Air Pollution, Fetal Development, and Children's Brains

Time to Act

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UCLA, FSPH
Air Pollution and Pregnancy

- Developing organism is uniquely sensitive to environmental toxins
- Immediate and long term health effects
  - Infant morbidity and mortality
  - Adverse effects on adult health (fetal programming hypothesis)?
- Fetal growth measures as sensitive indicators for organ development including *brain development*

Life course perspective...
Implications of the Observed Effect of Air Pollution on Birth Weight

*Louise Williams, †M. Anne Spence, and †Susan C. Tideman

*Department of Anthropology, University of California, Los Angeles, California; and †Neuropsychiatric Institute, MR Unit, Los Angeles, California

ABSTRACT: The purpose of this study was to ascertain whether air pollution in the Los Angeles Basin is affecting birth weight. The data base for the study consisted of daily air pollutant averages from the Air Pollution Control District of Los Angeles County, California, obstetric records of births at the University of California at Los Angeles Hospital for the year 1973, and smoking information on each gravida. The effect of total pollution level was significantly negatively associated with birth weight after removing the effects of other variables significantly associated with birth weight. Infants born to nonsmoking women who lived in the more polluted areas of the city weigh an average of 314 grams less than infants born to women living in the less polluted areas.
UCLA research team publications since 1999

(6) Wilhelm M, Ritz, B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California. Environ Health Perspect 2005 Sep;113(9):1212-21.

And counting....
Ambient air pollution and pregnancy outcome studies worldwide since 2000

Studies of many different pollutants conducted in Australia, Brazil, Canada, China, Czech Republic, Great Britain, S. Korea, Mexico, United States...
Table 2  Summary of combined effect estimates on pregnancy outcomes associated with PM$_{2.5}$ exposures

<table>
<thead>
<tr>
<th>Outcome and PM$_{2.5}$</th>
<th>Trimester</th>
<th>No. of studies</th>
<th>Test of association</th>
<th>Test of heterogeneity</th>
<th>Egger’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR/Beta</td>
<td>95% CI</td>
<td>$P$ value</td>
</tr>
<tr>
<td>BW and PM$_{2.5}$</td>
<td>Entire pregnancy</td>
<td>12</td>
<td>-14.58</td>
<td>-19.31 to -9.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>First trimester</td>
<td>7</td>
<td>-6.63</td>
<td>-13.65 to 0.39</td>
<td>0.064</td>
</tr>
<tr>
<td></td>
<td>Second trimester</td>
<td>5</td>
<td>-8.00</td>
<td>-14.52 to -1.48</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Third trimester</td>
<td>7</td>
<td>-14.91</td>
<td>-21.73 to -8.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBW and PM$_{2.5}$</td>
<td>Entire pregnancy</td>
<td>6</td>
<td>1.05</td>
<td>1.02 to 1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTB and PM$_{2.5}$</td>
<td>Entire pregnancy</td>
<td>8</td>
<td>1.10</td>
<td>1.03 to 1.18</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>First trimester</td>
<td>6</td>
<td>0.96</td>
<td>0.77 to 1.21</td>
<td>0.747</td>
</tr>
<tr>
<td></td>
<td>Second trimester</td>
<td>3</td>
<td>0.90</td>
<td>0.79 to 1.03</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>Third trimester</td>
<td>6</td>
<td>0.97</td>
<td>0.89 to 1.05</td>
<td>0.420</td>
</tr>
<tr>
<td>SGA and PM$_{2.5}$</td>
<td>Entire pregnancy</td>
<td>6</td>
<td>1.15</td>
<td>1.10 to 1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>First trimester</td>
<td>6</td>
<td>1.07</td>
<td>1.05 to 1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Second trimester</td>
<td>5</td>
<td>1.06</td>
<td>1.02 to 1.10</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Third trimester</td>
<td>5</td>
<td>1.06</td>
<td>1.04 to 1.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5-15% increase in risk per 10µg/m$^3$ PM$_{2.5}$

PM\textsubscript{2.5}

Ambient air pollution and low birthweight: a European cohort study (ESCAPE) 2013

Marie Pedersen, Lise Giorgis-Allemand, Claire Bernard, Inmaculada Aguilera, Anne-Marie Nybo Andersen, Ferran Ballester, Rob M J Beelen,

*Figure 1: Location of birth cohorts

*Figure 2: PM\textsubscript{2.5} concentrations in the ambient air during pregnancy by cohort and overall
Effect of pregnancy mean exposure to air pollutants on low birthweight at term estimated in pooled analyses using logistic regression with random effect of center adjusted for gestational age (weeks and [weeks]²), sex, parity (0, 1, 2, or more), maternal height, weight before pregnancy (broken stick model with a knot at 60 kg), maternal active smoking during second trimester (cigarettes per day), maternal age, maternal education (low, middle, high), and season of conception (January–March, April–June, July–September, October–December).

<table>
<thead>
<tr>
<th>One-pollutant models†</th>
<th>Total number with term birth*</th>
<th>Number with low birthweight at term</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM₂.₅</td>
<td>50 151</td>
<td>675</td>
<td>1.18 (1.06–1.33)</td>
</tr>
<tr>
<td>PM₂.₅-10</td>
<td>48 995</td>
<td>666</td>
<td>1.01 (0.88–1.15)</td>
</tr>
<tr>
<td>PM₁₀</td>
<td>50 151</td>
<td>675</td>
<td>1.16 (1.00–1.35)</td>
</tr>
<tr>
<td>PM₂.₅ absorbance</td>
<td>50 835</td>
<td>679</td>
<td>1.17 (0.95–1.39)</td>
</tr>
<tr>
<td>NO₂ in areas with PM₂.₅</td>
<td>49 285</td>
<td>656</td>
<td>1.05 (0.95–1.16)</td>
</tr>
<tr>
<td>NO₂ in all areas</td>
<td>61 452</td>
<td>1074</td>
<td>1.09 (1.00–1.19)</td>
</tr>
<tr>
<td>NOₓ in all areas</td>
<td>60 254</td>
<td>1046</td>
<td>1.04 (0.97–1.11)</td>
</tr>
<tr>
<td>Traffic density on nearest street</td>
<td>59 030</td>
<td>1000</td>
<td>1.06 (1.01–1.11)</td>
</tr>
<tr>
<td>Traffic load on major road within 100 m</td>
<td>60 254</td>
<td>1039</td>
<td>1.01 (0.96–1.07)</td>
</tr>
</tbody>
</table>
Neurodevelopmental Disorders: Autisms increase in California Birth Cohorts

1966-1991: 4 cases per 10,000 births
1994: 15 cases per 10,000 births
2001: 42.5 cases per 10,000 births
2008: 113 cases per 10,000 births

Figure: cumulative incidence per 10,000 births by birth cohort from 1990 to 2003, at ages 1–9 years, California, U.S.A.

Autism is a severe neurodevelopmental disorder

Air Pollution and Autisms

Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area

Gayle C. Windham,¹ Lixia Zhang,² Robert Gunier,¹ Lisa A. Croen,³ and Judith K. Grether¹

¹Division of Environmental and Occupational Disease Control, California Department of Health Services, Richmond, California, USA; ²Impact Assessment, Inc., La Jolla, California, USA; ³Kaiser Permanente Medical Care Program Division of Research, Oakland, California, USA

VOLUME 114 | NUMBER 9 | September 2006 • Environmental Health Perspectives

Perinatal Exposure to Hazardous Air Pollutants and Autism Spectrum Disorders at Age 8

Amy E. Kalkbrenner,⁴ Julie L. Daniels,⁴ Ji-Chiuan Chen,⁴ Charles Poole,⁴ Michael Emch,⁴ and Joseph Morrissey⁴


Residential Proximity to Freeways and Autism in the CHARGE Study

Heather E. Volk,¹ Irv Hertz-Picciotto,² Lora Delwiche,² Fred Lurmann,³ and Rob McConnell⁴

¹Departments of Preventive Medicine and Pediatrics, Zilkha Neurogenetic Institute, Keck School of Medicine, Children’s Hospital Los Angeles, University of Southern California, Los Angeles, California, USA; ²Department of Public Health Sciences, University of California–Davis, Davis, California, USA; ³Sonoma Technology Inc., Petaluma, California, USA; ⁴Department of Preventive Medicine, Keck School of Medicine, Unive

Environmental Health Perspectives • VOLUME 119 | NUMBER 6 | June 2011

Ambient Air Pollution and Autism in Los Angeles County, California

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

¹Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California, USA; ²Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

VOLUME 121 | NUMBER 3 | March 2013 • Environmental Health Perspectives
Traffic-Related Air Pollution and Autism Spectrum Disorder: A Population-Based Nested Case-Control Study in Israel

Raanan Raz*, Hagai Levine, Ofir Pinto, David M. Broday, Yuval, and Marc G. Weisskopf

* Correspondence to Dr. Raanan Raz, Braun School of Public Health and Community Medicine, The Hebrew University of Jerusalem and Hadassah Ein Kerem, Jerusalem 9112002, Israel (e-mail: raananr@ekmd.huji.ac.il).

Figure 1. Associations between exposure to nitrogen dioxide during pregnancy and during the 9 months after birth and risk of autism spectrum disorder among children born in central coastal Israel during 2005–2009. Odds ratios show the risk of autism spectrum disorder per interquartile-range increment (5.85 ppb) in nitrogen dioxide exposure. A) Results from 2 separate models, each adjusted for year of birth, calendar month of birth, population group, paternal age, and census poverty index. B) Results from 1 model, with mutual adjustment for both exposure periods in addition to all of the covariates listed above. Bars, 95% confidence intervals.
Autism Risk Increase by Modelled Air-Pollutants Levels in Denmark 1989-2013 (per IQR\textsuperscript{d})

Case N=15,387; Control N=68,139

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Exposure period</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted\textsuperscript{a}</td>
</tr>
<tr>
<td>(\text{NO}_2)</td>
<td>Pregnancy</td>
<td>1.19 (1.16, 1.22)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.20 (1.17, 1.23)</td>
</tr>
<tr>
<td>(\text{SO}_2)</td>
<td>Pregnancy</td>
<td>1.29 (1.23, 1.35)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.38 (1.31, 1.45)</td>
</tr>
<tr>
<td>(\text{PM}_{10})</td>
<td>Pregnancy</td>
<td>0.99 (0.95, 1.02)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.03 (0.99, 1.06)</td>
</tr>
<tr>
<td>(\text{PM}_{2.5})</td>
<td>Pregnancy</td>
<td>1.06 (1.02, 1.11)</td>
</tr>
<tr>
<td></td>
<td>9 months after birth</td>
<td>1.11 (1.07, 1.15)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} note: these are pair matched on gender, birth year
\textsuperscript{c} adjusted for all other covariates listed above and all exposure periods (pre-pregnancy, pregnancy and post-pregnancy).

\textsuperscript{d} IQRs in controls: NO\textsubscript{2}: 11.41 ug/m\textsuperscript{3}; SO\textsubscript{2}: 2.80 ug/m\textsuperscript{3}; PM\textsubscript{10}: 3.80 ug/m\textsuperscript{3}; PM\textsubscript{2.5}: 3.61 ug/m\textsuperscript{3}
In **high** (Los Angeles, California, Israel) and **low** pollution setting like Europe (ESCAPE) - especially in Denmark - with **excellent** exposure and health record systems adverse impacts of air pollution are seen on adverse pregnancy outcomes and autism.....
Global Burden of Disease (GBD) attributable to 20 leading risk factors in 2010, expressed as a percentage of global disability-adjusted life-years (DALYs)

Lim et al. 2012, Lancet

Neonatal disorders are absent from PM estimates

enough human evidence to add outcomes to GBD?
What could be missing for adverse birth outcomes and child brain development to qualify for GBD and/or policy and prevention efforts?
More sophisticated (better?) exposure models…

Map of SCAQMD Monitoring Stations and Zip Codes Included in Analysis
Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study

Jun Wu, Michelle Wilhelm, Judith Chung, Beate Ritz

**aOR for Preterm Birth per IQR increase in entire pregnancy in LA**

<table>
<thead>
<tr>
<th>Los Angeles</th>
<th>Cases (n)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>CO</td>
<td>3928</td>
<td>1.13 (1.09–1.18)</td>
<td>1.13 (1.08–1.19)</td>
</tr>
<tr>
<td>NO</td>
<td>3928</td>
<td>1.08 (1.05–1.12)</td>
<td>1.11 (1.06–1.16)</td>
</tr>
<tr>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3928</td>
<td>1.06 (0.97–1.15)</td>
<td>1.06 (0.95–1.18)</td>
</tr>
<tr>
<td>NO&lt;sub&gt;x&lt;/sub&gt;</td>
<td>3928</td>
<td>1.09 (1.05–1.14)</td>
<td>1.13 (1.07–1.19)</td>
</tr>
<tr>
<td>O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3928</td>
<td>0.99 (0.92–1.07)</td>
<td>1.00 (0.90–1.10)</td>
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<tr>
<td>PM&lt;sub&gt;10&lt;/sub&gt;</td>
<td>3928</td>
<td>1.05 (0.98–1.12)</td>
<td>1.06 (0.98–1.14)</td>
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<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>3174</td>
<td>1.02 (0.95–1.10)</td>
<td>1.04 (0.94–1.15)</td>
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<tr>
<td>NO LUR (unadjusted)</td>
<td>3928</td>
<td>1.01 (0.98–1.04)</td>
<td>1.01 (0.98–1.04)</td>
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<tr>
<td>NO&lt;sub&gt;2&lt;/sub&gt; LUR (unadjusted)</td>
<td>3928</td>
<td>1.13 (1.07–1.18)</td>
<td>1.07 (1.02–1.13)</td>
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<tr>
<td>NO&lt;sub&gt;x&lt;/sub&gt; LUR (unadjusted)</td>
<td>3928</td>
<td>1.09 (1.04–1.15)</td>
<td>1.05 (1.00–1.10)</td>
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<td>NO LUR (adjusted)</td>
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<td>1.00 (0.99–1.02)</td>
<td>1.02 (0.98–1.07)</td>
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<td>NO&lt;sub&gt;2&lt;/sub&gt; LUR (adjusted)</td>
<td>3928</td>
<td>0.98 (0.95–1.00)</td>
<td>0.92 (0.85–0.98)</td>
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<tr>
<td>NO&lt;sub&gt;x&lt;/sub&gt; LUR (adjusted)</td>
<td>3928</td>
<td>1.01 (0.99–1.03)</td>
<td>1.02 (0.95–1.08)</td>
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<tr>
<td>NO&lt;sub&gt;x&lt;/sub&gt; CALINE4</td>
<td>3928</td>
<td>1.05 (1.01–1.10)</td>
<td>1.04 (0.99–1.08)</td>
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<td>PM&lt;sub&gt;2.5&lt;/sub&gt; CALINE4</td>
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<td>1.06 (1.02–1.10)</td>
<td>1.04 (1.00–1.08)</td>
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<td>Traffic density</td>
<td>3928</td>
<td>1.03 (1.00–1.05)</td>
<td>1.02 (1.00–1.04)</td>
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</tbody>
</table>

<sup>a</sup> To compare results between regions, we used the inter-quartile range values for the entire region (see Table 2).

<sup>b</sup> Adjusted for maternal age, maternal race/ethnicity, parity, pyelonephritis, prenatal care insurance type, poverty, and season of conception.
Additional Epidemiologic Air Pollution Studies Outside of North America and Europe?

Where?
Africa?
South America?
Asia?
Associating airborne particle types with adverse health outcomes

Multi-Angle Imager for Aerosols (MAIA)
Potential target areas

- **Candidate Primary Target Area (PTA):** Under serious consideration for project epidemiological study

- **Potential PTA:** Further information and tradeoffs required

- **Secondary Target Area (STA):** Supports other air quality, aerosol and cloud climate studies

- **Calibration/Validation Target Area (CVTA):** Routinely observed site for vicarious calibration and instrument stability monitoring
Investigate Biologic Pathways in Animals and Humans?
Gestational Hypertension and Pre-eclampsia

Air Pollution, Blood Pressure, and the Risk of Hypertensive Complications During Pregnancy
The Generation R Study
(Hypertension. 2011;57:406-412.)


DOI 10.1007/s12012-012-9157-4

Prohypertensive Effect of Gestational Personal Exposure to Fine Particulate Matter. Prospective Cohort Study in Non-smoking and Non-obese Pregnant Women

Wieslaw A. Jedrychowski · Frederica P. Perera · Umberto Maugeri · John Spengler · Elzbieta Mroz · Elzbieta Flak · Laura Stöger · Renata Majewska · Irena Kaim

Environmental Research 117 (2012) 46–53

Contents lists available at SciVerse ScienceDirect
Environmental Research
general homepage: www.elsevier.com/locate/envres

Ambient air pollution exposure and blood pressure changes during pregnancy

Pei-Chen Lee a,*, Evelyn O. Talbott a, James M. Roberts a,b, Janet M. Catov a,b, Richard A. Bilionick c, Roslyn A. Stone d, Ravi K. Sharma e, Beate Ritz f

Association between Local Traffic-Generated Air Pollution and Pre-eclampsia and Preterm Delivery in the South Coast Air Basin of California

Jun Wu,1,2 Cizao Ren,2 Ralph J. Delfino,2 Judith Chung,3 Michelle Wilhelm,4 and Beate Ritz4
Inflammation in Pregnancy

Particulate Air Pollution Exposure and C-reactive Protein During Early Pregnancy

Pei-Chen Lee, Evelyn O. Talbott, James M. Roberts, Janet M. Catov, Ravi K. Sharma, and Beate Ritz

Environmental Health Perspectives • Volume 120 | Number 5 | May 2012

Chronic Air Pollution Exposure during Pregnancy and Maternal and Fetal C-Reactive Protein Levels: The Generation R Study

Edith H. van den Hooven, Yvonne de Kluizenaar, Frank H. Pierik, Albert Hofman, Sjoerd W. van Ratingen, Peter Y.J. Zandveld, Jan Lindemans, Henk Russcher, Eric A.P. Steegers, Henk M.E. Miedema, and Vincent W.V. Jaddoe

1Generation R Study Group, Erasmus Medical Center, Rotterdam, the Netherlands; 2Urban Environment and Safety, Netherlands Organisation for Applied Scientific Research (TNO), Utrecht, the Netherlands; 3Department of Epidemiology, 4Department of Clinical Chemistry, 5Department of Obstetrics and Gynaecology, and 6Department of Paediatrics, Erasmus Medical Center, Rotterdam, the Netherlands
Maternal exposure to diluted diesel engine exhaust alters placental function and induces intergenerational effects in rabbits

Placental mitochondrial methylation and exposure to airborne particulate matter in the early life environment: An ENVIRONAGE birth cohort study
UCLA scientists will study how pollution affects development of the placenta. Problems with the placenta can lead to preeclampsia, preterm birth and stillbirth.

September 29, 2015
Air monitoring during pregnancy

200 Women place Purple Air particle monitors in-and outdoors to measure particles of multiple sizes

Biosamples during pregnancy:

- Maternal/cord blood and placenta
- Maternal urine throughout pregnancy

Generate metabolomic, oxidative stress and inflammation markers
Expanded Alphafetoprotein Screening Program (XRAF) collects and stores mid-second trimester maternal serum samples

- identified serum from ~300 Autism Cases and 300 controls
- assessed air pollution exposure profiles

Air pollution and Autism
Feature selection using Variable Importance for Projection (VIP) based on PLSDA

Pathway enrichment analysis using Mummichog and m/z features with VIP>2

Higher in exposed group w/ Autism
Lower in exposed group w/ Autism
Air Pollution Studies of Birth Outcomes, and Child Brain Health Policy Relevant and Actionable!!!

06 February 2013

Nature | News

Air pollution delivers smaller babies
Study of 3 million infants suggests connection between inhaled particles and birth weight.

published in Environmental Health Perspectives

Associations of Pregnancy Outcomes and PM$_{2.5}$ in a National Canadian Study


¹Population Studies Division, Health Canada, Vancouver, British Columbia, Canada; ²Population Studies Division, Health Canada, Ottawa, Ontario, Canada; ³Geographic Information Health and Exposure Science Laboratory (GIS HEAL), School of Public Health, University of California, Berkeley, Berkeley, California, USA; ⁴Department of Environmental Health Sciences, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California, USA; ⁵Department of Sociology, University of New Brunswick, Fredericton, New Brunswick, Canada; ⁶Special Surveys Division, Statistics Canada, Ottawa, Ontario, Canada; ⁷Department of Physics and Atmospheric Science, Dalhousie University, Halifax, Nova Scotia, Canada; ⁸Harvard-Smithsonian Center for Astrophysics, Cambridge, Massachusetts, USA; ⁹Vaccine and Immunization Program Surveillance Division, Public Health Agency of Canada, Ottawa, Canada; ¹⁰Health Analysis Division, Statistics Canada, Ottawa, Ontario, Canada; ¹¹Maternal, Child and Youth Health, Surveillance and Epidemiology Division, Public Health Agency of Canada, Ottawa, Ontario, Canada; ¹²Air Health Science Division, Health Canada, Ottawa, Ontario, Canada
Prevention! But not like this.....

An L.A. driver in 1979
Los Angeles Times

Chinese Millionaire Sells Cans of Fresh Air, 2013

Women wearing masks in Beijing, where particulate matter levels can be tens of times higher than World Health Organization guidelines recommend.

Lintao Zhang/Getty Images
Special Thanks to Funders and Collaborators

- Liew, Yan, Heck, Ehrenstein, Cui, Ling, Turner, Wing UCLA Epidemiology
- Michael Jerrett – UCLA --COEH
- Jun Wu – UCI
- Jason Su - UC Berkeley
- Myles Cockburn, Denver CO
- Dean Jones, Emory