# Mitochondriomic Approaches to Children's Environmental Health

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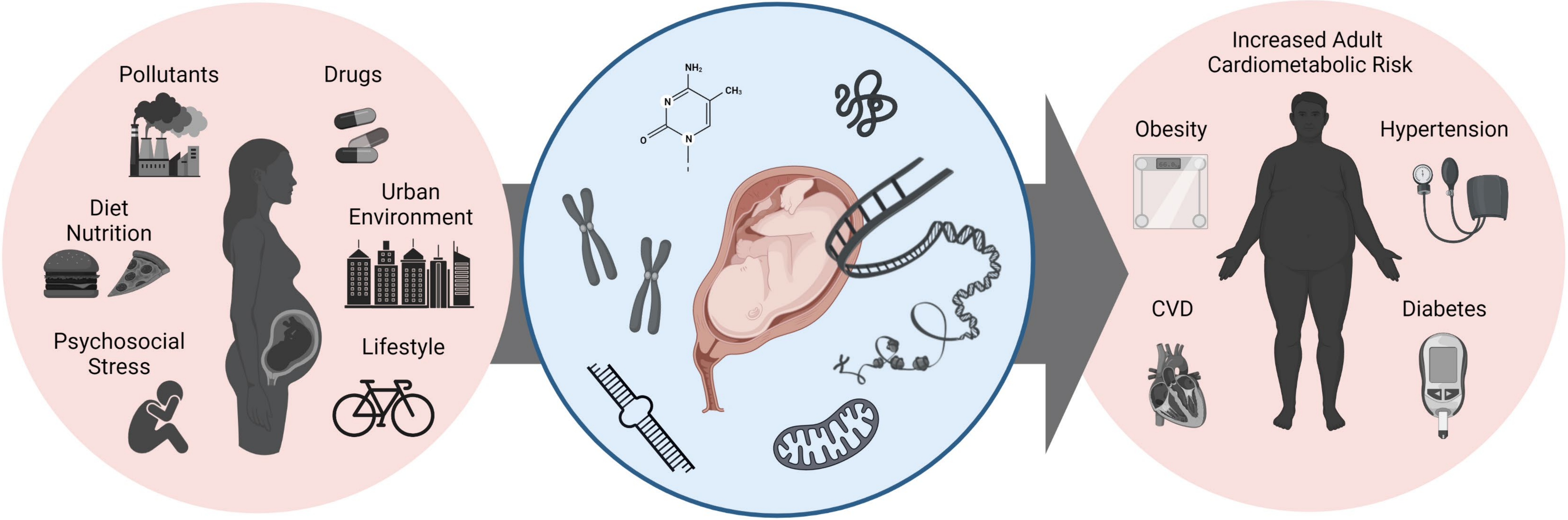
Pollutants
Drugs
Diet
Nutrition
Urban
Environment
Psychosocial
Stress
Lifestyle
?
Increased Adult
Cardiometabolic Risk
Obesity
Hypertension
CVD
Diabetes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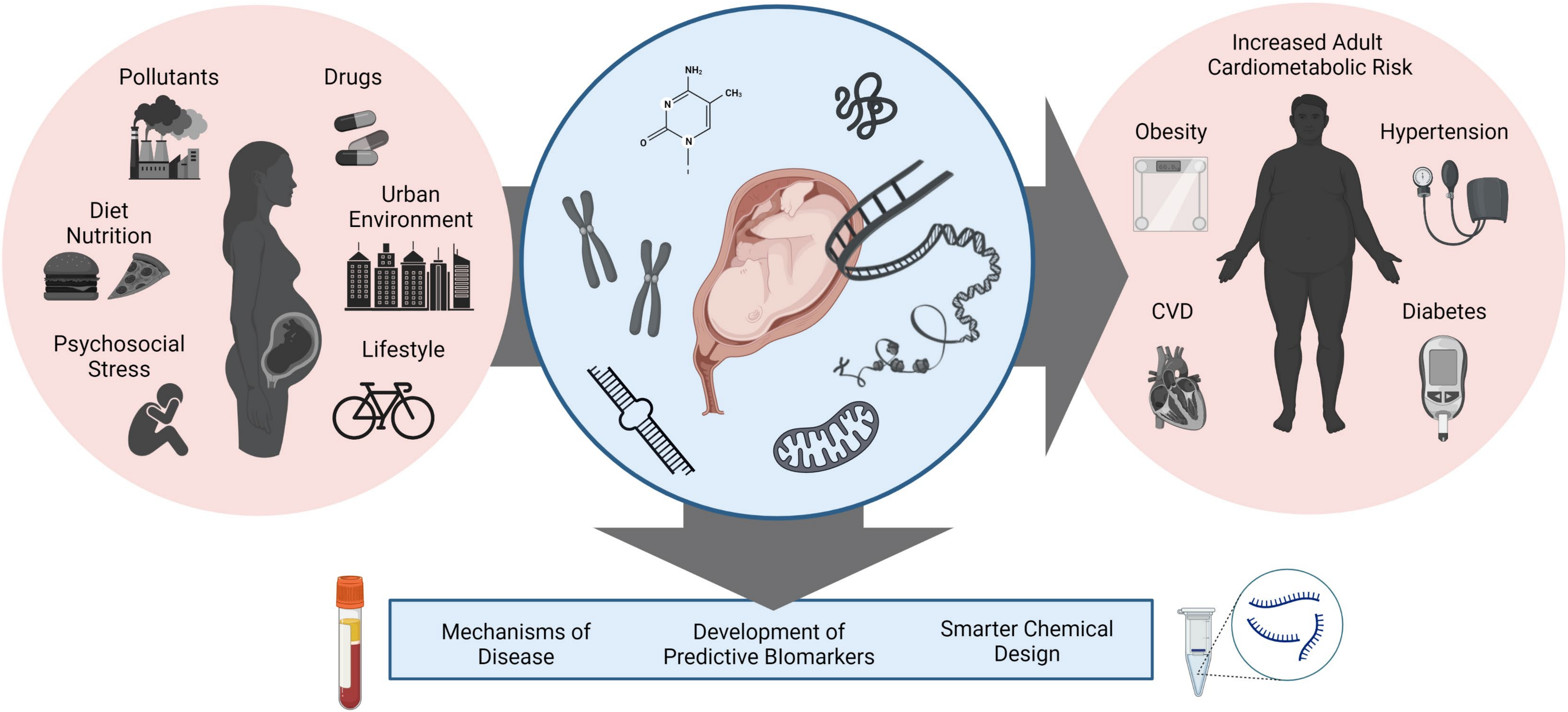

Pollutants
Drugs
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NH2
CH3
N
N
O
Increased Adult
Cardiometabolic Risk
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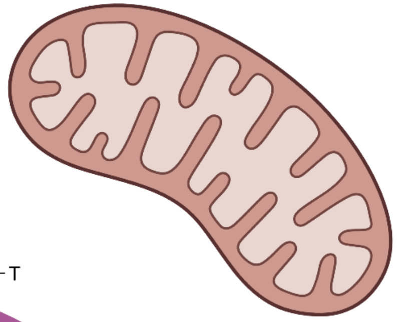
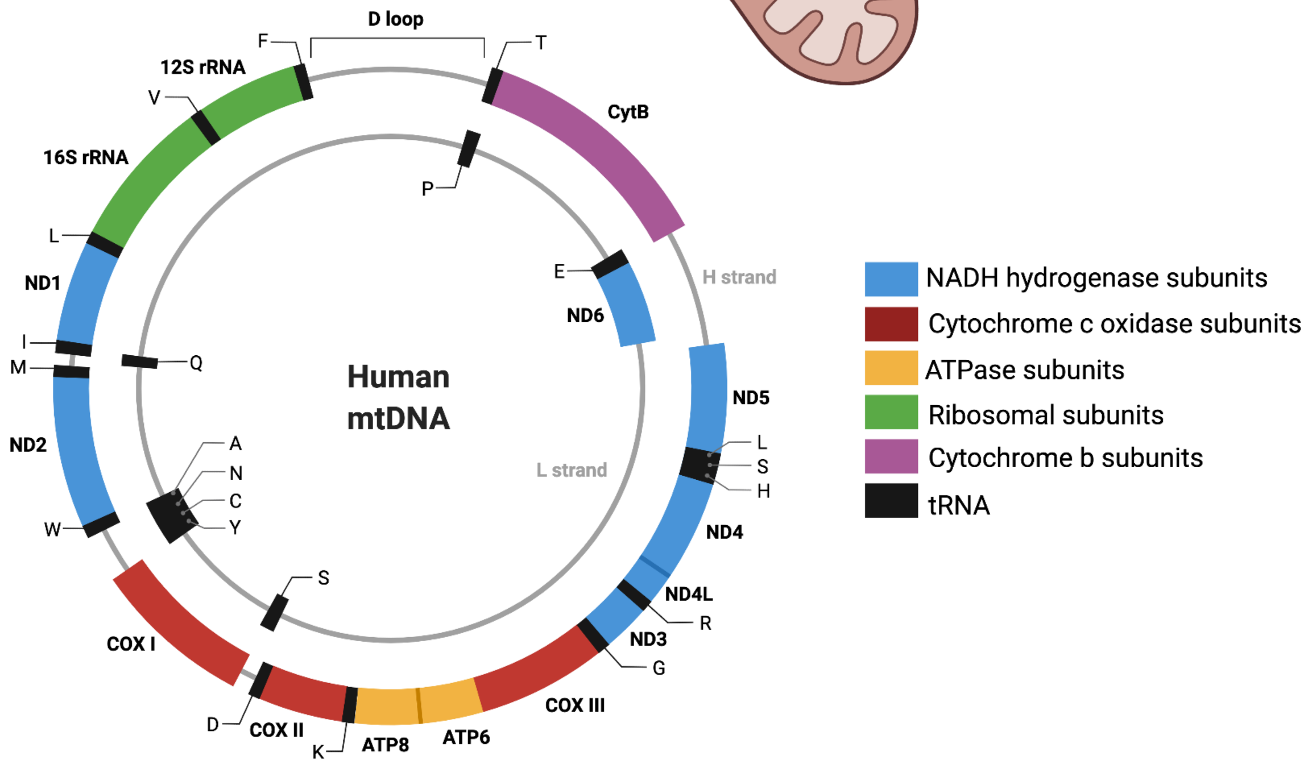
Hypertension
CVD
Diabetes
Mechanisms of
Disease
Development of
Predictive BIomarkers
Smarter Chemical
Design

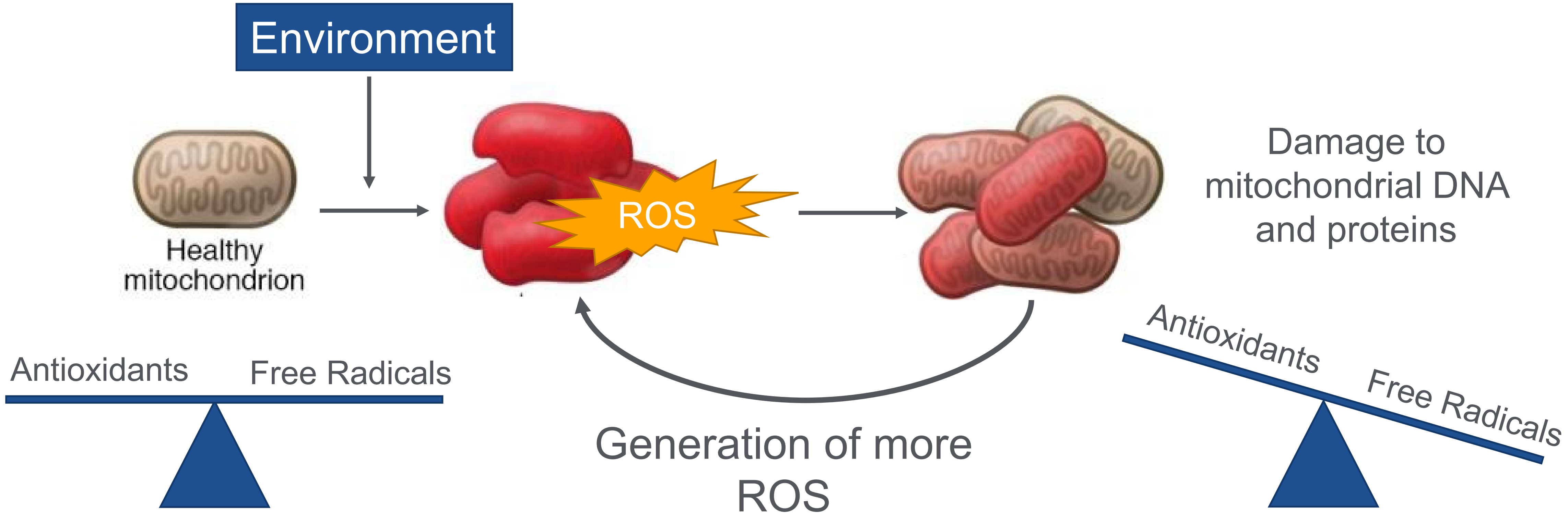
# Mitochondria and mtDNA

- Cellular organelle in the cytosol of most nucleated cells
- Turn glucose into ATP (energy) process of oxidative phosphorylation
- Extra-nuclear genome
- Small Circular DNA:16,569 bp
- 37 genes
    - 13 for proteins (oxidative phosphorylation enzymes)
    - 22 for tRNAs
    - 2 for rRNAs
- Primary source of intracellular oxidative stress.

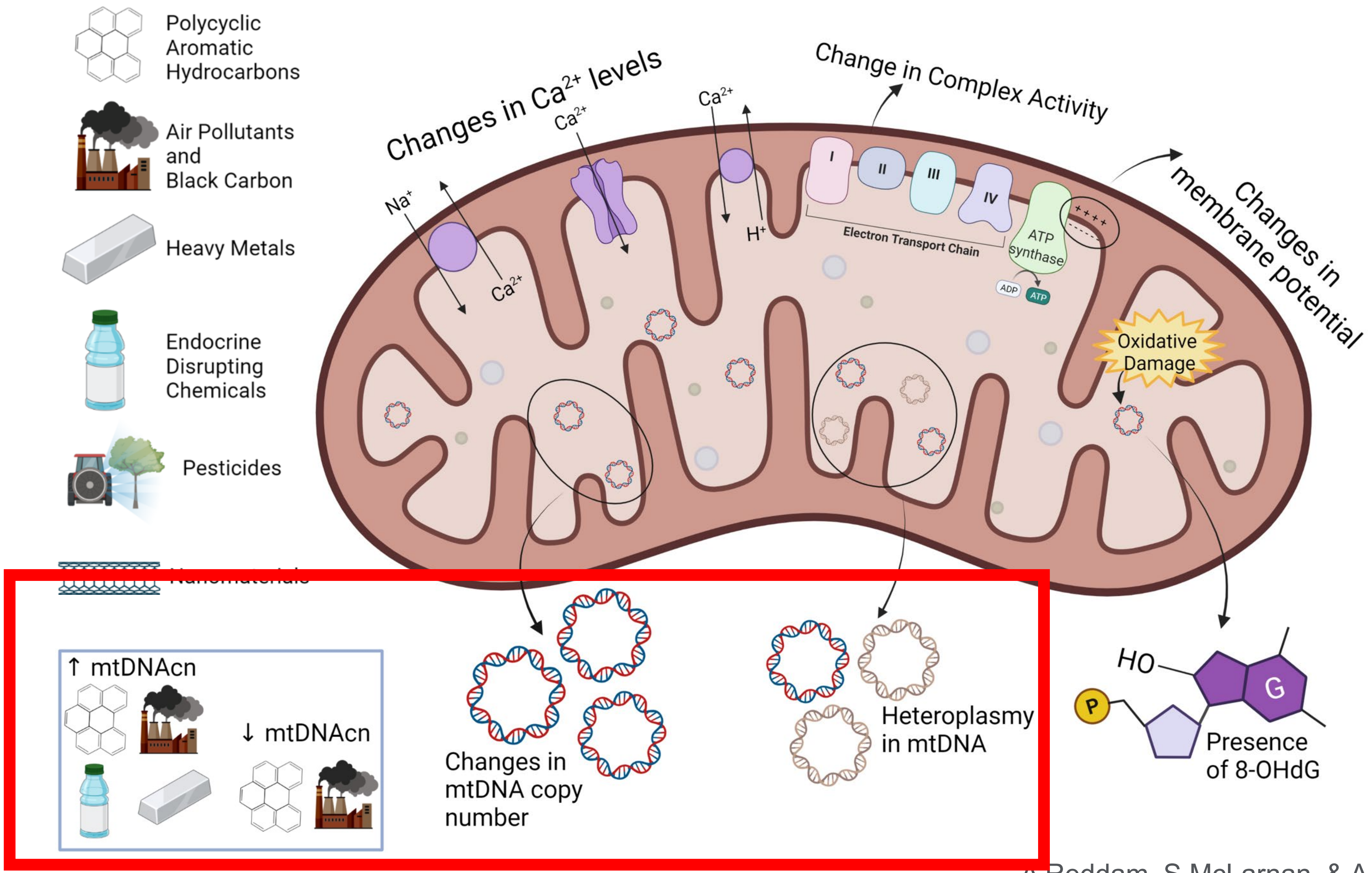




# A Vicious Cycle




ROS: Reactive Oxygen Species

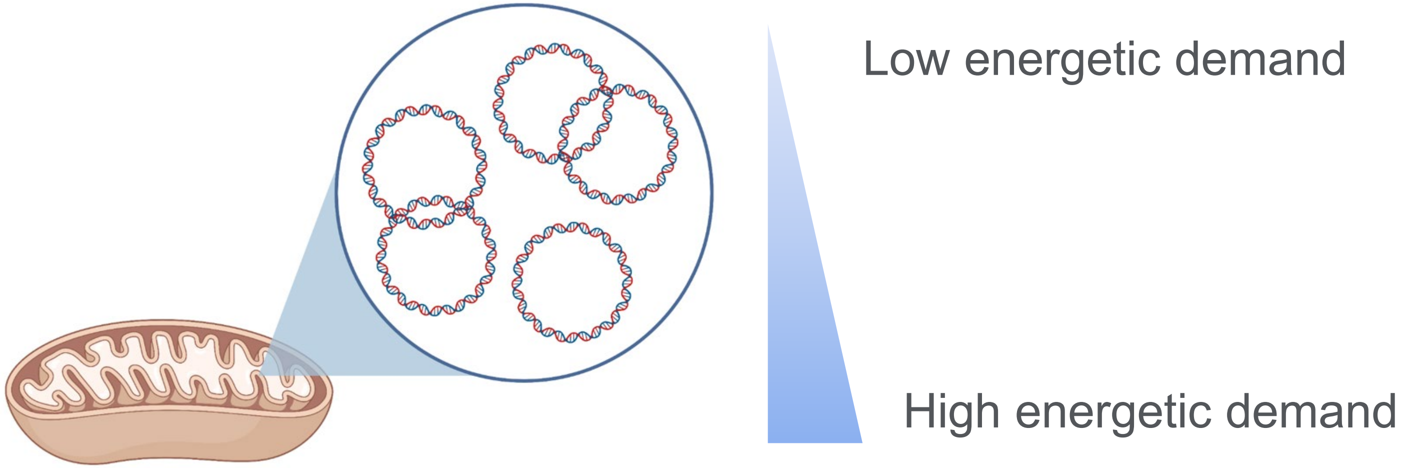



A Reddam, S McLarnan, & A Kupsco, under review

# Environmental Mitochondriomics

Systematic investigation of the mtDNA and its regulation in response to environmental exposures

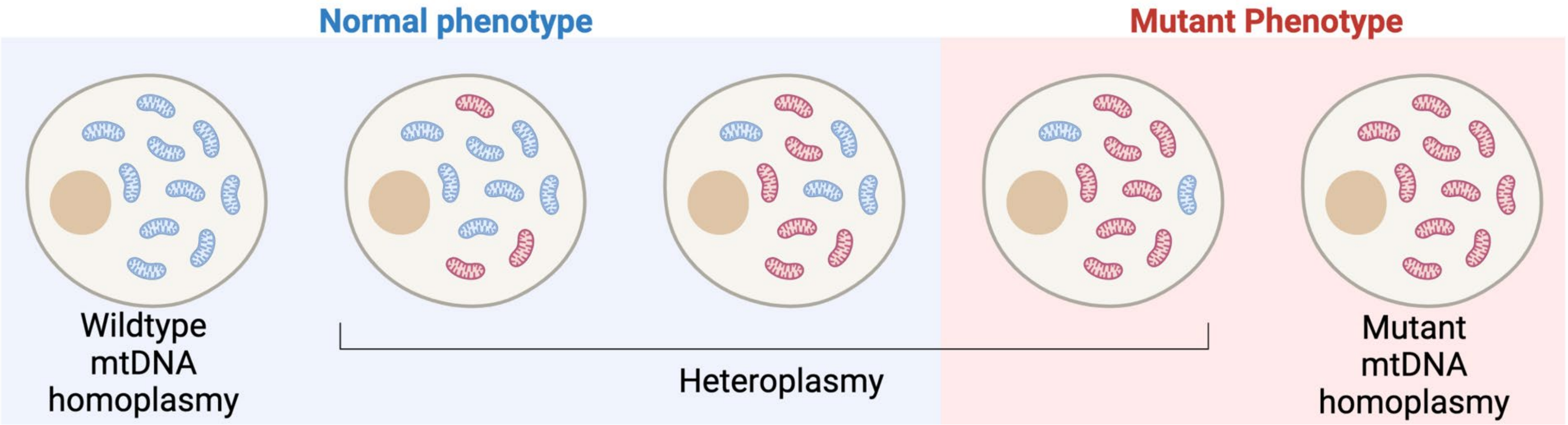
## mtDNA Copy Number (mtDNAcn)



# Environmental Mitochondriomics

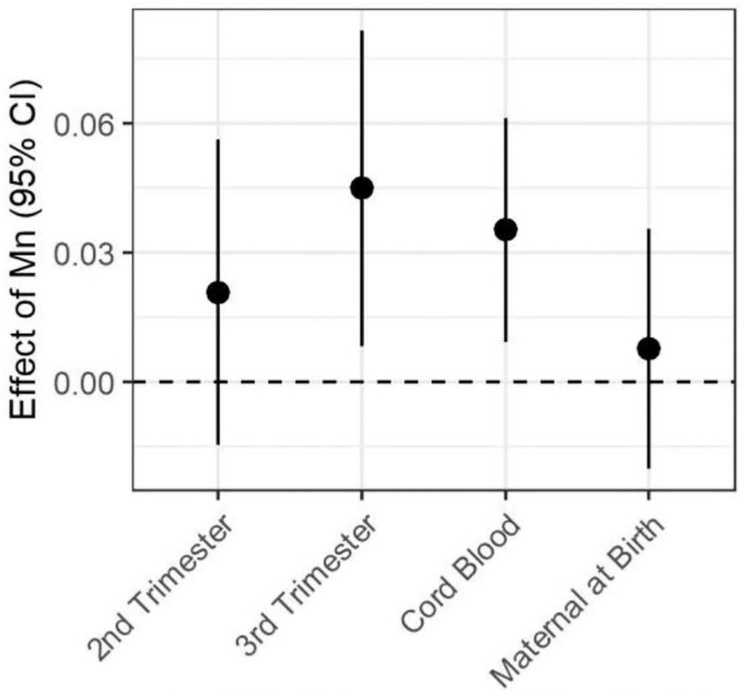
Systematic investigation of the mtDNA and its regulation in response to environmental exposures

## mtDNA
## Heteroplasmy

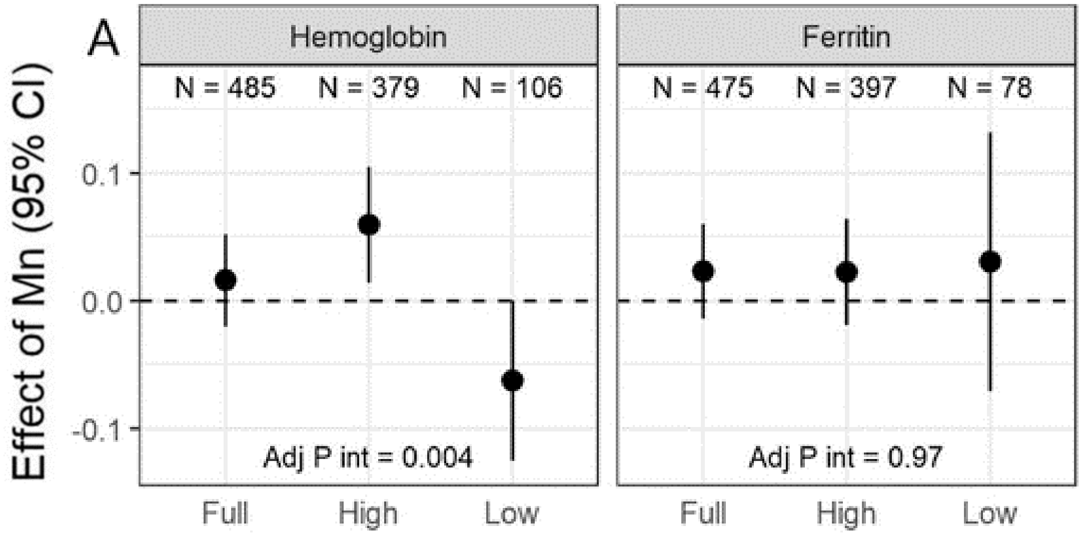


# Example: mtDNAcn in cord blood is associated with prenatal manganese (Mn) levels

Mn is an essential micronutrient that can be toxic at high levels



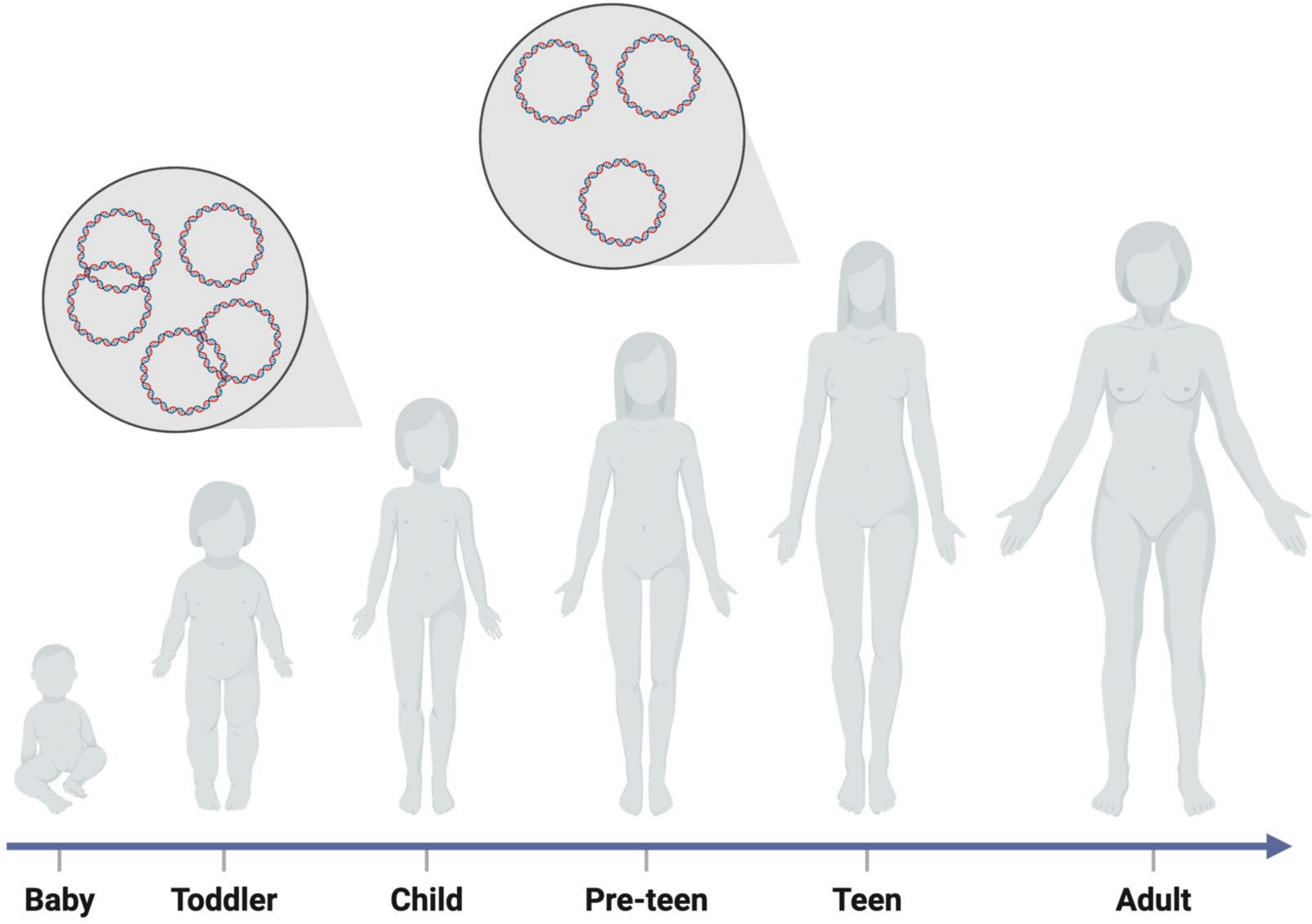

Associations of 2nd Trimester Mn by Maternal Anemic Status




Population by Hemoglobin and Ferritin Status

Kupsco et al., 2019

# But – mtDNA in childhood can only be interpreted in the context of dynamic changes in mtDNA throughout our lives



# mtDNA aging in human populations

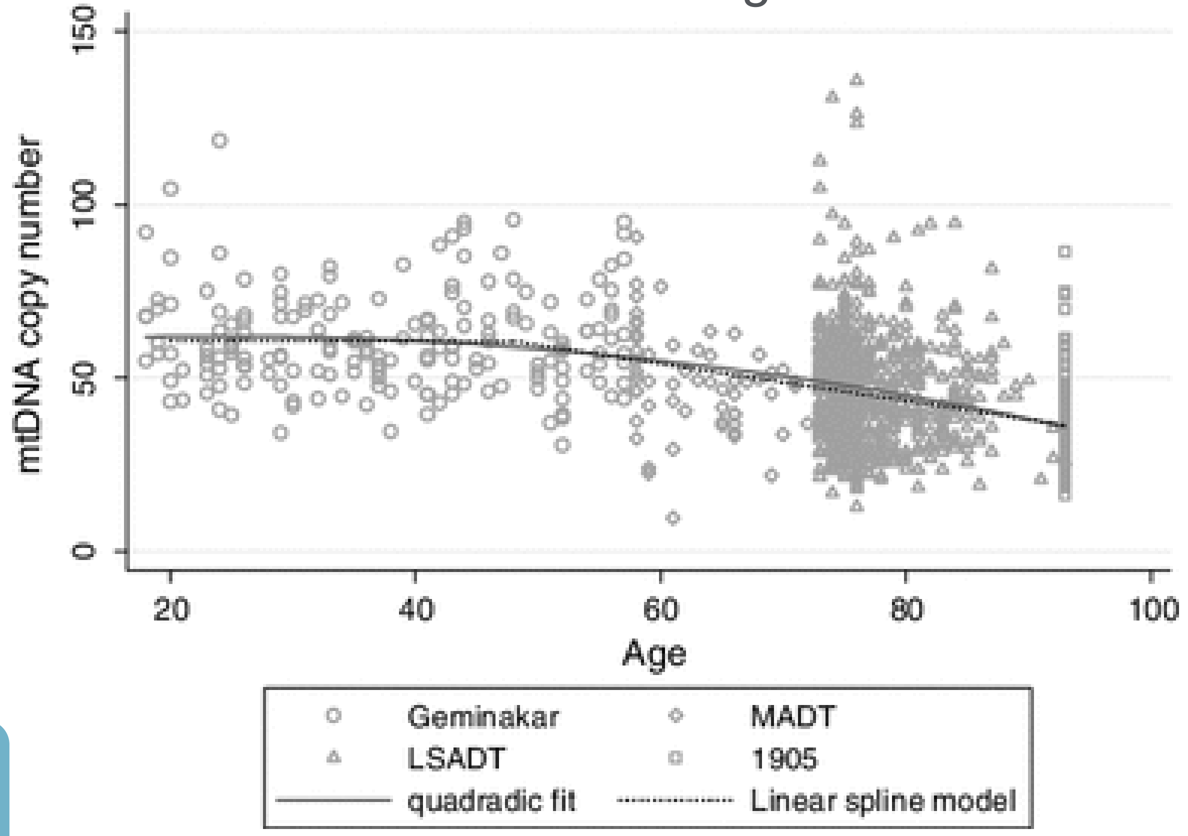
Mitochondrial function ↓ with age.

mtDNA content in blood ↓ with age

Associated with age-related diseases:
cardiovascular disease, cognitive decline, diabetes

But what about through childhood?

1000 individuals aged 19-83




Mengel-From et al., 2014

# Study Goals

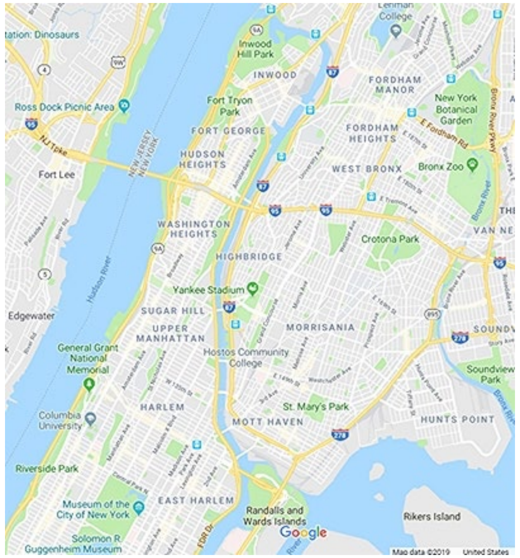
1. Characterize mtDNA copy number (mtDNAcn) trajectories from birth through adolescence

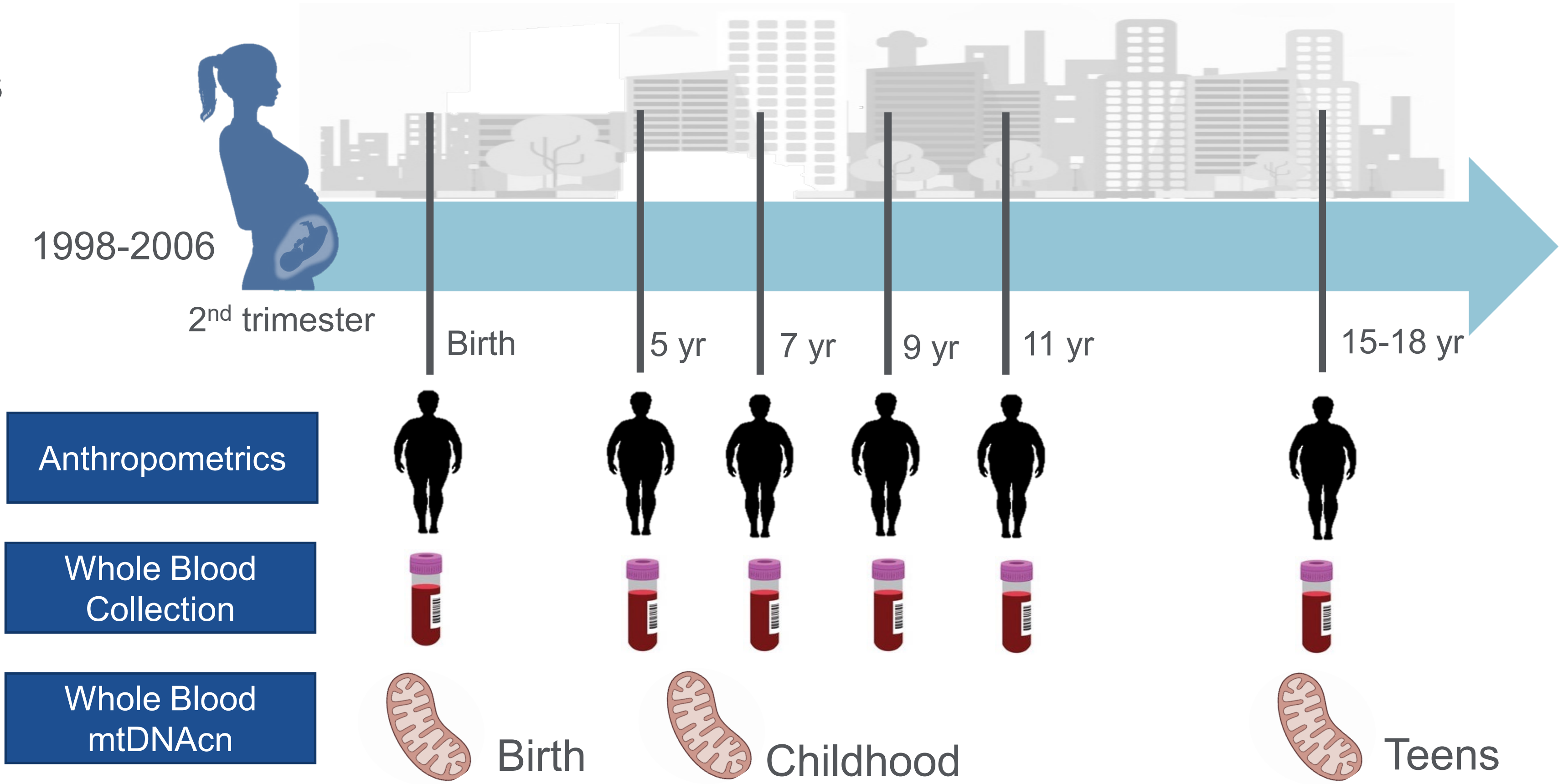
2. Determine maternal and child characteristics that associate with longitudinal mtDNAcn

# mtDNA in the Columbia Center for Children's Environmental Health (CCCEH)

Columbia Center For Children's Environmental Health
Mailman School of Public Health Columbia University

Enrolled 725 Pregnant Mothers of Dominican and African American descent.





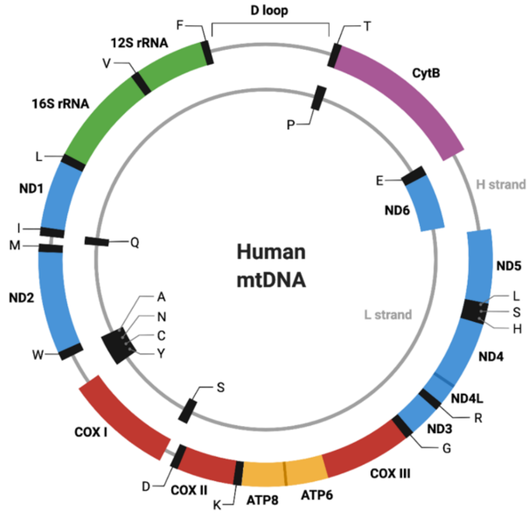
# Methods

Number of Samples

| | | | | |
|---|---|---|---|---|
| | | | | |

Quantified whole blood relative mtDNAcn using qRT-PCR.

Calculated as the ratio of a mitochondrial gene to a nuclear gene expression.

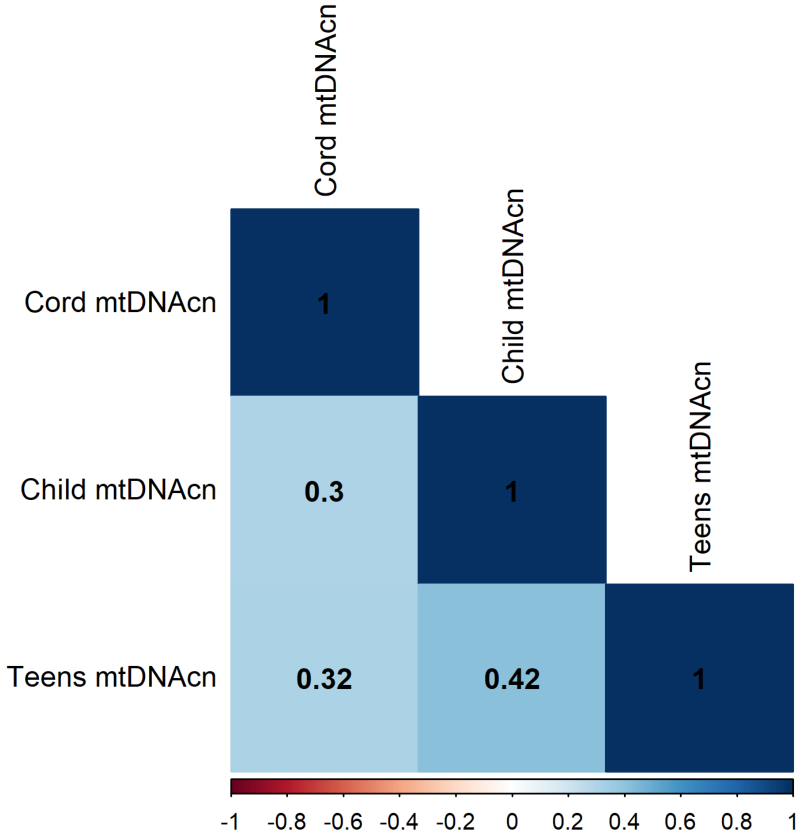


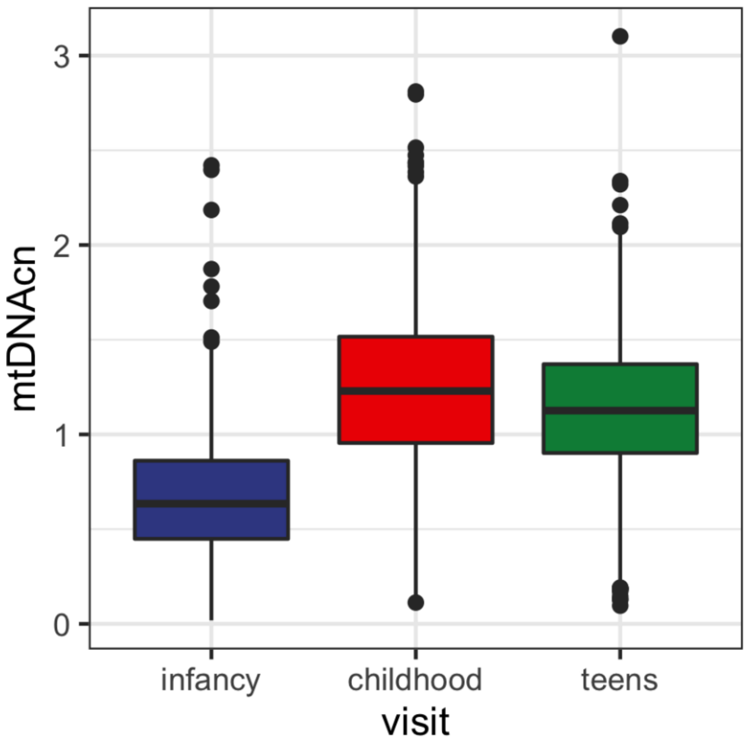

| | | | |
|---|---|---|---|
| | | | |

Examined longitudinal mtDNAcn trajectories and with potential prenatal covariates with mixed effects models.

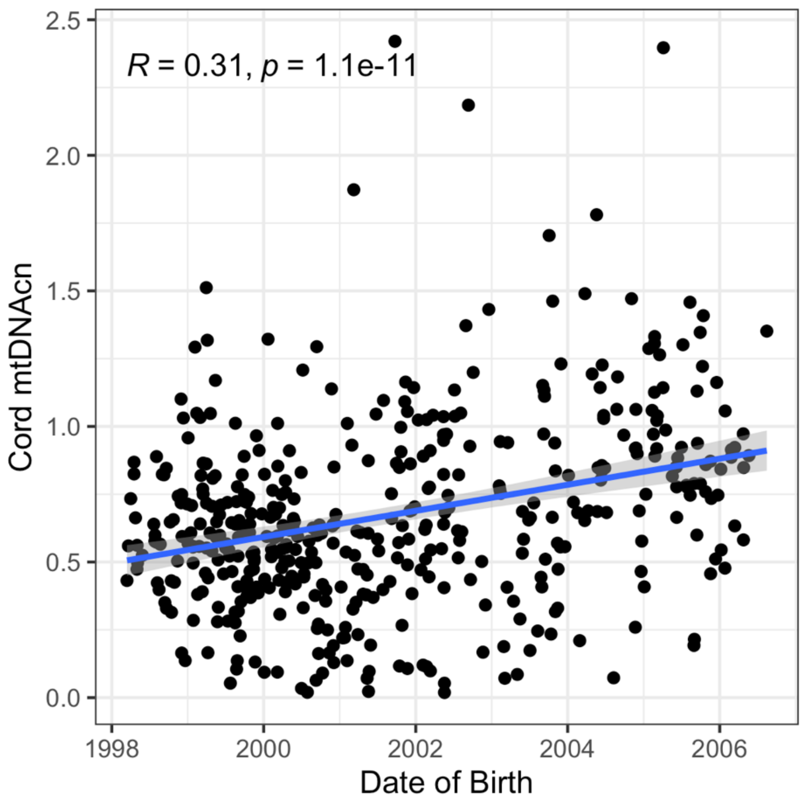
# Examination of mtDNAcn at three timepoints in childhood

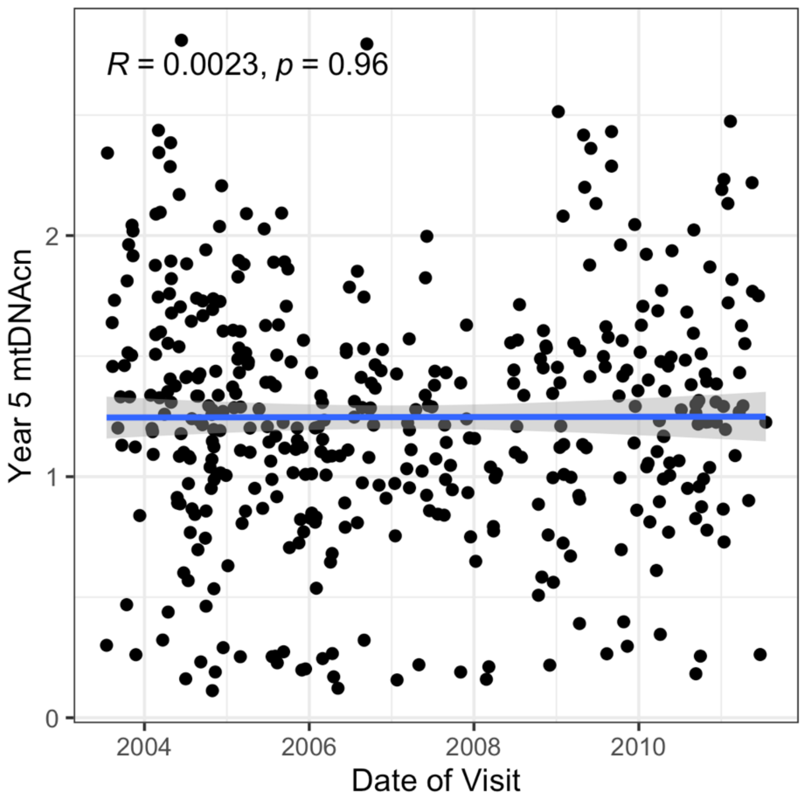
| Visit | Age (Years) | mtDNAcn |
|---|---|---|
| infancy | 0 | 0.67 ± 0.35 |
| childhood | 5.39 ± 0.77 | 1.24 ± 0.50 |
| teens | 17.2 ± 1.48 | 1.13 ± 0.44 |

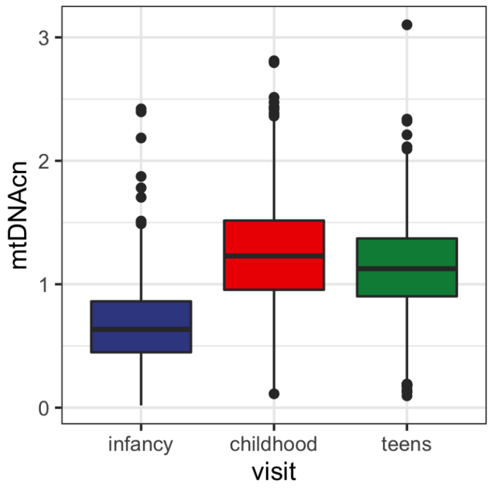


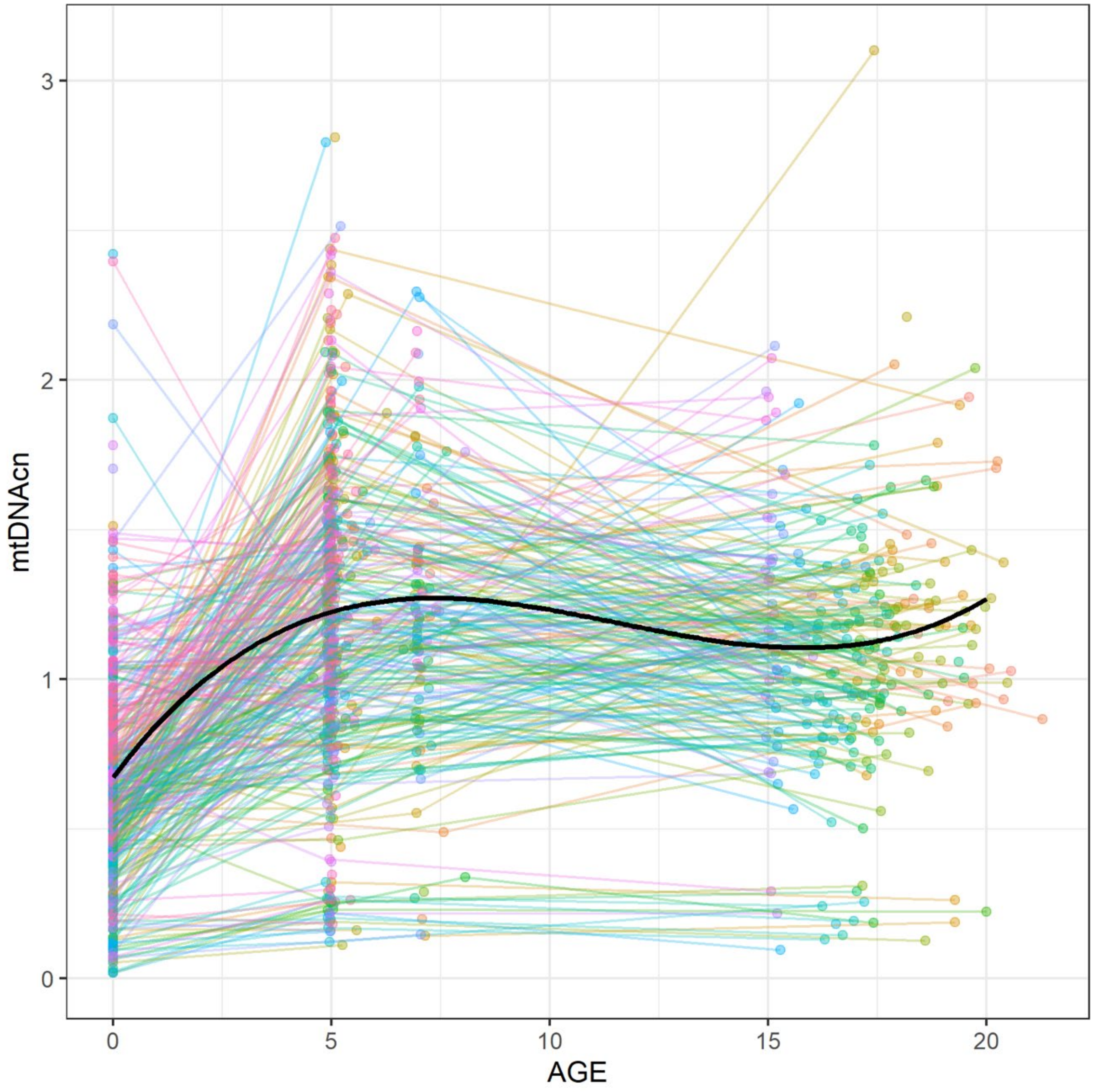
# Impact of Storage Time?




No clear association with storage date across all visits. Only within cord blood




# mtDNAcn Throughout Childhood

Each line and color corresponds to a single participant.

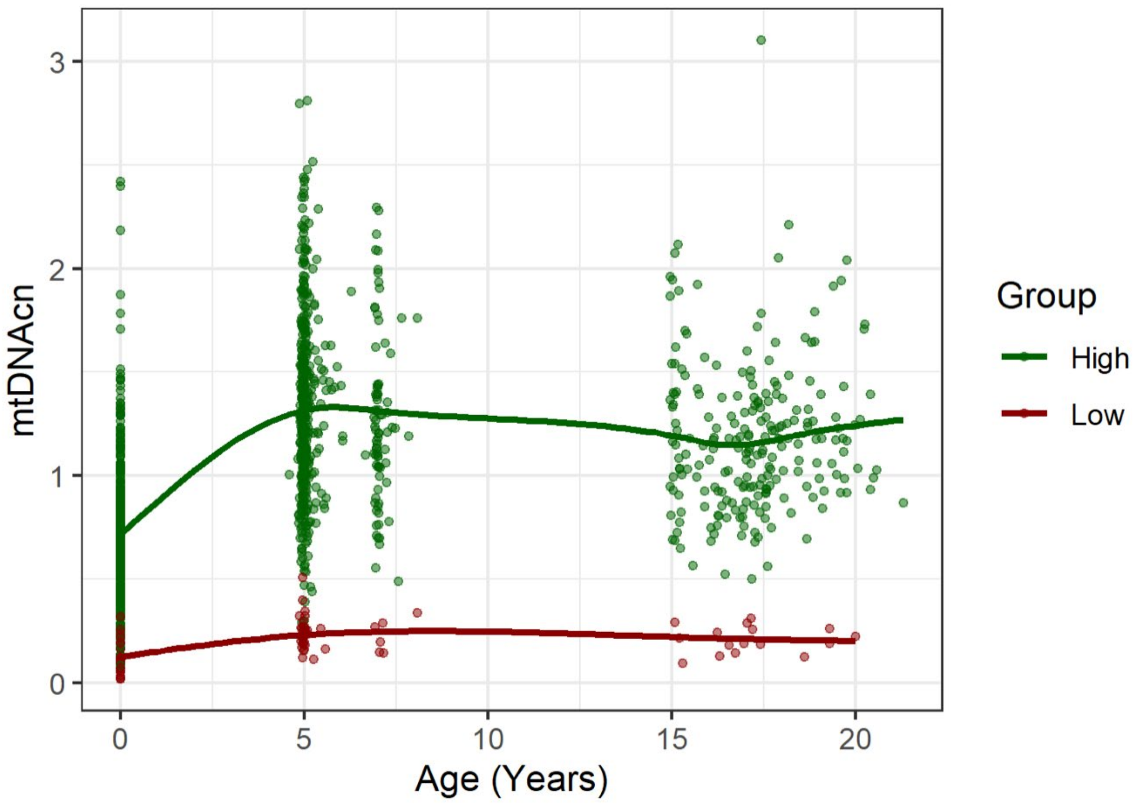
Black line is predicted association between age and mtDNAcn from mixed-effects models for age with natural splines.

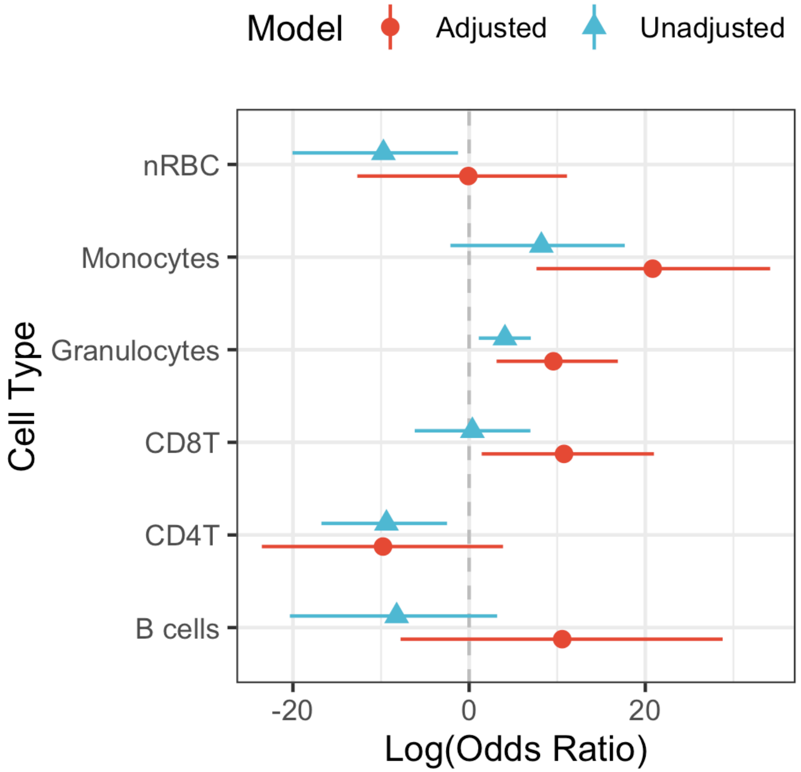
Lowest levels detected in cord blood.

Increases into childhood and remains relatively constant through to late adolescence.

# Latent Class Trajectory Modeling identifies two mtDNAcn trajectories

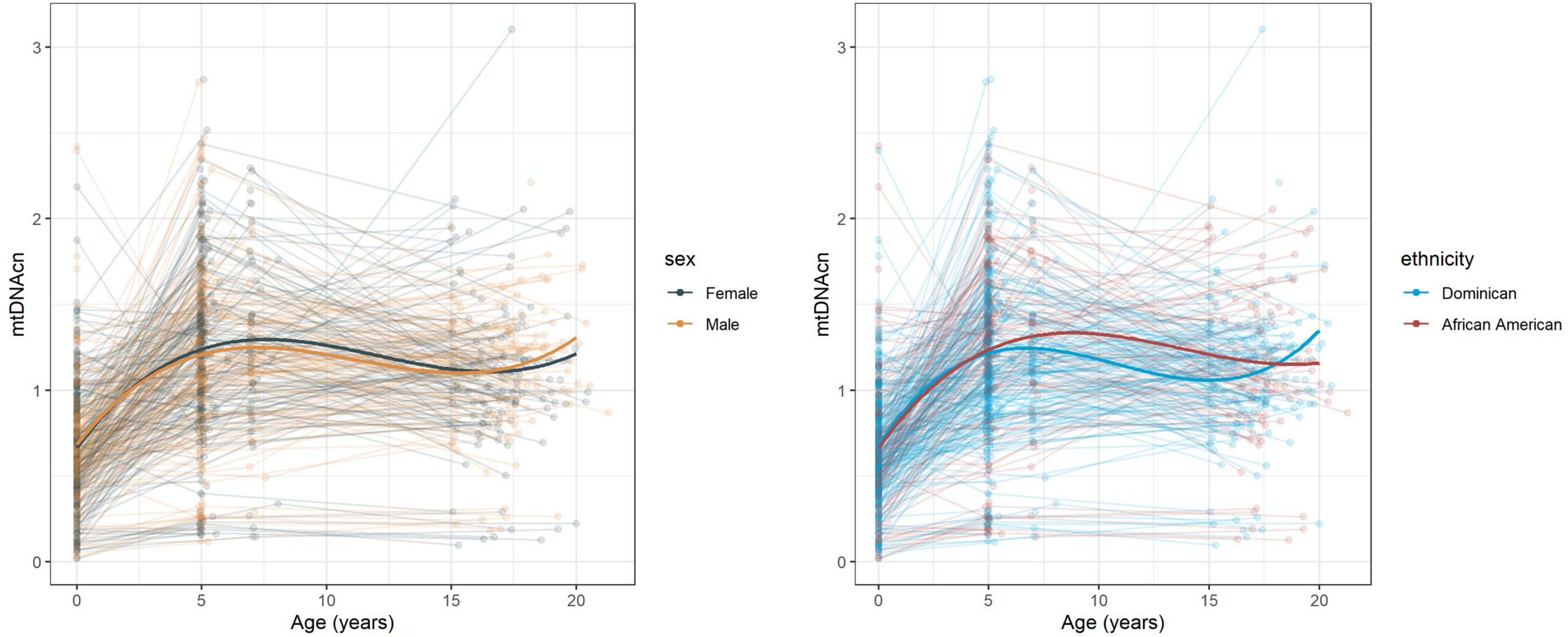
| High mtDNA | Low mtDNA |
|---|---|
| 615 | 47 |



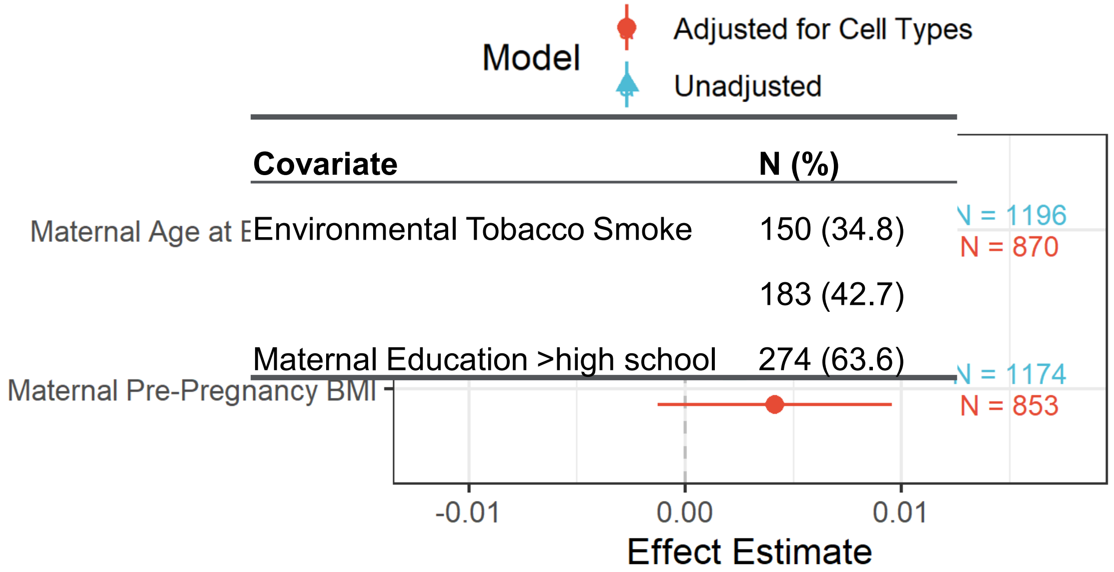




Reference: High mtDNAcn

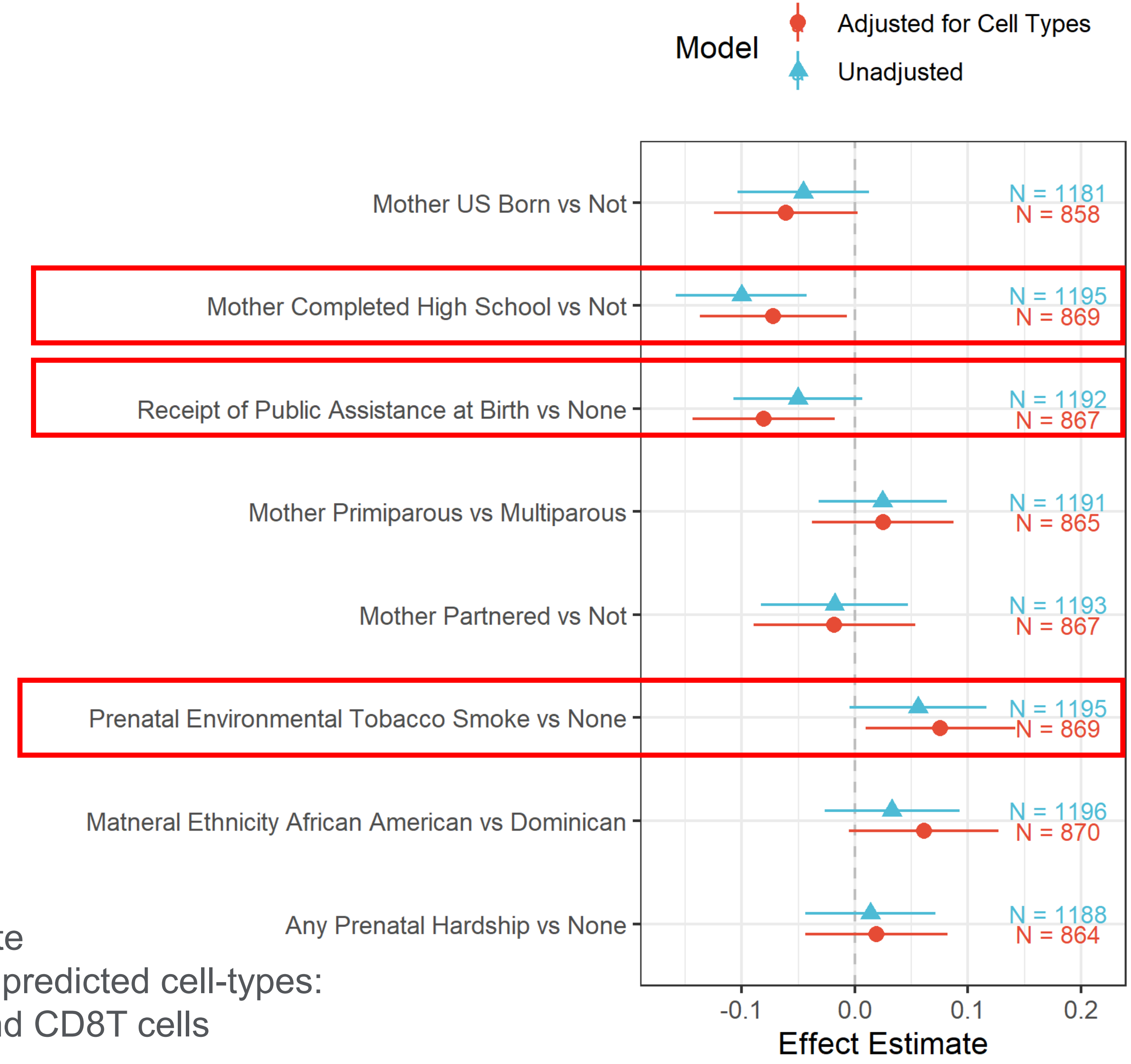
# No differences in mtDNAcn by sex or race/ethnicity



# Longitudinal mtDNAcn is associated with maternal factors




| Covariate | N (%) |
|---|---|
| Environmental Tobacco Smoke | 150 (34.8) |
| | 183 (42.7) |
| Maternal Education >high school | 274 (63.6) |



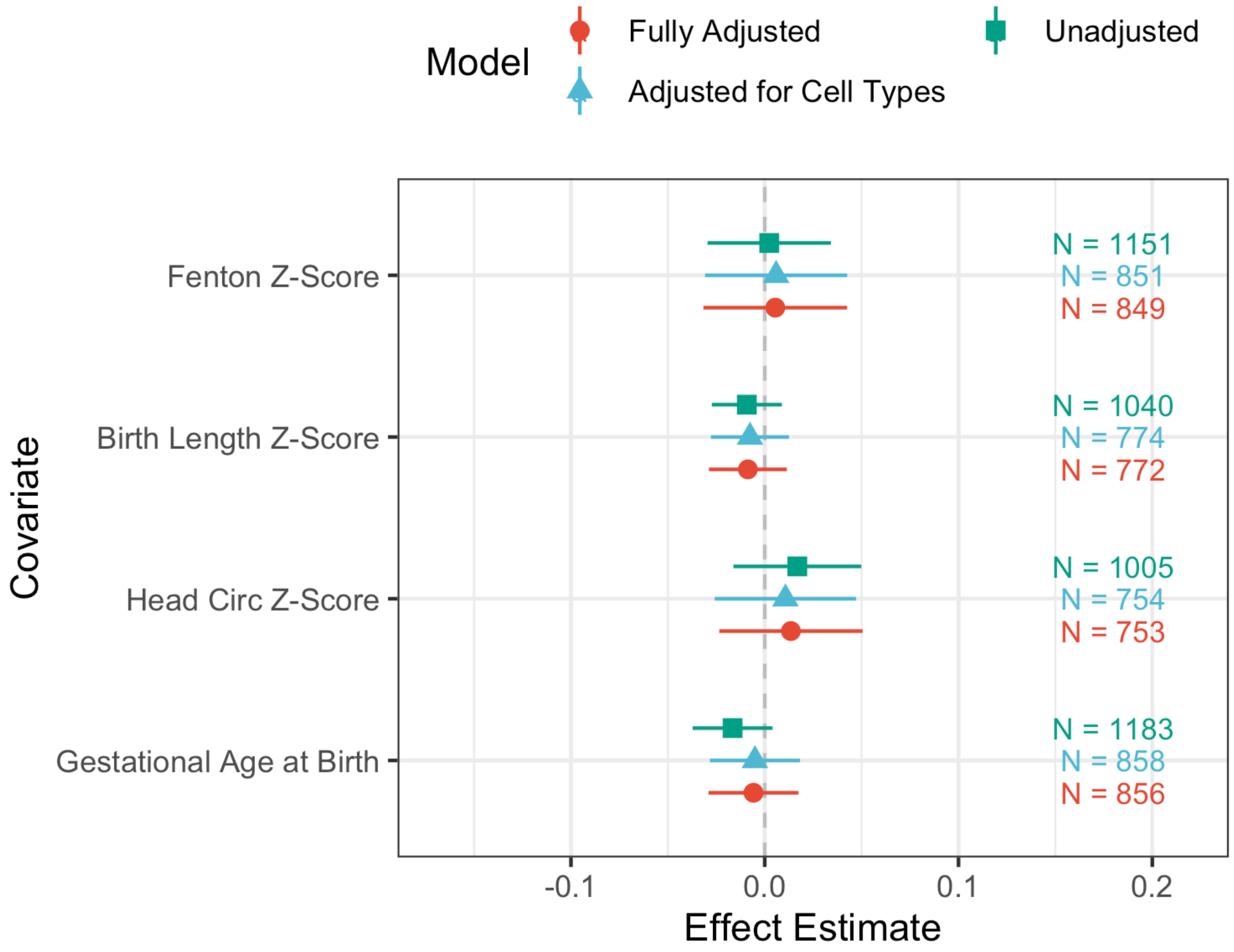

All models adjusted for child age at measurement and birth date
Cell type models are adjusted for cord blood DNA-methylation predicted cell-types: Nucleated red blood cells, granulocytes, monocytes, B cells and CD8T cells

# Birth outcomes are not associated with mtDNAcn in childhood

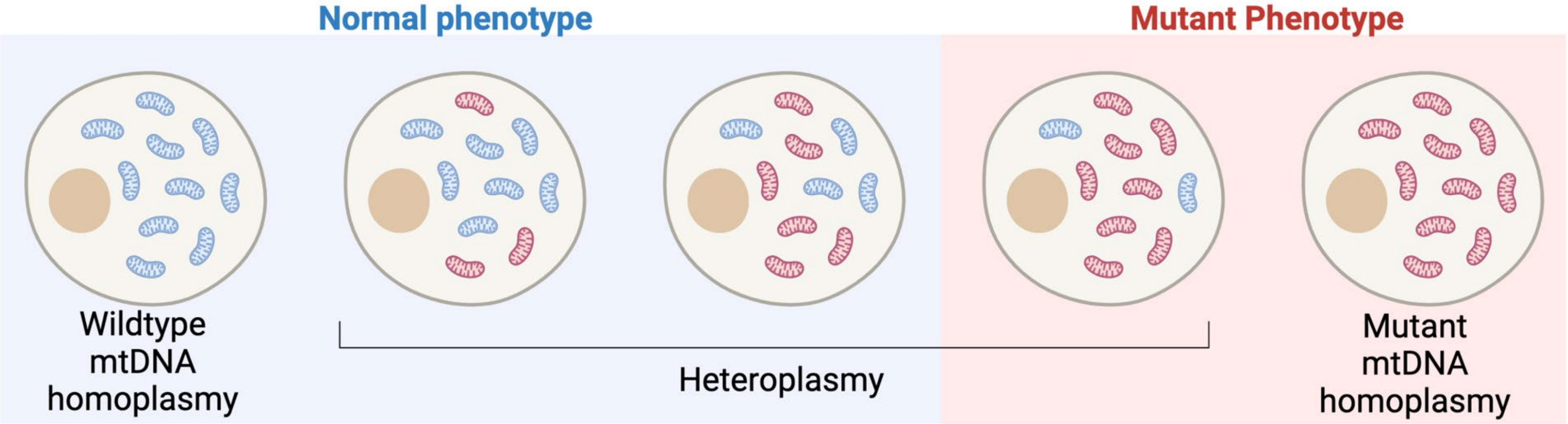
All models adjusted for child age at measurement and birth date.

Fully adjusted models additionally adjusted for:

Maternal school, maternal public assistance, Maternal age, child sex and cell type proportions



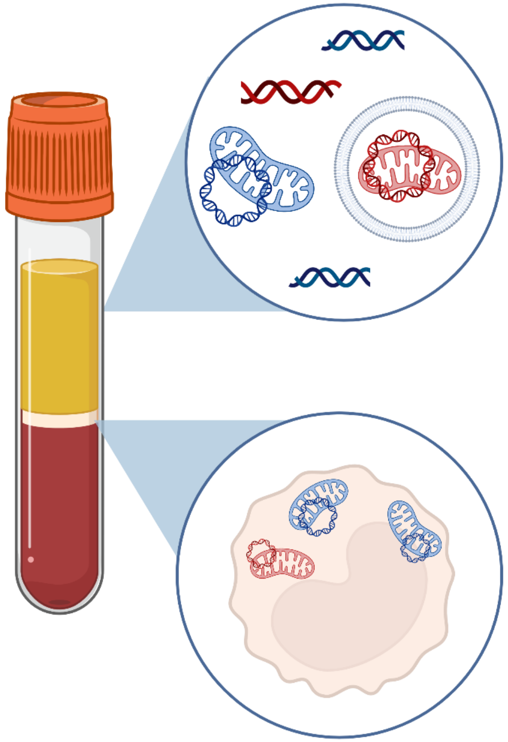
# Next Steps




Investigate associations with childhood growth and environmental exposures

Measure heteroplasmy in same samples

P30 Pilot Award:
Compare cellular to cell-free mtDNA content



Plasma mtDNA:

- Fragmented or whole in vesicles
- Originates from multiple target tissues
- Triggers inflammatory response
- Released from cell death

Buffy Coat mtDNA:

- Reflective of white blood cell response
- Highly dependent on immune cell type
- Changes with inflammation
- Easily measured

# Conclusions

Mitochondria are:

- Relevant at a population level for public health

Mitochondriomics has Limitations:

Challenges in interpretation of the direction of association

- mtDNAcn may not best reflect mitochondrial function

# Acknowledgements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Columbia Center For Children's Environmental Health

Mailman School of Public Health
Columbia University

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