Insulin, Insulin Resistance, and Exposure to Ambient Particulate Matter Air Pollution

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Particulate Matter

- Complex mixture of extremely small particles and liquid droplets in the air
- Made up of: acids, organic chemicals, metals, soil and dust particles
- Particles ≤10 microns pass through nose and throat and enter the lungs, and cause serious health effects.
Significance and Rationale

- WHO: nearly 7 million premature deaths due to air pollution worldwide in year 2012

- Particulate matter (PM) air pollution: one of the largest avoidable causes of death and illness

- 347 million people worldwide have diabetes; 9.3% of the US adults have type 2 diabetes (T2D)

- A recent study from Canada reported that for every 10 $\mu g/m^3$ $\uparrow$ PM2.5, there was a 11% $\uparrow$ in incident diabetes (Chen et al. 2013)
Potential mechanisms: Air pollution induced IR and diabetes.
### Background

**Ambient PM and T2D**

<table>
<thead>
<tr>
<th>References</th>
<th>Outcomes and Exposures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al. 2010</td>
<td>T2D; 5-year mean PM10</td>
<td>↑PM ↑T2D</td>
</tr>
<tr>
<td>Puett et al. 2011</td>
<td>T2D; 1-year mean PM2.5, PM10, PM10-2.5</td>
<td>No significant associations</td>
</tr>
<tr>
<td>Coogan 2012</td>
<td>T2D; 1-year mean PM2.5, NOx</td>
<td>↑NOx ↑T2D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No association with PM2.5</td>
</tr>
<tr>
<td>Chen 2013</td>
<td>T2D; 6-year mean PM2.5</td>
<td>↑PM2.5 ↑T2D</td>
</tr>
<tr>
<td>Park 2015</td>
<td>T2D prevalence and incidence; 1-year mean PM2.5 and NOx</td>
<td>↑PM2.5 and ↑NOx ↑T2D prevalence, but not with incidence</td>
</tr>
</tbody>
</table>
## Background

### Ambient PM and Glucose Homeostasis Measures

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<thead>
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<tbody>
<tr>
<td>Chuang 2011</td>
<td>Glucose, HBA1c; 1-year mean PM10 and PM2.5</td>
<td>↑PM ↑glucose and HBA1c</td>
</tr>
<tr>
<td>Thiering 2013</td>
<td>HOMA-IR; 2-year mean PM10, PM2.5</td>
<td>↑PM ↑HOMA-IR</td>
</tr>
<tr>
<td>Tamayo 2014</td>
<td>HBA1c; 1-year mean PM10</td>
<td>↑PM ↑HBA1c</td>
</tr>
<tr>
<td>Eze 2015</td>
<td>MetS components; 10-year mean PM10 and NO2</td>
<td>↑PM ↑MetS</td>
</tr>
</tbody>
</table>
Research Gaps

- Long-term PM exposures
- Cross-sectional designs
- Younger populations
- Heterogeneous definitions of diabetes
- Variable measures of glucose homeostasis
- Inconsistent exposure-outcome associations
To determine whether ambient PM is associated with impaired glucose homeostasis among women participating in the Women’s Health Initiative Clinical Trials (WHI CT)
Research Questions

1. Is short-term ambient PM exposure associated with impaired glucose homeostasis (insulin and insulin resistance) among post-menopausal women?

2. Is long-term ambient PM exposure associated with impaired glucose homeostasis (insulin and insulin resistance) among post-menopausal women?
Methods

Study Population
- WHI CT (Core analytes sample)

Design
- Longitudinal, repeated measures

Inclusions
- Center- and race-stratified 6% random minority oversample
- Data available at SV and AV 1,3 or 6

Exclusions
- Prevalent diabetes at SV (n=525 participants)
- Incident diabetes after baseline

Final Sample
- n=4,019 participants at SV
- n=15,221 observations over time
Outcomes: insulin (uIU/mL), insulin resistance (HOMA-IR), and insulin action (TG/HDL ratio)

Exposure: residential PM10 (2-day and 365-day mean)

Covariates: socio-demographic; clinical and behavioral; temporal and meteorological; and neighborhood socioeconomic
Methods

- **Exposure estimation method:** national scale, log normal ordinary kriging model (Liao et al. 2006)

- **Multiple imputation:** STATA using MI/CE method to impute missing outcomes, exposures and covariates
Methods

Statistical Analysis:

- 3-level, mixed-effects longitudinal models
  - Log-transformed outcomes
  - Random effects:
    - intercept & slope for PM @ center level (3)
    - intercept & slope for time @ participant level (2)
    - error @ measure level (1)
  - Implemented in STATA XTMIXED (MI ESTIMATE)
  - PM effects expressed as %Δ per 10 ug/m³ ↑ in PM

- All models were IPW for joint probability of sampling and attrition
Methods

3-level mixed effects model

\[
Y_{ijk} = \beta_1 + \beta_2 P_{ijk} + \beta_3 t_{ijk} + \beta_4 C_{ijk} + b_{1k}^{(3)} + b_{2k}^{(3)} (P_{ijk}) + b_{1jk}^{(2)} + b_{3jk}^{(2)} (t_{ijk}) + e_{ijk}^{(1)},
\]
Models:
- Model 1: unadjusted
- Model 2: + participant socio-demo attributes
- Model 3: + behavioral
- Model 4: + clinical
- Model 5: + temporal and meteorological
- Model 6: + Neighborhood SES
- Model 7: + CT arms
# Results:
## Demographics and Behavioral Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Weighted Mean (SE) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>62.6 (0.1)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>83.0</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>9.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.0</td>
</tr>
<tr>
<td>Others</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Less than college graduate</td>
<td>63.3</td>
</tr>
<tr>
<td>Bachelor degree and more</td>
<td>36.6</td>
</tr>
<tr>
<td><strong>Current Smoking</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.8</td>
</tr>
<tr>
<td>No</td>
<td>91.2</td>
</tr>
<tr>
<td><strong>Current Drinking</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57.1</td>
</tr>
<tr>
<td>No</td>
<td>42.8</td>
</tr>
</tbody>
</table>
### Results:
Clinical and Environmental Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Weighted Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical measures</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>94.2 (0.2)</td>
</tr>
<tr>
<td>Insulin, ul U/ mL</td>
<td>10.9 (0.1)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.6 (0.03)</td>
</tr>
<tr>
<td>TG/ HDL ratio</td>
<td>0.5 (0.01)</td>
</tr>
<tr>
<td><strong>PM(_{10}) exposure ((\mu g/ m^3))</strong> *</td>
<td>29.0 (0.2)</td>
</tr>
<tr>
<td><strong>PM(_{10}) exposure ((\mu g/ m^3))</strong> **</td>
<td>27.8 (0.1)</td>
</tr>
</tbody>
</table>

PM\(_{10}\), particulate matter of <10 μm in diameter.

* 2-day mean over exam day and prior day
** 365-day mean over exam day and 364 prior days
## Results:
### Short-term PM and Glucose Homeostasis Measures

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Models</th>
<th>%Δ</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Unadjusted</td>
<td>-0.71%</td>
<td>-1.43%, 0.02%</td>
</tr>
<tr>
<td></td>
<td>Fully Adjusted *</td>
<td>-0.87%</td>
<td>-1.69%, -0.03%</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Unadjusted</td>
<td>-1.01%</td>
<td>-1.81%, -0.20%</td>
</tr>
<tr>
<td></td>
<td>Fully Adjusted *</td>
<td>-1.11%</td>
<td>-2.00%, -0.21%</td>
</tr>
<tr>
<td>TG/HDL ratio</td>
<td>Unadjusted</td>
<td>0.11%</td>
<td>-0.95%, 1.17%</td>
</tr>
<tr>
<td></td>
<td>Fully Adjusted *</td>
<td>0.43%</td>
<td>-0.63%, 1.51%</td>
</tr>
</tbody>
</table>

*Adjusted for participant sociodemographic, behavioral, clinical, temporal, meteorological, neighborhood socioeconomic attributes & CT arms

%Δ = percent change per 10 ug/m³ ↑ 2-day mean PM
### Results:

#### Long-term PM and Glucose Homeostasis Measures

<table>
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<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Unadjusted</td>
<td>-0.71%</td>
<td>-2.09%, 3.58%</td>
</tr>
<tr>
<td></td>
<td>Fully Adjusted *</td>
<td>-1.72%</td>
<td>-5.23%, 1.91%</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Unadjusted</td>
<td>-0.06%</td>
<td>-2.99%, 2.95%</td>
</tr>
<tr>
<td></td>
<td>Fully Adjusted *</td>
<td>-2.51%</td>
<td>-6.37%, 1.51%</td>
</tr>
<tr>
<td>TG/HDL ratio</td>
<td>Unadjusted</td>
<td>-0.11%</td>
<td>-2.99%, 2.85%</td>
</tr>
<tr>
<td></td>
<td>Fully Adjusted *</td>
<td>-1.84%</td>
<td>-5.24%, 1.68%</td>
</tr>
</tbody>
</table>

*Adjusted for participant sociodemographic, behavioral, clinical, temporal, meteorological, neighborhood socioeconomic attributes & CT arms

%Δ = percent change per 10 ug/m³ ↑ 365-day mean PM
Sensitivity Analysis

Adjustments
- total caloric intake
- temporal/seasonal covariates (harmonics of time; season indicators; day of week)

Outlying/influential PM concentrations
- identified by an ESD multiple outlier procedure

PM Exposure Definitions
- 1- through 7-day means over lag days 0-7
- 2-day mean at different lags
- categorical (PM deciles)
- Used monthly PM estimates (Yanosky estimates) for long-term PM10 exposure

Alternative Models
- fixed effects
- one- & two-level
Conclusion

- Null to negative associations between glucose homeostasis measures and short- and long-term PM10 exposures
**Interpretation/Discussion**

- **Potential mechanisms** *(Wang 2009; Ozcan 2012)*
  
  **Short-term exposure**
  
  PM $\rightarrow$ endoplasmic reticulum (ER) stress  
  ER stress $\rightarrow$ unfolded protein response (UPR)  
  UPR $\rightarrow$ ↓protein misfolding $\rightarrow$ adaptive glucose homeostasis  

  **Long-term exposure**
  
  PM $\rightarrow$ ER stress $\rightarrow$ apoptosis  
  Apoptosis $\rightarrow$ exacerbated hyperglycemia
Limitations and Strengths

Limitations:
- Study of relatively healthy, postmenopausal female volunteers in a CT
- Focus on 1993-2005 PM exposures

Strengths:
- Longitudinal design with repeated measures
- Short- and long-term PM exposures
- Multiple glucose homeostasis outcomes
- Multi-level mixed model
- Weighting for sampling and selection probabilities
- Multiple imputation of missing variables using chained equations
Study Collaborators

- Eric Whitsel
- Regina Shih
- Beth Ann Griffin
- Gregory Wellenius
- Duanping Liao
- Jeff Yanosky
- Jamie Madrigano
- Jay Stewart
THANK YOU