Potential for dietary factors to mitigate toxic effects *in utero:* a complex story

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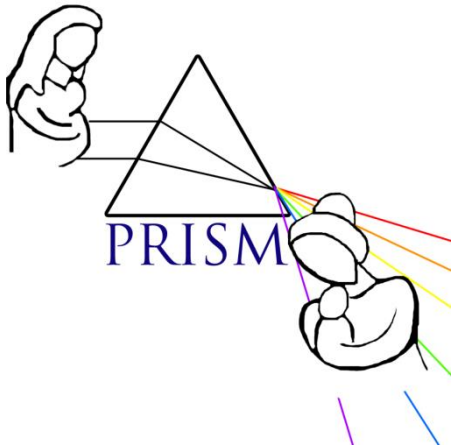
Institute for Exposomic Research

Examining associations among environmental exposures & micronutrients



Mexico City
2007-2011
N~941

PI: Robert Wright

Boston CHCs
2002~2010
N~945

PI: Rosalind Wright

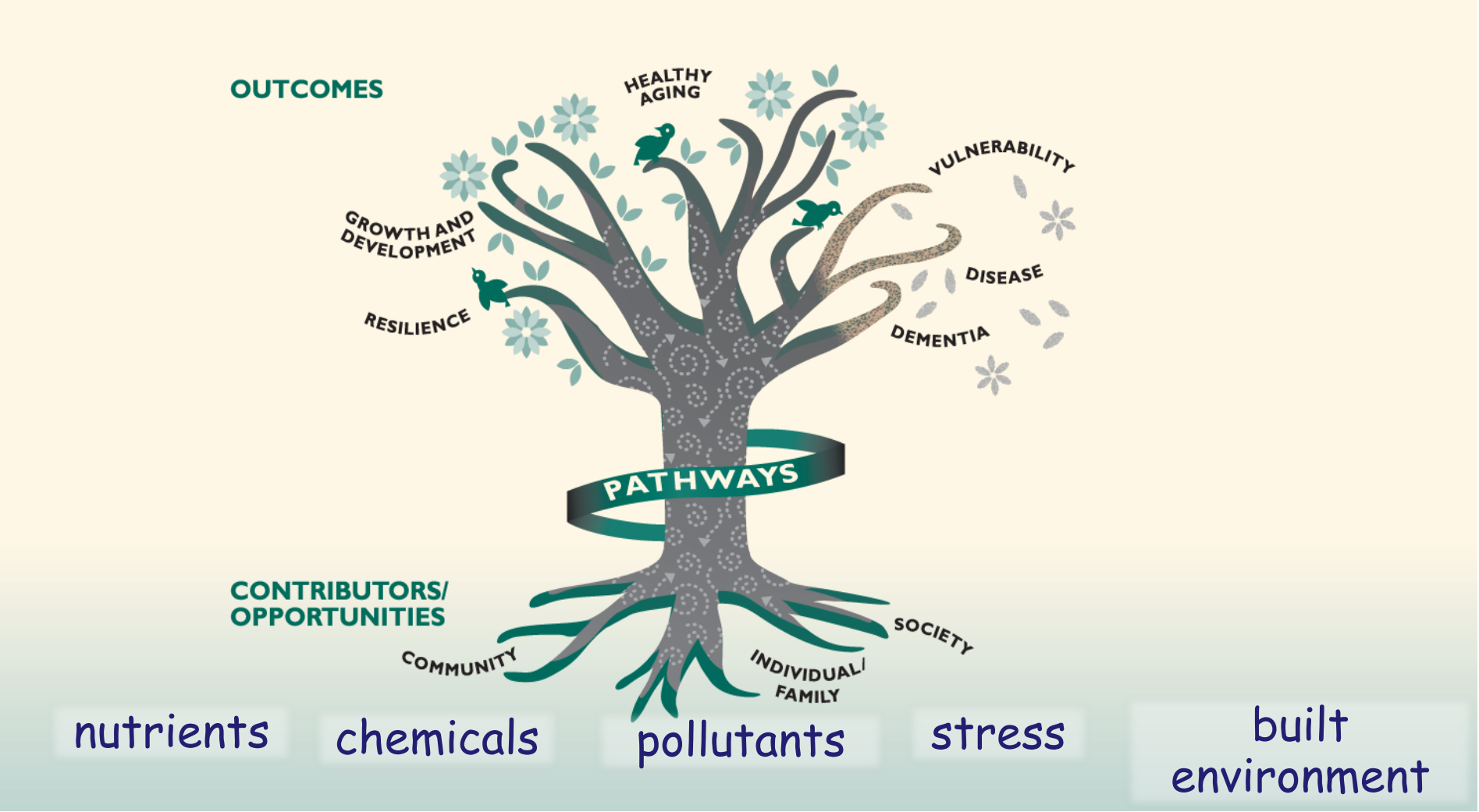
Boston
2011-2014
N~400

New York
2013 – ongoing
N~600

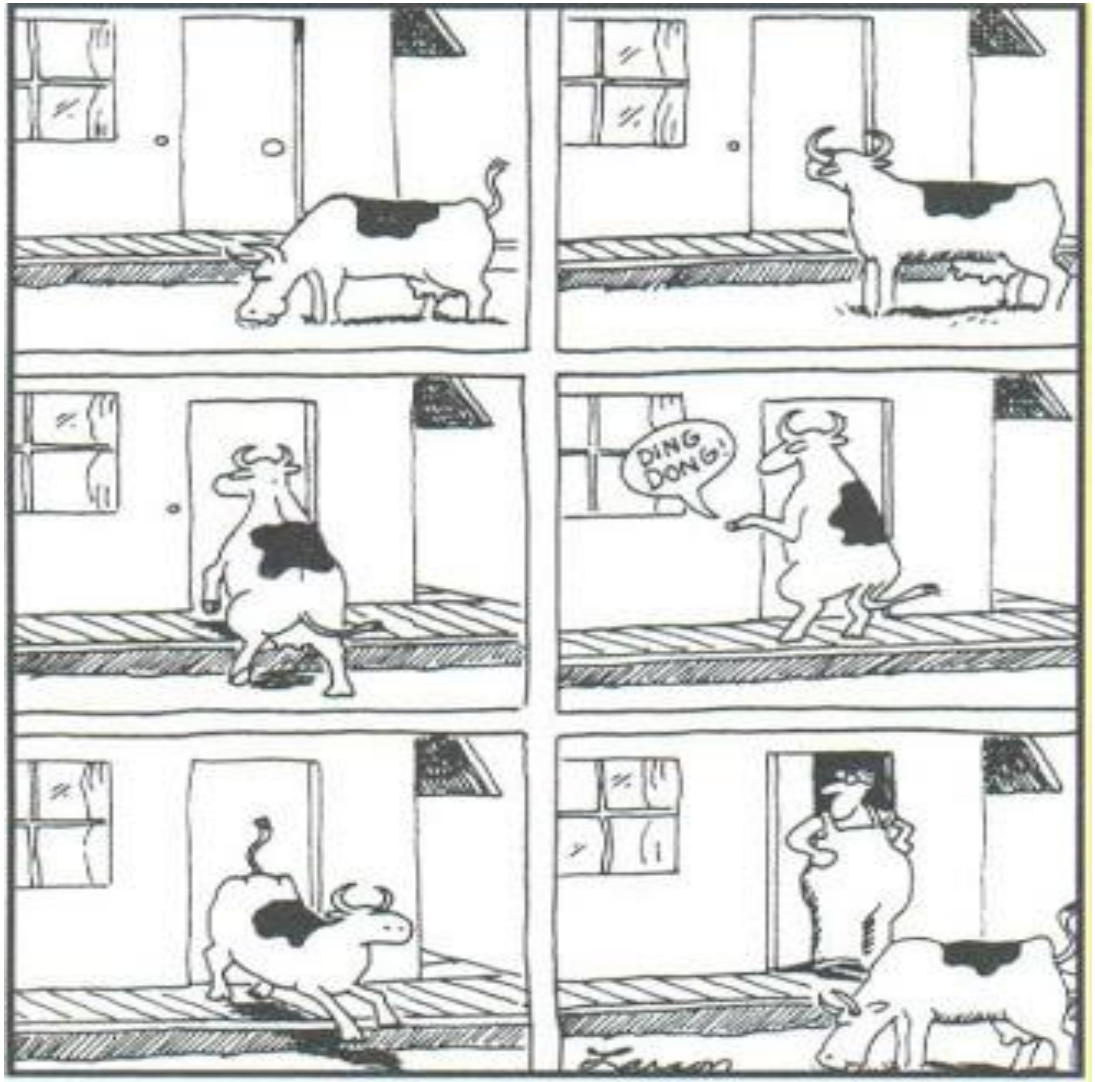
PI: Rosalind Wright

COPD - When does this story begin?

Multiple Factors Interact to Influence Health & Disease

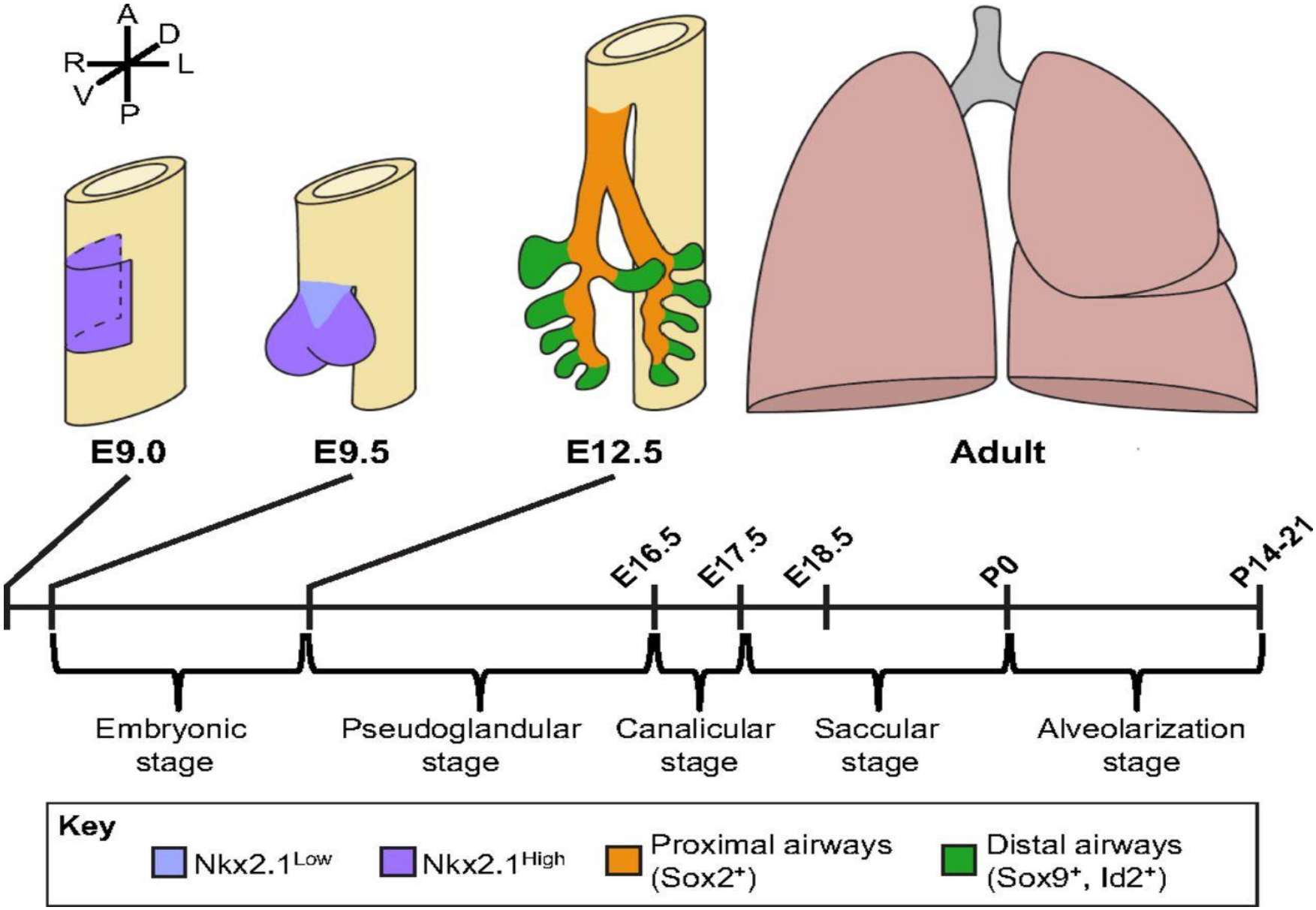


Diet may be a lever for building resilience

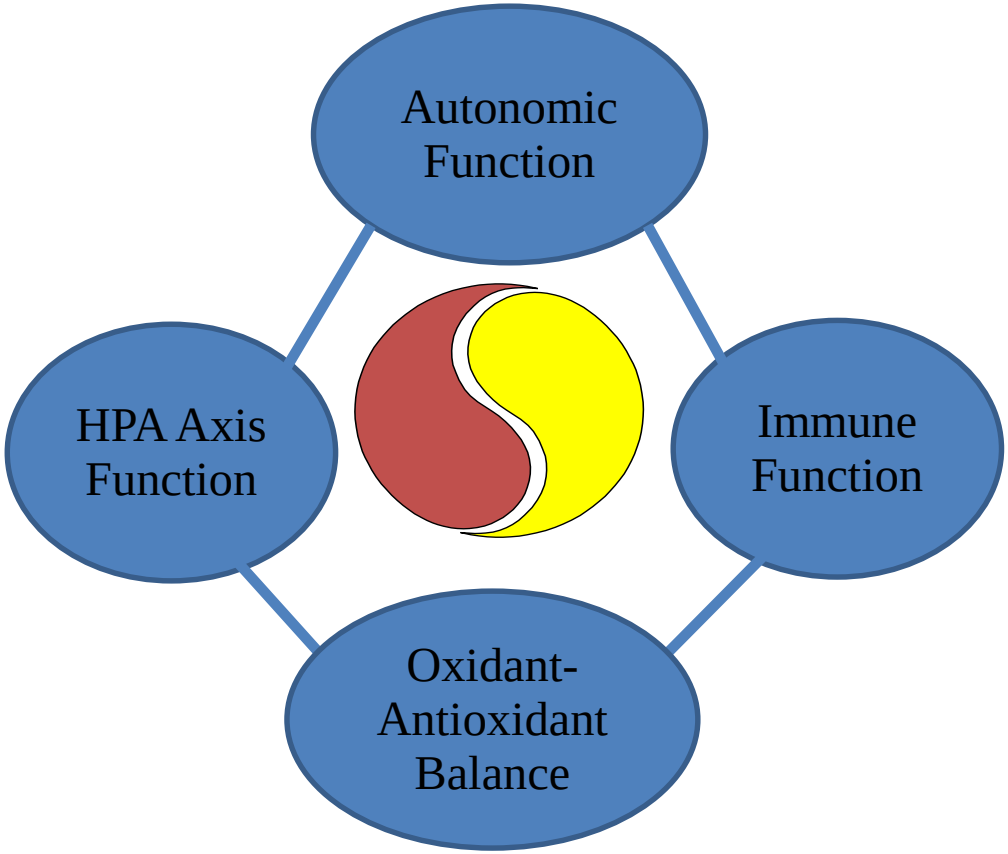


It’s all about the timing…

Stages of Lung Development

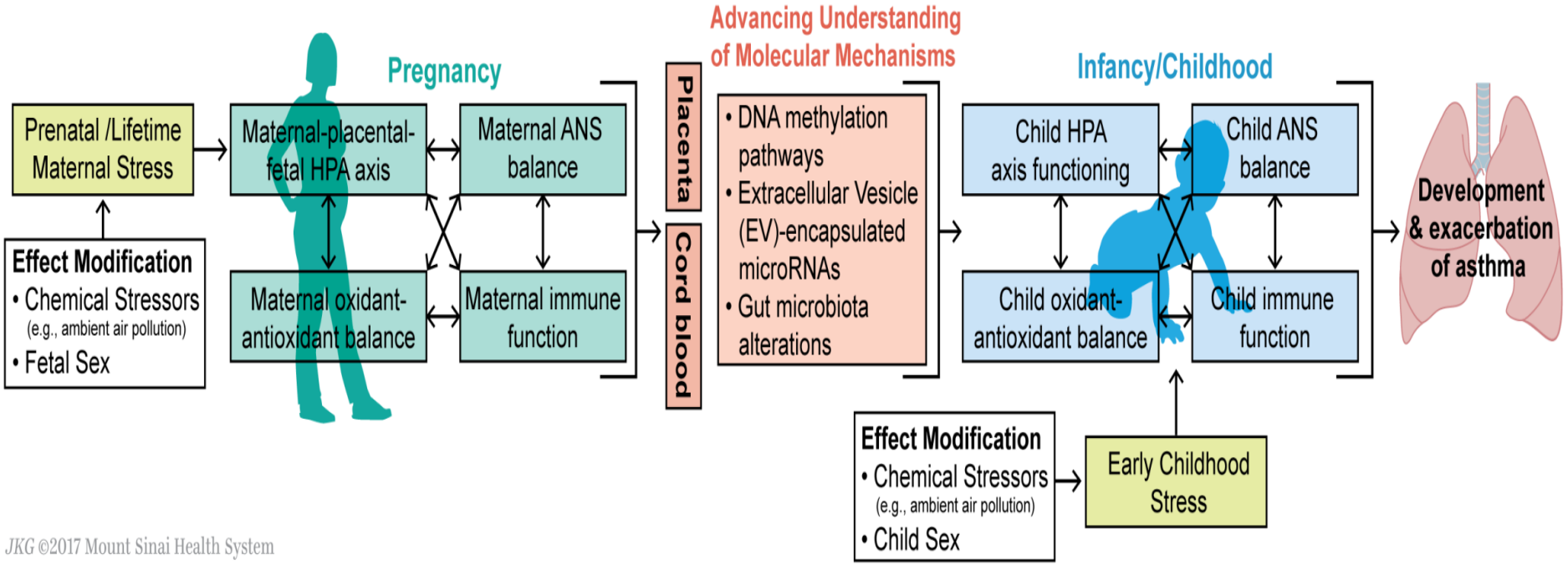


Key regulatory systems influencing development



OPTIMAL BALANCE = HEALTH

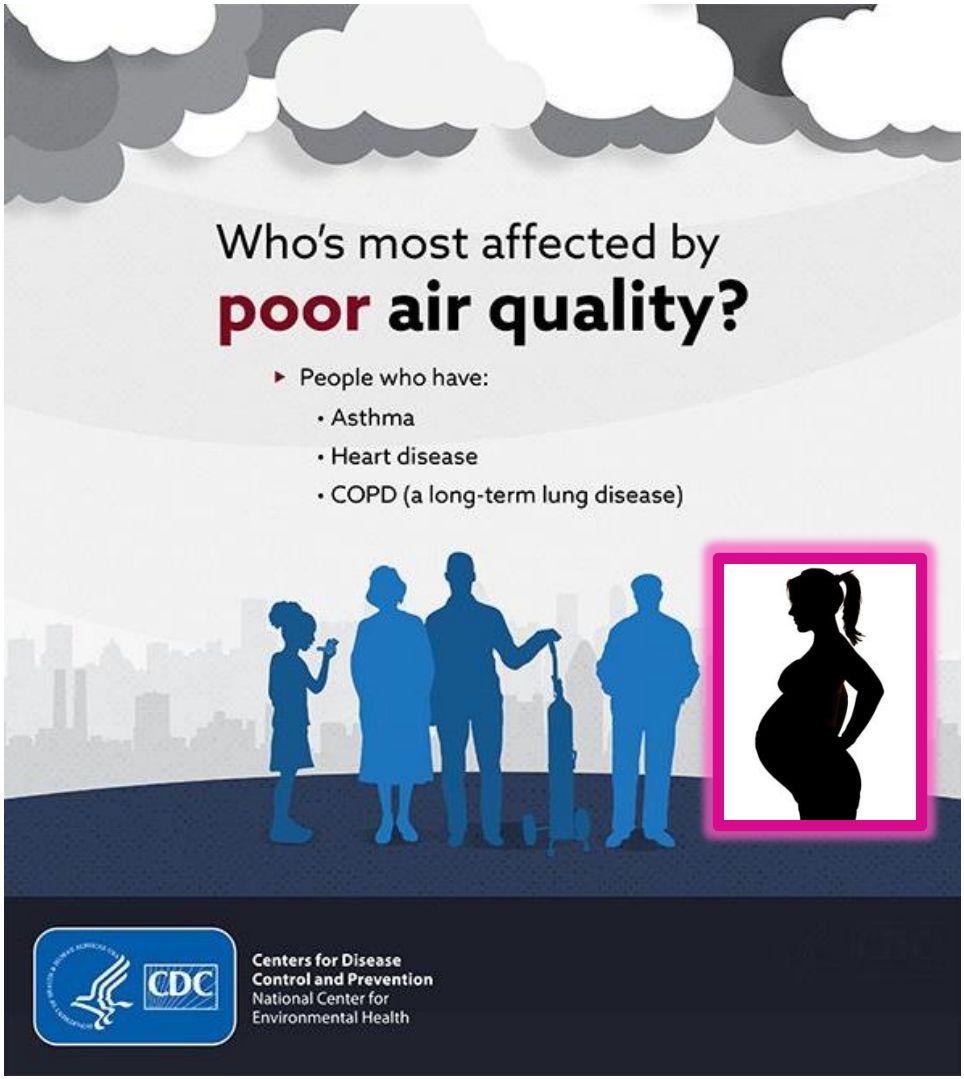
Key regulatory systems involved in respiratory system development



Rosa MJ, et al., *Curr Opin Allergy Immunol* 2018

Human fetus is uniquely vulnerable

- Gestation is period of rapid lung growth and maturation, particularly sensitive to insult
- Prenatal pollutant exposures linked to early childhood wheeze, asthma, deficits in lung function
- Time-sensitive windows within gestation not well understood



‘Place-based’ Exposures: Geomarker Data

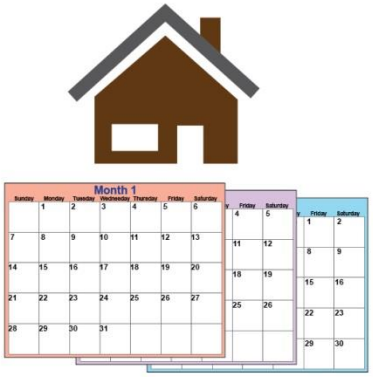
Addresses → **Geocode** → **Link / Derive Geomarker Data**

Home, school, work, etc addresses

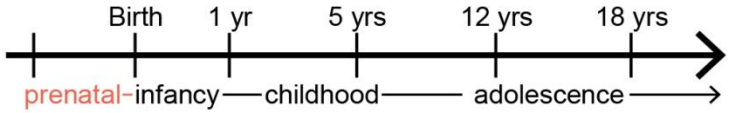
Convert address to coordinates to facilitate GIS

Link spatial locations to environmental, census, EHR data, etc.

1) Collect Addresses and Dates

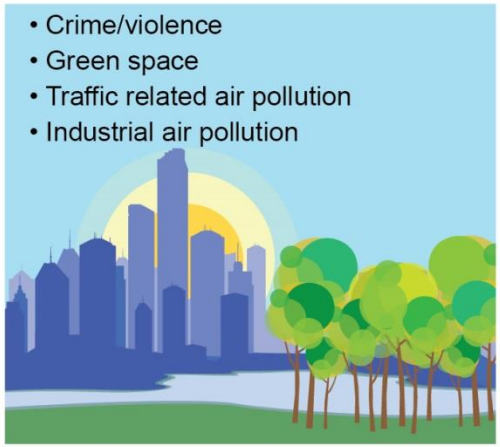


2) Construct Individual Residential Timelines

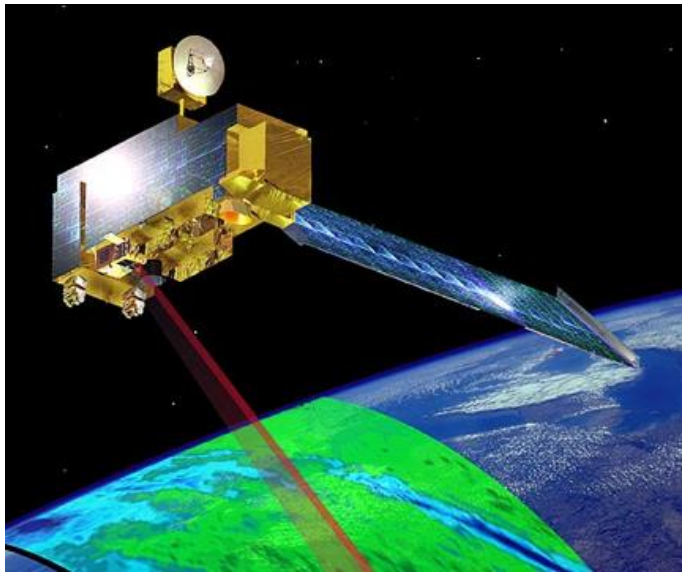


3) Geocode Addresses (lat/lon coordinates)

4) Assign Exposures

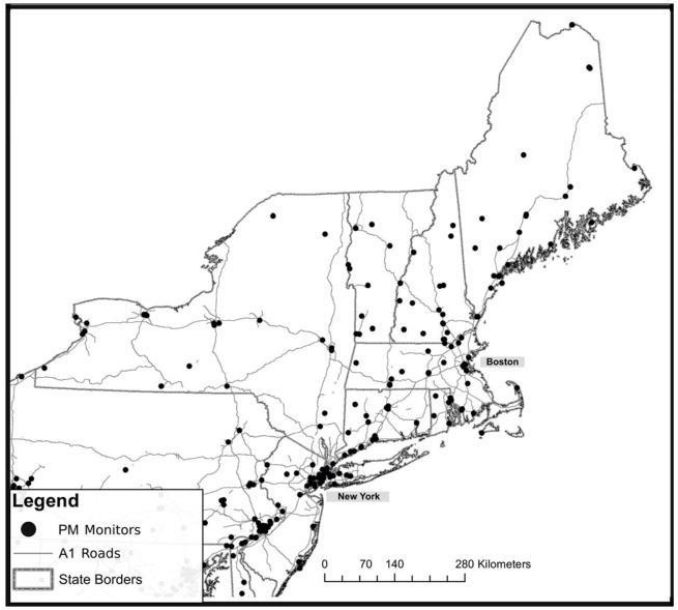


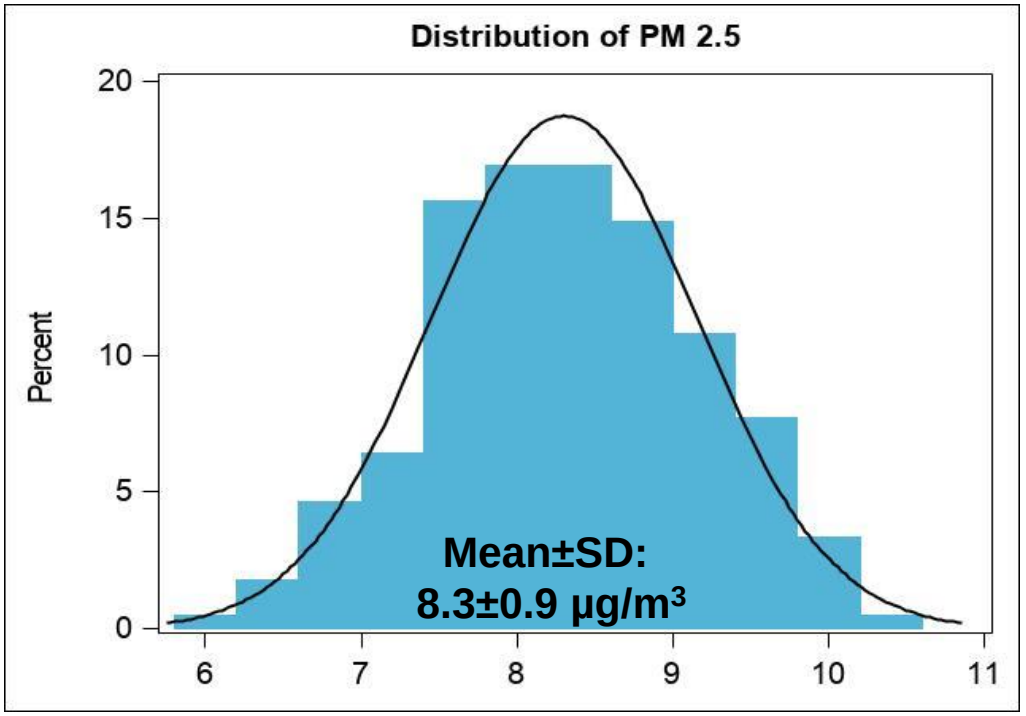
Exposure Assessment



Daily $PM_{2.5}$ exposure estimated for each study participant using a high-resolution satellite based hybrid model:

- AOD from MODIS satellite sensor (1x1 km)
- $PM_{2.5}$ monitoring data (EPA & IMPROVE)
- Spatiotemporal predictors (200x200 m)

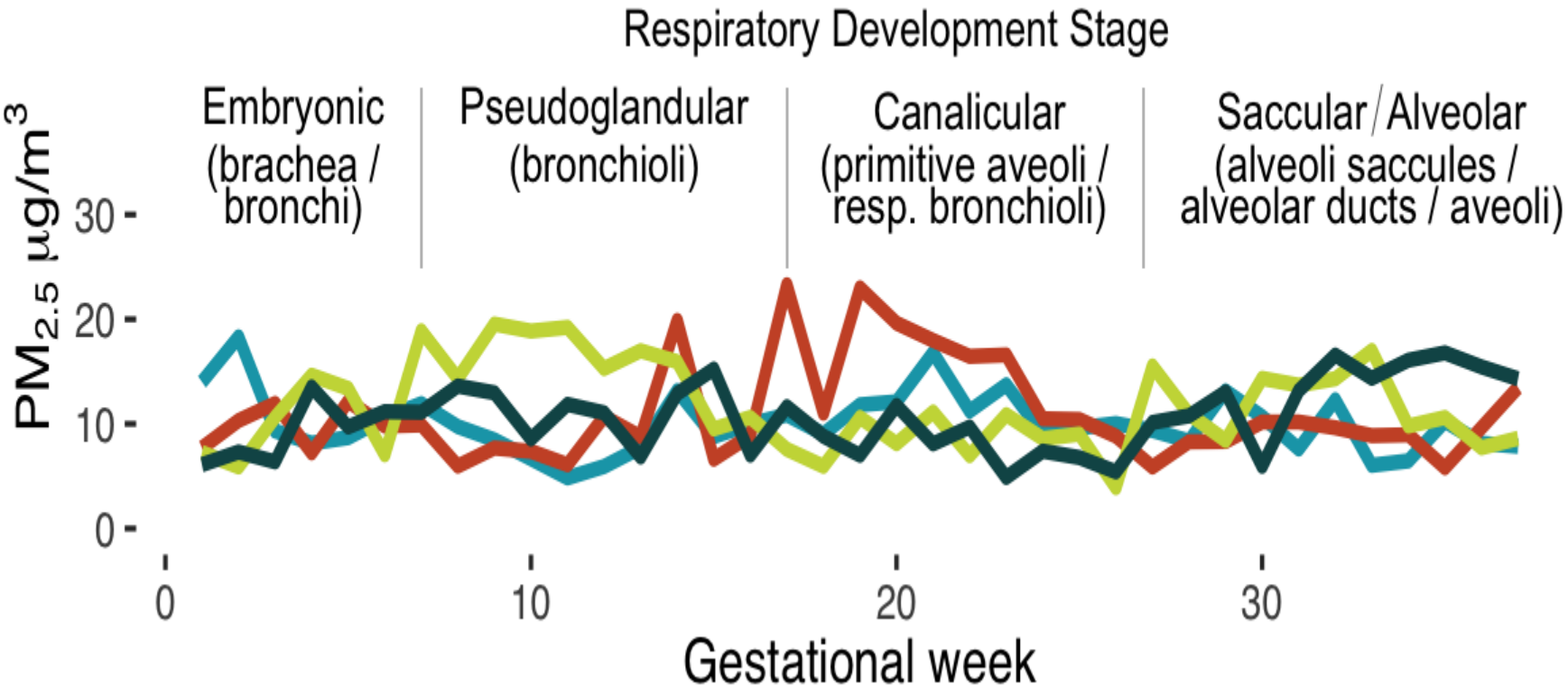




Kloog, I., et al. Atmos Environ (2014)

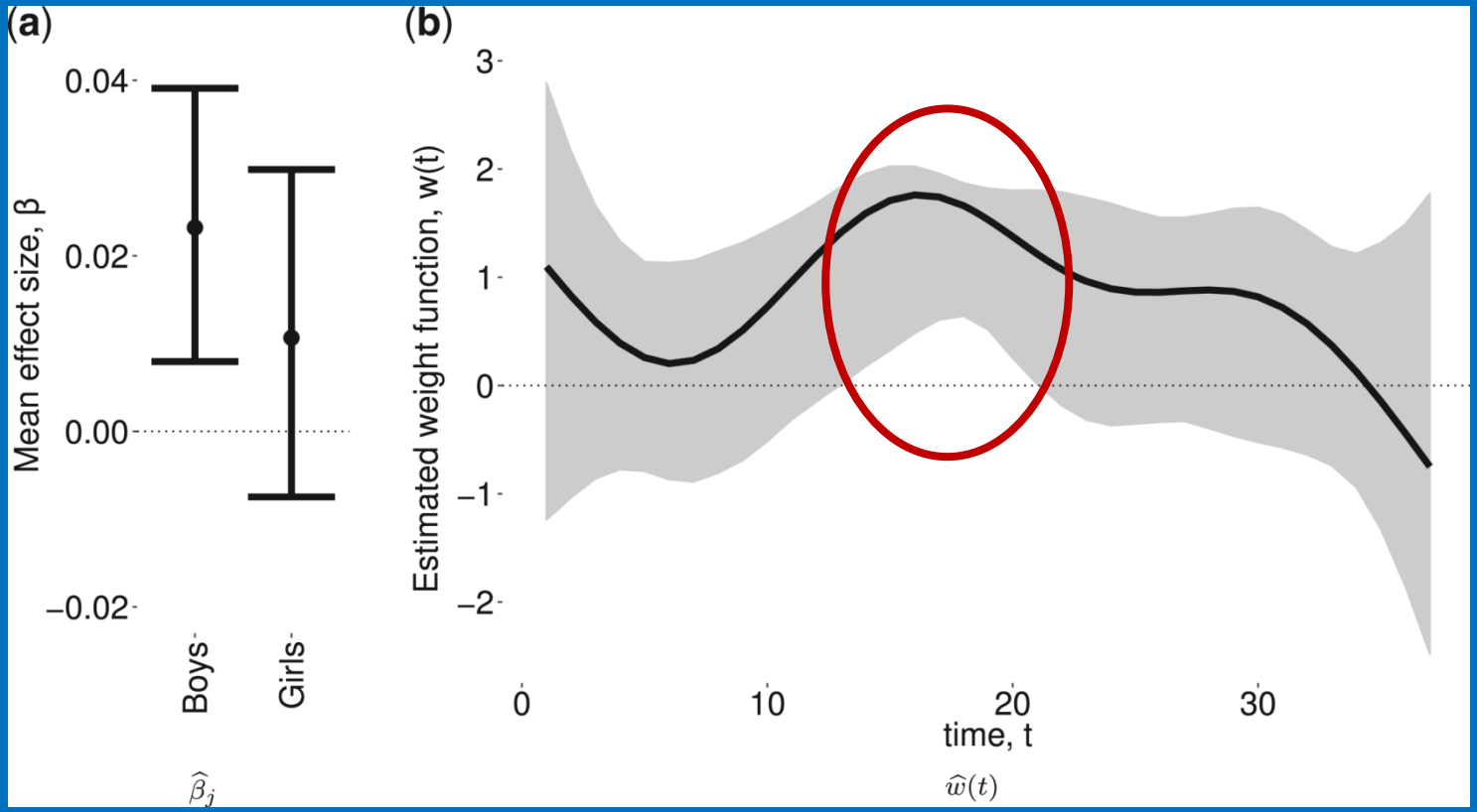
Critical/Sensitive Windows

Wilson A, et al., Potential for bias when estimating critical windows for air pollution in children's health. *A J Epidemiol* 2017



Bayesian DLIMs to identify perinatal windows of vulnerability to PM2.5 in children's asthma risk

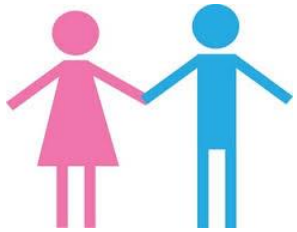
Wilson A, et al., Biostatistics 2017

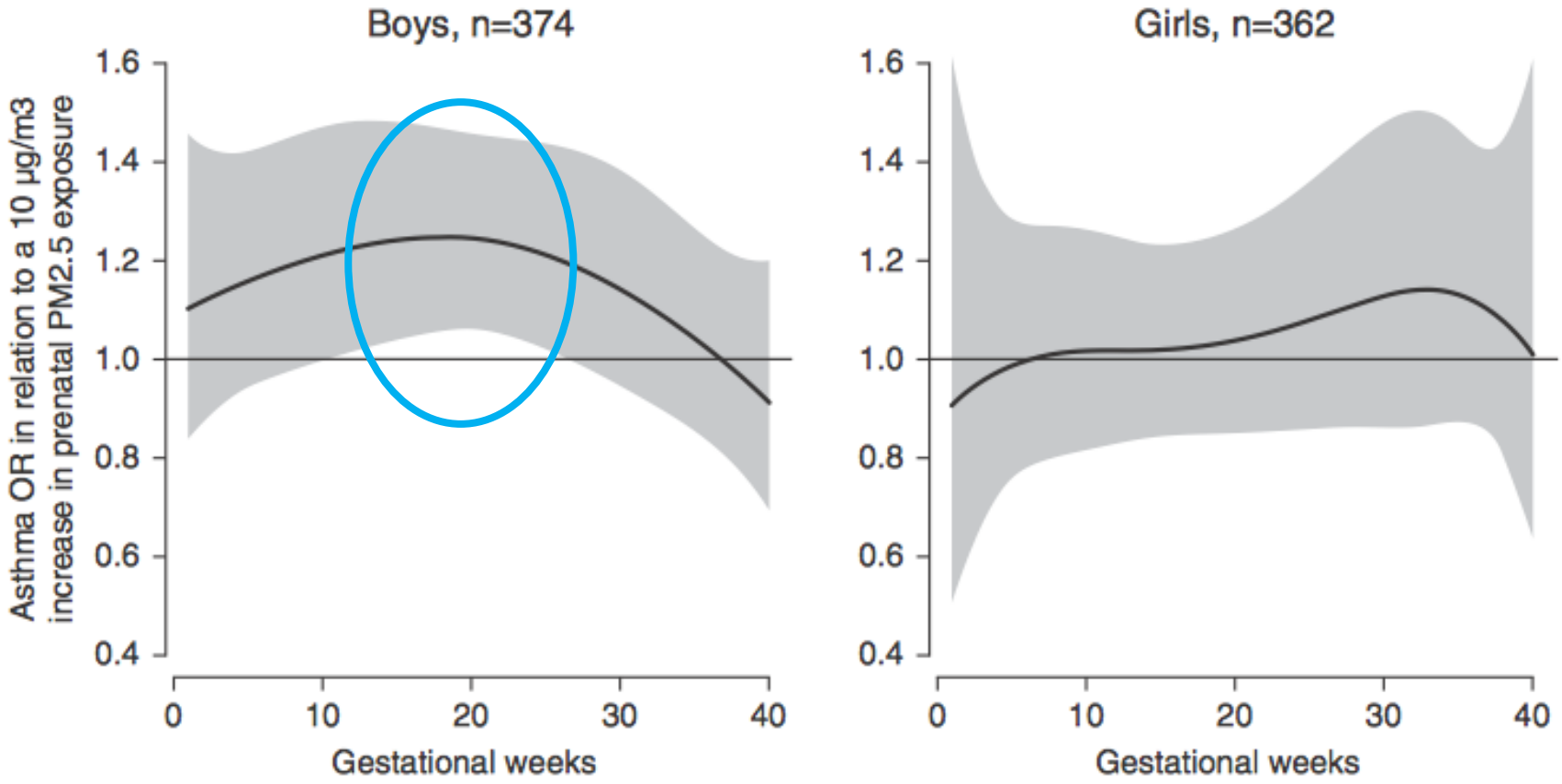


Also see: Hsu HH, et al Am J Respir Crit Care Med 2015

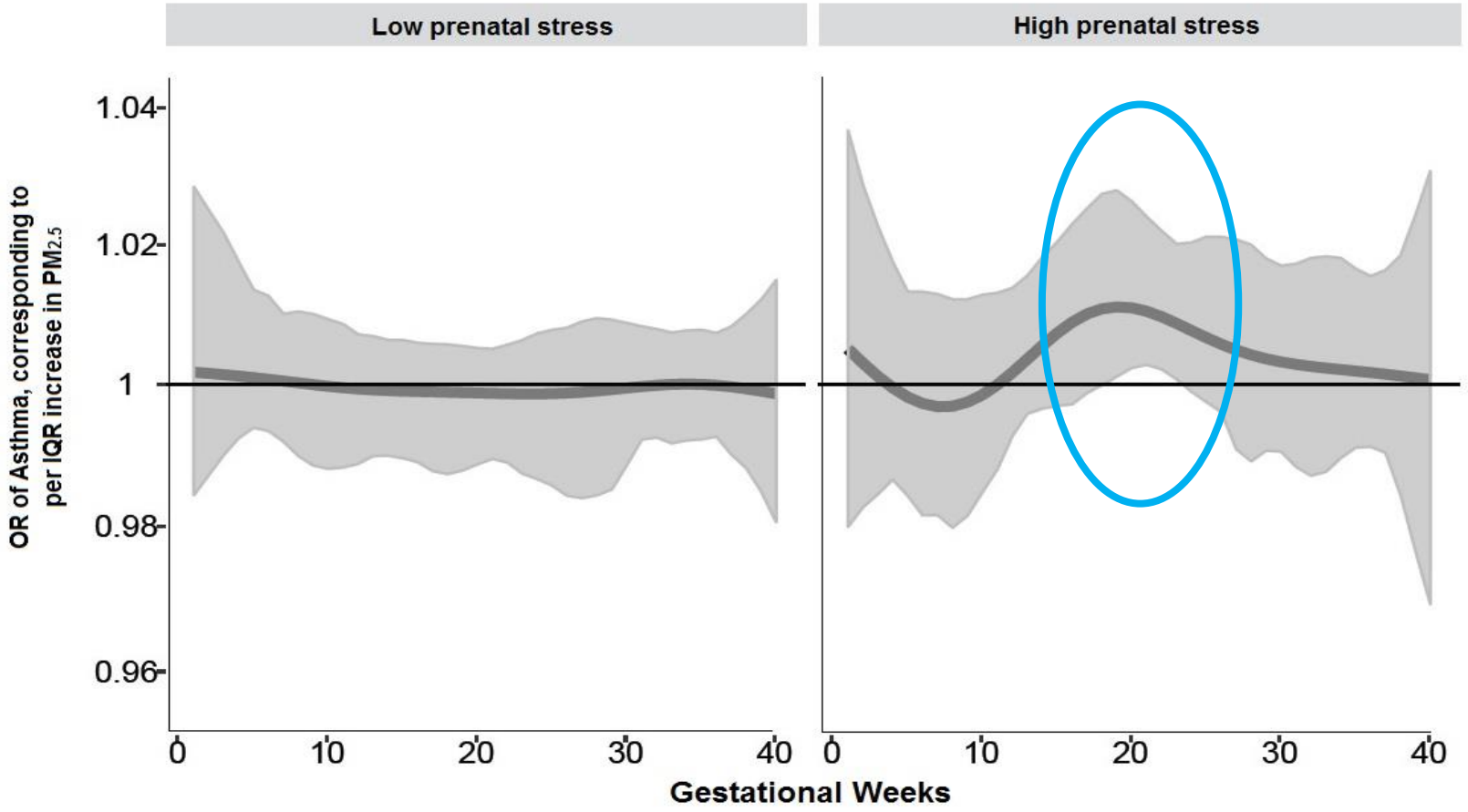
Prenatal PM2.5 and Asthma Onset by Age 6

Hsu et al. *AJRCCM* 2015; 192(9): 1052-1059





X



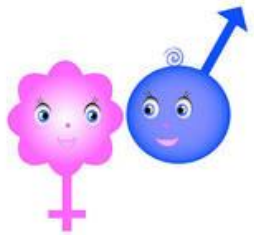
Lee A, et al., *JACI* 2018

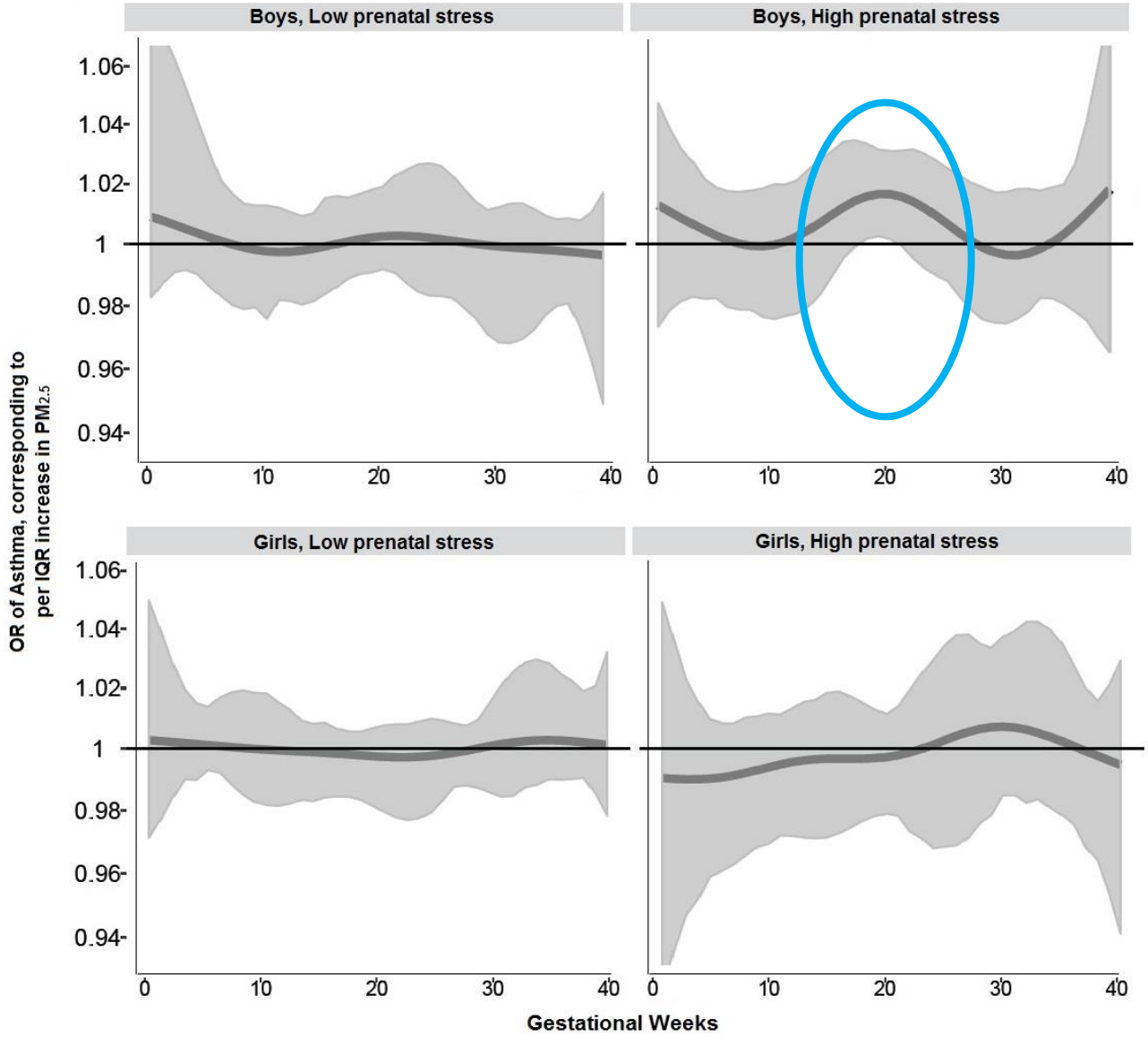

shutterstock

X


STRESS

X

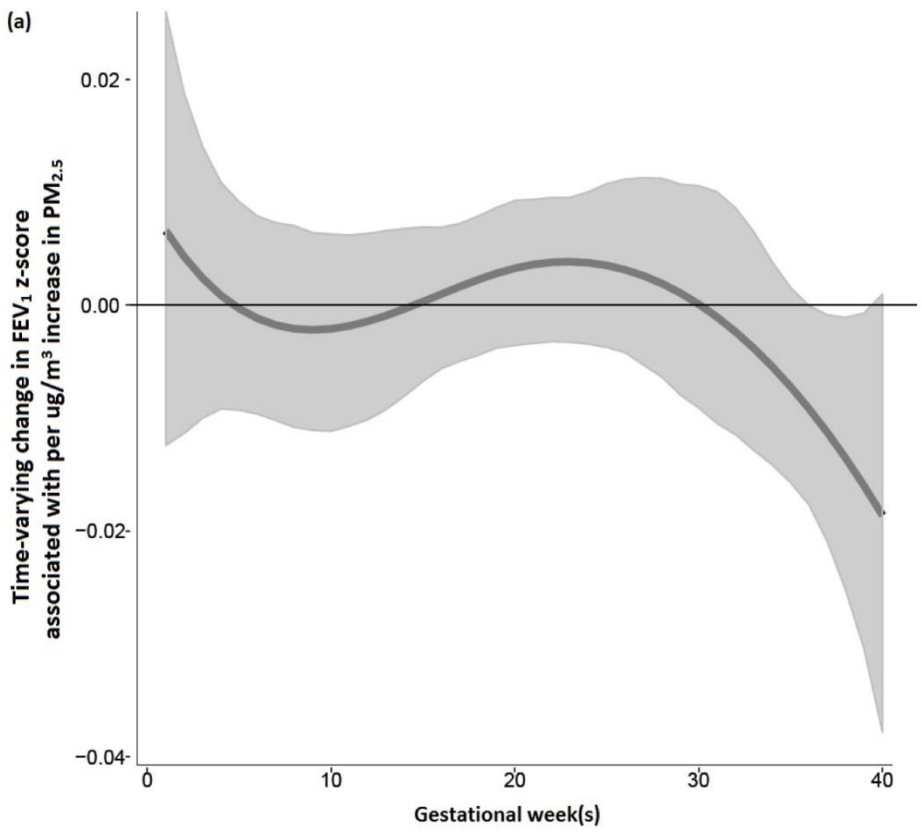


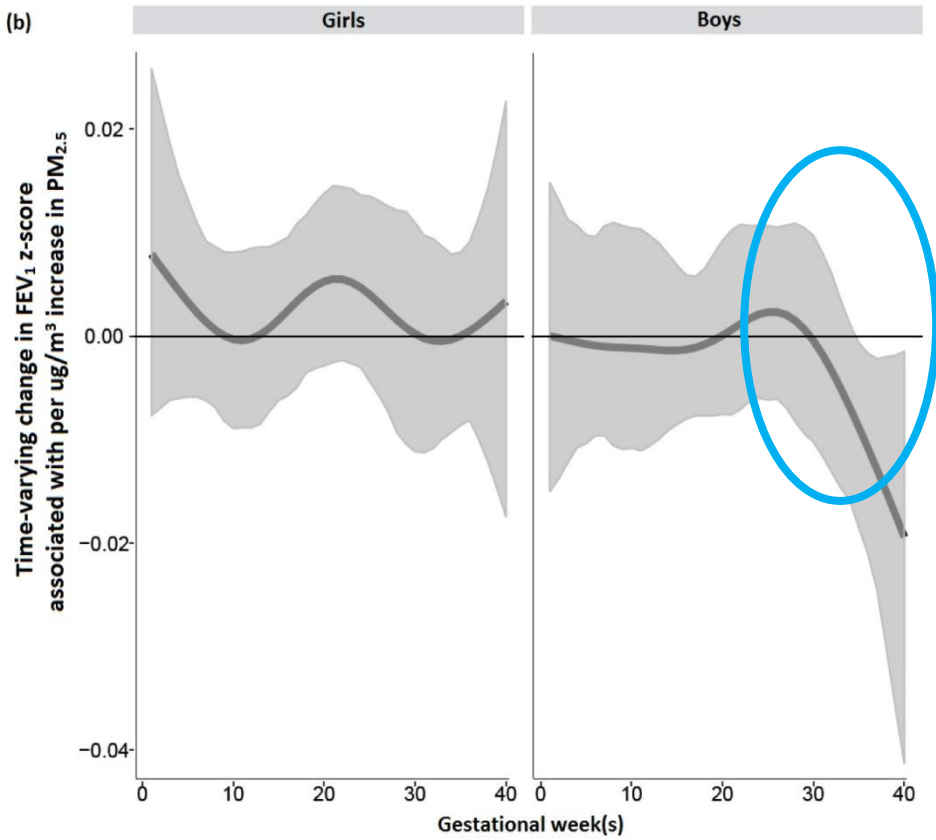

Boys, Low prenatal stress
Boys, High prenatal stress
Girls, Low prenatal stress
Girls, High prenatal stress
OR of Asthma, corresponding to per IQR increase in PM2.5
1.06
1.04
1.02
1
0.98
0.96
0.94
0
10
20
30
40
Gestational Weeks

Prenatal $PM_{2.5}$ and lung function age 7 yrs

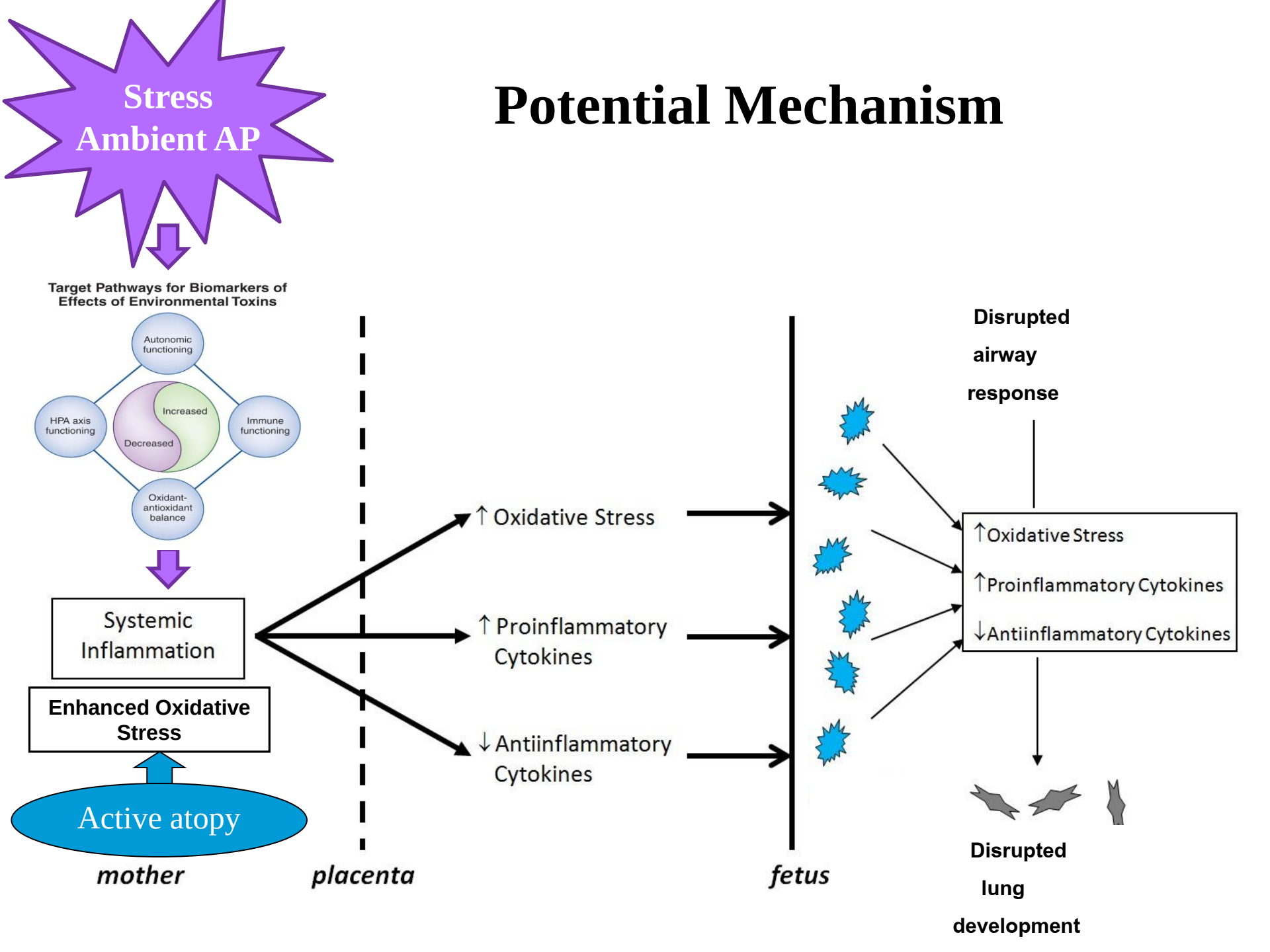
Lee AG, et al., *Respir Res* 2018

Lee A, et al., *JACI* 2018

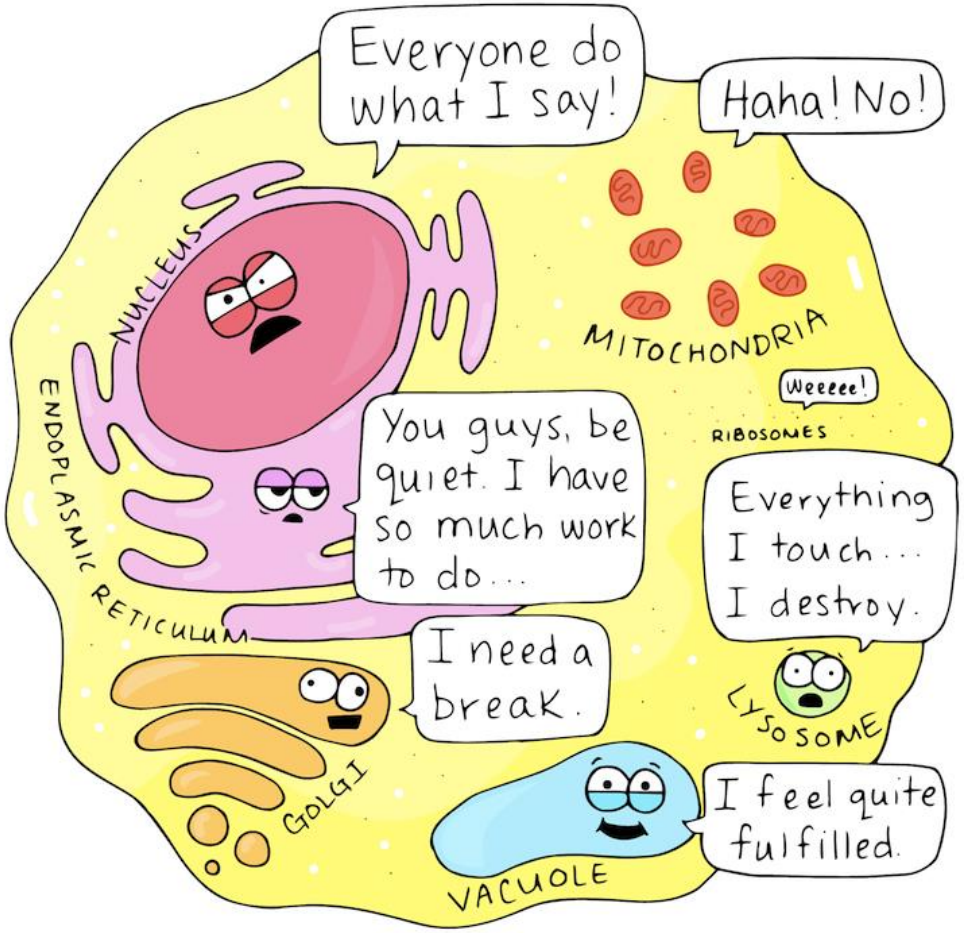




Potential Mechanism



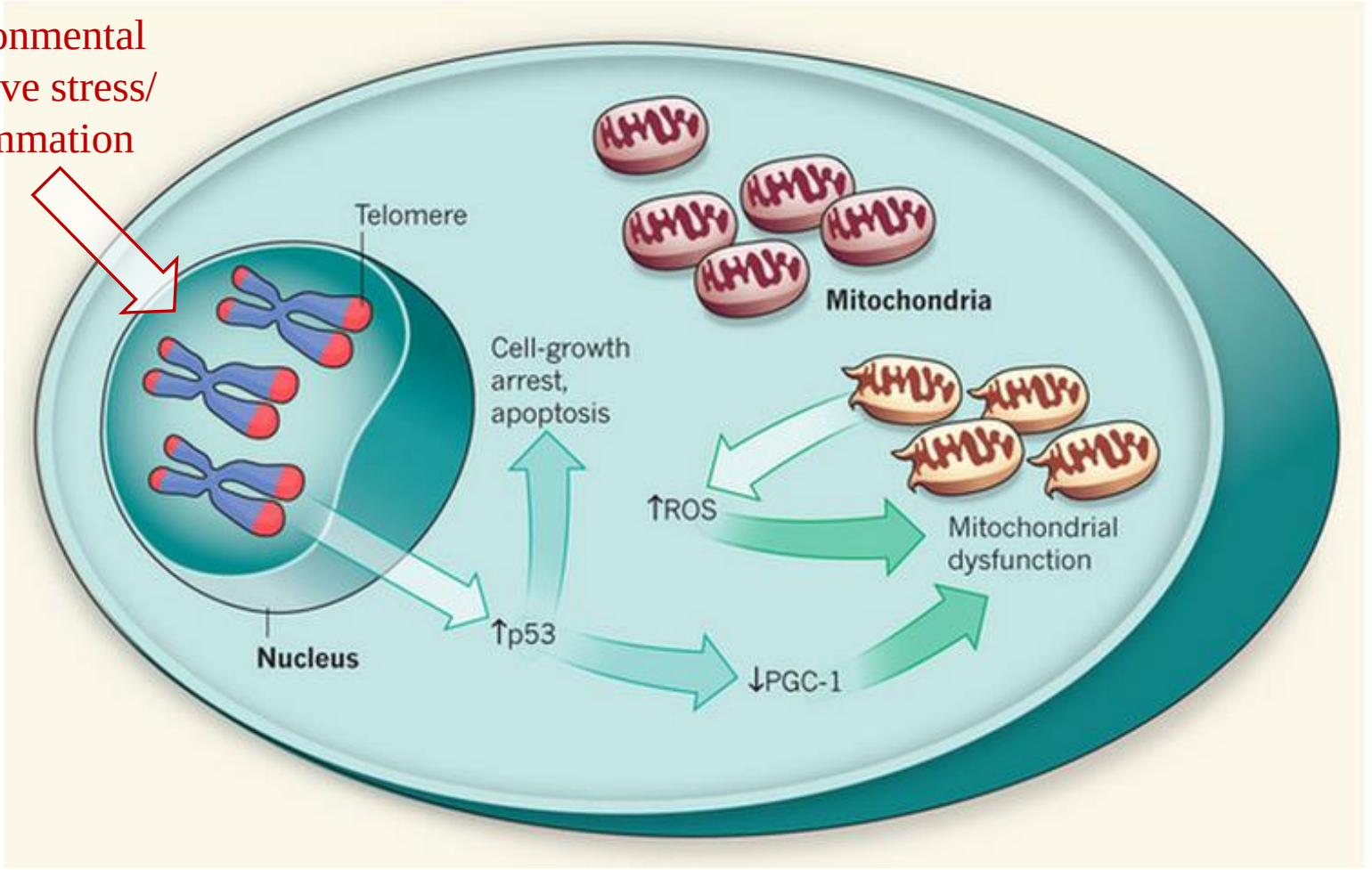
Dosimeters of environmentally-induced oxidative stress and inflammation over pregnancy



If organelles could talk.

Telomere-mitochondrial axis of aging

Environmental oxidative stress/ inflammation



Working hypothesis:
Fetal exposures to maternal environmental stress (pro-oxidants, pro-inflammatory)→ telomere damage & mitochondrial dysfunction → fetus predisposed to disease later in life

Kelly, DP. Nature 470, 342–343 (2011)

Assessment of telomere length and mitochondrial dysfunction in cord blood/placenta

- **Telomere length (TL)**
  - Real-time quantitative polymerase chain reaction (Q-PCR)
  - Ratio of telomere repeat (T) copy number to single copy gene (S) copy number (T/S ratio)
    - T/S ratio: T/36B4
    - Proportional to average TL in a cell

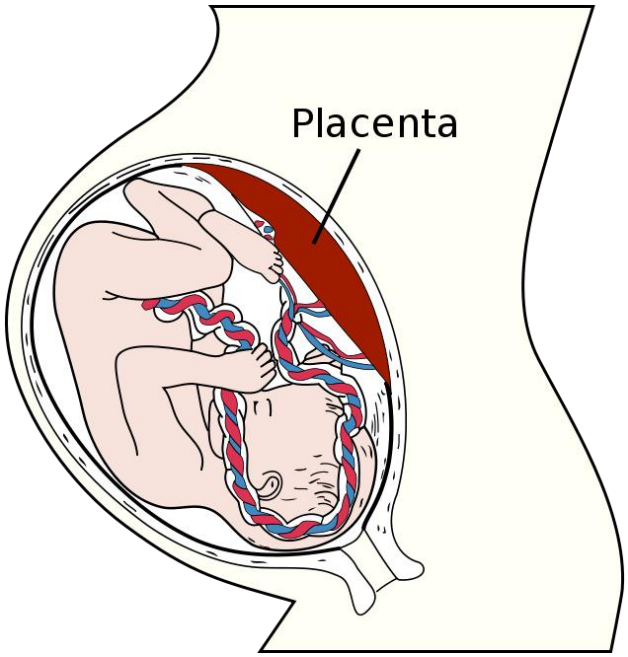
      (Cawton, RM. Nucleic Acids Res. 2002;30:e47)

- **Mitochondrial DNA copy number**
  - Q-PCR
  - Ratio of mitochondrial (MT) copy number to single copy gene (S) copy number
    - MT/S ratio: mt12s/RNAse P
    - Low copy number correlated with mitochondria-related metabolic disorders

      (Kim JH. et al. PLoS One. 2013 Jun 13;8(6))

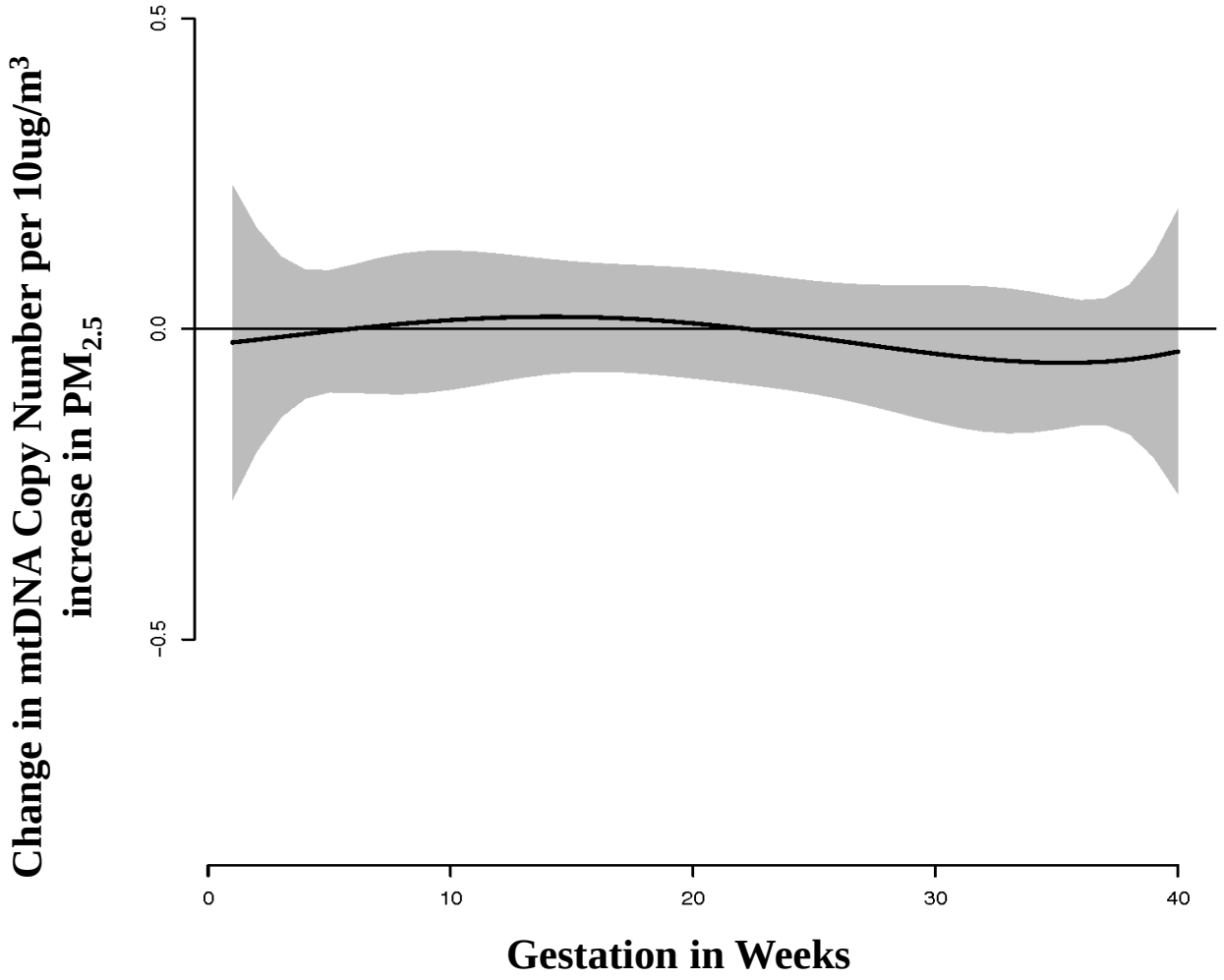
Why study the placenta?

- **Significant regulator of maternal-fetal signaling**
  - Cytokines
  - Neurosteroids and neurotransmitters
  - **Reactive oxygen species/oxidative balance**



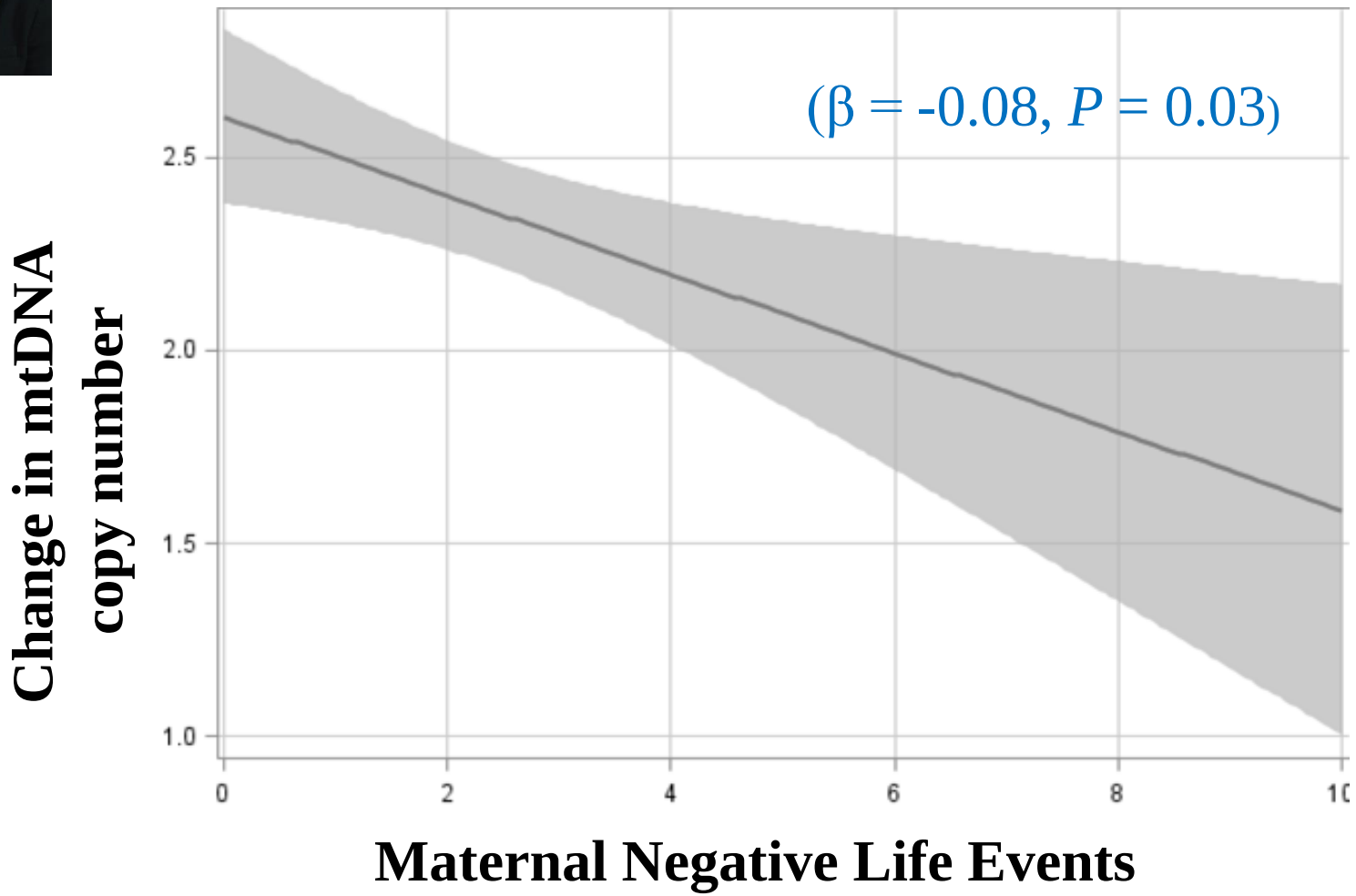
- **Exposures during pregnancy can alter placental function and signaling**
  - Impact fetal development

No main effect of $PM_{2.5}$ on placental mtDNA copy number



Brunst KJ, et al., Environ Int 2018; 112:49

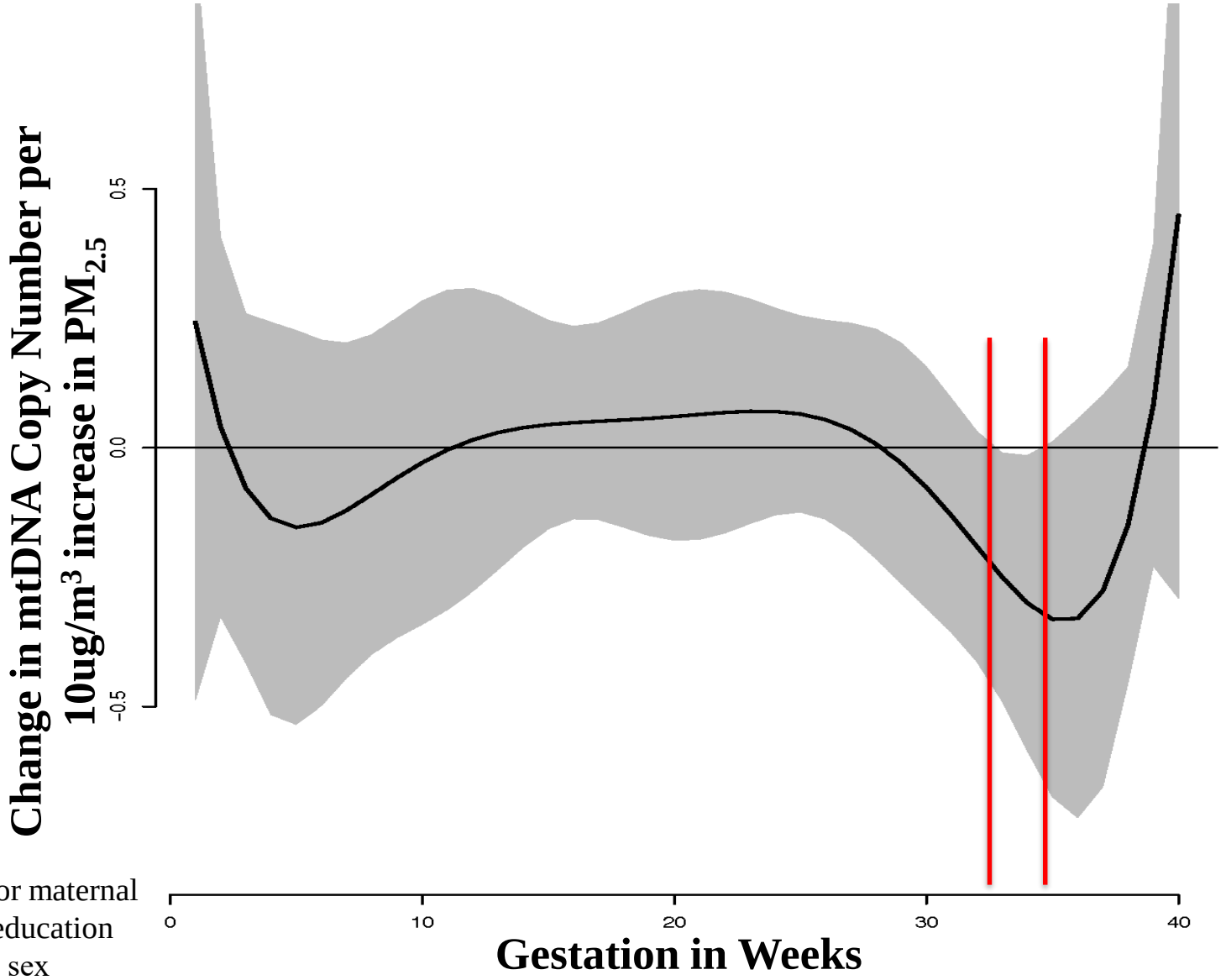
Maternal stress is associated with mtDNAcn in placenta



Brunst KJ, et al., Environ Int 2018; 112:49

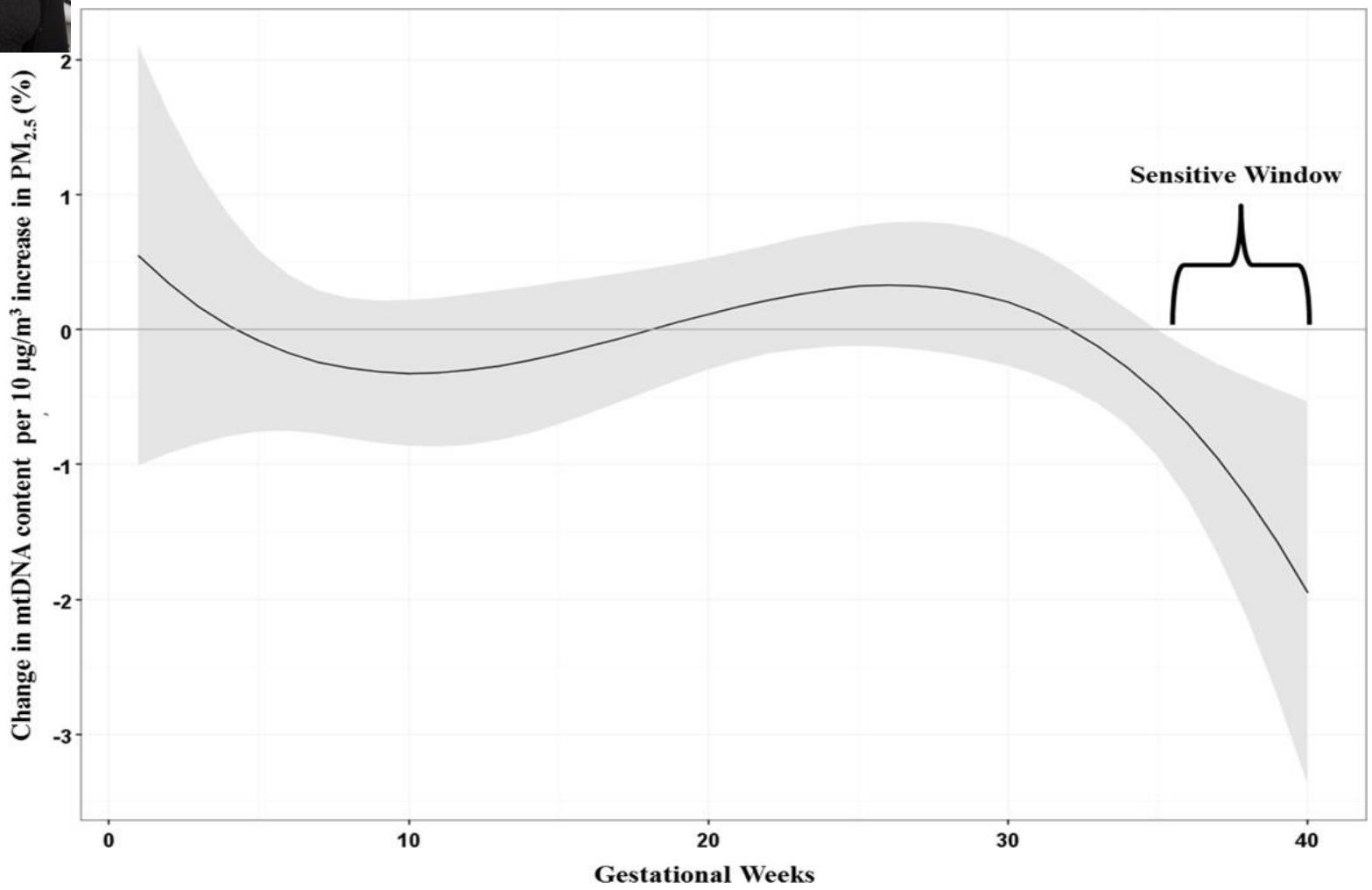
Also see: Brunst KJ, et al., Am J Epidemiol 2017; 186:1227

$PM_{2.5}$ exposure between 32-35 weeks gestation is associated with decreased mtDNAcn in women with high stress



Adjusted for maternal age, race, education and child's sex

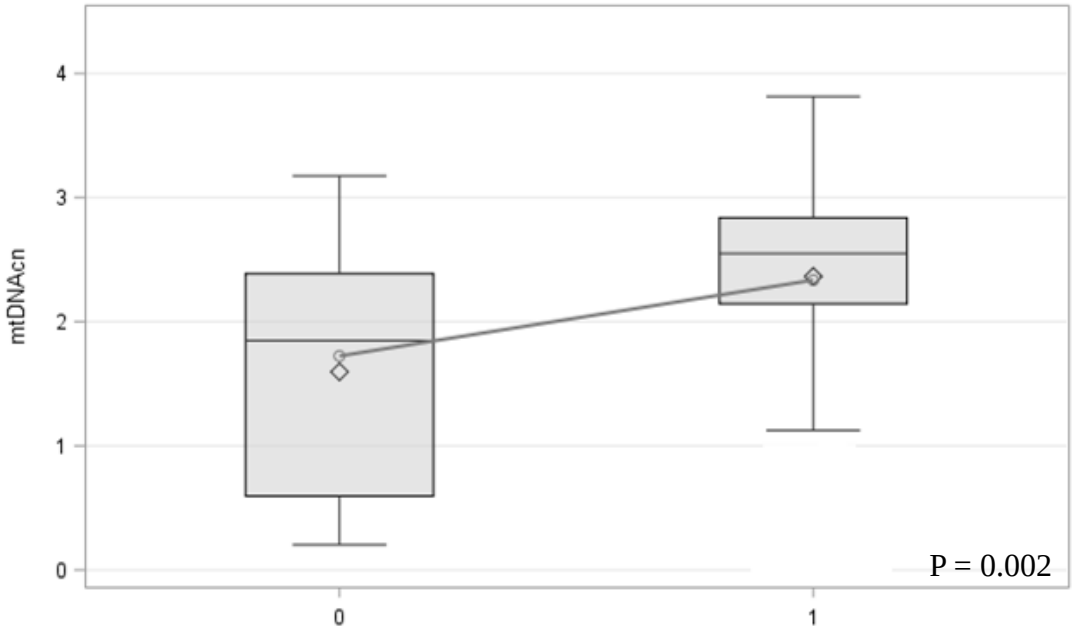
Mexico City PROGRESS Cohort – Prenatal $PM_{2.5}$ and mitochondrial DNA cn in cord blood



Rosa MJ, et al. Environ Int 2017; 98:198

Antioxidant Index

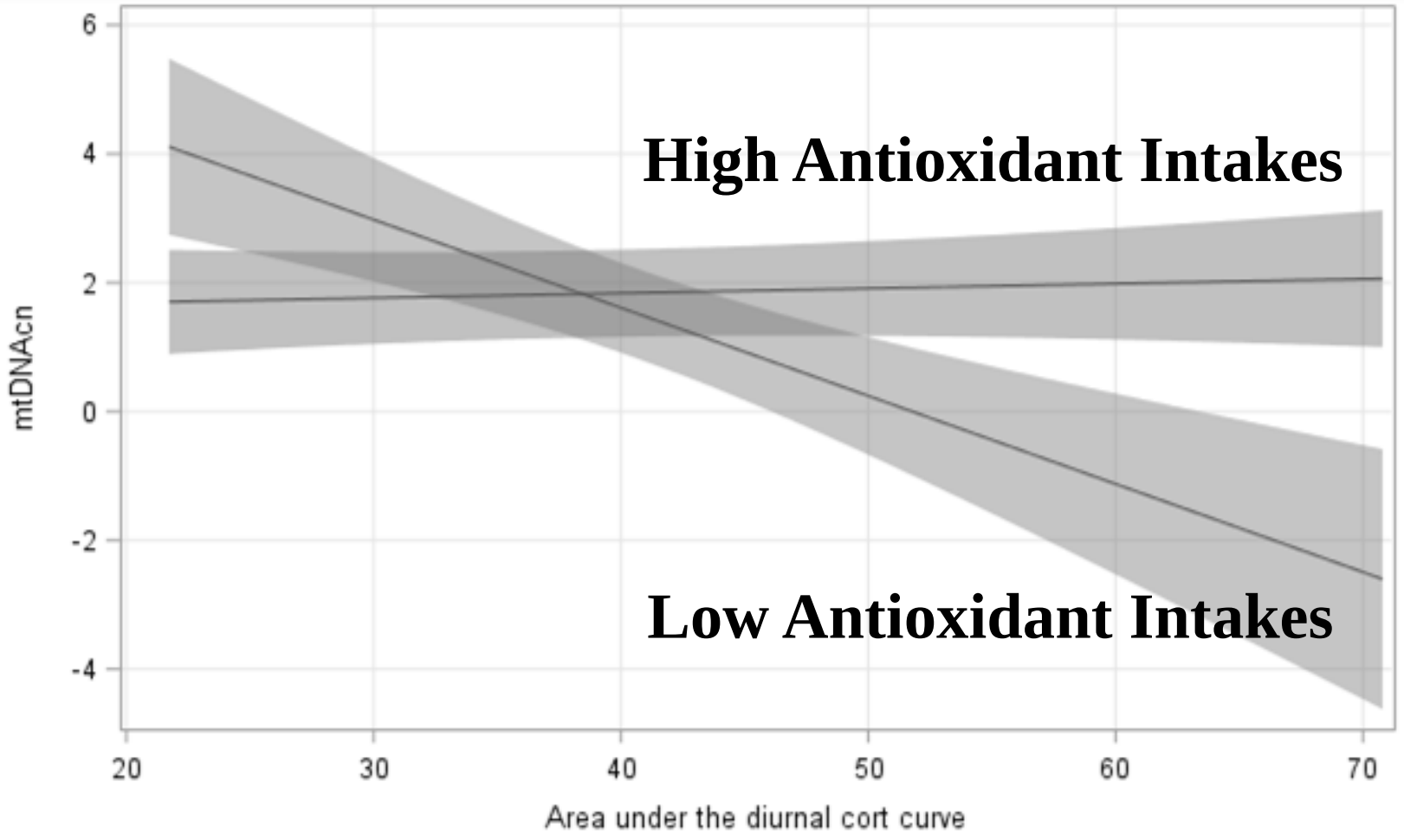
1) Converted antioxidant intakes into percentiles [Vit E, C, A, beta-carotene, zinc, magnesium, and selenium (dietary + suppl)]
2) Ranked percentiles relative to other participants' values
3) Final score reflecting a mean of the percentiles
4) Higher scores indicate higher overall antioxidant intakes



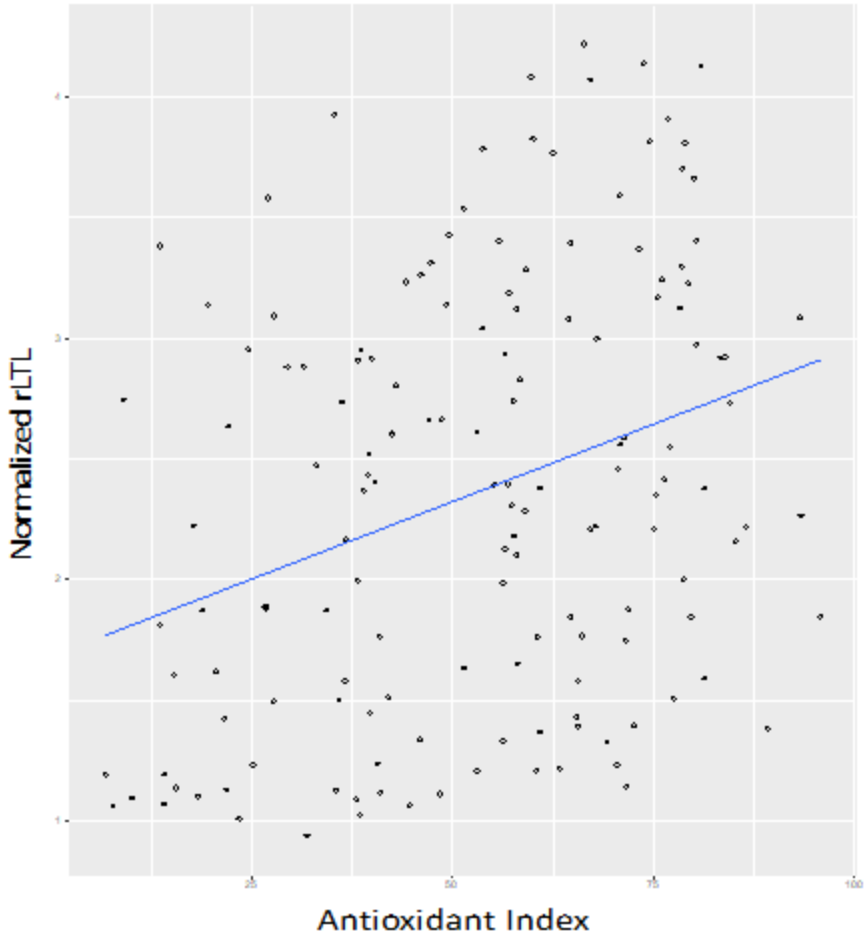
Low
(< 25th percentile)

High
(≥ 25th percentile)

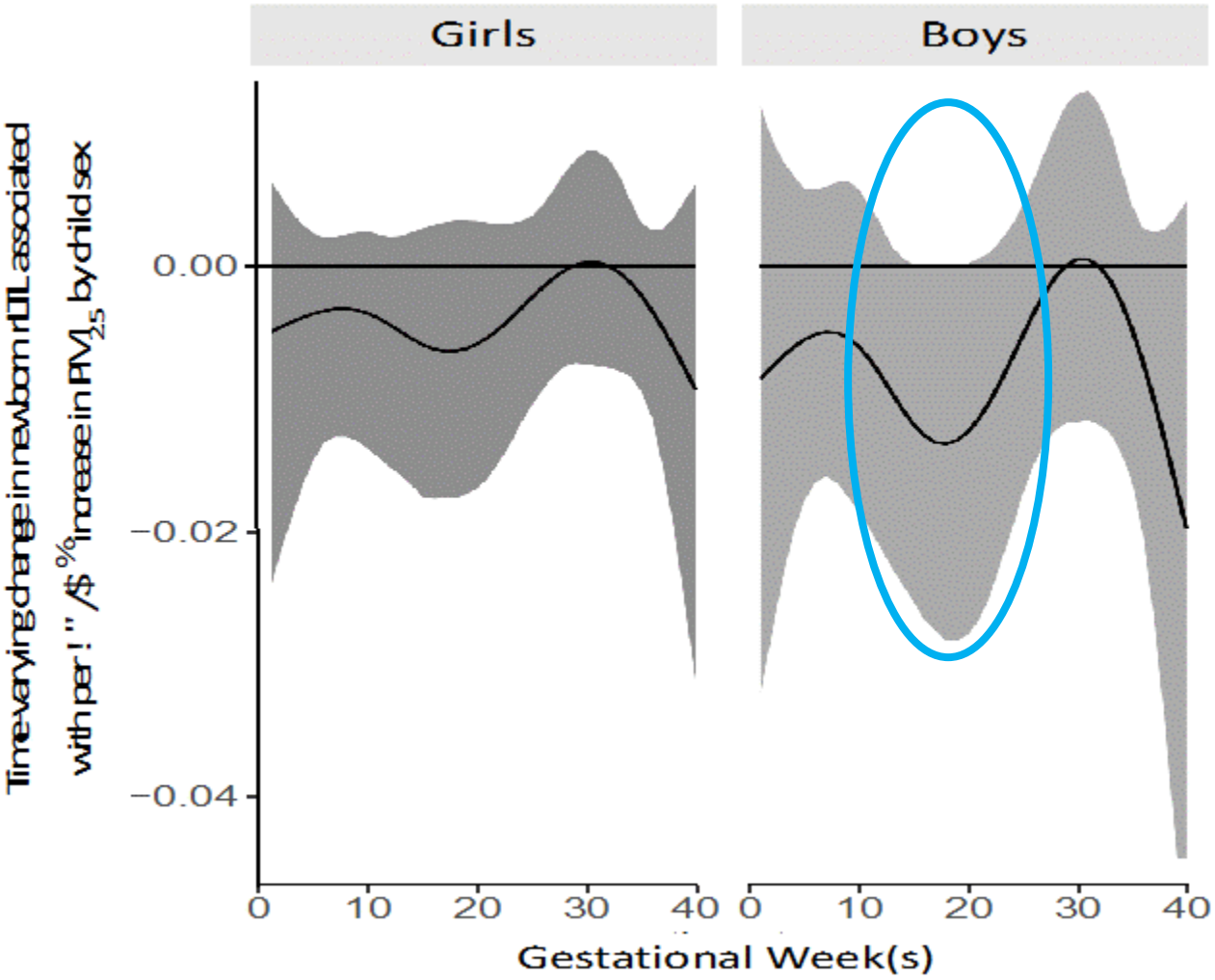
Prenatal Cortisol (AUC) & Placental mtDNAcn by Antioxidant Index



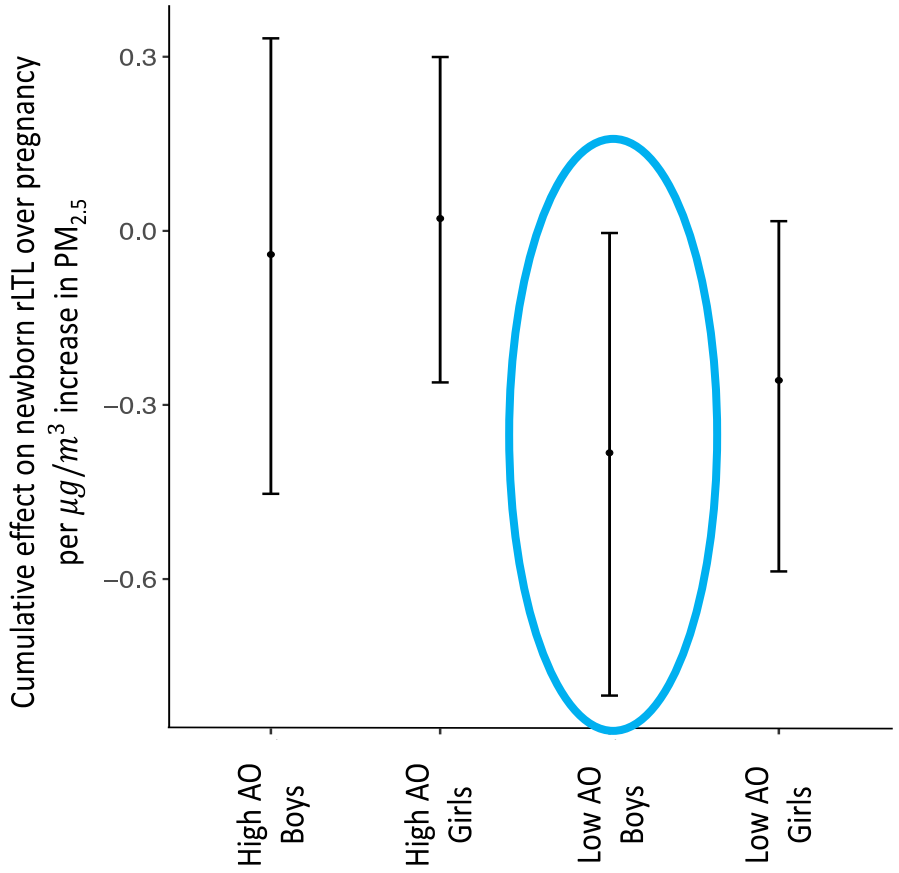
Cord Blood rLTL and Antioxidant Index



PM2.5 impacts telomere length at birth only among boys

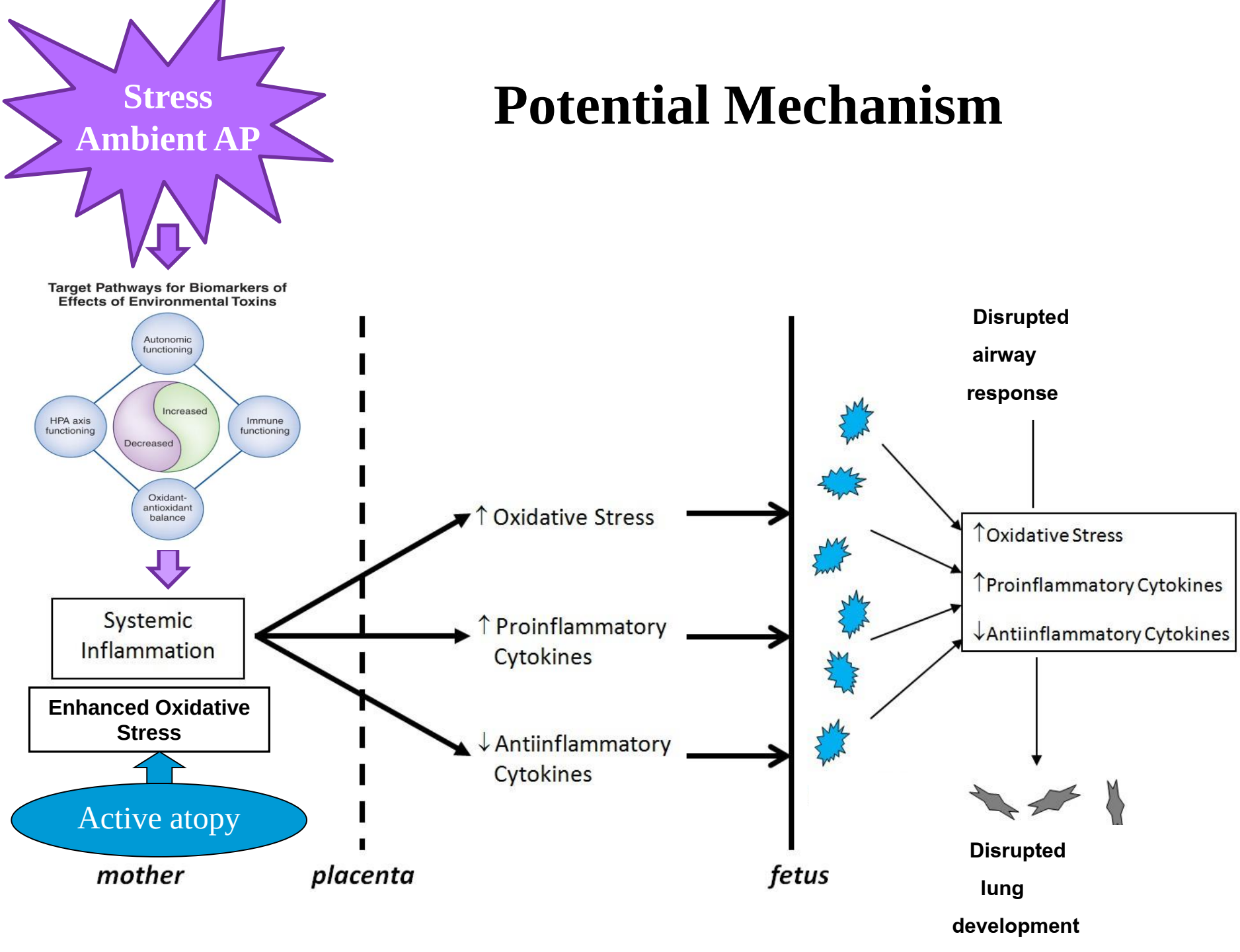


Cumulative effect PM2.5 on CB rLTL stratified by infant sex and AO intakes



In models examining effect modification by both child sex and maternal antioxidant intakes, the cumulative effect remained significant only in boys whose mothers reported low antioxidant intakes [CEE = -0.38 (95% CI -0.80 to -0.004)];

Potential Mechanism



the CANDLE study

Conditions **A**ffecting **N**eurocognitive **D**evelopment and **L**earning in **E**arly Childhood

CANDLE Study: Prenatal Prospective Cohort

- 1503 mother-infant dyads (2006-2011)
- Low-risk, singleton pregnancies
- Shelby County (Memphis), TN

Inclusion:

- Gestational Age ≥ 32 weeks
- Black/African American or White
- Follow-up at 4-6 years of age

Background

- Increasing prevalence of asthma/allergic disease linked to Western lifestyle changes, including changes in diet.

- Decrease in consumption of n-3 (omega-3) long-chain polyunsaturated fatty acids (PUFAs), and increase of n-6 PUFAs are a research topic of interest.

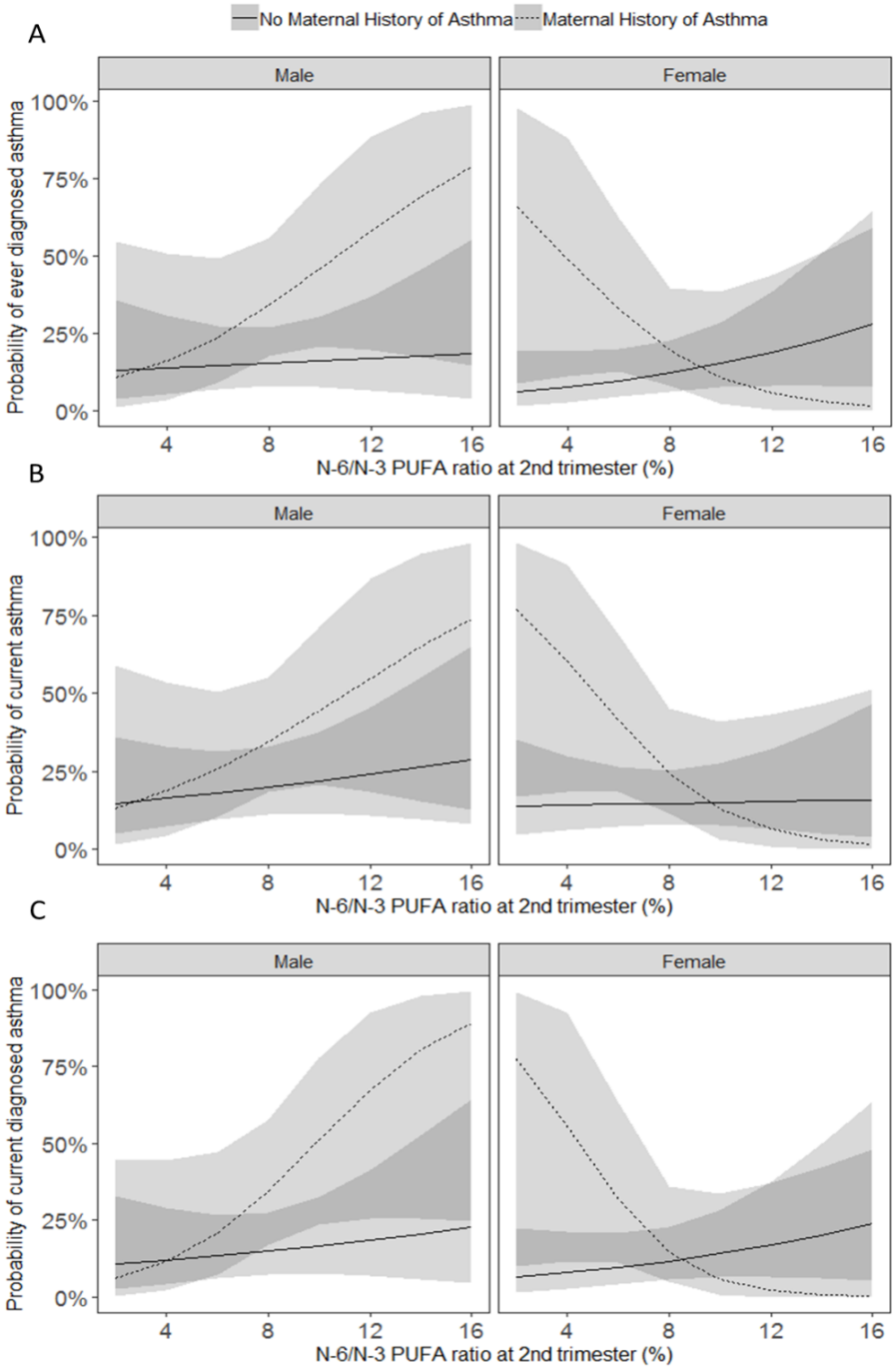
- Findings on prenatal polyunsaturated fatty acid (PUFA) intake and child wheeze and asthma have been inconsistent.

Background

- Few investigations have assessed how factors such as a familial predisposition to asthma, race, or child sex may influence association between prenatal PUFA status and child wheeze/asthma.

- Sex differences in childhood asthma development are well documented and previous work also demonstrates sexual dimorphism in fatty acid metabolism.

- The need to consider maternal history of atopic disease as an important effect modifier between the association of prenatal diet and child atopic disease has also been highlighted but this has not been examined.



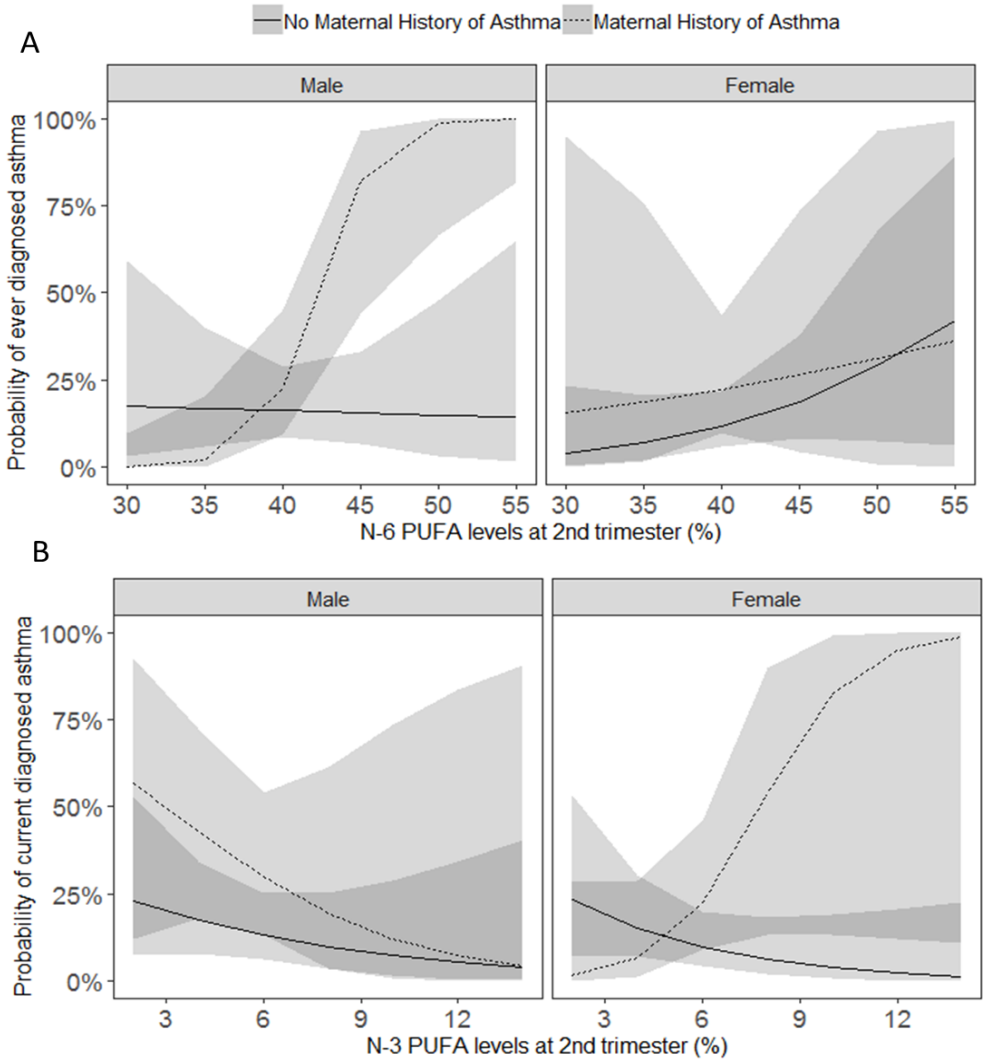
Multivariable analyses characterizing the association between continuous n-6/n-3 PUFA ratio at second trimester

(A) probability of ever diagnosed asthma ($p_{interaction}$=0.02)

(B) probability of current asthma ($p_{interaction}$=0.06)

(C) probability of current diagnosed asthma ($p_{interaction}$=0.01), by child sex and maternal history of asthma.

Rosa MJ, et al., manuscript under review



Multivariable analyses characterizing the association between:

(A) n-6PUFAs at second trimester and probability of ever diagnosed asthma ($p_{interaction}$=0.05)

(B) n-3PUFAs at second trimester and probability of current diagnosed asthma ($p_{interaction}$=0.04) by child sex and maternal history of asthma.

Rosa MJ, et al., manuscript under review

Conclusions: Main effects

- Higher maternal plasma n-6 PUFAs in pregnancy were associated with higher risk of ever being diagnosed with asthma and active asthma in their children at age 4-6 years.

- Lower risk of diagnosed current asthma with increasing n-3 PUFAs.

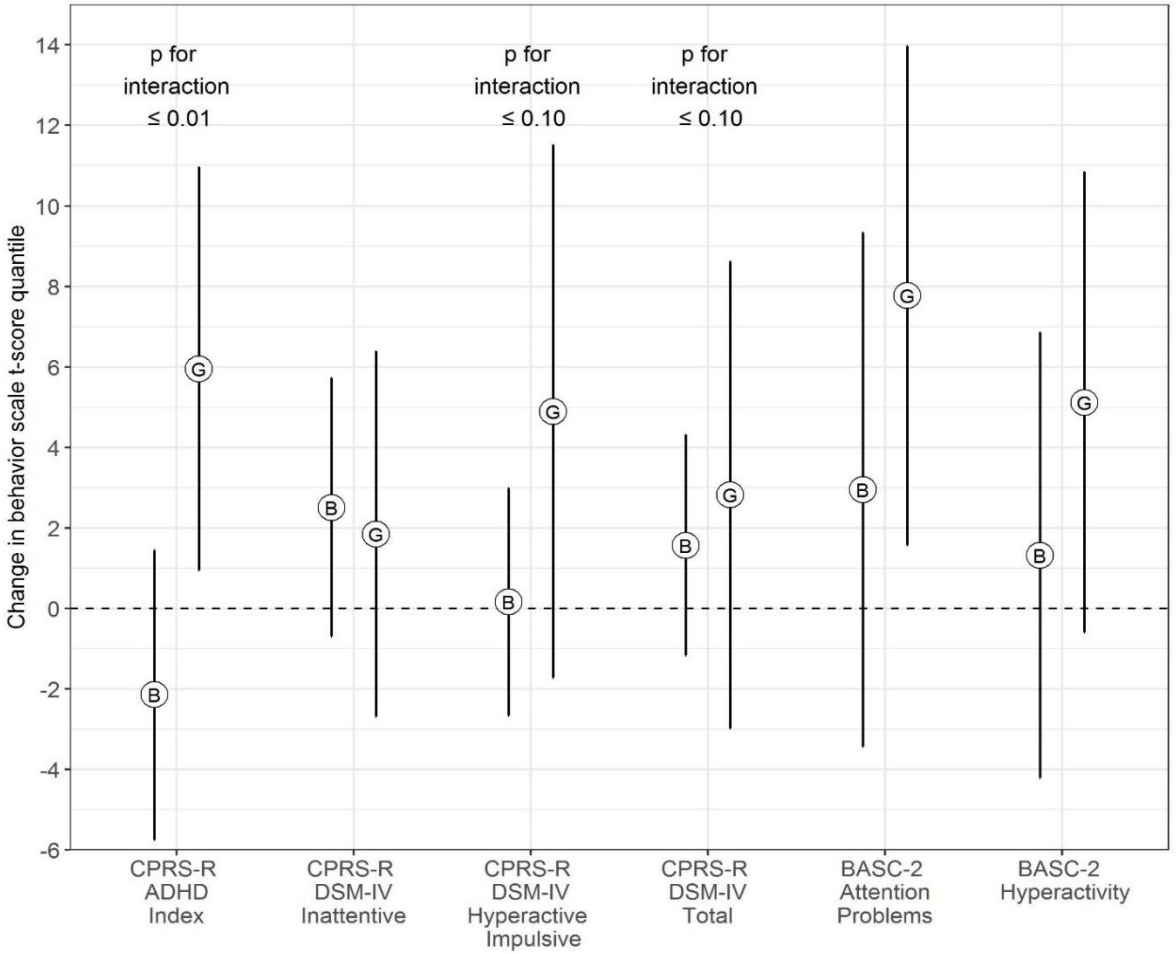
- No statistically significant associations between n-6/n-3 PUFA ratios and any respiratory outcomes in main effect models.

Conclusions: Interaction models

- Effects of n-6 PUFAs were modified by maternal asthma, with their effects being most pronounced in children born to women with asthma compared to those born to women without asthma.

- A significant three-way interaction between child sex, maternal asthma and n-6/n-3 PUFA indicated that male children born to women with asthma and a higher n-6/n-3 ratio had the highest risk across all outcomes.

Maternal active atopy in perinatal period and ADHD-like symptoms at age 6 years



Cowell W, et al., *Brain Behav Immun* 2019

Looking ahead…..

“It is easier to build strong children than to repair broken men.”

Frederick Douglas

Acknowledgements

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University of Michigan

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