A Tale of Traffic and Smog: How the Air We Breathe Can Affect the Developing Brain

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Autism Spectrum Disorder

**SOCIAL SKILLS**
- nonverbal interactions
- friendship
- joint attention
- reciprocity

**COMMUNICATION**
- language
- conversation
- play

**UNUSUAL BEHAVIORS**
- obsessive interests
- rigid rituals
- preoccupation with parts of objects
ASD Prevalence in the United States

Statistics from the Autism and Developmental Disabilities Monitoring Network (ADDM)

<table>
<thead>
<tr>
<th>Surveillance Year</th>
<th>Birth Year</th>
<th>Number Locations</th>
<th>Prevalence per 1,000 Children</th>
<th>~ 1 in X children...</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>1992</td>
<td>6</td>
<td>6.7</td>
<td>1/150</td>
</tr>
<tr>
<td>2002</td>
<td>1994</td>
<td>14</td>
<td>6.6</td>
<td>1/150</td>
</tr>
<tr>
<td>2004</td>
<td>1996</td>
<td>8</td>
<td>8.0</td>
<td>1/125</td>
</tr>
<tr>
<td>2006</td>
<td>1998</td>
<td>11</td>
<td>9.0</td>
<td>1/110</td>
</tr>
<tr>
<td>2008</td>
<td>2000</td>
<td>14</td>
<td>11.3</td>
<td>1/88</td>
</tr>
<tr>
<td>2010</td>
<td>2002</td>
<td>11</td>
<td>14.7</td>
<td>1/68</td>
</tr>
</tbody>
</table>
Family History

More likely to have ASD diagnosis if have a sibling with an ASD diagnosis

ASD indicates autism spectrum disorder. Shaded areas represent 95% 2-sided point-wise confidence interval bands. The siblings who had a full-sibling with ASD were followed for 76,481 person-years resulting in 634 ASD events. The siblings who had a full sibling without ASD were followed for 35,486,922 person-years resulting in 17,327 ASD events.
Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study

Sally Ozonoff, Gregory S. Young, Alice Carter, Daniel Messinger, Nurit Yirmiya, Lonnie Zwaigenbaum, Susan Bryson, Leslie J. Carver, John N. Constantino, Karen Dobkins, Ted Hutman, Jana M. Iverson, Rebecca Landa, Sally J. Rogers, Marian Sigman and Wendy L. Stone

Pediatrics 2011;128:e488; originally published online August 15, 2011;
DOI: 10.1542/peds.2010-2825

abstract

OBJECTIVE: The recurrence risk of autism spectrum disorders (ASD) is estimated to be between 3% and 10%, but previous research was limited by small sample sizes and biases related to ascertainment, reporting, and stoppage factors. This study used prospective methods to obtain an updated estimate of sibling recurrence risk for ASD.

METHODS: A prospective longitudinal study of infants at risk for ASD was conducted by a multisite international network, the Baby Siblings Research Consortium. Infants ($n=664$) with an older biological sibling with ASD were followed from early in life to 36 months, when they were classified as having or not having ASD. An ASD classification required surpassing the cutoff of the Autism Diagnostic Observation Schedule and receiving a clinical diagnosis from an expert clinician.

RESULTS: A total of $18.7\%$ of the infants developed ASD. Infant gender and the presence of $>1$ older affected sibling were significant predictors of ASD outcome, and there was an almost threefold increase in risk for male subjects and an additional twofold increase in risk if there was $>1$ older affected sibling. The age of the infant at study enrollment, the gender and functioning level of the infant’s older sibling, and other demographic factors did not predict ASD outcome.

CONCLUSIONS: The sibling recurrence rate of ASD is higher than suggested by previous estimates. The size of the current sample and prospective nature of data collection minimized many limitations of previous studies of sibling recurrence. Clinical implications, including genetic counseling, are discussed. Pediatrics 2011;128:e488–e495
Genetic Influences on ASD

- 3% de novo (N)
- 4% non-additive (D)
- 3% rare inherited (A)
- 49% common inherited (A)
- 41% unaccounted

Environmental Effects and GxE Interactions

Adapted from Gaugler et al., 2014
Autism Causation is Multifactorial

Likely to be many causes across the population and within an individual...

More Rare: 1 Cause

Possible: 2 Causes

More Common: 3 or More Causes

...from both genes and / or the environment(s)
Early Life Exposure Matters
Los Angeles

Beijing

London

New York

We are ALL exposed....
...air pollution involves more than just cars...
Air Pollution Is A Mixture

**Gases**
- Nitrogen Dioxide
- Ozone
- & More

**Particles**
- Coarse
- Fine
- Ultrafine
- Metals

**Volatile Agents**
- Polycyclic Aromatic Hydrocarbons
- & More
What Do We Mean When We Talk About Particles?
Health Effects of Air Pollution

- Cardiovascular Morbidity & Mortality
- CNS (Neurological)
- Respiratory Morbidity & Mortality
- Perinatal Development
- Assorted Birth Outcomes
- Cancer

MATES-III Modeled Cancer Risk
What Can Animal Studies Tell Us?

Direct Effects of Exposure
• Re-aerosolized UFPM from LA roadways
  – Increased inflammation in brain
  – Inflammatory cytokine activation
  – Changes in neuronal growth and differentiation
  – Depression symptoms

Trans-placental Effects
• *In utero* DEP exposure
  – Inflammation in brains of exposed pups
  – Male-specific effects

Kleinman et al., 2008
Morgan et al., 2011
Davis et al., 2013
Bolton et al., 2013
So What Does Air Pollution Do To the Brain?

Same Number

Different Differentiation

Less Fully Developed and Differentiated
Exposure to vehicle emissions results in altered blood brain barrier permeability and expression of matrix metalloproteinases and tight junction proteins in mice

Hannah A Oppenheim¹, JoAnn Lucero¹, Anne-Cécile Guyot², Lindsay M Herbert³, Jacob D McDonald¹, Aloïse Mabondzo² and Amie K Lund¹,⁴*

Conclusions: These data indicate that inhalation exposure to traffic-generated air pollutants promotes increased MMP activity and degradation of TJ proteins in the cerebral vasculature, resulting in altered BBB permeability and expression of neuroinflammatory markers.

Leaky Blood Brain Barrier
So What Does Air Pollution Do To the Brain? Can It Even GET There?

Developmental Exposure to Concentrated Ambient Ultrafine Particulate Matter Air Pollution in Mice Results in Persistent and Sex-Dependent Behavioral Neurotoxicity and Glial Activation.

Although mechanisms of these effects remain to be fully elucidated, findings suggest that neurodevelopment and/or adulthood air pollution exposure may represent a significant underexplored risk factor for central nervous system diseases/disorders and thus a significant public health threat even beyond current appreciation.
How Do We Measure This In Humans?

Personal Monitoring

Biologic Measures of Exposure

Geographic Linkages To Monitoring Networks
Measures of Air Pollution
Air Pollution Exposure and Early Life Neurodevelopment

Figure 1. Estimated effects of prenatal PAH exposure on cognitive development in children 12 months through 36 months of age by GEE. The model was adjusted for the child’s exact age at test administration, child’s sex, ethnicity, gestational age at birth, quality of the (caretaking) home environment, and prenatal exposure to ETS and CPF.

Perera et al., 2006

Decreased cognitive development score with increasing exposure
Roadway Proximity and Cognitive Development at Age 8

Figure 1. Mean differences (95% CIs) in cognitive assessment scores associated with residential proximity to major roadway at birth. (A) Results for standardized cognitive assessment scores scaled to mean ± SD = 100 ± 15 (KBIT-2 verbal and nonverbal IQ; WRAVMA visual motor). (B) Results for standardized cognitive assessment scores scaled to mean ± SD = 10 ± 3 (WRAML2 design memory and picture memory). All models were adjusted for characteristics of child (age, sex, breastfeeding duration, early childhood blood lead), mother (age, parity, race/ethnicity, education, IQ, marital/cohabitation status, and blood lead, smoking, secondhand smoke exposure, and alcohol in pregnancy), father (education), household (income, home caretaking environment, gas stove), and neighborhood (census tract median income).

Harris et al., 2015
Air Pollutants and ASD

Hazardous Air Pollutants

- Mercury, cadmium, nickel, vinyl chloride, DEP
  - California
  - Windham et al., 2006

- Methylene chloride, styrene, quinoline
  - North Carolina
  - Kalkbrenner et al., 2010

- Styrene, chromium, PAH, methylene chloride
  - Pennsylvania
  - Talbott et al., 2015

- Metals (lead, manganese, mercury), methylene chloride, DEP
  - Across USA
  - Roberts et al., 2013

- Traffic and industry emissions
  - LA County
  - Von Ehrenstein et al., 2014
Particles and Metals

Figure 2. Association of ASD with air pollutant concentration, highest quintile versus lowest quintile ORs by Wald two-sided $p$-value, children of the Nurses’ Health Study II ($n = 22,101$ controls, $n = 325$ cases).

Roberts et al., 2013
Air Pollutants and ASD

Near Roadway Air Pollution and NO₂ in the US

- California
  - Volk et al., 2011, 2013
- LA County
  - Becerra et al., 2011

Studies from Abroad

- No association with NO₂ in 4 European birth cohorts
  - Guxens et al., 2016
- No association with NO₂ in Sweden
  - Gong et al., 2014
- NO₂, Ozone, SO₂, CO in Taiwan
  - Jung et al., 2013

Particulate Matter (PM₂.₅ and PM₁₀)

- California
  - Volk et al., 2013
- Across USA
  - Raz et al., 2015
- California and North Carolina
  - Kalkbrenner et al., 2014
- Pennsylvania
  - Talbott et al., 2015
- LA County
  - Becerra et al., 2013
Study Design

• Childhood Autism Risks From Genetics and the Environment (CHARGE) Study
  – Born 1996-2007

• Autism Cases
  – First diagnosed by Regional Center (Department of Developmental Services (DDS)) or clinical referral
  – Positive for autism on gold standard assessments

• Controls
  – Typically developing children from birth records

NIEHS R01 ES015359, PI: Hertz-Picciotto
Air Pollution In CHARGE

CA Standard = 12 ug/m³

CA Standard = 20 ug/m³

CA Standard = 30 ppb
### Distance From Freeway at Birth
(304 Cases and 259 Controls)

<table>
<thead>
<tr>
<th>Birth Address</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Address &lt;309m</td>
<td>1.86 (1.04-3.45)</td>
<td>1.86 (1.03-3.45)</td>
</tr>
<tr>
<td>Birth Address 309-647m</td>
<td>0.98 (0.60-1.59)</td>
<td>0.96 (0.58-1.56)</td>
</tr>
<tr>
<td>Birth Address 647-1419m</td>
<td>1.14 (0.76-1.71)</td>
<td>1.11 (0.73-1.67)</td>
</tr>
<tr>
<td>Birth Address &gt;1419</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Model adjusted for child male gender, child ethnicity (Hispanic vs. White, Black/Asian/Other vs. White), maximum education in home (college degree or more), maternal age > 35 years, and prenatal smoking

SCEHSC Pilot Project, PI: Volk

Volk, et al., 2011
Near Roadway Air Pollution
(279 Cases and 245 Controls)

Probability of ASD Increases as NRAP Increases
Regional Pollutant Exposure  
(279 Cases and 245 Controls)

<table>
<thead>
<tr>
<th></th>
<th>First Year of Life OR*</th>
<th>All Pregnancy OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$</td>
<td>2.12 (1.45-3.10)</td>
<td>2.08 (1.93-2.25)</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>2.14 (1.46-3.12)</td>
<td>2.17 (1.49-3.16)</td>
</tr>
<tr>
<td>Nitrogen Dioxide</td>
<td>2.06 (1.37-3.09)</td>
<td>1.81 (1.23-2.65)</td>
</tr>
<tr>
<td>Ozone</td>
<td>1.15 (0.72-1.86)</td>
<td>1.09 (0.76-1.55)</td>
</tr>
</tbody>
</table>

*Regional pollution effects reflect risk of autism based on 2 standard deviations from the mean value, specifically per increase of 8.8 mg/m3 PM$_{2.5}$, 12.4 mg/m3 PM$_{10}$, 9.0 ppb NO$_2$, and 13.6 ppb ozone. The top TRP quartile refers to estimated exposure levels of 30.4ppb or greater.

Models adjusted for child male gender, child ethnicity (Hispanic vs. White, Black/Asian/Other vs. White), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 years vs. 35 years), prenatal smoking, population density.

Volk, et al., 2013
NIEHS R21 ES19002, PI: McConnell, Co-I: Volk
What Do We Know So Far?

• Air Pollution Associated with ASD
• Air Pollution Associated with Worse Functioning in ASD

What Do We Want To Know Next?

• So How Might This Work?
• What’s the Responsible Ingredient?
Where Do Genes Fit In?

3% de novo (N)

4% non-additive (D)

3% rare inherited (A)

49% common inherited (A)

41% unaccounted

ASD liability

Environmental Effects and GxE Interactions

Adapted from Gaugler et al., 2014
Simple Model for Gene and Environment Effects

Adapted from Geschwind et al., 2008
Prenatal PAH Exposure Reduces MET Protein Expression in Mouse Cortex (Benzo(a)Pyrene)

Sheng et al., 2010
Replications of *MET* rs1858830 Variant Association with Autism

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Sample Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Campbell et al. 2006. <em>PNAS</em>.</td>
<td>Family-based and case-control</td>
<td>Italy (Rome 1)</td>
</tr>
<tr>
<td>2 Campbell et al. 2006. <em>PNAS</em>.</td>
<td>Family-based and case-control</td>
<td>NIMH</td>
</tr>
<tr>
<td>7 Jackson et al. 2009. <em>Autism Res.</em></td>
<td>Case-control</td>
<td>Italy (Rome 2)</td>
</tr>
<tr>
<td>8 Thanseem et al. 2010. <em>Neurosci Res.</em></td>
<td>Family-based</td>
<td>Japan</td>
</tr>
<tr>
<td>9 Thanseem et al. 2010. <em>Neurosci Res.</em></td>
<td>Family-based</td>
<td>AGRE</td>
</tr>
<tr>
<td>10 Rajamma et al. 2011. SfN poster</td>
<td>Family-based</td>
<td>India</td>
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</table>
Joint Effect of *MET* rs1858830 and Air Pollution

<table>
<thead>
<tr>
<th>Near Roadway Air Pollution</th>
<th>MET rs1858830 Genotype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C/C</td>
<td>C/G or G/G</td>
</tr>
<tr>
<td>Exposed</td>
<td>2.9 (1.0-10.4)</td>
<td>1.3 (0.73-2.2)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>0.80 (0.47-1.4)</td>
<td>reference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Nitrogen Dioxide</th>
<th>MET rs1858830 Genotype</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C/C</td>
<td>C/G or G/G</td>
</tr>
<tr>
<td>Exposed</td>
<td>3.6 (1.3-12.7)</td>
<td>1.2 (0.71-2.1)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>0.72 (0.41-1.3)</td>
<td>reference</td>
</tr>
</tbody>
</table>

Volk et al, 2014
What Are The Next Steps?

Figure 6. EARLI Network core protocol data collection schedule
Prospective Evaluation of Air Pollution, Cognition, and Autistic Traits from Birth Onward (PEACABO)

• Collaboration with At-risk Infant Sibling Study Designs
  – Early Autism Risk Longitudinal Investigation (EARLI)
    • R01 ES016443 (Newschaffer)
  – Markers of Autism Risk in Babies-Learning Early Signs (MARBLES)
    • R01 ES020392 (Hertz-Picciotto)
Air Pollution on Development and ASD Over Time

Prenatal Exposure
Modeled Residential Exposure
Polycyclic Aromatic Hydrocarbon (PAH) Biomarkers

6, 12, 24, and 36 months
Cognitive Development
Adaptive Function
ASD and Related Traits

NIEHS R01 ES023780, PI: Volk
Virtual Consortium for Transdisciplinary Environmental Research (ViCTER)

• Understand the MECHANISM of the effect of air pollution on ASD
• Combine Both Human and Animal Models
Traffic and PM2.5 Prenatal Exposure

Child Cognitive Development ASD and Related Traits

Step 1 RNA seq Behavior

Step 2 Gene Expression Epigenetic Effects

Step 3 Genetic Associations

Prenatal Exposure Traffic and PM$_{2.5}$

12, 24, and 36 months Child Cognitive Development

ASD and Related Traits
Air Pollution Exposure Effects on Brain Structure

Effects of Prenatal Exposure to Air Pollutants (Polycyclic Aromatic Hydrocarbons) on the Development of Brain White Matter, Cognition, and Behavior in Later Childhood

Bradley S. Peterson, MD; Virginia A. Rauh, ScD; Ravi Bansal, PhD; Xuejun Hao, PhD; Zachary Toth, BA; Giancarlo Nati, BA; Kirwan Walsh, BA; Rachel L. Miller, MD; Franchesca Arias, MS; David Semanek, BA; Frederica Perera, DrPH, PhD

CONCLUSIONS AND RELEVANCE Our findings suggest that prenatal exposure to PAH air pollutants contributes to slower processing speed, attention-deficit/hyperactivity disorder symptoms, and externalizing problems in urban youth by disrupting the development of left hemisphere white matter, whereas postnatal PAH exposure contributes to additional disturbances in the development of white matter in dorsal prefrontal regions.

Peterson et al., 2015
IBIS Collaboration

Enrollment, 12, and 24 months
Brain Volume, Surface Area, EAF Volume, CC Morphology, WM Fiber Tract Structure

Prenatal Exposure
Modeled Residential Exposure

6, 12, 24 and 36 months
MSEL and VABS
ASD and Related Traits
Given the general consistency of findings across studies and the exposure-window-specific associations recently reported, the overall evidence for a causal association between air pollution and ASD is increasingly compelling.
What Might Be the Impact?

Population Attributable Risk Percent

\[=\]

The percent of cases that would **NOT** occur if that risk factor were eliminated
What Might Be The Impact?

We have room for improvement!

Population Attributable Risk Percent

% Population Exposed to Air Pollution

OR = 2.0
OR = 1.5
OR = 1.1
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