Neurotoxic effects of air pollution in early life

Mònica Guxens, MD MPH PhD
Assistant Research Professor

HEI’s 2015 Annual Conference
Philadelphia
May 5th 2015
Minamata 1956
Effects of prenatal exposure to mercury

- Outbreak of an unknown disease of the central nervous system
- Symptoms include ataxia, general muscle weakness, and damage of vision, hearing and speech
- In extreme cases, paralysis, coma, and death follow within weeks of the onset of symptoms
Lesson from Minamata

...in every case the mother was healthy, and it was not until more than three months after birth that the symptoms were recognized

Shoji Kitamura (1959)
“You have only one chance to develop a brain” – Prof. Philippe Grandjean

How do air pollutants reach the brain?
- based on animal studies -

Conceptual framework of the neuropsychological developmental process

Forns et al. Neuroepidemiology. 2012;38:203-8
How do we assess children’s neuropsychological development?

- Psychologist
- Computer-based tests
- Reported by mother, father, teacher, child himself

<table>
<thead>
<tr>
<th>Hyperactivity Scale</th>
<th>Not True</th>
<th>Somewhat True</th>
<th>Certainly True</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restless, overactive, cannot stay still for long</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Constantly fidgeting or squirming</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

- Clinical diagnosis by a doctor
Personal prenatal exposure to air pollution

Columbia Center for Children’s Environmental Health – F. Perera

Krakow, Poland

New York City
Personal prenatal exposure to air pollution

Columbia Center for Children’s Environmental Health – F. Perera

Birth cohort studies

3rd trimester pregnancy  Delivery  1 year  2 years  3 years  5 years  7 years  9 years

Personal monitor PAH - 48h  Maternal / Cord blood PAH-DNA adduct  Cognition (IQ), Psychomotor, Behaviour problems, Brain structural and functional MRI
# Personal prenatal exposure to air pollution

<table>
<thead>
<tr>
<th></th>
<th>1y NYC PAH air</th>
<th>2y NYC PAH air</th>
<th>3y NYC PAH air</th>
<th>5y NYC PAH air</th>
<th>7y NYC PAH-DNA cord blood</th>
<th>9y NYC PAH-DNA cord blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General cognition (IQ)</strong></td>
<td>—</td>
<td>—</td>
<td>✓</td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Verbal</strong></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Non-verbal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Psychomotor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total behaviour problems</strong></td>
<td>—</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td><strong>Anxious/depressed</strong></td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td><strong>DSM-Anxiety problems</strong></td>
<td>—</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td><strong>Attention problems</strong></td>
<td>—</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>DSM-ADHD problems</strong></td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Aggressive behaviour</strong></td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Other subscales</strong></td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Residential prenatal exposure to air pollution

ESCAPE Project – B. Brunekreef
Neuro working group – J. Sunyer/M. Guxens
Residential prenatal exposure to air pollution

ESCAPE Project – B. Brunekreef
Neuro working group – J. Sunyer/M. Guxens

Birth cohort studies
- Conception
- Delivery
- 1 year
- 2 years
- 3 years
- 4 years
- 5 years
- 6 years
- 7 years
- 10 years

Land use regression models –
Air pollution levels at participant’s address

Cognition (IQ), Psychomotor, Behaviour problems
Air Pollution During Pregnancy and Childhood Cognitive and Psychomotor Development

Six European Birth Cohorts


Epidemiology. 2014;25:636-47

Psychomotor development

N=9,482

A. NO₂ (per Δ10 μg/m³)

Cohort study, Country-region

GEN R, The Netherlands
DUISBURG, Germany
EDEN, France-Nancy
EDEN, France-Poitiers
GASPII, Italy
RHEA, Greece
INMA, Spain-Asturias
INMA, Spain-Gipuzkoa
INMA, Spain-Valencia
INMA, Spain-Sabadell
INMA, Spain-Granada

Overall -0.68 (-1.25, -0.10)
Air Pollution During Pregnancy and Childhood Cognitive and Psychomotor Development

Six European Birth Cohorts

Mònica Guxens, Raquel Garcia-Esteban, Lise Giorgis-Allemand, Joan Forns, Chiara Badaloni, Ferran Ballester, Rob Beelen, Giulia Cesaroni, Leda Chatzi, Maria de Agostini, Audrey de Nazelle, Marloes Eeftinck Schoppa, Francesco Forastiere, Ulrike Gehring, Akif M. Ceballos, Claudia Klümper, Manolis Kogevinas, Nerea Lertxundi, Mario Murcia, Vlado Vlaicu, Rosa Ramos, Theano Roumeliotaki, Rui Dorothea Sugiri, Adonina Tardón, Henn Tanja Vrijkotte, Michael Wilhelm.

N = 2,683

Cognitive development

Epidemiology. 2014;25:636-47
Air pollution exposure during pregnancy and childhood ADHD symptomatology in eight European cohort studies

Joan Forns, Raquel Garcia-Esteban, ..., Jordi Sunyer, Mònica Guxens

In preparation

<table>
<thead>
<tr>
<th>Cohort study, Country-area</th>
<th>Test</th>
<th>Age</th>
<th>OR (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATSS, Sweden</td>
<td>A-TAC</td>
<td>10y</td>
<td>0.79 (0.60, 1.05)</td>
<td>2439</td>
</tr>
<tr>
<td>DNBC, Denmark</td>
<td>SDQ</td>
<td>7y</td>
<td>0.94 (0.86, 1.03)</td>
<td>10049</td>
</tr>
<tr>
<td>ABCD, The Netherlands</td>
<td>SDQ</td>
<td>5y</td>
<td>0.85 (0.72, 1.00)</td>
<td>4223</td>
</tr>
<tr>
<td>GENERATION R, The Netherlands</td>
<td>CBCL 1/2-5</td>
<td>6y</td>
<td>0.89 (0.69, 1.16)</td>
<td>3718</td>
</tr>
<tr>
<td>GINI/LISA, Germany-Wesel</td>
<td>SDQ</td>
<td>10y</td>
<td>1.06 (0.70, 1.58)</td>
<td>1548</td>
</tr>
<tr>
<td>GINI/LISA, Germany-Munich</td>
<td>SDQ</td>
<td>10y</td>
<td>0.98 (0.76, 1.28)</td>
<td>2030</td>
</tr>
<tr>
<td>EDEN, France-Nancy</td>
<td>SDQ</td>
<td>3y</td>
<td>0.88 (0.64, 1.20)</td>
<td>395</td>
</tr>
<tr>
<td>EDEN, France-Poitiers</td>
<td>SDQ</td>
<td>3y</td>
<td>1.13 (0.60, 2.14)</td>
<td>386</td>
</tr>
<tr>
<td>GASPII, Italy</td>
<td>CBCL 1/2-5</td>
<td>4y</td>
<td>1.20 (0.93, 1.54)</td>
<td>483</td>
</tr>
<tr>
<td>INMA, Spain-Gipuzkoa</td>
<td>DSM-IV</td>
<td>4y</td>
<td>1.02 (0.26, 3.91)</td>
<td>284</td>
</tr>
<tr>
<td>INMA, Spain-Sabadell</td>
<td>DSM-IV</td>
<td>4y</td>
<td>1.03 (0.75, 1.41)</td>
<td>400</td>
</tr>
<tr>
<td>INMA, Spain-Valencia</td>
<td>DSM-IV</td>
<td>5y</td>
<td>0.98 (0.69, 1.40)</td>
<td>385</td>
</tr>
<tr>
<td>INMA, Spain-Granada</td>
<td>DSM-IV</td>
<td>4y</td>
<td>0.77 (0.43, 1.39)</td>
<td>121</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.752)</td>
<td></td>
<td></td>
<td>0.93 (0.88, 0.99)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

\[
\text{NO}_2 \text{ (per } \Delta 10 \text{ } \mu \text{g/m}^3) \]

N=26,461
Residential postnatal exposure to air pollution

Cincinnati Childhood Allergy and Air Pollution Study
Maternal-Infant Smoking Study of East Boston
INMA Project
Residential postnatal exposure to air pollution

Cincinnati Childhood Allergy and Air Pollution Study
Maternal-Infant Smoking Study of East Boston
INMA Project

Child cohort studies
- Delivery
- 1 year
- 4 years
- 7 years
- 8 years
- 11 years
- 14 years

Land use regression models – Air pollution levels at participant’s address
LUR models
Cognition (IQ), Psychomotor
LUR models
Cognition (IQ)
Behaviour problems
Attention function
## Residential postnatal exposure to air pollution

<table>
<thead>
<tr>
<th></th>
<th>INMA Project NO₂ 4y (n=210)</th>
<th>Cincinnati study EC 7y (n=576)</th>
<th>Boston study BC 7-14y (n=174)</th>
<th>Boston study BC 8-11y (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cognition (IQ)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>Verbal</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Non-verbal</td>
<td>—</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Memory</td>
<td>—</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Learning</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>Executive function</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>Working memory</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Attention function</td>
<td>—</td>
<td>—</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Gross motor</td>
<td>✓</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fine motor</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>✓</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Inattention</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Agression</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atypicality</td>
<td>—</td>
<td>—</td>
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</table>
Exposure to air pollution at school
Exposure to air pollution at school

<table>
<thead>
<tr>
<th></th>
<th>Breathe study EC, NO₂, UFP</th>
<th>Quanzhou NO₂, PM$_{10}$</th>
<th>Ranch study NO₂</th>
<th>Belgium study Combined traffic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-10y (n=2,715)</td>
<td>8-10y (n=861)</td>
<td>9-10y (n=719)</td>
<td>15y (n=606)</td>
</tr>
<tr>
<td></td>
<td>39 schools</td>
<td>2 schools</td>
<td>22 schools</td>
<td>---</td>
</tr>
<tr>
<td>Working memory</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Attention function</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuo-motor coordination</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-verbal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading comprehension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exposure to air pollution at school

Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study

Jordi Sunyer1,2,3,4, Mikel Esnaola1,2,3, Mar Alvarez-Pedrero1,2,3, Joan Forns1,2,3, Iloar Rivas1,2,3,5, Mònica López-Vicente1,2,3, Elisabet Suades-González1,2,3,6, Maria Foraster1,2,3, Raquel García-Esteban1,2,3, Xavier Basagaña1,2,3, Mar Viana5, Marta Cirach1,2,3, Teresa Moreno5, Andrés Alastuey5, Núria Sebastian-Galles2, Mark Nieuwenhuijsen1,2,3, Xavier Querol5


Dashed line = high traffic air pollution
Continuous line = low traffic air pollution
Gray shading = 95% CIs
Air pollution and autism spectrum disorders

Traffic-Related Air Pollution, Particulate Matter, and Autism

Heather E. Volk, PhD, MPH; Fred Lurmann; Bryan Penfold; Irva Hertz-Picciotto, PhD; Rob McConnell, MD
JAMA Psychiatry. 2013;70(1):71-7

Ambient Air Pollution and Autism in Los Angeles County, California

Tracy Ann Becerra,1 Michelle Wilhelm,1 Jørn Olsen,1 Myles Cockburn,2 and Beate Ritz1

Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case-Control Analysis within the Nurses’ Health Study II Cohort

Raanan Raz,1 Andrea L. Roberts,2 Kristen Lyall,3,4 Jaime E. Hart,1,5 Allan C. Just,1 Francine Laden,1,5,6 and Marc G. Weisskopf1,6
Environ Health Perspect. 2015;123:264-70

Particulate Matter Exposure, Prenatal and Postnatal Windows of Susceptibility, and Autism Spectrum Disorders

Amy E. Kalkbrenner,a Gayle C. Windham,b Marc L. Serre,c Yasuyuki Akita,c Xuexia Wang,a Kate Hoffman,a Brian P. Thayer,a and Julie L. Danielsc
Epidemiology. 2015;26:30-42

Air Pollution and Newly Diagnostic Autism Spectrum Disorders: A Population-Based Cohort Study in Taiwan

Chau-Ren Jung, Yu-Ting Lin, Bing-Fang Hwang*
Air pollution and autism spectrum disorders

Air pollution exposure during pregnancy and childhood autistic traits in four European population-based cohort studies

Mònica Guxens,1,2,3,4 Akhgar Ghassabian,4,5 Tong Gong,6 Raquel García-Esteban,1,2,3 Daniela Porta,7 Lise Giorgis-Allemand,6,9 Catarina Almqvist,6 Aritz Aranbarri,10,11 Rob Beelen,12 Chiara Badaloni,7 Giulia Cesaroni,7 Audrey de Nazelle,1,2,3,13 Marisa Estarlich,3,14 Francesco Forastiere,7 Joan Forns,1,2,3,12 Ulrike Gehring,13 Jesús Ibarluzea,3,11,16 Vincent W.V. Jaddoe,5,17,18 Michal Korek,19 Paul Lichtenstein,6 Mark J. Nieuwenhuijsen,1,2,3 Marisa Rebagliato,3,20 Rémy Slama,8,9 Henning Tiemeier,4,18,21 Frank C. Verhulst,4 Heather E. Volk,22 Göran Pershagen,19 Bert Brunekreef,12,23 Jordi Sunyer1,2,3,24

Environ Health Perspect 2015 (provisionally accepted)

NOTE: Weights are from random effects analysis

Overall (I-squared = 0.0%, p = 0.431)

<table>
<thead>
<tr>
<th>Cohort study, Country-area</th>
<th>Test</th>
<th>Age</th>
<th>OR (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATSS, Sweden</td>
<td>A-TAC</td>
<td>10y</td>
<td>0.92 (0.53, 1.62)</td>
<td>2437</td>
</tr>
<tr>
<td>GENERATION R, The Netherlands</td>
<td>CBCL</td>
<td>6y</td>
<td>0.85 (0.68, 1.07)</td>
<td>3706</td>
</tr>
<tr>
<td>GASPHI, Italy</td>
<td>CBCL</td>
<td>4y</td>
<td>0.94 (0.70, 1.25)</td>
<td>475</td>
</tr>
<tr>
<td>INMA, Spain-Gipuzkoa</td>
<td>CAST</td>
<td>4y</td>
<td>1.78 (0.47, 6.79)</td>
<td>317</td>
</tr>
<tr>
<td>INMA, Spain-Sabadell</td>
<td>CAST</td>
<td>4y</td>
<td>0.81 (0.41, 1.61)</td>
<td>271</td>
</tr>
<tr>
<td>INMA, Spain-Valencia</td>
<td>CAST</td>
<td>5y</td>
<td>1.35 (0.90, 2.01)</td>
<td>487</td>
</tr>
</tbody>
</table>

N=8,079

NOTE: Weights are from random effects analysis

NO₂ (per Δ10 µg/m³)
Air pollution and brain MRI

Mexico City – Calderón-Garcidueñas’ studies

New York City – Perera’s study
Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs

Lilian Calderón-Garcidueñas a,b,*, Antonieta Mora-Tiscareño Gilberto Gómez-Garza a, Gerardo Barragán-Mejía a, James B Gildardo Valencia-Salazar a, Valerie Jewells e, Robert R. Mar Beatriz Pérez-Guillé a, Ricardo Torres-Jardón h, Lou Herrit b, Maria E. Monroy a, Angelica González-Maciel a, Rafael Reyn Anna C Solt j, Randall W. Engle c,1

Brain Cogn. 2008;68(2):117-27

Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children

Lilian Calderón-Garcidueñas a,b, Randall Engle c, Antonieta Mora-Tiscareño a, Martin Styner d, Gilberto Gómez-Garza a, Hongtu Zhu e, Valerie Jewells f, Ricardo Torres-Jardón g, Lina Romero a, Maria E. Monroy-Acosta a, Christopher Bryant e, Luis Oscar González-González a, Humberto Medina-Cortina a, Amedeo D’Angiulli h,*

Brain Cogn. 2011;77(3):345-355

White Matter Hyperintensities, Systemic Inflammation, Brain Growth, and Cognitive Functions in Children Exposed to Air Pollution

Lilian Calderón-Garcidueñas a,b,*, Antonieta Mora-Tiscareño a, Martin Styner f, Gilberto Gómez-garza a, Hongtu Zhu a, Ricardo Torres-Jardón a, Esperanza Carlos a, Edelmira Solorio-López a, Humberto Medina-Cortina a, Michael Kavanagh b and Amedeo D’Angiulli h

J Alzheimers Dis. 2012;31:183-91
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; David Semanek, BA; Frederica Perera, DrPH, PhD

A Correlations with prenatal PAH levels

B Correlations with postnatal PAH levels

Correlations With WISC-IV Processing Speed
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; David Semanek, BA; Frederica Perera, DrPH, PhD

A Correlations with prenatal PAH levels

B Correlations with postnatal PAH levels

Prenatal PAH exposure → Reduced white matter surface → Slower information processing speed in childhood
Challenges

• Assess the appropriate brain function at the appropriate age and using the appropriate tool
• Which specific air pollutant is behind this association?
• Which is the role of noise exposure?
• Which is the most critical period of neurotoxicity?
• Why air pollution was associated to autism spectrum disorders in US studies but was not associated with autistic traits in European studies?
Future directions

• Brain structural and functional MRI will help to understand better which brain areas and brain functions are affected
• Studies including a more detailed exposure assessment (PM composition, UFP, source apportionment, multi-pollutant models, etc)
• Studies including noise exposure
• Studies including a more comprehensive exposure assessment along children’s lifetime
• Replicate US studies on autism spectrum disorder in Europe following a similar study design
Conclusions

• Air pollution exposure during pregnancy and in the first years of life seems to be associated to a decreased children’s brain development
Sick Individuals and Sick Populations

GEOFFREY ROSE

IQ

2 points

IQ
Thank you very much!

(mgxens@creal.cat)