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Risk Factors for Declines in Kidney Function in Sugarcane Workers in Guatemala

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Objectives: To characterize kidney function of sugarcane workers in Guatemala over the 6-month harvest and identify risk factors associated with changes in kidney function. **Methods:** Demographic and biological data were collected for 330 sugarcane cutters at the beginning and end of the harvest. Multivariable regression analyses were used to assess factors related to kidney function. **Results:** A decline in kidney function across the harvest was observed in 36% of the participants. Risk factors associated with this decline included working at a particular plantation mill, local area workers compared with highland workers, and current smokers. **Conclusion:** Results showed both occupational and behavioral factors play significant roles in declines in kidney function. These results underline the need for a comprehensive approach to the epidemic as well as further investigation of risk factors to guide research and interventions.

Keywords: agricultural workers, chronic kidney disease, international occupational health

An increase in chronic kidney disease morbidity and mortality rates has been observed in Latin America.[1–3] The epidemic of so-called chronic kidney disease of unknown origin (CKDu), also referred to as Mesoamerican nephropathy, has been observed mainly in agricultural communities. In El Salvador and Nicaragua, observed prevalence rates have ranged from 18% to 41%.[2,4,5] In a study based in Quezalguape, a rural municipality in the Department of Leon, Nicaragua, CKDu rates were 16 times higher than in age-matched 30 to 41-year-old men in the United States.[6] Notably, by definition, CKDu is not related to traditional risk factors such as hypertension, diabetes, or obesity.[7–9]

CKDu has been shown to be elevated particularly among male agricultural workers in their 20's to 40's, especially sugarcane cutters, who perform strenuous labor outdoors in hot temperatures and high humidity.[2,5,6,10] Researchers have hypothesized that CKDu is linked to repeated heat stress and recurrent dehydration during intense manual work.[11–16] One recent study reported a link between climate-related extreme heat exposure, dehydration, and volume loss and the prevalence of CKDu in sugarcane workers.[15,16] In 2015, the second International Research Workshop on Mesoamerican Nephropathy was convened by the Consortium on the Epidemic of Nephropathy in Central America and Mexico (CENCAM).[17] Consensus was reached that CKDu is characterized by an occupational component, and that the evidence is growing for a multi-causal role of strenuous work, heat, and insufficient rehydration, and that heat stress may play a central role in the causal pathway. Other proposed causal factors have been suggested, but not thoroughly examined, including nephrotoxic agrochemicals and heavy metals, tobacco use, nonsteroidal anti-inflammatory drug (NSAID) use, dietary fructose consumption, and infectious agents.[18–22] A recent review of studies examining pesticide exposure and CKDu indicates the need for better exposure assessment to determine the potential role of these chemicals, and particularly if they interact with other important risk factors like heat stress.[23]

In 2016, a Memorandum of Understanding (MOU) was executed between the University of Colorado and Pantaleon, an agribusiness and producer of sugar in Central America, to assess and improve the health, safety, and well-being of its sugarcane workers in Guatemala. While Guatemala has been cited as having high rates of CKD and renal failure mortality, at 16 per 100,000 males in 2008,[24] the prevalence of CKDu among the general population or high-risk populations such as sugarcane workers is not known. One of the few studies on CKD in Guatemala documented that one out of five patients on hemodialysis has CKDu compared with CKD in southwestern Guatemala.[25] We prospectively evaluated kidney function in workers across the 6-month harvest. Workers have been part of a Heat Illness Prevention Program since 2012 and, as part of that program, are provided with access to water, electrolyte supplements, rest periods, and shade but have anecdotally continued to experience kidney function changes. Although heat stress and dehydration have been the main focus of studies in Central America, the etiology of CKDu remains unknown. Other hypotheses for CKDu have been suggested in the literature, but with limited research. Therefore, we examined a number of potential risk factors in addition to hydration status. We hypothesized that reduced kidney function would continue to occur despite these measures and that multiple risk factors may contribute to risk of decline in kidney function across the harvest.

METHODS

Field Operations

In Guatemala, the sugarcane harvest season lasts 6 months from mid-November to early May. Cane cutters are assigned to

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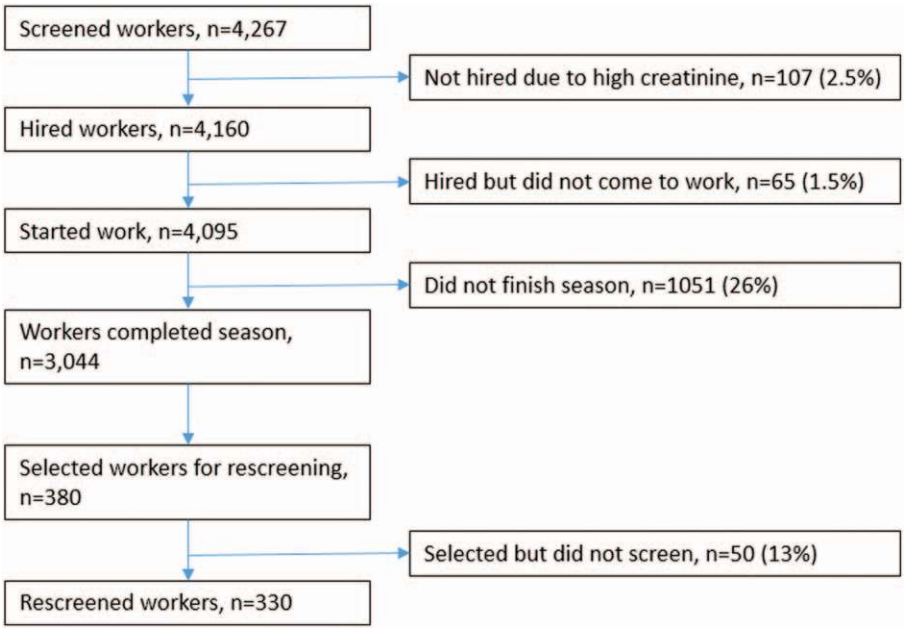

FIGURE 1. Evaluation flow chart.

cutting groups based on their home community, approximately 50 to 70 cane cutters are in each cutting group. Cutting groups are affiliated with one of two cane processing mills for the harvest season, referred to as Mill A and B. The majority of the cane cutters (70%) are assigned to the larger mill, Mill A. The two mills are located 33 km from each other in the Department of Escuintla and both are at approximately 445 m elevation. The mills are serviced by multiple interwoven plantations, ranging from sea level to 500 m elevation surrounding the mills. The cutting groups rotate through numerous plantations throughout the Department during the harvest. The field environments of these plantations servicing both mills are therefore very similar as are the cane cutting processes.

Each work week is 6 days long with a worker's daily shift averaging 10 hours in the field. Cutting sugarcane is intense labor. Crowe et al,[26] estimated that cutting cane results in a total metabolism of 261 W/m^2 (6.8 kcal/min). Workers are bused to and from the fields. They cut cane by swinging a machete from shoulder level to ground level to cut the cane and then workers lift, trim, and stack the cane.

Pantaleon promotes and monitors hydration, rest, and shade for their cane cutters which includes encouraging cane cutters to drink 16 L of water and 2.5 L of electrolyte solution (composition per liter: 4.6 g NaCl, 34 g carbohydrates [26 g sucrose], and 2 g KCl) and to take three 20-minute breaks and one 60-minute lunch break during the work shift. Field health aides, employed by Pantaleon, record how much water a small random subset of workers drinks during each day and conduct random urine specific gravity checks using urine dipsticks to monitor hydration status. During breaks, the aides educate the workers on topics including hydration, rest, hygiene, safe sexual practices, nutrition, and risks of using drugs and non-prescription medicines. Water and electrolyte solution are provided daily for free in the fields. Health aides and field physicians address health issues that arise during the day. Pantaleon also provides cane cutters with an ergonomically-designed machete to cut the cane, a personal, refillable 5-L container for water, and personal protective equipment including goggles, hat, long-sleeved shirt, gloves, wrist and shin guards, and boots.

Worker Population

For the 2015 to 2016 harvest season, Pantaleon performed a pre-employment medical screening on 4267 male cane cutters, more than or equal to 18 years of age, including 2026 local workers (47%) and 2241 highland workers (53%). A flow chart is shown in Fig. 1. For recruitment of local workers, Pantaleon announces the pre-employment dates for the upcoming harvest season through local radio and a mobile unit. Anyone in the local communities can apply. Highland workers come from the highland regions and are preselected based on whether they cut an average of 5 tons per day and worked at least 90 days the previous harvest. In addition, they must also not have any medical problems that would impact their ability to work. The people who pass the preselection are invited to apply for a position during the pre-employment process. New highland workers can also be invited to apply on-site by Pantaleon.

Of those workers screened, they employed 4160 cane cutters, including 1969 local workers (47%), and 2191 highland workers (53%). The 2% of the individuals not hired due to high creatinine measures ($n = 107$) were slightly older than hired workers (32 vs 28 years, respectively, P value <0.01) and reported having worked more harvests (seven vs six harvests, respectively, P value <0.01). They were not significantly different than the hired workers based on measured hypertension (7% vs 5%, respectively), body mass index (BMI) (23 kg/m^2 for both groups), self-reported current smoker status (4% vs 5%, respectively), and self-reported alcohol consumption (2% vs 3%, respectively). The non-hired workers had a median creatinine of 1.66 mg/dL (interquartile range [IQR]: 1.58 to 1.87) and a median estimated glomerular filtration rate (eGFR) of 53 mL/min/1.73 m^2 (IQR: 46 to 57) at time of screening.

Each workday, local workers commute from their home community on buses provided by their cutting group supervisor to their designated field and supply their own food. Local workers might travel from 30 minutes up to 2 hours to their worksite depending on the location of the field for that day. The majority of the local workers come from the Departments of Escuintla (61%) and Suchitepéquez (24%). The altitudes of the main source municipalities of the local workers in these departments range from 315 to 372 m. The highland workers are from the Departments of Quiché

(51%), Baja Verapaz (23%), and Chiquimula (17%). The altitudes of the main source municipalities of the highland workers in these departments range from 995 to 1827 m. Highland workers reside at the Pantaleon mills for the duration of the 6-month harvest and are provided with three daily meals, fresh water, and additional electrolyte solution that they can consume ad libitum.

Ethics review and approval for our analysis of the existing data was provided by the Colorado Multiple Institution Review Board (COMIRB).

Pre-Employment Screening

In late August to mid-November 2015, 4267 cane cutters participated in a pre-employment screening program to determine if they were fit for employment. The screening consisted of a medical examination (blood pressure, heart rate, height, weight, and physical examination), a survey that collected information about the individual's demographics, behaviors, and occupational and health history, and venipuncture to measure serum creatinine and calculate eGFR. Workers were asked to fast for 12 hours prior to the test and to avoid consumption of alcoholic beverages 1 day before the test.

As a health protection measure, it was the intention of the company to hire only individuals who had a serum creatinine level of 1.45 mg/dL or less. This screening practice has been in place since 2009. The cut-off was based on the concern that workers with a higher creatinine level would be at increased risk of kidney injury. The company doctors also screen for other acute and chronic illnesses that would inhibit an individual's ability to safely work. Workers with chronic illnesses such as uncontrolled hypertension have the opportunity to seek treatment with their own health care provider and once controlled can reapply for a position appropriate to their health condition.

End of Harvest Rescreening

To assess the incidence of kidney injury, Pantaleon rescreened a subset of 330 cane cutters during two mornings at the end of harvest in May 2016. To select this group, a stratified random sample was used to create a list of 380 cane cutters. Stratification was based on the 11 work area groups. Work area groups rotate to various plantations throughout the Department so work fields and conditions are very similar among the work area groups. Among the selected workers, 75% of the workers were associated with Mill A (eight work areas) and 55% were highland workers. Representation for each work area group ranged from 3% to 13%

Due to time constraints, 87% of the random sample of selected workers completed the rescreening ($n = 330$). A comparison of those selected and rescreened and those selected and not rescreened revealed no significant differences in age (27 and 28 years, respectively, P value 0.96), pre-employment BMI (23 and 22 kg/m^2, respectively, P value 0.08), pre-employment hypertension (3% and 6%, respectively, P value 0.37) or pre-employment eGFR (112 and 111 mL/min/1.73 m^2, respectively, P value 0.88). A higher proportion of selected local workers were more likely to not be rescreened compared with highland workers (62% and 38%, respectively, P value <0.01) and rescreened cane cutters worked, on average, more days than did workers selected but not rescreened (146 and 142 days, respectively, P value <0.01).

At the rescreening, workers completed a medical examination, an end-of-harvest survey, and a venipuncture. The interviewer-administered survey collected information on potential risk factors including demographics (age, sex, race/ethnicity, and place of residence); chronic health conditions (self-reported diabetes, heart disease, and kidney disease); occupation (type of work done off-season, average shift hours worked, and number of harvests worked); behaviors (water intake, electrolyte solution intake, sugary beverages per week, alcoholic drinks per day, applied pesticides or insecticides on own land, tobacco smoking, and medication use); and work-related symptoms (see supplemental material, http://links.lww.com/JOM/A416). Blood draws were performed early in the morning and workers were surveyed between 7:30 am and 12:00 pm. Similar to pre-employment screening, workers were asked to fast and avoid consumption of alcoholic beverages before the assessment.

Kidney Function Measures

All blood samples for both screenings were analyzed at an independent, licensed, and accredited clinical laboratory (Herrera Llerandi laboratory, Guatemala City, Guatemala). Serum creatinine was measured using a kinetic-rate Jaffe method and was used to calculate eGFR with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[27] Age, sex, and race are accounted for in the equation. In keeping with previous studies in Central America, race was considered ''non-black'' in the equation.[28,29]

We examined the 6-month, cross-season change in eGFR in two ways: (a) a continuous percent change in eGFR (%ΔGFR) from pre-employment to the end of harvest ([end of harvest eGFR – pre-employment eGFR/pre-employment eGFR] × 100), and (b) a dichotomized decline in eGFR from pre-employment to the end of harvest (less than 0%ΔGFR) compared with stable or increase in eGFR (more than or equal to 0%ΔGFR). We further categorized workers that had a decline in eGFR as having a mild decline versus a severe decline (0% to 20% decline vs more than 20% decline). It is unknown what degree of change in eGFR over a 6-month period indicates clinically significant progression. From the literature, we established that a decline of greater than 20% in eGFR was a conservative cutoff point indicating clinically significant kidney function decline.[30,31] We defined mildly reduced kidney function as an eGFR between 60 and 89 mL/min/1.73 m^2 and moderately reduced kidney function as an eGFR less than 60 mL/min/1.73 m^2.

Productivity Measures

The company provided investigators at the Center for Health, Work & Environment at the Colorado School of Public Health with a de-identified dataset of worker productivity that included total number of days worked and daily average tons of cane cut for each cane cutter. The individual average tons of cane cut across the season was calculated by averaging the daily total tons cut across the season.

Data Analysis

De-identified datasets were provided to investigators and all analyses and interpretation of results were performed independently by those investigators.

We examined the univariate relationships between the potential risk factors collected from the end of harvest medical examination and survey, and productivity data with %ΔGFR as continuous and categorical (more than or equal to 0% vs less than 0%ΔGFR) in the overall cohort ($n = 330$). We compared characteristics of those who declined in eGFR to those who did not using Mann–Whitney U (Wilcoxon) test for continuous variables and chi-squared or Fisher exact tests for dichotomous or categorical predictors. Continuous variables were expressed as median with IQR due to the non-normal distributions. Categorical variables were expressed as numbers and percentages. We then examined multivariable relationships using linear regression for the continuous outcome. We used stepwise multivariable regression analysis, using a P value of <0.10 for variable retention, to identify risk factors of the continuous and categorical outcomes. Characteristics were considered candidates for inclusion in the model if the P value on univariate testing was ≤ 0.10. All multivariable models adjusted for age, pre-employment eGFR, and self-reported water intake.

We ran logistic regression models for the dichotomized outcome with variables selected from variable selection process outlined above. We further stratified our outcome to mild (0% to 20% decline) and severe decline (more than 20% decline) and examined potential risk factors using multinomial logistic regression models. In these models the group of workers who were stable or had experienced an increase in eGFR over the harvest served as the reference group. We grouped former smokers with never smokers due to similarities observed in the bivariate analysis and to evaluate the effect of current smoking.[30] SAS version 9.4 (Cary, NC) was used for all analyses.

RESULTS

Participant Characteristics

The cohort of hired cane cutters, $N = 4160$, were all male, had a median age of 28 and BMI of 23 kg/m^2 (Table 1). About half of the hired workers were local (47%) and half were from the highland regions (53%). Only 3% of the cane cutters reported drinking alcohol, 5% reported being current smokers, and 5% reported being former smokers. Blood pressure was measured at pre-employment and 5% of the workers had hypertension, defined as systolic blood pressure more than or equal to 140 mmHg and/or diastolic blood pressure more than or equal to 90 mmHg. The median reported numbers of harvests worked was six harvests. In terms of kidney function, the median creatinine was 0.92 mg/dL and median eGFR was 110 mL/min/1.73 m^2.

At the end of harvest, 330 male participants completed a venipuncture, survey, and medical examination. The median age of participants was 28 years and BMI of 22 kg/m^2 (Table 2). Local workers made up 42% of participants and 58% were from the highlands. Few workers had hypertension (2%) at the end of harvest. Five of the participants reported having a history of kidney disease (1%), heart disease (1%), or diabetes (1%).

The majority of 330 respondents worked at Mill A (74%). Almost all had worked the sugarcane harvest the previous year (94%), with a median of eight harvests previously worked. The median individual average tons of cane cut across the season was 6 tons per day and the median days worked was 146 days.

As summarized in Table 2, the majority of survey respondents reported drinking 14 L or more of water per day (79%) and at least two cans/glasses of juice or soda per day (79%). Workers reported drinking, on average, five 500-mL bags of electrolyte solution per day. The majority of the workers reported that they never smoked (78%). Seventy percent reported taking an NSAID in the last 3 months. The two most common types of work done in the off-season were subsistence agriculture (60%) and commercial agriculture (10%). One-third reported applying pesticides or insecticides on their own land (39%). The most common work-related symptoms reported were headache (24%), painful urination (8%), fever (7%), and muscle cramping (4%). Symptom data are not shown.

Kidney Function

At pre-employment, 46 of the 330 participants (14%) had mildly reduced kidney function, with three participants meeting our case definition for moderately reduced kidney function (point prevalence, 1%, range: 56 to 59 mL/min/173 m^2). At the end of harvest, 32 participants (10%) had mildly reduced kidney function and 11 participants had moderately reduced kidney function (point prevalence, 3%). Ten workers developed moderately reduced kidney function during the harvest (6-month incidence, 3%, range: 45 to 59 mL/min/1.73 m^2), excluding three workers who had moderately reduced kidney function at pre-employment. Six of the 10 workers who developed moderately reduced kidney function during the harvest had mildly reduced kidney function at pre-employment (median: 82.3 mL/min/1.73 m^2, range: 65 to 125 mL/min/1.73 m^2). Among the three workers who had moderately reduced kidney function at pre-employment, one worker remained moderately reduced and had a severe decline and two workers improved slightly to mildly reduced kidney function at the rescreening.

TABLE 1. Pre-Employment Characteristics, $N = 4160$ Hired Workers (2015 to 2016)

Characteristics	Hired Workers *N* (%)
Demographics and health history	
Age, yr, median (IQR)	28 (23–35)
Body mass index, median (IQR)	23 (21–25)
Hypertension*	197 (5%)
Home of residence	
Local	1969 (47%)
Highland	2191 (53%)
Smoking status	
Never	3646 (90%)
Former	200 (5%)
Current	222 (5%)
Drinks alcohol	
No	3923 (97%)
Yes	122 (3%)
Creatinine, mg/dL, median (IQR)	0.92 (0.84–1.01)
Pre-employment eGFR, median (IQR)	110 (98–120)
≥90	3522 (85%)
60–89	615 (15%)
30–59	23 (<1%)
<30	0

eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2; IQR, interquartile range.

*Hypertension is defined as systolic blood pressure ≥140 and/or diastolic ≥90 mmHg.

As presented in Table 3, among the 330 workers, the median pre-employment eGFR was 111 mL/min/1.73 m^2 and end of harvest eGFR was 117 mL/min/1.73 m^2. On average, eGFR improved by 3 mL/min/1.73 m^2 during the harvest. Over the 6-month harvest, 63% of the workers' eGFR remained stable or improved (median: 10.52 mL/min/1.73 m^2, IQR: 3.90–17.86) (Fig. 2). However, eGFR declined in 37% of the workers, among whom 6% experienced a decline of more than 20% from pre-employment to the end of harvest (median: −7.29 mL/min/1.73 m^2, IQR: −15.36–−2.02).

One-quarter of the workforce (26%) left employment prior to the end of harvest. Anecdotally, there are a number of potential reasons why workers leave employment prior to the end of the season. Although we do not have information on the reasons why individual workers left employment early, we were able to analyze for the possible contribution of a healthy worker effect. Cane cutters who left early had clinically small, but statistically significantly higher creatinine at the start of the season compared with those who worked the entire season (median: 0.93 and 0.92 mg/dL, respectively, P value <0.01). Highland workers were significantly less likely to finish the season compared with local workers (29% vs 19%, respectively, P value <0.01).

Risk Factors

Univariate Analysis of Risk Factors

The factors associated with workers who had a decline in kidney function (less than <0%ΔGFR) in the univariate models are summarized in Table 2. Declines in kidney function were significantly more likely among local workers, workers at Mill A, workers who worked fewer days, and workers who did not report doing

TABLE 2. End of Harvest Rescreening Characteristics, Stratified by Percent Change in Estimated Glomerular Filtration Rate, eGFR

Characteristics	All Participants *N* (%)	%ΔGFR Decline *N* (%)	%ΔGFR Stable/Increase *N* (%)	*P*-Value*
Demographics and health history				
Overall, *N* (%)	330 (100%)	121 (37%)	209 (63%)	
Age, yr, median (IQR)	28 (23–36)	28 (24–36)	28 (23–36)	0.43
Body mass index, median (IQR)	22 (21–24)	23 (21–24)	22 (21–24)	0.06
Hypertension[a]	8 (2%)	4 (50%)	4 (50%)	0.44
Kidney disease[b]	2 (1%)	1 (50%)	1 (50%)	–
Heart disease[b]	2 (1%)	0	2 (100%)	–
Diabetes[b]	1 (1%)	0	1 (100%)	–
Home of residence				
Local	140 (42%)	68 (49%)	72 (51%)	<0.01
Highland	190 (58%)	53 (28%)	137 (72%)	
Work practices and work history				
Mill				
A	245 (74%)	103 (42%)	142 (58%)	<0.01
B	85 (26%)	18 (21%)	67 (79%)	
Number of harvests worked, $n = 322$, median (IQR)	8 (4–13)	8 (5–13)	8 (4–14)	0.54
Individual average tons cut/d[c], $n = 318$, median (IQR)	5.8 (5.4–6.3)	5.8 (5.3–6.3)	5.8 (5.4–6.3)	0.98
Total days worked[c], $n = 320$, median (IQR)	146 (140–150)	145 (137–149)	147 (142–150)	0.01
Behaviors				
Daily water intake (L)				
≤1	0	0	0	0.93
2–4	7 (2%)	3 (43%)	4 (57%)	
5–7	11 (3%)	3 (27%)	8 (74%)	
8–10	24 (7%)	10 (42%)	14 (58%)	
11–13	25 (7%)	10 (40%)	15 (60%)	
≥14	256 (79%)	94 (37%)	162 (63%)	
Sodas or juice drinks per week (can/glass)[d], $n = 319$, median (IQR)	6 (3–8)	7 (3–8)	6 (3–8)	0.22
Alcohol drinks per day, $n = 323$				
No	289 (90%)	104 (36%)	185 (64%)	0.65
1–2	17 (5%)	8 (47%)	9 (53%)	
≥3	16 (5%)	6 (38%)	10 (62%)	
Tobacco smoker				
Never	249 (78%)	85 (34%)	164 (66%)	0.07
Former	25 (8%)	9 (36%)	16 (64%)	
Current	44 (14%)	23 (52%)	21 (48%)	
Took NSAIDs[e], past 3 months				
No	98 (30%)	42 (43%)	56 (57%)	0.13
Yes	232 (70%)	79 (34%)	153 (66%)	
Daily electrolyte bags[f], $n = 311$, median (IQR)	5 (4–6)	5 (4–6)	5 (5–6)	0.83
Away from work practices				
Type of work during the off-season (top two responses)[g]				
Subsistence agriculture				
No	131 (40%)	60 (46%)	71 (54%)	0.01
Yes	199 (60%)	61 (31%)	71 (69%)	
Commercial agriculture				
No	296 (90%)	107 (36%)	189 (64%)	0.57
Yes	34 (10%)	14 (41%)	20 (59%)	
Applied pesticide or insecticides on own land				
No	186 (58%)	72 (39%)	114 (61%)	0.53
Yes	136 (42%)	48 (35%)	88 (65%)	
Kidney function				
Percent change in eGFR[h], median (IQR)	3.0 (−2.3–13.3)	−6.2 (−15.4–−1.8)	9.8 (3.5–17.7)	<0.01
Pre-employment eGFR				
≥90	281 (85%)	101 (35%)	180 (64%)	0.78
60–89	46 (14%)	19 (41%)	27 (59%)	
30–59	3 (1%)	1 (33%)	2 (67%)	
<30	0	0	0	
End of harvest eGFR				
≥90	287 (86%)	85 (30%)	202 (70%)	<0.01
60–89	32 (10%)	25 (78%)	7 (22%)	

(Continued on next page)

TABLE 2. (*Continued*)

Characteristics	All Participants *N* (%)	%ΔGFR Decline *N* (%)	%ΔGFR Stable/Increase *N* (%)	*P*-Value*
30–59	10 (3%)	10 (100%)	0	
<30	1 (1%)	1 (100%)	0	

eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2; IQR, interquartile range; L, liters; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg.
[b]Self-reported health history.
[c]Productivity dataset provided by employer.
[d]Multiplied survey responses from two questions: ''How many days a week do you drink sugar drinks?'' and ''How many cans/glasses each day?''.
[e]NSAIDs included ibuprofen, aspirin, or NSAID supplements (self-reported vitamins that contain NSAIDs).
[f]500 mL bags of electrolyte solution distributed by employer.
[g]Survey question: ''In the 6 months before coming to work what kind of work did you do?''.
[h]A minus sign indicates worsening kidney function.
*Mann–Whitney *U* (Wilcoxon) test, chi-squared, or Fisher exact test.

subsistence farming during the off-season. Total days worked was highly associated with home of residence, with highland workers having worked more days than local workers (median: 149 and 141 days, respectively). Those with declines in kidney function were more likely to end the season with reduced kidney function. Differences in BMI and smoking status approached statistical significance. BMI was slightly higher, on average, among workers with declines in kidney function compared with workers who were stable or had an improvement in kidney function. Current smokers were more likely to experience a decline in kidney function compared with former and never smokers. To further examine the relationship between kidney function, home of residence, and mill, we did separate analyses stratifying by home of residence and also by mill. Among only local workers, those at Mill A were more likely to experience a decline in kidney function compared with Mill B. The same relationship is seen among only highland workers. When stratified by mill, local workers at Mill A were more likely to have declines in kidney function compared with highland workers at Mill A. No significant difference is seen between local and highland workers at Mill B.

Table 3 summarizes the factors associated with %ΔGFR across the season in the univariate models. Highland workers showed a significantly greater improvement in %ΔGFR compared with local workers (5.14% and 0.33%, respectively). Workers at Mill B showed a significantly greater improvement in %ΔGFR over the season compared with workers at Mill A (12.37% and 1.34%, respectively). Workers who reported doing subsistence farming during the off-season showed a significantly greater improvement in %ΔGFR over the season compared with workers that did not report subsistence farming (5.14% and 0.81%, respectively). Subsistence farming is highly correlated with home of residence, where highland workers are significantly more likely to report doing subsistence farming in the off-season (75% highland workers and 25% local workers, P value <0.01). Average differences in %ΔGFR approached statistical significance between current smokers and never/former smokers (−0.63% and 3.22%, respectively).

Notably, several potential risk factors were not significantly associated with %ΔGFR including: age, BMI, hypertension, number of harvests worked, average tons cut per day, water intake, sugary beverages, NSAID use, electrolyte fluid consumption, commercial agriculture in off-season, pesticide or insecticide application on own land, and kidney function at pre-employment.

Multivariable Analysis of Risk Factors

To determine the contribution of each factor to %ΔGFR, a multivariable model based on potential risk factors for a decline in eGFR was constructed. The final model included water intake, pre-employment eGFR (less than 90 vs more than or equal to 90), Mill (A vs B), home of residence (local vs highland), and smoking status (current vs never/former) while controlling for age (Table 4). Workers at Mill A had an average 12.03% decline in eGFR compared with workers at Mill B. Local workers had an average 6.30% decline in eGFR compared with highland workers. Also, current smokers had an average 5.80% decline in eGFR compared with workers who reported that they never smoked or who had formerly smoked. Workers with a pre-employment eGFR less than 90 had an average 7.31% improvement in eGFR across the harvest compared with workers with an eGFR more than or equal to 90.

Using the logistic model, the odds of having a decline in kidney function (less than 0%ΔGFR) was significantly influenced by working at Mill A (odds ratio [OR]: 2.60, 95% confidence interval [CI]: 1.39:4.80), being a local worker (OR: 2.15, 95% CI: 1.28:3.60) and being a current smoker (OR: 2.33, 95% CI: 1.17:4.63), Fig. 3.

We also evaluated the odds of mild (0% to 20% decline) and severe decline (more than 20% decline) in kidney function. The group of workers with stable or in increase in kidney function served as the reference group. Higher risks were observed in workers with a severe decline (vs no decline) compared with a mild decline (vs no decline), as shown in Fig. 4. The model demonstrated that having a pre-employment eGFR less than 90 (OR: 4.23, 95% CI: 1.12:15.99), being a local worker (OR: 4.37, 95% CI: 1.41:13.52), and being a current smoker (OR: 5.27, 95% CI: 1.54:17.99) were significant risk factors for a severe decline in kidney function across the harvest. Being a local worker and working at Mill A were the only risk factors significant for having a mild decline in kidney function across the harvest (OR: 1.92, 95% CI: 1.12:3.30 and OR: 2.48, 95% CI: 1.30:4.72). Being a current smoker approached statistical significance as a risk factor for having a mild decline (OR: 1.99, 95% CI: 0.96:4.12). The 95% confidence intervals for the odds ratios comparing severe decline versus no decline were wide, due to the fact that there are a small number of severe decline outcome events. Thus, this association should be interpreted with caution.

DISCUSSION

Guatemalan sugarcane workers are at risk for reduced kidney function across the harvest season, as has been observed in other Central American countries. Although kidney function, on average, slightly increased during the 6-month harvest, a notable one-third of the workers worsened. We had the opportunity to evaluate one of the largest cohorts of sugarcane workers to date, affording the opportunity to examine a number of potential risk factors. Declines in kidney function were more likely to occur in local workers, workers employed at one of the two mills, and among current smokers.

TABLE 3. Comparison of Pre-Employment and End of Harvest eGFR and Percent Change in eGFR of 330 Cane Cutters

Characteristics	eGFR: Pre-Employment	eGFR: End of Harvest	%ΔGFR[c]	%ΔGFR *P*-Value*
	Median (IQR)			
Demographics and health history				
Overall	111 (99–121)	117 (103–125)	2.97 (−2.35–13.34)	
Age, yr[a]				0.84
<30 yrs, $n=187$	117 (104–124)	124 (112–128)	2.69 (−3.17–14.08)	0.64
30–39 yrs, $n=90$	110 (95–117)	113 (104–118)	2.29 (−2.94–12.64)	
≥40 yrs, $n=55$	98 (82–108)	103 (96–110)	3.60 (−1.01–12.37)	
Home of residence				
Local	111 (95–121)	112 (97–122)	0.33 (−7.63–7.33)	<0.01
Highland	110 (100–121)	120 (108–127)	5.14 (−0.62–16.59)	
Body mass index[a]				0.34
≥25, $n=51$	105 (95–118)	113 (98–122)	3.26 (−2.68–13.07)	0.87
<25, $n=274$	112 (99–121)	118 (105–126)	2.71 (−2.34–13.38)	
Hypertension[b]				
No	111 (98–121)	117 (104–125)	3.05 (−2.34–13.34)	0.76
Yes	99 (92–113)	111 (97–122)	−0.49 (−3.49–18.44)	
Work practices and work history				
Mill				
A	111 (99–120)	113 (100–123)	1.34 (−4.07–8.12)	<0.01
B	111 (97–121)	126 (116–132)	12.37 (1.44–25.16)	
Number of harvests worked[a]				0.92
≤2, $n=40$	124 (105–126)	127 (122–132)	4.41 (−1.07–17.60)	0.56
3–10, $n=164$	114 (102–121)	121 (105–126)	2.28 (−3.49–14.08)	
≥11, $n=120$	104 (86–115)	110 (98–116)	3.09 (−2.27–12.52)	
Average tons cut/d[a]				0.71
0–4, $n=30$	105 (90–116)	111 (94–120)	4.22 (−2.64–14.09)	0.63
5–7, $n=259$	112 (100–121)	118 (107–126)	2.91 (−2.06–13.18)	
≥7, $n=30$	117 (98–124)	119 (103–123)	2.74 (−10.25–9.30)	
Total days worked[a]				<0.01
<146 d, $n=164$	111 (97–121)	114 (100–124)	1.75 (−2.72–9.06)	0.02
≥146 d, $n=166$	111 (100–120)	119 (108–126)	4.57 (−1.78–16.18)	
Behaviors				
Daily water intake, L				
2–4	104 (72–119)	100 (70–125)	3.69 (−12.54–12.37)	0.93
5–7	111 (95–122)	113 (107–123)	3.03 (−2.21–14.85)	
8–10	105 (92–122)	113 (105–122)	3.81 (−2.77–21.85)	
11–13	106 (99–119)	112 (105–125)	4.04 (−1.27–12.39)	
≥14	111 (100–121)	118 (104–125)	2.66 (−2.45–13.34)	
Sodas or juice drinks per week[a]				0.21
0	112 (106–118)	121 (111–125)	8.54 (3.34–14.26)	0.53
1–7	110 (100–121)	116 (104–125)	2.69 (−2.21–14.08)	
8–14	112 (101–120)	118 (101–125)	2.66 (−2.95–12.21)	
≥15	115 (100–124)	121 (106–125)	1.02 (−8.96–16.73)	
Current tobacco smoker				
No, never/former	110 (99–121)	117 (105–125)	3.22 (−1.81–14.08)	0.06
Yes	111 (98–121)	115 (97–125)	−0.63 (−9.21–12.29)	
Took NSAIDs, past 3 mo				
No	114 (100–121)	114 (103–125)	1.61 (−3.16–14.08)	0.38
Yes	110 (98–121)	117 (104–125)	3.38 (−2.16–12.64)	
Daily electrolyte bags, $n=313$[a]				0.79
0–1, $n=10$	115 (106–120)	120 (113–124)	1.36 (−1.91–4.29)	0.85
2–4, $n=68$	113 (94–121)	116 (103–125)	1.15 (−2.53–13.23)	
5–7, $n=201$	110 (99–121)	117 (103–125)	4.15 (−3.17–14.4)	
≥8, $n=34$	115 (105–121)	115 (105–124)	2.00 (−0.70–9.06)	
Away from work practices				
Type of work during the off-season (top 2 responses)				
Subsistence agriculture				
No	112 (99–121)	115 (99–124)	0.81 (−3.16–7.34)	<0.01
Yes	110 (97–120)	118 (107–126)	5.14 (−1.75–16.26)	
Commercial agriculture				
No	110 (98–120)	116 (103–125)	3.30 (−2.35–14.08)	0.14
Yes	117 (104–124)	120 (104–127)	1.39 (−2.95–6.04)	
Applied pesticide or insecticides on own land				
No	113 (99–121)	117 (102–126)	2.62 (−2.46–10.49)	0.20
Yes	109 (97–119)	117 (105–124)	3.30 (−2.39–16.52)	

(Continued on next page)

TABLE 3. (*Continued*)

Characteristics	eGFR: Pre-Employment	eGFR: End of Harvest	%ΔGFR[c]	
	Median (IQR)			%ΔGFR *P*-Value*
Reduced kidney function at pre-employment				
No, ≥90	114 (104–122)	120 (110–126)	2.66 (0.50–12.92)	0.10
Yes, <90	79 (69–85)	79 (64–102)	9.30 (−12.54–29.74)	

eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2; IQR, interquartile range.
[a]Variables were analyzed for as continuous variables and categorical.
[b]Hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg.
[c]A minus sign indicates worsening kidney function across the harvest.
*Characteristics were analyzed with %ΔGFR using Mann–Whitney *U* (Wilcoxon) test or Kruskal–Wallis test. Linear regression was used to evaluate bivariate relationships between %ΔGFR and continuous characteristics.

Severe declines were more likely to occur in workers who had worse kidney function at pre-employment, local workers, and among current smokers. Thus, while dehydration may be an important contributor to reduced kidney function in sugarcane workers as suggested by the literature,[16,32,33] our findings do not show a relationship between kidney function and water intake. Our findings suggest that efforts to maintain kidney function by focusing on hydration alone may not be enough.

It is a common practice in Central America for agribusinesses to base hiring and placement decisions on pre-employment serum creatinine levels. Our results show that workers with reduced kidney function, on average, improved more across the season, however these workers are more likely to have a severe decline in kidney function (OR: 4.23, 95% CI: 1.12:15.99) compared with workers who start the harvest season with normal kidney function. These data suggest that poor kidney function at pre-employment should be considered in decisions about job placement, worker education, and level of vigilance in medical surveillance, including enhanced monitoring needs for this high-risk work group.

Although we reported that 3% of the workforce developed moderately reduced kidney function (Stage 3 chronic kidney insufficiency), this is likely an underestimate of the true incidence. Our analysis of pre-employment eGFR in the 26% of workers who quit before the end of the season demonstrated a probable healthy worker effect among cane cutters. It is likely that some workers who quit early may have experienced undiagnosed kidney injury during the season, leading up to their departure. Future research should be conducted at earlier time points during the season to construct a more accurate incidence rate and to assess reasons why workers quit prematurely.

This evaluation adds to the small body of published evidence on the change in kidney function that occurs in sugarcane workers. A study conducted in Brazil among 25 sugarcane workers found no change in serum creatinine from pre- to post-harvest.[34] Other studies in Nicaragua have found that the average eGFR decreased over the sugarcane harvest depending on job type.[28,29] The sugarcane company in Nicaragua where the Laws et al[28,29] study was conducted applied a hiring cut-off, more than 1.4 mg/dL serum creatinine, similar to the cut-off used by Pantaleon reported here. In another study in Nicaragua, eGFR decreased by a mean of 10 mL/min/1.73 m^2 after 9 weeks in 23 sugarcane workers (decreasing from 109 to 99 mL/min/1.73 m^2).[35] In that study, the employer excluded workers with a serum creatinine of more than or equal to 1.0 mg/dL.

While our assessment focuses on potential explanations for the decline in kidney function seen in one-third of the workforce, there is merit in considering factors that may explain why two-thirds of the workers showed stable or improved eGFR under the same work conditions. The differences seen in these two groups are

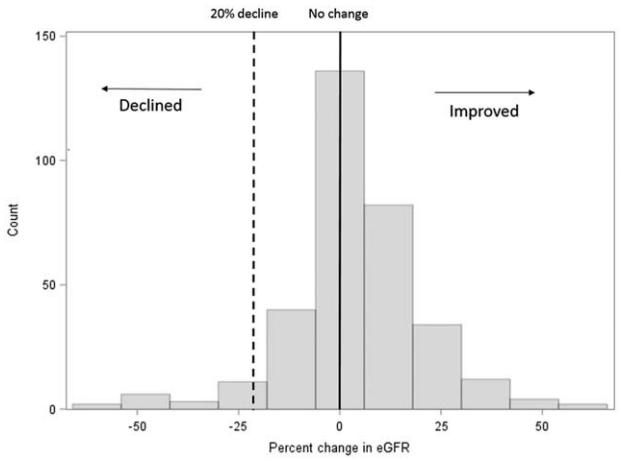

FIGURE 2. Distribution of percent change in estimated glomerular filtration rate (eGFR), across the harvest.

TABLE 4. Multivariable Analysis of Percent Change in eGFR During the Harvest (2015 to 2016)

Variables	% Change in eGFR (*N* = 317)	
	Mean Difference, β (95% CI)	*P*-Value
Age (per yr)	−0.03 (−0.22:0.17)	0.77
Daily water intake (per category increase)[a]	−1.25 (−3.26:0.76)	0.22
Pre-employment eGFR		<0.01
<90	7.31 (2.41:12.22)	<0.01
≥90	Ref	
Mill		
A	−12.03 (−15.98:−8.08)	<0.01
B	Ref	
Residence		
Local	−6.30 (−10.01:−2.60)	<0.01
Highland	Ref	
Tobacco smoker		
Current	−5.80 (−10.70:−0.91)	0.02
Never/Former	Ref	

Values are regression coefficients (β) expressed in percent change in estimated glomerular filtration rate, eGFR.
A negative β value is equivalent to a decrease in eGFR.
[a]Water categories, liters (L): 2–4, 5–7, 8–10, 11–13, ≥14.

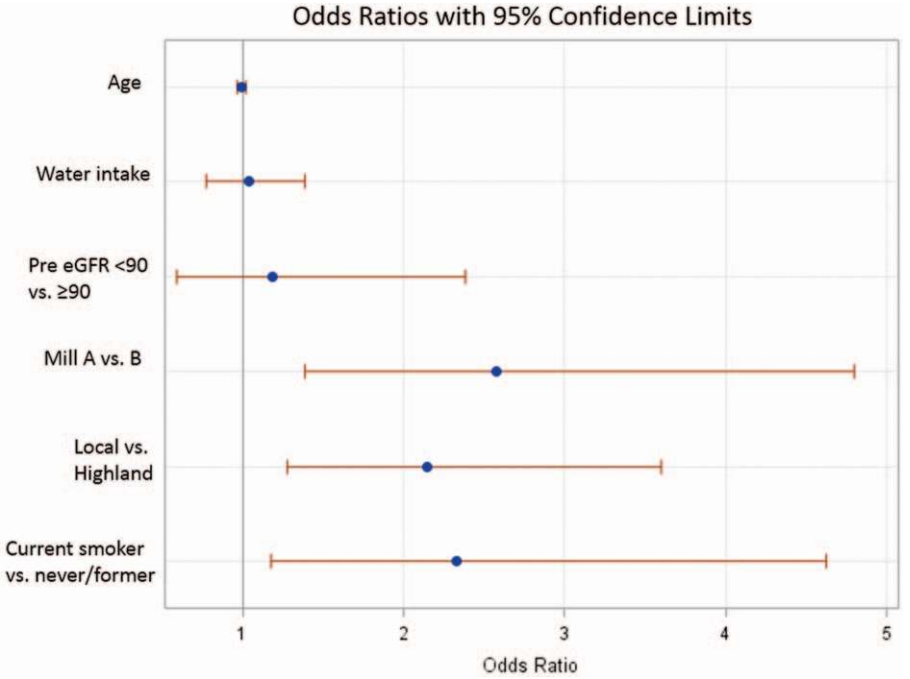

FIGURE 3. Multiple logistic regression model with risk factors of a percent decline in estimated glomerular filtration rate (eGFR) (less than 0%ΔGFR) compared with stable/improving in eGFR (more than or equal to 0%ΔGFR).

unlikely to be explained by differences in baseline health status, given that we observed no differences in age, measured blood pressure, or in self-reported medical history of chronic illnesses known to contribute to kidney injury (ie, diabetes and pre-existing kidney disease). Based on the prevailing theory that CKDu is caused principally by heat stress and dehydration,[19,33] it is possible that workers whose kidney function was stable or improved did better at complying with company guidelines adapted from the US Occupational Safety and Health Administration's Water. Rest. Shade (WRS) program.[15,36] A recent study in El Salvador tested a WRS intervention coupled with efficiency improvements and found reduced impact of heat stress across a harvest season[15] and, in turn, better kidney function during the workday in a study of 40 workers.[32] We observed no significant differences in self-reported consumption of water, electrolyte solution intake, or in the amount of physical exertion (as estimated by average daily tons of cane cut). The majority of the workers in this evaluation reported drinking large amounts of water (more than or equal to 14 L), offering a plausible explanation for why water consumption was not associated with declines in kidney function.

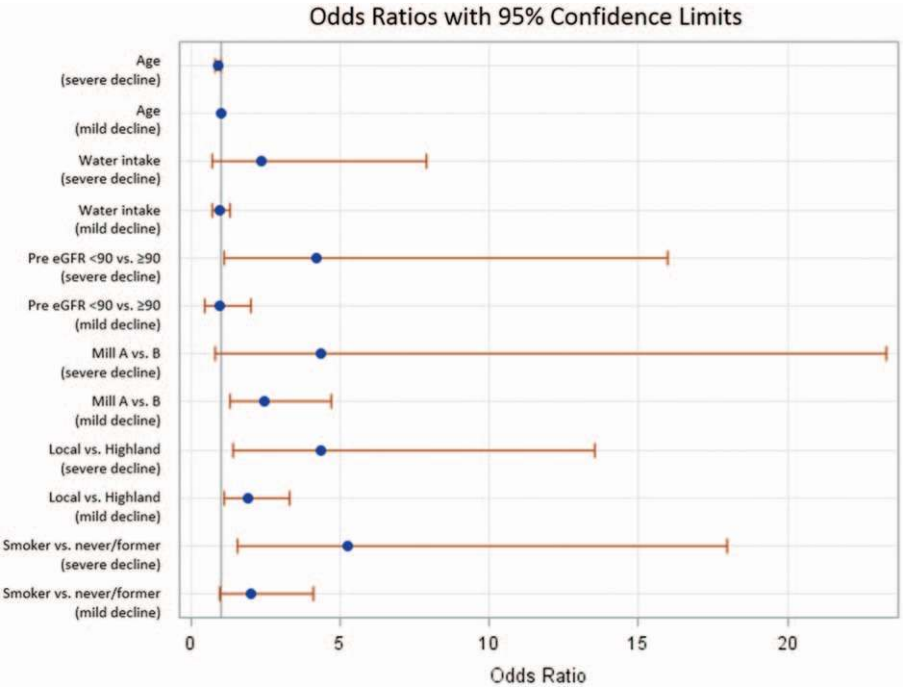

FIGURE 4. Multinomial logistic regression with three groups of %ΔGFR as the outcome variable (severe decline [more than −20%], mild decline [0% to −20%], and stable or increasing as the reference group [more than or equal to 0%]).

The reported amount of water consumed per day by the Guatemala cohort is higher than what has been reported in other comparable studies, and yet we observed approximately the same or greater end-of-season prevalence as has been reported in cohorts that reported drinking half as much water.[28,29,34] It could be that the rates of moderately reduced kidney function would be worse in our population if not for the large amounts of water consumed by the workers. Further research, like the above El Salvador study, is needed to test how well interventions that prevent dehydration reduce CKDu incidence. Our results suggest that there may be other drivers in addition to dehydration and physical exertion that contribute to renal insufficiency in sugarcane workers.

A clue to the difference in kidney function may lie in the observed difference between local and highland workers. We found that highland workers show greater improvement and are at a lower risk of experiencing a decline in eGFR compared with local workers. Possible explanations for the differences observed between local and highland workers include (1) adaptation to conditions during the harvest season, (2) exposures while not at work and during the off-season, (3) diet during the workday, (4) daily commutes to and from the worksite, and (5) daily recovery after the work shift, such as more rest, eating more nutritious food, and increased water intake. Highland workers live in dormitories at the mills during the harvest with all meals and water provided by the employer. Contrary to this finding, the drop out data for the cane cutters showed that highland workers were more likely to not finish the season.

Because of the size of our cohort, we were able to run robust multivariable models that suggest additional risk factors for the decline in kidney function observed. Importantly, our data show that workers who smoke tobacco are at a significantly greater risk for a decline in kidney function over the harvest. In a study in Sri Lanka, smoking was found likely to increase susceptibility to renal disease and be a contributory factor to CKDu.[37] Another study in El Salvador found a univariate association between elevated serum creatinine, history of ever smoking, and nephrolithiasis.[2] The nephrology literature provides both mechanistic and epidemiologic support for the relationship between tobacco use and kidney function.[38] We conclude that future studies should examine smoking frequency and duration with more detail and perhaps even measure cotinine as a biomarker.

Some of the independent risk factors may offer clues to other contributing causes of renal insufficiency in this population, however further research is needed. For example, our results show a clear difference in the vulnerability of workers at Mill A. Future research is needed to consider environmental factors such as exposure to heavy metals or other nephrotoxins at the two mills, as these two mills have different drinking water sources. Local differences in the implementation of WRS guidelines should also be considered.

Several limitations should be acknowledged. In terms of the screened population, self-selection in applying for a job presents a selection bias. We are unable to compare those applying for sugarcane work with those not applying for work, and thus do not know if individuals who applied are representative of the general population in the source communities and if they are systematically different than those that did not apply. One can assume that those that applied are healthy than those that did not apply. Due to a 2-day time limitation for conducting the rescreening at the end of the season, we were only able to collect rescreening data on 87% of the workers that had been randomly selected to participate. Although eligible participants who were not rescreened may have been absent for that work shift due to kidney disease, we consider this unlikely based on their demographic similarities to those who participated. Highland workers and workers who worked more days were more likely to be rescreened but these workers were more likely to have improved kidney function, thus biasing estimates toward the null. It also bears note that because 26% of workers left employment early, we may have underestimated declines in eGFR and bias estimates toward the null. This bias towards healthier participants screened at the end of harvest may have weakened the true relationship between risk factors and %ΔGFR. Because we relied on self-reported survey data, there may have been a misclassification of survey data including water and electrolyte intake, NSAID use, pesticide or insecticide application, and sugary beverage intake. Self-reported water intake may not be an accurate proxy for hydration status. Most prior studies of hydration in such cohorts have also relied on self-reported water intake, with its obvious limitations. Details on quantity and duration of NSAID use, pesticide or insecticide application, sugary beverage intake, and tobacco use and biomarkers of hydration status merits further attention, including future research examining possible interactions with heat stress. Future studies should assess objective measurements such as cotinine and urinary drug concentration. Another potential limitation is that the interpretation of eGFR may be confounded by diet, specifically protein intake. Dietary protein consumption increases serum creatinine level which is used to calculate eGFR, the primary outcome. However, since highland workers are provided meals by the company and may consume more protein, we would have observed lower eGFR values among these workers, which we did not observe. Finally, we did not measure the potential impact of heat exposure in this study. We acknowledge that heat stress could play an important role in the etiology of this disease, therefore, our future research will also examine heat and humidity exposure measured by wet bulb globe temperature (WBGT) as it relates to kidney health outcomes as well as productivity.

CONCLUSION

This evaluation establishes that there is a risk for CKDu among Guatemalan sugarcane workers. We identified risk factors for decline in kidney function over a 6-month harvest including mill, being a local worker, smoking, and having a low pre-employment eGFR level. Results suggest that a decline in kidney function may be related to both occupational and behavioral factors and that future research on these factors is warranted. A comprehensive, Total Worker Health®[39] approach to this epidemic may be needed in order to integrate efforts to promote both a safe work environment and healthy behaviors.

Efforts to better characterize risk factors will require access to cohorts at least as large as the one examined in this project, and should include detailed quantitative measurements of exposures to nephrotoxic agrochemicals and heavy metals, NSAID use, tobacco use, hydration status, and heat exposure. Epidemiological studies are needed to confirm our findings, given the limited research on the role of risk factors in the decline of kidney function.

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