



Chronic Kidney Disease of Unknown Aetiology in a Seasonal Agricultural Worker: A Narrative Review of Heat Stress and Occupational Causation

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Abstract

A young agricultural worker with declining kidney function, no diabetes, no hypertension and minimal proteinuria does not fit the categories nephrology is organised around. The pattern has been described across three continents, it tracks occupation rather than geography, and its likeliest cause is the work itself.

Objectives: To review the published evidence on chronic kidney disease of unknown aetiology in agricultural workers: how prevalent it is, what distinguishes it clinically, how strong the evidence for heat stress is against the alternatives, and what this means for a worker presenting in a receiving country.

Material and Methods: Narrative review of prospective occupational cohorts, cross-shift and cross-harvest studies, biopsy series, intervention studies and systematic reviews indexed in PubMed and the major nephrology, occupational and environmental health journals. No new patient data were generated; every estimate quoted is one published by the original investigators.

Results: In a prospective cohort of 569 workers without known diabetes, hypertension or kidney disease, baseline prevalence of chronic kidney disease was 7.4 per cent, with age-standardised prevalence highest in Salvadoran sugarcane at 14.1 per cent and Salvadoran corn at 11.6 per cent. Among 103 Guatemalan cane harvesters, 29 per cent showed repeated severe cross-shift creatinine fluctuations. Progression to chronic disease occurred in 8.4 per cent of 586 cane workers with acute kidney injury, with a median eGFR change of -33.3 mL/min/1.73m² from normal function eight months earlier.

Conclusion: The occupational pattern is consistent and the heat and workload evidence is the strongest available, with pesticide and infectious hypotheses largely negative. Causation is not settled, and the practical implication does not depend on settling it: the diagnosis is missed when nobody asks what the patient does for a living.

Abbreviations: AKI – Acute Kidney Injury, CKDu – Chronic Kidney Disease of Unknown Aetiology, CKDnt – Chronic Kidney Disease of Non-Traditional Origin, eGFR – Estimated Glomerular Filtration Rate, MeN – Mesoamerican Nephropathy, WRS – Water-Rest-Shade.

Keywords: Chronic Kidney Disease of Unknown Aetiology; Heat Stress Nephropathy; Agricultural Workers; Occupational Health; Mesoamerican Nephropathy

Introduction

An epidemic of chronic kidney disease not attributable to diabetes, hypertension or glomerular disease has been described over the past two decades among agricultural communities in Central America, Sri Lanka, India and elsewhere [1,2,3]. Mortality along the Pacific coast of Central America is extremely high, particularly among sugarcane workers [4,5].

The regional nephropathies share a recognisable set of features: they affect low-and-middle-income countries with tropical climates, predominantly rural agricultural communities, with male predominance, absence of significant proteinuria or hypertension, and chronic tubulointerstitial nephritis on biopsy [3,6,7]. Biopsy in established disease shows chronic interstitial change, tubular atrophy and inflammation [1,8].

Proposed causes include heat stress and volume depletion, agrochemicals, contaminated water and heavy metals [3,9,10]. This review examines the strength of each, and what the pattern means for a clinician meeting such a patient outside the regions where the disease was described.

Material and Methods

Search strategy: PubMed and the archives of the major nephrology, occupational medicine and environmental health journals were searched for studies of chronic kidney disease of unknown aetiology. Search terms combined chronic kidney disease of unknown aetiology, Mesoamerican nephropathy and heat stress nephropathy with agricultural workers, sugarcane, cross-shift, biopsy and water rest shade. Reference lists of systematic reviews [3,11] were screened by hand for primary sources.

Eligibility: Studies were included if they reported prevalence or incidence in defined occupational populations, measured kidney function across a shift or harvest, described histology, or evaluated a preventive intervention. Ecological and time-trend analyses are cited where they test a hypothesis and are identified as such.

Data extraction and handling: Design, setting, occupation, sample size, the definition of kidney disease used and the reported estimate were extracted as published. The occupation and the exclusion of traditional causes are reported alongside every prevalence figure, because the entity is defined by exclusion and studies differ in how rigorously that exclusion was applied. No pooling or re-analysis was performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

Prevalence by occupation: A prospective cohort recruited 569 workers with no known diabetes, hypertension or chronic kidney disease from sugarcane, corn, plantain, brickmaking and road construction in El Salvador and Nicaragua, observing them across three consecutive workdays and resampling at six months. Baseline prevalence of chronic kidney disease, defined as eGFR of 60 mL/min/1.73m² or below at both time points, was 7.4 per cent. Age-standardised prevalence was highest in Salvadoran sugarcane at 14.1 per cent, followed by Salvadoran corn at 11.6 per cent (Figure 1) [12].

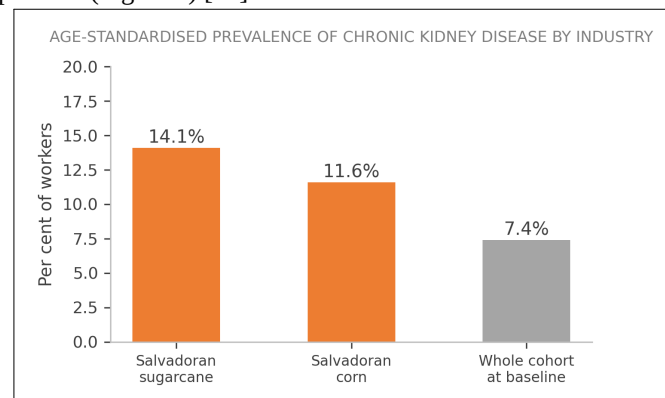


Figure 1: Age-standardised prevalence of chronic kidney disease by industry in a prospective occupational cohort [12]

The occupational gradient: The distribution follows work intensity and heat exposure rather than residence. Disease has been reported in sugarcane and other high-intensity agriculture, and in non-agricultural occupations involving heavy manual labour in hot environments, but not among subsistence farmers [13]. Coastal agricultural communities show higher prevalence of reduced eGFR than those living 500 metres above sea level, and sugarcane and cotton workers higher prevalence than coffee or subsistence farmers in the same coastal areas [3,14,27,28,29]. Systematic reviews of risk factors and of the epidemiological literature reach compatible conclusions [31,32].

What happens within a shift: Cross-shift studies show measurable change in kidney function and hydration biomarkers across a single working day [13,15]. Among 103 Guatemalan cane harvesters studied over six consecutive days, 29 per cent experienced repeated severe fluctuations in creatinine across the shift, and those fluctuations forecast end-of-season kidney function (Figure 2) [16]. This is the observation that converts an epidemiological association into a plausible mechanism. Experimental work supports a route from repeated dehydration and raised core temperature to nephron loss [25,26].

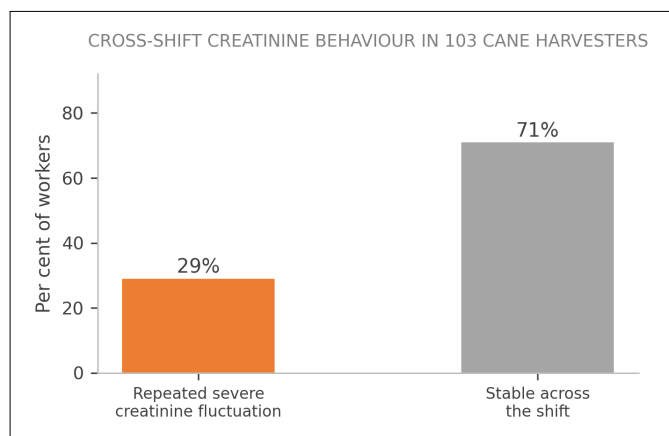


Figure 2: Cross-shift creatinine behaviour among Guatemalan cane harvesters [16]

From acute injury to chronic disease: Progression to chronic kidney disease occurred in 49 of 586 sugarcane workers with acute kidney injury (8.4 per cent), with a median eGFR change of $-33.3 \text{ mL/min/1.73m}^2$ from normal kidney function eight months earlier (Figure 3) [1,17]. The reviewers of that finding noted an important limitation: no comparison was made with workers who had no history of acute injury, so whether repeated acute kidney injury is a genuine risk factor for chronic disease remains to be established [1].

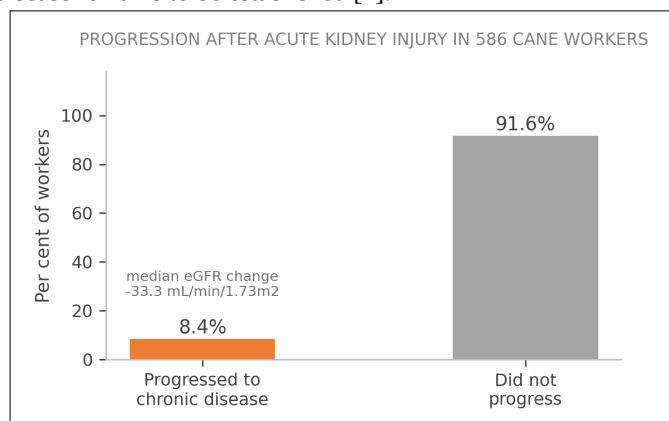


Figure 3: Progression to chronic kidney disease after acute kidney injury in sugarcane workers [1,17]

Weighing the hypotheses: Studies of pesticides and of infectious risk factors have been largely negative, and non-occupational risk factors do not explain the observed epidemiological patterns (Figure 4) [13]. The heat hypothesis is not unchallenged: analysis of time trends and mortality patterns in Central America from 1997 to 2013 concluded that heat stress could not fully explain the epidemic, and a separate study reported no association between high ambient temperature and occurrence in El Salvador [3,18,19]. Considerable regional disparities in research make a single causal link difficult to establish [3].

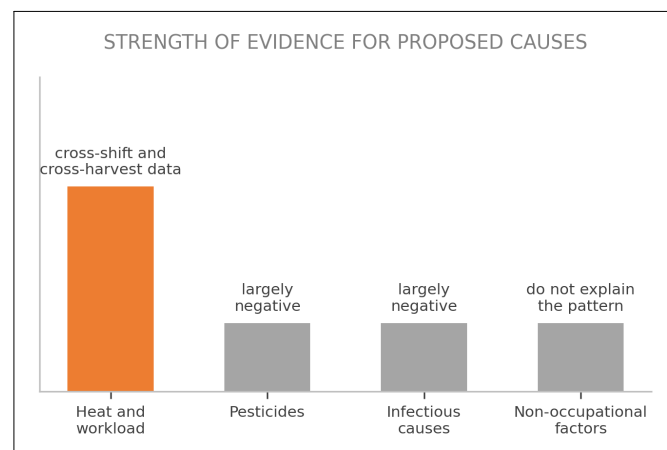


Figure 4: Relative strength of evidence for the principal proposed causes [3,13,18]

Study	Design and cohort	Principal reported finding
MANOS cohort [12]	Prospective, 569 workers, 5 industries	Baseline CKD 7.4%; Salvadoran sugarcane 14.1%
Guatemalan harvesters [16]	103 workers, 6 consecutive days	29% with repeated severe cross-shift creatinine fluctuation
Cane worker cohort [17]	586 workers with acute kidney injury	8.4% progressed; median eGFR change -33.3
Wesseling et al. 2020 [13]	Review of occupational evidence	Heat and workload supported; pesticides largely negative
Garcia-Trabanino et al. 2015 [15]	Cross-shift study, cane cutters	Heat stress, dehydration and kidney function measured directly
Glaser et al. 2016 [9]	Review of heat stress nephropathy	Frames the disease as climate-related occupational injury
Wijkstrom et al. [8]	Biopsy series, Sri Lanka	Histological similarities and differences with Mesoamerican disease

Table 1: Principal studies reviewed, with the finding as reported by the original investigators

What prevention shows: The strongest practical evidence is interventional. Implementation of a water-rest-shade programme midharvest in El Salvador appeared to halt declining kidney function among cane cutters [13]. In Nicaragua the same approach appeared sufficient to prevent damage among workers with low to moderate workload but not among cutters with the heaviest workload [13,20]. Workplace screening in Guatemala identified clinically significant and potentially reversible kidney injury and evaluated an educational and behavioural intervention on the trajectory of decline [21]. If the disease responds to rest, water and shade, its cause is difficult to place anywhere other than the work.

The patient outside the endemic region: Seasonal and migrant agricultural labour means this presentation now appears in receiving countries, where the differential is unfamiliar and the occupational history is rarely taken in a nephrology clinic [22,23]. The clinical signature is reasonably distinctive: a young or middle-aged manual worker, usually male, with reduced eGFR, bland urinary sediment, minimal proteinuria, normal or

low-normal blood pressure and no diabetes [3,6,7]. Hyperuricaemia, hypokalaemia and hypomagnesaemia have been described [1,24], and early tubulointerstitial nephritis has been detected at the genesis of the disease [30].

Feature	Typical finding	Contrast with common causes
Age and sex	Young to middle-aged, predominantly male	Diabetic and hypertensive disease occur later [3,6]
Proteinuria	Absent or minimal	Prominent in diabetic and glomerular disease [3,7]
Blood pressure	Normal or low-normal	Hypertension usually precedes hypertensive disease [6,7]
Histology	Chronic tubulointerstitial nephritis	Not a glomerular pattern [1,8]
Occupation	Heavy manual work in heat	The single most useful question [12,13]
Course	Progressive, often silent until advanced	Few early symptoms; found on screening [21]

Table 2: Clinical signature of the disease and how it differs from traditional causes

Discussion

The occupational patterning is the most persuasive element of this literature. Disease appears in sugarcane cutters and in other heavy manual work performed in heat, and not in subsistence farmers living in the same communities, drinking the same water and exposed to broadly similar agrochemicals [13,14]. That contrast is difficult to explain by anything in the environment that is shared, and it points at what differs, which is the physical work and the thermal load.

The cross-shift data strengthen that considerably. Measuring a change in creatinine across a single working day, and showing that the magnitude of those fluctuations forecasts kidney function at the end of the season, links an exposure to a mechanism to an outcome within one cohort [15,16]. Very few environmental disease hypotheses have that structure.

Honesty requires reporting the contrary evidence, which is real. A time-trend analysis across Central America concluded that heat stress could not fully account for the epidemic, and a study in El Salvador found no association between ambient temperature and disease occurrence [18,19]. These are not fringe objections. They suggest either that ambient temperature is a poor proxy for the relevant exposure, which is core body temperature during exertion, or that heat is necessary but not sufficient. The distinction matters for prevention, since shading a field and shortening a shift address different things.

For the individual patient the causal debate is largely beside the point. The diagnosis is made or missed on whether an occupational history is taken. A young man with an eGFR of 45, no proteinuria, no diabetes and normal blood pressure will otherwise be investigated at length and labelled idiopathic. Asking what he does for a living, and for how many seasons, converts an unexplained finding into a recognised entity with a literature behind it and, importantly, with a preventive intervention that has been shown to work for his colleagues

[13,21].

Study limitations

The limitations belong to the underlying literature. The entity is defined by exclusion, and studies differ in how rigorously diabetes, hypertension and glomerular disease were ruled out [3,12]. Occupational cohorts recruit workers well enough to work, so the most affected are systematically absent, which biases prevalence downward [12]. Cross-shift creatinine change reflects volume status as well as injury and is an imperfect marker of nephron loss [15,16]. The progression cohort had no comparison group without acute kidney injury, so the causal link between repeated acute injury and chronic disease is unestablished [1,17]. Intervention studies are largely uncontrolled before-and-after evaluations conducted by parties with an interest in the result [13,21]. Ecological analyses testing the heat hypothesis reach conflicting conclusions [18,19]. Biopsy series are small [8]. And almost all evidence comes from Central America and Sri Lanka, with the applicability to European seasonal labour unstudied [3,22,33]. Occupational heat strain is nonetheless a recognised global threat to worker health and productivity [34,35].

Conclusion

Chronic kidney disease of unknown aetiology in agricultural workers is unexplained only in the narrow sense that no single cause has been proven. The pattern is clear enough to act on: it follows heavy manual work in heat rather than residence, it produces measurable injury within a single shift, and it appears to respond to water, rest and shade. Contrary evidence exists and should not be filtered out, particularly the analyses finding that ambient temperature alone does not explain the epidemic. For a clinician meeting a young agricultural worker with reduced eGFR and a bland urinary sediment, none of that uncertainty changes the useful step, which is to ask about the work before concluding the disease has no cause.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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