



Brigham and Women's Hospital

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Mesoamerican Nephropathy:

A Chronic Kidney Disease Epidemic in Central America

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DISCLOSURES

No relevant disclosures

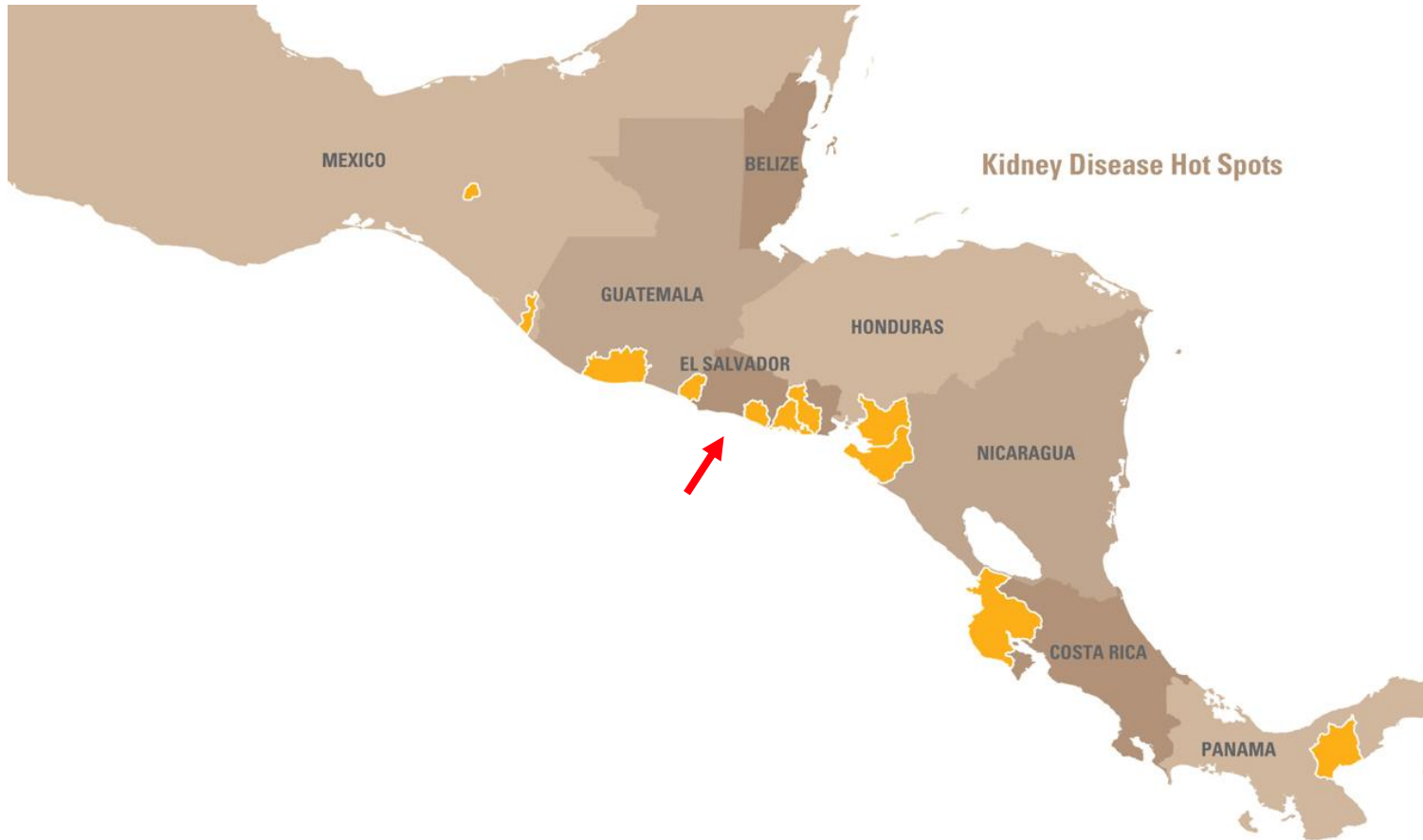
OBJECTIVES

- Understand the epidemiology, clinical characteristics, and suspected causes of Mesoamerican Nephropathy.
- Appreciate the emerging role of heat in chronic kidney disease.

Mesoamerican Nephropathy (MeN)



Mesoamerican Nephropathy (MeN)



Nefropatía terminal en pacientes de un hospital de referencia en El Salvador

Ramón García Trabanino,¹ Raúl Aguilar,² Carlos Reyes Silva,¹ Manuel Ortiz Mercado¹ y Ricardo Leiva Merino³

Rev Panam Salud Publica/Pan Am J Public Health 12(3), 2002

Diabetes: ~ 15%

HTN: ~ 7%

No diagnosis: ~ 67%



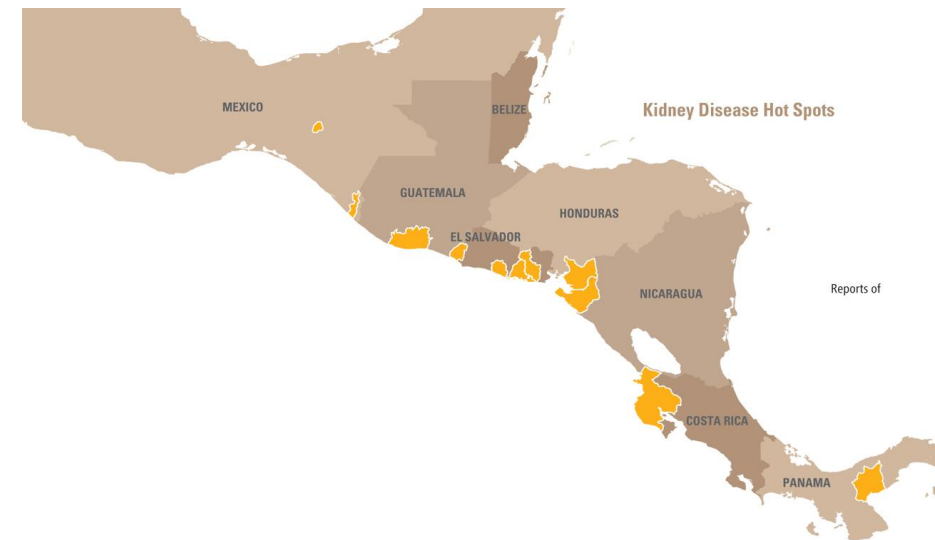
Beat the heat. Cane cutters in El Paisnal, El Salvador, start work at the break of dawn to take advantage of the cooler morning hours.

Mesoamerica's Mystery Killer

Scientists have come up with a gallery of rogues to explain an epidemic of kidney disease in Central America. But the culprit has stayed one step ahead

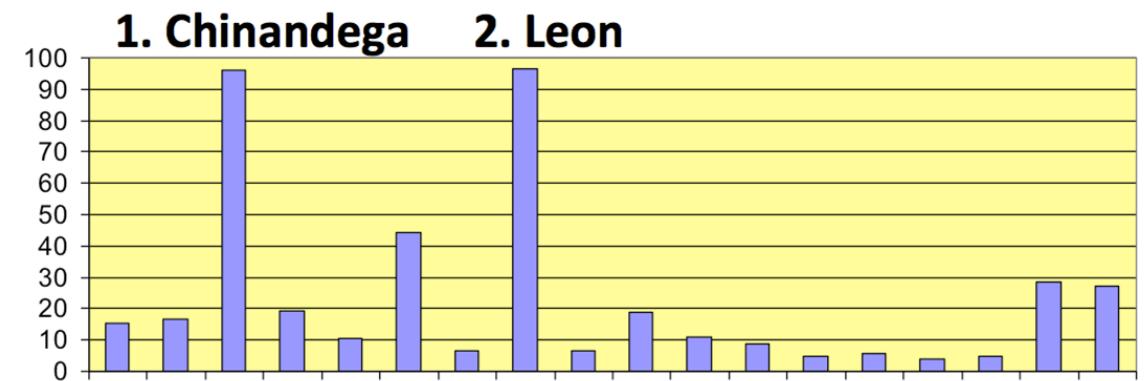
Mesoamerican Nephropathy (MeN) Demographics

- Coastal, low altitude
- Pacific vs. Caribbean
- Agricultural workers
- Other manual laborers
- Males >> Females
- 40% men in some communities



Common risk factor across countries and communities is strenuous labor in hot, humid climates

What is a hotspot?



Mortality rate/100,000 from kidney disease
in the Americas

Clinical characteristics of MeN

Consistent

Young age
No traditional risk factors
Minimal proteinuria
Small echogenic kidneys
Bx: tubulointerstitial dz
>> glomerular dz

Frequent

Hyperuricemia
Family history

Sometimes

Hyponatremia
Hypokalemia
HypoMg
Leukocyturia



Leading suspects . . .

Toxins

Agrichemicals
Aristolochia

Medications

NSAIDs
Gentamicin

Heat

Heavy Metals

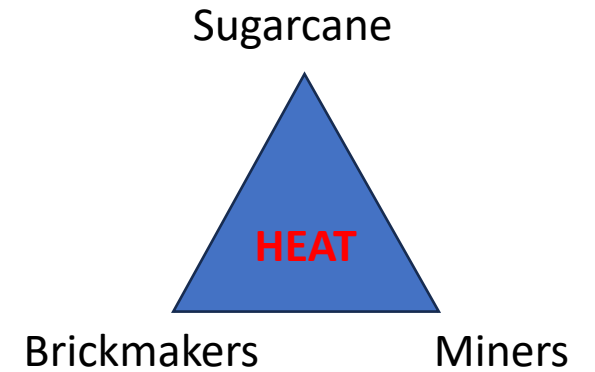
Lead
Nickel
Cadmium
Arsenic

Infectious

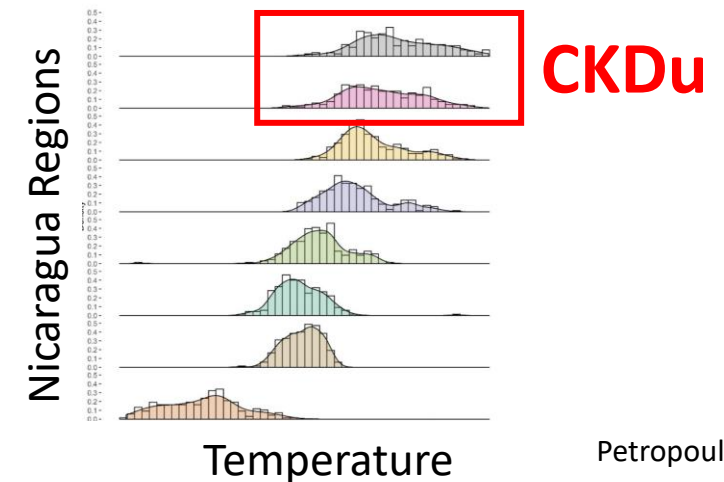
Leptospirosis, Hantavirus
(Malaria, Dengue, Zika, etc.)

Epidemiological evidence that heat causes MeN

- Heat and heat stress are the common risk factor across high-risk occupations.
- Risk of MeN highly correlated with heat stress of specific job tasks.
- Risk of MeN increases with rising temperature within regions.

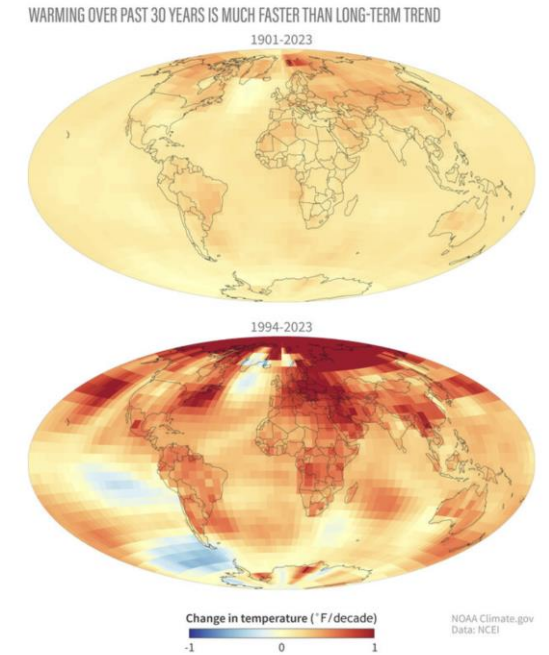
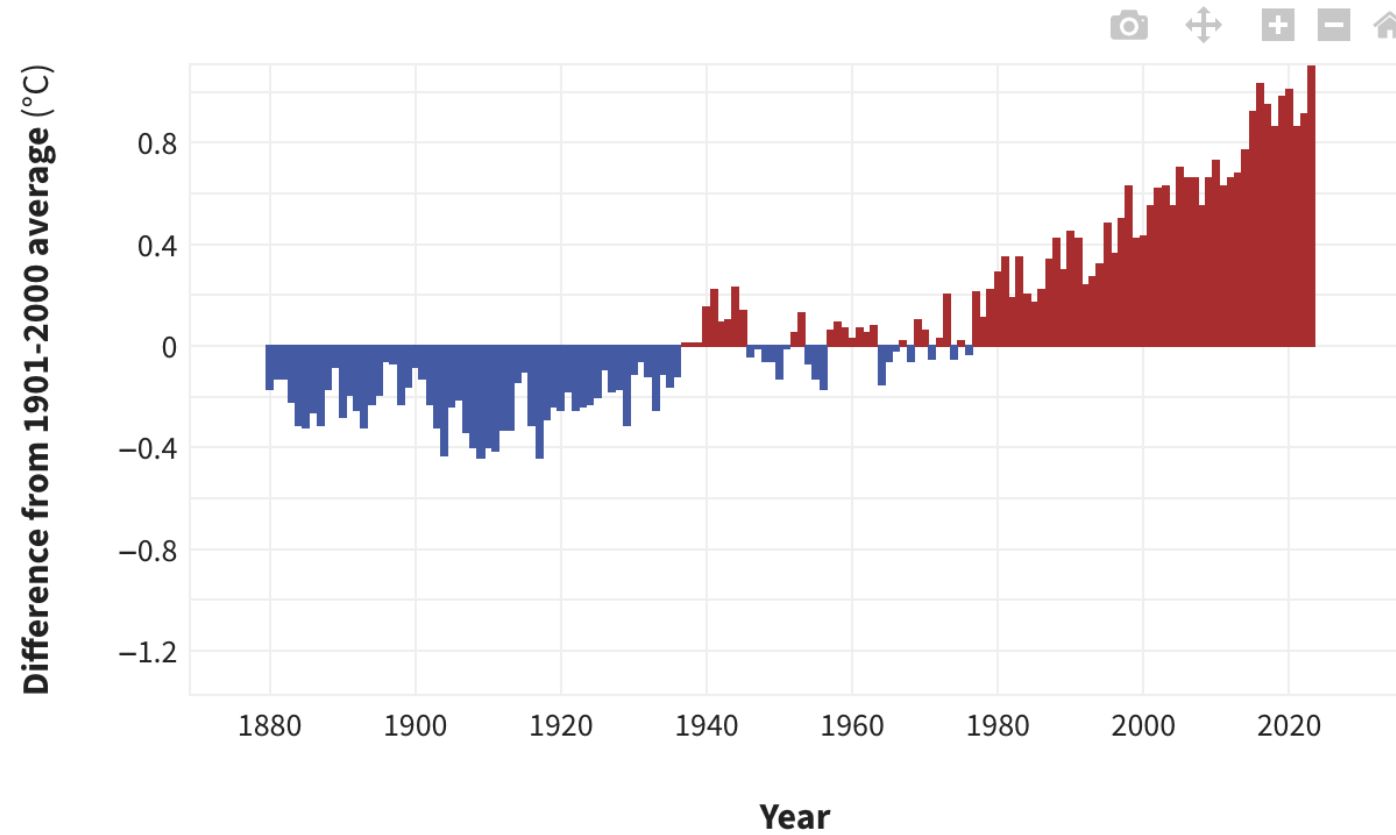


Cane Cutters >
Irrigators >
Fumigators >
Other workers



Rising temperatures worldwide

GLOBAL AVERAGE SURFACE TEMPERATURE



Heat-induced CKD in South African Miners

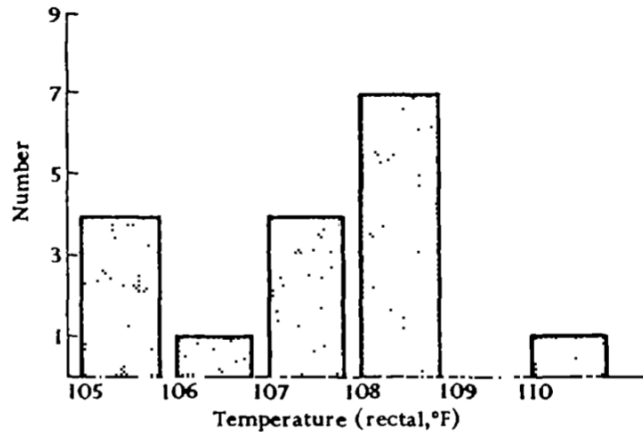


FIG. 3. The initial temperatures in 17 cases of heatstroke.

CHRONIC INTERSTITIAL NEPHRITIS AS A CONSEQUENCE OF HEATSTROKE¹

By M. C. KEW, C. ABRAHAMS, AND H. C. SEFTTEL

(From Department of Medicine, Johannesburg Hospital and University of the Witwatersrand, and South African Institute for Medical Research, Johannesburg)

CHRONIC INTERSTITIAL NEPHRITIS AFTER HEATSTROKE

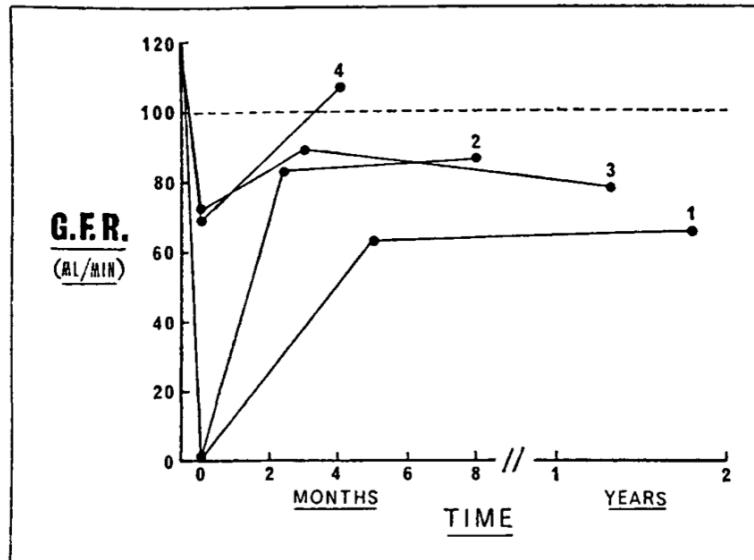


FIG. 1. Serial estimations of the glomerular filtration rates in the four patients.

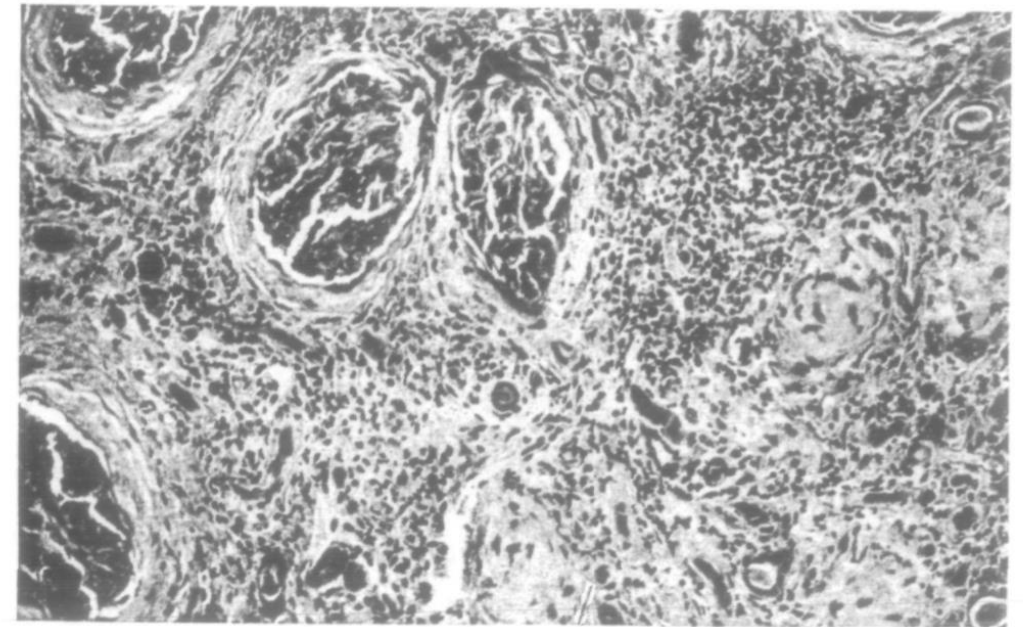


FIG. 5. Photomicrograph of third renal biopsy in *Case 1* showing a marked periglomerular fibrosis, interstitial fibrosis, round-cell infiltrate into the interstitial tissue and tubular atrophy. (Haematoxylin and eosin $\times 200$.)

Renal Plasma Flow

GFR

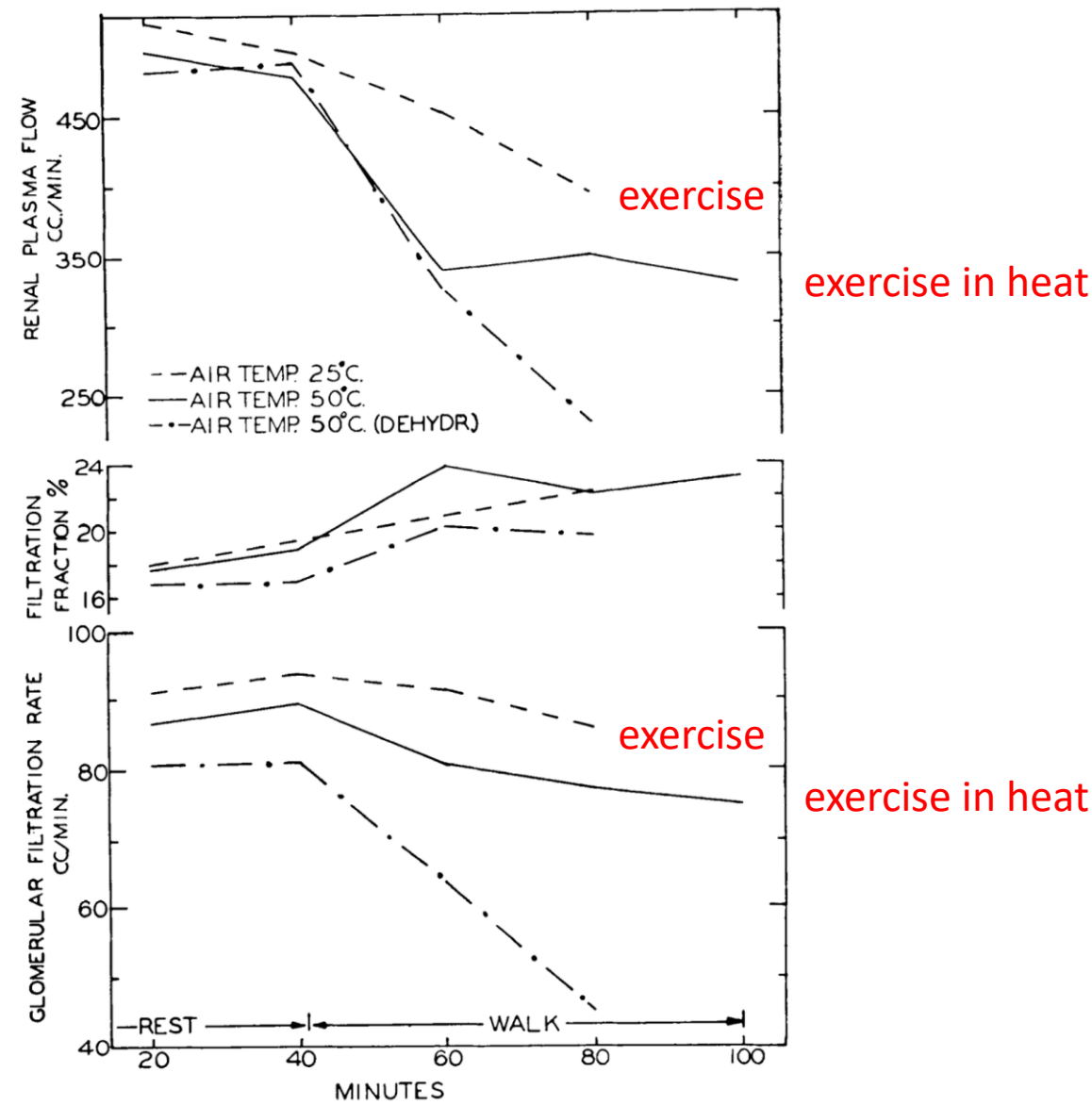


Fig. 1. EFFECT OF WORK, HEAT STRESS AND DEHYDRATION on glomerular filtration rate, renal plasma flow and filtration fraction. The data are average values of subjects S. R., D. M., R. C. and J. S., who completed all clearance periods in all experiments.

Renal Plasma Flow

GFR

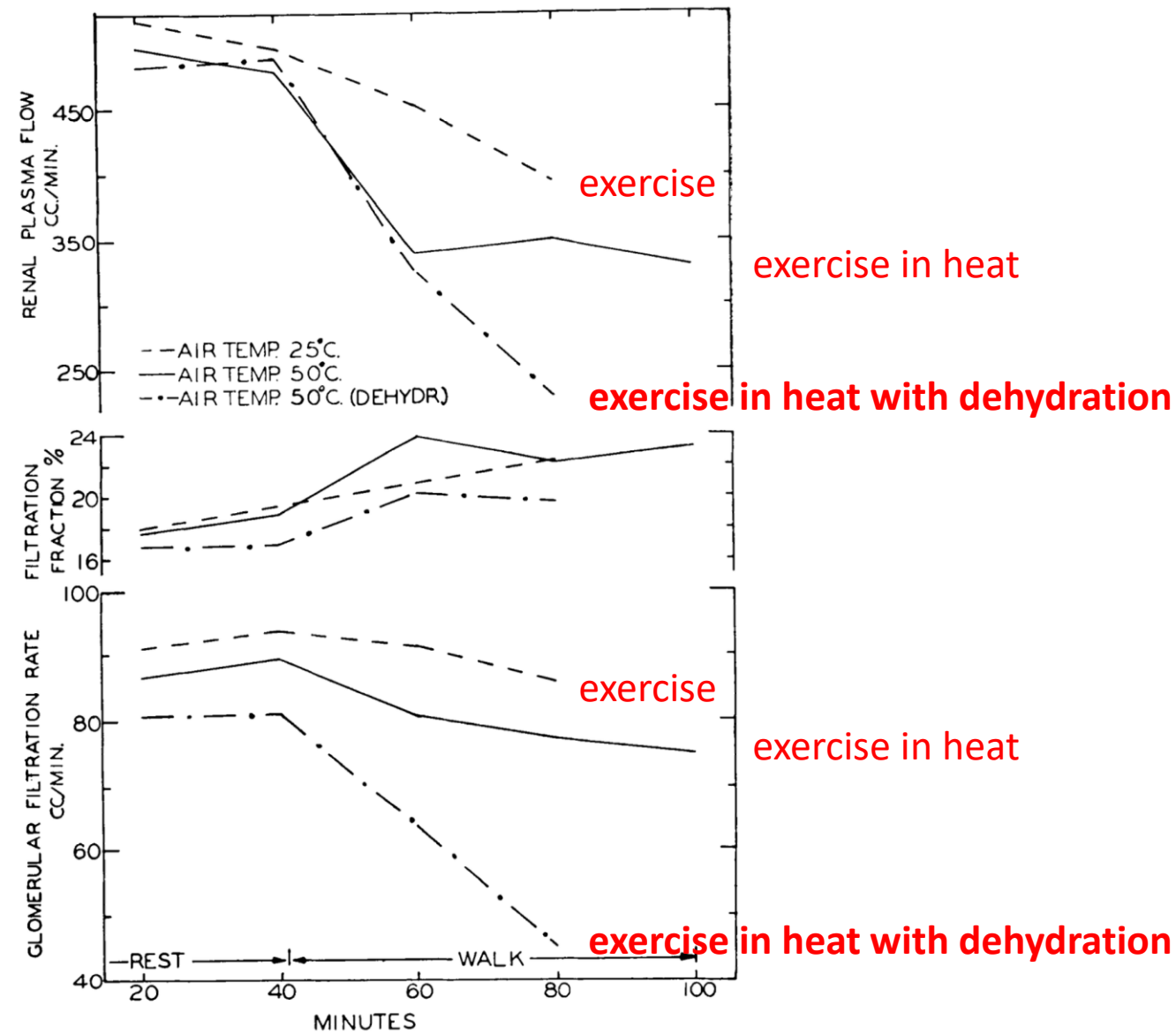


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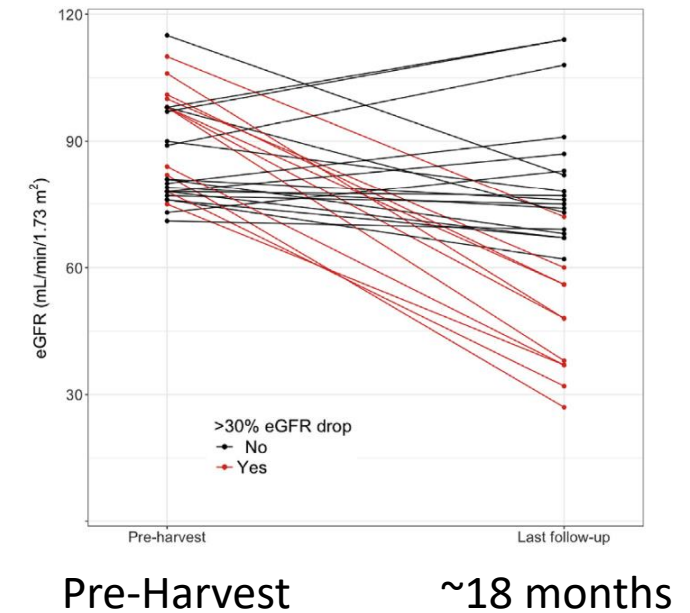
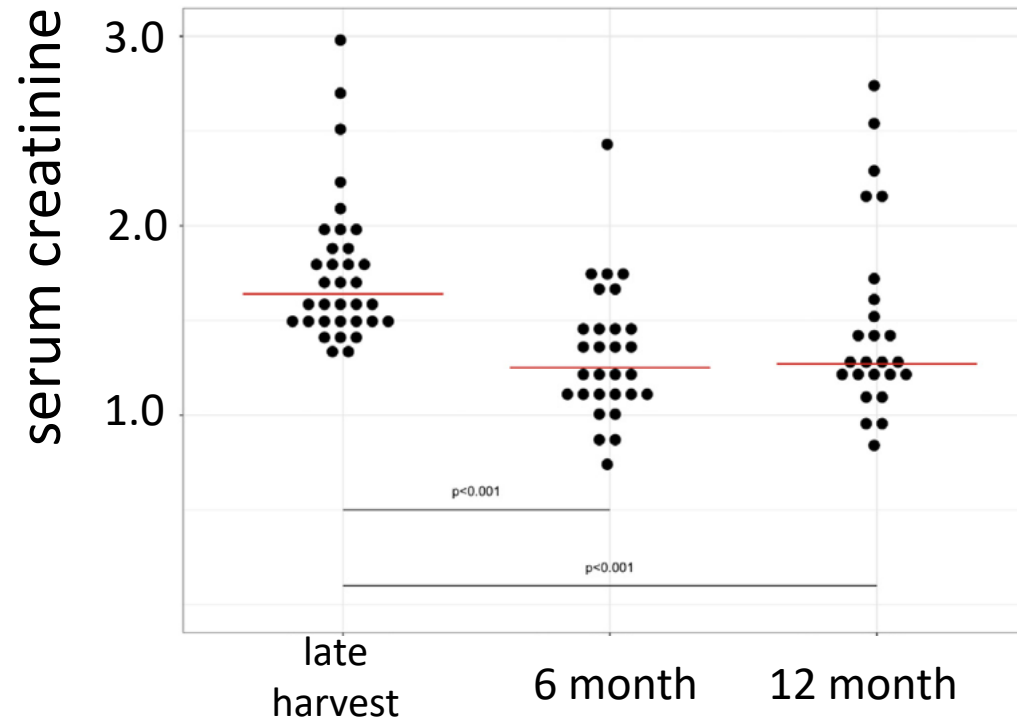
Cyclic AKI episodes

Original Investigation



Acute Kidney Injury in Sugarcane Workers at Risk for Mesoamerican Nephropathy

Joseph Kupferman,* Oriana Ramírez-Rubio,* Juan José Amador, Damaris López-Pilarte, Elissa H. Wilker, Rebecca L. Laws, Caryn Sennett, Ninoska Violeta Robles, Jorge Luis Lau, Alejandro José Salinas, James S. Kaufman, Daniel E. Weiner, Madeleine K. Scammell, Michael D. McClean, Daniel R. Brooks, and David J. Friedman



>10% of workers had acute or sub-acute kidney injury

Biopsies from Sugarcane workers with AKI

www.kidney-international.org

clinical investigation

Early detection of acute tubulointerstitial nephritis in the genesis of Mesoamerican nephropathy

Rebecca S.B. Fischer^{1,9}, Chandan Vangala^{2,9}, Luan Truong^{2,3}, Sreedhar Mandayam², Denis Chavarria⁴, Orlando M. Granera Llanes⁵, Marcos U. Fonseca Laguna⁵, Alvaro Guerra Baez⁵, Felix Garcia⁶, Ramón García-Trabanino^{7,8} and Kristy O. Murray¹

www.kidney-international.org

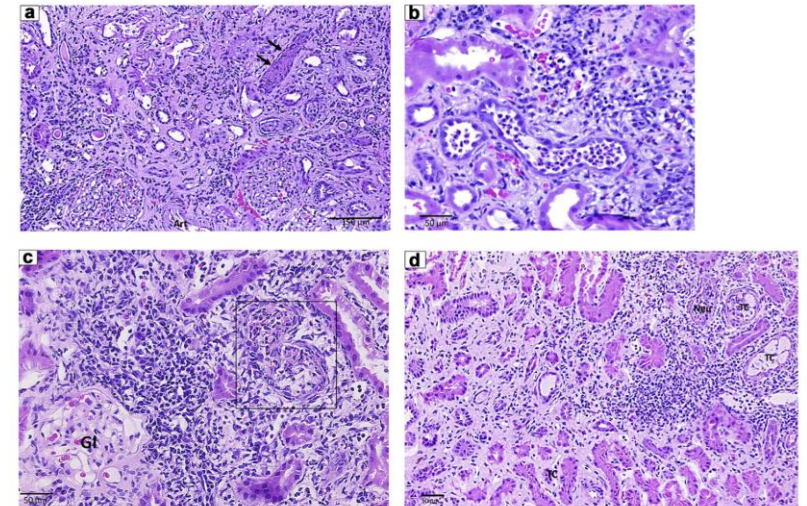
clinical investigation

Clinical markers to predict progression from acute to chronic kidney disease in Mesoamerican nephropathy

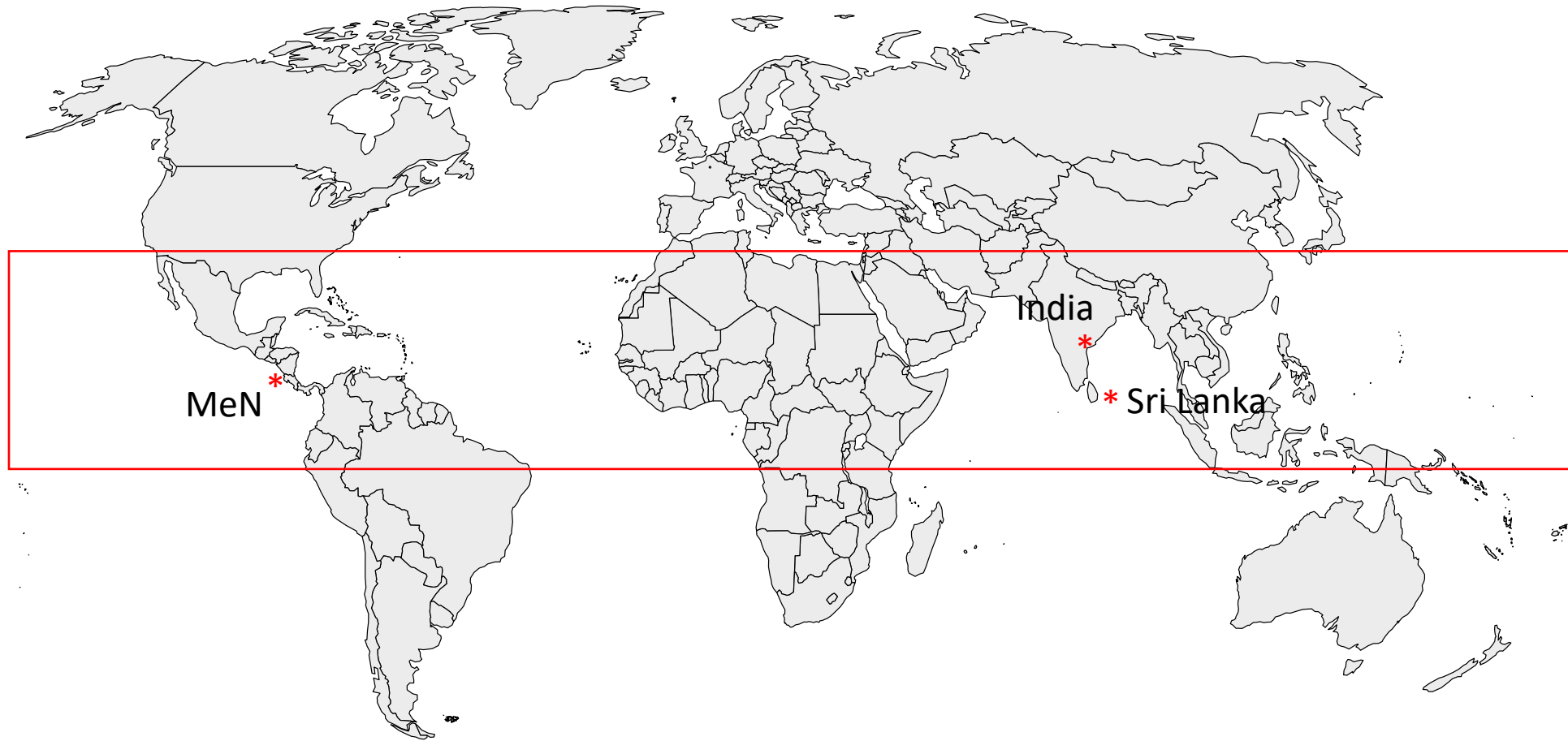
Rebecca S.B. Fischer¹, Chandan Vangala², Sreedhar Mandayam², Denis Chavarria³, Ramón García-Trabanino^{4,5}, Felix Garcia⁶, Linda L. Garcia¹ and Kristy O. Murray¹



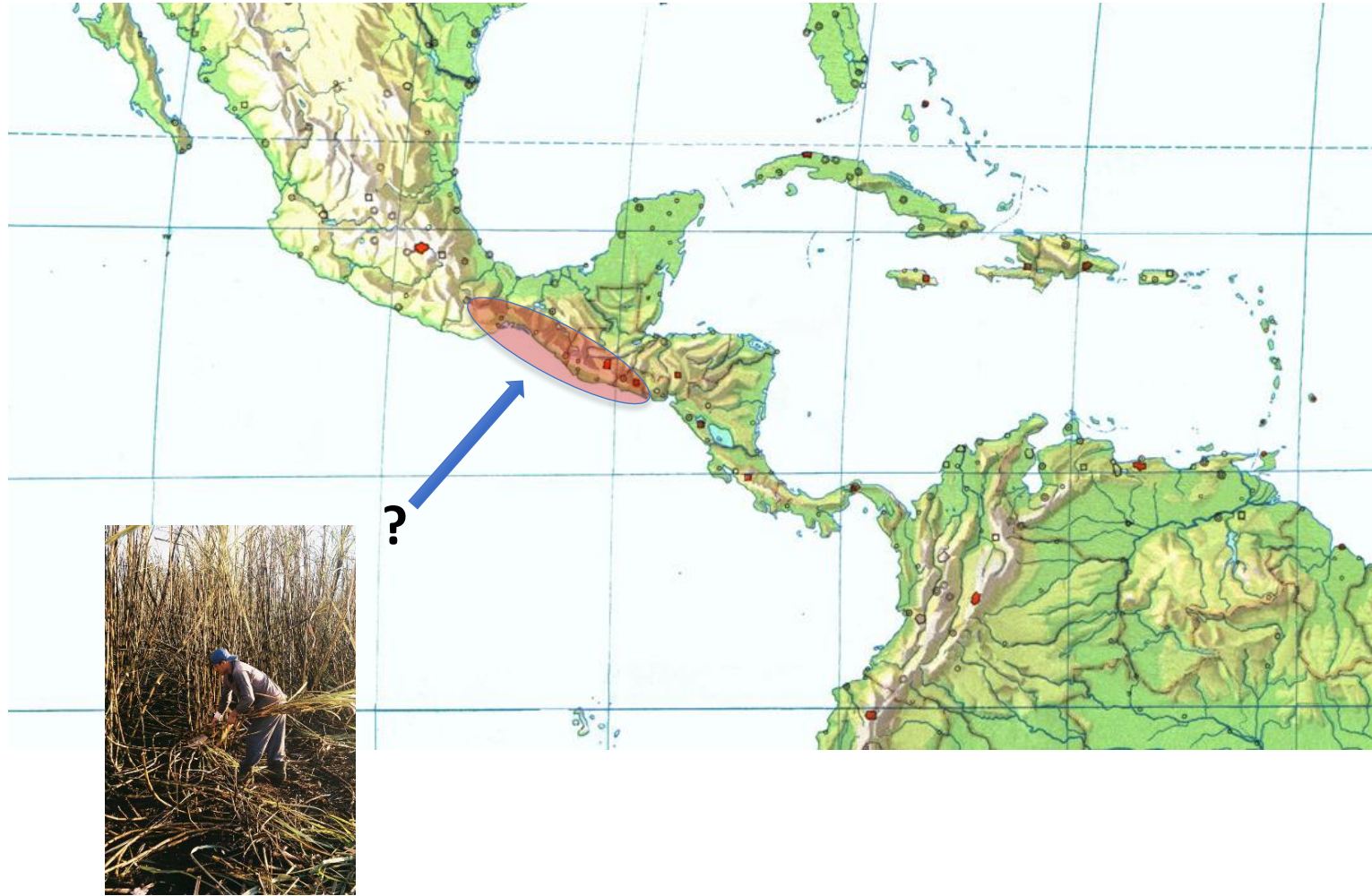
Workers present with:
Elevated Temperatures
Elevated Creatinine
Symptoms of volume loss
Sterile Urine



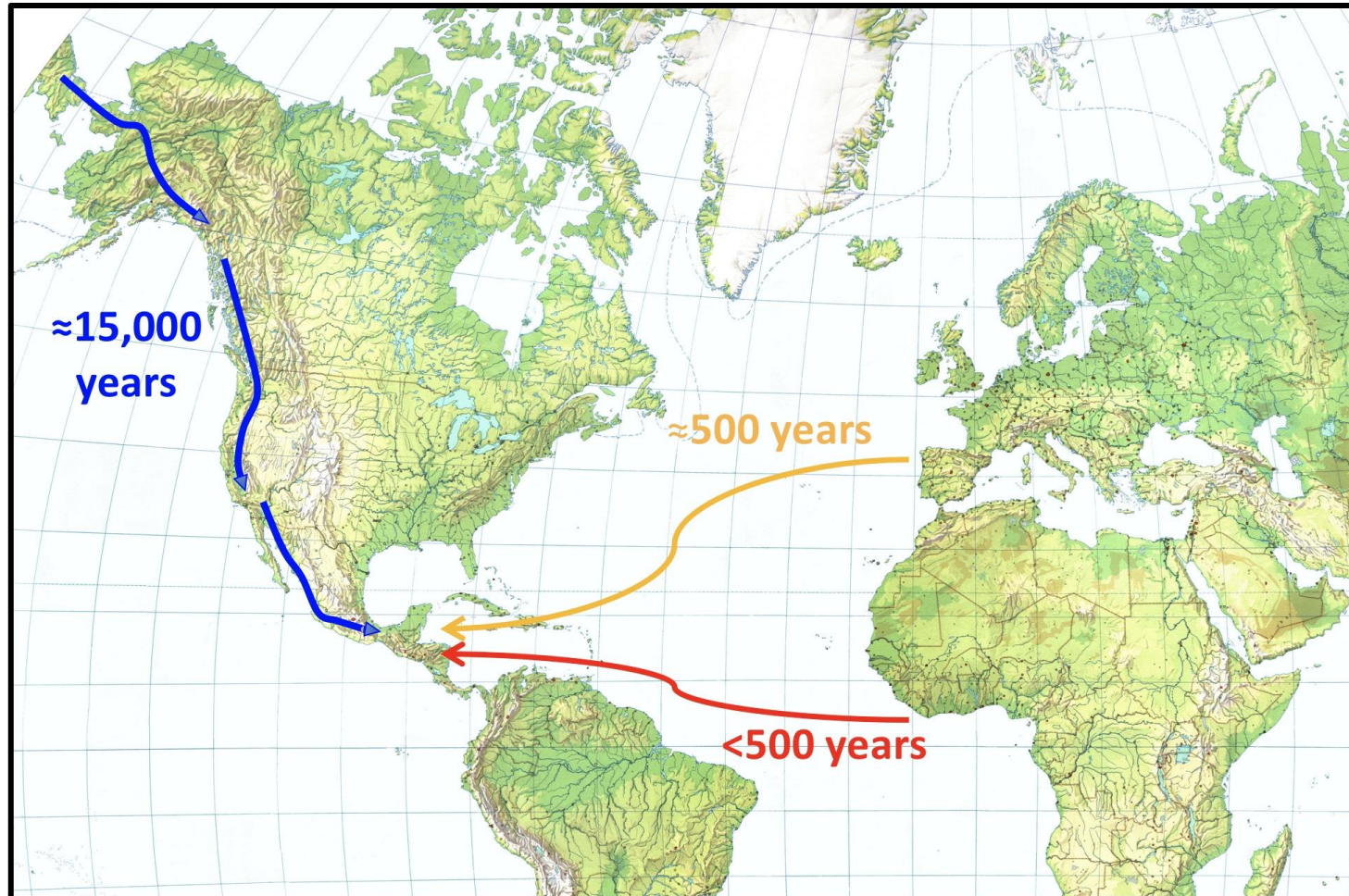
Why the restricted range of CKDu?



What is unique about this environment?



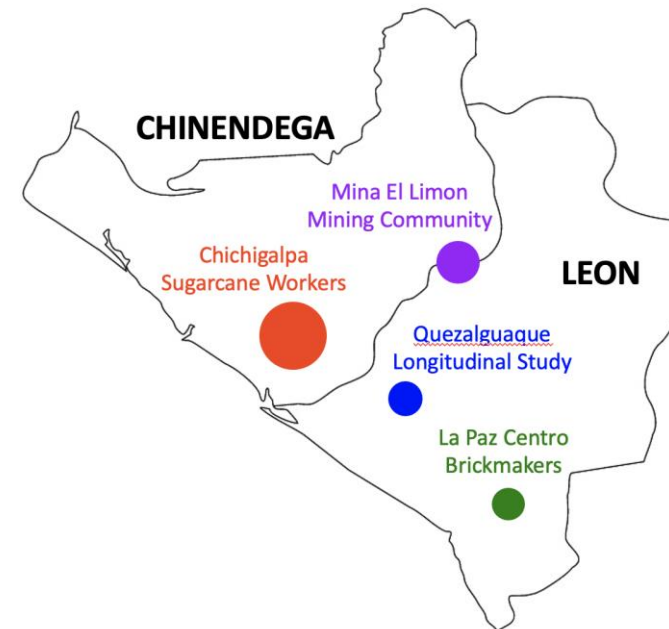
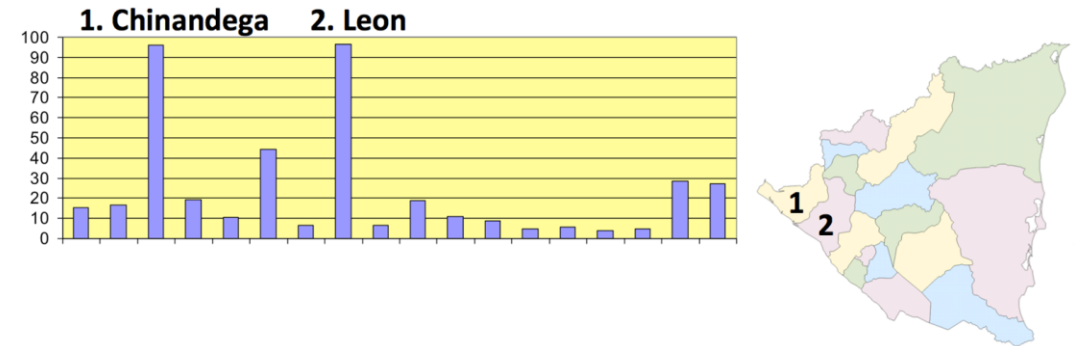
What is unique about the inhabitants?



Genetic Studies of Mesoamerican Nephropathy

Rationale:

1. People working under similar conditions and exposed to similar risk factors in many other tropical climates do not develop kidney disease at high rates
2. Hard to explain why some workers get kidney disease while others working side by side do not get kidney disease



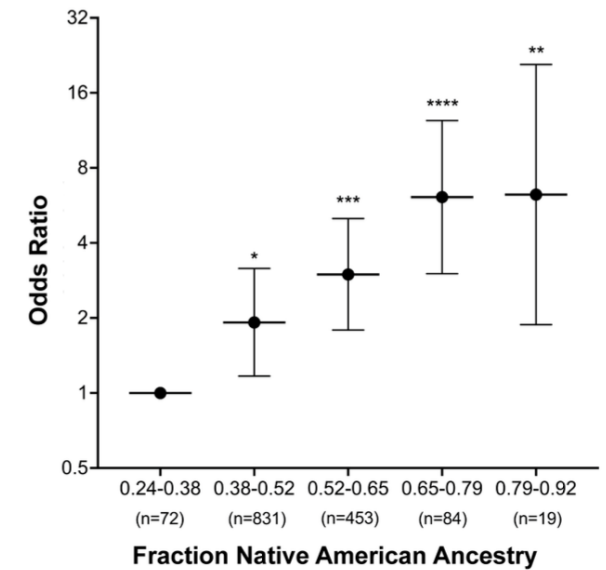
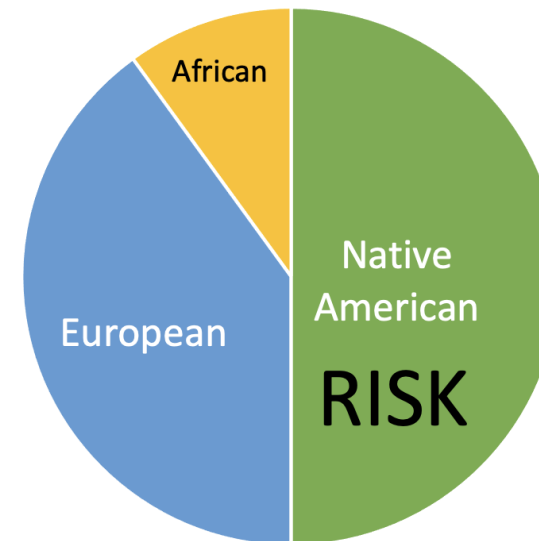
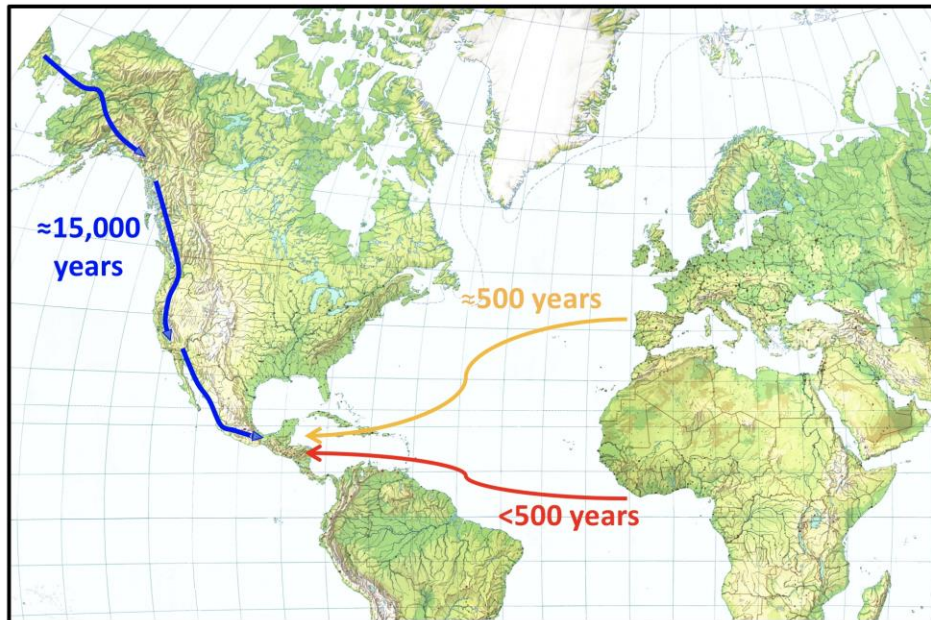
Genetic Susceptibility to Mesoamerican Nephropathy?

PNAS

RESEARCH ARTICLE | GENETICS

Genetic risk factors for Mesoamerican nephropathy

David J. Friedman^{a,b,c,1}, Dominick A. Leone^d, Juan José Amador^{d,e}, Joseph Kupferman^{a,b}, Lauren J. Francey^a, Damaris Lopez-Pilarte^e, Jorge Lau^f, Iris Delgado^g, W. Katherine Yih^{b,g,h}, Alejandro Salinas^{f,2}, Minxian Wang^c, Giulio Genovese^c, Shrijal Shah^g, Jessica Kelly^g, Calum F. Tattersfield^g, Nathan H. Raines^{a,b}, Magaly Amador^e, Leny Dias^g, Achilleas Pitsillidesⁱ, Oriana Ramirez-Rubio^{d,j}, Alda G. Amador^e, Marissa Cortopassi^k, Katie M. Applebaum^l, Seth L. Alper^{a,b,c}, Alex S. Banks^{b,k}, Michael D. McClean^m, Jessica H. Leibler^m, Madeleine K. Scammell^m, Josée Dupuis^{i,n}, and Daniel R. Brooks^{d,1}



Genetic risk factors for Mesoamerican nephropathy

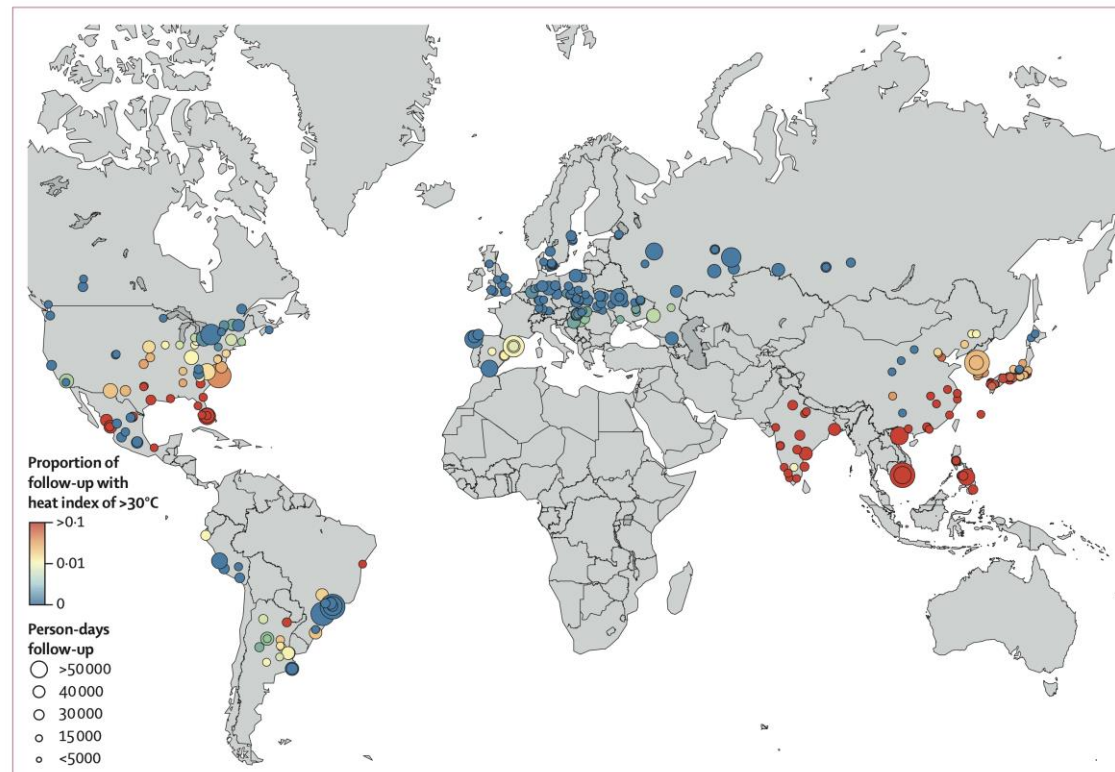
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- Genetic Variants in OPCML associated with Mesoamerican nephropathy
- OPCML is a brain gene originally described in vasopressin-secreting cells of the hypothalamus
- Protective variants associated with enhanced urine concentrating capacity among sugarcane workers
- Mouse knock-out models suggest OPCML regulates salt and water handling, temperature regulation

Ambient heat exposure and kidney function in patients with chronic kidney disease: a post-hoc analysis of the DAPA-CKD trial

Zhiyan Zhang, Hiddo J L Heerspink, Glenn M Chertow, Ricardo Correa-Rotter, Antonio Gasparrini, Niels Jongs, Anna Maria Langkilde, John J V McMurray, Malcolm N Mistry, Peter Rossing, Robert D Toto, Priya Vart, Dorothea Nitsch*, David C Wheeler*, Ben Caplin*

Lancet Planet Health 2024



Ambient heat exposure and kidney function in patients with chronic kidney disease: a post-hoc analysis of the DAPA-CKD trial

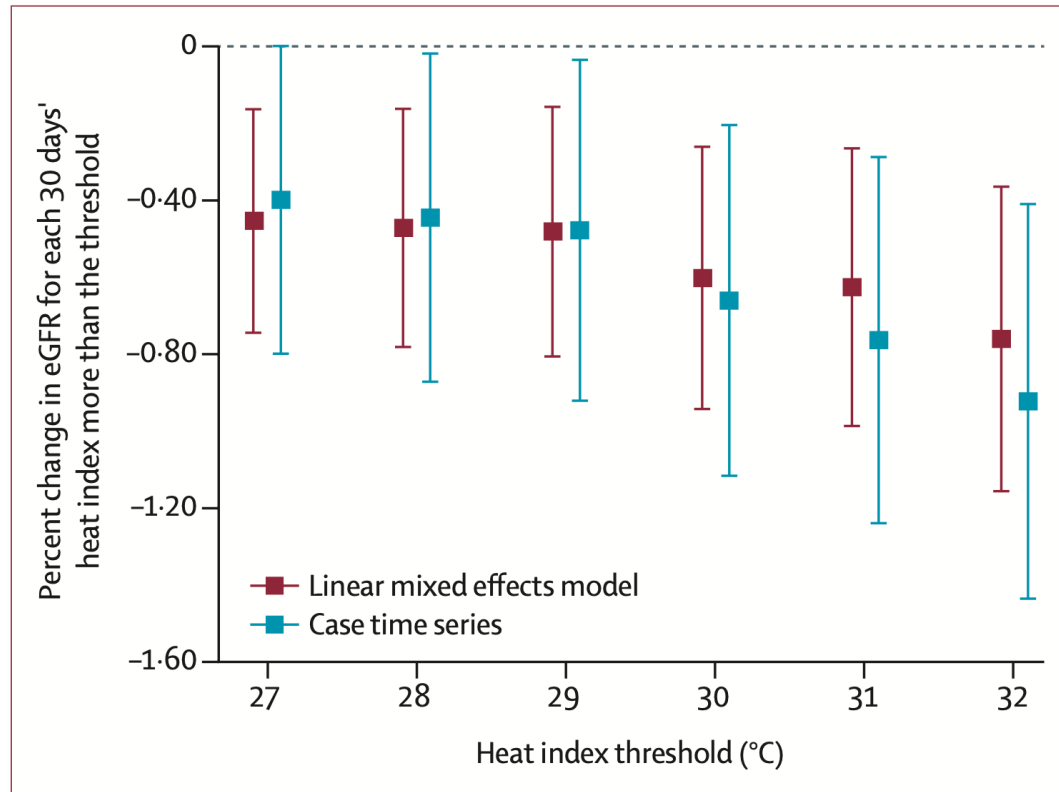


Figure 2: Association between heat index and change in eGFR at different heat index thresholds

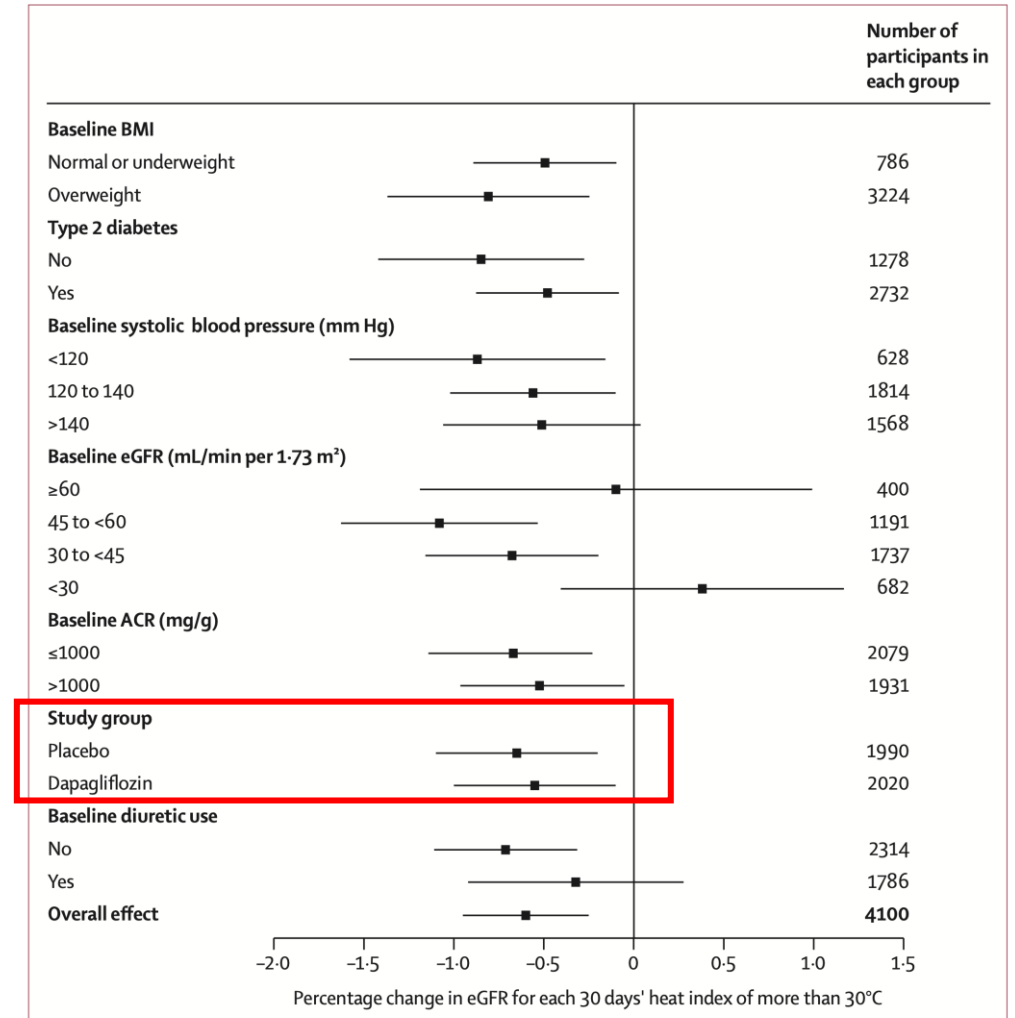
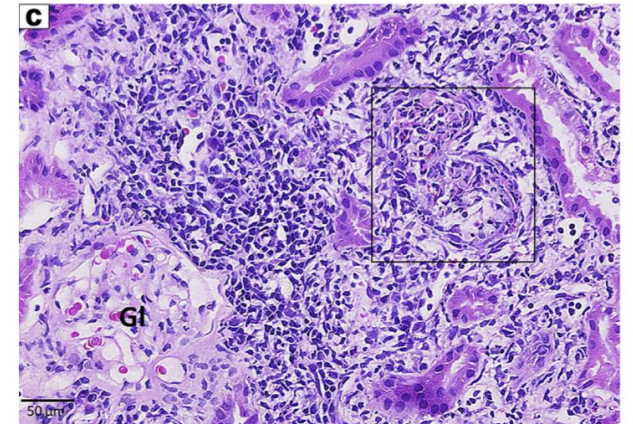
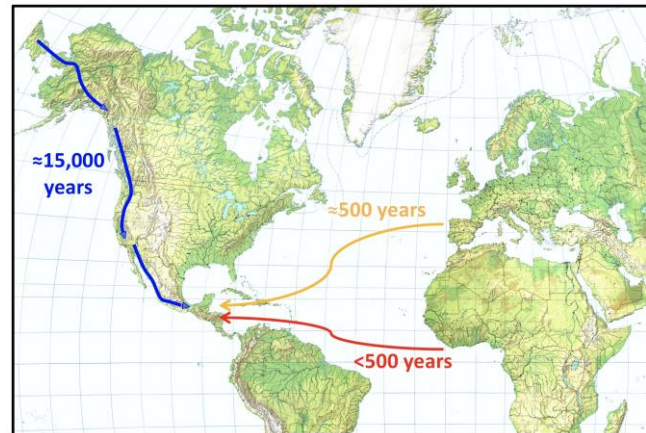


Figure 3: Associations between heat index and change in eGFR in subgroups

3.7 ml/min/year faster eGFR decline in hottest sites vs. median temperature sites

TAKE HOME MESSAGES

- MeN occurs in “hotspots” where one common element is strenuous labor in hot, humid climates
- Repetitive AKI episodes may lead to accumulated kidney injury
- Biopsies tend to show tubulointerstitial nephritis with varying degrees of inflammatory infiltrate
- There are differences in susceptibility between populations and between individuals within a population
- Other environmental factors are probably important in specific hotspots



Questions

Which feature of Mesoamerican Nephropathy is correct:

- a. Occurs about equally in males and females
- b. Associated with high grade proteinuria
- c. Hard to distinguish from diabetic nephropathy
- d. Often associated with high uric acid levels

Mesoamerican Nephropathy is one presentation of CKDu. Other major hotspots of CKDu include:

- a. Sri Lanka and India
- b. Australia and New Zealand
- c. The Balkan states
- d. South America

References

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Johnson RJ, Wesseling C, Newman LS.
NEJM 2019

Genetic Risk Factors for Mesoamerican Nephropathy
Friedman D et al
PNAS 2025

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Elinder CG
J Internal Med 2025