60,000 Trucks per day: Diesel Exhaust Exposure, Wheezing and Sneezing

Cincinnati Childrens Allergy and Air Pollution Study

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David I Bernstein MD

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- NIAID funded T32 (PI)
- Research Contracts – Glaxo, Merck, Amgen, Johnson and Johnson, Medimmune
TEAM

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  – Marepalli Rao PhD
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  Abraham Research
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  Bernstein Clinical Research
  – Sherry Evans RN CNP
  – Kristen Klefas
  – Patrick Reilly

• Washington University
  – Pratim Biswas PhD
CCAAPS and the Mission of the Center for Clinical and Translational Science and Training

1. Interdisciplinary Team of Scientists and Mentors
   – Training facilitated by Institutional T32s
     Allergy Immunology NIAID; Environmental Health NIEHS

2. Trainees (partial list)
   – Jocelyn Biagini PhD*
   – Chris Codispoti MD, MS
   – Tolly Epstein MD, MA*
   – Haejin Kim MD
   – Pat Ryan PhD*
   – Andrew Smith MD, MA*
   – Heidi Sucharew PhD*

* Joined faculty of UC or CCHMC
Objectives

1. Review issues regarding the origins of atopy and traffic related air pollutants.
2. Frame the background and questions posed by the CCAAPS study.
3. Present study design and methods
4. Review key epidemiologic / clinical findings of CCAAPS.
Putative Risk Factors: Childhood Asthma

1. Gender  *Boys > Girls*
2. Reduced Lung function in Infancy
3. Airway Hyperreactivity
4. Atopy or elevated total IgE
5. Indoor allergen exposure – unknown
6. Environmental tobacco smoke
   – Active and passive; pre-natal exposure
7. Allergic rhinitis, Atopic dermatitis
Risk Factors for Childhood Asthma

7. Antibiotics in infancy – hygiene hypothesis?
8. Endotoxin, microbial exposure, innate immunity
   – Enhance or reduce risk
9. Early respiratory infections
10. Exposure to Traffic Pollutants and Diesel Exhaust?
Early epidemiologic evidence

• Truck traffic or living close to highways is associated with atopic sensitization in children (Janssen et al. 2003)

• Traffic exposure associated with ↓ in lung function, wheeze and asthma

• PM$_{2.5}$ exposure correlates with ↓ $FEV_1$ & respiratory symptoms (Ward et al. 2005)
Nasal challenge with diesel exhaust particles (DEP) can act as an adjuvant or “synergize” to induce a specific IgE response to a neo-allergen, keyhole limpet hemocyanin (KLH)

*Diaz-Sanchez et al. JACI 1999*
Epidemiologic evidence lacking →

• Does early traffic exhaust exposure contribute to aeroallergen sensitization?
• Do such effects partially explain the rising incidence of atopic sensitization and asthma in developed countries?
• Does traffic exhaust contribute to the burden of asthma in children?
What is Traffic-Related Air Pollution (TRAP)?

• Derived from the combustion of gasoline and diesel traffic
  - Particulate Matter
  - NO\textsubscript{x}
  - Polycyclic Aromatic Hydrocarbons
  - Metals

• High spatial variability
PM Size Definitions

- **Coarse particles (PM\textsubscript{10})**
  - Diameter $> 2.5$ microns and $< 10$ microns
  - Produced primarily by mechanical processes (tire wear, grinding, re-suspension of ground particles)

- **Fine particles (PM\textsubscript{2.5})**
  - Diameter $\leq 2.5$ microns
  - Produced primarily from combustion sources and principally from diesel

- **Ultrafine particles (PM\textsubscript{0.1})**
  - Diameter $< 0.1$ micron (100 nm)
- 450 compounds generating reactive oxidative species (ROS)
- Large surface area – adsorb and carry protein allergens?

Direct resp effects
- Induce Oxidative stress
- ↑ sputum neutrophils
- ↑ bronchial mast cells
- ↑ IL-6, IL-8, ICAM-1
- ↑ methacholine AHR

Diesel particles are carbon at their core with toxics and carcinogenic substances attached to their surfaces.
Hypothesis

CCAAPS study

Infants with high exposure to traffic pollutants will have a different pattern of early aeroallergen sensitization and greater relative risk for atopic disorders versus infants living distant from traffic.
Study Design

High-risk birth cohort: ages 1, 2, 3 and 4 → Age 7 2001→2011

CCAAPS

Live Births (n=762)
- Atopic parent
- Live <400 m or >1500 m from major road

Data collected:
- Validated Health Questionnaire
- Physical Exam
- Traffic related air pollution
- Home assessment – house dust sample
- Skin Prick testing

Wheezing age 1
- Allergic Rhinitis age 3
- Wheezing age 3
- Eczema age 4
- Asthma age 7
Population: Cincinnati Childhood Allergy & Air Pollution Study (CCAAPS)

• 762 children of atopic parents
  – Parents recruited (2001-2003) from public birth records in Cincinnati metropolitan area
  – Parents had symptoms of an allergic disease and a positive skin prick test (SPT) to an aeroallergen
  – **Control Cohort Design** – Proximity model subjects lived <400 m or >1500 m from a major road
Data collected at Annual visits (Ages 1-4 years)

- In-person health itemized questionnaire, including items adapted from the International Study on Allergies & Asthma in Childhood (ISAAC)\(^1\)
- Physical exam and clinicians’ global assessment
- Skin prick tests (SPTs) to Egg, Milk, and 15 aeroallergens, including:
  - *Dog*, *Cat*, *Dust-mite (Der f + Der p)*, *German cockroach*, *Elm*, *Oak*, *Cedar*, *Maple*, *Ragweed*, *Fescue*, *Timothy*, *Alternaria*, *Aspergillus*, *Penicillium*, and *Cladosporium*

Data collected at Home Visits (Age 1 year)

- Types and numbers of pets

- Home dust samples from a 2 m² area of floor surface in the infant’s primary activity room
  - Endotoxin and \((1\rightarrow 3)\) β-D-glucan analyzed with a limulus amebocyte lysate assay \(^1\)
  - Cat allergen (Fel d 1), Dog allergen (Can f 1), Cockroach (Bla g 1) and Dust-mite allergen (Der f 1) analyzed with a monoclonal sandwich ELISA assay \(^2\)

Prevalence of atopy by aeroallergen for all tested parents and their infants at age one

*J Pediatr* 2006;149:505-11

<table>
<thead>
<tr>
<th>Category</th>
<th>Individual Allergens</th>
<th>(4) SPT+ Infan With at Least One SPT+ n = 193 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollen</td>
<td>Meadow fescue</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Timothy</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>White oak</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>Maple mix</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>American elm</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Red cedar</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Short ragweed</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Alternaria</td>
<td>8.8</td>
</tr>
<tr>
<td>Mold</td>
<td><em>Aspergillus fumigatus</em></td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td><em>Penicillium</em></td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td><em>Cladosporium</em></td>
<td>9.3</td>
</tr>
<tr>
<td>Dust</td>
<td>Dust mite</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td><em>German cockroach</em></td>
<td>6.2</td>
</tr>
<tr>
<td>Animal</td>
<td>Cat</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>4.7</td>
</tr>
<tr>
<td>Food</td>
<td>Milk</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>43.0</td>
</tr>
</tbody>
</table>

**Skin test Results - Infants**

- 28% Skin test + any allergen
- 18% ST+ to aeroallergen(s)
Traffic pollutant exposure?

**Proximity Model**
- Distance of infant from primary residence to major roads using known information about types of vehicles (buses, trucks) on those roads.
- Classified as: stop and go, moving, unexposed

**Land Use Regression Model**
- Area sampling – PM2.5
- Elemental carbon attributable to traffic (ECAT)
- Takes into account variates other than proximity – may avoid exposure mis-classification
How do we estimate a child’s level of DEP exposure?

*Ryan et al. 2007*

**ECAT**-- **E**lemental **C**arbon **A**ttributable to **T**raffic

- 27 Air sampling sites
- Ambient collections PM < 2.5
- Elemental carbon - xray fluorescence, thermal optical transmittance
- Fraction of EC calculated due to diesel sources

**Land-use regression (LUR) Model**

- Predict pollution concentrations at a given location based on surrounding land and traffic data
- Predictive Variables in model:
  - wind direction, length of bus routes within 300 m of the sample site, a measure of truck intensity within 300 m of the sampling site, and elevation
CCAAPS PM$_{2.5}$ monitoring network
Wheezing and Asthma Outcomes
Adjusted OR of recurrent wheezing, and combined high endotoxin (EU/mg) with ≥ 2 dogs in the home

 Campo, Kalra et al. JACI 2006 Dec;118(6):1271-8

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recurrent wheeze* OR (95% CI)</th>
<th>Recurrent wheeze with an event† OR (95% CI)</th>
<th>Any wheeze‡ OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin (EU/mg)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Dogs</td>
<td>1.3 (0.8-1.9)</td>
<td>1.1 (0.7-1.8)</td>
<td>1.1 (0.8-1.6)</td>
</tr>
<tr>
<td>1 Dog</td>
<td>0.7 (0.4-1.1)</td>
<td>0.6 (0.4-1.1)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>≥2 Dogs</td>
<td>0.4 (0.1-0.9)</td>
<td>0.4 (0.1-1.0)</td>
<td>0.3 (0.1-0.8)</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.5 (0.9-2.3)</td>
<td>1.6 (1.0-2.8)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Day care</td>
<td>2.6 (1.3-5.5)</td>
<td>3.2 (1.5-6.9)</td>
<td>2.6 (1.3-5.1)</td>
</tr>
<tr>
<td>No. of siblings</td>
<td></td>
<td></td>
<td>2.0 (1.1-3.7)</td>
</tr>
<tr>
<td>No. of colds in the past year¶</td>
<td>1.3 (1.1-1.6)</td>
<td>1.3 (1.1-1.6)</td>
<td>1.4 (1.1-1.6)</td>
</tr>
<tr>
<td>Mother smoked (cigarettes/d)#</td>
<td>13.2 (P &lt; .001; df = 2)</td>
<td>13.2 (P &lt; .001; df = 2)</td>
<td>9.4 (P &lt; .001; df = 2)</td>
</tr>
<tr>
<td>Either parent had asthma</td>
<td>2.3 (1.4-3.6)</td>
<td>2.7 (1.6-4.6)</td>
<td>1.8 (1.2-2.8)</td>
</tr>
</tbody>
</table>

*Recurrent wheeze: ≥ 2 wheezing episodes in the past 12 months.
†Recurrent wheeze with an event: ≥2 wheezing episodes in the past 12 months that required a medical intervention or sleep disturbance caused by wheezing. Denominator does not include 26 infants who wheezed but did not require treatment.
‡Control group: ≤ 1 wheezing episodes in the past 12 months.
Is proximity to truck and bus traffic associated with infant wheezing?

Ryan et al. J Allergy Clin Immunol 2005

Stop-Go: < 100 m from bus route / highway < 50 mph
Moving: < 400 m from major road (>1000 trucks / day)
Unexposed: > 400 m from bus route / major road
### TABLE II. Unadjusted and adjusted* ORs and 95% CIs for wheezing without a cold  Year 1

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR</th>
<th></th>
<th>Adjusted OR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Stop-and-go exposure†</td>
<td>3.41</td>
<td>1.71-6.81</td>
<td>2.50</td>
<td>1.15-5.42</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>2.80</td>
<td>1.54-5.08</td>
<td>2.39</td>
<td>1.20-4.76</td>
</tr>
<tr>
<td>Paternal asthma</td>
<td>2.63</td>
<td>1.29-5.37</td>
<td>2.35</td>
<td>1.08-5.13</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.93</td>
<td>1.04-3.58</td>
<td>2.49</td>
<td>1.21-5.10</td>
</tr>
<tr>
<td>Only child‡</td>
<td>0.47</td>
<td>0.23-0.96</td>
<td>0.42</td>
<td>0.19-0.93</td>
</tr>
</tbody>
</table>

*Adjusted for maternal smoking, breast-feeding, pet ownership, visible mold, maternal asthma, care outside the home, and monthly diaries returned.

†Reference category = unexposed.

‡Reference category = 2 or more siblings.

*Ryan et al JACI 2005*
Estimated levels of DEP exposure associated with infant wheezing without a cold prior to age one

*Ryan et al. 2007*

<table>
<thead>
<tr>
<th>Exposure to ECAT (µg/m³)</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>0.3</td>
<td>1.23 (1.01–1.50)</td>
</tr>
<tr>
<td>0.4</td>
<td>1.51 (1.01–2.26)</td>
</tr>
<tr>
<td>0.5</td>
<td>1.86 (1.02–3.39)</td>
</tr>
<tr>
<td>0.6</td>
<td>2.29 (1.03–5.09)</td>
</tr>
<tr>
<td>0.7</td>
<td>2.82 (1.04–7.65)</td>
</tr>
<tr>
<td>0.8</td>
<td>3.46 (1.05–11.49)</td>
</tr>
<tr>
<td>0.9</td>
<td>4.26 (1.06–17.26)</td>
</tr>
</tbody>
</table>

*a*Adjusted for sex, race, maternal smoking, child care attendance, breast-feeding, pet ownership, and visible mold in the home.
Exposure to Traffic-related Particles Infancy and Wheezing Phenotypes at Age 3 Years
Ryan P, Bernstein D, Lockey J et al. AJRCCM 2009

Exposure: Land use regression model (ECAT)

Outcomes

1. Recurrent wheeze (≥2 episodes x 12 mos)
2. Persistent wheezing at age 36 months (24 months)
3. Persistent allergic wheezing at age 36 months and SPT + ≥ 1 aeroallergen
4. Asthma Predictive Index
   - recurrent wheezing at age 36 months and at least 1/3 major criteria (parental asthma, sensitization ≥ 1 aeroallergen, and eczema) or
   - 2/3 minor criteria (wheezing, allergic rhinitis, sensitization to milk/egg.
   - Positive predictive value of 59% ages 6-13

Guilbert et al. JACI 2004
Exposure to Traffic-related Particles during Infancy Is Associated with Wheezing Phenotypes at Age 3 Years

Ryan P, Bernstein D, Lockey J et al. AJRCCM 2009

Univariate analysis

<table>
<thead>
<tr>
<th>Quartile ECAT</th>
<th>Estimated ECAT (μg/m³)</th>
<th>Persistent Wheeze</th>
<th>Recurrent Wheeze</th>
<th>Asthma Predictive Index*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% Wheeze</td>
<td>OR† (95% CI)</td>
<td>% Wheeze</td>
</tr>
<tr>
<td>&lt;25th percentile</td>
<td>≤ 0.30</td>
<td>9.0</td>
<td>1</td>
<td>13.5</td>
</tr>
<tr>
<td>≥25th percentile to 50th percentile</td>
<td>0.31–0.34</td>
<td>12.2</td>
<td>1.4 (0.7–2.9)</td>
<td>14.1</td>
</tr>
<tr>
<td>≥50th percentile to 75th percentile</td>
<td>0.35–0.40</td>
<td>12.8</td>
<td>1.5 (0.7–3.1)</td>
<td>16.7</td>
</tr>
<tr>
<td>≥75th percentile</td>
<td>≥0.41</td>
<td>18.6</td>
<td>2.3 (1.2–4.6)</td>
<td>21.8</td>
</tr>
</tbody>
</table>

*OR† = Odds Ratio (95% CI)
Synergistic Effect of Traffic Pollutants and Endotoxin on Persistent Wheeze at Age Three

Adjusted for ECAT, endotoxin, smoking, parental asthma, gender and breast feeding;
High ECAT: >75th percentile (0.41 mg/m3); low ECAT: < 75th percentile.
Childhood Exposure to TRAP and Wheezing Phenotypes at Age 7: Preliminary Results

Figure 1.c Adjusted* Associations Between ECAT Exposure at Birth and Wheezing Phenotypes at Age Seven

*Adjusted for parental history of asthma, gender, race, mother’s education, breastfeeding, daycare attendance, ETS exposure, pets in the home
Studies of Traffic pollutant/childhood wheezing

Methodological Issues

• Misclassification of Outcomes
  – wheezing phenotypes based on questionnaire responses in young children do not accurately predict asthma

• Objective measures of lung function, airway hyperresponsiveness, and airways inflammation will confirm the childhood asthma phenotype at age 7
Asthma at Age 7 in “high risk” CCAAPS Cohort

- Parental report of asthma symptoms
  - Tight of clogged chest or throat in the previous 12 months
  - Difficulty breathing or wheezy after exercise
  - Wheezing or whistling in the chest in the previous 12 months
  - Previous doctor-diagnosed asthma
    AND
- Demonstrated airway reversibility
  - >12% increase in FEV1 following administration of bronchodilator
    OR
- Positive methacholine challenge test
  - > 20% decline in FEV1

- Asthma: 16.6%
CCAAPS Clinical Evaluation -- Age 7

- Age 7
- Questionnaire
- BASC-2
- SPT
- Physical examination
- Hair sample
  - Nicotine / Cotinine
- Saliva sample
  - DNA Isolation
- Blood Collection
- Exhaled Nitric Oxide (eNO)
- Spirometry
  - Bronchodilator
  - MCCT
Childhood Exposure to TRAP and Asthma at Age 7: Preliminary Results

Figure 2.a Unadjusted Associations Between ECAT Exposure and Asthma at Age Seven
Summary of Cincinnati Birth Cohort
Traffic pollutants and wheezing

1. Proximity to stop and go traffic was associated with wheezing in Year 1, and greater in African American infants.
2. ECAT measured at Year 1 was associated with recurrent wheeze in Year 1 and with multiple wheezing phenotypes at age 3.
3. Co-exposure to endotoxin/ECAT during year 1 increased risk for persistent wheeze at age 3.
4. High level of TRAP exposure increased risk for asthma at age 7.
Hypothesis
Early exposure to DEP enhances risk of allergic rhinitis in childhood at age 3
Outcomes – Age 3

- **Allergic rhinitis (Primary outcome)**
  - In the past 12 months, has your child ever had a problem with sneezing, or a runny or a blocked nose when he/she did not have a cold or flu (ISAAC) ?
  
  AND

  - SPT (+) to ≥ 1 of 15 aeroallergens compared to non-atopic, non-symptomatic children.
  - Comparator Group – No symptoms and negative SPTs.

- **“Rhinitis” (Secondary outcome)**
  - Positive response to rhinitis questionnaire item, and the comparator group included
  - Comparator Group - All children without symptoms.

1 Asher MI et al. European Resp Journal 1995
Predictors of Allergic Rhinitis and Rhinitis – Multivariate logistic regression

Codispoti et al. J Allergy Clin Immunol 2010

<table>
<thead>
<tr>
<th>Predictor in infancy</th>
<th>Allergic Rhinitis N=100/322 (31%) aOR (95% CI)</th>
<th>Rhinitis N=189/549 (34%) aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breastfeeding duration (months) in African-Americans</strong></td>
<td>0.8 (0.6, 0.9)**</td>
<td>0.8 (0.7, 0.9)**</td>
</tr>
<tr>
<td><strong>Breastfeeding duration (months) in non-African-Americans</strong></td>
<td>1.0 (0.96, 1.1)</td>
<td>1.0 (0.96, 1.1)</td>
</tr>
<tr>
<td><strong>Season of birth:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Autumn</td>
<td>2.2 (1.0, 4.7)*</td>
<td>1.4 (0.9, 2.2)</td>
</tr>
<tr>
<td>Spring</td>
<td>2.9 (1.3, 6.6)*</td>
<td>2.0 (1.2, 3.4)**</td>
</tr>
<tr>
<td>Summer</td>
<td>2.1 (0.9, 4.9)</td>
<td>1.7 (1.0, 3.0)</td>
</tr>
<tr>
<td><strong>SPT+ trees:</strong></td>
<td>8.7 (3.0, 24.8)*****</td>
<td>2.6 (1.2, 5.4)*</td>
</tr>
<tr>
<td><strong>SPT + milk and/or egg:</strong></td>
<td>4.5 (2.1, 9.8)*****</td>
<td>1.6 (0.96, 2.7)</td>
</tr>
<tr>
<td>≥2 children in home in infancy:</td>
<td>0.5 (0.3, 0.9)*</td>
<td>0.8 (0.5, 1.2)</td>
</tr>
<tr>
<td><strong>Low HDE (EU/mg) in infancy:</strong></td>
<td>0.5 (0.3, 0.8)*</td>
<td>0.8 (0.5, 1.1)</td>
</tr>
<tr>
<td><strong>Medium HDE (EU/mg) in infancy:</strong></td>
<td>6.3 (2.3, 17.2)*****</td>
<td>1.8 (1.0, 3.5)</td>
</tr>
<tr>
<td><strong>High HDE (EU/mg) in infancy:</strong></td>
<td>0.002 (&lt;0.001, 0.1)****</td>
<td>0.4 (0.1, 1.5)</td>
</tr>
</tbody>
</table>
FIG 1. Smooth plot of AR prevalence in relation to HDE concentration.

Clinical Implications for High Risk Children

• Breast feeding should be encouraged in infants born to African American parents.
• Indoor bio-contaminant exposure (e.g. house dust endotoxin) may influence development of allergic rhinitis (positively or negatively) in high risk children.
• Skin testing is useful in high risk infants.
Other findings

Kalra et al. *Chest* 2006
- Atopy is a risk factor for habitual snoring at age 1 year.

Iossifova et al. *Allergy* 2007
- (1-3)-beta-D-glucan in house dust associated with less risk for recurrent wheezing among infants.

Smith et al. *J Peds* 2008
- IL 4RA snp (C-589T) and smoking increases risk of wheezing in African-American infants

Schroer et al. *J Peds* 2009
- DEP exposure in children with GST-P1 Val(105) allele increases risk of persistent wheezing at 12 and 24 mos.
Other findings

**Epstein et al. J Pediatrics**
- Dog ownership significantly reduced the risk for eczema at age 4 years among dog-sensitized children, cat ownership combined with cat sensitization significantly increased the risk.

**Biagini et al. J Investigative Dermatology 2010**
- Children with dog in home less likely to have eczema at ages 1, 2 and 3.
Hypothesis

CCAAPS study

Infants with high exposure to traffic pollutants will have a different pattern of early aeroallergen sensitization and greater relative risk for atopic disorders versus infants living distant from traffic.
Summary and Discussion points

• ECAT Exposure during infancy did not predict:
  – Aeroallergen sensitization years 1-4
  – Allergic rhinitis ages three and four
  – Atopic dermatitis at age four

• ECAT exposure during infancy predicts:
  – Wheezing without a cold at age 1
  – Persistent wheeze at age 3
  – Persistent wheeze at age 7
  – Asthma at age 7

• Exposure interactions are important determinants of clinical outcomes
The end or just the beginning?