NEURODEVELOPMENTAL EFFECTS

Health Effects Institute 2019 Annual Conference
Early-Life Exposure to Air Pollution

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Overview

• Introduction to neurodevelopmental outcomes
  • Vulnerability of the developing brain
  • Neuropsychological assessment

• Air pollution and neurodevelopment
  • Prenatal exposure
  • Childhood exposure

• Discussion and future directions
Brain development continues after birth

Developmental course of human brain development

- Experience-dependent synapse formation and dendritic arborization
- Prefrontal cortex
- Parietal and temporal association cortex
- Sensorimotor cortex
- Synaptogenesis and synaptic pruning

Myelination

Neurulation

- Cell proliferation and migration

Conception

-8 -6 -4 -2 0 2 4 6 8 10 Months

Birth

Years

0 2 4 6 8 10 12 14 16 18 20
Neurotoxicants

Fetal alcohol syndrome

Mercury poisoning Minimata, Japan

Lead
Environmental pollutants with known or potential neurotoxic effects

- Metals (arsenic, lead, mercury)
- Persistent organic pollutants (PCBs, PBDEs, PFASs)
- Solvents (ethanol, toluene)
- Pesticides (organophosphates)
- Consumer products chemicals
  - (e.g., phthalates, BPA, phenols)
- Air pollution, second hand smoke
Neurodevelopmental domains

- Language/verbal skills
- Memory and learning
- Visuospatial abilities
- Motor function
- Attention
- Executive function/working memory
- Behavioral inhibition
- Social behavior

- Domains may be differentially sensitive to environmental exposures
Neuropsychological assessment

• Types of assessment
  • Neuropsychological performance
  • Reporting scales (parent, teacher, self)

• Battery of tests designed by a neuropsychologist

• Impairment measured on a continuum
  • Along dimensions/domains

• Diagnosis of developmental disorder
  • Extreme impairment can result in classification of a neurodevelopmental disorder, e.g. ADHD, autism spectrum disorder, intellectual disability

ADHD = Attention-deficit/hyperactivity disorder
Intellectual disability
ADHD = Attention-deficit/hyperactivity disorder

Attention, impulsivity/hyperactivity

ADHD = Attention-deficit/hyperactivity disorder
Autism Spectrum Disorder

Social behavior (social communication, restricted interests and repetitive behaviors)
Public health significance

• Prevalence of neurodevelopmental disorders is high and rising, e.g., ADHD (5-10%), autism (1.5-2%)
  • *Increasing incidence?*

• Features persist across the life course

• Impacts on long-term health and well-being (*among those with and without clinical diagnosis*)
  • Education and employment
  • Mental health, e.g., anxiety, depression
  • Behavioral health, e.g., substance use
  • Higher morbidity, risk for early mortality

ADHD = Attention-deficit/hyperactivity disorder
AIR POLLUTION AND NEURODEVELOPMENT
Air pollution: a complex mixture

- EPA criteria pollutants
- Traffic-related pollutants (PM, NO₂)
- Distance to roadways, traffic density
- Polycyclic aromatic hydrocarbons (PAHs)

- 2 fractions of particulate matter most relevant to CNS:
  - PM₂.₅: particles with a diameter < 2.5 μm
  - Ultrafine PM (UFPM): particles with a diameter < 100 nm

- PM as a vehicle for neurotoxicants
  - E.g., metals, organics

PM = particulate matter
NO₂ = nitrogen dioxide
CNS = central nervous system
PRENATAL EXPOSURE
Biologic plausibility

- Cross placenta
- Fetal growth
- Prenatal neurodevelopment
- Air pollution
- Maternal infection, inflammation
Prenatal PAHs and MRI (n=40, NYC)

Prenatal PAHs associated with lower volume of cerebral surface in left hemisphere

Derive from reductions in white matter

Peterson et al. JAMA Psychiatry 2015. 72(6): 531-40

PAHs = polycyclic aromatic hydrocarbons
MRI = magnetic resonance imaging
Mediated effects on performance/behavior

- Slower processing speed
- More ADHD-related behaviors

PAHs = polycyclic aromatic hydrocarbons
ADHD = Attention-deficit/hyperactivity disorder
Roadway proximity & IQ, visual motor age 7-10y
(Proposal Viva: Boston, MA, n=1,109)

Null associations for PM$_{2.5}$ and black carbon


PM$_{2.5}$ = fine particulate matter
NO₂ & road traffic and Full Scale and Verbal IQ
(Gene and Environment Prospective Study on Infancy in Italy (GASPII), n=474)

NO$_2$ & PM$_{2.5}$ and psychomotor age 1-6y
(European Study of Cohorts for Air Pollution Effects (ESCAPE): pooled analysis of 6 European Cohorts, n=9,482)

- **BUT general cognition and language development not associated with any of the studied pollutant exposures (but most children assessed at age 2 or younger)**

NO$_2$ and attention at 4-5y
(Spanish INMA Project n=1,298)

**Omission Errors**

<table>
<thead>
<tr>
<th>Region</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabadell</td>
<td>1.08 (1.00, 1.17)</td>
</tr>
<tr>
<td>Valencia</td>
<td>1.06 (0.98, 1.15)</td>
</tr>
<tr>
<td>Asturias</td>
<td>1.07 (0.93, 1.22)</td>
</tr>
<tr>
<td>Gipuzkoa</td>
<td>0.96 (0.82, 1.13)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.06 (1.01, 1.11)</td>
</tr>
<tr>
<td>(I-squared = 0.0%, p = 0.648)</td>
<td></td>
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</tbody>
</table>

**Response time variability**

<table>
<thead>
<tr>
<th>Region</th>
<th>Coef (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabadell</td>
<td>1.03 (-0.77, 2.83)</td>
</tr>
<tr>
<td>Valencia</td>
<td>1.03 (-0.11, 2.18)</td>
</tr>
<tr>
<td>Asturias</td>
<td>2.15 (-0.89, 5.18)</td>
</tr>
<tr>
<td>Gipuzkoa</td>
<td>0.85 (-3.00, 4.70)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.12 (0.22, 2.02)</td>
</tr>
<tr>
<td>(I-squared = 0.0%, p = 0.921)</td>
<td></td>
</tr>
</tbody>
</table>


NO$_2$ = nitrogen dioxide
NO$_2$ & PM$_{2.5}$ and ADHD symptoms age 3-10y
(ESCAPE: pooled analysis of 8 European Cohorts, n=29,127)


ADHD = Attention-deficit/hyperactivity disorder
PM$_{2.5}$ = fine particulate matter
NO$_2$ = nitrogen dioxide
Study design advantages of air pollution

• Prenatal exposures → prospective study design
  • Typically requires a birth cohort study to measure exposure during the relevant time period (pregnancy)
  • Underpowered to look at neurodevelopmental disorders (typically focus on quantitative traits)

• BUT: Air pollution less subject to these constraints
  • Exposure can be assessed via residential history
  • Adequate power to look at neurodevelopmental disorders
PM$_{2.5}$ and Autism Spectrum Disorders (ASD)

<table>
<thead>
<tr>
<th>Source</th>
<th>PM$_{2.5}$ (per 10 μg/m$^3$)</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becerra et al, 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guxens et al, 2016</td>
<td></td>
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<tr>
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<tr>
<td>Meta-analyses</td>
<td></td>
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</tr>
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<td>Flores-Pajot et al, 2016</td>
<td></td>
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</tr>
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<td></td>
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</tr>
</tbody>
</table>

PM$_{2.5}$ and Autism Spectrum Disorders (ASD)

Associations with autistic traits

<table>
<thead>
<tr>
<th>Source</th>
<th>Cohort study, country-area</th>
<th>Test</th>
<th>Age</th>
<th>PM$_{2.5}$ (per Δ5 μg/m$^3$)</th>
<th>OR (95% CI)</th>
<th>% weight</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becerra et al, 2013</td>
<td>CATSS, Sweden</td>
<td>A-TAC</td>
<td>10y</td>
<td></td>
<td>0.08 (0.01, 0.68)</td>
<td>7.97</td>
<td>1,585</td>
</tr>
<tr>
<td>Guxens et al, 2016</td>
<td>GENERATION R, The Netherlands</td>
<td>CBCL</td>
<td>6y</td>
<td></td>
<td>0.76 (0.53, 1.11)</td>
<td>44.72</td>
<td>3,706</td>
</tr>
<tr>
<td>Raz et al, 2015</td>
<td>GASPII, Italy</td>
<td>CBCL</td>
<td>4y</td>
<td></td>
<td>1.20 (0.73, 1.97)</td>
<td>40.17</td>
<td>475</td>
</tr>
<tr>
<td>Talbott et al, 2015</td>
<td>INMA, Spain-Sabadell</td>
<td>CAST</td>
<td>4y</td>
<td></td>
<td>0.28 (0.03, 2.73)</td>
<td>7.14</td>
<td>271</td>
</tr>
<tr>
<td>Volk et al, 2013</td>
<td>Overall (I$^2$ = 61.2%, p = 0.052)</td>
<td>CAST</td>
<td>4y</td>
<td></td>
<td>0.71 (0.37, 1.37)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Note: Weights are from

**NO₂ and Autism Spectrum Disorder (ASD)**

**Source**
- This study
- Becerra et al, 2013
- Guxens et al, 2016
- Raz et al, 2015
- Raz et al, 2017
- Talbott et al, 2015
- Volk et al, 2013

**Meta-analyses**
- Flores-Pajot et al, 2016
- Lam et al, 2016

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NO$_2$ and Autism Spectrum Disorder (ASD)

Associations with autistic traits

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Year</th>
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<td>This study</td>
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<td>2016</td>
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<tr>
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<td>2016</td>
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CHILDHOOD EXPOSURE
Children are not small adults!

- immature blood brain barrier
- rapid brain development
- higher breathing rate to body size ratio
- ↑ time spent outdoors
Inhaled airborne PM via nasal epithelium

Passage of pollutants in blood serum through BBB


BBB = blood brain barrier
PM = particulate matter
Black carbon and cognition at age 9y
(Maternal-Infant Smoking Study of East Boston, n=202)

TABLE 2. Relation of predicted black carbon levels (average of summer and winter) at children’s residences to scores on subscales of the Kaufman Brief Intelligence Test in linear regression models (n = 202), Maternal Infant Smoking Study of East Boston, 1986–2001†

<table>
<thead>
<tr>
<th>Black carbon model</th>
<th>Vocabulary</th>
<th>Matrices</th>
<th>Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI‡</td>
<td>Estimate</td>
</tr>
<tr>
<td>Adjusted for demographic factors§</td>
<td>-2.0</td>
<td>-5.3, 1.3</td>
<td>-4.2</td>
</tr>
<tr>
<td>Adjusted for above factors + in-utero tobacco smoke + secondhand smoke</td>
<td>-2.0</td>
<td>-5.3, 1.4</td>
<td>-4.0</td>
</tr>
<tr>
<td>Adjusted for above factors + birth weight</td>
<td>-2.0</td>
<td>-5.4, 1.3</td>
<td>-4.0</td>
</tr>
<tr>
<td>Adjusted for above factors + blood lead level</td>
<td>-2.2</td>
<td>-5.5, 1.1</td>
<td>-4.0</td>
</tr>
</tbody>
</table>

* p < 0.05.
† Change in subscale score per interquartile-range (0.4-μg/m³) increase in log black carbon level.
‡ CI, confidence interval.
§ Adjusted for age, gender, primary language spoken at home, and mother’s education.

Black carbon executive function at 7y (Project Viva, Boston, MA, n=1,212)

Harris et al. Neurotox and Teratology 2016. 57:60-70
Mean Difference in Teacher-Rated BRIEF BRI score per IQR Increase in Black Carbon Exposure

Year 1: 0.2
Year 2: 0.6
Year 3: 0.9
Year 4: 1.4
Year 5: 1.4
Year 6: 1.6
Birth-Age 6: 1.0

IQR = interquartile range

Harris et al. Neurotox and Teratology 2016. 57:60-70
Prenatal vs. infant AP exposure and ASD (Denmark nation-wide (ca=15,387;co=68,139))

<table>
<thead>
<tr>
<th>Exposure (IQR ↑)</th>
<th>Exposure period</th>
<th>OR (95% CI) Unadjusted(^a)</th>
<th>Adjusted(^b)</th>
<th>Mutually adjusted(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{NO}_2)</td>
<td>Pregnancy</td>
<td>1.19 (1.16, 1.22)</td>
<td>1.10 (1.06, 1.13)</td>
<td>1.00 (0.93, 1.08)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.20 (1.17, 1.23)</td>
<td>1.11 (1.07, 1.14)</td>
<td>\textbf{1.08 (1.01, 1.15)}</td>
</tr>
<tr>
<td>(\text{SO}_2)</td>
<td>Pregnancy</td>
<td>1.29 (1.23, 1.35)</td>
<td>1.12 (1.07, 1.18)</td>
<td>0.96 (0.90, 1.04)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.38 (1.31, 1.45)</td>
<td>1.21 (1.15, 1.28)</td>
<td>\textbf{1.21 (1.13, 1.29)}</td>
</tr>
<tr>
<td>(\text{PM}_{10})</td>
<td>Pregnancy</td>
<td>0.99 (0.95, 1.02)</td>
<td>0.97 (0.94, 1.01)</td>
<td>0.95 (0.91, 1.00)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.03 (0.99, 1.06)</td>
<td>1.01 (0.97, 1.05)</td>
<td>\textbf{1.04 (1.00, 1.09)}</td>
</tr>
<tr>
<td>(\text{PM}_{2.5})</td>
<td>Pregnancy</td>
<td>1.06 (1.02, 1.11)</td>
<td>1.00 (0.96, 1.04)</td>
<td>0.96 (0.91, 1.02)</td>
</tr>
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<td>1.11 (1.07, 1.15)</td>
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</tbody>
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\(\text{AP} = \text{air pollution}\)
\(\text{ASD} = \text{Autism Spectrum Disorder}\)
\(\text{OR} = \text{odds ratio}\)
\(\text{CI} = \text{confidence interval}\)
Prenatal vs. infant NO$_2$ and ASD
(Israel nation-wide (ca=2,098; co=54,191))


BREATHE Study

Brain Development and Air Pollution Ultrafine Particles in School Children

- 39 schools in Barcelona
- High vs. low traffic
- Matched on socioeconomic status
- N=2,897 age 7-10y

Elemental carbon and behavior (BREATHE Study, n=2,714)

<table>
<thead>
<tr>
<th>Variable</th>
<th>EC indoor IQR = 1.01 µg/m³</th>
<th>EC outdoor IQR = 0.86 µg/m³</th>
<th>NO₂ indoor IQR = 21.01 µg/m³</th>
<th>NO₂ outdoor IQR = 22.26 µg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total difficulties score (SDQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-exposure</td>
<td>1.07 (1.01, 1.12)*</td>
<td></td>
<td>1.02 (0.96, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Multi-exposure</td>
<td>1.08 (1.02, 1.14)**</td>
<td></td>
<td>1.02 (0.95, 1.10)</td>
<td></td>
</tr>
<tr>
<td>Outdoor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-exposure</td>
<td>1.07 (1.03, 1.12)**</td>
<td></td>
<td>1.07 (1.01, 1.14)*</td>
<td></td>
</tr>
<tr>
<td>Multi-exposure</td>
<td>1.08 (1.03, 1.13)**</td>
<td></td>
<td>1.08 (1.01, 1.16)*</td>
<td></td>
</tr>
</tbody>
</table>

NO₂ = nitrogen dioxide  
IQR = interquartile range

“Acute” associations of NO₂ with attention (BREATHE Study)

Sunyer et al. Epidemiology 2017. 28(2): 181-189

NO₂ = nitrogen dioxide
Discussion

• Neurodevelopmental outcomes: complex, sensitive and important

• Number of studies on air pollution and neurodevelopment have exploded in the last 5-10 years
air pollution AND (neurodevelopment* OR cogniti* OR ADHD OR autism OR intell* OR behavior*)
air pollution AND autism

Number of Publications

Year

Discussion

• Neurodevelopmental outcomes: complex, sensitive and important

• Number of studies on air pollution and neurodevelopment have exploded in the last 5-10 years

• Literature shows associations of both prenatal and childhood air pollution exposure with adverse cognitive and behavioral function
  • Child exposure associated with higher risk for some endpoints?

• Regulatory implications
  • Fetuses and children more vulnerable to neurodevelopmental impacts of air pollution
Thoughts on Future Directions

• Cognitive/behavioral domains vulnerable to air pollution

• Critical time windows during prenatal AND postnatal periods
  • More investigation of childhood exposure and “acute” effects

• Autism Spectrum Disorder (ASD) associations: inconsistency between U.S. and European studies

• Residual confounding (e.g., socioeconomic status, noise)

• Accounting for air pollution mixtures
  • Particulate matter → chemical composition

• Ultra fine particles

• Neuroimaging
Thank you for your attention!

*Thanks to Maria Harris for providing some of the slides for this talk