Epidemic of Diabetes in the U.S.

- ~25 million Americans are diabetic
- Diabetes in children is usually type 1, but rate of type 2 increasing, especially among non-whites

![Graph showing rate of new cases of type 1 and type 2 diabetes among youth ages younger than 20 years, by race/ethnicity, 2002–2005]
Epidemic of Obesity in U.S.

- 34% of Americans are overweight (BMI 25-29.9) and 34% are obese (BMI $\geq$30)
- Percent of children who are obese
  - age 12-19 years: 18.1
  - age 6-11 years: 19.6
  - age 2-5 years: 10.4
Obesity Epidemic

- Thought to be due primarily to:
  - increased caloric intake from high consumption of sugar-containing drinks and high-caloric-density fast food
  - decreased energy expenditure from a sedentary lifestyle
- Animal evidence suggests that chemicals in the environment may be “obesogens”
  - ? ambient air pollutants
Linkage of Diabetes and Obesity

• Diabetes is a disorder of glucose metabolism
  – the body’s cells fail to take up glucose from the blood due to insulin resistance
• 80% of those who develop type 2 diabetes are obese
  – obesity is associated with insulin resistance
• Both diabetes and obesity are associated with increased systemic inflammation
Air Pollution and Obesity

• Jerrett et al. found that higher levels of traffic were associated with higher attained BMI in children aged 10–18 (Prev Med 2010)

• This team later showed that traffic-related air pollution was positively associated with growth in BMI (Environ Health 2014)

• Rundle et al. found that early-life exposure to PAHs was associated with increased BMI and obesity at age 7 (Am J Epidemiol 2012)

• Calderón-Garcidueñas reported that children exposed to high concentrations of ambient PM$_{2.5}$ in Mexico City had high blood leptin levels (Environ Res 2015)
Air Pollution and Diabetes

- Several studies have shown associations between diabetes in adults and exposure to traffic-related air pollution (TRAP)
- Few studies in children
  - Two studies have shown associations between ozone and type 1 diabetes (Hathout et al., *Pediatr Diabetes* 2006; Malmquist et al., *Environ Res* 2015*)
  *also NO₂*
  - Thiering et al. found an association with TRAP and insulin resistance (*Diabetologia* 2013)
Potential Mechanism

- Air pollution can induce oxidative stress and systemic inflammation
- PM$_{2.5}$ induced adipose tissue inflammation and insulin resistance in a mouse model of diet-induced obesity (Sun et al. Circulation 2009)

Hypotheses:
- Exposure to air pollution in utero and in early childhood increases risk of abnormal glucose metabolism later in childhood
- Exposure to air pollution in utero and in early childhood increases risk of obesity in later childhood

CHAPS
Children’s Health & Air Pollution Study
Specific Aim 1

• To determine whether chronic exposure to ambient air pollution, especially PAHs, is associated with:
  – increased HbA1c
  – increased BMI (ponderal index for infants)
  – increased levels of 8-isoprostane (biomarker of oxidative stress), CRP (biomarker of systemic inflammation), leptin, adiponectin, and high-density lipoprotein (biomarkers of abnormal fat and glucose metabolism)

CHAPS
Children’s Health & Air Pollution Study
Specific Aims 2 and 3

- To determine whether chronic exposure to air pollution-induced Treg and Teff cell dysfunction is associated with:
  - increased HbA1c
  - increased BMI (ponderal index for infants)
- To determine whether epigenetic modification of FOXP3 underlies the associations between Treg dysfunction and abnormal glucose regulation/increased BMI

![Schematic View of Human Foxp3 CpG Islands](image)
CHAPS Study Design

• Follow birth cohort to be recruited (birth data, including cord blood; annual visit ages 1 and 2; n=200)
• Child cohort (age 7, follow-up visit at age 9; n=200)
• Adolescent cohort (mean age 16, had previous P20 visit for comparison; n=200)
• For all participants
  – HbA1c, adiponectin and leptin, 8-isoprostane, CRP, IL-6, immune biomarkers (CyTOF), anthropometry, dietary and physical activity data at each visit
  – Estimated air pollution exposure pre-natal to present
Characteristics of first 100 adolescent participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Latino</td>
<td>48.9%</td>
</tr>
<tr>
<td>%White</td>
<td>40.6%</td>
</tr>
<tr>
<td>%African-American</td>
<td>7.3%</td>
</tr>
<tr>
<td>%Male</td>
<td>50.0%</td>
</tr>
<tr>
<td>%≥18</td>
<td>33.0%</td>
</tr>
<tr>
<td>%asthma</td>
<td>35.0%</td>
</tr>
<tr>
<td>%Rent</td>
<td>39.2%</td>
</tr>
<tr>
<td>%Income&lt;$15000</td>
<td>27.5%</td>
</tr>
<tr>
<td>%Income&gt;$50,000</td>
<td>39.6%</td>
</tr>
<tr>
<td>%Health Insurance</td>
<td>88.9%</td>
</tr>
</tbody>
</table>
Distribution of Outcome Variables (first 100 adolescent participants)

<table>
<thead>
<tr>
<th>Variable</th>
<th>25th percentile</th>
<th>Median</th>
<th>75th percentile</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>55.2</td>
<td>64.4</td>
<td>79.5</td>
<td>69.2</td>
<td>20.3</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.58</td>
<td>1.66</td>
<td>1.74</td>
<td>1.66</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI</td>
<td>20.7</td>
<td>22.5</td>
<td>27.3</td>
<td>25.8</td>
<td>10.1</td>
</tr>
<tr>
<td>% Body Fat</td>
<td>21.4</td>
<td>26.6</td>
<td>35.6</td>
<td>28.4</td>
<td>9.3</td>
</tr>
<tr>
<td>Waist Circumference (in)</td>
<td>29.3</td>
<td>31.3</td>
<td>35.2</td>
<td>33.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Waist-Height-Ratio</td>
<td>0.45</td>
<td>0.48</td>
<td>0.55</td>
<td>0.52</td>
<td>0.11</td>
</tr>
<tr>
<td>Diastolic BP (avg of 3)</td>
<td>55.0</td>
<td>60.7</td>
<td>69.3</td>
<td>61.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Systolic BP (avg of 3)</td>
<td>103.5</td>
<td>113.2</td>
<td>124.8</td>
<td>114.4</td>
<td>14.0</td>
</tr>
<tr>
<td>HbA1c (15-19 y/o)</td>
<td>5.0</td>
<td>5.1</td>
<td>5.3</td>
<td>5.13</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Median values (16 y/o)  
Boys   | Girls  | NHANES
---|--------|--------
BMI   | 22.3   | 22.1   |
% Body Fat | 21.4   | 32.4   |
Waist Circumference | 31.2   | 30.4   |
Waist-Height Ratio  | 0.45   | 0.48   |
HbA1c (15-19 y/o)  | 4.9    |        |
Summary

• The prevalence of both obesity and diabetes is high among Latino youth in the SJV
• Air pollution may increase the risk of both conditions by inducing oxidative stress and systemic inflammation
• PAH-induced immune dysfunction may be on the pathway
• The CHAPS design allows investigation of this potential pathway in multiple age cohorts (birth, child, and adolescent)
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