Air Pollution and Adverse Birth Outcomes

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Disclosures

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Outline

• Air pollution
  ▫ Preterm birth
    • Socioeconomic factors
  ▫ Birth Defects
    • Social factors
    • Genetic factors

• Cumulative pollution and preterm birth
  ▫ CalEnviroScreen

• Future directions
  ▫ PFAS in water and preterm birth
Air Pollution
Air Pollution

The impact of air pollution

2 Million premature deaths per year worldwide

source: World Health Organization

Severity of Effects

Death
Emergency Room visits, Hospital Admissions
Doctor visits, school absences
Respiratory symptoms, asthma attacks, medication use
Lung function decrements, inflammation, susceptibility to infection, cardiac effects
Pregnant Women + Air Pollution Don’t Mix

- 40% increase in volume of air inhaled/exhaled per minute
- 20% increase in oxygen consumption
- 50% increase in cardiac output

Physical changes in pregnancy make women more susceptible to pollutants.
Development and Periods of Susceptibility

- **Fertilized Egg**
- **Embryo**
- **Fetus**
- **Infant**
- **Child Teenager**
Air Pollution - San Joaquin Valley of California

- Carbon monoxide (CO)
- Nitrogen dioxide (NO₂)
- Nitrogen oxide (NO)
- Particulate matter <2.5 µm (PM₂.₅)
- Particulate matter <10 µm (PM₁₀)
- Traffic density (within 300m)
- Polycyclic aromatic hydrocarbons
Particulate Matter

HUMAN HAIR
50-70 µm
(microns) in diameter

PM$_{2.5}$
Combustion particles, organic compounds, metals, etc.
< 2.5 µm (microns) in diameter

PM$_{10}$
Dust, pollen, mold, etc.
< 10 µm (microns) in diameter

90 µm (microns) in diameter
FINE BEACH SAND

Image courtesy of the U.S. EPA
Counties that do not meet the annual $\text{PM}_{2.5}$ Standard

66 counties don’t currently meet 12 $\mu$g/m$^3$

EPA will not decide who needs to improve air quality to meet the standard until 2014 at the earliest. States will have until 2020-2025 to meet the standard.
Preterm Birth
Air Pollution & Preterm Birth

Traffic-related air pollution

Carbon Monoxide (CO)
Nitrogen Dioxide (NO₂)
Particulate Matter < 10 and 2.5 μm (PM₁₀, PM₂.₅)
Traffic Density (within 300m)

Preterm birth

Birth at...
- 34-36 weeks gestation (8%)
- 32-33 weeks gestation (2%)
- 28-31 weeks gestation (1%)
- 20-27 weeks gestation (1%)

N=250,000 2000-2006
Air Pollution Exposure Assessment

- Daily 24-hour averages of NO$_2$, NO, CO, PM$_{10}$, PM$_{2.5}$ and a daily 8-hour maximum of O$_3$ and were averaged over the first 2 months of pregnancy

- Air quality data from US EPA’s Air Quality System database were spatially interpolated by using inverse distance-squared weighting from up to 4 quality measurement stations

- Maximum interpolation radius of 50 km (25km for NO and CO)

- Traffic density indicators were calculated from distance-decayed annual average daily traffic volumes within a 300-m radius
### Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California

Amy M. Padula PhD, MSc, Kathleen M. Mortimer ScD, MPH, Ira B. Tager MD, MPH, S. Katharine Hammond PhD, MS, Frederick W. Lurmann MS, Wei Yang MD, MS, MA, David K. Stevenson MD, Gary M. Shaw DrPH

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>N</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO</td>
<td>NO₂</td>
</tr>
<tr>
<td>37-42 (term)</td>
<td>232,241</td>
<td>1.0</td>
</tr>
<tr>
<td>34-36</td>
<td>22,321</td>
<td>1.1</td>
</tr>
<tr>
<td>32-33</td>
<td>4,011</td>
<td>1.0</td>
</tr>
<tr>
<td>28-31</td>
<td>2,938</td>
<td>1.2</td>
</tr>
<tr>
<td>24-27</td>
<td>1233</td>
<td>1.8</td>
</tr>
<tr>
<td>20-23</td>
<td>460</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Exposure to the highest quartile in the 2nd trimester (weeks 14-26)
Preterm Birth & $PM_{2.5}$

The graph shows the odds ratio of preterm birth associated with $PM_{2.5}$ exposure across different gestational ages. The x-axis represents the gestational age in weeks, while the y-axis represents the odds ratio. The data points are color-coded to indicate the trimester:
- First Trimester (diamonds)
- Second Trimester (squares)
- Third Trimester (triangles)

The graph indicates a trend where the odds ratio increases as gestational age decreases, particularly noticeable in the first trimester. The black line represents the baseline odds ratio, which remains relatively constant across different gestational ages.
Preterm Birth & \( \text{PM}_{10} \)

The graph shows the odds ratio of preterm birth associated with \( \text{PM}_{10} \) exposure across different gestational ages and trimesters. The x-axis represents gestational age (weeks), while the y-axis represents the odds ratio. 

- **First Trimester** is indicated by diamond markers.
- **Second Trimester** is indicated by square markers.
- **Third Trimester** is indicated by triangle markers.

The graph illustrates a trend where the odds ratio increases with gestational age, particularly noticeable in certain trimesters.
Multi-pollutant Score

- Number of exposures in the highest quartile of...
  - CO
  - NO$_2$
  - PM$_{10}$
  - PM$_{2.5}$
  - traffic density
Multi-pollutant score for 2\textsuperscript{nd} trimester

34-36 weeks
Multi-pollutant score for 2^{nd} trimester

![Graph showing multi-pollutant score for 2^{nd} trimester with points indicating score values for 32-33 weeks and 34-36 weeks.]
Multi-pollutant score for 2nd trimester

![Graph showing multi-pollutant score for different weeks of pregnancy.]

- **34-36 weeks**
- **32-33 weeks**
- **28-31 weeks**
Multi-pollutant score for 2nd trimester
Role of Neighborhood SES

- Odds ratio of birth at 20-27 weeks for each exposure during the 2nd trimester of pregnancy

*defined as those living in a block group with >10% unemployment, >15% with income from public assistance and >20% families below poverty level
Exposure to airborne polycyclic aromatic hydrocarbons during pregnancy and risk of preterm birth

Amy M. Padula a,*, Elizabeth M. Noth b, S. Katharine Hammond b, Fred W. Lurmann c, Wei Yang a, Ira B. Tager b, Gary M. Shaw a

<table>
<thead>
<tr>
<th>PAH exposure period</th>
<th>Gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34-36 weeks</td>
</tr>
<tr>
<td>Entire Pregnancy</td>
<td>0.99</td>
</tr>
<tr>
<td>1st trimester</td>
<td>0.92</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>0.98</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>1.00</td>
</tr>
<tr>
<td>Last 6 weeks</td>
<td>0.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PAH Level</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd quartile</td>
<td>1.49</td>
<td>(1.08, 2.06)</td>
</tr>
<tr>
<td>3rd quartile</td>
<td>2.63</td>
<td>(1.93, 3.59)</td>
</tr>
<tr>
<td>4th quartile</td>
<td>3.94</td>
<td>(3.03, 5.12)</td>
</tr>
</tbody>
</table>
Birth Defects
Study Population

• California Center
  • 1997-2006 (-2011)
  • 2,493 cases (58 phenotypes)
  • 849 controls
    » PIs: Gary Shaw & Suzan Carmichael
The Association of Ambient Air Pollution and Traffic Exposures With Selected Congenital Anomalies in the San Joaquin Valley of California

Amy M. Padula*, Ira B. Tager, Suzan L. Carmichael, S. Katharine Hammond, Frederick Lurmann, and Gary M. Shaw

- Anencephaly: N=77
- Spina bifida: N=138
- Cleft lip: N=293
- Cleft palate only: N=129
- Gastroschisis: N=169
- Controls: N=849

- CO, NO, NO₂, PM₂.₅, PM₁₀, O₃, traffic density
- First 2 months of pregnancy
- Each quartile of exposure vs. lowest quartile
- Associations with neural tube defects
- No associations with...
  - cleft lip, with or without cleft palate
  - cleft palate only
  - gastroschisis (stratified by </>20 yrs old)
# The Association of Ambient Air Pollution and Traffic Exposures With Selected Congenital Anomalies in the San Joaquin Valley of California

Amy M. Padula*, Ira B. Tager, Suzan L. Carmichael, S. Katharine Hammond, Frederick Lurmann, and Gary M. Shaw

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Anencephaly (N=77)</th>
<th>Spina bifida (N=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide</td>
<td>1.6 (0.7, 3.8)</td>
<td><strong>2.0 (1.1, 3.8)</strong></td>
</tr>
<tr>
<td>Nitrogen oxide</td>
<td><strong>2.8 (1.3, 5.9)</strong></td>
<td>1.4 (0.8, 2.5)</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>1.7 (0.9, 3.4)</td>
<td><strong>1.7 (1.0, 3.0)</strong></td>
</tr>
<tr>
<td>Particulate Matter &lt;2.5μ</td>
<td>1.6 (0.7, 3.4)</td>
<td>1.4 (0.7, 2.6)</td>
</tr>
<tr>
<td>Particulate Matter &lt;10μ</td>
<td>1.1 (0.5, 2.1)</td>
<td>1.3 (0.8, 2.2)</td>
</tr>
<tr>
<td>Ozone</td>
<td>0.6 (0.4, 0.9)</td>
<td><strong>0.5 (0.2, 0.9)</strong></td>
</tr>
</tbody>
</table>

*Adjusted for maternal race/ethnicity, education and multivitamin use.
### Congenital Heart Defect Cases

- **Pulmonary valve stenosis**
- **Ventricular septal defects** – perimembranous, muscular, conal
- **Secundum atrial septal defects**
- **Hypoplastic left heart syndrome**
- **Coarctation of the aorta**
- **Heterotaxia**
- **Dextro-transposition of the great arteries**
- **Teratology of Fallot**

- **Other atrial septal defects**
- **Single ventricle or other complex**
- **Total anomalous pulmonary venous return**
- **Aortic stenosis**
- **Pulmonary atresia**
- **Tricuspid atresia**
- **Double outlet right ventricle – other**
- **Double outlet right ventricle – TGA**
- **Atrioventricular septal defects**

\[ n = 822 \text{ cases} \]
\[ n = 849 \text{ controls} \]
Ambient Air Pollution and Traffic Exposures and Congenital Heart Defects in the San Joaquin Valley of California

Amy M. Padula, Ira B. Tager, Suzan L. Carmichael, S. Katharine Hammond, Wei Yang, Frederick Lurmann, Gary M. Shaw

### Positive Associations

<table>
<thead>
<tr>
<th>PM$_{10}$</th>
<th>PM$_{2.5}$</th>
<th>Traffic Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY VALVE STENOSIS</td>
<td>PERIMEMBRANOUS VENTRICULAR SEPTAL DEFECTS</td>
<td>TRANSPOSITION OF THE GREAT ARTERIES</td>
</tr>
</tbody>
</table>

95% confidence intervals

- adjusted for maternal race/ethnicity, education and multivitamin use
Inverse Associations

- PM$_{2.5}$
- CO
- Traffic Density

95% confidence intervals

- Perimembranous Ventricular Septal Defects
- Secundum Atrial Septal Defects
- Secundum Atrial Septal Defects
- Transposition of the Great Arteries

...adjusted for maternal race/ethnicity, education and multivitamin use...
Traffic-Related Air Pollution and Selected Birth Defects in the San Joaquin Valley of California

Amy M. Padula, Ira B. Tager, Suzan L. Carmichael, S. Katharine Hammond, Wei Yang, Frederick W. Lurmann, and Gary M. Shaw

1Stanford University, Stanford, California
2University of California, Berkeley, Berkeley, California
3Sonoma Technology Inc., Petaluma, California

- Anotia/microtia (106)
- Anorectal atresia/stenosis (91)
- Craniosynostosis (87)
- Hypospadias second or third degree (67)
- Diaphragmatic hernia (66)
- Transverse limb deficiency (63)
- Intestinal atresia/stenosis (52)
- Amniotic band syndrome and limb body wall complex (49)
- Hydrocephaly (46)
- Longitudinal limb deficiency (45)
- Esophageal atresia (44)
Traffic-Related Air Pollution and Selected Birth Defects in the San Joaquin Valley of California

Amy M. Padula, 1* Ira B. Tager, 2 Suzan L. Carmichael, 1,2 S. Katharine Hammond, 2 Wei Yang, 1 Frederick W. Lurmann, 3 and Gary M. Shaw 1

1 Stanford University, Stanford, California
2 University of California, Berkeley, Berkeley, California
3 Sonoma Technology Inc., Petaluma, California

- 11 phenotypes that had at least 40 cases
  - traffic density $\rightarrow$ esophageal atresia (OR=2.8, 95% CI, 1.1–7.4)
  - PM$_{10}$ $\rightarrow$ esophageal atresia (OR 4.9; 95% CI, 1.4–17.2)
  - PM$_{10}$ $\rightarrow$ hydrocephaly (OR=0.3; 95% CI, 0.1–0.9)
  - CO $\rightarrow$ anotia/microtia (OR=0.4; 95% CI, 0.2–0.8)
  - CO $\rightarrow$ transverse limb deficiency (OR=0.4; 95% CI, 0.2–0.9)
- adjusted for maternal race/ethnicity, education, and vitamin use
Social factors as effect modifiers

Neighborhood Socioeconomic Status Acculturation among Hispanic Mothers
• **Poverty**  (>20% living below federal level)
• **Income**  (median <$30,000)
• **Education**  (<HS education >30%)
• **Unemployment**  (>10%)
• **Public assistance**  (>10% with income)
• **Home value**  (median <$100,000)
• High $\text{PM}_{10}$ was associated with spina bifida in neighborhoods with...
  • High poverty aOR = 2.6 (95% CI: 1.1, 6.0)
  • Low income aOR = 5.1 (95% CI: 1.7, 15.3)
  • Low education aOR = 3.2 (95% CI: 1.4, 7.4)

• After adjusting for maternal race/ethnicity, education and vitamin use
• Do individual and neighborhood acculturation factors modify the associations between air pollution and neural tube defects among Hispanic women?

• **Spina bifida**=94; **Anencephaly**=45; **Controls**=466

• Proportion of seven neighborhood acculturation factors from the U.S. Census
  - Spanish language
  - US citizenship
  - Year of entry
  - English proficiency
  - Foreign born
  - Hispanic population
  - “Acculturation index”

• Adjusted for maternal education and multivitamin use in the first 2 months of pregnancy
• Stratification by nativity
Stronger associations between CO, NO and NO$_2$ and NTDs were observed in neighborhoods that were more acculturated.

Stronger associations between PM$_{10}$ and NTDs were observed in neighborhoods that were less acculturated.
Genetic factors

Gene-Environment Interactions
Genetic variation in biotransformation enzymes, air pollution exposures, and risk of spina bifida

Amy M. Padula¹  |  Wei Yang²  |  Kathleen Schultz³  |  Fred Lurmann⁴  |  S. Katharine Hammond⁵  |  Gary M. Shaw²

- Bloodspots and buccal cells in 86 cases and 208 controls
- 104 gene variants (158 assayed)
- Adjusted for race/ethnicity, folic acid vitamin and smoking
- Tested for effect modification by race/ethnicity and folic acid vitamin
Gene-environment interactions between pollutants and several gene variants in metabolic enzymes:

- NO (ABCC2)
- NO$_2$ (ABCC2, SLC01B1)
- PM$_{10}$ (ABCC2, CYP1A2, CYP2B6, CYP2C19, CYP2D6, NAT2, SLC01B1, SLC01B3)
- PM$_{2.5}$ (CYP1A1 and CYP1A2)
Genetic variation in biotransformation enzymes, air pollution exposures, and risk of spina bifida

Amy M. Padula¹ | Wei Yang² | Kathleen Schultz³ | Fred Lurmann⁴ | S. Katharine Hammond⁵ | Gary M. Shaw²

ABCC2 rs3740066
Genetic variation in biotransformation enzymes, air pollution exposures, and risk of spina bifida

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Particulate Matter <10 µm
Future Plans

- Polycyclic aromatic hydrocarbons
- Gene-environment interactions
- Wildfires and preterm birth
Cumulative Pollution

CalEnviroScreen
Environmental pollution and as contributors to preterm birth

Investigation of association between environmental and socioeconomic factors and preterm birth in California

Amy M. Padula, Hongtai Huang, Rebecca J. Baer, Laura M. Laura L. Jellife-Palowski, Marina Sirota and Tracey J. Woodruff

Associations with Preterm Birth

Fresno County

- Exposures score
  - Low SES OR=1.16 (1.06, 1.25)
  - High SES OR=1.07 (0.98, 1.17)
- Drinking Water score
  - Low SES OR=1.29 (1.09, 1.52)
  - High SES OR=1.00 (0.90, 1.12)

California State

- Pollution Burden
  - OR=1.03 (1.01, 1.04)
- PM2.5
  - OR=1.03 (1.02, 1.04)
- Drinking Water Scores
  - OR=1.04 (1.03, 1.05)

Pollution Burden Score

<table>
<thead>
<tr>
<th>Percentile Range</th>
<th>Pollutant Burden Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 19th percentile</td>
<td>Reference</td>
</tr>
<tr>
<td>20 – 39th percentile</td>
<td>1.38 (0.79, 2.40)</td>
</tr>
<tr>
<td>40 – 59th percentile</td>
<td>1.78 (1.09, 2.88)</td>
</tr>
<tr>
<td>60 – 79th percentile</td>
<td>1.98 (1.23, 3.19)</td>
</tr>
<tr>
<td>80 – 100th percentile</td>
<td>1.98 (1.23, 3.19)</td>
</tr>
</tbody>
</table>

Adjusted odds ratios (OR) & 95% Confidence intervals
Collaborations
PFAS in Drinking Water and Preterm Birth

• R01 to resubmit in July

• PFAS
  ▫ Monitored drinking water (2013-2015)
  ▫ 2\textsuperscript{nd} trimester serum (banked samples from screening test)

• Preterm birth (birth certificate)

• Social factors (neighborhood deprivation)
PFAS & PTB proposal

Water Contaminants
- 6 Perfluoralkyl substances
- 13 co-contaminants

Aim 3

Sera Analyses
- 35 Perfluoralkyl substances
- Thyroid Hormones
- Corticotropin-Releasing Hormone

Social Stressors
- Maternal Race/Ethnicity
- Maternal Education, Insurance
- Neighborhood Socioeconomic Status
- Neighborhood Deprivation

Aim 2

Outcomes
- Preterm Birth
  - Spontaneous preterm birth
  - Early preterm birth

Aim 1
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S. Katharine Hammond, University of California Berkeley