Occupational heat exposure and kidney disease

Studies on the role of heat stress in the Mesoamerican epidemic of Chronic Kidney Disease of non-traditional origin

Erik Hansson

School of Public Health and Community Medicine

Institute of Medicine

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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erik.hansson@amm.gu.se

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ABSTRACT

This thesis examines the association between heat stress and kidney disease in Mesoamerica using different perspectives and methods. An ecologic study found that hot, sugarcane-cultivating regions had elevated chronic kidney disease (CKD) mortality. In a longitudinal workplace study, kidney injury incidence was higher among sugarcane harvest workers with high physical workload, and decreased with an intervention reducing heat stress. Low liquid intake and consumption of NSAIDs were additional risk factors for kidney injury. Kidney injury coincided with fever and elevated levels of inflammation biomarkers, suggesting that inflammation mediated kidney injury. These findings are consistent with excessive heat strain from high internal heat production and external heat load being a main cause of the Mesoamerican epidemic of CKD of non-traditional origin (CKDnT). Kidney injury assessed by repeat serum creatinine (SCr) measurements corresponded well to increasing levels of urine kidney injury markers and decreasing serum erythropoietin, strengthening SCr increase as an intermediary outcome. The implications of the findings for future research, and public and occupational health practice in low-income settings facing global warming are discussed.

Keywords: Heat stress, heat strain, chronic kidney disease, acute kidney injury, occupational medicine

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SAMMANFATTNING PÅ SVENSKA

Lantbruksarbetare i Centralamerika drabbas ofta av kronisk njursjukdom. Den bakomliggande orsaken är ofullständigt känd, men tidigare forskning pekar på att fysiskt krävande arbete i värme skulle kunna orsaka njursjukdom. I doktorandprojektet studerades samband mellan värmestress och njursjukdom i Centralamerika med olika metoder, med fokus på sockerrörsarbetare som i samband med skörden utför ett fysiskt krävande arbete i ett varmt klimat.

I en studie (delarbete I) med rumslig analys av registerdata var dödligheten i njursjukdom betydligt högre i låglänta, varma områden med mycket sockerrörsodling i Mexiko, Guatemala, El Salvador, Nicaragua och Costa Rica än i områden där vädret är svalare eller andra grödor odlas. I nästa delarbete följde vi sockerrörsarbetare på plantagen Ingenio San Antonio (ISA) i Nicaragua över en säsong. Risken för njurskada var förhöjd hos de med de fysiskt mest krävande arbetena. Njurskada definierades som en ökning av kreatinin i serum på minst 0.3 mg/dl. För att ytterligare studera sambandet mellan värmestress och njurskador fick arbetarna ta längre raster varje timme och bättre tillgång till skugga och vätska (delarbete III). Denna intervention förebyggde njurskador, åtminstone i arbetsgrupper där förändringarna verkligen genomförts.

För att förstå mer om hur värmestress kan orsaka njurskador ställdes frågor om symtom och läkemedels- och vätskeintag till sockerrörsarbetarna, och blod- och urinprov togs före och efter skördesäsongen. De som rapporterade att de känt feber, tagit anti-inflammatoriska läkemedel eller druckit sötade drycker snarare än vatten och elektrolyttillskott hade högre risk för njurskada. Förhöjda nivåer av urinsyra eller en inflammationsmarkör i blodet, lågt kaliumvärde, och sjunkande blodvärde var också associerat med njurskada (delarbete IV). Samtidigt med njurskada definierad enligt ovan, steg även ett flertal markörer för njurskada i urinen, vilket stödjer att de njurskador som uppmätts hos sockerrörsarbetarna sannolikt ger konsekvenser på sikt (delarbete V).

Sammantaget visar resultaten på ett samband mellan långvarig värmestress och utveckling av njursjukdom, och bidrar till en ökad förståelse av möjliga mekanismer bakom detta samband, där återkommande inflammation och skador troligen gradvis ger kroniska skador. Den pågående globala uppvärmningen kan förväntas förvärra denna problematik. Värmestress på arbetet kan förebyggas, men mer forskning behövs, i synnerhet i låginkomstländer. En ökad förståelse av mekanismerna som orsakar njursjukdom vid värmestress behövs för utveckling av mer specifika åtgärder.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Hansson E, Mansourian A, Farnaghi M, Petzold M, Jakobsson K. An ecological study of chronic kidney disease in five Mesoamerican countries: associations with crop and heat. BMC Public Health. 2021 May 1;21(1):840.

II. Hansson E, Glaser J, Weiss I, Ekström U, Apelqvist J, Hogstedt C, Peraza S, Lucas R, Jakobsson K, Wesseling C, Wegman DH. Workload and cross-harvest kidney injury in a Nicaraguan sugarcane worker cohort. Occup Environ Med. 2019 Nov;76(11):818-826.

III. Glaser J, Hansson E, Weiss I, Wesseling C, Jakobsson K, Ekström U, Apelqvist J, Lucas R, Arias Monge E, Peraza S, Hogstedt C, Wegman DH. Preventing kidney injury among sugarcane workers: promising evidence from enhanced workplace interventions. Occup Environ Med. 2020 Aug;77(8):527-534.

IV. Hansson E, Glaser J, Jakobsson K, Weiss I, Wesseling C, Lucas RAI, Wei JLK, Ekström U, Wijkström J, Bodin T, Johnson RJ, Wegman DH. Pathophysiological Mechanisms by which Heat Stress Potentially Induces Kidney Inflammation and Chronic Kidney Disease in Sugarcane Workers. Nutrients. 2020 Jun 2;12(6):1639.

V. Hansson E, Wegman DH, Wesseling C, Glaser J, Schlader ZJ, Wijkström J, Jakobsson K. Markers of kidney tubular and interstitial injury and function among sugarcane workers with cross-harvest serum creatinine elevation. Occup Environ Med. 2021 Dec.

CONTENT

ABBREVIATIONS

ACGIH	American College of Governmental Industrial Hygienists
ACMS	American College of Sports Medicine
AKD	Acute Kidney Disease
AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
CKD-EPI	CKD Epidemiology Collaboration
CKDnT	Chronic Kidney Disease of non-traditional origin
CKDu	Chronic Kidney Disease of unknown etiology
CRP	C-Reactive Protein
DEGREE	Disadvantaged Populations eGFR Epidemiology Study
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
GFR	Glomerular Filtration Rate
GIS	Geographical Information System
IKI	Incident Kidney Injury
IR	Incidence Ratio
ISA	Ingenio San Antonio
ISO	International Standardization Organization
KIM-1	Kidney Injury Molecule 1
LoA	Limit of Agreement

MeN	Mesoamerican Nephropathy
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NIOSH	National Institute of Occupational Safety and Hygiene
OSH	Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
PHS	Predicted Heat Strain
SCr	Serum Creatinine
WBGT	Wet-Bulb Globe Temperature
WRS	Water, Rest, Shade

1 INTRODUCTION

Reports of an epidemic of chronic kidney disease among young male agricultural workers, not related to traditional risk factors such as diabetes or hypertension, started appearing in Mesoamerica in the early 2000's.[2] [3] Analyses of mortality records however indicate that kidney disease mortality among men started increasing in the Costa Rican sugarcane cultivation regions of Guanacaste in the 1970's,[4] and that the Nicaraguan sugarcane cultivation regions Chinandega, Leon and Granada had elevated kidney disease mortality in the 1990's.[5]

Globally, this epidemic is most often referred to as CKDu, as in Chronic Kidney Disease of unknown etiology. In Mesoamerica, it is also referred to as Mesoamerican Nephropathy (MeN). The Pan-American Health Organization (PAHO) refer to the Mesoamerican epidemic as Chronic Kidney Disease of non-traditional origin (CKDnT).[6] CKDnT will be used in this thesis.

After the initial reports from Mesoamerica, a similar disease condition has been described also in Sri Lanka[7] and India.[8] Although rural populations are mostly affected in all these separate locales, it remains unclear to what extent the disease entities in Mesoamerica and South Asia are the same.[8] This thesis focuses on Mesoamerica, recognizing that disease characteristics, pathophysiology and etiology may or may not overlap with those in other regions.

Twenty years after recognizing the CKDnT epidemic, uncertainty on etiology remains. Research has focused on potential roles of metal or pesticide exposure, nephrotoxic medication, consumption of unregulated alcohol,[5] and excessive heat exposure.[9] [10] Considering that previously incompletely understood endemic nephropathies later have been attributed to toxins (e.g. Balkan nephropathy caused by aristolochic acid contaminated crops[11] and Itai-itai caused by cadmium-contaminated food[12]), and the volcanic soil and pesticide-intense Mesoamerican agriculture, toxins have been sought as a cause of CKDnT. However, to date no toxin has been identified as the cause of the CKDnT epidemic.

Already from the very first reports of CKDnT,[3] heat stress has been proposed as a cause. At the latest international research workshop on CKDnT, it was noted that a large number of epidemiological studies found an association between heat exposure and CKDnT.[10] However, the workshop report also concludes that a causal role of heat in CKDnT pathogenesis cannot be determined.[10] Considering ongoing global warming, there is an even greater need to better understand the relationship between heat and kidney disease.

1.1 THE KIDNEY

1.1.1 Anatomy and physiology

The kidneys are paired retroperitoneal organs each consisting of 1 million functional units known as nephrons, each consisting of a capillary ball called glomerulus and a winding tube called tubuli.[13] Small blood vessels transport blood to and from the glomerulus, and then form the peritubular capillaries surrounding the tubuli. The glomeruli are predominantly located in the outer (cortical) parts of the kidney. The tubuli stretches into the inner (medullary) parts of the kidney and then returns to the cortex to empty into the collecting ducts which transport the urine onwards in the urinary tract.

The main functions of the kidneys are to eliminate water-soluble substances and regulate volume homeostasis and thereby blood pressure.[13] Briefly, this is achieved by filtering fluid and solutes out from the circulation in the glomeruli, and then reabsorbing large proportions again in the tubuli. In the glomerulus, a proportion of the plasma is filtered across the glomerular filtration barrier made up of endothelial cells, a basement membrane and podocytes, into Bowman's capsule, which is connected to the proximal tubuli. This filtrated fluid, the primary urine, contains water-soluble compounds such as electrolytes and other small substances, while larger molecules cannot pass through the pores in the glomerular filtration barrier. The primary urine pass through several tubular segments, with specialized functions at which water, electrolytes, amino acids etc. are reabsorbed, and waste products secreted. These processes are carefully orchestrated by hormonal systems signaling from within the kidney, and from other organs; the adrenal cortex, the vascular system and the pituitary gland, enabling the body to maintain water and electrolytes homeostasis and blood pressure. The kidneys also contribute to regulating blood pressure via renin synthesis in response to low blood pressure. Renin activate the renin-angiotensin-aldosterone system with effects on blood pressure regulation involving multiple responses.

The reabsorption of water depend on maintaining a high concentration of solvents in the medulla, something which mandates a restricted blood flow to this region.[13] At the same time, absorption of sodium is an energy and thus oxygen-demanding process,[14] and this combination of high metabolic demands and low oxygen availability puts the transition zone between the cortex and medulla (the corticomedullary junction) at the "brink of hypoxia".[15]

The kidneys regulate synthesis of red blood cells via the hormone erythropoietin (EPO).[13] Specific cells located in the interstitial space surrounding the tubuli in the corticomedullary junction release this hormone in response to reduced oxygen partial pressure. By regulating the tubular reabsorption of calcium and phosphate, and via synthesis of the active form of vitamin D, which in turn influence intestinal absorption and bone reabsorption of calcium, the kidneys have a key role in maintaining stable calcium levels. Another crucial role of the kidneys is regulating the body acid-base balance. Typically, the kidneys reabsorb almost all bicarbonate and excrete ammonium and other acids, giving a net loss of acids.[13]

1.1.2 Biochemical assessment

Kidney function is primarily assessed by glomerular filtration rate (GFR), which is the volume of blood cleared from a compound eliminated via the kidney through glomerular filtration per time unit.[13] This is typically expressed in relation to the standard body surface area (ml/min/1.73 m^2). The gold standard for measuring glomerular filtration is by injecting an exogenous substance which is completely filtered by the glomeruli, not reabsorbed or secreted by the tubuli or in other way eliminated (e.g. via bile), and then repeatedly measure serum concentrations of this substance at fixed time points. This is a resource-demanding procedure, and equations have been constructed to calculate estimated GFR (eGFR) from serum concentrations of endogenous substances, accounting for age and sex. The filtrating function of the kidney, GFR, varies with age and sex. In men, normal GFR declines from approximately 140 ml/min/1.73 m^2 at age 20 to 120 at age 50.[16]

Creatinine is the endogenous compound most often used for calculation of eGFR ($eGFR_{cr}$). It is a 113 Dalton waste product of creatine metabolism in muscle cells, which is eliminated primarily via glomerular filtration but also to a minor extent tubular secretion. Aside from GFR, creatinine levels depend on meat (especially boiled) consumption, muscle mass, age, and sex. Cystatin C is a small protein (13.3 kiloDalton) which is more expensive and less accessible to measure than creatinine. The populations included in construction of eGFR estimation equations are from Europe or the US, meaning potential genetic, diet and constitutional differences compared to other populations may lead to significant bias when applying them in other populations.[17]

Cystatin C concentrations are not influenced by muscle mass or creatine metabolism. This makes cystatin C-derived eGFR ($eGFR_{cy}$) assessment attractive when analyzing changes in eGFR in physically highly active individuals. As cystatin C is a much larger molecule than creatinine, it may however also be that $eGFR_{cy}$ better reflect the glomerular filtration of larger molecules, such as proteins. A low ratio of $eGFR_{cy}/eGFR_{cr}$ has been suggested to represent a disease entity named "shrunken pore syndrome", in which the elimination of large compounds are more impaired than the elimination of smaller compounds, and has been associated with elevated mortality as well as higher circulating levels of pro-inflammatory and pro-aterosclerotic proteins.[18 19]

Another commonly used, and easily accessible, method for assessing another aspect of kidney function and damage is urine albumin concentration.[20] Only small quantities of albumin are filtered through the glomerular membrane, and virtually all are reabsorbed by healthy tubuli.[21] As the concentration of albumin in urine depends on the urine flow rate, urine levels of albumin are typically normalized to the urine creatinine concentration,[20] with rate of creatinine excretion in urine assumed to be constant. Thereby, urine albumin levels can be assessed in spot urine samples and does not need 24 hour urine collection. Levels of protein in urine may be assessed semi-quantitatively using dipsticks,[20] but this is less reliable than quantification of urine albumin/creatinine ratio. Urine can also be analyzed for specific protein markers of tubular injury, such as kidney injury molecule 1 (KIM-1) or neutrophil gelatinase-associated lipocalin (NGAL), which are considered proxy markers for kidney damage.[22] A large number of such potential biomarkers exist, but unlike eGFR and albumin, none of them are yet widely implemented in clinical care.

1.1.3 Kidney disease

1.1.3.1 Classification and nomenclature

Kidney disease classifications are primarily based on GFR and the trajectory of this function parameter in time.[20 22 23]

Acute kidney injury (AKI) is defined as an abrupt decrease in GFR resulting in low urine output (0.5 ml/kg/h) during a 6 h period and/or increasing serum creatinine (SCr) levels over a period of 48 hours to 7 days.[22] An increase in SCr >0.3 mg/dL in 48 hours or >50% in 7 days is consistent with an AKI diagnosis.[22] These clinical criteria are adapted for clinical settings in which individuals may have daily serum samples taken, but less well suited for occupational or community settings in which such frequent monitoring is not feasible. Rather than a single disease entity, AKI is considered a heterogeneous syndrome of multiple possible causes and consequences.[22]

Acute kidney disease (AKD) includes AKI, but also recent (≤3 months) decrease of eGFR to <60 ml/min/1.73 m^2, a decrease of eGFR by ≥35% or an increase in SCr by >50% in the past ≤3 months, or the onset of other markers of kidney damage within this time period not necessarily associated with GFR decline.[23]

Diagnostic criteria for chronic kidney disease (CKD) overlap with some of those for AKD (<60 ml/min/1.73 m^2 and markers of kidney damage), but these abnormalities have persisted for >3 months. CKD stages 1-5 are classified by underlying cause, GFR category (G1 ≥90 ml/min/1.73m^2, G2 60-89 ml/min/1.73m^2, G3 30-59 ml/min/1.73m^2, G4 15-29 ml/min/1.73m^2 and G5 <15 ml/min/1.73m^2 or dialysis) and albuminuria (A1 < 3 mg/mmol creatinine, A2 3-30 mg/mmol creatinine and A3 >30 mg/mmol creatinine).[20]

1.1.3.2 Etiology

There are a wide range of possible causes of AKI, which may be classified as decreased renal blood perfusion, urinary tract obstruction, or other specific or non-specific renal causes, which however may occur simultaneously.[22]

Dehydration and circulatory failure, e.g. in heart failure, can cause kidney injury as the renal blood perfusion is reduced.[15 22] Interacting effects of several drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, and diuretics (or dehydration), may together lead to a much increased risk of reduced renal perfusion and thereby AKI.[24] Obstruction of the flow of urine from the kidney, such as from renal calculi or benign prostatic hyperplasia, may cause AKI.[22]

Other causes of AKI include infectious agents causing interstitial nephritis (e.g. leptospirosis[25]), glomerulonephritis, coagulation disorders, myeloma, systemic inflammation (e.g. sepsis), ischemia and toxins.[22] Examples of toxicants include X-ray contrast[22] and aminoglycoside antibiotics,[22] but also endogenous compounds, such as myoglobin,[26] a protein released from damaged or dying muscle cells, may cause severe kidney injury. In clinical practice, it is generally considered that adequate hydration can help prevent kidney injury from toxic substances, with ensuring good hydration status used to prevent e.g. X-ray contrast[27] toxicity and kidney injury during rhabdomyolysis, the clinical syndrome caused by myoglobin release.[28]

The risk of developing CKD, or worsening of existing CKD, is elevated among AKI survivors.[29 30] It is however not established whether this reflects a causal mechanism (injury suffered during AKI episode cause CKD), or a confounded association (an underlying condition putting patients at risk of both AKI and

CKD).[29 30] Determining the direction of causality requires intervening to prevent AKI and study the effect of this on CKD incidence.

The most common causes of CKD worldwide are hypertension and diabetes.[16 31] There are several more rare causes of CKD.[16] Chronically reduced perfusion, as in renal artery stenosis, may cause CKD. Congenital, e.g. polycystic kidney disease, and glomerulonephritis (e.g. IgA nephritis), most of which are caused by inflammation of various origins (autoimmune, post-infectious), are other etiological groups. Several different metals, such as cadmium, lead, mercury, lithium, and platinum may cause kidney injury and disease,[32] as well as other exogenous but naturally occurring toxins such as mycotoxins.[33] Occupational exposure to certain specific pesticides has been associated with a higher risk of CKD in a US cohort of agricultural workers,[34] but the large number of substances considered mean that there is a risk for false-positive findings. Use of the pesticide paraquat was however also associated with a higher risk of CKD among the wives of these agricultural workers,[35] strengthening that this substance may be a risk factor for CKD. A recent conference abstract described positive associations between the pesticides 2,4-D, chlorpyrifos, malathion, and a deltamethrin metabolite, and CKD not due to hypertension or diabetes in the large US National Health and Nutrition Examination Survey,[36] but these findings need to be more carefully examined.

1.1.3.3 Clinical and biochemical manifestation

Fluid retention, hypertension, and electrolyte imbalance resulting in edema with circulatory and respiratory disturbances are dramatic and potentially fatal manifestations of kidney failure. However, chronic kidney disease often present much more insidiously and can progress silently without any clinical manifestations for years. Early stages of CKD are typically asymptomatic, but accumulation of waste products may cause tiredness, nausea and itching at more advanced stages. Risks of cardiovascular disease and death is much elevated in CKD patients.[16] Disturbed calcium/phosphate homeostasis can lead to bone disease and vascular calcification.[37] Loss of renal regulation of acid-base balance cause metabolic acidosis.[13] Mild acute kidney injury does not necessarily present with any symptoms at all although more severe forms causing anuria will rapidly lead to symptoms prompting clinical care.

For kidney disease types associated with an increased permeability of the glomerulus to large proteins such as albumin (nephrotic syndrome), frothy urine may be one presentation, combined with edema as intravascular albumin concentration decrease. Anemia is a common manifestation in CKD stages 4-5, resulting from the loss of erythropoietin-producing cells, and regular assessment of hemoglobin levels are recommended for CKD patients with eGFR <60 ml/min/1.73 m^2.[16]

1.1.3.4 Treatment

Optimized management of the underlying cause of kidney disease, e.g. hypertension and diabetes, are prioritized prevention/treatment approaches in early stages of CKD caused by these conditions.[16] In later stages, treatment of biochemical disturbances such as metabolic acidosis, hyperphosphatemia and low erythropoietin levels becomes necessary in order to avoid manifestations such as fractures, cardiovascular disease and anemia. At the ultimate stage (CKD stage 5), it becomes necessary to replace the kidneys as regulators of fluid homeostasis and eliminators of waste products, either by hemo- or peritoneal dialysis, or transplantation. These advanced therapies are very expensive and carry medical risks.

1.1.4 Chronic Kidney Disease of non-traditional origin

1.1.4.1 Case definitions

The Pan-American Health Organization has developed case definitions for CKDnT intended for clinical practice and surveillance.[38] Possible cases have eGFR <60 ml/min/1.73m^2 at one single measurement and are aged <60 years, and have no history of hypertensive disease, type 1 diabetes, or other known causes of CKD such as congenital malformations, polycystic kidney disease, glomerulonephritis, vasculitis, etc.. A repeated eGFR assessment after 3 months at <60 ml/min/1.73m^2 is required for the probable case definition. The confirmed case definition further includes an ultrasonography examination to rule out urinary tract obstruction or renal polycystic disease, includes other kidney damage markers than eGFR, and formalizes some exclusion criteria.

For the purpose of epidemiological prevalence studies, the Disadvantaged Populations eGFR Epidemiology Study (DEGREE) protocol recommends only one SCr measurement, as it is considered unlikely that a large proportion of survey participants will have an acute reduction in kidney function at the time of sampling,[39] and the logistics of following individuals for 3 months greatly complicate field research.

1.1.4.2 Demographic characteristics

Men younger than 50 years of age is the group primarily affected by CKDnT.[2 40] The male-to-female ratio of prevalence of reduced renal function in affected communities is approximately 4.[41] The CKD mortality and dialysis initiation male-to-female ratio was 10 in a severely affected area of El Salvador.[42]

Several studies report a pronounced variation by place of residence and occupation,[41] with inhabitants in lowland rural areas[4 9 43-45] and workers performing heavy labor in hot conditions worse affected, e.g. agricultural workers in general,[46-49] sugarcane workers,[46 48 50] fishermen,[46] miners,[25 46 51] brick-makers,[52] and construction[51] and port workers.[51]

1.1.4.3 Symptoms, natural history and biochemical findings

CKDnT is characterized by no or low levels of protein- and albuminuria,[38] meaning a urine sample for these parameter is unlikely to detect disease. Thereby, serum samples need to be obtained in occupational studies and population surveys of CKDnT. Ideally, repeat serum sample measurements after 3 months are needed to confirm CKD status.

Several studies have found that inflammation (fever and raised inflammation biomarkers) and concomitant serum creatinine >0.3 mg/dl increase across a few months is common in populations at risk of CKDnT.[53-55] Dysuria in the absence of urinary tract infections has frequently been reported in populations at risk of CKDnT,[51 56-58] but the link between this symptom, kidney injury and changes in kidney function has not been established.

Interpreting changes in eGFR in the context of CKDnT is associated with a number of challenges. First, the population at risk of CKDnT are typically young, meaning they have eGFR values in a range in which eGFR is a more inaccurate estimate of actual GFR[59], at least in absolute numbers. Therefore, changes in either direction at high eGFR values is difficult to interpret. Secondly, increased eGFR may be a sign of glomerular hyperfiltration.[60] Comparing mean changes between groups can thus be misleading as decreasing eGFR in some individuals may be masked by hyperfiltration in others, a condition which is also pathological. Third, studies of rapid changes in eGFR, such as across a work shift, need to consider that glomerular function can only be reliably estimated if the serum marker from which it is estimated is at a steady state.[59 61] In the context of heavy physical work, the possibility that work leads to an increased muscle release of creatinine further perturbing this steady state, in addition to reduced GFR, needs consideration. Last, GFR estimating equations have not been validated in Mesoamerican populations.

Studies on kidney disease progression among workers at risk of CKDnT have often used the term AKI for increases in serum creatinine occurring over a 6 month period,[53-55 62] although this term is defined as a SCr increase occurring over a maximum 1 week period (see above). Other longitudinal studies have grouped individuals by rapidly progressive loss of or stable kidney function, [63-66] categories which lack established definitions but which were identified using regression modelling of the longitudinal data. Within this thesis, a definition and term developed for epidemiological studies in populations at risk of CKDnT is utilized, named Incident Kidney Injury (IKI). This is defined as a >0.3 mg/dL or 50% increase in SCr from one pre-shift measurement to a pre-shift measurement 5-6 months later (Paper II-V). Several workers with SCr increase >0.3 mg/dL during harvest have been reported to develop CKDnT within some months,[54 62] but the link between this acute condition and CKDnT remains to be better explored.

Hyperuricemia is often seen among CKDnT patients and is also common in other forms of CKD. However, uric acid levels among CKDnT patients are generally higher than expected based on eGFR levels and age.[67] Unlike many other forms of CKD, patients with CKDnT often have low potassium levels.[53 54 68-71] Blood hemoglobin (Hb) levels are often decreased,[53 54 68 72] and low Hb has been shown to correlate with a higher risk of CKDnT among sugarcane workers suffering from AKI.[54]

1.1.4.4 Histopathological findings

Kidney biopsy findings among Mesoamerican CKDnT patients seem to differ somewhat between disease phases. Among current or former sugarcane workers with CKDnT recruited at a Nicaraguan university hospital (N=19)[69] and Salvadoran tertiary hospital (N=8),[70] glomerulosclerosis and glomerular hypertrophy was widespread. Interstitial fibrosis and inflammation were mild to moderate, with infiltration primarily of lymphocytes. In a study of sugarcane workers (N=11) presenting to a sugarcane mill hospital with recent SCr increase, and in most cases signs and symptoms consistent with a systemic inflammatory response, findings of tubulointerstitial inflammation were more pronounced.[55] T lymphocytes and neutrophils infiltration in the corticomedullary junction interstitium was common, while glomeruli were mostly preserved.[55]

1.2 HEAT

1.2.1 Heat balance, stress and strain

The heat balance of the human body is determined by the balance of metabolic heat production and the net transfer of heat to the external environment.[73 74] This can be expressed using the heat balance equation:

$$M - W = R + C + E + K + L + S$$

In this equation, M is the rate at which energy is produced in the body from its metabolism and W is the mechanical work the body exerts on external objects. The difference between M and W is the internal heat production. R is radiation of heat energy (e.g. from sun) to or from the body. C is heat energy loss or gain from convection, i.e. heat energy transferred via air surrounding the body. E is evaporation, i.e. loss of heat energy as fluid turns from liquid to vapor at the skin. K is conduction, heat energy transfer via direct contact with clothes or surfaces. L is heat energy losses via respiration. The remaining term, S, is the rate at which the body accumulates or lose heat energy. S is 0 when the body is at a steady state and heat production equals heat losses. If S is positive, the body will accumulate heat and is under heat stress.

Heat stress is the combined effect of external conditions, metabolic heat production and clothing.[75] Ambient temperature obviously determine heat exposure, but other external factors can also have a large impact; convection will be reduced if there is no wind, evaporation is less effective the more humid the surrounding air is, and radiation is higher under full sunlight than shade. A body at rest produce much less heat energy than one conducting physically heavy work. Clothing is an important determinant of heat energy transfers as clothes trap air heated and humidified by the body, thus limiting convection and evaporation.

Heat strain are the responses which occur as the body is affected by heat stress.[75] The physiological responses to heat stress increase skin blood flow and sweat rate, which increase heat losses from convection and evaporation. Sweating leads to losses of water and electrolytes, putting heat-strained workers at risk of dehydration. Hyperthermia and dehydration are related but distinct aspects of heat strain.[76] It is possible to suffer from hyperthermia without being dehydrated, and vice versa.

1.2.2 Heat stress and strain assessment

According to the International Labor Organization Code of Practice on Ambient Factors at the Workplace from 2001, thermal conditions should be measured in the workplace, taking into account the temperature and humidity in each work task cycle, the clothing worn, and physical activity performed.[77]

1.2.2.1 External heat

The Wet-Bulb Globe Temperature (WBGT) is perhaps the most well-known and widely utilized of many different indices of the external component of human heat stress exposure.[74] It is an International Standardization Organization (ISO) standard (7243:2017). It was developed based on observations of heat illness among US Army and Marine Corps soldiers in the 1950s, where guidelines based on this index effectively reduced heat illness among soldiers.[78] It is measured using three different thermometers, the readings of which are combined using a simple formula.

$$WBGT = 0.7 * T_W + 0.2 * T_g + 0.1 * T_d$$

T_W is the natural wet-bulb temperature, which is measured using a thermometer covered by a wetted cloth. Due to evaporation, it records a lower temperature than a standard thermometer when relative humidity is low. T_g is the globe thermometer temperature, which is recorded inside of a 15 cm diameter black globe, something which makes it record a higher temperature when there is radiation from the sun or other radiating heat source. T_d is the dry-bulb temperature, measured with a standard thermometer not influenced by moisture or radiation.

One important limitation of WBGT is that it underestimates heat stress when evaporation is restricted by high humidity or clothing with low water vapor permeability.[24 78]

Due to the size of WBGT measurement equipment, personalized WBGT monitoring cannot be performed. Simpler devices, which log temperature and humidity only, can instead be mounted on the individual to provide personalized exposure assessments of these parameters.

1.2.2.2 Physical workload, i.e. internal heat production

There are different methods, with widely different logistic demands and accuracies, for assessing physical workload and thereby internal energy production (ISO 8996:2021).[73] Calorimetry measure heat production or oxygen consumption to calculate how much energy is consumed. Oxygen consumption can be measured outside of laboratory settings using a breathing mask, but this relatively inconvenient equipment may interfere with the way activities are conducted, making this option difficult to use in occupational settings. Less exact and expensive estimates of physical workload include measuring body movements using accelerometers, or heart rate.

Triaxial accelerometers are small devices which sense movements in three dimensions using piezoelectric materials. Accelerometer-based techniques are sometimes used to measure physical activity in epidemiological studies.[79] Several different available equations validated against more exact methods of energy expenditure calculation translates the movements recorded to energy expenditure estimates. These estimates are generally worse at assessing energy expenditure of tasks which are more complex and involve upper body work, as estimation equations were not developed for such activities,[80] and as accelerometers are typically worn on the hip.

Heart rate can be measured using an optical sensor in a wristband, or using an electrical sensor worn in a chest strap. The latter is considered more reliable in occupational settings as hand grasping, arm movements and dirt may interfere with optical sensing of pulsations at the wrist. Heart rate is closely associated with physical workload if environmental temperature, emotive state, mental load, age, physical fitness, medication and several other individual characteristics are constant.[73] Heart rate increase relatively more in response to upper than lower body activity.[73] The increase in heart rate from increasing temperatures can be problematic in settings where heat stress is substantial, as it risk overestimating physical workload at high external temperatures.[81]

Physical workload may also be assessed by observations rather than measurements. The ISO standard on heat determination of metabolic rate (8996:2004) describe two different levels of detail for such assessments. In level 1 assessments of the mean physical intensity of the activity is broadly described as resting, low, moderate, high and very high (Table 1). This method is considered to have very low accuracy, and may also change with time as jobs are increasingly mechanized.[82] In level 2, an observer notes each specific activity, and the duration of these activities, in order to calculate the time-weighted average metabolic rate using a table with measured metabolic rates for detailed activities. The skills and knowledge of the observer determine how accurate this method is.[82]

Table 1. Classification of workload in the Adelante cohort based on ISO 8996:2021, level 1 assessment.

Metabolic rate class	ISO 8996:2021 Example task	Adelante cohort job category
Low	Standing, light activity (e.g. laboratory)	Field support staff
Moderate	Sustained hand and arm work (e.g. polishing)	Irrigation repair work
High	Intense arm and trunk work with hand tools	Seed cutters
Very high	Working with an axe	Burned cane cutters

1.2.2.3 Clothing

The degree of transfer of heat between the body and the surrounding environment is affected by the evaporative resistance and thermal insulation of clothing.[83] Garments with a high evaporative resistance, such as protective equipment against some toxic and infectious agents, have a high resistance to water vapor which reduce the cooling effect of sweating.[83] Thermal insulation is mainly determined by the volume of still air trapped in the garment, as air has a low thermal conductivity. Thermal insulation may protect against heat from radiant sources,[83] but also conserve metabolic heat in the body. Evaporative resistance and thermal insulation can be measured using manikins simulating human body heat production, sweating and movements,[83] but can also be estimated by summarizing known values of typical clothes (ISO 9920:2007).

1.2.2.4 Core body temperature

Core body temperature can be estimated using the predicted heat strain (PHS)[84] model described in ISO 7933, which calculates heat accumulation based on the heat balance equation and detailed information on environmental characteristics such as temperature and humidity, clothing and physical workload. Calculation of the PHS model has been implemented in web calculators[85] and free software including R packages.[86]

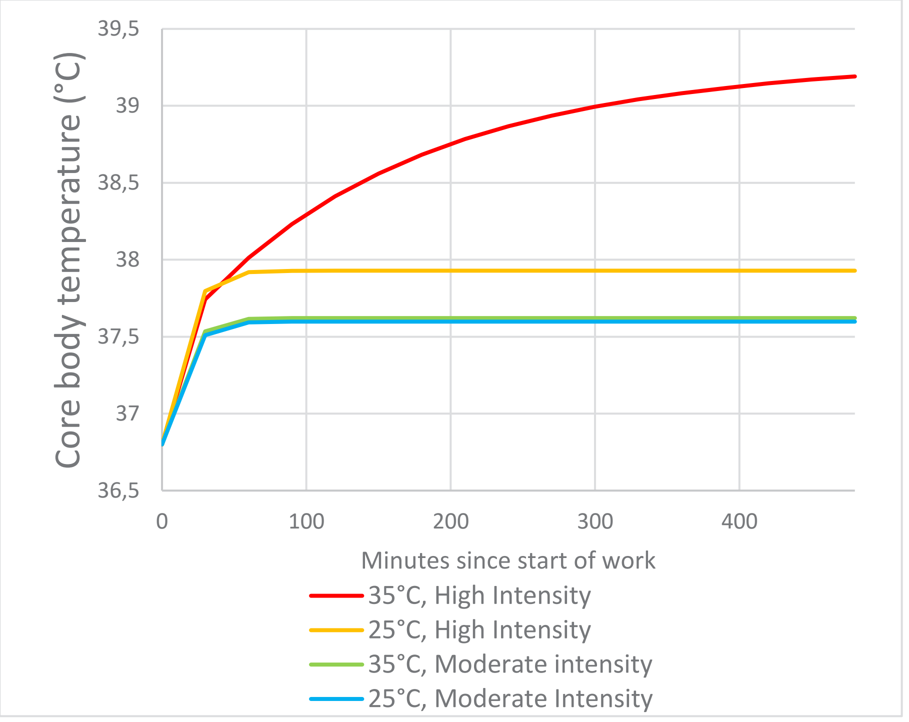

Figure 1. *Predictions of T_c using the predicted heat strain model (ISO 7933) for an acclimatized worker in 40% relative humidity, work clothes, no solar radiation. Calculated using https://www.eat.lth.se/fileadmin/eat/Termisk_miljoe/PHS/PHS.html*

In exercise and occupational research settings T_c is typically measured in the gastrointestinal tract, either by a nasogastric or rectal probe, or by an ingestible thermometer pill which send temperature readings to an external data logger. The latter method is most easily applied in occupational settings. Ingestion of cold (5-8°C) drinks may however lead to temporary decreases in temperature measurements for up to 8 hours after thermometer pill ingestion.[87] Among commonly used surrogate measurement sites of T_c, tympanic temperatures are probably more accurate reflections of T_c than oral and axillar measurements.[88] The accuracy of tympanic temperature measurements may vary by equipment quality and measurement technician.[88]

Core body temperature may also be estimated from continuous heart rate. At least two methods exist for this. Buller et al (2013)[89] developed an estimation algorithm, with an overall bias of -0.03°C, and 95% limit of agreement (LoA) of 0.63°C compared to gastrointestinal (i.e. T_c) temperatures in hot conditions. There was a tendency towards underestimating core temperature at low workloads, which however did not lead to missing relevant hyperthermia, and to overestimate T_c at high workloads, thus erring on the side of caution.[89] Ioannou et al (2019) developed a method using the PHS model to predict T_c from heartrate, reporting an overall bias of 0.06 with a 95% LoA of 0.58°C in a small validation study.[90] Differences of ~0.6°C may be considered large, but are comparable to the agreement between esophageal and rectal temperatures.[89]

1.2.2.5 Dehydration

It has been argued that there is no gold standard for assessing hydration status at one time point.[91] The most accurate measurement technique: isotope-based measurement of total body water content combined with plasma osmolality relies on control of posture, diet, water intake, physical activity and environment, and requires several hours until equilibrium is reached.[91] It is therefore not feasible in occupational settings. Rather, it has been suggested that repeated measurements of body weight at several time points throughout the day is the best way of estimating hydration status among free-moving individuals: decreasing body weight indicates ongoing uncompensated loss of body water, i.e. dehydration.[92] This view is supported by considering hydration status, and the euhydrated state, as having a sinusoidal variation, rather than something which ever reaches a steady state between the various compartments within which body fluids are distributed.[91-93] Body weight is an apparently simple measurement. However, measurements should be in the nude or underwear only, without sweaty clothing,[92] something which is problematic in occupational settings.

One concern with using urine-based markers of hydration (e.g. osmolality, specific gravity, color, or creatinine concentration) is that tubular kidney disease may lead to a reduced ability to concentrate urine, meaning a pathologically non-concentrated sample may theoretically be erroneously interpreted as a state of adequate hydration. Another potential problem of urine-based markers of dehydration is that large fluid boluses may be rapidly excreted by the kidneys as dilute urine even if there is dehydration in intracellular compartments.[91] This is due to avoiding intravascular fluid overload being a key homeostatic aim, and the time it takes to reach fluid equilibrium between intra- and extracellular compartments.[91] Despite these limitations, urine specific gravity still may have a role to play in assessing hydration status,[93] also at workplaces. Urine density may be an important indicator of pre-shift hydration status, as the worker then more likely can be assumed to be in a steady state, and weight change is not applicable.

1.2.2.6 Physiological strain index

The physiological strain index, PSI, combining measurements of T_c and heart rate has been suggested to estimate combined physiological strain from physical work, environmental heat exposure, and dehydration, and respond rapidly to rest.[94] It is calculated from rectal temperature (T_{re}) and heart rate (HR) at baseline ($_0$) and during work ($_t$), using the formula:

$$PSI = 5 \times \frac{(T_{re,t} - T_{re,0})}{39.5 - T_{re,0}} + 5 \times \frac{(HR_t - HR_0)}{180 - HR_0}$$

This index has been found to increase in agricultural worker groups with kidney injury during harvest[95]. In that study, T was assessed using spot tympanic membrane measurements as surrogates of T_c, and HR_t was assessed using spot measurements of heart rate. Although this keep data collection costs very low, the agreement between PSI measured this way and measured using continuous heart rate and gastrointestinal/core temperature measurements in occupational settings is not known.

1.2.3 Health effects of heat

Acute effects of heat on health are known to range from minor skin disorders (heat rash), via benign temporary weakness and loss of consciousness (heat collapse) to life-threatening multi-organ failure (heat stroke).[96] Heat stroke is characterized by the collapse of thermoregulatory functions, leading to hot, dry skin, rapidly rising T_c, a pronounced systemic inflammatory reaction associated with injury to multiple organs including kidneys, and blurred consciousness or coma. Heat stroke is usually divided into two distinct entities, exertional heat stroke occurring in persons engaged in heavy physical activity and classical heat stroke which more often occur among elderly with underlying health conditions or medication putting them at increased risk of elevated T_c at rest during heat waves.[96]

The pathophysiology of heat stroke is not completely understood, although current theories stress the role of an aberrant systemic inflammatory reaction.[96] Increased gut permeability as splanchnic blood flow is reduced may compromise the gut's barrier function, increasing blood levels of pro-inflammatory bacterial waste-products (i.e. endotoxin), initiating a systemic inflammatory reaction with circulatory disturbances and organ injury. Increased body temperatures may also directly cause cell death and impair coagulation system function, mechanisms which may also contribute to inflammation and heat stroke pathogenesis.[96]

The health effects of prolonged exposure to heat are less well understood than the acute.[92] Although studies point to an association between acute heat exposure and AKI,[97 98] recurrent, prolonged exposure to heat is not universally accepted as a cause of CKD.[10]

1.2.4 Regulation of occupational heat strain

World Health Organization guidelines consider that T_c above 38.0°C due to occupational heat stress carry unacceptable risks,[99] whereas American College of Governmental Industrial Hygienists (ACGIH) guidelines make an exception for medically selected, acclimatized workers to reach up to 38.5°C.[75]

Heart rate is more easily measured than T_c, and ACGIH provides two guidelines for interpreting heart rate as an indicator of acceptable heat strain during work: 1) heart rate should not exceed 180-age beats per minute during three consecutive minutes and 2) recovery heart rate one minute after maximum effort should not exceed 110 beats per minute.[75] The ACGIH guidelines also emphasize monitoring symptoms of heat strain: sudden and severe fatigue, nausea, dizziness or lightheadedness should lead to work discontinuation.[75]

1.2.5 Heat illness prevention

1.2.5.1 Hydration

In a recent study among agricultural and construction workers in Spain, Cyprus and Qatar, advising on a hydration schedule of 750 ml/h led to a decrease in T_c in most settings. It was concluded that this is the single most important and feasible technical way of mitigating effects of occupational heat stress.[100] When heat-exposed exercising or working humans themselves choose how to hydrate, many become dehydrated,[92 101] and institutions such as the US Army provide guidelines for the hourly consumption of water for different WBGT and workloads.[102] Dehydration has been associated with a lower sweat rate, something which may increase core body temperatures.[92] Working while dehydrated has been associated with increased T_c in experimental conditions,[101] and it is generally considered important that exercise is initiated when not dehydrated.[103] Following a scheduled fluid intake rate rather than ad libitum drinking during exercise is however more controversial.[76 103] Experimental, athletic and occupational conditions differ, and the symptoms and reduced performance which dehydration cause may lead to different changes in behavior depending on the setting.[76] Hyperhydration is not better than euhydration for limiting hyperthermia,[101] and voices have been raised warning against employers relying too much on hydration as an approach to mitigate dangers from heat stress.[76]

Excessive water intake can be dangerous. US Army and National Institute of Occupational Safety and Hygiene (NIOSH) guidelines state that water intake should not exceed 1.4 L/h or 11 L/24 h.[92 102] Extreme water intake is primarily dangerous due to the risks of cerebral edema associated with hyponatremia.[92] In an intervention study among Guatemalan sugarcane workers,[104] workers were incentivized to drink by giving lottery tickets to those with a urine specific gravity <1.020, which is indicative of absence of dehydration.[105] However, the majority of workers ended the workday with a very dilute urine (67% <1.005), most of them drinking much more than recommended above. The mean sodium concentration among these workers at post-shift was approximately 135 mmol/L,[104] indicating a large proportion were hyponatremic.

The American College of Sports Medicine (ACMS) and NIOSH recommend electrolyte solution for replacing salt if sweating is prolonged (>2 hours).[92 93] However, both NIOSH and ACMS stress the importance of meals for stimulating hydration and as a source of electrolytes which in most cases is sufficient.[92 93] Long term effects of electrolyte imbalances and supplementation are not well understood.[92]

Fluid containers worn at the back, connected via a tube to a mouth piece allow for continuous hydration during activity, and have successfully been trialed among sugarcane cutters.[106 107] A theoretical benefit of these are that small fluid volumes continuously added may more efficiently be absorbed and distributed in the body compared to large boluses. However, breaks needed to hydrate may also have benefits for reducing core body temperatures.

1.2.5.2 Rest breaks

Several institutions, such as NIOSH[92] and the US Army[102] have made recommendations for at which ambient temperatures and/or WBGT levels physical work at different intensities heat stress may lead to dangerous heat strain, and how much rest is needed per hour to avoid this (Table 2). Such guidelines can be used to screen for settings where heat strain assessment by more detailed techniques such as estimation using the PHS model or measurements of core body temperature or heart rate are needed.[75 108] However, rather than stipulating mandatory rest break schedules, some researchers argue for allowing workers to self-pace as a safe way of regulating work intensity which minimizes productivity losses.[109]

There seems to be only little research on the effect of mandatory versus spontaneous, worker-initiated breaks on heat strain. In an experimental setting, self-determined breaks were too short to allow the body to cool down sufficiently.[100 110] Paradoxically, mandating planned breaks for agricultural and construction workers in one study increased HR, something the authors attributed to higher HR when standing or walking during breaks rather than crouching to pick fruits, and too short breaks (90 seconds every 30 minutes of work or 10 minutes every 1 h).[100]

The effects of planned, mandatory breaks vs. relying on self-pacing is likely dependent on the workers' perception on possibilities to adapt their workload to the environmental conditions without this having severe economic consequences. In agricultural[100] and construction[109] workers who were able to self-pace, external heat did not correlate with T_c, or T_{ear} and HR respectively, something which was interpreted as self-pacing being sufficient to limit hyperthermia in these settings.

Rest/work schedule according to US Army guidelines[102], combat uniform							
WBGT range (°C)		Easy work		Moderate work		Heavy work	
Low	High	Work	Rest	Work	Rest	Work	Rest
25.6	27.8	-	-	-	-	40	20
27.8	29.4	-	-	50	10	30	30
29.4	31.1	-	-	40	20	30	30
31.1	32.2	-	-	30	30	20	40
>32.2		50	10	20	40	10	50

Rest/work schedule according to NIOSH guidelines[92], normal work clothing							
Adjusted* air temperature range (°C)		Easy work		Moderate work		Heavy work	
Low	High	Work	Rest	Work	Rest	Work	Rest
34.4	35.0	-	-	-	-	45	15
35.0	35.6	-	-	-	-	45	15
35.6	36.1	-	-	-	-	40	20
36.1	36.7	-	-	-	-	35	25
36.7	37.2	-	-	-	-	35	25
37.2	37.8	-	-	45	15	30	30
37.8	38.3	-	-	40	20	30	30
38.3	38.9	-	-	35	25	25	35
38.9	39.4	-	-	30	30	20	40
39.4	40.0	-	-	30	30	20	20
40.0	40.6	-	-	25	35	15	45
40.6	41.1	45	15	20	40	Caution	
41.1	41.7	40	20	15	45	Caution	
41.7	42.2	35	25	Caution		Caution	
42.2	42.8	30	30	Caution		Caution	
42.8	43.3	15	45	Caution		Caution	
>43.3		Caution		Caution		Caution	

*Table 2. WBGT, Wet-bulb globe temperature. NIOSH, National Institute of Occupational Safety and Health. *Naturally ventilated settings with 30% relative humidity, perceptible air movement and work in shade/at night. Subtract 2.2°C for each 10% relative humidity below 30% (down to 10%). Add 1.7°C for each 10% relative humidity above 30% (up to 60%). Add 3.9°C in partly shaded conditions. Add 7.2°C in full sun.*

1.2.5.3 Shade

Radiant heat from the sun can be substantial, especially in tropical areas where the sun angle is high. NIOSH recommend adjusting their temperature-guided rest-schedule recommendations by adding 7°C to ambient temperatures when in full sun (Table 1).[92] Climate-CHIP add 2.5°C when estimating WBGT in sunny compared to shaded conditions,[111] an adjustment which has large implications when applying WBGT-based rest/work schedules. A small trial of the effect of shade tents used at Ingenio San Antonio (ISA) on WBGT (reported in e-mail from Denis Chavarria, 2020-04-18) was performed by measuring WBGT every 10 minutes from 10:30 to 12:00 on a single day, finding that WBGT was on average 2.0°C lower in a black shade tent and 2.7°C lower inside a green shade tent (the latter used in Harvest 2, Paper III).

1.2.5.4 Worker empowerment and payment structures

It has been concluded that "empowering laborers to self-pace is the basis of heat mitigation".[100] In occupational settings, the possibilities to adapt behavior by heat stress may be limited as there may be no available shade, and protection from other hazards require a certain type of clothing. Further, per-piece payment is common for agricultural workers,[112-114] and has been associated with higher physical activity and risk-taking, and higher risk of kidney and other types of injuries among workers in agriculture and other sectors.[113-118] However, at least among Californian agricultural workers, who work in a hot and dry climate characterized by cold morning and hot afternoons, per piece payment may enable workers to adapt their pace when heat levels increase.[114] The payment structure can affect how agricultural worker views heat stress regulations such as breaks, with piece-paid workers viewing these as "imposed" and hourly-paid workers as "acts of compliance".[118]

1.2.5.5 Technological aids

A textbook chapter on applied work physiology begins by stating that "With the development of mechanization, automation, and many work-saving devices, modern technology has eliminated much heavy physical work".[73] While this may be true in many high-income settings, much heavy physical work is still performed in low-income settings,[82] where the climate is often hot. Further, providing technological aids do not necessarily lead to reduced efforts. Among Cypriot fruit pickers, providing a machine for carrying fruit lead to increased productivity, but not decreased HR or T_c,[100] indicating that at least these agricultural workers maintained effort and increased output rather than decreased efforts and maintained output when given the possibility.

However, technological improvements that enable workers to remain productive under heat stress may nevertheless be important. Reduced productivity as heat increase may become a significant burden for economies in hot regions as temperatures increase,[97] something which is likely to have important secondary effects on health.

1.2.5.6 Acclimatization

An acclimatization period is promoted by the US Department of Labor Occupational Safety & Health Administration (OSHA) in addition to water, rest and shade (WRS).[119] Large proportions of hospitalized heat-related kidney injury[120] and fatal heat illness[121] occur in newly hired workers. While individual susceptibility may be one reason underlying this, as well as inadequate experience of work tasks, the physiological changes that the body undergo after 7-14 days of gradually increasing heat stress is likely another contributing cause, which should be utilized to decrease the risks of working in heat.

During gradually increasing heat stress, sweating and skin blood vessel vasodilation is initiated at a lower T_c.[103] Thereby, heat losses through evaporation of sweat is larger, and conductive heat losses are greater as a larger temperature gradient between the skin and surrounding remains.[73] Having high aerobic fitness may also prevent elevation of core body temperatures due to similar mechanisms as heat acclimatization, and effects of physical aerobic training and heat acclimatization overlap.[103]

1.3 SUGARCANE CULTIVATION IN MESOAMERICA AND AT INGENIO SAN ANTONIO

Sugarcane in Mesoamerica is cultivated by large-scale mills in monocultures covering thousands of acres and small farmers selling cane to the mills (outgrowers). The mills produce molasses, sugar, ethanol (as biofuel and liquor) and electricity. Workers are hired and/or subcontracted for various outdoor tasks related to planting, irrigation, weed and pest control, and harvest. Employment forms among outgrowers are likely less formalized. Workforce size vary much over the year. Sugarcane workers in Mesoamerica are recruited from local communities, or migrate for the harvest season.[122]

Ingenio San Antonio (ISA), situated in the north-western Nicaraguan Chinandega province, is the largest sugarcane mill in the country, employing thousands of workers during harvest season.[123] It farms its own land and buys cane from outgrowers. ISA was founded in the 1890 and production has increased seven-fold over the past 60 years.[123] Most ISA workers live within 20 km from the mill, but some workers commute for more than approximately 1 hour each day to work (unpublished data). The mill arranges for buses to pick workers up in their communities and drive them directly to their field.

1.3.1 Field workers

ISA employs workers for many different field work tasks. Four jobs are analyzed in the papers included in this thesis: burned cane cutters, seed cutters, irrigation repair workers and field support staff. Workers in most job categories are organized into 60-person groups called *cuadrillas*, who are transported by the same bus from home to work. *Cuadrillas* are headed by supervising and managerial staff monitoring production and the per-piece payment system, and supported by health promotors and staff organizing water and electrolyte solution distribution, together constituting the “field support staff” category. Level of education and employment between harvest seasons differ by job categories, with burned cane cutters being the least educated and those most often conducting jobs in other physically demanding sectors outside of sugarcane between harvests (Table 3).

Sugarcane in Mesoamerica is harvested during the November-April dry season. Fields are burned prior to harvesting in order to remove leaves which makes harvest work more difficult. Burned cane cutters are typically paid by how many tons of cane they cut. A machete is used for cutting cane.

New sugarcane plants are sown by putting the cane stalks cut in 30 cm pieces in the ground. These stalks are obtained by seed cutters, who harvest living green cane, cut it in 30 cm pieces, and put these in a bundle or bag. Seed cutters are also paid by the piece. Both burned and seed cane cutting can be mechanized by the use of harvesters. These machines are however very expensive, does not function well in uneven terrain, and cannot go to fields not connected to adequate roads. Mechanized sugarcane harvesting started in 2002 at ISA, and has been increasing gradually since then.[27]

Seeder workers put cane stalks in furrows previously made by a tractor, and then cover the furrows by shoveling. At least at ISA, payment is per furrow finalized.[27]

Irrigation repair workers identify leaks in underground irrigation tubes, and dig a few decimeters to locate and fix the leak using a rubber tube. As the water is flowing in the underground tubes, the underarms of the workers are submerged for parts of the work cycle. Another type of irrigation is performed by letting a canal temporarily flood a field, a process known as gravity irrigation. Gravity irrigation workers make a hole in the canal wall, wait for the field to be flooded, and then repair the hole again. Both of these activities involve digging, but not for extended periods and work is paid at a fixed rate.

The majority of agrichemicals applied at ISA are herbicides. In 2010, 11 agrichemicals were listed as used at ISA of which three were considered possibly nephrotoxic: glyphosate, cypermethrin and carboxin+captan, and although it could not be quantified, it was likely that some workers were exposed to these substances.[27] Workers applying pesticide wear personal protective equipment with high evaporative resistance possibly exposing them to high heat stress.[83] Weed control is also performed by manual uprooting of weeds by pulling them up by hand. This work involves rather small dynamic muscle activity.

Table 3. Education and employment between harvest seasons for four categories of ISA workers

	Education, median years (IQR)	N	Proportion of workers returning for work reporting ≥2 months of work in						
			Sugarcane between-harvest			Construction	Transportation*	Agriculture (other than sugarcane)	Unemployment
			Heavy work	Moderate work	Light work				
Burned cane cutters	4 (1-6)	97	34%	4%	1%	8%	10%	29%	39%
Seed cutters	6 (4-7)	102	91%	4%	0%	0%	1%	14%	29%
Irrigation repair workers	6 (6-9)	83	7%	92%	1%	1%	2%	1%	50%
Field support staff	10 (6-14)	32	13%	25%	72%	6%	0%	0%	44%

*Tri-cycle driver, loader, ambulating salesperson, push-cart operator etc.

1.3.2 Existing occupational health interventions

ISA has been aware of the high toll of CKD among its workers for at least 30 years.[124] Recommendations on limiting heat stress by limiting workday length to 8 hours and ensuring adequate hydration were made by a local doctor 20 years ago.[3] Approximately 10 years ago, a research team from Boston University conducted an investigation on the possible causes of CKDnT at ISA, which also describe some of the preventive and treatment efforts at that point in time.[27] Workers were then allowed, but not obliged, to take breaks, had poor access to shade, and cane cutters sometimes worked until 3 pm. Workers were provided with electrolyte solution but brought their own water from home (they could however refill from the company buses). Some workers received training on hydration at the start of the harvest season, but there was no acclimatization period.[27]

In 2017, the mill had an occupational safety and health (OSH) organization training workers in heat stress management and supplying workers with tested purified water, electrolyte solution, protective clothing, and shade tents. A two-week acclimatization period was implemented and there was also a schedule for planned breaks. Cutters at ISA were then hired directly by the company and not subcontracted, which used to be the practice in 2010.[27] The mill arranged a pre-employment and mid-harvest screening for kidney disease. Male workers with a serum creatinine exceeding 1.3 mg/dL (115 µmol/L) and female workers exceeding 1.0 mg/dL (88 µmol/L) are not hired. Workers exceeding these threshold at mid-harvest are placed on a two-week sick leave and re-tested at the end of this period. If serum creatinine normalizes, they may then start working again. Otherwise they risk losing their employment.

The mill runs a hospital with inpatient facilities at which workers and their family may seek care. Workers can also be referred there if health promotors find that they are not well in the field. Serum creatinine testing is routinely performed when unwell workers present to the hospital, and it is not uncommon that workers are found to have acute kidney injury.[53] Workers requiring care for kidney injury will also be put on sick leave until creatinine normalizes.

The present procedures at ISA likely represent one of the most formalized structures for heat stress management and kidney disease prevention and care in the Mesoamerican sugarcane industry. The German Development Bank (DEG) provided a loan to ISA's owners to expand their operations in 2017. As part of the loan conditions, DEG funded the research network La Isla Network (LIN) to in partnership with Bonsucro, Nicaragua Sugar Estates Limited and The Nicaraguan Sugar Producers Association launch the Adelante Initiative, which aimed to develop, test and disseminate a heat stress intervention program in the Mesoamerican sugarcane industry.[125]

2 AIM

The overarching aim of this thesis is to advance understanding of the relationship between heat and CKDnT in Mesoamerica.

An ecologic study (Paper I) will be used to visualize the spatial distribution of CKDnT in Mesoamerica, and how this distribution relates to heat and agricultural factors at an area level. The study findings provide a rationale for focusing the rest of the thesis on sugarcane worker populations.

Among sugarcane workers at ISA, Paper II aims to explore the hypothesis that the physically most strenuous jobs are at highest risk of kidney injury, and describe the external heat exposure in relation to established guidelines for heat stress. In the Adelante study, the impact of improving access to water, rest and shade on kidney injury incidence among sugarcane workers is tested using the preceding year as a historical control (Paper III). The thesis then aims to construct a theoretical framework of how heat stress may cause kidney injury and CKDnT which incorporates inflammation, and to test aspects of this framework using questionnaire and biochemical data collected among sugarcane workers (Paper IV).

An important long-term research goal is to understand to what extent kidney injury experienced during prolonged heat stress is relevant for risk of developing CKDnT. In order to provide a basis for this future line of research, Paper V aims to explore the association between the creatinine-based definition of IKI used in Papers II-IV and other markers of kidney injury and dysfunction, thereby also better understanding which kidney structures and functions are impacted. This can help assess whether a mechanistic link between these injury episodes and CKDnT is likely.

Table 4. Thesis at a glance: overview of aims, analytical approaches and papers

Level	Aim	Analytical approach	Paper
Meso-america	Map CKD mortality in five countries and identify area-level risk factors	Ecologic study using routine data, Bayesian hierarchical spatial regression modeling	I.
Sugarcane plantation	Observe work conditions and workload-kidney injury association	Exposure assessment, cross-harvest SCr measurements, regression modeling	II.
	Trial workplace water-rest-shade intervention	Historical control intervention study, regression modeling	III.
Sugarcane worker	Develop organism-level pathophysiological framework	Literature review, IKI biochemistry and behavior risk factor regression modeling	IV.
	Assess validity of IKI as intermediary outcome	IKI case-control comparison of alternative kidney injury markers	V.

CKD, Chronic kidney disease. IKI, incident kidney injury. SCr, serum creatinine.

3 METHODS

3.1 ECOLOGIC STUDY

3.1.1 Data collection

3.1.1.1 Routinely collected mortality or hospital admission data

Routinely collected data refer to data collected not for research purposes, but for example through hospital records, insurance systems, systems for mandatory notification of communicable or malignant disease and vital registries. Such data sources may be useful for developing initial etiological hypotheses by comparing across time periods, geographical areas or population groups.[126] Disadvantages include that routinely collected data is often available only in an aggregated form that does not allow linkage to information on additional risk factors, and that the completeness, validity and accuracy of data are less known than if the researcher collected the data.[126] Routine data on kidney disease mortality on a subnational or national level formed one part of the initial source of epidemiological information on CKDnT in Mesoamerica,[5] and later research studies have utilized datasets with a higher resolution.[4 43 44] However, presentation of the data have often not been done at a high spatial resolution.

Registries on cause of death in several low- and middle countries are often of low or unknown quality.[127] Further, kidney disease may not be an evident direct or contributing cause of death unless laboratory analyses are performed before death. The extent to which such diagnostics are available will therefore influence what proportion of kidney disease mortality is ascertained in routinely available statistics.

Openly available data was sought on health and statistic department webpages and extracted when available (Nicaragua, Guatemala and Mexico). Contacts with researchers having published reports on area-level distribution of CKD was available for some countries (El Salvador and Costa Rica). For Honduras, Panama, and Belize, no area-level data on CKD mortality covering more than one single year could be obtained from e-mail contacts with officials and/or researchers.

3.1.1.2 Climate data source

Assessment of heat exposure at individual level has been described in section 1.2.1. At an area level, heat exposure may be estimated using data from satellites and weather stations. Accuracy of these estimates depend on the distance to weather stations, and this may be quite far in hot low-income countries. In occupational settings, variation in heat exposures at a very local level (microclimate) may have a large impact on heat stress.[128] High-resolution data on the built environment may be used to estimates microclimate.[129]

Ideally, the combined effects of ambient temperatures, humidity, solar radiation and wind speed at relevant time points throughout the day should be considered. Methods exist for estimating WBGT from weather station data rather than measuring it.[130] Climate-CHIP is a website which use historical meteorological data and climate projections to estimate WBGT for indoor and outdoor conditions for each 0.5°×0.5° cell of the world,[111] i.e. a crude estimate as this translates to approximately 50km×50km at the equator. ClimApp is a mobile phone application which calculates a heat stress index based on the weather forecast at the user's Global Positioning System location, and user-defined input on clothing and activity level.[131] Neither of these tools currently allow for export of historical heat stress index estimates to spatial layers which can be integrated in a geographical information system (GIS). This limits their usefulness for assessment of heat exposure between different geographical regions. Within the present study, the external component of heat stress in each geographical area was approximated by the mean maximum monthly temperature in the centroid of each area, interpolated from weather stations data from 1970-2000,[132 133] dichotomized at 30°C.

3.1.2 Statistics of spatial disease mapping

Spatial autocorrelation is the "first law of geography": observations which are near each other are generally more similar than those that are far away. With information about a parameter of interest from one area, one will generally be able to guess that same parameter in a neighboring area with higher accuracy, while it provides less information on a far-away area. This dependence between observations violates assumptions in standard regression models and statistical tests, which require observations to be independent. Not accounting for such autocorrelation will lead to overly certain conclusions about effects.[134]

Hierarchical regression models, in which the dependence between observations is included in the regression model, have been developed in order to account for spatial autocorrelation and is now often used in disease mapping studies.[134] These are random effects models in which observations are seen as nested in structures influencing them through unmeasured factors, similar to methods used for repeated measurements within patients, or children within families etc.. In disease mapping regression models these structures are described either as a function of distance or adjacency between areas. The latter is computationally easier.[134]

As granularity of spatial data increase, so does the noise level. In areas with a very small number of inhabitants, a small number of individuals with the outcome will lead to extreme rates. These extreme areas, which often represent completely random events, can become visually dominating in a map, leading to a noisy, largely uninterpretable map of disease rates. One solution may be to aggregate data and present it at a higher administrative level. This however reduce accuracy in a way which is arbitrary in relation to the actual process giving rise to the data and leads to a loss of information. Another solution may be to color-code only areas with a "statistically significant" low or high disease rate ratio. However, if this does not consider disease rates in neighboring areas it neglects that several neighboring areas may together have a disease rate which is unexpectedly high or low, even if each area on its own does not reach "significance".

Incorporating information on spatial relationships through hierarchical regression models improves utilization of data with important benefits for visualization of spatial patterns.[134] Using such models, it is possible to visualize the underlying process giving rise to the data rather than the noisy data in itself, displaying a modelled effect estimate for each area. This can be seen as a way of "smoothing" the data for improved visualization. A spatially correlated random effects structure smooth the effect estimate towards the local mean, and an uncorrelated random effects structure smooth towards the overall mean, and both can be employed. The expected number of outcomes in each area determines how much smoothing is performed: effect estimates of areas with small populations will be more drawn towards the local and global mean, reflecting the higher uncertainty in such areas.

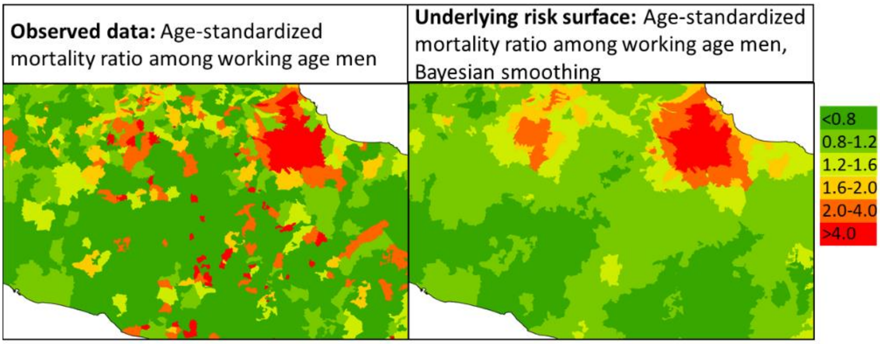

Figure 2. *Maps of CKD mortality in central Mexico: comparison of raw rates (left) and modeled estimates (right). The right figure is part of Paper I* [1]

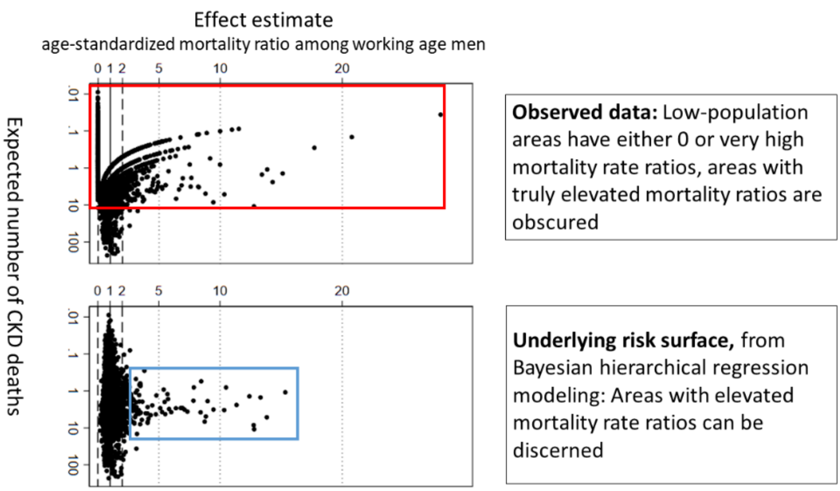

Figure 3. *Illustration of Bayesian smoothing on CKD municipality-level mortality rate ratio estimates for working-age men in Guatemala, Mexico and Costa Rica*

The hierarchical regression models described above have been criticized for potentially obscuring relationships between exposures, which in themselves have a strong spatial variation, and outcomes.[134 135] This occurs as spatial hierarchical regression models may confuse spatial structures with exposure effects, attributing an overly large variation in outcomes to unmeasured spatial factors. More advanced modelling approaches have been developed to solve this issue.[135]

Bayesian statistical approaches are popular for disease mapping. In a Bayesian framework, inference on a parameter of interest is based on the data and the prior, which represent the researcher's belief about the parameter before seeing the data. In the absence of substantial information, this prior can be vaguely specified. The prior and the information in the data are combined to yield a posterior distribution - which can be interpreted as the distribution of the possible parameter values after updating the prior with information from the available data.[136] Inference in a frequentist statistical framework, which currently are more often taught and used in biomedicine and epidemiology, is based on the sampling distribution. The findings of a statistical analysis performed in a frequentist framework describes how often a parameter will be found to be within a certain range, or exceed a certain value, if the same sampling procedure is repeated an infinite number of times.[136]

It has been argued that Bayesian statistics are more in line with how most persons perceive probabilities and uncertainty, and thus is a more intuitive approach.[136 137] However, the main reason for adopting Bayesian statistics in disease mapping applications seem be that these allow for estimation of a larger number of parameters than is feasible to estimate using frequentist statistical approaches, and that large numbers of parameters need to be estimated in the type of hierarchical models utilized in disease mapping.[134]

3.2 WORKPLACE STUDIES

3.2.1 Adelante and WE intervention studies

The sugarcane industry has been in focus of research on CKDnT in Mesoamerica since the recognition of the epidemic, and most occupational studies have included sugarcane workers. As previously described, sugarcane mills employ workers for various outdoor tasks, ranging from strenuous cane cutting to relatively low-workload tasks of irrigation tube repair and the supervisors monitoring fieldwork. This enables identification of contrasts in exposure to heat stress while other environmental exposures and sociodemographic factors are held relatively constant. Sugarcane mills also constitute relatively stable and well-functioning institutions in Mesoamerica, within which it may more easily be possible to conduct workplace intervention studies than in more small-scale and informal sectors.

Two previous studies including different categories of outdoor sugarcane worker categories have been performed at ISA. One of these studies suffered from large losses to follow-up during the harvest season and found that cutters and gravity irrigation workers had a similarly large decrease in eGFR, which however was larger than factory workers, drivers, seeders and agrichemical applicators.[51 138] In a later study, cane cutters had a much higher rate of AKI during harvest season than seed cutters, weeders, irrigation workers and pesticide applicators.[62] In Guatemala, sugarcane cutters had higher incidence of cross-shift AKI than those cutting and planting seed cane.[139] Important extensions of the Adelante[125] study which forms the basis of the workplace studies in this thesis (Papers II-V) beyond the mentioned studies was the ambition to follow workers over a three-year period with gradually improved heat-related working conditions.

Interventions aiming to reduce heat stress among sugarcane workers have been studied at two sites before or in parallel with the Adelante Study: the Worker Efficiency (WE) project at the mill El Angel in El Salvador, and a research project led by Colorado University at a Pantaleon mill in Guatemala. The WE Project has been described in detail previously.[106 107] It built on OSHA's WRS principles, emphasizing also training of workers in ergonomic and efficient cane cutting techniques. At Pantaleon, reports on working conditions interventions so far focus on improving workers' hydration, such as requesting a certain electrolyte or water intake[140] and incentivizing low urine density,[104 105] while workers worked 10-hour days, albeit with three 20 minute breaks and a one-hour lunch break.[105 141]

In the first year of the Adelante study, drip irrigation repair workers were included as an "exploratory examination" of "labor groups believed to have a lower degree of heat stress" than cutters.[142] The plan was to observe the existing working conditions in the first year, and then integrate lessons learned at the WE Project[106 107] to the existing ISA practices for cutters as a way to intervene towards reducing heat strain.[142] Current ISA heat stress prevention practices were not being evaluated for health impact, and it was set as an objective to evaluate whether kidney function levels could remain stable over three years under current or improved heat-related working conditions. The intervention can be seen as consisting of four different aspects: hydration, rest, shade, and efficient and ergonomic cutting. Hydration, rest and shade practices are described in Papers II and III, while interventions to improve cutting is briefly mentioned here.

In the WE Project, workers were given a new type of machete, which was lighter and had a blade with an angle at the middle.[107] They were also instructed how to distribute cutting of rows and stacking of cane to improve efficiency.[107] Workers at ISA already had a machete with a bent blade and the advice on redistribution of cutting were not applicable by the first year of the Adelante study. In Adelante, improvement of machete design continued, with the aim of enabling local production of ergonomically optimized machetes that improve worker efficiency, while reducing muscle damage and musculoskeletal pain. This sub-project has not yet been evaluated.

While the main outcome of both the WE Project and Adelante study were kidney injury and function decline during harvest, and the main exposure workload and WRS intervention, additional data were collected before and after harvest from the workers. Information collected include such proposed as risk factors in previous studies, and a basic biochemical assessment focusing on hydration indicators, inflammation and muscle injury. These datasets formed a rich source of information for testing several of the etiological and pathophysiological hypotheses which have evolved over the past decades. Paper IV was initially developed as a review of heat and exercise physiology on the link between heat exposure and systemic inflammation, inspired by the observation in Paper II that high C-reactive protein (CRP) levels very clearly was associated with IKI. However, during the writing process, more and more related topics became integrated, and with that an analysis of much of the data collected in the WE Project and Adelante study.

3.2.2 Statistical analysis

3.2.2.1 Healthy worker effect and missing data

The healthy worker effect arise as workers with disease are more likely to leave the workforce, leaving a sample of relatively healthy individuals in the workforce. At ISA, screening using serum creatinine before and in the middle of the harvest amplify this pressure towards eliminating workers with kidney disease from the workforce. Mid-harvest kidney injury screening created a challenge in the analysis of cross-harvest kidney outcomes, as who were lost during the harvest season was, at least partly, depending on the outcome. The Adelante study was one of the first in the field to actively follow-up workers who did not show up for testing at the end of harvest.

As outcome data was not missing at random, complete case analysis (i.e. including only workers with serum creatinine assessments before and after harvest) would be biased. As workers who the company had identified as having kidney disease during harvest, through their mid-harvest screening or as patients in their hospital, would be less likely to finish harvest work and thus be completely observed, this bias would lead to an underestimate of the incidence of cross-harvest kidney disease, and could reduce the possibility to see an effect of different job groups (Paper II). When analyzing whether reducing heat stress reduce kidney injury (Paper III), including only workers finishing harvest could lead to erroneously making the conclusion that there is an intervention effect if identification of kidney injury during harvest improved.

Workers who did not attend end-harvest measurements were contacted after harvest to investigate the reason that they did not attend. Substantial proportions indicated that they had left due to kidney disease, information which could also be verified in mill OSH and hospital records. Having a strategy for follow-up of drop-out workers, both in the field-work and statistical analysis, is an important lesson learned for future occupational studies on CKDnT, especially in settings where screening during follow-up amplify healthy worker selection bias.

3.2.2.2 Continuous and binary creatinine-based kidney outcomes

Unless explicitly written, eGFR refers to $eGFR_{cr}$ estimated using the CKD-EPI equation,[143] as it was the only method of GFR estimation utilized in this thesis.

Kidney function estimated as eGFR is measured on a continuous scale. Some inter-individual variation in assessed kidney function is to be expected: variations in diet, hydration status, and time of day may lead to slight variations in serum creatinine, and creatinine is also measured with an error (the coefficient of variation at the laboratory was approximately 1.5%). Within individuals one would therefore expect changes in eGFR across the 6-month harvest season ($\Delta eGFR_{cross\text{-}harvest}$) to fluctuate up and down without this necessarily representing pathology but rather “noise”.

The concordance between eGFR and GFR worsen at high (>90 ml/min/1.73m^2) GFR levels. The change in eGFR estimated for each unit change in SCr is larger at low SCr values than higher. Therefore, small and uncertain fluctuations in SCr at a low range may lead to large fluctuations in eGFR which link poorly to actual GFR.[59] One needs to be aware that a relatively large proportion of the changes in eGFR is likely to be noise among healthy workers, and that declines as well as increases (due to glomerular hyperfiltration) may be pathological when using a continuous outcome for $\Delta eGFR_{cross\text{-}harvest}$.

We analyzed a dichotomized change in kidney function outcome in addition to the continuous $\Delta eGFR_{cross\text{-}harvest}$ outcome for a number of reasons. First, it enabled us to combine the SCr measurements among workers attending end of harvest examinations with workers not finishing harvest reporting that they were not there due to kidney disease detected during harvest. In Papers II and III, a distinction is made between $IKI_{measured}$ and IKI_{all}, with $IKI_{measured}$ including only those with a measured creatinine across the harvest season, and IKI_{all} including also those who lack an end-harvest SCr measurement, but report that they left work due to kidney disease. Second, we wanted an outcome which translated to clinical criteria for kidney disease and injury. Last, having a dichotomized case status definition allows for case-control studies, which when nested in cohort studies are an efficient design for investigating exposures which can be analyzed in stored samples.[144] As both cases and controls are selected from the same well-defined cohort, these kind of case-control studies are less likely to be subject to selection bias.[144] Paper V is an example of a study using these stored samples, and more investigations are being prepared. The criteria of a cross-harvest increase in SCr of 0.3 mg/dL was chosen based on its analogy with the definition of AKI, and inspection of the normal distribution of $\Delta SCr_{cross\text{-}harvest}$ (Figure 3).

Departure from the normal distribution is often used to identify when a biological process is not following an expected pattern. The theory behind this is that the distribution of a sum of a very large amount of influencing factors will have a normal distribution.[136] Therefore, an outcome which is the combined result of a large number of small contributing causes will also be normal. An example is body height: it is affected by several genes, and the influence of dietary intake and health at different time points of a child's growth periods including in utero, and perhaps even factors in the child's parents and grandparents. Together, these factors constitute a huge number of complex and interacting causes all contributing a small proportion to the final result, which when summarized have a normal distribution.[136] Individuals which do not fall within this distribution are more likely to be affected by a strong and specific causal factor, in this case a pathological condition.

Figure 3 displays the distribution of $\Delta SCr_{cross\text{-}harvest}$ among male burned cane and seed cutters during harvest 1 (i.e. Paper II), visualizing two workers with a clear decrease in SCr across the harvest, a central group containing the majority displaying relatively stable SCr values, and a tail of workers with SCr increase which does not fit into the normal distribution. The beginning of this right tail is well approximated by the 0.3 mg/dL threshold which is used as a threshold for AKI over shorter time spans in clinical settings. Workers above this threshold are denoted to have IKI in Papers II-V.

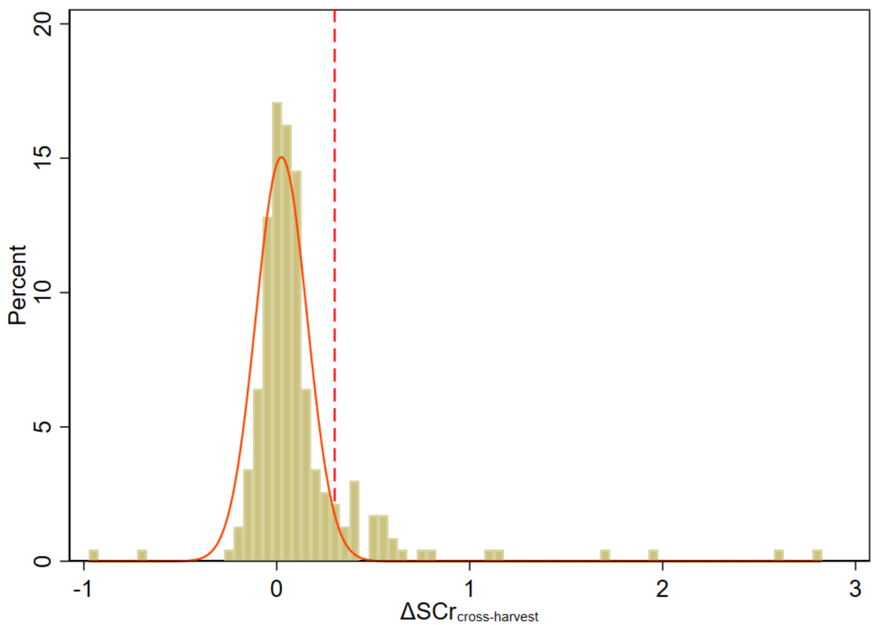

Figure 3. Distribution of cross-harvest serum creatinine changes in Harvest 1. Red solid line describe the normal distribution in workers with $\Delta SCr_{cross\text{-}harvest}$ <±0.3 mg/dL. Red dotted line denote the 0.3 mg/dL threshold for IKI, incident kidney injury

3.2.2.3 Alternative estimation of GFR

Serum cystatin C was measured in parallel with creatinine in the Adelante and the WE Project, something which is novel in this setting. The relationship between $eGFR_{cy}$ and $eGFR_{cr}$ among male sugarcane cutters has been described in parallel with this thesis, finding that $eGFR_{cy}$ is generally much lower than $eGFR_{cr}$.[145]

The difference between $eGFR_{cy}$ and $eGFR_{cr}$ is pronounced also in other work categories in the Adelante study (Figure 4). Without measuring GFR, it is not possible to tell which of $eGFR_{cy}$ or $eGFR_{cr}$ is the most accurate.

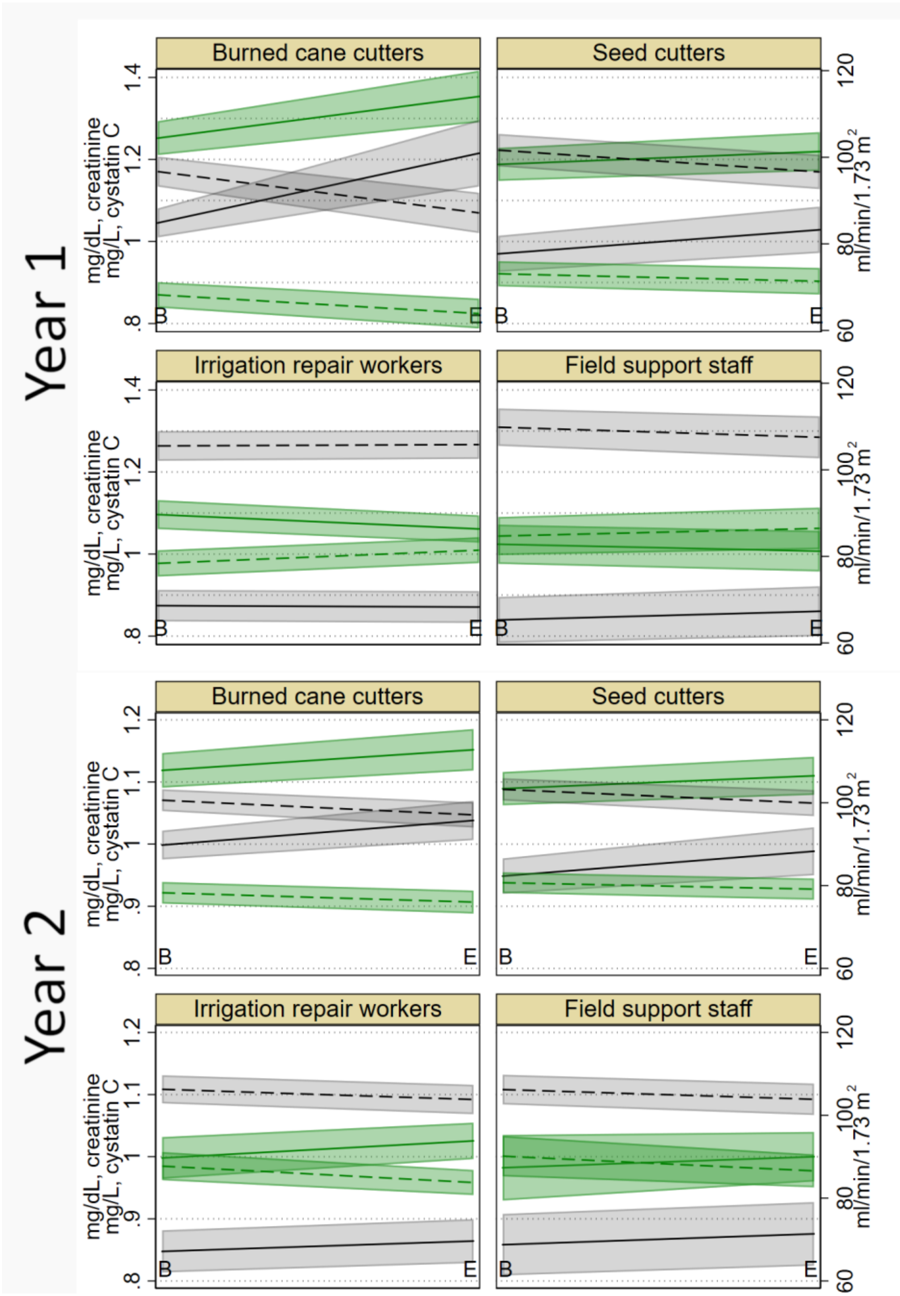

Figure 4 Mean cystatin C, creatinine, eGFRcy and eGFRcr by job category in the Adelante study. Lines represents means and fields their 95% confidence intervals. Dashed lines denote eGFR, solid serum concentrations. Green denote cystatin C, gray creatinine. B: Baseline, E: End-harvest.

3.2.2.4 Urine-based kidney injury markers

As mentioned in section 1.1.2, kidney injury and disease progression risk can be assessed using urine measurements of albumin, which is filtered at a very low fraction through healthy glomeruli and largely reabsorbed by healthy tubuli.[21] There are also several emerging urine markers of kidney injury considered specific to tubular injury, which have been associated with a worse kidney disease prognosis.[146 147] A selection of such markers were analyzed in Paper V.

Understanding the relationship between kidney injury markers and the overall concentration and flow of urine is important for interpreting concentration of compounds in urine spot samples. Urine albumin concentration is typically divided by the creatinine concentration, which is reasonable as creatinine is also (mainly) excreted via glomerular filtration and concentrations thereby will change in a similar way as fluid is reabsorbed along the tubuli. For markers which are actively secreted or synthesized in response to injury in distal parts of the tubuli, it is less clear that indexing to urine creatinine is appropriate.[148] Even if a cohort study of CKD patients found that indexing the tubular injury marker to creatinine and adjusting for urine creatinine concentrations generally yielded similar results when analyzing associations between the tubular injury marker and kidney disease outcomes,[148] urine creatinine excretion in sugarcane workers could be expected to be importantly influenced by physical activity.[149]

The few studies which have analyzed urine tubular injury markers in relation to physical activity have handled this issue differently. In a study of marathon runners, Mansour et al report only tubular injury markers not adjusted for creatinine, not mentioning the possibility that cross-run increases in urine tubular injury markers may be due to more concentrated urine.[150] Chapman et al used different adjustment approaches: no adjustment, and adjustment to urine creatinine, osmolality and flow rate.[151] Different ways of adjusting for urine flow or concentration yielded somewhat different results in this experimental setting. Laws et al[138] adjusted for urine concentration using creatinine in their study among sugarcane workers, assessing cross-harvest changes in the tubular injury marker NGAL concentrations while Sorensen et al[104] did not in their cross-shift assessment of the same biomarker. There is no established method for accounting for urine dilution when analyzing tubular injury markers after physical exercise, but it is important to try to minimize influence of factors such as physical activity, diurnal variation, diet and muscle mass by analyzing repeated samples in the same worker before and after exposure. When feasible, collecting information on urine flow rate as an alternative indexing variable should be considered. Tubular creatinine excretion increase during the night as eGFR falls,[152] leading to higher urine creatinine concentrations in the morning.

3.2.2.5 Repeated measurements

When considering repeated measurements of e.g. a kidney function or injury marker within individuals, the hierarchical structure of data needs consideration as the kidney function measured in an individual at one time point will be correlated with the kidney function at another point in time. Mixed effects models in which fixed effects for parameters of interest and confounders are included together with individual-level random effects (intercepts and/or slopes) were used for analysis of this type of data in Papers II-V, of which the analysis in Paper III will be discussed in more detail here.

Paper III aimed to describe the change in change in kidney function trajectory during harvest between Harvest 1 to Harvest 2 for different work categories, in order to evaluate the intervention effect. In this analysis, it is important to consider that different workers have different starting eGFR, and that there are also individual characteristics determining how quickly their kidney function decline with time. Both this individual intercept and slope will influence correlation between observations in the dataset, and should be accounted for when modelling.[153] The pattern of correlation within individuals need to be specified when having multiple observations within individuals. Common choices include specifying no specific correlation pattern between repeated measurements (unstructured covariance structure), and an autoregressive structure, in which measurements which are closer in time are assumed to be more correlated.[153] The former is the most general choice and was chosen in the present analysis.

Running separate models for each job category, the group-level effect of each of the four measurement occasions (i.e. pre- and end-harvest Harvest 1 and 2) on eGFR were calculated, accounting for the structure of repeated measurements as described above. From these group-level effects of measurement occasion, the difference between pre- and end-harvest for each harvest, and the difference in these differences, could then be calculated as an estimate of the intervention effect on cross-harvest change in eGFR.

4 RESULTS

4.1 ECOLOGIC STUDY (PAPER I)

Five Mesoamerican countries (Costa Rica, Nicaragua, Guatemala, Mexico and El Salvador) could provide outcome data at a municipal level for more than one year. Areas with the most intense cultivation of sugarcane and yearly mean monthly maximum temperatures above 30°C had the highest CKD mortality or hospital admission rate. The association between sugarcane cultivation and CKD mortality at area level was stronger for men than women in the three countries from which sex-stratified data could be provided (Costa Rica, Guatemala and Mexico).

There was no consistent association between CKD mortality or admission, and crop cultivation intensity for rice, coffee or banana, at above or below 30°C in the five included countries.

4.2 WORKPLACE OBSERVATION AND INTERVENTION (PAPERS II – III)

Wet-bulb globe temperature monitoring in sugarcane worker fields recorded heat levels exceeding those recommended for continuous heavy work for a large proportion of the workday. From approximately 10 am onwards, workers performing heavy work would need to rest half the time on most days in order to be estimated to safely avoid excessive heat strain.

Among 427 outdoor sugarcane workers measured before and after the harvest season 2017-2018 (Harvest 1), there were clear differences in kidney outcomes by physical workload. Those with low-moderate physical work (field supervisors and irrigation repair workers) did not have $IKI_{measured}$ during the 6-month sugarcane harvest season, while 3% and 21% of those with heavy (seed cutters) and very heavy workload (burned cane cutters), respectively, had. The heavy and very heavy workload job categories had worse cross-harvest eGFR decline, at 4 ml/min/1.73m^2 and 9 ml/min/1.73m^2 worse than the workers with low-moderate physical workload, respectively. A large proportion (31 out of 98 reached, 15 not reached) reported leaving harvest work due to kidney injury. After including workers who did not finish harvest, the gradient between heat stress and kidney outcomes remained, with IKI_{all} rates at 2%, 9% and 27% in each of the three job categories.

Less than half (204/427) of the workers who were sampled before and after Harvest 1 were sampled also before and after the 2018-2019 harvest (Harvest 2). However, new workers were hired, and 488 workers were sampled before and after Harvest 2. Cross-harvest eGFR trajectories improved in Harvest 2 among burned cane cutters (from -9 to -4 ml/min/1.73m^2/harvest), remained relatively stable in seed cutters (from -5 to -3 ml/min/1.73m^2/harvest), and worsened slightly among irrigation repair workers and field support staff, albeit still at low levels (from 0 to -2 ml/min/1.73m^2/harvest). $IKI_{measured}$ and IKI_{all} rates improved among burned cane cutters, from 21% to 5% and 27% to 7% respectively. Among seed cutters, there was a trend towards worse IKI rates in Harvest 2, with $IKI_{measured}$ and IKI_{all} rates at 7% and 10% respectively compared to 3% and 9% in Harvest 1. Post-hoc analysis of IKI rates by seed cutter *cuadrilla* revealed that IKI events during Harvest 2 strongly clustered in *cuadrillas* independently judged by the mill OSH lead physician to have worse implementation of the intervention. Rates of IKI remained low among field support staff and irrigation repair workers in Harvest 2.

Among seed cutters, which consist of both male and female workers, men had a higher incidence of IKI, with only 1 $IKI_{measured}$ event in 88 worker-harvests for women compared to 17 in 223 worker-harvests for men.

4.3 PATHOPHYSIOLOGY (PAPERS IV – V)

Elevated levels of inflammation biomarkers was a consistent finding in studies reporting this in workers at risk of CKDnT with recent kidney injury, a finding also replicated in the Adelante and WE Project cohorts.

The increased blood flow demands of the skin and working muscle during work in heat causes a diversion of blood flow from the kidneys by increased vascular resistance in the renal and splanchnic vessels.[73 154 155] Dehydration augments strain on the kidney as blood flow is reduced and urine concentration needs to be increased, leading to increased metabolic demands in the tubuli and simultaneously lowered blood perfusion.[14] This mismatch may lead to cell injury and death, which could cause inflammation.[156] However, also the blood flow to the gut decrease during exercise, heat and dehydration,[157-161] something which may lead to increased permeability to bacterial endotoxin possibly sparking a systemic inflammatory reaction.[96] Non-steroidal anti-inflammatory drugs (NSAIDs) both decrease blood flow to kidney[162] and increase gut permeability[163] during exercise. In our study, intake of NSAID was associated with a higher rate of kidney injury during harvest.

Another potential cause of inflammation during exercise in heat is uric acid, which may precipitate in urine to form crystals which are inflammatory.[72 164] A role of uric acid in CKDnT pathogenesis has been considered,[68 164-167] but it remains difficult to establish whether hyperuricemia represents a cause, consequence or epiphenomenon, as hyperuricemia may also be caused by reduced kidney function. Uric acid may arise from fructose metabolism from consumed sugary drinks. In our study, consuming sugary drinks and having high uric acid levels were associated with a higher risk of kidney injury.

Muscle release cytokines during exercise, which may both stimulate and suppress the immune system.[168] Further, compounds released from injured muscle, such as uric acid,[62] may also contribute to systemic inflammation. In our study, creatinine phosphokinase, a marker of muscle injury, increased during harvest in the work categories with kidney injury, but was not consistently higher among workers with IKI.

Hypokalemia may be both a consequence and possibly a contributing cause of kidney disease. Reduced tubular function may cause potassium wasting, as the fractional excretion of potassium is increased. On the other hand, low potassium levels might also potentially contribute to kidney disease, secondarily to disturbed renal angiogenesis.[169 170] In our study, hypokalemia was more often seen among workers with kidney injury.

Anemia was found to be associated with IKI in Paper IV. Anemia may contribute to worse oxygen delivery to the kidney and could thus contribute to kidney injury and inflammation during the stressful conditions described above. However, anemia may also be a consequence of kidney injury, as EPO is produced in cells situated in structures (tubulointerstitium) found to be inflamed and injured during initial stages of CKDnT. This potential vicious cycle had not been explored previously among workers at risk of CKDnT, and Paper V describe decreasing Hb and EPO levels during sugarcane harvest among workers with IKI. This suggest that kidney injury contributes to the anemia seen in early stages of CKDnT.

Urine concentrations of tubuli-specific markers of kidney injury; KIM-1, monocyte chemoattractant protein 1, calbindin and glutathione S-transferase π increased during harvest in IKI cases, while clusterin did not.

5 DISCUSSION

5.1 ECOLOGIC STUDY (PAPER I)

The ecologic analysis of five Mesoamerican countries indicate that men in hot sugarcane cultivating areas have an increased risk of CKD, something which likely is due to an increased risk of CKDnT among heat-stressed workers. It does however not rule out a causal role of factors not related to heat but associated with sugarcane cultivation in low-land regions, e.g. a soil type or pest leading to a specific metal and or pesticide exposure among populations in such regions, and not the occupationally exposed subpopulation. Ruling out such mechanisms based on this analysis would incur a risk of committing an ecologic fallacy, in which the association at an area level is translated to the individual level.[171] As previously mentioned, there are however previous individual-level studies indicating an association between sugarcane work and CKDnT.[46 48 50] The ecologic approach was useful for obtaining large contrasts in exposure (climate and occupation) in a large dataset with mortality as an end-point, something which would have been very expensive and time-consuming to obtain by individual-level cohort studies in five countries. It also provides a picture of the extent to which sugarcane cultivation in heat affect the distribution of CKDnT in Mesoamerica.

One aim of the research project underlying Paper I was to provide an example of how GIS could be used to describe existing health and environment data, specifically applied to CKDnT. This could then serve as an inspiration and guide for similar studies in other settings, studies that can form an initial assessment of the CKDnT situation in those regions. The possible utility of this approach crucially depend on the availability and quality of outcome data, and this has so far not been demonstrated outside of Mesoamerica. Vital registries are less well-functioning in several other low- and middle income countries.[127] Population-level heat stress exposure data, integrating information on ambient temperature, humidity, wind speed and solar radiation, with physical workload in prevalent occupations is another important component for ecologic studies aiming to further explore links between chronic heat stress and disease, and there is a need for such spatial datasets to be developed. The extent to which GIS and spatial regression modelling has been successfully introduced in the CKDnT community is too early to evaluate.

A number of challenges are associated with interpreting routine data of kidney disease, especially in the context of CKDnT. Kidney disease outcomes may not be adequately captured in settings where possibilities to diagnose kidney disease are limited, or for population groups for which healthcare is less accessible. Migrant workers, who often perform heavy agriculture or construction work, constitute one group where kidney disease may not easily be recognized in routinely available statistics. Epidemiological patterns may not be obvious in returning workers unless detailed occupational history is considered.

Verbal autopsies are utilized to quantify causes of death in low- and middle-income settings where vital registries are not well-functioning. However, kidney disease is probably difficult to identify as a contributing cause of death from interviews with relatives, especially in settings where laboratory analyses to identify kidney disease are not routinely performed or where awareness of kidney disease is low. Standardized prevalence surveys, e.g. utilizing the DEGREE protocol, giving comparable kidney disease prevalence estimates in various populations have been considered an important next step for understanding CKDnT etiology,[39] and this need remains in many parts of the world.

5.2 WORKPLACE OBSERVATION AND INTERVENTION (PAPERS II – III)

5.2.1 Heat exposure assessment

In the sugarcane fields at ISA, workers performing heavy and very heavy work have a non-negligible risk of experiencing hyperthermia unless they rest most of the time after 10 am according to established guidelines for heat stress prevention. However, these guidelines are intended primarily to screen for settings where heat stress is a potential problem and more in-depth assessment should be performed. Such assessments have been performed, but have not yet been published. However, they indicate that worker T_c indeed increase above 38.0°C during a workday.

Adopting a rest/work schedule as outlined by ACGIH or other institutions would undoubtedly lead to a large loss of worktime and thus productivity. Slight increases in rest:work ratio were implemented between Harvest 1 and 2, and could be accepted by the mill and workers. A further increase in rest:work ratio was suggested for Harvest 3.

5.2.2 Workload effect

Heat stress is strengthened as an important cause of CKDnT in Paper II, by finding that the jobs with higher levels of heat stress (cutters) have higher rates of IKI than workers experiencing less heat stress but otherwise work at the same workplace (field support staff and irrigation repair workers) and live in the same municipalities, albeit along different bus routes. Further studies should explore to what extent workers from these job categories are recruited from different communities, and if so, to what extent kidney disease risk vary by residence after considering occupational exposure. Residual variation by residential location, as a proxy for unmeasured environmental exposures, and reduced association between job types and IKI, would then indicate that non-occupational factors confound the very clear gradient seen between job categories in Papers II and III. Preliminary analyses indicate that spatial clustering of IKI among workers at ISA is weak and can be explained by workers from different job categories living in different areas.

The regression modelling analyses in Papers II and III do not adjust for education or other socio-economic variables. These variables are likely to be distal determinants influencing both which job category a worker is hired into, and possibly also workers' understanding of heat stress prevention information, risk perception, and non-occupational exposures and health-related behavior. Thereby, education may be a confounder of the association between job category (as an indicator of workload) and kidney injury. Information on number of completed school years was collected in harvest 1 (Table 1). Accounting for age and sex differences, burned cane cutters had approximately 1 year of schooling shorter than seed cutters, 2 years shorter than irrigation repair workers and 6 years shorter than field support staff. Each year of schooling was associated with a 10% lower incidence of IKI_{all} (incidence ratio (IR) 0.90 [95% confidence interval (CI) 0.84-0.96]). However, after adjusting for job category during harvest, there was no association between education and IKI_{all} (IR 1.01 [95% CI 0.93-1.09]). Conversely, adjusting for education yielded essentially no change in job category effect estimates. This indicates that education does not confound the association between workload and IKI_{all}, and that the effect of education on IKI_{all} is explained by differences in workload.

5.2.3 Intervention effect

In Paper III, an intervention providing better access to water, rest and shade was associated with a reduced rate of IKI among burned cane cutters, and seed cutter groups where the intervention was appropriately implemented. This lends further support to the hypothesis that heat stress is an important cause of kidney injury in populations at risk of CKDnT and demonstrate that heat stress is a modifiable risk factor. Rather than a randomized controlled trial, the intervention in Paper III utilizes historical control observations (Paper II), something which has both advantages and disadvantages. A major reason of this design is ethical; it was considered unethical to withhold water, rest and shade improvements from a control group of workers as these conditions are so basic that they should be fulfilled at work. An advantage is that external validity and generalizability increase as the intervention is carried out in real-world conditions, within the constraints put by being set in an organization with commercial interests rather than an artificial laboratory setting constructed for the intervention itself. An experimental study replicating repeatedly excessive heat stress over several months would not be ethical, and so time-consuming it is impossible to perform in a sufficient number of volunteers. However, interventions in the real world are more difficult to control, especially when implementation of the intervention is within the employer's rather than the researchers' responsibility, and this may have impaired internal validity.

As an example, it became evident after the data had been collected that the intervention may have been differentially well implemented within job categories. In retrospect, individual workers were nested within job groups, *cuadrillas*, and the management in each of these groups were responsible for implementation. Including effects for the cross-harvest slope and IKI risk for each *cuadrilla* may have improved assessments of job category and intervention effects, as there turned out to be marked differences in kidney outcomes and probably intervention implementation between *cuadrillas*. However, the potential importance of *cuadrilla* membership was not recognized at the time of planning the analytical approach.

Collecting more data on implementation of intervention during the harvest would have enabled a quantitative and more objective assessment of the degree of intervention each worker was actually benefitting from. This need of an evaluation of implementation of working condition improvements is an important lesson learned from the Adelante study.[172] What metrics to focus on for this monitoring to be meaningful, and how it can be integrated into employers' self-monitoring are important to understand.

With only one year of comparison, and an unknown background variation in IKI rates between years, it is possible that the apparent improvement from one year to another can be attributed to fluctuation in unmeasured factors not considered here such as epidemic disease outbreaks. Another factor which may have contributed is the breakdown of mechanical harvesters during Harvest 1, which may have disturbed preventive measures otherwise in place. There was however not a clear difference in heat levels between Harvest 1 and 2 (Figure 5). A longer time series before and after intervention would have improved the strength of evidence, but such historical data were not easily obtained from mill records, especially as creatinine measurements seem less well standardized in the years preceding the intervention and there were no systematized end-harvest measurements.

A high worker turnover between Harvest 1 and 2 reduced power to find differences. Workers who are included in both harvests provide more information on intervention effect as they are exposed to both "treatments" (i.e. intervention). Depending on the reason that the workforce changed, it may also have led to other limitations for concluding an intervention effect. If a new group of workers with a smaller or higher risk of kidney injury, for other reasons than occupational exposure, were hired in Harvest 2, then that may have made the comparison of harvests less valid as an estimate of intervention effect. The reason that a large number of workers who were hired in Harvest 1

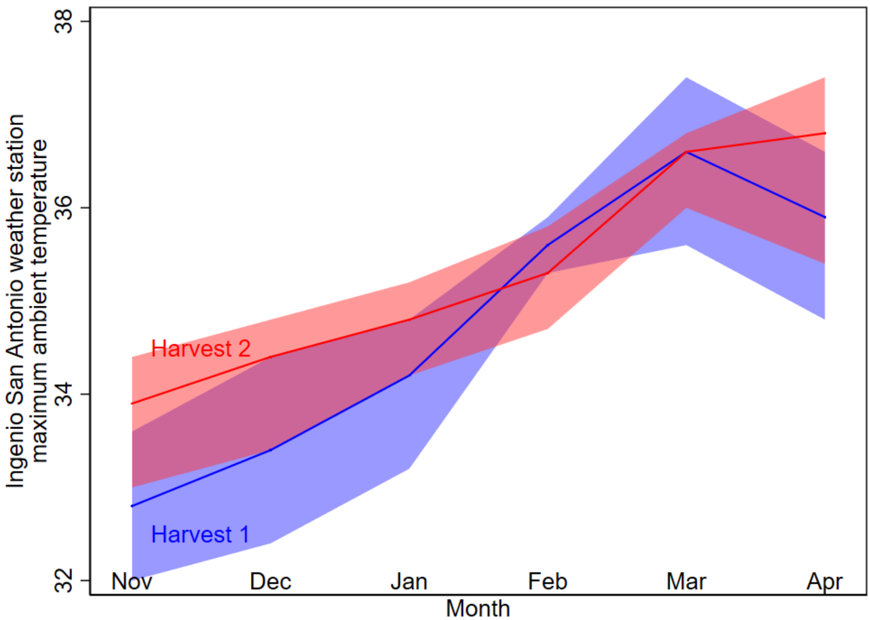

Figure 5 Maximum ambient temperatures during Harvest 1 and Harvest 2 at Ingenio San Antonio weather station. Line is median, shaded area is interquartile range.

were not hired again in Harvest 2 was that ISA changed the bus routes from which workers were sourced, a decision which as I understand it was due to logistic reasons only. Possibly important confounders such as age, sex and number of previous harvests worked were similar within job categories in Harvest 1 and 2.

On the other hand, keeping only workers who participated in Harvest 1 in Harvest 2 could have increased the risk that healthy worker selection bias would induce an artificial protective effect. This can arise as workers who experienced kidney injury during Harvest 1 can be assumed to be less likely to become hired in Harvest 2, and these may have some degree of individual susceptibility to kidney disease. Workers in this way more susceptible to kidney injury would then have been eliminated from the workforce and not replaced by new, and therefor possibly more susceptible, workers as they had been ahead of Harvest 1.

5.2.4 Reflections on the water, rest, shade intervention

An intervention at a workplace allows studying intervention uptake within that organization. This is of key importance for understanding how the intervention can successfully be implemented at scale (chapter 7.1). Such qualitative research has been performed within the Adelante Initiative.[173] External monitoring, a stronger and more out-spoken mandate from high-level to mid-level managers to focus on occupational health alongside with productivity, and communication of health outcomes back to the organization[173] may have led to improved enforcement of the company's previously stipulated but likely less strongly enforced guidelines on heat stress management. This may well have been more important for improving kidney outcomes than the actual changes suggested to rest schedule, and hydration and shade practices between Harvests 1 and 2.

Encouraging proper hydration by educating and enabling workers is likely a safer way to ensure sufficient hydration than enforcing a certain volume and electrolyte intake rate. Factors which may be important for making workers able to drink enough include offering water which is, and is perceived as, safe to drink (not contaminated) and palatable (e.g. non-chlorinated taste),[118] and that workers are obliged to take breaks during which they may hydrate, refill fluid containers, and access acceptable sanitary facilities. Piece-paid workers might choose between hydrating, which takes time, and productivity/incomes.[174] This means that in research in real-life occupational settings, it may be difficult to separate effects of hydration and scheduled rest, as they are linked by hydrating taking time away from work – breaks are necessary for hydration. Focus group discussions with US Latino agricultural workers have identified that beliefs about water consumption and temperatures may hinder appropriate hydration practices,[118] and identifying such within the workforce may improve intervention acceptance and uptake.

ISA has recommendations for hourly water and electrolyte solution intake,[175] and there is a system for monitoring hydration among its workers. With a focus on cutters, a health promoter monitors groups of approximately eight workers each day for liquid intake volume, urine output volume, urine density and weight change during the work shift. If the health promoter thinks the worker does not hydrate sufficiently, the worker will be informed and monitored a subsequent day, until hydration behavior improves. To my knowledge, the effectiveness of this system has not been evaluated, but it provides an example of how hydration can be monitored and promoted at an individual level utilizing easily available technology.

Rest in shade will be more effective than unshaded rest, at least as long as the workers do not have to walk far to reach shade. Moving the tents as the workforce move across the field should therefore not be overlooked.[176] It is also important that the shade tents impair convection as little as possible, meaning that sides of the tent not facing the sun should be kept open for the wind, and that the tent fabric is semipermeable.[176] Workers should also not have to congregate so densely in the shade that convection is impaired.

5.3 PATHOPHYSIOLOGY (PAPERS IV – V)

The combined literature review and data analysis in Paper IV contributed to constructing and strengthening a theoretical framework of how heat stress may lead to kidney injury and disease via activation of a systemic inflammatory reaction. Among the hypotheses put forth and analyzed in this paper, hyperuricemia, muscle injury and renal hypoxia have previously been considered, but novel hypotheses include the role that increased gut permeability to bacterial endotoxin may have in fueling systemic inflammation and kidney injury and disease, and that loss of renal EPO production is a cause of anemia in sugarcane workers with IKI.

Paper IV has an unusual structure, combining elements of a literature review with analysis of original data. It was considered that this format was more suitable for untangling the possible contributing pathophysiological mechanisms linking heat and kidney injury, than a more traditional research paper focusing on a single hypothesis. The approach taken does not allow for directly testing the overall hypothesis that heat exposure is the cause of kidney disease. Rather, several hypotheses, which would be supported by the data if heat is a contributing cause and heat affects physiology the way previous literature is understood, are developed and tested. As the same process was not performed for other proposed etiologies (e.g. pesticides and metals) it is not possible to use the approach taken in this paper for comparing the plausibility of different possible etiologies.

Indeed, the same observation, raised inflammation markers, have also been interpreted by Fischer et al as signs of an “exogenous etiology, such as an infectious agent or toxin”,[53] rather than heat. Fischer et al also interpreted anemia as a finding consistent with Ni intoxication,[177] arguing that the time between anemia and last healthy kidney assessment (a few months) is too short for anemia to be due to kidney disease. These differences illustrate how researchers, perhaps influenced by personal opinions and ongoing research projects, may interpret the same observations differently.

Since the publication of Paper IV, one study has measured a marker of endotoxemia, lipopolysaccharide-binding protein, among heat-stressed workers with kidney injury, providing initial support of this hypothesis.[178]

For some of the findings in Paper IV, such as the association between hypokalemia and hyperuricemia, and IKI, the direction of causality is difficult to determine. Trials of pharmaceutical agents and supplements may be one way of determining these directions in future research. Allopurinol reduce production of uric acid and decreased kidney injury in mice exposed to heat stress.[165] Studies in humans at risk of CKDnT have not been performed although some sugarcane workers with AKD receive allopurinol.[53] Despite the low cost, potassium supplementation has not been studied as prevention or early treatment except for as an electrolyte solutions component.

Paper V corroborates the findings in Papers II-IV by showing that an increase in SCr across the harvest season is associated with an increase in other kidney injury parameters than SCr. This finding indicates that IKI represents actual tissue damage rather than merely a temporarily reduced glomerular filtration. This understanding is important for further longitudinal studies of the link between IKI and CKDnT. Paper V also elucidate a potential mechanism explaining the high rates of anemia in workers with early stages of CKDnT, by finding decreasing levels of EPO among workers with IKI. This may suggest that EPO-producing cells in the tubuli transform to pro-fibrotic myofibroblasts during IKI,[179] something which could explain the negative prognostic value of anemia in early CKDnT.[54]

Further strengthening the findings in Papers II-V, a recent study demonstrated good agreement between cross-harvest changes in $eGFR_{cr}$ and $eGFR_{cy}$ among sugarcane cutters,[145] indicating that reduced $eGFR_{cr}$ is not merely the result of increased creatine metabolism during harvest work.

6 CONCLUSION

The findings of this thesis support that prolonged, repeated strenuous work in heat cause kidney injury among sugarcane workers, a population which previously has been identified to be at high risk of CKDnT. Considering the spatial distribution of CKD in Mesoamerica and its association with sugarcane cultivation in heat, differences in this exposure seem to drive the impact of CKDnT on public health in Mesoamerica at large. Workers with the physically most demanding jobs during excessive external heat stress were more often found to have biochemical evidence of kidney injury and had larger kidney function decline. Further strengthening the evidence of a causal role of heat stress, and demonstrating that this is a modifiable exposure, intervening to reduce heat stress improved kidney outcomes.

It is hypothesized that CKDnT arise secondarily to repeated events of inadequately resolved inflammation-mediated acute kidney injury events. In support of a mechanistic link between IKI and CKDnT, biomarkers linked to long-term worse kidney outcomes were elevated in workers with IKI.

Risk factors for IKI among the workers conducting the most physically intense labor in heat are consistent with those expected if heat stress is an important cause: an inflammatory response, use of NSAIDs, and low electrolyte and water intake.

7 FUTURE PERSPECTIVES

7.1 PUBLIC HEALTH

A large-scale ecologic study support that the sugarcane industry is the key sector driving the CKDnT epidemic in Mesoamerica (Paper I). Intervention studies at three sugarcane mills in Mesoamerica[104 106 139 141] (Paper III) support pathophysiological theories that kidney injury during harvest season can be prevented by limiting dehydration and hyperthermia during work, by making water and electrolyte solution easily available (or even incentivized) and instituting a mandatory rest period each hour. In addition to these modified working conditions, prevention by temporarily removing individual workers with early stages of kidney injury (as identified based on symptoms and/or routine monitoring of easily available biochemical analyses) from heat exposure may be effective as it could be expected to favor resolution of kidney inflammation and injury. Whether these improved working conditions and early injury detection systems can be implemented at a large scale across the sugarcane industry in Mesoamerica, and beyond, needs consideration.

One cannot expect a linear path from research findings to policy[180], and health behavior change may not occur despite overwhelming evidence[181]. Rather than a “common-sense” approach to research impact, i.e. assuming people will adopt research findings because it is the best available knowledge, Kelly et al.[180 181] argue for considering the social structures in which the intervention is supposed to occur and the not purely rational factors which drive human behavior.

Three levels have been considered to influence how research findings impact public health policy[180]; 1) the political/social level, corresponding to the “macro” and “structure” concepts of analytical sociology, at which political viability, public opinion and congruency with current strategies are important factors, 2) the organizational level, similar to the “micro” and “agency” concepts, at which perceived risks, current organizational priorities, leadership commitment, and implementation support availability matter, and 3) the intervention level, which is the technicalities of the intervention as such. Public health interventions, especially those targeting vulnerable populations which aim to reduce health disparities, can also be analyzed using Diderichsen’s and Hallqvist’s[182] theoretical framework on how social disparities in health arise from the interplay between contextual factors and individual vulnerability at various points in the chain between social position, risk of exposure, susceptibility to exposure, and consequence of disease.

This sub-chapter aims to consider occupational heat stress interventions in the Mesoamerican sugarcane industry in relation to the concepts outlined in the previous paragraphs, thereby exploring what may motivate actors at different levels to promote, implement, and ultimately to internalize the changes in work practices likely needed to stop the CKDnT epidemic. While the analysis focuses on the specific case of kidney disease among sugarcane workers in Nicaragua, it may be applicable to other settings where heat stress is a significant risk at the workplace.

7.1.1 Political/social/macro level, and structure

As witnessed by availability of research funds, there is a political will in high-income countries to contribute towards building climate change resilient societies in low-income countries. More or less explicit concerns over increased migration as the climate gets hotter may be one factor motivating efforts to create decent, healthy and heat-insensitive job opportunities in low-income countries. Production of biofuel from sugarcane could help making low-income countries less dependent on energy imports and may become a source of large revenues.

Development banks lend money to biofuel production projects, such as by lending money to build distilleries. CKDnT patients and activists have utilized these institutions' grievance mechanisms to mitigate CKDnT negative impact on health and communities by securing funding for healthcare and alternative local livelihoods.[183] Loan conditions and funding from development banks also enabled one of the first epidemiological investigation of CKDnT etiology[27 183] and most of the research activities underlying Papers II-V of the present thesis.

Public relation risks may be an incentive of change. After its rum "Flor de Caña" received impactful negative publicity,[184] ISA committed to adopting a heat stress intervention program evaluated by external researchers.[185] The sustainable sugarcane platform Bonsucro, which collects stakeholder in the sugarcane industry including several multinational companies such as Coca-Cola, Shell and BP, are revising their production guidelines to include heat stress management (personal communication via Ilana Weiss).

To provide a background on the socioeconomic conditions of the sugarcane worker population, sugarcane cutters at ISA have shorter education than the average Nicaraguan population, and often face difficult economic conditions[186]. The north-west part of the country is dominated by sugarcane monoculture, meaning it may be difficult to find work in other industries. Among the Adelante cohort workers included in harvest 1 and then again interviewed at the baseline of harvest 2, a large proportion of workers report not working for ≥2 months outside of the harvest season (Table 1). Nicaraguan social security systems do not include sickness absence benefits compensating workers prescribed rest due to biochemical evidence of reversible initial stages of kidney injury.

The harsh economic situation facing the workers likely affect their evaluation of trade-off between income today and future health and the way they pace themselves while working. Piece-paid seasonal workers need to have a high accumulated workload during a prolonged period in order to earn an income which can cover expenses during periods of no or less intense employment. Systematized, routine monitoring of workers for early injury markers may not be acceptable to workers as it may increase their economic vulnerability in the short term if findings of early disease cause them to lose income. It will probably be difficult to implement such monitoring without a system for compensation of workers who are prescribed rest or for relocating workers to alternative employments.

Many local physicians and pharmacists attribute CKDnT to excessive heat exposure[58], but little is known about levels of such understanding in the populations employed as sugarcane workers. A household survey found that the proportion of ISA sugarcane workers with CKDnT's household heads who can read was 84%.[186] However, it is more difficult to quantify the level of critical health literacy, which goes beyond being able to read simple instructions and is important for being able to interpret health information and utilize it to improve one's health.[187]

The balance between heat and cold is an important concept in many traditional medical systems, including in Central America.[174 188-190] In Nicaragua, I have encountered beliefs about the health hazards of drinking cold water when it is hot, or taking a cold shower after being hot, and such perceptions are also found among Hispanic agricultural workers in the US.[118] Other cultural concepts are gender norms which some authors link to worse safety culture at male-dominated workplaces such as construction.[191] Male Hispanic agricultural workers were found to identify fewer early heat-related symptoms than female workers, mentioning mostly severe symptoms such as fainting or irritability.[118] Although biological differences could contribute to the increased risk of IKI among men in Papers II and III, these gender differences also likely contribute.

CKDnT has sparked political conflict in Nicaragua for at least 15 years. Workers with CKDnT have protested in the capital Managua and raised road-blocks.[192] There is a history of police violence against protests related to

CKDnT and unwanted police presence at CKDnT victim's funerals.[192] The Nicaraguan government and police force has generally become more repressive and violent following the 2018 protests against pension cuts.[193] [194] While there is a legal right to labor union membership, it has previously been documented that workers engaging in union activities have been punished by not being given food baskets, and that company labor unions disturb independent union activities.[192]

7.1.2 Organizational/micro level, and agency

One reason why the heat stress intervention was difficult to implement at Ingenio El Angel in El Salvador was inadequate support from mid-level management. This highlights the need to understand factors at the organizational level relevant for implementation. Interventions which are based on research funds are unlikely to be sustained as this funding rarely last beyond a few years. That the intervention cause no decrease in productivity is important for companies,[173] but under piece-paid conditions perhaps even more so to workers.

One study has attempted to understand the organizational psychology concerning the heat stress intervention program at ISA from interviewing foremen.[173] A paternalistic view on the workers as unable to care for their own health, in need of education, correction and supervision in order to comply with the heat stress intervention emerges from these interviews. Cultural reasons and low appreciation of risks appear as explanations, although some foremen also express how workers are concerned that the stipulated longer and more frequent breaks makes them earn less. The interviews with foremen also indicate that support and commitment from upper management and monitoring of the health impacts of the intervention are important motivational factors, and that there is a need to have a strong support in the organization on how to balance health and productivity demands. At El Angel in El Salvador, focus group discussions were carried out with workers,[107] who generally welcomed the intervention although not always complied with rest schedules.

7.1.3 Achieving impact

7.1.3.1 Research in more settings

From the foremen at ISA,[173] it seems like the research process, and the feedback of research results is a factor which motivate improving working conditions. There had been efforts aiming to reduce heat stress at ISA previously, but these had not been monitored and evaluated as now. Perhaps the intervention-based research needs to be replicated elsewhere not only as there is a need to replicate research findings in order to build a stronger evidence base, but also because the research activities in themselves lead to implementation. Likewise, one could hope that awareness among workers on improved outcomes at the worksite/research project they work at/participate in reduce resistance to rest schedules, or even inspire demands of changed workplace practices. This is also in line with how Gentry et al.[180] identify conducting research in collaboration with local policy-maker as one way of achieving impact. The quality of previously implemented heat stress interventions needs to continue to be monitored and evaluated after research projects are finalized, with the employees and company rather than researchers in charge.

7.1.3.2 Proximal vs. systemic level action

There is a lack of information on how sugarcane workers themselves perceive heat stress interventions. From the perspective of the ISA foremen, it seems there is some resistance to the rest schedule.[173] The voices of the foremen may however rather express wishes to be seen as resolute and aware of mill policy and priorities. Nonetheless, if the workers themselves are not enthusiastic about a mandatory rest schedule it seems unlikely this way of working would be internalized and maintained.

The term "structural vulnerability" has been used to describe conditions facing migrant Latino farmworkers in the US,[174 195] and considering the lack of alternative livelihoods and indebtedness of many households around ISA,[186] the sugarcane worker population does also not seem to have "unfettered agency".[157] There are economic factors which limit workers' possibilities to negotiate better pay. Large proportions of Mesoamerican sugarcane is already harvested by mechanical harvesters, one of which can replace 60 cutters on even, accessible fields. What happens if the costs for manual labor increase? At what wage level will cutters lose their jobs and the uneven, inaccessible sugarcane fields they now harvest be laid fallow or made accessible to mechanical harvesters?

Munro[185] criticized heat stress interventions by arguing that injustice and vulnerability is perpetuated by addressing proximal rather than structural/systemic causes of CKDnT. Political questions of power, exploitation and inequality are rendered technical by framing CKDnT as a medical question of the amount of rest and water per hour. However, she concludes that impact on health and human rights may more easily be achieved with heat stress interventions within the current system. The Diderichsen model of the cycle which maintain social disparities in health[182] (Figure 6) highlight the role that ill health has in social stratification, something which is also seen in sugarcane worker populations. Workers with kidney disease are actively screened out from the workforce, losing income opportunities. This stratification may also operate across generations as adolescents in families where someone has fallen ill with CKDnT often leave school early to contribute to family income,[186] and for collectives, such as communities and countries, as the costs of CKDnT treatment and death of working-age individuals are high.

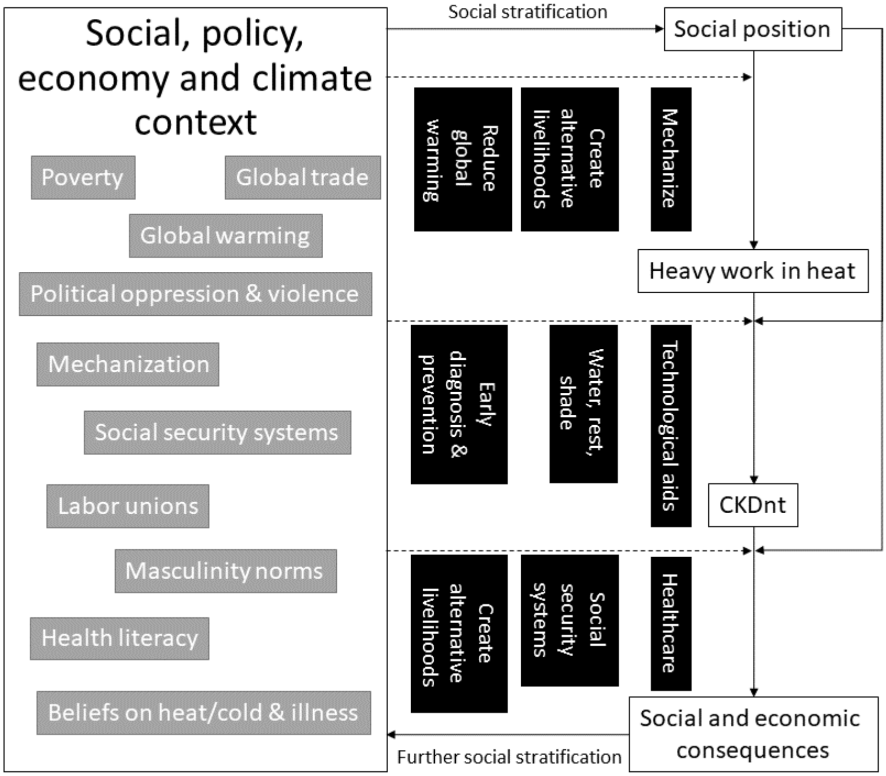

Figure 6 Conceptual framework of social disparities in chronic kidney disease of non-traditional origin, with potential interventions aiming to ameliorate these (dashed lines and black boxes). Adapted from Diderichsen and Hallqvist [182].

7.2 RESEARCH

7.2.1 Linking acute and chronic kidney disease

A better understanding of the natural history of CKDnT is needed in order to fully understand its etiology. Whether exposures during growth and development predispose workers to suffer from kidney disease when they start working in heat-stressed jobs is important to understand, and future research focusing on newly recruited workers may help elucidate this. Further, understanding the relationship between the acute changes in kidney function documented in this thesis (i.e. IKI) among workers at high risk of CKDnT and actual development of CKDnT is key.

Longitudinal studies are needed to determine if there is an association between these conditions. So far, longitudinal studies over 1-3 years supports an association between AKD and CKDnT.[54 62] In Paper II, IKI was associated with a worse 1-year eGFR decline. However, are these associations between rapid, likely reversible and long-term, likely irreversible eGFR loss causal? As mentioned, observational studies have documented a link between AKI (primarily suffered at hospital), and later CKD,[29 30] but an intervention study reducing heart surgery-induced AKI does not give as strong support.[196] There are however important differences between heart surgery patients and sugarcane workers, with heart surgery patients having a high prevalence of other CKD risk factors and receiving best available care for AKI. Among the sugarcane workers, the absence of recovery period after injury during which inflammation may adequately resolve may be a key mechanism behind CKDnT (Paper IV). This makes it difficult to translate findings on the link between AKD and CKD between clinical and occupational settings. Evaluating the impact of heat stress interventions not only against IKI, but also for CKDnT, dialysis and death is of large interest, but necessitates a long-term commitment from study participants, employers, researchers and funders.

Rather than only intervening to prevent IKI, improving possibilities for early detection of IKI and individual-level risk-factor elimination (rest or change to lower workload), should be considered as a way of both studying the link between acute and chronic kidney disease in this setting, but also better understand etiology. Such a line of research, and individual-level care and prevention, depends on identifying cheap and easily available markers of kidney injury in populations at risk of CKDnT, and constructing the economic structures needed to enable workers to abstain from continued heavy work in heat when they have early kidney injury. Evaluation of the current system for sick leave due to kidney injury or elevated serum creatinine at mid-harvest testing currently in place at ISA could be an initial next step. Urine specific gravity has been proposed as a simple indicator of kidney injury in heat stressed workers as it was associated with urine nephrin concentrations.[197] However, that overall urine concentration (i.e. specific gravity) is associated with concentrations of a specific injury marker in the same sample may well be confounded by urine flow rate. Urine dipstick leukocyturia[53 56 104] (Paper IV), decreasing hemoglobin[54] (Paper IV and V), and C-reactive protein[54]

(Papers II and IV) are other markers available as point-of-care analyses to consider as these have been linked to eGFR loss.

A related field of research is to better understand how to measure kidney injury and function in this population. The marked changes in $eGFR_{cr}$ during a harvest correspond well to changes in $eGFR_{cy}$[145] and tubular injury markers (Paper V), but at least eGFR changes are to a large extent reversible. The marked difference between $eGFR_{cr}$ and $eGFR_{cy}$ raises the question of which is the best marker of glomerular function in this population, and how well either of these actually correspond to measured GFR, and manifest kidney disease, or whether there are other function or injury markers which may better identify ongoing kidney injury and future risk of disease.

A cohort study has reported that anemia at AKD hospital admission predicted CKDnT progression among sugarcane workers.[54] This finding is interesting considering Paper V, in which EPO levels decreased during harvest among workers with IKI, indicating that EPO-producing fibroblasts may have transformed to pro-inflammatory and -fibrotic myofibroblasts no longer expressing EPO.[179 198] Further exploring these molecular pathways may provide insights on the transition between AKD and CKD.

7.2.2 Heat stress versus other etiologies

Although there are initial reports of likely links between occupational heat exposure and kidney injury or disease from the US,[113 178 199] Brazil,[200] Lebanon,[201] Nepalese Gulf state and Malaysia migrants,[202 203] Thailand,[204 205] and Taiwan[206 207], it remains possible that heat stress leads to high levels of CKDnT in Mesoamerica as it interacts with one or more hitherto unidentified cause, such as a genetic trait, infectious agent or artificial or naturally occurring toxin prevalent in parts of Mesoamerica.

Infection is considered a risk factor for developing heat illness,[96] meaning even minor infections may be assumed to increase the risk of heat-related kidney injury. Hantavirus and leptospirosis are known to infect the kidneys and are endemic to Mesoamerica, but were not found to be associated with CKDnT in Nicaragua.[25]

An interaction between heat stress and exposure to toxic agents have been proposed as the cause of CKDnT as heat stress leads to a larger liquid intake and as dehydration may potentiate nephrotoxic effects,[27 208] but studies examining such interaction hypotheses have not been performed in the context of CKDnT. However, so far no, or only small studies which have not been replicated, have found evidence of elevated exposure to known nephrotoxins among populations at risk of CKDnT, or demonstrated clear associations between such toxins and kidney outcomes.[10 177 209-211] Thus, on-going research is utilizing the samples bio-banked as part of the Adelante and WE Project for investigating other possible causes of CKDnT in Mesoamerica.

However, in the face of an epidemic severely affecting already disadvantaged communities, a relevant question is for how long the quest to find an overlooked potential toxin should be continued before action on more established risk factors preventable now is initiated.

7.3 CONCLUSIONS

The population at risk of CKDnT are susceptible to adverse health effects of a hot climate due to poverty and lack of alternative employment opportunities, which makes it difficult to avoid heavy physical work. The combination of heavy work in heat leads to high heat stress. Poor health literacy, norms on masculinity and cultural beliefs on heat and cold may also limit their possibility to avoid heavy work and increase susceptibility to it by not demanding adequate protection at work, and the potential role of these factors needs to be better explored.

There is a lack of understanding of how the workers themselves perceive heat interventions, but it is understandable if fear of losing income opportunities in the context of piece-pay, mechanization and global competition cause resistance towards taking breaks. Considering the high costs to individuals and society of CKDnT, the possible negative spiral of disease and worse economic development, and the most likely huge and utopian changes in global economic structures which would be necessary to abolish physically demanding work in heat without mass unemployment, actions at the “proximal” level of worksite interventions should be considered, especially as the climate gets warmer.

Continued research on workplace heat-stress interventions at multiple worksites may increase both the evidence base and research impact as more sites and stakeholders are engaged. Biofuel production development projects are prone to industrialized agriculture with working conditions linked to CKDnT, but institutions such as developing banks funding these can be held accountable and enable research and action. Jeopardizing employers’ public relations may be necessary to access vulnerable working populations.

CKDnT can be seen as a symptom of climate injustice, with those having contributed the least to global warming facing its worst consequences. Further, increased demands of “green” energy from sugarcane in high-income countries may make more workers exposed to conditions which when combined with high environmental temperatures put them at high risk of CKDnT. In order to mitigate effects of global warming on workers' health and productivity, and thereby on livelihoods and communities, there is a need of further research on the molecular and cellular basis of heat pathophysiology, heat stress prevention interventions, as well as research explaining the economy and power structures that underlie excessive heat exposure.

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