, or hazardous, levels of metals. Also, from Sri Lanka [273] in a speculative review suggests that '*some pesticide metabolites'* interacts with 'certain renal enzymes' but to mot provide any evidence that this any clinical or whatsoever importance.

A **Sri Lanka** study report on the progression of CKDu[274]. Records of 379 CKDu patients from 2005-14 at Girandurukotte, an endemic area for CKDu were analysed. Mean age was 53 years, male-to-female ratio of 2.5. Mean follow-up period was 85 months. The annual eGFR decline varied from 0.3 to 10.5 mL/min/1.73 m^2/year. Faster eGFR decline rate was seen in younger patients, those that had a higher eGFR at start, and smoked. It was suggested that continued exposure to environmental risk factors influence the rate of progression, but no evidence for this is presented. Nevertheless, this report show that patients diagnosed with CKDu in Sri Lanka relatively often deteriorate quite rapidly in eGFR.

A field test of using the **Disadvantaged Populations eGFR Epidemiology (DEGREE) protocol**[181]has been carried it on outdoor Hispanic workers in the USA [275]. Fifty workers were interviewed and examined in Houston. Administration of DEGREE and CKDu questionnaires averaged 10 and 5 min, respectively, with all questions easily understood. Implementation of DEGREE and the new CKDu module was straightforward and well understood.

Clinical and experimental studies

A 5-to-7-year follow-up of eGFR in 26 patients, with biopsy-confirmed Mesoamerican nephropathy (MeN) from **El Salvador and Nicaragua** has been reported [33]. The mean eGFR decline was -1.7 mL/min/1.73 m^2 per year, with 15 % of participants having a rapid progression, 35 % a decline in eGFR between -5 and -1 mL/min/1.73 m^2 per year, and 50 % stable or improved eGFR. Individuals with moderate/severe interstitial fibrosis in biopsies had a higher risk of progressive disease, and

segmental sclerosis and albuminuria were more common in patients with rapid progression and may indicate a more active disease.

In a shoe-making factory in West Java, **Indonesia** 119 heat exposed workers were followed with measurements ty of urine specific gravity and early indicators renal heat stress; urinary nephrin and urinary kidney injury molecule-1 (KIM-1) Subjects were indoor heat-exposed to a wet-bulb globe temperature (WBGT) of 28-30 degrees C for 8 hours daily with 1 hour break, 5 days a week. There were 15 (12.6%) subjects who had eGFR <90 mL/min, but >/=60 mL/min. High serum vasopressin levels were found in 79 subjects with a mean of 6.5 ng/mL. Most subjects had nephrinuria (87.4%) with preserved renal function (87.4%). Several subjects had elevated urinary KIM-1 (10.9%) and albuminuria (7.6%). A cut-off value of >/=1.018 for urine specific gravity has sensitivity of 71.2% and specificity of 80% for detecting elevation of urinary nephrin levels. It was concluded that a urine specific gravity cut-off value of >/=1.018 could be used to detect nephrinuria among heat-exposed workers.

A review on renal pathology in MeN/CKDu

Publications from renal biopsy studies related to CKDu - Sri Lanka and Mesoamerican nephropathy in thirteen studies have been assessed [276]. Interstitial fibrosis was the seen in all studies. Tubulointerstitial and glomerular abnormalities showed a more variable distribution. No characteristic histopathological feature was reported other than a proximal tubular lysosomal inclusion body which was claimed to indicate a toxic etiology. Three main pathogenetic mechanisms were postulated: repeated acute insults leading to scarring, low-grade chronic insults leading to non-inflammatory fibrosis, and tubulointerstitial damage in combination with glomerular injury. The interpretation and comparative analysis of these studies are hampered by the heterogeneity in case selection and biopsy reporting. No characteristic histopathological feature could be found. There are noticeable differences between in CKDu-Sri Lanka or Mesoamerican nephropathy, in the frequency and severity of the glomerular and tubulointerstitial changes which warrant more explorative studies preferably on kidneys in early stages of the disease.

Overview/review/discussion papers

Reviews and discussion papers on MeN/CKDu are continuously being published, e.g. *Demystifying Chronic Kidney Disease of Unknown Etiology (CKDu): Computational Interaction Analysis of Pesticides and Metabolites with Vital Renal Enzymes* [273], *Kidney developmental effects of metal-herbicide mixtures: Implications for chronic kidney disease of unknown etiology* [200], and *The Utility of Novel Renal Biomarkers in Assessment of Chronic Kidney Disease of Unknown Etiology (CKDu): Mesoamerican nephropathy: A not so unknown chronic kidney disease*[277] *A Review* [240] but really does not add much for the understanding of this disease and CKD epidemic.
There are really a lot of them now – review papers that make attempt to summarize and conclude about what is often considered as an enigmatic disease. ‘Chronic Kidney Disease of Unknown Origin: A Mysterious Epidemic’ is a recent example [278]. After eight pages of text and 58 references the authors conclude ‘*As a definitive etiology has not been postulated for CKDu to date, this comprehensive review was undertaken to throw light on the poorly understood epidemiologic risk factors and the course of the disease.’* Another similar review [279] ‘*critically reviewing relevant primary studies*’ concludes, ‘*The current body of evidence for any aetiological agent as the cause of CKDu in Sri Lanka is limited. Further research with stronger study designs is necessary to increase knowledge of aetiology of CKDu in Sri Lanka to identify and eliminate exposure to possible causative agent(s) prior to concluding that the disease is multifactorial.* Likewise [280]in a ‘multi-pronged research on endemic chronic kidney disease of unknown etiology in Sri Lanka: a systematic review’ summarizes as follows: ‘*This compilation of research studies on CKDu in Sri Lanka has explored the probable causative agents of the disease, yet present conflicting conclusions on CKDu etiology. Thus, relevant, well-planned, high-quality research studies are critically warranted. However, the research findings reported here, it may be hypothesized that CKDu is a multifactorial disease linked to the environment, agricultural practices, and genetic predispositions.*’

Most of the review from Sri Lanka tend to emphasise that we don't know what is causing the CKDu/MeN epidemic and often suggest rather far-fetched hypothesis whereas a review in Spanish from Central America in Nefrologia is more specific and useful [277].

The unresolved epidemic of chronic kidney disease of uncertain origin (CKDu) around the world: A review and new insights [281] is a relatively extensive non-systematic review. However, the 'clinical presentation' of CKDu is not in full concert with what has been reported by others and neither the conclusion that 'mounting body of evidence suggesting that the disease may be the result of exposure to a variety of water contaminants combined with volume depletion'.

In a '*Scoping review on Heat Stress and Kidney Function in Farmworkers in the US*. [282] found evidence that more work is needed within the US to understand the relationship between working in the heat and kidney function in agricultural and other workers who experience high heat conditions at work and are susceptible to the deleterious effects of working in heat.

A review paper in the major European kidney journal, NDT [283] points out climate change should be of special concern for the nephrologist as the kidney has a critical role in protecting dehydration, and that there is increasing evidence that climate change and heat stress may be involved epidemics of chronic kidney disease of uncertain etiology in various regions of the world, including Mesoamerica, Sri Lanka, India and Thailand.

A systematic review and meta-analysis of population-level prevalence studies in South Asia (**Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, India, Pakistan, and Sri Lanka**) indicate that the pooled prevalence of CKD among the general population was 14%. The proportion of CKD of unknown origin was 8%. The prevalence of CKDu in the endemic population was 8% [284]. According to the authors of this repost CKD represents a serious public health challenge in South Asia, but no conclusions nor suggestions of its cause is presented.

As I see is, and I hope those that care to read this summary report agree, we do have come further than most of these reviews suggest, regarding the cause, consequences from and prevention of MeN and CKDu.
A recent and excellent review with title *Occupational heat exposure and the risk of chronic kidney disease of non-traditional origin in the United States* published in November 2021 [285]. This review comes much further than most of the extensive but superficial overviews and concludes as follows; *'Occupational heat exposure is linked to the development of kidney injury and disease in individuals who frequently perform physically demanding work in the heat. For instance, in Central America, an epidemic of chronic kidney disease of non-traditional origin (CKDnt) is occurring among manual laborers, whereas potentially related epidemics have emerged in India and Sri Lanka. … One of the leading hypotheses is that repetitive kidney injury caused by physical work in the heat can progress to CKDnt. Whether heat stress is the primary causal agent or accelerates existing underlying pathology remains contested. However, the current evidence supports that heat stress induces tubular kidney injury, which is worsened by higher core temperatures, dehydration, longer work durations, muscle damaging exercise, and consumption of beverages containing high levels of fructose'….* and states in the end '*Overall, the surprisingly limited available evidence characterizing occupational heat exposure in US workers supports the need for future investigations to understand this risk of CKDnt'.*

2022

According to a report from Georgia, USA chronic kidney disease of unknown aetiology (CKDu) has also been seen in immigrants in the United States who work in agricultural occupations.
[286]. Fifty undocumented immigrants receiving emergent-only hemodialysis were interviewed about their work history. The average age was 49.5 years (SD +/- 11.5), and the majority (52%) were female and originated from Mexico (66%). In decreasing order of frequency, the interviewed occupations with documented renal toxicant exposures, such as applying pesticides in landscaping, heat exposure in agriculture, construction, landscaping, and dry cleaning, and lead paint fumes in construction.

The relationship between creatinine and cystatin C based estimated glomerular filtration rate (eGFR) in actively working sugarcane cutters was examined in 458 sugarcane cutters from **Nicaragua** and **El Salvador** [287]. Serum samples were taken before and at end of harvest seasons and analysed for creatinine and cystatin C. The mean eGFRcr was significantly higher than eGFRcys in both cohorts; absolute difference 22 mL/min/1.73 m^2 in Nicaragua and 13 mL/min/1.73 m^2 in El Salvador. It is suggested that the discrepancy between eGFRcr and eGFRcys may indicate reduced glomerular filtration of larger molecules and/or systemic bias in CKD-EPI performance in this population. Overall, all eGFR calculations showed a similar decrease from before to end of harvest of about 3% in El Salvador, and a decrease of about 4% in Nicaragua. This is in accordance with several other reports, which show that occupational cane cutting cause a decrease in the renal function.

Assessment and evaluation of a Workplace Intervention for Heat Stress programme in a major sugar mill located in Chichigalpa, **Nicaragua**, has been presented [28]. This mill produces refined sugar, ethanol, rum, and power for the grid. The mill has a fully equipped hospital and laboratory that attends to workers and their family's health needs (free of charge) and likely captures all hospitalized acute kidney injury (AKI) in the workforce. Around 3000 manual field laborers are employed in the cultivation and harvesting of sugar cane, the majority hired for the 6-month harvest period, but many are hired throughout the year for specific manual jobs as needed. Workers are not migrants and are drawn from many small communities in the area. The climate during the harvest months of November–April is hot and relatively humid. Temperatures in the sugarcane fields rise rapidly and reach about 34 ◦C by about 10 a.m. (wet bulb globe temperature–WBGT, 30 ◦C) and 37 ◦C at 2 p.m. (WBGT 31 ◦C). The prevention program key components were:

1. Acclimatization for a 2-week period at the start of harvest,
2. Stopping work at noon or as shortly after as possible,
3. Regular rest breaks that varied by job type, and
4. Shade tent along with a water reservoir and electrolyte solution for each work group.

Albeit this prevention programme faced many problems and obstacles threw out and there many possibilities for improvements it should be regarded as a success. After introduction of the prevention programme cross-harvest kidney injuries dropped from 27 to 7% among workers at the highest risk (Burned-cane cutters) and hospitalizations for AKI from a harvest incidence of 9.4% to less than 1%.

Sugarcane workers in Mesoamerica are at high risk of chronic kidney disease and several studies have shown increasing serum creatinine levels during harvest, something which may be a sign of acute kidney injury. In a report from **Nicaragua** examines whether increase in S-Cr is associated with more specific markers of kidney tubular and interstitial injury and function, during prolonged heat stress among workers at high risk of chronic kidney [288]. Urine monocyte chemoattractant protein-1 (MCP-1), kidney injury molecule-1 (KIM-1), calbindin, glutathione S-transferase-pi (GST-pi), clusterin, interleukin 18 and albumin, fractional excretion of potassium (FEK), blood haemoglobin, serum potassium, ferritin and erythropoietin were measured before and after harvest in a sample of 30 workers with an S-Cr increase across harvest (cases), and 53 workers with stable S-Cr (controls). Urine MCP-1, KIM-1, calbindin, GST-pi, albumin, and FEK increased in cases, whereas blood haemoglobin and serum erythropoietin decreased. This study provides additional support that workers regularly exposed to heat stress develop acute kidney injury in and that repeated injury may initiate the development of MeN/CKDu.

A study from **Costa Rica** to evaluate heat exposure, dehydration, and kidney function in rice workers provide results which are consistent with the hypothesis that occupational heat exposure is a critical risk factor for CKDu in Mesoamerica [289]. Biological and questionnaire data were collected from male field (n = 27) and other (n = 45) workers from a rice company where chronic kidney disease of unknown origin (CKDu) is endemic. Field workers were above recommended limits for occupational heat exposure during most of the shifts. Dehydration (USG≥1.025) was common in both groups, but field workers were more exposed to heat and had higher workloads. Low eGFR (<60 mL/min/1.73 m^2) was more prevalent in field workers at start (19% vs. 4%) and follow-up (26% vs. 7%), and field

workers experienced incident kidney injury (IKI) more frequently than other workers: 26% versus 2%, respectively.

In June 2022 Erik Hansson, in a thesis report [39], presented his extensive research work, carried out together with several other of the key investigators on MeN/CKDu/CKTnt, in **Nicaragua and Central America**, using different perspectives and methods. An ecologic study found that hot, sugarcane-cultivating regions had elevated chronic kidney disease (CKD) mortality. In a longitudinal workplace study, kidney injury incidence was higher among sugarcane harvest workers with high physical workload and decreased with an intervention reducing heat stress. Low liquid intake and consumption of NSAIDs were additional risk factors for kidney injury. Kidney injury coincided with fever and elevated levels of inflammation biomarkers, suggesting inflammation-mediated injury. The findings are consistent with excessive heat strain from high internal heat production and external heat load being a main cause of the Mesoamerican epidemic of CKD of non-traditional origin (CKDnT).

I another report from **Salvadoran and Nicaraguan** sugarcane cutters Hansson et al 2022 [290] attempts to identify easily available early markers of rapid kidney function decline in a population at high risk of CKDnt. 39 male Salvadoran sugarcane cutters sampled on several occasions before and after work shift during harvest. Results obtained were compared with previous results from371 male Nicaraguan sugarcane cutters sampled as part of routine monitoring program. Cutters worked at high physical intensity at wet-bulb globe temperatures mostly above 29 degrees C for 6-8 hours per day 6 days a week during the 5-6 months harvest season.: Dipstick leukocyturia after work shift in the El Salvadoran group was the most promising marker of change in estimated glomerular filtration rate across the harvest season, explaining >25% of the eGFR change(cross-harvest). Leukocyturia was also associated with experiencing fever, little or dark urine, cramps, headache, dizziness and abdominal pain in the preceding 2-week period. Decreasing blood haemoglobin (Hb) and eGFR during harvest were also predictive of eGFR loss. In the Nicaraguan confirmation dataset, those having leukocyturia at any sampling during harvest had a 13 mL/min/1.73 m^2 drop in eGFR.

In a case report from the USA typical CKDu/MeN is described in a migrant from **Nicaragua** [291]. An unemployed poor 39-year-old male, who had a history of gout, presented at the emergency department with elevated creatinine and uric acid levels, but low potassium and magnesium levels in plasma. He had mildly elevated blood pressure of 137/87 and normal urinalysis, but trace protein. Renal biopsy revealed moderate chronic tubulointerstitial nephropathy and secondary focal global glomerulosclerosis with glomerulomegaly. Findings like those in patients with MeN in El Salvador and Nicaragua. Unfortunately, occupational history was not available.

According to one retrospective study CKDu may occur also in **Panama** [292]. From 224 patients with CKD a group of 15 patients were diagnosed according to diagnostic criteria proposed by PAHO [113] with CKDnt (same as CKDu), These patients were compared to 91 patients with CKD of traditional causes. Patients with CKDnt had a median age of 58 years which was lower than a median of 71 for patients with identified causes of CKD. Patients with CKDnt significantly more often had a history of being agricultural (60%) and transportation (20%) workers, than patients with identified causes of CKD.

The Mesoamerican Nephropathy Occupational Study (MANOS) is a prospective cohort study of CKDu among agricultural and non-agricultural workers in **El Salvador** and **Nicaragua**. A report [293] describe cohort recruitment, baseline data collection, and CKDu prevalence Workers with no known diabetes, hypertension, or CKD were recruited from sugarcane, corn, plantain, brickmaking, and road construction industries (n = 569). Prevalence of CKD at baseline was unexpected high; 7.4%, and highest among Salvadoran sugarcane workers (14.1%), followed by Salvadoran corn (11.6%), and Nicaraguan brickmaking (8.1%). As often observed in other cross-sectional studies the prevalence of CKD (eGFR< 60 ml/min) increased markedly with age; in agegroup18–24 (0.6%), 25-34 (5.6%), and 35-45 /18.4%). As no quantitative data on previous occupational exposures (such as years of work in sugarcane) was available in this cohort it is impossible to infer if lowered eGFR had any relation to

previous such exposures, but future follow-up studies may give useful information on risk factors and the role of hazardous exposures for a deteriorating renal function (GFR).

In **Mexico** a high prevalence of CKDu has been seen in Aguascalientes. In a cross-sectional study of serum creatinine, and the albumin:creatinine ratio (ACR), was determined in 513 school students aged 10 and 17 years old [294]. A kidney biopsy was performed in patients with persistent albuminuria. The prevalence of persistent albuminuria was 3.7%. Only one individual had a decreased GFR. Eighteen kidney biopsies were performed; 72% had glomerulomegaly and only one patient had mild fibrosis. Podocyte abnormalities were evident on electron microscopy, including partial fusion (100%), microvillous degeneration (80%) and increased organelles (60%). The authors suggest that exposure to environmental toxins such as pesticides, even prenatally, may be responsible for this pathological entity, but also 'family clustering'[295]. It is hard to know to what extent these observations of young students have with proteinuria has any bearings on the MeN/CKDu epidemic in other regions of Central America.

In **Sri Lanka** 39 locally blended black tea samples were collected from a village where chronic kidney disease with undetermined origin (CKDu) is prevalent. The fluoride content in tea was around 2 mg/l and with groundwater in many dry zone regions in Sri Lanka showing high fluoride levels that exceed 0.5 mg/L, the additional daily intake can rapidly exceed recommended thresholds of 2 mg/day [296]. This amount of fluoride may perhaps cause dental fluorosis in some individuals, but in contrast to what is suggested in this paper fluoride has not been linked to ant form kidney disease.

Two reports from **Sri Lanka** addresses the issue of trace metals as being a cause of, or contributing to, the development of CKDu. In one study [297] samples of rice consumed by 32 clinically diagnosed CKDu cases were analysed for possible nephrotoxic trace elements. The results revealed that the mean values of Cd, As, and Pb consumed by patients were low. In another report [298]102 rice soil samples were collected from main climatic zones viz. wet and dry zones including CKDu hotspots. It was concluded that rice soils are not alarmingly contaminated with toxic trace elements.

Duplicated diets from 62 individuals in an area of **Sri Lanka** where there is a high incidence of CKDu has analysed by inductively coupled plasma mass spectrometry[254]. After a lot of measurements of nine different metals including Cd, Pb and calculations of likely daily intake, and it's variation between individuals it is concluded that 'potential dangerous effects' from Cs and As are minimal. But that protective measurements against Pb are recommended.

In another report from **Sri Lanka** hydrogeochemical factors controlling the occurrence of chronic kidney disease of unknown etiology (CKDu) was examined [299]. Groundwater from CKDu endemic areas had significantly higher Si (average 30.1 mg/L) and F (average 0.80 mg/L) concentrations than those of non-CKDu groundwater (average 21.0 and 0.45 mg/L, respectively). Not that much of a difference as I see it and disagree on the conclusion in this paper 'This study highlights the CKDu potential risk factors regarding groundwater geochemistry and their enrichment factors, which helps in preventing the prevalence of CKDu.'

Whereas most investigators nowadays tend to rule out the possible role of metals for development of CKDu/MeN this has been examined in **Guatemala** [300]. Urinary metals (arsenic, cadmium, nickel, and uranium) were examined in 222 sugarcane cutters. Arsenic, cadmium, and nickel were detected in the majority of the 340 urine samples and were generally within limits previously considered not be nephrotoxic. However, a few significant associations were found between, e.g. between urine cadmium and eGFR and urinary neutrophil gelatinase-associated lipocalin (NGAL), and urine arsenic was associated with eGFR. In the case of cadmium confounding from age and smoking is likely to occur, and for urine arsenic speciation and consumption of seafood need to be considered.

In another report from **Guatemala** [301] it is shown that adults living in rural areas are considerably shorter in length than in North American population that has been used to calculate the eGFR formulas (CKD-EPI) equation). The mean height in rural Guatemala was 151 cm, compared with 170 cm in the North American CKD-EPI cohort. Mean weight was 62 kg compared with 82 kg and BSA was 1.57 m^2 compared with 1.93 m^2. If adjustments for individually calculated BSA is made prevalence of individual eGFR in small individuals become lower and the prevalence of CKD in the population increases,

Experimental work

Silica nanoparticles (SiNPs) released during the burning of sugarcane have been postulated to have a role in CKDu/MeN. To test this in animals 200- or 300-nm amorphous SiNPs was administrated twice weekly (4 mg/dose), or vehicle by oropharyngeal aspiration for 13 wk to rats. Both sizes of SiNPs caused local inflammation in the lung and kidney and were detected in the serum and urine. Both sizes of SiNPs caused kidney damage, with early tubular injury and inflammation (at week 13) that continued to inflammation and chronic fibrosis at week 26 despite discontinuation of the SiNP administration. The findings give some support to the hypothesis that human exposure to amorphous silica nanoparticles found in burned sugarcane fields could have a participatory role in CKDu. However, oropharyngeal aspiration of SiNPs in rats is a considerably different type of exposure as that from inhalation of silica nanoparticles released from burning of sugarcane.

In a paper, which comprise a mix of a clinical observational, epidemiological, and animal experimental results, it is suggested that paraquat may be the culprit for CKDu/MeN [302]. In the clinical part 52 migrants with Mesoamerican Nephropathy (MeN) suspected as being the cause of kidney failure necessitating dialysis treatment were identified. Renal biopsy material was available from 6 to 8 of these patients. In a cross-sectional study comparison was made regarding several factors with demographically similar patients with kidney failure from other causes (n=63), and age/sex/place of origin-matched healthy participants (n=16). In an experimental part mice (n=73) received 10-15 weekly intraperitoneal injections of paraquat (a reactive oxygen species-generating herbicide) or vehicle. Patients with suspected MeN and kidney failure were young agricultural workers, almost exclusively men; the majority were from **Mexico and El Salvador**; and (27%) had prior exposures to agrochemicals, including paraquat. But possibly also many other types of exposures, such as heat strain, but this was not assessed or discussed in this report. Nevertheless paraquat-treated male mice developed kidney failure and tubulointerstitial nephritis consistent. Paraquat is an infamous highly toxic substance giving rise to multiorgan inflammation and damage. Thus, tubulointerstitial nephritis in paraquat exposed mice is an expected finding but provide no evidence that paraquat is the cause of end-stage renal disease in tentatively caused by MeN.

The capacity of different eGFR creatinine, and cystatin C, based formulas to accurately estimate the iohexol measured GFR has been 50 men in **Nicaragua**, living in MeN endemic areas [303]. Bias and misclassification was considerable for several of the commonly used formulas for eGFR in MeN/CKDu research in the region, in particular that using only cystatin C, whereas a new creatinine and cystatin eGFR formula which do not use any ‘race term’[304]perform better. That cystatin C based formula tend to underestimate GFR is in accordance with another comparison of eGFR calculations of in 458 sugarcane cutters from Nicaragua and El Salvador [287]

Overview/review/discussion papers

Baseline characteristics including socio-demographic details, risk factors, disease characteristics and laboratory measurements were compared between urban and rural participants in The **Indian Chronic Kidney Disease (ICKD) study** enrolling patients with estimated glomerular filtration rate (eGFR) 15-60 mL/min/1.73 m^2, or >60 mL/min/1.73 m^2 with proteinuria [305]. Of total of 4,056 patients with a mean age of 50 years, 67.2% were males, two-thirds of patients lived in rural areas and the median eGFR was 40 mL/min/1.73 m^2. About 87% were hypertensive, 37% had diabetes, 22% had CVD,

6.7% had history of acute kidney injury and 23% reported prior use of alternative drugs. Diabetic kidney disease, chronic interstitial nephritis (CIN) and CKD-cause unknown were the leading causes. Rural participants had more occupational exposure and tobacco use but lower educational status and income. CIN and unknown categories were leading causes in rural participants. CKDu, as used in this summary report, was not mentioned in this Indian report. But CKDu was discussed in a review entitled '*Chronic kidney disease of unknown etiology in **India**: a comparative study with Mesoamerican and Sri Lankan nephropathy'* [306] which unfortunately adds nothing new, or that has already been written in a great number of reviews before.

A systematic literature review of 119 publications on CKDu in **Sri Lanka** indicated the absence of a comprehensive plan of action to mitigate this situation [307]. A "One Health" approach is suggested as a potential way forward to alleviate the CKDu epidemic in Sri Lanka. This enables the representation of multiple causative agents (and interactions thereof) among environmental, animal, and human systems, in concert with the "exposome" that provides the totality of exposure the individual has undergone since birth. – not an easy task as I see it!

A review entitled *Rising of a global silent killer: critical analysis of chronic kidney disease of uncertain aetiology (CKDu) worldwide and mitigation steps* analysed more than 200 articles to understand the disease responsible for more than 30,000 and suggest further studies to overcome the mysterious nature of this disease [308].

An interesting approach to find out where important research on if exposure to heat can impact kidney health has been taken [309]. A total of 226 published articles related to the impact of heat on kidney health were identified as of November 20, 2021. Research on heat-related kidney injury has witnessed rapid development in recent decades, motivated by the emergence of chronic kidney disease of unknown etiology and climate change. Most of these articles (93%) were published within the last decade. The United States was the most prominent country in terms of research productivity and collaboration.

A text in UNDARK by Reveley provide more personal and social consequences of CKDu in poor El Salvador communities [310]

2023

Self-reported CKD, and work-related CKD, and suspected CKDu risk factors were collected from 9,032 workers in the Central American Survey of Working Conditions and Health. High physical work demands were associated with work-related CKD [311]. The majority of work-related CKD were reported in the western parts of Honduras and Nicaragua, in hot temperature regions, and overlapped with those areas with a high density of CKDu risk factors.

Overview/review/discussion papers

An overview of plant species used traditionally in Mesoamerica by Mayan groups to treat kidney-related conditions has been presented [312], but no results (bad or beneficial) from its use is presented.

The International Society of Nephrology Consortium of Collaborators on CKDu in early 2023 in *Kidney International* reported on challenges and opportunities in interventions for chronic kidney disease of unknown origin (CKDu) [313]. It is summarized that the disease was first described two decades ago, much of the pathophysiology remains unclear, and that a leading hypothesis is occupational exposure to recurrent heat stress leading to recurrent acute kidney injury (AKI). The Consortium presents the few trials on prevention of CKDu that has been published and give suggestions, and advice, how to perform useful interventional research on prevention and treatment of CKDu. Nonrandomized intervention study designs are likely to continue to play an important role.

In an excellent multiauthor review ‘Climate change and nephrology’ causes, pathogeneses, and clinical findings, including renal effects from classic heatstroke, exertional heatstroke and heat-related illness is presented in NDT in early 2023 [314]. CKDu is presented and discussed in detail and about etiology it is concluded that it represents a type of heat stress–related injury. Often subjects develop subtle injury to their kidneys each day while they are in the field that causes CKD over time, or they may have an occasional more severe AKI that progress to CKD. Evidence for supporting this theory is listed below.

- There is evidence, especially in Sri Lanka and Mesoamerica, that the epidemics are not simply due to better diagnosis and recognition, but rather represent a true increase in the prevalence of CKD since the 1970s and 1980s.
- The sites where CKDu is occurring typically represent some of the hottest areas in the region.
- Occupations with a high CKDu prevalence are associated intense heat exposure and symptoms of dehydration are common.
- Cross-shift studies in Mesoamerica that individuals are often becoming mildly dehydrated and develop cross-shift evidence for acute reductions in kidney dysfunction and the development of hyperuricemia and similar findings have been demonstrated for volunteers who exercise in the heat.
- In rats, CKD has experimentally been possible to induce by repeated exposure to heat and dehydration.
- There is increasing evidence that measures to reduce heat stress, such as the implementation of better hydration, shade and rest, can reduce the frequency of individuals developing cross-shift

Additional review papers and proceedings from meetings on CKDu and MeN that may be relevant to cite and consider

First International conference on Mesoamerican Nephropathy 2013 in Costa Rica [12] [13] [14].

Second International conference on Mesoamerican Nephropathy 2015 [315, 316].

Report from the Third International Workshop on Chronic Kidney Diseases of Uncertain/Non-Traditional Etiology in Mesoamerica and Other Regions. [317]

Thesis of Julia Wijkström, which present clinical and renal morphology data from patients with CKDu from three counties, El Salvador, Nicaragua and Sri Lanka [318]

A text on Mesoamerican Nephropathy [319]is presented, and repeatedly updated, in the clinically much used web-based Evidence based Clinical decision support UpToDate https://www.uptodate.com/home

Jah and Modi in a review paper for Kidney International [320]. The estimated global crude prevalence of CKD was about 150 per million in 1990, which increased to 275 per million cases in 2016. This change in prevalence is mostly related to ageing. It is pointed out that the adverse health impact from CKD is not limited to end-stage kidney failure.

A recently published review '*A Systematic Review of Complications Associated With Percutaneous Native Kidney Biopsies in Adults in Low- and Middle-Income Countries* '[321] is very relevant as renal biopsies has been made used in several studies on MeN/CKDu. Thirty-nine studies on a total of than 19,500 renal biopsies from 18 countries were assessed in this systematic review. Hematomas and gross haematuria after the procedure was seen in 1-2% of the patients, transfusions were needed in 0.2% and nephrectomy was rare; 0.04%. Fatality was one ten thousand. It was concluded in this review complications associated with kidney biopsies are low and that its use for making diagnosis and decisions on treatment should be promoted.

In 2014 a previously ill-defined autosomal dominant renal diseases which originate from tubular cells and lead to tubular atrophy and interstitial fibrosis was described in more detail [322]. Ten families were examined, and specific mutations was found in 7 of 9 families. Based on clinical and pathological characteristics we propose the term 'Autosomal Dominant Tubulointerstitial Kidney Disease' was suggested. The morphological changes described to are not identical but share similarities with those seen in MeN.

Kew at el already in 1970 reported that acute renal damage was a common and important complication of heatstroke among South African goldminers, but that this sometimes may progress to CKD. The effects of heatstroke on renal structure and function have been studied in 40 Bantu goldminers. During the acute stage all showed evidence of renal damage, which was classified as mild in 19, moderate in 12, e 10 of those with moderate damage have been followed for periods of up to four years with serial studies of renal function and structure. In most of both severe and moderate cases the impaired renal function of the acute stage was completely reversible, and renal histology either returned to normal or showed only a minimal degree of residual patchy interstitial fibrosis. However, four of the patients subsequently developed chronic progressive interstitial nephritis with persistent or progressive impairment of renal function [323].

Reports of nephrotoxicity from pesticides are rare [324]. In the chapter on Organic solvents, silicon-containing compounds, and pesticide, in Clinical Nephrotoxins. Renal Injury from Drugs and Chemicals by M. E. De Broe and G. A. Porter, present that AKI from pesticides is mainly seen in connection with full-blown systemic toxicity from pesticides. Nothing about renal toxicity is mentioned a chapter on occupational risk from pesticide use in Zenz classical textbook on Occupational Medicine [325].

A special issue in the Lancet [326] was in 2018 devoted to health consequences of climate change. In this report focus is given to decreased outdoor labour productivity and migration and socio-economic

consequences. Soma attention is given to the possibility of an increase of infectious diseases, such as dengue fever. Kidney diseases and CKD is not discussed.

Some aspects on using p-creatinine and/or cystatin to estimate the glomerular filtration rate (GFR).

Measurement of plasma or serum) makes it possible estimate the glomerular function (eGFR) with reasonably accuracy. Age and gender must be considered, and a sophisticated formula used; usually the so-called CKD-epi formula. In the US also ethnicity, black or non-black, is needed. Measurement of a cystatin C, a small plasma protein, can also be used for eGFR with similar good accuracy. A thorough systematic review on which estimate of eGFR that provided the best accuracy under different conditions (age, gender and various GFR ranges) from Sweden [327, 328] concluded that creatinine and cystatin C provide equally and reasonably accurate eGFR, and that the average of these to eGFR (creatinine) and eGFR (cystatin C) is even more accurate.

eGFR from cystatin C has some important advantages though, it's not influenced by muscle mass or ingestion of meat and creatinine rich food such as meat goulash. A few hours after a goulash serving containing 250-300 of meat the p-creatinine concentration double [329]. An increase in p-creatinine of about 20 umol/l is typically seen 3-4 h after meat containing meals as compared to non-meat meals, whereas cystatin C remains unchanged [330]. Heavy physical exercise may also change the p-creatinine concentration. After a marathon run, or worse, p-creatinine on average may increase with 10-30 umol/l [331] whereas the increase in cystatin C is much less pronounced [332].

Another, and often neglected, factor when interpreting p-creatinine changes and eGFR, is that the calculations behind eGFR presume a stable renal function (GFR). A sudden drop in GFR will not result in increasing p-creatinine until sometime has passed. This because of basic pharmacokinetic principles. When assessing and treating acute kidney injury specific formulas, based on the change of p-creatinine over time, has been suggested to calculate the actual change in GFR [132]. From a model of the pharmaco-kinetics of creatinine, which is produced at a more or less constant rate from the muscle cells, I've calculated that a sudden 50% drop in the GFR will produce merely a 20% increase in creatinine after 8h. This latency of achieving a new steady-state level of creatinine in plasma (enabling accurate eGFR calculations) possibly hold true also for p-cystatin C.

Could metals or silica be the culprit for CKDu?

Exposure to metals has repeatedly been suggested to be the cause of MeN and CKDu. In connection with the second International workshop on MeN (2015) Elinder[197] submitted a working paper entitled 'Does exposure to toxic metals have a role in the development of Mesoamerican Nephropathy (MeN)?' and concluded 'When scrutinizing available knowledge on renal effects and exposure to toxic metals (arsenic, cadmium, lead, lithium and mercury) and information about exposure to these metals in MeN/CKDu endemic area, the clinical presentation and morphological findings, it is unlikely that this epidemic is primarily caused by exposure to these metals.' Also, when considering what has been published since 2015. I consider this conclusion to be valid.

In the fifth rewritten and updated comprehensive of Handbook on the Toxicology of Metals, [53, 333, 334]nothing suggests any associations between exposure to metals and CKDu. Likewise, an extensive recent review on health effects from environmental exposure to arsenic [335], do not indicate that arsenic exposure may cause CKDu.

Arsenic concentration in toenail clippings was analysed in 3,768 in the US, and the association between toenail arsenic levels and CKD incidence over a mean of 24 years of follow-up was examined [336]. CKD was identified if having estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or albuminuria >30 mg/g. After controlling for potential confounders, including demographics, socioeconomics, lifestyle factors, clinical measurements of blood pressure, lipids, and glucose, and medical history, arsenic exposure measured in toenails was not associated with CKD.

Silica, a metalloid which was not discussed in my review [197]and has been suggested to have a role in the development of CKDu. Mascarenas et al 2017 analysed ground/drinking water from areas were patients with severe CKD and control with no CKD and found higher silica and lead concentration in water (99 mg Si/l and 8 ug Pb/l) in areas where CKD patients resided than in the control areas (11-12 mg Si/l and 0,7-0,8 ug Pb/l). The concentration of other metal, including Al, As, Cd, and Hg, was similar [337].
In this context is it worth noting that silica is the eighth most common element in the universe by mass, but that very rarely occurs as the pure element in the Earth's crust because of its high chemical affinity for oxygen. It is most widely distributed in dusts, sands, planetoids, and planets as various forms of silicon dioxide (silica) or silicates. More than 90% of the Earth's crust is composed of silicate minerals, making silicon the second most abundant element in the Earth's crust (about 28% by mass) after oxygen. There is some evidence that silicon is important to human health for their nail, hair, bone, and skin tissues, and has been considered an essential element (https://en.wikipedia.org/wiki/Silicon). Despite silicas abundance in our environment there are a few reports that suggest that silica may exert direct nephrotoxic effects in humans [338] but there are a few studies and on animals.

In dogs' high daily doses of silica in the form of sodium- and magnesium silicate in the diet (1.8-2.4 g/day) caused renal lesions with interstitial inflammation [339]. In rabbits silica in the form of magnesium-trisilicate in water (250 mg/l, corresponding to 50 to 100 mg/day and kg) caused renal lesions with interstitial inflammation after four months [340]. Interestingly, it was shown that some silica was absorbed after ingestion and eliminated via urine.

It is well known that exposure to silica from inhalation of stone dust may cause silicosis [341]. It has also been reported in series of studies that individuals with silicosis have an increased risk of getting CKD [342], and glomerulonephritis from autoimmunity of an ANCA-associated vasculitis (AAV) type. In a systematic review and meta-analysis silicosis ANCA-associated vasculitis 158 potentially relevant manuscripts and 3 abstracts related to silica exposure and risk of AAV were scrutinized. An overall significant summary effect estimate of silica "ever exposure" with development of AAV gave an OR of 2.56, 95% CI 1.51-4.36)[343]. Recently (2021) a group of epidemiologists in Denmark [344] examined the association between respirable crystalline silica exposure and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus and small vessel vasculitis the total Danish working population, 1 541 505 male and 1 470 769 female workers followed since entering the labour market 1979-2015. Adjusted for age and calendar year, men exposed to high levels of respirable crystalline silica compared with non-exposed showed increased incidence rate ratio (IRR) for the four diseases combined of 1.53 [95% confidence interval (CI): 1.39-1.69], for systemic sclerosis of 1.62 (1.08-2.44) and rheumatoid arthritis of 1.57 (1.41-1.75). However, rates of CKD were not examined.

It has been shown that granite workers with heavy exposure to silica had glomerular and proximal tubular dysfunction evidenced by increased urinary excretions of albumin, alpha-1-microglobulin (AMG), and beta-N-acetyl-glucosaminidase (NAG). The urinary excretion of albumin, alpha-1-microglobulin (AMG), beta-2-microglobulin (BMG), and beta-N-acetyl-glucosaminidase (NAG) was determined in two groups of granite workers with low and high exposure to silica. Low molecular weight proteinuria and enzymuria were significantly correlated with duration of exposure in the high but not the low exposure group. These increases were most pronounced in those with 10 or more years of heavy exposure, and in those with radiological evidence of pulmonary fibrosis, particularly those with rounded small opacities denoting classical silicosis[345]. Massive proteinuria and acute renal failure in a patient with acute silicoproteinosis has been presented [346]. In another study a cohort of 2412 white male gold miners were studied. Eligible gold miners worked underground for at least 1 year between 1940 and 1965 in a South Dakota Eleven cohort members was identified to treated for end stage renal disease (ESRD) The standardised incidence ratio (SIR) of ESRD caused by glomerulonephritis or interstitial nephritis was 4.2 (95% CI, 1.5-9.2), increasing to 7.7 among workers with 10 or more years of employment underground[347].

Albeit inhalation of quartz and silica containing particles may cause inflammation and sclerosis in the lung, and possibly induce secondary systemic inflammation with the precipitation of autoimmunity and also with renal vasculitis and/or glomerulonephritis [348], this is however far from evidence that ingestion and gastrointestinal absorption of small amounts of silica from the diet or soluble in drinking water may cause CKD.

In recent years it has been suggested that exposure via inhalation to silica may have a role for developing MeN/CKDu. Sugarcane field workers in Guatemala are exposed to potentially high concentrations of particles containing amorphous silica due to emissions from burning and harvesting sugarcane [349]. Measurements suggest that particles are occurring in size fractions that likely impact in the upper airways and that penetrate the unciliated region of the lungs. Concentrations as high as 1500 and 1170 ug/m^3 were observed. In the UK Silica dust has a workplace exposure limit (WEL) of 100 ug/m^3, expressed as an 8-hour time-weighted average (TWA). In the US the ACGIH 2000 revised its Threshold Limit Value (**TLV**) for respirable crystalline **silica** (quartz) to 50 ug/m^3, (ISO) and has since further lowered its **TLV** to 25 ug/m^3. To what extent this exposure to silica may contribute to the development of MeN/CKDu will be examined in the future.
It should be noted that silicosis has not, yet, been seen sugar cane field workers.

Herbal medication, traditional medicines, and CKD

In most countries, herbal products are not regulated as medicines. Nevertheless, the use of herbal therapy may lead to renal injury or various toxic insults. Herbal poisoning may be secondary to the presence of undisclosed drugs or heavy metals, interaction with the pharmacokinetic profile of concomitantly administered drugs, or association with a misidentified herbal species. Various renal syndromes were reported after the use of medicinal plants, including tubular necrosis, acute interstitial nephritis, Fanconi's syndrome, hypokalemia or hyperkalemia, hypertension, papillary necrosis, chronic interstitial nephritis, nephrolithiasis, urinary retention, and cancer of the urinary tract [350].
Traditional medicines (TM) are a principal form of health care for many populations, particularly in low- and middle-income countries, and they have gained attention as an important means of health care coverage globally.
In an extensive review *Traditional Medicines and Kidney Disease in Low- and Middle-Income Countries: Opportunities and Challenges* [351] it concluded that kidney diseases may be caused, treated, prevented, improved, or worsened by traditional medicines depending on the setting, the person, and the types, modes, and frequencies of traditional medicine use. Traditional medicines are used extensively in sub-Saharan Africa, China, India and across Latin America. Examples of common traditional medicines in use for the treatment of kidney diseases and kidney-related disorders across Latin America are Examples of common TMs in use for the treatment of kidney diseases and kidney-related disorders across Latin America are.

Scientific Name	Common Local Name	Common English Name	Common Uses or Indications	Pharmacology/effects
Arrabidaea brachypoda	Cipó-una (Brazil)	Bureau roots	Nephrolithiasis Arthritis/arthralgia	Anti-oxidative, anti-inflammatory (COX-2 inhibition), analgesic, and antimicrobial, antiparasitic
Vitex polygama	Tarumã	Leaf tea	Nephrolithiasis Inflammation	Anti-inflammatory, analgesic, anti-oxidative, and diuretic
Cecropia species	Embauba (Brazil)	Pumpwood Trumpet Tree	Hypertension Nephrolithiasis	Have anti-inflammatory effects

including pachystachya and obtusifolia	Guaramo (Central America)		Cystitis and nephritis Asthma/bronchitis Diabetes Wound healing Arthritis/arthralgia	through the reduction of renal arginase activity, and TGF-β expression
Hibiscus sabdariffa	Agua de Jamaica (Mexico) Flor de Jamaica (Mexico) Sorrel (Belize, Trinidad, and Tobago)	Hibiscus	Hypertension Edema Diabetes Constipation	Present hypocholesterol-emic, anti-oxidants, hypoglycemic (inhibits α-glucosidase), and diuretic effects

Albeit traditional medicines (TM) possibly cause AKI as well as CKD in Central and Latin America there do not appear to be any TM that cause typical CKDu/MeN or TM that has been reported to be used often in CKDu/MeN endemic areas and/or among sugar cane cutters.
However, one paper in J Ethnopharmacology published in 2022 [352]suggest that several herbs used in traditional Mayan medicine for renal-associated diseases may have nephroprotective effects, but no date or results are presented.

Air pollution, with fine particulate matter, and CKD

Fine particulate matter (PM2.5) is an important environmental risk factor for cardiopulmonary diseases. In recent years exposure to ambient air pollution has also been associated with CKD.

One-year averaged exposure to small particles (PM2.5) and renal function decline over time was investigated in an prospective cohort study of 669 older men living in the Boston metropolitan area[353]. A 2.1 ug/m^3-higher 1-year PM2.5 was associated with an additional annual decrease in eGFR of 0.60 mL/min/1.73 m^2 per year. This was not possible to explain by confounding. Fully adjusted models included additional adjustment for BMI, total cholesterol, diabetes, coronary heart disease, ARB medication, ACEI medication, other anti-hypertensive medication, years of education, percentage below poverty level in census tract, parental homeownership, smoking status, cumulative pack-years smoked, and daily alcohol intake, and distance to roadway.

In a much larger cohort study, in Taiwan, the association between long-term exposure to particulate matter (PM) with small aerodynamic diameter and the development of CKD incident CKD (defined as eGFR<60mL/min/1.73m^2) in a large cohort was examined [354]. A total of 100,629 Taiwanese residents age >20 yr were included between 2001 and 2014. During the follow-up, 4,046 incident CKD cases were identified, and the incidence rate was 6.2 per 1,000 person-years. Participants with the fourth and fifth quintiles of particulate exposure of had an increased risk of CKD development, adjusting for age, sex, educational level, smoking, drinking, body mass index, systolic blood pressure, fasting glucose, total cholesterol, and self-reported heart disease or stroke, with an HR [95% confidence interval (CI)] of 1.11 (1.02, 1.22) and 1.15 (1.05, 1.26), respectively.

In an even larger observational cohort of 2,482,737 United States veterans the association of PM2.5 concentrations and risk of incident eGFR <60 ml/min per 1.73 m^2, eGFR decline >30%, and ESRD over a median follow-up of 8.52 years was examined [355]. County-level exposure was defined at baseline as the annual average PM2.5 concentrations in 2004, and separately as time-varying where it was updated annually and as cohort participants moved. A 10-microg/m^3 increase in PM2.5 concentration was associated with increased risk of eGFR<60 ml/min per 1.73 m^2 (hazard ratio (HR), 1.21), eGFR decline 30% (HR, 1.28), and ESRD (HR, 1.26). Again, results hard to explain from confounding as models were adjusted for age, race, sex, cancer, cardiovascular disease, chronic lung disease, diabetes mellitus, hyperlipidaemia, hypertension, T_0 eGFR, BMI, smoking status, angiotensin-

converting enzyme inhibitor/angiotensin receptor blocker use, county population density, number of outpatients eGFR measurements, number of hospitalizations, and county percent in poverty.

From the US comes also an extensive epidemiological study that association of ambient fine particulate matter air pollution (PM2.5) with kidney transplant outcomes [356]. An amazing number of 112,098 patients with kidney transplants was follow-up for an average 6.0 (3.9-8.9) years. Increased PM2.5 levels were associated with increased risk of death-censored graft failure (adjusted hazard ratio [aHR] per 10 mug/m3 increase, 1.17) and all-cause death (aHR per 10 mug/m3 increase, 1.21), after adjusting for all possible available confounders.

Exposure to particles (PM2.5), and mortality from renal failure (RF) among elderly in Hong Kong, China from 1998 to 2010 has been examined [357]. PM2.5 concentration at the residential address of each participant was estimated based on a satellite-based spatiotemporal model. 61,447 individuals were included in the analyses. 443 RF deaths was seen during the 10 years of follow-up. For an interquartile-range increase in PM2.5 concentration (3.2 mug/m^3), hazard ratios for RF mortality were 1.23 among all cohort participants and 1.42 for patients with prevalent chronic kidney disease.

The association between long-term exposure to ambient PM2.5 and CKD prevalence in China was explored [358] in 47,204 adults. Annual exposure to PM2.5 was assessed. Participants with eGFR <60 ml/min per 1.73 m^2 or albuminuria were defined as having CKD. An increase of 10 mug/m^3 in PM2.5 was positively associated with CKD prevalence (OR 1.3) and albuminuria (OR, 1.4). In this report is however not clear how CKD was defined or how adjustments for confounding factors were performed. In a commentary [359] this report is considered meritorious and adding to the understanding the relationship between high levels of PM2.5 and kidney disease. However, the cross-sectional design weakens the evidence.

Ambient temperature, mortality, and CKD

Humans have considerable ability to adapt to the local climate type, but both mor than usual cold and hot temperatures are associated with increased risk of mortality. This has been noticed and reported from many epidemiological studies and reports. Below a few not systematically selected examples.

Data on temperature and mortality daily in 306 communities from 12 countries/regions (Australia, Brazil, Thailand, China, Taiwan, Korea, Japan, Italy, Spain, United Kingdom, United States, and Canada) was analysed [360]. A Poisson regression nonlinear model was used to estimate the community-specific temperature-mortality relation. A multivariate meta-analysis was used to pool the nonlinear and delayed effects of ambient temperature at the national level, in each country. Meta-analysis results showed that both cold and hot temperatures increased the risk of mortality in all the countries/regions. Temperatures associated with the lowest mortality were around the 75th percentile of temperature in all the countries/regions, ranging from 66th (Taiwan) to 80th (UK) percentiles.

The impact of extreme temperatures on mortality in 12 counties across Hubei Province, central **China**, during 2009-2012 have been examined [361]. An inverse J-shaped relationship was observed between temperature and mortality at the provincial level. Heat effect occurred immediately and persisted for 2-3 days, whereas cold effect was 1-2 days delayed and much longer lasting. Higher mortality risks were observed among females, the elderly aged over 75 years, persons dying outside the hospital and those with high education attainment, especially for cold effects.

Heat-related mortality at the beginning of the twenty-first century in **Rio de Janeiro** has been examined [362]. The highest absolute mortality values during heat-related events were linked to circulatory illnesses, but the highest excess of mortality was related to diabetes, particularly for women within the elderly age groups.

Heat-mortality relationship in the two largest urban areas in **Belgium**, Antwerp and Brussels was assessed for the warm seasons from 2002 until 2011, also considering the effect of air pollution [363]. An increase in mortality occurred above a maximum temperature of 25.2 degrees C in Antwerp and 22.8 degrees C in Brussels. It was estimated that above these thresholds, there is an increase in mortality of 4.9% per 1 degree C in Antwerp and of 3.1% in Brussels. During the study period, 1.5% of the deaths in Antwerp and 3.5% of the deaths in Brussels could be attributed to the effect of heat. Adjustment for air pollution attenuated the effect of temperature on mortality.

Also in **Sweden**, in the north of Europe, heat waves on a national as well as a regional level, significantly increased both all-cause mortality and CHD mortality by approximately 10% and 15%, respectively [364]. Another epidemiological report examined the incidence of hospitalizations from hyponatremia in Sweden between October 2005 and December 2014 in relation to the 24h average ambient temperature [365]. The incidence of hyponatremia was stable at 0.3 per million person-days from -10°C to 10°C but increased rapidly at 24h mean temperatures above 15°C, with 1.96 hospitalizations per million days at the highest recorded temperature of 26°C. Women and elderly carried the greatest risk. To what extent this association between ambient temperature and hospitalizations is seen also in other populations and in other regions of the world need to be examined. The report underlines the importance, and likely health risks, from increasing global temperatures and from living in ‘temperature hotspots.

Recently empirical data from 732 locations in 43 countries was used to estimate the mortality burdens associated with the additional heat exposure that has resulted from recent human-induced warming, during the period 1991–2018[366]. Across all study countries, it was found that 37.0% of warm-season heat-related deaths could be attributed to anthropogenic climate change and that increased mortality is evident on every continent. Burdens varied geographically but were of the order of dozens to hundreds of deaths per year in many locations. The findings support the urgent need for more ambitious mitigation and adaptation strategies to minimize the public health impacts of climate change.

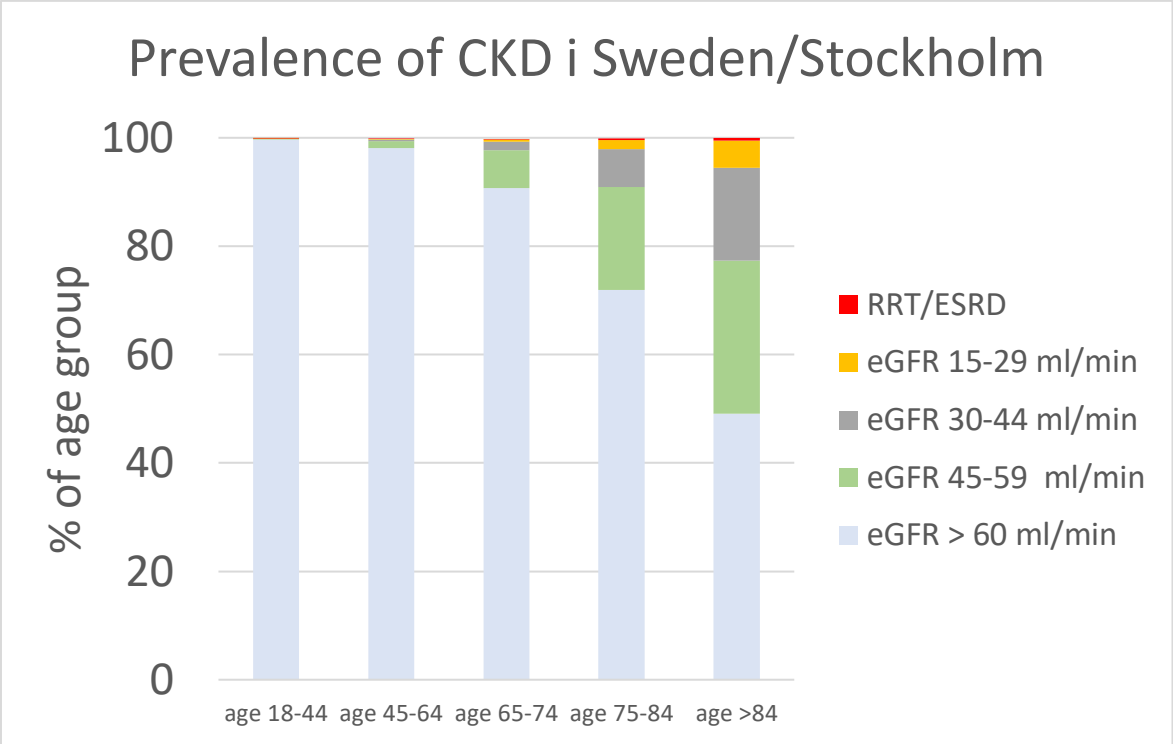
Qatar is a major destination country for Nepali migrant workers where they are exposed to various occupational hazards, including excessive heat. The majority are working in high wet bulb globe temperature (WBGT) exceeding 31 degrees C each working day during hot months The average annual death rate for Nepali migrant workers in Qatar was 150 deaths/100,000. The major cause of these deaths was recorded as cardiovascular problems (cardiovascular disease; CVD). It is likely that a large proportion of these CVD deaths during hot months were due to serious heat stroke. A close temporal association was found between deaths rates due to cardiovascular causes and monthly WBGT [367]. Recently the catastrophically poor working conditions, and lack of medical and health monitoring of migrant workers in the preparation of 2022 World Cup football event in Quatar has been pointed out [368].

Of particular interest in the context of this Summary report on MeN and CKDu is publication in the Lancet in October 2021 [369]. The association between ambient temperature and hospitalization for renal diseases was examined in **Brazil** during 2000−2015. For every 1 dgr C increase in daily mean temperature, the estimated risk of hospitalization for renal diseases over lag 0−7 days increased by 0.9% at the national level. The associations between temperature and renal diseases were largest at day zero but remained for lag 1−2 days. The risk was more prominent in females, children aged 0−4 years, and the aged over 79 years. However, cases were classified into glomerular diseases (N00-N08), renal tubulo-interstitial diseases (N10N16), and kidney failure (N17-N19), and neither Mesoamerican Nephropathy nor CKDu or CKDnT was mentioned in this report which focus on acute hospitalisations rather than chronic kidney disease. Nevertheless, this nationwide study provides evidence that more policies should be developed to prevent heat-related hospitalizations and mitigate climate change.

Already in 2014 Gronlund et al examined hospital admissions and city-specific data on temperature, humidity, and ozone from 1992 through 2006 in the **US**. Extreme heat was associated with a 3% (95% CI: 2%, 4%) in all-cause hospital admissions over the subsequent 8 days. Extreme heat was associated with 15% increased hospitalizations for renal 95% CI: 9%, 21%) but not for cardiovascular diseases. This was seen particularly among the elderly [370].

Prevalence of CKD in relation to age in 'normal' population

'This figure, which present the proportion on different eGFR levels in different age groups in Sweden [371], may serve as a reference to compare results from cross-sectional studies cited above.



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