Heat stress, hydration and uric acid: a cross-sectional study in workers of three occupations in a hotspot of Mesoamerican nephropathy in Nicaragua

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ABSTRACT

Objectives: To study Mesoamerican nephropathy (MeN) and its risk factors in three hot occupations.

Design: Cross-sectional.

Setting: Chinandega and León municipalities, a MeN hotspot on the Nicaraguan Pacific coast, January–February 2013.

Participants: 194 male workers aged 17–39 years: 86 sugarcane cutters, 56 construction workers, 52 small-scale farmers.

Outcome measures: (1) Differences between the three occupational groups in prevalences/levels of socioeconomic, occupational, lifestyle and health risk factors for chronic kidney disease (CKD) and in biomarkers of kidney function and hydration; (2) differences in prevalences/levels of CKD risk factors between workers with reduced estimated glomerular filtration rate (eGFRCKD-EPI <80 mL/min/1.73 m2) and workers with normal kidney function (eGFRCKD-EPI ≥80 mL/min/1.73 m2).

Results: Sugarcane cutters were more exposed to heat and consumed more fluid on workdays and had less obesity, lower blood sugar, lower blood pressure and a better lipid profile. Reduced eGFR occurred in 16%, 9% and 2% of sugarcane cutters, construction workers and farmers, respectively (trend cane > construction > farming, p=0.003). Significant trends (cane > construction > farming) were also observed for high serum urea nitrogen (blood urea nitrogen (BUN) >20 mg/dL), high serum creatinine (Scr >1.2 mg/dL), low urinary pH (<5.5) and high BUN/Scr ratio (>20) but not for high urinary specific gravity (>1.030). Sugarcane cutters also more often had proteinuria and blood and leucocytes in the urine. Workers with eGFR <80 mL/min/1.73 m2 reported a higher intake of water and lower intake of sugary beverages. Serum uric acid levels related strongly and inversely to eGFR levels (adj β −10.4 mL/min/1.73 m2, 95% CI −12.2 to −8.5, p<0.001). No associations were observed for other metabolic risk factors, pesticides, non-steroidal anti-inflammatory drugs or alcohol. Among cane cutters, consumption of electrolyte hydration solution appeared preventive (adj β 8.1 mL/min/1.73 m2, p=0.09).

Conclusions: Heat stress, dehydration and kidney dysfunction were most common among sugarcane cutters. Kidney dysfunction also occurred to a lesser extent among construction workers, but hardly at all among small-scale farmers. High serum uric acid was associated with reduced kidney function.

INTRODUCTION

Mesoamerican nephropathy (MeN), an epidemic of chronic kidney disease (CKD), is a chronic tubulointerstitial disease unrelated to traditional CKD risk factors, affecting predominantly young male workers in Pacific coastal communities of Central America and possibly southern Mexico.1–4 Several tens of thousands of people have died of this...
A consistent risk factor for MeN appears to be heavy manual labour in extreme heat. Manual sugarcane cutters exert substantial amounts of energy, often in environmental temperatures over 35°C and high humidity. Besides heat stress, some sugarcane workers are also exposed to pesticides, either at sugarcane plantations or while labouring in other crops. Consumption of non-steroidal anti-inflammatory drugs (NSAIDs) to manage muscle pain is common. Exposure to heavy metals may occur through contaminated pesticide formulations and fertilisers, as has been shown in Sri Lanka, contaminated drinking water, or even during burning of the cane. Overall, exposure of sugarcane workers to different potential CKD risk factors has not been described in detail.

A leading hypothesis is that recurrent dehydration, possibly in combination with exposure to other agents (eg, NSAIDs, heavy metals, agrochemicals, high fructose intake) may be a driving factor. Animal experiments have shown that dehydration and hyperosmolarity may induce tubular injury via activation of the polystreptokinase pathway in the kidney. Recently, a mechanism of hyperuricaemia and cyclical uricosuria associated with volume loss and dehydration has also been proposed.

Studies suggest that MeN may also occur among miners and construction workers, and subsistence farmers. However, these cross-sectional data mostly consider current occupation and are therefore not conclusive. Cane cutting is seasonal and many sugarcane workers are also subsistence farmers or work in construction. Contrary to contracted workers, independent small-scale farmers have control over their work hours and are able to avoid the hottest temperatures. Prevalence studies have been recommended to assess exposure to CKD risk factors and kidney dysfunction in different occupations.

The aim of this study was to compare the prevalence of a range of potential CKD risk factors among sugarcane cutters, construction workers and small-scale farmers labouring in the same hot environment, along with biomarkers of hydration and kidney function. We hypothesise that sugarcane cutters experience more heat stress, more dehydration and more signs of kidney dysfunction than small-scale farmers, with construction workers somewhere in between.

METHODS
Study population and recruitment
This is a cross-sectional study. We recruited 194 male workers aged 17–39 years, all living in the municipalities of Chinandega and León in the Pacific region of Nicaragua, a major epicentre for the MeN epidemic. Of these, 86 were sugarcane cutters, 56 construction workers and 52 small-scale farmers. cane cutters from several sugarcane villages were recruited with the help of community leaders; a trade union assisted in recruiting construction workers employed by private companies at three construction sites; and a rural farmer association helped to recruit associated farmers dedicated full time to the cultivation of subsistence crops. The response rate was 86% among cane cutters and there were no refusals among construction workers and farmers.

The study was approved by the Ethical Review Board of UNAN-León, Nicaragua. All participants provided written informed consent.

Data collection
Data were collected for sugarcane cutters during January 2013, 2 months after the sugarcane harvest started, and during February 2013 for construction workers and farmers under similar climatic conditions. In each of the sugarcane and farming villages a well-known public place was selected as the data collection station; construction workers were evaluated at their work site. Data collection started between 05:30 and 06:00 hours on the morning after a workday and blood and urine samples were collected after overnight fasting.

Medical measurements and biological samples
Blood pressure was measured with a calibrated digital sphygmomanometer with the participant seated after resting for 10 min. Weight was measured with a calibrated digital flat mobile scale and height with a foldable stadiometer. Certified technicians collected blood samples in vacuum tubes for centrifugation and serum separation and in a tube with anticoagulant for blood cell count. Samples without coagulant were centrifuged on the spot at 3500 rpm for 10 min at room temperature. All samples were placed on ice and transported the same day to the laboratory at the Research Center on Health, Work and Environment (CISTA) at UNAN-León where haematocrit and haemoglobin were determined with a Mindray 2300 haematology analyser and the serum samples were frozen at −80°C. After finalising all data collection, serum samples were transported to the National Diagnostic and Reference Center of the Ministry of Health (CNDR-MINSA) of Nicaragua, which takes part in an international interlaboratory quality control programme. Samples were analysed with Cobas Integra 400, an automated equipment which uses a photometric test to determine levels of serum glucose, lipid profile, serum uric acid (S-UA) and blood urea nitrogen (BUN) and a Jaffe compensated method for quantification of serum creatinine (SCr). SCr was calibrated against IDMS-traceable creatinine. Blind spiked and duplicate blood samples from each tenth participant were in 95% within 1 SD. A urinalysis dipstick was performed on a spot morning sample using a Bayer Clinitek 50 Urine Chemistry Analyser with Multistix 10SG reagent strips (Siemens Diagnostics, USA) with
semi-quantitative measurements of protein (≥30–
<100 mg/dL) and ≥300 mg/dL, glucose (positive at
≥100 mm Hg), or a self-reported medical history of hyper-
self-reported social and work history items, diseases
and medications, and heat stress exposure variables were
dichotomised. A category of high tobacco consumption
was created with subjects in the upper quartile of ever
smokers (≥3 pack-years) and a category of high alcohol
consumption composed of subjects in the upper tertiles
of lifetime alcohol consumption (≥80 000 g) or average
weekly consumption (≥125 g). Total fluid intake was
defined as drinking water plus sugary drinks (natural
fruit refreshments, sodas, coffee, tea and electrolyte solu-
tion) and reported as litres of total liquids consumed
the previous (work) day and for comparison also for a
typical non-work day, with subcategories into water only
and sugary drinks. Total fructose intake was estimated
from all food and fluids consumed including chewed
cane and stratified into fructose from food sources and
added sugars. Fructose variables were categorised into
quartiles. The cut-off for body mass index was set at
≥25 kg/m^2. Hypertension was defined as systolic blood
pressure ≥140 mm Hg and/or diastolic blood pressure
≥90 mm Hg, or a self-reported medical history of hyper-
tension. Diabetes was defined as serum glucose
≥125 mg/dL in the fasting serum sample or a self-
reported medical history of diabetes. Use of nephrotoxic
medications was recorded if taken at least three times
per week for more than 3 months in the case of NSAIDs
and other analgesics, or administered for at least a week
in the case of nephrotoxic antibiotics, during the last
year. Blood and urine biochemical parameters were
explored as continuous variables or defined as normal
versus abnormal using standard clinical cut-off values.

Differences between occupations were assessed with
ANOVA and Kruskal-Wallis tests for normally and not
normally distributed continuous variables, respectively,
and Pearson χ^2 test for categorical variables or Fisher’s
exact test when the χ^2 test was not applicable. Post hoc
tests were performed with Tukey’s HSD test for continu-
ous results and post-hoc χ^2 as described by Franke
et al.

With occupation as the main proxy for heat
stress, we assessed trends for sugarcane cutters > con-
struction workers > farmers for prevalences of markers
of kidney dysfunction and dehydration over the ordered
occupational groups with the gamma statistic.

Differences in the distribution of risk factors between
subjects with reduced and normal kidney function were
explored for all occupations combined (n=194) and
restricted to sugarcane cutters (n=86), with Whitney
U-tests for continuous variables and χ^2 tests or Fisher’s
exact test for categorical variables. Exact p values are
reported and p values ≤0.05 were considered statistically
significant. Multivariate linear regression models were
constructed for all workers and restricted to sugarcane
cutters, with factors that were different between subjects
with reduced and normal kidney function at p<0.10.
Residuals from the regressions were checked to assess
the fit of the models.

RESULTS
Potential risk factors for CKD/MeN among the three
occupations
Socioeconomic and health-related CKD risk factors
Socioeconomic CKD risk indicators were unfavourable
for all workers, but somewhat less for construction
workers (table 1A). Farmers had the lowest income
and sugarcane cutters were significantly less educated
with an average of 4 years of elementary schooling. With
regard to lifestyle and medical factors (table 1B), sugarcane cutters had lower prevalences of high tobacco and alcohol consumption. There were no major differences in the use of nephrotoxic drugs between the groups. None of the workers had been previously diagnosed with diabetes and only 5 had hyperglycaemia >125 mg/dL (2 sugarcane cutters, 2 construction workers and 1 farmer). Sugarcane cutters showed less obesity, better lipid profiles, lower heart rates and lower blood pressure but more anaemia (36% with haemoglobin <13 g/dL). There were no differences in total leucocyte count between occupations.

Table 1 Socioeconomic and health indicators relevant for chronic kidney disease/Mesoamerican nephropathy risk among workers in three occupations, municipalities of Chinandega and León, Nicaragua, 2013

|                        | Sugarcane (N=86) | Construction (N=56) | Farming (N=52) | p Value* differences between groups |
|------------------------|------------------|---------------------|----------------|-----------------------------------|
| **(A) Demographics, employment and social indicators** |                  |                     |                |                                   |
| Age (years)            | 25.6±5.5         | 27.3±6.0            | 25.2±5.1       | 0.11                              |
| Education (years)      | 3.9±3.0†         | 7.8±3.6             | 8.0±4.1        | <0.001                            |
| Drinking water from well, % | 84.9†           | 12.5                | 13.5           | <0.001                            |
| Temporary contract, %  | 93.0†            | 75.0†               | 21.1†          | <0.001                            |
| Without work ≥4 months/year, % | 20.9            | 17.9                | 34.6†          | 0.089                             |
| No current social security, % | 15.1            | 8.9                 | 92.3†          | <0.001                            |
| Monthly household income per person in family (25 córdobas=1 US$) | 1808±1156†       | 2267±1124†          | 1343±1059†     | <0.001                            |
| **(B) Lifestyle, medical history and health indicators** |                  |                     |                |                                   |
| High tobacco consumption, % | 10.5†           | 26.8                | 23.1           | 0.031                             |
| High alcohol consumption, % | 18.6            | 28.6                | 32.7           | 0.145                             |
| Non-steroidal anti-inflammatory drugs ≥3 months, % | 5.8            | 7.1                 | 7.7            | 0.901                             |
| Nephrotic antibiotics, % | 1.2             | 1.8                 | 0.0            | 0.648                             |
| History of kidney stones, % | 1.2             | 5.4                 | 1.9            | 0.287                             |
| History of urinary tract infections, % | 23.3‡           | 33.9                | 42.3‡          | 0.058                             |
| Not feeling in good health, % | 10.5§           | 37.5§               | 17.5           | <0.001                            |
| Body mass index ≥25 kg/m², % | 17.4§           | 58.9§               | 40.4           | <0.001                            |
| Blood pressure>140/90, % | 5.8†            | 17.9                | 26.9           | 0.003                             |
| Heart rate (beats/min) | 62±12†           | 73±14               | 72±13          | <0.001                            |
| Blood glucose (mg/dL)  | 89±11            | 90±14               | 90±12          | 0.874                             |
| Triglycerides (mg/dL)  | 120±67†          | 168±108             | 177±124        | <0.001                            |
| Cholesterol (mg/dL)    | 170±36§          | 188±41§             | 178±44         | 0.032                             |
| HDL cholesterol (mg/dL) | 48±12†          | 42±10               | 38±8           | <0.001                            |
| LDL cholesterol (mg/dL) | 93±28           | 101±33              | 91±32          | 0.120                             |
| VLDL cholesterol (mg/dL) | 24±13†         | 34±22               | 35±25          | <0.001                            |
| Haematuric (%)¶        | 46.8±5.9         | 48.5±4.8            | 50.8±4.0†      | <0.001                            |
| Haemoglobin (g/dL)¶    | 13.4±1.6†        | 14.8±1.5            | 15.4±1.3       | <0.001                            |
| Haemoglobin <13 g/dL, %¶ | 35.8†         | 8.9                 | 3.8            | <0.001                            |
| White cell counts/µL¶,** | 7184±2048       | 7307±1656           | 7580±1882      | 0.503                             |
| % neutrophils¶,**      | 38.6±10.6        | 38.6±8.8            | 36.5±9.0       | 0.421                             |
| % lymphocytes¶,**      | 21.2±6.6†        | 18.5±4.9†           | 14.5±4.7†      | <0.001                            |
| % other cells¶,**      | 40.2±10.0        | 43.0±8.2            | 49.1±10.6†     | <0.001                            |
| Erythrocytes×10¹²/µL¶ | 4.87±0.59†       | 5.27±0.47†          | 5.53±0.50†     | <0.001                            |
| Platelets×10¹³/µL¶    | 299.4±76.7       | 315.6±67.7          | 292.8±62.8     | 0.218                             |

Values are mean±SD unless indicated otherwise.
* p Value for differences between groups: ANOVA for normally distributed continuous variables, Kruskal-Wallis for not normally distributed continuous variables, χ² test for categorical variables.
† Significantly different from the other two categories in post hoc tests.
‡ Significant difference only between sugarcane cutters and farmers.
§ Significant difference only between sugarcane cutters and construction workers.
¶ Missing data for sugarcane workers due to technical error.
** Exclusion of one farmer with outlier for white blood cell count (WBC count=17500/µL).
HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

Occupational heat exposure, fluid and fructose intake and pesticides
On average, construction workers had an effective work time of 8 hours and farmers had the shortest with 5 hours, whereas sugarcane workers actively cut cane for 6.5 hours per day (table 2A). A higher proportion of sugarcane workers perceived a very rapid work pace and had to take rest breaks in the absence of shade; 83% received incentives for cutting more cane and almost half started harvesting within 12 hours of burning the cane. Sugarcane cutters more often reported weight loss related to the current job (over the last 2 months) and Wesseling C, et al. BMJ Open 2016;6:e011034. doi:10.1136/bmjopen-2016-011034
fainting on the job (6% compared with 2% of farmers and no construction workers). Dysuria (‘chistata’), a common symptom in MeN affected areas thought to be related to dehydration,15 24 was not different between the three groups.

With regard to fluid intake (table 2B), sugarcane cutters reported on average 6.2 L of total fluid intake the previous (work) day, 70% (4.4 L) as water and almost 30% (1.8 L) as sugary drinks. This was higher than for construction workers and farmers. Intake of

| Table 2 | Occupational heat stress, fluid and fructose intake and pesticide exposure indicators among workers in three occupations, municipalities of Chinandega and León, Nicaragua, 2013 |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (A) Current occupational heat stress                                                                                                                                   |
| Effective work hours per day (work hours minus breaks)                                                                                                                  |
| Sugarcane (N=86)                                                                                                                                                    |
| 6.5±1.2†                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 8.1±0.7†                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 5.3±2.0†                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| <0.001                                                                                                                                                    |
| Very rapid work pace, %                                                                                                                                           |
| Sugarcane (N=86)                                                                                                                                                    |
| 74.4†                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 53.6                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 40.4                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| <0.001                                                                                                                                                    |
| No shade during breaks, %                                                                                                                                          |
| Sugarcane (N=86)                                                                                                                                                    |
| 20.9†                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 1.8‡                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 11.5                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| 0.004                                                                                                                                                    |
| Lifting weights >50 lbs, %                                                                                                                                            |
| Sugarcane (N=86)                                                                                                                                                    |
| 18.6†                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 66.1                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 65.4                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| <0.001                                                                                                                                                    |
| Awkward work postures, %                                                                                                                                             |
| Sugarcane (N=86)                                                                                                                                                    |
| 58.1                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 76.8                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 69.2                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| 0.063                                                                                                                                                    |
| Incentives to cut more cane, %                                                                                                                                           |
| Sugarcane (N=86)                                                                                                                                                    |
| 82.6                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| –                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| –                                                                                                                                                    |
| Hours post-burning at field entrance                                                                                                                                     |
| Sugarcane (N=86)                                                                                                                                                    |
| 11.7±6.2                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| –                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| –                                                                                                                                                    |
| Self-reported weight loss on the current job (last 2 months), %                                                                                                           |
| Sugarcane (N=86)                                                                                                                                                    |
| 77.9†                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 39.3                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 36.5                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| <0.001                                                                                                                                                    |
| Fainted at work, %                                                                                                                                                    |
| Sugarcane (N=86)                                                                                                                                                    |
| 5.8                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 0                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 1.9                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| 0.126                                                                                                                                                    |
| Dysuria (‘chistata’), %                                                                                                                                                    |
| Sugarcane (N=86)                                                                                                                                                    |
| 43.0                                                                                                                                                    |
| Construction (N=56)                                                                                                                                             |
| 48.2                                                                                                                                                    |
| Farming (N=52)                                                                                                                                                    |
| 44.2                                                                                                                                                    |
| p Value*                                                                                                                                                    |
| 0.827                                                                                                                                                    |

(B) Fluid and fructose intake

Fluid intake previous day (workday)

| Total fluid (L) | Sugarcane (N=86) | Construction (N=56) | Farming (N=52) | p Value* |
|----------------|------------------|---------------------|----------------|---------|
| 6.2±4.1†       | 4.4±2.1          | 4.0±2.7             | 0.003          |
| Water          | 4.4±3.9†         | 2.9±2.1             | 2.8±2.4        | 0.002   |
| Sugary drinks  | 1.8±1.8          | 1.5±0.9             | 1.2±0.8        | 0.208   |
| Electrolyte    | 1.2±1.1          | –                   | –              |         |
| solution (N=31)|                  |                     |                |         |
| Lowest quartile total fluid (≤2.5 L), % | 18.6 | 19.6 | 40.4† | 0.009 |
| Highest quartile total fluid (≥7.0 L), % | 40.7† | 8.9 | 13.5 | <0.001 |

(C) Fluid intake on typical non-work day

| Total fluid (L) | Sugarcane (N=86) | Construction (N=56) | Farming (N=52) | p Value* |
|----------------|------------------|---------------------|----------------|---------|
| 4.2±2.3        | 3.8±1.7          | 4.1±2.2             | 0.503          |
| Water          | 3.0±2.0          | 2.2±1.3             | 2.7±2.0        | 0.053   |
| Sugary drinks  | 1.2±1.1          | 1.6±1.1             | 1.4±1.9        | 0.117   |

(D) Fructose intake previous day (workday)

| Total fructose intake (g) | Sugarcane (N=86) | Construction (N=56) | Farming (N=52) | p Value* |
|---------------------------|------------------|---------------------|----------------|---------|
| 103.1±72.1†              | 80.1±46.1        | 70.9±36.8           | 0.008          |
| From food sources       | 8.4±10.7†        | 15.9±16.6           | 17.4±16.7      | <0.001  |
| From added sugar        | 94.7±70.5†       | 64.2±38.1           | 53.2±30.7      | <0.001  |
| During work hours       | 58.6±44.7†       | 28.6±21.4           | 26.1±16.5      | <0.001  |
| Sugary drinks (‘frescos’, sodas, coffee) | 22.5±15.7 | 28.6±21.4 | 26.1±16.3 | 0.108   |
| Sugarcane chewing (N=53) | 35.0±18.5        | –                   | –              |         |
| Electrolyte solution (N=31) | 40.3±35.2 | –                   | –              |         |
| Outside (before and after) work hours | 36.1±39.3 | 35.6±31.4 | 27.1±25.9 | 0.350   |
| Highest quartile total fructose intake (>107 g), % | 40.7† | 19.6 | 15.7 | 0.002   |

(E) Work and pesticide use history

| Cumulative time on current job (months) | Sugarcane (N=86) | Construction (N=56) | Farming (N=52) | p Value* |
|----------------------------------------|------------------|---------------------|----------------|---------|
| 77±60                                   | 68±80            | 116±67†             | 0.001          |
| Ever sugarcane work, %                  | 100.0†           | 3.6                 | 3.8            | <0.001  |
| Ever plantation (other than sugarcane), % | 24.4        | 5.4†                | 21.2           | 0.012   |
| Ever work in small-scale agricultural (%) | 61.6†            | 25.0†               | 100.0†         | <0.001  |
| Ever construction work, %              | 5.8              | 100.0†              | 11.5           | <0.001  |
| Ever any pesticide use, %              | 46.5†            | 10.7†               | 71.2†          | <0.001  |
| Glyphosate, %                          | 19.8†            | 0.0                 | 3.8            | <0.001  |
| 2,4-D, %                               | 23.3†            | 0.0†                | 9.6†           | <0.001  |
| Paraquat, %                            | 9.3              | 3.6                 | 25.0†          | 0.002   |
| Chlorpyrifos, %                        | 0.0              | 0.0                 | 23.1†          | <0.001  |
| Cypermethrin, %                        | 18.6†            | 3.6†                | 42.6†          | <0.001  |

Values are mean±SD unless indicated otherwise.

*p Value for differences between groups: ANOVA for normally distributed continuous variables, Kruskal-Wallis for not normally distributed continuous variables, χ² test for categorical variables.

†Significantly different from the other two categories in post hoc tests.

‡Significant difference only between sugarcane cutters and construction workers.

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Water and sugary beverages were not correlated ($r_p=0.01$). In contrast, there was no difference between the three groups for total fluid intake on non-work days.

Fructose intake during the previous day was highest for sugarcane cutters and 41% of sugarcane cutters belonged to the category of highest quartile of consumption of total fructose (>107 g) (table 2B). Fructose intake from food was low among sugarcane cutters and most came from added sugars during work hours, specifically from sweetened beverages, electrolyte hydration solution (one-third of cutters) and cane chewing (about two-thirds). Fructose intake outside work hours was not different between the groups.

With regard to pesticide exposures (table 2C), farmers used pesticides most frequently (71%) compared with almost half of sugarcane cutters and only 11% of construction workers. Glyphosate and 2,4-D use was more prevalent in sugarcane cutters (17%) and construction workers (16%) than among farmers (6%).

Regarding markers of dehydration, the prevalence of concentrated urine (USG ≥1.030) was not statistically different between groups (table 3B). Low urinary pH occurred in 29% of sugarcane cutters versus 12% of construction workers and farmers (p=0.01) and sugarcane cutters (17%) and construction workers (16%) than among farmers (6%).

### Table 3 Biomarkers of kidney function and dehydration among workers in three occupations and trend over categories ordered by exposure to occupational heat stress (sugarcane > construction > farming), municipalities of Chinandega and León, Nicaragua, 2013

| Variable | Sugarcane (N=86) | Construction (N=56) | Farming (N=52) | p Value: differences between groups* | p Value: trend† |
|----------|------------------|---------------------|----------------|-------------------------------------|-----------------|
| (A) Indicators of kidney function | | | | | |
| BUN (mg/dL), mean±SD (range) | 13.9±5.0† | 10.1±5.1 | 9.2±3.6 | <0.001 |
| BUN >20 mg/dL (%) | 15.1‡ | 5.4 | 1.9 | 0.017 | 0.003 |
| Serum creatinine (SCR) (mg/dL), mean±SD (range) | 0.84±0.39 | 1.00±1.16 | 0.78±0.22 | 0.393 |
| SCr >1.2 mg/dL, % | 17.4‖ | 8.9 | 5.8‖ | 0.088 | 0.024 |
| eGFR<sub>CKD-EPI</sub>, mean±SD (range) | 121±31 (34–160) | 118±30 (7–161) | 125±18 (49–158) | 0.299 |
| eGFR<sub>CKD-EPI</sub> <80 mL/min/1.73 m<sup>2</sup>, % | 16.3‖ | 8.9 | 1.9‖ | 0.025 | 0.003 |
| S-UA (mg/dL), mean±SD (range) | 6.0±1.7 (3.0–12.7) | 5.8±1.6 (3.6–11.0) | 5.0±1.1‖<sup>‡</sup> | 0.001 |
| S-UA >7.2 mg/dL, % | 17.4 | 16.1 | 5.8 | 0.136 | 0.055 |
| Proteinuria >30 mg/dL, % | 14.7 | 5.4 | 6.1 | 0.128 | 0.081 |
| Leucocytes in urine, % | 22.1‡ | 0 | 1.9 | <0.001 | <0.001 |
| Nitrites in urine, % | 0 | 0 | 0 | – | – |
| Blood in urine, % | 5.8 | 1.8 | 1.9 | 0.339 | 0.186 |
| (B) Indicators of dehydration | | | | | |
| Urinary specific gravity ≥1.030, % | 15.3 | 28.6 | 20.4 | 0.161 | 0.255 |
| Urinary pH ≤5.5, % | 29.4‡ | 12.5 | 12.2 | 0.014 | 0.006 |
| BUN/SCr ratio >20, % | 25.6‡ | 0 | 3.8 | <0.001 | <0.001 |

* p Value for differences between groups: ANOVA for normally distributed continuous variables, Kruskal-Wallis for not normally distributed continuous variables, χ<sup>2</sup> test for categorical variables.
† Gamma statistic for trend over ordered categories.
‡ Significantly different from the other two categories in post hoc tests.
‖ Significant difference only between sugarcane cutters and construction workers.

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; S-UA, serum uric acid.
cutters more commonly had an elevated BUN/SCr ratio (26% vs 0 and 4% of construction workers and farmers, p<0.001). Trends over ordered categories were significant for urinary pH and BUN/SCr ratio. Although sugarcane cutters as a group had a lower prevalence of concentrated urine, within the group low fluid intake was strongly associated with concentrated urine (OR 3.5, p=0.06) and acidic urine (OR 8.7, p<0.001), which was not the case among construction workers and farmers (table 4).

**Risk factors for reduced kidney function**

In bivariate analyses of differences in kidney, urinary and metabolic biomarkers, work practices, hydration practices and lifestyle characteristics between subjects with reduced kidney function (eGFR <80 mL/min/1.73 m²) and subjects with normal kidney function (eGFR ≥80 mL/min/1.73 m²) (see online supplementary table S1), reduced kidney function was significantly associated with work as a sugarcane cutter, high intake of water, low intake of sugary beverages, increasing age, low haemoglobin and high tobacco consumption. In analyses restricted to sugarcane cutters the results were similar and, in addition, workers with reduced kidney function had cut cane for a considerably longer time than those with normal kidney function (cumulative time on the job: median 108 vs 60 months, p=0.06). Sugarcane cutters with reduced kidney function reported almost three times higher water intake and three times lower intake of sugary beverages than cutters with normal kidney function, with only one of the 14 reporting intake of the electrolyte solution. In addition, the cane cutters with reduced kidney function had a worse lipid profile than those with normal kidney function and more often had hypertension, but none had diabetes or hyperglycaemia and only one was overweight (see online supplementary table S1).

In backwards stepping multivariate linear regression analyses with inclusion of variables with p<0.10 in the bivariate analyses (except haemoglobin due to missing data), age (β −1.3, 95% CI −1.8 to −0.8; p<0.001) and S-UA (β −10.4, 95% CI −12.2 to −8.5; p<0.001) were significantly associated with reduced kidney function among all workers, which was identical in models with total fluid intake and with intake of water and sugary beverages separately (table 5A). In the subset of sugarcane cutters, too many variables had a p value ≤0.10 in bivariate analyses (see online supplementary table S1) and therefore the regression was done in two steps. Hypertension, lipid profile tests and blood sugar were not associated with reduced kidney function in a model also including age and S-UA (data not shown) and were not further considered. In a model with water intake, intake of sugary drinks (without electrolyte solution) and intake yes/no of electrolyte solution, age, S-UA, high tobacco consumption and high alcohol consumption (table 5B), reduced kidney function was associated significantly with age and S-UA and non-significantly with the intake of electrolyte solution (β 8.1, 95% CI −1.2 to 17.5, p=0.09). Age and cumulative months on the job correlated (r_p 0.68, p<0.001), and substituting age with time cutting cane yielded similar results.

**DISCUSSION**

This study found evidence for more frequent heat stress, dehydration and kidney dysfunction among sugarcane

| Table 4 | Associations between low intake of fluids and markers of dehydration among sugarcane cutters (n=86) and non-cutters (construction workers and small-scale farmers) (n=108) |
|---|---|---|
| **Lowest quartiles of fluid intake** | USG ≥1.030* OR (95% CI) p Value† | pH ≤5.5* | BUN/SCr ratio >20* |
| **Total fluids ≤2.5 L** |  |  |  |
| Sugarcane cutters (n=16) | 3.5 (1.0 to 13) p=0.06 | 8.7 (2.6 to 29) p<0.001 | 1.2 (0.3 to 4.3) p=0.67 |
| Construction workers and farmers (n=32) | 1.4 (0.5 to 3.5) p=0.51 | 2.3 (0.7 to 7.5) p=0.17 | – |
| **Water ≤1.5 L** |  |  |  |
| Sugarcane cutters (n=16) | 3.0 (0.7 to 12) p=0.14 | 2.9 (0.9 to 9.6) p=0.08 | 2.3 (0.7 to 7.3) p=0.17 |
| Construction workers and farmers (n=32) | 1.9 (0.7 to 4.9) p=0.18 | 1.7 (0.5 to 5.6) p=0.42 | – |
| **Sugary drinks ≤0.75 L** |  |  |  |
| Sugarcane cutters (n=28) | 2.5 (0.7 to 9.2) p=0.16 | 2.5 (0.9 to 7.1) p=0.08 | 0.3 (0.2 to 1.1) p=0.06 |
| Construction workers and farmers (n=21) | 1.8 (0.6 to 5.2) p=0.28 | 0.7 (0.2; 3.6) p=0.69 | – |

*Markers of dehydration: high USG (≥1.030), acidic urine (urinary pH ≤5.5), high BUN/SCr ratio (>20).
†The ORs and 95% CIs for water and sugary drinks are adjusted for each other.
‡Not computed because only two non-cutters had BUN/SCr ratio >20.
BUN, blood urea nitrogen; SCr, serum creatinine; USG, urinary specific gravity.
cutters, as expected, and to a lesser degree also reduced kidney function among construction workers but not among small-scale farmers. Also, as expected, SUA levels increased with decreasing eGFR.

**Evidence of reduced kidney function**

We used a cut-off of eGFR of 80 mL/min/1.73 m² to evaluate differences in renal function because only 11 workers had eGFR <60 due to their young age (all under age 40) and also because sugarcane workers were screened by employers before the start of the harvest 2 months earlier and workers with SCr >1.2 mg/dL were not hired and, thus, were not part of our study population. Despite this, approximately one-quarter of sugarcane cutters had evidence for either eGFR <80 mL/min/1.73 m² or proteinuria ≥30 mg, and these findings were, respectively, eight-, three- and twofold more common than those observed in subsistence farmers and about twofold more common than in construction workers (table 3). However, although to a lesser degree than cane cutters, construction workers also had an unusually high prevalence of decreased kidney function, which is in accordance with a previous unpublished study in the same area. In contrast, the single small-scale farmer with reduced kidney function had worked previously in sugarcane. Thus, our results show that not all agricultural workers are at increased risk for CKD, as is commonly stated, but rather workers in certain types of agriculture and other jobs in the heat such as work in the construction industry. The absence of reduced kidney function among subsistence farmers is consistent with a study in a MeN epidemic area in El Salvador, where subsistence farmers without a history of plantation work had a significantly lower prevalence of abnormal SCr than men who had worked on sugar or cotton plantations (15% vs 33%). Reduced kidney function was accompanied by a higher frequency of anaemia among sugarcane cutters (36% vs 4% in the other groups). The prevalence of anaemia was higher than the prevalence of reduced kidney function and cannot be simply ascribed to the higher frequency of reduced renal function. Marked anaemia, defined as Hb <10 g/dL, was not observed in any of the groups. Reduced kidney function was not associated with traditional risk factors for CKD. Notably, there were no cases of confirmed diabetes in the entire population. Importantly, sugarcane workers showed significantly worse renal function despite an overall lower frequency of abnormal lipid profile, hypertension and obesity compared with the other two groups (see table 1). Increasing age (>50 years) is a known risk factor for CKD, but in our study increasing age was associated with a decline in renal function despite the young age of the study participants. This is possibly related to an increased risk with continued job exposure over time, in particular among the sugarcane cutters. Thus, our study

| Table 5 | Multivariate linear regression models of estimated glomerular filtration rate (eGFRCKD-EPI) among all workers (sugarcane cutters, construction workers and farmers) and restricted to sugarcane cutters |
|---------|---------------------------------------------------------------------------------|
|          | β coefficient (95% CI) | Standardised β coefficient | p Value | Adjusted R² |
| **(A) All subjects (N=194)** | | | | |
| Step 1 | | | | |
| Water intake (L) | −0.7 (−1.7 to 0.3) | −0.08 | 0.15 | 0.47 |
| Sugary beverages intake (L) | 1.2 (−0.8 to 3.3) | 0.06 | 0.24 |
| Sugarcane cutter ever | 3.6 (−2.5 to 9.6) | 0.07 | 0.25 |
| Age (years) | −1.2 (−1.7 to −0.6) | −0.24 | <0.001 |
| Serum uric acid (mg/dL) | −10.0 (−12.0 to −8.1) | −0.57 | <0.001 |
| High tobacco consumption | −4.5 (−11.6 to 2.7) | −0.07 | 0.22 |
| High alcohol consumption | 1.2 (−5.6 to 8.1) | 0.02 | 0.72 |
| **Final step** | | | | |
| Age (years) | −1.3 (−1.8 to −0.8) | −0.27 | <0.001 | 0.47 |
| Serum uric acid (mg/dL) | −10.4 (−12.2 to −8.5) | −0.59 | <0.001 |
| **(B) Sugarcane cutters (N=86)** | | | | |
| Step 1 | | | | |
| Water intake (L) | −0.7 (−1.9 to 0.5) | −0.09 | 0.25 | 0.58 |
| Sugary beverages intake (without electrolyte solution) (L) | 1.2 (−3.7 to 6.0) | 0.04 | 0.63 |
| Electrolyte solution (yes/no) | 6.4 (−4.5 to 17.3) | 0.10 | 0.24 |
| Age (years) | −1.7 (−2.5 to −0.8) | −0.29 | <0.001 |
| Serum uric acid | −10.9 (−13.8: −8.1) | −0.59 | <0.001 |
| High tobacco consumption | −10.1 (−22.5 to 2.3) | −0.12 | 0.11 |
| High alcohol consumption | −7.8 (−19.5 to 3.9) | −0.10 | 0.19 |
| **Final step** | | | | |
| Age (years) | −1.9 (−2.7 to −1.1) | −0.34 | <0.001 | 0.57 |
| Serum uric acid (mg/dL) | −11.3 (−14.0 to −8.6) | −0.61 | <0.001 |
| Electrolyte solution (yes/no) | 8.1 (−1.2 to 17.5) | 0.13 | 0.09 |
suggests that most cases of reduced kidney function are related to MeN and not classic CKD.

Evidence for heat stress
There was evidence for a greater risk of heat stress among sugarcane cutters. Sugarcane cutters labouring at a faster pace, had less exposure to shade, reported more weight loss during the ongoing harvest and had more fainting episodes. While sugarcane cutters had greater heat stress exposure, they also drank more fluids during the course of the day, amounting to an average of 6.2 L per day (although this varied considerably, with approximately 20% drinking <2.5 L/day and 40% >7 L/day). However, the type of exertion and sweating that occurs with cane harvesting could still result in a dramatic loss of fluids such that dehydration can occur despite high fluid consumption. Cade et al found that college football players could lose as much as 8 quarts (about 7.6 L) of water in a 2-hour period, associated with loss of salt, decrease in blood glucose and a fall in blood pressure.

Potential mechanisms involved in inducing kidney damage
Daily heat stress and dehydration may cause repeated renal hypoperfusion episodes, and intermittent subclinical rhabdomyolysis associated with excessive exertion may also induce repeated acute kidney injury through the release of inflammatory mediators including cytokines and uric acid which, over time, leads to glomerular and tubulointerstitial disease in animals.32

Confirmation of this hypothesis, S-UA might rise as a consequence of subclinical rhabdomyolysis, followed by its crystallisation in the urine. One factor that increases the risk of urate crystal formation is acidic urine, which could result from the release of lactic acid associated with strenuous exercise and the effects of dehydration to reclaim sodium with hydrogen ion excretion. Urine pH was significantly lower in the sugarcane workers compared with the other groups (see table 3) and was strongly associated with low fluid intake on the previous (work) day in the subset of sugarcane workers (see table 4). This might reflect the effects of greater volume depletion (with aldosterone stimulation), lactic acid generation during the previous day, or other mechanisms.

Hydration and fructose
We had expected that low water intake or high sugary fluid intake would be associated with reduced renal function, based on studies in animals. However, workers with eGFR <80 mL/min/1.73 m² drank more water and consumed fewer sugar-based drinks during the workday than subjects with normal kidney function (4.5 vs 2.2 L water, p=0.08; 0.6 vs 1.25 L sugary beverages, p=0.001) (see online supplementary table S1). This was particularly so among the sugarcane cutters with reduced kidney function who drank about 4 L more water and 1 L less sugary beverages. Excessive thirst from decreased concentration capacity of impaired kidneys may partially explain these counterintuitive findings, as well as the very high water requirements during the great heat stress exposure, they also drank more fluids during the course of the day, amounting to an average of 6.2 L per day (although this varied considerably, with approximately 20% drinking <2.5 L/day and 40% >7 L/day). However, the type of exertion and sweating that occurs with cane harvesting could still result in a dramatic loss of fluids such that dehydration can occur despite high fluid consumption. Cade et al found that college football players could lose as much as 8 quarts (about 7.6 L) of water in a 2-hour period, associated with loss of salt, decrease in blood glucose and a fall in blood pressure.

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Other risk factors for kidney disease

There was no association with NSAIDs or alcohol intake. A history of high tobacco consumption was more frequent among subjects with reduced kidney function (p=0.02) but lost significance in multivariate analyses. A history of pesticide exposure was more common among farmers, although exposure to herbicides was more common among sugarcane cutters, especially glyphosate and 2,4-D, both of special interest. However, analyses failed to identify pesticide exposures as an independent risk factor for reduced kidney function (see online supplementary table S1).

Study limitations

The main limitation of our study is its cross-sectional design. The kidney function parameters are based on single determinations in blood and urine without a chronicity criterion (presence during at least 3 months) for a proper clinical diagnosis of CKD.39 Recently, attention has been drawn to the fact that single biomarker determinations and consequent categorisations into CKD stages based on a cut-off value, without consideration of age- and sex-specific criteria for GFR, are inadequate as the basis for population-based CKD prevalences because these practices can lead to over-diagnosis among the elderly and under-diagnosis in younger age groups, with large unexplained differences between nations.40 41 However, the main purpose of our study is not a clinical diagnosis but to distinguish differences in kidney function parameters between three occupational groups of the same sex and same young age distribution, and comparisons therefore remain valid on the group level. In addition, in the same region, at the time of this study, we also followed a small group of heat-exposed sugarcane cutters and a group of control workers unexposed to heat over the harvest season. The cutters showed an important decline in kidney function,42 which provides support for the cross-sectional findings, although no cohort data exist for construction workers or farmers.

Another limitation is that our heat exposure and hydration data were self-reported, but these data were collected through carefully designed questionnaires. Workers were asked to fast and did not consume any food before providing blood and spot urine samples between 05:30 and 06:00 hours (see Methods), but they did ingest water or other fluids during the evening, night and early morning. Nonetheless, we observed a lower U-pH and more frequent high BUN/SCr ratio among cane cutters and, to a lesser extent, among construction workers compared with subsistence farmers, which is an indication of incomplete recovery of adequate hydration status after the previous work day among the more heat stress-exposed workers.

Our sample size was based on a pre-study power calculation of 80% to detect CKD among 100 sugarcane cutters and100 non-cutters at α 0.05. Post hoc, we achieved a power of 0.68 for an increased risk of reduced eGFR among cutters versus non-cutters, but the post hoc power of the comparison between cutters and farmers was 80%. Therefore, our results seem sufficiently reliable, also considering the significant trends for indicators of heat stress, dehydration and kidney dysfunction in support of our main hypothesis of cane cutting>construction>farming. Finally, we did not have resources for examining biomarkers of early damage such as neutrophil gelatinase associated lipocalin (NGAL) and N-acetyl-β-D-glucosaminidase (NAG), which are important to include in future studies.

CONCLUSIONS

Compared with construction workers and, in particular, subsistence farmers from the same MeN epidemic region of Nicaragua, sugarcane cutters have higher heat stress, more dehydration and worse renal function despite the fact that other health indicators of the cutters were significantly better. Our study supports the need for improved work practices and even more hydration with adequate access to water for sugarcane cutters, as well as for workers in other hot occupations such as construction. The associations between intake of water and sugary drinks and kidney function as well as the role of hyperuricaemia need to be assessed in carefully designed follow-up studies.

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REFERENCES

1. Wesseling C, Crowe J, Hogstedt C, et al. Resolving the enigma of the Mesoamerican nephropathy—MeN—a research workshop summary. Am J Kidney Dis 2014;63:396–404.

2. Wijkström J, Leiva R, Elinder CG, et al. Clinical and pathological characterization of MeN—a longitudinal study of workers at risk of Mesoamerican nephropathy. Am J Kidney Dis 2014;63:506–20.

3. Torres C, Aragón A, González M, et al. Decreased kidney function of unknown cause in Nicaragua: a community-based survey. Nefrolempa study, 2009. MEDICC Rev 2011;55:485–96.

4. Wesseling C, Crowe J, Hogstedt C, Johnson RK. CKD of unknown origin in Central America: the case for a Mesoamerican nephropathy. Am J Kidney Dis 2014;63:506–20.

5. Laws RL, Brooks DR, Amador JJ, et al. Changes in kidney function and associated risk factors in two Salvadoran farming communities, 2012. MEDICC Rev 2014;16:55–60.

6. Orantes CM, Herrera R, Almaguer M, et al. Chronic kidney disease of unknown etiology in Mesoamerica: a call for interdisciplinary research and action. Am J Public Health 2013;103:1927–30.

7. Nakagawa T, Mazzali M, Kang DH, et al. Hyperuricemia causes glomerular hypertrophy in the rat. Am J Physiol Renal Physiol 2003;284:F100–8.

8. Vanholder R, Sever MS, Erek E, et al. Rhabdomyolysis. J Am Soc Nephrol 2000;11:1553–60.

9. Knochel JP, Dotin LN, Hamburger RJ. Heat stress, exercise, and muscle injury: effects on urate metabolism and renal function. Ann Intern Med 1974;81:321–8.

10. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant 2013;28:2221–8.

11. Nakagawa T, Mazzali M, Kang DH, et al. Hyperuricemia causes glomerular hypertrophy in the rat. Am J Physiol Renal Physiol 2003;284:F100–8.

12. Crowe J, Wesseling C, Román-Solano B, et al. Heat exposure in sugarcane harvesters in Costa Rica. Am J Ind Med 2011;54:117–24.

13. Lucas RA, Bodin T, García-Trabanino R, et al. Heat stress and workload associated with sugarcane cutting—an excessively strenuous occupation! Extrem Physiol Med 2015;4(Suppl 1):A23.

14. Raines N, González M, Wyatt C, et al. Risk factors for reduced glomerular filtration rate in a Nicaraguan community affected by Mesoamerican nephropathy. MEDICC Rev 2014;16:16–22.

15. Ramírez-Rubio O, Brooks DR, Amador JJ, et al. Chronic kidney disease in Nicaragua: a qualitative analysis of semi-structured interviews with physicians and pharmacists. BMC Public Health 2013;13:350.

16. Reyes-Díaz J, Fonseka S, Fernando A, et al. Phosphate fertilizer is a main source of arsenic in areas affected with chronic kidney disease of unknown etiology in Sri Lanka. Springerplus 2014;4:90.

17. Laws RL, Brooks DR, Amador JJ, et al. Changes in kidney function among Nicaraguan sugarcane workers. Int J Occup Environ Health 2015;21:241–50.

18. Paula Santos U, Zanetta DM, Terra-Filho M, et al. Burnt sugarcane harvesting is associated with acute renal dysfunction. Kidney Int 2015;87:782–9.

19. Roncal-Jimenez CA, Ishimoto T, Lanasa MA, et al. Fructokinase activity mediates dehydration-induced renal injury. Kidney Int 2014;86:294–302.

20. Roncal-Jimenez CA, Lanasa MA, Jensen T, et al. Mechanisms by which dehydration may lead to chronic kidney disease. Ann Nutr Metab 2015;66(Suppl 3):P10–13.

21. Roncal-Jimenez CA, Garcia-Trabanino R, Barregard L, et al. Heat stress nephropathy from exercise-induced uric acid crystalluria: a perspective on Mesoamerican nephropathy. Am J Kidney Dis 2016;67:20–30.

22. McClean MA, Amador JJ, Laws R, et al. Biological sampling report: Investigating biomarkers of kidney injury and chronic kidney disease among workers in Western Nicaragua. Boston: University School of Public Health: Compliance Advisor Ombudman, 2012. http://www. caso-ombudsman.org/documents/Biological_Sampling_Report_April_2012.pdf (accessed 2 Jan 2016).

23. Peraza S, Wesseling C, Aragón A, et al. Decreased kidney function among agriculture workers in El Salvador. Am J Kidney Dis 2012;59:531–40.

24. Crowe J, Nilsson M, Kjellström T, et al. Heat-related symptoms in sugarcane harvesters. Am J Ind Med 2015;58:541–8.

25. Madero M, Arriaga JC, Jalal D, et al. The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. Proc Nutr Soc 2013;72:151–9.

26. Agricultural Research Service. National Nutrient Database for Standard Reference Release 27. United States Department of Agriculture. http://ndb.nal.usda.gov/ndb/foods/show/62167?fg=&man=&ifacet=&count=&max=25&sort=&qlookup=cane&offset=&format=Full&new=&measureby (accessed 2 Jan 2016).

27. Franke TM, Ho T, Christie CA. The chi-square test: often used and often misinterpreted. Am J Evaluation 2012;33:450–8.

28. Cade JR, Free HJ, De Quessa AM, et al. Changes in body fluid composition and volume during vigorous exercise by athletes. J Sports Med Phys Fitness 1971;11:172–8.

29. Vanholder R, Sever MS, Erek E, et al. Rhabdomyolysis. J Am Soc Nephrol 2000;11:1553–60.

30. Knochel JP, Dotin LN, Hamburger RJ. Heat stress, exercise, and muscle injury: effects on urate metabolism and renal function. Ann Intern Med 1974;81:321–8.

31. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is causing which? Nephrol Dial Transplant 2013;28:2221–8.

32. Nakagawa T, Mazzali M, Kang DH, et al. Hyperuricemia causes glomerular hypertrophy in the rat. Am J Physiol Renal Physiol 2003;284:F100–8.

33. Pang MX, Li H, Guo J, et al. Heat stress nephropathy from exercise-induced uric acid crystalluria: a perspective on Mesoamerican nephropathy. Am J Kidney Dis 2016;67:20–30.

34. Sánchez-Lozada LG, Tapia E, Santamaría J, et al. Fructose, but not dextrose, accelerates the progression of chronic kidney disease. J Am Physiol Renal Physiol 2007;293:F1256–61.

35. Shoham DA, Durazo-Arvizu R, Kramer H, et al. Sugary soda consumption and albuminuria: results from The National Health and Nutrition Examination Survey, 1999–2004. PLoS ONE 2008;3:e3431.

36. Steens PE, Levin A. Fructose ingestion acutely elevates blood pressure in healthy young humans. Am J Physiol Regul Integr Comp Physiol 2008;294:R750–7.

37. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825–50.

38. Benghanem Gharbi M, Elseviers M, Zamd M, et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid “over”- and “under”-diagnosis of CKD. Kidney Int 2016;89:1363–71.

39. Le MT, Frye RF, Rivard CJ, et al. Effects of high-fructose corn syrup and sucrose on the pharmacokinetics of fructose and acute metabolic and hemodynamic responses in healthy subjects. Metab Clin Exp 2012;61:641–51.

40. Brown CM, Dulloo AG, Yenpu G, et al. Fructose ingestion acutely elevates blood pressure in healthy young humans. Am J Physiol Regul Integr Comp Physiol 2008;294:R750–7.

41. De Broe ME, Gharbi MB, Elseviers M, Maremard, prevalence of chronic kidney disease, how to avoid over-diagnosis and under-diagnosis. Nephrol Ther 2016;12(Suppl 1):S57–63.

42. Wesseling C, Aragón A, González M, et al. Kidney function in sugarcane cutters in Nicaragua—a longitudinal study of workers at risk of Mesoamerican nephropathy. Environ Res 2016;147:125–32.