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

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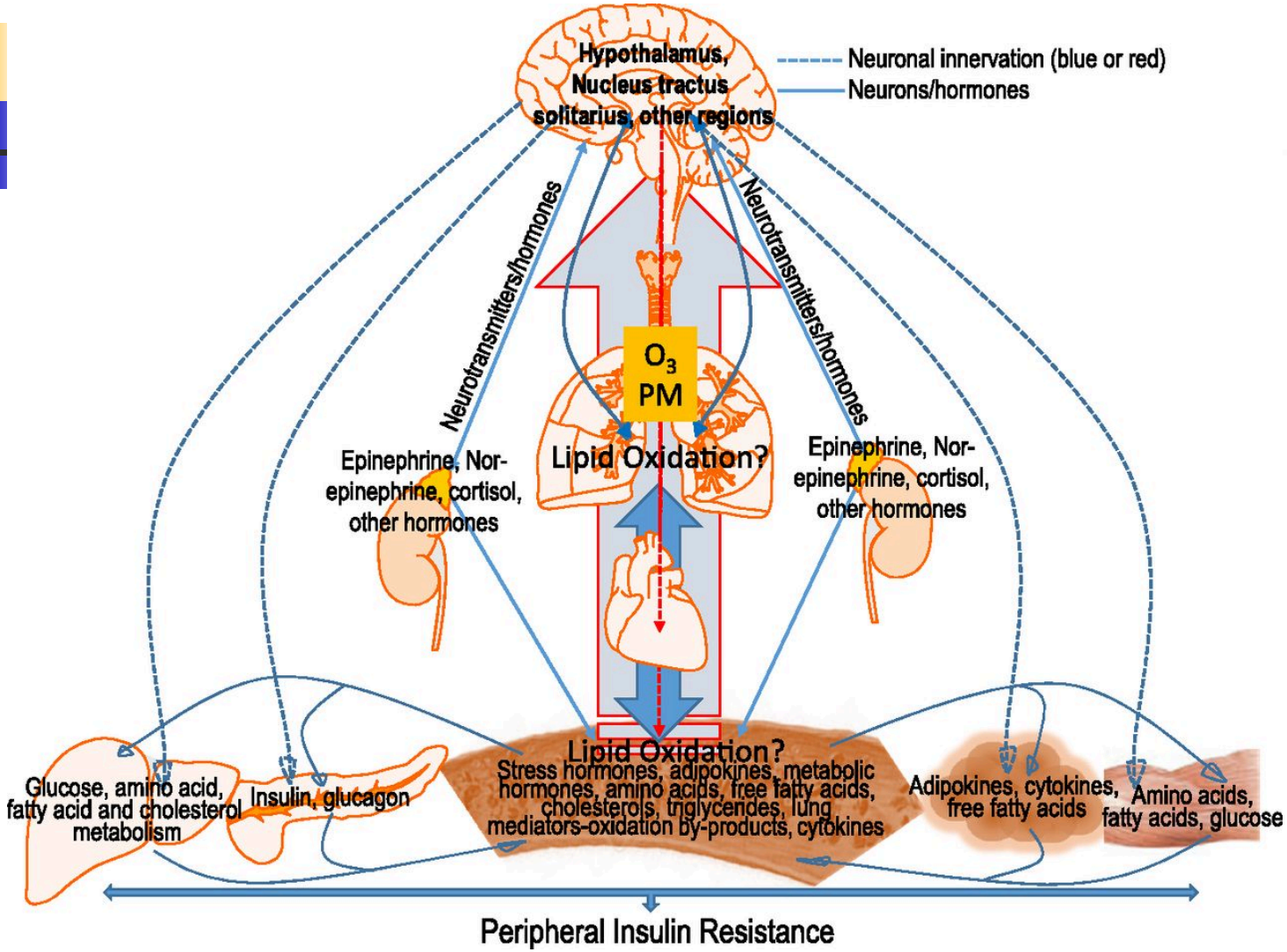
Particulate Matter

- 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 μg/m3 ↑PM2.5, there was a 11%↑in incident diabetes (Chen et al. 2013)

Potential mechanisms: Air pollution induced IR and diabetes.



Urmila P. Kodavanti Diabetes 2015;64:712-714

American Diabetes Association.

Background

Ambient PM and T2D

References	Outcomes and Exposures	Results
Kramer et al. 2010	T2D; 5-year mean PM10	↑PM ↑T2D
Puett et al. 2011	T2D; 1-year mean PM2.5, PM10, PM10-2.5	No significant associations
Coogan 2012	T2D; 1–year mean PM2.5, NOx	↑NOx ↑T2D No association with PM2.5
Chen 2013	T2D; 6-year mean PM2.5	↑PM2.5 ↑T2D
Park 2015	T2D prevalence and incidence; 1-year mean PM2.5 and NOx	↑PM2.5 and ↑NOx ↑T2D prevalence, but not with incidence

Background

Ambient PM and and Glucose Homeostasis Measures

References	Outcomes and Exposures	Results
Chuang 2011	Glucose, HBA1c; 1-year mean PM10 and PM2.5	↑PM ↑glucose and HBA1c
Thiering 2013	HOMA-IR; 2-year mean PM10, PM2.5	↑PM ↑HOMA-IR
Tamayo 2014	HBA1c; 1-year mean PM10	↑PM ↑HBA1c
Eze 2015	MetS components; 10-year mean PM10 and NO2	↑PM ↑MetS

Research Gaps

- Long-term PM exposures
- Cross-sectional designs
- Younger populations
- Heterogeneous definitions of diabetes
- Variable measures of glucose homeostasis
- Inconsistent exposure-outcome associations

Study Aim

- 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

Methods

- **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 MICE method to impute missing outcomes, exposures and covariates

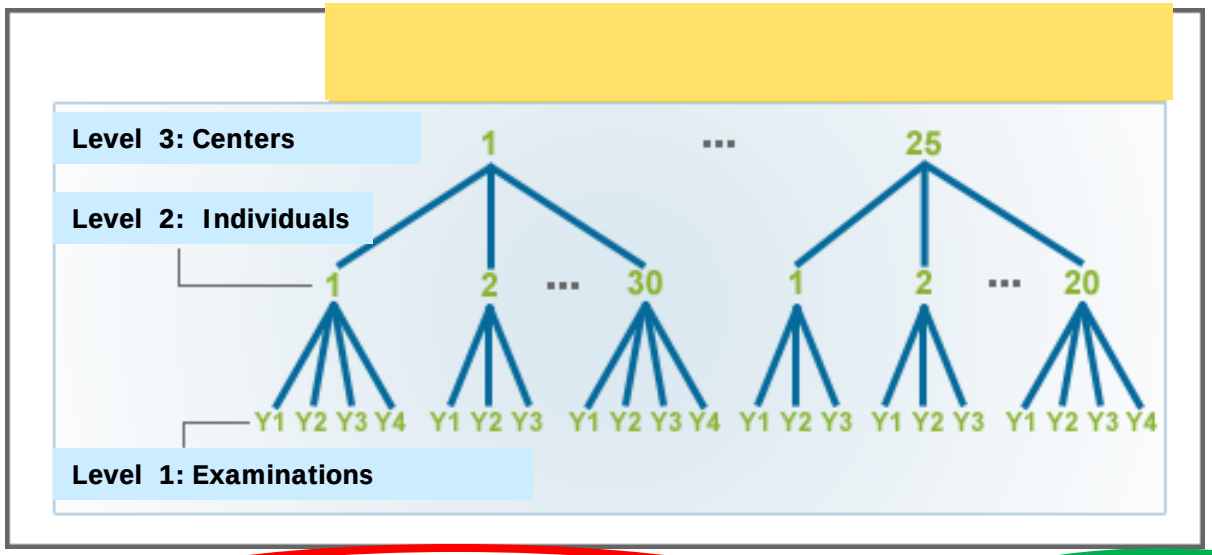
Methods

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/m^3 ↑in PM
- All models were IPW for joint probability of sampling and attrition

Methods

3-level mixed effects model



$$Y_{ijk} = \beta_1 + \beta_2 P_{ijk} + \beta_3 t_{ijk} + \beta_4 C_{ijk} + b^{(3)}_{1k} + b^{(3)}_{2k}(P_{ijk}) + b^{(2)}_{1jk} + b^{(2)}_{3jk}(t_{ijk}) + e^{(1)}_{ijk},$$

Methods

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

Characteristics	Weighted Mean (SE) or %
Age, years	62.6 (0.1)
Race / ethnicity	
Non-Hispanic White	83.0
Non-Hispanic Black	9.2
Hispanic	4.0
Others	3.7
Education	
Less than college graduate	63.3
Bachelor degree and more	36.6
Current Smoking	
Yes	8.8
No	91.2
Current Drinking	
Yes	57.1
No	42.8

Results:
Clinical and Environmental Characteristics

Characteristics	Weighted Mean (SE)
Clinical measures	
Glucose, mg/dL	94.2 (0.2)
Insulin, uIU/mL	10.9 (0.1)
HOMA-IR	2.6 (0.03)
TG/HDL ratio	0.5 (0.01)
PM_{10} exposure ($\mu g/m^3$)*	29.0 (0.2)
PM_{10} exposure ($\mu g/m^3$)**	27.8 (0.1)

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

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

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

%Δ = percent change per 10 ug/m^3 ↑ 2-day mean PM

Results:

Long-term PM and Glucose Homeostasis Measures

Outcomes	Models	%Δ	95% CI
Insulin	Unadjusted	-0.71%	-2.09%, 3.58%
	Fully Adjusted *	-1.72%	-5.23%, 1.91%
HOMA-IR	Unadjusted	-0.06%	-2.99%, 2.95%
	Fully Adjusted *	-2.51%	-6.37%, 1.51%
TG/HDL ratio	Unadjusted	-0.11%	-2.99%, 2.85%
	Fully Adjusted *	-1.84%	-5.24%, 1.68%

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

%Δ = percent change per 10 ug/m^3 ↑ 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 → endoplasmic reticulum (ER) stress

  ER stress → unfolded protein response (UPR)

  UPR → ↓protein misfolding → adaptive glucose homeostasis

  Long-term exposure

  PM → ER stress → apoptosis

  Apoptosis → 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
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THANK YOU