

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

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## 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.<sup>1</sup> 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);<sup>2-4</sup> (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 ratio 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 ( $\leq 5$  liters/day, and  $> 5$  liters/day). Water hardness was grouped based as soft/moderately hard (0-120 mg/L), and hard/very hard ( $\geq 121$  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.<sup>5</sup> 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<sup>2</sup>/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)
<b>Heat-related/dehydration symptoms</b>			
Headache (n, %)			
<b>Yes</b>	139 (39.7)	103 (39.2)	36 (41.4)
<b>No</b>	211 (60.3)	160 (60.8)	51 (58.6)
Tachycardia (n, %)			
<b>Yes</b>	40 (11.4)	27 (10.3)	13 (14.9)
<b>No</b>	310 (88.6)	236 (89.7)	74 (85.61)
Muscle cramps in the arms or legs (n, %)			
<b>Yes</b>	42 (12.0)	32 (12.2)	10 (11.5)
<b>No</b>	308 (88.0)	231 (87.8)	77 (88.5)
Muscle weakness (n, %)			
<b>Yes</b>	6 (1.7)	2 (0.8)	4 (4.6)
<b>No</b>	344 (98.3)	261 (99.2)	83 (95.4)
Fever (n, %)			
<b>Yes</b>	36 (10.3)	32 (12.2)	4 (4.6)
<b>No</b>	314 (89.7)	231 (87.8)	83 (95.4)
Nausea (n, %)			
<b>Yes</b>	25 (7.1)	22 (8.4)	3 (3.5)
<b>No</b>	325 (92.9)	241 (91.6)	84 (96.5)
Difficulty breathing (n, %)			
<b>Yes</b>	16 (4.6)	11 (4.2)	5 (5.8)
<b>No</b>	334 (95.4)	252 (95.8)	82 (94.2)
Dizziness (n, %)			
<b>Yes</b>	26 (7.4)	15 (5.7)	11 (12.6)
<b>No</b>	324 (92.6)	248 (94.3)	76 (87.4)
Vomiting (n, %)			
<b>Yes</b>	8 (2.3)	8 (3.0)	0 (0)
<b>No</b>	342 (97.7)	255 (97.0)	87 (100.0)
Fainting (n, %)			
<b>Yes</b>	7 (2.0)	5 (1.9)	2 (2.3)
<b>No</b>	343 (98.0)	258 (98.1)	85 (97.7)
Dysuria (n, %)			
<b>Yes</b>	94 (26.9)	72 (27.4)	22 (25.3)
<b>No</b>	256 (73.1)	191 (72.6)	65 (74.7)
Dry mouth (n, %)			
<b>Yes</b>	75 (21.4)	56 (21.3)	19 (21.8)
<b>No</b>	275 (78.6)	207 (78.7)	68 (78.2)
Very dark urine (n, %)			
<b>Yes</b>	21 (6.0)	12 (4.6)	9 (10.3)
<b>No</b>	329 (94.0)	251 (95.4)	78 (89.7)
Very little urine (n, %)			
<b>Yes</b>	30 (8.6)	16 (6.1)	14 (16.1)
<b>No</b>	320 (91.4)	247 (93.9)	73 (83.9)
Extremely tired (n, %)			
<b>Yes</b>	29 (8.3)	19 (7.2)	10 (11.5)
<b>No</b>	321 (91.7)	244 (92.8)	77 (88.5)
Confusion (n, %)			
<b>Yes</b>	12 (3.4)	8 (3.0)	4 (4.6)
<b>No</b>	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 poor	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 water	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; <sup>†</sup> n (%)			
Yes	42 (19.7)	7 (28.0)	6 (24.0)
No	171 (80.3)	18 (72.0)	19 (76.0)
Dysuria <sup>†</sup>			
Yes	61 (28.6)	8 (32.0)	3 (12.0)
No	152 (71.4)	17 (68.0)	22 (88.0)
Fever <sup>†</sup>			
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 <sup>2</sup> ; 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 <sup>2</sup> ; 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 <sup>2</sup> ; 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 <sup>2</sup> ; 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 <sup>2</sup> ; 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. <sup>†</sup>over the last 6-months; <sup>‡</sup>over the last week; <sup>§</sup>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 poor	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 water	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; <sup>†</sup> n (%)		
Yes	8 (9.5)	0 (0)
No	76 (90.5)	3 (100.0)
Dysuria <sup>†</sup>		
Yes	21 (25.0)	1 (33.3)
No	63 (75.0)	2 (66.7)
Fever <sup>†</sup>		
Yes	4 (4.8)	0 (0)
No	80 (95.2)	3 (100.0)
Baseline eGFR, mL/min/1.73m <sup>2</sup> ; median (IQR)	121.8 (115.8 – 127.1)	136.3 (123.3 – 136.4)
Second eGFR, mL/min/1.73m <sup>2</sup> ; median (IQR)	118.9 (109.1 – 128.2)	107.5 (91.5 – 136.7)
Third eGFR, mL/min/1.73m <sup>2</sup> ; median (IQR)	119.5 (113.0 – 126.6)	102.3 (93.1 – 108.2)
Fourth eGFR, mL/min/1.73m <sup>2</sup> ; median (IQR)	119.4 (112.7 – 124.9)	99.9 (95.9 – 108.0)
Final eGFR, mL/min/1.73m <sup>2</sup> ; 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. <sup>†</sup>over the last 6-months; <sup>‡</sup>over the last week; <sup>§</sup>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)**

<b>Characteristic</b>	<b>Preserved and stable eGFR (n=176)</b>	<b>Rapid decline in eGFR (n=18)</b>	<b>Dysfunction at baseline (n=19)</b>
<b>Total liquid in last 24hrs; n (%)</b>			
≤ 5.0 litres	18 (10.2)	2 (11.1)	2 (10.5)
>5.0 litres	158 (89.8)	16 (88.9)	17 (89.5)
<b>Current occupation; n (%)</b>			
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)
<b>Predominant sugarcane role;† n (%)</b>			
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)
<b>Months in sugarcane;† mean (SD)</b>	2.9±2.7	4.2±2.5	1.2±2.2
<b>Months in agriculture;† mean (SD)</b>	1.6±2.3	0.4±1.4	3.0±2.5
<b>Work carried out;‡ n (%)</b>			
Indoors	39 (22.2)	3 (16.7)	5 (26.3)
Outdoors	137 (77.8)	15 (83.3)	14 (73.7)
<b>Work in a hot environment;‡ n (%)</b>			
Irregularly	36 (20.5)	4 (22.2)	7 (36.8)
Regular/frequently	140 (79.5)	14 (77.8)	12 (63.2)
<b>Shade availability;‡ n (%)</b>			
Yes or inside	161 (91.5)	17 (94.4)	18 (94.7)
No	15 (8.5)	1 (5.6)	1 (5.3)
<b>Duration of breaks;‡ n (%)</b>			
≤ 10 minutes	69 (39.2)	8 (44.4)	7 (36.8)
>10 minutes	107 (60.8)	10 (55.6)	12 (63.2)
<b>Physical effort at work;‡ n (%)</b>			
Slight	60 (34.1)	5 (27.8)	4 (21.1)
Moderate/hard	116 (65.9)	13 (72.2)	15 (78.9)
<b>Weight loss at work;‡ n (%)</b>			
Yes	41 (23.3)	3 (16.7)	2 (10.5)
No	135 (76.7)	15 (83.3)	17 (89.5)
<b>Heat/dehydration symptoms;† n (%)</b>			
Yes	127 (72.2)	12 (66.7)	14 (73.7)
No	49 (27.8)	6 (33.3)	5 (26.3)
<b>Dysuria †</b>			
Yes	58 (32.9)	3 (16.7)	3 (15.8)
No	118 (67.1)	15 (83.3)	16 (84.2)
<b>Fever†</b>			
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
<b>Alcohol consumption</b>			
Any	1.00	1.04	0.38 to 2.78
None	1.00	Reference	Reference
<b>Total liquid in last 24hrs</b>			
≤ 5.0 litres	1.00	1.08	0.22 to 5.16
>5.0 litres	1.00	Reference	Reference
<b>Current occupation</b>			
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
<b>Main sugarcane role<sup>†</sup></b>			
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
<b>Months in sugarcane<sup>†</sup></b>	1.00	1.20	0.98 to 1.46
<b>Months in agriculture<sup>†</sup></b>	1.00	0.71	0.49 to 1.02
<b>Work carried out<sup>a</sup></b>			
Outdoors	1.00	1.25	0.33 to 4.65
Indoors	1.00	Reference	Reference
<b>Work in a hot environment<sup>†</sup></b>			
Regular/frequently	1.00	0.81	0.24 to 2.70
Irregularly	1.00	Reference	Reference
<b>Shade availability<sup>†</sup></b>			
No	1.00	0.58	0.07 to 4.75
Yes or inside	1.00	Reference	Reference
<b>Duration of breaks<sup>†</sup></b>			
≤ 10 minutes	1.00	1.27	0.47 to 3.42
>10 minutes	1.00	Reference	Reference
<b>Physical effort at work<sup>‡</sup></b>			
Moderate/hard	1.00	1.27	0.43 to 3.77
Slight	1.00	Reference	Reference
<b>Heat/dehydration symptoms<sup>†</sup></b>			
Yes	1.00	0.81	0.28 to 2.29
No	1.00	Reference	Reference
<b>Dysuria<sup>†</sup></b>			
Yes	1.00	0.42	0.11 to 1.52
No	1.00	Reference	Reference
<b>Fever<sup>†</sup></b>			
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
<b>Alcohol consumption</b>			
Any	1.00	0.85	0.36 to 1.99
None	1.00	Reference	Reference
<b>NSAID use</b>			
Daily/regularly	1.00	2.00	0.65 to 6.10
Never/occasionally	1.00	Reference	Reference
<b>Water sources</b>			
Piped water	1.00	0.74	0.32 to 1.74
Dug well/drilled well	1.00	Reference	Reference
<b>Water hardness</b>			
Softly/moderately hard	1.00	2.13	0.86 to 5.29
Hard/very hard	1.00	Reference	Reference
<b>Total liquid in last 24hrs</b>			
>5.0 litres/day	1.00	1.18	0.49 to 2.83
≤ 5.0 litres/day	1.00	Reference	Reference
<b>Current occupation</b>			
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
<b>Main sugarcane role (if ever worked in sugarcane)</b>			
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
<b>Current or historical banana work</b>			
Yes	1.00	9.40	3.79 to 23.30
No	1.00	Reference	Reference
<b>Years in sugarcane</b>	1.00	1.03	0.90 to 1.18
<b>Years in agriculture</b>	1.00	1.02	0.93 to 1.11
<b>Work carried out<sup>†</sup></b>			
Outdoors	1.00	1.39	0.51 to 3.78
Indoors	1.00	Reference	Reference
<b>Work in a hot environment<sup>†</sup></b>			
Regular/frequently	1.00	1.03	0.42 to 2.55
Irregularly	1.00	Reference	Reference
<b>Shade availability<sup>†</sup></b>			
No	1.00	0.79	0.27 to 2.23
Yes or inside	1.00	Reference	Reference
<b>Duration of breaks<sup>†</sup></b>			
≤ 10 minutes	1.00	2.36	1.01 to 5.55
>10 minutes	1.00	Reference	Reference
<b>Physical effort at work<sup>‡</sup></b>			
Moderate/hard	1.00	1.00	0.43 to 2.33
None/slight	1.00	Reference	Reference
<b>Agrochemicals<sup>†,§</sup></b>			
Yes	1.00	0.61	0.26 to 1.45
No	1.00	Reference	Reference
<b>Heat/dehydration symptoms<sup>†</sup></b>			
Yes	1.00	1.22	0.47 to 3.12
No	1.00	Reference	Reference
<b>Dysuria<sup>†</sup></b>			
Yes	1.00	0.33	0.09 to 1.17
No	1.00	Reference	Reference
<b>Fever<sup>†</sup></b>			
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 <sub>Scr-Scys</sub> (mL/min/1.73m <sup>2</sup> /year)	95% confidence interval
<b>Alcohol consumption</b>			
Any	141	-0.19	-2.14 to 1.75
None	122	Reference [-1.99]	Reference
<b>NSAID use</b>			
Daily/regularly	29	-1.04	-4.13 to 2.04
Never/occasionally	234	Reference [-1.96]	Reference
<b>Water sources</b>			
Piped water	139	-0.71	-2.65 to 1.23
Dug well/drilled well	124	Reference [-1.69]	Reference
<b>Water hardness</b>			
Softly/moderately hard	67	-0.37	-2.58 to 1.82
Hard/very hard	196	Reference [-1.95]	Reference
<b>Total liquid in last 24hrs</b>			
>5.0 litres/day	85	-0.33	-2.42 to 1.74
≤ 5.0 litres/day	178	Reference [-1.97]	Reference
<b>Current occupation</b>			
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
<b>Main sugarcane role (if ever worked in sugarcane)</b>			
<i>Cane/seed cutter</i>	137	-0.25	-2.92 to 2.41
<i>Seeder</i>	47	-1.18	-4.44 to 2.07
<i>Other cane jobs</i>	33	0.04	-3.51 to 3.59
<i>Never worked in sugarcane</i>	46	Reference [-1.81]	Reference
<b>Current or historical banana work</b>			
Yes	47	0.90	-1.57 to 3.39
No	216	Reference [-2.46]	Reference
<b>Years in sugarcane</b>	--	-1.10	-2.03 to -0.17
<b>Years in agriculture</b>	--	0.11	-0.47 to 0.69
<b>Work carried out<sup>†</sup></b>			
Outdoors	194	-3.08	-5.23 to -0.92
Indoors	69	Reference [0.19]	Reference
<b>Work in a hot environment<sup>†</sup></b>			
Regular/frequently	171	1.17	-0.84 to 3.18
Irregularly	92	Reference [-2.82]	Reference
<b>Shade availability<sup>†</sup></b>			
No	73	-3.70	-5.79 to -1.61
Yes or inside	190	Reference [-1.01]	Reference
<b>Duration of breaks<sup>†</sup></b>			
≤ 10 minutes	86	-2.16	-4.22 to -0.09
>10 minutes	177	Reference [-1.37]	Reference
<b>Physical effort at work<sup>‡</sup></b>			
Moderate/hard	149	-1.31	-3.25 to 0.62
None/slight	114	Reference [-1.35]	Reference
<b>Agrochemicals<sup>†,§</sup></b>			
Yes	135	-1.26	-3.20 to 0.67
No	128	Reference [-1.45]	Reference
<b>Heat/dehydration symptoms<sup>†</sup></b>			
Yes	175	-0.69	-2.75 to 1.35
No	88	Reference [-1.62]	Reference
<b>Dysuria<sup>†</sup></b>			
Yes	72	-0.26	-2.45 to 1.92
No	191	Reference [-1.99]	Reference
<b>Fever<sup>†</sup></b>			
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. <sup>†</sup>over the last 6-months.; <sup>‡</sup>over the last week; <sup>§</sup>Data collected at second visit, includes glyphosate, cypermethrin, paraquat and methomyl

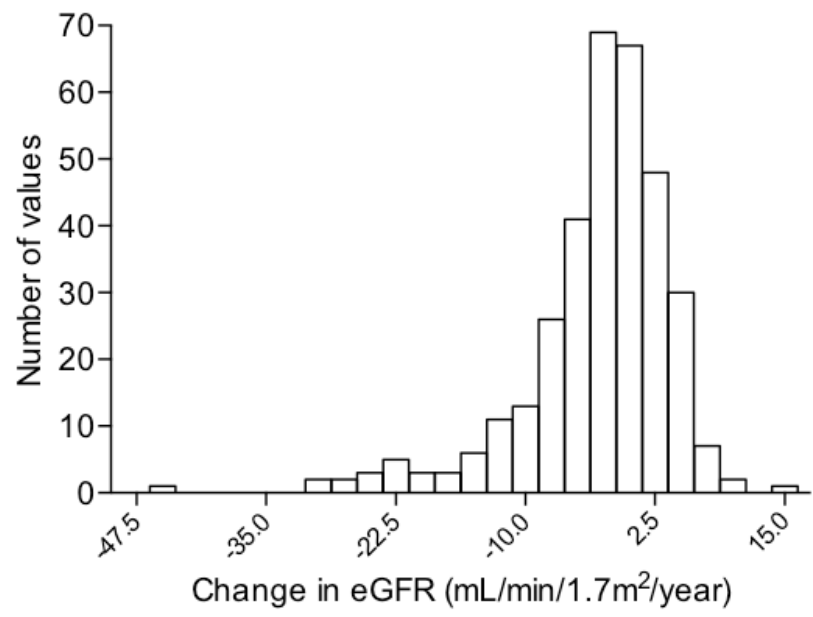
## Supplementary Figures

**Supplementary Figure 1: Distribution of eGFR trajectories in the study population.** eGFR decline calculated 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  $-20\text{mL}/\text{min}/1.7\text{m}^2/\text{year}$ .

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

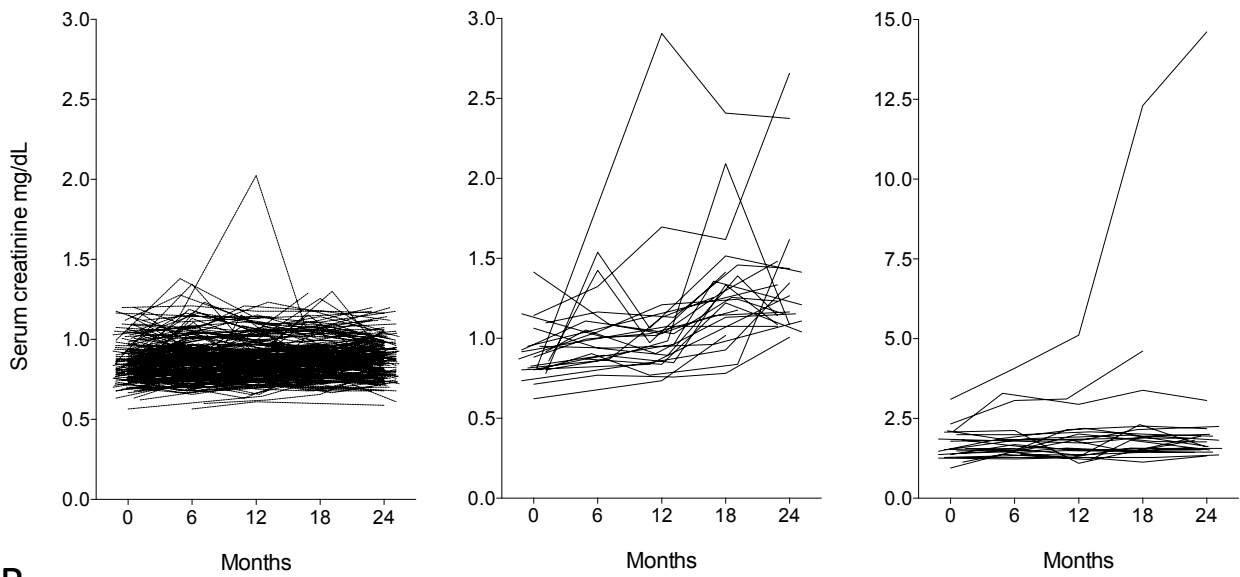


Supplementary Figure 1



Supplementary Figure 2.

A



B

