Fetal Health & the Environment

Michael Leung

8/16/2021

Roadmap

- Overview
- Paper 1: Live birth bias
- Paper 2: Particulate Matter and Fetal Growth
- Paper 3: Ambient Temperature and Fetal Growth
- Conclusion & Future Directions

Overview of Fetal Health Literature

- Many studies on environmental risk factors for fetal health
- Most use birth weight as the data are easily accessible
- However, there are several limitations:
  - Birth weight poorly reflects fetal growth restriction
  - Driven mainly by fat accumulation & so may be a poor proxy for the development of other organs
  - Assessment at birth requires the production of live births

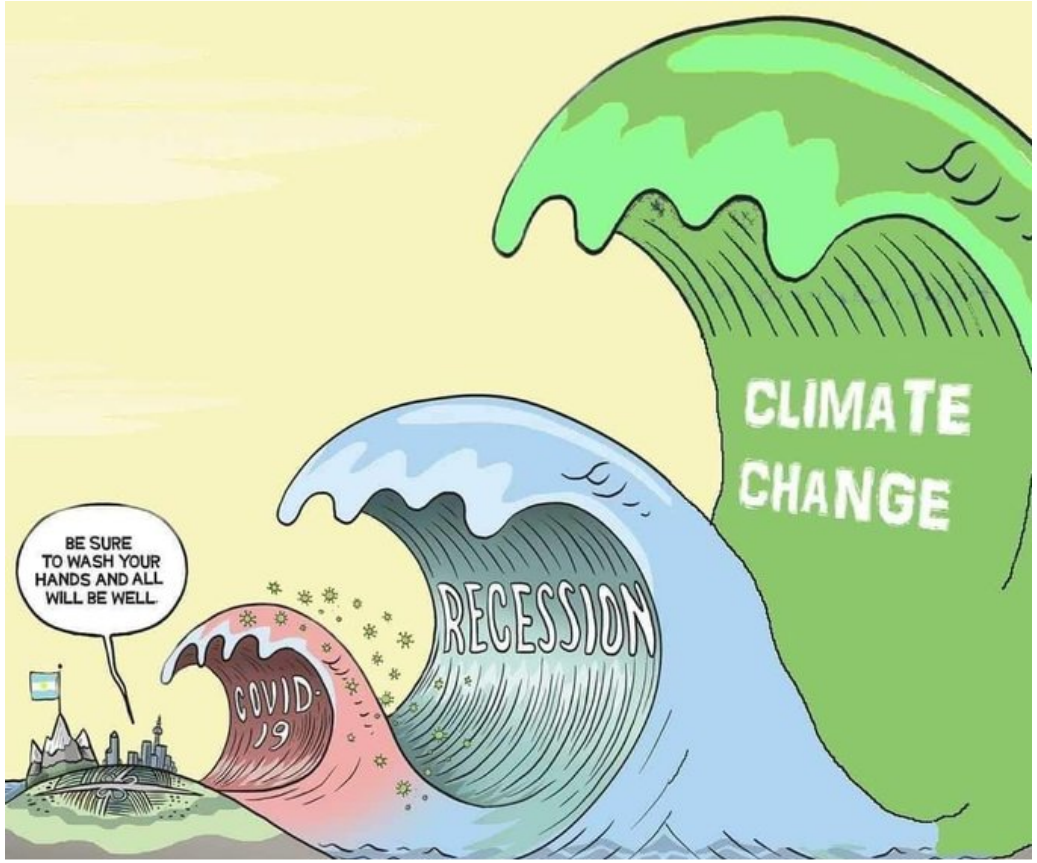
What is this dissertation about?

- It asks the question - how do environmental exposures affect *in utero* fetal development during pregnancy rather than at its conclusion, and what are some of the implications?

Paper	Aim
1	Assess through simulations the bias due to selection on live births
2	Examine the association between particulate matter < 2.5 microns and fetal growth measures
3	Examine the association between ambient temperature and fetal growth measures

Why $PM_{2.5}$ and Temperature?

- The current climate crisis is a threat to human health ("code red")
- Heat & air pollution exacerbated by climate change, with more extreme weather events
- Pregnant individuals & their fetuses are a vulnerable group

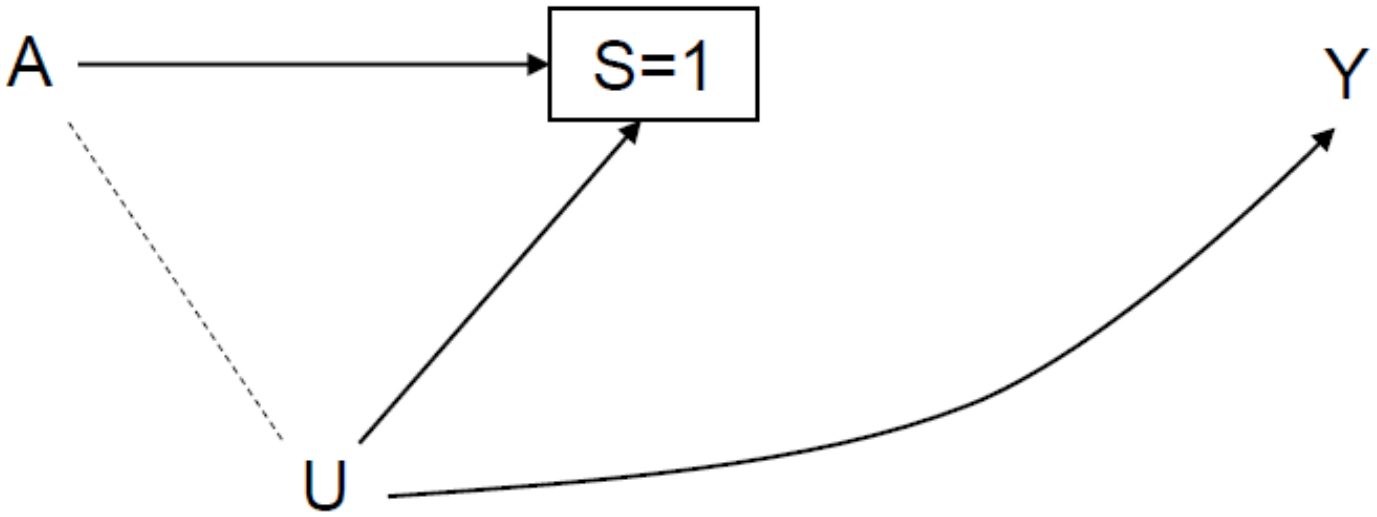


Bias due to selection on live births in studies of environmental exposures during pregnancy: A simulation study

Michael Leung, Marianthi-Anna Kioumourtzoglou, Raanan Raz & Marc Weisskopf

Background

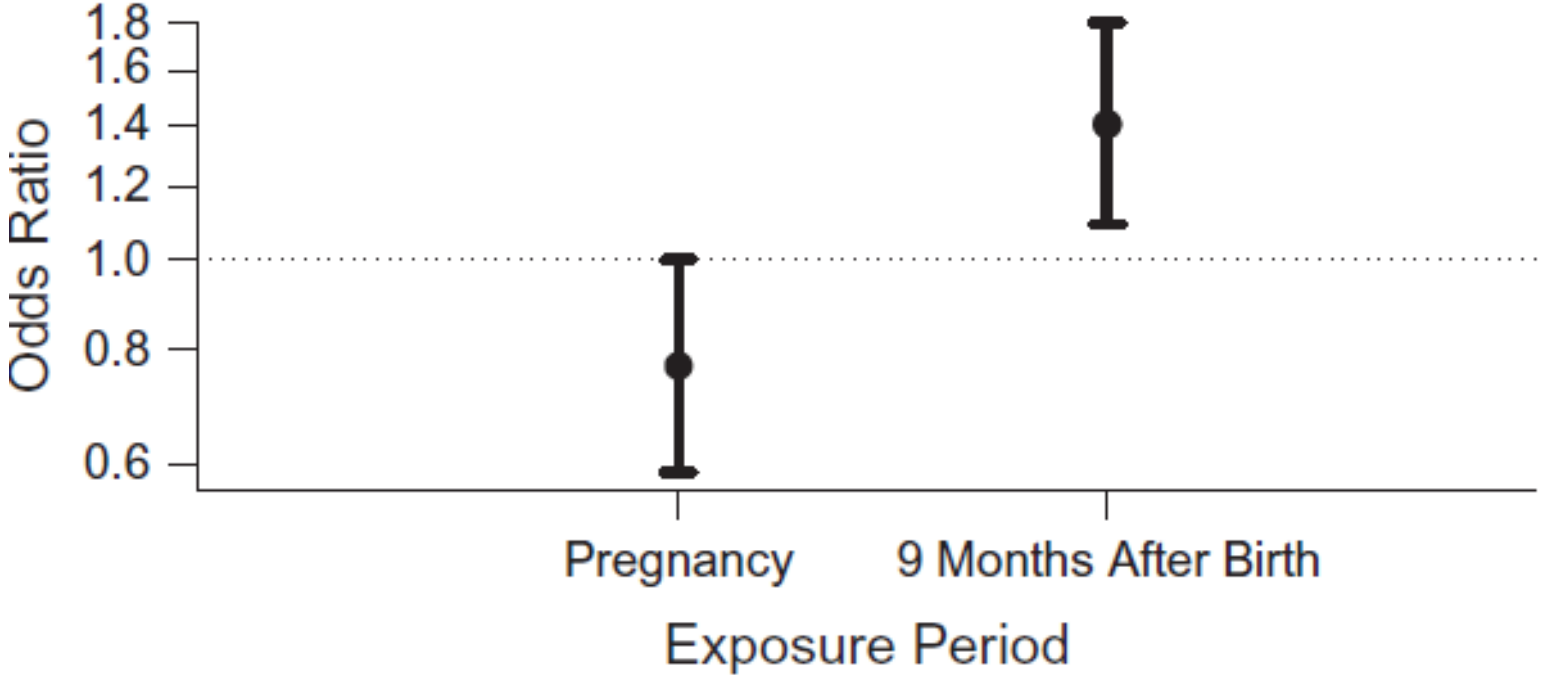
- Environmental studies of prenatal exposures are vulnerable to live birth bias (LBB), which is the bias that arises from the restriction of the analysis to live births when that is driven by both exposure A and unmeasured factors U that also affect the outcome



- LBB strength determined by selection effects (OR_S), and prevalence of U (π_U)

Background

- An example of possible LBB is a recent analysis of nitrogen dioxide (NO_2) and autism spectrum disorder (ASD), where the odds ratio for prenatal NO_2 exposure was 0.77 per IQR (Raz et al. 2018)



Background

- LBB difficult to study with real data
- Few simulation studies have showed that LBB is generally weak, but they presuppose no A-U interaction
- Here, we relax these assumptions and consider three survival (selection) mechanisms
  1. Collider-stratification without interaction (M1): A and U independently affect selection
  2. Depletion of susceptibles (M2): Selection is dependent on the presence of both A and U (i.e., the interaction-only effect)
  3. When both 1 and 2 operate simultaneously (M1+2)

- **Aim**: To examine what parameters would be needed to account for this protective association through LBB

Methods

- Simulated the magnitude of bias under the null, under three selection mechanisms (M1, M2, M1+2) in a hypothetical pregnancy cohort of 100,000 conceptions

$$P(loss_i) = \frac{e^{\beta_0+\beta_1 A_i+\beta_2 U_i+\beta_3 A_i \cdot U_i}}{1+e^{\beta_0+\beta_1 A_i+\beta_2 U_i+\beta_3 A_i \cdot U_i}}$$

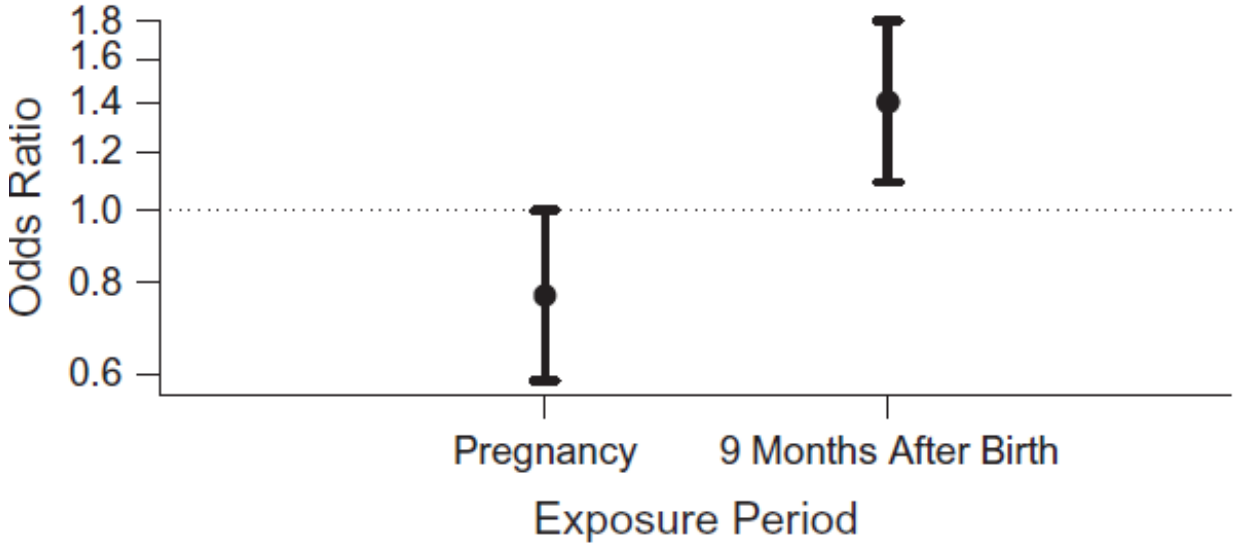
$$P(ASD_i) = \frac{e^{\gamma_0+\gamma_1 U_i}}{1+e^{\gamma_0+\gamma_1 U_i}}$$

- M1: $e^{\beta_1} = e^{\beta_2} = OR_S$, $e^{\beta_3} = 1$
- M2: $e^{\beta_1} = e^{\beta_2} = 1$, $e^{\beta_3} = OR_S$
- M1+2: $e^{\beta_1} = e^{\beta_2} = e^{\beta_3} = OR_S$

where $OR_S = 1.5, 2.0, 2.5, 3.0$, and $\pi_U = 0.25, 0.50, 0.75$

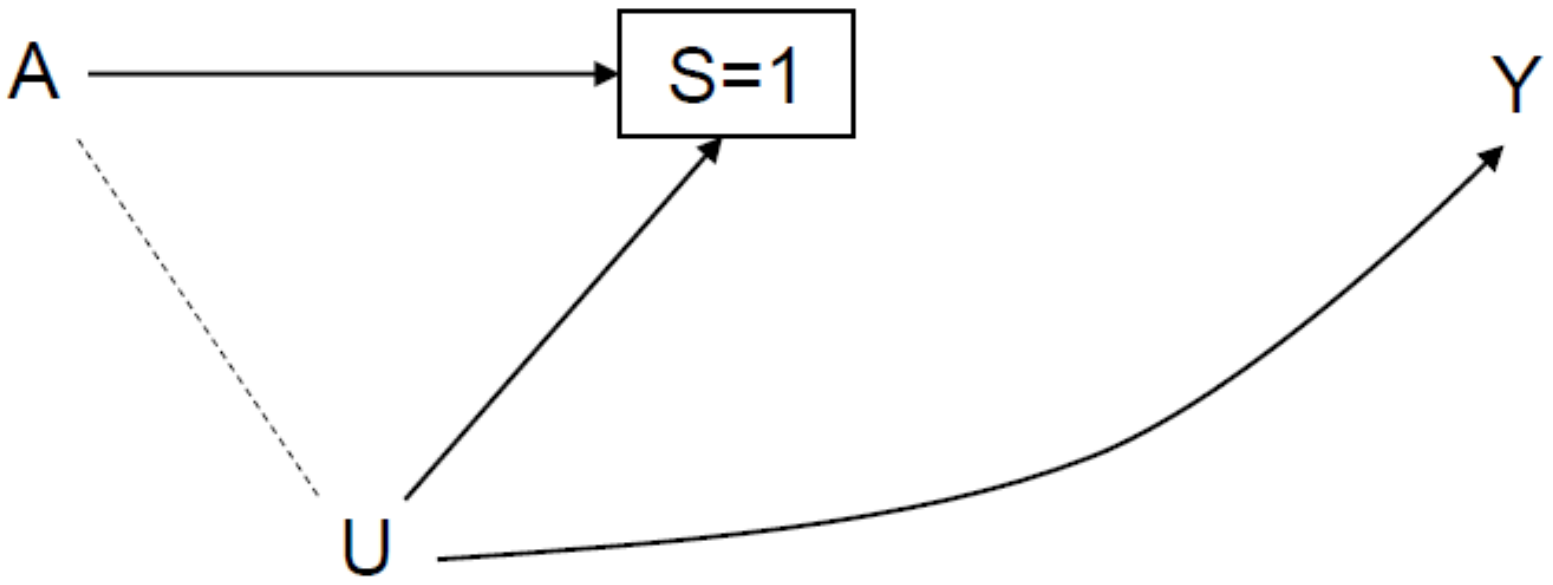
Methods

- Other inputs were based on the characteristics of the original NO_2-ASD study:
  - $NO_2 \sim \mathcal{N}(16.7, 4.3^2)$
  - Baseline odds of Y was set to be 0.015 (reflect low incidence of ASD)
  - Baseline odds of fetal loss was set to be 0.05
- Each scenario was simulated 1000 times
- Determined observed OR for ASD and NO_2 among live births ($S = 1$) in each simulation with logistic regression ($OR_{AY|S=1}$)



Methods

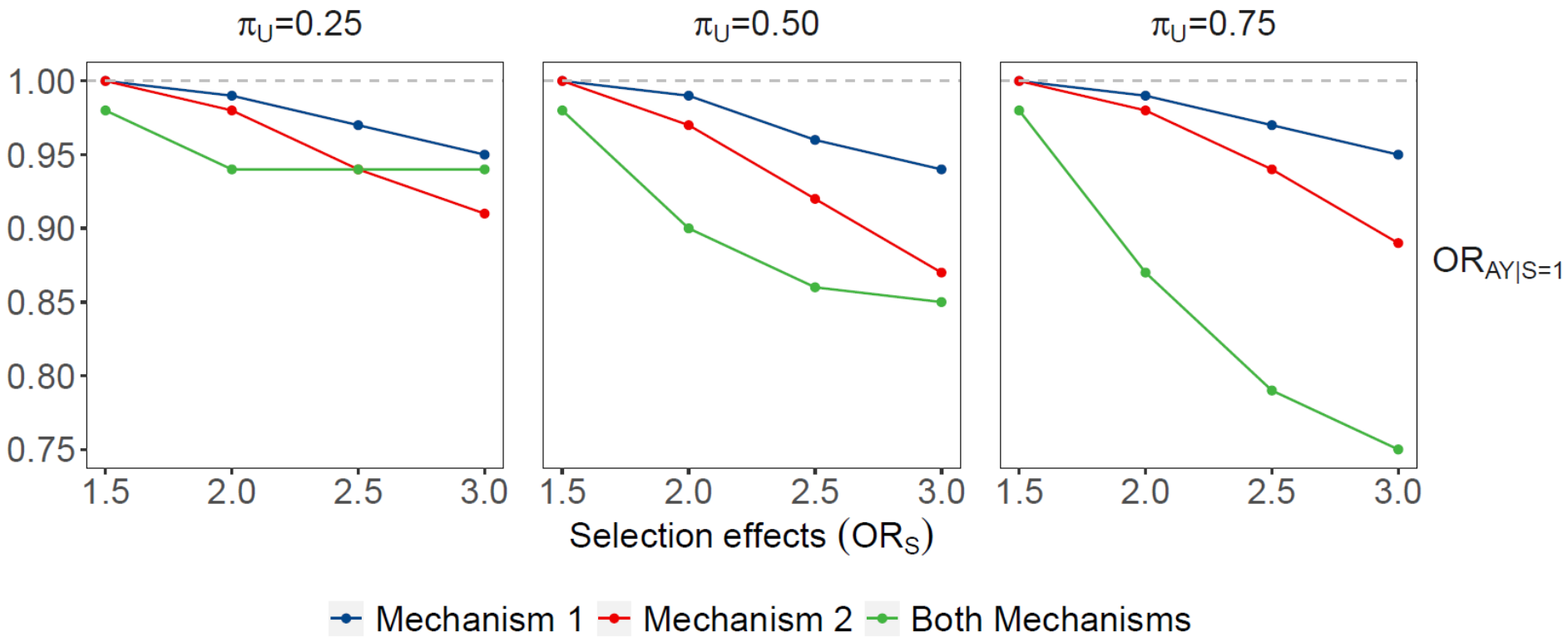
- Obtained mean of the "bias parameters" among $S = 1$:
  - NO_2-U association ($OR_{AU|S=1}$)
  - prevalence of U ($\pi_{U|S=1}$)



- Repeated these scenarios in the presence of two, and three Us, where all Us were set to have the same prevalence and effect on selection

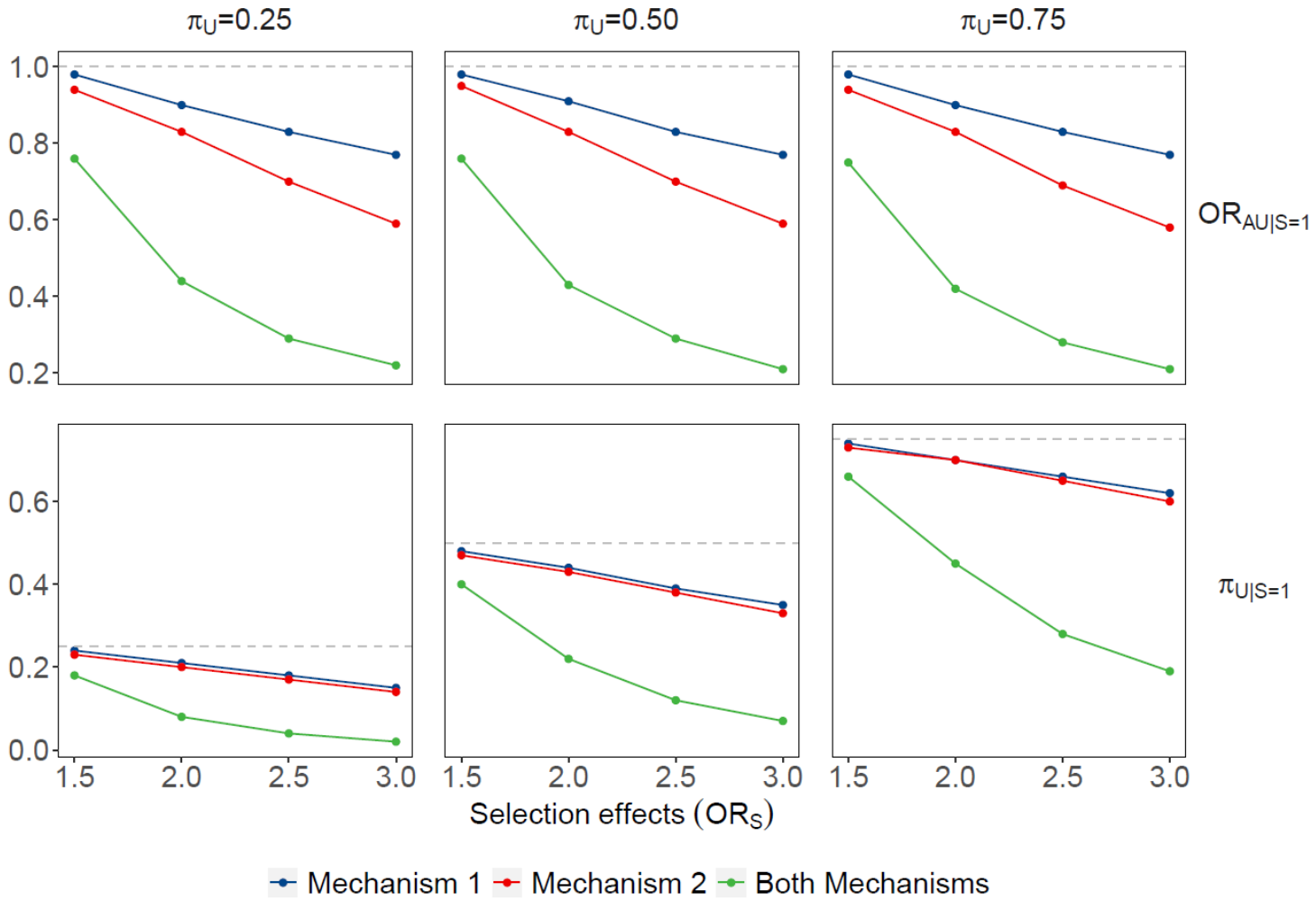
Simulation Results: Observed NO_2-ASD Association

- Magnitude of LBB: M1 < M2 < M1+2



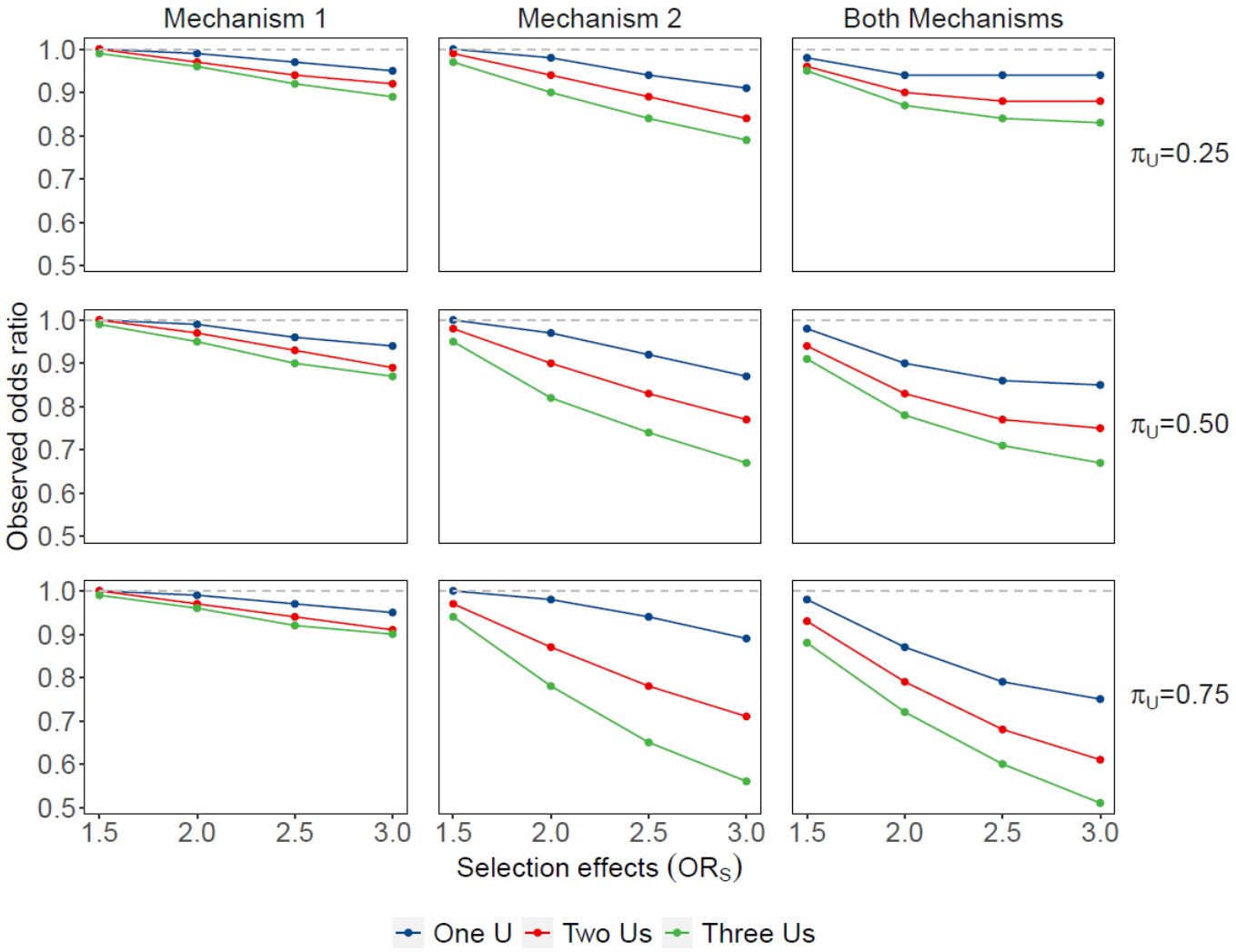
Simulation Results: Bias Parameters

- ↑ deviation from population parameters = ↑ LBB



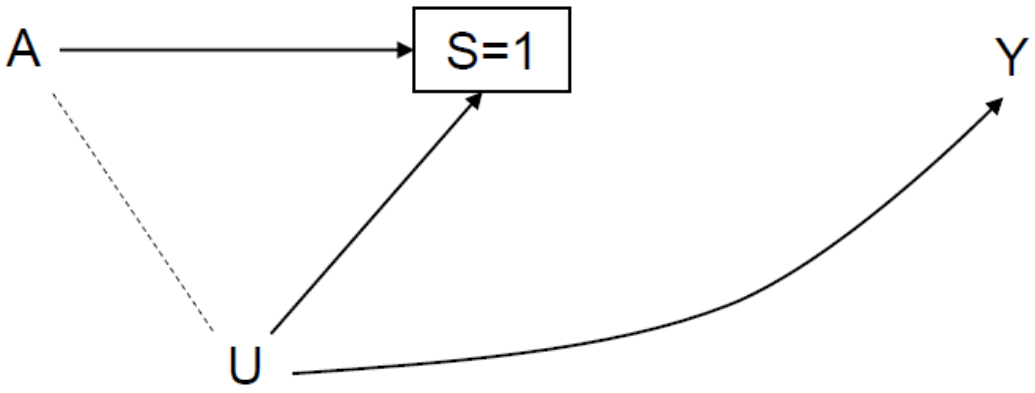
Simulation Results: Multiple *U*s

- Bias is amplified with multiple *U*s, with the extent of amplification dependent on the mechanism



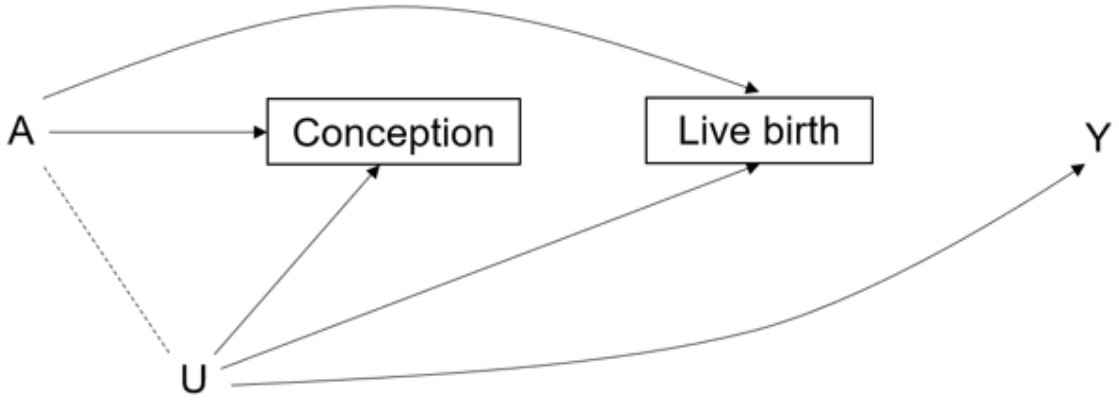
Key Findings

- LBB generally weak for M1, and thus unlikely to account for observed NO_2-ASD association
- LBB due to M2 or M1+2 more likely to account for observed NO_2-ASD association
- More likely if U was a composite of uncontrolled variables
  - e.g., prenatal stress, maternal smoking, genetic factors, endocrine-disrupting chemicals etc.



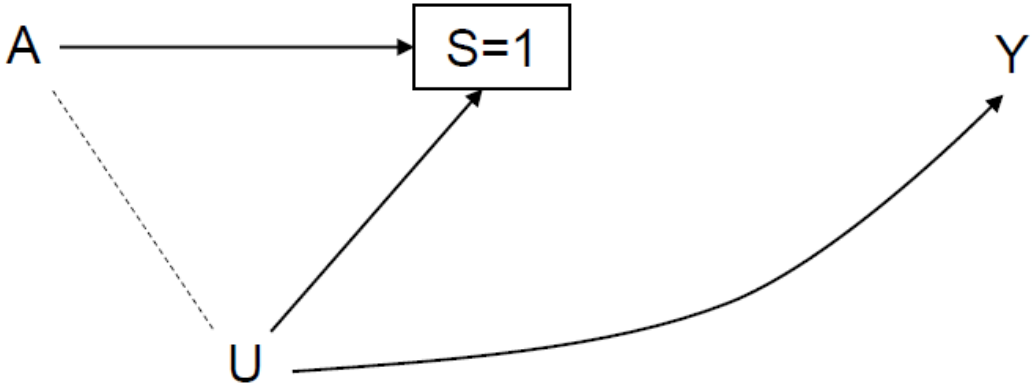
Potential Limitations

- Simplified depictions of potential causal structures
- Simulation assumptions:
  - no confounding of exposure effects
  - no loss to follow-up among live-born children
  - no measurement error
  - no seasonal or time trends in exposure/outcome
  - equal magnitude and sign of selection effects
  - conceptions are not affected by pre-conception exposures



Conclusion & Future Directions

- LBB leads to associations that are biased downwards and limits identification of harmful exposures
  - Truly adverse effects may appear not as harmful, null, or even protective
- What can we do?
  - Need to be able to study pregnancy loss (measure selection)
  - To rule out LBB, we could show that the exposure does not affect selection
  - If it does affect selection, we would need to collect information on U



Exposure to $PM_{2.5}$ during pregnancy and fetal growth in Massachusetts, USA

Michael Leung, Marc Weisskopf, Francine Laden, Brent Coull, Anna Modest, Michele Hacker, Blair Wylie, Yaguang Wei, Joel Schwartz & Stefania Papatheodorou

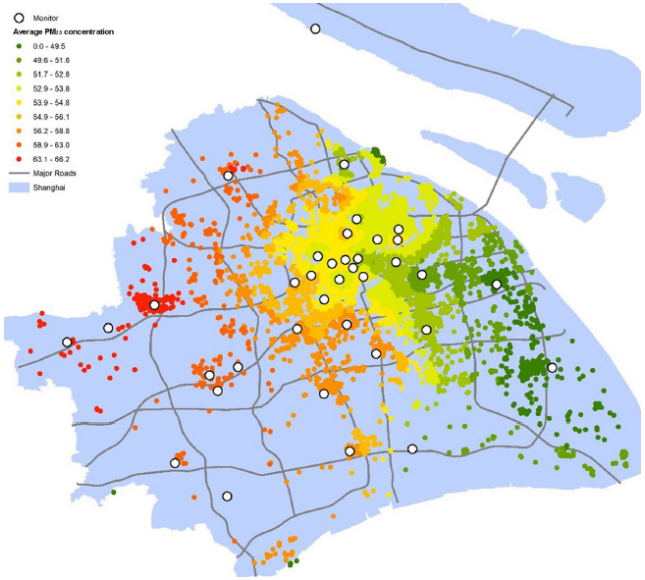
Background

- Pregnancy is a period of increased vulnerability to air pollution
- Systematic review showed that air pollution was consistently associated with reduced birth weight (Bekkar 2020)
- Birth weight poorly reflects fetal growth restriction
- Additional insights using routine ultrasound data

x

Background: Evidence from Prior Studies

- Three studies have examined the association between $PM_{2.5}$ and ultrasound parameters of fetal growth (Clemens 2017, Cao 2019, Lin 2020)
  - Increased exposure associated with reduced fetal growth
  - Limitations:
    - Limited spatial resolution (e.g., nearest monitor)
    - Only assessed cumulative $PM_{2.5}$ exposure



Methods: Study Population

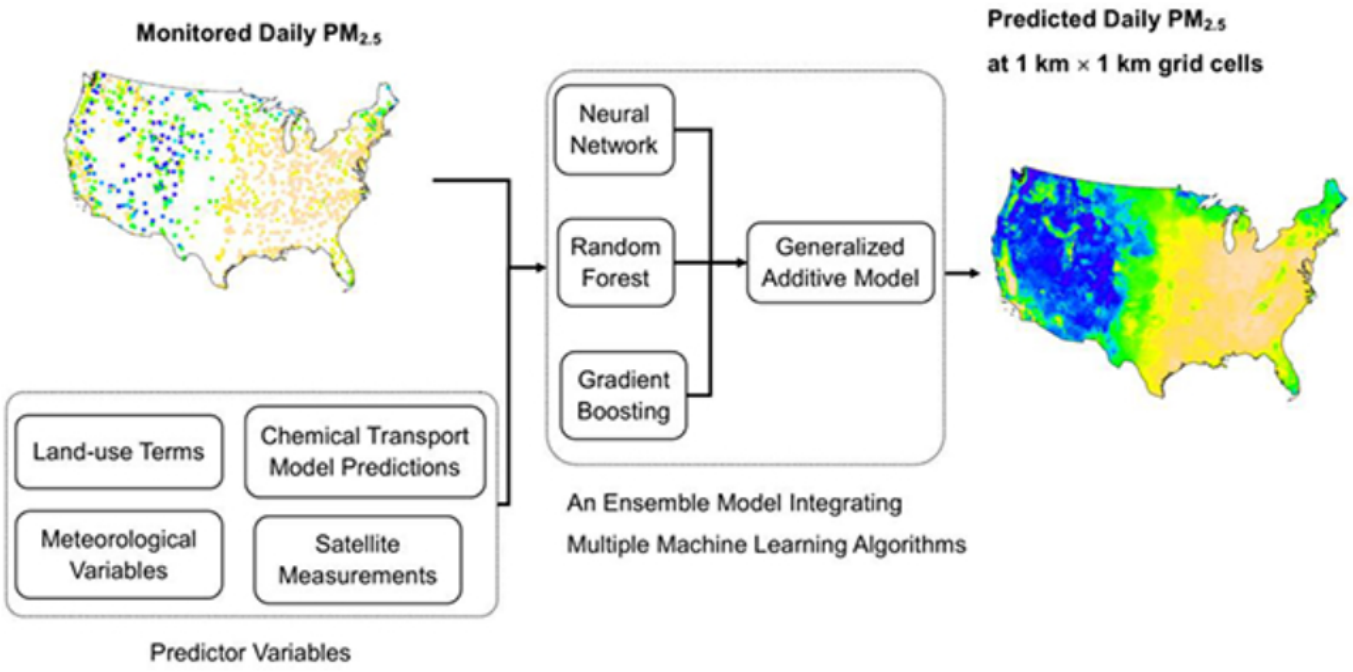
- Deliveries at Beth Israel Deaconess Medical Center (BIDMC), 2011-2016
  - Pregnancies that are expected to undergo routine ultrasound as part of standard prenatal care at BIDMC
- BIDMC is a large tertiary-care hospital which covers a wide area & no specific pattern of referral
- Exclusions: multiple gestations & residential addresses outside of Massachusetts

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

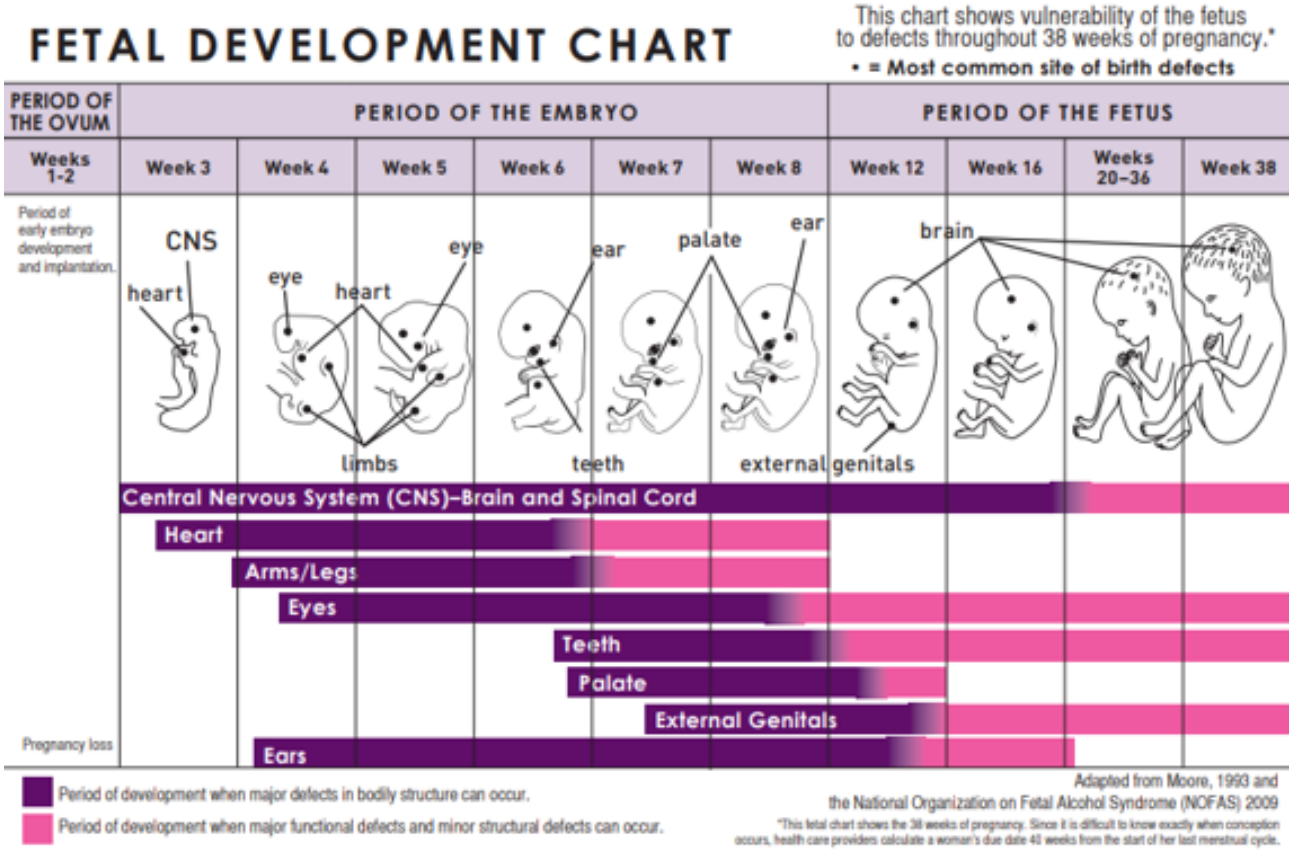
Methods: $PM_{2.5}$

- Spatiotemporal model that estimates daily $PM_{2.5}$ exposure in each 1x1 km grid across the Continental US (R^2=0.86)
- Assigned based on pregnant individual's address at delivery



Methods: $PM_{2.5}$

- Two exposure windows:
  - Primary window: first 16 weeks
  - Secondary window: from conception to fetal growth assessment



Methods: Fetal Growth Measures

- Ultrasound measures from BIDMC (OB/GYN and Radiology)
  - Biparietal diameter (BPD), head circumference (HC), femur length (FL), and abdominal circumference (AC) standardized using INTERGROWTH-21st fetal growth standards.
  - Scans categorized into two types of scans: anatomic scans (<24 weeks) & growth scans ($\geq$ 24 weeks)
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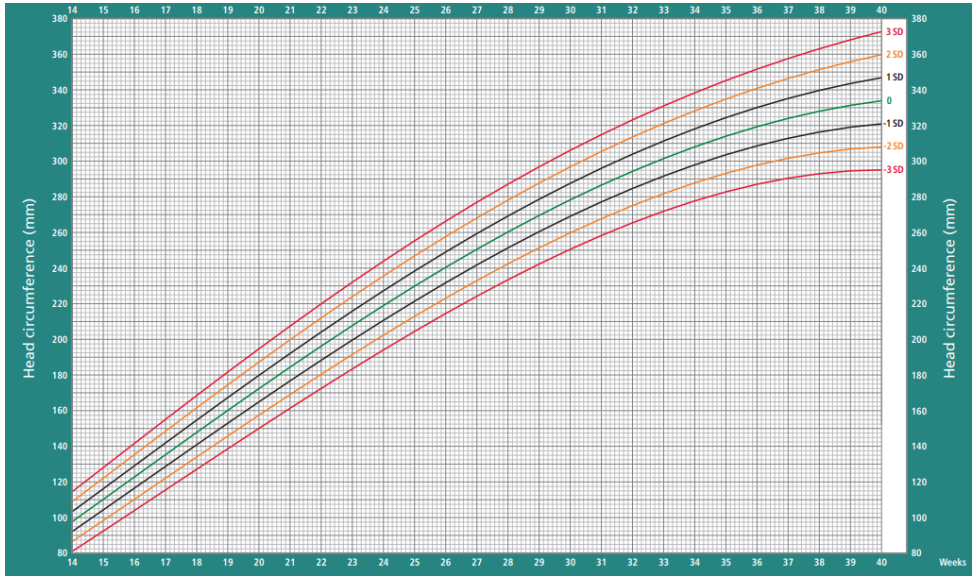
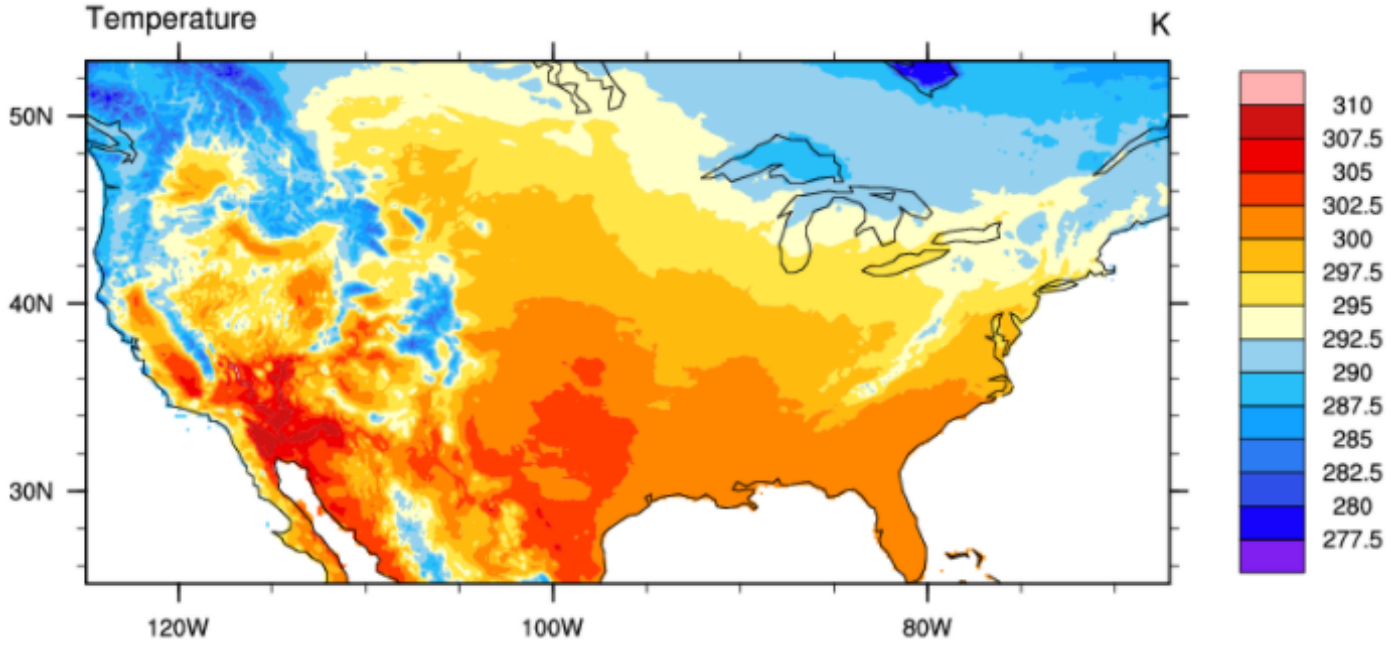


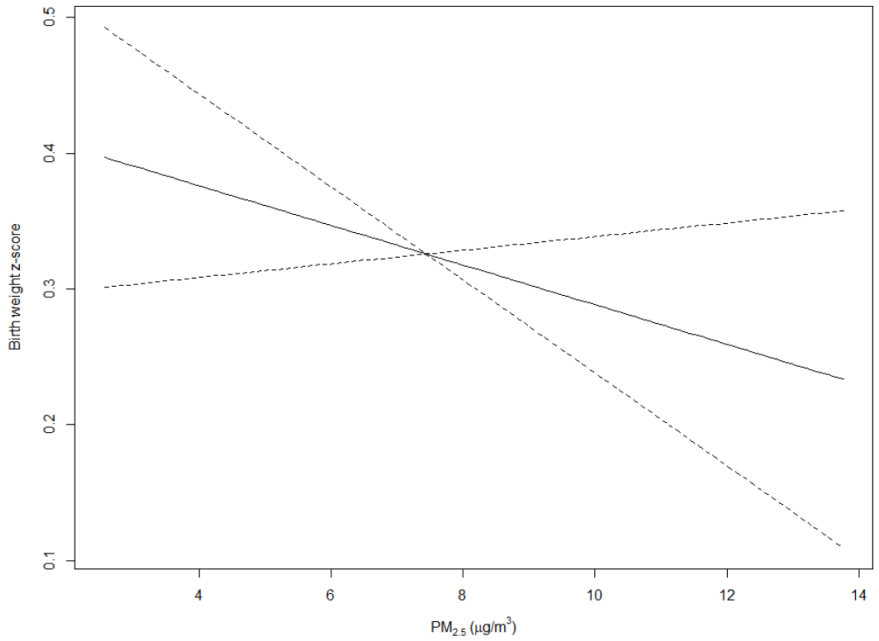
Methods: Covariates

- Temperature from NASA North American Land Data Assimilation Systems (NLDAS-2), 12x12 km
- Maternal age, race, educational attainment, insurance type, parity, fetal sex
- Area Deprivation Index (ADI), census block group level
  - Neighborhood disadvantage metric derived from 17 census variables on income, education, employment & housing quality

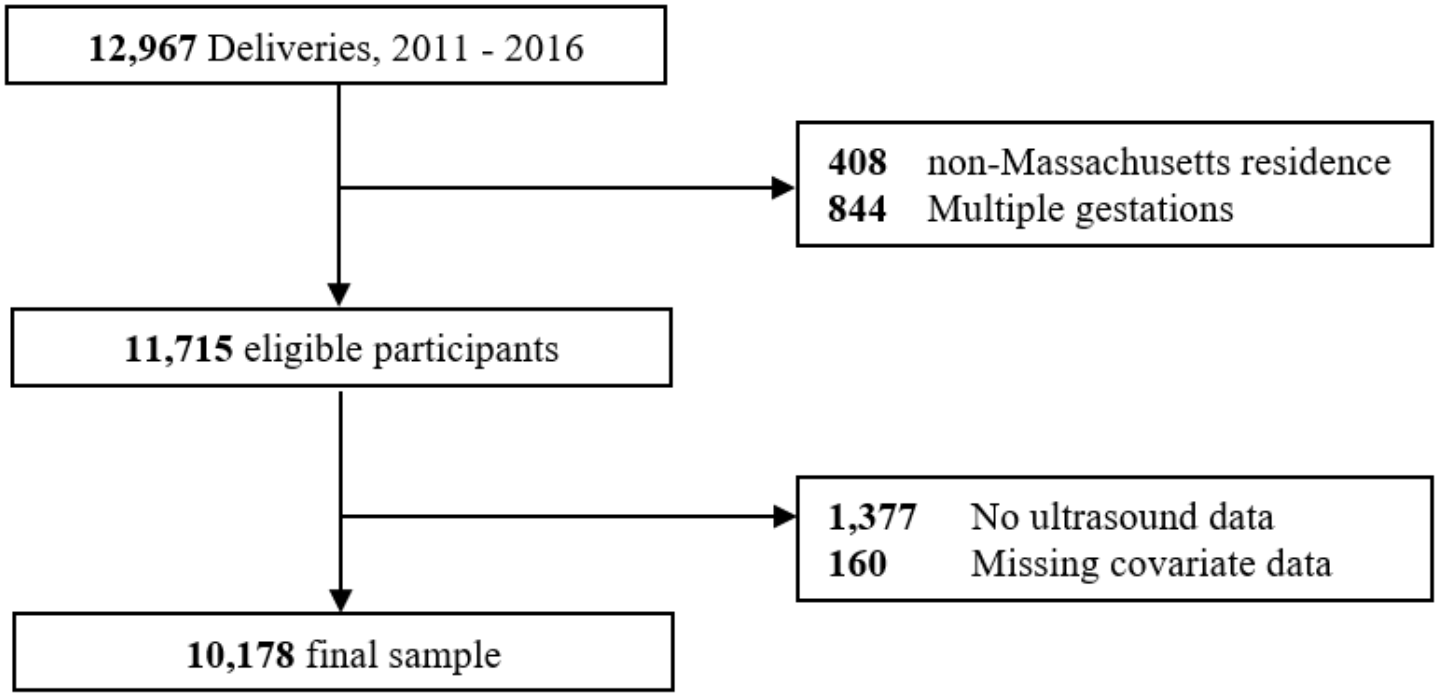


Methods: Analysis

- General additive mixed model (GAMM)
  - Penalized spline for $PM_{2.5}$
  - All covariates listed previously, term for conception year & natural spline with 4 df/year for conception day of the year
  - Random intercept for each pregnancy
  - Effect modification by fetal sex, race, education & ADI
- Since GAMMs showed approximately linear associations, present estimates from model with linear term

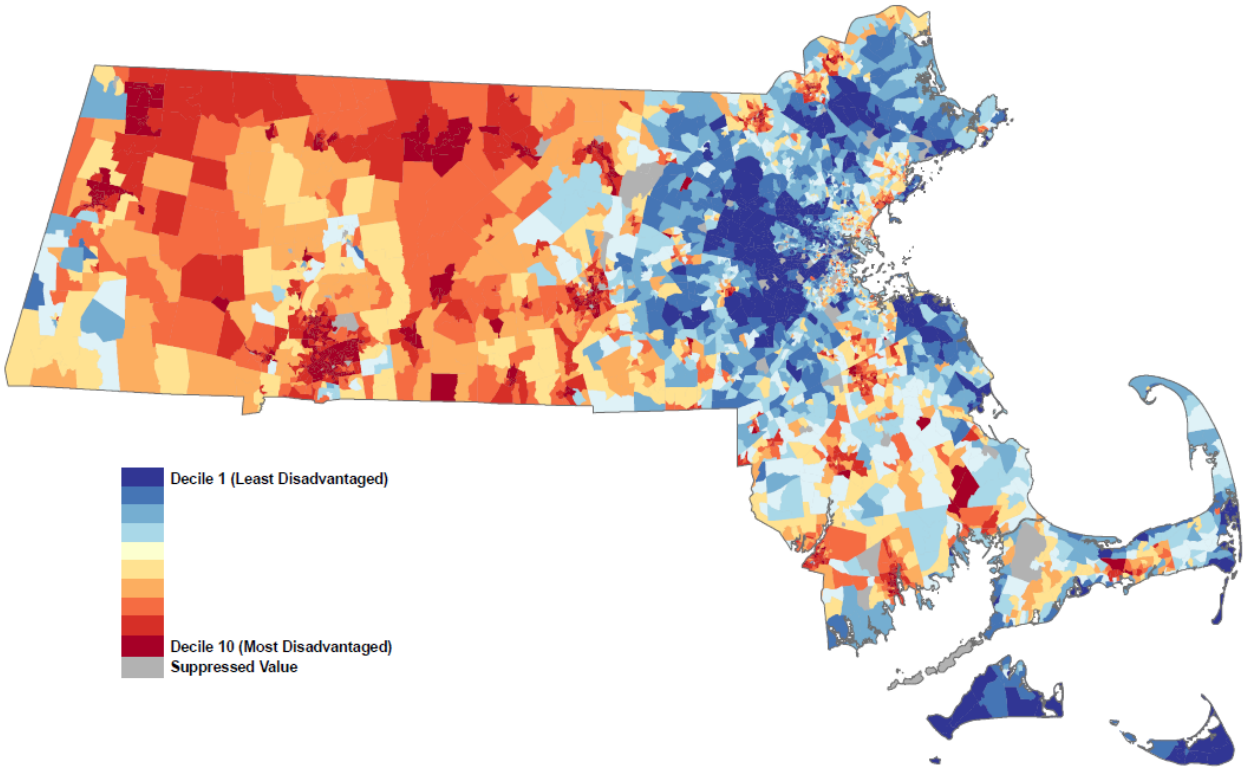


Results: Participant Selection



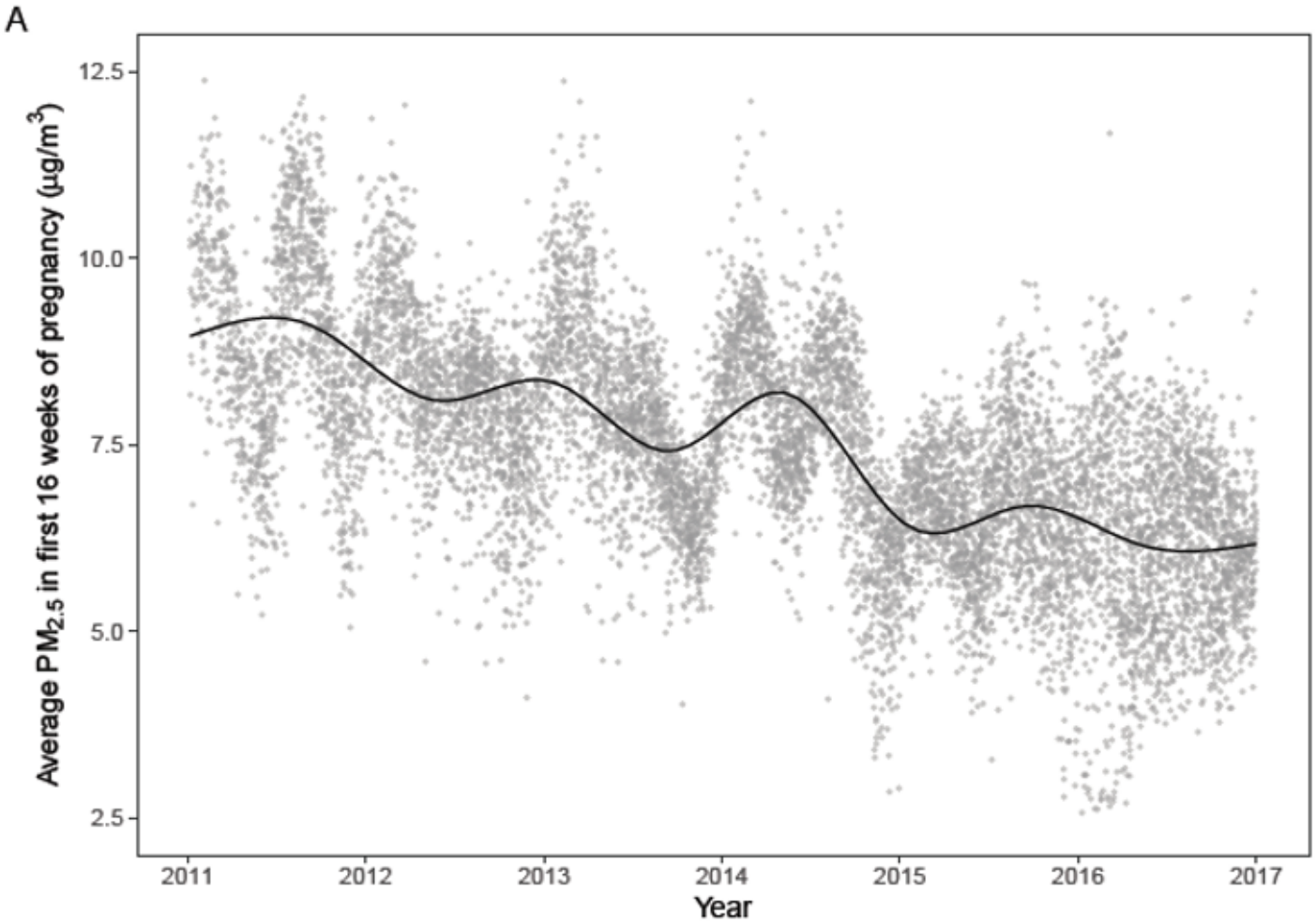
Results: Maternal Characteristics

- Race: **51%** white
- Education: **48%** College or higher
- ADI: mean of **22** (1: least disadvantage, 100: most disadvantage)

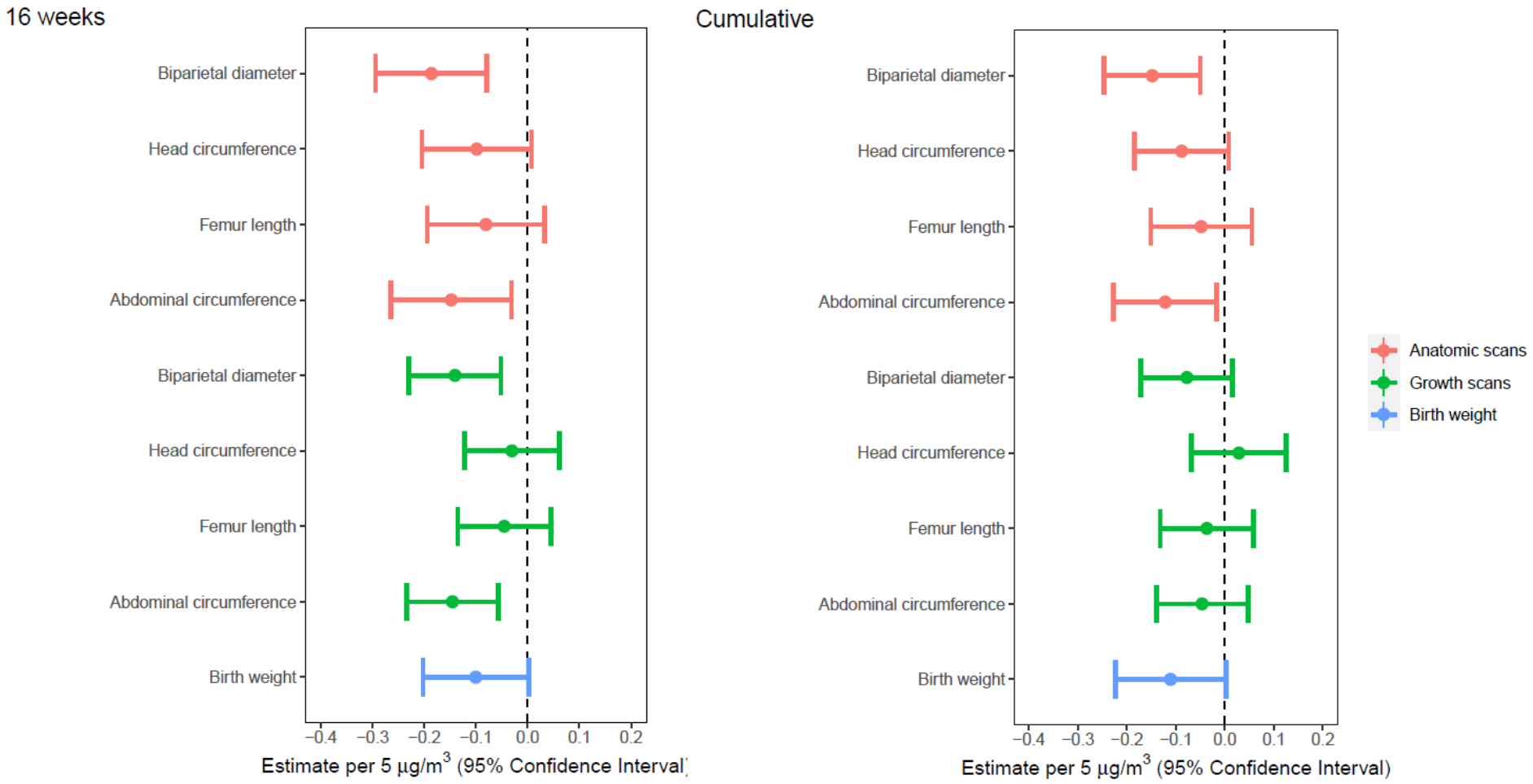


Results: Temporal Trend of $PM_{2.5}$

- Low pollution environment: levels below the national standards of 12 $\mu g/m^3$



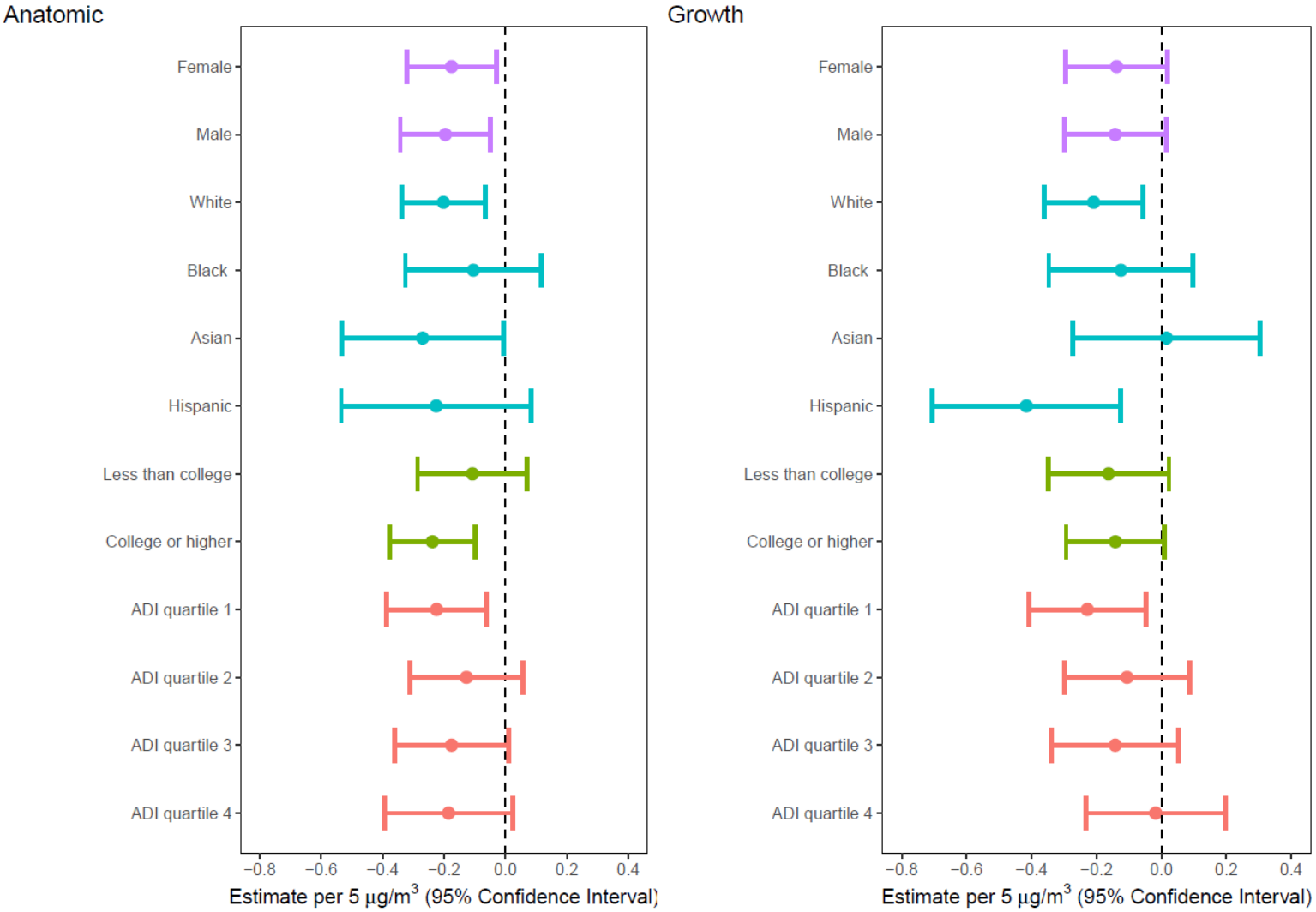
Results: Main Results



- $PM_{2.5}$ potentially interferes with early fetal tissue development rather than period of rapid growth later in pregnancy

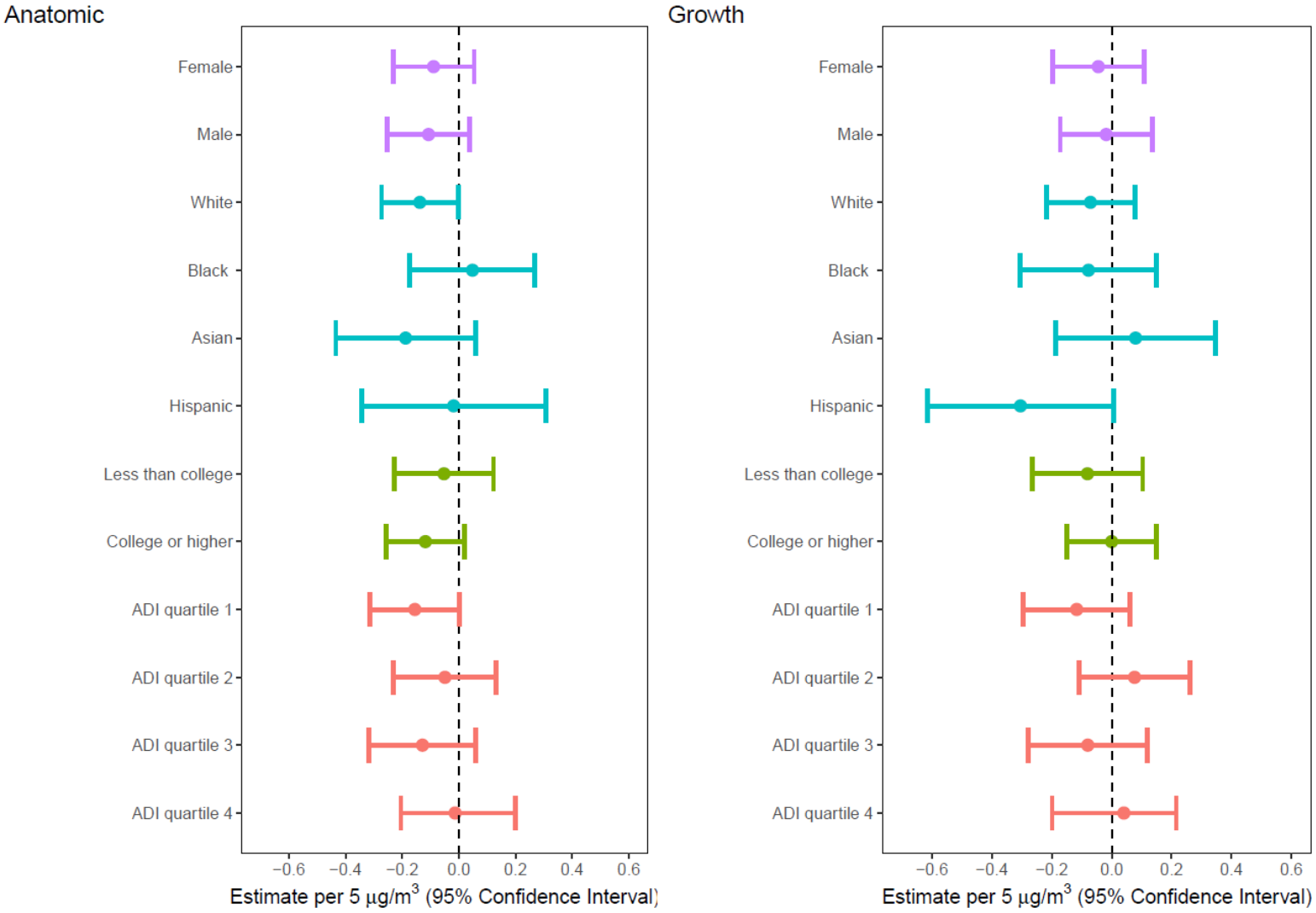
Results: Effect Modification BPD

- Potential modification by race, education & ADI



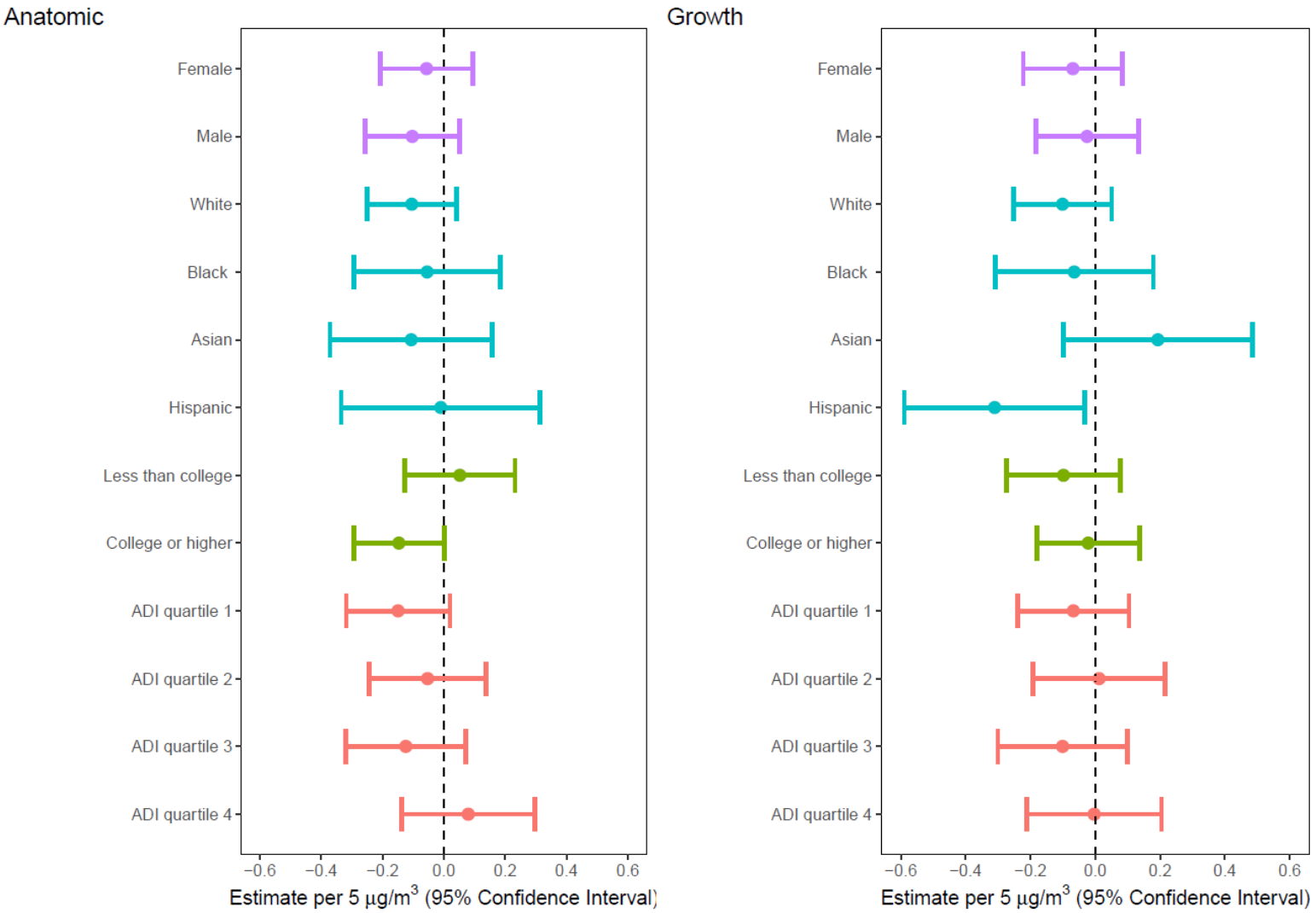
Results: Effect Modification HC

- Potential modification by race, education & ADI



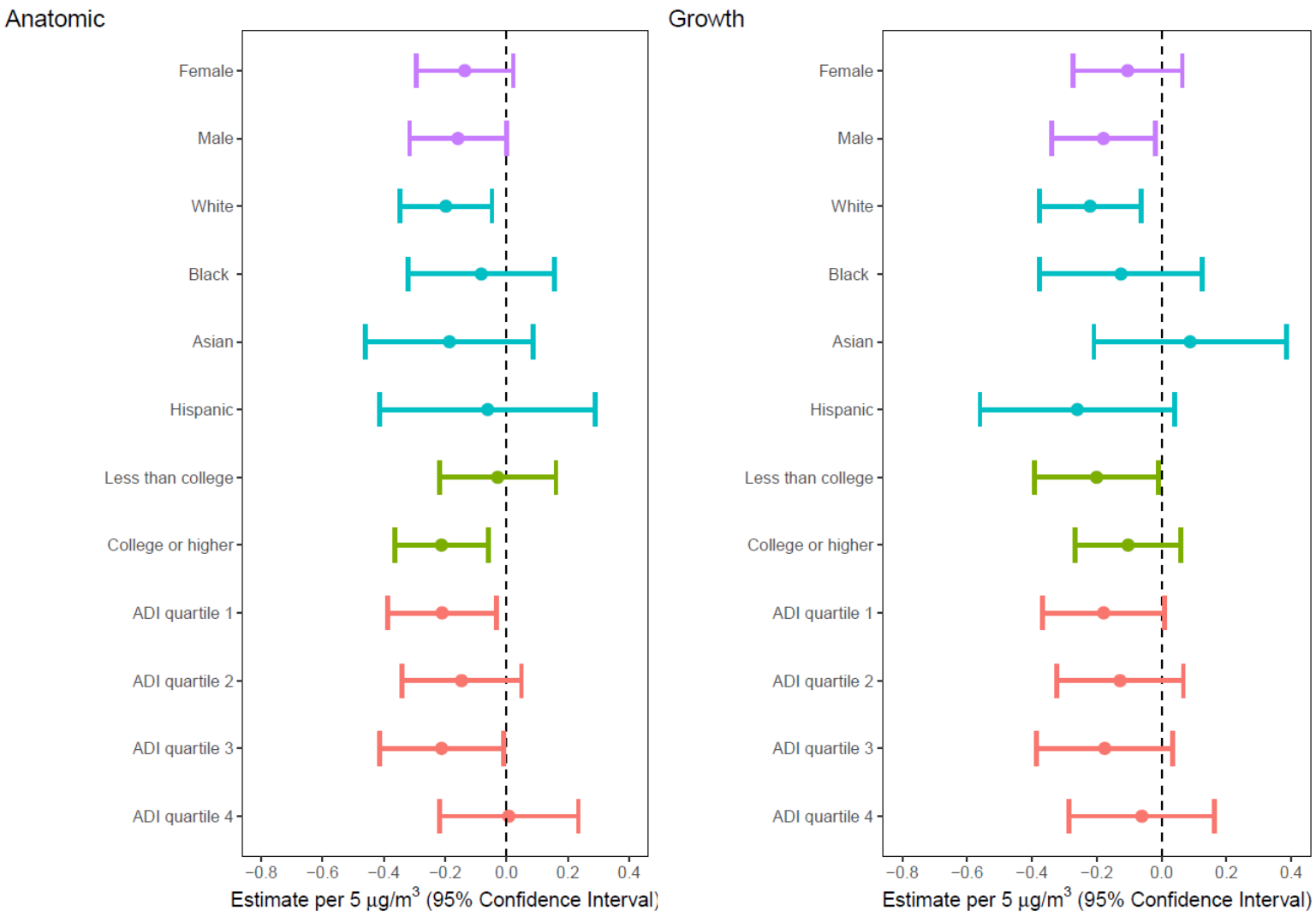
Results: Effect Modification FL

- Potential modification by race, education & ADI



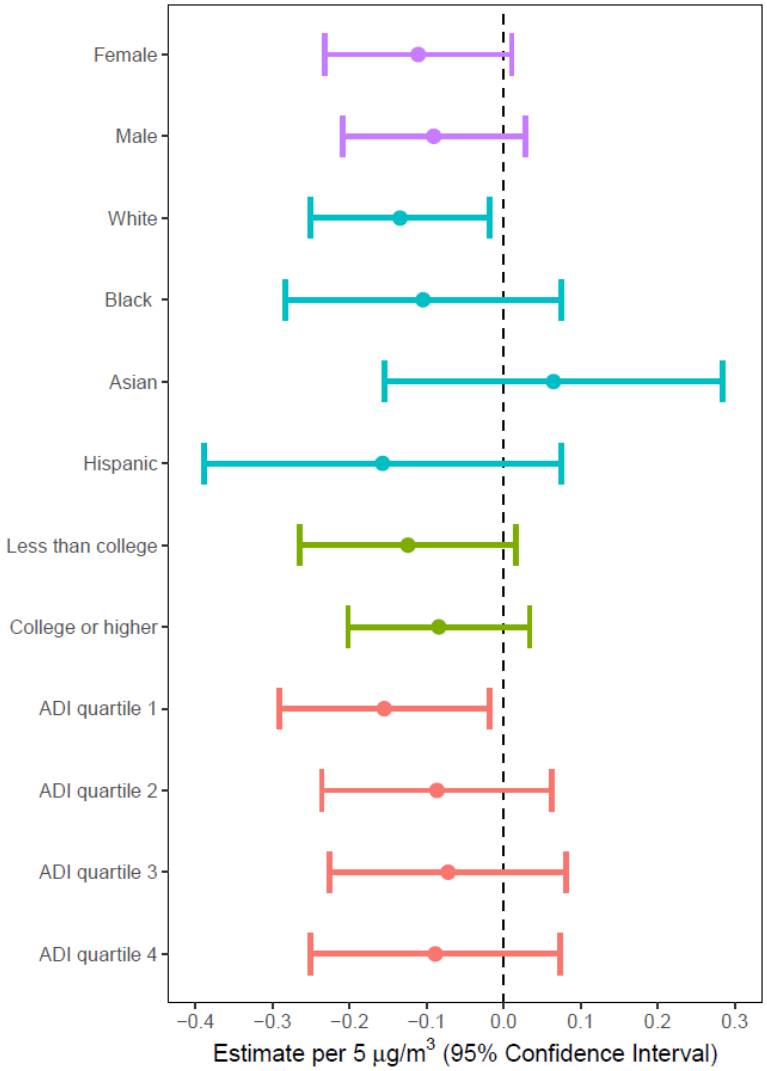
Results: Effect Modification AC

- Potential modification by race, education & ADI



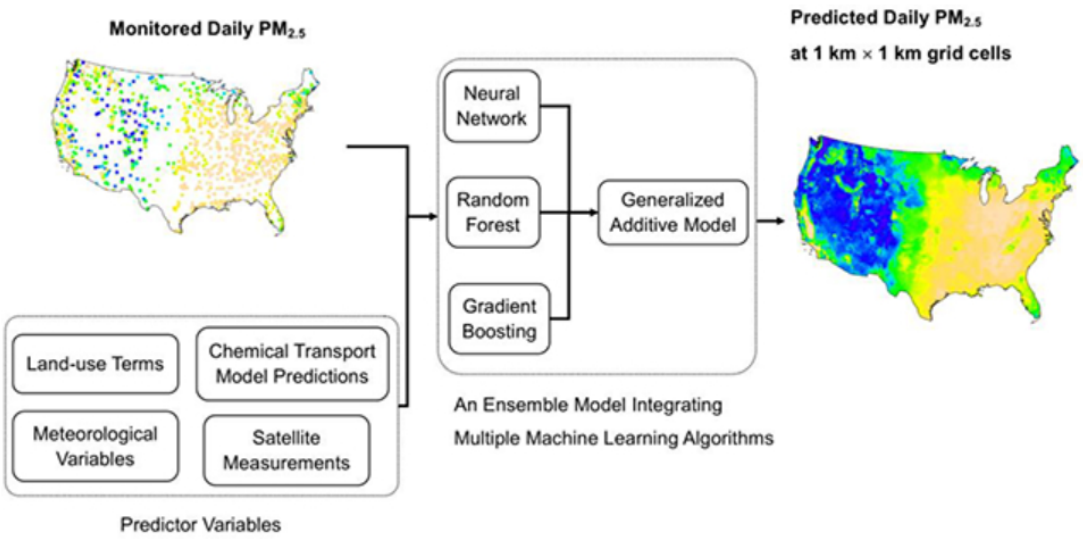
Results: Effect Modification Birth weight

- Potential modification by race, education & ADI



Potential Limitations

- Exposure measurement error (non-differential)
  - modelled outdoor values
  - residential mobility during pregnancy
  - time-activity pattern during pregnancy
- Live birth bias since analysis restricted to live births
- Not everyone had growth scans (72%), so analyses of growth scans should be interpreted with caution



Conclusion & Future Directions

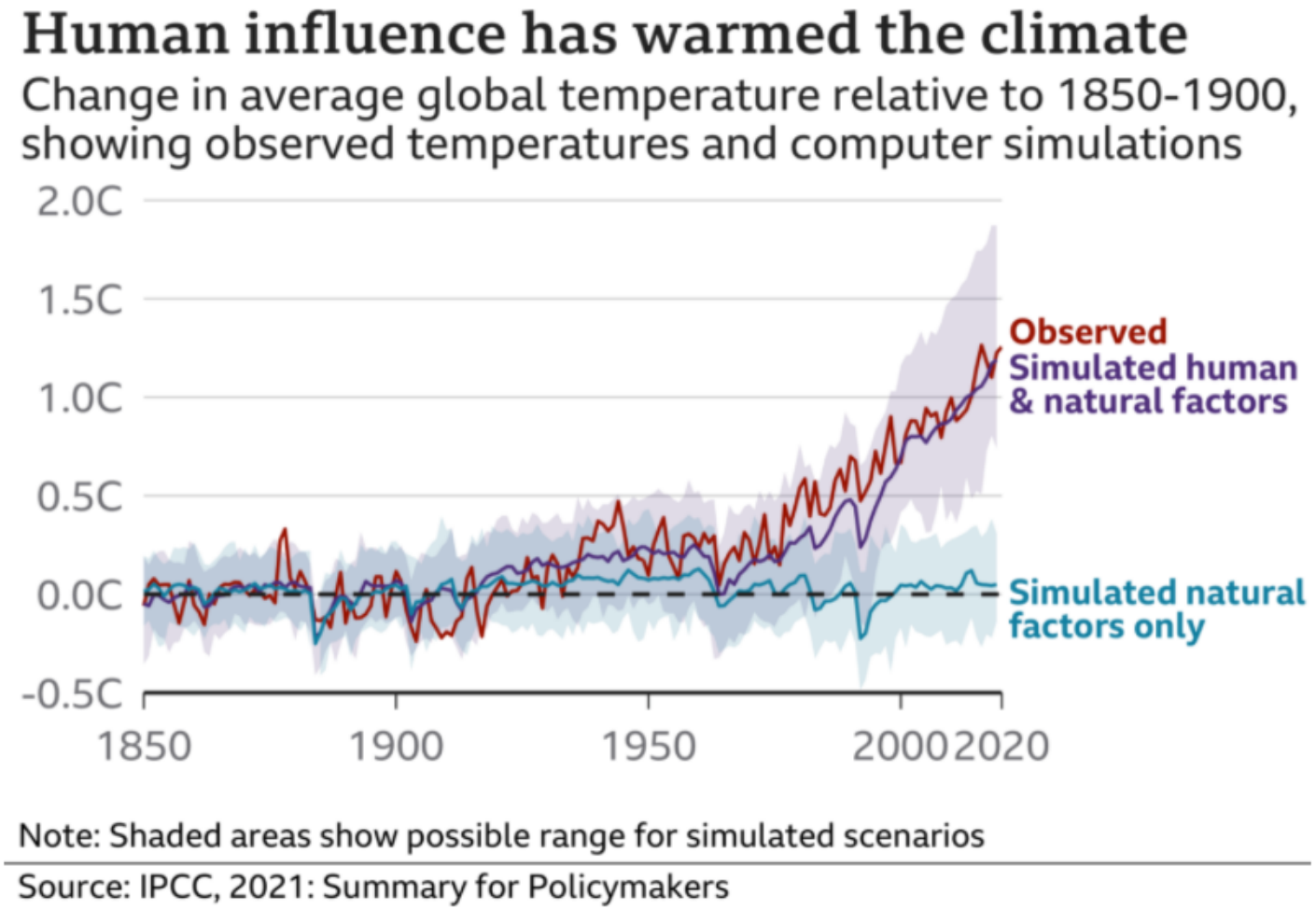
- Gestational exposure to $PM_{2.5}$ was associated with $\downarrow$ fetal ultrasound parameters and birth weight
- No effect modification by sex, but potential disparities by race, education & ADI
- Future work
  - different demographic distributions
  - higher exposure levels
  - consider early pregnancy as a critical window
  - decompose contributions of different $PM_{2.5}$ pollutants

Ambient temperature during pregnancy and fetal growth in Massachusetts, USA

Michael Leung, Francine Laden, Brent Coull, Anna Modest, Michele Hacker, Blair Wylie, Yaguang Wei, Joel Schwartz, Stefania Papatheodorou & Marc Weisskopf

Background

- Climate crisis has led to warmer global temperatures

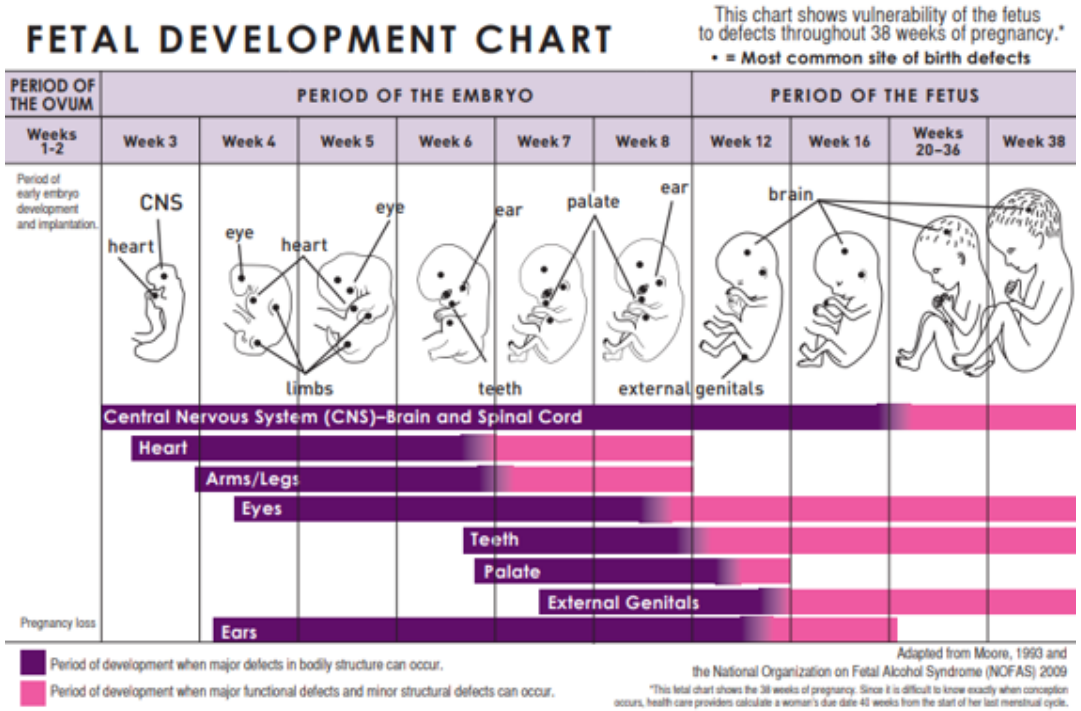


Background

- Pregnant individuals and their fetuses have been recognized as one group that is particularly vulnerable to heat stress
  - Physiological and anatomical changes present challenges to thermoregulation
- Two systematic reviews have shown that ↑ heat during pregnancy → ↓ birth weight (Bekkar 2020, Chersich 2020)
- No study has examined associations using ultrasound parameters of fetal growth

Temperature

- Temperature from NASA NLDAS-2 (12x12 km grid), assigned based on address at delivery
- Two exposure windows:
  - Primary window: first 16 weeks
  - Secondary window: from conception to fetal growth assessment



Fetal growth outcomes

- Ultrasound measures from BIDMC (OB/GYN and Radiology)
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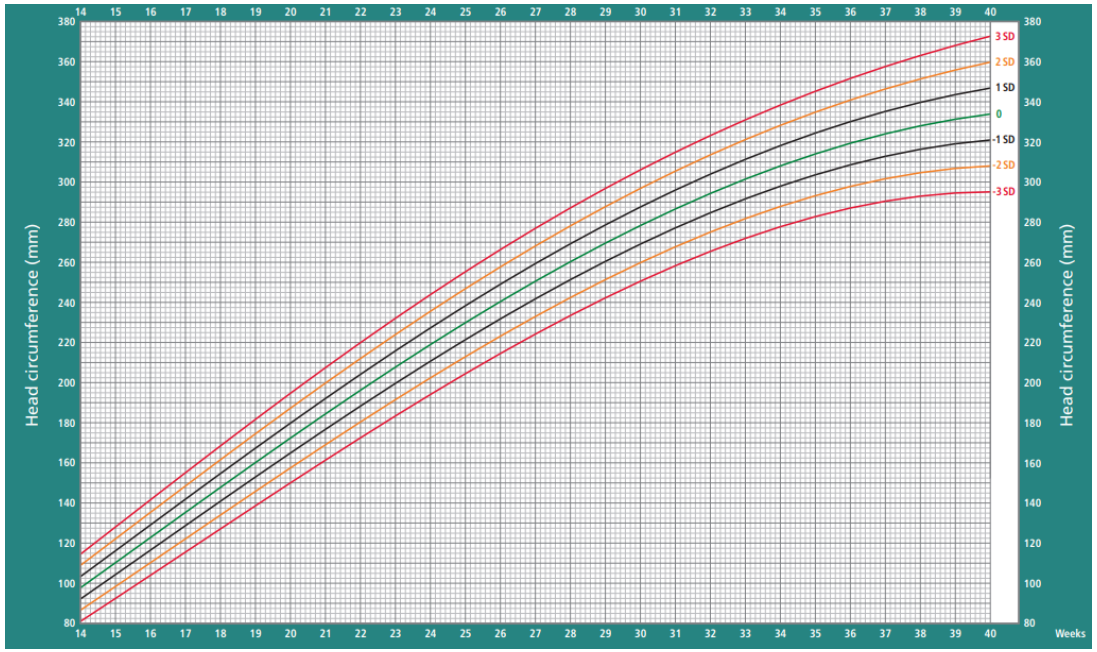
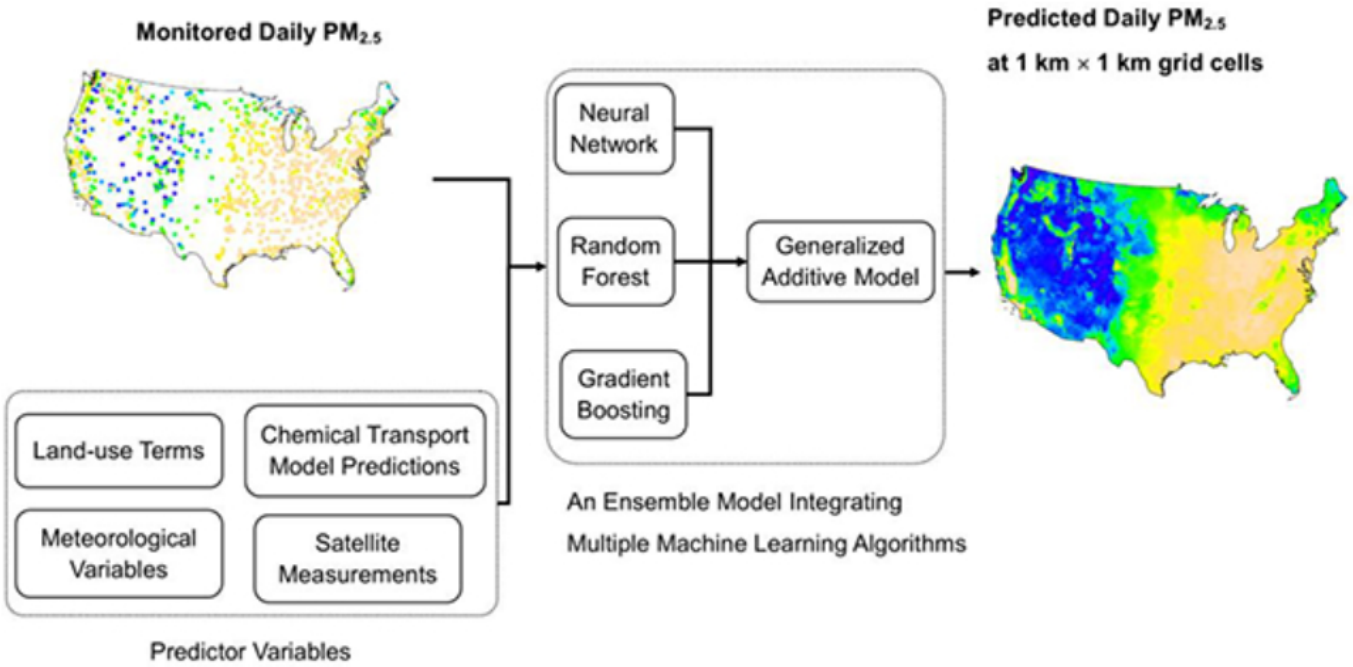


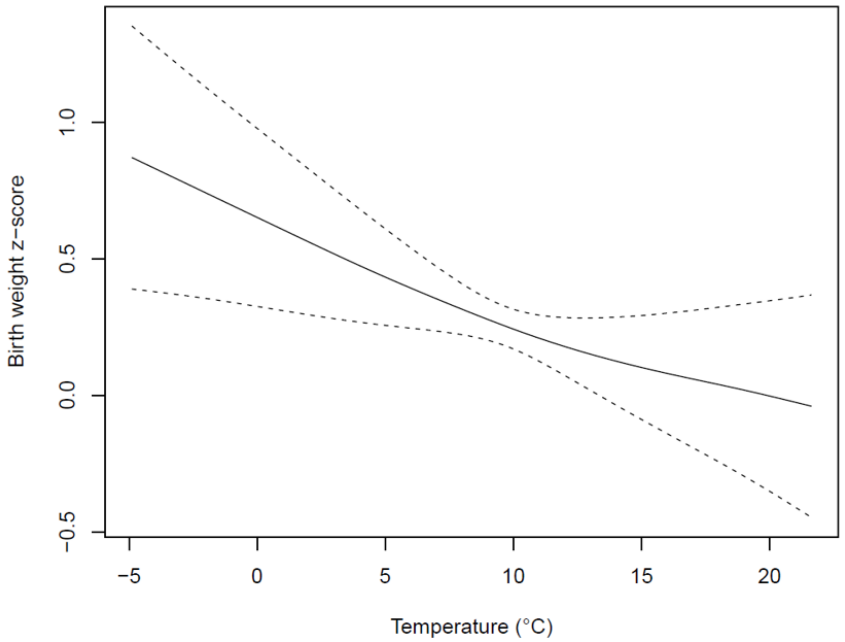
Covariates

- Specific humidity from NASA NLDAS-2, 12x12 km
- $PM_{2.5}$ from spatiotemporal model, 1x1 km grid
- maternal age, race, educational attainment, insurance type, parity, fetal sex
- Area Deprivation Index (ADI), census block group level

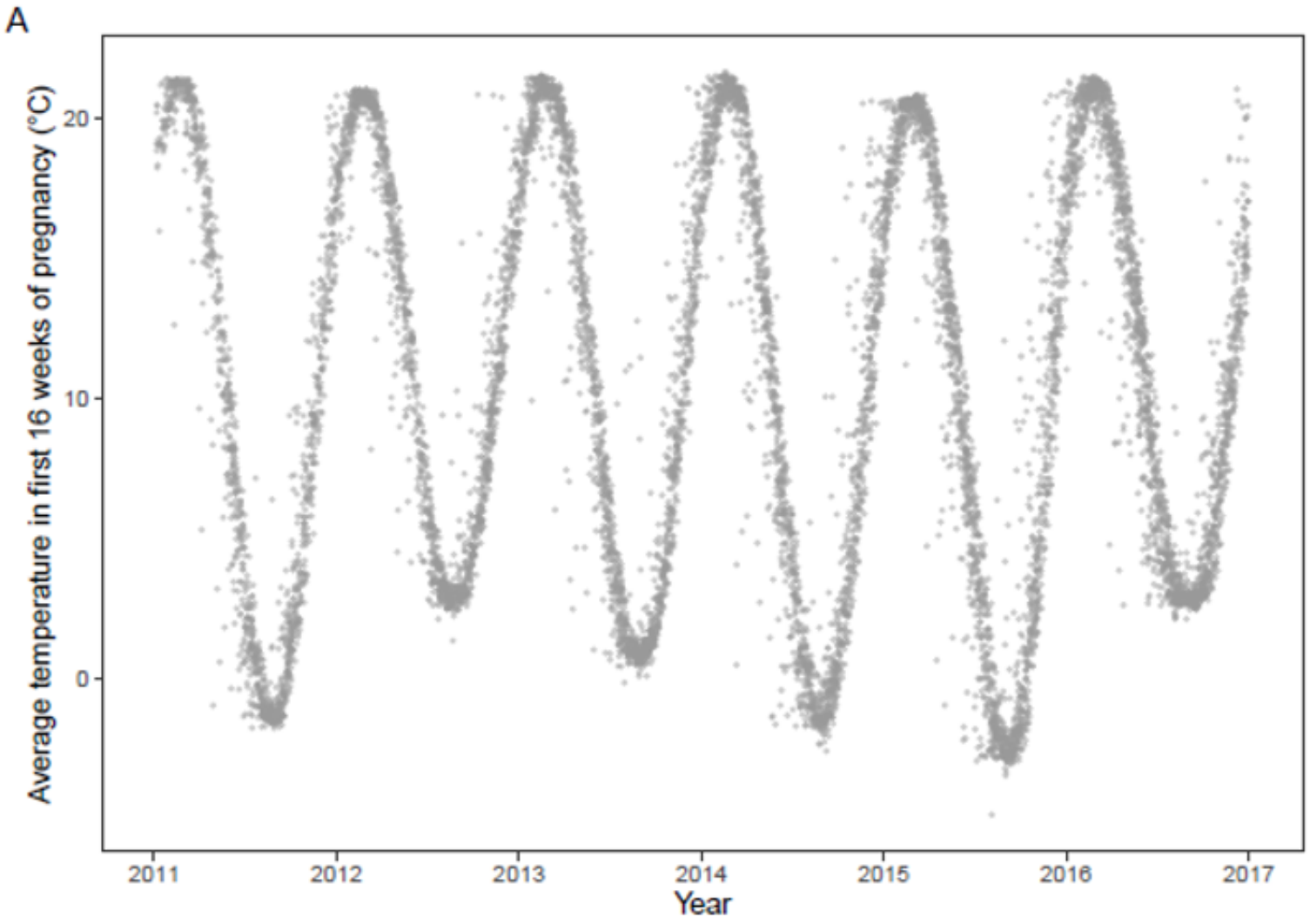


Analysis

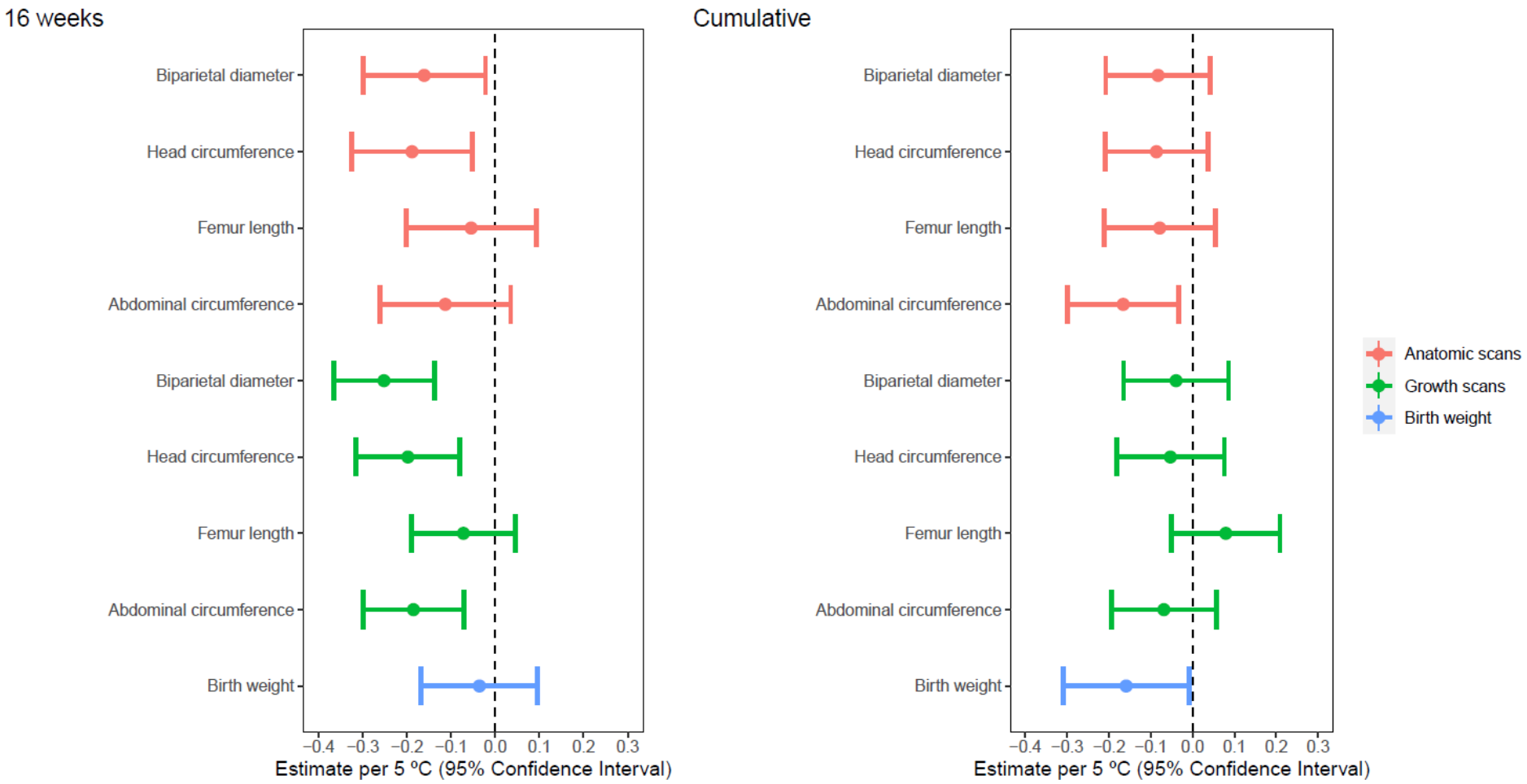
- General additive mixed model (GAMM)
  - Penalized spline for temperature
  - All covariates listed previously, term for conception year, and natural splines with 4 df/year for conception day of the year
  - Random intercept for each pregnancy
  - Effect modification by fetal sex, maternal age, race, educational attainment, ADI
- Since GAMMs showed approximately linear associations, present estimates from model with linear term



Results: Temporal Trend of Temperature



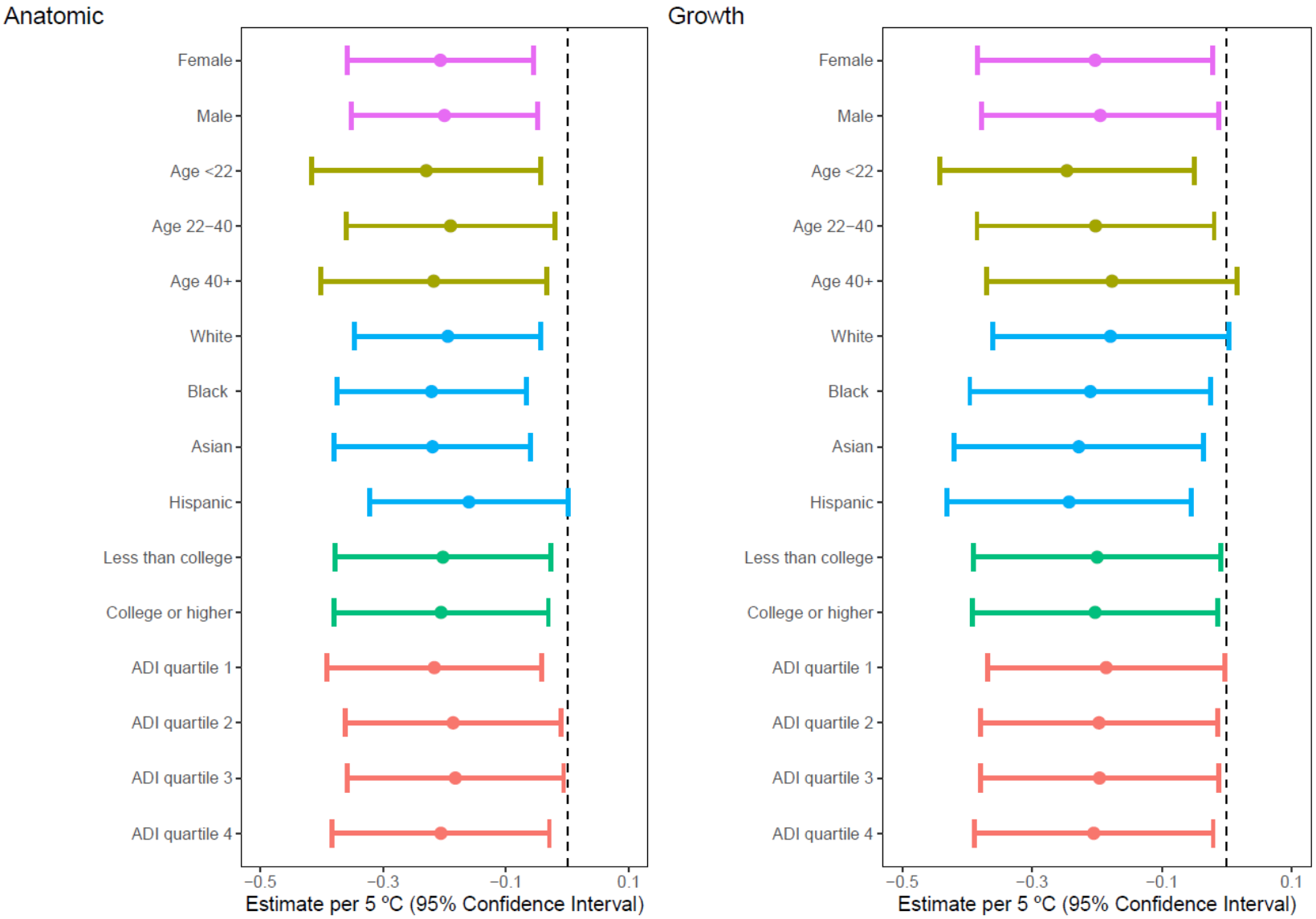
Results: Main results



- Heat potentially interferes with early fetal tissue development, with head size parameters appear sensitive

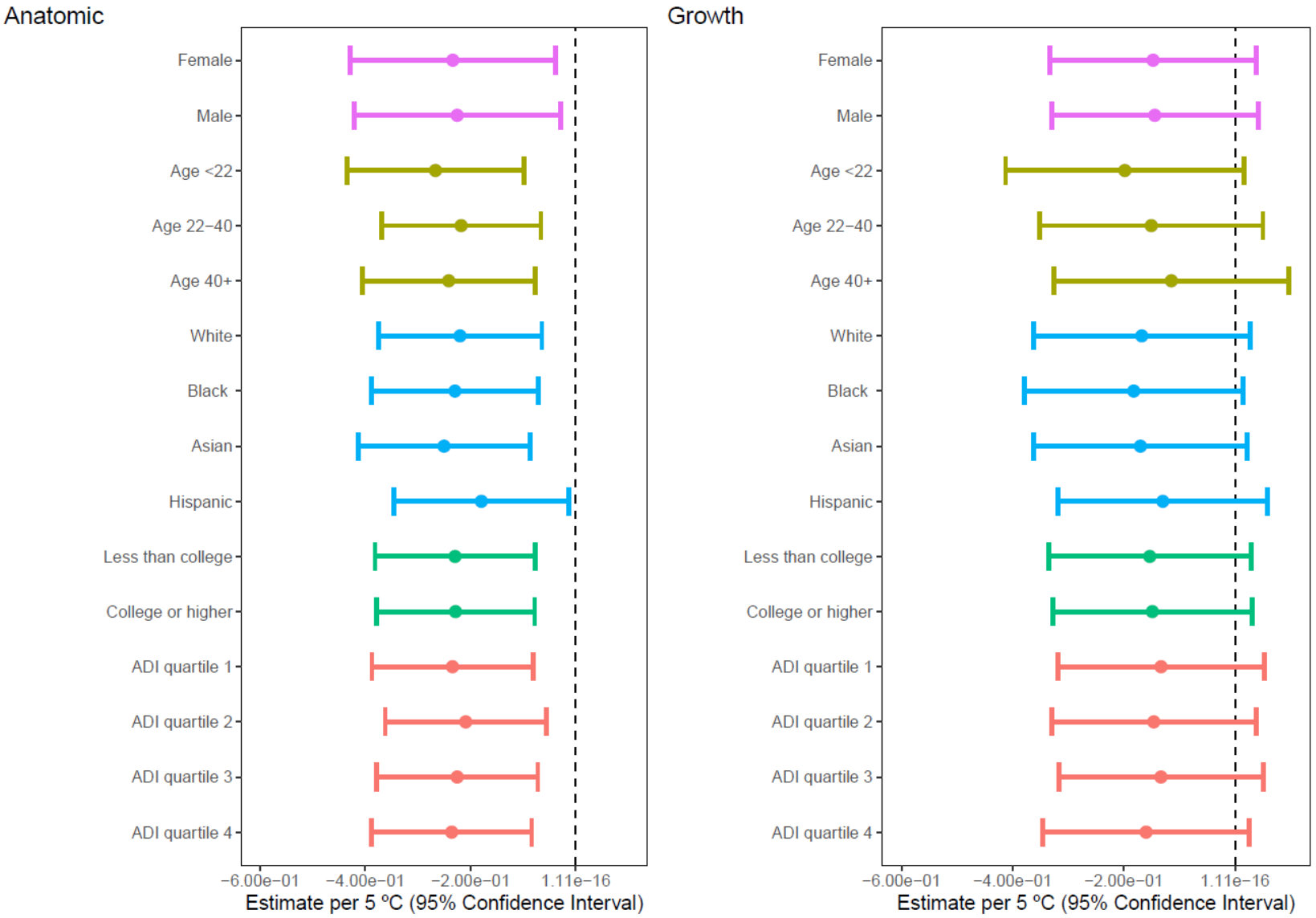
Results: Effect Modification BPD

- No effect modification



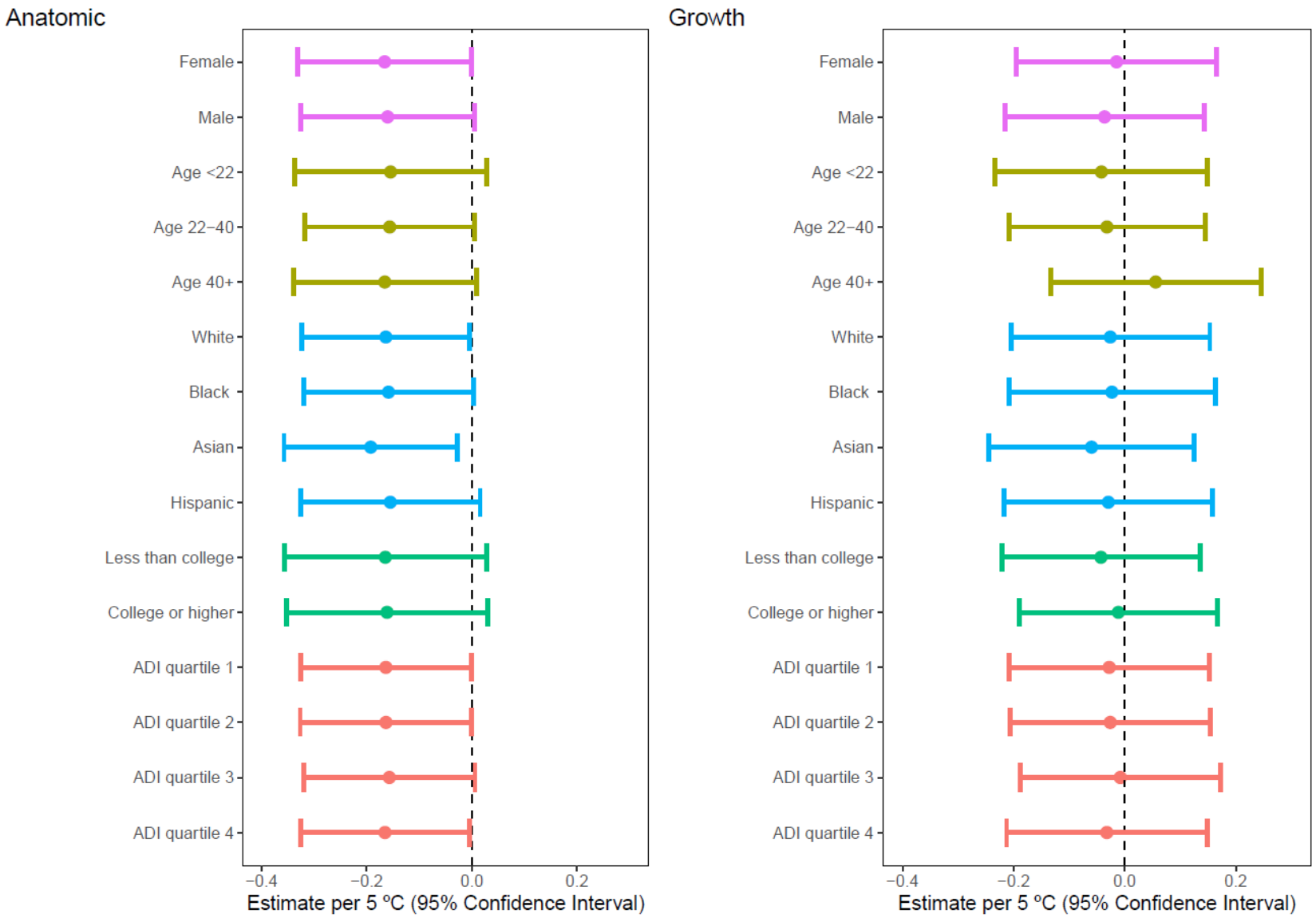
Results: Effect Modification HC

- No effect modification



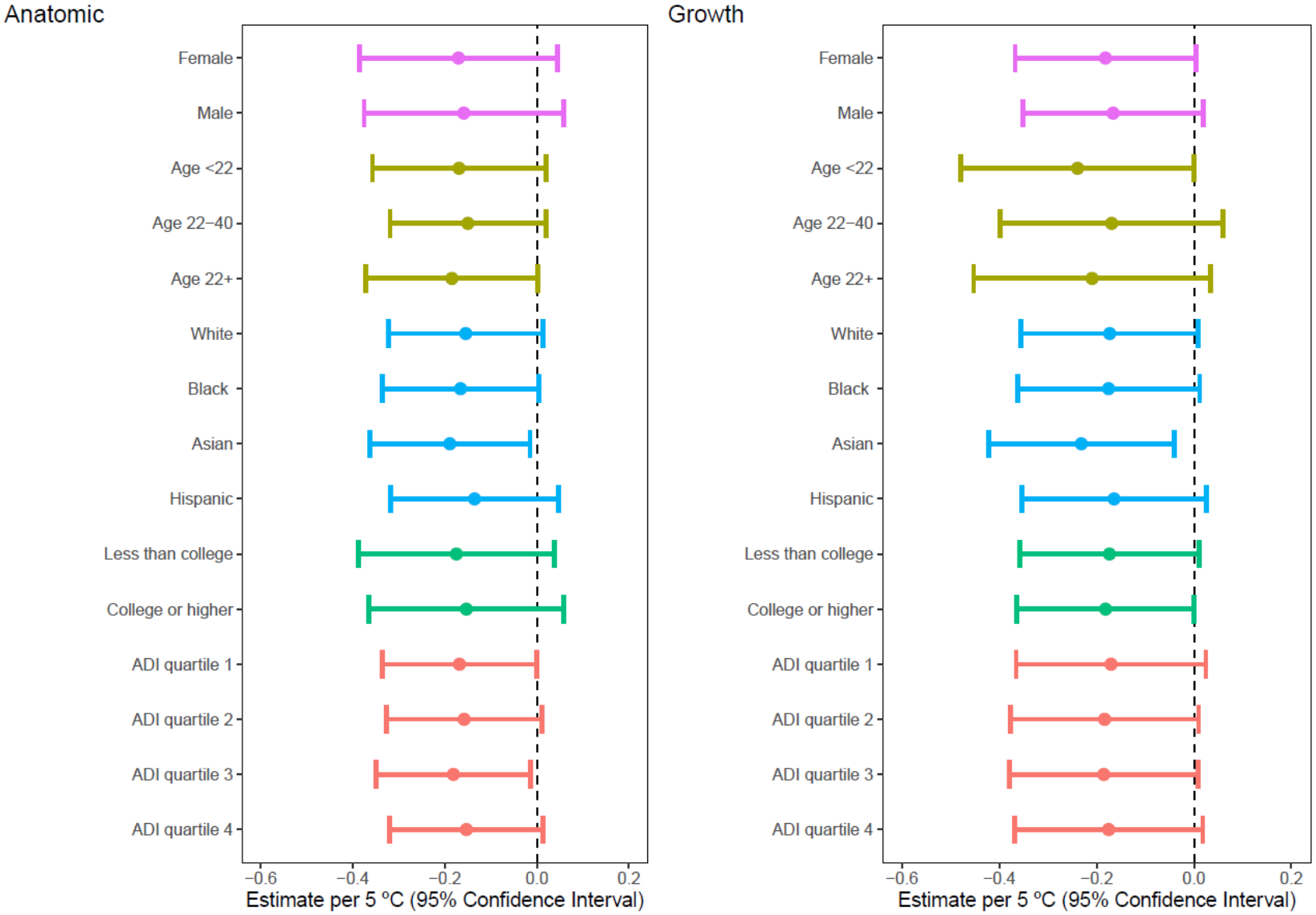
Results: Effect Modification FL

- Potential modification by maternal age



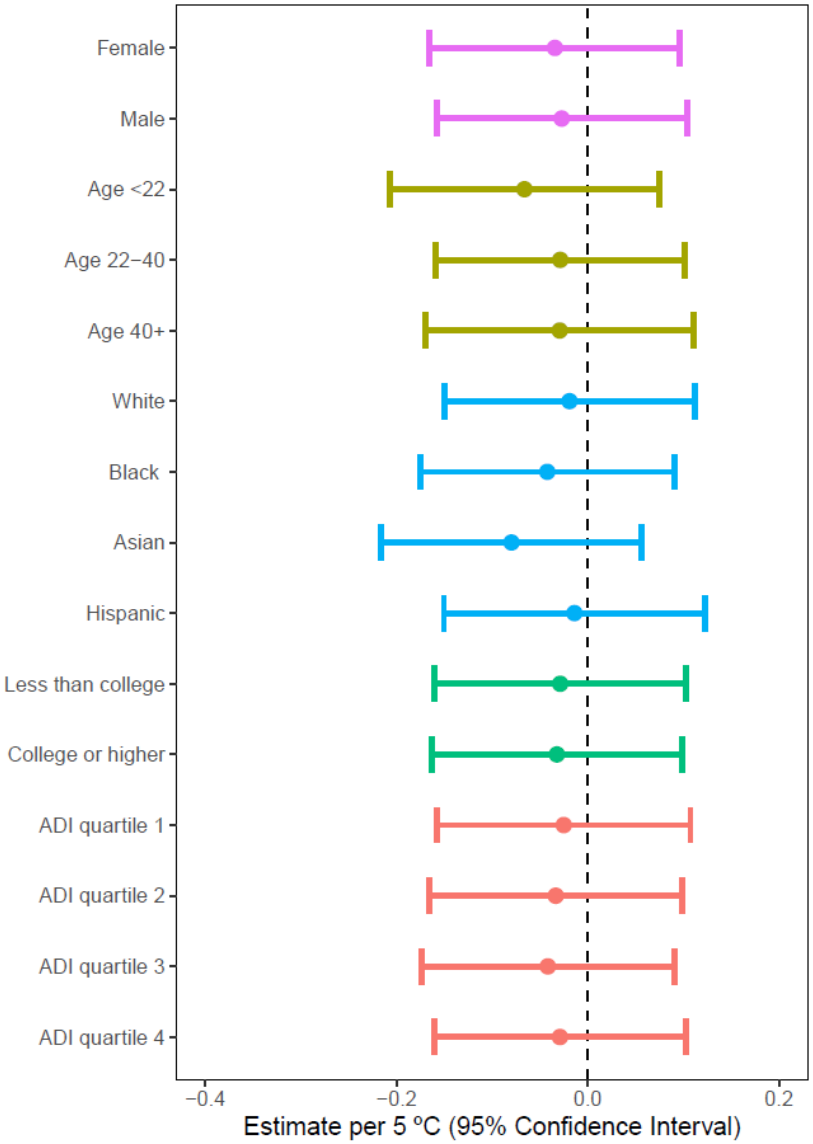
Results: Effect Modification AC

- No effect modification



Results: Effect Modification Birth weight

- Potential modification by maternal age & race



Potential Limitations

- 12 km grid may not capture urban heat islands
  - Potentially important for racial disparities

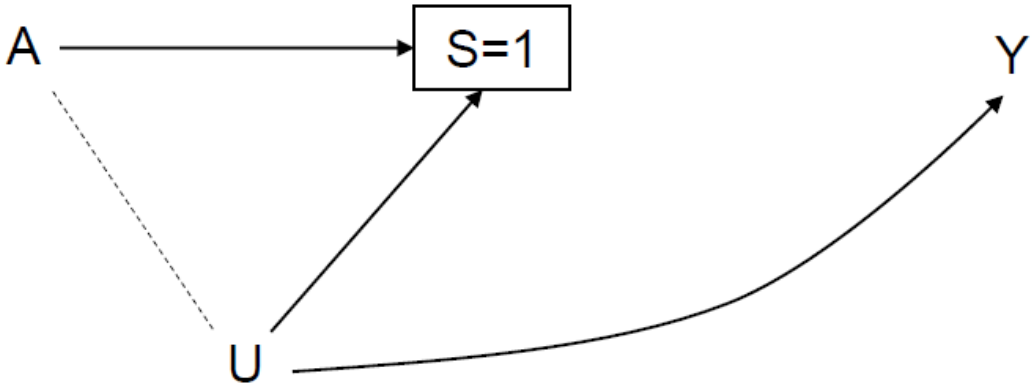
Boston has the sixth hottest heat island in the US, new report says

By Brittany Bowker Globe Staff, Updated July 16, 2021, 11:33 a.m.

Boston was ranked as having one of the hottest heat islands in the country. DAVID L. RYAN/GLOBE STAFF

Potential Limitations

- Exposure measurement error (non-differential):
  - temperature based on outdoor values
  - assignment based on residential address at delivery
- Live birth bias since analysis restricted to live births
- Not everyone had growth scans (72%), so analyses of growth scans should be interpreted with caution



Conclusion & Future Directions

- Heat exposure during pregnancy was associated with ↓ fetal ultrasound parameters (head parameters especially) & birth weight
- Future studies
  - different temperature distributions/seasonality
  - different demographic/socioeconomic compositions
  - temperature data with finer spatial resolution
  - follow-up studies of brain/neurodevelopment

Conclusions & Future Research

Reviewing the Three Papers

- This dissertation asks the question - how do environmental exposures affect *in utero* fetal development during pregnancy rather than solely at its conclusion, and what are some of the implications?
  - **Answer**: Exclusively focusing on birth outcomes may miss *in utero* events that are relevant for health

Paper	Key Findings
1	Ignoring the effects on pregnancy loss can lead to bias
2	Higher PM was associated with impaired fetal growth
3	Higher temperature was associated with impaired fetal growth

- Investment into studying *in utero* health events
- Importance of mitigating climate change cannot be understated

Future Directions

- Identify risk factors for pregnancy loss
- Assess whether observed results are clinically meaningful
- Identify at-risk populations/disparities
- Interactions between air pollution & temperature

Acknowledgements

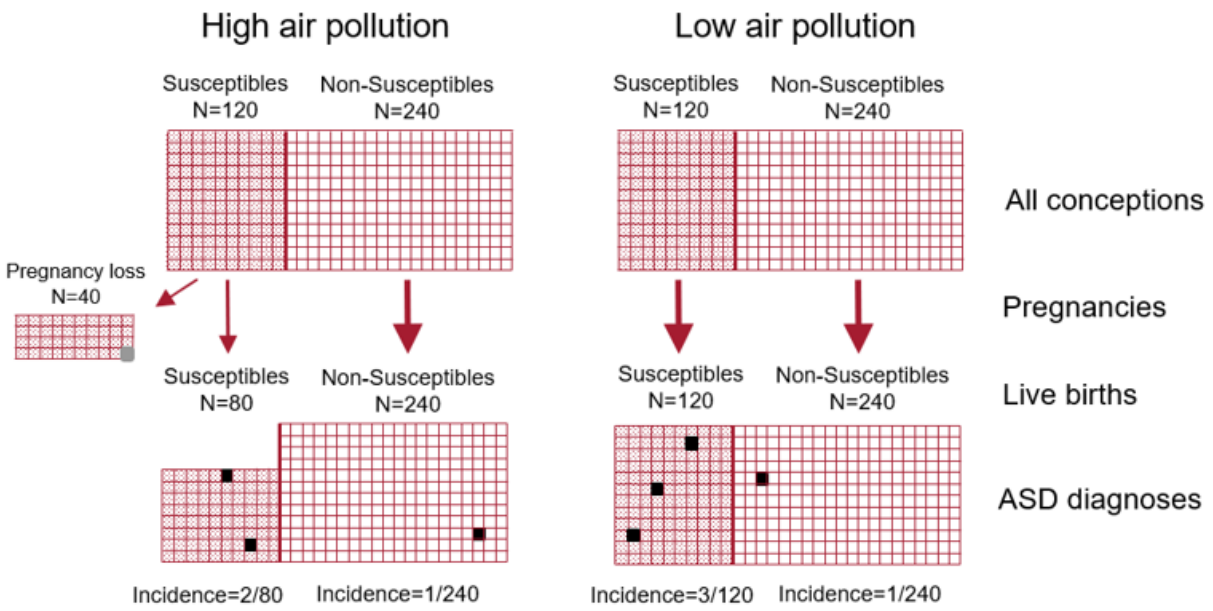
- Marc
- Stefania, Francine & Brent
- Michele, Anna, Joel, Yaguang, Marianthi, Raanan & Blair
- Eric, Ellen, Warisha, Caroline, Bruce & Matthew
- Miguel, Sonia, Murray & Barbra
- Family & Friends

Thank You!

Additional Slides

Examples of Survival Mechanisms

- Collider-stratification without interaction (M1)
  - Air pollution and endocrine-disrupting chemicals
- Depletion of susceptibles (M2)
  - Gene-environment interaction (loss occurs in those with gene U)

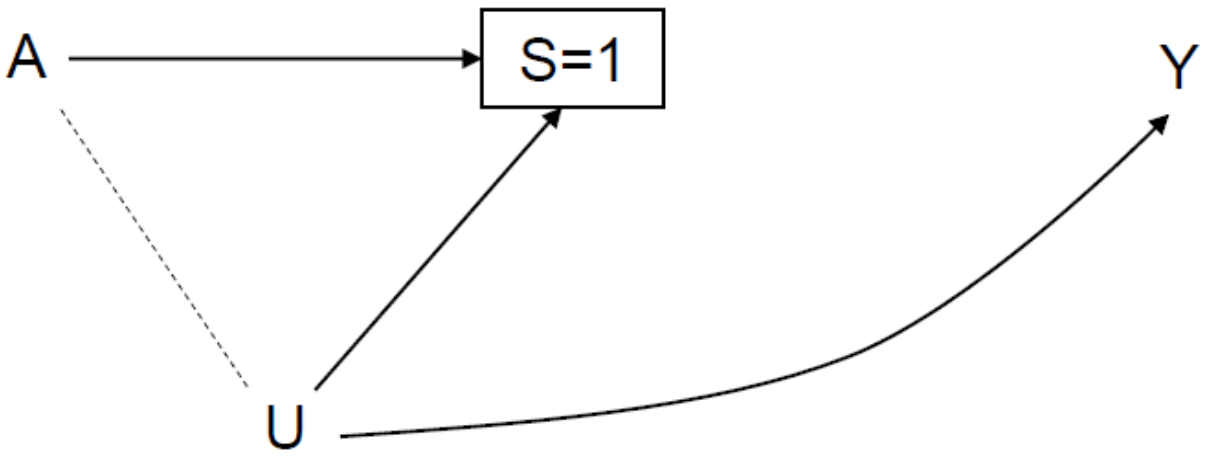


	No ASD	ASD	Total
Low air pollution	356	4	360
High air pollution	317	3	320
Total	673	7	680

$$\text{Relative Risk} = \frac{\frac{3}{320}}{\frac{4}{360}} = 0.85$$

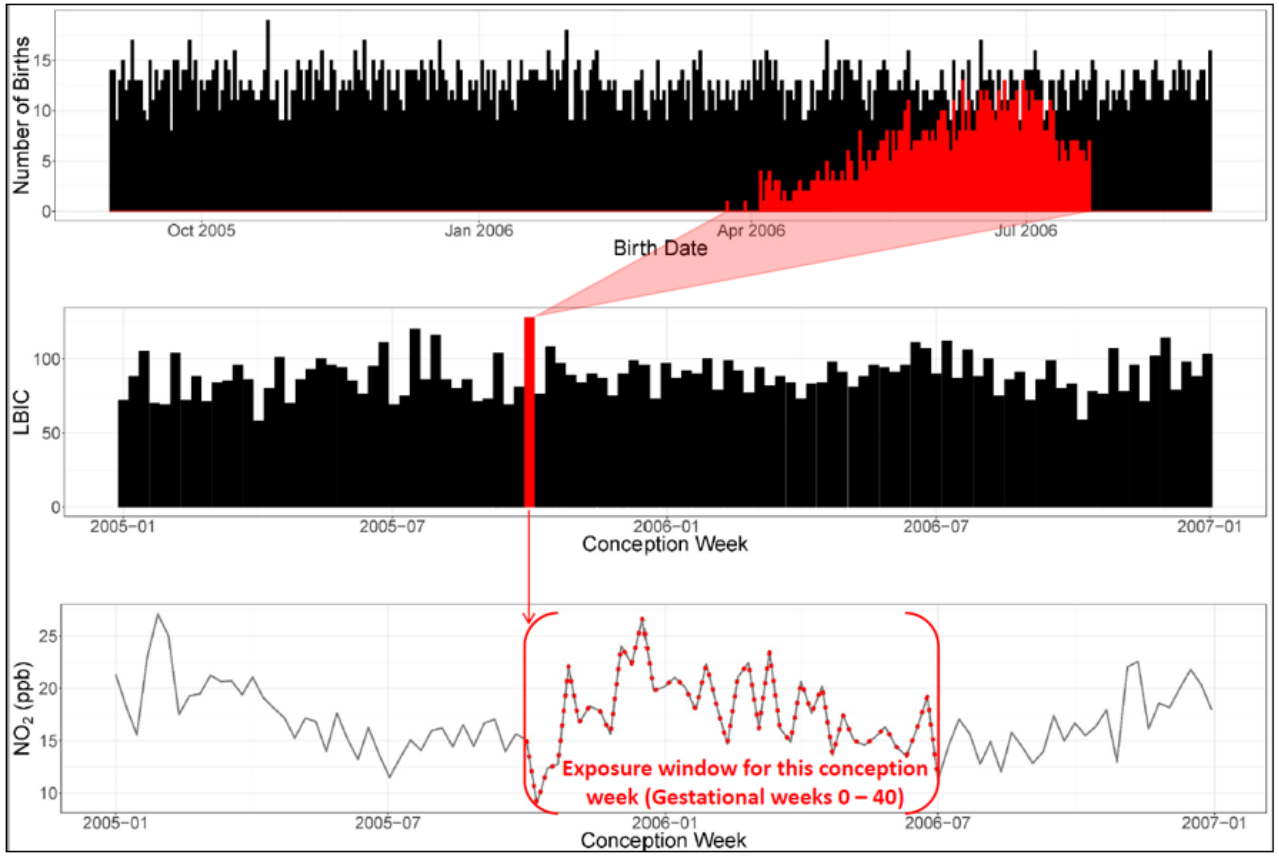
LBB Parameters

- NO_2-loss associations
  - OR = 1.04 - 1.27 (Grippo 2018)
- U-loss associations
  - Smoking: OR = 1.47 (Marufu 2015)
  - EDC: OR = 1.6 - 2.52 (Krieg 2016, Tsukimori 2008)
- U-ASD associations
  - Smoking: OR = 1.56 (Caramaschi 2018)
  - EDC: OR = 1.20 - 1.97 (Bernardo 2019)



How to study pregnancy loss

- Live birth identified conceptions (LBIC): conceptions in a given time window that result in live births (Kioumourtzoglou 2019)



- Poisson model (count data) with forward lag

How to study pregnancy loss

- **Model**: $E[LB|A, Z_k] = \beta_0 + \beta_1 A + Z_k^T \beta_k$

$$
\begin{aligned}
\beta_1 &= E[LB|A+1, Z_k^T] - E[LB|A, Z_k^T] \\
&= E[TC - PL|A+1, Z_k^T] - E[TC - PL|A, Z_k^T] \\
&= E[TC|A+1, Z_k^T] - E[PL|A+1, Z_k^T] - E[TC|A, Z_k^T] + E[PL|A, Z_k^T] \\
&= E[PL|A, Z_k^T] - E[PL|A+1, Z_k^T]
\end{aligned}
$$

- Exposures during pregnancy do not affect number of conceptions, so TC drops out in expectation
- Variant of time-series design can infer effects on pregnancy loss based on live births

How to adjust for LBB

- Many different ways proposed (Chiu 2020)

Approach	Causal Estimands[a]
1. Total effect of treatment on a composite event	$\Pr[Q^{a=1}]-\Pr[Q^{a=0}]$
2. Total effect of treatment on the event of interest	$\Pr[Y^{a=1}]-\Pr[Y^{a=0}]$
3. Direct effect of treatment on the event of interest, not mediated through competing events[b]	$\Pr[Y^{a=1,d=1}]-\Pr[Y^{a=0,d=1}]$
g-formula estimator	
IP-weighted estimator	
Doubly robust estimator	
4. Separable direct and indirect effects[b,c]	
Separable direct effect when the component of letrozole that affects competing event is kept and the component of gonadotropin that affects competing event is eliminated[d]	$\Pr[Y^{a_Y=1,a_D=1}]-\Pr[Y^{a_Y=0,a_D=1}]$
g-formula estimator	
IP-weighted estimator 1	
IP-weighted estimator 2	
Separable indirect effect when the component of letrozole that affects neonatal complications is eliminated and the component of gonadotropin that affects neonatal complications is kept	$\Pr[Y^{a_Y=0,a_D=1}]-\Pr[Y^{a_Y=0,a_D=0}]$
g-formula estimator	
IP-weighted estimator 1	
IP-weighted estimator 2	

Observed A-Y associations

Inputs		Average NO_2-ASD odds ratio among live births, $OR_{AY\|S=1}$ (95% SI)		
π_U	OR_S	Mechanism 1: Collider-stratification without interaction[a]	Mechanism 2: Depletion of susceptibles[b]	Both Mechanisms: Mechanism 1 + Mechanism 2[c]
0.25	1.5	1.00 (0.93,1.07)	1.00 (0.93,1.07)	0.98 (0.91,1.06)
	2.0	0.99 (0.92,1.06)	0.98 (0.91,1.04)	0.94 (0.86,1.04)
	2.5	0.97 (0.89,1.06)	0.94 (0.88,1.01)	0.94 (0.84,1.04)
	3.0	0.95 (0.86,1.06)	0.91 (0.85,0.97)	0.94 (0.83,1.06)
0.50	1.5	1.00 (0.93,1.07)	1.00 (0.93,1.06)	0.98 (0.91,1.05)
	2.0	0.99 (0.91,1.06)	0.97 (0.91,1.03)	0.90 (0.82,0.99)
	2.5	0.96 (0.88,1.04)	0.92 (0.86,0.98)	0.86 (0.77,0.96)
	3.0	0.94 (0.86,1.03)	0.87 (0.82,0.94)	0.85 (0.74,0.97)
0.75	1.5	1.00 (0.93,1.06)	1.00 (0.94,1.06)	0.98 (0.91,1.05)
	2.0	0.99 (0.92,1.06)	0.98 (0.92,1.04)	0.87 (0.78,0.96)
	2.5	0.97 (0.89,1.05)	0.94 (0.89,1.00)	0.79 (0.69,0.90)
	3.0	0.95 (0.86,1.04)	0.89 (0.83,0.94)	0.75 (0.64,0.89)

Bias Parameters

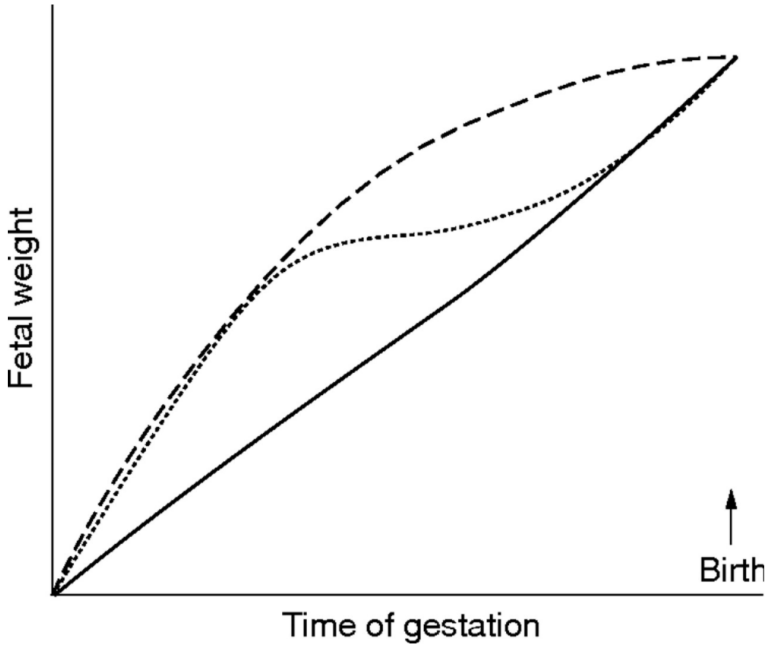
Inputs		Average bias parameters among live births (95% SI)					
		Mechanism 1: Collider-stratification without interaction[a]		Mechanism 2: Depletion of susceptibles[b]		Both Mechanisms: Mechanism 1 + Mechanism 2[c]	
π_U	OR_S	$OR_{AU\|S=1}$	$\pi_{U\|S=1}$	$OR_{AU\|S=1}$	$\pi_{U\|S=1}$	$OR_{AU\|S=1}$	$\pi_{U\|S=1}$
0.25	1.5	0.98 (0.96,1.00)	0.24 (0.23,0.24)	0.94 (0.93,0.96)	0.23 (0.23,0.23)	0.76 (0.74,0.78)	0.18 (0.18,0.18)
	2.0	0.90 (0.88,0.93)	0.21 (0.21,0.21)	0.83 (0.81,0.85)	0.20 (0.20,0.20)	0.44 (0.42,0.46)	0.08 (0.08,0.09)
	2.5	0.83 (0.80,0.85)	0.18 (0.17,0.18)	0.70 (0.69,0.72)	0.17 (0.17,0.17)	0.29 (0.27,0.31)	0.04 (0.04,0.04)
	3.0	0.77 (0.74,0.80)	0.15 (0.15,0.15)	0.59 (0.58,0.61)	0.14 (0.14,0.14)	0.22 (0.20,0.24)	0.02 (0.02,0.03)
0.50	1.5	0.98 (0.96,1.00)	0.48 (0.48,0.49)	0.95 (0.93,0.96)	0.47 (0.47,0.48)	0.76 (0.74,0.77)	0.40 (0.39,0.40)
	2.0	0.91 (0.89,0.93)	0.44 (0.44,0.45)	0.83 (0.82,0.85)	0.43 (0.43,0.43)	0.43 (0.42,0.45)	0.22 (0.21,0.22)
	2.5	0.83 (0.81,0.85)	0.39 (0.39,0.40)	0.70 (0.69,0.71)	0.38 (0.38,0.38)	0.29 (0.27,0.30)	0.12 (0.11,0.12)
	3.0	0.77 (0.75,0.80)	0.35 (0.34,0.35)	0.59 (0.57,0.60)	0.33 (0.33,0.33)	0.21 (0.20,0.23)	0.07 (0.07,0.07)
0.75	1.5	0.98 (0.96,1.00)	0.74 (0.73,0.74)	0.94 (0.93,0.96)	0.73 (0.73,0.73)	0.75 (0.73,0.77)	0.66 (0.66,0.67)
	2.0	0.90 (0.88,0.93)	0.70 (0.70,0.71)	0.83 (0.81,0.85)	0.70 (0.69,0.70)	0.42 (0.41,0.44)	0.45 (0.45,0.46)
	2.5	0.83 (0.81,0.85)	0.66 (0.66,0.67)	0.69 (0.68,0.71)	0.65 (0.64,0.65)	0.28 (0.27,0.30)	0.28 (0.28,0.29)
	3.0	0.77 (0.75,0.80)	0.62 (0.61,0.62)	0.58 (0.56,0.59)	0.60 (0.59,0.60)	0.21 (0.19,0.22)	0.19 (0.18,0.19)

Multiple *U*s

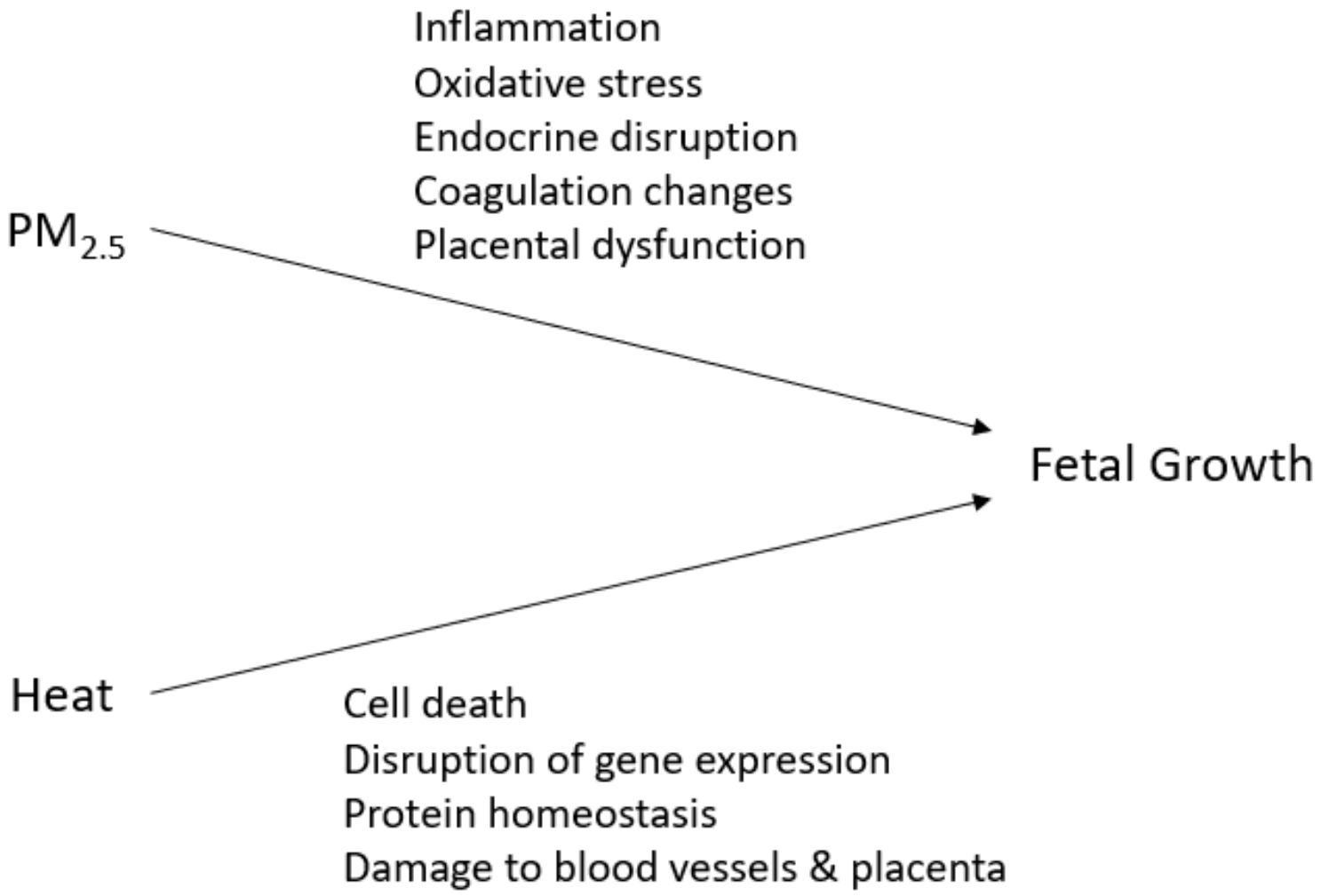
Inputs		Average NO_2-ASD odds ratio among live births, $OR_{AY\|S=1}$ (95% SI)								
		Mechanism 1: Collider-stratification without interaction[a]			Mechanism 2: Depletion of susceptibles[b]			Both Mechanisms: Mechanism 1 + Mechanism 2[c]		
π_U	OR_S	One U	Two Us	Three Us	One U	Two Us	Three Us	One U	Two Us	Three Us
0.25	1.5	1.00 (0.93,1.07)	1.00 (0.93,1.07)	0.99 (0.93,1.06)	1.00 (0.93,1.07)	0.99 (0.92,1.05)	0.97 (0.91,1.04)	0.98 (0.91,1.06)	0.96 (0.89,1.03)	0.95 (0.88,1.02)
	2.0	0.99 (0.92,1.06)	0.97 (0.90,1.05)	0.96 (0.90,1.03)	0.98 (0.91,1.04)	0.94 (0.89,1.01)	0.90 (0.85,0.96)	0.94 (0.86,1.04)	0.90 (0.82,1.00)	0.87 (0.78,0.96)
	2.5	0.97 (0.89,1.06)	0.94 (0.87,1.02)	0.92 (0.85,0.99)	0.94 (0.88,1.01)	0.89 (0.84,0.95)	0.84 (0.79,0.90)	0.94 (0.84,1.04)	0.88 (0.78,0.99)	0.84 (0.74,0.94)
	3.0	0.95 (0.86,1.06)	0.92 (0.82,1.01)	0.89 (0.80,0.98)	0.91 (0.85,0.97)	0.84 (0.79,0.90)	0.79 (0.74,0.85)	0.94 (0.83,1.06)	0.88 (0.77,1.00)	0.83 (0.70,0.96)
0.50	1.5	1.00 (0.93,1.07)	1.00 (0.93,1.06)	0.99 (0.93,1.05)	1.00 (0.93,1.06)	0.98 (0.92,1.04)	0.95 (0.89,1.01)	0.98 (0.91,1.05)	0.94 (0.87,1.01)	0.91 (0.83,0.99)
	2.0	0.99 (0.91,1.06)	0.97 (0.90,1.03)	0.95 (0.89,1.01)	0.97 (0.91,1.03)	0.90 (0.84,0.95)	0.82 (0.77,0.87)	0.90 (0.82,0.99)	0.83 (0.74,0.92)	0.78 (0.69,0.89)
	2.5	0.96 (0.88,1.04)	0.93 (0.86,1.00)	0.90 (0.84,0.97)	0.92 (0.86,0.98)	0.83 (0.77,0.88)	0.74 (0.68,0.79)	0.86 (0.77,0.96)	0.77 (0.67,0.89)	0.71 (0.59,0.84)
	3.0	0.94 (0.86,1.03)	0.89 (0.82,0.97)	0.87 (0.80,0.95)	0.87 (0.82,0.94)	0.77 (0.71,0.82)	0.67 (0.62,0.72)	0.85 (0.74,0.97)	0.75 (0.63,0.88)	0.67 (0.53,0.84)
0.75	1.5	1.00 (0.93,1.06)	1.00 (0.94,1.06)	0.99 (0.94,1.05)	1.00 (0.94,1.06)	0.97 (0.91,1.04)	0.94 (0.88,0.99)	0.98 (0.91,1.05)	0.93 (0.86,1.01)	0.88 (0.80,0.98)
	2.0	0.99 (0.92,1.06)	0.97 (0.91,1.03)	0.96 (0.91,1.02)	0.98 (0.92,1.04)	0.87 (0.82,0.93)	0.78 (0.73,0.84)	0.87 (0.78,0.96)	0.79 (0.70,0.90)	0.72 (0.59,0.86)
	2.5	0.97 (0.89,1.05)	0.94 (0.88,1.01)	0.92 (0.87,0.99)	0.94 (0.89,1.00)	0.78 (0.73,0.83)	0.65 (0.60,0.70)	0.79 (0.69,0.90)	0.68 (0.57,0.82)	0.60 (0.44,0.77)
	3.0	0.95 (0.86,1.04)	0.91 (0.83,0.99)	0.90 (0.83,0.98)	0.89 (0.83,0.94)	0.71 (0.66,0.76)	0.56 (0.51,0.61)	0.75 (0.64,0.89)	0.61 (0.48,0.77)	0.51 (0.34,0.73)

Markers of Fetal Growth

- Birth weight poorly reflects fetal growth restriction (FGR)
- Cannot characterize growth trajectory - hard to distinguish a healthy newborn from one that experiences FGR early in pregnancy but later catches up



Biological Mechanism



Growth Standards

NICHD

LOCATION

12 U.S. Sites
New York [2], New Jersey, Delaware, Rhode Island, Massachusetts, South Carolina, Alabama, Illinois, and California [3]

RACE & ETHNIC

Highly statistically significant differences in fetal growth by race/ethnicity

Racial/ethnic-specific derived standards

INCLUSION/ EXCLUSION

A priori exclusion of pregnancy complications, preterm delivery < 37 weeks' gestation, stillbirth and fetal factors including all structural anomalies and karyotype abnormalities

ANALYTIC APPROACHES

Data transformation: log

Model assumptions: linear mixed models, assuming a normal distribution of the fetal growth trajectories (after log transformation)

Smoothing technique over gestational age: cubic splines

ESTIMATED FETAL WEIGHT

Calculated EFW from HC, AC and FL using the Hadlock 1985 formula[26]

INTERGROWTH

LOCATION

8 Countries
Brazil, China, India, Italy, Kenya, Oman, U.K. and U.S.

RACE & ETHNIC

One overall growth chart

No statistical testing for differences among countries

INCLUSION/ EXCLUSION

Exclusion of pregnancy complications and fetal factors such as congenital anomalies and stillbirth

ANALYTIC APPROACHES

Data transformation: none

Model assumptions: linear mixed models with location and scale assumptions, assuming a normal distribution of the fetal growth trajectories

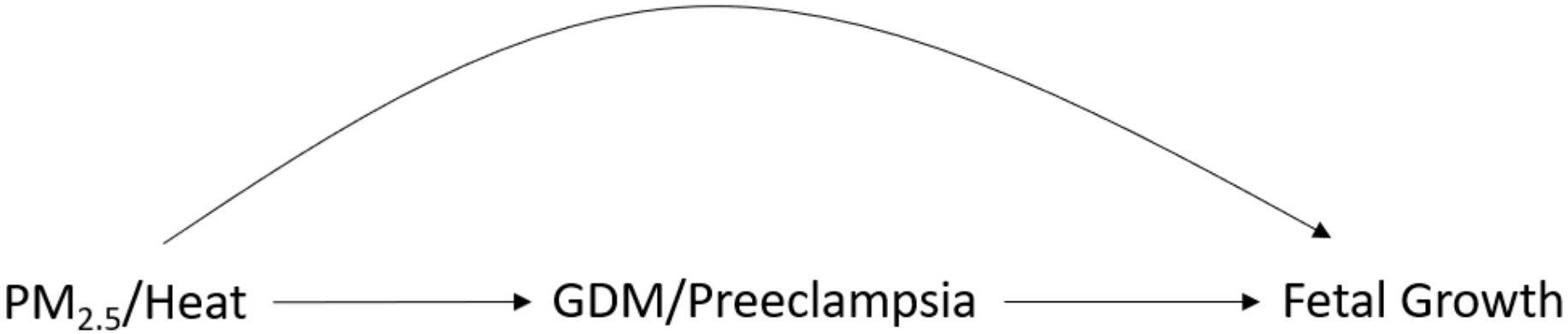
Smoothing technique over gestational age: second-degree fractional polynomials

ESTIMATED FETAL WEIGHT

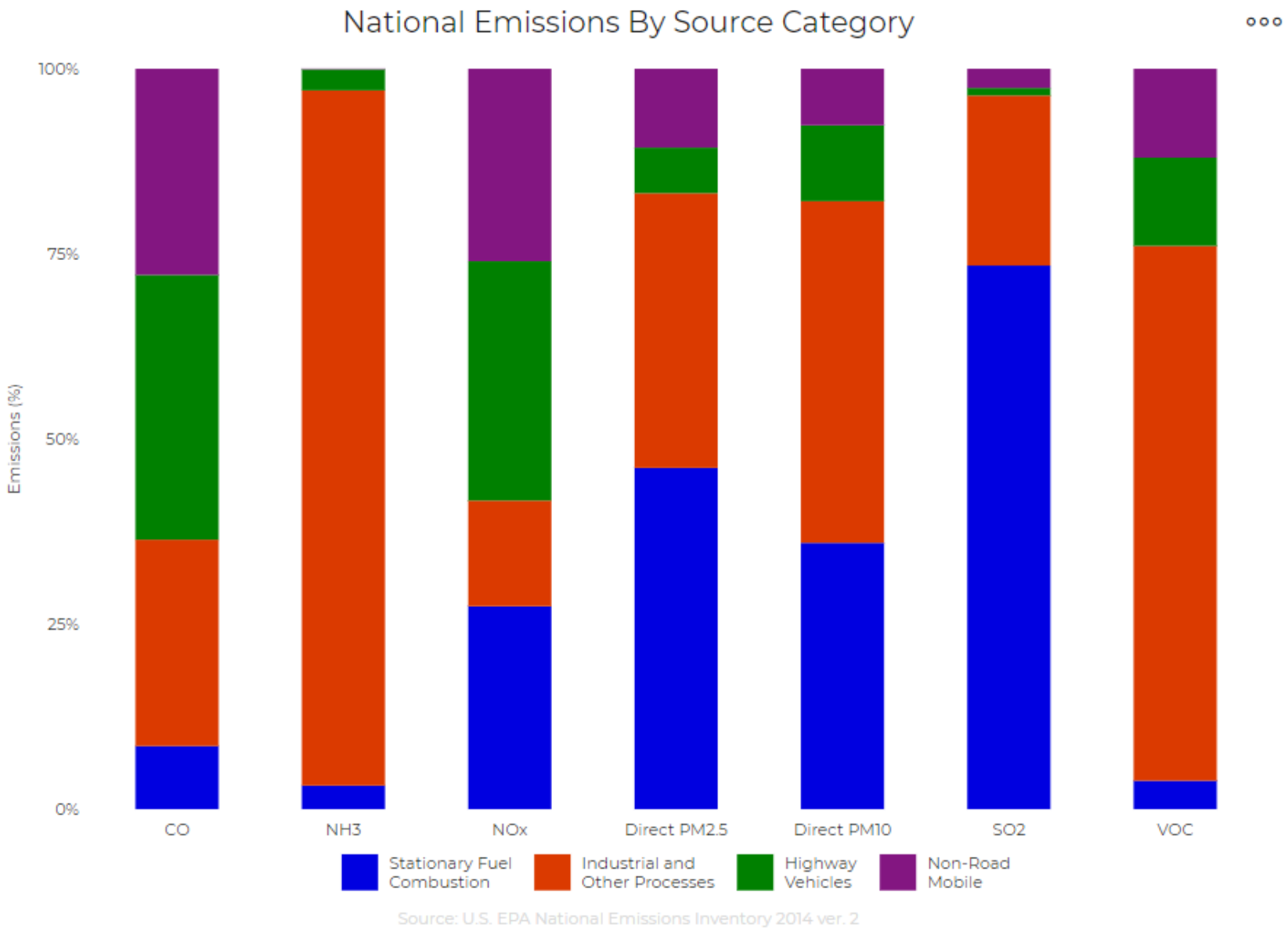
Created a new formula[12] based on only HC and AC, making the comparison of EFW less meaningful

GDM and Preeclampsia?

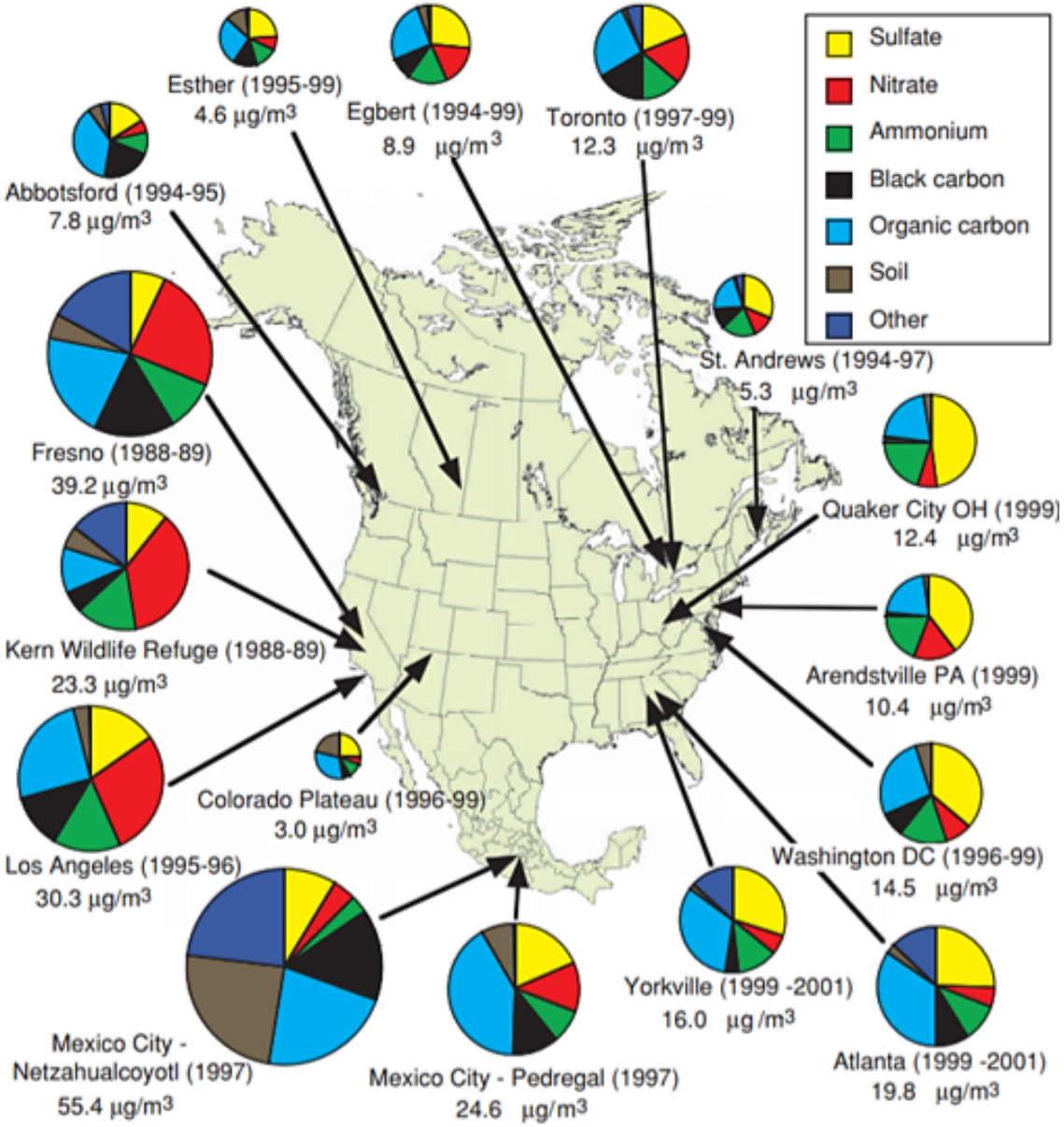
- GDM and preeclampsia may be on the causal pathway



$PM_{2.5}$ Composition



$PM_{2.5}$ Composition



Temperature

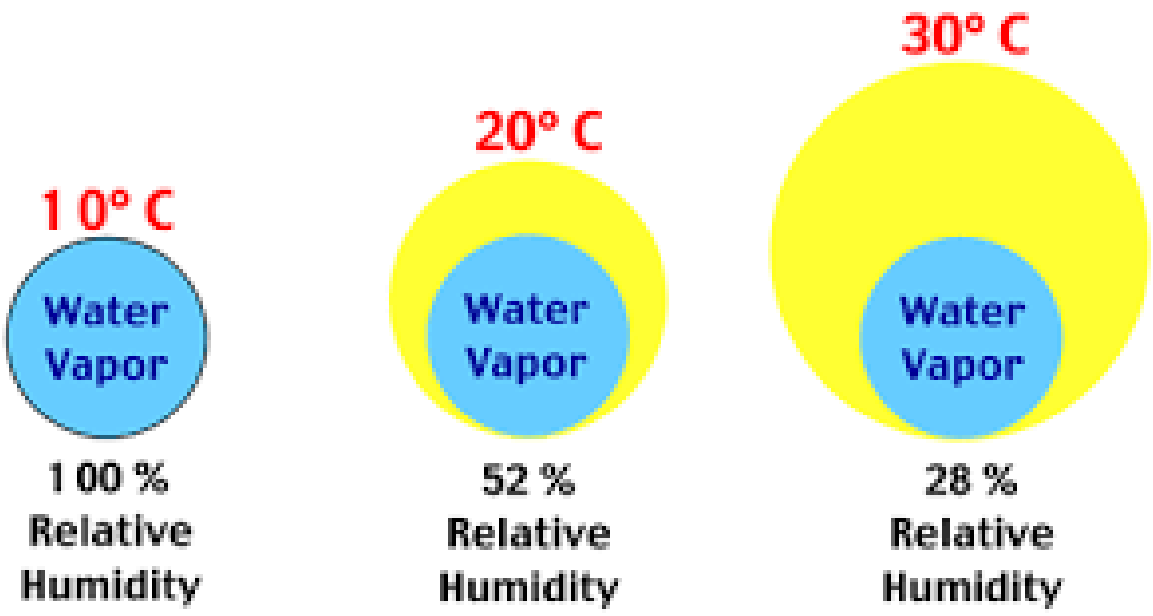
- Air temperature
- Heat Index ("feels like" temperature):
  - air temperature + relative humidity
- Apparent Temperature:
  - air temperature + relative humidity + wind speed + solar radiation

Relative Humidity (%)	temperature (°F)															
	80	82	84	86	88	90	92	94	96	98	100	102	104	106	108	110
40	80	81	83	85	88	91	94	97	101	105	109	114	119	124	130	136
45	80	82	84	87	89	93	96	100	104	109	114	119	124	130	137	
50	81	83	85	88	91	95	99	103	108	113	118	124	131	137		
55	81	84	86	89	93	97	101	106	112	117	124	130	137			
60	82	84	88	91	95	100	105	110	116	123	129	137				
65	82	85	89	93	98	103	108	114	121	128	136					
70	83	86	90	95	100	105	112	119	126	134						
75	84	88	92	97	103	109	116	124	132							
80	84	89	94	100	106	113	121	129								
85	85	90	96	102	110	117	126	135								
90	86	91	98	105	113	122	131									
95	86	93	100	108	117	127										
100	87	95	103	112	121	132										

Caution | Extreme Caution | Danger | Extreme Danger

Humidity

- Specific humidity: mass of water vapor per unit mass of air
- Relative humidity: amount of water vapor in the air relative to the maximum amount possible
  - maximum humidity determined by temperature of the system
  - same amount of water vapor results in ↑ humidity in cool air than warm air



GAM

- can think of as GLM with penalization

$$g(E(Y)) = \alpha + s_1(x_1) + ... + s_p(x_p)$$

- $s_1(x_1), ...s_p(x_p)$ denote smooth non-parametric functions (i.e., functional form determined by the data)
- Estimates smooth relationships simultaneously and then predicts $g(E(Y))$ by adding them up
- smoothness determined by generalized cross validation

Results: Maternal and Fetal Characteristics

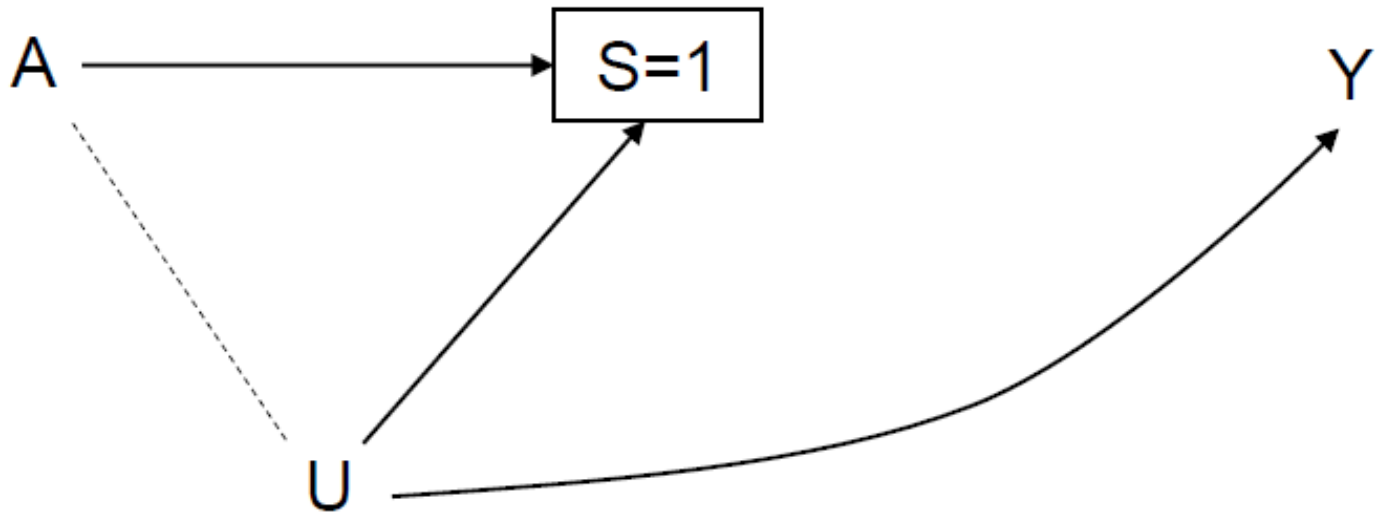
Characteristics	N (%)
Age (years)	
Mean (SD)	31 (5.4)
Education	
College or higher	4872 (48)
Lower than college	3458 (34)
Not specified	1848 (18)
Race	
White	5223 (51)
Black	1771 (17)
Asian	964 (9)
Hispanic	940 (9)
Not specified	1280 (13)
Parity	
Nulliparous	5023 (49)
Parous	5155 (51)
Child sex	
Female	5014 (49)
Male	5164 (51)
Insurance	
Private	7935 (78)
Public or uninsured	2243 (22)
Area Deprivation Index (percentile)	
Mean (SD)	22 (20)
Average $PM_{2.5}$ in first 16 weeks of pregnancy ($\mu g/m^3$)	
Mean (SD)	7.4 (1.5)
Average temperature in first 16 weeks of pregnancy (° C)	
Mean (SD)	10 (7.5)
Number of ultrasounds	
2+ ultrasounds	7340 (72)
1 ultrasound	2838 (28)

Results: Summary of Fetal Growth Measures

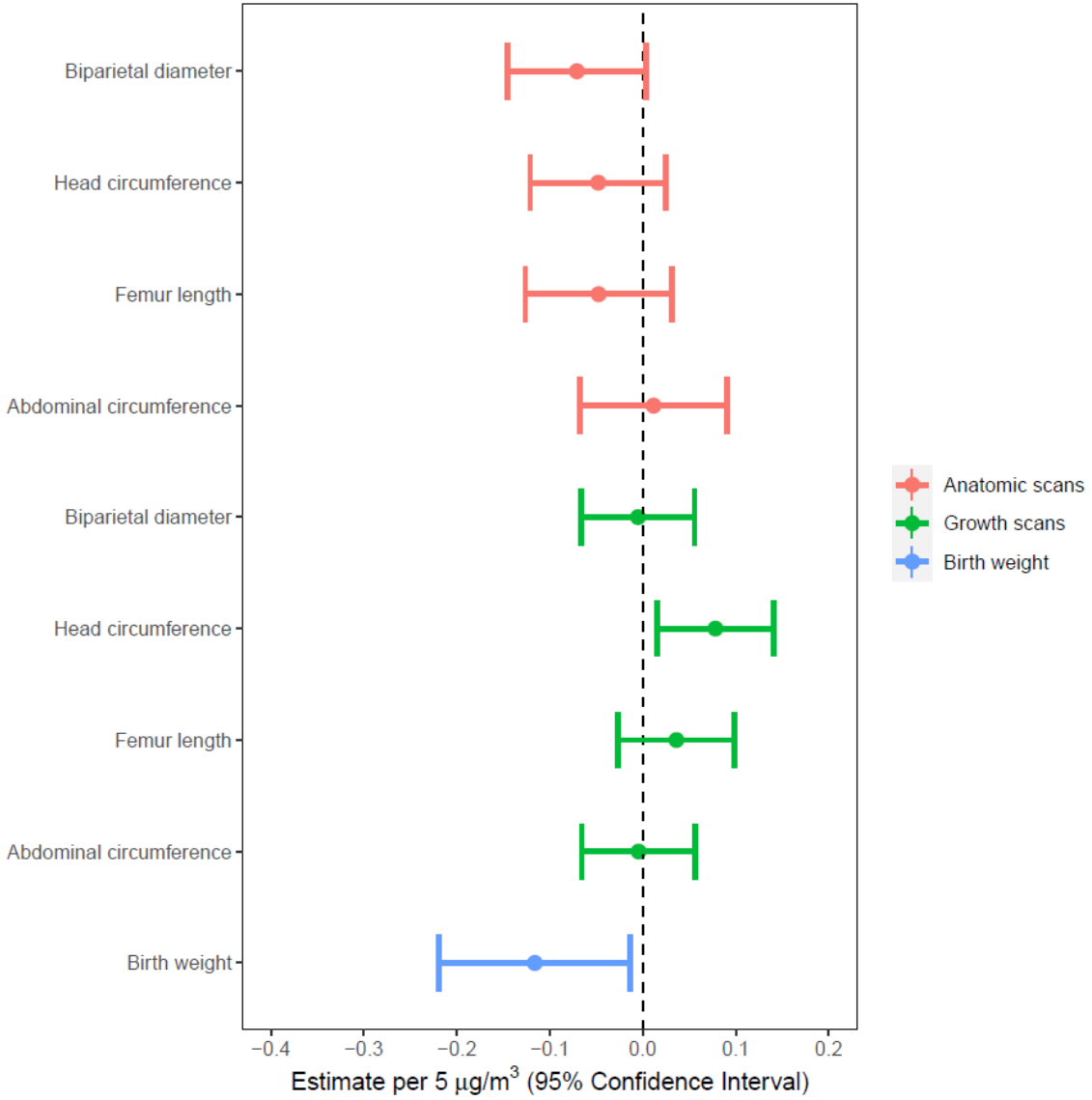
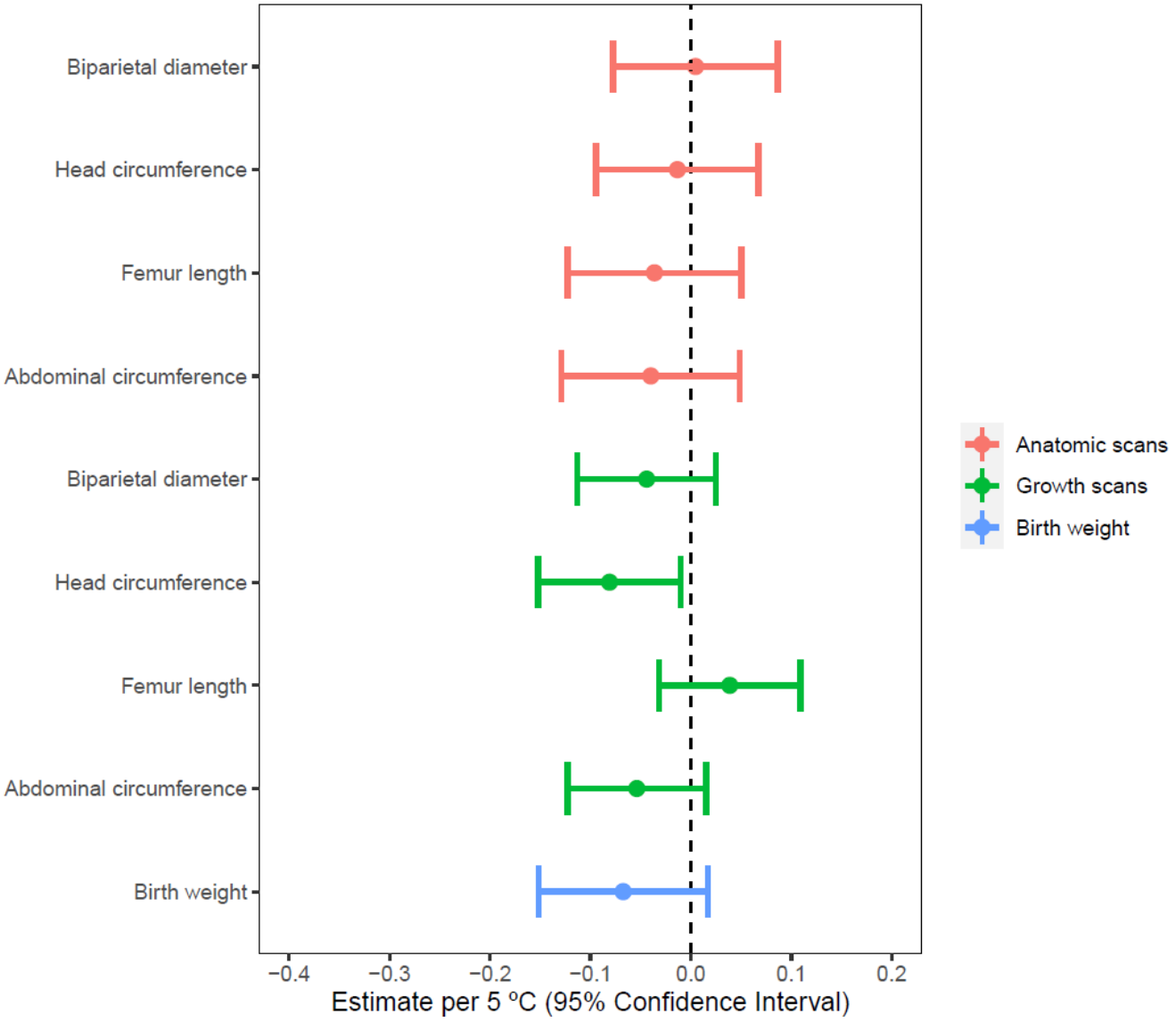
Growth outcome	N	Mean (SD)
Anatomic scans (<24 weeks)		
BPD z-score	10,207	-0.67 (1.10)
HC z-score	10,164	0.37 (1.10)
FL z-score	10,143	0.82 (1.14)
AC z-score	10,112	0.52 (1.17)
Growth scans (≥24 weeks)		
BPD z-score	15,944	-0.86 (1.12)
HC z-score	15,874	0.33 (1.15)
FL z-score	15,892	1.11 (1.10)
AC z-score	15,866	0.56 (1.10)
Birth weight z-score	9,991	0.33 (1.00)

LBB in papers 1 & 2

- $PM_{2.5}$ & stillbirth
  - OR: 1.15, range: 1.06-1.23 (Bekkar 2020)
- Temperature & stillbirth
  - OR: 1.06 per 1 °C, and 1.10 per IQR (Bekkar 2020)
- Candidate *U*s
  - e.g., substance/drug use, nutrition/eating disorders, anemia, altitude, social deprivation, placental/cord anomalies, infection, maternal illness, air pollution, temperature



Paper 2: Exposure 1 month prior



Paper 3: Exposure 1 month prior