The Mechanisms of Air Pollution Mediated Cardiovascular Disease

Sanjay Rajagopalan
Case Cardiovascular Research Institute
Case Western Reserve University
University Hospitals, Harrington Heart and Vascular Institute
Cleveland OH

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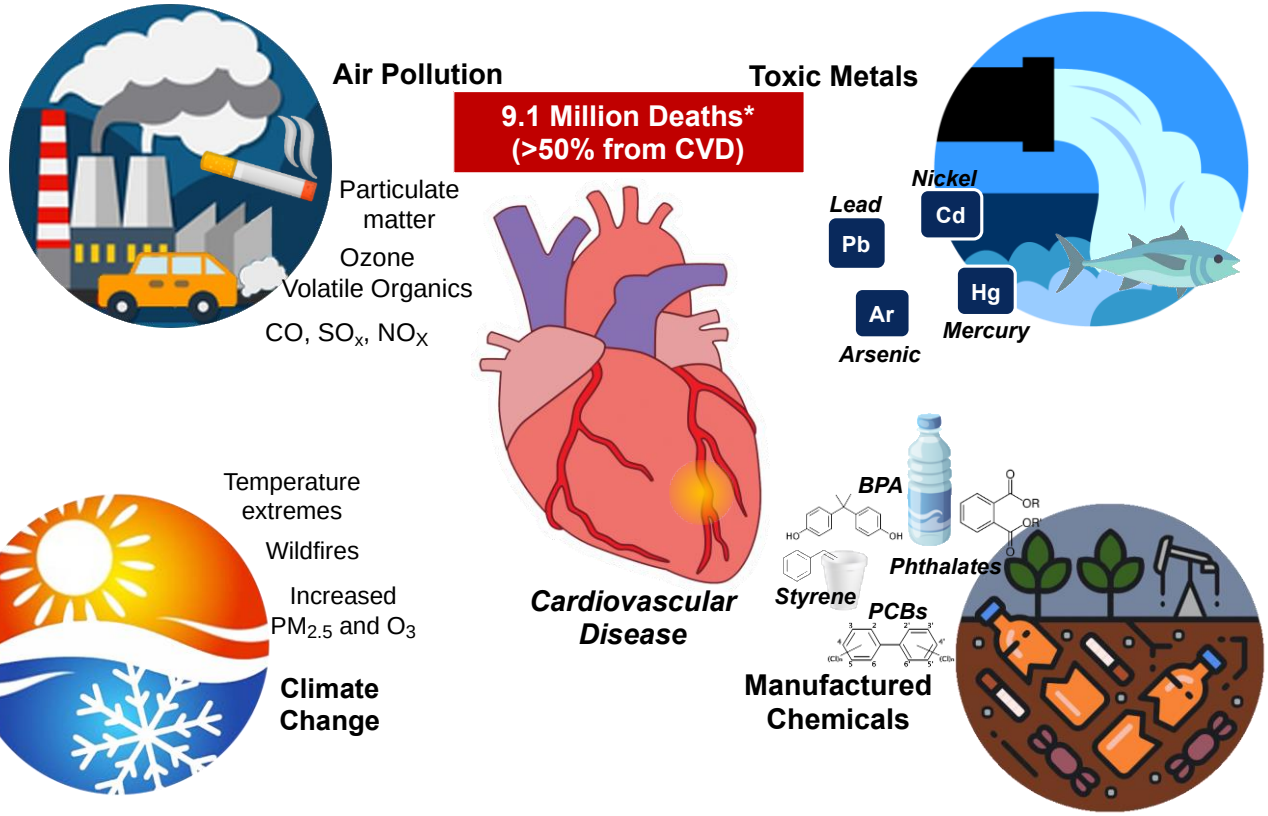
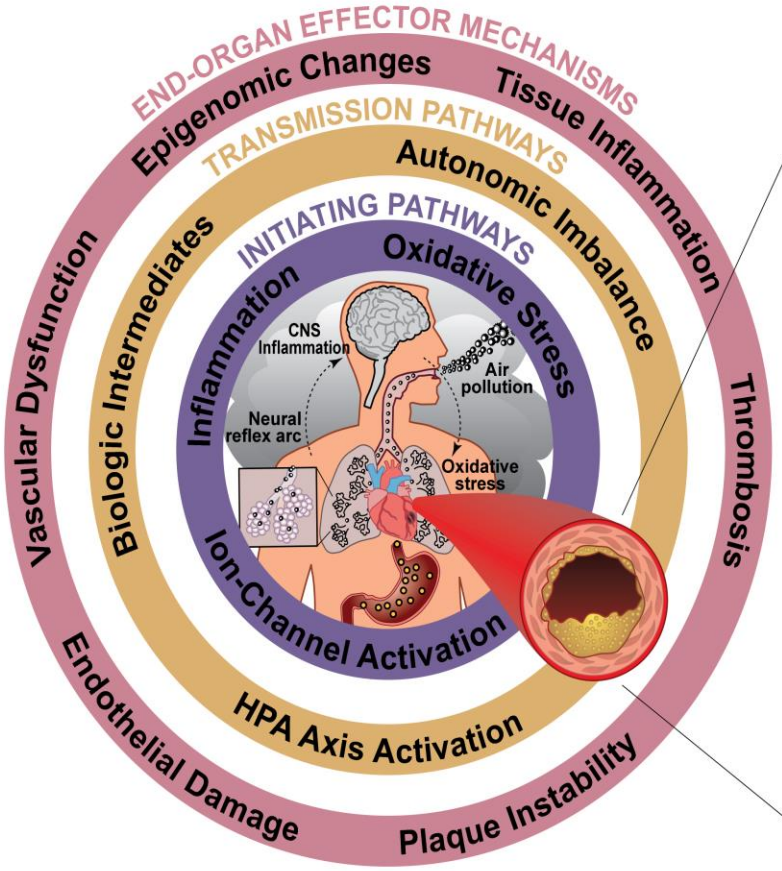
The Footprint of Pollution in the Anthropocene Era

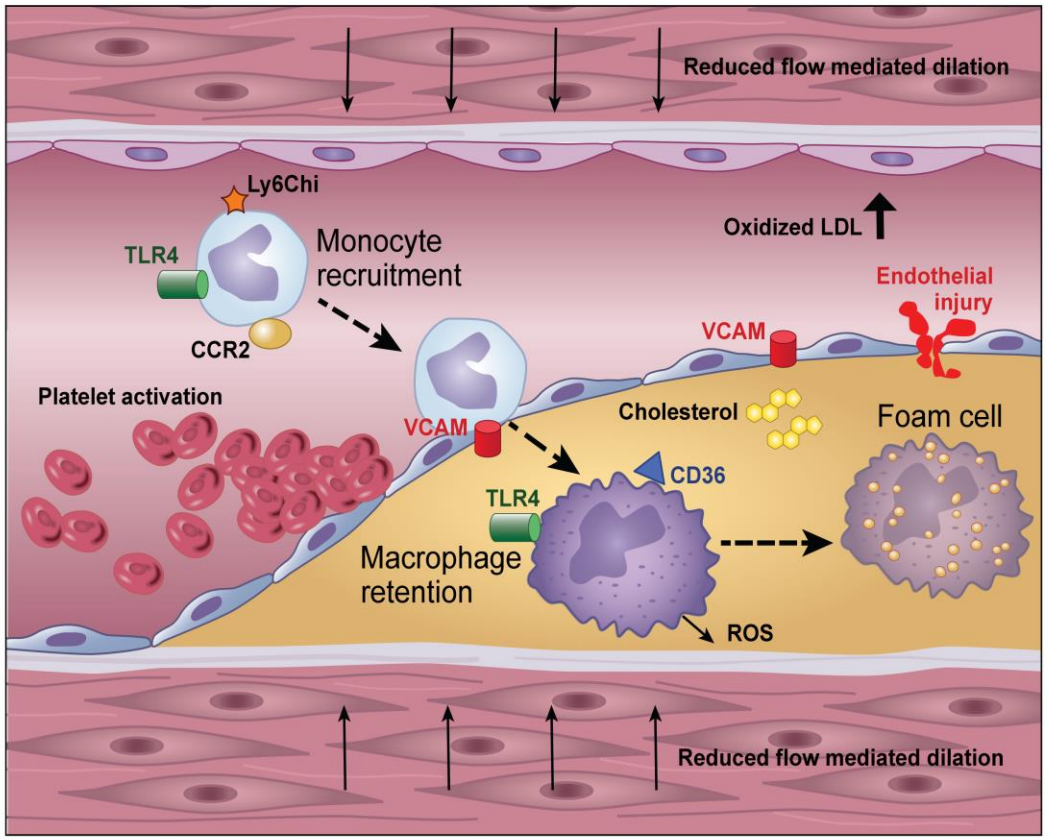
Air Pollution Major Determinant of Climate Change

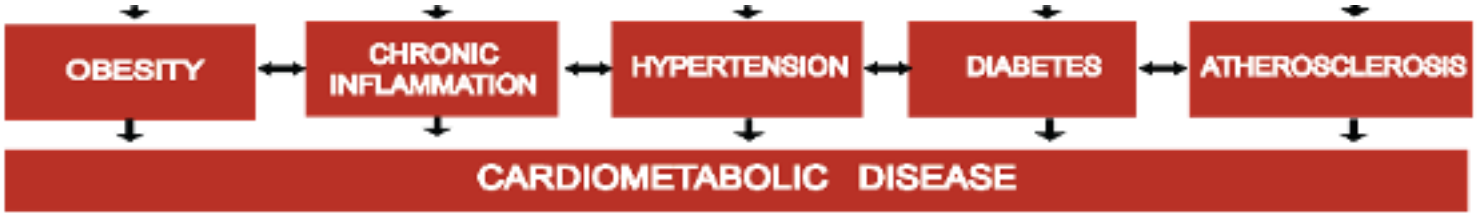


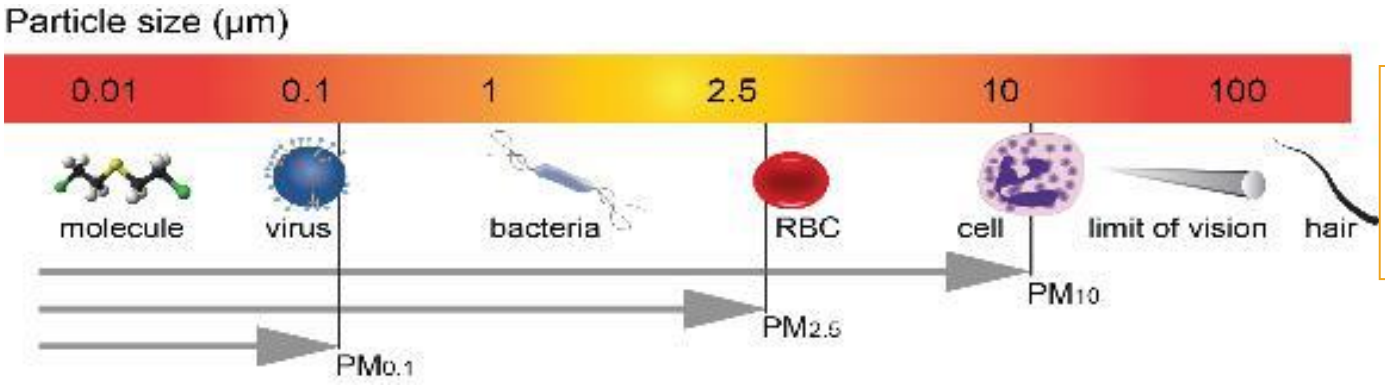
Rajagopalan S. Landrigan P. N Engl J Med 2021 Nov 11;385(20):1881-1892.

Air Pollution Pathways Mediating Cardiovascular Risk

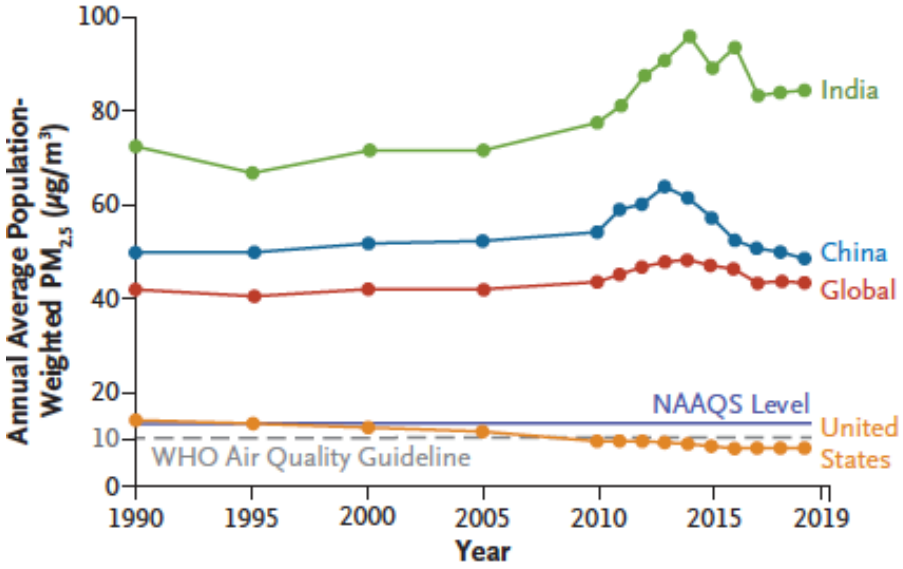


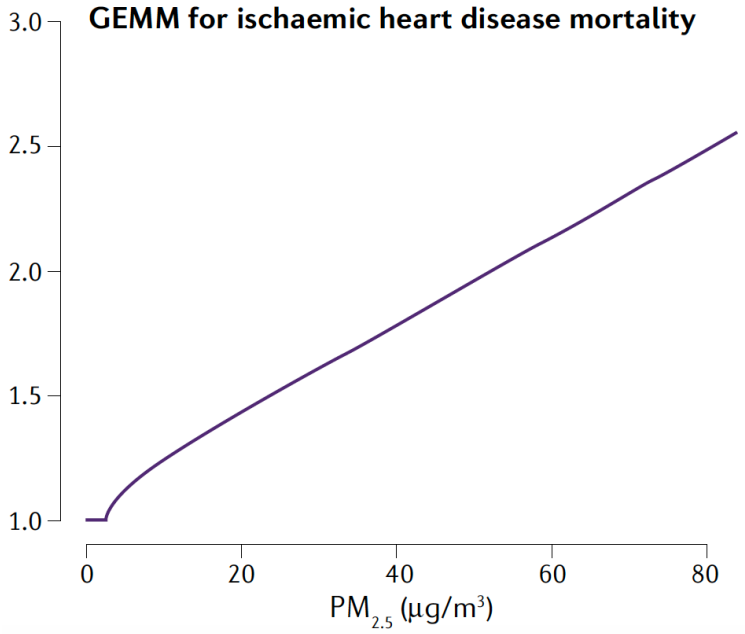






$PM_{2.5}$ Consistently Strongest Component

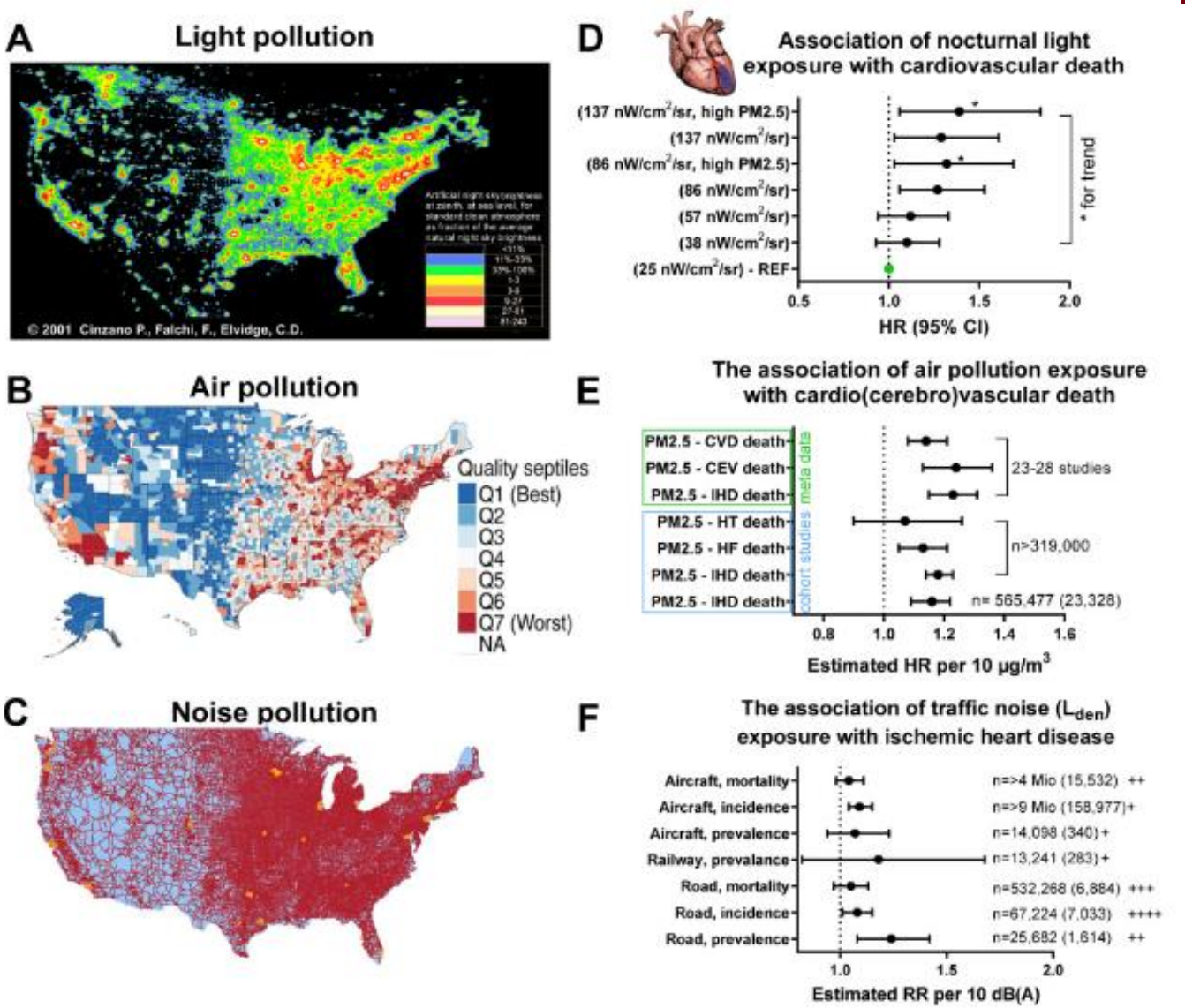




Levels in the US are mostly below NAAQS Annual Level of 12 µg/m³

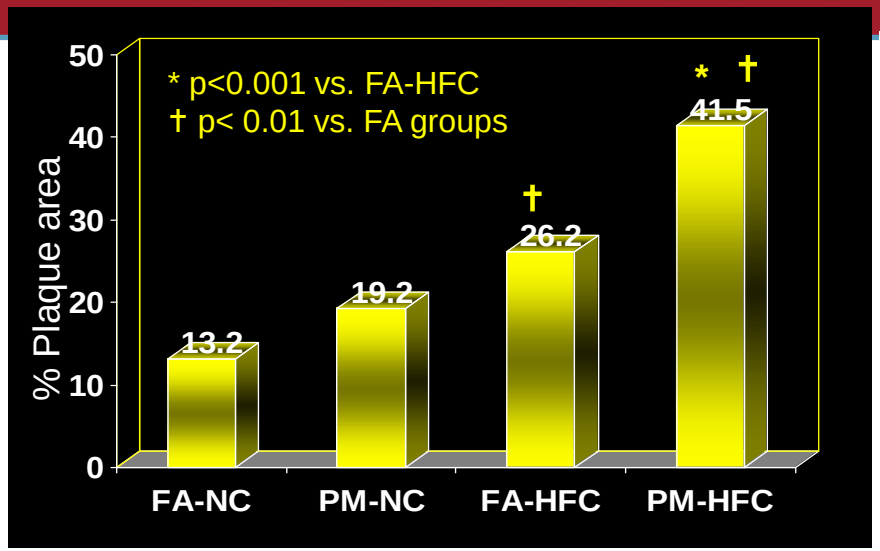
No lower threshold dose response

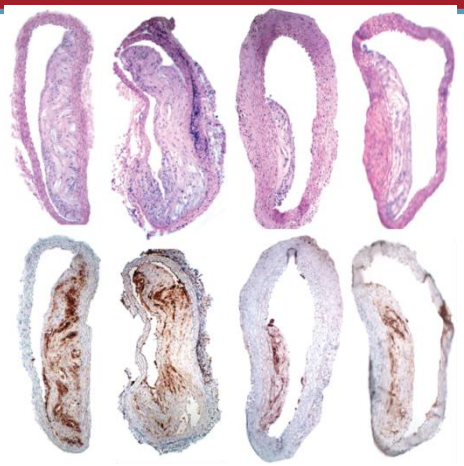
Al-Kindi, S, Rajagopalan S. et al. Nature Reviews Cardiology (May 2020)

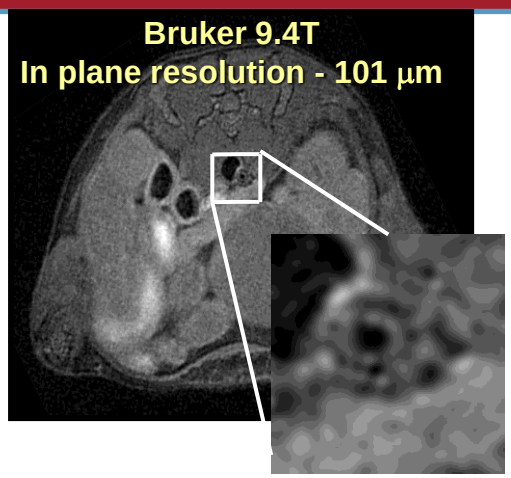


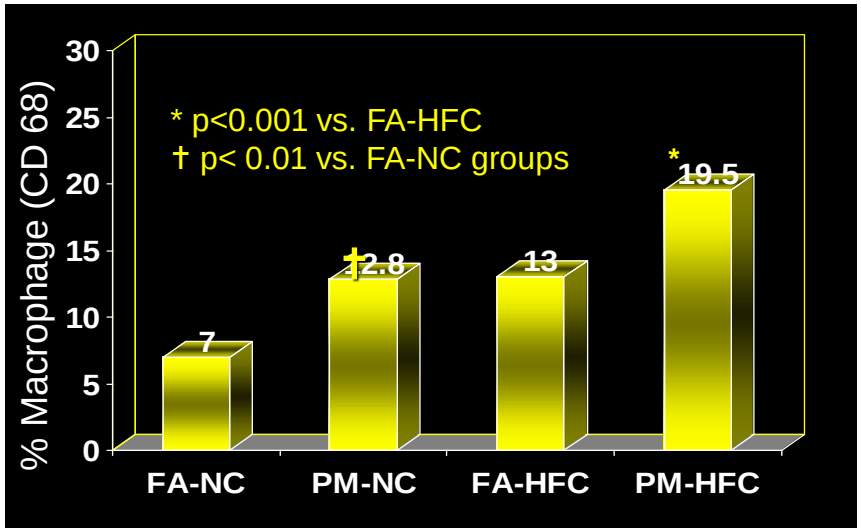
Eur Heart J. 2021 Jul 1;42(25):2422-2438

Chronic PM Exposure Potentiates Atherosclerosis and Vascular Inflammation

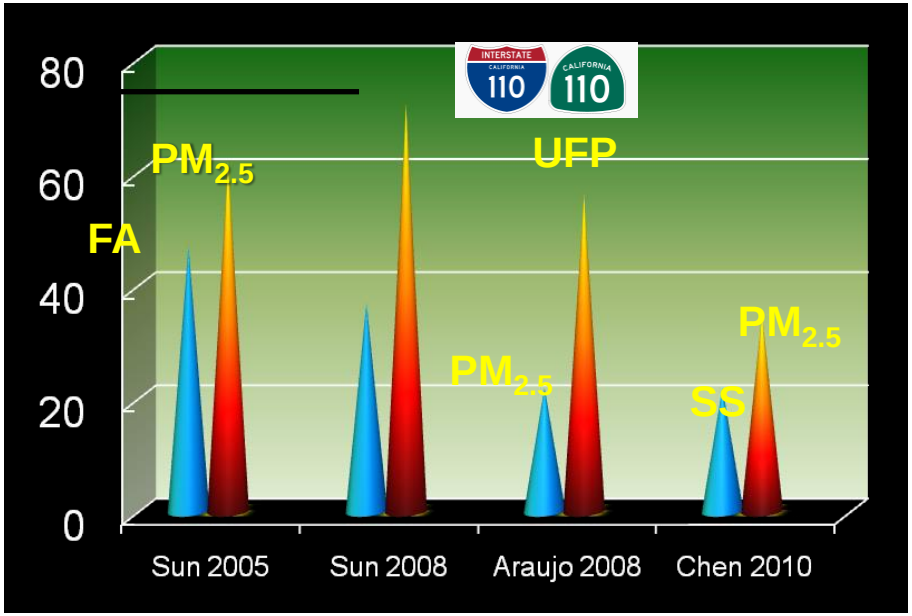




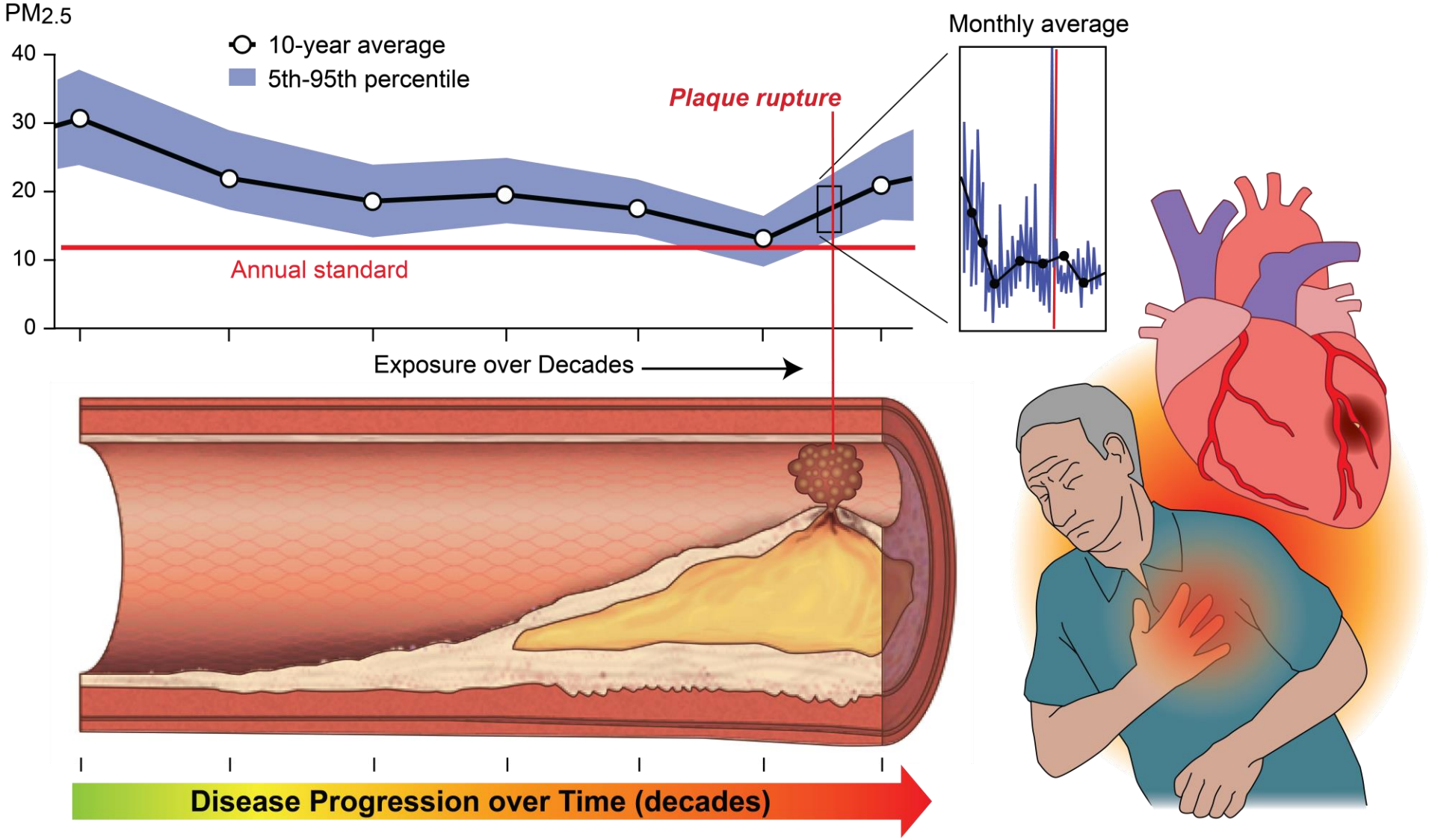




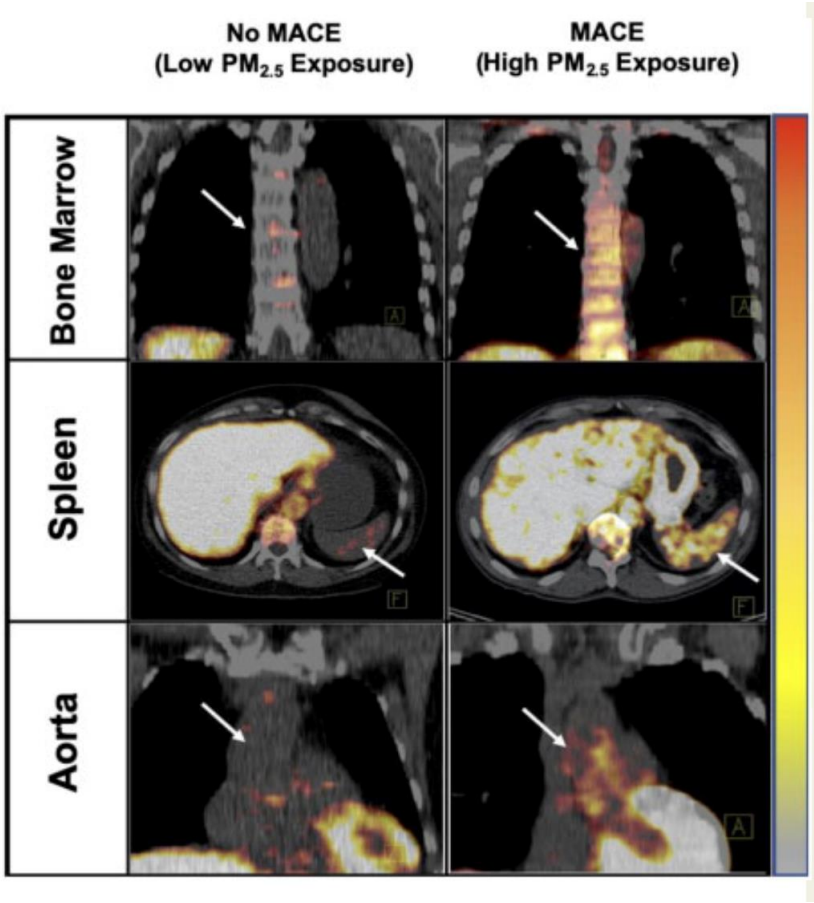
Sun et al. JAMA 2006.; 294



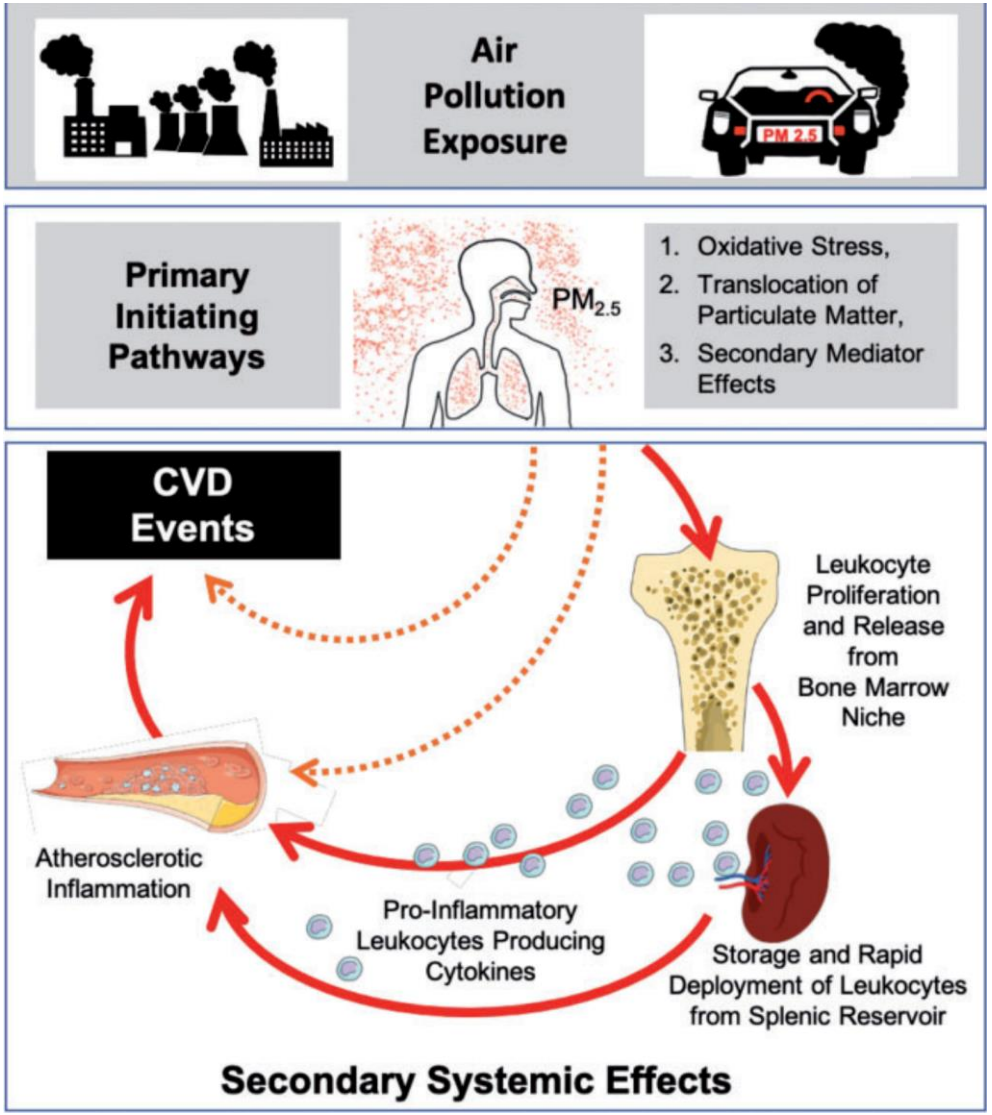
Inhal Toxicol. 2008;20:127–137; Circ Res. 2008;102:589–596; Toxicol Sci. 2009 80-88 . Inhal Toxicol. 2010;22;449-59.



Bevan G and Rajagopalan S et al. Arterioscler Thromb Vasc Biol. 2021 Feb;41(2):628-637



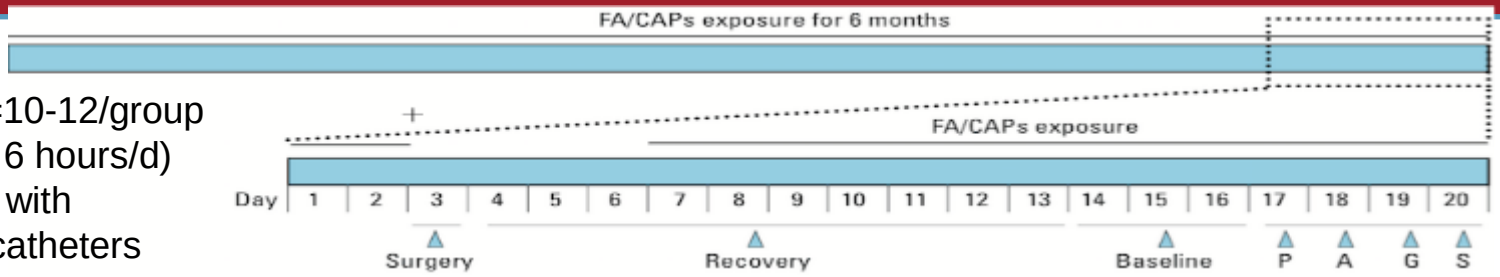
Tissue activities on ^{18}F-FDG-PET/CT by $PM_{2.5}$ exposure. Tissue FDG increased with PM2.5 exposure and major adverse cardiovascular event.

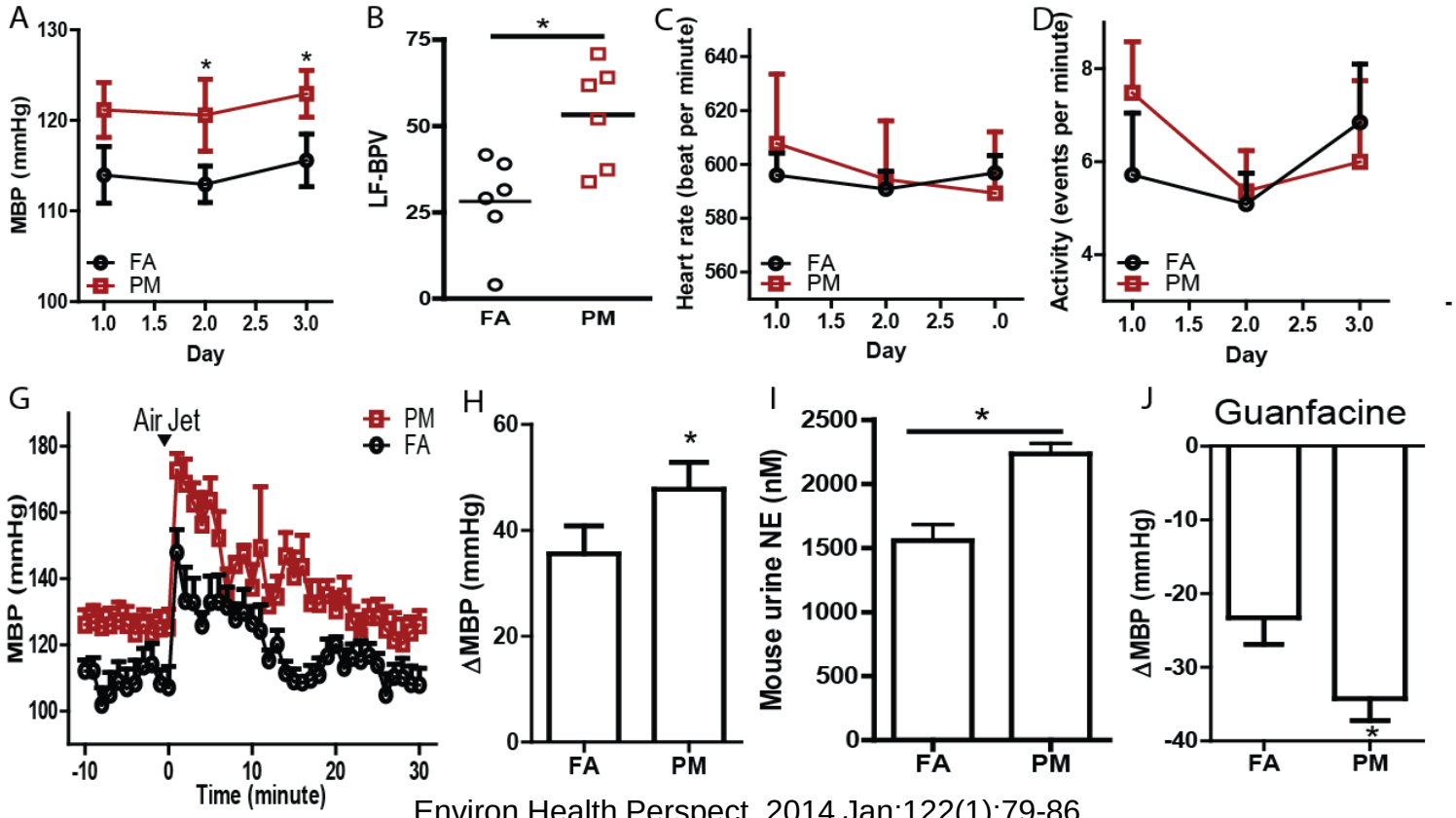


Abohashem S, Rajagopalan, S, Tawakol A. et al. European Heart Journal (2021) 42, 761–772

Central Sympathetic Activation with $PM_{2.5}$ 12 Week Exposure (C57/Bl6)

C57Bl/6 (n=10-12/group
(5 days/wk, 6 hours/d)
Cannulated with
indwellling catheters
prior to exposure





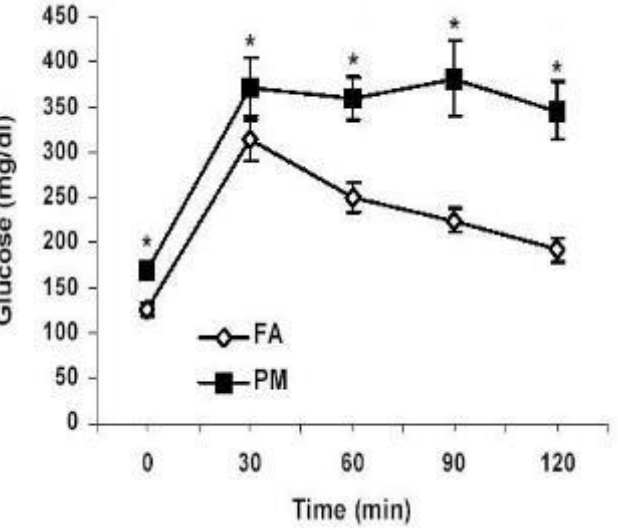
Environ Health Perspect. 2014 Jan;122(1):79-86

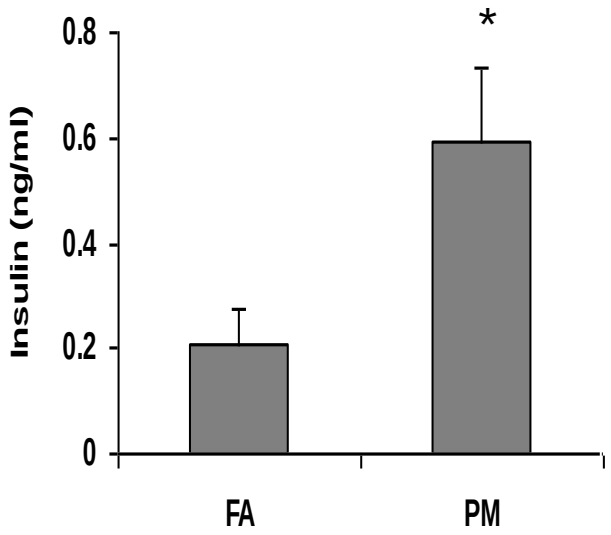
Links Between Hypertension and Air Pollution: Summary of Evidence

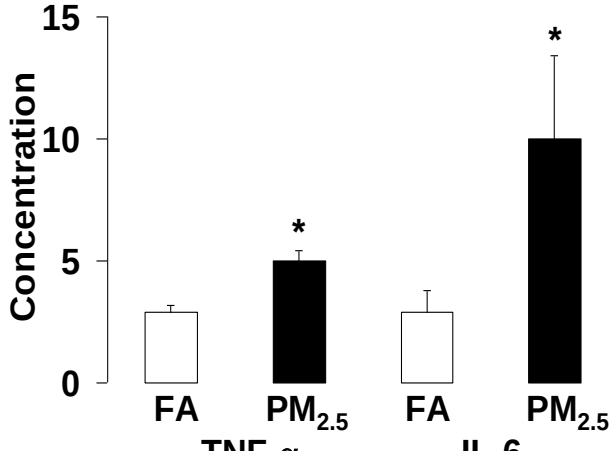
- BP positively related to PM2.5 exposure (↑ of 1.4 mmHg, 95% CI (0.87-1.91) and 0.89 mmHg, 95% CI (0.49-1.29) per 10 mcg/m3 increase for SBP and DBP respectively (1).
- Both ultrafine and course particles mediate blood pressure increase acutely (2, 3, 4, 5)
- Evidence suggests a slower effect (hours to days) with ambient air pollution compared to controlled chamber studies

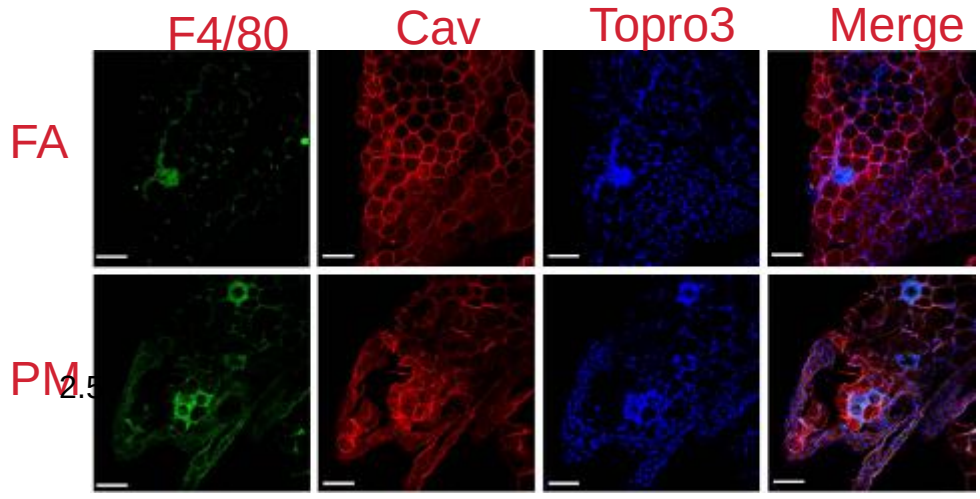
1. Liang et al. J Hypertens. 2014 Nov;32(11):2130-4.
2. Zhao and Rajagopalan S et al. Hypertension. 2014 Apr;63(4):871-7
3. Cosselman K E et al. Hypertension 2012;59:943-948.
4. Brook RD and Rajagopalan S et al. Environ Health Perspect. 2014 Jun;122(6):624-30.
5. 5. Byrd JB and Brook RD et al .J Am Soc Hypertens. 2016 Feb;10(2):133-139.e4

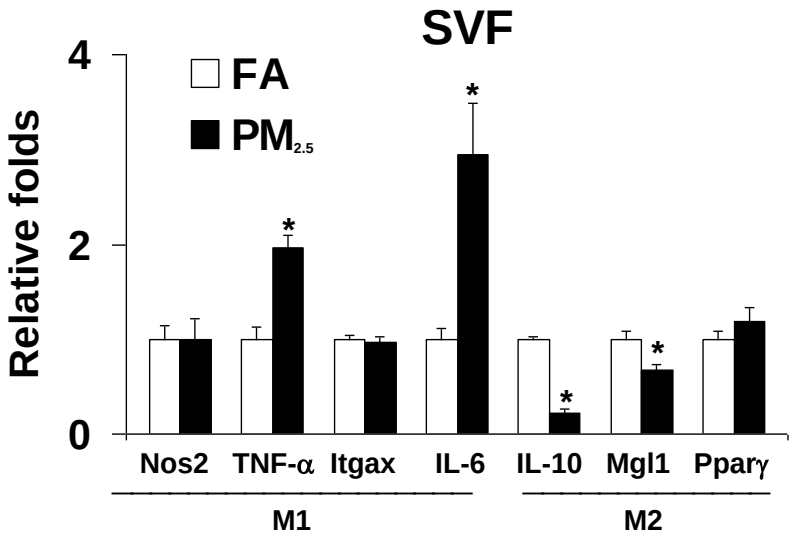
Chronic $PM_{2.5}$ Ambient Exposures (20 wk) Potentiates Inflammation/Insulin Resistance





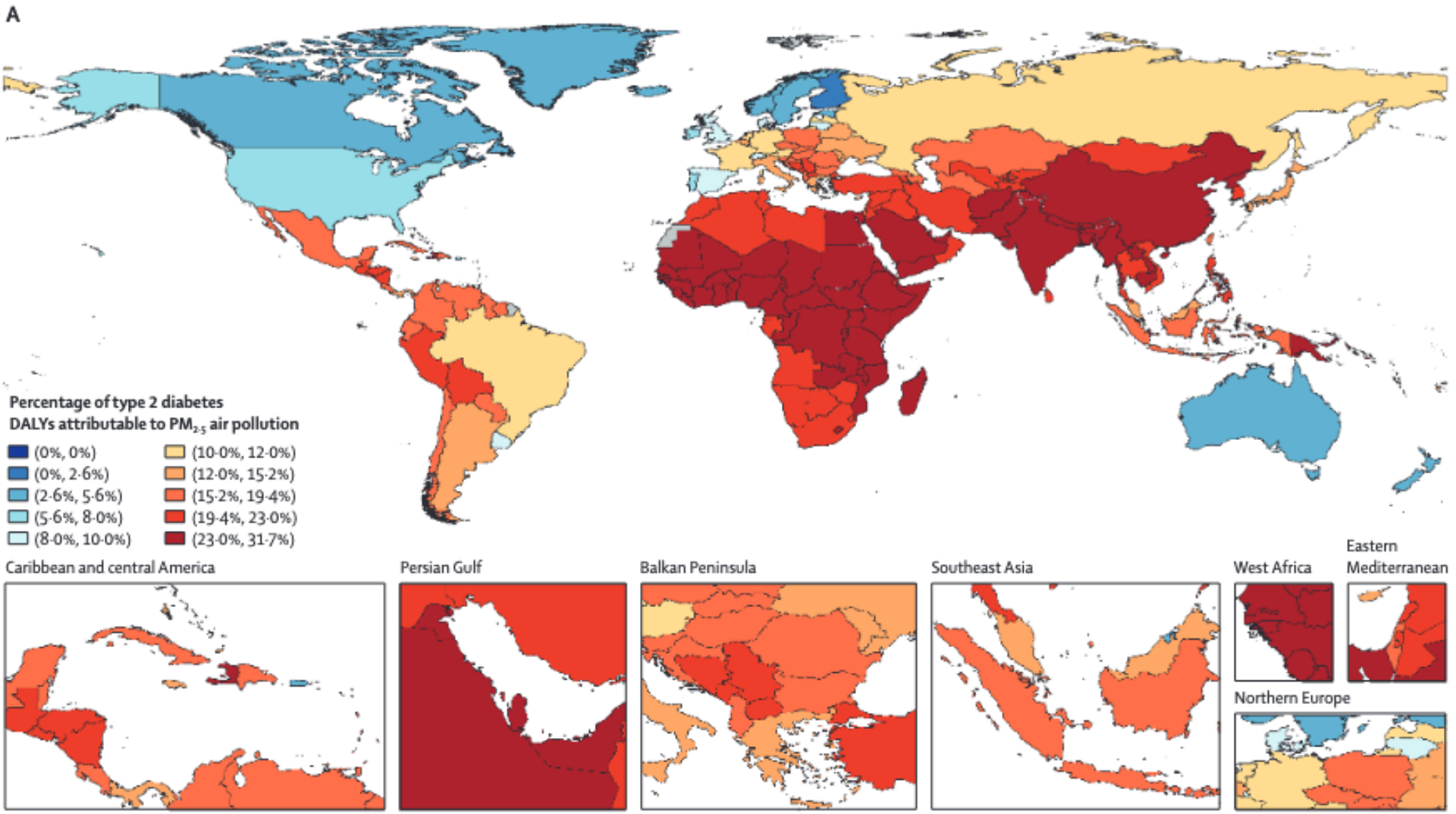




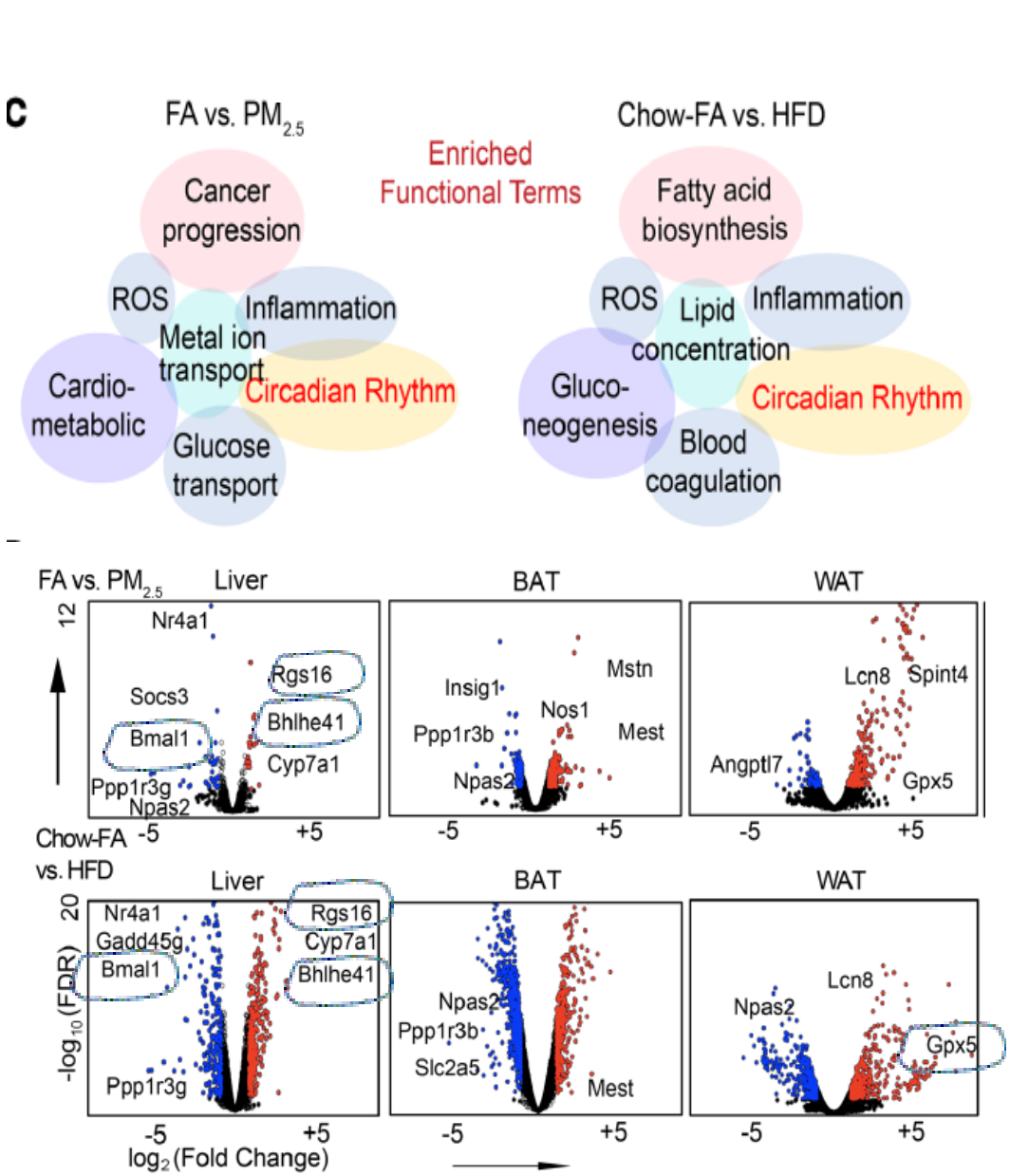


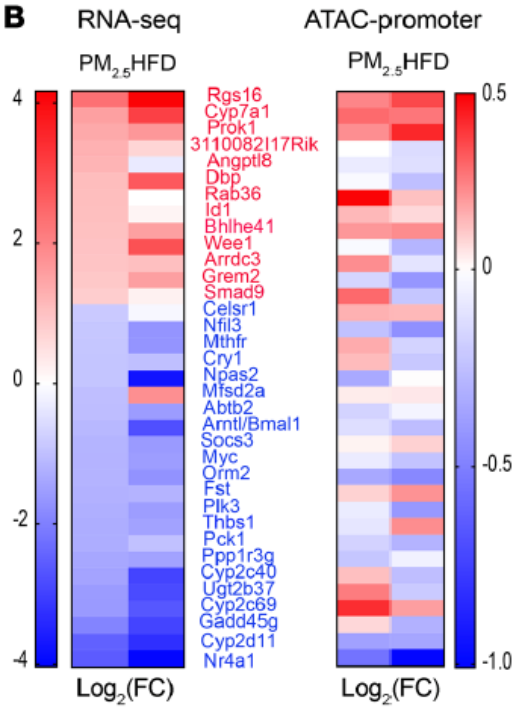
Sun Q, Yue et al. Circulation 2009; 119(4):538-46.

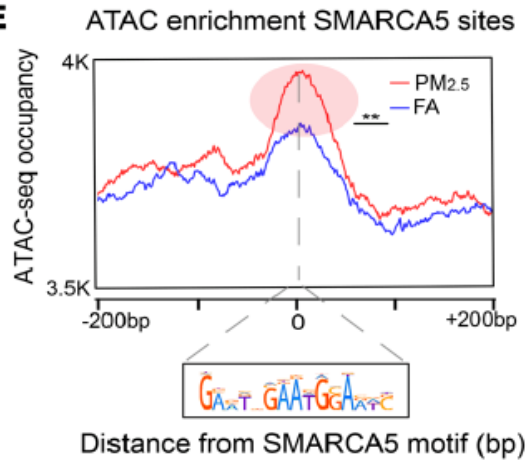
In 2019, 20% of the Global Burden of Type 2 Diabetes is Attributable to $PM_{2.5}$ Exposure



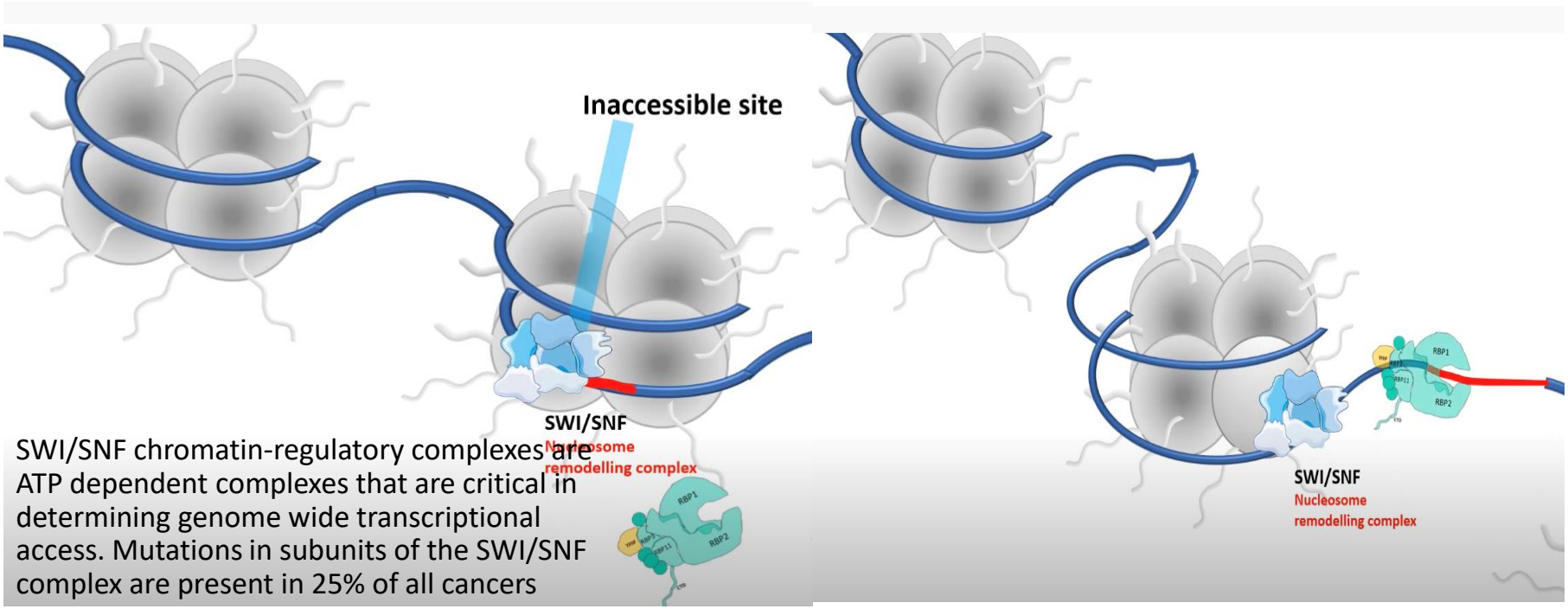
Lancet Planet Health 2022; 6: e586–600


C
FA vs. PM2.5
Chow-FA vs. HFD
Enriched Functional Terms
Cancer progression
ROS
Inflammation
Metal ion transport
Cardio-metabolic
Circadian Rhythm
Glucose transport
Fatty acid biosynthesis
ROS
Lipid concentration
Inflammation
Gluco-neogenesis
Circadian Rhythm
Blood coagulation
FA vs. PM2.5
Liver
BAT
WAT
Nr4a1
Rgs16
Socs3
Bhlhe41
Bmal1
Cyp7a1
Ppp1r3g
Npas2
Insig1
Mstn
Nos1
Ppp1r3b
Mest
Npas2
Lcn8
Spint4
Angptl7
Gpx5
Chow-FA vs. HFD
Liver
BAT
WAT
Nr4a1
Gadd45g
Bmal1
Rgs16
Cyp7a1
Bhlhe41
Ppp1r3g
Npas2
Ppp1r3b
Slc2a5
Mest
Lcn8
Npas2
Gpx5
-log10(FDR)
log2(Fold Change)


B
RNA-seq
ATAC-promoter
PM2.5HFD
PM2.5HFD
Rgs16
Cyp7a1
Prok1
3110082I17Rik
Angptl8
Dbp
Rab36
Id1
Bhlhe41
Wee1
Arrdc3
Grem2
Smad9
Celsr1
Nfil3
Mthfr
Cry1
Npas2
Mfsd2a
Abtb2
Arntl/Bmal1
Socs3
Myc
Orm2
Fst
Plk3
Thbs1
Pck1
Ppp1r3g
Cyp2c40
Ugt2b37
Cyp2c69
Gadd45g
Cyp2d11
Nr4a1
Log2(FC)
Log2(FC)

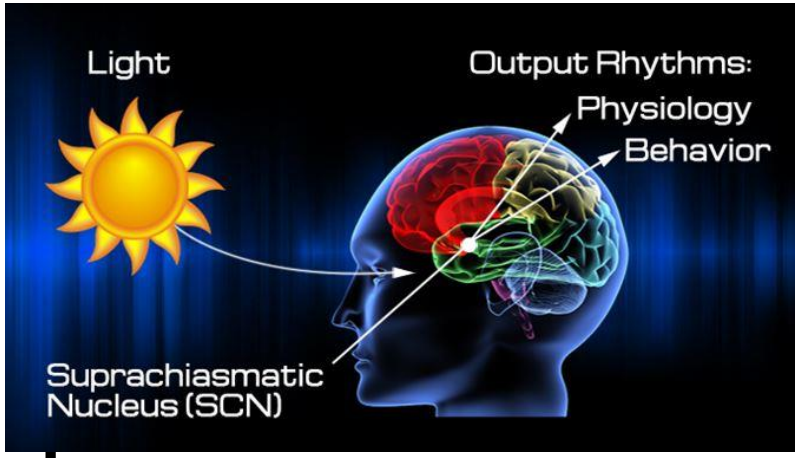

E
ATAC enrichment SMARCA5 sites
ATAC-seq occupancy
PM2.5
FA
-200bp
0
+200bp
Distance from SMARCA5 motif (bp)

SWItch-Sucrose Non-Fermentable (SWI-SNF) Nucleosomal Remodeling Complex

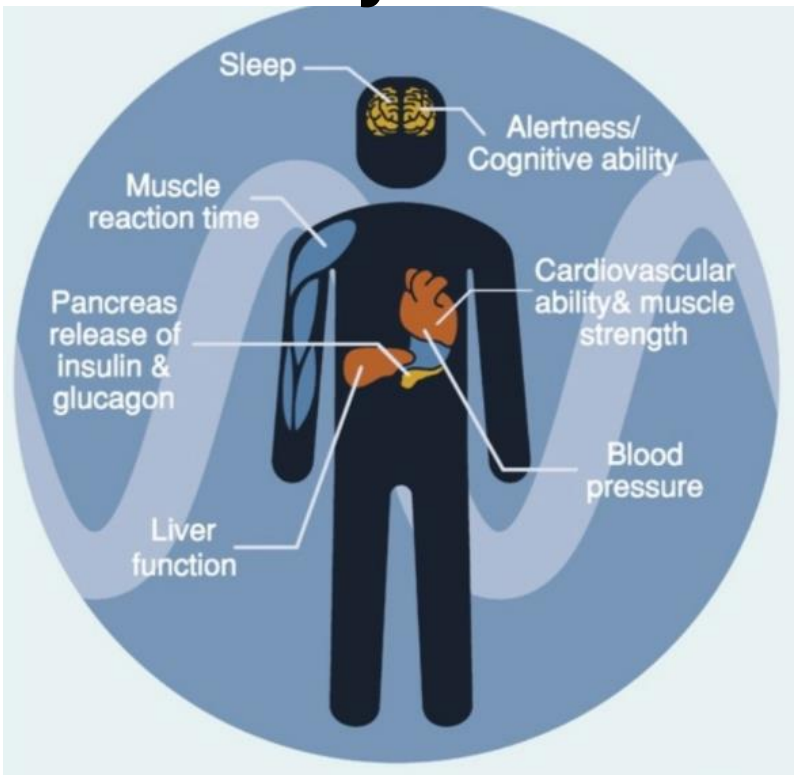


SWI/SNF chromatin-regulatory complexes are ATP dependent complexes that are critical in determining genome wide transcriptional access. Mutations in subunits of the SWI/SNF complex are present in 25% of all cancers

Adapted from The SWI/SNF complex in cancer — biology, biomarkers and therapy. Nature Reviews Clinical Oncology volume 17, pages435–448(2020

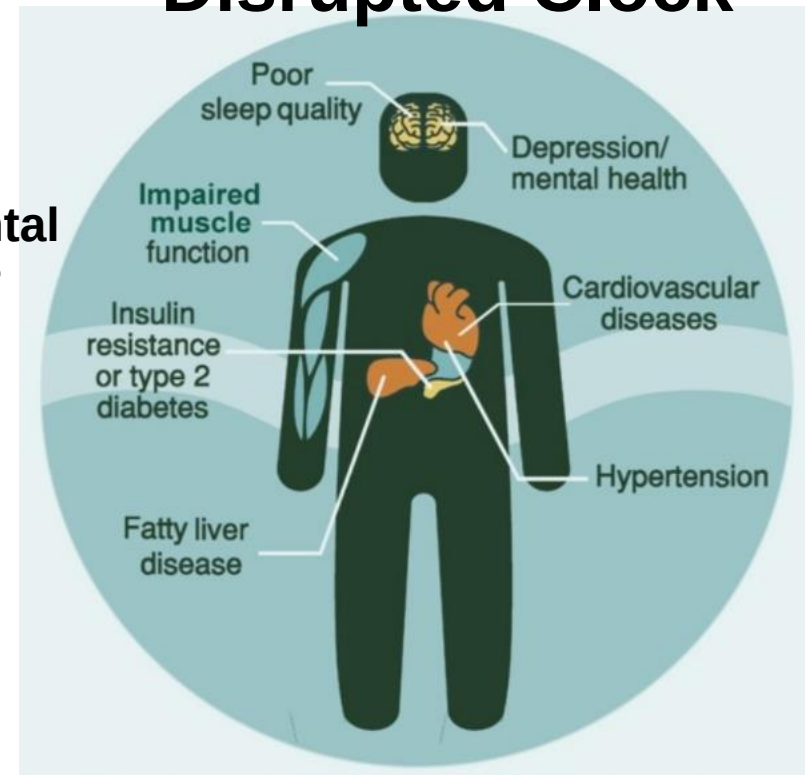


Healthy Clock

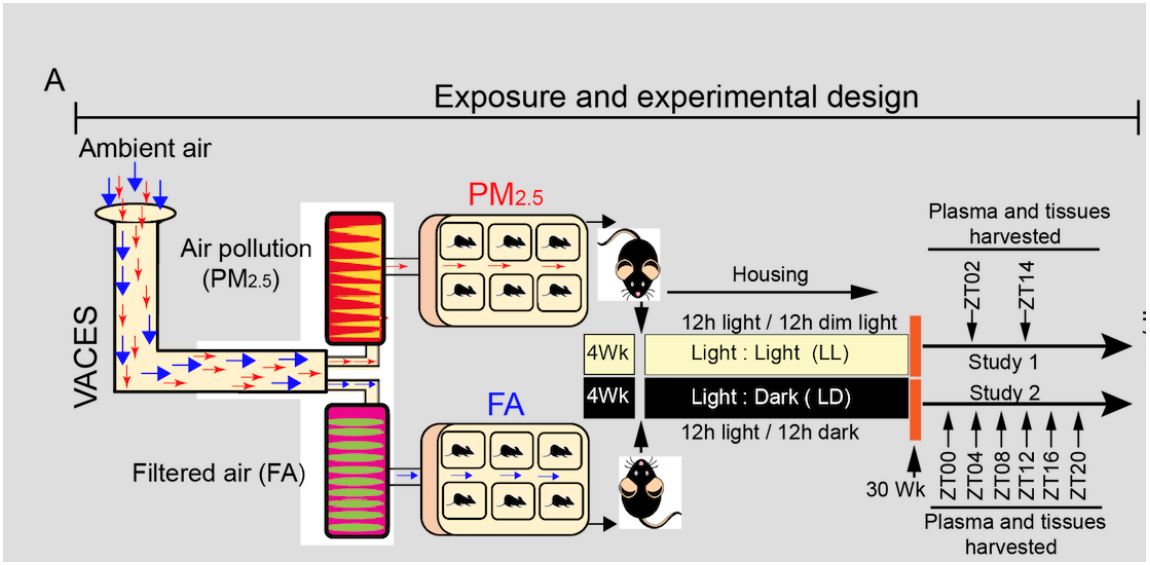


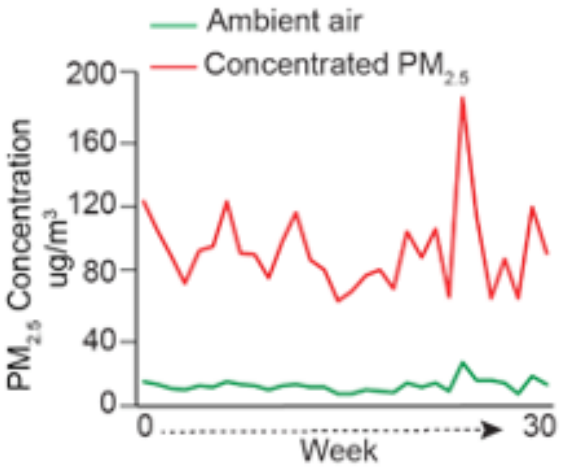
Light
Environmental
Triggers?

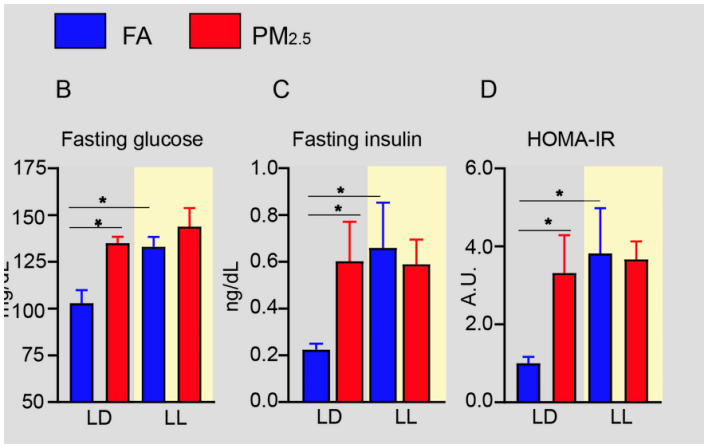
Disrupted Clock

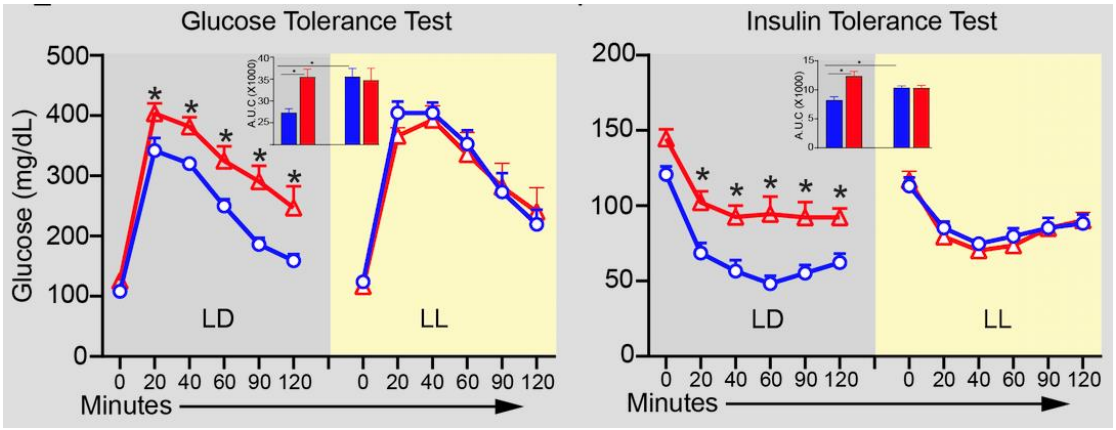


$PM_{2.5}$ Induces Insulin Resistance and Causes Circadian Disruption Similar to Light at Night Exposure



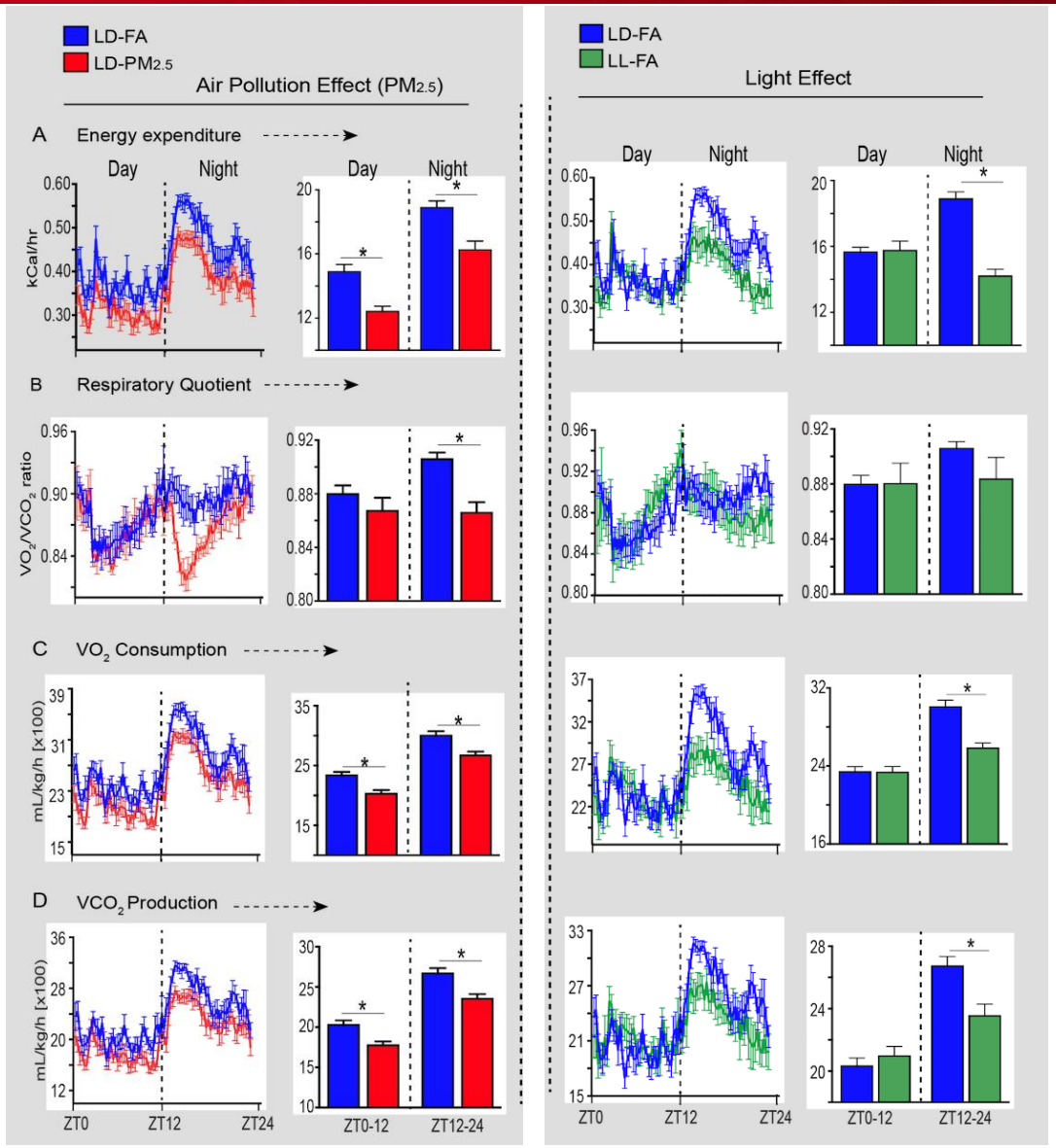


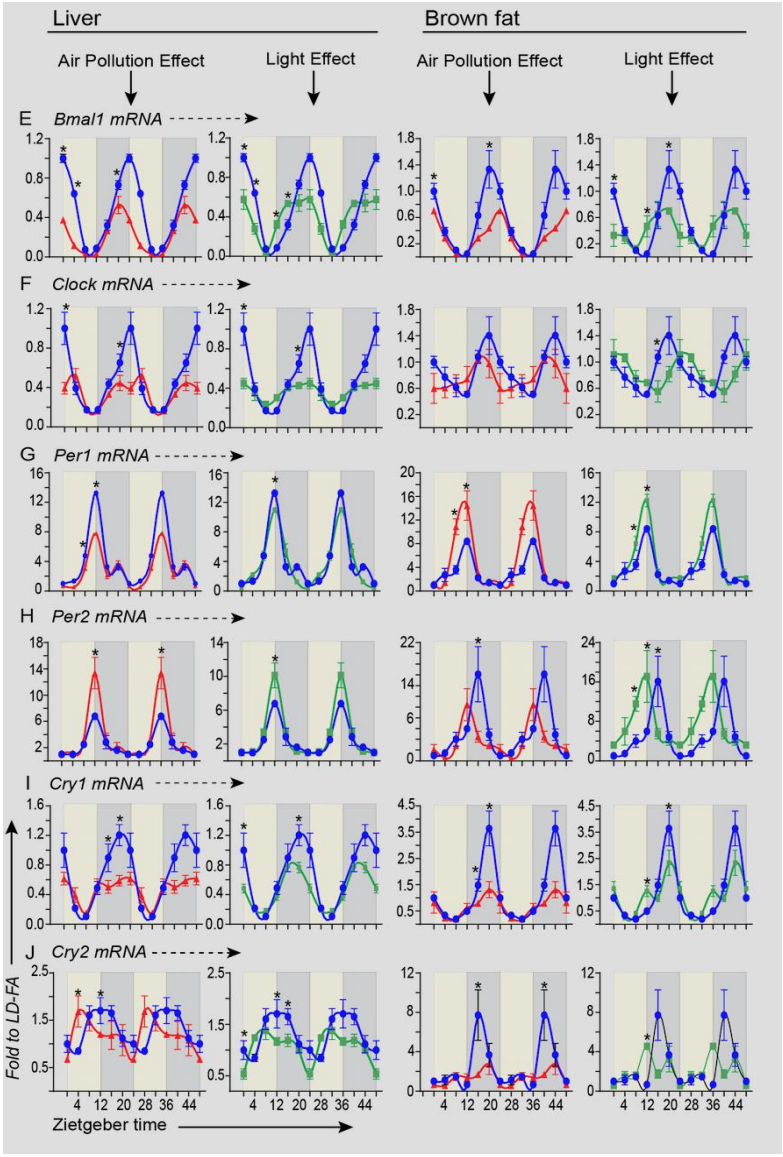




Rangasamy P. Vinayachandran V et al. iScience. 2020 Oct 24;23(11):101728.
doi: 10.1016/j.isci.2020.101728. eCollection 2020 Nov 20

$PM_{2.5}$ Disrupts Metabolism and Circadian Function





Rangasamy P. Vinayachandran V et al. iScience. 2020 Oct 24;23(11):101728. doi: 10.1016/j.isci.2020.101728. eCollection 2020 Nov 20

Conclusions

- $PM_{2.5}$ is the leading environmental cause of death and disability and the 4th leading cause of global mortality
- Atherosclerotic cardiovascular disease (ASCVD) dominates the mode of death due to $PM_{2.5.}$
- Compelling epidemiologic and mechanistic data implicates $PM_{2.5}$ in ASCVD initiation, progression and complications
- Coarse, fine and ultrafine $PM_{2.5}$ potentiates blood pressure through alerations in vascular autonomic tone. These changes occur acutely in response to exposure.
- $PM_{2.5}$ exposure induces hyperinsulinemia, adipose inflammation and altered metabolism (including impaired O2 consumption and energy expenditure)
- Air Pollution may induce circadian disruption akin to light at night exposure.

Case Western Reserve/UH

Palanivel Rangasamy*
Vinesh Vinayachandran*
Sadeer Al-Kindi
Lopa Das
Andrew Maiseyeu
Jeffrey Deiulis

Wayne State University
Michigan State
Robert Brook

University of Toronto
Health Canada
Jeffrey Brook

Michigan State University
Jack Harkema

New York University
Lung chi Chen
Terry Gordon

JHU Bloomberg School of Public Health

Shyam Biswal
Bongsoo Park

Peking Union Medical College/Fuwai
Zhongjie Fan
Dong Feng Gu

Peking University
Wei Huang

Public Health Foundation of India
Dorairaj Prabhakaran

University of Mainz
Thomas Muenzel
Andreas Daiber

EPA
Robert Devlin
Wayne Cascio
Dan Costa

Technischen Universität Dresden
Henning Morawietz