Project report:

Particulate Matter and High Density Lipoprotein Dysfunction:

A Pilot Study involving the Global Range of Ambient Exposure Levels

Jianping Li, MD, PhD
PKU First Hospital
**UM-PKU Joint Initiative - Hypotheses and Aims**

**HDL DYSFUNCTION AS A MECHANISTIC LINKAGE BETWEEN PM$_{2.5}$ AND CV DISEASES**

Our overarching hypothesis is that PM$_{2.5}$ exposure (across the global range of ambient concentrations) is capable of impairing several facets of HDL functionality which after serve as key mechanistic pathways in the instigation of adverse CV changes induced

Specific Aim 1 (UM Site): To determine the effect of sub-acute ambient PM$_{2.5}$ exposures at “low levels” (range: 5-35 µg·m$^3$) in Southeastern Michigan on HDL function and its associations with CV biomarker outcomes among 50 healthy adults without CV disease

Specific Aim 2 (PKU Site): To determine the effect of sub-acute ambient PM$_{2.5}$ exposures at “high levels” (range: 50-150 µg·m$^3$) in the Beijing area on HDL functionality and its impact upon CV biomarker outcomes among 50 adults without CV disease

**Main Outcomes**

1) Myeloperoxidase (MPO)-induced HDL oxidation products (chlorotyrosine, nitrotyrosine) by MS
2) HDL-induced cholesterol efflux capacity
3) Detailed assessment of the HDL proteome (protein cargo) by MS
STUDY TEAM OF INVESTIGATORS

PU Investigators

1. Jianping Li (PI) (Cardiology): Oversight of entire study and completion of CV biomarker protocols at PU.

2. Wei Huang (Co-PI) (Epidemiology): Responsible for air pollution/environmental exposure assessments at PU.

3. Lemin Zheng (Co-I) (Biochemistry): Responsible for HDL function (RCT, endothelial assays) of PU samples.

UM Investigators

1. Robert Brook (PI) (Cardiology): Oversight of entire study and completion of CV biomarker protocols at UM.

2. Sub Pennathur (Co-I) (Nephrology): Mass-spectrometry HDL function assays from samples at both sites.

3. Eugene Chen (Co-I) (Cardiology): Determine HDL-C efflux capacity of UM blood samples.

4. Masako Morishita (Co-I) (UM SPH): Analyzing all air pollution exposure assessments at the UM study site.

5. Lu Wang (Co-I) (SPH): Responsible for all data management and analyses (both sites).
UNIQUE ASPECTS OF JI STUDY

1. First study of the effect of ambient PM$_{2.5}$ levels on HDL function

2. Multiple HDL functionality outcomes evaluated using cutting-edge methods in experienced lab (proteome)

3. Harmonized protocols at PU and UM site
   - Single core at UM for all HDL outcomes
   - Similar subjects & exposure measures at both sites
   - Unprecedented opportunity to explore full exposure range impact of air pollutants on HDL function and linkages to similar CV outcomes

4. Both ambient community and personal-level air pollutants monitored

5. Highly-experience team with track record of collaborations
Study subjects enrollment and following

Screened: 95
Enrolled: 78

Follow up:
1st: Nov.24, 2014~Jan.8, 2015
3st: Sep. 21, 2015~Nov. 9, 2015


HDL cholesterol efflux capacity (HDL-CEC)
HDL oxidization index (HDL-OI)
Data analyses, Manuscript preparation and submission

• Main result of the project (Effect of air pollution on HDL function) had been sent to JAMA-Cardiology

• Combined data analyses (i.e. Effect of air pollution on blood pressure is under preparation)

• Effect of air pollution on other cardiovascular biomarkers (i.e. Micro-particles, endothelial functions, are under preparation)
Funding applied based on this project:

- National Nature Science Foundation Project: The Influence of PM2.5 on the Level of Particulates and Its Effects on Inducing Cardiovascular injuries.(81470025)
- National Nature Science Foundation Project: The role of loss-of-function HDL-C in PM2.5 induced endothelial injury(2017, funded)
- National Nature Science Foundation Key Project: Underlying Pathophysiologic Pathways and Mechanisms in PM2.5 and its organic constituents exposure attributed Cardiovascular Dysfunction In Vulnerable and Healthy Groups (being estimated)
Ambient Air Pollution is Associated with High Density Lipoprotein Dysfunction among Healthy Adults in Beijing, China

Jianping Li 1#, Changping Zhou 2#, Hongbing Xu 3#, Robert D. Brook4, Shengcong Liu 1, Yang Wang 3, Tieci Yi 1, Qian Zhao 3, Jie Chen 3, Xiaoming Song 3, Yi Zhang 3, Subramaniam Pennathur 5, Sanjay Rajagopalan 6, Lemin Zheng 2*, Wei Huang 3*
Effect of personal exposure to air pollution

A

Changes in HDL-C (mg/dL)

PM$_{2.5}$  BC

Changes in non-HDL-C (mg/dL)

PM$_{2.5}$  BC

C

Changes in HDL-C% (C)

PM$_{2.5}$  BC

D

Changes in HDL-OL (RUC/µg HDL-C·min)

PM$_{2.5}$  BC

Lag Hours
Effect of ambient air pollution
University of Michigan-Peking

University
JOINT INSTITUTE PROJECT
Cardiometabolic effects of PM across the global spectrum of air pollution levels

Robert D. Brook, MD
Director, Comprehensive Hypertension Center
Professor of Cardiovascular Medicine
University of Michigan
Summary of Michigan Study Results

- Trial has been completed (April 2016)
  - N=50 participants
  - Exposures: Personal & ambient PM/temp twice per participant
  - Outcomes: BP, endothelial function (FMD), heart rate variability (HRV), aortic compliance
  - HDL function: oxidative stress and cholesterol efflux

Publications - UM Site

- Personal-Level Exposure to Environmental Temperature is a Superior Predictor of Endothelial-Dependent Vasodilatation than Outdoor-Ambient Level. J Am Soc Hypertens 2017 (in press)
- 3 manuscripts in review/preparation for 2017
Personal-Level Exposure to Environmental Temperature is a Superior Predictor of Endothelial-Dependent Vasodilatation (FMD) than Outdoor-Ambient Level

- Colder outdoor-temperatures (per -10° C) over the previous 1-6 days were associated with decreases in FMD: -0.57% to -0.62% (p=0.006). Mean temp: 4.4C [range: -3.9 to 23.2]

- 10° C decrease in personal-level temperature exposure in the prior 24-hours was associated with a greater decrement in FMD: **-2.44% (p=0.038)**.

- Short-term exposures to colder environmental temperatures reduced endothelial-dependent vasodilatation, supporting the epidemiological link between cold and cardiovascular events. We show for the first time that temperature exposures at the personal-level are more robust predictors of FMD than outdoor-ambient levels.

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PM levels in Beijing

<table>
<thead>
<tr>
<th>PM&lt;sub&gt;2.5&lt;/sub&gt; (µg/m³)</th>
<th>Obs</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>25&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Median</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal</td>
<td>253</td>
<td>52.4 ± 79.2</td>
<td>2.5</td>
<td>13.8</td>
<td>27.1</td>
<td>62.8</td>
<td>785.0</td>
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<tr>
<td>Outdoor 7-day average</td>
<td>255</td>
<td>86.7 ± 52.1</td>
<td>30.6</td>
<td>46.8</td>
<td>69.8</td>
<td>117.0</td>
<td>236.2</td>
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</table>

PM levels in Michigan

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>25&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Median</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Max</th>
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<tr>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt; (µg/m³)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Personal</td>
<td>95</td>
<td>12.2 ± 16.9</td>
<td>0.2</td>
<td>4.0</td>
<td>6.9</td>
<td>13.3</td>
<td>94.0</td>
</tr>
<tr>
<td>Outdoor 7-day average</td>
<td>94</td>
<td>9.1 ± 1.8</td>
<td>5.5</td>
<td>7.7</td>
<td>9.1</td>
<td>10.7</td>
<td>12.4</td>
</tr>
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</table>
Short-term Blood Pressure Responses to Ambient Fine Particulate Matter Exposures at the Extremes of Global Air Pollution Concentrations

Ambient PM2.5 exposures in Beijing raise BP over 1-7 days
Short-term Blood Pressure Responses to Ambient Fine Particulate Matter Exposures at the Extremes of Global Air Pollution Concentrations

<table>
<thead>
<tr>
<th>BMI_Index</th>
<th>BMI&lt;25</th>
<th>BMI&gt;=25</th>
</tr>
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No BP responses to much lower ambient PM2.5 levels in Michigan.
CONCLUSIONS

Short-term exposures to ambient fine particulate matter in a highly-polluted environment (BEIJING) promote elevations in blood pressure even among healthy young adults. The fact that no adverse responses were observed in a clean location (MICHIGAN) supports the key public health importance of international efforts to improve global air quality.
Short-term exposure to ambient fine particulate matter reduced HDL function (lowers CEC) even at low PM2.5 levels encountered in Michigan
谢谢