Summary and comments on available and published reports on MeN/CKDu/CKDnT/CINAC.

Publications are presented in chronological order, i.e. when presented/published. Review papers are presented at the end of each calendar year.

I’ve attempted to make this presentation as comprehensive as possible. Information about pertinent papers that are not, but may well be cited, is appreciated.

I’ve read most of the cited reports thoroughly and I have subsequently made a short summary. Often – but not always – based on the abstract. Often specific comments are given.

I’d like to draw attention to two recently published reports (2019) [1],[2] and an experimental study [3] that are presented in this summary report. These studies provide important evidence that strenuous heat exposure, such as during cane cutting, in a dose-effect and dose response related manner contribute to the development of MeN/CKDu whereas this is not the case for ‘agrochemicals’. The experimental work suggest that different ethnic populations may have different susceptibly to heat.

This is in contrast to what is suggested by Benjamin A Vervaet and others in a report currently in press in Kidney International entitled Chronic interstitial nephritis in agricultural communities is a toxin induced proximal tubular. The observation of proximal tubular cell cytoplasmic granules in cases with CKDu/CINAC is interesting and certainly worth exploring when attempting to elucidate the cause of CKDu. They may well indicate some nonspecific tubular disturbance, or dysfunction, but do not provide evidence that CKDu is caused by environmental toxins.

After the chronological presentation I’ve included a few pages with citations of other reports that may be pertinent. A discussion on how to interpret p-creatinine (and cystatin C) when attempting to identify changes in the glomerular filtration rate (GFR), the key renal function variable, can silica be the culprit for CKDu, and finally a graph on the prevalence of different levels of CKD (I to V) in a ‘normal population’. This may be useful for comparisons.

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2002
Trabanino RG, et al 2002. Possibly 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 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 [4].

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-cut cause for CKD. Farmer living, pesticides exposure and alcohol consumption were found to be very common characteristics in both populations and were not associated to the presence of proteinuria [5].

2006
Overview/review/discussion paper: 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 that 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 [6].

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 138 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. The majority 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 past 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 [7].

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[8].

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 [9].

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/subsistence 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 m² 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 m². 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. [10]

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 m². In a case- control approach various exposure and demographic factors where compared with those having an eGFR>60 ml/min per 1.73 m². 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 [11].

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 m², 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. Most of the ‘cases’ with low eGFR (<60 ml/min per 1.73 m²) 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 [12].

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 m². 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 [13].

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 from serum creatinine using the MDRD formula. The prevalence of eGFR<60 ml/min per 1.73 m² 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 [14].

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) [15]. In particular as also people living elsewhere may develop AAN after food, or tea, containing (AA) [16].

Chandrajith et al 2011 from Sri Lanka called attention to a high prevalence of CKD of unknown cause in certain areas of the country, in particular the north central dry zone. It was suggested that genetic predisposition and some or several environmental factors are involved in the pathogenesis [17].

2012

Nanayakkara et al 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 [18].

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 life style 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. In particular 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 m² 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 m² 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 CKDu in the area [19].

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 1.73m². 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) [20].

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 1.73m² 2003 had died within two years. Out of nine aged over 65 having an eGFR < 60 ml/min per 1.73m² three (33%) had died. High blood pressure was a risk factor for disease progression and death in this cohort [21].

Overview/review/discussion paper: Brooks et al 2012 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 [22].

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 [23].

2013

Jayasumana et al 2013 [24] 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 [25]. Furthermore, monitoring of exposure to the toxic form of arsenic (i.e. inorganic arsenic) is complicated by the fact that organic forms of non-toxic arsenic is common in several forms seafood (such as shrimps and shellfish). Consumption of certain types of common seafood may thus increase the urinary excretion of arsenic considerably. In order 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 was not considered be unusually high or frequently diagnosed. Despite the media attention given to the potential role of agrichemicals 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 [26].

That heat exposure during sugarcane harvesting in Costa Rica has been shown. Non-participatory observation and Wet Bulb Globe Temperatures (WBGT) measurements were carried out during two typical working-week 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 hours 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 [27].

The first detailed clinical and pathological characterization of what has been named Mesoamerican Nephropathy (MeN) was published 2013[28]. 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 equetion, 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 [28].

Overview/review/discussion papers: Wesseling et al 2013 in AJPH. A summary and 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 considered to be 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. However 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 [29].

Lewington et al (2013) in KI make an attempt 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 [30].
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 [31].

In 2014 two medical students, Kinsky 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 Víduas’ 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, unsufficient training and medical support and in particular poor hygienic facilities at the homes of affected individuals [32].

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 m² was 42% among men 9.8% in women. Among participants with GFR <60 mL/min/1.73 m², 44% had proteinuria ≥30 mg/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 m² and controls defined by an eGFR >90 mL/min/1.73 m². 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 bolus 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 [33].

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 located in the south-western municipalities of La Paz Department. This area is the region of highest ambient temperatures (33–36 °C) 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 [34].

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 m²) 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 m². 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 [35].
Herrera et 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 m². 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: nocturia (65%), and dysuria (39.1%). Markers of renal damage where often abnormal in this group of selected patient 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-off 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 [36].

López-Marín et al 2014 performed renal biopsies of the patient’s characterized by Herrera 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 [37].

Vela et al 2014 present another descriptive cross-sectional study from two El Salvadoran 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 [38].

Orduñez 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) which is 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 is occurring in these two countries [39].

The incidence prevalence distribution of pediatric chronic kidney disease (CKD) in Guatemala has been presented [40]. 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 is most prevalent among adults.

Santos et al 2014 examined 28 healthy non-African Brazilian workers engaged in sugar cane harvesting during 2009. 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 were 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 m² 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 [41]. 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%!). It may be speculated that the increase in p-creatinine is a result of creatinine release from muscle cells rather than change in GFR.

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, 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 [42].

Wesseling et al 2014 examined the geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica. Standardized mortality ratios (SMRs) were compared for three time periods between provinces and counties. In the Guanacaste province at the NW Pacific coast of Costa Rica, where MeN is known to occur, the CKD mortality increased from the mid-1970s. Age-standardised rates per 100.000 in men aged over 29 increased from 5.8 in the early seventies to 75.0 in 2007-2012, compared to 5.9 to 16.2 in the rest of Costa Rica. For women, rates increased from 4.5 to 20.7 in Guanacaste versus 4.2 to 9.7 in the rest of the country [43].

42 male patients with confirmed CKDu were interviewed about how they used pesticides in three communities of Bajo Lempa region, El Salvador [44]. Interviewed did not use appropriate personal protective equipment; hazardous pesticides were often misused, 95% of interviewed mixed different types 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 [45] but included also some environmental measurements of cadmium and arsenic.

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.’ [46].
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.

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 [47].

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 [48].

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 [49].

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 commonly 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, as yet, mainly circumstantial [50].

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 [51].

Gronlund et al (2014) 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 [52].

In review paper on CKD hotspots around the world [53] Mesoamerican nephropathy is mentioned along with Balkan nephropathy, Chinese herb nephropathy and the high prevalence of CKD in the Australian Aboriginal population.

Another review [54] 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 [39]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 [55].

2015

Laws et al (2015) investigated changes and job-specific differences 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 m²) and irrigators (–4.9 ml/min/1.73 m²) 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. 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 m²) and irrigators (–4.9 ml/min/1.73 m²) but was not seen in drivers and factory workers not exposed to ‘heat stress’. One weakness in this study is that eGFR is calculated from serum creatinine and 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 well be influenced by a physically demanding work, such as cane cutting. Another methodological problem is the circumstance that workers with elevated creatinine already at the start of the season where not hired. Thus, the examined group to some extent comprise a selection of healthy individuals.

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 m²) 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 also among women. Unfortunately, exposure to heat and water and salt depletion was not reported [56].

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 m². Histopathiological 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 [57].
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 [58].

Laux et al (2015) analysed enrolment rates in RRT Guatemala and found the rates were significantly 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 [59].

Lebov et al (2015) conducted a cross-sectional study of 2275 residents in Leon, Nicaragua. CKD (eGFR<60 ml/min/1.73 m²) 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 [60].

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 work-time 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 [61].

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 [62].

In a cross-sectional epidemiological study Jayasumana et al (2015) compared 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, 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 [63].

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 [64].

Overview/review/discussion papers: Elinder et al (2015) in an extensive 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 [65].

Another review text on MeN, which is updated regularly and available on line, appear in UpToDate since 2015 [66] [67].

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 recently 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 [68].

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 [69].

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 [70].

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 [71].

Murray et al 2015 [72] 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.
Dehydration directly injures renal tubules. Thus, MeN may result from exercise and heat stress associated with 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

Regional variations in prevalence the prevalence of chronic kidney disease (CKD) in Costa Rica have been analysed and reported 2019 [73]. 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 m². 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 [74].

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 [75].

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 [76]. Prevalence of microalbuminuria 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 [77].

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 [78].

Laux et al in 2016 [59] interviewed patients on hemodialysis in southwestern Guatemala who had chronic kidney disease (CKD) of non-traditional causes (CKDnt). Of 242 total patients (including 171 non-diabetics) 45 (18.6% of total patients and 26.3% of non-diabetics) lacked traditional CKD risk factors. 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.

Wesseling et al (2016) performed a cross-sectional study in Chinandega and Leon municipalities, a MenN 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 m² reported a higher intake of water and lower intake of sugary beverages. Serum uric acid levels related strongly and inversely to eGFR levels [79].

Wesseling et al (2016) 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 [80].

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 [81].

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 [82].

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 [83].

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 [84].
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 [85].

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%) [86].

**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 [87].

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 [88].

**Debate:** 'Should we consider renaming 'Mesoamerican Nephropathy' as Nephropathy of Unknown Cause in Agricultural Labourers (NUCAL)?’[89].

Jayasumana et al (2016) [90] 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 tubulointerstitial 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 heat 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 has been criticized [91].

Lozier et al (2016) propose a case-definition and a new name for CKDu; chronic kidney disease of non-traditional cause CKDnT [92]. 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. CKDnT.

The concept of case-definition, which is very useful in surveillance programs, has been further developed [93]. In short, this proposal includes:

1) Estimated glomerular filtration rate (eGFR) <60 ml/ min/1.73 m².

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 undergone 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 would be found in e.g. Sweden in northern Europe.

2017

Wijkstrom et al (2017 studied kidney biopsies from 19 male sugarcane workers in Nicaragua with suspected MeN in Nicaragua. Participants had a mean eGFR cr of 57 (range, 33-96) mL/min/1.73m². 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/1.73m² per year [94].

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 leukocytosis (81%), and neutrophilia (86%) was common. Mean serum creatinine was 2.0 +/- 0.6 mg/dL. In urine almost, all patients displayed leucocyturia (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 [95].

Largely the same group of investigators have also reported from examination of renal biopsies of 11 patients with suspected acute MeN in this Nicaraguan population [95], 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 edema, 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 differ from that of Wijkström et al 2015 and 2017 from MeN patients in El Salvador and Nicaragua respectively [28] [94] 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 [95] included leucocyturia, and leucocytosis and/or neutrophilia i.e. displaying acute evidence of ongoing acute inflammation and renal disease whereas Wijkstrom et al[28] [94] patients with established CKD taken, without signs of acute inflammation that were not currently working or exposed. Nevertheless, the results by [95] that the chronic glomerular changes seen in typical cases of MeN may indeed be 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) made an attempt 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/1.73m2 [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/1.73m2 (95% CI -5.5 -1.3) than in the reference -5.3 (95% CI -7.9 -2.7) [96].

From Sri Lanka Gamage et al (2017) report 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. 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[97].

**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 [98].
Madero et al 2017 [99] in the journal Current Opinion in Nephrology and Hypertension gave a review on Mesoamerican nephropathy (MeN) and concluded that the evidence supports 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 etiology was presented by Valcke et al 2017[100]. 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 [101], while Zoccatelli argued cyclic dehydration hypothesis alone could hardly explain the epidemics outside Mesoamerica [102] while Campese (2017) [103] suggested 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) [104]. 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) [105] 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 (2017 in press) [106] 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 [107] 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/1.73m2. 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 [108] in 2018 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 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 in particular seen at high, WBGT from 30 up to 34C [109]. 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 [110]. 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 [111]. 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. The short term (post-shift) increase in p-creatinine, according to my interpretation, more likely to indicate changes in the muscle- and protein metabolism, than actual effect in 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 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 [112].

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 [113]. 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 m² per year), and 9.5% that had a baseline dysfunction (58 ml/min per 1.73 m² experienced an average drop in eGFR of -3.8 ml/min per 1.73 m² 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[114]. In a logistic model to predict prediction rapid eGFR decline however U-NAGL alone was not able to predict individuals with rapidly declining eGFR[115].

Another important follow-up study of the kidney function was published from an area in the Pacific low-land of Nicaragua with an established high prevalence of CKD/MeN in 2018 [116]. From February 2015 to May 2017, 586 previously overall healthy agricultural workers (median age 27.8 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 organisation (PAHO) [117] 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, 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 [118]. 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 ESRD such as CVD and infections in will then not be recorded as death from CKD. The uptake rate in RRT the countries 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 [119]. 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 [120]. 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 [121]. 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 [122] summarizes a 54-page document from the Pan American Health organisation (PAHO) on diagnosing and surveillance of CKDnT [122]. This PAHO document presents a background to the CKD 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 [122].

Ordunez and associated researchers has in several review 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 [123] [117]. The name chronic interstitial nephritis of agricultural communities (CINAC) rather than MeN or CKDu has been suggested [106, 117]. But this proposal has not been generally accepted but criticised by others [91] [124] 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 [65]in a review wrote ‘Although pesticides can be responsible for both acute and occasionally chronic health effects [125], they are rarely nephrotoxic unless associated with a serious systemic intoxication with multiorgan damage [126]. 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 [106] in this 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 around 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 [127].

2019

A high a prevalence of CKD has also reported from Uddanam in Western India [128]. 2210 individuals (age >18 years) living in a rural area were examined. CKD with eGFR <60 ml/min per 1.73 m² 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 [129]. 12 500 individuals without diabetes, hypertension or heavy proteinuria was examined between 2010 and 2014. The prevalence overall prevalence of eGFR <60 ml/min per 1.73 m² 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 m² 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 [130] 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). This third report from Guatemala is interesting as it shows that post-shift increase is recorded more often in workers with higher specific gravity in urine pre- and post-shift and loss so in those with lower intake of rehydration fluids – but the report suffers from the same problem as previous pre- and post-shift evaluations of AKI. A short term (post-shift) increase in p-creatinine presumably mainly indicate changes in the muscle- and protein metabolism, rather than a real effect in 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 [58].

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 [131]. 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/1.73m². The CKD prevalence was 12.1% (n = 27), 100% of cases were male, 8 had stage 5 CKD (eGFR < 15mL/min/1.73m²), 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 [1]. 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 stronium) were analysed by inductively coupled plasma-mass spectrometry. Twelve pesticides or their metabolites (2,4-dichlorophenoxyacetic acid, 3-phenoxbenzoic acid, 4-fluoro-3-phenoxbenzoic 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, ethlenethiourea, glyphosate, 4-chloro-2-methylphenoxy acetic acid, 3-hydroxypyrimetanil, 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 of not special precautions are taken, and that arsenic in urine needs to be speciated to be evaluated [132].

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 (Hansson, 2019 #7698. 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 m² in the low-moderate category to -5 mL/min/1.73 m² in the high and -9 mL/min/1.73 m² 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 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 $\geq$28.9) and not exposed to heat have been examined [Nerbass, 2019 #7682]. 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 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 [133] 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/1.73m²) 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[134]. In a review report based on previous cross-sectional studies in El Salvador [133] 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 include, 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 now also are being published from Mexico [135]. 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: 20.1 vs. 10.4%, and proteinuria: 36.1 vs. 11.0%). The prevalence of proteinuria in children was also higher (44.4 vs. 4.8%). 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 [136]. 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 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 $\geq$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 etiology (CKDu) in the North Central Province of Sri Lanka has been analysed [137]. 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 [138]. 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 possible to analyze blood or urine samples and the results are based on interviews only.
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 [139]. This infection is considered to 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 [140]. Fifty kidney disease patients and 270 controls from Kandy and 104 kidney disease patients and 242 controls from Girandurukotte were examined. Seropositivities 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.

However, 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 the 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 [141].

Also in Sri Lanka an attempt has been made to use urinary biomarkers for Diagnosis of CKDu [142]. 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 [143], the SPRINT trial in the USA, been associate with a somewhat elevated risk to get AKI again.

Currently in press is an experimental study that may great importance for the understanding of MeN and CKDu [3]. 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 in particular 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 into the Americas 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 [144]. 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** has been published but provides no new or pertinent information [145]. Another review suggests that ‘Glyphosate's synergistic health effects in combination with exposure to other pollutants, in particular paraquat, and physical labor in the ubiquitous high temperatures of lowland tropical regions, could result in renal damage consistent with CKDu in **Sri Lanka**’ [Gunatilake, 2019 #7660], but provide no hard data or evidence to support this suggestion. 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 {Herrera Valdes, 2019 #7700}. 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 early 2019 researchers at the Pan American Health Organization (PAHO) presented a systematic review of the most frequent exposures suspected to be possible causes of CKDnT[146]. 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 this 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.

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 [147].

To improve research and reporting on CKDu a standardised protocol for cohort studies in high-risk communities has been suggested[148] [149]: 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/1.73m²), 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 [150]. 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 [151]. 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 [152]. 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 hyperosmolality 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.

Vervaet and collaborators [153] have presented a report which is about to be published in Kidney International 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-interstitial nephritis. Already in 2017 [90] 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) are now presented and compared to biopsies obtained from non CINAC cases. 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 is in contrast to several other case series [28] [94] [107]. 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 a number of 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, defined by the presence of 2 or more clusters of >3 lysosomes which meet the criteria of aggregates and dysmorphism, smaller than 1.2 μm in greatest diameter, 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. Thus, these morphological findings are non-specific and possible to relate to exposure to any specific toxic substance.

The observation of proximal tubular cell cytoplasmic granules in cases with CKDu/CINAC is interesting and certainly worth exploring when attempting to elucidate the cause of CKDu. They may well indicate some nonspecific tubular disturbance, or dysfunction, but do not provide evidence that CKDu is caused by environmental toxins. 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 [154]. Indeed such relationships, between heat exposure and lowered eGFR or CKD, have been reported from a number of 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, as yet, detect or exclude any specific cause.

Additional papers and facts that may be pertinent in the context of discussions of CKDu and MeN that may relevant to cite and consider;

Second International conference on Mesoamerican Nephropathy 2015 [155].

Thesis of Julia Wijkström, which present clinical and renal morphology data from patients with CKDu from three counties, El Salvador, Nicaragua and Sri Lanka [156]

Jah and Modi in a review paper for Kidney International [157]. The estimated global crude prevalence of CKD is 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.

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 [158]. Ten families were examined, and specific mutations was found in 7 of 9 families. On the basis of 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 gold-miners. 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 were followed for periods of up to four years with serial studies of renal function and structure. In the majority 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 [159].

Reports of nephrotoxicity from pesticides are rare [160]. 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 [161].

A special issue in the Lancet [162] 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 have to 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 [163, 164] 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 [165]. 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 [166]. 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 [167] whereas the increase in cystatin C is much less pronounced [168].

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 [112]. From a model of the pharma-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 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[169] 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. However, silica, a metalloid which was not discussed in that review 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 [170].

In this context it is 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 [171] 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 [172]. 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 [173]. Interestingly, it was shown that some silica was absorbed after ingestion and eliminated via urine.

It is well established of extensive exposure to silica from inhalation stone dust may cause silicosis (Schlueter, 1994). It has also been reported in series of studies that individuals with silicosis have an increased risk of getting CKD [174], 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[175].

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, 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.

**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 [176], may serve as a reference to compare results from cross-sectional studies cited above.

![Prevalence of CKD in Sweden/Stockholm](image)

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