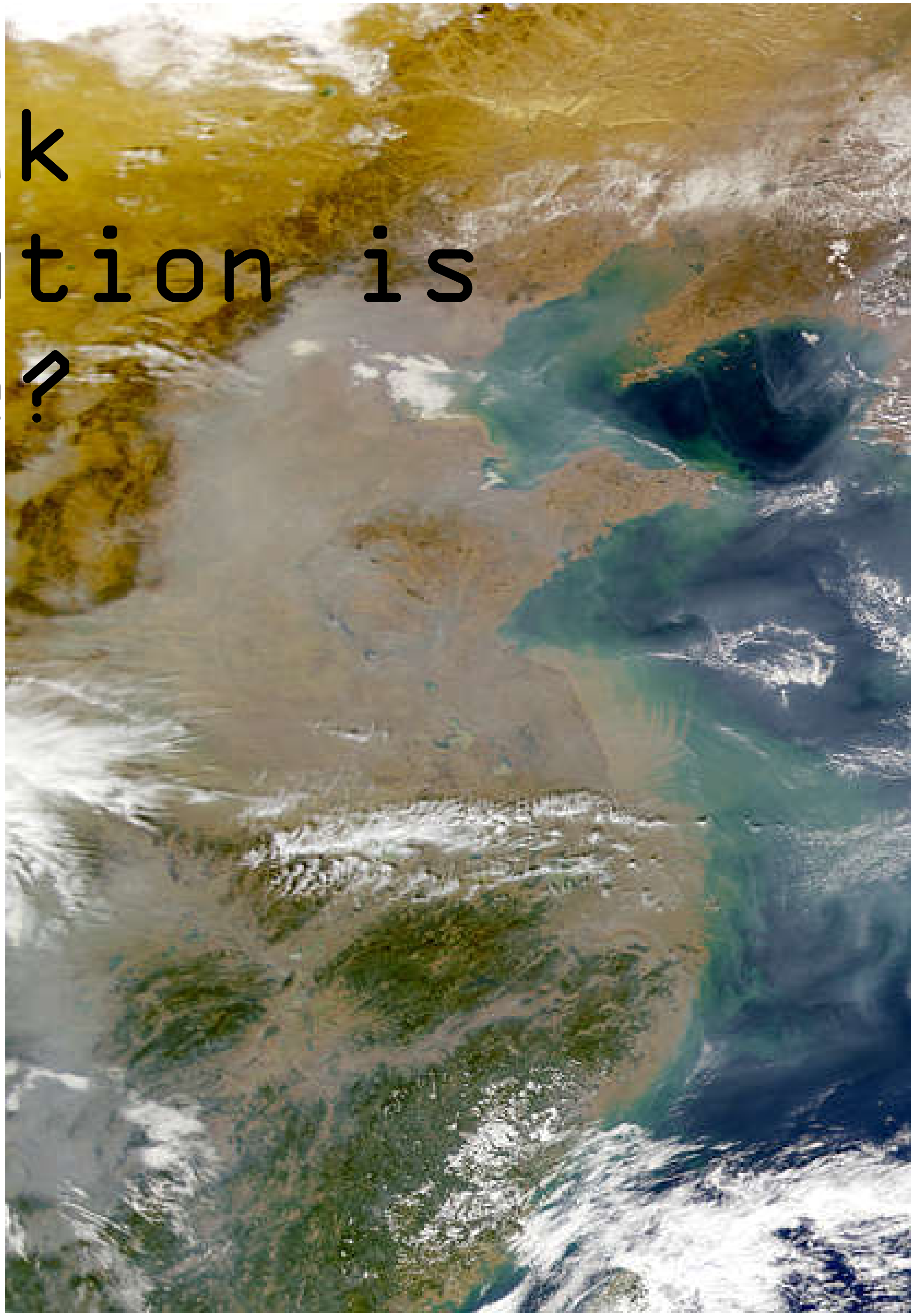
Why do we Think that Air Pollution is Killing People?



Joel Schwartz

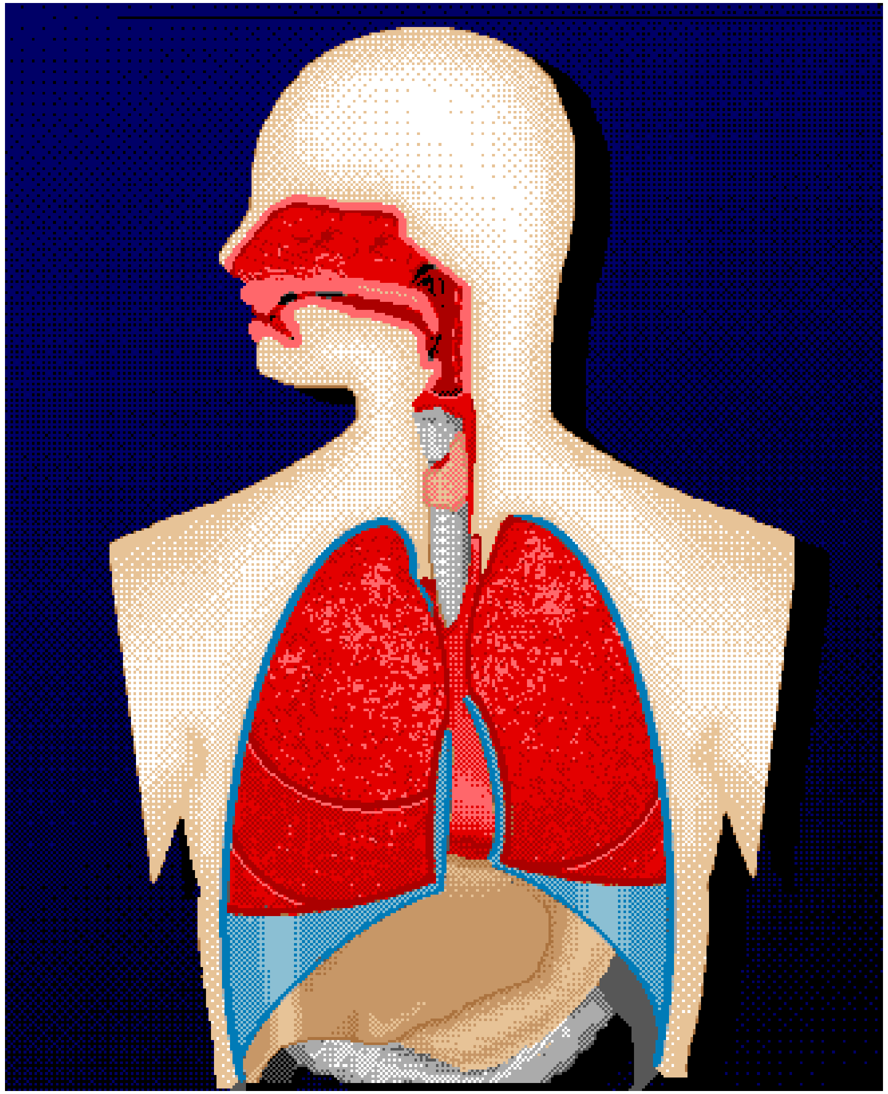
Harvard University

Outline

- How the Lung Works
- Observational Data on PM2.5
- What Happens When We Change Air Pollution?
- How is this Happening?
- What About Ozone?

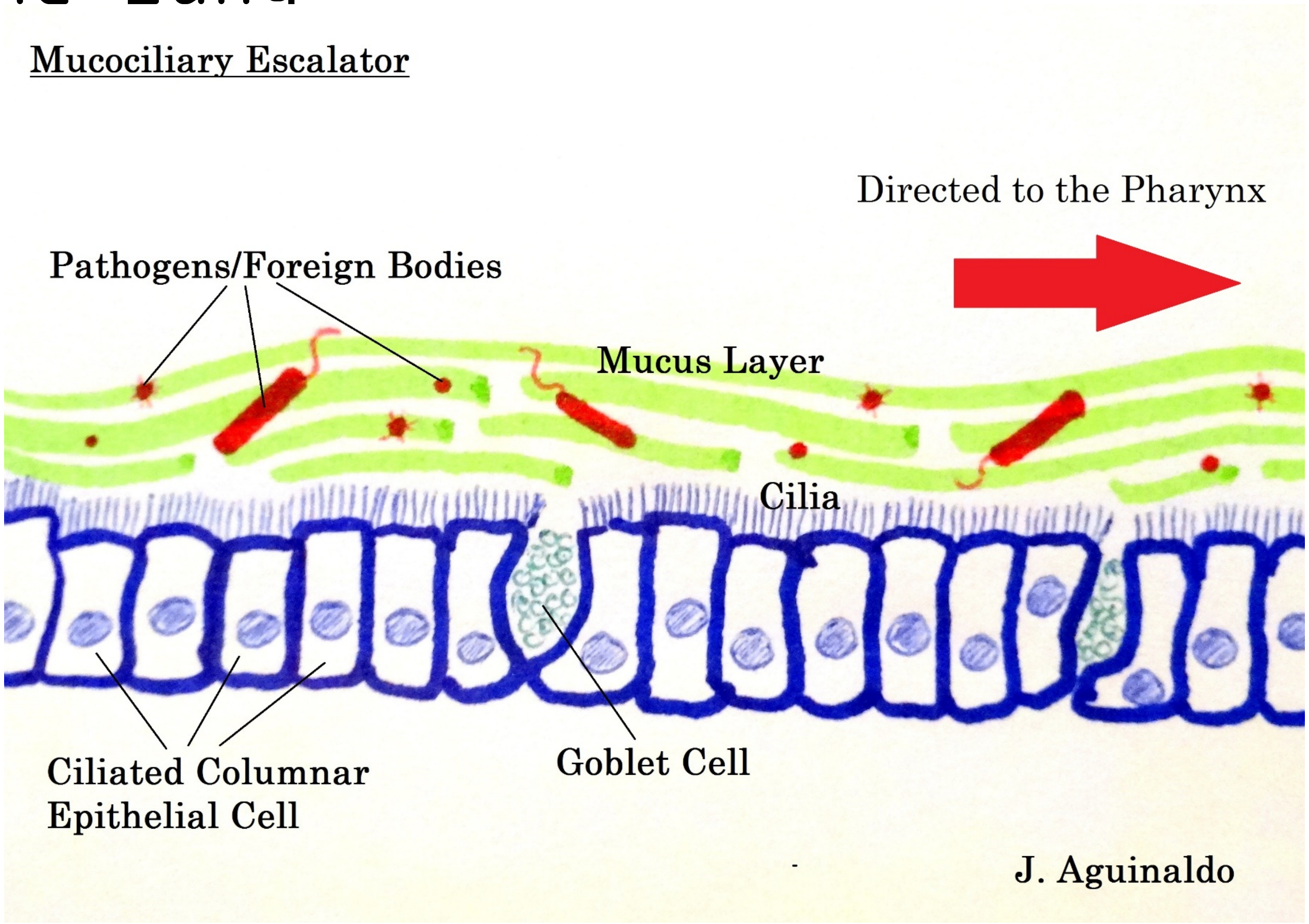
In Evolutionary Time Lungs Saw

- Mostly non-biologic particles that were the product of mechanical processes
  - Erosion, Wind blown dust
  - Median Diameter of ~ 3-7 µM
- Nasal passages and upper Airways evolved to remove substantial amounts of these particles



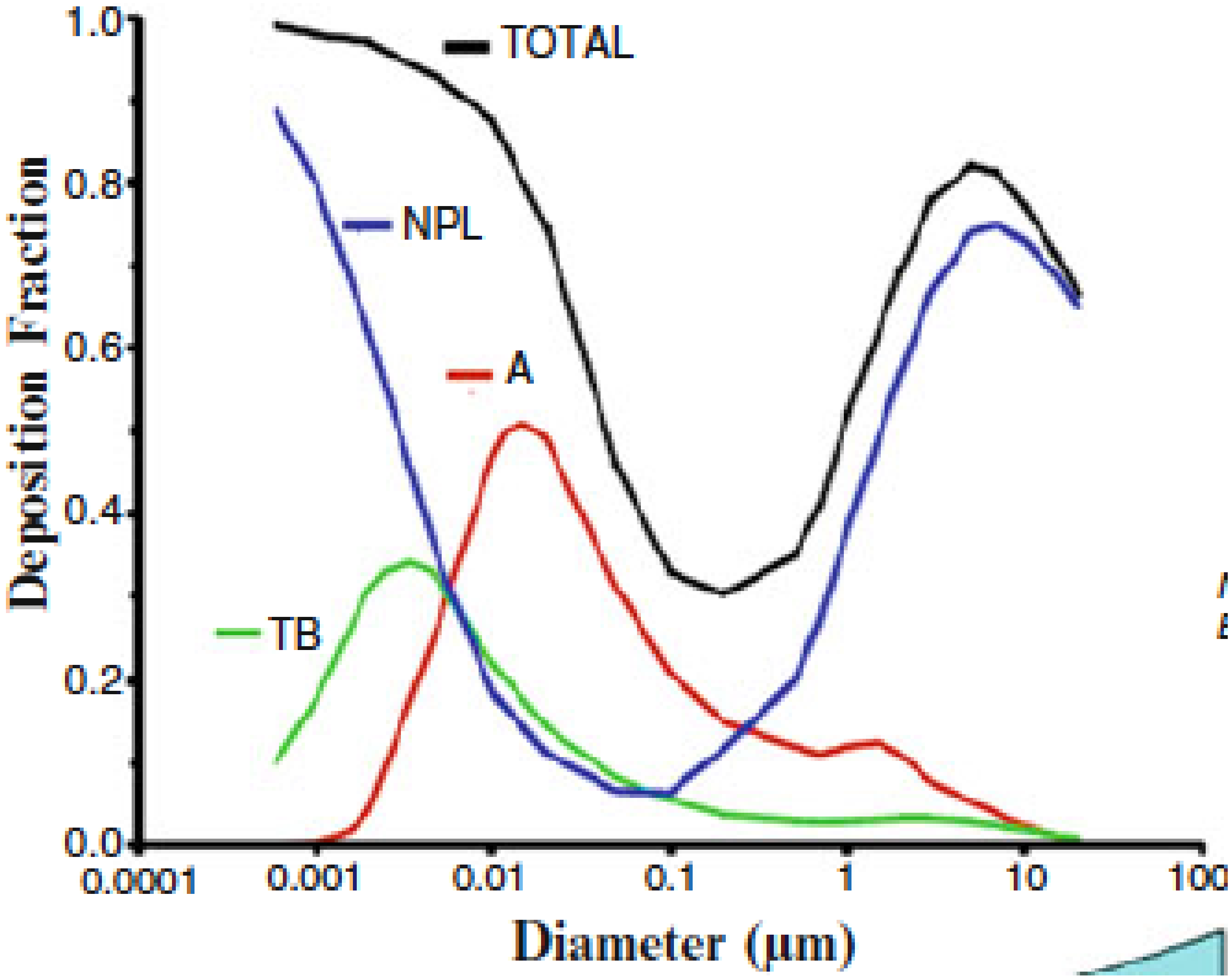
Within the Lung

- Mucociliary Clearance
  - transport particles up out of the lung
- Alveolar Macrophage deals with particles that penetrate to the alveolar region, but much more slowly



The Domestication of Fire Brought a New Challenge

- Combustion Particles have
  - Different Size, Chemistry
- Generally less than 1 mM in diameter, with Primary Combustion Particles in the Nano-Particle Range
- Nano-particles have greater deposition in both upper and lower airways
- 80-98% of particles deposited in alveoli in urban areas are combustion particles

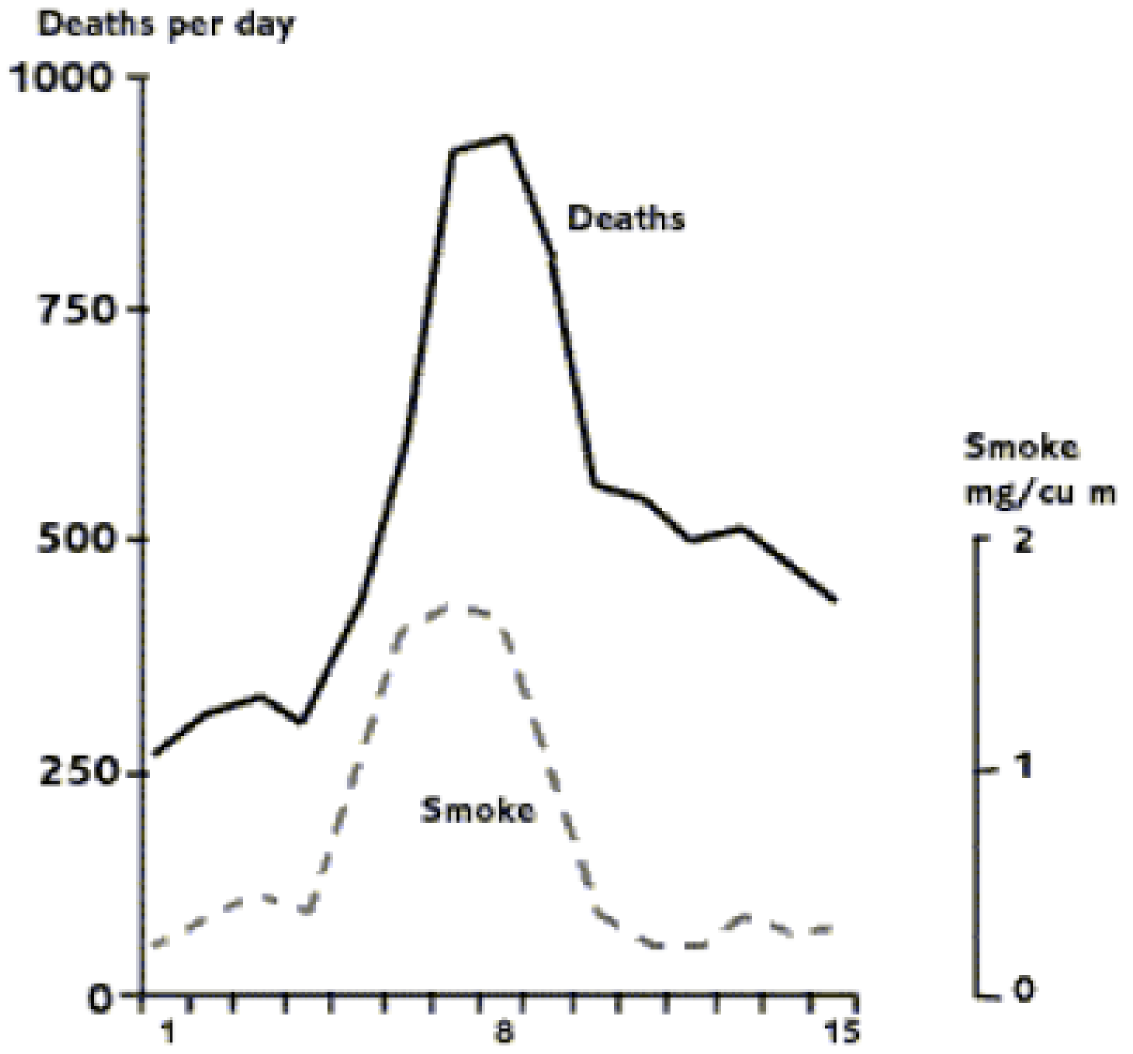


TOTAL
NPL
A
TB
Deposition Fraction
1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
100
Diameter (µm)

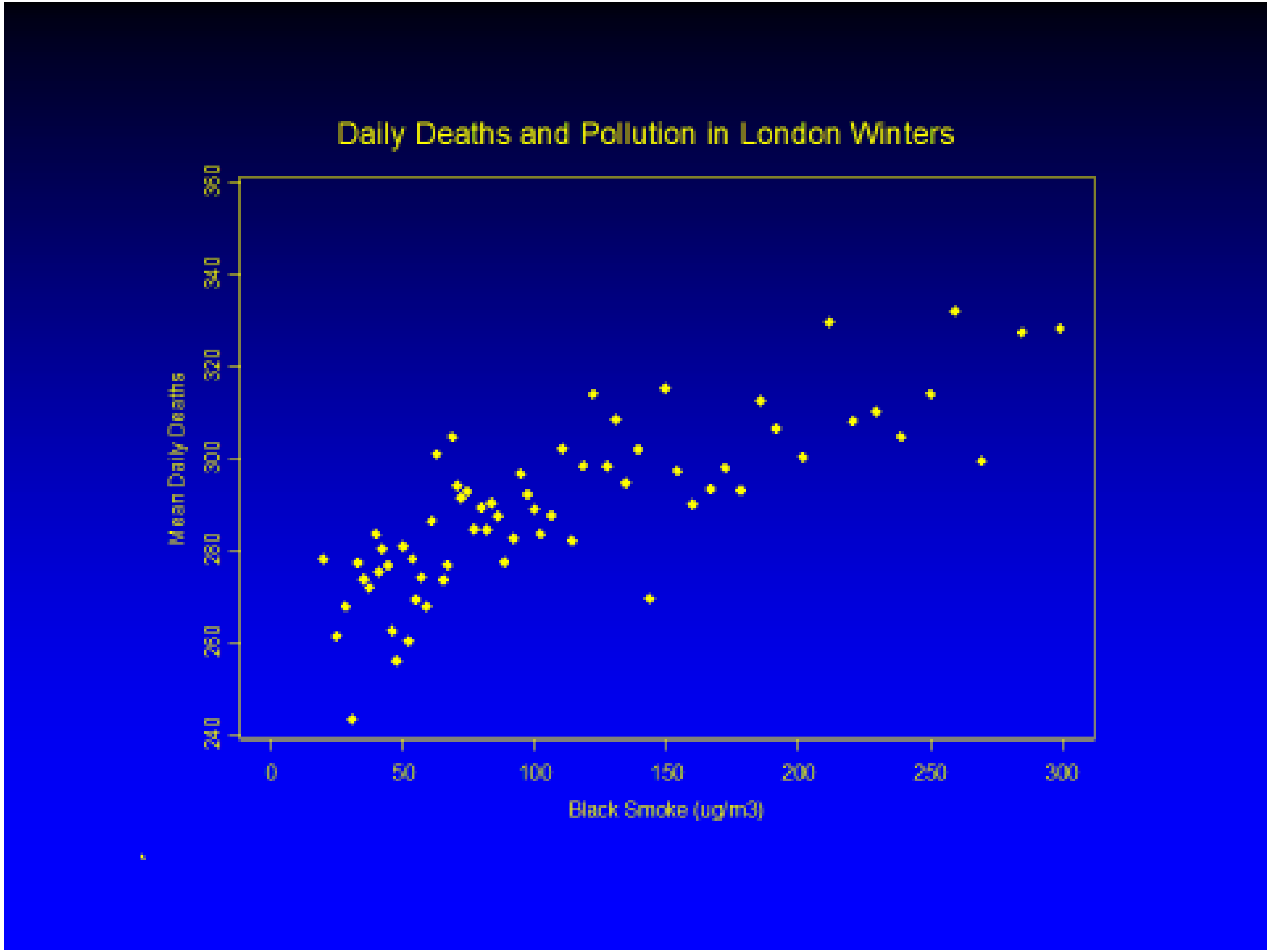
So Combustion Particles Go Where They Don't Belong

- What do they do there?

They Kill People at High Dose

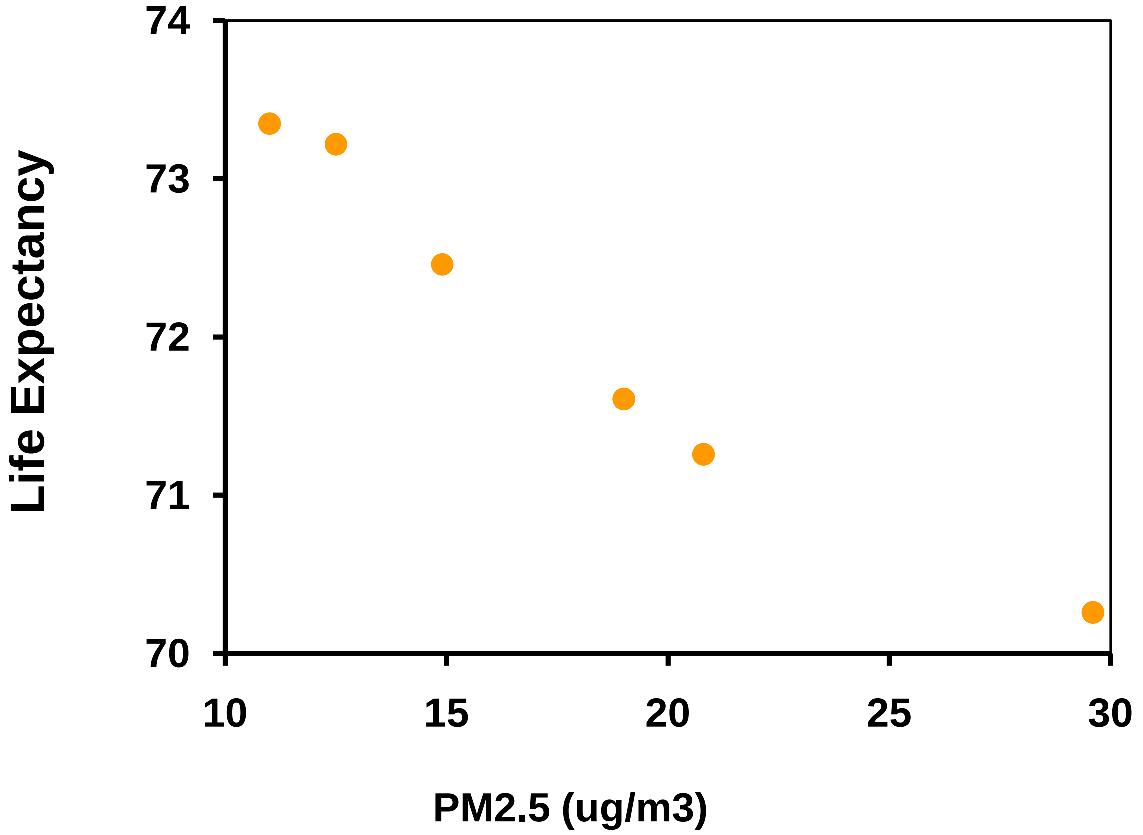


And Lower Concentrations



Schwartz & Marcus, Am J Epi 1990

They Kill People at Low Dose

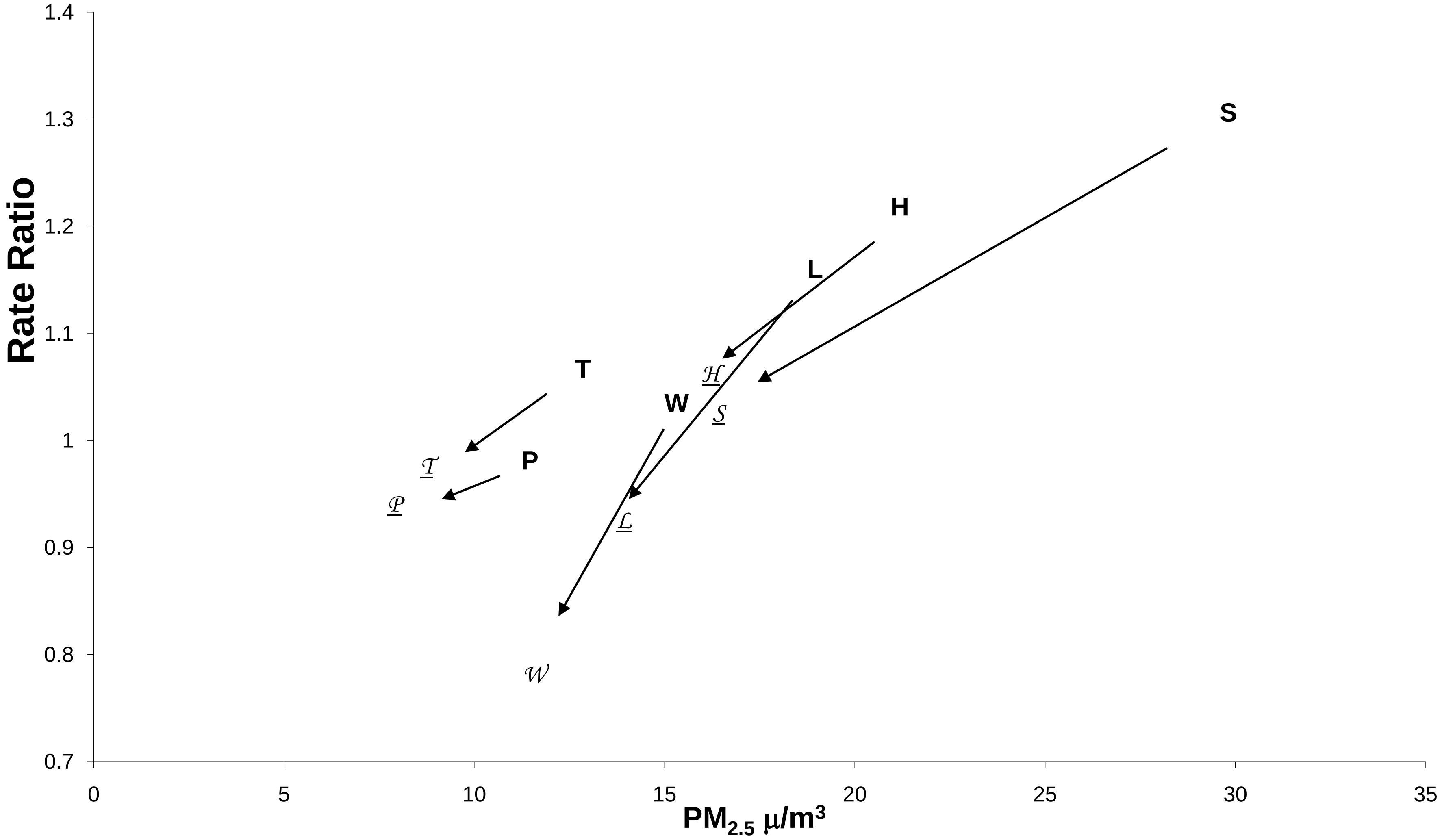


Dockery 1993

If You Reduce Particles

- Fewer People Die

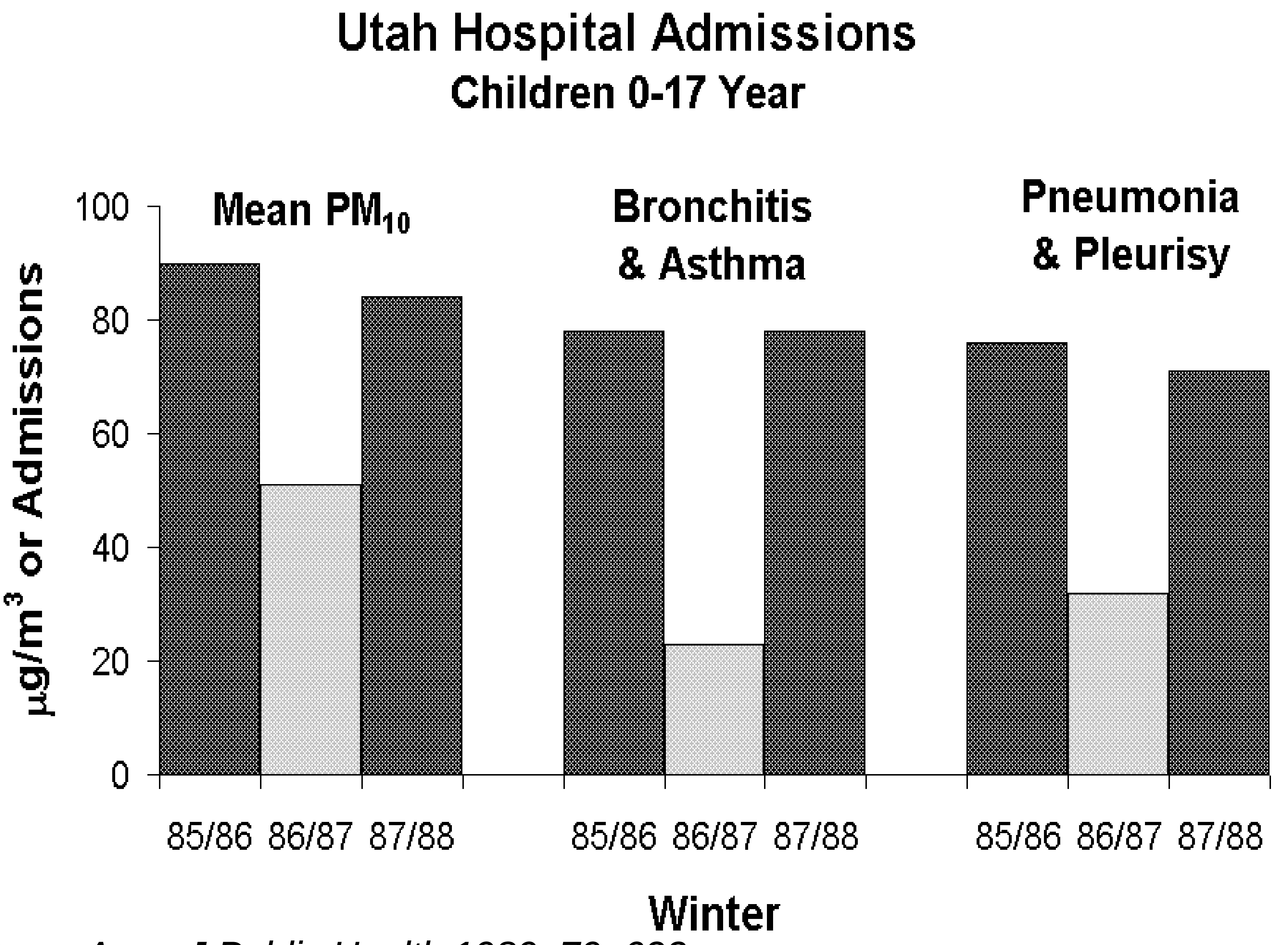
Relative Risk of Death in Six US Cities during Two Follow-up Periods



Laden 2006

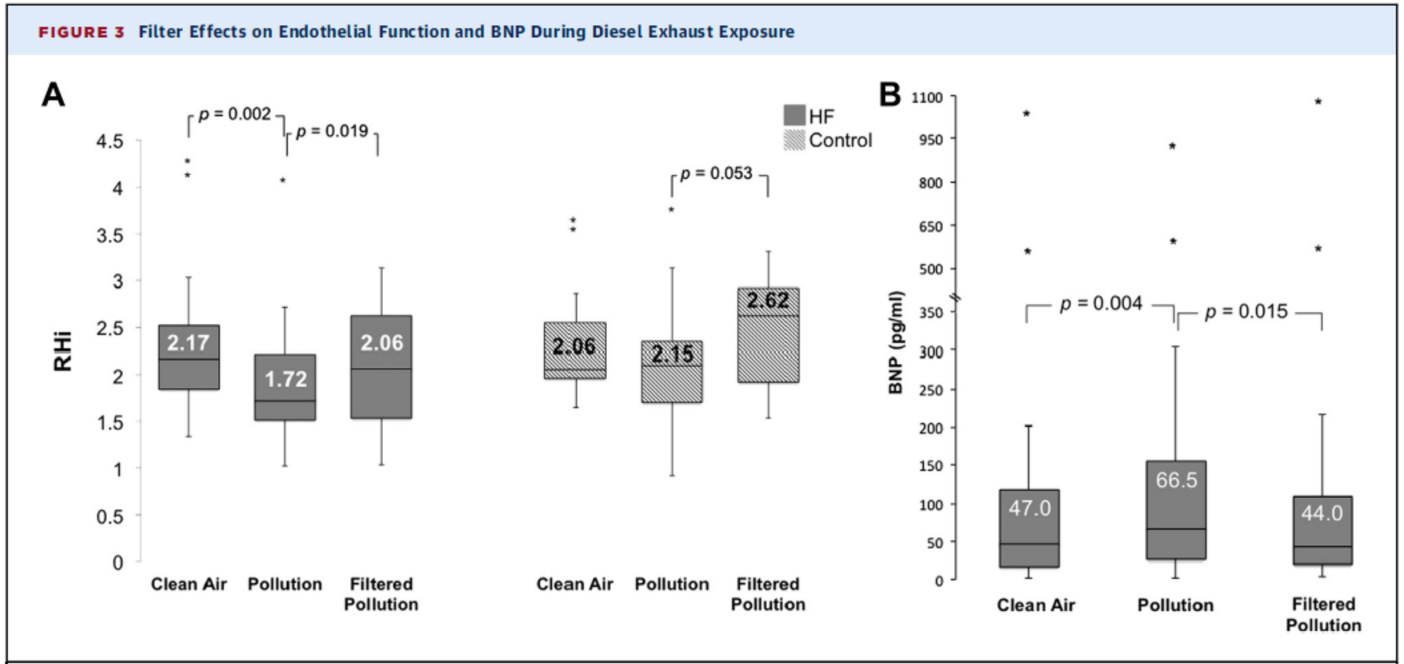
Pope Smelter Strike

- Smelter Strike Reduced Sulfates in U.S. Southwest by ~60%
- 2.5 ug/m^3 decrease in Sulfates
- 2.5% Reduction in Mortality
- Avol Lung Function Growth in Southern California Children' s Cohort
  - Children who moved to more polluted areas had slower growth
  - Children who moved to less polluted areas had faster growth



Pope, Amer J Public Health 1989; 79: 623

Filtering Particles from the Air Improves Endothelial Function



(A) Endothelial function assessed by using the reactive hyperemia index (RHi) in patients with heart failure and control volunteers after exposure to clean air, diesel

This Also worked in the Home

- Randomized trial of air filtration
- 8% improvement in endothelial function with Filtered air

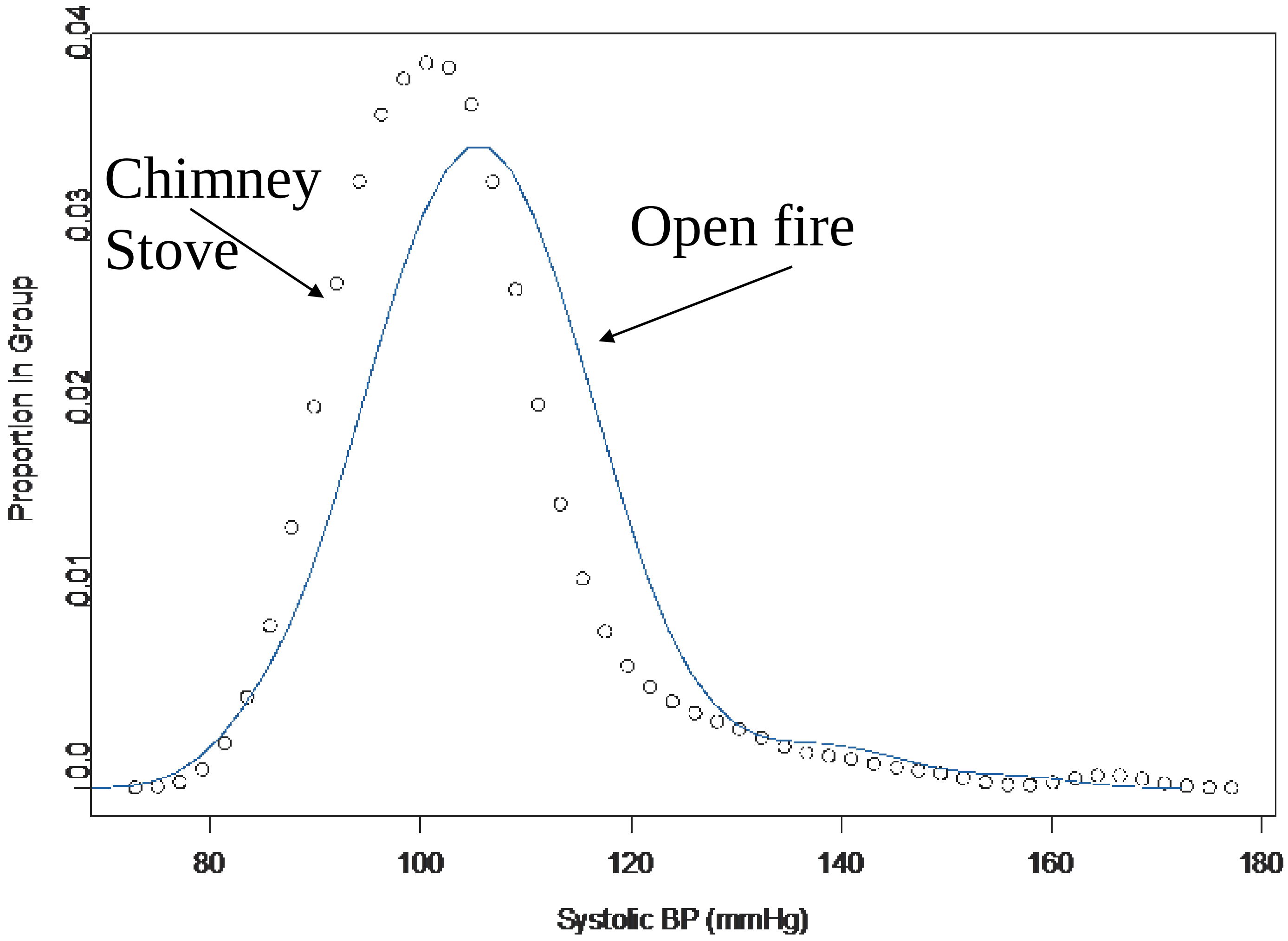
    (Brauner et al 2008)

Beijing Particle Mask Study

- People walked the same route twice
- Once wearing a mask that filtered out particles, once without the mask
- Blood pressure was 3 mmHg lower when they were wearing the mask
- ST segment depression was less wearing mask

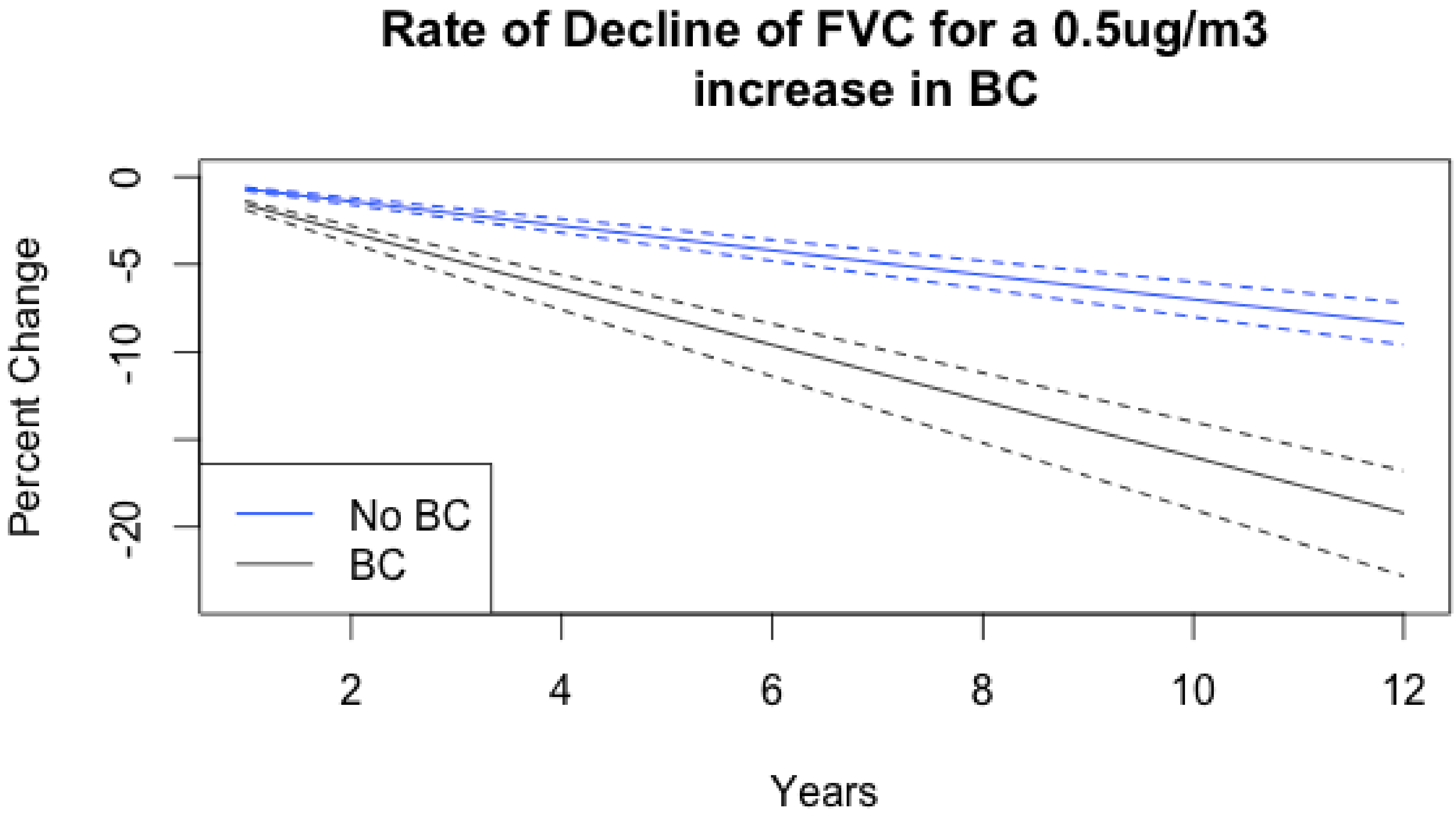
Langrish 2012

Randomized Trial: Effect of Stove on Distribution of Systolic Blood Pressure



That is not All Particles Do

Lung function decline according to black carbon exposure



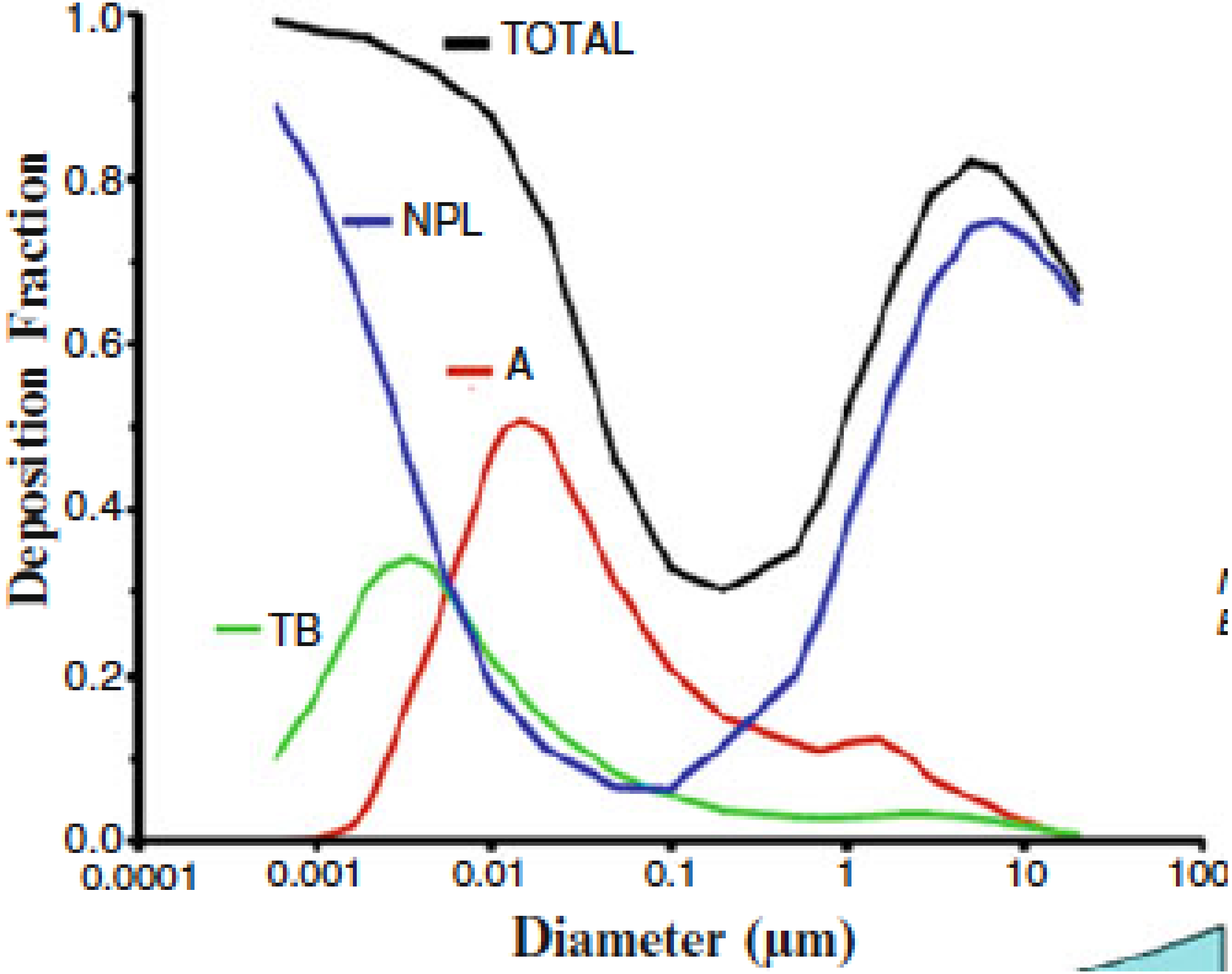
Lepeule, 2014

- Calderón-Garcidueñas showed (2008)
  - That animals living in Mexico City had increased inflammation and beta-amyloid than animals in a less polluted city
  - That Children in Mexico City had reduce brain volume and increased beta-amyloid compared to the less polluted city.

Particles and Cognitive Ability

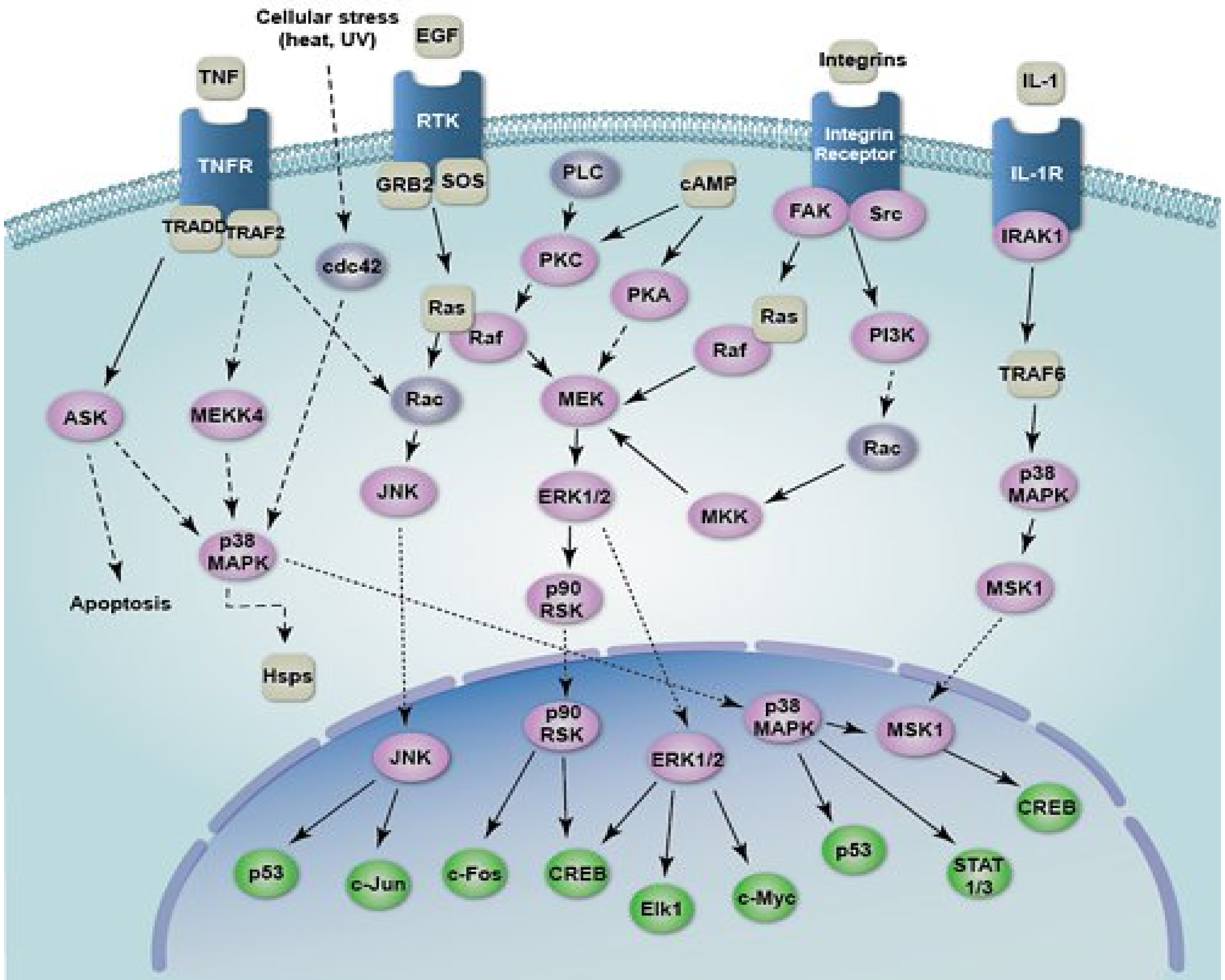
- Children exposed to traffic particles have lower IQ (Franco-Suglia 2008)
- Adults exposed to PM2.5 have faster rates of cognitive decline (Weuve 2012)
- Elderly exposed to traffic particles have lower cognitive ability (Power 2012)
- Animals exposed to particles have brain inflammation, particularly in the hippocampal area, which is key to memory (Campball 2005, Fonken 2011)

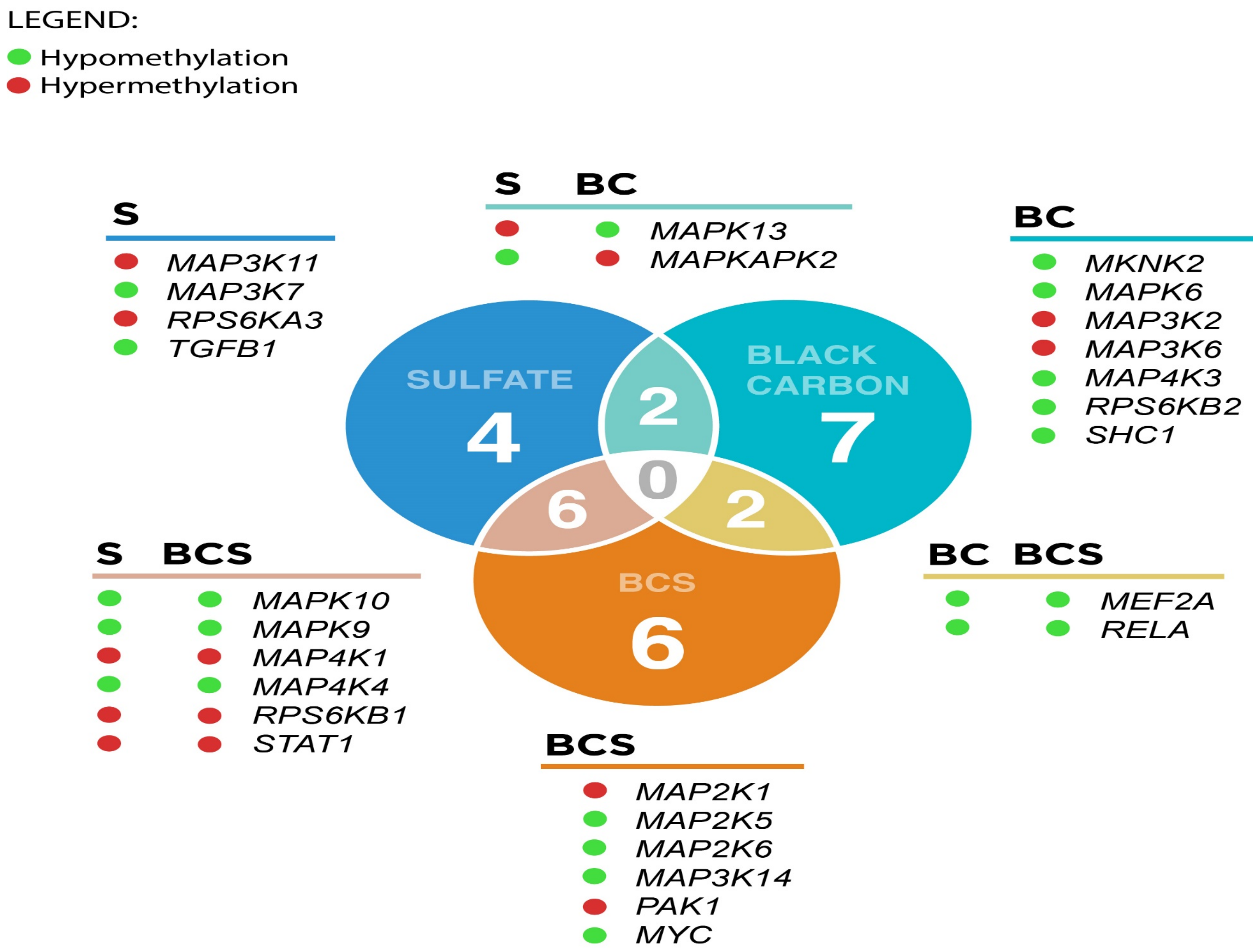
How is this Happening?



1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
100
Deposition Fraction
Diameter (µm)
TOTAL
NPL
A
TB

MAPK Signalling

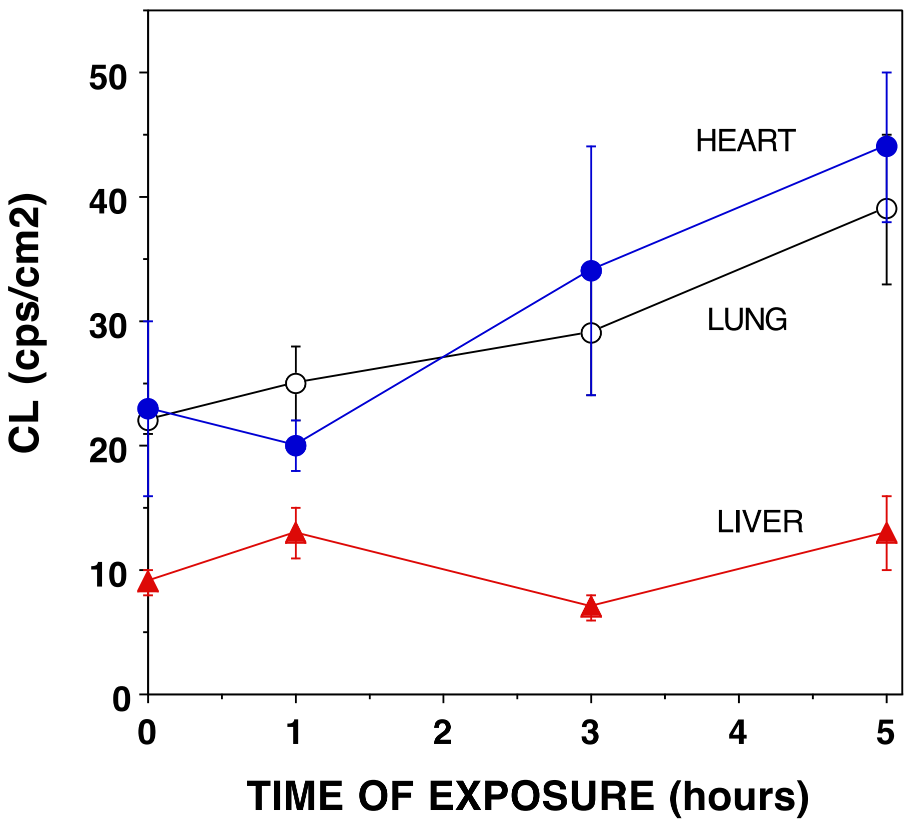




LEGEND:
Hypomethylation
Hypermethylation
S
MAP3K11
MAP3K7
RPS6KA3
TGFB1
S BC
MAPK13
MAPKAPK2
BC
MKNK2
MAPK6
MAP3K2
MAP3K6
MAP4K3
RPS6KB2
SHC1
SULFATE
4
BLACK CARBON
7
2
0
6
2
BCS
6
S BCS
MAPK10
MAPK9
MAP4K1
MAP4K4
RPS6KB1
STAT1
BC BCS
MEF2A
RELA
BCS
MAP2K1
MAP2K5
MAP2K6
MAP3K14
PAK1
MYC

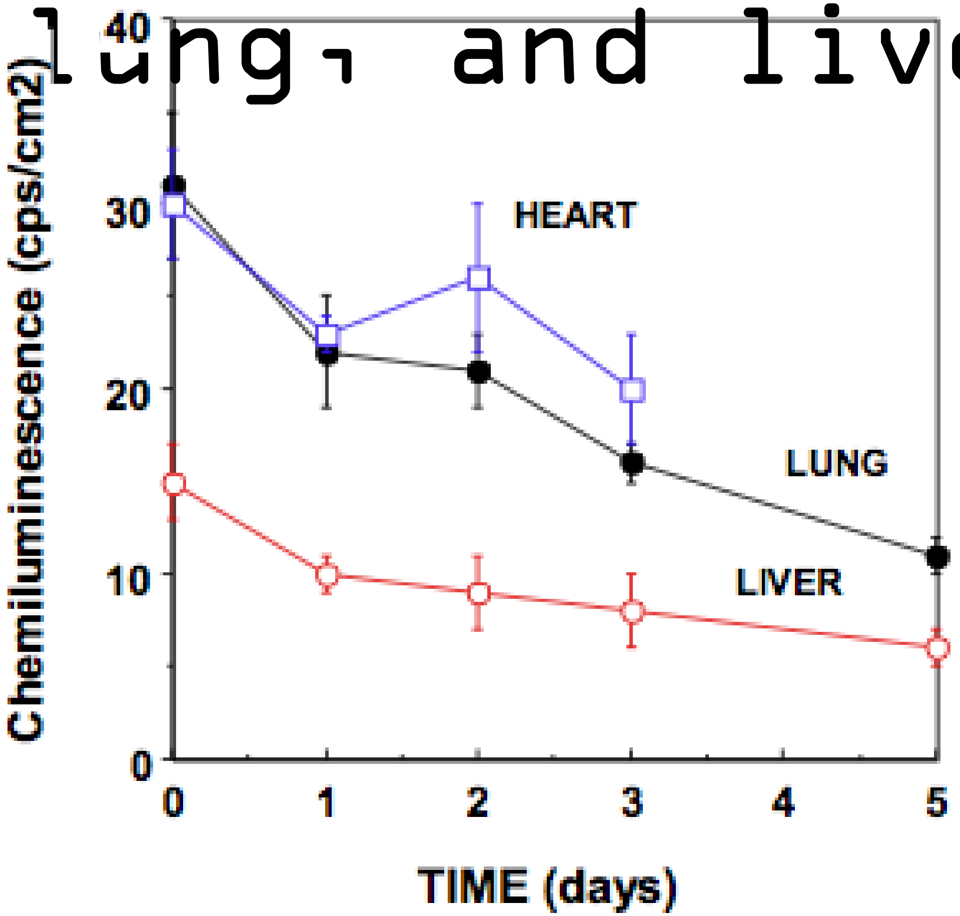
Particles Induce oxidants in the Heart and Lung

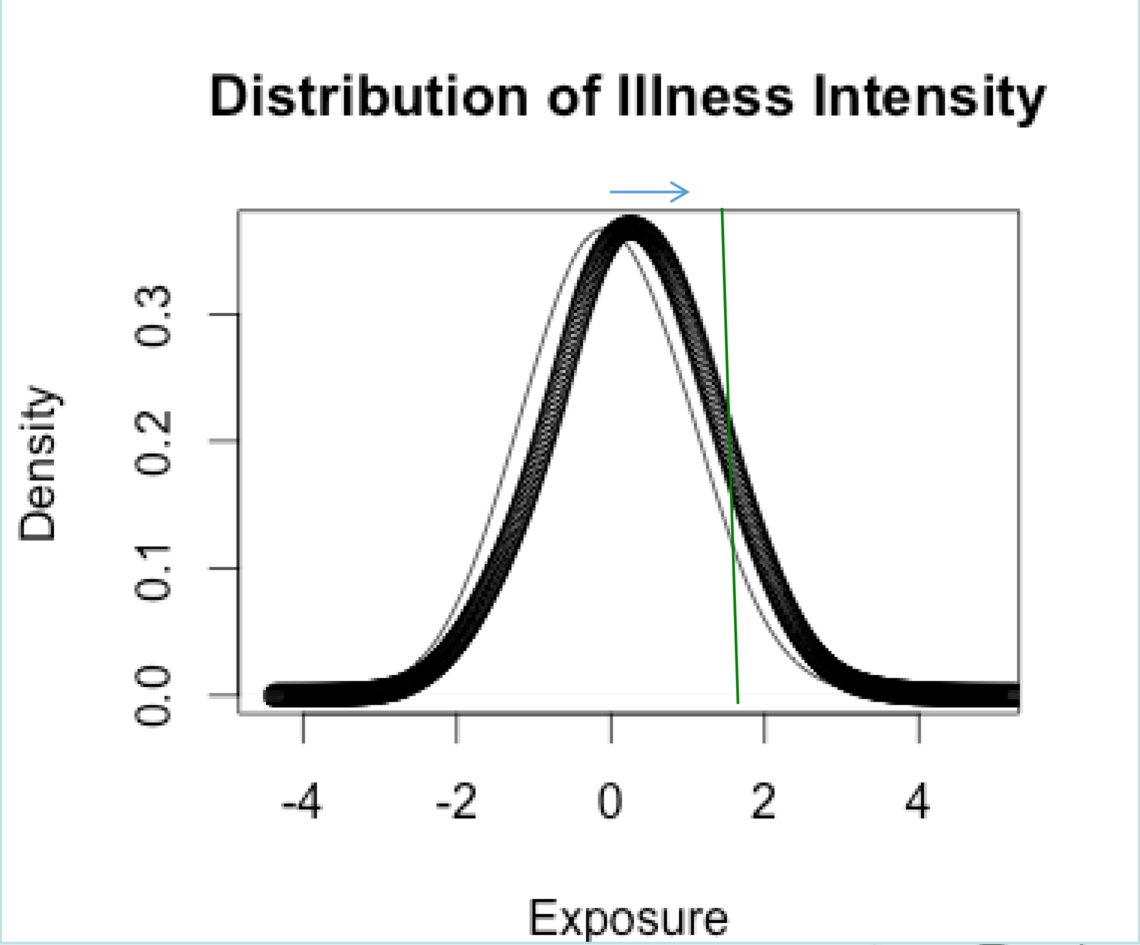
- Gurguera et al EHP 2003)

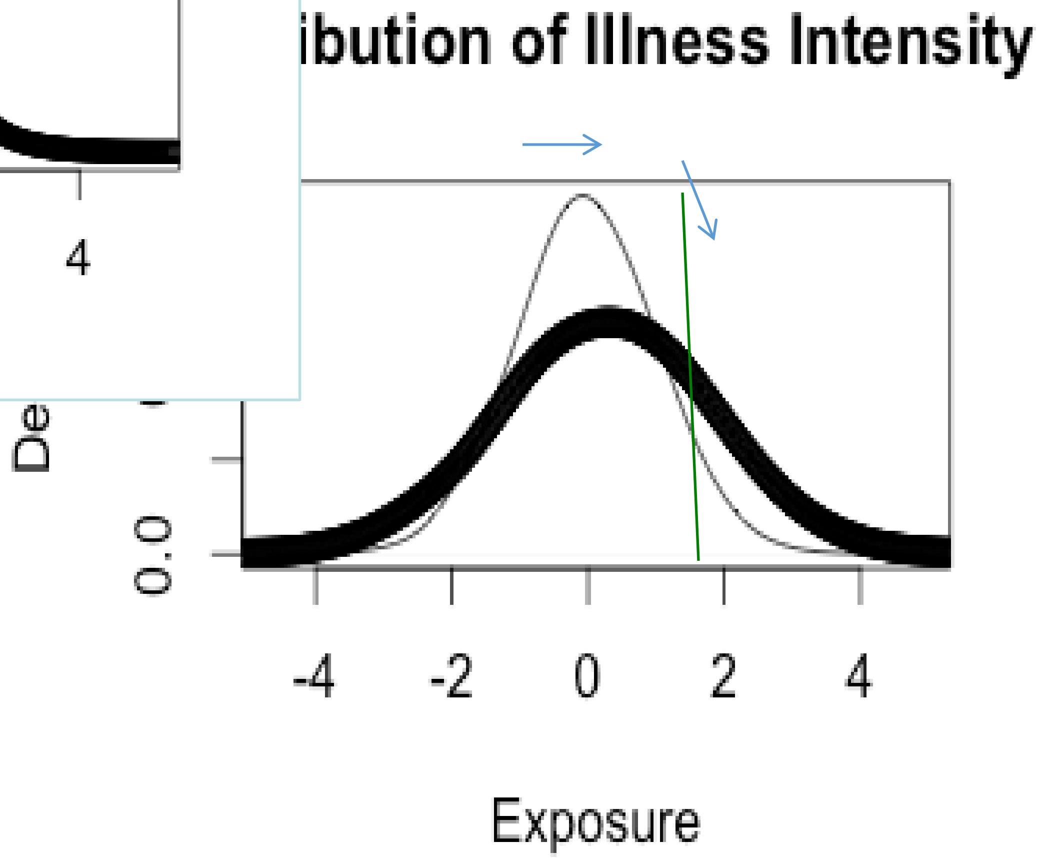


Chemiluminescence (CL) of lung, heart, and liver after various durations of Particle exposure.

Effect of putting animals in filtered air on oxidative stress in their heart, lung, and liver

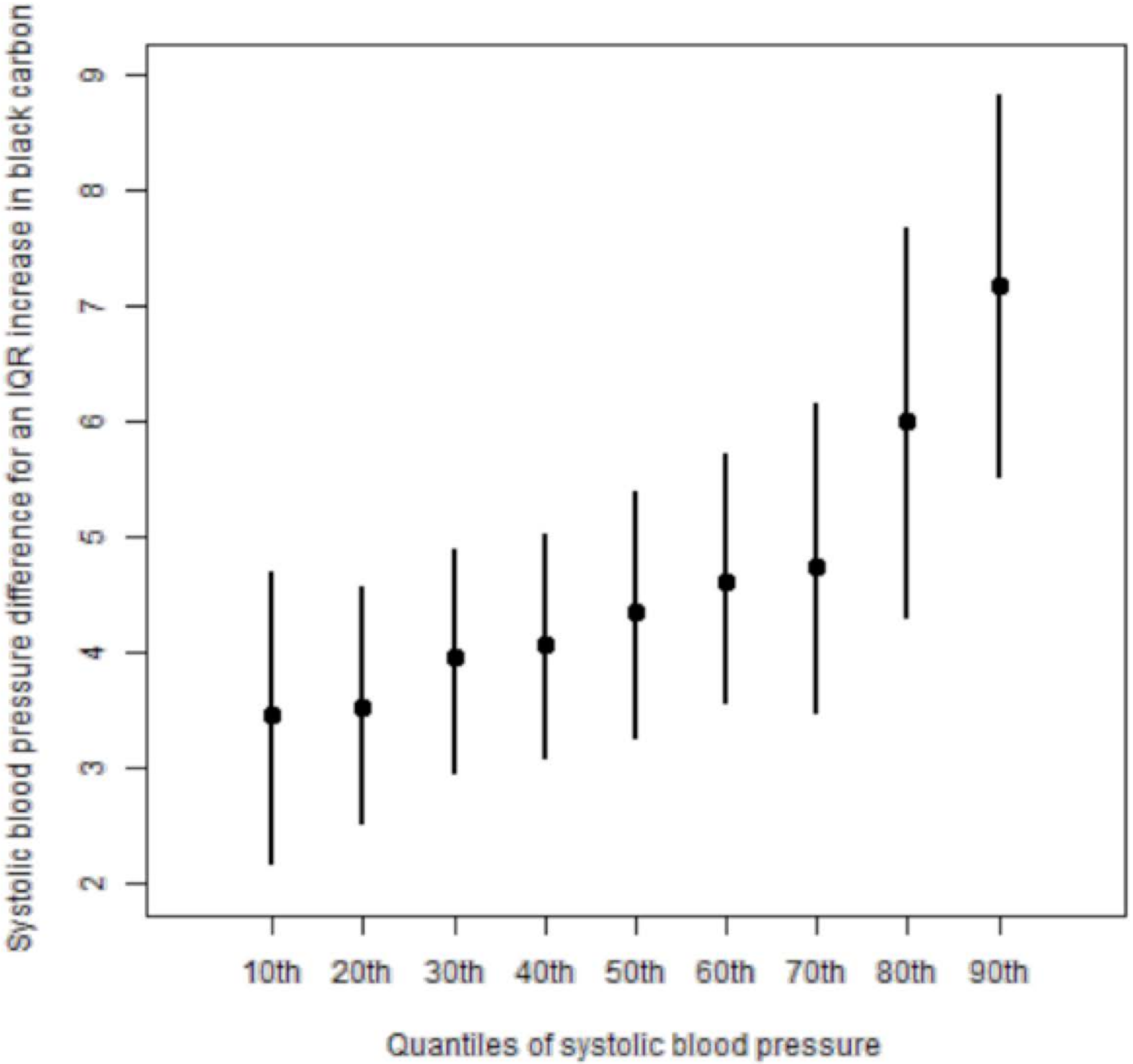



Distribution of Illness Intensity
Density
0.0
0.1
0.2
0.3
-4
-2
0
2
4
Exposure


ibution of Illness Intensity
De
0.0
-4
-2
0
2
4
Exposure

Quantile
Regression!

Bind 2016



What About Ozone?

Ozone and Survival in Four Cohorts with Potenti[al] Predisposing Diseases

Antonella Zanobetti[1] and Joel Schwartz[1]

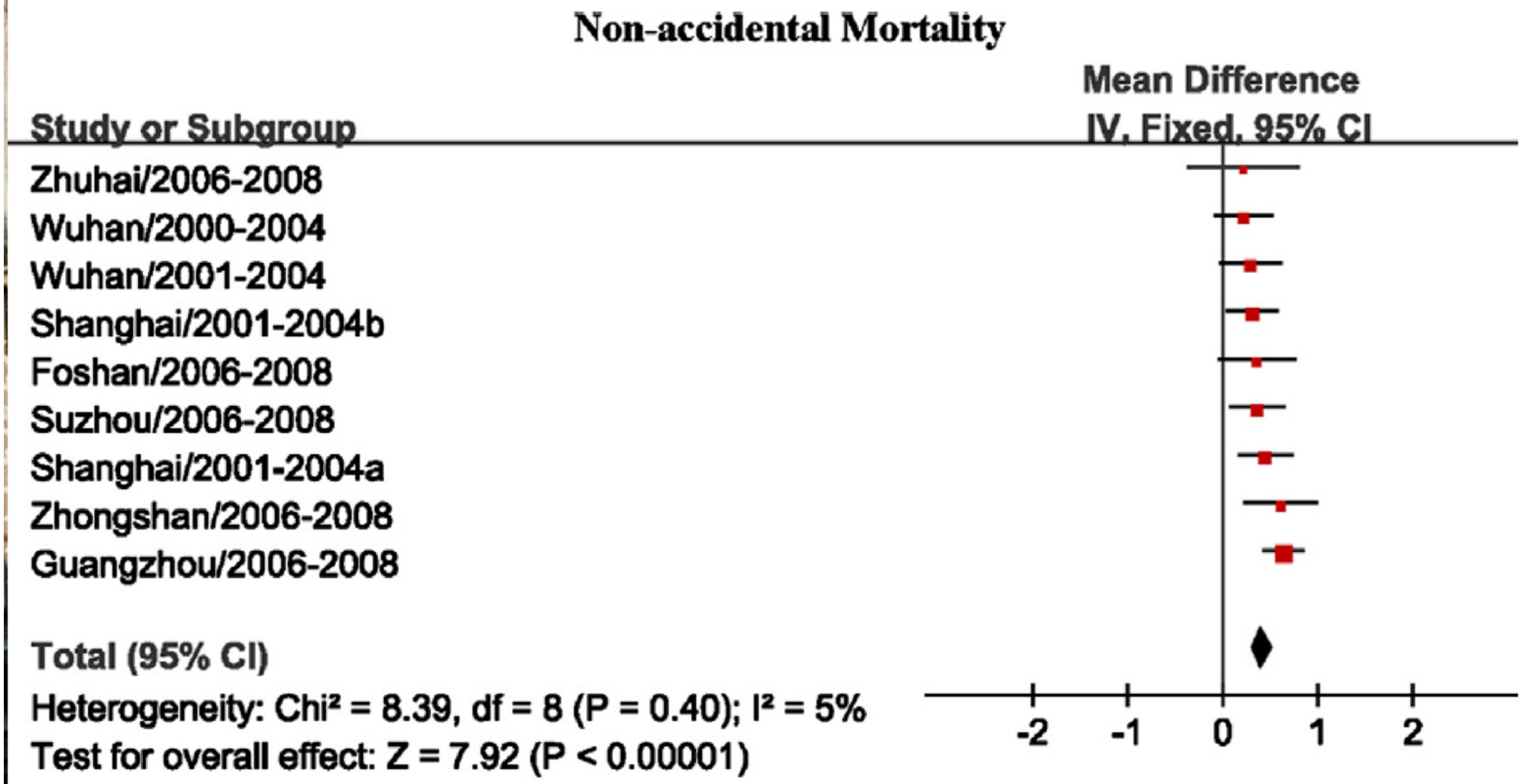
TABLE 2. HAZARD RATIO AND 95% CONFIDENCE INTERVALS FOR 5-ppb INCREASE IN 8-HOUR OZONE FOR THE YEAR OF FAILURE, ACROSS THE 105 CITIES

	Ozone Average May to September		Ozone Average Spring and Autumn	
	HR	95% CI	HR	95% CI
CHF	1.06	1.03–1.08	1.02	0.99–1.05
MI	1.09	1.06–1.12	1.04	1.00–1.08
Diabetes	1.07	1.05–1.10	1.03	1.00–1.07
COPD	1.07	1.04–1.09	1.03	1.00–1.06

Meta-analysis of the Chinese studies of the association between ambient ozone and mortality

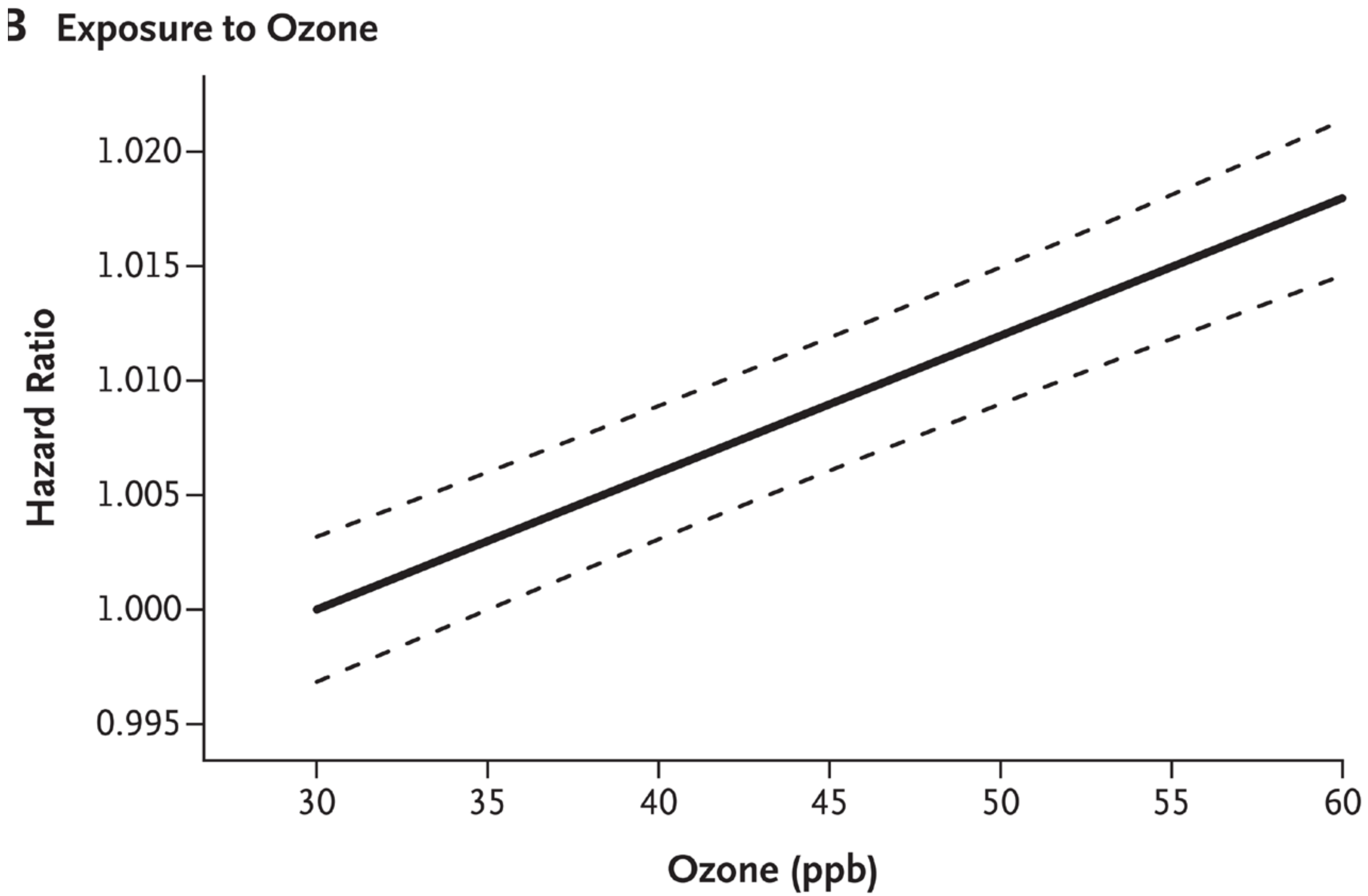
Chemosphere 2013

Meilin Yan[a], Zhaorong Liu[a,*], Xiaotu Liu[a], Hengyi Duan[a], Tiantian Li[b,*]



0.42% increase per 10 μg/m3

Di 2017 61 Million Medicare Participants



Air pollution: a nationwide prediction model and health effect
空气污染的全美预测模型及其健康危害

Qian Di （底骞）, Joel Schwartz
Harvard University
哈佛大学

INTRODUCTION 引言

- The health effects of $PM_{2.5}$ and ozone have been well-documented；
- 细颗粒物（$PM_{2.5}$）和臭氧的健康危害已经得到充分研究；
- The effect of ozone on mortality in cohort studies is still relatively unexplored;
- 但臭氧和总死亡率之间的关系在队列研究中尚不清楚；
- The effects of both ozone and $PM_{2.5}$ at levels below the National Ambient Air Quality Standards (NAAQS) need further exploration;
- 在低于"全美空气质量标准"以下的低浓度空气污染仍会危害健康吗？
- Health effect of air pollution in the general population?
- 空气污染对于一般人群的危害？

Method Overview 方法简述

- Two identical groups living in two areas: polluted area and clean area
- 两群人各种条件相同，分别生活空气污染地区和干净的地区
- Continue to follow them for some years and observe the health outcome (e.g. death)
- 持续跟踪这群人若干年，记录健康结果（例如死亡）

Method Overview 方法简述

- Survival Analysis: Study the statistical association between time to event (e.g. time to death) and exposure (e.g. air pollution)
- 生存分析：利用统计模型研究生存时间和空气污染暴露之间的关系
- Estimate how exposure increases mortality rate ， i.e., the risk estimate of air pollution
- 估计空气污染把死亡率提高了多少——作为空气污染危害的量化指标

DATA 数据

- All Medicare particiants (n=67,682,479) in the continental United States from 2000 to 2012;
- 美国本土48州2000年到2012年所有“联邦医疗保险”参保人员（6700万）
- Outcome: all-cause mortality
- 本研究仅考察总死亡率
- Covariate: date of death, age of entry, year of entry, sex, race, whether eligible for Medicaid (proxy for SES), and ZIP code of residence
- 提供的信息：死亡日期、参保年龄、参保年份、性别、种族，是否符合联邦医疗辅助保险（作为社会经济状况的指标），居住地邮政编码

DATA 数据

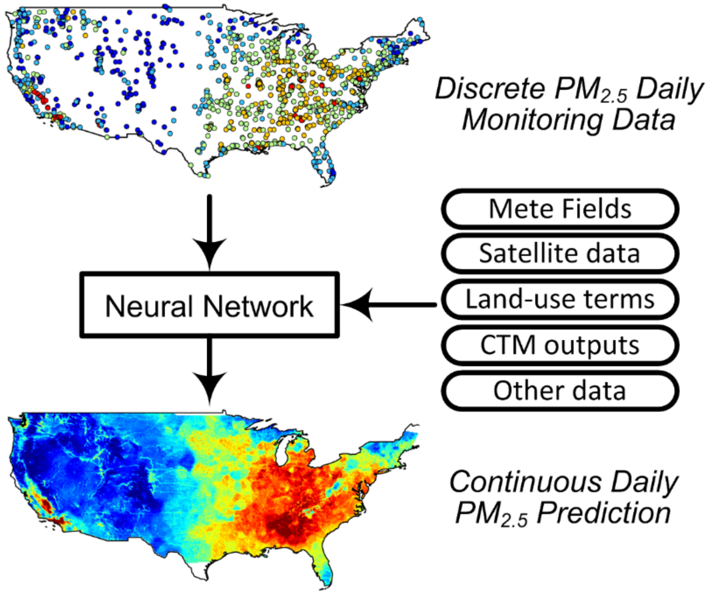
- ZIP code-level and county-level covariates
- 其他控制变量：邮政编码级别和县级别的各种变量
- U.S. censuses
- 全美统计局的资料
    - % of Hispanic people, % of black, median household income, median value of owner occupied housing, % of population above age 65 living below the poverty level, % with less than high school education (above age of 65), % of owner occupied housing units, and population density.
    - 墨西哥裔居民比例，黑人比例，平均家庭收入，家庭自有住房比例，65岁以上人口贫困率，65岁以上高中以下学历比例，家庭拥有住房价格，人口密度

DATA 数据

- Behavioral Risk Factor Surveillance System (BRFSS) of the Centers for Disease Control and Prevention (CDC)
- 全美疾病与控制中心的行为检测系统数据
  - Ever smoking rate, BMI、
  - 吸烟率，体重指数（县级别）
- The Dartmouth atlas of health care
- 达特茅斯保险数据
  - % of Medicare enrollees having a blood lipid (LDL-C) test, a hemoglobin A1c test, and at least one ambulatory visit to a primary care clinician – proxy for healthcare quality
  - “联邦医疗保险”参保人员中进行血脂蛋白测试、血红蛋白测试和造访医生的比例——作为医疗服务质量的指标

Method 方法

- Exposure assessment: a neural network to incorporate satellite-based measurements, simulation outputs from a chemical transport model (CTM), land-use terms and other ancillary data to model monitored $PM_{2.5}$ and ozone.
- 暴露评估：利用神经网络模型，整合卫星气溶胶光学厚度数据，大气化学模型模拟数据，土地利用数据，以及其他辅助数据来预测细颗粒物和臭氧浓度



Model training At monitors: $PM_{2.5} \sim \beta_1 Mete + \beta_2 Satellite + \beta_3 land + \beta_4 CTM + \beta_5 others$

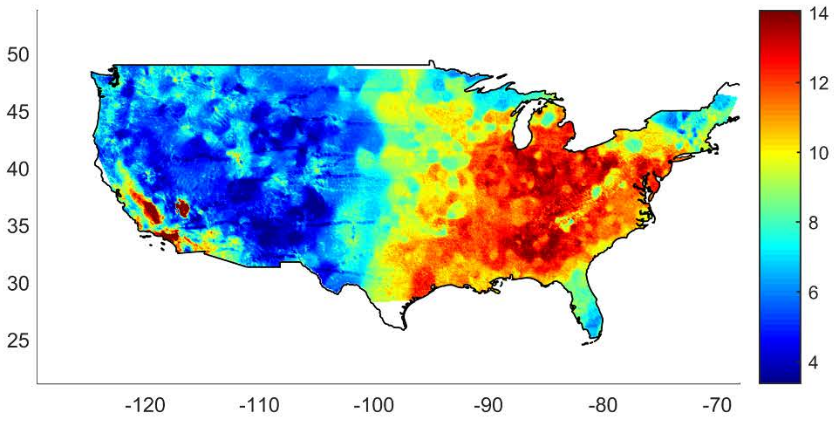
在监测站点处训练模型：细颗粒物~气象变量+卫星数据+土地利用数据+大气化学模型模拟数据+其他数据

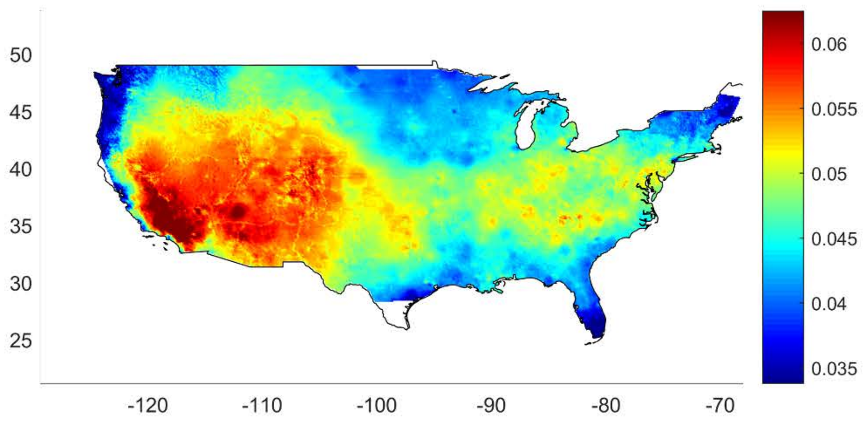
Modeling prediction without monitors: $\widehat{PM_{2.5}} \sim \beta_1 Mete + \beta_2 Satellite + \beta_3 land + \beta_4 CTM + \beta_5 others$

模型经过训练，在没有监测站点的地方可以预测细颗粒物浓度

Method 方法

- Exposure assessment results:
- 暴露评估结果：
  - Cross-validated correlation: R^2=0.84 for $PM_{2.5}$; R^2=0.76 for ozone on held out monitors
  - 检查检验相关系数，对细颗粒物和臭氧分别为0.84和0.76.





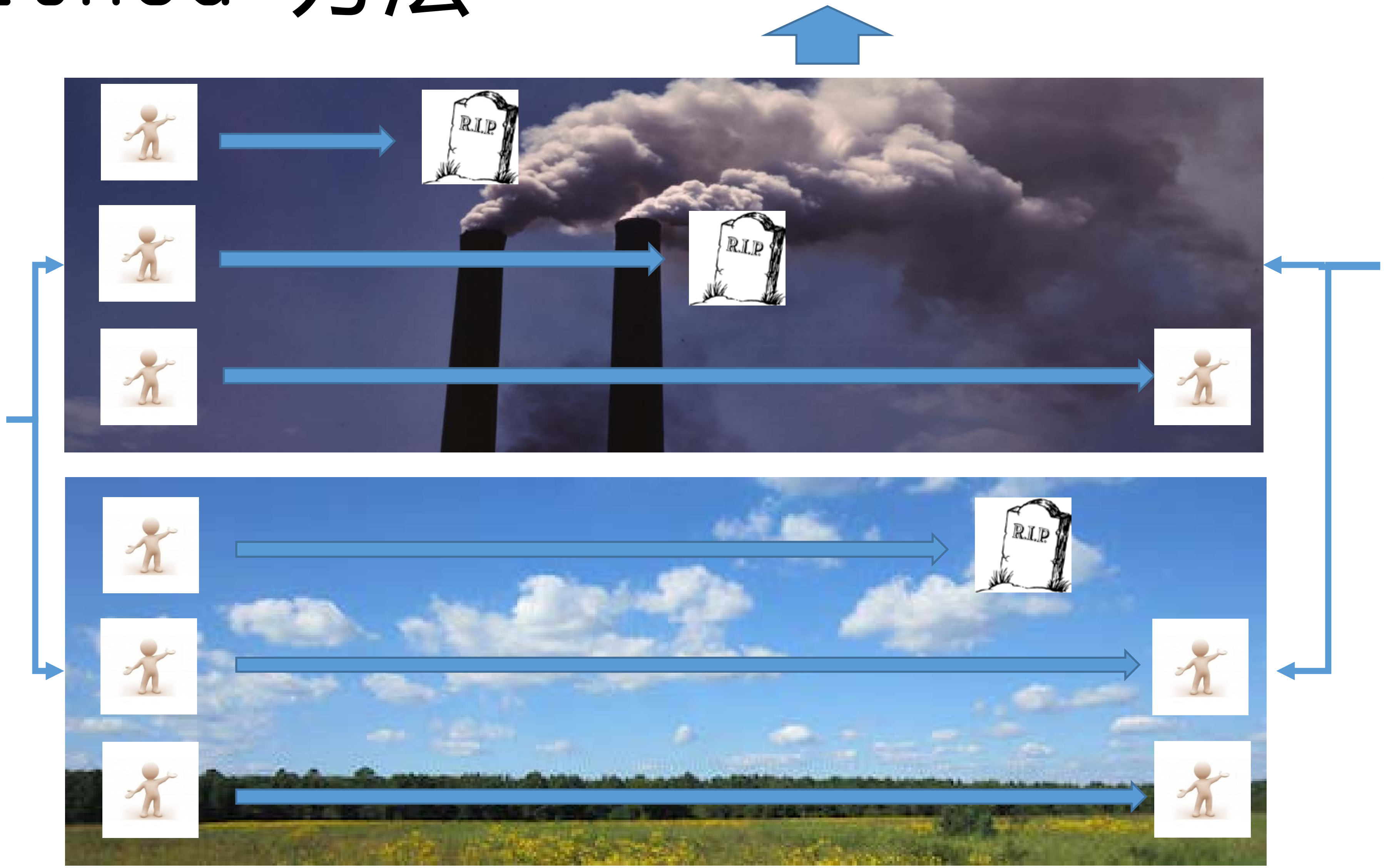
Di, Q., Kloog, I., Koutrakis, P., Lyapustin, A., Wang, Y. and Schwartz, J., 2016. Assessing PM2. 5 Exposures with High Spatiotemporal Resolution across the Continental United States. *Environmental science & technology*,*50*(9), pp.4712-4721.
Di, Q., Rowland, S., Koutrakis, P. and Schwartz, J., 2016. A Hybrid Model for Spatially and Temporally Resolved Ozone Exposures in the Continental United States. *Journal of the Air & Waste Management Association*, (just-accepted).

Method 方法

- Cox proportional hazards model
- 生存分析模型
  - Stratified by sex, race, SES, and 5-year categories of age at entry; the remaining covariates described above were directly entered into the model
  - 根据性别、种族、社会经济状况、参保年龄（五年一组）分层分析，其他的控制变量直接加入生存分析模型
- Two-Pollutant Analysis
- 双污染物模型——细颗粒物和臭氧同时加入模型
- Random intercepts for each ZIP (account for geographic variation)
- 每个邮政编码有一个随机截距来控制地理差异

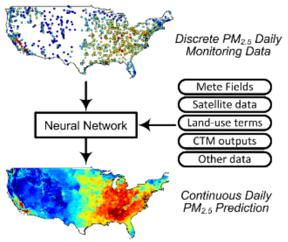
Method 方法

Survival Analysis 生存分析模型



67 million Medicare participants

“联邦医疗保险”参保人员（6700万）



Results 结果

	Two-Pollutant Analysis (prediction model) 双污染物模型	Low Exposure Analysis (prediction model) 在低浓度下	Two-Pollutant Analysis (monitoring data) 使用检测站点数据
$PM_{2.5}$ 细颗粒物	1.073 (1.071–1.075)	1.136 (1.131–1.141)	1.061 (1.059–1.063)
Ozone 臭氧	1.011 (1.010–1.012)	1.010 (1.009–1.011)	1.001 (1.000–1.002)

- 10 μg/m^3 increase in $PM_{2.5}$ ~ 7.3% increase in mortality;
- 细颗粒物浓度每升高10微克每立方米~总死亡率增加7.3%
- 10 μg/m^3 increase in $PM_{2.5}$ ~ 13.6% increase in mortality below 12 μg/m^3;
- 细颗粒物浓度低于12微克每立方米时，细颗粒物浓度每升高10微克每立方米~总死亡率增加13.6%
- 10 ppb increase in ozone ~ 1.1% increase in mortality;
- 臭氧浓度升高10 ppb~总死亡率增加1.1%
- 10 ppb increase in ozone ~ 1.0% increase in mortality below 50 ppb;
- 在低于50ppb浓度时，臭氧浓度升高10 ppb~总死亡率增加1.0%
- Subgroup analysis: among African Americans, the effect estimate for PM2.5 was three times as high as that for the overall population
- 亚组分析：细颗粒物造成的黑人死亡率增加是人群平均的三倍

Di, Q., Wang, Y., Zanobetti, A., Wang, Y., Koutrakis, P., Choirat, C., Dominici, F. and Schwartz, J.D., 2017. Air pollution and mortality in the Medicare population. *New England Journal of Medicine*, *376*(26), pp.2513-2522.

Discussion 讨论

- Health effect at low concentrations: significant and elevated association
- 低浓度空气污染的健康效应更加明显
  - Evidence supporting more stringent air quality standards
  - 更严格的空气质量标准迫在眉睫
  - Elevated marginal health benefits by mitigating air pollution to lower levels
  - 继续降低空气污染的边际健康收益更大
- Association between ozone and all-cause mortality
- 臭氧的长期暴露和总死亡率之间的关系
  - More than just respiratory mortality
  - 臭氧的健康效应不仅限于呼吸道死亡
- Consistency with previous study
- 印证之前的研究