Maternal Malnutrition: A Global Challenge

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

- ~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

Many health impacts of Climate Change mediated via Agricultural & Nutritional Domains

- Warmer temp
- High CO2
- Anthropogenic activities

- Droughts & crop failures
- Nutritional quality of foods
- Water quality
- Extreme heat exposures
- Vector-based diseases

- Food Insecurity
- Environmental exposures
- Infectious disease

Mosquitos V. Cholerae
Intersection of Nutrition, Climate (Heat) & Health: Translating to Research Targets

**Vulnerable Populations**

1000+ days
Malnourished & impoverished

**Health Effects/Systems**

- Pregnancy
- Lactation
- Heme/anemia
- Renal function
- GI - Hep
- Respiratory
- Immune Fxn
- Inflammation

**Outcomes**

- 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

**Participants**
- Rural LMI communities

**Study Design**
- Arm 1: Pre-conception (3 mo pre-conception)
  - 3 mo precon
- Arm 2: Pregnancy (12 wk of pregnancy)
- Arm 3: Control (Non-Intervention Control)
  - Iron & Folic Acid

**Biospecimen & Data**
- Maternal Health: BMI, Weight gain, SES, Parity, Education
- Maternal Serum: 12 wk, 34 wk
- Placenta: RNA, DNA, protein
- Infant Birth Variables: Weight, LAZ, Head circumference (birth to 2 y of age)

**Study Design Diagram**

- **Participants**
  - Rural LMI communities
  - Arm 1: Pre-conception (3 mo pre-conception)
  - Arm 2: Pregnancy (12 wk of pregnancy)
  - Arm 3: Control (Non-Intervention Control)

- **Study Design**
  - 3 mo precon
  - 12 wk
  - 34 wk

- **Biospecimen & Data**
  - Maternal Health
  - Maternal Serum
  - Placenta
  - Infant Birth Variables

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

Non-intervention Control
Iron & Folic Acid
Pakistan ranks 9th highest: Children’s Climate Risk Index (UNICEF)

Heat Effects During Pregnancy: WF Trial

Participants
- Rural LMI communities
  - Arm 1: Pre-conception (3 mo pre-conception)
    - 3 mo precon
    - 12 wk
    - 34 wk
  - Arm 2: Pregnancy (12 wk of pregnancy)
  - Arm 3: Control (Non-intervention Control (Iron & Folic Acid))

Study Design

Exposures
- Avg maximal daily temperature
- Number of days when $T_{max} > 39^\circ C$ (Heat stress days)
- Heat Index

Outcomes
- Linear regression with birth outcomes
  - Birth length
  - Birth weight
  - Head circumference

Environmental Variables: Thatta, Pakistan

A. Avg Daily $T_{\text{max}}$

B. Avg Daily Relative Humidity

C. Avg Daily Heat Index

D. PM$_{2.5}$
Birth Length is Influenced by Season of Birth

Days with $T_{\text{max}} > 39 \, ^\circ\text{C}$

A

Season of Birth

B

C

ANOVA p-value $p < 2.2e^{-16}$

$\text{p} = 8.9e^{-05}$

$0.008$

$< 0.001$

$0.48$

$\text{p} = 0.0096$

$0.011$

$0.05$

$0.79$

Season of Birth

Number of Heat Stress Days in T1

$\text{p} < 2.2e^{-16}$
Birth Length is Negatively Associated with $T_{1-\max}$

- For each 5°C increase in the $T_{\text{max}}$ in the first trimester
  - LGAZ decreased by 0.15 z-scores.
  - HCGAZ decreased by 0.11 z-scores.

- Excessive heat stress (>20 d of >39°C) was associated with
  - Lower birth length (LGAZ, $p < 0.01$, $\beta = -0.35$).
  - Lower head circumference z-scores ($p < 0.01$; $\beta = -0.29$).

- Shankar et al, PNAS Nexus, In press 2023

https://doi.org/10.1093/pnasnexus/pgac309
Heat Stress and Placental Changes

Pregnancy heat stress

Placental Changes

Growth (LGAZ, WGAZ)
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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>Thatta</th>
<th>Belagavi</th>
<th>Nagpur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers, n</td>
<td>127,366</td>
<td>40,722</td>
<td>43,624</td>
<td>43,020</td>
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</tbody>
</table>
Association of Trimester Average Daily Maximum Temperatures With Birth Outcomes, Overall

![Graphs showing relative risks with corresponding 95% CI and p-values obtained from modified Poisson approach with a sandwich estimator for each categorical outcome and 5°C in trimester average daily maximum temperatures.](image-url)
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

Fetal weights at dpc 17.5

B

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

C

DEGs in Clusters

D

Number of DEGs per Cluster

- Decidual Stromal cells: 113
- Endothelial cells: 112
- Lab Trophoblasts: 105
- Spiral Artery TGCs: 89
- Junct Trophoblasts: 80
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)

\[ R = -0.3, \ p = 0.00084 \]

\[ R = -0.29, \ p = 0.0011 \]
Lactogenic Differentiation: HC11 Cells

Un-differentiated Day 5

Differentiated Day 5 (37°C)

Differentiated Day 5 (38°C)
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 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

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Puujee Jambal, MS. MPH
Stephanie Gilley, MD. Ph.D.
Season of Birth and Postnatal Growth

Are there other aspects of postnatal growth influenced by temp?

Breast milk composition?
Heat Stress and Maternal Metabolites

Arms 1, 2 & 3

34 wk pregnancy

Dried blood spots

Linear regression

Targeted metabolomics

1-C metabolites & amino acids (29)
Maternal Metabolites Associated with Ambient Temperature

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>β</th>
<th>SE</th>
<th>p-value</th>
<th>FDR p-value</th>
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</thead>
<tbody>
<tr>
<td>Choline</td>
<td>-0.063</td>
<td>0.009</td>
<td>4.30E-10</td>
<td>1.16E-08</td>
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<tr>
<td>Glutamine</td>
<td>0.046</td>
<td>0.008</td>
<td>1.96E-07</td>
<td>2.65E-06</td>
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<td>Histidine</td>
<td>0.034</td>
<td>0.010</td>
<td>0.0007</td>
<td>0.0055</td>
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<tr>
<td>Arginine</td>
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<td>0.005</td>
<td>0.0008</td>
<td>0.0055</td>
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<tr>
<td>SDMA</td>
<td>0.012</td>
<td>0.004</td>
<td>0.004</td>
<td>0.0211</td>
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<tr>
<td>Methionine</td>
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<td>0.007</td>
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<td>0.0211</td>
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<td>Cysteine</td>
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<td>Homoarginine</td>
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<td>Targinine</td>
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<td>0.005</td>
<td>0.035</td>
<td>0.0942</td>
</tr>
</tbody>
</table>

Multiple linear regression models adjusted for cluster and supplement arm.
Association of Trimester Average Daily Maximum Temperatures With Preeclampsia / HTN

3rd trimester heat and PE/ HTN

Overall

*P* = 0.005

Thatta

*P* = 0.002

Belagavi

*P* = 0.02

Nagpur

*P* = 0.002