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

Summer Program in Quantitative Sciences
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Overview

• Evolution of Research

• Meet Our Data

• Methods

• Models

• Stratified Models

• Results and Limitations
Evolution of our Research

- 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 $\rightarrow$ Childhood Wheeze
• Previous Research done:
  • Elevated maternal cortisol levels $\rightarrow$ reduced childhood IQ$^2$
  • Elevated maternal cortisol levels $\rightarrow$ 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

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
Let's 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
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
## Summary Statistics

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cort1</td>
<td>2.646</td>
<td>0.437</td>
</tr>
<tr>
<td>Cort2</td>
<td>2.680</td>
<td>0.522</td>
</tr>
<tr>
<td>Cort3</td>
<td>2.206</td>
<td>0.461</td>
</tr>
<tr>
<td>Cort4</td>
<td>1.816</td>
<td>0.495</td>
</tr>
<tr>
<td>Cort5</td>
<td>1.597</td>
<td>0.575</td>
</tr>
<tr>
<td>CAR</td>
<td>0.037</td>
<td>0.475</td>
</tr>
<tr>
<td>PM Slope</td>
<td>-0.217</td>
<td>0.481</td>
</tr>
<tr>
<td>Daily Slope</td>
<td>-1.049</td>
<td>0.668</td>
</tr>
<tr>
<td>Enrollment Age</td>
<td>26.69</td>
<td>5.932</td>
</tr>
</tbody>
</table>
Total Maternal Cortisol Levels vs Time of Day
## Summary Statistics

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoke</td>
<td>57 (19.4%)</td>
</tr>
<tr>
<td>BMI (obese)</td>
<td>94 (32.5%)</td>
</tr>
<tr>
<td>Maternal Atopy</td>
<td>109 (37.2%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>35 (11.9%)</td>
</tr>
<tr>
<td>Black</td>
<td>79 (26.8%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>158 (53.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (7.7%)</td>
</tr>
</tbody>
</table>
## Wheeze Cortisol Associations

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

Cortisol

Wheeze

NonWheeze

time
Adjusted Model

- Logistic Regression

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

- 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
- \( p_i/(1-p_i) \): odds ratio of wheezing vs. not wheezing
- Slope coefficient \( \beta_j \): implies that one unit change in \( X_j \) results in a \( \beta_j \) change in the log odds of the outcome Y.
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.

\[
\log\left(\frac{p_i}{1 - p_i}\right) = \alpha + \beta_1 \text{Cort5} + \beta_2 \text{Obese} + \beta_3 \text{Smoke} + \beta_4 \text{NonWhite} + \beta_5 \text{Age} + \beta_6 \text{Matopy} + \beta_7 \text{Cort5} \times \text{Obese}
\]
Output Results

<table>
<thead>
<tr>
<th></th>
<th>Coefficient Estimates</th>
<th>Standard Error</th>
<th>Z-Value</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.51</td>
<td>1.61</td>
<td>-0.94</td>
<td>0.35</td>
</tr>
<tr>
<td>Cortisol 5</td>
<td>-0.10</td>
<td>0.61</td>
<td>-0.18</td>
<td>0.86</td>
</tr>
<tr>
<td>Obese</td>
<td>-2.90</td>
<td>1.72</td>
<td>-1.69</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoke</td>
<td>-0.85</td>
<td>0.76</td>
<td>-1.11</td>
<td>0.27</td>
</tr>
<tr>
<td>Non-White</td>
<td>-0.99</td>
<td>1.11</td>
<td>-0.89</td>
<td>0.37</td>
</tr>
<tr>
<td>Age</td>
<td>-0.04</td>
<td>0.04</td>
<td>-0.92</td>
<td>0.36</td>
</tr>
<tr>
<td>Mother’s Atopy</td>
<td>0.27</td>
<td>0.49</td>
<td>0.56</td>
<td>0.58</td>
</tr>
<tr>
<td>Cortisol 5 x Obese</td>
<td>2.33</td>
<td>0.95</td>
<td>2.47</td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>

- 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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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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References

• 1. http://www.hsph.harvard.edu/news/magazine/fall09wrights/

