The Double-Burden of Heat Stress and Maternal Malnutrition on Maternal-Child Health Outcomes

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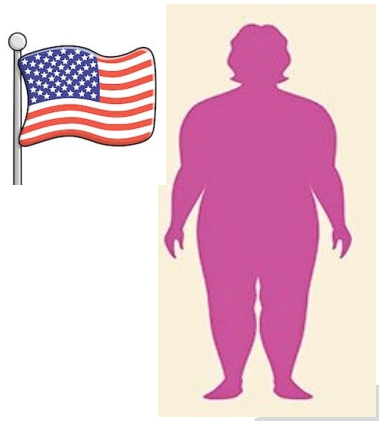
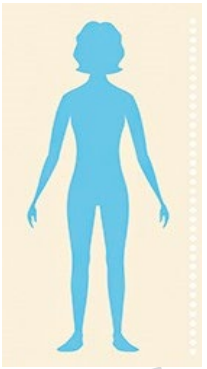
NICHD Council Meeting
January 24, 2023

Maternal Malnutrition: A Global Challenge

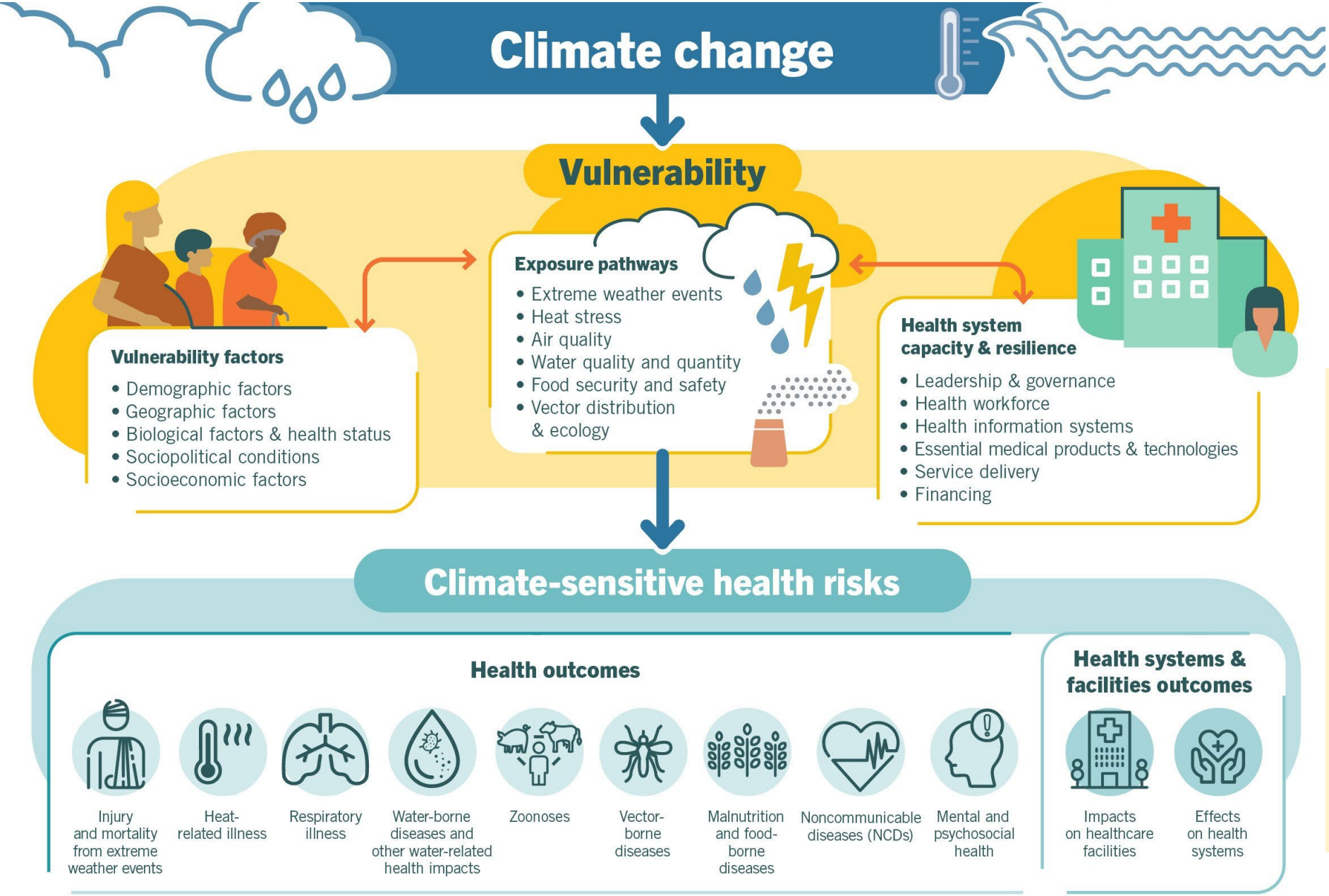
Malnutrition
- Undernutrition
- Overnutrition (Obesity)
- Micronutrient deficiencies (hidden hunger)





Undernutrition
Malnutrition
Poverty

- ~**120 million** women are underweight in LMIC
- **372 million** (> 50%) WRA with micronutrient deficiencies
- *Undernutrition→↑↑ risk of death*



Climate Change & Human Health

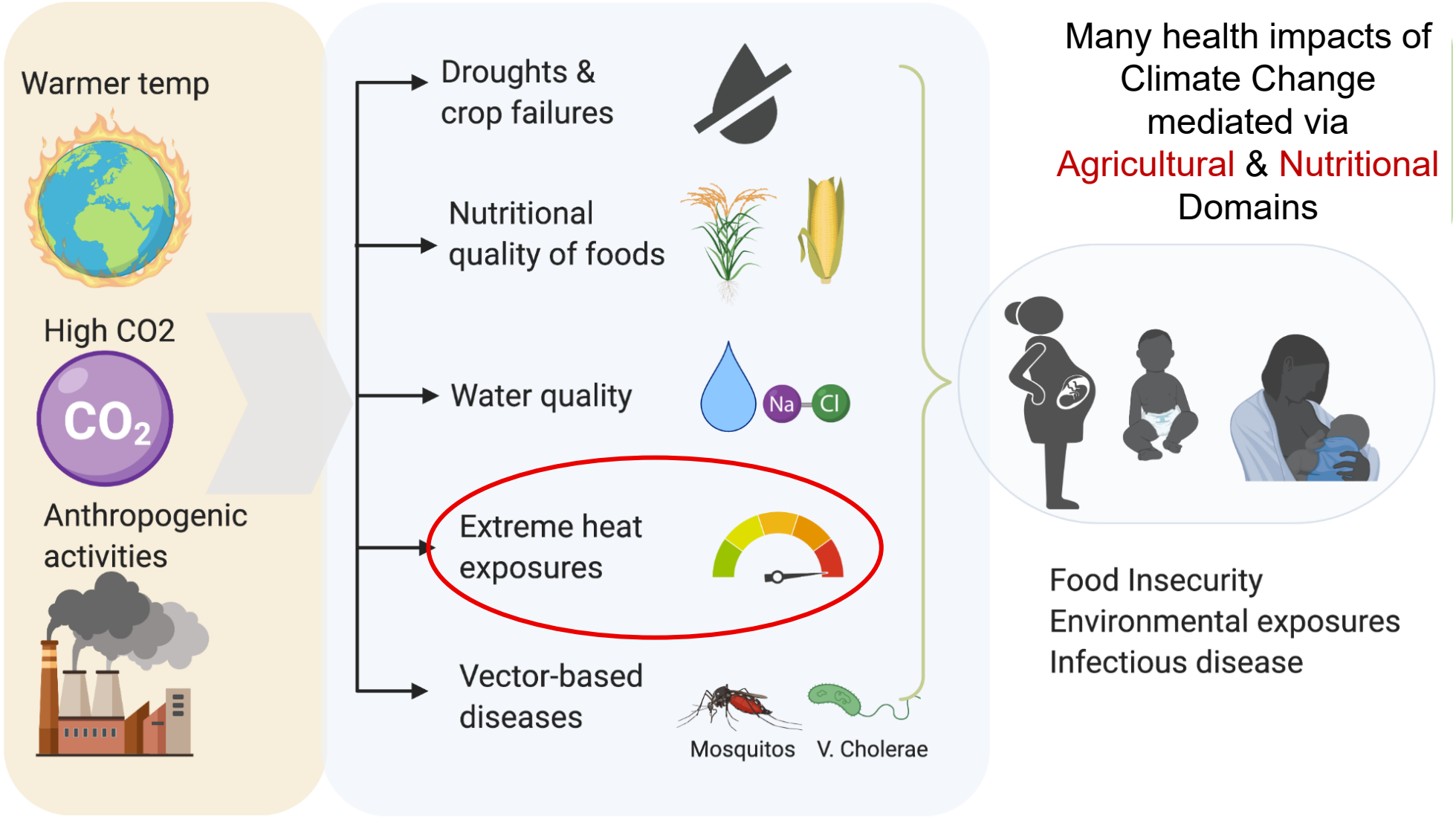
Impacts on social & environmental **determinants of health**

2030 – 2050 climate change → **~250,000 additional deaths/yr** malnutrition, malaria, diarrhea, & heat stress

Direct damage costs to health estimated at $2-4 B/year by 2030

WHO Climate and Health Fact Sheet

Impacts of Climate Change on Health



Intersection of Nutrition, Climate (Heat) & Health:
Translating to Research Targets

Vulnerable Populations	Health Effects/Systems	Outcomes
1000⁺days Malnourished & impoverished	• Pregnancy • Lactation • Heme/anemia • Renal function • GI - Hep • Respiratory • Immune Fxn • Inflammation	• Obstetric (HDP, PPH) • SB, PTB, SGA • Infant growth • Neurodevelop • ***Resilience***

NUTRITION – QUANTITY & QUALITY

All Children Globally Are At-Risk to Heat Stress

- Already 559 million children are exposed to high heatwave frequency*.
- In 2020, around 740 million children (1 in 3 children) lived in countries with at least 83 days/year exceeding 35°C.
- By 2050, virtually every child (~2 billion) on the planet will face more frequent heatwaves, irrespective of warming scenarios.

*>4.5 heatwaves/ year

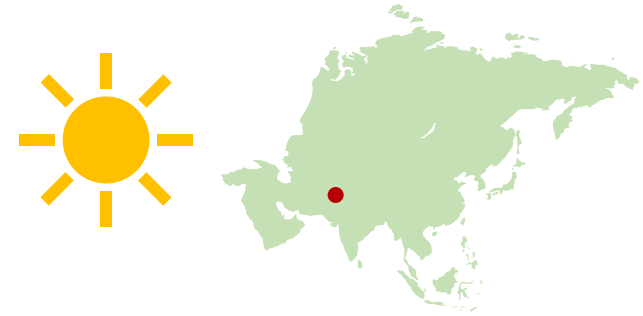
UNICEF October 2022

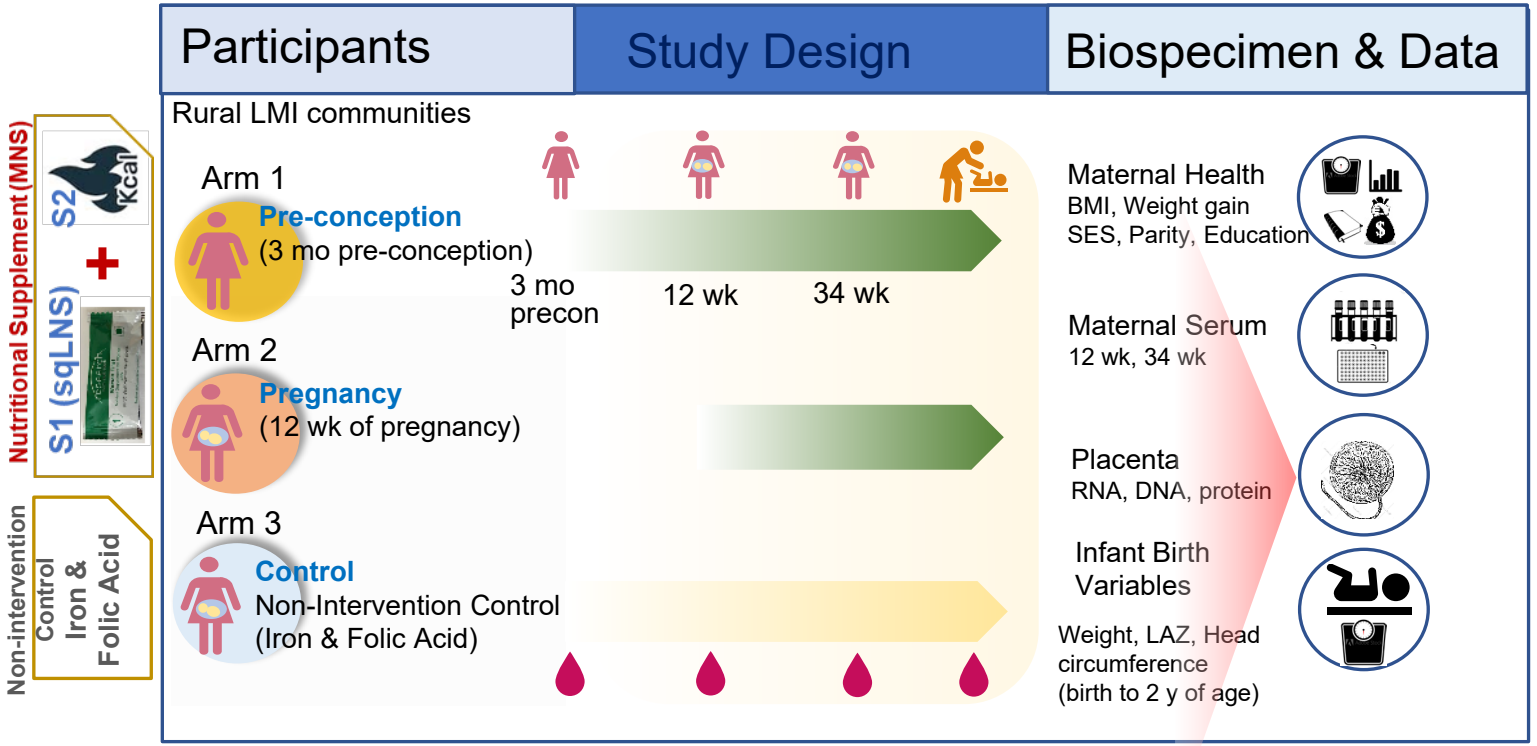
Heat Stress: Imminent Threat To Human Health

Dangerous heat takes over Midwest, Northeast

Heat waves in resource-limited settings

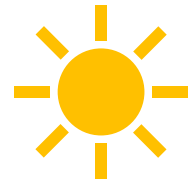
Women First Preconception Nutrition Trial





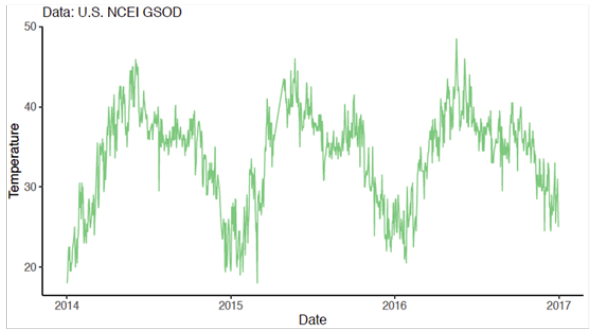
PIs: K. Michael Hambidge, MD
Nancy Krebs, MD

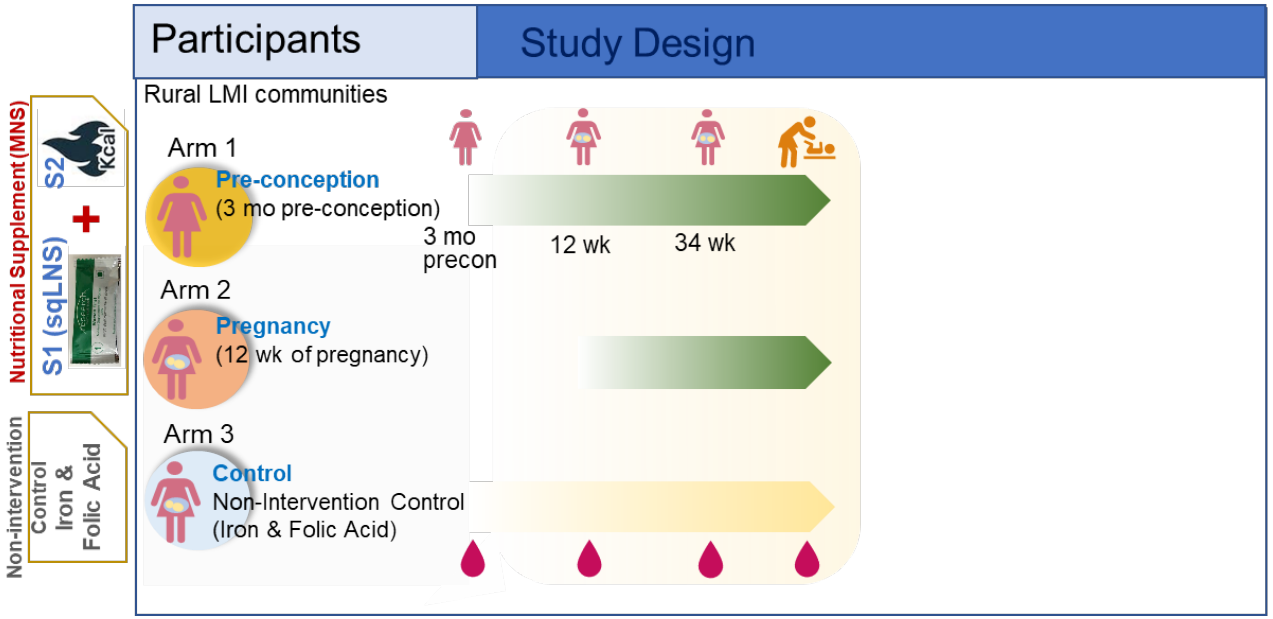
Heat Effects During Pregnancy: WF Trial



Pakistan ranks 9th highest: Children's Climate Risk Index (UNICEF)

NCEI GSOD





For each subject over pregnancy

- Avg maximal daily temperature
- Number of days when T_{max} > 39ºC (Heat stress days)
- Heat Index

Exposures

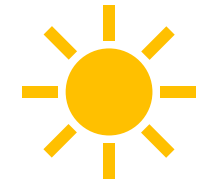
Linear regression with birth outcomes

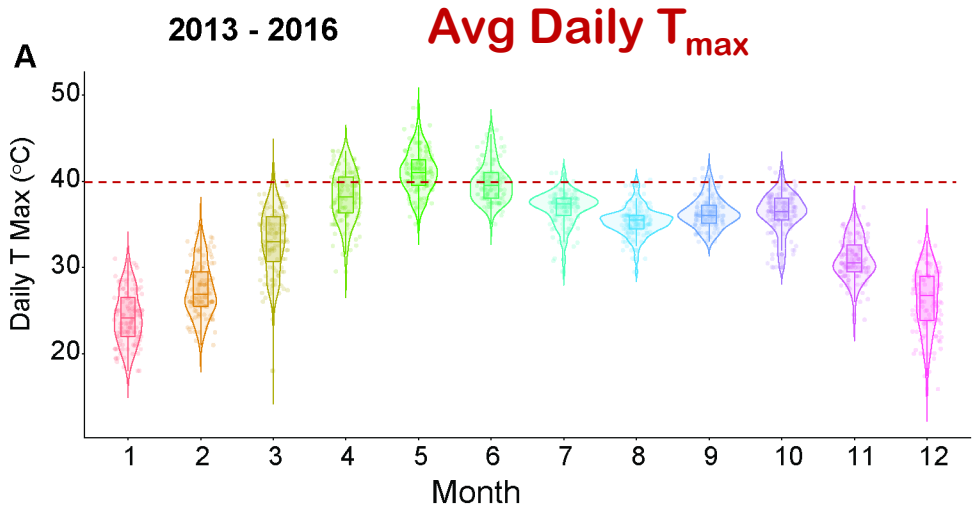
- Birth length
- Birth weight
- Head circumference

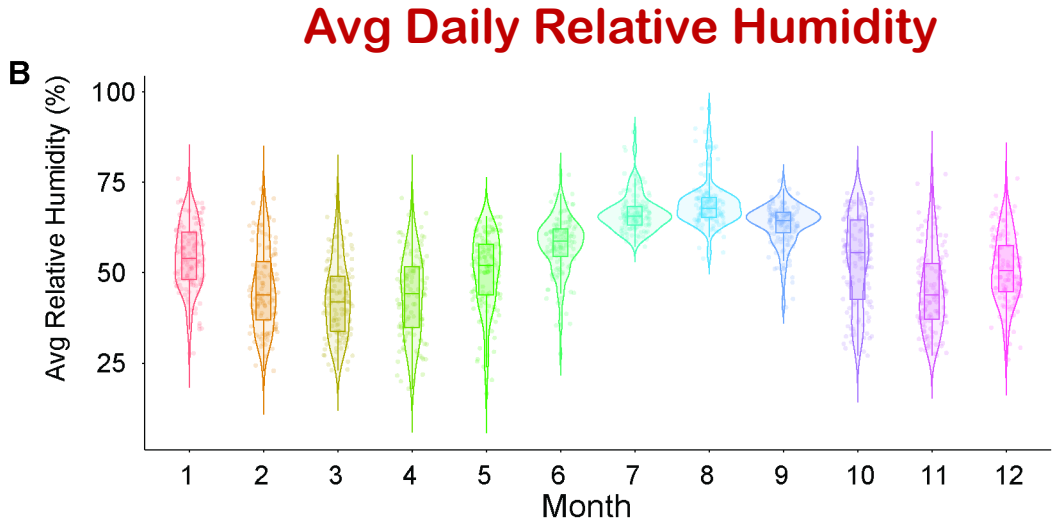
Outcomes

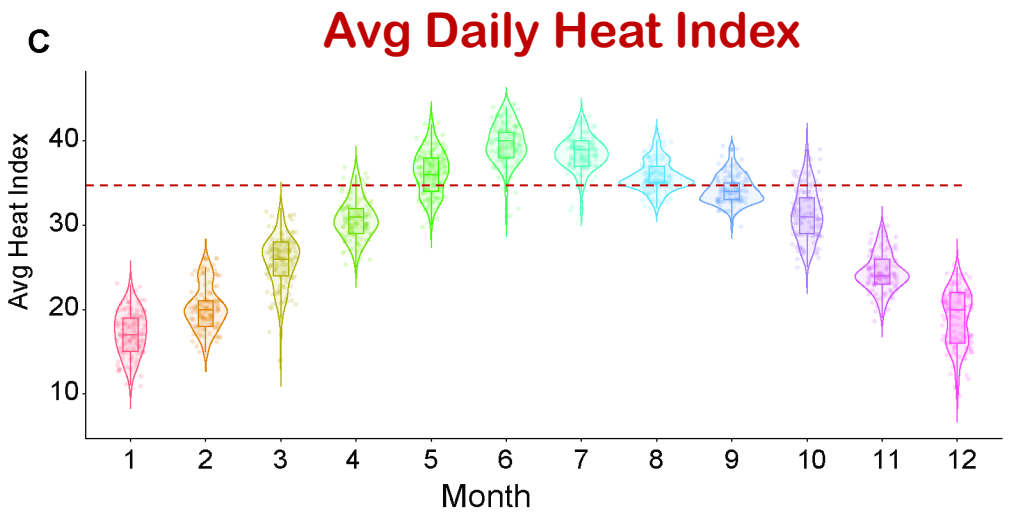
https://data.unicef.org/resources/childrens-climate-risk-index-report/

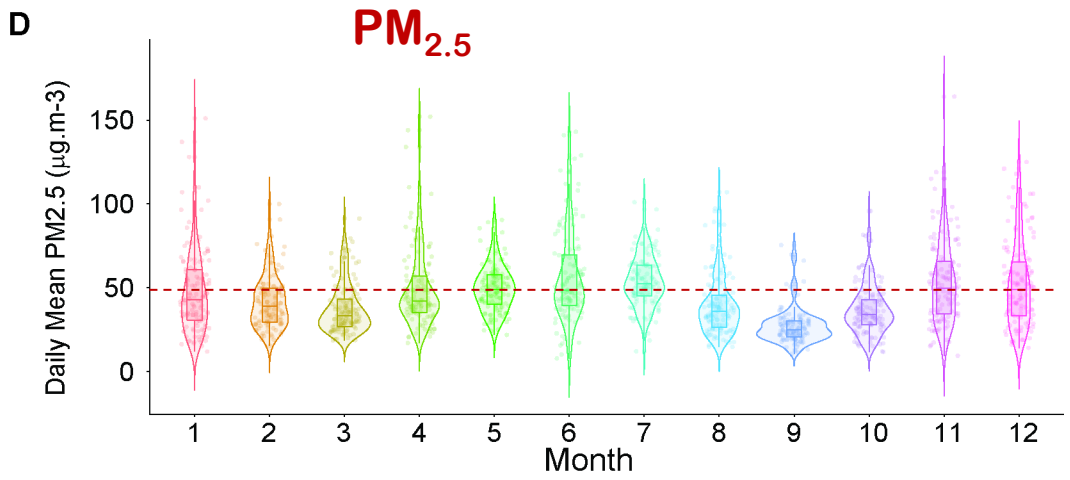
Environmental Variables: Thatta, Pakistan



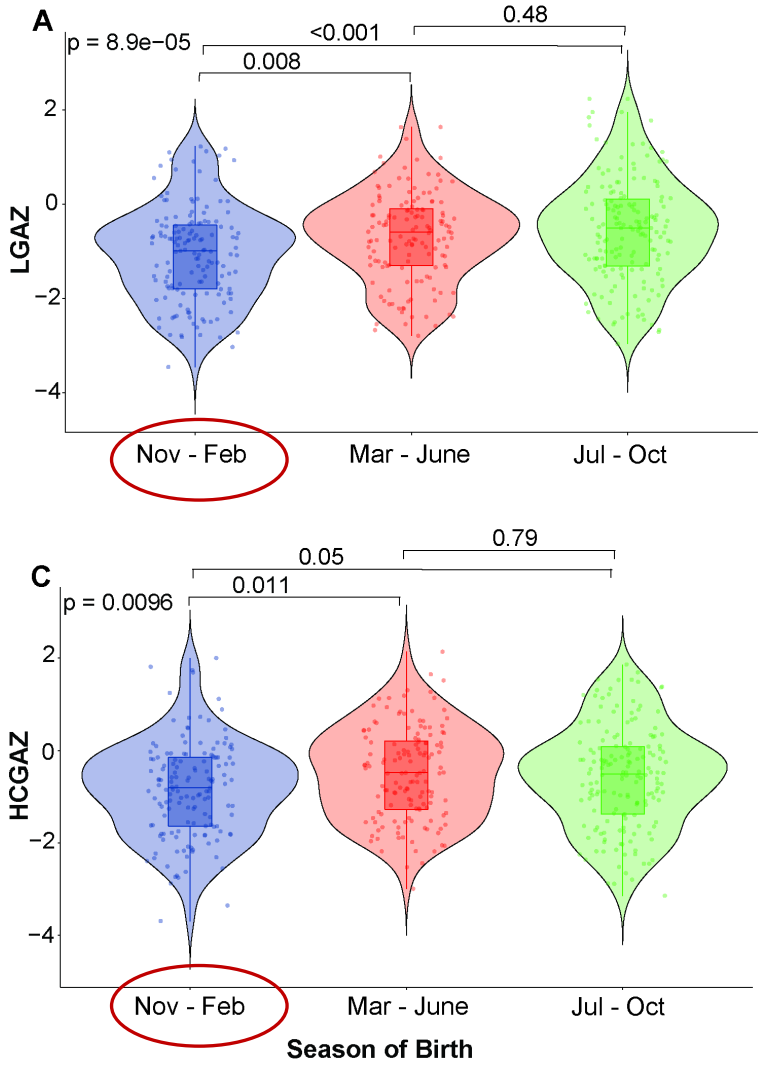


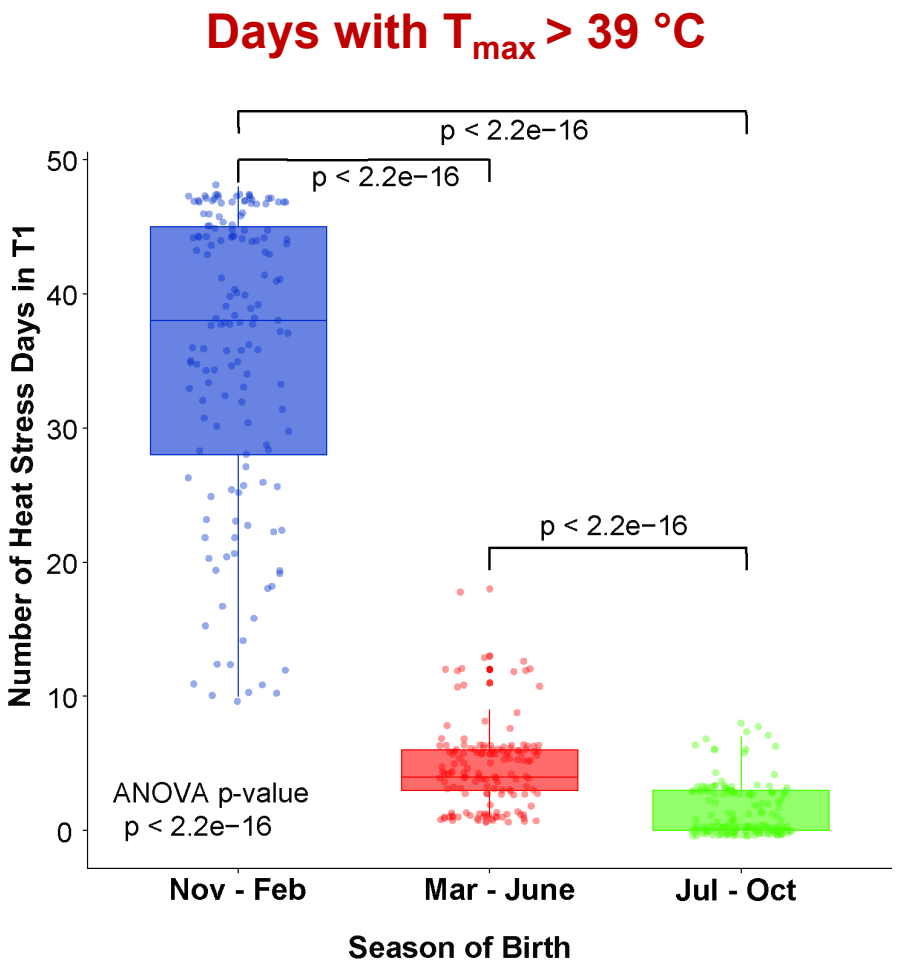




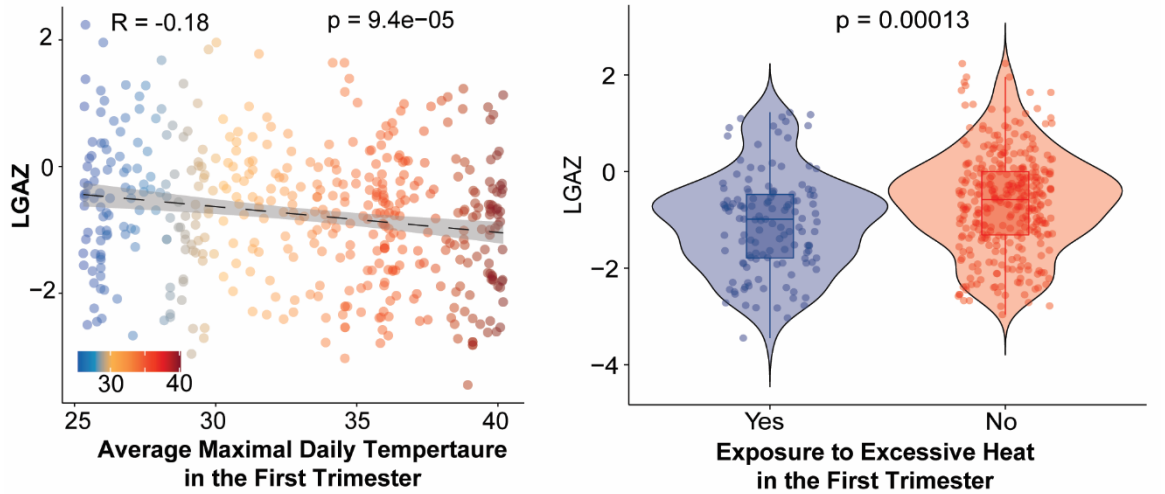


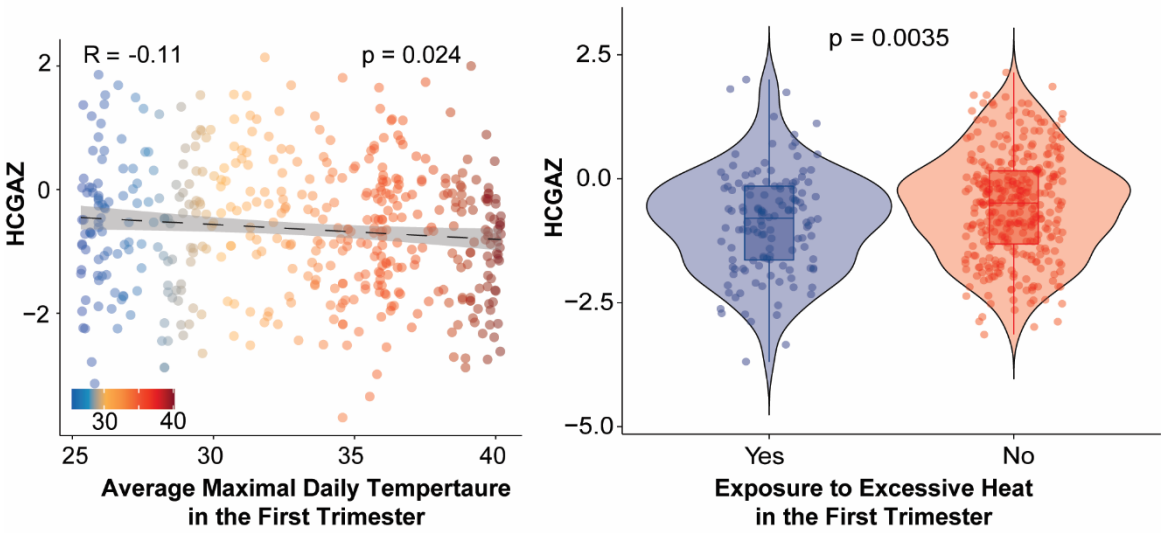
Birth Length is Influenced by Season of Birth





Birth Length is Negatively Associated with T1- T_{max}



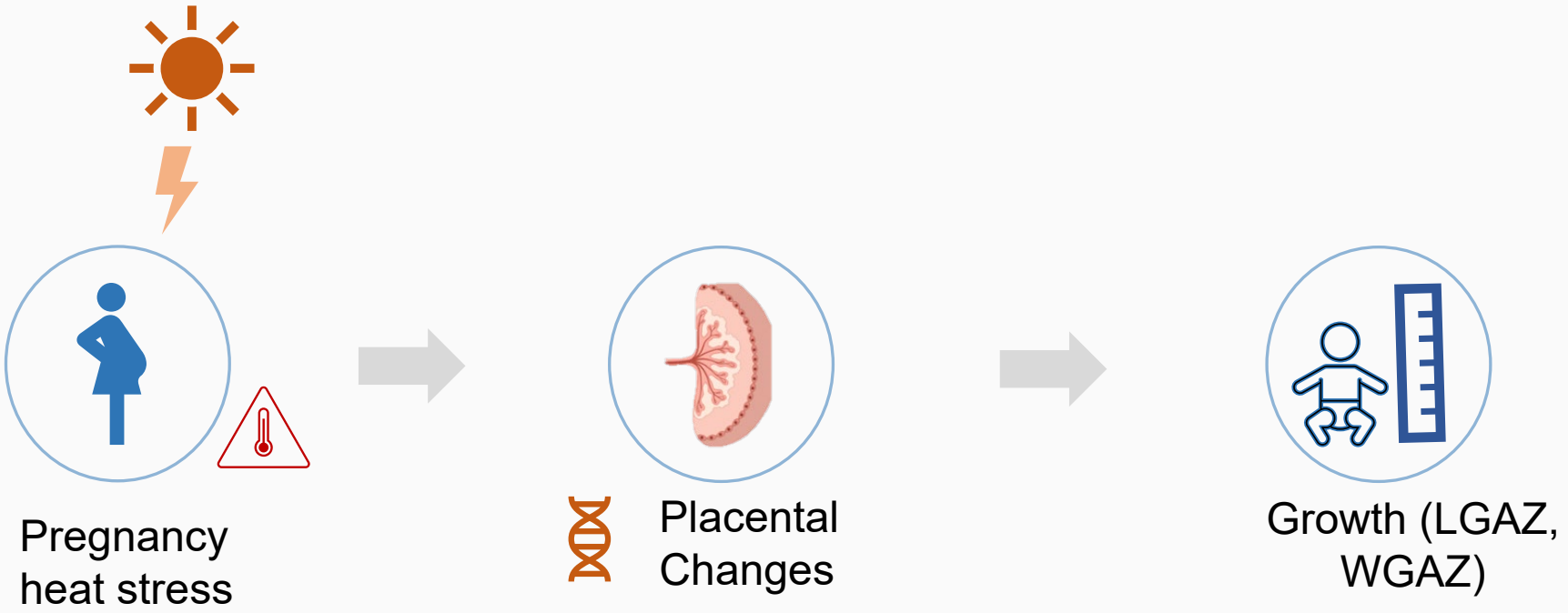


- For each 5°C increase in the T_{max} in the first trimester
  - LGAZ decreased by 0.15 z-scores.
  - HCGAZ decreased by 0.11 z-scores.
- Excessive heat stress (>20 d of >39ºC) was associated with
  - Lower birth length (LGAZ, $p < 0.01$, $\beta = -0.35$).
  - Lower head circumference z-scores ($p < 0.01$; $\beta = -0.29$).

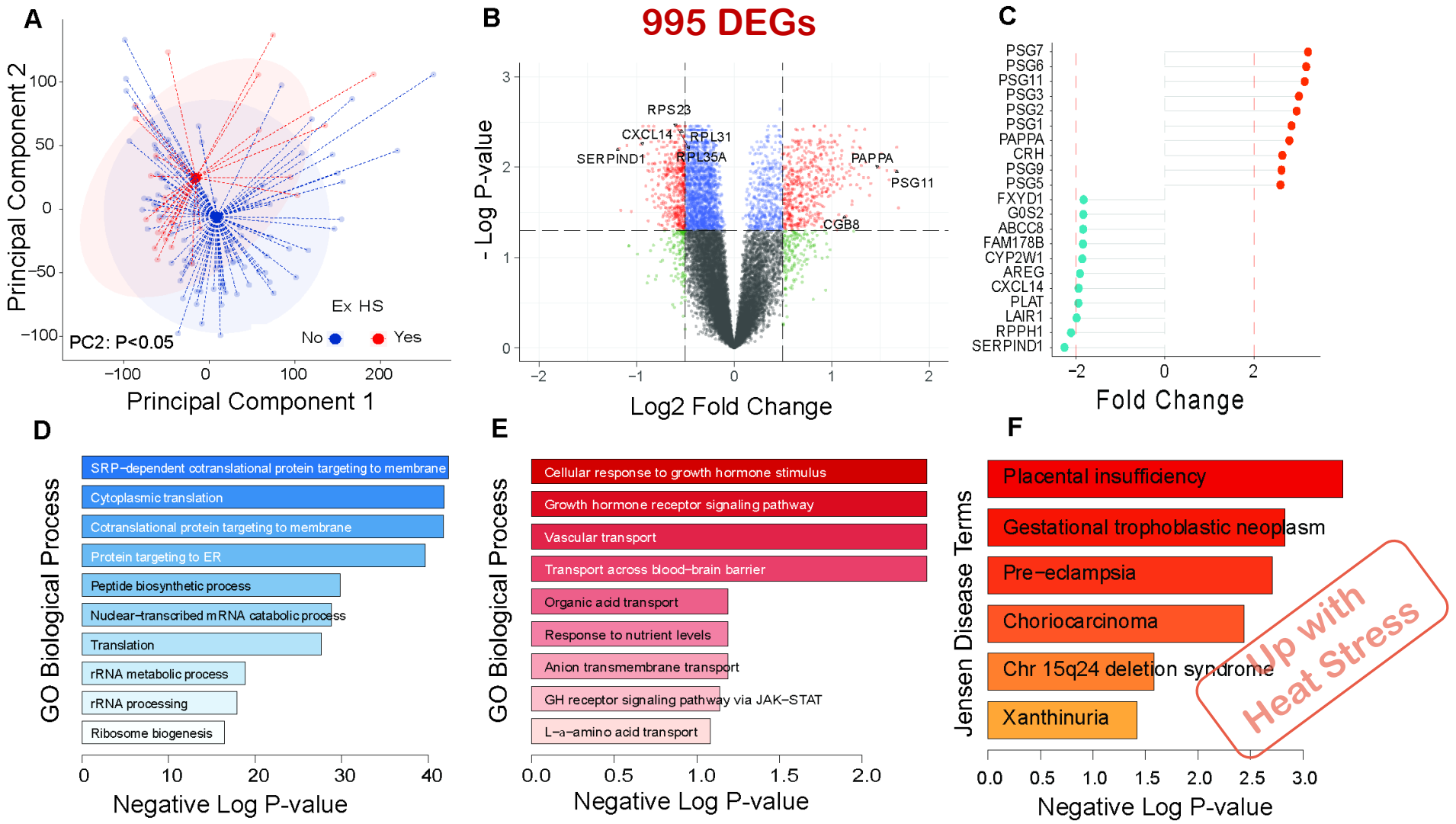
Models adjusted for rel. humidity, $PM_{2.5}$, age, parity, mode of delivery, GWG

Shankar et al, PNAS Nexus, In press 2023
https://doi.org/10.1093/pnasnexus/pgac309

Heat Stress and Placental Changes



Heat Stress Impacts Placental Protein Translation

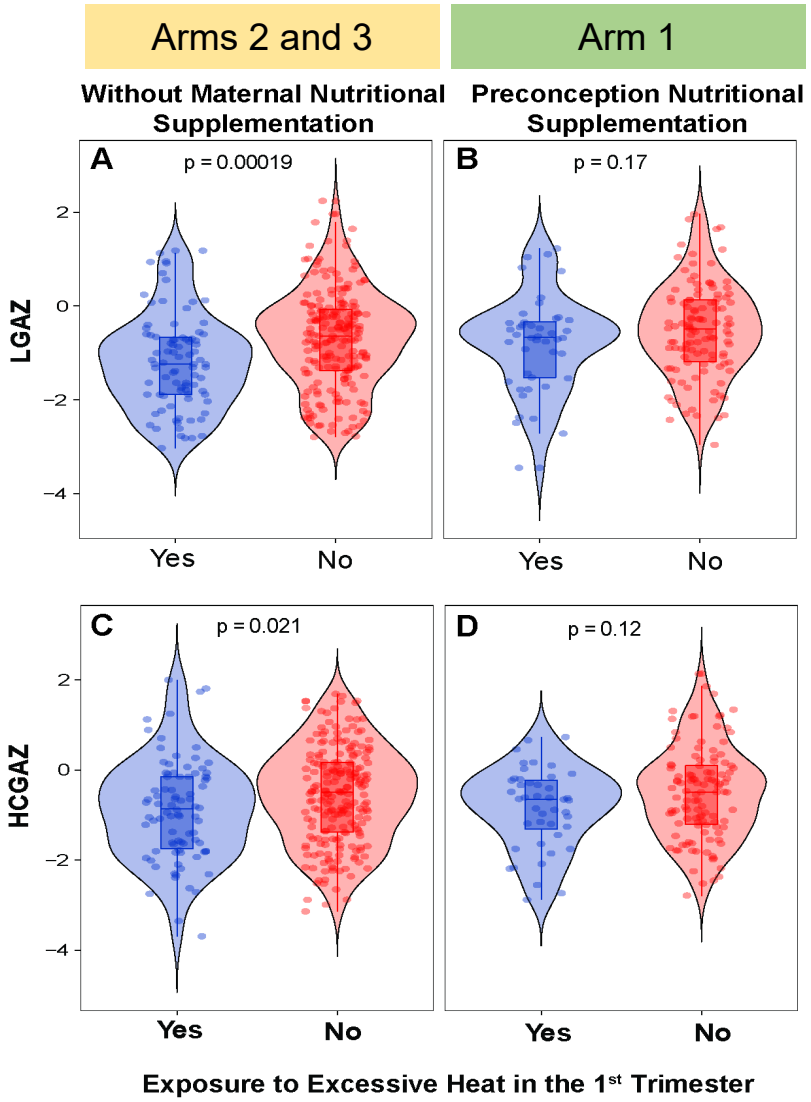


Decreased by Heat

Increased by Heat

Shankar et al, PNAS Nexus, In press 2023

Preconception MNS Mitigates Heat Effects on LGAZ & HCGAZ



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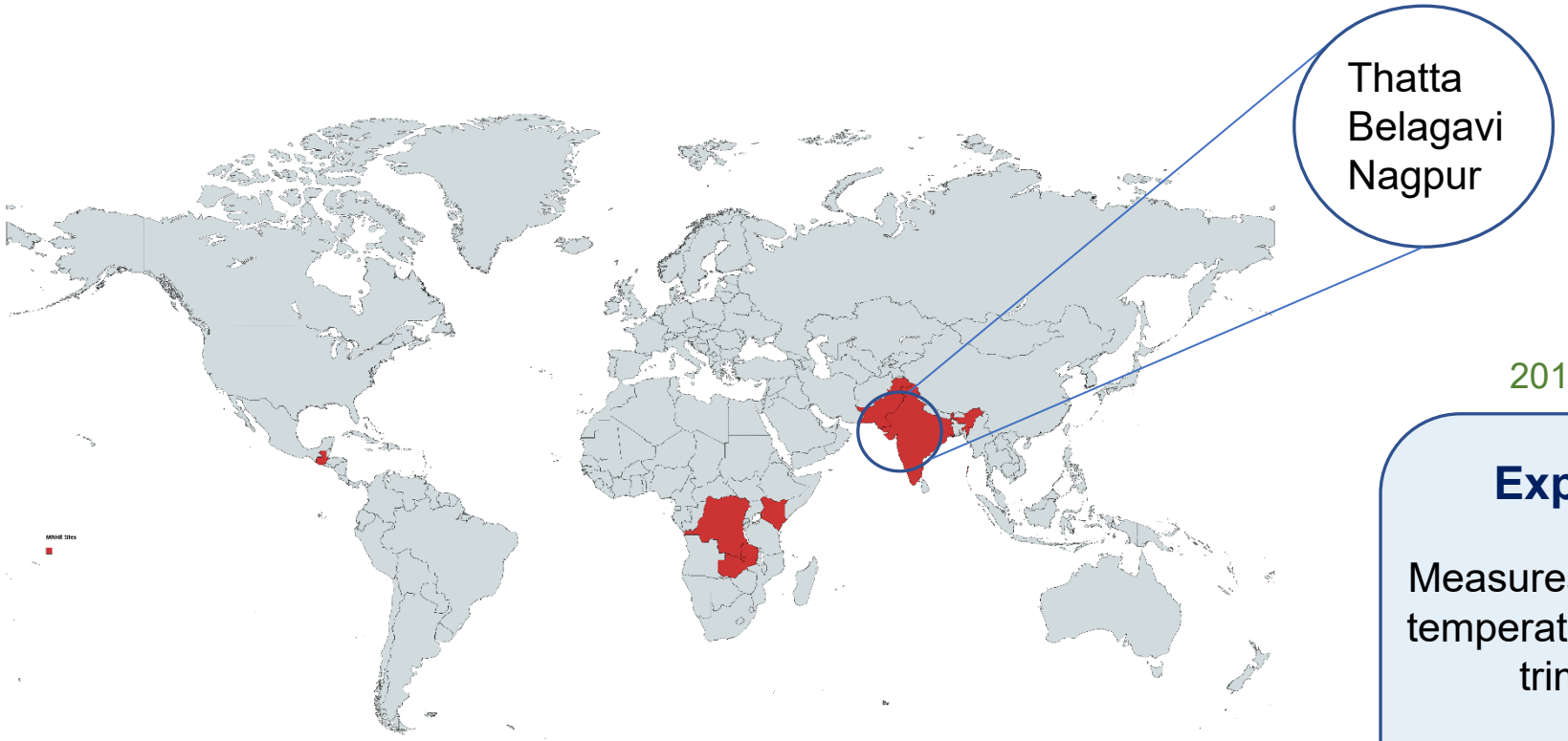
Maternal Newborn Health Registry:
NICHD Global Network



DR Congo
Zambia
Guatemala
India (2)
Pakistan
Kenya
Bangladesh

~500,000 births

2012 to 2022

2015 to 2020

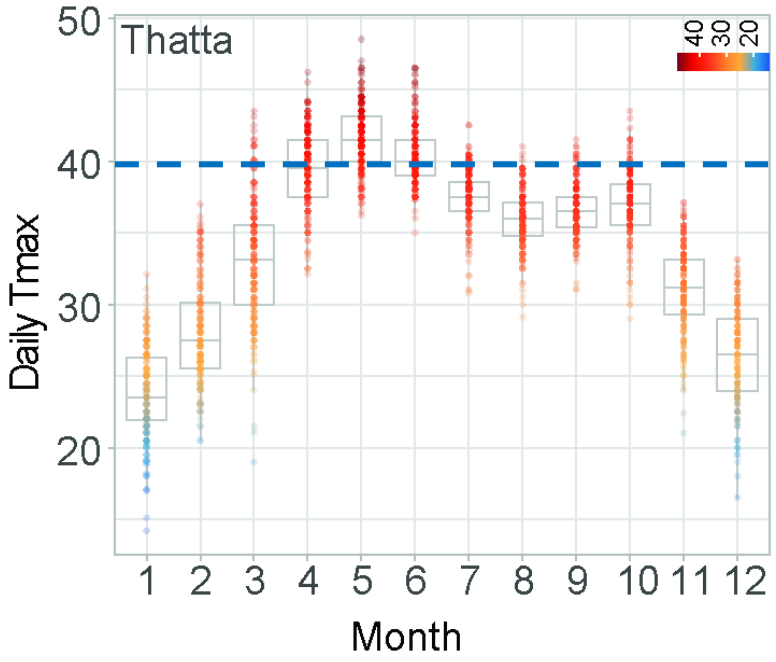
Exposure

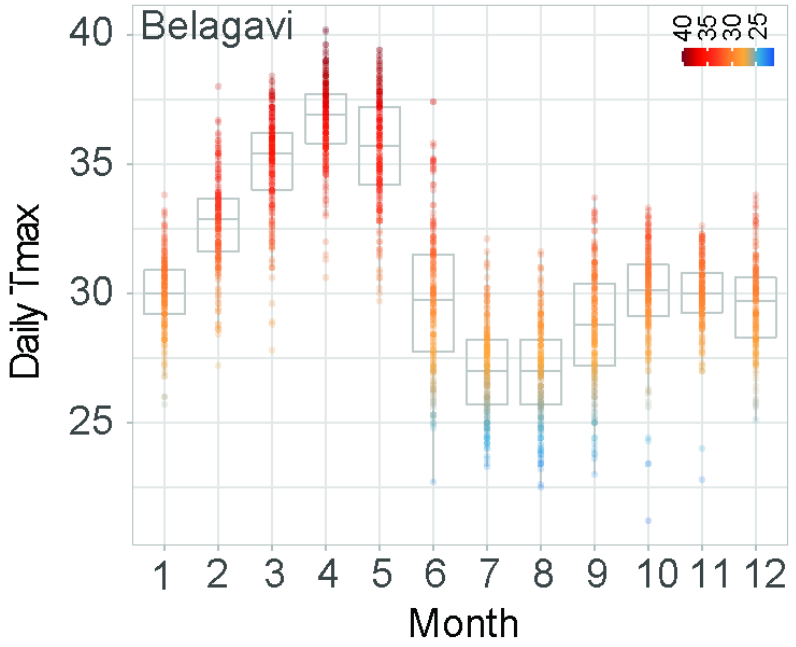
Measures of ambient temperatures in each trimester

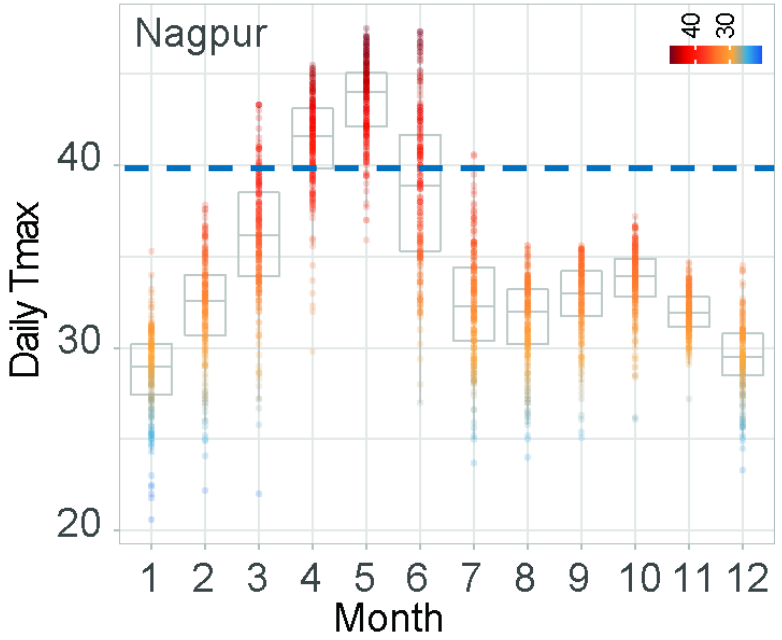
Outcomes

Pregnancy HTN
Stillbirth
Low birth weight
PTB

Daily Maximum Temp: 3 Sites (India & Pakistan)

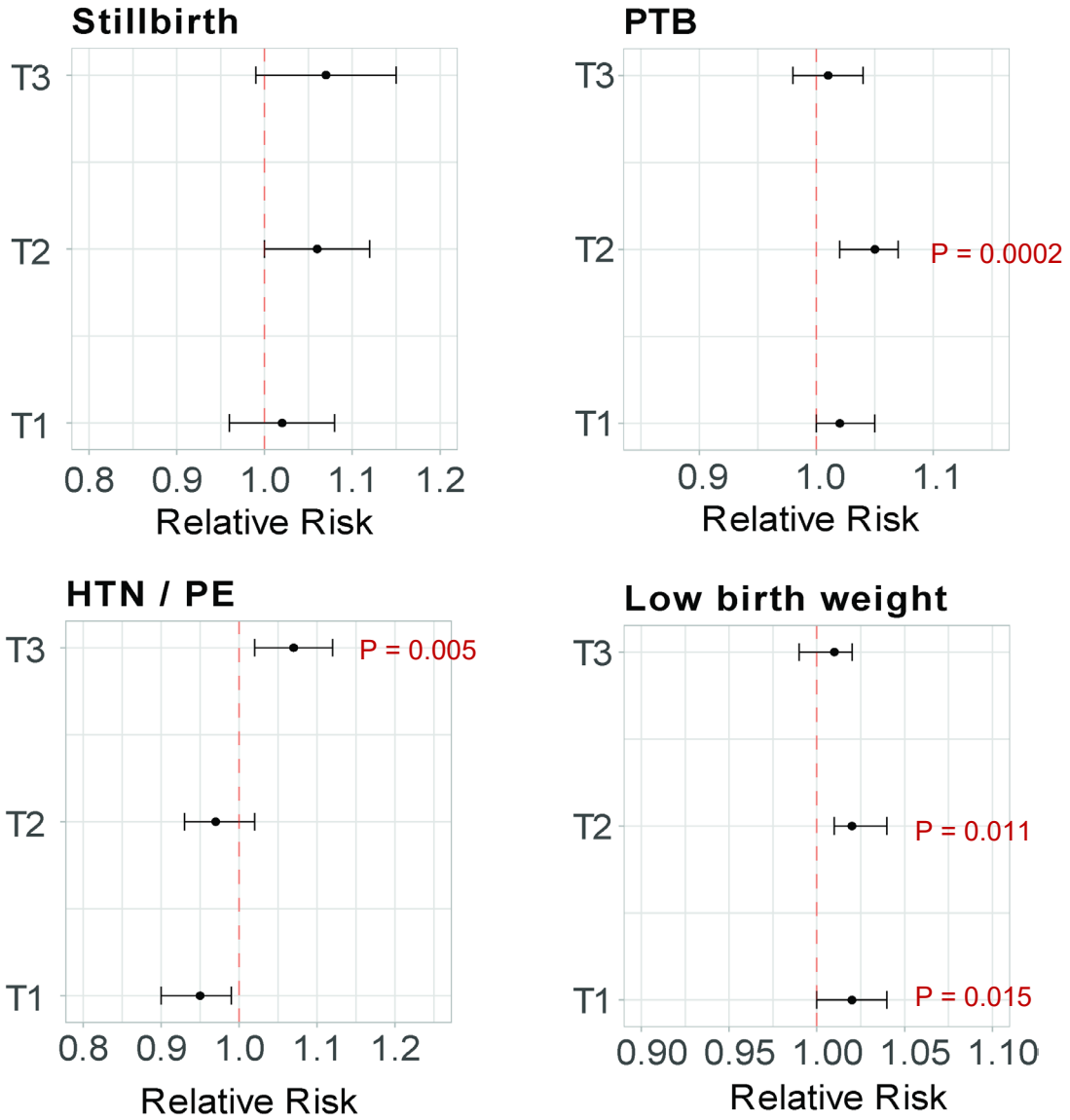






Characteristics	Overall	Thatta	Belagavi	Nagpur
Mothers, n	**127,366**	40,722	43,624	43,020

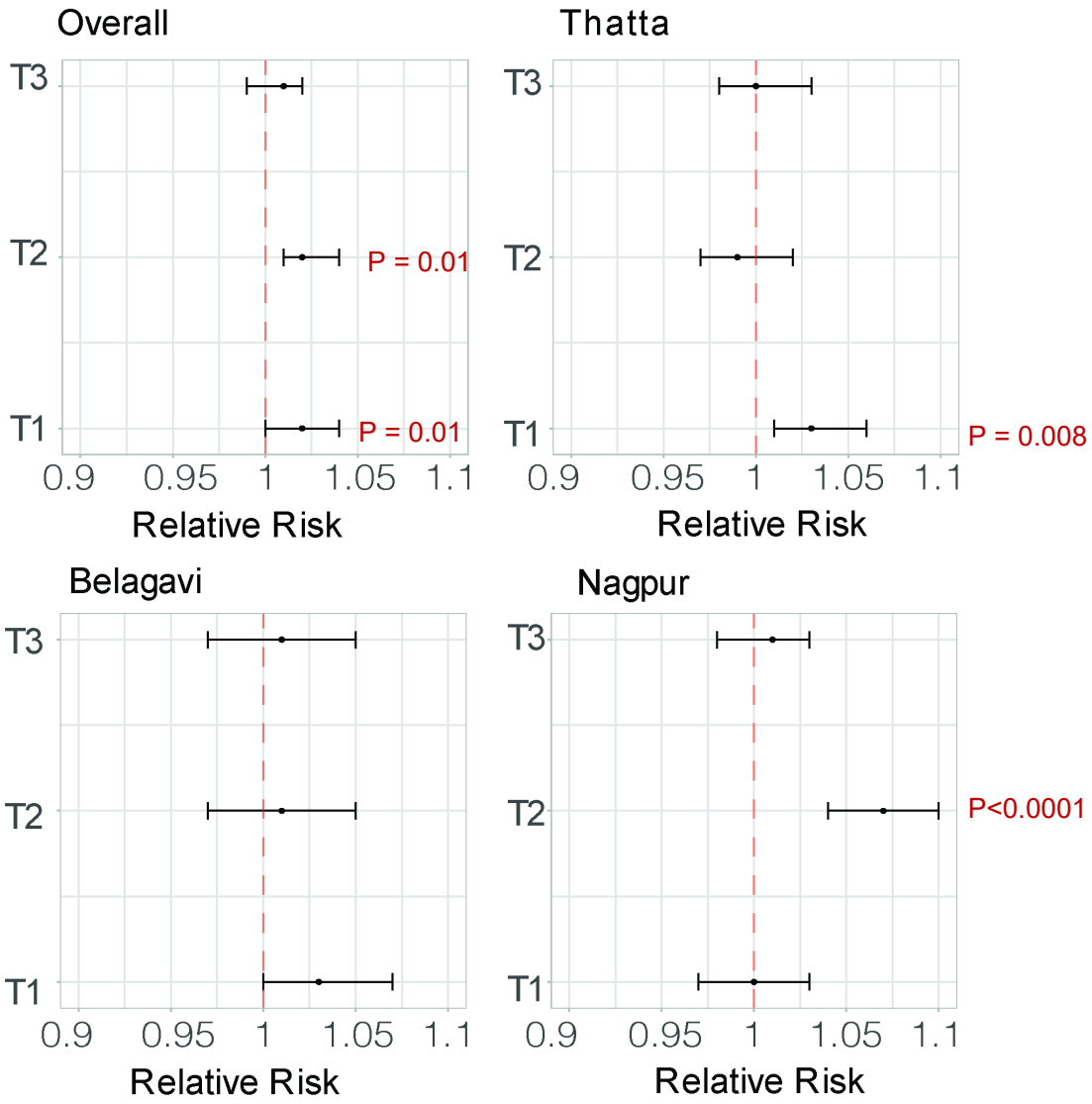
Association of Trimester Average Daily Maximum Temperatures With Birth Outcomes, Overall



Relative risks with corresponding 95% CI and p-values obtained from modified Poisson approach with a sandwich estimator for each categorical outcome and 5℃ in trimester average daily maximum temperatures.

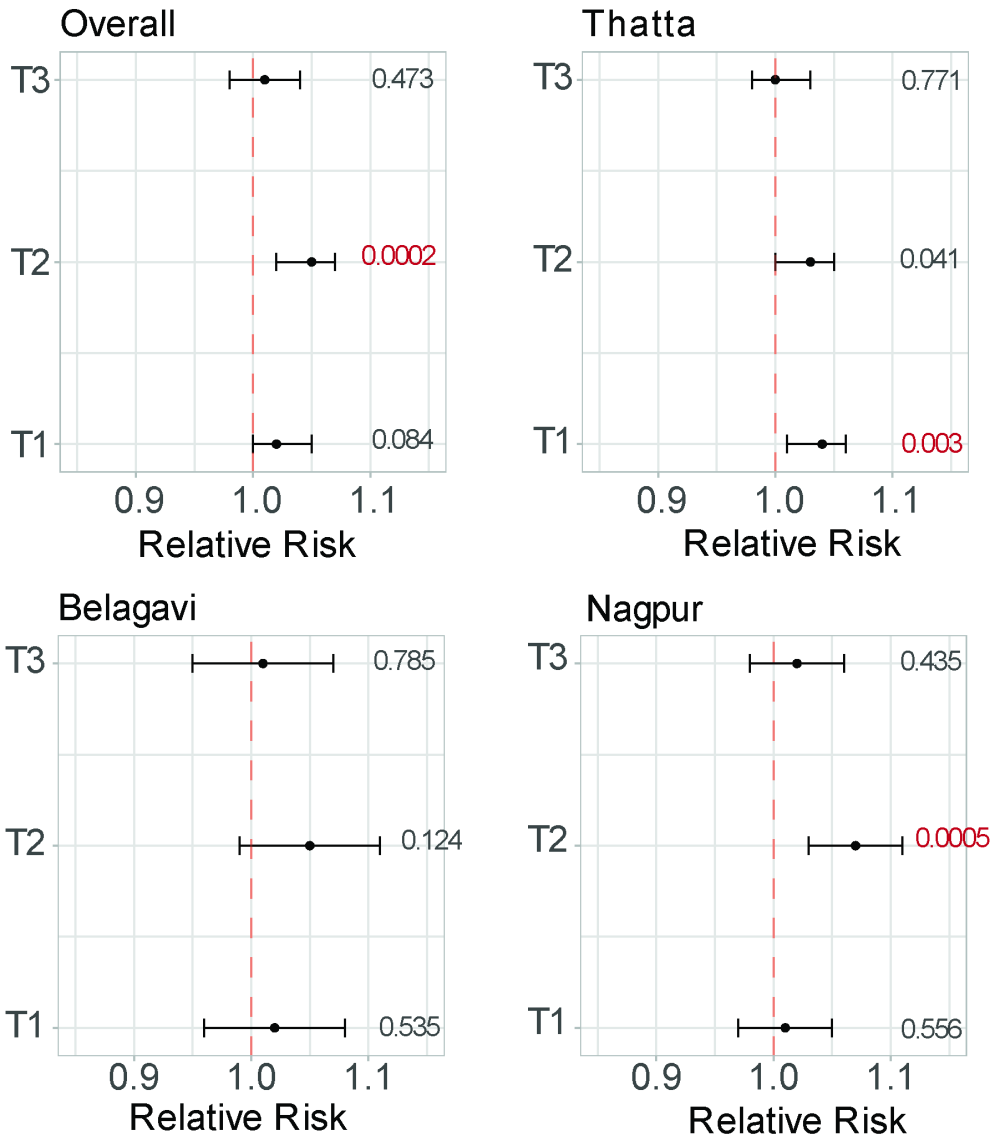
Association of Trimester Average Daily Maximum Temperatures With Low-Birth Weight

1st & 2nd trimester heat and LBW



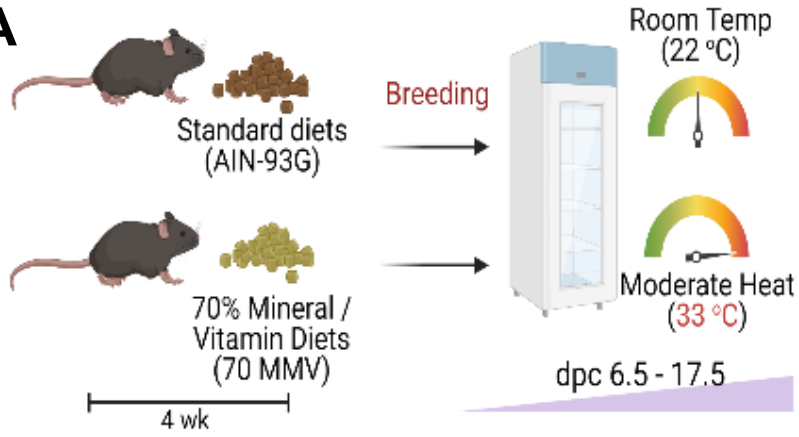
Association of Trimester Average Daily Maximum Temperatures With Preterm Birth

2nd trimester heat and PTB



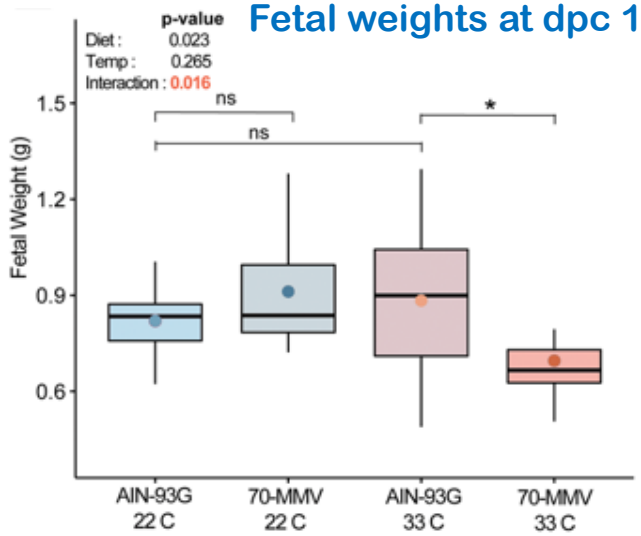
Employing Mouse Models: Heat Stress + Malnutrition

A



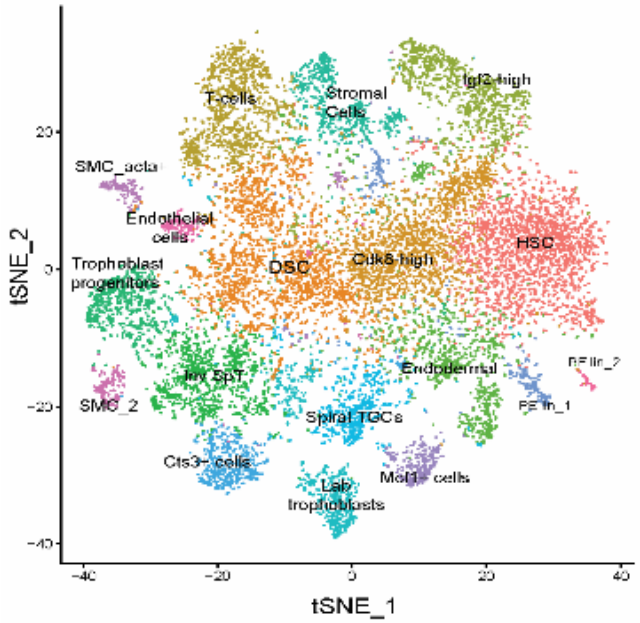
B

Fetal weights at dpc 17.5



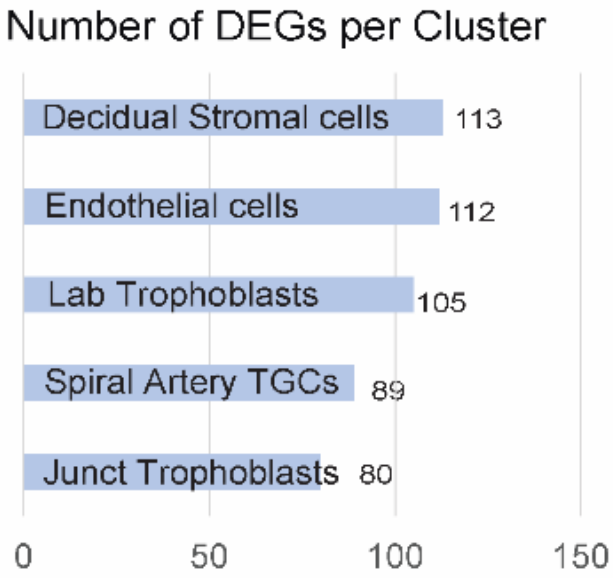
Single-nuclei RNA-seq of dpc 17.5 placenta (~20,000 nuclei)

C



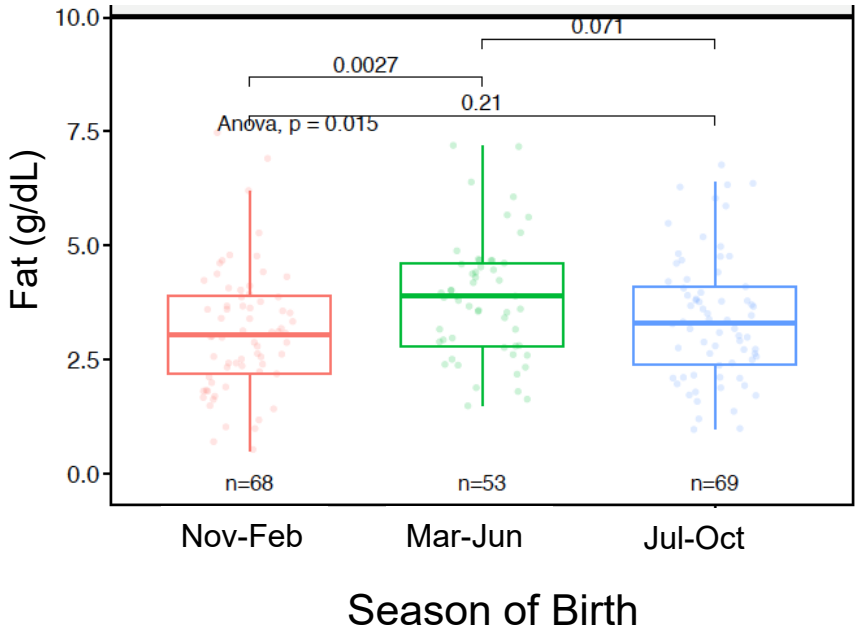
DEGs in Clusters

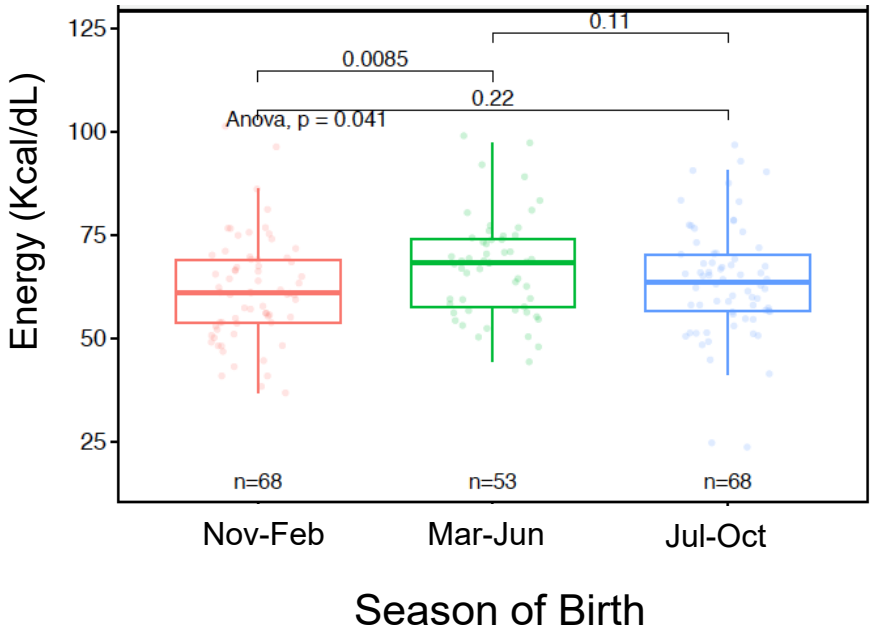
D



Seasonal Changes In Breast Milk (Women First Trial)

Breast milk composition 3 months post-partum

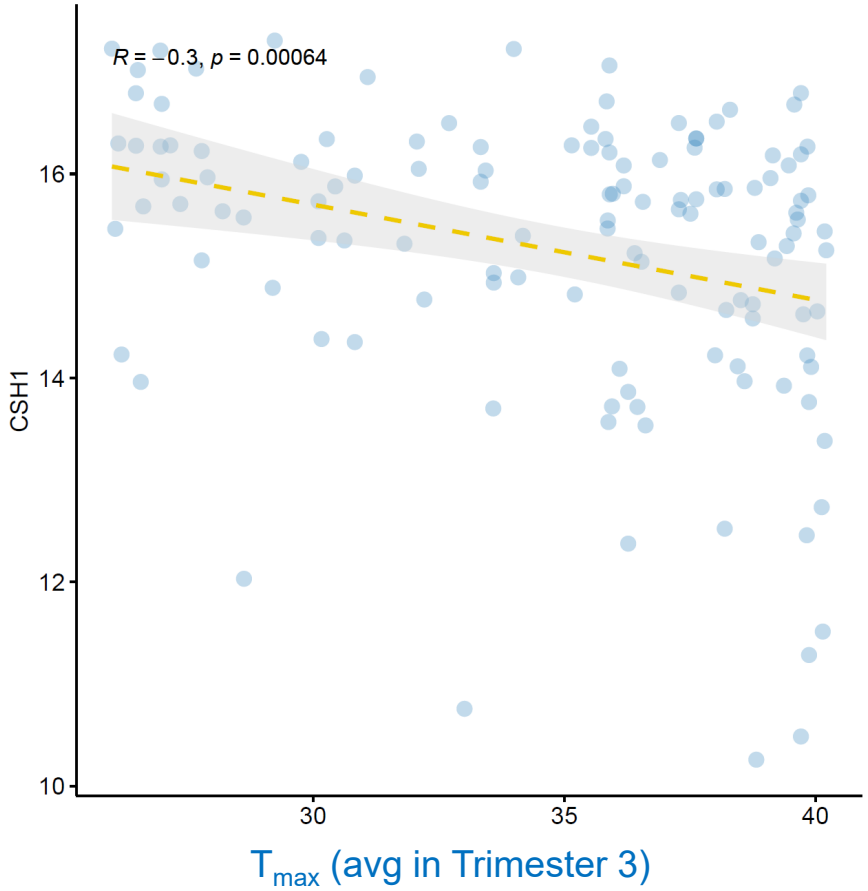


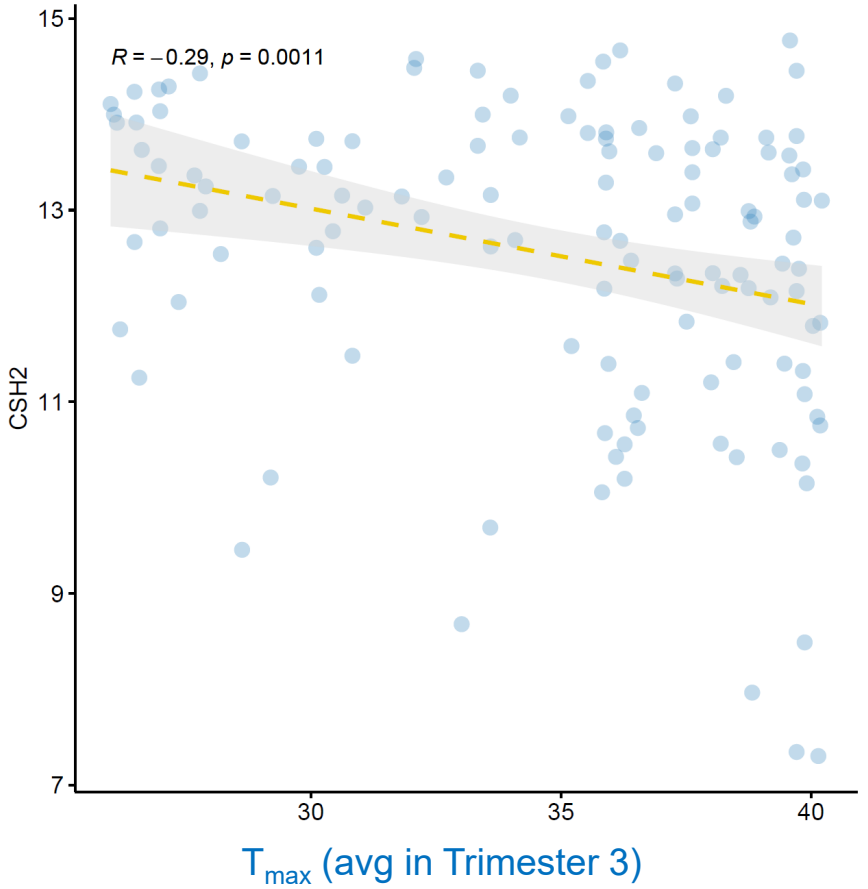


We don’t know about milk quantity!

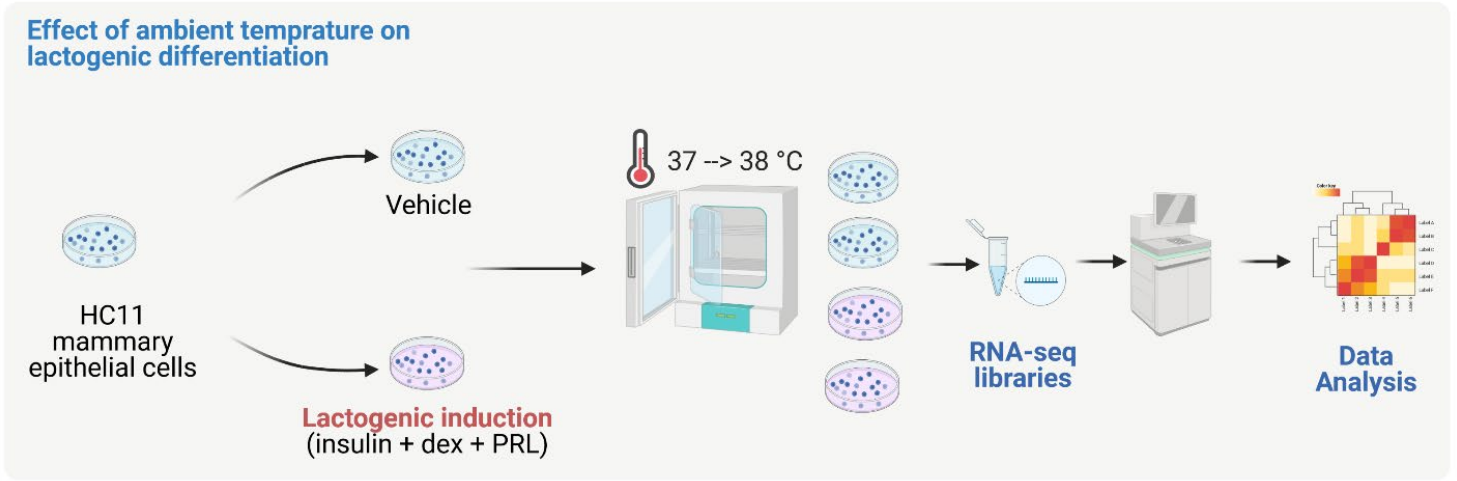
Placental Expression Of Lactogenic Genes And Ambient Temperature

Chorionic somatomammotropin hormone (Placental Lactogen)

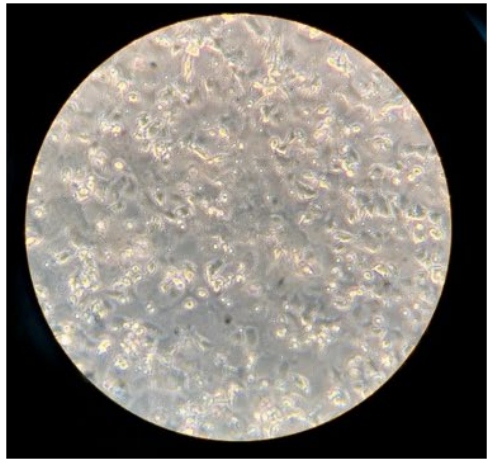




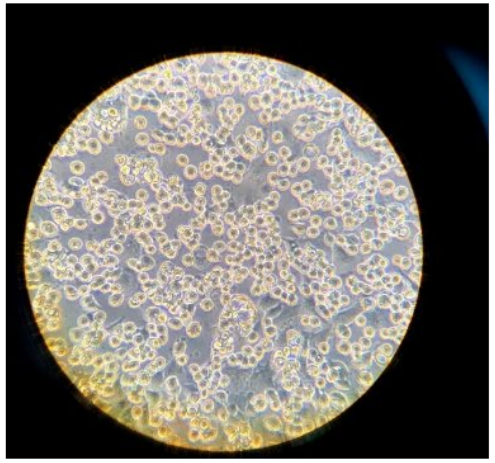
Lactogenic Differentiation: HC11 Cells



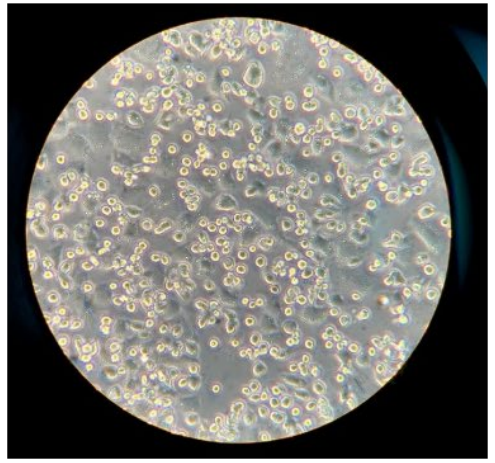
Un-differentiated
Day 5



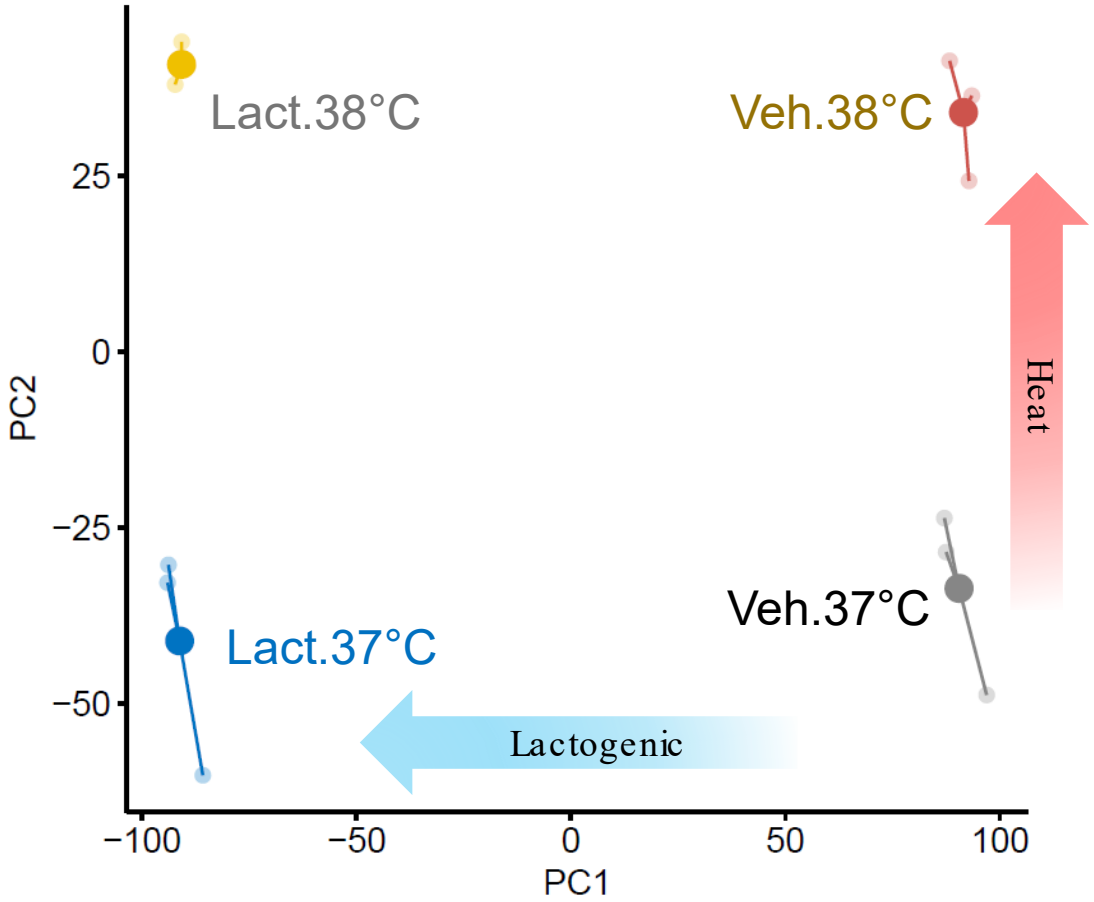
Differentiated
Day 5 (37ºC)



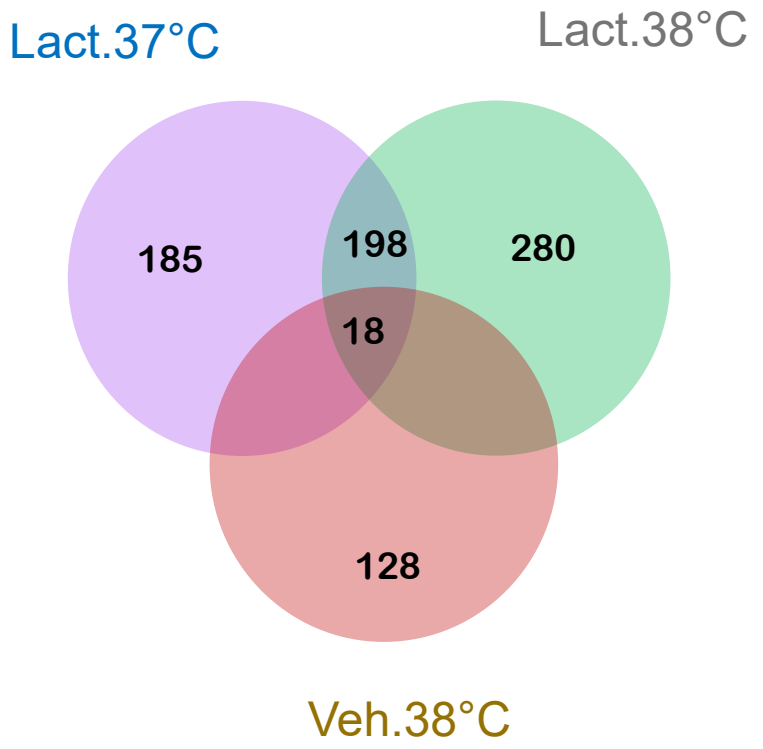
Differentiated
Day 5 (38ºC)



Global Gene Expression Changes With Lactogenic Differentiation And Ambient Temperature

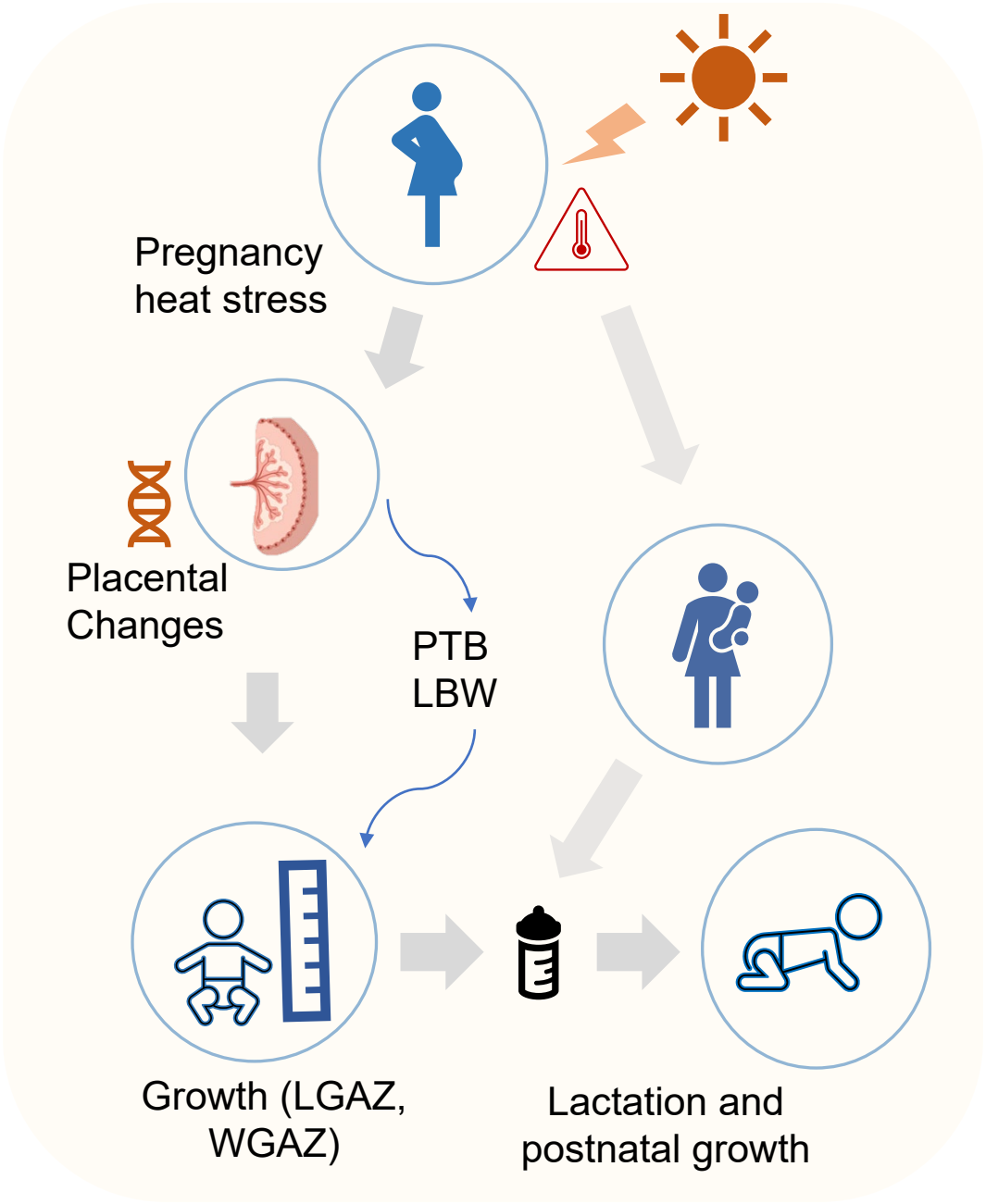


Min 2-FC and p < 0.05 (FDR)



Take Home Messages

- In the context of maternal malnutrition, ambient heat stress has detrimental effects on intrauterine growth.
- Improved maternal nutritional status provides resilience against heat-induced growth restriction.
- Excessive heat exposure in diminishes placental genes involved in protein translation.
- Ambient heat during pregnancy and lactation is likely to have detrimental effects through multiple pathways.
- Prospective intervention and mechanistic are necessary to further elucidate mechanisms.



Acknowledgments

Women First Investigators & Participants
Eunice Kennedy Shriver NICHD Global Network (GN) for Women's and Children's Health Research.

Sumera A. Ali, Ph.D.
Sarah Saleem, M.D., MPH.
Robert Goldenberg, M.D.
K. Michael Hambidge, M.D.

Krebs Lab members
Jamie Westcott
Jennifer Kemp
Sarah Borengasser, Ph.D.

Meghan Ruebel, Ph.D.
Puujee Jambal, MS. MPH
Stephanie Gilley, MD. Ph.D.

NIH
Eunice Kennedy Shriver National Institute of Child Health and Human Development

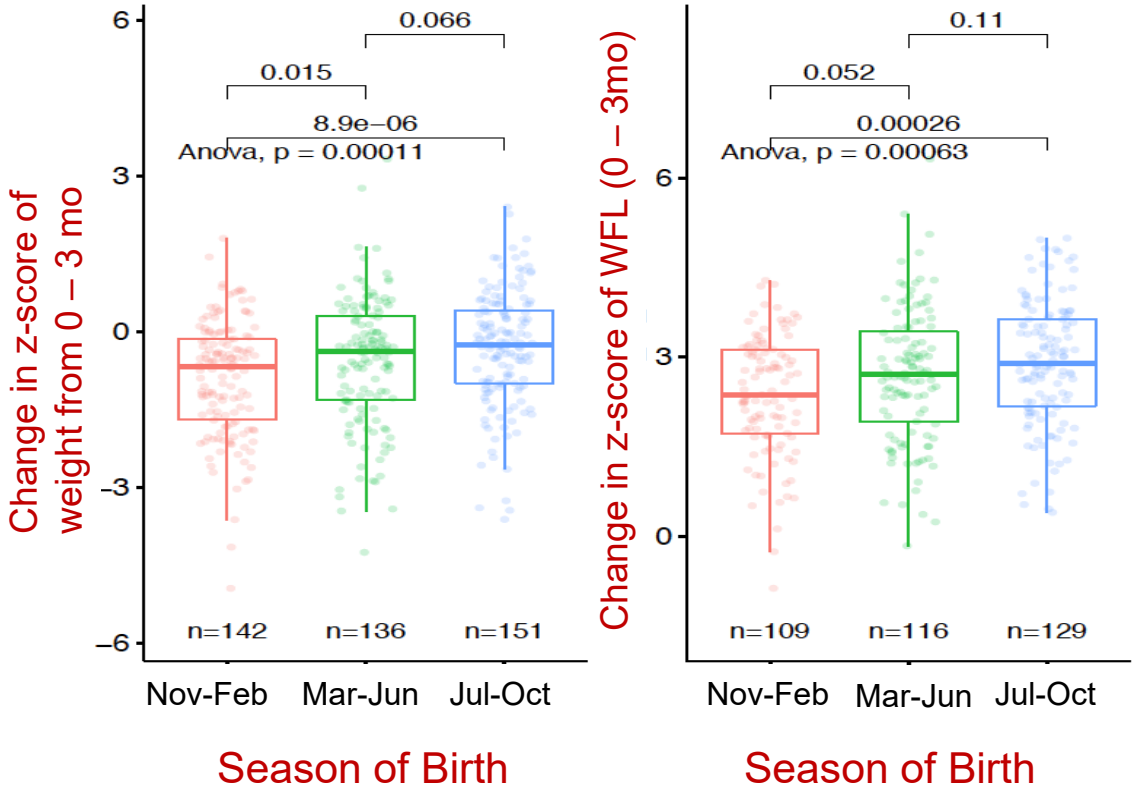
BILL & MELINDA GATES *foundation*

University of Colorado Anschutz Medical Campus

School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Children's Hospital Colorado

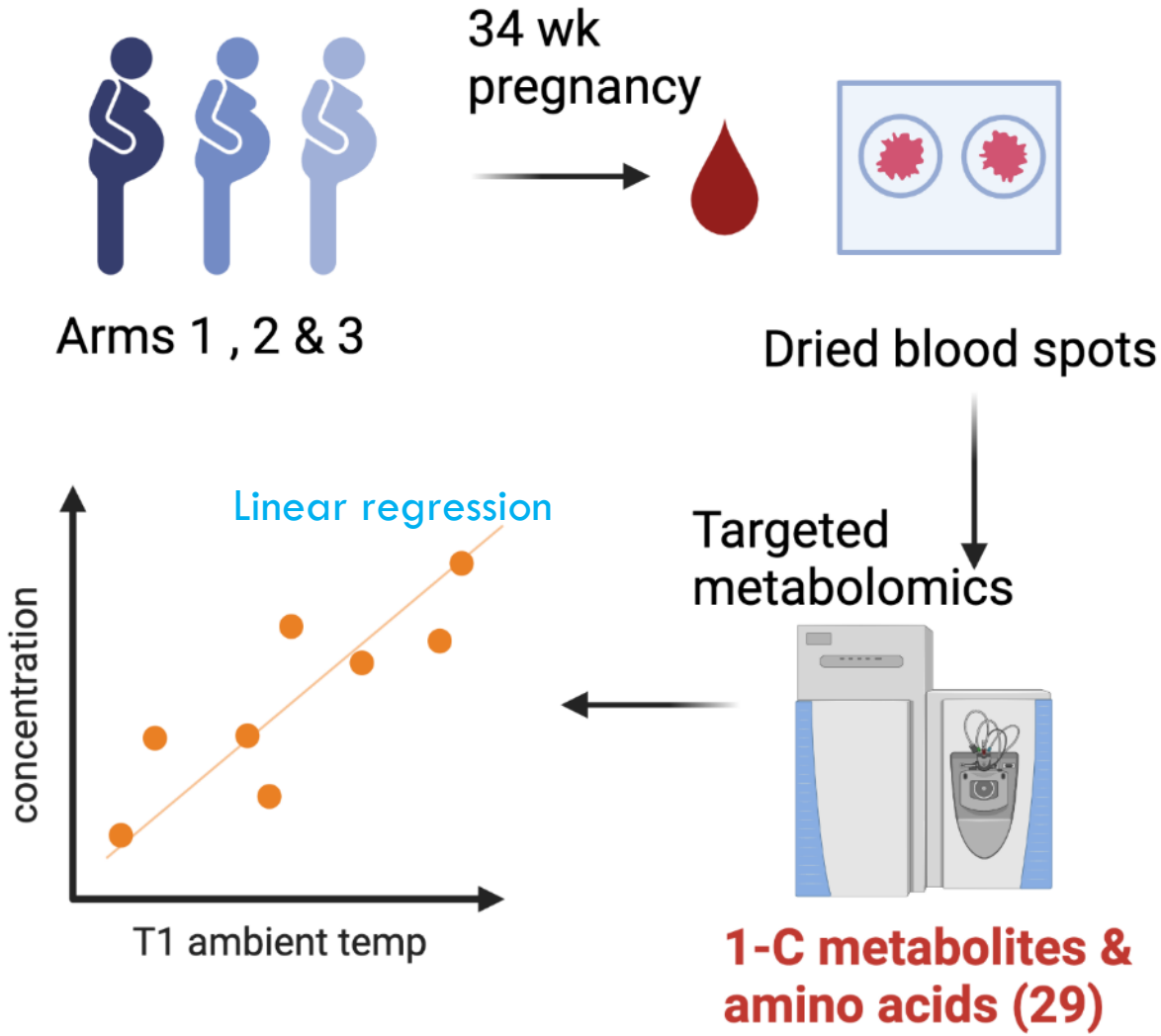
Season of Birth and Postnatal Growth



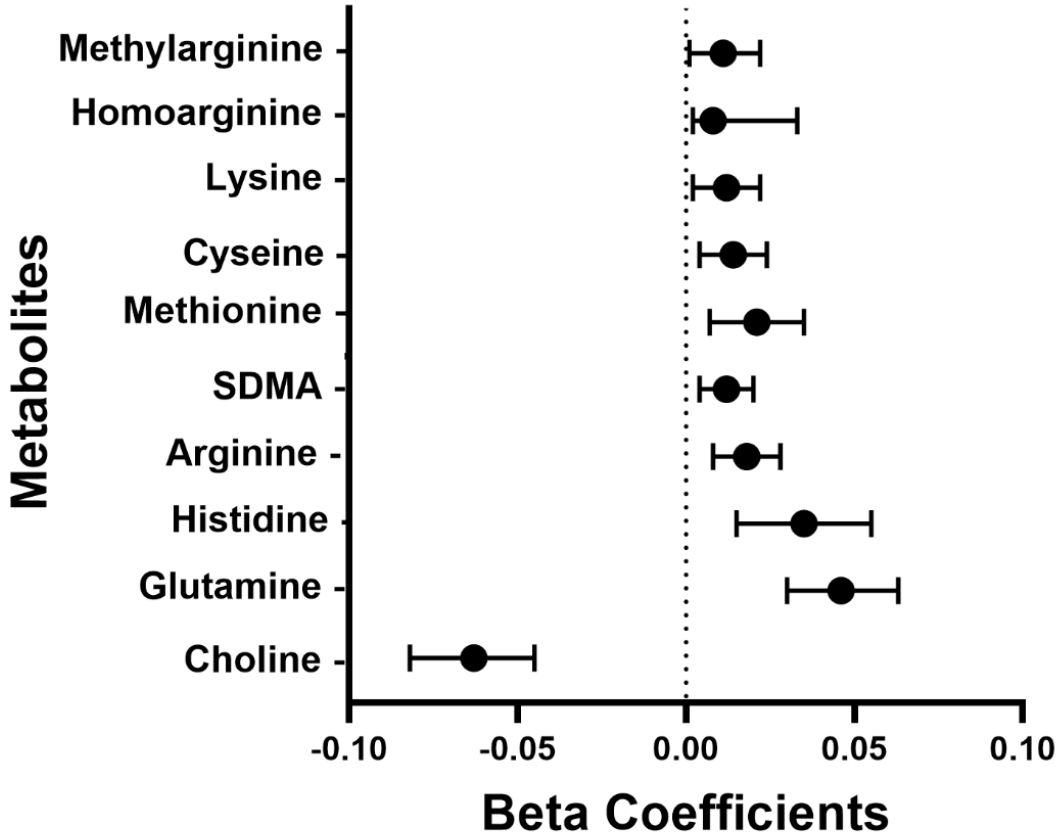
Are there other aspects of postnatal growth influenced by temp?

Breast milk composition?

Heat Stress and Maternal Metabolites



Maternal Metabolites Associated with Ambient Temperature



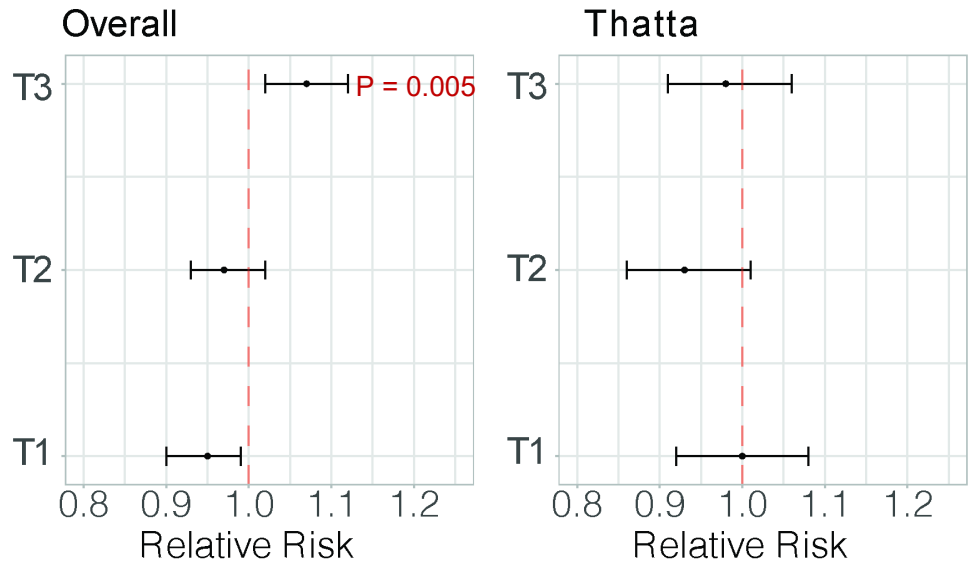
Metabolite	β	SE	p-value	FDR p-value
Choline	-0.063	0.009	4.30E-10	1.16E-08
Glutamine	0.046	0.008	1.96E-07	2.65E-06
Histidine	0.034	0.010	0.0007	0.0055
Arginine	0.017	0.005	0.0008	0.0055
SDMA	0.012	0.004	0.004	0.0211
Methionine	0.020	0.007	0.004	0.0211
Cysteine	0.013	0.005	0.008	0.0313
Lysine	0.012	0.005	0.016	0.0545
Homoarginine	0.018	0.008	0.027	0.0820
Targinine	0.011	0.005	0.035	0.0942

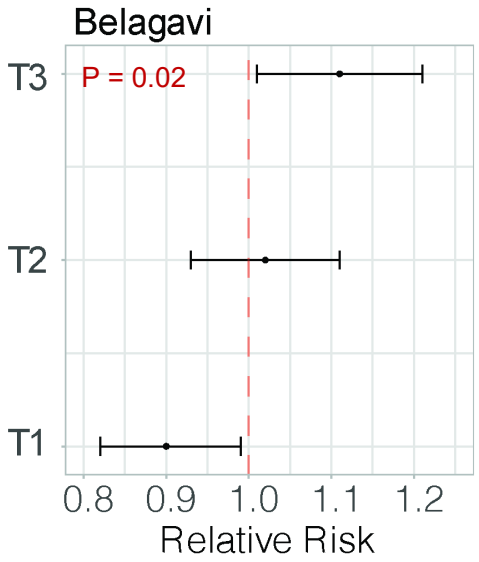
Multiple linear regression models adjusted for cluster and supplement arm

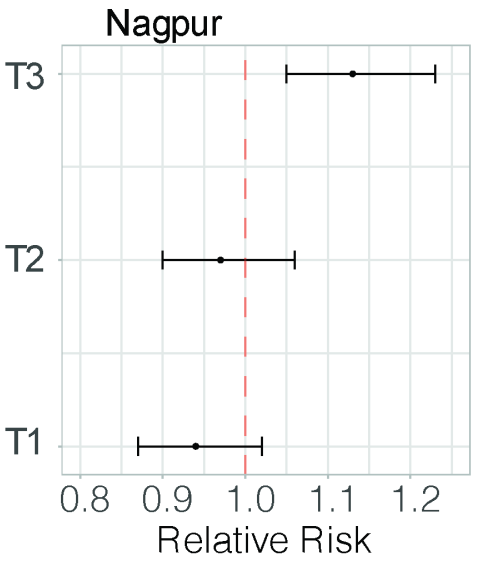
Shankar et al, PNAS Nexus, In press 2023
https://doi.org/10.1093/pnasnexus/pgac309

Association of Trimester Average Daily Maximum Temperatures With Preeclampsia / HTN

3rd trimester heat and PE/ HTN







P = 0.002

3rd trimester heat and PE/ HTN