Air Pollution and Autism Spectrum Disorder (ASD)

Overview of the Research

Lynne Pavlic Marshall, PhD
Allegheny County Health Department
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Outline:

• Autism Spectrum Disorder (ASD)
  • Historical Context
  • Description and Prevalence
  • Possible risk factors
• Association between air pollutants and ASD
ASD: Historical context

• First described in the literature in 1943 (Kanner)
• In 1952 it was referred to early onset schizophrenia and was then renamed infantile autism in 1980 and then autism disorder in 1987
• In the past decade the common name autism has covered a broad range of behavioral, communication, and social disorders under the umbrella term Autism Spectrum Disorder

ASD: Description

Heterogeneous neurological disease

• Defined by
  • Impairments in social interactions
  • Verbal and non-verbal communication
  • Relationships
  • Repetitive actions or behaviors
• Can be accompanied by
  • Epileptic seizures
  • Impaired speech
  • Intellectual disability
### ASD: Prevalence

<table>
<thead>
<tr>
<th>Surveillance Year</th>
<th>Birth Year</th>
<th>Number of ADDM Sites Reporting</th>
<th>Prevalence per 1,000 Children (Range)</th>
<th>This is about 1 in X children</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>1992</td>
<td>6</td>
<td>6.7 (4.5 – 9.9)</td>
<td>1 in 150</td>
</tr>
<tr>
<td>2002</td>
<td>1994</td>
<td>14</td>
<td>6.6 (3.3 – 10.6)</td>
<td>1 in 150</td>
</tr>
<tr>
<td>2004</td>
<td>1996</td>
<td>8</td>
<td>8.0 (4.6 – 9.8)</td>
<td>1 in 125</td>
</tr>
<tr>
<td>2006</td>
<td>1998</td>
<td>11</td>
<td>9.0 (4.2 – 12.1)</td>
<td>1 in 110</td>
</tr>
<tr>
<td>2008</td>
<td>2000</td>
<td>14</td>
<td>11.3 (4.8 – 21.2)</td>
<td>1 in 88</td>
</tr>
<tr>
<td>2010</td>
<td>2002</td>
<td>11</td>
<td>14.7 (14.3 – 15.1)</td>
<td>1 in 68</td>
</tr>
</tbody>
</table>

Source: Surveillance data from the CDC funded Autism and Developmental Disabilities Monitoring (ADDM) Network

### Reasons for Increase in ASD Prevalence

ASD: Prevalence

• ASD occurs in all racial, ethnic, and socioeconomic groups
• ASD is almost 5 times more common among boys (1 in 42) than among girls (1 in 189)
• Studies in Asia, Europe, and North America have identified individuals with ASD with an average prevalence of about 1%

ASD: Challenges

1. It takes diverse forms

2. Does not have clear diagnostic parameters
   • ASD diagnosis is based on clinical presentation and judgment
   • Numerous instruments are used

3. Prevalence is increasing but reasons are unclear
ASD: Genetics or Environment

Etiology is unknown

- Has strong genetic origins, but specific genes have not yet been identified
- Recent research suggests
  - as much as 55% of cases are caused by environmental factors
  - a timeframe of the prenatal or early postnatal period
- Likely a combination of genetics AND environment

Environmental (non-genetic) risk factors suggested by prior research
Previous findings:
On the association of air pollutants and ASD

Rationale:

• Air pollution is associated with many health outcomes
  • Respiratory disease
  • Cardiovascular disease
  • Cancer
  • Adverse birth outcomes
    • Low birth weight (LBW)
    • Preterm birth
    • Birth defects
Rationale:

• Many air pollutants are considered developmental and/or neurological toxicants
  • Fetus can be exposed to the pollutant itself
    • Many cross the placenta and the blood-brain barrier
  • Fetal exposure to elevated maternal inflammatory cytokines resulting from maternal exposure

Major Challenge: Exposure Assessment

• National Air Toxics Assessment
• Proximity to:
  • Highways
  • Agricultural pesticide use
  • Industry - pollutants measured by Toxic Release Inventory (TRI)
• Air Monitor data
National Air Toxics Assessment (NATA):

- EPA modeled concentration, exposure, and risk assessments for 187 air toxics
  - Use information from the National Emissions Inventory, meteorological data, and traffic density
  - Census tract level estimates

Previous Studies:

- Four studies to date have explored the association between ASD and concentrations of air pollutants as estimated by NATA
  - Windham, 2006
  - Kalkbrenner, 2010
  - Roberts, 2013
  - Talbott, 2015 (not yet published)
Findings using NATA estimates

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Odds Ratio (95% CI)</th>
<th>Investigator</th>
<th>Study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium</td>
<td>1.54 (1.08, 2.20)</td>
<td>Windham</td>
<td>San Francisco Bay area, CA</td>
</tr>
<tr>
<td>Chromium</td>
<td>1.66 (1.11, 2.46)</td>
<td>Talbott</td>
<td>Western Pennsylvania</td>
</tr>
<tr>
<td>Diesel particulate matter</td>
<td>1.44 (1.03, 2.02)</td>
<td>Windham</td>
<td>San Francisco Bay area, CA</td>
</tr>
<tr>
<td>Lead</td>
<td>1.6 (1.1, 2.3)</td>
<td>Roberts</td>
<td>Across the US</td>
</tr>
<tr>
<td>Manganese</td>
<td>1.5 (1.1, 2.2)</td>
<td>Roberts</td>
<td>Across the US</td>
</tr>
<tr>
<td>Mercury</td>
<td>2.0 (1.2, 3.3)</td>
<td>Roberts</td>
<td>Across the US</td>
</tr>
<tr>
<td></td>
<td>1.92 (1.36, 2.71)</td>
<td>Windham</td>
<td>San Francisco Bay area, CA</td>
</tr>
<tr>
<td>Nickel</td>
<td>1.7 (1.1, 2.5)</td>
<td>Roberts</td>
<td>Across the US</td>
</tr>
<tr>
<td></td>
<td>1.46 (1.04, 2.06)</td>
<td>Windham</td>
<td>San Francisco Bay area, CA</td>
</tr>
<tr>
<td>Styrene</td>
<td>1.97 (1.13, 3.43)</td>
<td>Talbott</td>
<td>Western Pennsylvania</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1.47 (1.03, 2.08)</td>
<td>Windham</td>
<td>San Francisco Bay area, CA</td>
</tr>
<tr>
<td>Vinyl Chloride</td>
<td>1.75 (1.25, 2.43)</td>
<td>Windham</td>
<td>San Francisco Bay area, CA</td>
</tr>
<tr>
<td>PAH</td>
<td>1.52 (1.00, 2.30)</td>
<td>Talbott</td>
<td>Western Pennsylvania</td>
</tr>
</tbody>
</table>

Proximity:

- Highways
  - Volk, 2011
- Agricultural pesticide use
  - Roberts, 2007
- Industry - TRI sites
  - Palmer, 2009
Findings using proximity to represent exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Association with ASD</th>
<th>How close is exposed group</th>
<th>Investigator</th>
<th>Study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury emitting TRI sites</td>
<td>2% decrease</td>
<td>Per each 10 miles</td>
<td>Palmer</td>
<td>Texas</td>
</tr>
<tr>
<td>Agricultural pesticide use (organochlorines)</td>
<td>6.1 (2.4, 15.3)</td>
<td>≤ 500 m</td>
<td>Roberts</td>
<td>California</td>
</tr>
<tr>
<td>Highways</td>
<td>1.86 (1.04, 3.45)</td>
<td>≤ 309 m</td>
<td>Volk</td>
<td>California</td>
</tr>
</tbody>
</table>

Air Monitor Data: Exposure Assessment

- Assign concentration of nearest monitor
  - Becerra, 2013
  - von Ehrenstein, 2014

- Use monitor data to create an exposure surface with air modeling techniques
  - Becerra, 2013 → Land Use Regression (LUR)
  - Jung, 2013 → Inverse distance weighting (IDW)
  - Volk, 2013 → CALINE4 line-source air quality dispersion model (traffic-related air pollution) and IDW
  - Talbott, 2015 → LUR (not yet published)
## Findings using air monitor data: CAPs

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Odds Ratio (95% CI)</th>
<th>Exposure measure</th>
<th>Investigator</th>
<th>Study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>1.49 (1.23, 1.81)</td>
<td>IQR (13.6 ng/m³)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>1.37 (1.31, 1.44)*</td>
<td>100 ppb</td>
<td>Jung</td>
<td>Taiwan</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>1.07 (1.03, 1.12)</td>
<td>IQR (5.41 ppb)</td>
<td>Becerra</td>
<td>Los Angeles County, CA</td>
</tr>
<tr>
<td></td>
<td>4.43 (3.33, 5.90)*</td>
<td>10 ppb</td>
<td>Jung</td>
<td>Taiwan</td>
</tr>
<tr>
<td></td>
<td>1.81 (1.23, 2.65)</td>
<td>2 SD (14.1 ppb)</td>
<td>Volk</td>
<td>California</td>
</tr>
<tr>
<td>Ozone</td>
<td>1.06 (1.01, 1.12)</td>
<td>IQR (11.54 ppb)</td>
<td>Becerra</td>
<td>Los Angeles County, CA</td>
</tr>
<tr>
<td></td>
<td>1.59 (1.42, 1.78)*</td>
<td>10 ppb</td>
<td>Jung</td>
<td>Taiwan</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>1.15 (1.06, 1.24)**</td>
<td>IQR (4.68 µg/m³)</td>
<td>Becerra</td>
<td>Los Angeles, CA</td>
</tr>
<tr>
<td></td>
<td>2.08 (1.93, 2.25)</td>
<td>2 SD (8.7 µg/m³)</td>
<td>Volk</td>
<td>California</td>
</tr>
<tr>
<td></td>
<td>1.50 (1.16, 1.94)</td>
<td>IQR (4.40 µg/m³)</td>
<td>Raz</td>
<td>Across the US</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>2.17 (1.49, 3.16)</td>
<td>2 SD (14.6 µg/m³)</td>
<td>Volk</td>
<td>California</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>1.18 (1.09, 1.28)*</td>
<td>1 ppb</td>
<td>Jung</td>
<td>Taiwan</td>
</tr>
</tbody>
</table>

SD = standard deviation; IQR = interquartile range; * = hazard ratio; ** = only in the model that also includes ozone

## Findings using air monitor data: HAPs

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Odds Ratio(s) (95% CI)</th>
<th>Exposure measure</th>
<th>Investigator</th>
<th>Study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde</td>
<td>1.20 (1.07, 1.34)</td>
<td>IQR (0.50 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>1.34 (1.17, 1.52)</td>
<td>IQR (1.93 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Copper</td>
<td>1.09 (1.02, 1.16)</td>
<td>IQR (0.10 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Benzene</td>
<td>1.46 (1.12, 1.89)</td>
<td>IQR (0.78 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>1.59 (1.18, 2.15)</td>
<td>IQR (0.28 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>1.48 (1.25, 1.75)</td>
<td>IQR (0.19 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Toluene</td>
<td>1.37 (1.12, 1.67)</td>
<td>IQR (1.68 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Xylene: ortho</td>
<td>1.42 (1.19, 1.70)</td>
<td>IQR (0.28 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Meta/para</td>
<td>1.51 (1.26, 1.82)</td>
<td>IQR (0.88 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Perchloroethylene</td>
<td>1.40 (1.09, 1.80)</td>
<td>IQR (0.24 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1.14 (1.03, 1.27)</td>
<td>IQR (0.14 ppb)</td>
<td>von Ehrenstein</td>
<td>California</td>
</tr>
<tr>
<td>Traffic-related air pollution</td>
<td>1.98 (1.20, 3.31)</td>
<td>≥ 31.8 ppb to 9.7 ppb</td>
<td>Volk</td>
<td>California</td>
</tr>
</tbody>
</table>
Strengths of previous studies

- Individual level data for adjustment
- ASD cases diagnosed by a physician
- Use of birth certificates
  - Representative population control
  - Unbiased ascertainment of risk factors
  - Limitations in data collection are non-differential
- Some have looked at other interesting questions
  - Affect of exposure in males only and in females only
  - Affect of exposure during critical pregnancy time periods

Limitations of previous studies

- Exposure assessment
  - NATA lacks spatial and temporal precision
  - Proximity measures do not take meteorology into account
- Most assessed exposure at residence of birth only, no consideration for
  - Moving during pregnancy
  - Any exposures outside of residence or residential census tract
- Air exposure to pollutants only
  - Water, soil, and food are also potential sources of exposure
Future directions

• National autism registry
• Improved spatial and temporal ascertainment of exposures
  • Monitored levels of air pollutants
  • Assess exposure by gestational age
• Investigate gene/environment interactions

Interaction of Genes and Environment

Volk, 2014

• Children with highest quartile of exposure to nitrogen dioxide AND the MET CC genotype were statistically significantly more likely to have ASD than children with in lower quartiles of exposure AND the MET CG or GG genotype.
• PM$_{10}$ exposure has a significant association with ASD regardless of MET genotype (although the association is stronger for the CC genotype).