Prenatal Exposure to Stress Modifies the Association between Prenatal Lead and Infant Neurodevelopment

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National Institute of Public Health, Mexico
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Background: **Lead**

“Lead exposure can affect nearly every system in the body”

http://www.cdc.gov/nceh/lead/
Background: Lead

http://www.cdc.gov/nceh/lead/Recalls/default.htm
Background: **Stress**
Background: *Health Effects of Psychosocial Stress*

- Cardiovascular disease
- Digestive, fertility, urinary problems
- Weakened immune system
- Behaviors that increase risk to cancer
Background: *Exposure to Lead and Psychosocial Stress likely co-occur*
Background: The Prenatal Period

- Vulnerable time for exposures.
- Not only the dose.
- Critical windows of susceptibility.
- Effects later in life: “Fetal Programming”.

SCIENCEphotoLIBRARY
Background

• Lead and stress are independently associated with reduced neurodevelopmental scores

• Disrupt similar but not completely overlapping mechanisms

• Exposure to both during gestation may have modifying effects

Biological Mechanism

PRENATAL LEAD + PRENATAL STRESS → NEURODEVELOPMENT

- Glucocorticoid receptors
- Hippocampus
- Learning processes.
Study Design

PROGRESS Birth Cohort

Programming Research in Obesity, Growth, Environment and Social Stressors

(Robert Wright P.I.)
Between July 2007 and February 2011

Pregnant women receiving health insurance and prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social [IMSS]).

1054 pregnant women were recruited and followed since their 2nd trimester.
Eligibility criteria for PROGRESS cohort:

- <20 weeks gestation
- be 18 years or older
- have access to a telephone
- plan to reside in Mexico City for the next 3 years
- be free of heart or kidney disease
- not be using steroids or anti-epilepsy drugs
- not be consuming alcohol on a daily basis
Timing of Exposure and Outcome

- 690 children Bayley at either 12 or 24
- <1,500 g or <32 weeks excluded
- 680 final simple size

<table>
<thead>
<tr>
<th>Maternal Lead in Blood</th>
<th>681</th>
<th>611</th>
<th>568</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Lead in Tibia Bone</td>
<td></td>
<td></td>
<td>541</td>
</tr>
<tr>
<td>Maternal Stress: CRYSIS</td>
<td>636</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Neuro-development</td>
<td></td>
<td></td>
<td>548</td>
</tr>
</tbody>
</table>
## Maternal Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at delivery, yrs</td>
<td>27.9 (5.5)</td>
</tr>
<tr>
<td>Education, total years</td>
<td>11.9 (2.8)</td>
</tr>
<tr>
<td>Maternal IQ</td>
<td>84.9 (12.6)</td>
</tr>
<tr>
<td>2(^{nd}) trimester blood lead (µg/dl)</td>
<td>3.6 (2.6)</td>
</tr>
<tr>
<td>3(^{nd}) trimester blood lead (µg/dl)</td>
<td>3.9 (2.9)</td>
</tr>
<tr>
<td>Delivery blood lead (µg/dl)</td>
<td>3.7 (2.6)</td>
</tr>
<tr>
<td>Tibia lead (µg/g)</td>
<td>5.25 (5.6)</td>
</tr>
<tr>
<td>NLE score</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>
# Infant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>356 (52)</td>
</tr>
<tr>
<td>Breastfed (never)</td>
<td>39 (6)</td>
</tr>
<tr>
<td>Gestational Age, weeks</td>
<td>38.4 (1.6)</td>
</tr>
<tr>
<td>Birth Weight, kg</td>
<td>3.1 (0.4)</td>
</tr>
<tr>
<td>HOME evaluation score</td>
<td>31.6 (5.5)</td>
</tr>
<tr>
<td>Cognitive</td>
<td>92.4 ± 8.5</td>
</tr>
<tr>
<td>Language</td>
<td>89.7 ± 9.1</td>
</tr>
<tr>
<td>Motor</td>
<td>94 ± 9.4</td>
</tr>
</tbody>
</table>
Statistical Analyses

Multivariable regression models

• Separate analyses for 12-month & 24-month Bayley scores

• Separate models for each lead exposure indicator (2nd trimester, 3rd trimester, birth and tibia)

• Stress was dichotomized at the median (3 NLE)

• Interaction term continuous Pb x NLE

• All models where adjusted for:
  
  infant
  
  ○ sex, birth weight, gestational age
  
  maternal
  
  ○ age at delivery, IQ, HOME score
Results: Multivariable Models

Lead Effect Estimates by Stress Category on 12-Month Cognitive Scores
Results: Multivariable Models

Lead Effect Estimates by Stress Category on 12-Month Language Scores

<table>
<thead>
<tr>
<th>Stress Category</th>
<th>2\textsuperscript{nd} Trimester BPb</th>
<th>3\textsuperscript{rd} Trimester BPb</th>
<th>Birth BPb</th>
<th>Tibia Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td><img src="image1" alt="1st Data Point" /></td>
<td><img src="image2" alt="2nd Data Point" /></td>
<td><img src="image3" alt="3rd Data Point" /></td>
<td><img src="image4" alt="4th Data Point" /></td>
</tr>
<tr>
<td>High</td>
<td><img src="image5" alt="5th Data Point" /></td>
<td><img src="image6" alt="6th Data Point" /></td>
<td><img src="image7" alt="7th Data Point" /></td>
<td><img src="image8" alt="8th Data Point" /></td>
</tr>
</tbody>
</table>

- p for interaction 0.03
- p for interaction 0.05
Results: Multivariable Models

Lead Effect Estimates by Stress Category on 12-Month Motor Scores

2\textsuperscript{nd} Trimester BPb

3\textsuperscript{rd} Trimester BPb

Birth BPb

Tibia Pb

p for interaction 0.08

p for interaction 0.07
Conclusions

• 12 months of age more sensitive time point

• Stress modifies the association between prenatal lead and 12-month Bayley scores
  
  o 12 month infants high stress →lower scores compared to those with low stress

• Low stress: slightly positive associations
  
  o protective effect against lead

Surkan, Schnaas et al. 2008; Roseboom, Painter et al. 2011
Implications

*Prenatal lead neurotoxicity modified by prenatal stress*

- Relevance of studying mixed exposures
  - not only chemical exposures may be relevant

- Importance of interventions targeting early life
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