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DECLINE IN KIDNEY FUNCTION AMONG APPARENTLY HEALTHY YOUNG ADULTS AT RISK OF MESOAMERICAN NEPHROPATHY

Marvin Gonzalez-Quiroz, MSc[1,2,3], Evangelia-Theano Smpokou, MSc[3], Richard J. Silverwood, PhD[4], Armando Camacho, BSc[1], Dorien Faber, MSc[5], Brenda La Rosa Garcia, BSc[3], Amin Oomatia, MBChir[3], Michael Hill, PhD[6], Jason Glaser, BSc[5], Jennifer Le Blond, PhD[7], Catharina Wesseling, PhD[8], Aurora Aragon, PhD[1], Liam Smeeth, PhD[2], Neil Pearce, PhD[2,4], Dorothea Nitsch, MD[2], Ben Caplin, PhD[3]

1. Research Centre on Health, Work and Environment, National Autonomous University of Nicaragua at León, León, Nicaragua.

2. Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK.

3. Centre for Nephrology, Division of Medicine, University College London, London, UK

4. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.

5. La Isla Network, Ada, MI, USA.

6. Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford. Oxford, UK.

7. Royal School of Mines, Imperial College London, London, UK.

8. Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

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Corresponding author: Ben Caplin.

Centre for Nephrology, Division of Medicine, University College London, London, UK

Address: Rowland Hill Street London NW3 2PF, United Kingdom

Email: b.caplin@ucl.ac.uk; Tel: +44 020 7830 2695

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Significance statement

Chronic kidney disease of undetermined cause is the leading cause of death among working-age adults in a number of Central American countries. This is the first community-based longitudinal study undertaken in the at-risk population. The results demonstrate an unprecedented evolution of disease with a substantial proportion of initially apparently healthy men and a small proportion of women experiencing rapid loss of kidney function over the 2-year follow-up. Although a number of occupational risk-factors were identified, the range of study participants that sustained loss of eGFR suggests that other factors also play a role. These findings describe a highly prevalent, uniquely aggressive, kidney disease with no clear cause. Gaining insight into the etiology should be a global health research priority.

ABSTRACT

Background: There are epidemic levels of chronic kidney disease (CKD) of undetermined cause clustering in agricultural communities in low-and-middle income countries, most prominently in Central America. We aimed to investigate the natural history of, and factors associated with, loss of kidney function in a high-risk population.

Methods: A 2-year prospective community-based longitudinal study with 6-monthly follow-up was conducted in nine rural communities in North-western Nicaragua, including all men (n=263) and a random sample of women (n=87), aged 18-30, without self-reported CKD, diabetes or hypertension. Growth mixture modelling was used to identify subgroups of estimated glomerular filtration rate (eGFR) trajectory and weighted multinomial logistic regression to examine associations with proposed risk factors.

Results: Three sub-populations of eGFR trajectory among men were identified: 81% remained stable (mean baseline eGFR: 116mL/min/1.73m^2; mean change in eGFR over follow-up: -0.6mL/min/1.73m^2/year); 9.5% experienced rapid decline despite normal baseline kidney function (112mL/min/1.73m^2; -18.2mL/min/1.73m^2/year); whilst 9.5% had baseline renal dysfunction (58mL/min/1.73m^2; -3.8mL/min/1.73m^2/year). Two sub-populations were identified in women: 96.6% remained stable (121mL/min/1.73m^2; -0.6mL/min/1.73m^2/year); and 3.4% experienced rapid decline (132mL/min/1.73m^2; -14.2mL/min/1.73m^2/year, n=3 cases). Among men, at baseline, outdoor and agricultural work along with lack of available shade during work-breaks were associated with rapid decline status.

Conclusion: There is an aggressive kidney disease in Nicaragua that is without clear cause. While associated with agricultural work the range of study participants that sustained loss of eGFR suggests that other factors also play a role.

INTRODUCTION

Chronic kidney disease of undetermined cause (CKDu), also termed Mesoamerican Nephropathy (MeN) in Central America, has led to the death of tens of thousands of young adults in rural Nicaragua and El-Salvador.[1,2] Cross-sectional studies have demonstrated low (<60mL/min/1.73m^2) estimated glomerular filtration rates (eGFR) at a prevalence of between 2 and 50% among lowland agricultural communities in the region.[3-6] Forms of CKDu occur in other tropical climates with reports of high prevalence in Sri Lanka[7,8] (where similar but not identical histopathological findings have been reported[9]), India[10] and Egypt[11] although whether this represents the same disease entity remains unclear.

Men from communities affected by MeN predominantly work in agriculture, primarily sugar production from cane. Agricultural activity in this industry is concentrated in the dry season, which in Nicaragua occurs between November and May. Although a leading hypothesis in Mesoamerica is that the disease relates to heat stress, a number of other causes, including agrichemicals, infection and heavy metals, have been proposed.[1,12-14]

Empirical evidence for causes of CKDu has to date been limited to identification of factors associated with either reduced eGFR in cross-sectional studies,[3,15,16] or loss of eGFR across the harvest season in two workplace-based follow-up studies[17,18]. Given the potential for reverse causation (i.e. reduced eGFR resulting in changes in exposure) and misclassification of exposures and/or outcome in the cross-sectional designs, along with the non-generalizability, and substantial loss to follow-up that occurred in the longitudinal workplace studies, evidence on risk factors for, and evolution of, CKDu is extremely limited.[19]

Our aim was to investigate the natural history of disease, specifically early loss of kidney function, along with risk factors and urinary markers (albumin: creatinine ratio; ACR, and neutrophil gelatinase associated lipocalin; NGAL) associated with decline in eGFR. Therefore, we conducted a community-based longitudinal study of an initially apparently healthy young rural population in Northwest Nicaragua.

METHODS

Cohort

Both local and UK based institutional review boards approved the study and participants provided written informed consent. The rationale and description of the study design has been published elsewhere.[20] Briefly, this was a two-year longitudinal community-based study following 350 participants aged 18 to 30 years in Leon and Chinandega regions, Nicaragua (Figure 1). Following engagement work we performed a census of all adults aged 18-30 in nine rural communities. As we were specifically interested in associations with early kidney injury in MeN all potential participants with a self-reported diagnosis of chronic kidney disease (CKD), diabetes, or hypertension were excluded. All remaining men (as men have been reported to suffer more CKDu), and women selected at random (in numbers leading to a male: female ratio of 3:1) were invited to take part. Participants were predominantly recruited in November 2014, with an additional 7% in May 2015 as recruitment targets had not been met in November.

Procedures

Questionnaire data, clinical measurements and biosamples were collected at baseline and then every six months until November 2016. Participants were asked to respond to questions on demography, occupational history and current job, lifestyle factors and symptoms. Urinary tract infection (UTI) was recorded where participants reported a clinical diagnosis (which is common in this part of Nicaragua) typically without urinalysis or microbiological confirmation. Body weight was measured with minimal clothes using electronic scales and height using a portable stadiometer (both Seca, Birmingham, UK). Blood pressure and heart rate was measured in a sitting position using a calibrated digital sphygmomanometer (Omron, Kyoto, Japan) after five minutes of quiet seated rest. A mean of three measurements was recorded. Participants were asked to attend fasted, first thing in the morning (prior to work) in an attempt to reduce within- and between person variation in serum creatinine.

Biochemical methods

Serum creatinine and cystatin C were both measured in a single batch using quality control referenced to international standards (for creatinine: isotope dilution mass-spectrometry quantified National Institute of Standards and Technology Standard Reference Material 967). eGFR was calculated using the CKD-EPI formula combining creatinine and cystatin C.[21] ACR along with semi-quantitative protein and specific gravity by test-stick was performed in baseline urine samples thawed for the first time. In addition, 55 samples (thawed for a second time) selected using a nested case-control approach were analysed for NGAL.

Statistical methods

The collection and categorization of exposure variables is described in the Supplementary Material. As eGFR trajectories clustered in discrete subgroups (see Supplementary Figure 1), and differently between sexes, we used growth mixture modelling (GMM) separately in men and women to empirically derive latent classes of eGFR trajectory.[22] The GMM is a longitudinal finite mixture model that allows identification of unobserved latent classes of individuals following similar progression of the outcome over time without imposing a priori constraints on the levels of eGFR or rates of eGFR change (or the proportion of participants experiencing any class of change). Each individual's probability of belonging to a particular latent class is derived entirely from the observed eGFR measurements, with individual departures from the mean trajectory within each class represented by random effects. We primarily used the Bayesian Information Criterion to determine the optimal number of classes as suggested in this setting.[23] The GMM was estimated by maximum-likelihood using an expectation maximisation (EM) algorithm, with confidence intervals for the mean rate of eGFR decline derived using conventional standard errors.

Each individual was assigned a probability of each class (eGFR trajectory) and then for the purposes of the descriptive figure, tables and urinary findings allocated to the highest probability group.

To test whether proposed causal exposures (alcohol or NSAID use, occupational factors, heat-stress, agrochemical exposure, fever, dysuria, water quantity/quality/source in males only) were associated with rapidly declining eGFR trajectory we conducted age and educational-level adjusted analyses using probability-weighted logistic regression (with weighting according to the participant's probability of each eGFR trajectory as per the GMM) examining exposures individually using stable with preserved eGFR trajectory as a reference. Associations where the 95% confidence intervals (CI) of the odds ratio (OR) did not include unity were interpreted as significant. We also performed a sensitivity analysis using exposures assessed at Visit 2 (only in those men recruited at Visit1) and rapid decline given the seasonal variation in occupational exposures. Those with baseline dysfunction were not the primary focus of this study but a further analysis additionally exploring associations between risk factors and this eGFR trajectory was also performed using probability-weighted logistic regression (see Supplementary Material).

Differences in urinary markers in each eGFR trajectory group (defined based on highest probability as above) were investigated either in the whole population for ACR or using a nested-case control approach in the case of NGAL. Differences between groups were explored using analysis of variance with Dunnett's post-hoc test. Positive and negative predictive values were calculated for urinary NGAL for the rapid decline versus stable group.

RESULTS

Cohort and follow-up

520 adults aged 18-30 were identified in the study communities. After exclusion of 4% of the potential participants because of self-reported CKD, diabetes or hypertension, 350 participants (of the 360 invited after random selection of eligible women; 97%) were included in the study.[20] Overall, participants attended a total of 1581 study visits over the two-year follow-up (92% of planned visits).

Two participants died from end-stage renal disease during the study period. The cohort is described in Figure 1 and Table 1.

The median eGFR in men was 116.2 mL/min/1.73m^2 (interquartile range [IQR], 102.4–124.6) at baseline, and 110.4 mL/min/1.73m^2 (IQR, 92.5–120.5) at end of follow-up. The corresponding figures for women were 122.0 mL/min/1.73m^2 (IQR, 116.3-127.2) at baseline, and 120.2 mL/min/1.73m^2 (IQR, 110.6-126.6). The eGFR varied by season (Figure 2) with a median of 116.0 mL/min/1.73m^2 (IQR, 102.7-123.8) at the end of the rainy season (November; i.e. pre-sugarcane harvest, all years combined) compared to 113.4 mL/min/1.73m^2 (IQR, 100.8-122.4) at the end of the dry season (May; i.e. post-sugarcane harvest, all years combined). This effect was greatest in those participants with lower eGFRs but was also present in those with stable kidney function (Supplementary Table 2).

eGFR trajectory groups

Using GMM we identified three different subgroups in men and two in women based on the model intercept (baseline eGFR) and slope (change in eGFR over time). Among men (Figure 3A) the majority (81%) of men had preserved and stable eGFR, however 9.5% (n=25) had baseline kidney dysfunction (eGFR ~60mL/min at recruitment) and a further 9.5% experienced rapid decline in eGFR (with a mean loss of 18mL/min/1.72m^2/year) despite preserved eGFR at baseline. Almost all the women (Figure 3B) had preserved and stable eGFR but 3.4% (n=3) also experienced rapid decline (with a mean loss of 14mL/min/1.72m^2/year). No differences were seen between communities in the proportions of participants in these subgroups.

Baseline socio-demographic, occupational history, occupational exposures, lifestyle factors, and symptoms stratified by the assigned kidney trajectory groups are presented in Supplementary Tables 2 and 3. The frequencies of indoor work and availability of shade were both lower in the rapidly declining subgroup. Of the three women who fell into the rapid decline group, one had worked in (non-sugarcane) agriculture and two worked exclusively at home.

Adjusted associations with rapid decline trajectory

Baseline age and educational-level adjusted, probability-weighted associations with the rapid decline in eGFR trajectory in men using the preserved and stable trajectory as the reference are presented in Table 2. Outdoor work (OR, 10.35, 95% CI, 1.35 to 79.24), (non-sugarcane) agricultural work (OR, 3.57, 95% CI 1.14 to 11.13) and lack of shade available during work breaks (OR, 3.74, 95% CI, 1.59-8.76) were associated with this outcome. However, we found no evidence for associations between rapid decline and years of work in sugarcane, or agriculture; self-reported physical effort in the last week at work or occupational heat exposure; self-reported agrochemical exposure over last six months; alcohol consumption, self-reported fluid consumption, water quality or source; heat/dehydration-related symptoms; or use of NSAIDs.

We were concerned that the questionnaire administered at baseline might fail to capture important occupational exposures as, for most participants, it was conducted 6-months after the harvest season. Therefore, we conducted a sensitivity analysis (men recruited at the November visit only, n=213) examining the association with the same rapid decline eGFR trajectory as above, and occupational exposures, hydration variables and heat-related symptoms captured at the second study visit (May 2015, immediately post-harvest; Supplementary Table 4). At this time point, no associations were detected between working outdoors or lack of shade and rapid decline in eGFR trajectory (although very few participants were not exposed). There was an association between both those working in a sugarcane cutting role (OR: 3.84 95% CI, 1.17 to 12.58) and those reporting fever over the last 6-months (OR: 5.77, 95% CI, 2.03 to 16.33) and rapid decline trajectory but in line with the baseline exposure analysis no associations were observed between self-reported measures of heat exposure, combined heat-related symptoms, or fluid intake and outcome (Supplementary Table 5).

Urinary findings

No associations were found between dipstick proteinuria, specific gravity or ACR and eGFR trajectory subgroups (Tables 3 and 4). Urinary NGAL levels among males differed between the three groups tested (Figure 4). The positive and negative predictive values of NGAL ≥5.5pg/mmol for rapid decline were 28.5%, and 62.5% respectively.

DISCUSSION

This is the first community-based cohort study from an area with high reported prevalence of MeN, and the first longitudinal study of at least moderate size with follow-up of more than 6 months in area at high-risk of disease. Even after excluding those with self-reported CKD, 9.5% of the apparently healthy men, but no women, in the study had evidence of baseline renal dysfunction. Rapid loss of eGFR from normal baseline levels was found in a further 9.5% of men and 3.4% of women. Among men, risk factors at baseline for rapid decline included working outdoors, agricultural work and lack of shade availability but none of the other questionnaire responses aimed at capturing heat stress, time-accumulated occupation or other proposed causes of MeN were associated with the outcome at baseline. Due to small numbers, we were unable to examine associations in women.

Other important findings from our study include the cyclical annual fluctuation in renal function across the entire population with the average eGFR approximately 2.5 mL/min/1.73m^2 lower following the dry (harvest) season as compared to 6-months earlier. Furthermore, although there were no differences in albuminuria between those with different kidney function trajectories, urinary NGAL was substantially higher among those with baseline dysfunction, and marginally elevated in the rapid decline group.

Although CKDu has been anecdotally reported as an aggressive disease[1], the rate of loss of kidney function in the rapid decline group who make up almost 10% of the unselected young male population in our study is to our knowledge without precedent. Even when compared to eGFR decline in other forms of CKD seen in clinic populations the observed loss of kidney function is alarming. Although a recent biopsy study that enrolled patients with established CKDu reported a rate of decline in eGFR of 7.0mL/min/1.73m^2/year among men with a history of work in the sugarcane[24] there have been no longitudinal studies which have examined medium- or long-term (>1-year) changes in kidney function in the at-risk population. The rate of eGFR decline has been explored in more detail in other forms of CKD, for example, a longitudinal study in fifty-five clinic patients with diabetic nephropathy from Belgium reported that approximately 15% of patients suffered severe decline in kidney function (defined as eGFR loss >4mL/min/1.73m^{2}year).[25] Most recently, Boucquemont et al. examined eGFR decline in a CKD patient population in France using a similar latent class-based modelling approach to that used in this analysis.[26] This study reported severe eGFR decline in only 0.6% of patients (~50mL/min/1.73m^2 over almost 6 years). Therefore, our study findings underline the unique, and severe nature of kidney disease in this region.

The associations with rapid decline trajectory in men suggests that occupation (outdoor agricultural work) is an important risk factor for loss of kidney function and is consistent with previous reports[18]. The temporary nature of work in this population makes distinguishing relationships between specific occupations and eGFR loss challenging however it is interesting to note that neither time-accumulated sugarcane or agricultural work was associated with outcome. Furthermore, the association between lack of available shade at baseline, and rapid decline trajectory, suggests that working environment may play an important role in disease evolution, either by (not reducing) solar exposure or as a surrogate for generally poor occupational conditions. Consistent with this, and line with previous cross-harvest studies[17] we identified an association between rapid decline and a cane/seed cutting role (a job role that has been associated with particularly hot working conditions) in a sensitivity analysis examining associations with exposures assessed post-harvest.

The lack of association of self-reported physical effort the previous week at work, and both work in very hot environment and combined dehydration/heat stress symptoms in the last 6 months, with the outcome measure both at baseline, and in the sensitivity analysis with exposures assessed at visit 2 raises further questions. Although self-reported measures of thermal sensation and physical exertion have been shown to robustly capture acute physiological heat stress[27] our (similar) instruments (and/or our combined measure of heat-symptoms) may not be valid in the rural Nicaraguan population or may not reflect time-accumulated heat stress. Alternatively, we may have had inadequate power to detect heat stress as a partial contributor to eGFR decline or otherwise it may be that non-heat related occupational exposures promote the development of CKDu. Finally the association between self-reported fever over the previous 6-months at the second study visit and rapid decline trajectory might support a proposed infective/inflammatory contributor to MeN[28], though this finding was from a sensitivity analysis and should be treated with caution.

In summary, our data do not provide clear evidence for a cause to the disease. Along with occupation the importance of non-occupational factors is supported by: (i) the range of jobs undertaken by the men experiencing rapid decline, and (ii) the 3.4% of women in our study who also showed a rapid loss of eGFR. As others have suggested,[2] separate initiating and exacerbating factors should be considered as occurs in other forms of CKD. For example, the progression of kidney disease due to known causes (e.g. diabetes, glomerulonephritis) can be exacerbated by episodes of volume depletion. Therefore, the possibility of an initial (currently unknown) sub-clinical insult, which is then exacerbated by the harsh working conditions might explain the increased rates of eGFR loss and excess of advanced disease in men.

Although other studies have identified changes in urinary biomarkers in sugarcane workers over the harvest season in Mesoamerica[29] none have examined associations with subsequent eGFR loss over the medium-term. There were no associations between dipstick proteinuria or ACR, and eGFR trajectory group. Although albuminuria is a strong risk factor for renal decline in most populations, this is consistent with previous reports from Mesoamerica where patients with established CKDu show only low-grade proteinuria.[6,24,30] Urinary NGAL levels were substantially raised in those with baseline dysfunction but levels in the rapid decline group overlapped with the stable group making this test poorly predictive at an individual level.

Finally, it is worth noting the seasonal variation of eGFR in the population. Other studies (unrelated to CKDu) have described similar seasonal differences in renal function[31,32] so whether this this variation is in any way related to the factors that cause MeN is unclear but this finding does need to be considered when interpreting the change in eGFR reported in cross-harvest studies[5,18]. Ideally, any future longitudinal biomarker study should be of more than one-year duration to ensure that small falls in eGFR do not reflect cyclical seasonal changes.

Our study has several strengths. Overall response rates were high and the eGFR was estimated using robust methods. We excluded those with self-report of diabetes and hypertension in an attempt to focus our study on eGFR decline due to MeN and the prospective nature of our study enabled us to identify those with aggressive disease without necessarily meeting definitions for CKD. Furthermore we excluded those with established renal disease (either by self-report from the study as a whole or by examining only those with preserved eGFR at baseline for the risk-factor analysis) and hence overcome issues associated with reverse causation.

Our study also has limitations. We did not formally exclude diabetes in our participants. Although often undiagnosed,[33] the prevalence of diabetes is low in Nicaraguans of this age-group[34] and none of those in the rapid decline group demonstrated albuminuria (or glycosuria; data not presented) making an underlying diabetic lesion highly unlikely. We also relied on self-report to quantify the majority of occupational and environmental exposures. Although questionnaire-based assessments are useful instruments, none of them have been validated in the Nicaraguan population so some exposures may be prone to misclassification. The study took place in a confined geographical area which limits generalizability. Resources restricted our study to a moderate sample size and we had to alter our statistical approach. We were nonetheless able to detect a number of strong associations with eGFR trajectory but the analytical change did lead to a reduction in power. Therefore we would have expected to identify associations with a primary cause of disease that had been reliably captured by questionnaire but may have missed weaker associations particularly with contributing exposures. The baseline dysfunction group are unrepresentative due to selection criteria (those with established CKD were intentionally excluded at recruitment) and possibly survivor bias (due to the small number of deaths in this group) and the nature of the study design means the relationship between rapid decline in eGFR and hard outcomes could not be described. However, we hope to perform extended follow-up to investigate the longer-term outcomes in the cohort. Finally, the CKD-EPI formula has not been validated for this population, although as we were interested in within-person change in eGFR this is unlikely to be of major importance.

In conclusion, this is the first community-based cohort study that describes the natural history of eGFR in those at risk of MeN. Almost 10% of apparently healthy young men, and 3.4% of young women showed a marked decline in kidney function. Additional studies with at least 1-year follow-up are needed to understand the causes of this decline, including the risks associated with outdoor (agricultural) work. Efforts to identify biomarkers of this early loss of eGFR, rather than established disease, are essential to gain a better understanding of aetiology, as well as to identify the population(s) that would benefit from interventions. A combined, multidisciplinary approach is called for, in partnership with the affected communities and local employers, to address this devastating disease.

AUTHOR CONTRIBUTIONS

BC and NP conceived the project. MG-Q, DN, CW, JG, JLeB, AA, LS NP and BC designed the study. MG-Q, AC, DF, JLeB, and BC performed the fieldwork along with the fieldwork team. MG-Q, RS, DN, NP and BC analysed and interpreted the data. ES, BG, AO and MH analyzed the biological samples. MG-Q, RS, DN, NP and BC drafted the manuscript. All authors read, critically appraised and approved the final manuscript.

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Table 1. Selected demographic, lifestyle and occupational characteristics of the study cohort

Characteristic	Overall (*n*=350)	Males (*n*=263)	Females (*n*=87)
	Personal and Lifestyle Factors		
Age in years; mean (SD)	23.9 (3.7)	23.7 (3.8)	24.2 (3.6)
Educational level; n (%)			
Illiteracy	18 (5.1)	18 (6.8)	0 (0)
Primary school	176 (50.3)	133 (50.6)	43 (49.4)
Secondary school	138 (39.5)	100 (38.0)	38 (43.7)
Higher education	18 (5.1)	12 (4.6)	6 (6.9)
Body mass index; median (IQR)	22.7 (21.0–25.0)	22.4 (20.8–24.1)	24.5 (21.9–30.0)
Systolic blood pressure mmHg; median (IQR)	117 (109 – 124)	119 (111 – 125)	109 (103 – 119)
Diastolic blood pressure mmHg; median (IQR)	68 (63 – 73)	68 (63 - 74)	68 (63 – 72)
Household income in Córdobas/month; median (IQR)	6000 (4000–9200)	6000 (4000–10000)	5120 (3380–8144)
Family history of CKD; n (%)			
Yes	165 (47.1)	126 (47.9)	39 (44.8)
No	185 (52.9)	137 (52.1)	48 (55.2)
Annual alcohol consumption in grams; median (IQR)	0·0 (0–849)	82.9 (0–1350)	0.0 (0–0)
Smoking pack-year; median (IQR)	0·0 (0–0)	0·0 (0–1)	0.0 (0–0)
NSAID use ever; n (%)			
Never	58 (16·6)	49 (18·6)	9 (10·3)
Occasionally	251 (71·7)	185 (70·3)	66 (75·9)
Regularly	31 (8·9)	23 (8·8)	8 (9·2)
Daily	10 (2·8)	6 (2·3)	4 (4·6)
Water sources; n (%)			
Piped wáter	186 (53.1)	139 (52.9)	47 (54.0)
Dug well	126 (36.0)	98 (37.2)	28 (32.2)
Drilled well	38 (10.9)	26 (9.9)	12 (13.8)
Water Hardness; n (%)			
Soft	0 (0·0)	0 (0·0)	0 (0·0)
Moderately hard	97 (27·7)	67 (25·4)	30 (34·5)
Hard	160 (45·7)	123 (46·8)	37 (42·5)
Very hard	93 (26·6)	73 (27·8)	20 (23·0)
Total liquid in last 24hrs; median (IQR)	5.0 (3.7–6.3)	5.6 (4.2–6.7)	3.6 (2.5–4.5)
	Occupational Factors		
Current occupation; n (%)			
Sugarcane	55 (15.7)	45 (17.1)	10 (11.5)
Banana work	14 (4.0)	13 (4.9)	1 (1.1)
Other agricultural work	115 (32.9)	109 (41.5)	6 (6.9)
Commerce	14 (4.0)	5 (1.9)	9 (10.3)
Construction	10 (2.9)	10 (3.8)	0 (0)
Fishing	7 (2.0)	7 (2.7)	0 (0)
Homeworker	54 (15.4)	0 (0)	54 (62.1)
Student	6 (1.7)	4 (1.5)	2 (2.3)
Unemployed	51 (14.6)	49 (18.6)	2 (2.3)
Other occupations*	24 (6.8)	21 (8.0)	3 (3.5)
Main sugarcane role (if ever worked in sugarcane); n (%)			
Cane cutter	81 (23.2)	81 (30.8)	0 (0)
Seed cutter	56 (16.3)	56 (21.3)	0 (0)
Seeder	67 (19.2)	47 (17.9)	21 (24.1)
Cane cleaner	26 (7.4)	17 (6.5)	9 (10.4)
Pesticide applicator	4 (1.1)	4 (1.5)	0 (0)
Cane irrigator	8 (2.3)	8 (3.0)	0 (0)
Driver	4 (1.1)	4 (1.5)	0 (0)
Never worked in sugarcane	103(29.4)	46 (17.5)	57 (65.5)
Current or previous banana work; n (%)			
Yes	56 (16.0)	47 (17.9)	9 (10.3)
No	294 (84.0)	216 (82.1)	78 (89.7)
Years in sugarcane; mean (SD)	2.2 (2.8)	2.8 (2.8)	0.67 (1.7)
Years in agricultura; mean (SD)	3.6 (4.4)	4.3 (4.5)	1.2 (3.3)

Characteristic	Overall (*n*=350)	Males (*n*=263)	Females (*n*=87)
Work carried out ;[†] n (%)			
Indoors	136(38.9)	69 (26.2)	67 (77.0)
Outdoors	214 (61.1)	194 (73.8)	20 (23.0)
Work in a hot environment;[†] n (%)			
Irregularly	137 (39.2)	92 (35.0)	45 (51.7)
Regularly	74 (21.1)	57 (21.7)	17 (19.5)
Frequently	139 (39.7)	114 (43.3)	25 (28.8)
Always	0 (0)	0 (0)	0 (0)
Shade availability;[†] n (%)			
Yes	254 (72.6)	190 (72.2)	64 (73.6)
No	96 (27.4)	73 (27.8)	23 (26.4)
Duration of breaks in mins;[†] median (IQR)	20 (10-30)	15.0 (10 - 30)	30.0 (20- 60)
Physical effort at work;[‡] n (%)			
Did not work	15 (4.3)	14 (5.3)	1 (1.2)
Slight	142 (40.6)	100 (38.0)	42 (48.3)
Moderate	155 (44.2)	119 (45.3)	36 (41.4)
Hard	38 (10.9)	30 (11.4)	8 (9.2)
Glyphosate use;[†,§] n (%)			
Yes	77 (22.0)	77 (29.3)	0 (0)
No	273 (78.0)	186 (70.7)	87 (100.0)
Paraquat use;[†,§] n (%)			
Yes	44 (12.6)	44 (16.7)	0 (0)
No	306 (87.4)	219 (83.3)	87 (100.0)
Cypermethrin use;[†,§] n (%)			
Yes	75 (21.4)	73 (27.7)	2 (2.3)
No	275 (78.6)	190 (72.2)	85 (97.7)
Methomyl use;[†,§] n (%)			
Yes	12 (3.4)	12 (4.6)	0 (0)
No	338 (96.6)	251 (94.4)	87 (100.0)
	Clinical history/symptoms		
Heat/dehydration symptoms;[†] n (%)			
Yes	240 (68·6)	175 (66·5)	65 (74·7)
No	110 (31·4)	88 (33·5)	22 (25·3)
UTI in the previous year; n (%)			
Yes	91 (26.0)	56 (21.3)	35 (40.2)
No	259 (74.0)	207 (78.7)	52 (59.8)
Weight loss;[†] n (%)			
Yes	63 (18.0)	55 (20.9)	8 (9.2)
No	287 (82.0)	208 (79.1)	79 (90.8)
Dysuria[†]			
Yes	94 (26.9)	72 (27.4)	22 (25.3)
No	256 (73.1)	191 (72.6)	65 (74.7)
Fever[†]			
Yes	36 (10.3)	32 (12.2)	4 (4.6)
No	314 (89.7)	231 (87.8)	83 (95.4)
	Study Visits and Outcome		
Initial serum creatinine, mg/dl; median (IQR)	0.81 (0.70–0.90)	0.84 (0.77–0.94)	0.63 (0.57–0.68)
Final serum creatinine, mg/dl; median (IQR)	0.81 (0.70–0.90)	0.91 (0.80–1.03)	0.64 (0.57–0.72)
Initial cystatin C, mg/L; median (IQR)	0.82 (0.74–0.92)	0.85 (0.77–0.95)	0.72 (0.67–0.80)
Final cystatin C, mg/L; median (IQR)	0.84 (0.76–0.94)	0.88 (0.80–1.01)	0.72 (0.67–0.80)
Initial eGFR, mL/min/1.73m^2; median (IQR)	118.3 (106.6 – 125.4)	116.2 (102.4 – 124.6)	122.0 (116.3 – 127.2)
Final eGFR, mL/min/1.73m^2; median (IQR)	113.1 (99.4 – 122.3)	110.4 (92.5 – 120.1)	120.2 (110.6 – 126.6)

Abbreviations: CKD: Chronic Kidney Disease; NSAID: Non-steroidal anti-inflammatory drug; eGFR: estimated glomerular filtration rate using CKD EPI equation based on creatinine and cystatin c; UTI: diagnosed with a urinary tract infection typically without microbiological or dipstick confirmation. *Other occupations include: teacher, painter, shoemaker, security, manufacturing operator and barber; [†]over the last 6-months; [‡]over the last week; §Data collected at second visit; Questionnaire data prior to recoding are presented in Appendix Table 1.

Table 2. Age and education level adjusted associations of rapid decline in kidney function by baseline exposure in male study participants*

Characteristic	Preserved and stable eGFR	Rapid decline in eGFR	
	Reference	OR	95% CI
Alcohol consumption			
Any	1.00	1.69	0.70 to 4.10
None	1.00	Reference	Reference
NSAID use			
Daily/regularly	1.00	1.28	0.34 to 4.74
Never/occasionally	1.00	Reference	Reference
Water sources			
Piped water	1.00	0.79	0.34 to 1.81
Dug well/drilled well	1.00	Reference	Reference
Water hardness			
Softly/moderately hard	1.00	1.21	0.47 to 3.11
Hard/very hard	1.00	Reference	Reference
Total liquid in last 24hrs			
>5.0 litres/day	1.00	1.01	0.43 to 2.38
≤ 5.0 litres/day	1.00	Reference	Reference
Current occupation			
Sugarcane	1.00	1.51	0.31 to 7.29
Agricultural work	1.00	3.57	1.14 to 11.13
Other occupations/EIP	1.00	Reference	Reference
Main sugarcane role (if ever worked in sugarcane)			
Cane/seed cutter	1.00	2.15	0.57 to 8.06
Seeder	1.00	1.82	0.40 to 8.20
Other cane jobs	1.00	0.94	0.14 to 6.08
Never worked in sugarcane	1.00	Reference	Reference
Current or historical banana work			
Yes	1.00	1.77	0.60 to 5.18
No	1.00	Reference	Reference
Years in sugarcane	1.00	1.02	0.87 to 1.19
Years in agriculture	1.00	0.99	0.89 to 1.09
Work carried out†			
Outdoors	1.00	10.35	1.35 to 79.24
Indoors	1.00	Reference	Reference
Work in a hot environment†			
Regular/frequently	1.00	0.46	0.20 to 1.06
Irregularly	1.00	Reference	Reference
Shade availability†			
No	1.00	3.74	1.59 to 8.76
Yes or inside	1.00	Reference	Reference
Duration of breaks†			
≤ 10 minutes	1.00	1.86	0.80 to 4.33
>10 minutes	1.00	Reference	Reference
Physical effort at work‡			
Moderate/hard	1.00	1.40	0.59 to 3.32
None/slight	1.00	Reference	Reference
Agrochemicals†,§			
Yes	1.00	1.70	0.72 to 4.03
No	1.00	Reference	Reference
Heat/dehydration symptoms†			
Yes	1.00	1.40	0.55 to 3.55
No	1.00	Reference	Reference
Dysuria†			
Yes	1.00	1.18	0.48 to 2.89
No	1.00	Reference	Reference
Fever†			
Yes	1.00	2.41	0.80 to 7.27
No	1.00	Reference	Reference

Abbreviations: OR: odds ratio; NSAID: Non-steroidal anti-inflammatory drug; UTI: urinary tract infection: EIP: Economically Inactive Population. Agricultural work includes all non-sugarcane agricultural work. * Probability weighted according to results of growth mixture model; † over the last 6-months.; ‡ over the last week; § Data collected at second visit, includes glyphosate, cypermethrin, paraquat and methomyl

Table 3: Description of urinary findings at baseline by assigned eGFR trajectory groups in males

Urine findings	Overall (*n*=263)	Preserved and stable eGFR (*n*=213)	Rapid decline in eGFR (*n*=25)	Baseline dysfunction (*n*=25)
Urinary specific gravity (n, %)				
≤ 1020	256 (97.3)	207 (97.2)	24 (96.0)	25 (100.0)
>1020	7 (2.7)	6 (2.8)	1 (4.0)	0 (0)
Protein (n, %)				
Negative	224 (85.2)	181 (85.0)	22 (88.0)	21 (84.0)
Trace	25 (9.5)	19 (8.9)	2 (8.0)	4 (16.0)
Positive	14 (5.3)	13 (6.1)	1 (4.0)	0 (0)
ACR (n, %)				
≥ *30 mg/g*	15 (5.7)	11 (5.2)	0 (0)	4 (16.0)
< *30 mg/g*	248 (94.3)	201 (94.8)	25 (100.0)	21 (84.0)

Participants assigned to the group with the highest probability in growth mixture model. Abbreviations: ACR: Albumin creatinine ratio. *P*=NS by Fishers exact test for differences by group.

Table 4: Description of urinary findings at baseline by assigned eGFR trajectory groups in females.

Urine findings	Overall (*n*=87)	Preserved and stable eGFR (*n*=84)	Rapid decline in eGFR (*n*=3)
Urinary specific gravity (n, %)			
≤ *1020*	81 (93.1)	79 (94.1)	2 (66.7)
>1020	6 (6.9)	5 (5.9)	1 (33.3)
Protein (n, %)			
Negative	70 (80.5)	68 (81.0)	2 (66.7)
Trace	13 (14.9)	12 (14.3)	1 (33.3))
Positive	4 (4.6)	4 (4.7)	0 (0)
ACR (n, %)			
≥ *30 mg/g*	9 (10.3)	9 (10.7)	0 (0)
< *30 mg/g*	78 (89.7)	75 (89.3)	3 (100.0)

Participants assigned to the group with the highest probability in growth mixture model. Abbreviations: ACR: Albumin creatinine ratio. Given the small number in some cells no statistical tests were performed.

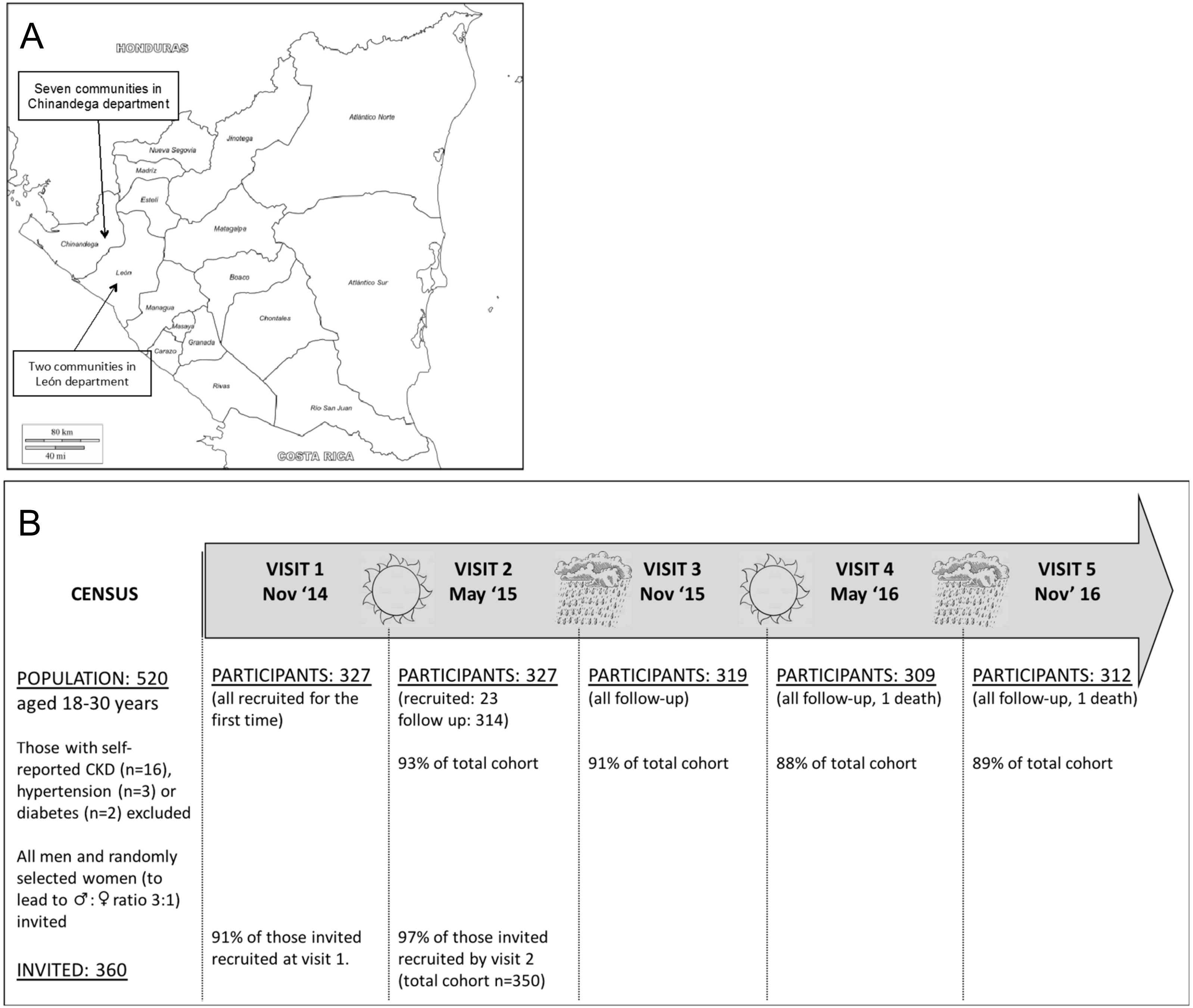
FIGURE LEGENDS

Figure 1: Study outline. Location of the nine study communities in Nicaragua (A). Cartoon showing study timeline along with population, recruitment and follow-up numbers (B). Two participants died from end-stage renal disease.

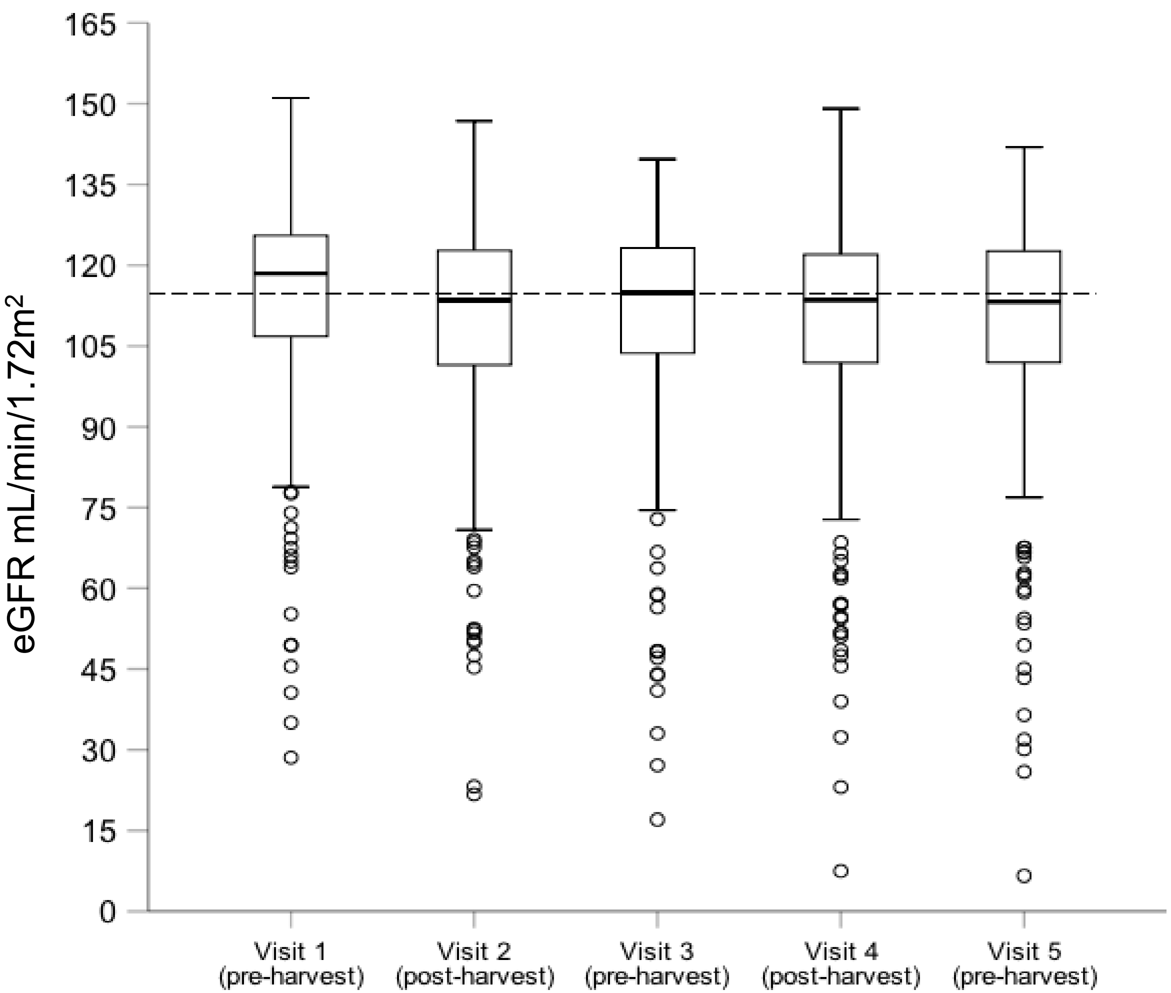
Figure 2: Box-and whisker plot of eGFR across the study population. Median eGFR was lower post-harvest than pre-harvest. The dashed line represents the median eGFR in the population at baseline.

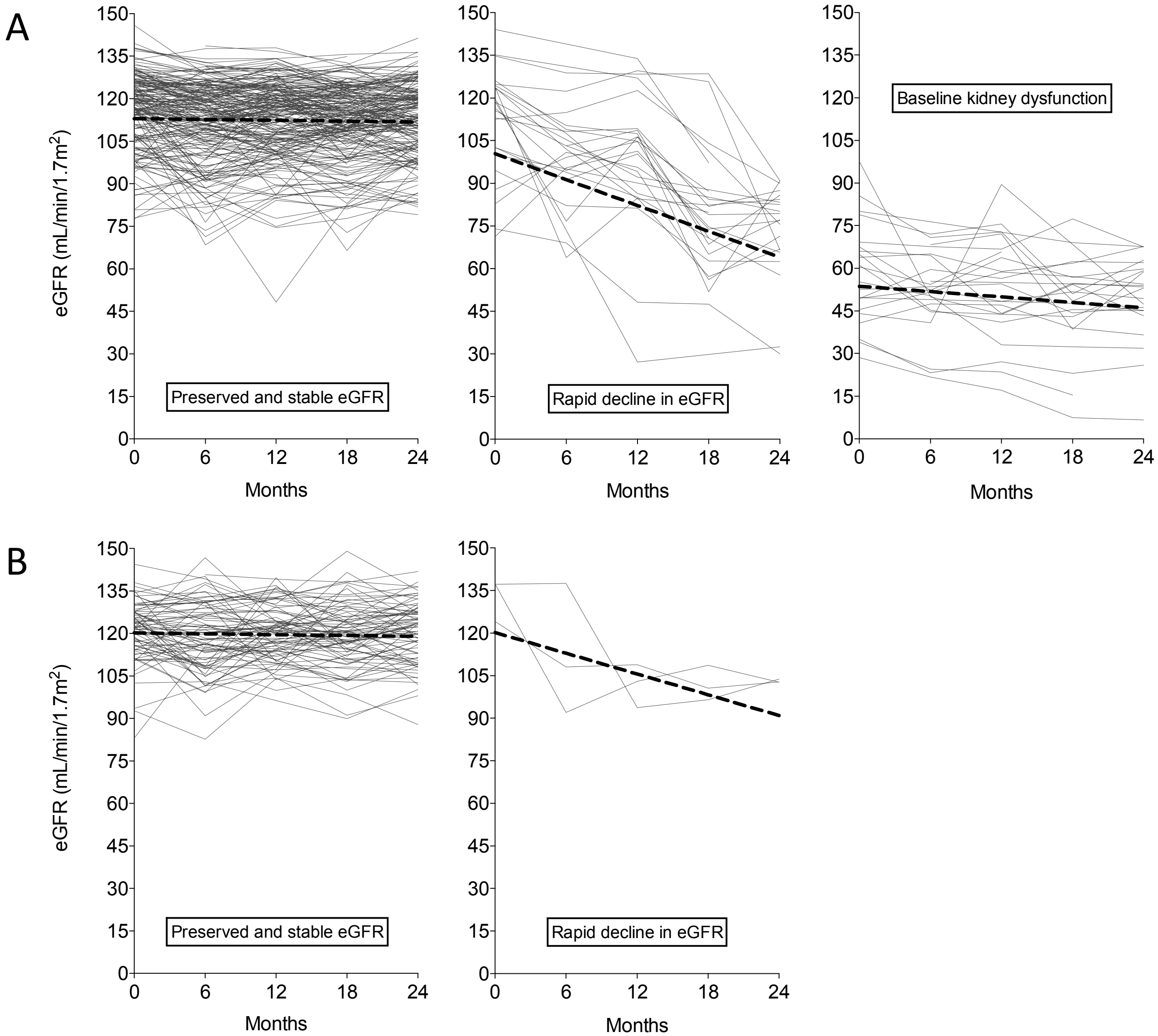
Figure 3: eGFR in the assigned kidney trajectory groups over the 2-year follow-up period. Three subgroups were identified in the 263 males (A) and two in 87 females (B). Each blue line represents the individual eGFR of a single participant. Each participant was allocated to the group of highest probability derived from the growth mixture model. Coefficients for the three male groups: preserved and stable eGFR (*n*=213; intercept [mean eGFR at baseline], 113.3 mL/min/1.73m^2, 95% CI, 111.3 to 115.3; slope [mean eGFR decline over time] -0.6 mL/min/1.73m^2/year, 95% CI, 0.0 to -0.9); rapid decline in eGFR (*n*=25; intercept, 109.5 mL/min/1.73m^2, 95% CI, 99.1 to 119.9; slope, -18.2 mL/min/1.73m^2/year, 95% CI, -13.5 to -22.9; and baseline dysfunction (*n*=25; intercept 55.6 mL/min/1.73m^2, 95% CI, 48.5 to 62.7; slope, -3.8 mL/min/1.73m^2/year, 95% CI, -0.7 to -6.9 . Coefficients for the two female groups: preserved and stable eGFR (*n*=84; intercept, 120.5 mL/min/1.73m^2, 95% CI, 118.1 to 122.9; slope, -0.6 mL/min/1.73m^2/year, 95% CI, 0.2 to -1.4) but we also identified a small number with rapid decline in kidney function (*n*=3; intercept, 127.5 mL/min/1.73m^2, 95% CI, 119.3 to 135.7; slope, -14.6 mL/min/1.73m^2/year, 95% CI,-7.5 to -21.7).

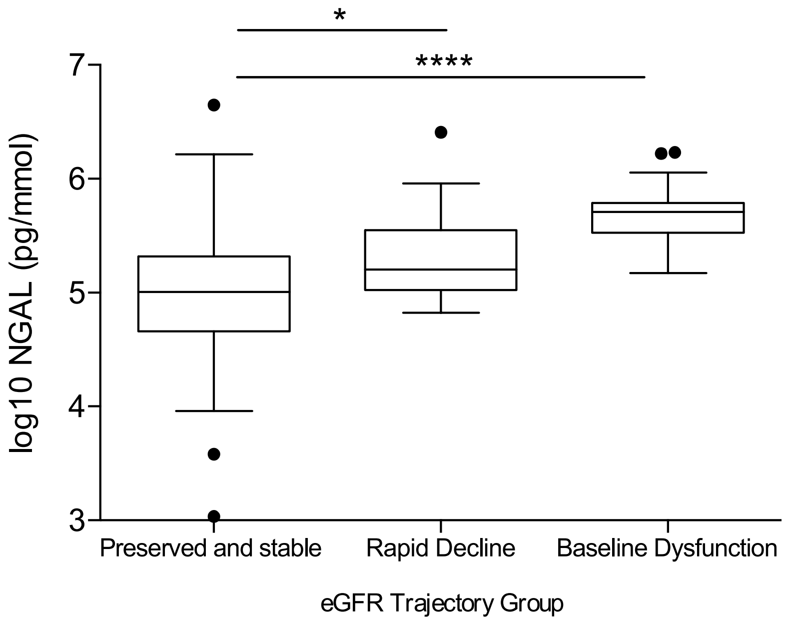
Figure 4: Box-and-whisker plot of urinary NGAL/creatinine concentrations by assigned eGFR trajectory group among male study participants. Lines: median; Boxes: interquartile range; Whiskers: 1.5x interquartile range; Dots: outlying values. Stable group, n=55; Rapid decline group, n=25; Baseline dysfunction, n=24. *P=0.031; ****P= <0.001 using ANOVA followed by Dunnett's multiple comparisons test (using stable and preserved eGFR group as reference).



A
HONDURAS
Seven communities in Chinandega department
Two communities in León department
Nueva Segovia
Jinotega
Atlántico Norte
Madriz
Estelí
Matagalpa
Chinandega
León
Boaco
Atlántico Sur
Managua
Masaya
Chontales
Carazo
Granada
Rivas
Río San Juan
80 km
40 mi
COSTA RICA
B
CENSUS
VISIT 1 Nov '14
VISIT 2 May '15
VISIT 3 Nov '15
VISIT 4 May '16
VISIT 5 Nov' 16
POPULATION: 520
aged 18-30 years
Those with self-reported CKD (n=16), hypertension (n=3) or diabetes (n=2) excluded
All men and randomly selected women (to lead to ♂:♀ ratio 3:1) invited
INVITED: 360
PARTICIPANTS: 327
(all recruited for the first time)
91% of those invited recruited at visit 1.
PARTICIPANTS: 327
(recruited: 23
follow up: 314)
93% of total cohort
97% of those invited recruited by visit 2 (total cohort n=350)
PARTICIPANTS: 319
(all follow-up)
91% of total cohort
PARTICIPANTS: 309
(all follow-up, 1 death)
88% of total cohort
PARTICIPANTS: 312
(all follow-up, 1 death)
89% of total cohort


165
150
135
120
105
90
75
60
45
30
15
0
eGFR mL/min/1.72m2
Visit 1
(pre-harvest)
Visit 2
(post-harvest)
Visit 3
(pre-harvest)
Visit 4
(post-harvest)
Visit 5
(pre-harvest)


A
B
eGFR (mL/min/1.7m²)
150
135
120
105
90
75
60
45
30
15
0
Months
0
6
12
18
24
Preserved and stable eGFR
Rapid decline in eGFR
Baseline kidney dysfunction



*
****
7
6
5
4
3
log10 NGAL (pg/mmol)
Preserved and stable
Rapid Decline
Baseline Dysfunction
eGFR Trajectory Group

Decline in kidney function among apparently healthy young adults at risk of Mesoamerican Nephropathy.

Marvin Gonzalez-Quiroz, MSc[1,2,3], Evangelia-Theano Smpokou, MSc[3], Richard J. Silverwood, PhD[4], Armando Camacho, BSc[1], Dorien Faber, MSc[5], Brenda La Rosa Garcia, BSc[3], Amin Oomatia, MBChir[3], Michael Hill, PhD[6], Jason Glaser, BSc[5], Jennifer Le Blond, PhD[7], Catharina Wesseling, PhD[8], Aurora Aragon, PhD[1], Liam Smeeth, PhD[2], Neil Pearce, PhD[2,4], Dorothea Nitsch, MD[2], Ben Caplin, PhD[3]

1. Research Centre on Health, Work and Environment, National Autonomous University of Nicaragua at León, León, Nicaragua.
2. Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK.
3. Centre for Nephrology, Division of Medicine, University College London, London, UK
4. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.
5. La Isla Network, Ada, MI, USA.
6. Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford. Oxford, UK.
7. Royal School of Mines, Imperial College London, London, UK.
8. Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

Supplementary Material

1. Supplementary Methods

Communities and population: The study was conducted in 9 rural communities in Leon and Chinandega regions of Northwest Nicaragua. Most of these communities had not previously taken part in CKD research but one had taken part in previous studies. Following engagement activities the study team enumerated the *de jure* population aged 18-30 of each village by visiting dwellings and liaison with families and community leaders. Comparison with current local government data suggests the sampling frame n=520 represented 10-15% of the total population (including children) of the area. Internal and external migration means that numbers of adults in this age range are relatively underrepresented in these rural communities.

Questionnaire data, clinical measures and water samples: We collected exposure variables using a questionnaire, the details of which are available elsewhere.[1] In addition, at the second visit, we also asked participants to report any use of glyphosate, paraquat, methomyl, and cypermethrin with assistance from a visual catalogue**.**
Questionnaire data were collected at baseline and each study visit on:
A. Demographics: age, education, household income per month, water sources, and social security status.
B. Occupational history: current occupation, history of sugarcane work ever, predominant sugarcane job if ever worked in sugarcane, current and historical banana work, previous job duration, and number of sugarcane harvests or pre-harvests worked.
C. Current occupational exposures: daily work hours, duration of breaks, location of work, experience of a hot working environment, availability of shade during work breaks, physical effort last week at work, weight loss at work.
D. Lifestyle factors: grams of alcohol consumption over the last year, smoking pack-years, liquid (water and soft drinks) intake in last 24-hours, and use of nephrotoxic medications at any time.
E. Self-reported symptoms in the last 6-months, separated into: (i) heat-related/dehydration symptoms: headache, tachycardia, muscle cramps in the arms, or legs, fever, nausea, difficulty breathing, muscle weakness, dizziness, vomiting, fainting, dysuria, dry mouth, very dark urine, very little urine, extremely tired and confusion);[2-4] (ii) self-reported weight loss (iii) self-reported diagnoses of urinary tract infection in the previous year. Original symptom questionnaire responses for the whole population are summarised in Supplementary Table 1.

Height, weight and blood pressure were measured using standard procedures and calibrated devices.

Water was collected from participants' primary water source at baseline and second visit only. Water was collected and stored in polypropylene containers at 4°C. Water hardness was calculated from the sum of calcium and magnesium cations (as calcium carbonate, in mg/L), measured using inductively coupled plasma mass-spectrometry at Imperial College London.

Urine and serum markers: All biosamples were stored at 4°C on collection, frozen at the end of the study day (-20°C, for up to 2 weeks), and then stored at -80°C following transfer to the UK. Dipstick (Siemens multistix, SG10) analysis was performed on previously frozen urine samples to assess protein, and specific gravity semi-quantitatively. Albumin was quantified using a colorimetric method with bromocresol green Albumin Assay Kit (Sigma-Aldrich, MAK124). Baseline urine samples from men, previously frozen, and stored at -80°C for 2.5 years were analysed for Neutrophil Gelatinase-Associated Lipocalin (NGAL): fifty-five randomly selected from the stable kidney function group and all of those in the rapid decliners in kidney and established renal dysfunction at baseline status groups. NGAL was measured using enzyme-linked immunoassay (ELH-Lipocalin2, RayBiotech) according to manufacturer's instructions. Albumin and NGAL were expressed as the ration to urinary creatinine measured using the Jaffe method (Sigma-Aldrich C4255).

Serum creatinine (sCr) and cystatin C (sCys) were both measured in a single batch analysis of all 1581 stored study samples at Nuffield Department of Population Health Wolfson Laboratories from the Clinical Trials Services Unit (CTSU), Oxford University, using quality control referenced to isotope dilution mass spectrometry traceable international standards. sCr was quantified using a Beckman AU680 Chemistry Analyser (Jaffe compensated method) and sCys was measured using Siemens BN ProSpec (nephelometry). Mean expanded uncertainty values: 3% at both 2.2mg/dL and 4.7mg/dL for sCr; 8% at 0.7mg/L and 6% at 2.1mg/L for sCys. The CKD EPI formula for serum creatinine - cystatin C was then used to estimate GFR.

Exposure variables: The original frequencies of self-reported symptoms (prior to recoding) are presented in Supplementary Table 1. Prior to association analyses income was recoded using the World Bank definition of poverty of an income of US $1.90/day and educational level as illiteracy or attendance at primary-level education versus attendance at secondary- or higher-level education. Current occupation was grouped into sugarcane work, other agricultural work, and other occupations/economically inactive population; predominant sugar cane role was categorised (by potential heat exposure) as (cane/seed) cutters, seeders or other roles; work breaks as <10 minutes or >10 minutes; self-reported occupational agrochemical exposure as use of any of glyphosate, paraquat, cypermethrin, or methomyl; and, the degree of physical effort in last week at work as none or slight versus moderate or hard. Lifestyle risk factors included daily alcohol consumption averaged over the last year was defined as none (0 grams for both sexes) versus any (1-60 grams for males and 1-40 grams for females), and current smoking status classified as never smokers (0 pack-years) versus light smokers (1-20 pack-years). Non-steroidal anti-inflammatory drugs use was recoded as daily or regularly versus occasionally or never. Self-reported diagnosis of urinary tract infection was also recorded. Self-reported symptoms were categorized as positive for any one heat-related/dehydration symptom, alongside fever, dysuria and self-reported weight loss.

Three variables related to fluid consumption were analysed: water sources (piped water, water from a dug well/drilled well) and total liquid intake in last 24 hours (≤5 liters/day, and >5 liters/day). Water hardness was grouped based as soft/moderately hard (0-120 mg/L), and hard/very hard (≥121 mg/L).

Additional statistical methods

Continuous variables were summarized by means and standard deviations or medians and interquartile range, and categorical variables by frequency/percentages. For the further analyses, non-normally distributed continuous variables were categorised, and ordinal variables were recoded to avoid small cell numbers (see Supplementary Table 1).

We found a multi-level linear model had poor fit with non-normally distributed residuals as eGFR trajectories clustered in sub-populations and differently between men and women. Therefore we used a growth mixture modeling (GMM) approach. We identified three subpopulations of eGFR trajectory in men and two in women, primarily by using the Bayesian Information Criterion as suggested in this setting.[5] Adjustment for season of follow-up visit did not substantially affect the estimation of eGFR trajectories so was not included in the model.

Associations between individual exposure variables and outcome were examined using probability-weighted multinomial logistic regression. Individuals' probabilities of each kidney function status were obtained from the GMM. These models were adjusted for age and educational level as these variables might confound the association between casual factors of interest and outcome. 95% confidence intervals of odds ratios that did not include unity were accepted as significant. As these association models consisted of exploratory analyses no formal adjustments for multiple testing were performed.

The original study sample of 350 was calculated to achieve 90% power to detect associations with acceleration in eGFR decline of 5.0 mL/min/1.73m^2/year in a linear model to which at least 20% of the population were exposed, at alpha 0.01. Given the change in analysis strategy we performed a post-hoc power calculation. Using a chi-squared test to detect differences in kidney function status (e.g. stable versus rapid decline) associated with an exposure (to which half the population are exposed) there would be over 80% power to detect an odds ratio of 3.8 or greater. With a non-exposed prevalence of 4.5% this reflects a similar power to detect an exposure that multiplies the risk by 3.3. This estimate is likely to be conservative as the analysis was based on a probability-weighted kidney function status, an outcome that is likely to be a more precise measure of disease spectrum than an absolute categorical grouping.

The coefficients for exposures from the poorly fitting multi-level model, with eGFR measures clustered within participants including random intercept and slope, are included as Supplementary Table 7 (for information).

Analyses were performed using Stata v14 (Stata Corp.), Prism v7 (Graphpad Software) and Mplus (Muthén & Muthén).

2. Ethics approval and consent to participate

All participants signed a written informed consent to participate in the follow-up study, in accordance to the Declaration of Helsinki. The study was approved by the bioethical review board at the Medical Faculty of UNAN-León (Ref: FWA00004523/IRB00003342), and the research ethics committee of the London School of Hygiene and Tropical Medicine (Ref: 8643/14363) in 2014.

3. Supplementary References

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4. Supplementary Tables

Supplementary Table 1. Symptoms reported over the last 6 months reported at baseline

Symptom	Overall (%) (*n*=350)	Males (*n*=263)	Females (*n*=87)
Heat-related/dehydration symptoms			
Headache (n, %)			
Yes	139 (39.7)	103 (39.2)	36 (41.4)
No	211 (60.3)	160 (60.8)	51 (58.6)
Tachycardia (n, %)			
Yes	40 (11.4)	27 (10.3)	13 (14.9)
No	310 (88.6)	236 (89.7)	74 (85.61)
Muscle cramps in the arms or legs (n, %)			
Yes	42 (12.0)	32 (12.2)	10 (11.5)
No	308 (88.0)	231 (87.8)	77 (88.5)
Muscle weakness (n, %)			
Yes	6 (1.7)	2 (0.8)	4 (4.6)
No	344 (98.3)	261 (99.2)	83 (95.4)
Fever (n, %)			
Yes	36 (10.3)	32 (12.2)	4 (4.6)
No	314 (89.7)	231 (87.8)	83 (95.4)
Nausea (n, %)			
Yes	25 (7.1)	22 (8.4)	3 (3.5)
No	325 (92.9)	241 (91.6)	84 (96.5)
Difficulty breathing (n, %)			
Yes	16 (4.6)	11 (4.2)	5 (5.8)
No	334 (95.4)	252 (95.8)	82 (94.2)
Dizziness (n, %)			
Yes	26 (7.4)	15 (5.7)	11 (12.6)
No	324 (92.6)	248 (94.3)	76 (87.4)
Vomiting (n, %)			
Yes	8 (2.3)	8 (3.0)	0 (0)
No	342 (97.7)	255 (97.0)	87 (100.0)
Fainting (n, %)			
Yes	7 (2.0)	5 (1.9)	2 (2.3)
No	343 (98.0)	258 (98.1)	85 (97.7)
Dysuria (n, %)			
Yes	94 (26.9)	72 (27.4)	22 (25.3)
No	256 (73.1)	191 (72.6)	65 (74.7)
Dry mouth (n, %)			
Yes	75 (21.4)	56 (21.3)	19 (21.8)
No	275 (78.6)	207 (78.7)	68 (78.2)
Very dark urine (n, %)			
Yes	21 (6.0)	12 (4.6)	9 (10.3)
No	329 (94.0)	251 (95.4)	78 (89.7)
Very little urine (n, %)			
Yes	30 (8.6)	16 (6.1)	14 (16.1)
No	320 (91.4)	247 (93.9)	73 (83.9)
Extremely tired (n, %)			
Yes	29 (8.3)	19 (7.2)	10 (11.5)
No	321 (91.7)	244 (92.8)	77 (88.5)
Confusion (n, %)			
Yes	12 (3.4)	8 (3.0)	4 (4.6)
No	338 (96.6)	255 (97.0)	83 (95.4)

.

Supplementary Table 2. Baseline demographic, lifestyle characteristics of male study participants, stratified by assigned eGFR trajectory group* (n=263)

Characteristic	Preserved and stable kidney function (*n*=213)	Rapid decline in eGFR (*n*=25)	Dysfunction at baseline (*n*=25)
Age, years; mean (SD)	23.6 (3.8)	23.3 (3.6)	25.4 (2.9)
Educational level; n (%)			
Illiteracy/primary	121 (56.8)	14 (56.0)	16 (64.0)
Secondary/higher	92 (43.2)	11 (44.0)	9 (36.0)
Body mass index; n, (%)			
Normal	176 (82.6)	18 (72.0)	21 (84.0)
Overweight/Obese	37 (17.4)	7 (28.0)	4 (16.0)
Systolic blood pressure mmHg; median (IQR)	118 (110 – 124)	120 (113 – 127)	126 (119 – 129)
Diastolic blood pressure mmHg; median (IQR)	69 (63 – 73)	70 (66 – 76)	74 (68 – 78)
Income; n (%)			
Poor	108 (50.7)	16 (64.0)	14 (56.0)
Not por	105 (49.3)	9 (36.0)	11 (44.0)
Family history of CKD; n (%)			
Yes	103 (48.4)	11 (44.0)	12 (48.0)
No	110 (51.6)	14 (56.0)	13 (52.0)
Alcohol consumption; n (%)			
Any	112 (52.6)	16 (64.0)	13 (52.0)
None	101 (47.4)	9 (36.0)	12 (48.0)
Smoking history; n (%)			
Light smokers	81 (38.0)	10 (40.0)	12 (48.0)
Never smokers	132 (62.0)	15 (60.0)	13 (52.0)
NSAID use; n (%)			
Daily-regularly	21 (9.9)	3 (12.0)	5 (20.0)
Never-occasionally	192 (90.1)	22 (88.0)	20 (80.0)
Water sources; n (%)			
Piped wáter	115 (54.0)	12 (48.0)	12 (48.0)
Dug well/drilled well	98 (46.0)	13 (52.0)	13 (52.0)
Water hardness; n (%)			
Soft/moderately hard	51 (23.9)	7 (28.0)	9 (36.0)
Hard/very hard	162 (76.1)	18 (72.0)	16 (65.0)
Total liquid in last 24hrs; n (%)			
≤ 5.0 litres	86 (40.4)	10 (40.0)	9 (36.0)
>5.0 litres	127 (59.6)	15 (60.0)	16 (64.0)
Current occupation; n (%)			
Sugarcane	38 (17.8)	3 (12.0)	4 (16.0)
Agricultural work	98 (46.0)	18 (72.0)	15 (60.0)
Other occupations/EIP	77 (36.2)	4 (16.0)	6 (24.0)
Main sugarcane role (if ever worked in sugarcane) (%)			
Cane/seed cutter	103 (48.4)	15 (60.0)	19 (76.0)
Seeder	39 (18.3)	5 (20.0)	3 (12.0)
Other cane Jobs	30 (14.1)	2 (8.0)	1 (4.0)
Never worked in sugarcane	41 (19.3)	3 (12.0)	2 (8.0)
Current or historical banana work; n (%)			
Yes	27 (12.9)	5 (20.0)	15 (60.0)
No	186 (87.3)	20 (80.0)	10 (40.0)
Years in sugarcane; mean (SD)	2.7±2.9	2.7±2.7	3.6±2.8
Years in agriculture; mean (SD)	4.3±4.5	4.0±3.9	5.4±4.5
Work carried out;† n (%)			
Indoors	62 (29.1)	1 (4.0)	6 (24.0)
Outdoors	151 (70.9)	24 (96.0)	19 (76.0)
Work in a hot environment;† n (%)			
Irregularly	71 (33.3)	13 (52.0)	8 (32.0)
Regular/frequently	142 (66.7)	12 (48.0)	17 (68.0)
Shade availability;† n (%)			
Yes or inside	159 (74.7)	11 (44.0)	20 (80.0)
No	54 (25.3)	14 (56.0)	5 (20.0)
Duration of breaks;† n (%)			
≤ 10 minutes	63 (29.6)	11 (44.0)	12 (48.0)
>10 minutes	150 (70.4)	14 (56.0)	13 (52.0)
Physical effort at work;‡ n (%)			
None/slight	94 (44.1)	9 (36.0)	11 (44.0)
Moderate/hard	119 (55.9)	16 (64.0)	14 (56.0)
Agrochemicals;†, § n (%)			
Yes	109 (51.2)	16 (64.0)	10 (40.0)
No	104 (48.8)	9 (36.0)	15 (60.0)
Heat/dehydration symptoms;† n (%)			
Yes	139 (65.3)	18 (72.0)	18 (72.0)
No	74 (34.7)	7 (28.0)	7 (28.0)

Characteristic	Preserved and stable kidney function (*n*=213)	Rapid decline in eGFR (*n*=25)	Dysfunction at baseline (*n*=25)
UTI diagnosis in the previous year; n (%)			
Yes	42 (19.7)	5 (20.0)	9 (36.0)
No	171 (80.3)	20 (80.0)	16 (64.0)
Weight loss;† n (%)			
Yes	42 (19.7)	7 (28.0)	6 (24.0)
No	171 (80.3	18 (72.0)	19 (76.0)
Dysuria †			
Yes	61 (28.6)	8 (32.0)	3 (12.0)
No	152 (71.4)	17 (68.0)	22 (88.0)
Fever†			
Yes	21 (9.9)	5 (20.0)	6 (24.0)
No	192 (90.1)	20 (80.0)	19 (76.0)
Baseline eGFR, mL/min/1.73m^2; median (IQR)	117.9 (107.6 - 125.4)	116.5 (102.6 - 123.8)	55.5 (49.4 - 67.5)
Second eGFR, mL/min/1.73m^2; median (IQR)	114.7 (104.5 - 122.3)	101.4 (91.2 - 108.9)	51.6 (44.6 - 64.6)
Third eGFR, mL/min/1.73m^2; median (IQR)	115.3 (104.0 - 123.1)	103.0 (85.7 - 108.9)	55.0 (43.9 - 65.7)
Fourth eGFR, mL/min/1.73m^2; median (IQR)	113.4 (105.5 - 121.6)	74.3 (62.7 - 84.3)	48.5 (39.0 - 56.8)
Final eGFR, mL/min/1.73m^2; median (IQR)	113.7 (103.8 - 121.9)	77.1 (66.6 - 84.3)	53.2 (45.0 – 59.7)

Abbreviations: CKD: Chronic Kidney Disease; NSAID: Non-steroidal anti-inflammatory drug; eGFR: estimated glomerular filtration rate using CKD EPI equation based on creatinine and cystatin c; UTI: urinary tract infection. EIP; Economically Inactive Population. Agricultural work includes all non-sugarcane agricultural work. *Participants assigned to the group with the highest probability in growth mixture model. †over the last 6-months; ‡over the last week; §Data collected at second visit. Includes glyphosate, cypermethrin, paraquat and methomyl

Supplementary Table 3. Baseline demographic, lifestyle characteristics of female study participants, stratified by assigned eGFR trajectory group* (n=87)

Characteristic	Preserved and stable eGFR (*n*=84)	Rapid decline in eGFR (*n*=3)
Age, years; mean (SD)	24.3 ± 3.6	21.7 ± 3.0
Educational level; n (%)		
Illiteracy/primary	41 (48.8)	2 (66.7)
Secondary/higher	43 (51.2)	1 (33.3)
Body mass index; n, (%)		
Normal	46 (54.8)	1 (33.3)
Overweight/Obese	38 (45.2)	2 (66.7)
Systolic blood pressure mmHg; median (IQR)	109 (102 – 117)	125 (103 – 133)
Diastolic blood pressure mmHg; median (IQR)	67 (63 – 72)	74 (67 – 75)
Income; n (%)		
Poor	50 (59.5)	1 (33.3)
Not por	34 (40.5)	2 (66.7)
Family history of CKD; n (%)		
Yes	37 (44.1)	2 (66.7)
No	47 (55.9)	1 (33.3)
Alcohol consumption; n (%)		
Any	7 (8.3)	1 (33.3)
None	77 (91.7)	2 (66.7)
Smoking history; n (%)		
Light smokers	1 (1.2)	0 (0)
Never smokers	83 (98.8)	3 (100.0)
NSAID use; n (%)		
Daily-regularly	11 (13.1)	1 (33.3)
Never-occasionally	73 (86.9)	2 (66.7)
Water sources; n (%)		
Piped wáter	45 (53.6)	2 (66.7)
Dug well/drilled well	39 (46.4)	1 (33.3)
Water hardness; n (%)		
Soft/moderately hard	28 (33.3)	2 (66.7)
Hard/very hard	56 (66.7)	1 (33.3)
Total liquid in last 24hrs; n (%)		
≤ 5.0 litres	70 (83.3)	3 (100.0)
>5.0 litres	14 (16.7)	0 (0)
Current occupation; n (%)		
Sugarcane	10 (11.9)	0 (0)
Agricultural work	6 (7.1)	1 (33.3)
Other occupations/EIP	68 (81.0)	2 (66.7)
Main sugarcane role (if ever worked in sugarcane); n (%)		
Cane/seed cutter	0 (0)	0 (0)
Seeder	21 (25.0)	0 (0)
Other cane Jobs	9 (10.7)	0 (0)
None	54 (64.3)	3 (100.0)
Current or historical banana work; n (%)		
Yes	9 (10.7)	0 (0)
No	75 (89.3)	3 (100.0)
Years in sugarcane; mean (SD)	0.6±1.7	0±0
Years in agriculture; mean (SD)	1.2±3.4	0.3±0.5
Work carried out;† n (%)		
Indoors	65 (77.4)	2 (66.7)
Outdoors	19 (22.6)	1 (33.3)
Work in a hot environment;† n (%)		
Irregularly	43 (51.2)	2 (66.7)
Regular/frequently	41 (48.8)	1 (33.3)
Shade availability;† n (%)		
Yes or inside	62 (73.8)	2 (66.7)
No	22 (26.2)	1 (33.3)
Duration of breaks;† n (%)		
≤ 10 minutes	14 (16.7)	1 (33.3)
>10 minutes	70 (83.3)	2 (66.7)
Physical effort at work;‡ n (%)		
None/slight	42 (50.0)	1 (33.3)
Moderate/hard	42 (50.0)	2 (66.7)
Agrochemicals;†, § n (%)		
Yes	12 (14.3)	0 (0)
No	72 (85.7)	3 (100.0)
Heat/dehydration symptoms;† n (%)		
Yes	63 (75.0)	2 (66.7)
No	21 (25.5)	1 (33.3)
UTI diagnosis in the previous year; n (%)		
Yes	34 (40.5)	1 (33.3)

Characteristic	Preserved and stable eGFR (*n*=84)	Rapid decline in eGFR (*n*=3)
No	50 (59.5)	2 (66.7)
Weight loss;† n (%)		
Yes	8 (9.5)	0 (0)
No	76 (90.5)	3 (100.0)
Dysuria †		
Yes	21 (25.0)	1 (33.3)
No	63 (75.0)	2 (66.7)
Fever†		
Yes	4 (4.8)	0 (0)
No	80 (95.2)	3 (100.0)
Baseline eGFR, mL/min/1.73m^2; median (IQR)	121.8 (115.8 – 127.1)	136.3 (123.3 – 136.4)
Second eGFR, mL/min/1.73m^2; median (IQR)	118.9 (109.1 – 128.2)	107.5 (91.5 – 136.7)
Third eGFR, mL/min/1.73m^2; median (IQR)	119.5 (113.0 – 126.6)	102.3 (93.1 – 108.2)
Fourth eGFR, mL/min/1.73m^2; median (IQR)	119.4 (112.7 – 124.9)	99.9 (95.9 – 108.0)
Final eGFR, mL/min/1.73m^2; median (IQR)	121.4 (112.1 – 126.6)	102.2 (102.0 – 103.1)

Abbreviations: CKD: Chronic Kidney Disease; NSAID: Non-steroidal anti-inflammatory drug; eGFR: estimated glomerular filtration rate using CKD EPI equation based on creatinine and cystatin c; UTI: urinary tract infection. EIP; Economically Inactive Population. Agricultural work includes all non-sugarcane agricultural work. *Participants assigned to the group with the highest probability in growth mixture model. †over the last 6-months; ‡over the last week; §Data collected at second visit. Includes glyphosate, cypermethrin, paraquat and methomyl

Supplementary Table 4. Occupational characteristics, heat symptoms and liquid intake at visit 2 for males recruited at the first study visit only, stratified by assigned eGFR trajectory group* (n=213)

Characteristic	Preserved and stable eGFR (n=176)	Rapid decline in eGFR (n=18)	Dysfunction at baseline (n=19)
Total liquid in last 24hrs; n (%)			
≤ 5.0 litres	18 (10.2)	2 (11.1)	2 (10.5)
>5.0 litres	158 (89.8)	16 (88.9)	17 (89.5)
Current occupation; n (%)			
Sugarcane	89 (50.6)	10 (55.6)	5 (26.3)
Agricultural work	54 (30.7)	4 (22.2)	11 (57.9)
Other occupations/EIP	33 (18.7)	4 (22.2)	3 (15.8)
Predominant sugarcane role;† n (%)			
Cane/seed cutter	32 (18.1)	9 (50.0)	4 (21.1)
Seeder	33 (18.8)	4 (22.2)	0 (0)
Other cane jobs	39 (22.2)	0 (0)	4 (21.1)
Not worked in sugarcane	72 (40.9)	5 (27.8)	11 (57.9)
Months in sugarcane;† mean (SD)	2.9±2.7	4.2±2.5	1.2±2.2
Months in agriculture;† mean (SD)	1.6±2.3	0.4±1.4	3.0±2.5
Work carried out;† n (%)			
Indoors	39 (22.2)	3 (16.7)	5 (26.3)
Outdoors	137 (77.8)	15 (83.3)	14 (73.7)
Work in a hot environment;† n (%)			
Irregularly	36 (20.5)	4 (22.2)	7 (36.8)
Regular/frequently	140 (79.5)	14 (77.8)	12 (63.2)
Shade availability;† n (%)			
Yes or inside	161 (91.5)	17 (94.4)	18 (94.7)
No	15 (8.5)	1 (5.6)	1 (5.3)
Duration of breaks;† n (%)			
≤ 10 minutes	69 (39.2)	8 (44.4)	7 (36.8)
>10 minutes	107 (60.8)	10 (55.6)	12 (63.2)
Physical effort at work;‡ n (%)			
Slight	60 (34.1)	5 (27.8)	4 (21.1)
Moderate/hard	116 (65.9)	13 (72.2)	15 (78.9)
Weight loss at work;† n (%)			
Yes	41 (23.3)	3 (16.7)	2 (10.5)
No	135 (76.7)	15 (83.3)	17 (89.5)
Heat/dehydration symptoms;† n (%)			
Yes	127 (72.2)	12 (66.7)	14 (73.7)
No	49 (27.8)	6 (33.3)	5 (26.3)
Dysuria †			
Yes	58 (32.9)	3 (16.7)	3 (15.8)
No	118 (67.1)	15 (83.3)	16 (84.2)
Fever†			
Yes	36 (20.4)	10 (55.6)	7 (36.8)
No	140 (79.6)	8 (44.4)	12 (63.2)

Abbreviations: EIP; Economically Inactive Population. Agricultural work includes all non-sugarcane agricultural work. . *Participants assigned to the group with the highest probability in growth mixture model. †Over the last 6-months; ‡over the last week;

Supplementary Table 5. Age and education level adjusted associations* of rapid decline trajectory with exposures at visit 2 among in male study participants (*n*= 213)

Characteristic	Preserved and stable eGFR (n=176)	Rapid decline in eGFR (n=18)	
	Reference	OR	**95% CI**
Alcohol consumption			
Any	1.00	1.04	0.38 to 2.78
None	1.00	Reference	Reference
Total liquid in last 24hrs			
≤ 5.0 litres	1.00	1.08	0.22 to 5.16
>5.0 litres	1.00	Reference	Reference
Current occupation			
Sugarcane	1.00	0.84	0.24 to 2.96
Agricultural work	1.00	0.59	0.13 to 2.59
Other occupations/EIP	1.00	Reference	Reference
Main sugarcane role†			
Cane/seed cutter	1.00	3.84	1.17 to 12.58
Seeder	1.00	1.59	0.38 to 6.52
Other cane Jobs	1.00	--	--
Not worked in sugarcane	1.00	Reference	Reference
Months in sugarcane†	1.00	1.20	0.98 to 1.46
Months in agriculture†	1.00	0.71	0.49 to 1.02
Work carried out[a]			
Outdoors	1.00	1.25	0.33 to 4.65
Indoors	1.00	Reference	Reference
Work in a hot environment†			
Regular/frequently	1.00	0.81	0.24 to 2.70
Irregularly	1.00	Reference	Reference
Shade availability†			
No	1.00	0.58	0.07 to 4.75
Yes or inside	1.00	Reference	Reference
Duration of breaks†			
≤ 10 minutes	1.00	1.27	0.47 to 3.42
>10 minutes	1.00	Reference	Reference
Physical effort at work‡			
Moderate/hard	1.00	1.27	0.43 to 3.77
Slight	1.00	Reference	Reference
Heat/dehydration symptoms†			
Yes	1.00	0.81	0.28 to 2.29
No	1.00	Reference	Reference
Dysuria †			
Yes	1.00	0.42	0.11 to 1.52
No	1.00	Reference	Reference
Fever†			
Yes	1.00	5.77	2.03 to 16.33
No	1.00	Reference	Reference

Abbreviations: OR: odds ratio; Agricultural work includes all non-sugarcane agricultural work. EIP: Economically Inactive Population. *Probability weighted according to results of growth mixture model; †over the last 6-months.; ‡over the last week;

Supplementary Table 6. Age and education level adjusted associations* of baseline kidney dysfunction with baseline exposures in male study participants

Characteristic	Preserved and stable eGFR	Baseline dysfunction	
	Reference	OR	95% CI
Alcohol consumption			
Any	1.00	0.85	0.36 to 1.99
None	1.00	Reference	Reference
NSAID use			
Daily/regularly	1.00	2.00	0.65 to 6.10
Never/occasionally	1.00	Reference	Reference
Water sources			
Piped water	1.00	0.74	0.32 to 1.74
Dug well/drilled well	1.00	Reference	Reference
Water hardness			
Softly/moderately hard	1.00	2.13	0.86 to 5.29
Hard/very hard	1.00	Reference	Reference
Total liquid in last 24hrs			
>5.0 litres/day	1.00	1.18	0.49 to 2.83
≤ 5.0 litres/day	1.00	Reference	Reference
Current occupation			
Sugarcane	1.00	1.82	0.46 to 7.20
Agricultural work	1.00	2.26	0.81 to 6.32
Other occupations/EIP	1.00	Reference	Reference
Main sugarcane role (if ever worked in sugarcane)			
Cane/seed cutter	1.00	3.16	0.69 to 14.47
Seeder	1.00	1.36	0.21 to 8.79
Other cane jobs	1.00	0.59	0.05 to 7.01
Never worked in sugarcane	1.00	Reference	Reference
Current or historical banana work			
Yes	1.00	9.40	3.79 to 23.30
No	1.00	Reference	Reference
Years in sugarcane	1.00	1.03	0.90 to 1.18
Years in agriculture	1.00	1.02	0.93 to 1.11
Work carried out†			
Outdoors	1.00	1.39	0.51 to 3.78
Indoors	1.00	Reference	Reference
Work in a hot environment†			
Regular/frequently	1.00	1.03	0.42 to 2.55
Irregularly	1.00	Reference	Reference
Shade availability†			
No	1.00	0.79	0.27 to 2.23
Yes or inside	1.00	Reference	Reference
Duration of breaks†			
≤ 10 minutes	1.00	2.36	1.01 to 5.55
>10 minutes	1.00	Reference	Reference
Physical effort at work‡			
Moderate/hard	1.00	1.00	0.43 to 2.33
None/slight	1.00	Reference	Reference
Agrochemicals†,§			
Yes	1.00	0.61	0.26 to 1.45
No	1.00	Reference	Reference
Heat/dehydration symptoms†			
Yes	1.00	1.22	0.47 to 3.12
No	1.00	Reference	Reference
Dysuria†			
Yes	1.00	0.33	0.09 to 1.17
No	1.00	Reference	Reference
Fever†			
Yes	1.00	2.58	0.88 to 7.54
No	1.00	Reference	Reference

Abbreviations: OR: odds ratio; NSAID: Non-steroidal anti-inflammatory drug; UTI: urinary tract infection: EIP: Economically Inactive Population. Agricultural work includes all non-sugarcane agricultural work. *Probability weighted according to results of growth mixture model; †over the last 6-months.; ‡over the last week; §Data collected at second visit, includes glyphosate, cypermethrin, paraquat and methomyl

Supplementary Table 7. Age and education level adjusted multilevel analysis of association of baseline exposures with eGFR change over follow-up in the male population*

Characteristic	n	Difference in rate of change in $eGFR_{Scr-Scys}$ (mL/min/1·73m^2/year)	95% confidence interval
Alcohol consumption			
Any	141	-0.19	-2·14 to 1·75
None	122	Reference [-1·99]	Reference
NSAID use			
Daily/regularly	29	-1.04	-4·13 to 2·04
Never/occasionally	234	Reference [-1·96]	Reference
Water sources			
Piped water	139	-0.71	-2·65 to 1·23
Dug well/drilled well	124	Reference [-1·69]	Reference
Water hardness			
Softly/moderately hard	67	-0.37	-2·58 to 1·82
Hard/very hard	196	Reference [-1·95]	Reference
Total liquid in last 24hrs			
>5.0 litres/day	85	-0.33	-2·42 to 1·74
≤ 5.0 litres/day	178	Reference [-1·97]	Reference
Current occupation			
Sugarcane	45	-0.28	-3·23 to 2·67
Agricultural work	131	-2.51	-4·65 to -0·37
Other occupations/EIP	87	Reference [-0·67]	Reference
Main sugarcane role (if ever worked in sugarcane)			
Cane/seed cutter	137	-0.25	-2·92 to 2·41
Seeder	47	-1.18	-4·44 to 2·07
Other cane jobs	33	0.04	-3·51 to 3·59
Never worked in sugaracane	46	Reference [-1·81]	Reference
Current or historical banana work			
Yes	47	0.90	-1·57 to 3·39
No	216	Reference [-2·46]	Reference
Years in sugarcane	--	-1.10	-2.03 to -0.17
Years in agriculture	--	0.11	-0.47 to 0.69
Work carried out†			
Outdoors	194	-3.08	-5·23 to -0·92
Indoors	69	Reference [0·19]	Reference
Work in a hot environment†			
Regular/frequently	171	1.17	-0·84 to 3·18
Irregularly	92	Reference [-2·82]	Reference
Shade availability†			
No	73	-3.70	-5·79 to -1·61
Yes or inside	190	Reference [-1·01]	Reference
Duration of breaks†			
≤ 10 minutes	86	-2.16	-4·22 to -0·09
>10 minutes	177	Reference [-1·37]	Reference
Physical effort at work‡			
Moderate/hard	149	-1.31	-3·25 to 0·62
None/slight	114	Reference [-1·35]	Reference
Agrochemicals†,§			
Yes	135	-1.26	-3·20 to 0·67
No	128	Reference [-1·45]	Reference
Heat/dehydration symptoms†			
Yes	175	-0.69	-2·75 to 1·35
No	88	Reference [-1·62]	Reference
Dysuria †			
Yes	72	-0.26	-2·45 to 1·92
No	191	Reference [-1·99]	Reference
Fever†			
Yes	32	-1.74	-4·71 to 1·22
No	231	Reference [-1·89]	Reference

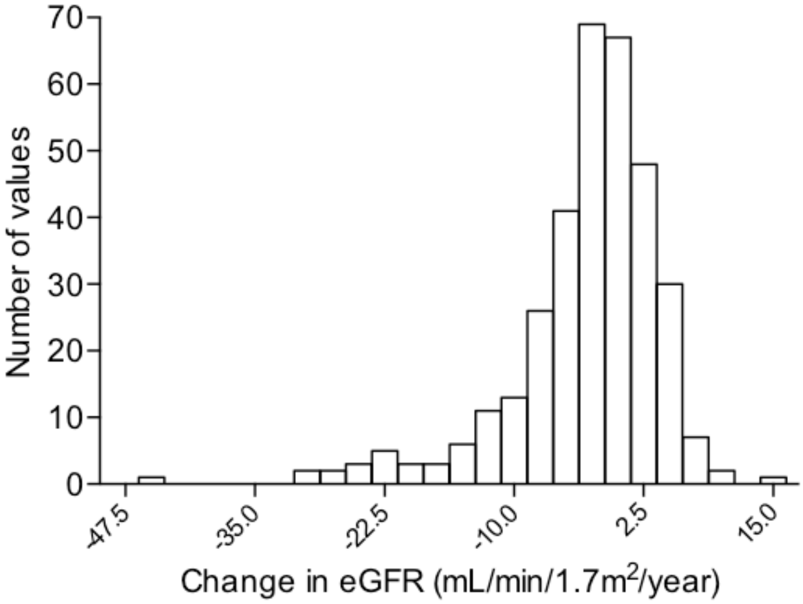
Abbreviations: NSAID: Non-steroidal anti-inflammatory drug; UTI: urinary tract infection: EIP: Economically Inactive Population. Agricultural work includes all non-sugarcane agricultural work. *Coefficients estimated from the eGFR*time interaction. Model demonstrates poor fit and provided for information only. †over the last 6-months.; ‡over the last week; §Data collected at second visit, includes glyphosate, cypermethrin, paraquat and methomyl

Supplementary Figures

Supplementary Figure 1: Distribution of eGFR trajectories in the study population. eGFR decline calcuated by ordinary least squares. The sub-group of those with rapid eGFR decline can be seen as a small but distinct group of values centring at -20mL/min/1.7m^2/year.

Supplementary Figure 2: Serum creatinine levels in the different eGFR trajectory groups over time in (A) men and (B) women.

Supplementary Figure 1



Supplementary Figure 2.