Prenatal Exposure to Maternal Stress and Childhood Wheeze in an Urban Boston Cohort

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SCHOOL OF PUBLIC HEALTH

Overview

- Evolution of Research
- Meet Our Data
- Methods
- Models
- Stratified Models
- Results and Limitations

Evolution of our Research[1]

- Dr. Rosalind Wright and Dr. Robert Wright
- "Transdisciplinary" research
  - statistical genetics with social and physical environments
  - ranging from brain development to pollution exposure
- Asthma ⟶ Violence
- Lead ⟶ Childhood health outcomes

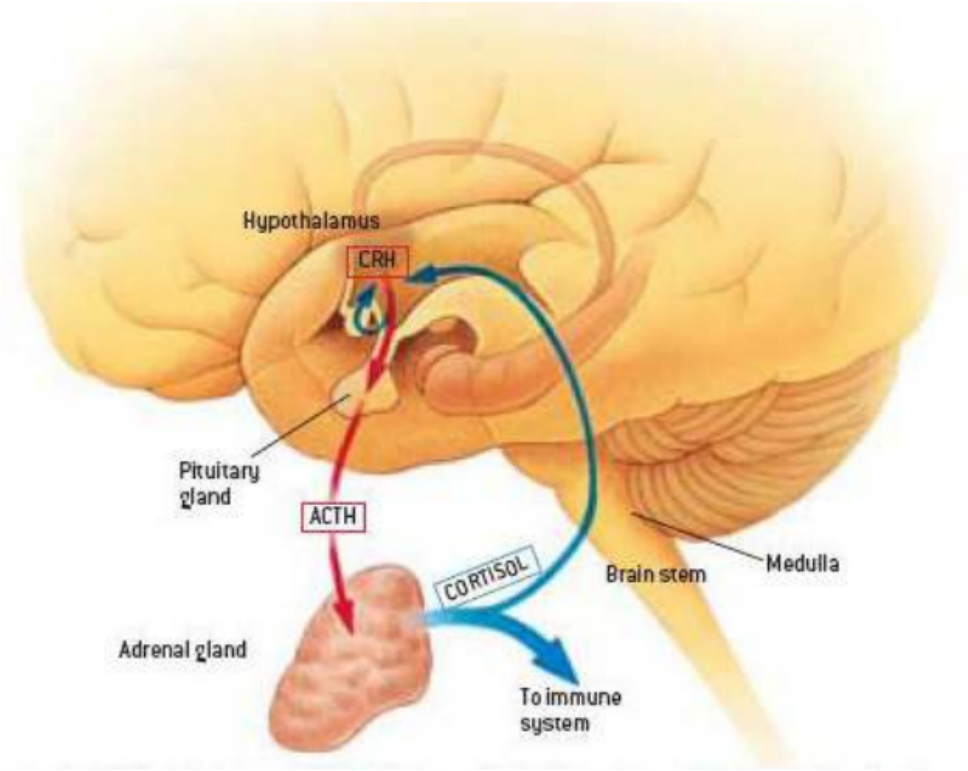
Our Research

- Prenatal Exposure to stress $\xrightarrow{?}$ Childhood Wheeze
- Previous Research done:
  - Elevated maternal cortisol levels $\longrightarrow$ reduced childhood IQ[2]
  - Elevated maternal cortisol levels $\longrightarrow$ reduced birth weight [3]

"Specifically, these studies need to address how fetal exposure to stress may influence human immune and neuroendocrine development, whether such effects are independent of postnatal exposures, and how these pathways may, in turn, influence asthma development."

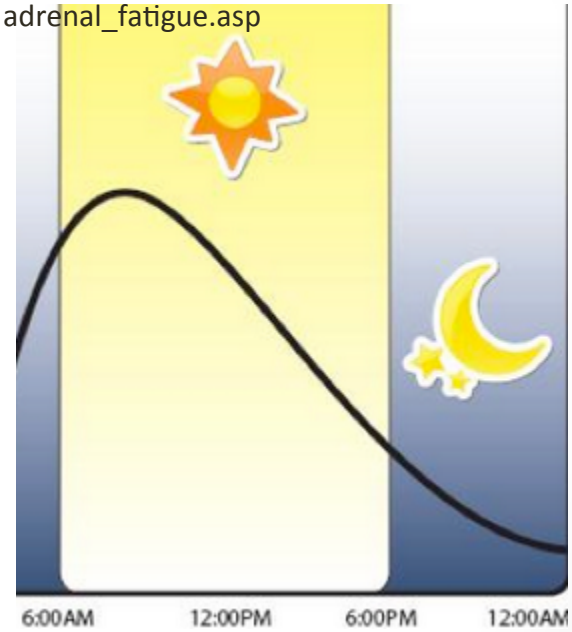
Wright et al., 2007

Cortisol Levels



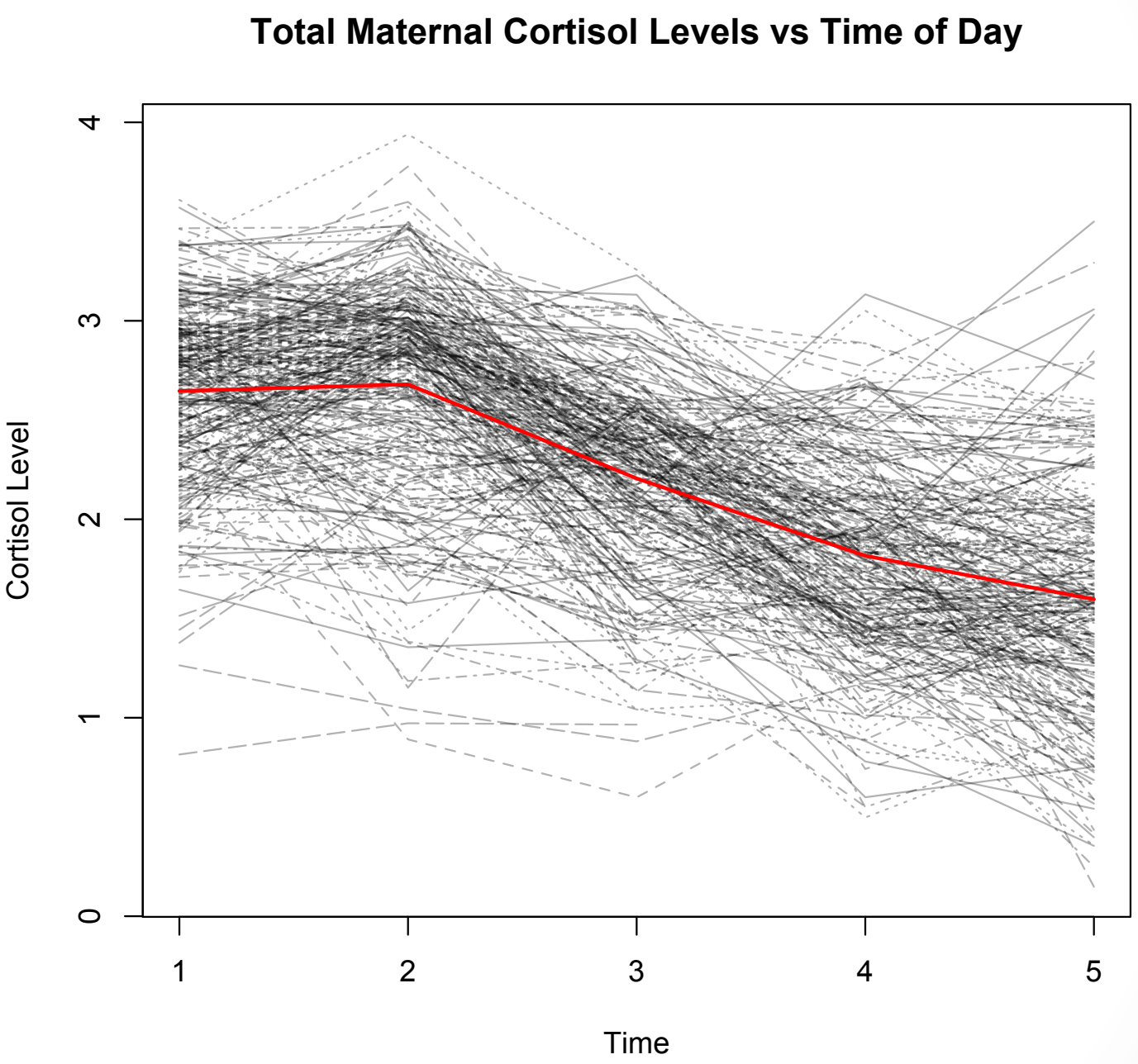
Cortisol functions
http://www.cbs.mpg.de/depts/singer/arb3/stress

Average daily cortisol levels
www.drlam.com/articles/adrenal_fatigue.asp



Meet our Data

- Boston cohort, ACCESS
  - 297 women
  - Brigham & Women's Hospital, Boston Medical Center, and affiliated clinics
  - August 2002 and December 2009
  - Mid to late pregnancy
- Cortisol levels
  - Swabs
  - Average levels of three days
- Infant Wheeze
- 22 Wheezers


Total Maternal Cortisol Levels vs Time of Day
Cortisol Level
0
1
2
3
4
1
2
3
4
5
Time

Lets Take a Look at Our Data…

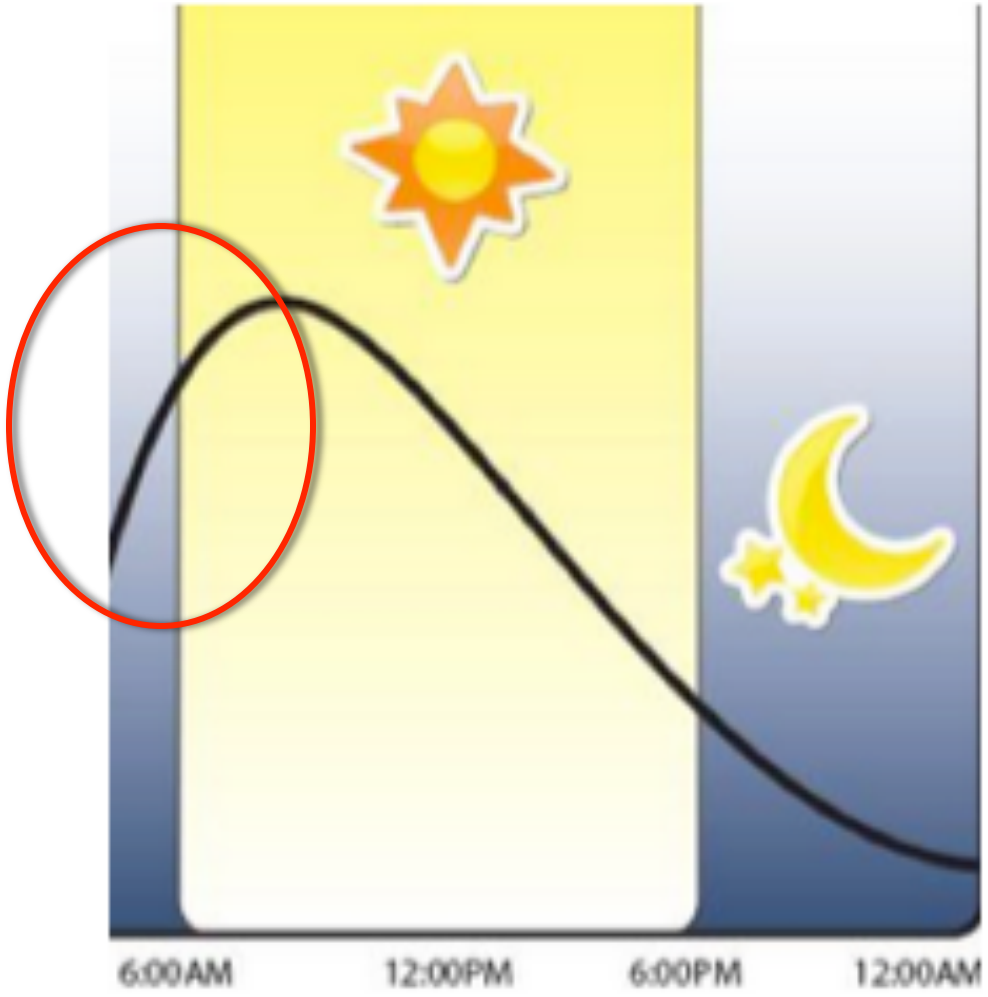
- Many variables included, with a primary focus on…
  1. Repeated Wheeze: dichotomous variable; primary outcome of interest of whether or not the child wheezes during the first two years of life
  2. Maternal BMI: dichotomized by whether or not the mother was overweight
     a) 0 = BMI < 30
     b) 1 = BMI ≥ 30
  3. Smoke: dichotomous variable on maternal smoking at second trimester of pregnancy

Lets Take a Look at Our Data…

4. Mother's Atopy: self report of exzema, wheezing, etc
5. Race: Race of the pregnant mother categorized as…
   a) 0 = White
   b) 1 = Black
   c) 2 = Hispanic
   d) 3 = Other
6. Enrollment Age: Continuous variable; age of mother at pregnancy measured in years

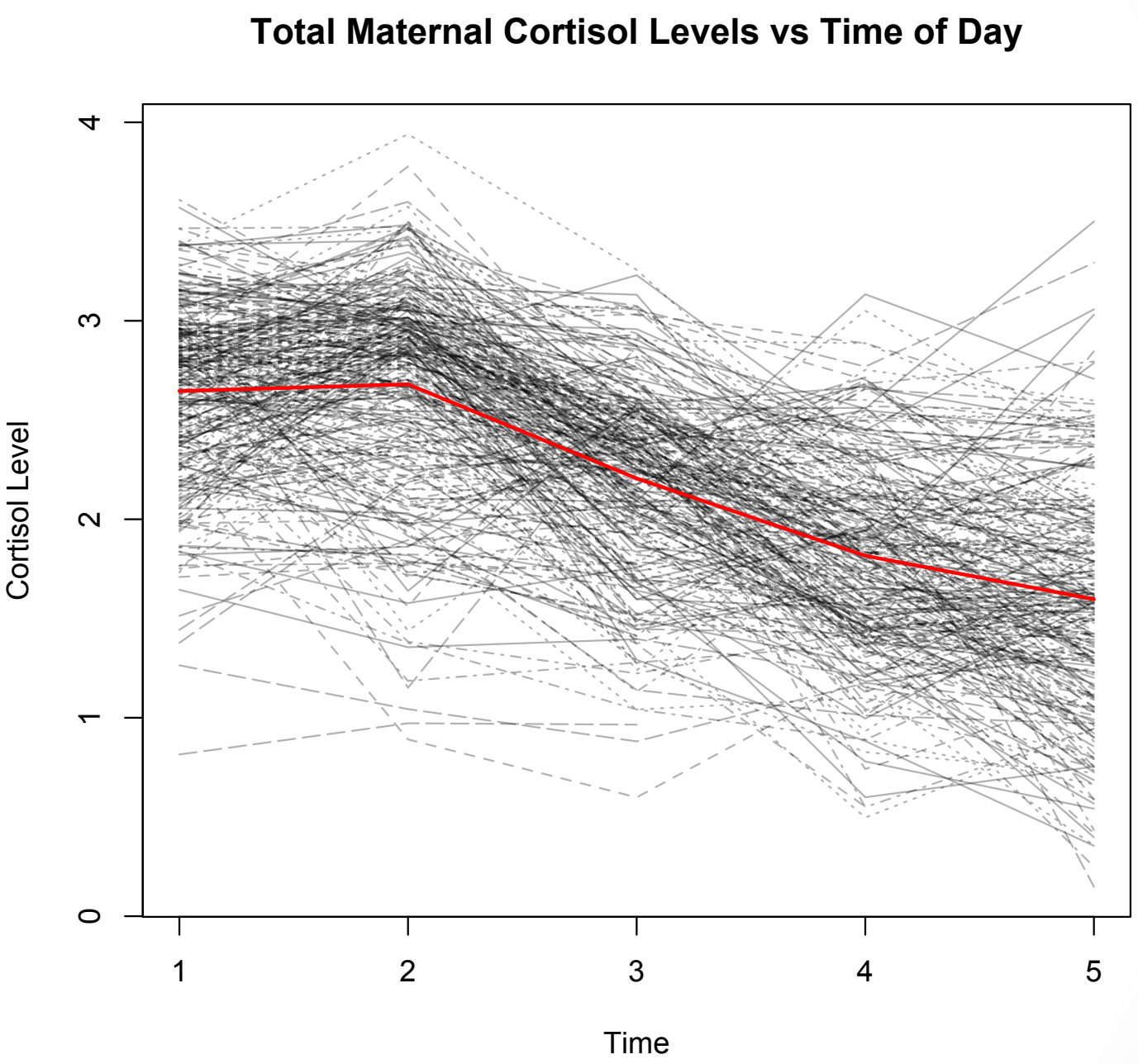
What is "Stress"?

- Stress is measured by cortisol levels in pregnant mother
- Measurements taken at 5 different points during the day
  - "Cort1" → measured immediately after waking up
  - "Cort2" → 30 minutes following wake up time
    - CAR: Cort2 – Cort1; most important due to 'peak' in stress response
  - "Cort3" & "Cort4" → measured midday to late afternoon
  - "Cort5" → measured before mother goes to bed
    - PM Slope: Cort5 – Cort4; captures decline in stress in evening
    - Daily Slope: Cort5 – Cort1; captures overall daily decline


6:00AM
12:00PM
6:00PM
12:00AM

Summary Statistics

	Mean	Standard Deviation
Cort1	2.646	0.437
Cort2	2.680	0.522
Cort3	2.206	0.461
Cort4	1.816	0.495
Cort5	1.597	0.575
CAR	0.037	0.475
PM Slope	-0.217	0.481
Daily Slope	-1.049	0.668
Enrollment Age	26.69	5.932

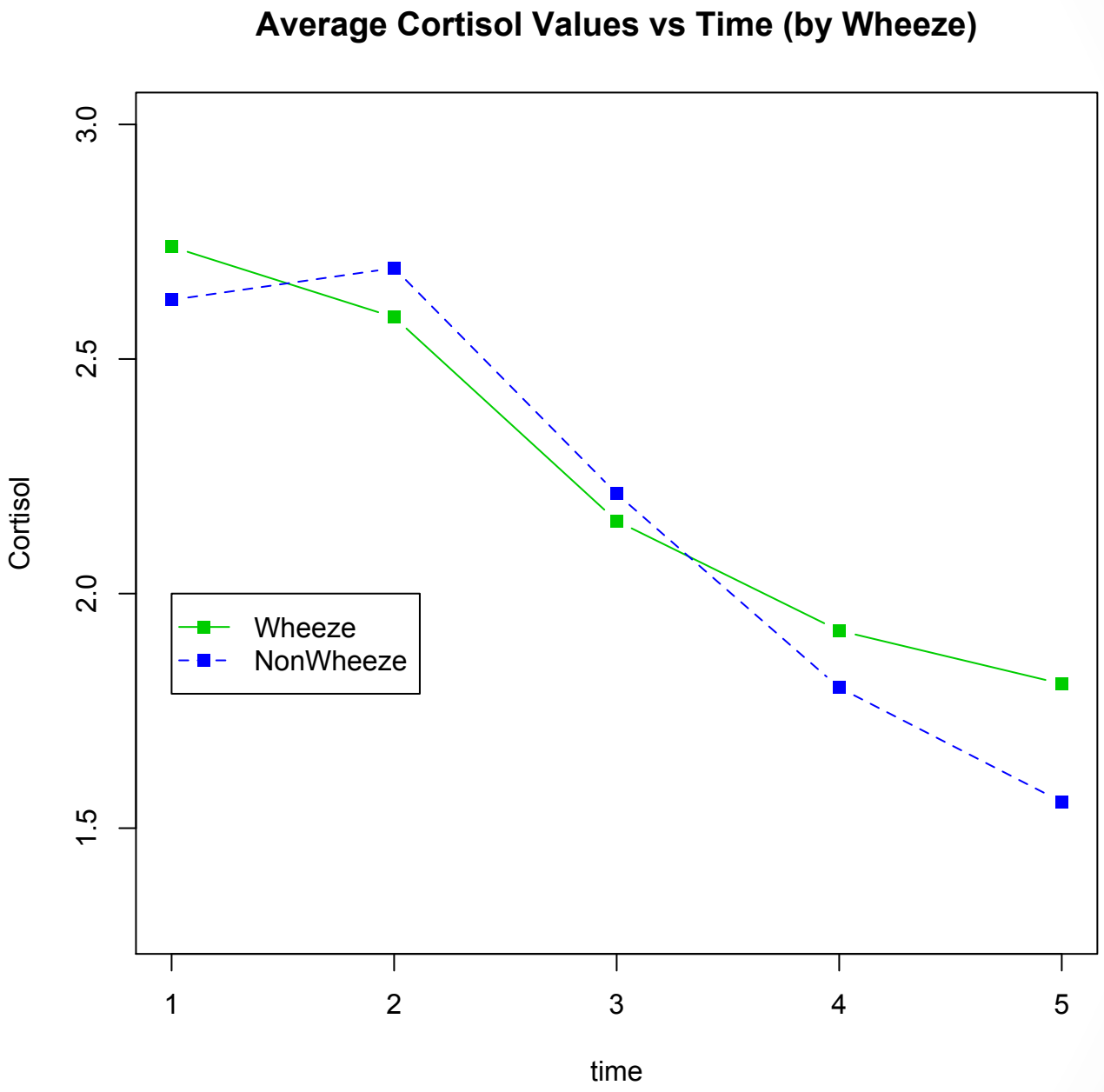

Total Maternal Cortisol Levels vs Time of Day
Cortisol Level
0
1
2
3
4
1
2
3
4
5
Time

Summary Statistics

	Count (Percentage)
Smoke	57 (19.4%)
BMI (obese)	94 (32.5%)
Maternal Atopy	109 (37.2%)
Race	
White	35 (11.9%)
Black	79 (26.8%)
Hispanic	158 (53.6%)
Other	23 (7.7%)

Wheeze Cortisol Associations

	No wheeze= 0	Wheeze= 1	95% CI	p-value
Cort 1	2.626 (0.440)	2.739 (0.362)	(-0.282, 0.056)	0.1802
Cort 2	2.694 (0.521)	2.589 (0.505)	(-0.127, 0.337)	0.3618
Cort 3	2.213 (0.465)	2.155 (0.442)	(-0.145, 0.262)	0.5622
Cort 4	1.799 (0.487)	1.921 (0.566)	(-0.380, 0.137)	0.3415
Cort 5	1.556 (0.572)	1.808 (0.570)	(-0.514, 0.010)	0.05909
CAR	0.068 (0.472)	-0.150 (0.489)	(-0.006, 0.442)	0.05569
PM Slope	-0.425 (0.508)	-0.234 (0.579)	(-0.456, 0.074)	0.1497
Daily Slope	-1.067 (0.661)	-0.932 (0.681)	(-0.450, 0.174)	0.3713


Average Cortisol Values vs Time (by Wheeze)
Cortisol
3.0
2.5
2.0
1.5
Wheeze
NonWheeze
1
2
3
4
5
time

Adjusted Model

- Logistic Regression

$$\log\left(\frac{p_i}{1-p_i}\right) = \alpha + \beta_1 "Stress" + \beta_2 Obese + \beta_3 Smoke + \beta_4 NonWhite + \beta_5 Age + \beta_6 Matopy$$

- Fitted for each stress variables
  - *Cort1, Cort2, Cort3, Cort4, Cort5, CAR, PM Slope, Daily Slope*
- outcome Y in model is “Repeated Wheeze”:
- p_i : probability that individual i wheezes twice in the two years of life
- $p_i/1\text{-}p_i$: odds ratio of wheezing vs. not wheezing
- Slope coefficient $\beta_{j:}$ implies that one unit change in X_j results in a β_j change in the log odds of the outcome Y.

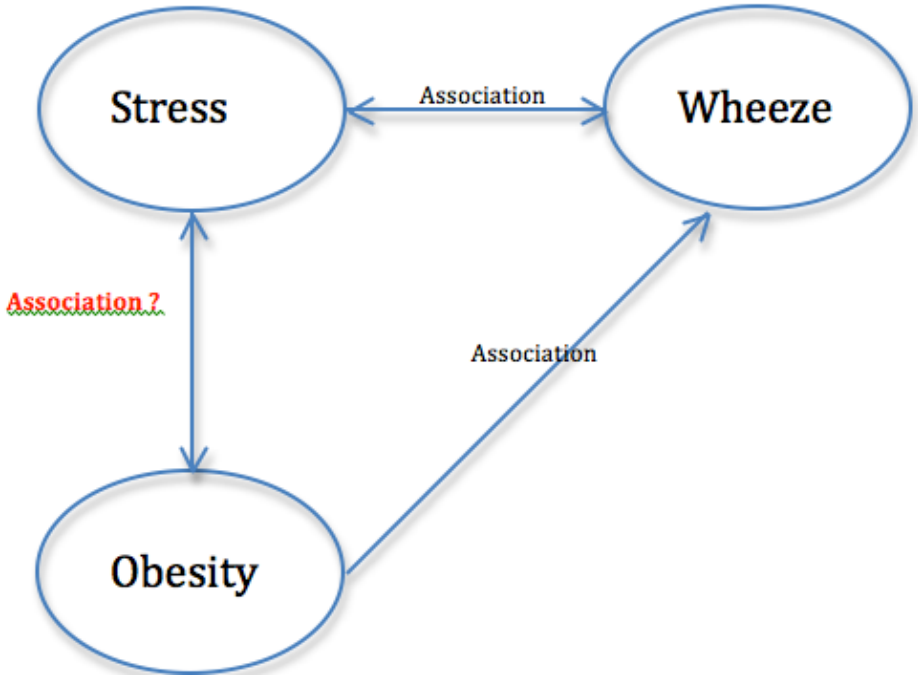
Output Example

	Coefficients Estimates	Standard Error	Z-value	P-value
(Intercept)	-3.50	1.39	-2.49	0.01
Cortisol 5	0.95	0.42	2.26	0.02
Obese	1.19	0.48	2.50	**0.01**
Smoke	-0.69	0.70	-0.99	0.32
Non-White	-0.98	1.07	-0.92	0.36
Age	-0.03	0.04	-0.85	0.40
Mother's Atopy	0.30	0.48	0.62	0.53

- RESULT: For each model, the p-values for obese only were significant at 5% significance level. So, there is evidence to suggest that obesity has an effect on wheezing after all other variables are accounted for.

- The log odds ratio of wheezing vs. not increases by a factor of 1.19 for obese mothers.

Effect Modification by Obesity



- Effect modification tested by adding an interaction term to the model.

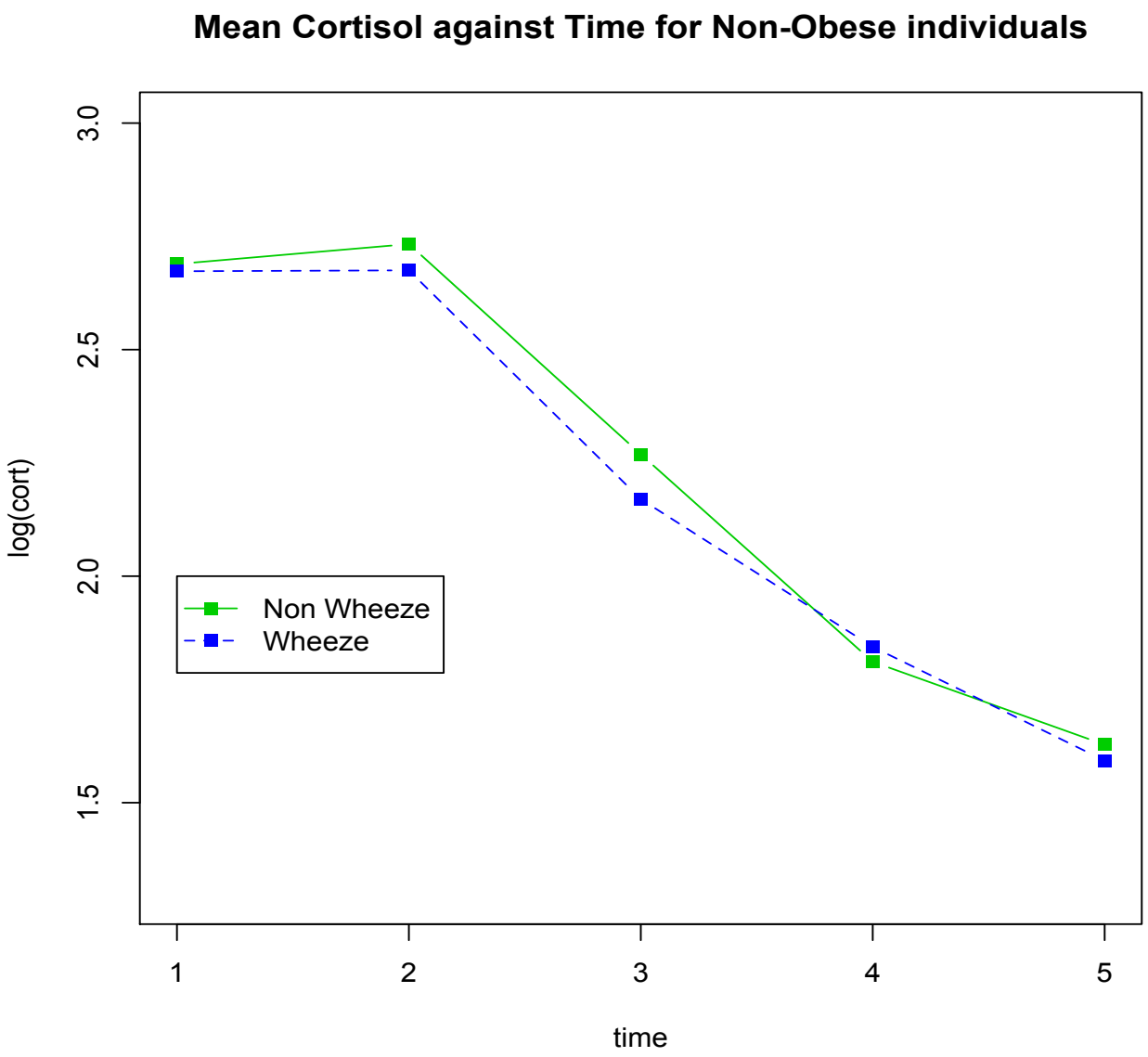
$$\log\left(\frac{p_i}{1-p_i}\right) = \alpha + \beta_1 Cort5 + \beta_2 Obese + \beta_3 Smoke + \beta_4 NonWhite$$

$$+\beta_5 Age + \beta_6 Matopy + \beta_7 Cort5 \times Obese$$

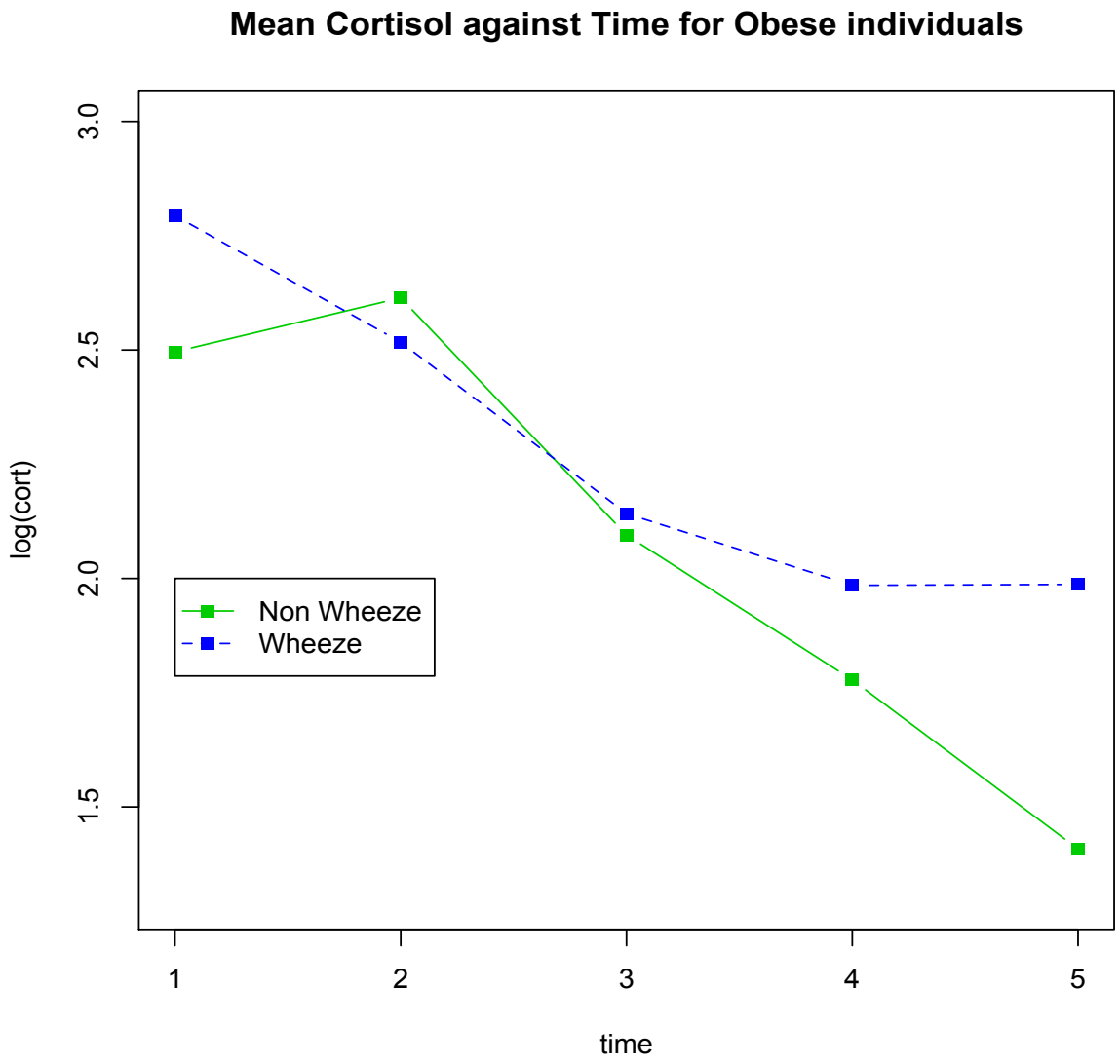
Output Results

	Coefficient Estimates	Standard Error	Z-Value	P-Value
(Intercept)	-1.51	1.61	-0.94	0.35
Cortisol 5	-0.10	0.61	-0.18	0.86
Obese	-2.90	1.72	-1.69	0.09
Smoke	-0.85	0.76	-1.11	0.27
Non-White	-0.99	1.11	-0.89	0.37
Age	-0.04	0.04	-0.92	0.36
Mother's Atopy	0.27	0.49	0.56	0.58
Cortisol 5 x Obese	2.33	0.95	2.47	**0.01**

- The interaction term is significant at the 5% significance level.
- The effect of Cortisol Level (at Time 5 in this case) on repeated wheeze is different for obese and non-obese



For Non-Obese mothers, there is no significant difference in cortisol levels throughout the day between wheezers and non-wheezers



For obese mothers, there is a significant difference in cortisol levels throughout the day between wheezers and non-wheezers.

Limitations

- Potential inflated associations
- Standard definition of repeated wheeze
- Cortisol measures taken at 2nd and 3rd trimester
- Possible inaccuracy of self –reported data
  - i.e Smoking, Mother's Atopy

Take Away

- Stress deserves more attention in combination with existing factors in the field of public health when examining maternal and childhood health associations.

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