ORIGINAL RESEARCH

Workload and cross-harvest kidney injury in a Nicaraguan sugarcane worker cohort

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ABSTRACT

Objectives To examine the association between workload and kidney injury in a fieldworker cohort with different levels of physically demanding work over a sugarcane harvest, and to assess whether the existing heat prevention efforts at a leading occupational safety and health programme are sufficient to mitigate kidney injury.

Methods Biological and questionnaire data were collected before (n=545) and at the end (n=427) of harvest among field support staff (low workload), drip irrigation workers (moderate), seed cutters (high) and burned sugarcane cutters (very high). Dropouts were contacted (87%) and reported the reason for leaving work. Cross-harvest incident kidney injury (IKI) was defined as serum creatinine increase ≥0.30 mg/dL or ≥1.5 times the baseline value, or among dropouts reporting kidney injury leading to leaving work.

Results Mean cross-harvest estimated glomerular filtration rate change was significantly associated with workload, increasing from 0 mL/min/1.73 m^2 in the low-moderate category to −5 mL/min/1.73 m^2 in the high and −9 mL/min/1.73 m^2 in the very high workload group. A similar pattern occurred with IKI, where low-moderate workload had 2% compared with 27% in the very high workload category. A healthy worker selection effect was detected, with 32% of dropouts reporting kidney injury. Fever and C reactive protein elevation were associated with kidney injury.

Conclusions Workers considered to have the highest workload had more cross-harvest kidney damage than workers with less workload. Work practices preventing heat stress should be strengthened and their role in preventing kidney damage examined further. Future occupational studies on chronic kidney disease of unknown aetiology should account for a healthy worker effect by pursuing those lost to follow-up.

Key messages

What is already known about this subject?
► In Mesoamerica, a region affected by chronic kidney disease of unknown aetiology, sugarcane workers are at a high risk of kidney injury during harvest.

What are the new findings?
► There was evidence of more kidney injury with physically more demanding sugarcane harvest jobs.
► A healthy worker selection effect was revealed when dropouts were interviewed, with results showing a higher incidence of cross-harvest kidney injury in this group.
► Elevated C reactive protein and self-reported fever were more common in those with kidney injury.

How might this impact on policy or clinical practice in the foreseeable future?
► This study describes the baseline of the 3-year Adelante Initiative intervention study, indicating the need for further improvements of working conditions for manual workers with heavy physical workload in a hot climate.

INTRODUCTION

Chronic kidney disease in the absence of diabetes, hypertension or other known risk factors, thus of unknown aetiology (CKDu),[1] is estimated to have caused tens of thousands of deaths in Mesoamerica.[2]

Hypotheses of the aetiology of CKDu include repeated heat stress and dehydration, pesticides, drinking water contaminants, infectious diseases, and non-steroidal anti-inflammatory drugs.[3] Studies have presented increased prevalence of reduced kidney function[4 5] and increased kidney injury incidence across work shifts[6–11] and across harvests[10–14] among sugarcane workers, a group performing strenuous manual work in high temperatures,[15] indicating that heat stress and dehydration likely contribute to initiation or progression of CKDu.

There is some evidence to suggest reducing heat stress and dehydration may reduce cross-harvest kidney injury.[10 16] The sugarcane mill Ingenio San Antonio (ISA) in Chinandega, Nicaragua, has gradually enhanced efforts to improve occupational health among fieldworkers[17–19] and has added water intake, rest and shade to injury prevention efforts via the following principles:
► Harvest employment starts with a 2-week acclimatisation period.
► Fieldworker groups considered at high risk of kidney injury have access to tents for rest in shade during mandated breaks. Movable tents made of a netted fabric are open on two sides, thus giving shade while also being ventilated.
► Cane and seed cutters have stools for seated, shaded rest.

Table 1 Demographic composition, heat and physical effort exposure, intervention, and sampling strategy of studied job categories of fieldworkers

	Burned cane cutters	Seed cutters	Drip irrigation repair workers	Field support
n*	158	190	128	54
Demographics				
% men	100	72	53	65
Age, median (IQR)	30 (25–37)	26 (23–33)	29 (23–34)	31 (25–35)
Work characteristics				
Previous harvests, median (IQR)	7 (4–13)	4 (2–6)	4 (2–6)	5 (1–8)
First ever harvest, n (%)	0	14 (7)	10 (8)	6 (11)
Work setting	Cane fields burned 12 hours earlier	Green cane	Open fields	Open fields
Work task	Cut burned cane, top foliage and leave in rows on ground.	Cut cane at stem, then into 3–4 pieces. Later, pieces are bundled into packages of 10–11.5 kg.	Repair underground drip irrigation tubes requiring digging, bending, prolonged squatting.	Supervisors, work organisers, health promoters, hydration operators. Some occasionally walk long distances.
Physical demands†	Very high	High	Moderate	Light
Work schedule	06:00–noon	06:00–14:00, cutting ends at noon	06:00–14:00	06:00–noon–14:00
Mobile clinic	Daily	Daily or every other day	None	Many are implementers of the intervention with access to water and shade, but no clear rest recommendations.
Health promoter	Yes	Yes	Every other day	
Water distribution	Yes	Yes	Yes	
Lunch provided	Yes, end of work	Yes, during noon rest	No	
Tent	Yes	Yes	Yes	
Stool provided	Yes	Yes	No	
Population sampling				
Sampling strategy	All	All	Two of four work groups (one female, one male)	All present in fields with job groups studied
Mid-harvest testing, n (%)	137 (87)	151 (79)	96 (75)	19 (35)
Dropout, n‡ (%)	33 (21‡)	46 (23‡)	23 (17‡)	12 (21‡)
Baseline eGFR, median (IQR) (mL/min/1.73 m^2)	97 (80–114)	110 (87–122)	109 (93–123)	112 (96–121)
Questionnaire				
Pesticide use during harvest§, n (%)	6 (5)	3 (2)	3 (3)	2 (5)
Incident fever§, n (%)	12 (9)	16 (11)	12 (11)	4 (10)
Chikungunya during harvest, n (%)	5 (3)	3 (2)	0	1 (2)
NSAID use, n (%)	40 (25)	39 (21)	29 (23)	8 (15)
Current smoking, n (%)	55 (35)	55 (29)	23 (30)	10 (19)
Daily liquid intake end-harvest vs baseline change§ (L), median (IQR)	4.9 (2.1–8.3)	2.8 (0.1–5.9)	4.4 (1.8–5.8)	2.6 (1.0–4.4)
End-harvest electrolyte solution (boli) intake§ (L), median (IQR)	0.75 (0–1.05)	0.6 (0–0.9)	0.9 (0–1.2)	0.9 (0.6–2)
End-harvest daily sugary beverage intake§ (L), median (IQR)	0.5 (0.2–1)	0.5 (0.2–0.9)	0.5 (0.2–0.9)	0.5 (0.4–0.8)
Diabetes, n (%)	0	1 (1)	1 (1)	1 (2)
Hypertension (self-reported and/or measured (>140/90 mm Hg)), n (%)	5 (3)	6 (3)	2 (2)	1 (2)

*Number of workers including those followed up at the end of harvest and dropouts contacted after harvest.
†Physical demands order based on observation.
‡Denominator includes all recruited and also those who had no follow-up at all.
§Only includes those finishing the harvest.
eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.

► Hydration operators refill personal thermoses and distribute 0.3 L electrolyte solution (bolis) hourly.
► Mandated breaks and workday lengths are adapted to avoid the most strenuous work after noon (table 1).
► Workers are given sun-protective clothing, including hat, eye shield or sunglasses, long-sleeved wicking shirt, and personal thermos in addition to other personal protective equipment.
► Mobile health clinics provide support for cutters in the field throughout the harvest.

The ISA is cooperating with the sustainable sugarcane round-table Bonsucro,[20] the Nicaraguan Sugarcane Producers Association and the non-governmental organisation La Isla Network[21] in the 3-year Adelante Initiative[22] intervention study. The long-term objective is to assess the impact of improved workplace interventions on preventing heat stress and kidney dysfunction. This paper reports on the first year evaluating the already existing occupational safety and health programme, informing recommendations for improvements. The observations will

form a baseline for evaluation of further interventions. Here, we examine risk factors for baseline cross-harvest kidney injury with a specific focus on job tasks. A long-term aim is to determine if a sustainable programme of heat stress management can diminish kidney injury, and if successful can be adapted for use throughout the sugarcane industry and other impacted industries.

All workers were apprised of the study objectives and procedures and any questions were answered before signing an informed consent before enrolment in the study. This was done by our trained staff.

METHODS

Study participants and data collection

During sugarcane harvest (November–April), seasonal workers from Nicaragua, predominantly from areas close to the ISA, were employed directly by the mill after a routine pre-employment health screening (October–November 2017). Men with serum creatinine (SCr) ≥1.3 mg/dL and women with SCr ≥1.0 mg/dL applying for fieldwork jobs could be hired after re-evaluation 10–15 days later if retested values fell below those thresholds. At mid-harvest (February 2018) SCr was measured at the ISA laboratory in fieldworkers, as part of the ISA routine. Those with SCr elevation were placed on sick leave and dismissed if SCr remeasurement did not return to below cut-offs within a few weeks. Workers presenting with elevated creatinine could also be given leave, and a case series suggests this is common.[23]

Among the several manual field jobs, four were selected to represent a range of physical work: manual cutters of burned cane (very high physical demands), cutters of green cane for seeding (high physical demands), drip irrigation repair workers (medium physical demands) and field support staff (foremen and auxiliary logistics staff, health promoters, hydration operators; low physical demands) (table 1). Ranking of the physical demands of occupational groups was based on repeated qualitative observations by occupational hygienists and senior occupational physicians, taking into account postures, movements, handling of tools and weight carrying. We included all hired burned cane and seed cutters, together with half of the irrigation repair workers (one each of the two male and two female work teams), irrespective of baseline creatinine (table 1). All field support staff accompanying these fieldworkers were also included. A convenience sample of ISA administrative workers unexposed to fieldwork (n=68) were recruited to provide an estimate of normal values in the region for an unexposed population. Those starting work were considered cohort participants, excluding one worker who worked only 4 days.

We organised the study baseline examination to accompany the ISA pre-employment screening: a brief questionnaire administered by our trained interviewers and an aliquot of morning blood and urine samples for analyses at Lund University. Workers were retested at end-harvest by prework shift serum and urine sampling and an extended questionnaire.

The questionnaire covered demographics, medical history, fever during the last week, symptoms within the past 2 weeks and liquid intake 24 hours prior to the interview at baseline and at the end of harvest. Height, weight, blood pressure and heart rate (HR) were measured at baseline and at end-harvest (height just baseline). At end-harvest, questions on personal habits, occupational history, infectious disease occurrence and pesticide exposure during harvest were added to the questionnaire.

Wet-bulb globe temperature (WBGT) was measured by trained ISA mobile health clinic personnel accompanying the workforce using QUESTemp34 (3M). Measurements were done hourly from 06:00 until shift end, with sample days distributed across the harvest.

Serum was separated from the cells at the ISA laboratory, frozen at −77°C and transported to Sweden after each data collection period. Analyses were performed at Skåne University Hospital in Lund, Sweden, on a Cobas 701 instrument (Roche Diagnostics, Basel, Switzerland). Each individual's baseline and end-harvest samples were analysed during the same session. Sodium concentrations indicated that part of the serum samples had been inadequately mixed after thawing. Thus, all analytes were corrected using sample-specific correction factors, based on the ratio of measured sodium/true sodium level (assumed to be 140 mmol/L; online supplementary 1).

Workers absent at end-harvest testing were visited at home, asked why they left work and administered a shortened end-harvest questionnaire. No blood or urine samples were taken.

Outcome

Two outcomes were examined. The first was a dichotomous measure for cross-harvest kidney injury, an event we named incident kidney injury (IKI), and the second was continuous cross-harvest estimated glomerular filtration rate (eGFR) change (ΔeGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. IKI was subdivided into IKI-Measured: SCr elevation at the end-harvest ≥0.30 mg/dL higher than or ≥1.5 times the baseline value; or IKI-All: combining IKI-Measured with self-report by dropouts who left work or had been on sick leave due to SCr elevation. This subdivision enabled inclusion of dropouts in the analysis to account for healthy worker selection effect. IKI is an epidemiological measure distinct from the clinical criteria for acute kidney injury (AKI). The SCr elevation cut-offs were equal to the Kidney Disease Improving Global Outcomes (KDIGO) clinical criteria for AKI, which refer to shorter-term SCr changes rather than cross-harvest changes.[24] Definitions of sugarcane worker cross-harvest kidney injury similar to IKI have been reported.[11 13 14]

Statistical analysis

Categories of potential risk factors were created. Job, the main exposure, is described in table 1. Age was divided into four 10-year categories. Change in reported daily liquid intake at end-harvest versus baseline was categorised as reduced, increased by 0–5 L, 5–10 L and >10 L. Daily boli intake was categorised to 0, 1–3 and >3 300 mL bags, and sugary drinks (sweetened diluted fresh fruit drinks and soft drinks) intake to <0.5 L, 0.5–1.5 L and >1.5 L. Recent incident fever was defined as fever within the past week reported by participants who did not report fever at baseline. Baseline eGFR was categorised to >90, 75–89, 60–74 and <60 mL/min/1.73 m^2.

Proportions with IKI-Measured and IKI-All by risk factor category were calculated and incidence ratios (IR) with 95% CI estimated using univariate Poisson regression. Multivariate Poisson regression was performed by entering potential risk factors separately into a model with job as main exposure variable and age (continuous) and sex as covariates. Other factors were not adjusted for in the model as they may be on the causal pathway between job and outcome, but we tried a model with adjustment for baseline eGFR. To reduce the number of parameters, irrigation repair workers and field support staff were merged because there was no risk difference between them (table 2). Multivariate analyses were performed only for IKI-All due to insufficient number of workers with IKI-Measured. The IR for

Table 2 Baseline and cross-harvest eGFR and IKI by risk factor category

	Harvest finishers only					Including also dropouts			
		Continuous eGFR (mL/min/1.73 m²)		IKI			IKI		
				IKI-Measured* event			IKI-All† event		
	Total (n)	Mean difference at baseline§ (95% CI)	Mean cross-harvest eGFR slope (ΔeGFR) difference§ (95% CI)	n (%)	Univariate IR (95% CI)	Total (n)	n (%)	Univariate IR (95% CI)	Adjusted‡ IR (95% CI)
All	427	Not applicable	Not applicable	32 (7)	Not applicable	525	63 (12)	Not applicable	Not applicable
Sex									
Female	111	Ref	Ref	0 (0)	Not applicable	131	5 (4)	1 (–)	1 (–)
Male	316	−6.1 (−11 to 1.5)	−0.4 (−3.8 to 3.0)	32 (10)	Not applicable	394	58 (15)	3.89 (1.55 to 9.62)	1.24 (0.44 to 3.50)
Age									
18–29	233	Ref	Ref	19 (8)	1 (–)	292	36 (12)	1 (–)	0.98 (0.94 to 1.01)
30–39	153	−13 (−17 to 8.6)	1.5 (−1.4 to 4.5)	11 (7)	0.88 (0.42 to 1.85)	178	21 (12)	0.96 (0.56 to 1.64)	
40–49	32	−20 (−26 to 13)	3.4 (−1.8 to 8.6)	2 (6)	0.77 (0.18 to 3.29)	43	5 (12)	0.94 (0.37 to 2.40)	
50–60	9	−26 (−38 to 13)	7.0 (−2.4 to 16)	0 (0)	Not applicable	12	1 (8)	0.68 (0.09 to 5.00)	
Job category									
Cane cutters	128	−6.1 (−11 to 1.2)	−9.2 (−13 to 5.6)	27 (21)	6.24 (2.40 to 16.2)	157	43 (27)	14.2 (1.96 to 103)	11.8 (3.93 to 35.4)
Seed cutters	148	−5.8 (−10 to 1.5)	−4.3 (−7.5 to 1.0)	5 (3)	1 (–)	188	16 (9)	4.55 (0.59 to 33.4)	3.54 (1.17 to 10.7)
Irrigation repair	109	Ref	Ref	0 (0)	Not applicable	128	3 (2)	1.22 (0.13 to 11.7)	1 (–)
Field support	42			0 (0)	Not applicable	52	1 (2)	1 (–)	
Pesticide use									
No	415	Ref	Ref	29 (7)	1 (–)	Pesticide use data were not collected among dropouts.			
Yes	13	−3.4 (−14 to 7)	−7 (−15 to 0.8)	3 (23)	3.29 (1.00 to 10.8)				
Incident fever									
No	383	Ref	Ref	23 (6)	1 (–)	Symptoms data were not collected among dropouts.			
Yes	43	−0.9 (−6.8 to 5.1)	−4.7 (−9.1 to 0.3)	9 (21)	3.49 (1.77 to 9.22)				
Chikungunya during harvest									
No	425	Ref	Ref	31 (7)	1 (–)	516	59 (11)	1 (–)	1 (–)
Yes	2	−9.0 (−35 to 17)	−13 (−32 to 6.8)	1 (50)	6.85 (0.94 to 50.2)	9	4 (44)	3.89 (1.41 to 10.7)	2.58 (0.93 to 7.14)
NSAID use									
No	330	Ref	Ref	21 (6)	1 (–)	409	47 (11)	1 (–)	1 (–)
Yes	97	−1 (−5.3 to 3.3)	−2.9 (−6.1 to 0.3)	11 (11)	1.78 (0.86 to 3.70)	116	16 (14)	1.2 (0.68 to 2.12)	1.14 (0.64 to 2.02)
Current smoking¶									
No	303	Ref	Ref	19 (6)	1 (–)	373	39 (10)	1 (–)	1 (–)
Yes	124	3.9 (−0.3 to 8)	−1.3 (−4.4 to 1.9)	13 (11)	1.67 (0.83 to 3.39)	147	24 (16)	1.56 (0.94 to 2.60)	1.25 (0.74 to 2.11)
Change in 24-hour liquid intake over harvest (L)									
<0	74	1.6 (−5.0 to 2.6)	−1.2 (−5.0 to 2.6)	6 (8)	1.28 (0.48 to 3.40)	Liquid intake data were not collected among dropouts.			
+0–5	189	Ref	Ref	12 (7)	1 (–)				
+5–10	140	3.1 (−1.0 to 7.3)	1.6 (−1.5 to 4.6)	10 (7)	1.13 (0.49 to 2.60)				
+>10	23	3.2 (−5.1 to 12)	4.8 (−1.4 to 11)	4 (18)	2.74 (0.88 to 8.49)				

Electrolyte solution intake per 24 hours at end of harvest (number of 300 mL bags)

Table 2 continued

| | Harvest finishers only | | | | | Including also dropouts | | | |
| | | Continuous eGFR (mL/min/1.73 m²) | | IKI-Measured* event | | | IKI-All† event | | |
	Total (n)	Mean difference at baseline§ (95% CI)	Mean cross-harvest eGFR slope (ΔeGFR) difference§ (95% CI)	n (%)	Univariate IR (95% CI)	Total (n)	n (%)	Univariate IR (95% CI)	Adjusted‡ IR (95% CI)
0	126	Ref	Ref	8 (6)	1 (–)	Liquid intake data were not collected among dropouts.			
1–3	188	1.4 (–2.8 to 5.7)	1.9 (–1.3 to 5.0)	18 (10)	1.51 (0.66 to 3.47)				
≥4	112	–1.3 (–6.0 to 3.5)	4.8 (1.3 to 8.4)	6 (5)	0.84 (0.29 to 2.43)				
Sugary beverage intake per 24 hours at end of harvest (L)									
<0.5	184	Ref	Ref	8 (4)	1 (–)	Liquid intake data were not collected among dropouts.			
0.5–1.5	188	0.8 (–3 to 4.6)	–3.9 (–6.7 to 1)	18 (10)	2.2 (0.96 to 5.06)				
>1.5	54	–2.2 (–7.9 to 3.6)	–2.9 (–7.2 to 1.3)	6 (11)	2.56 (0.89 to 7.37)				
Baseline eGFR (mL/min/1.73 m²)									
>90	305	Ref	Ref	16 (5)	1 (–)	373	31 (8)	1 (–)	1 (–)
75–90	67	–28 (–30 to 25)	3.3 (–0.6 to 7.1)	7 (10)	1.99 (0.82 to 4.84)	83	13 (16)	1.88 (0.99 to 3.60)	1.52 (0.77 to 2.97)
60–74	43	–43 (–46 to 40)	3.3 (–1.4 to 7.9)	8 (19)	3.55 (1.52 to 8.29)	52	13 (25)	3.01 (1.57 to 5.75)	2.76 (1.38 to 5.49)
<60	12	–59 (–64 to 53)	7.9 (–0.2 to 16)	1 (8)	1.59 (0.21 to 12.0)	17	6 (35)	4.25 (1.77 to 10.2)	3.48 (1.42 to 8.50)
Diabetes (self-reported)									
No	425	Ref	Ref	32 (8)	1 (–)	522	63 (12)	Not applicable	Not applicable
Yes	2	4.3 (–22 to 31)	–4.8 (–24 to 15)	0 (0)	Not applicable	3	0 (0)		
Hypertension (self-reported and/or measured (>140/90 mm Hg))**									
No	412	Ref	Ref	31 (8)	1 (–)	508	60 (12)	1 (–)	1 (–)
Yes	12	–8.1 (–19 to 3)	3.5 (–4.8 to 12)	1 (8)	1.11 (0.15 to 8.11)	14	3 (21)	1.81 (0.57 to 5.78)	1.95 (0.59 to 6.42)

*SCr at the end of harvest ≥0.30 mg/dL higher than or ≥1.5 times the baseline value.
†SCr at the end of harvest ≥0.30 mg/dL higher than or ≥1.5 times the baseline value or self-reported elevated SCr during harvest leading to sick leave or dismissal from job.
‡Model: job category (combining irrigation repair workers and field support staff), age (continuous), sex and risk factor.
§Adjusted for job, sex and age category and their interaction with test occasion.
¶15 with missing data on smoking.
**3 with missing data on hypertension.
eGFR, estimated glomerular filtration rate; IKI, incident kidney injury; IR, incidence ratio; NSAID, non-steroidal anti-inflammatory drug; SCr, serum creatinine.
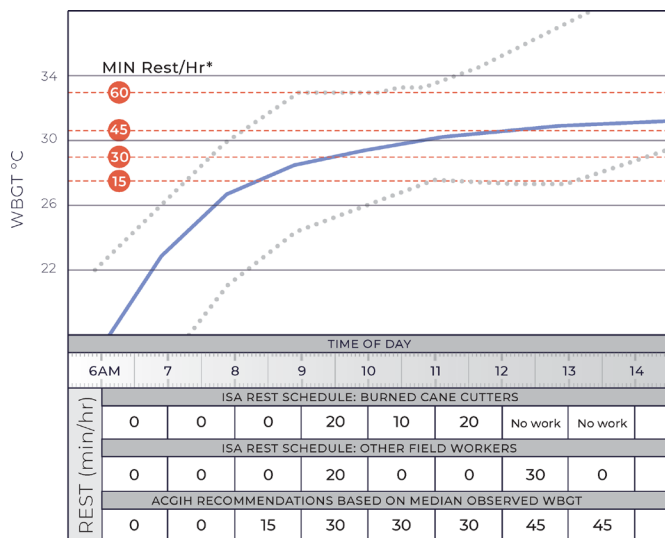
Figure 1 Median (solid blue line) and 90% range (grey dotted lines) wet-bulb globe temperature (WBGT) in the sugarcane fields of Ingenio San Antonio (ISA) during harvest in 2017–2018. The ISA rest schedules during harvest in 2017–2018 are compared with the American Conference of Governmental Industrial Hygienists (ACGIH) recommendations for heavy physical work according to the median WBGT. *Threshold limit values (red dashed lines) for the number of minutes of rest per hour recommended by the ACGIH[25] for heavy physical work.

sex was calculated restricted to seed cutters as there were no female burned cane cutters (table 1) and very few events in other work groups (table 2).

eGFR was modelled with mixed-effects linear regression using an unstructured covariance matrix for the random intercept and slope for each worker, estimated using the *mixed* command. Age group, sex and job were included as fixed effects in all models and other risk factors were entered separately. Interactions between test occasion and risk factors were assessed to model mean eGFR trends (ΔeGFR) with 95% CI across harvest.

To further explore self-reported fever, we assessed median baseline and cross-harvest change in C reactive protein (CRP) between IKI and job groups. All statistical analyses were conducted using Stata V.15.

RESULTS
WBGT measurements
WBGT measurements were plotted against the WBGT/rest limits at which the American Conference of Governmental Industrial Hygienists (ACGIH) considers there to be a risk of heat illness during heavy physical activity.[25] This revealed a gap between practice and guidelines (figure 1).

Participation
After preharvest testing, 545 fieldworkers in the teams selected for the study were employed (figure 2). Five workers lacked Lund University serum samples either from baseline or end-harvest and were excluded. Workers were predominantly men under 40 (67%), with some variation by job (table 1).

Between baseline and end-harvest, 113 (21%) workers dropped out. Of these, 98 (87%) were contacted. Only 15 (3% of all enrolled in the study) were lost completely. Dropout was more common among those with low baseline eGFR (33% among those with <60 mL/min/1.73 m^2 vs 20% among those with >90 mL/min/1.73 m^2) and higher age (26% above 40 years vs 20% below), but relatively constant between jobs (range 17%–23%).

Kidney injury incidence and cross-harvest eGFR trends
Of the 427 workers examined at baseline and end-harvest, 32 (7%) had IKI (table 2). Among the 98 located dropouts, 31 (32%) self-reported creatinine elevation. Of those, 19 indicated leaving before end-harvest due to high SCr and the other 12 had been on sick leave due to creatinine elevation. Among these 12, 3 did not return to work because work was too hard or for personal reasons and 9 were not present or notified the day of testing. In total, 63 (12%) of the 525 participating fieldworkers had IKI-All during harvest.

Overall eGFR decreased by 4.6 (95% CI 3.2 to 6.0) mL/min/1.73 m^2 during harvest.

Kidney injury risk factors
IKI varied significantly by job category. IKI-Measured only occurred in men among burned cane cutters (21%) and seed cutters (3%). For IKI-All, incidence increased to 27% among burned cane cutters and to 9% among seed cutters (including
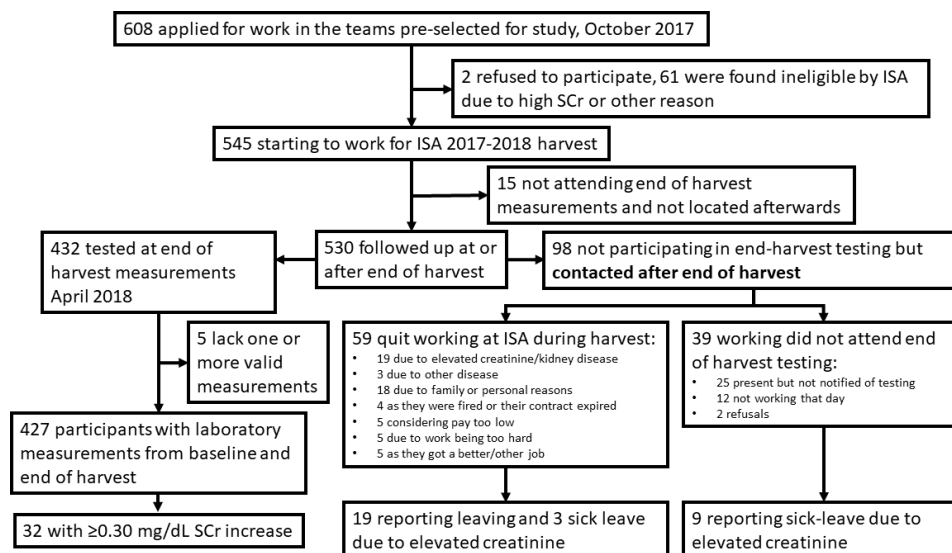
Figure 2 Participant flow chart. ISA, Ingenio San Antonio; SCr, serum creatinine.
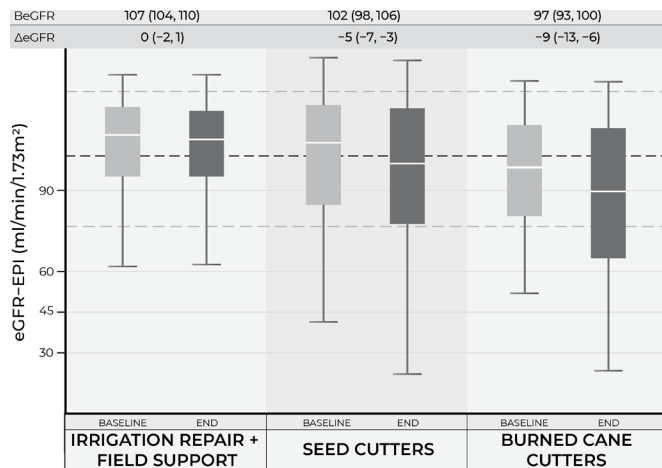
Figure 3 Renal function (eGFR) by job and time of testing. Dashed lines indicate median (black) and 90% range (grey) eGFR in administrative staff at baseline. BeGFR denotes mean (95% CI) baseline eGFR. ΔeGFR denotes mean (95% CI) cross-harvest change in eGFR. Includes only workers measured before and at the end of harvest. eGFR, estimated glomerular filtration rate. EPI denotes eGFR is estimted according to the Chronic Kidney Disease Epidemiology Collaboration equation.

five women) (table 2). After age and sex adjustment, IKI-All incidence remained significantly elevated among cane and seed cutters compared with irrigation repair workers and field support staff. Adjusting for baseline eGFR reduced the age-adjusted and sex-adjusted IKI-All IR to 9.3 (95% CI 3.2 to 28.3) for burned cane cutters and 3.3 (95% CI 1.1 to 9.9) for seed cutters.

Cross-harvest eGFR declines varied by job (figure 3), with age-adjusted and sex-adjusted ΔeGFR −9.2 (95% CI −12.9 to 5.6) among burned cane cutters and −4.3 (95% CI −7.5 to −1.0) mL/min/1.73 m^2 among seed cutters, with field support staff and irrigation repair workers as referent (table 2). The difference between burned cane and seed cutter was statistically significant (p=0.01). These results did not change markedly after adjustment for baseline eGFR.

IKI-All incidence sex differences were non-significant among seed cutters (male/female IR 0.87, 95% CI 0.30 to 2.51), and there were no sex differences in age- and job-adjusted ΔeGFR. Age was inversely associated with ΔeGFR and IKI, which was strengthened when adjusting for baseline eGFR category, with a 1-year age increase associated with a 0.96 (95% CI 0.92 to 0.99) IR decrease.

IKI-All increased with decreased baseline renal function, while ΔeGFR was worse among those with higher baseline renal function. Cross-harvest change in liquid intake was not clearly associated with IKI nor ΔeGFR, neither was absolute liquid intake. There was a tendency towards more IKI with increased sugary drink intake. High boli intake was associated with less ΔeGFR decline, but not associated with IKI. Self-reported pesticide use, although infrequent (n=13, from various job categories), was borderline significantly associated with IKI-Measured in univariate analysis and ΔeGFR. End-harvest incident fever was associated with IKI-Measured, as was the inflammatory marker CRP, which increased eightfold in IKI workers during harvest while remaining stable in others. Workers self-reporting fever had significantly elevated CRP levels (online supplementary 2).

DISCUSSION

IKI among sugarcane fieldworkers during harvest was frequent (12% IKI-All), with events concentrated among burned cane

cutters (27%; table 2). The IKI term was chosen as an epidemiological measure of substantial change in renal function over a specific time frame longer than that specified for AKI.[24] Similar studies have found high cross-harvest kidney injury incidence, especially among burned cane cutters, 14%[11] and 19%,[14] with the first study following cutters after only 9 weeks and the latter not reporting on loss to follow-up.

Our results reflect a substantial healthy worker selection effect. Most dropouts were tracked, and the rate of self-reported IKI (elevated SCr) among the dropouts was four times higher than among those measured at end-harvest (32% vs 7.5%). Neglecting dropouts introduces selection bias and impedes future evaluation of intervention effects: improved outcomes among non-dropouts could be attributed to intervention effects but may also arise if the mill improves detection of ill workers and/or applies stricter criteria for return to work.

We assessed the validity of the use of IKI including self-reported IKI. Twenty-six out of 32 workers with measured and 23 out of 31 with self-reported IKI in year 1 returned for pre-employment testing at year 2, as did 372 workers without IKI. In a mixed-effects linear regression model adjusting for age, sex and job, the baseline-to-baseline eGFR decline was 9.6 (95% CI 14.3 to 4.8) and 5.3 (10.2 to 0.5) mL/min/1.73 m^2 larger in the measured and self-reported IKI groups, respectively, than in non-IKI workers. Worse kidney function at year 2 baseline 12 months later strengthens IKI-Measured as a valuable intermediate endpoint[14] and indicates the validity of self-reported IKI, respectively. Further, reliable self-report of elevated SCr is not surprising as the importance of this biomarker is well understood in the community of workers, especially as it determines eligibility for hiring and for maintaining employment.

A nearby community cohort reported a small seasonal kidney function decline.[26] The marked differences between workers in different jobs with similar outdoor heat exposure at work during the harvest indicate that seasonal effects alone cannot explain our findings.[27]

Cross-harvest eGFR declines were smaller and IKI events rare among workers judged to have low-moderate physical demands, but who share the very hot climatic conditions with their colleagues working more intensely. This suggests that an important driver of kidney injury in this setting is heavy physically demanding work. As in all observational research, unmeasured risk factors cannot be ruled out, but such factors must then be highly prevalent in cutters, but not in field support staff working just a few metres away.

Very few workers reported pesticide use during harvest. Considering that their jobs at the mill do not imply direct pesticide exposure and the low proportion reporting pesticide use, it is unlikely that a large proportion of IKI events could be attributed to pesticide exposure during harvest, a finding in line with previous studies.[4 9 12 13] To better understand a possible role of pesticides, exposure during non-harvest must be thoroughly assessed in all workers. Also, detailed information on pesticide use from the mill and investigations in workers with potentially higher exposure (weeders) are needed and planned for years 2 and 3, as these could overcome potential validity problems of self-reported pesticide use. Most other explanatory variables are also self-reported, which is a limitation of this study.

Reduced baseline kidney function was a risk factor for IKI-All but not for ΔeGFR decline. This is probably explained by three mechanisms: (1) a few individuals had extreme changes (ΔeGFR restitution by >20 or loss by >50 mL/min/1.73 m^2) on the two ends of baseline eGFR distribution; (2) the relationship between SCr and eGFR is non-linear (a 0.3 mg/dL SCr increase at low

eGFR implies much smaller eGFR decrease than at high eGFR); and (3) workers with low initial eGFR were more likely to drop out with IKI.

Evidence suggested inflammation may be associated with kidney injury, as others have reported.[7 8 12 23 26 28] To our knowledge, no study has identified the cause of inflammation or made a clear distinction between inflammation from heat injury[29] versus infection. Reverse causation is unlikely as end-harvest CRP levels among IKI workers (online supplementary 2) were higher than normally seen in dialysis patients[30] and middle-income country predialysis patients,[31 32] despite those patients having lower eGFR.

Reverse causation, residual confounding and measurement error limit interpretation concerning the role of hydration. While low liquid intake may predispose to kidney injury, high intake may indicate kidney injury causing poor urine concentration ability or strenuous work,[3] potentially explaining why some studies[4 33] identify high liquid intake as a risk factor and we find no association. Acute kidney damage has been reported in well-hydrated workers.[7] Likewise, exertional heat stroke, a condition also characterised by systemic inflammation and organ damage,[29] may also occur in well-hydrated individuals.[34] A more complex interaction between water intake, physical labour and heat exposure is likely, with avoidance of dehydration not necessarily incurring complete protection against effects of heat on the kidney.

Nonetheless, hydration status should be assessed during repeated work shifts to adequately understand the role of dehydration in CKDu pathogenesis, but such measurements are complex in a field setting.[35] Electrolyte solution intake has been associated with less kidney injury,[4 6 12 13] and our results agree partially: less cross-harvest eGFR decline, but no clear protective effect against IKI among those drinking the most bolis. A potential harmful effect of sugary beverages should be further considered.[36] Drinking water contamination is unlikely considering that no nephrotoxic substances have been found in drinking water at the mill or within its vicinity,[17 37] nor in routine monitoring by the mill.

Muscular mass and diet could influence SCr levels and thus our results. Future studies should consider using glomerular filtration rate markers independent of this, for example, cystatin C.

The error introduced by incomplete mixing at the laboratory is a limitation, reduced by the correction using an internal standard. The correction procedure has been validated experimentally, and the assumed true sodium level of 140 mmol/L for the correction is in accordance with observations in sugarcane workers in the region. Associations observed are likely real, but we acknowledge there might be associations not observed due to the increased non-differential noise introduced by the error and the introduction of a correction factor.

Our assessment of workload for year 1 was observation-based, but preliminary analysis of HR measurements from year 2 confirms workload ordering (based on $\%HR_{Max}$): burned cane cutters had the highest proportion of the work shift at high levels of $\%HR_{Max}$, followed by seed cutters and irrigation repair workers, and with field support staff not yet measured.

Efforts are in process in years 2 and 3 to track the impact of interventions improvements, as current preventive measures seem inadequate for cutters. Improvements include adoption of rest schedules closer to the ACGIH guidelines, breaks earlier in the workday, and guaranteeing accessibility to water, tents for all job groups and increased adherence to the prescribed interventions. The current study of existing practices will be used as a historical control to evaluate the effectiveness of these measures.

CONCLUSION

Our results provide evidence for an association between physically demanding job tasks and kidney injury in a population exposed to high environmental heat levels. Workers considered to have the highest workload had more cross-harvest kidney damage than workers with less workload. Work practices preventing heat stress should be strengthened in design and implementation and their role in preventing kidney damage examined further. Research is needed to measure core body temperature, and the impact of an enhanced rest schedule and better access to water, and to investigate the role of inflammation. Future occupational studies should include longitudinal designs and account for a healthy worker effect by pursuing those lost to follow-up.

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