Outdoor Air Pollution and Asthma

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Outdoor Air Pollution

• 14% of new cases and 15% of exacerbations of childhood asthma attributed to TRAP in a study of 10 European cities (*Eur Respir J*, 2013)
• Rapidly increasing pollution in mega-cities of the developing world
Outdoor Air Pollution

- Multiple sources
- Mixture of gases and particulate matter
- Traffic-related air pollution
Long-range transport of aerosols and gases

- Natural and anthropogenic emissions from the Earth (CH₄, CO, CO₂, VOCs, sulphate, black carbon, dust, N₂O, CFCs, NOₓ, ozone)
- Chemical transformation and deposition of pollutants
- Sulphur emissions from oceans
- Evaporation and convection

Aircraft emissions (NOₓ, black carbon, sulphate)

Halocarbons (CFCs)

Chemical transformation

Ozone destruction

Water vapour

Stratosphere

Troposphere

Free troposphere

Boundary layer

Cities

Agriculture

Desert dust

Transportation

Biomass burning

Forests and other ecosystems

Oceans

Chemical transformation

Ozone production
Air Pollution and Asthma

• Exacerbation
  – Multiple studies support short-term worsening of asthma with exposure to PM, O$_3$, NO$_2$ or traffic emissions

• New onset
  – Evidence less clear-cut, but accumulating for O$_3$, NO$_2$, and traffic
WHY THE SAN JOAQUIN VALLEY?

• High air pollution
  – Primarily mobile source
  – Valley topography
• Rapidly growing population
  – Fastest in California
  – 45% Latino
• Economic hardship
  – High unemployment
• High rates of asthma
Fresno Asthmatic Children’s Environment Study (FACES)

• Study of a panel of asthmatic children living within 20 km of the Fresno EPA monitoring station

• Goal: follow course of asthma in relation to air pollution

Funded by CA Air Resources Board and NHLBI
Short-term effects of air pollution on wheeze in asthmatic children in Fresno

- 315 children with asthma, 6-11 years of age, were recruited for FACES
- Ambient air quality data from the Fresno monitoring station were used to assign exposures to pollutants
- Wheeze was significantly associated with short-term exposures to
  - \( \text{NO}_2 \) [OR = 1.10 (1.02-1.20)];
  - \( \text{PM}_{10-2.5} \) [OR = 1.11 (1.01-1.22)]

Mann J, et al. *Environ Health Perspect* 2010;118:1497..
Regulatory T cells (Tregs) in Asthma

• **Treg** (CD4+CD25^{hi}CD127^{lo}) cells can control other immune cells
• **Foxp3** is a transcription factor associated with Treg function
• Children lacking Foxp3 have severe allergies, asthma, GI disease, and type I diabetes.
• Treg cells can inhibit effector T cells

Does exposure to air pollution decrease Treg function in asthma?

Is Foxp3 expression altered? If so, how?
Ambient air pollution impairs regulatory T-cell function in asthma

• FACES participants
  – Children 8-12 yrs with asthma (FA: n=71)
  – Serial spirometry and clinical symptom score
  – Blood samples
  – Individual estimates of exposure to PAHs

• Age-matched and sex-matched comparison groups
  – Fresno control children with no asthma and no allergies (FC: n=40)
  – Stanford children with asthma (SA: n=30)
  – Stanford control children with no asthma and no allergies (SC: n=30)

Treg Foxp3 expression is associated with asthma severity

Nadeau K, et al. 2010
**FOXP3** CpG regions are hypermethylated in FACES subjects

**Schematic View of Human Foxp3 CpG Islands**

- **Upstream CpG islands (-5786 to -5558 bp)**
- **Promoter islands (-210 to -25)** N=8
- **Intronic Enhancer** (no CpG islands)
- **Intronic islands (+3826 to +4321)** N=13

Binding site to:
- MeCP2, MBD2, DNTM1, DNTM3b
- SP1, AP1, TIEG1, NFAT, STAT5
- SMAD3, NFAT
- STAT5, CREB, ATF

**Percentage of Methylated CpG Motifs**

- **Foxp3 promoter**
- **Foxp3 intronic**
  - p≤0.001
  - p≤0.001
  - p≤0.001

Nadeau K, et al. 2010
Polycyclic Aromatic Hydrocarbons (PAHs)

- PAHs are formed by incomplete combustion of carbon-containing materials (wood, coal, diesel, gas; also cooked food and tobacco smoke)
Association between PAH exposure and methylation of \textit{FOXP3} in FA subjects

Nadeau K, et al. 2010
PAH exposure and wheeze in the FACES cohort

• Estimates of PAH exposure were associated with increased wheeze (n=283)
• The odds ratios for asthmatic children exposed to PAHs (ng/m3) ranged from 1.01 (95% CI, 1.00-1.02) to 1.10 (95% CI, 1.04-1.17)].
• This trend for increased wheeze persisted among all PAHs measured.
  – Phenanthrene was found to have a higher relative impact on wheeze.

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