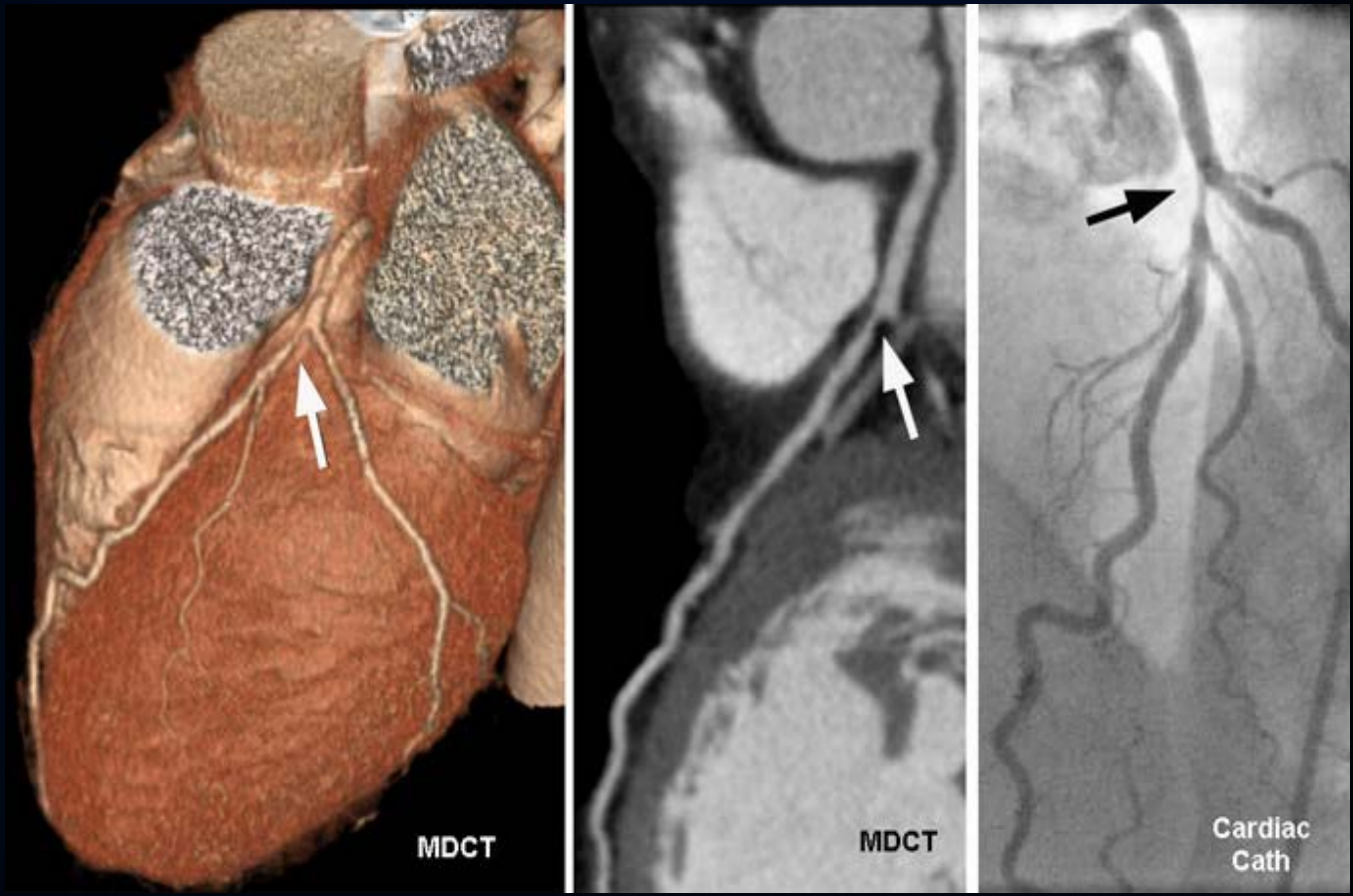
Mechanistic insights into air pollution and Type 2 diabetes.

Sanjay Rajagopalan, MD

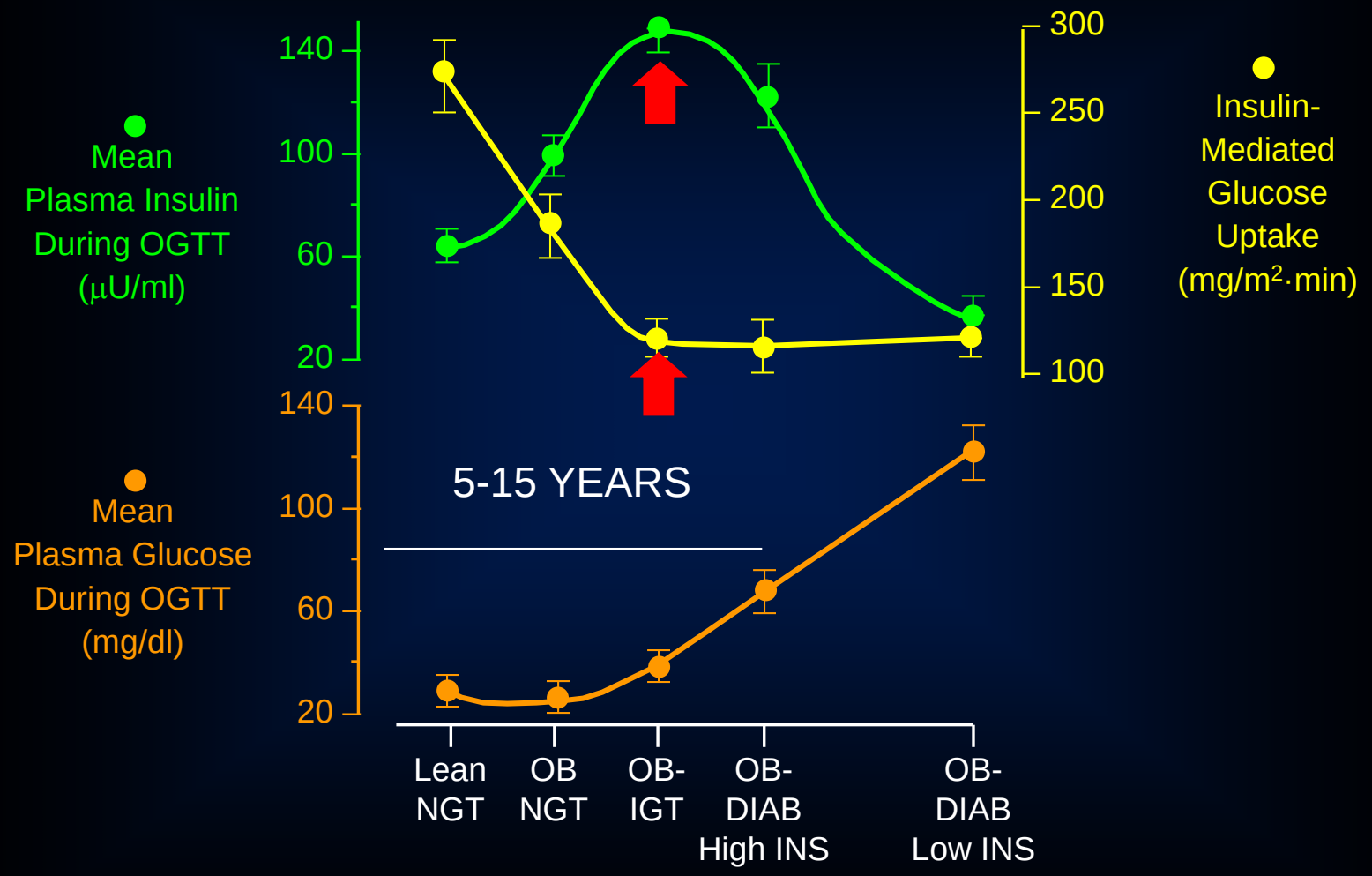
HEI Conference April 30, 2018

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%

Natural History of T2DM

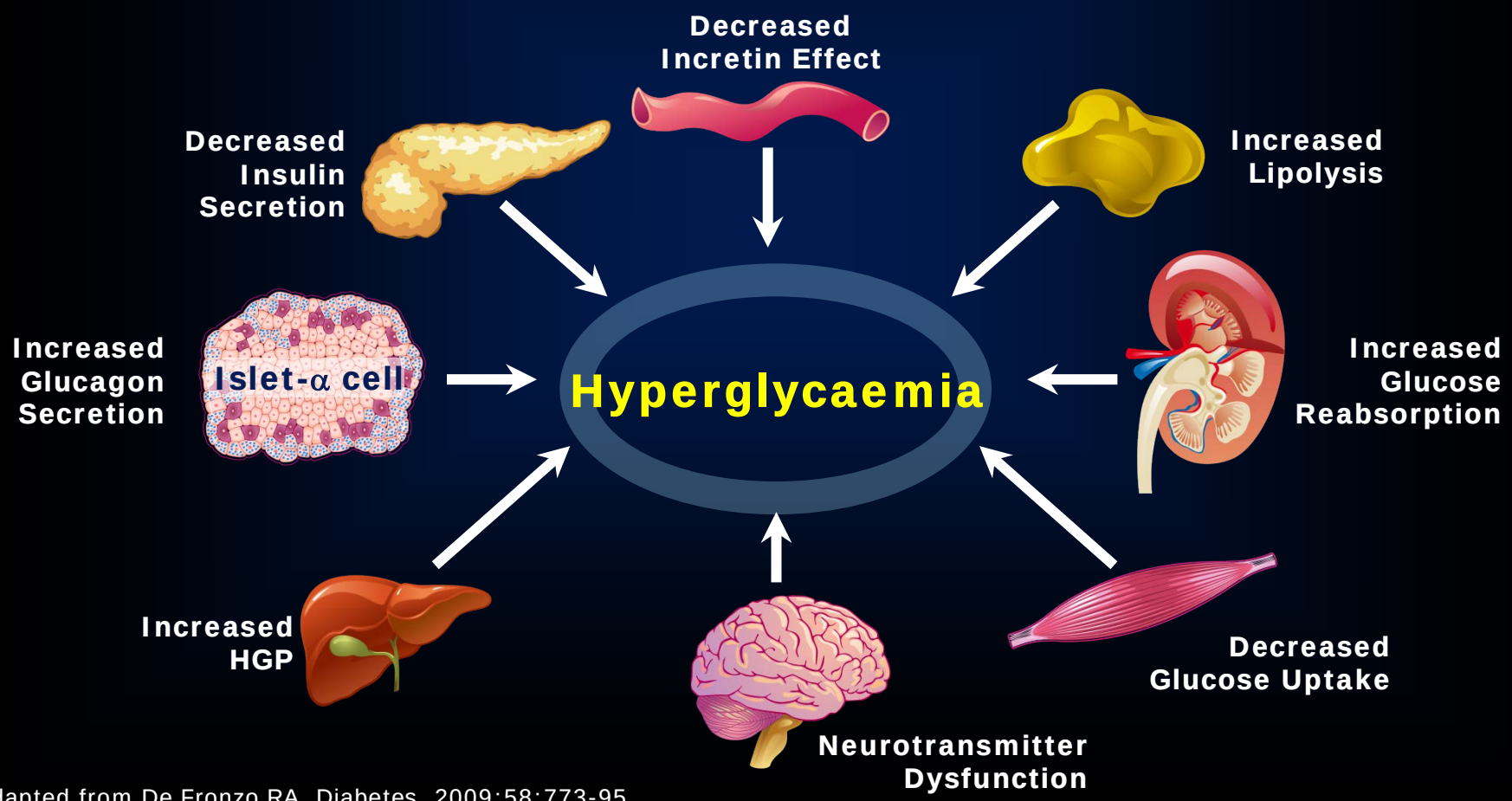


OGTT = oral glucose tolerance test
OB = obese NGT = no glucose intolerance
IGT = initial glucose intolerance
INS = insulin resistant

Defronzo & Felber. *Diabetes*. 1988; 37: 667-687 and *Metabolism*. 1990; 39: 1068-75.

Multiple defects contribute to the progression of type 2 diabetes mellitus

De Fronzo's Ominous Octet



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 = ?

Number of Pollution Related Deaths = ?

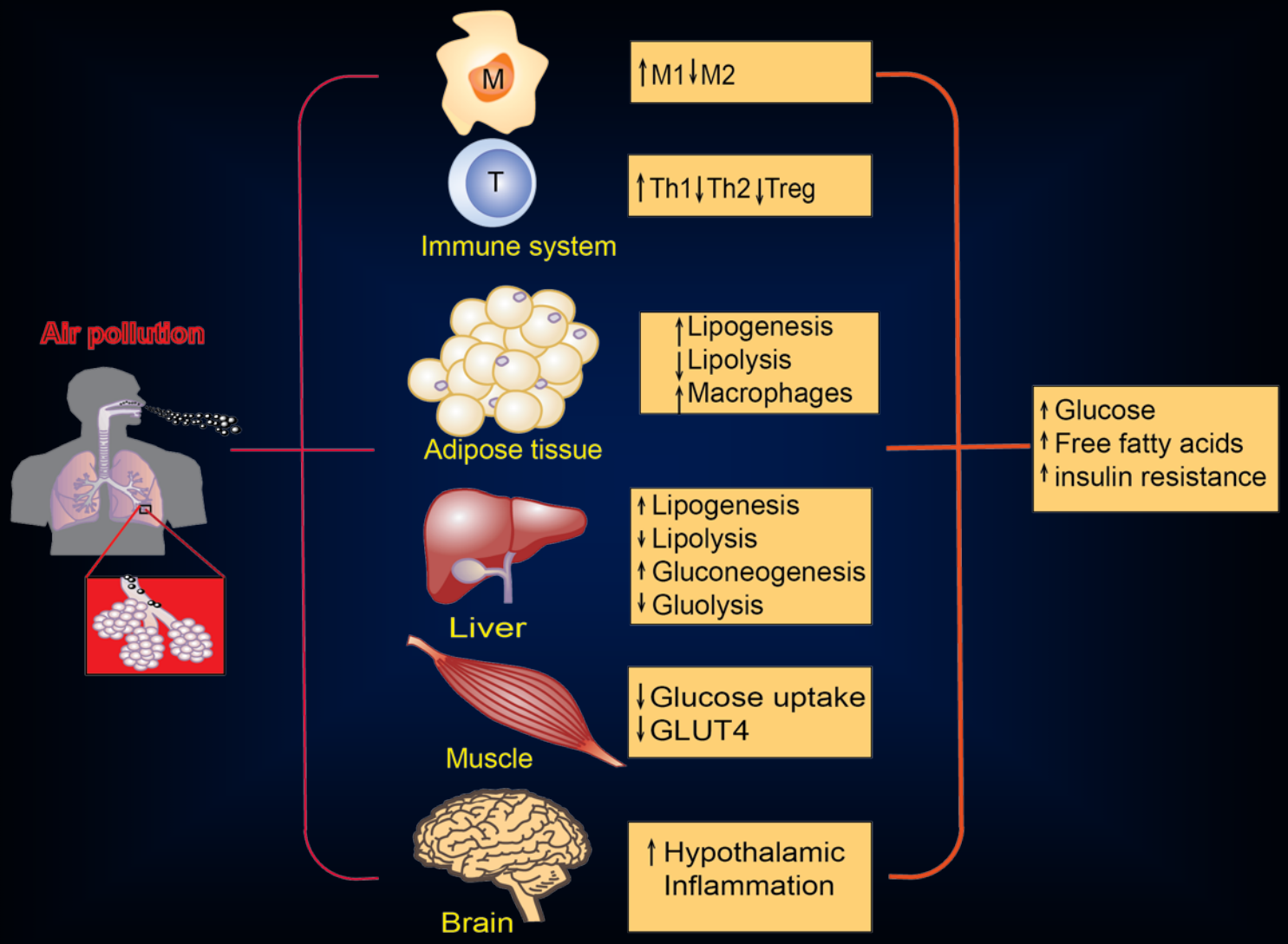
Zone 1
Well characterized health effects of well studied pollutants.

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

Zone 3
Inadequate characterized health effects of emerging pollutants.

Landrigan P et al. The Lancet Commission on pollution and health Lancet. 2017 Oct 17.

How may Air Pollution Cause Type 2 DM?



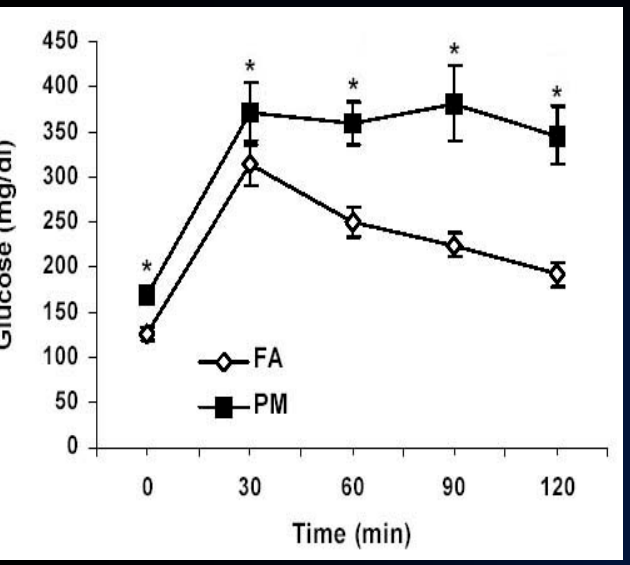
M = macrophage
T = T cell
GLUT = glucose transporter

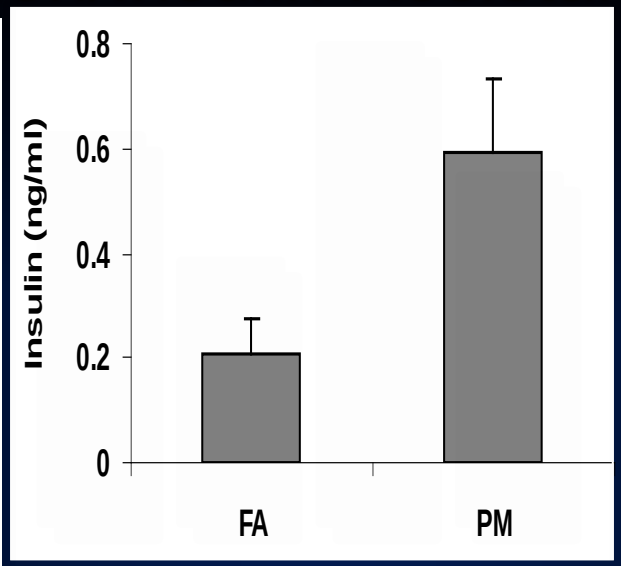
Rao X et al. Toxicol Sci. 2015 Feb;143(2):231-41

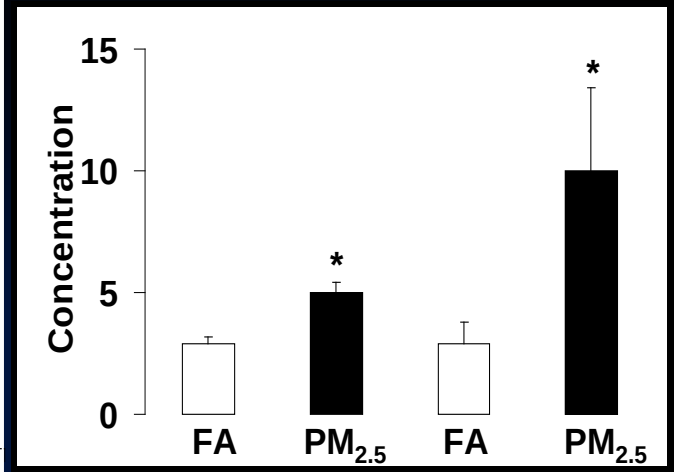
- Chronic low level inflammation represents a convergent pathway for multiple diseases
- Cellular inflammation has emerged as a primary determinant of many components of the metabolic syndrome

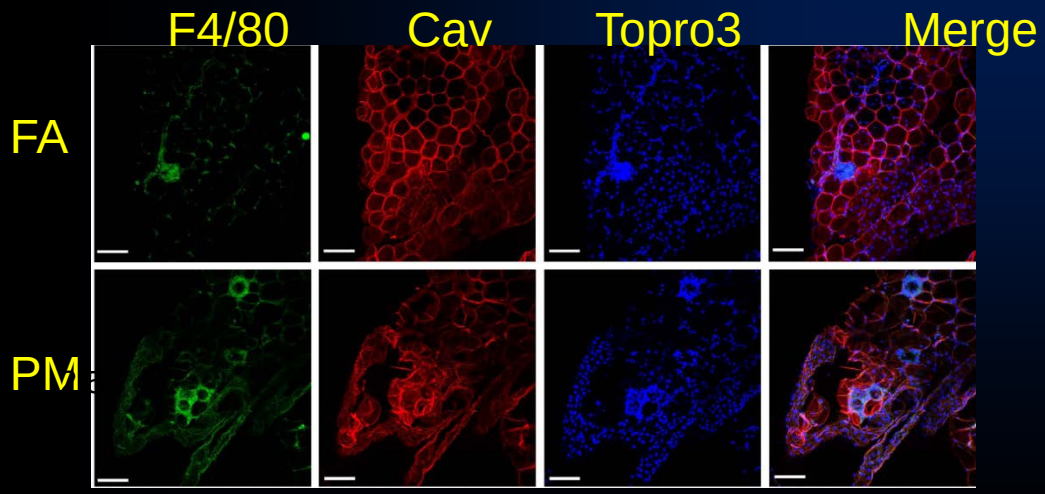
Hotamisligil G et al. Nature 2006; 444; 86-67; Shoelson S et al. JCI 2006; 116; 3015-26; Olefsky et al. Ann Rev Physiol 2010; 72; 1-28

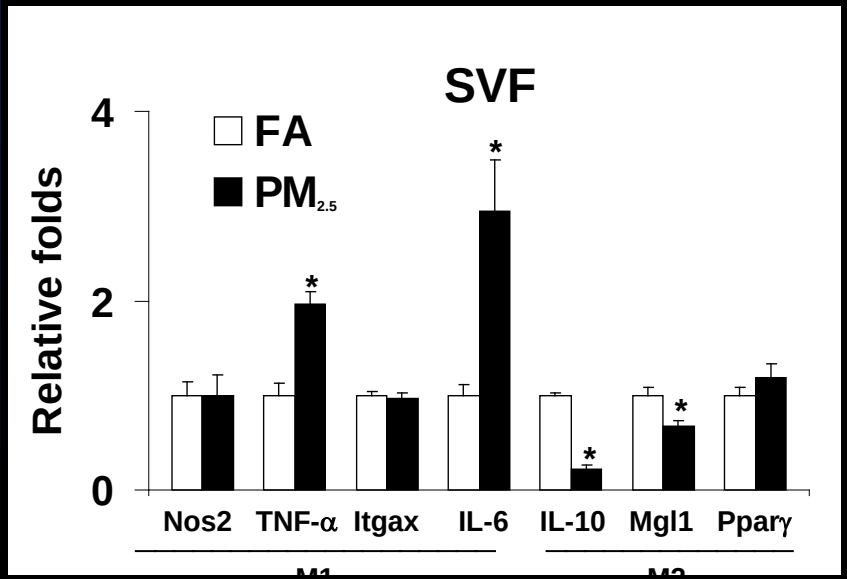
Chronic $PM_{2.5}$ Ambient Exposures (20 wk) Potentiates Inflammation/Insulin Resistance in Mice





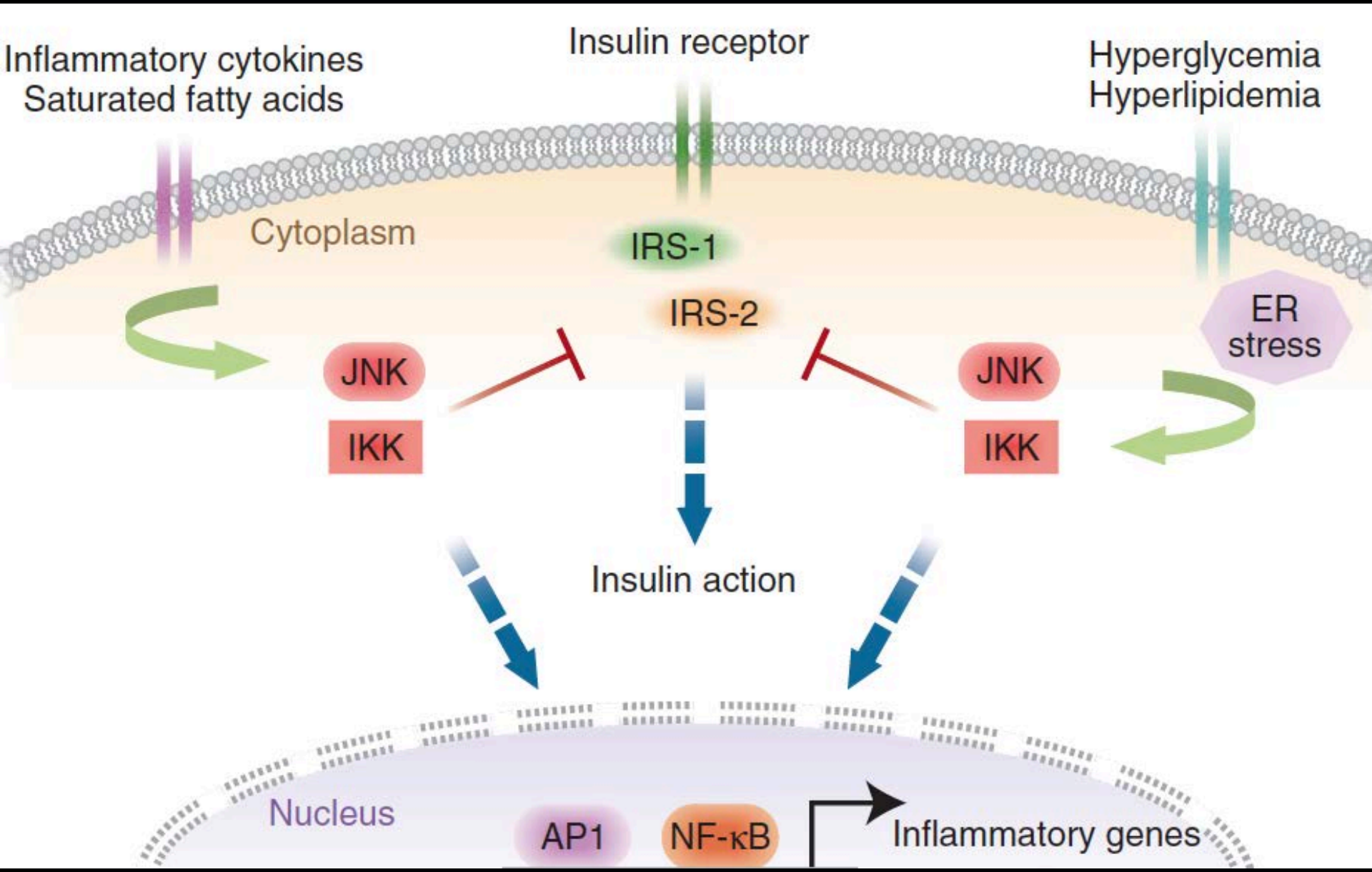


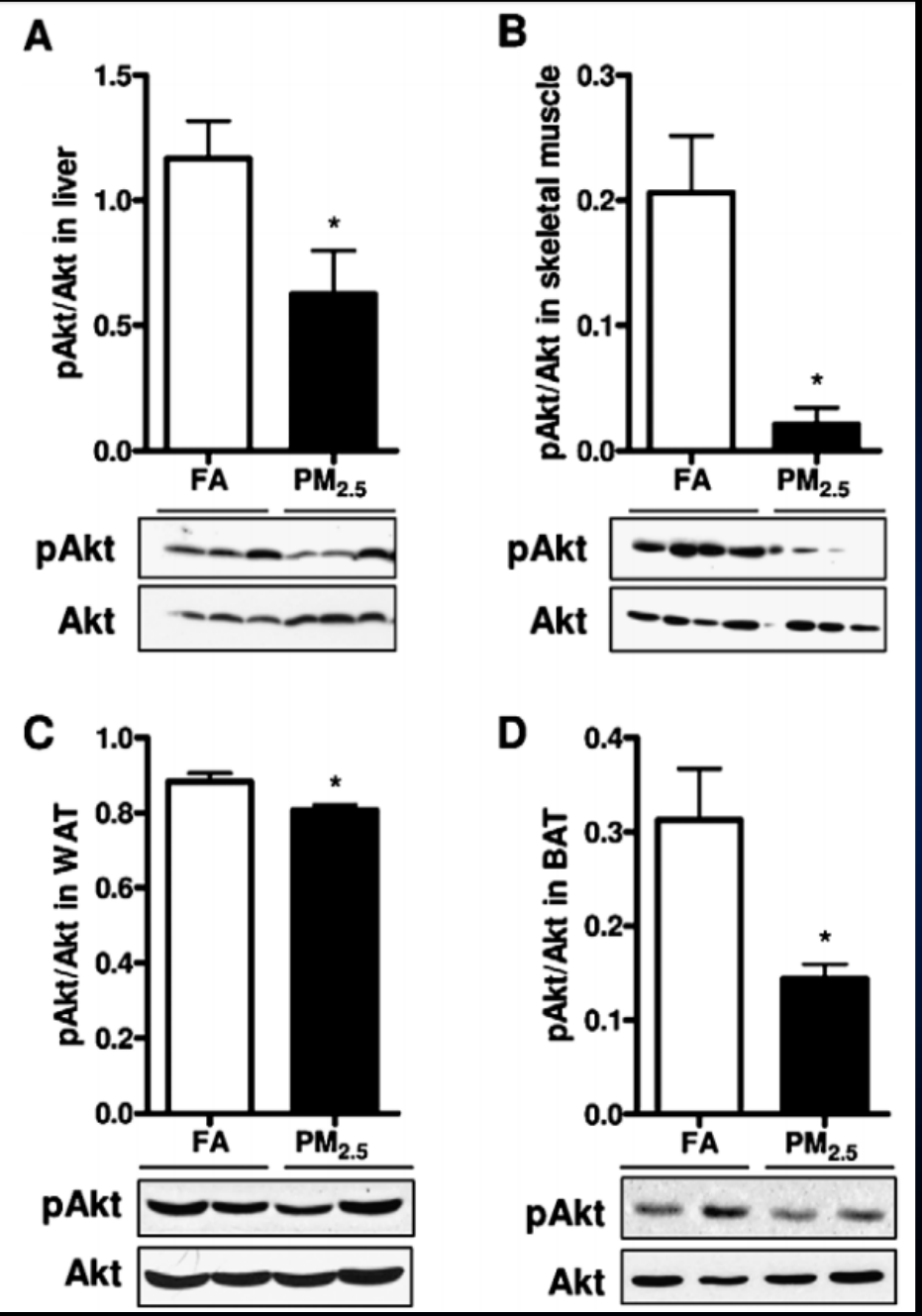




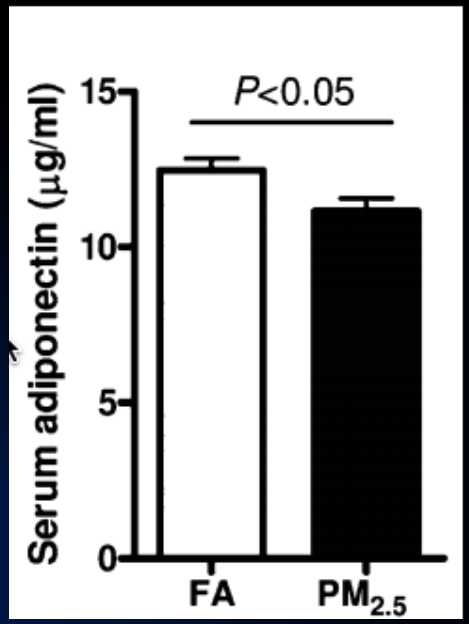
Sun Q, Yue et al. Circulation 2009; 119(4):538-46.

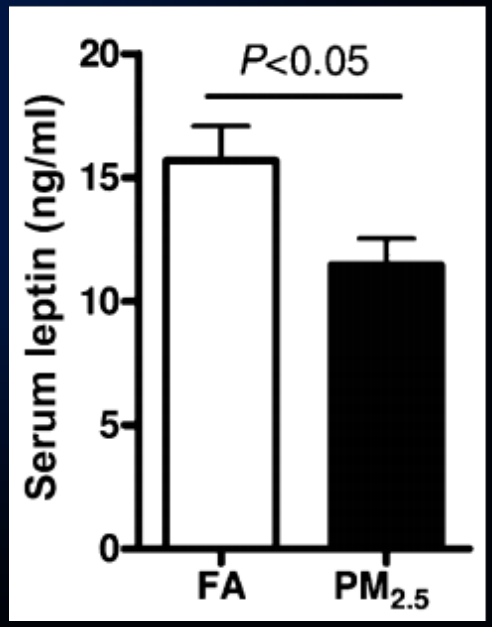
FA = filtered air PM = particulate matter SVF = ??


Inflammatory cytokines
Saturated fatty acids
Insulin receptor
Hyperglycemia
Hyperlipidemia
Cytoplasm
IRS-1
IRS-2
ER stress
JNK
IKK
JNK
IKK
Insulin action
Nucleus
AP1
NF-κB
Inflammatory genes



WAT = white adipose tissue
BAT = brown adipose tisse



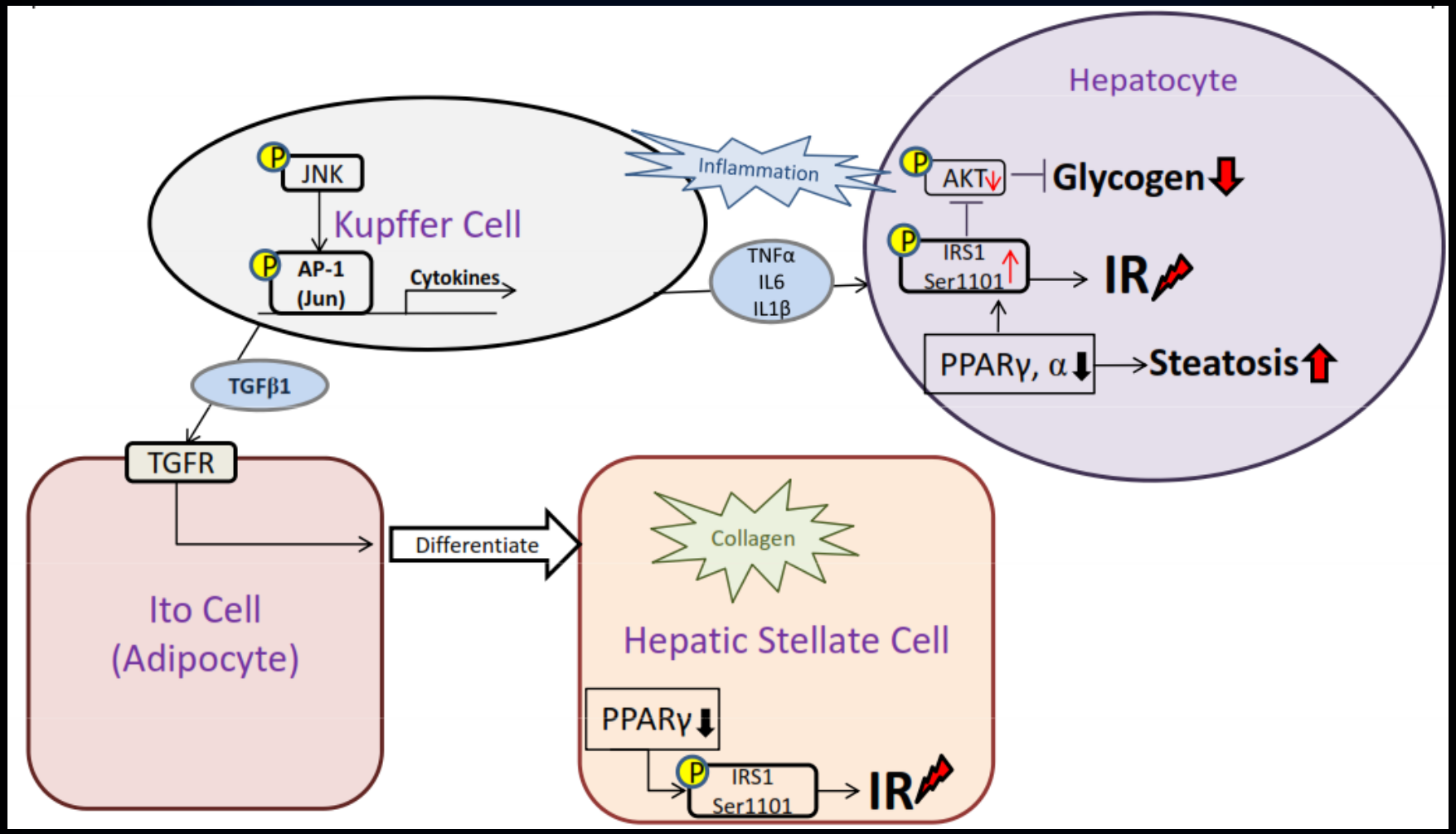


FA = filtered air
PM = particulate matter

Toxicol Pathol. 2013 Feb;41(2):361-73. doi: 10.1177/0192623312464531

TOXICOLOGICAL SCIENCES 124(1), 88–98 (2011)

Hypothetical Model of $PM_{2.5}$ Mediated Hepatic Insulin Resistance (IR) and Steatosis

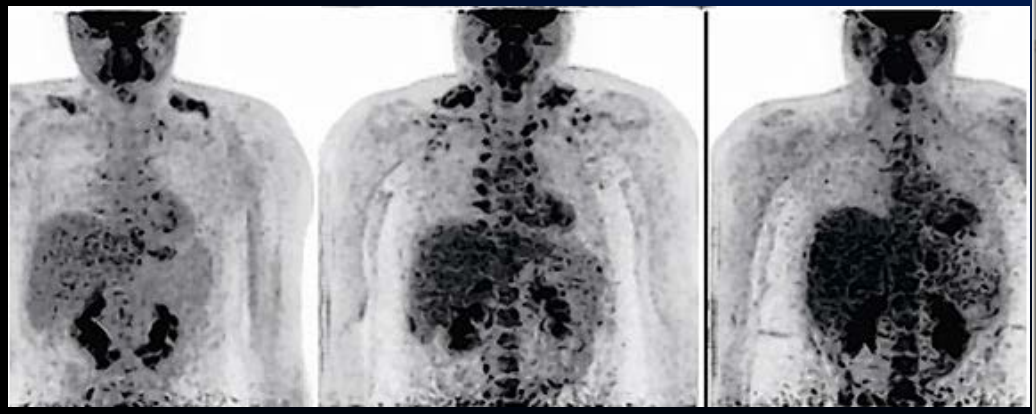


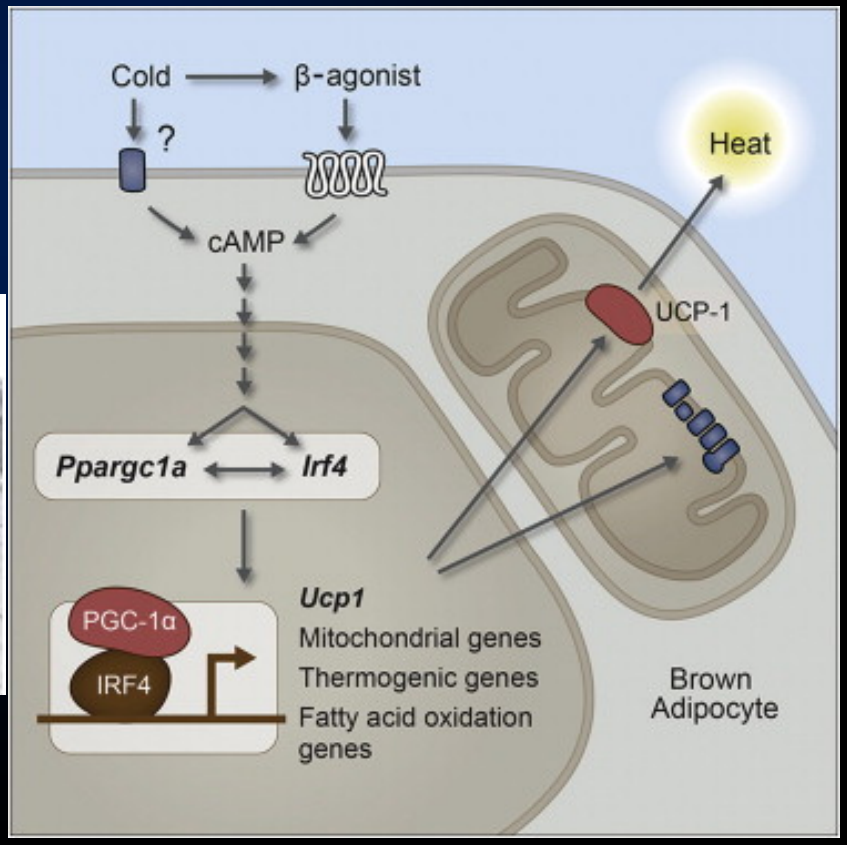
Zheng et al. J Hepatol. 2013 Jan;58(1):148-54.

Does Air Pollution Induce Metabolic Changes and Shift in Thermogenesis?

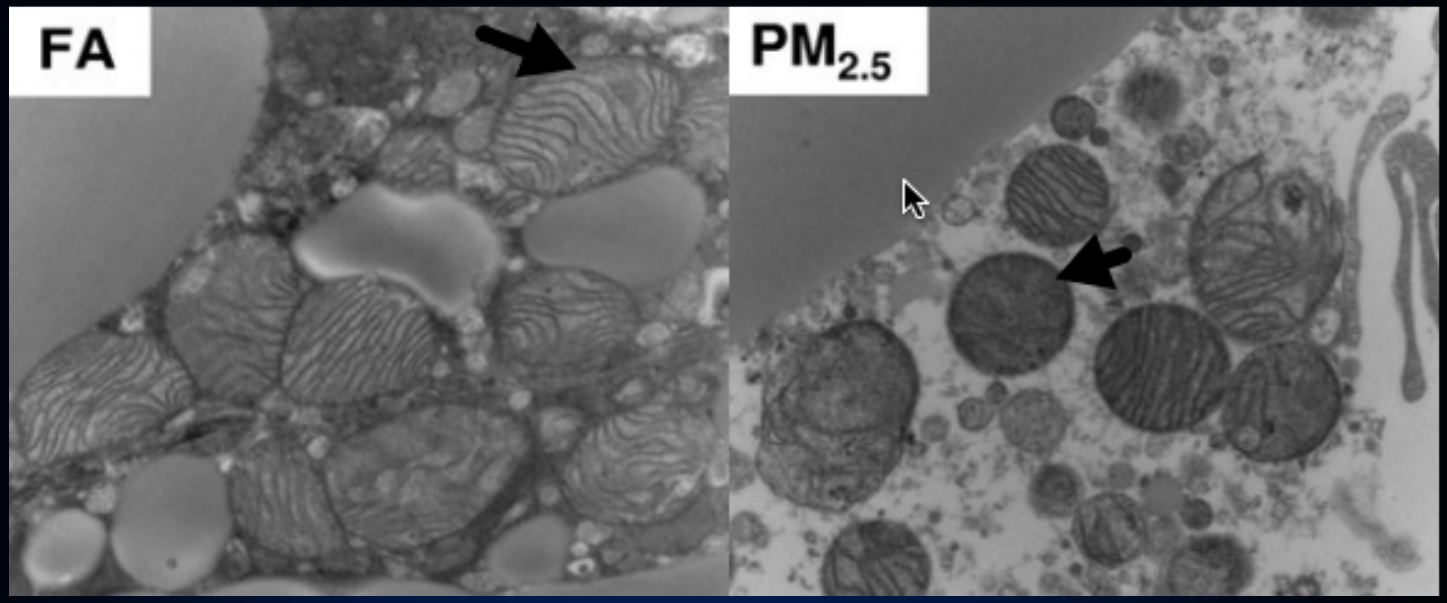
Does Air Pollution Alter Brown Adipose Structure and Function?

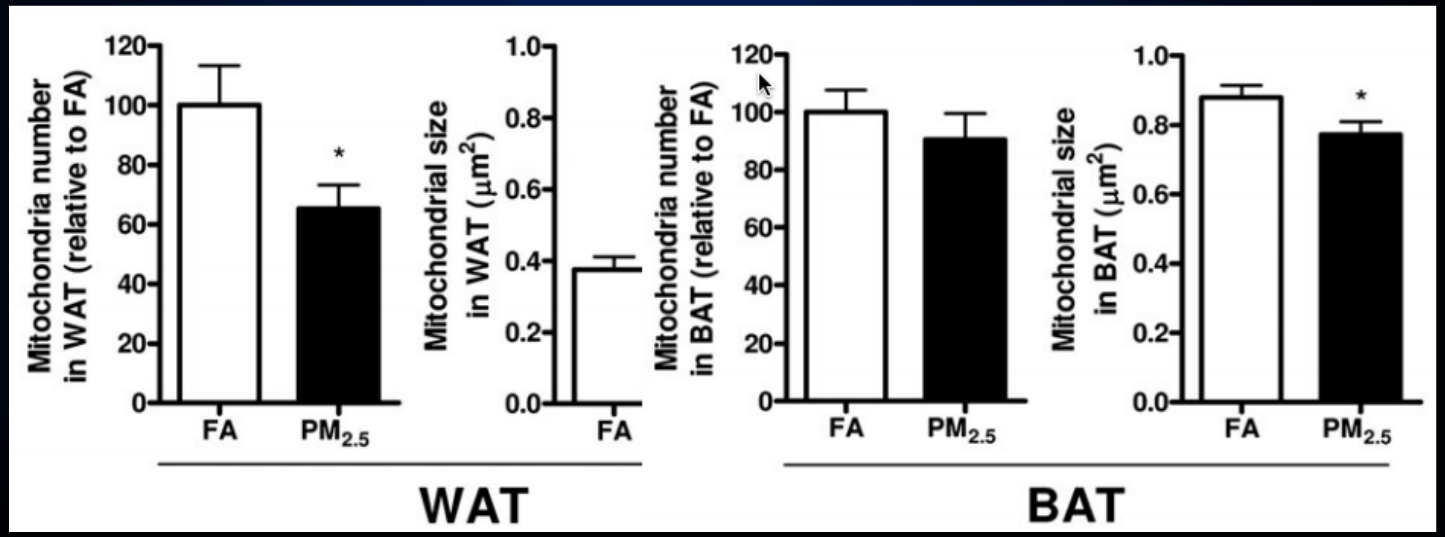
Baby Fat May Help You Lose Weight





Long Term $PM_{2.5}$ Exposure (40 weeks): Impact on Mitochondrial Structure

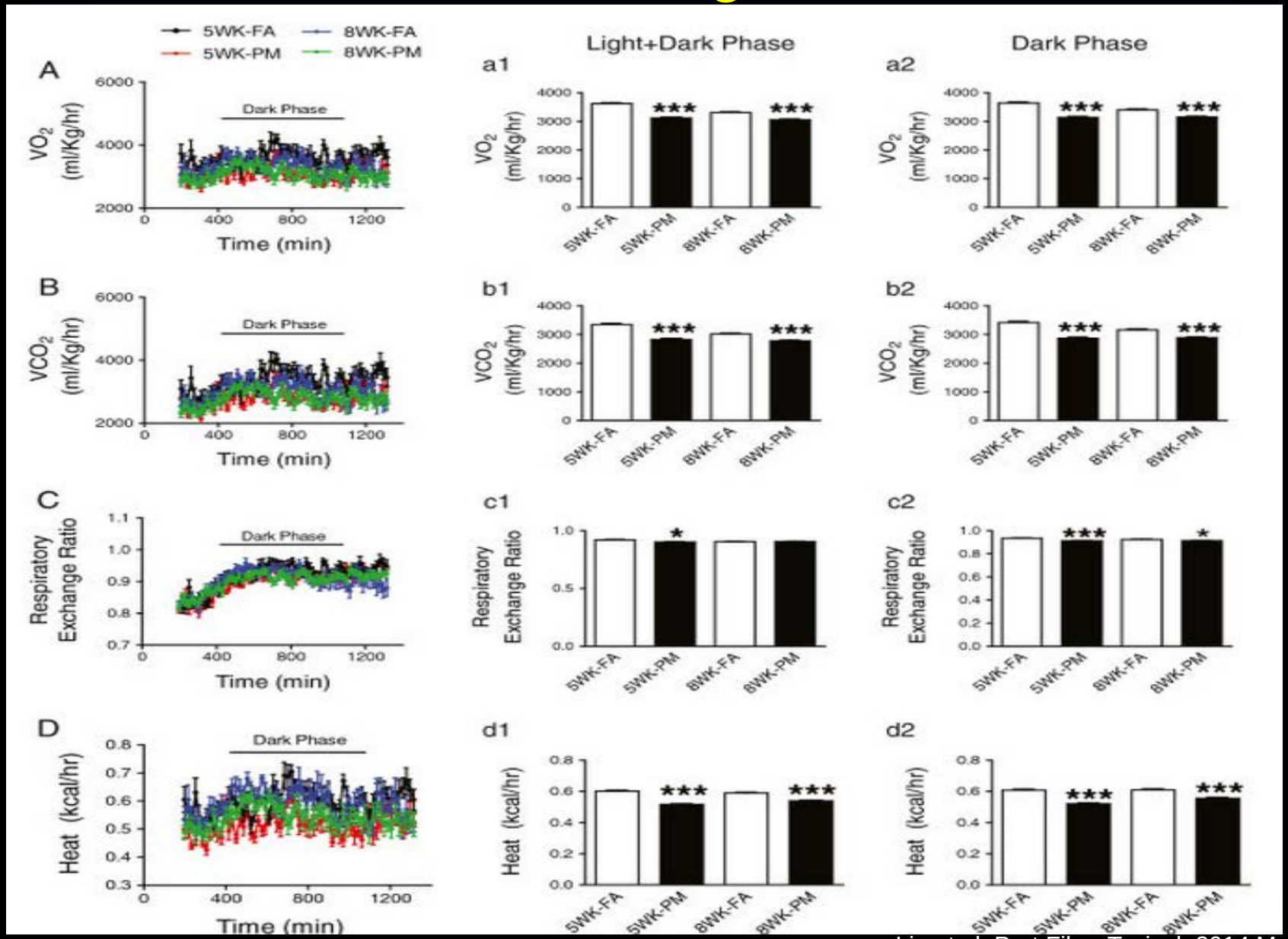




FA = filtered air PM = particulate matter
WAT = white adipose tissue BAT = brown adipose tissue

Tox Sciences 2011; 124; 88-98

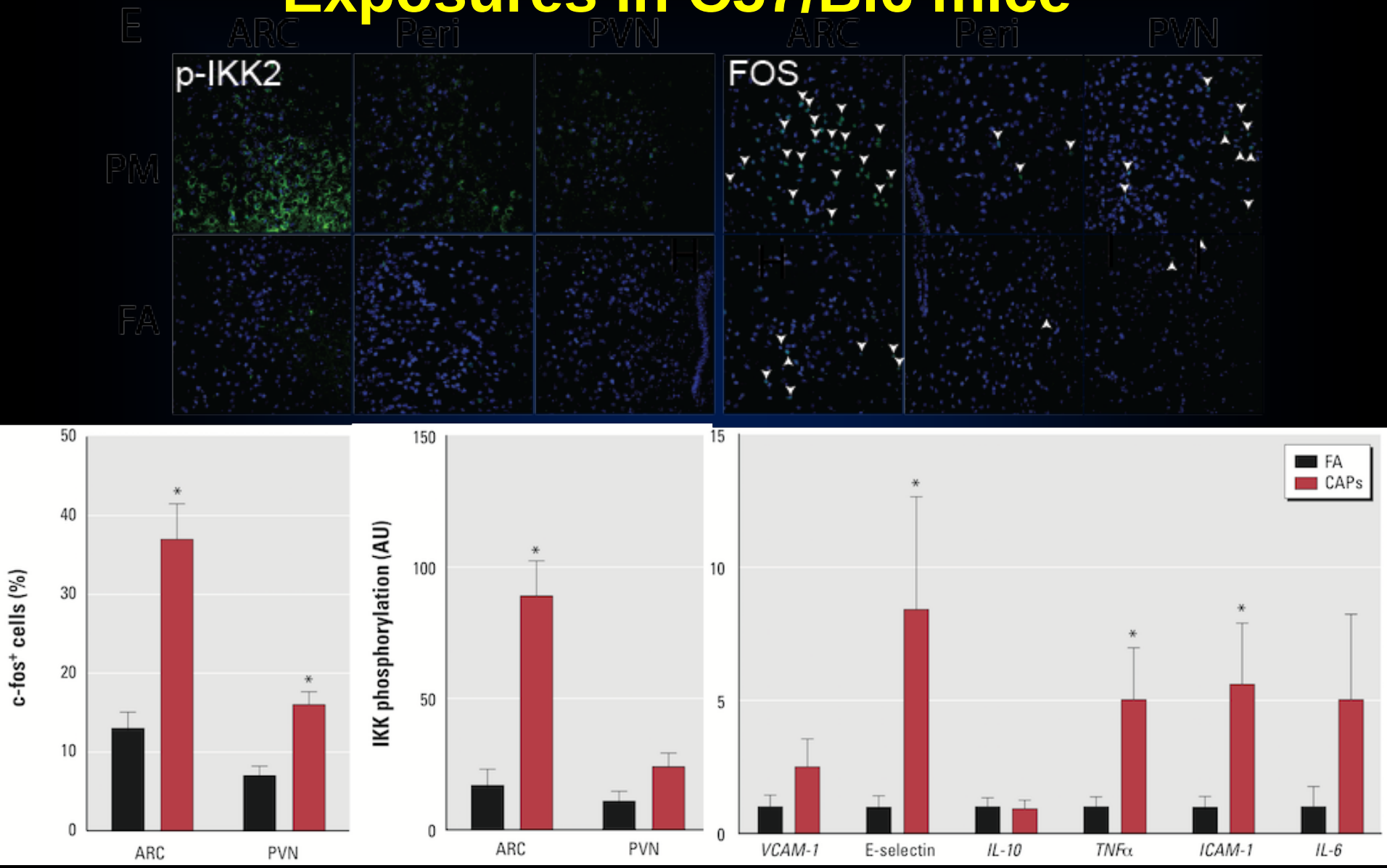
$PM_{2.5}$ Mediated Changes in Whole Body Metabolism and Thermogenesis



Liu et al. Part Fibre Toxicol. 2014 May 30;11:21

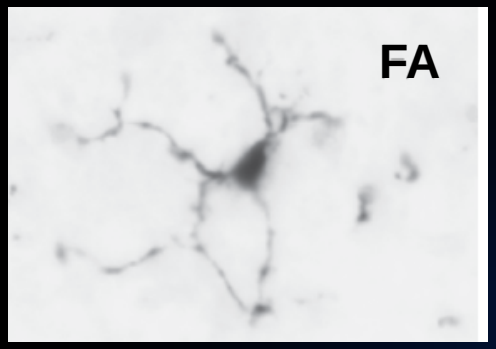
Are Central Nervous System Pathways Responsible for Metabolic Control Involved?

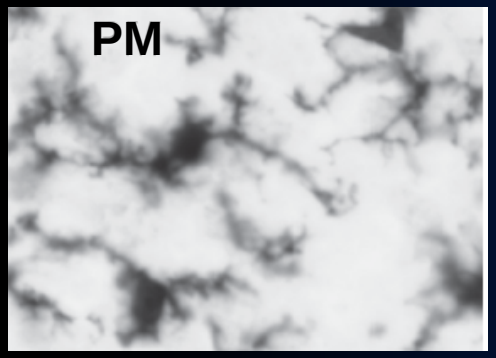
Hypothalamic Inflammation with Long-Term Exposures in C57/Bl6 mice

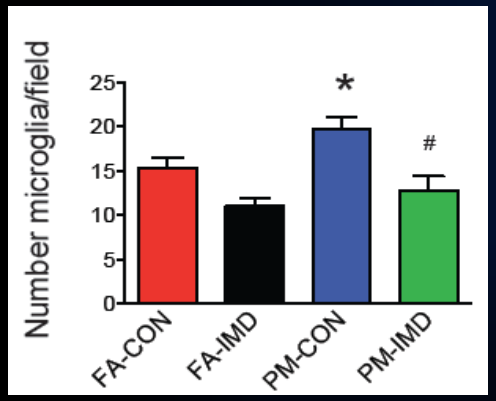


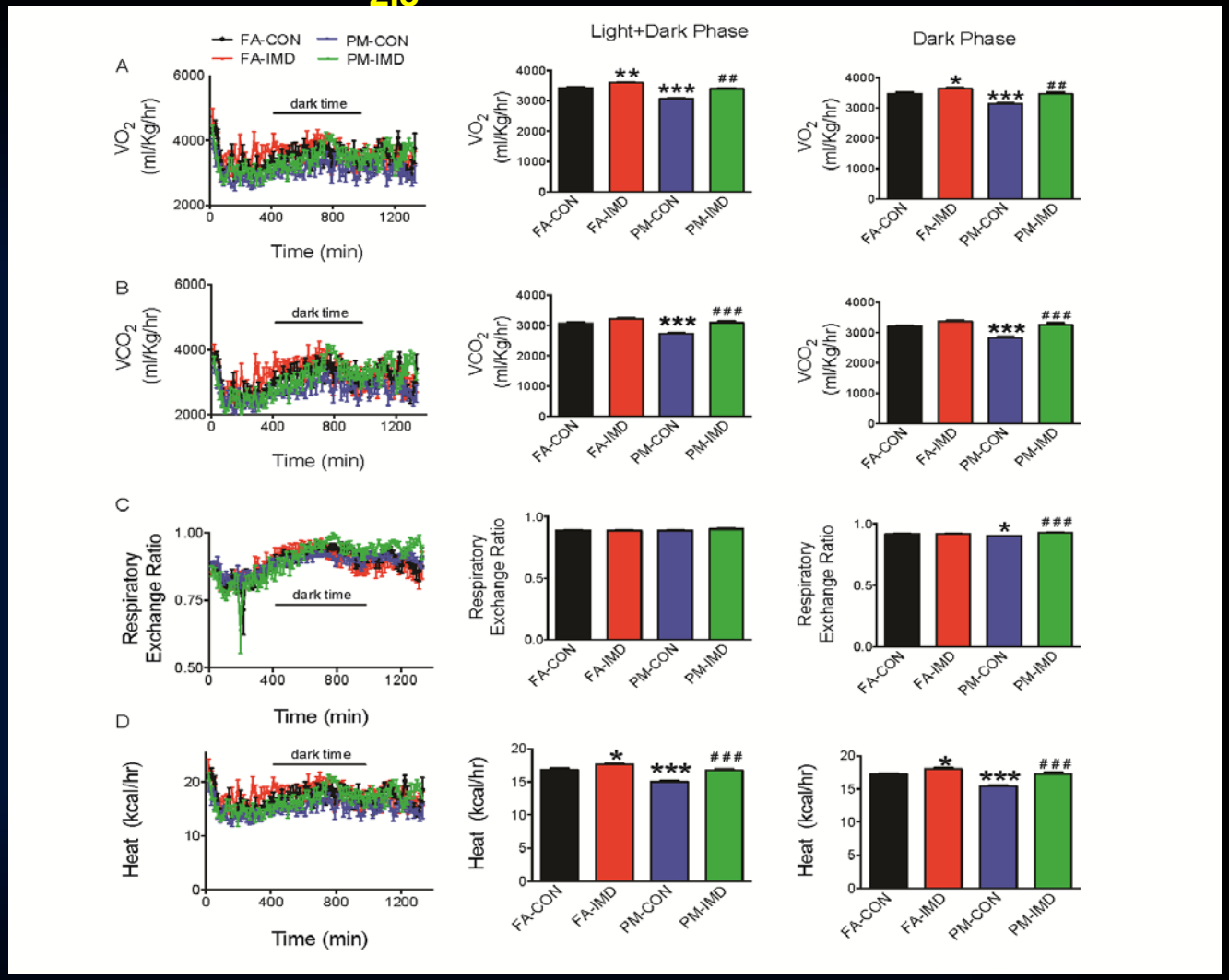
Environ Health Perspect. 2014 Jan;122(1):79-8

Intracerebroventricular (ICV) infusion of IKKβ Inhibitor (IMD-0354) Inhibits $PM_{2.5}$ Effects





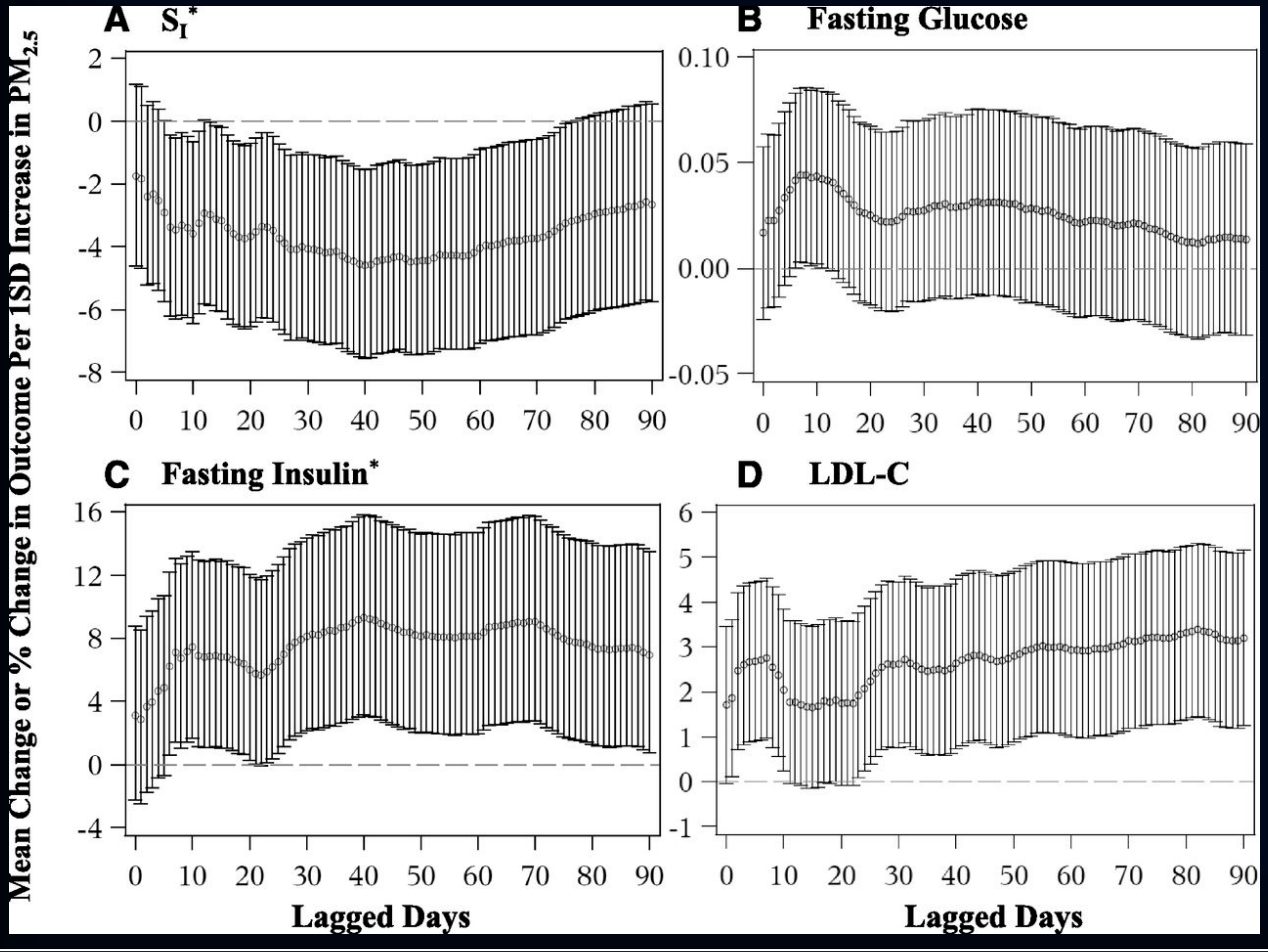




- O_2 consumption (A), CO_2 production (B), respiratory exchange ratio (C) and heat production (D) of mice measured by indirect calorimetry over a 24 hrs period (from 10:00 am to 10:00 am the next day) after 4 wks of $PM_{2.5}$ exposure and IKKβ inhibitor treatment. *P<0.05, **P<0.01, ***P<0.001 compared 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.

FSIGT = frequently sampled intravenous glucose tolerance

Zhanghua Chen et al. Dia Care 2016;39:547-554

Original Article

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/m^3 and 0.2 to 24.5 μg/m^3, 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) mm Hg per SD increase (67.2 μg/m^3), 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) mm Hg per SD increase (3.6 μg/m^3). 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/HYPERTENSIONAHA.115.06237.**)

- **Online Data Supplement**

ASPIRE: AIR POLLUTION: STRATEGIES FOR PERSONALIZED INTERVENTION TO REDUCE EXPOSURE

SPONSOR: National Institutes of Health (NIH)

Location: Beijing China

Collaborators: Peking University, Peking Union Medical College. Fuwai Hospital

Principal Investigator(s): Sanjay Rajagopalan, Robert D. Brook

Co-Investigators: Wei Huang (Peking University)
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