Mechanistic insights into air pollution and Type 2 diabetes.

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58-year-old patient with Type 2 Diabetes Mellitus (T2DM): HbA$_{1c}$=7.5 and Blood Pressure (BP)=135/80

10-year Cardiovascular (CV) event = 5%

OGTT = oral glucose tolerance test
OB = obese   NGT = no glucose intolerance
IGT = initial glucose intolerance
INS = insulin resistant
Multiple defects contribute to the progression of type 2 diabetes mellitus

De Fronzo’s Ominous Octet

- Decreased Insulin Secretion
- Increased Glucagon Secretion
- Increased HGP
- Islet-α cell
- Decreased Incretin Effect
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction
- Increased Lipolysis

Adapted from De Fronzo RA. Diabetes. 2009;58:773-95.
IF TRADITIONAL RISK FACTORS WERE WORSENED BY AIR POLLUTION... THE GLOBAL RISK POSED WOULD BE EVEN LARGER...
Number of Pollution Related Deaths = 9 Million

If traditional risk factors WERE WORSEned BY AIR POLLUTION… the global risk posed would be even larger…

Number of Pollution Related Deaths = ?

Zone 1
Well characterized health effects of well studied pollutants.

Zone 2
Emerging, but still unqualified, (Hypertension, diabetes, and others)

Zone 3
Inadequate characterized health effects of emerging pollutants.

Number of Pollution Related Deaths = ?

How may Air Pollution Cause Type 2 DM?

M = macrophage
T = T cell
GLUT = glucose transporter

M1↓M2

Th1↓Th2↓Treg

↑Lipogenesis
↓Lipolysis
↑Macrophages

↑Lipogenesis
↓Lipolysis
↑Gluconeogenesis
↓Gluolysis

↓Glucose uptake
↓GLUT4

↑Hypothalamic Inflammation

↑Glucose
↑Free fatty acids
↑insulin resistance

Rao X et al. Toxicol Sci. 2015 Feb;143(2):231-41
• Chronic low level inflammation represents a convergent pathway for multiple diseases
• Cellular inflammation has emerged as a primary determinant of many components of the metabolic syndrome

Chronic PM\textsubscript{2.5} Ambient Exposures (20 wk) Potentiates Inflammation/Insulin Resistance in Mice


FA = filtered air   PM = particulate matter SVF = ??
Inflammatory cytokines
Saturated fatty acids

Cytoplasm

IRS-1

IRS-2

JNK
IKK

Insulin receptor

Hyperglycemia
Hyperlipidemia

ER stress

Insulin action

Nucleus

AP1
NF-κB

Inflammatory genes
Hypothetical Model of PM$_{2.5}$ Mediated Hepatic Insulin Resistance (IR) and Steatosis

Does Air Pollution Induce Metabolic Changes and Shift in Thermogenesis?
Does Air Pollution Alter Brown Adipose Structure and Function?

Baby Fat May Help You Lose Weight
Long Term PM$_{2.5}$ Exposure (40 weeks): Impact on Mitochondrial Structure

FA = filtered air   PM = particulate matter
WAT = white adipose tissue   BAT = brown adipose tissue
PM$_{2.5}$ Mediated Changes in Whole Body Metabolism and Thermogenesis

Liu et al. Part Fibre Toxicol. 2014 May 30;11:27
Are Central Nervous System Pathways Responsible for Metabolic Control Involved?
Hypothalamic Inflammation with Long-Term Exposures in C57/Bl6 mice

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[Graph and images showing expression levels of various markers in different hypothalamic regions.]
Intracerebroventricular (ICV) infusion of IKKβ Inhibitor (IMD-0354) Inhibits PM$_{2.5}$ Effects

- **O$_2$** consumption (A), **CO$_2$** production (B), respiratory exchange ratio (C) and heat production (D) of mice measured by indirect calorimetry over a 24 hrs period (from 10:00 am to 10:00 am the next day) after 4 wks of PM$_{2.5}$ exposure and IKKβ inhibitor treatment. *P<0.05, **P<0.01, ***P<0.001 compared to FA-CON group; ###P<0.01, ####P<0.001 when compared PM-IMD group with PM-CON group. n=6 per group.

Liu et al 2014  Part Fib Tox
Regression associations between cumulative averages of daily PM$_{2.5}$ and metabolic outcomes over 0–90 days prior to FSIGT

1-SD (5.1 μg/m$^3$) increase in 0–40 days’ PM$_{2.5}$ was significantly associated with a 4.9% decrease in SI. Effect size similar to 1% increase in body fat.
Extreme Air Pollution Conditions Adversely Affect Blood Pressure and Insulin Resistance

The Air Pollution and Cardiometabolic Disease Study

Robert D. Brook, Zhichao Sun, Jeffrey R. Brook, Xiaoyi Zhao, Yanping Ruan, Jianhua Yan, Bhramar Mukherjee, Xiaoquan Rao, Fengkui Duan, Lixian Sun, Ruijuan Liang, Hui Lian, Shuyang Zhang, Quan Fang, Dongfeng Gu, Qinghua Sun, Zhongjie Fan, Sanjay Rajagopalan

Abstract—Mounting evidence supports that fine particulate matter adversely affects cardiometabolic diseases particularly in susceptible individuals; however, health effects induced by the extreme concentrations within megacities in Asia are not well described. We enrolled 65 nonsmoking adults with metabolic syndrome and insulin resistance in the Beijing metropolitan area into a panel study of 4 repeated visits across 4 seasons since 2012. Daily ambient fine particulate matter and personal black carbon levels ranged from 9.0 to 552.5 μg/m³ and 0.2 to 24.5 μg/m³, respectively, with extreme levels observed during January 2013. Cumulative fine particulate matter exposure windows across the prior 1 to 7 days were significantly associated with systolic blood pressure elevations ranging from 2.0 (95% confidence interval, 0.3–3.7) to 2.7 (0.6–4.8) mmHg per SD increase (67.2 μg/m³), whereas cumulative black carbon exposure during the previous 2 to 5 days were significantly associated with ranges in elevations in diastolic blood pressure from 1.3 (0.0–2.5) to 1.7 (0.3–3.2) mmHg per SD increase (3.6 μg/m³). Both black carbon and fine particulate matter were significantly associated with worsening insulin resistance (0.18 [0.01–0.36] and 0.22 [0.04–0.39] unit increase per SD increase of personal-level black carbon and 0.18 [0.02–0.34] and 0.22 [0.08–0.36] unit increase per SD increase of ambient fine particulate matter on lag days 4 and 5). These results provide important global public health warnings that air pollution may pose a risk to cardiometabolic health even at the extremely high concentrations faced by billions of people in the developing world today. (Hypertension. 2016;67:00-00. DOI: 10.1161/HYPERVENTIONAHA.115.06237.)

Online Data Supplement
ASPIRE: AIR POLLUTION: STRATEGIES FOR PERSONALIZED INTERVENTION TO REDUCE EXPOSURE

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