Motor Vehicle Exhaust and Allergic Disease in a Birth Cohort

The Cincinnati Childhood Allergy and Air Pollution Study
(Institute of Medicine 2007)

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CCAAPS Central Questions

1. Are infants who are exposed to truck and bus diesel exhaust particles (DEP) at an increased risk for developing allergies and allergic diseases?

2. How do the proximity and land-use regression models compare when characterizing exposure?

3. Is there a gene*environment interaction between genotype and DEP exposure and childhood wheezing?
Why are we interested in allergic diseases?

- Prevalence rates differ among developed/less developed countries and urban/rural areas supporting hypothesis of environmental factors\(^1\)

- 52% of children ages 6-17 are SPT\(^2\)

- Allergic respiratory diseases doubled in previous 2 decades\(^3\)

- Sensitization to allergens in early childhood (< 2 years) is more important than later in childhood for development of persistent wheeze and asthma\(^4\)

- In children, most asthma is allergic asthma

- Asthma attack prevalence rate is 44% higher for African-American children compared to Caucasian children\(^3\)

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2 Third National Health and Nutritional Examination Survey (1988-94)
Why are we concerned about diesel exhaust particles (DEP)?

- > 90% are fine (0.1 – 2.5 µm) or ultrafine (< 0.1 µm) in size

- Inert carbon core with large surface area per unit of mass
  Ideal for absorbing heavy metals and organic PAHs

- ~25% of all PM from fuel combustion is derived from diesel

- Buses, trucks, and other heavy vehicles are major sources of ambient DEP
What is the relationship of DEP and health effects?

- Increases TH$_2$ cytokine production
- Enhances allergen specific IgE production in the upper airway after intranasal allergen exposure
- Binds with allergens and can be co-deposited into the airways
- Generates reactive oxygen species (ROS) associated with inflammation and lung damage
- Produces ROS after co-exposure with endotoxin in animal studies
Up to 60,000 Trucks/Day on Cincinnati’s Interstates
Infant Eligibility and Recruitment

- Full-term infants born in the Ohio/Kentucky River Valley region were identified from birth records (2001-2003)

- Birth address geocoded and initially grouped:
  
  **EXPOSED:** Infants residing < 400 meters (m) from highway (> 1000 trucks/day)

  **UNEXPOSED:** Infants residing > 1500 m from major road

- Parents recruited at infants’ age 6 months and screened for allergy symptoms and tested for SPT+
Recruitment Results
(over 20 months)

• **7352 letters sent to families**

• **2265 completed eligibility survey (31%)**

• **881 parents had allergy symptoms and were SPT+ to 1+/15 aeroallergens**

• **758 infants enrolled (SPT to 15 pollen, mold, dust, or animal and milk and egg)**
CCAAPS Methods

- **Annual study visits ages 1-4**
  - SPT (15 aeroallergens, milk and egg)
  - Physical examination
  - Health questionnaire (ISAAC)
  - Hair sample
  - DNA sample

- **Home Assessments (8, 24 mo)**
  - Measure visible mold in home
  - Collect dust sample
    - (cat, dog, dust mite, cockroach, (1-3)-β-glucan & endotoxin)
Central Question 1

Are infants who are exposed to truck and bus traffic exhaust particles at an increased risk for developing allergies and allergic diseases?
Traffic Exposure Models

1. Proximity model using distance and type of truck and bus traffic

2. Ambient air sampling for estimates of DEP applied with land-use regression model
Proximity Model of Truck and Bus Exposure*

Geocode Address

Exposed to interstate, state route, or bus route?

Exposed to interstate?

Exposed to state route?

Exposed to bus route?

Speed limit greater than 50 m.p.h.?

Moving

Stop / Go

Unexposed

> 400 m from interstate
> 100 m from state route
> 100 m from bus route

Is proximity to truck and bus traffic associated with infant wheezing?

Proximity Model

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

CCAAPS Outdoor Air Sampling Methods

- **Outdoor ambient air sampling over 5 years**
  - 27 sampling sites
  - Collect PM 2.5
  - Elemental analysis
  - Elemental / Organic carbon (EC/OC)

- **ECAT-- Elemental Carbon Attributable to Traffic**
  - Portion of sampled EC attributed to traffic combustion
  - Ambient PM 2.5 + Trace Metals + Source apportionment + EC/OC analysis
  - Marker of diesel combustion
Estimated Individual Exposure to DEP for Each Child Using Land-use Regression Model
Multiple linear regression results for the association between sampled ECAT and land-use variables

**Final LUR Model Including Six Validation Sites \((R^2 = 0.74)\)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta)</th>
<th>(p)</th>
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</thead>
<tbody>
<tr>
<td>Elevation</td>
<td>-0.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of bus routes within 300 m</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>Truck intensity within 300 m</td>
<td>0.01</td>
<td>0.12</td>
</tr>
<tr>
<td>Wind index</td>
<td>0.09</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Are estimated levels of DEP exposure associated with wheezing without a cold at age 1 year?

<table>
<thead>
<tr>
<th>Exposure to ECAT (µg/m³)</th>
<th>aOR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>0.2</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>0.3</td>
<td>1.2 (1.01 – 1.50)</td>
</tr>
<tr>
<td>0.4</td>
<td>1.5 (1.01 – 2.26)</td>
</tr>
<tr>
<td>0.5</td>
<td>1.9 (1.02 – 3.39)</td>
</tr>
<tr>
<td>0.6</td>
<td>2.3 (1.03 – 5.09)</td>
</tr>
<tr>
<td>0.7</td>
<td>2.8 (1.04 – 7.65)</td>
</tr>
<tr>
<td>0.8</td>
<td>3.5 (1.05 – 11.49)</td>
</tr>
<tr>
<td>0.9</td>
<td>4.3 (1.06 – 17.26)</td>
</tr>
</tbody>
</table>

Adjusted for sex, race, maternal smoking, child care attendance, breast-feeding, pet ownership, and visible mold in the home.

Parents reported all addresses where their child spent ≥ 8 hours/week in the previous year
- Change in home address
- Relatives’ homes
- Daycare/Babysitters

All addresses reported for the first 36 months of the child’s life were geocoded

Time weighted average daily DEP exposure for each address calculated using the LUR model

Home dust endotoxin measured prior to age 1 year
Exposure to DEP Through Age One is Associated with Wheezing at 3 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High DEP*</th>
<th>High DEP/High Endotoxin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Aeroallergen Sensitization</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>(0.8 - 1.8)</td>
<td>(0.2 - 2.1)</td>
</tr>
<tr>
<td>Persistent Wheeze</td>
<td>1.5</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>(0.9 - 2.5)</td>
<td>(1.5 - 11.7)</td>
</tr>
<tr>
<td>Persistent Allergic Wheeze</td>
<td>2.1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>(1.02 - 4.31)</td>
<td>(0.8 - 14.1)</td>
</tr>
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</table>

* Adjusted for gender, race, and parental history of asthma

**Persistent wheeze at age three**: Report of recurrent wheezing at two consecutive annual visits or physician diagnosis of asthma

Ryan P. 2007 PhD dissertation
Effect Modification of High Endotoxin Exposure on the Association Between DEP and Persistent Wheeze

High diesel is defined as cumulative DEP exposure to 12 months $\geq 151 \mu g/m^3 \times$ year (top quartile)
High endotoxin is defined as $\geq 165$ EU/mg (top quartile)
OR adjusted for gender, race and parental history of asthma
Persistent wheeze at age three: Recurrent wheezing at 2 consecutive annual visits or physician DX of asthma
“Are infants who are exposed to truck and bus traffic exhaust particles at an increased risk for developing allergies and allergic diseases?”

- Residential proximity (< 100 m) to stop/go bus and/or truck traffic was significantly associated with infant wheezing

- LUR derived DEP estimates were associated with early childhood wheezing

- Exposure to DEP during critical periods of lung development may promote chronic inflammation leading to airway remodeling
Central Question 2

How do the proximity and land-use regression models compare when characterizing exposure?
Are unexposed infants really unexposed?

![Bar chart showing the distribution of ECAT (µg/m³) for unexposed infants (n = 347). The x-axis represents ECAT concentrations ranging from 0.2 to 0.9, and the y-axis represents the number of infants. The chart indicates that most unexposed infants have ECAT levels below 0.32 µg/m³.](image-url)
What is the exposure of infants in the moving group compared to the unexposed group?
How does the exposure of the stop/go group compare?
Answers to Central Question 2

“How do the proximity and land-use regression models compare when characterizing exposure?”

• Within each proximity group there is a continuum of exposure
  Exposure misclassification?
  All infants had some level of DEP exposure (0.20 -1.02 µg/m³)

• Infants designated as ‘unexposed’ by proximity had the lowest estimated DEP levels

• Exposure to moving or stop/go traffic had similar ranges of DEP
Central Question 3

Is there a gene*environment interaction between genotype and DEP exposure and childhood wheezing?
Glutathione S-transferase P1 (GST-P1)

- Chemicals in DEP induce the production of ROS, oxidative stress
  *Candidate gene: GST enzymes

- Predominant cytosolic GST expressed in lung epithelium

- A single nucleotide polymorphism (SNP) that converts an adenine → guanine results in a isoleucine → valine (Ile → Val) substitution in codon 105
  
  The Val^{105} allele has been shown to significantly lower GST enzyme activity impairing detoxification of ROS (Watson et al., Carcinogenesis, 1998)
Low and High DEP Exposure Estimate, GST-P1 Genotype, and Infant Wheeze

Low DEP (< 0.5 µg/m³)

High DEP (≥ 0.5 µg/m³)
Answers to Central Question 3

“Is there a gene*environment interaction between genotype and DEP exposure and childhood wheezing?”

• At low levels of DEP, no increased risk in wheezing, regardless of genotype.

• High levels of DEP may only impact those who are genetically at risk.

• Evidence exists for a gene:environment interaction between GSTP1 and DEP and wheezing in children

• Carriers of Val^{105} allele
  (22% African Americans, 15% Caucasians)
# Acknowledgements

<table>
<thead>
<tr>
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**Epidemiology/Statistics Team**

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THE DIESEL MADE 'EM DO IT.