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## **Biological pathways from heat exposure to preterm birth: longitudinal studies across three countries in sub-Saharan Africa**

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# Outline

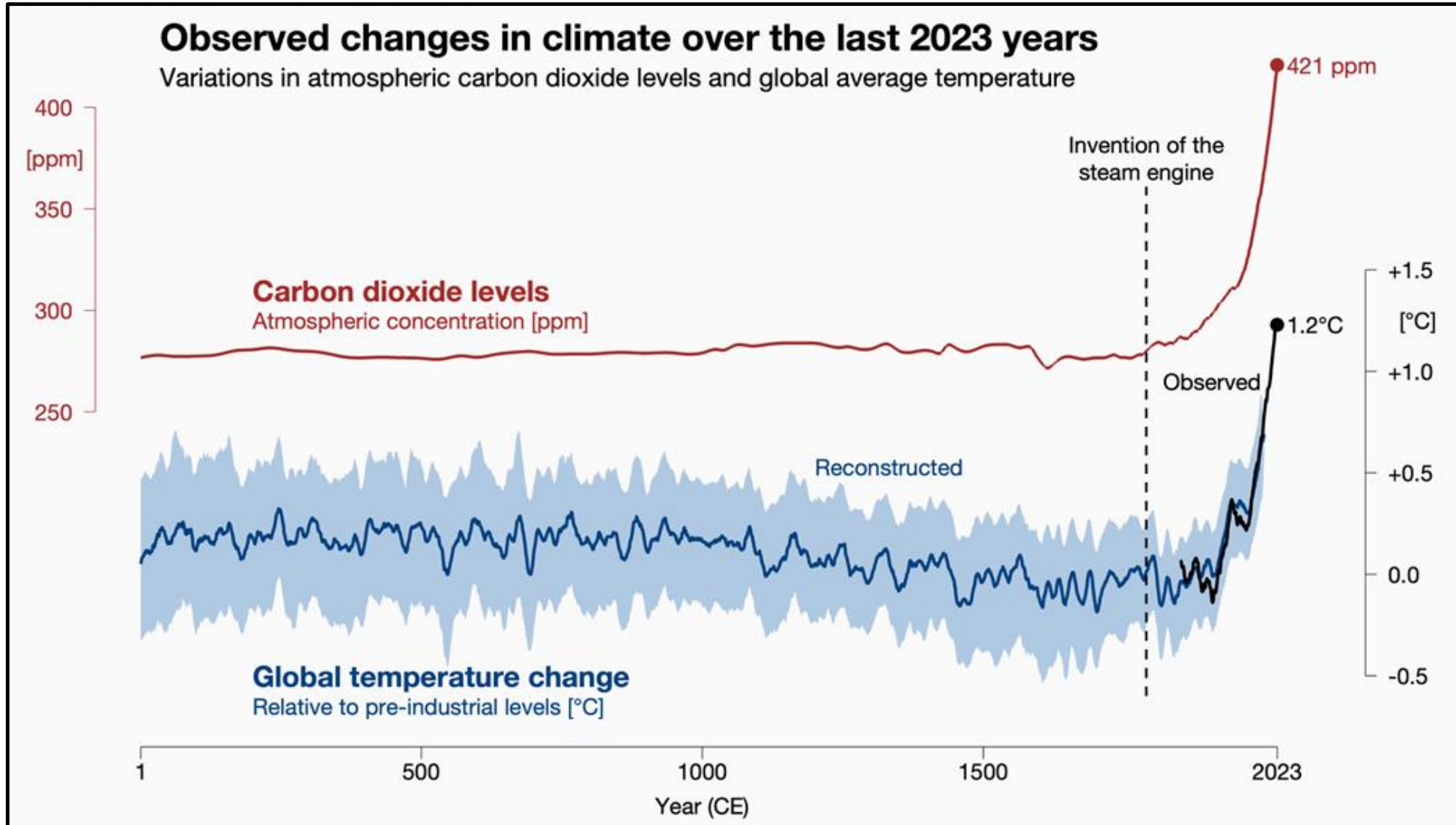
- Background climate change, heat and pre-term births
- Rationale of the three linked studies
- Details of the three linked studies
- Conclusion



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## Impact of human activities



<https://ed-hawkins.github.io/climate-visuals/indicators.html>

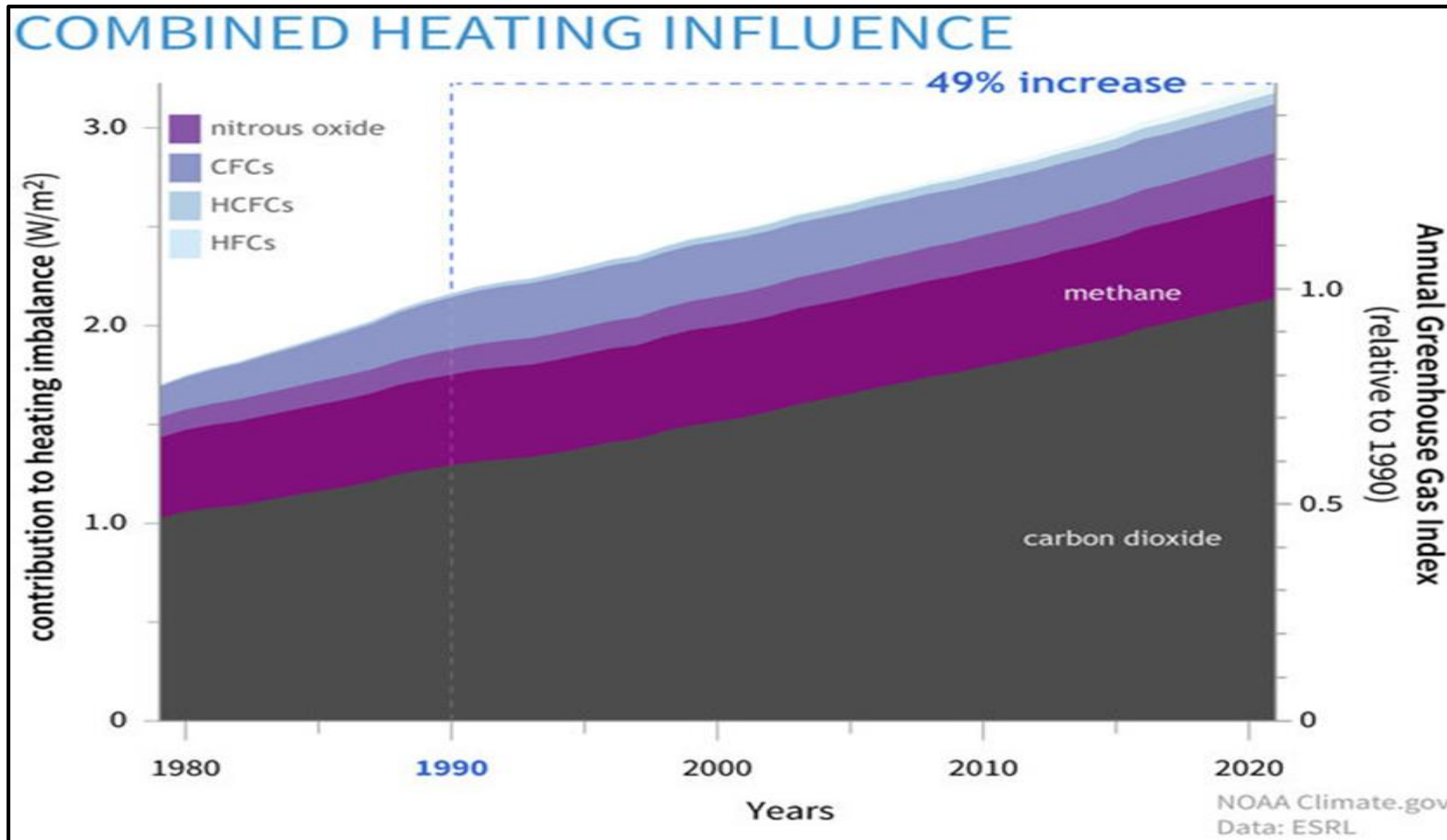




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## Impact of human activities



[Climate.gov](https://climate.gov)

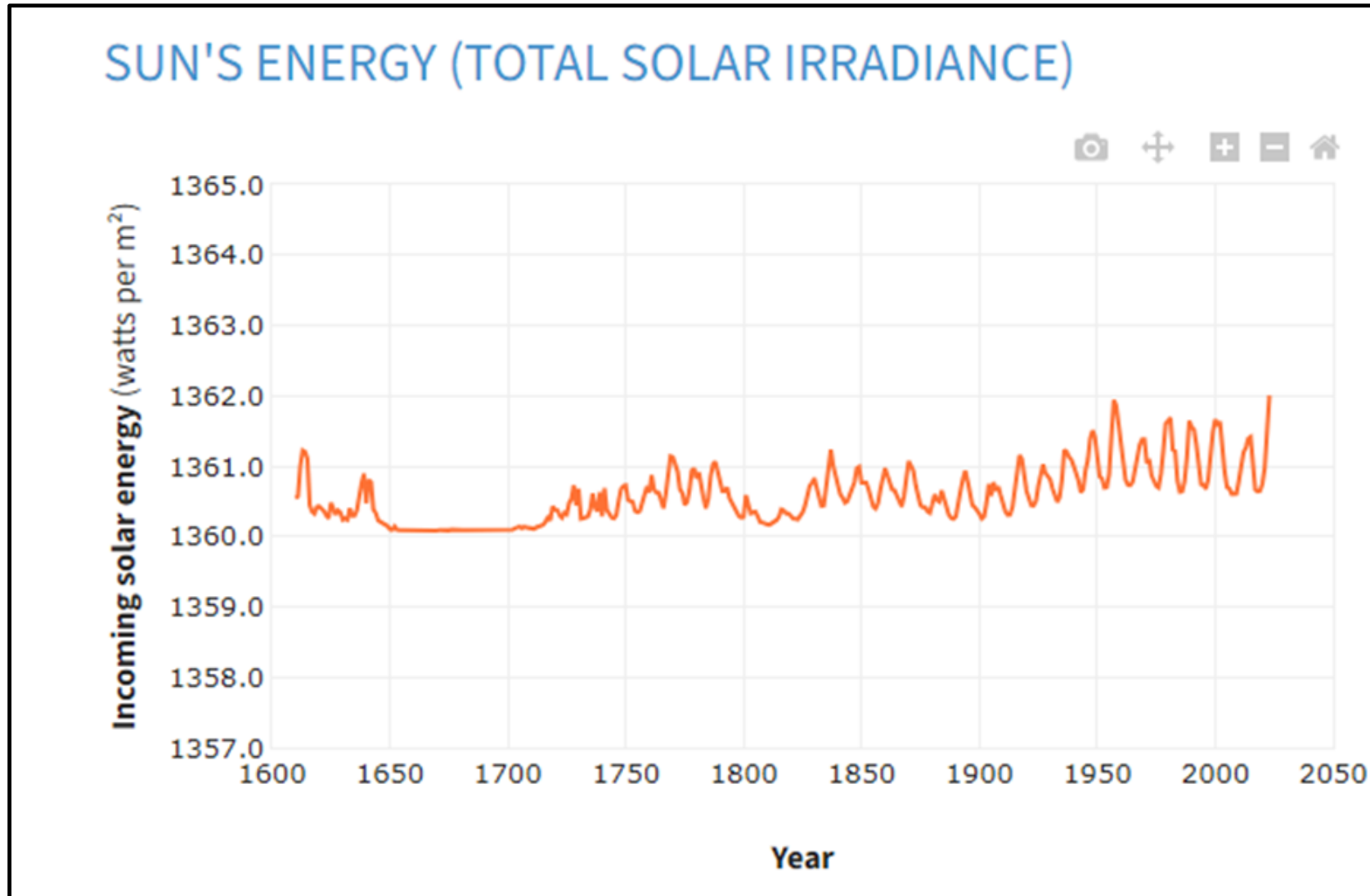




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## It is not the sun!



Climate.gov



# Preterm birth

- Birth of a child before 37 completed weeks of gestation
- Leading cause of death and disability in children under 5 yr worldwide (11%)
- **Short-term sequelae:** Admission to Neonatal High Care and Intensive Units
  - Respiratory Distress Syndrome, Neonatal Jaundice, Sepsis, Early Neonatal Death
- **Long-term sequelae:** Early development of adult-onset diseases
  - Cancers, cardiovascular disease, insulin resistance and obesity, diabetes
  - Neurological and social disability

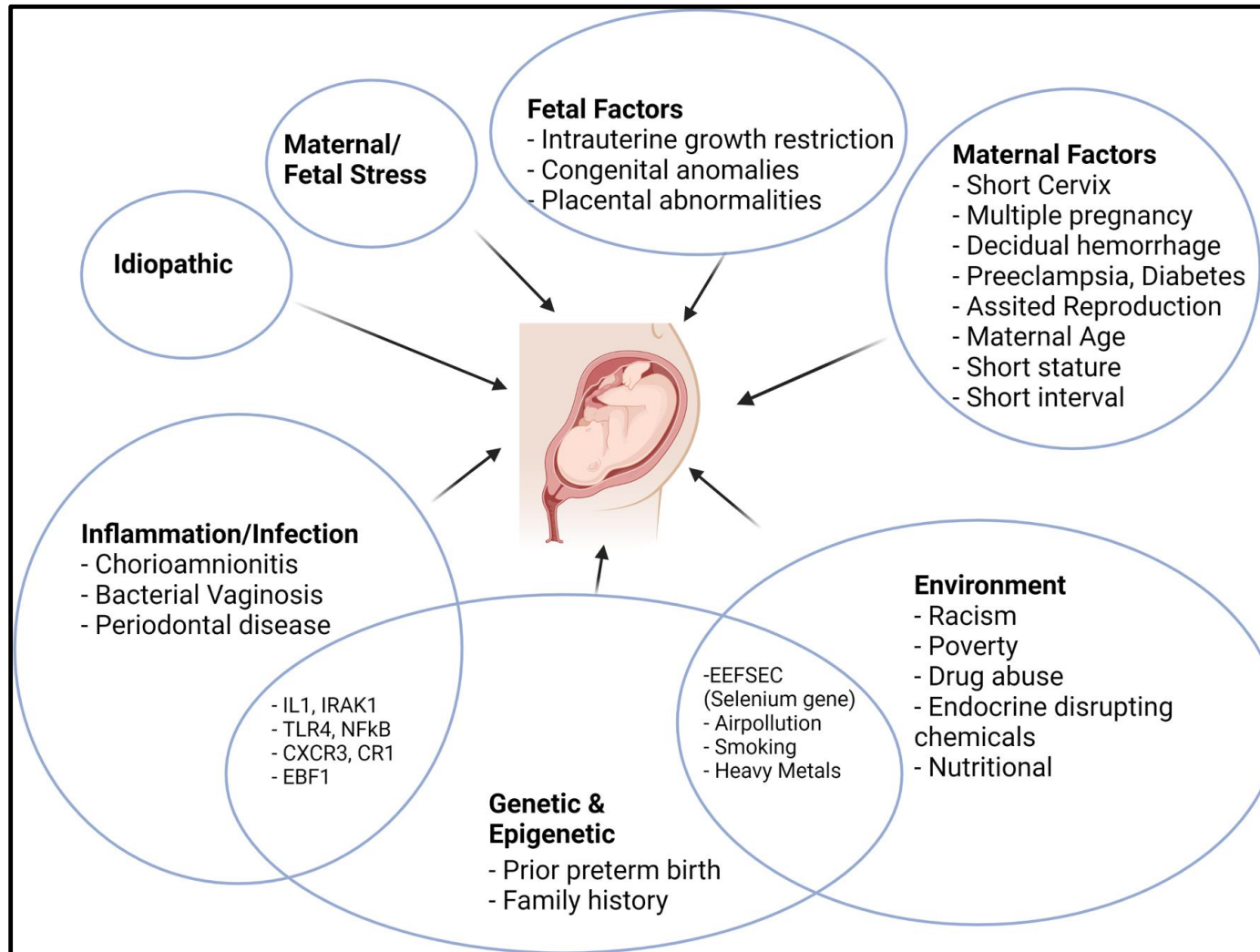




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## Causes of preterm birth



Jain et al., Am J Reprod Immunol, 2022

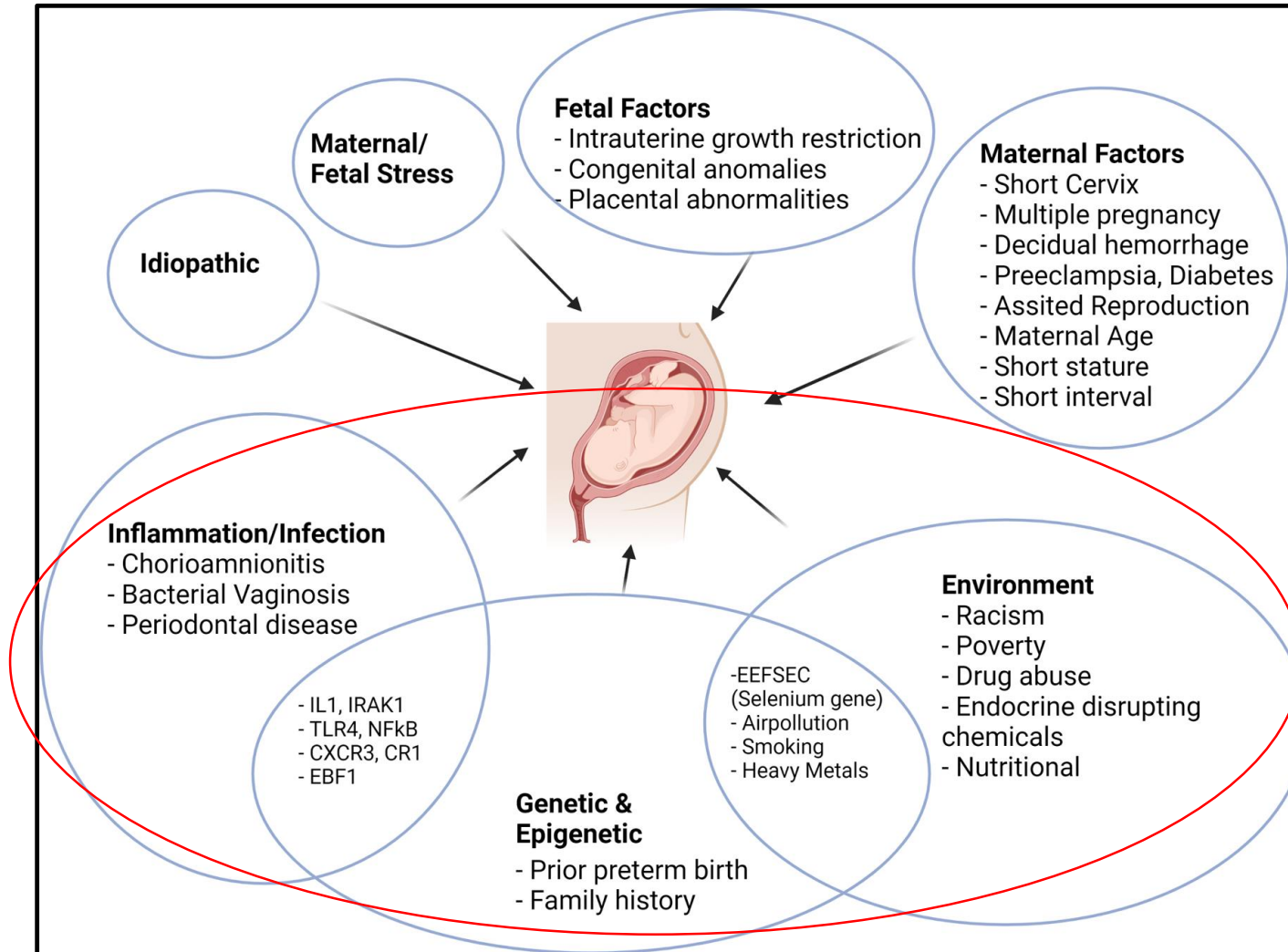




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## Causes of to preterm birth



Jain et al., Am J Reprod Immunol, 2022



# Heat exposure to preterm birth

- Studies show linkages between heat exposure and pregnancy outcomes
- Very few have investigated the underlying biological pathways in humans
- Plausible biological sequelae of heat exposure include:
  - Epigenetic and immunological changes;
  - Sympathetic system activation and release of hormones that trigger labour;
  - Dehydration, aberrant placental implantation and impaired placental flow;
  - Altered fetal membrane integrity and microbiome;

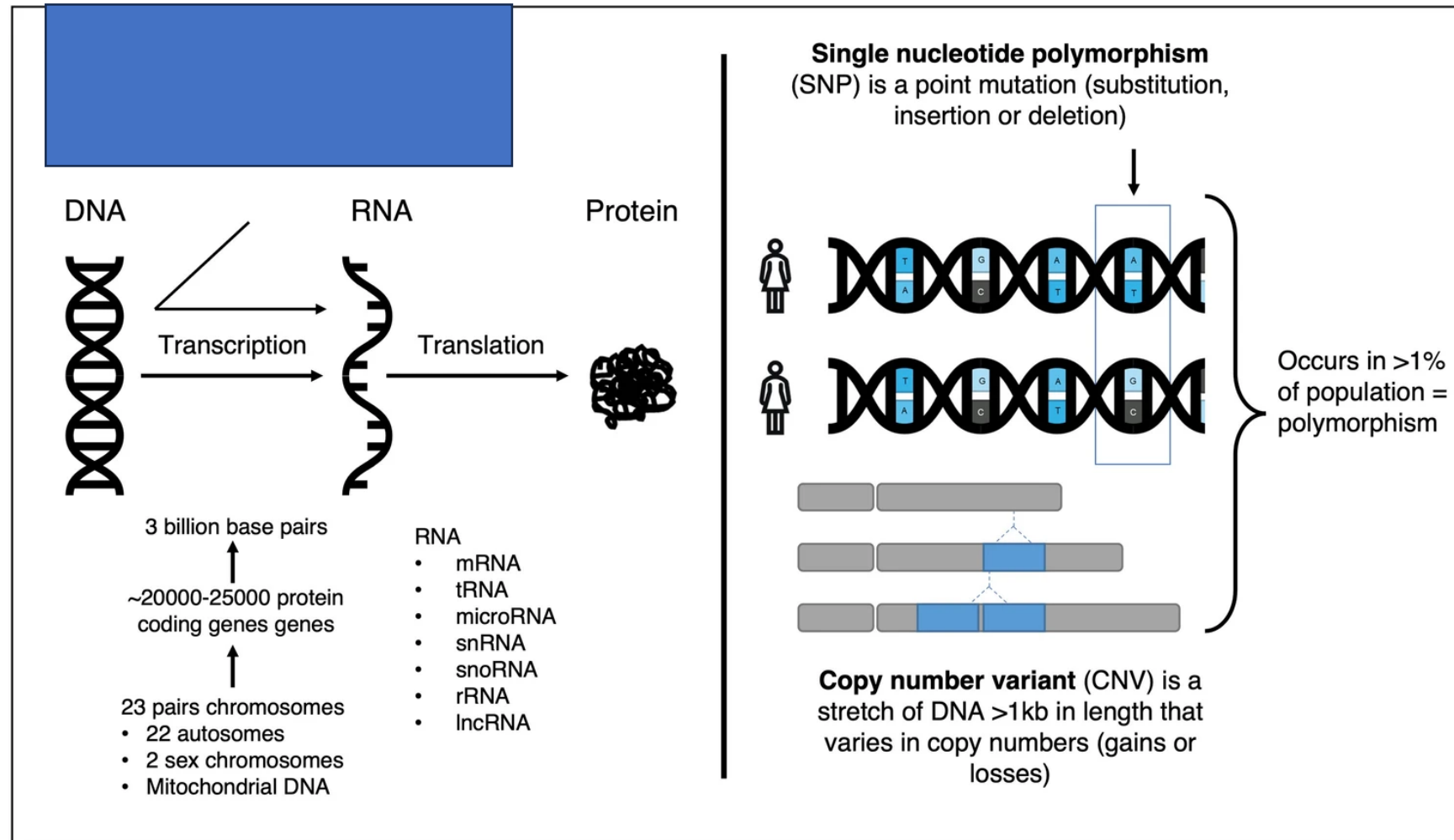
Samuels et al., *International Journal of Biotechnology*, 2022



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## Heat, genetics and preterm birth



Wadon et al., Ann Hum Genet, 2020

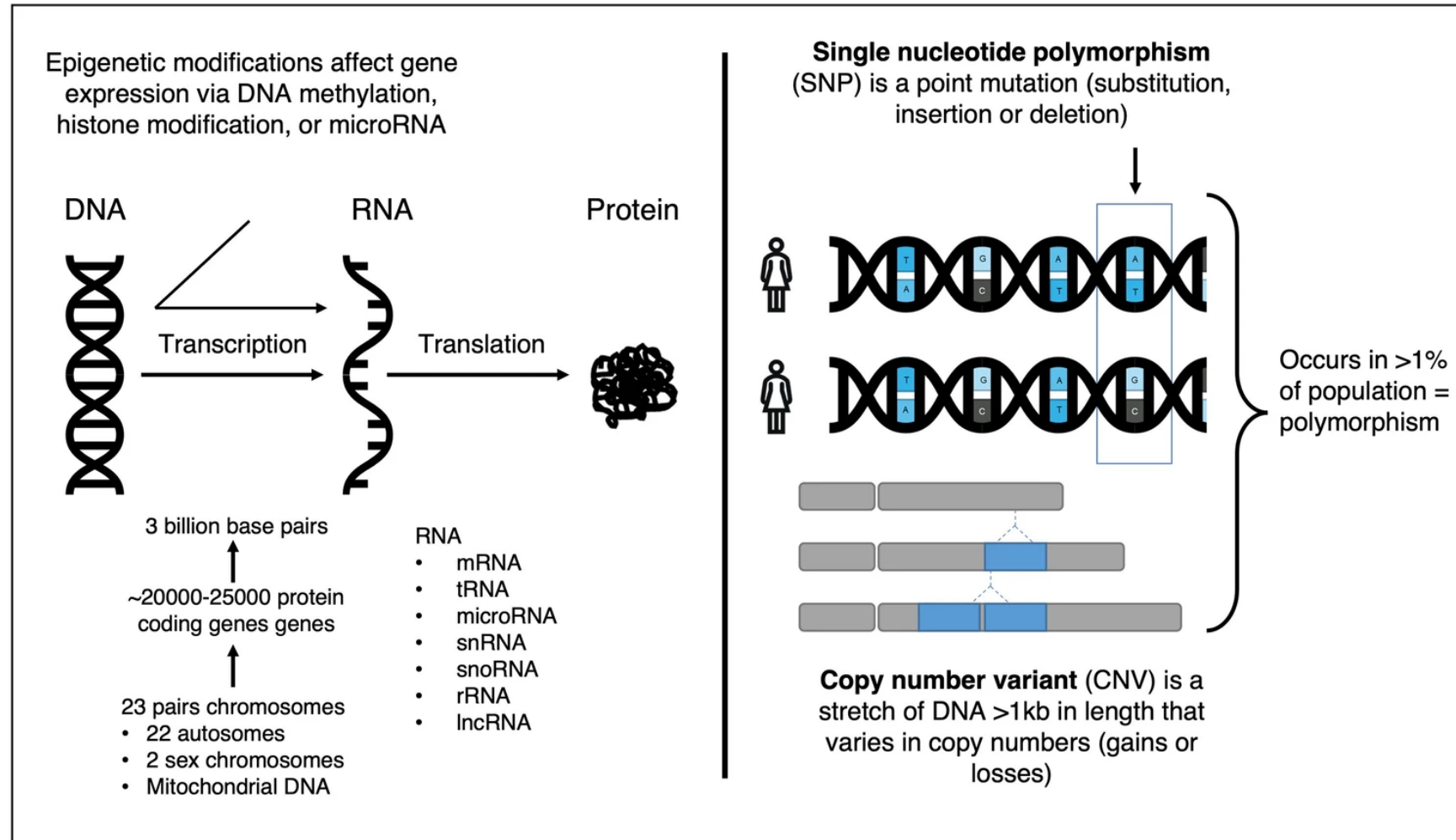




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## Genetics of preterm birth

| Genomic                              | Transcriptomic          | Epigenomic |
|--------------------------------------|-------------------------|------------|
| RAB31                                | RAB31                   | RAB31      |
| RBPJ                                 | RBPJ                    | RBPJ       |
| Heat shock family                    | Heat shock family       | TTN        |
| Nuclear receptor genes               | Nuclear receptor genes  |            |
| Immune signaling (IL-1, TLR4, NFKB1) | Immune signaling (IL-1) |            |
| IGF signalling                       | IGF signalling          |            |
| EBF1, EEFSEC, AGTR2                  | SOD1                    |            |
| CR1                                  |                         |            |
| PAI-2                                |                         |            |



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## Genomics of preterm birth

| Genomic                              | Transcriptomic          | Epigenomic   |
|--------------------------------------|-------------------------|--------------|
| RAB31                                | RAB31                   | <b>RAB31</b> |
| RBPJ                                 | RBPJ                    | <b>RBPJ</b>  |
| Heat shock family                    | Heat shock family       | <b>TTN</b>   |
| Nuclear receptor genes               | Nuclear receptor genes  |              |
| Immune signaling (IL-1, TLR4, NFKB1) | Immune signaling (IL-1) |              |
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| EBF1, EEFSEC, AGTR2                  | SOD1                    |              |
| CR1                                  |                         |              |
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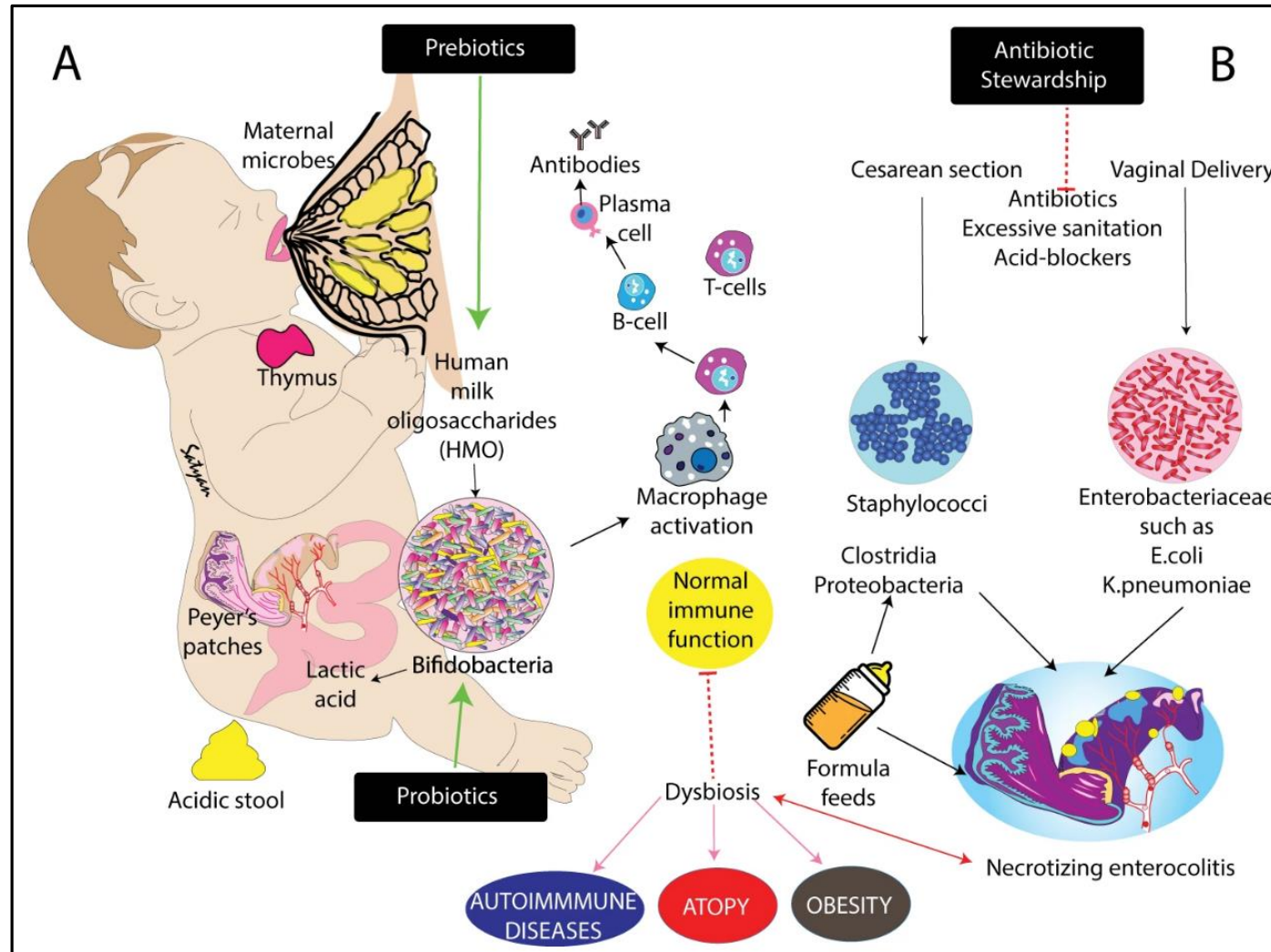




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# Heat and neonatal microbiome



Underwood et al., Nature, 2020

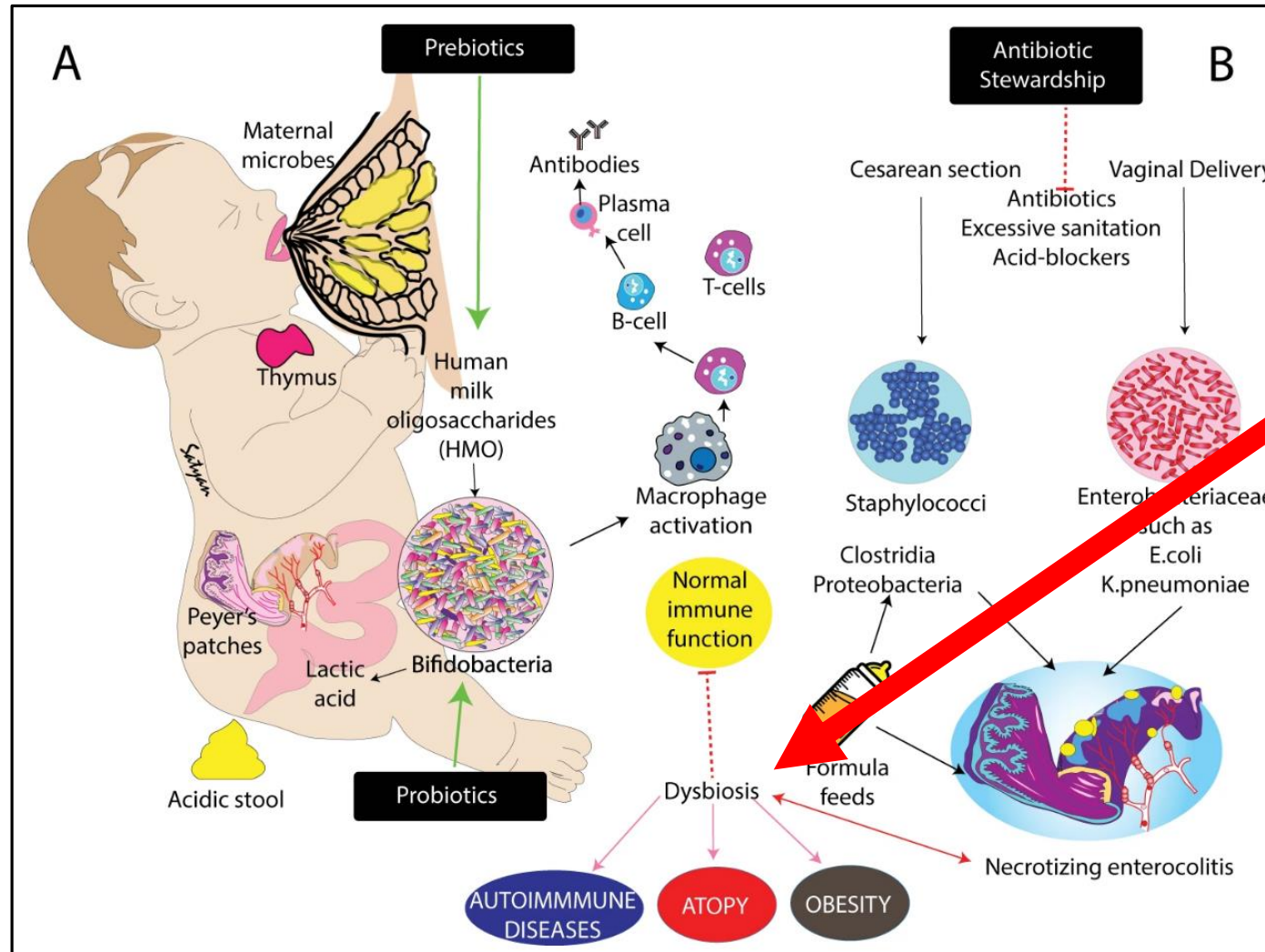




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## Heat and neonatal microbiome

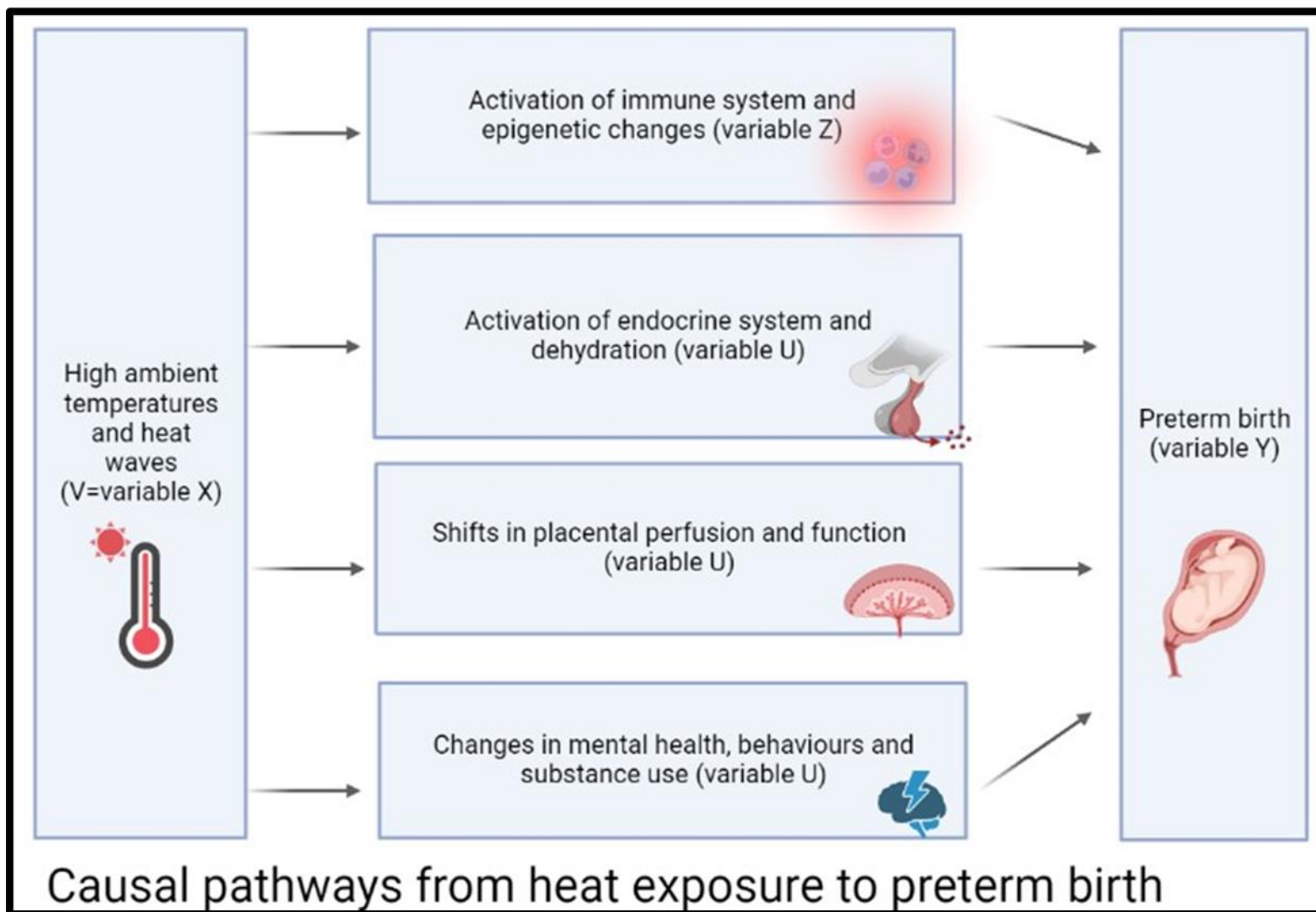


Heat exposure

Underwood et al., Nature, 2020



# Pathways to preterm birth



# Overarching goal of 3 linked studies

**Investigate biological mechanisms from heat stress to preterm birth**

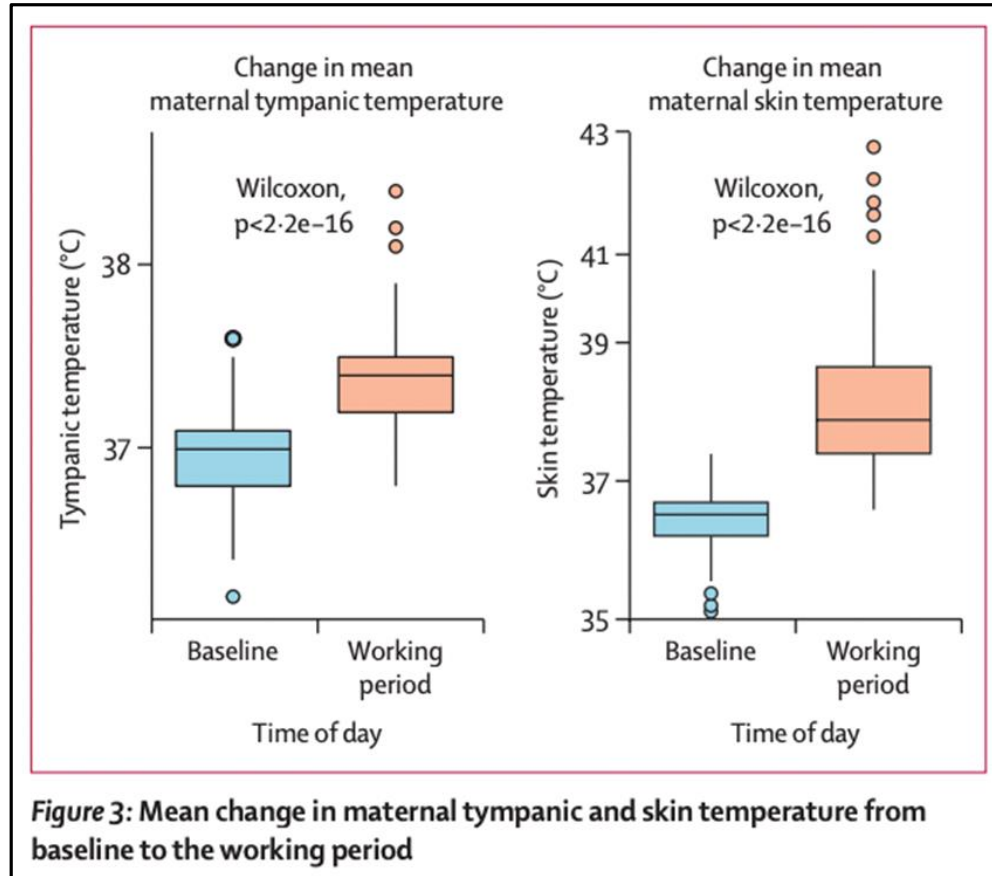




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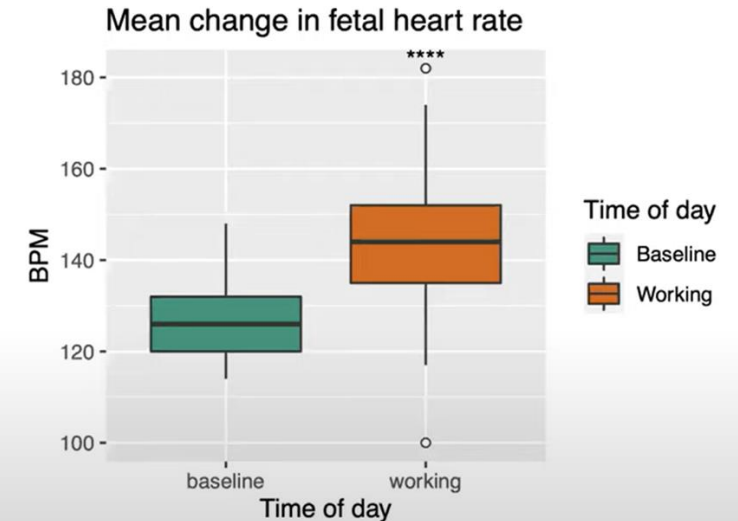
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## Heat In Pregnancy Study (HIPS):



### Impact on fetus

- 41/122 (33.6%) episodes of fetal stress
- 21/122 (17%) experienced fetal heart rates >160 or < 115 bpm.
- 22/40 (55%) experienced an increase in RI from baseline





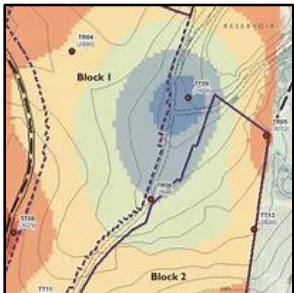
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# Heat In Pregnancy Study (HIPS):

**Overall aim:** to determine the physiological and biochemical changes that occur in pregnancy due to heat stress and how these impact maternal, fetal and newborn health and well-being.

**Micro-climate mapping by remote data monitoring:** cover regions from where participants will be recruited for the duration of the study



## Chronic Heat Prospective

**Cohort study:** Intensive follow-up including wearable devices to measure personal heat, humidity and air pollution exposure



**Placenta and microbiome work:** fetal size, umbilical doppler assessments, placental hormones and rectal swabs for infant microbiota



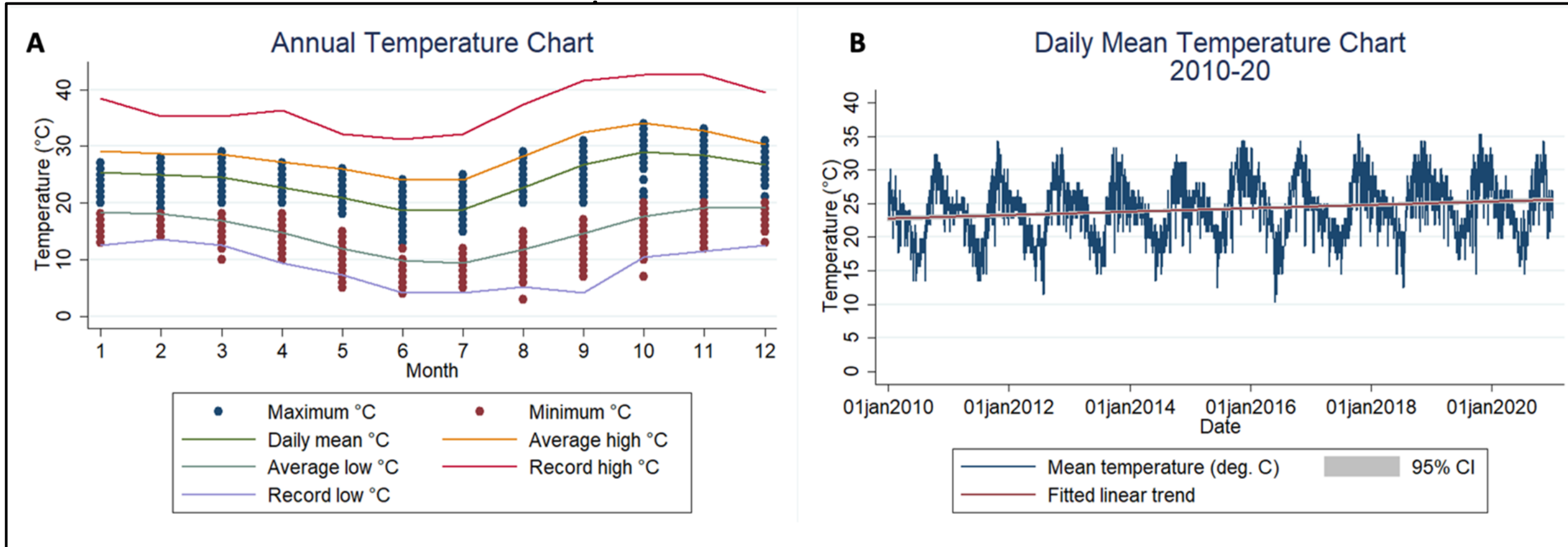




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## Extreme heat and preterm birth in rural Zimbabwe



Climate change in Shurugwi: (A) Intra-annual variation in temperature (B) Average daily temperature by year



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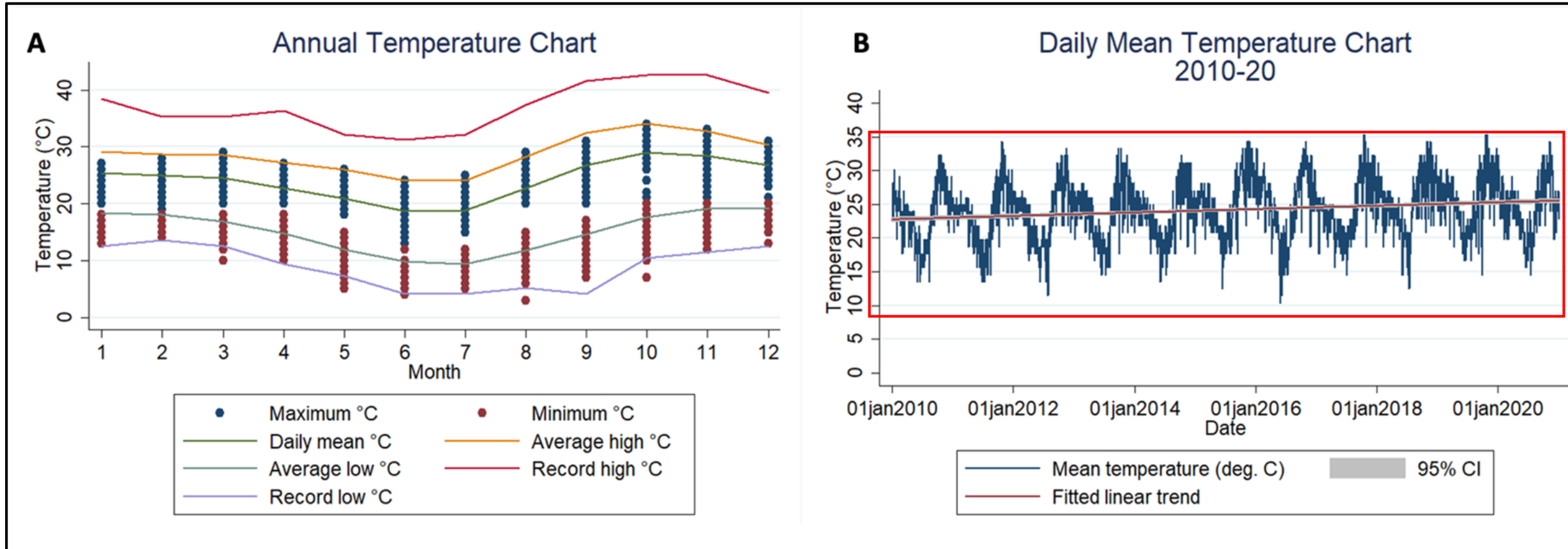


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# Extreme heat and preterm birth in rural Zimbabwe

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Climate change in Shurugwi: (A) Intra-annual variation in temperature (B) Average daily temperature by year



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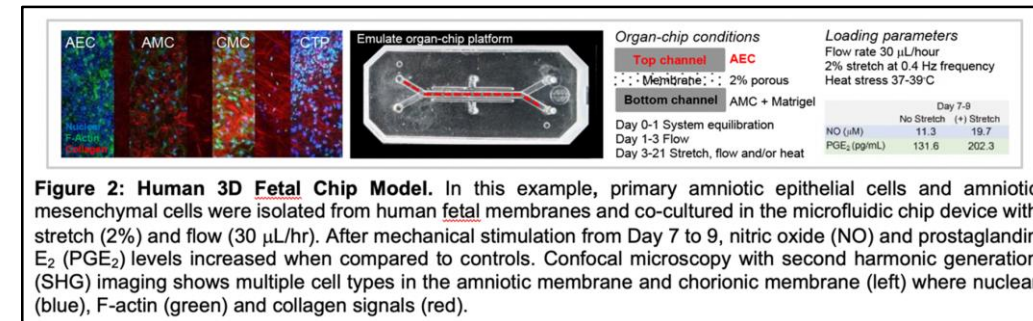
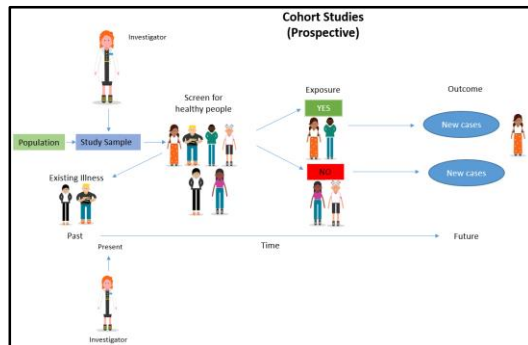
# Extreme heat and preterm birth in rural Zimbabwe

**Overall aim:** define the biological mechanism linking extreme heat with preterm birth

**Two cohorts:** evaluate association between extreme heat and preterm birth

**Nested sub-study:** explore associations between extreme heat and inflammatory pathways underlying preterm birth

**Human fetal chip model:** to provide a cellular level understanding of the response of fetal membranes to environmental changes in heat.



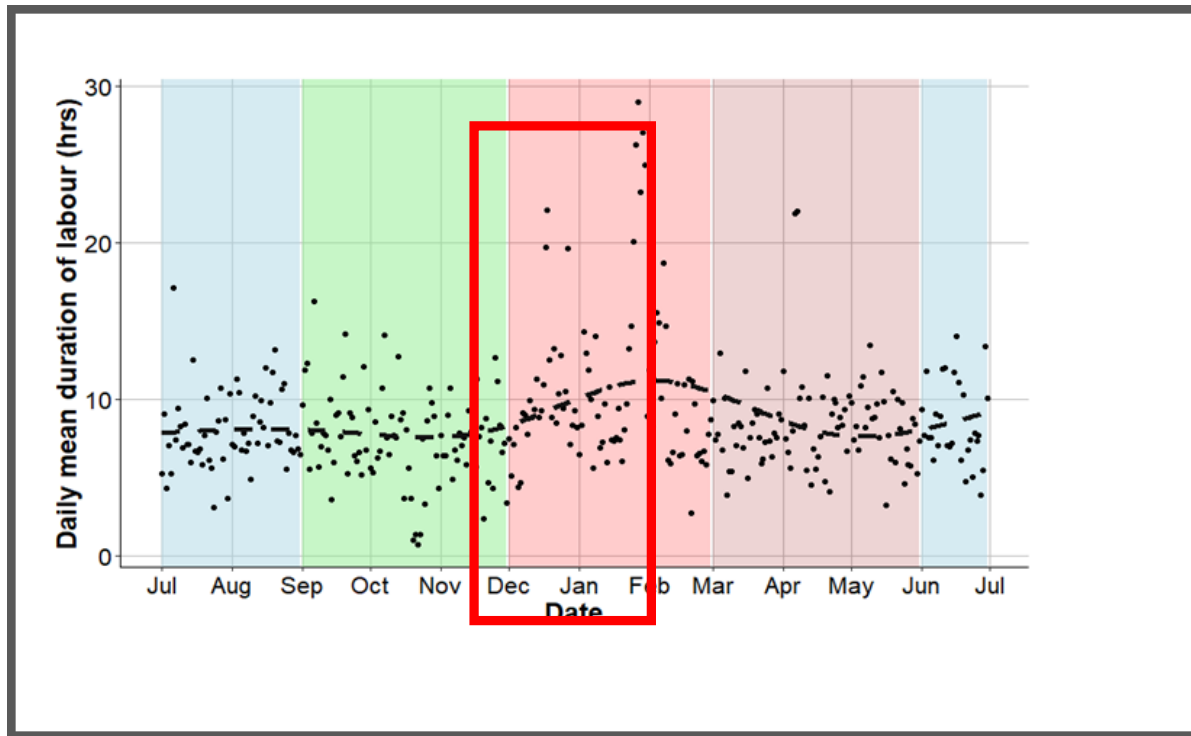


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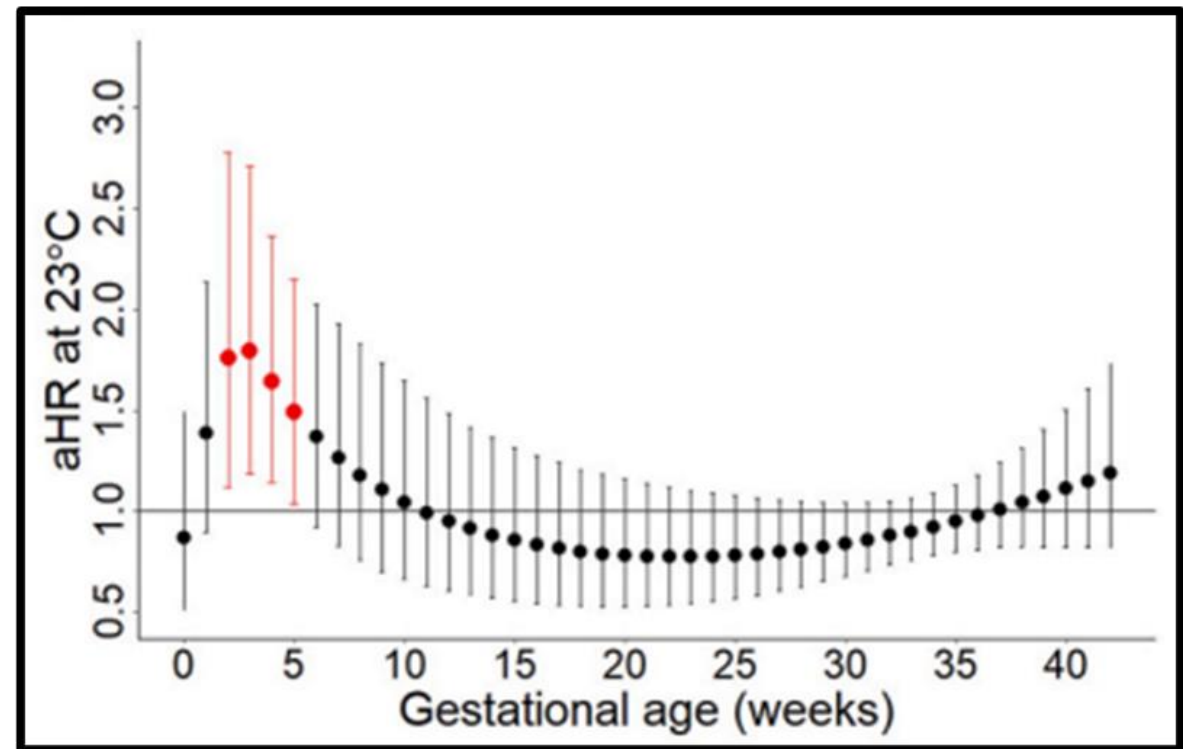
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## Bio-HEAT study:

Investigating the Biological pathways from HEAT exposure to preterm birth and other adverse maternal and child health outcomes



Provisional analysis 7996 birth records in Jhb, Mean duration of labour with fitted natural cubic spline ( $df = 6$ ). Median duration in summer=7.7 hours (IQR=1.8-13.8), winter=6.4 hours (IQR=1.3-12.4), spring=6.3 hours (IQR=1.2-12.0) and autumn=6.2 hours (IQR=1.3-12.3). Wilcoxin signed rank test  $p < 0.001$ . EMCS due to foetal distress=396 (21% of births) versus winter=292 (14% of births)



Ambient temperature during pregnancy and risk of maternal hypertensive disorders: A time-to-event study in Johannesburg, South Africa

Chérie Part<sup>a,\*</sup>, Jean le Roux<sup>b</sup>, Matthew Chersich<sup>b</sup>, Shobna Sawry<sup>b</sup>, Véronique Filippi<sup>c</sup>, Nathalie Roos<sup>d</sup>, Lee Fairlie<sup>b</sup>, Britt Nakstad<sup>e,f</sup>, Jeroen de Bont<sup>g</sup>, Petter Ljungman<sup>g,h</sup>, Massimo Stafoggia<sup>i</sup>, Sari Kovats<sup>a</sup>, Stanley Luchters<sup>j,k,l</sup>, Shakoor Hajat<sup>a</sup>



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# Bio-HEAT study:

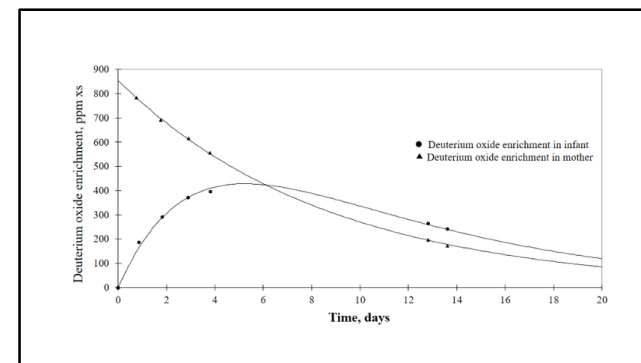
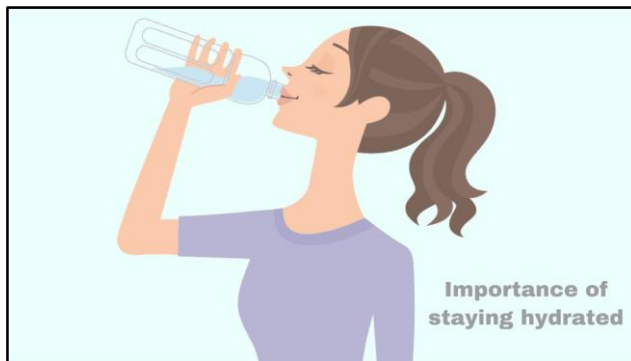
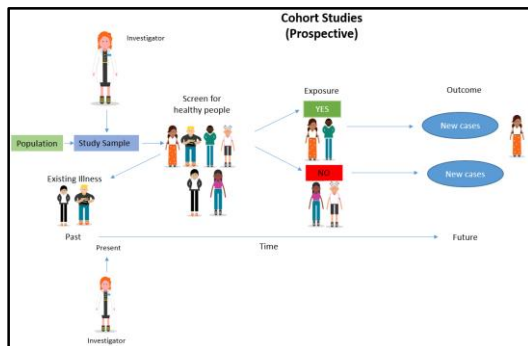
Investigating the Biological pathways from HEA**T** exposure to preterm birth and other adverse maternal and child health outcomes

Overall aim: understand the causal relations between heat exposure and pregnancy, intrapartum and postpartum outcomes

**Pregnant women cohort:** elucidate the biomarkers and other factors mediating preterm birth in extreme heat.

**Intrapartum cohort:** explore the impact of potential protective interventions (space cooling, hydration) on outcomes using a historical comparative analysis.

**Breast feeding cohort:** explore the breast-feeding frequency, breast milk composition and breastmilk volumes changes with ambient temperature





# Summary of the three studies

| Study                                                   | PTB | Inflammatory biomarkers                                                                                                                          | Genetics and Epigenetics             | Innovative work                                                 |
|---------------------------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------|
| <b>HIPS study (The Gambia)</b>                          | Yes | <b>Placental hormones:</b> PAPP-A, PLGF,<br><b>Immune markers:</b> TNF- and IL-6                                                                 | Placenta and Infant epigenetics      | Infant rectal microbiome and Placental work                     |
| <b>Extreme heat and preterm birth in rural Zimbabwe</b> | Yes | <b>Immune markers:</b> CRP, IL-4-13, TNF, CCL3<br><b>Lipid profiles:</b> Resolvins, eicosanoids<br><b>Intestinal barrier function:</b> Neopterin | DAMPS and PAMPS: S100B, hsp70, hsp90 | Human fetal chip model                                          |
| <b>Bio-Heat study (South Africa)</b>                    | Yes | <b>Immune markers:</b> IL-6 and other cytokines<br><b>Sympathetic system:</b> cortisol and adrenaline                                            | Epigenetics                          | Intra-partum protective interventions and breast milk sub-study |

# Anticipated outcomes

- Collectively, studies focus across rural & urban settings, in 2 African regions
- Evidence of complex interplay between heat, and maternal and infant health
- Synthesising findings from these & related studies fill major knowledge gaps
- Inform the development of targeted, evidence-based interventions.

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- **Conflicts of Interest:**
- **Project websites :**
- <https://www.lshtm.ac.uk/research/centres-projects-groups/gambia-heat-in-pregnancy-study#:~:text=While%20thermoregulation%20in%20pregnancy%20is,rate%20and%20placental%20blood%20flow>
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# THANK YOU

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