How evidence from epidemiological studies can be used to answer causality questions

The case of air pollution - cause or correlation?

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Air pollution epidemiology in risk assessment:

- Cause or correlation – evidence from epidemiological studies
- Evidence synthesis
- Getting the numbers right – how to get unbiased population-based health effect estimates

Summer 2023

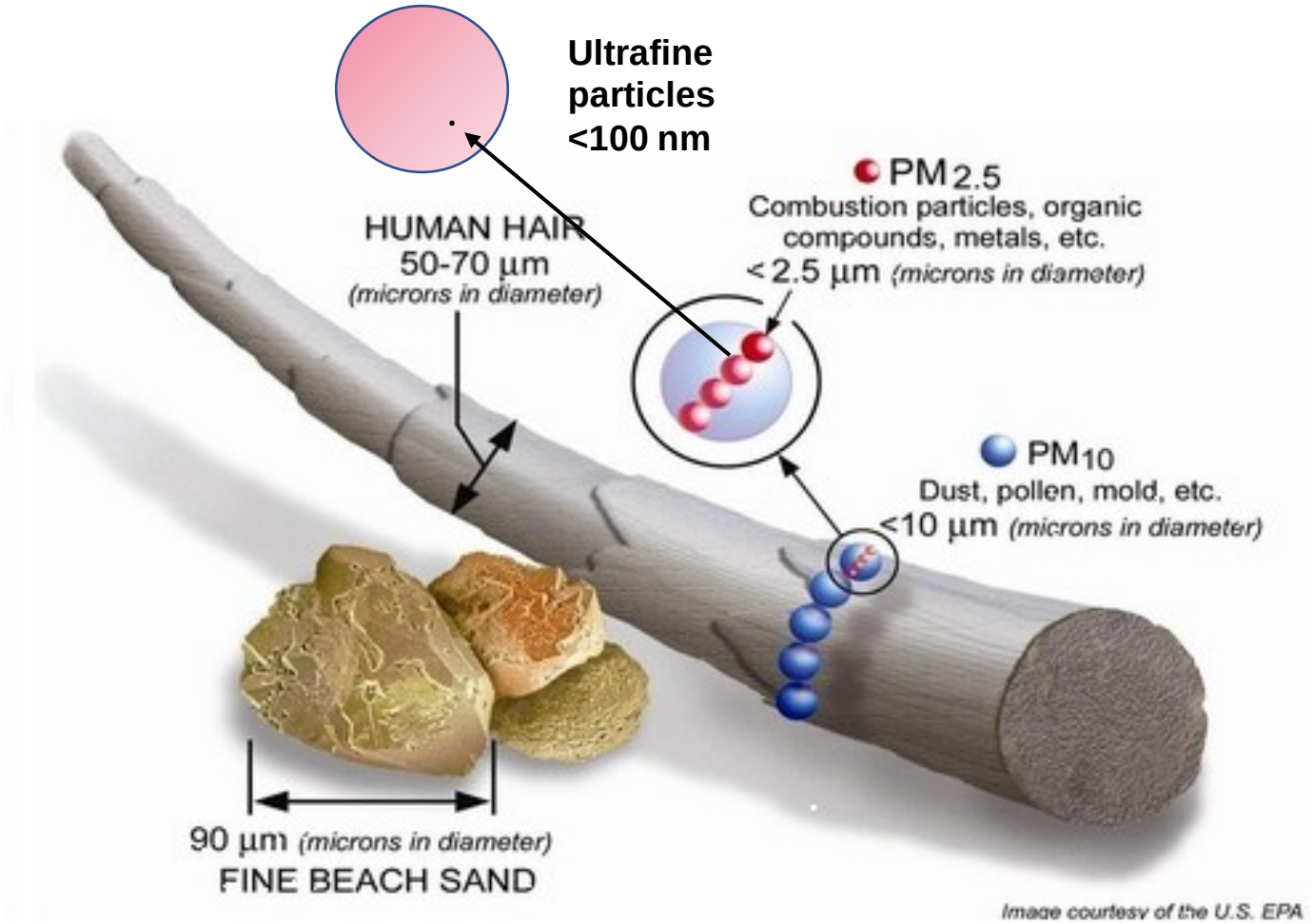
„Air pollution is the **only man-made** object you can see from space with the **naked eye**“

Joel Schwartz

Air pollution: Mixture of gases and particles

Most important gases
Ozone, NO_2, SO_2

Most important particles
PM_{10}, $PM_{2.5}$, UFP



Biological Mechanisms

- Oxidative stress
- Inflammation
- Carcinogenic
- Activation of nerval reflexes
- Transfer of inflammatory mediators, particles, and carcinogens through blood stream to far away organs

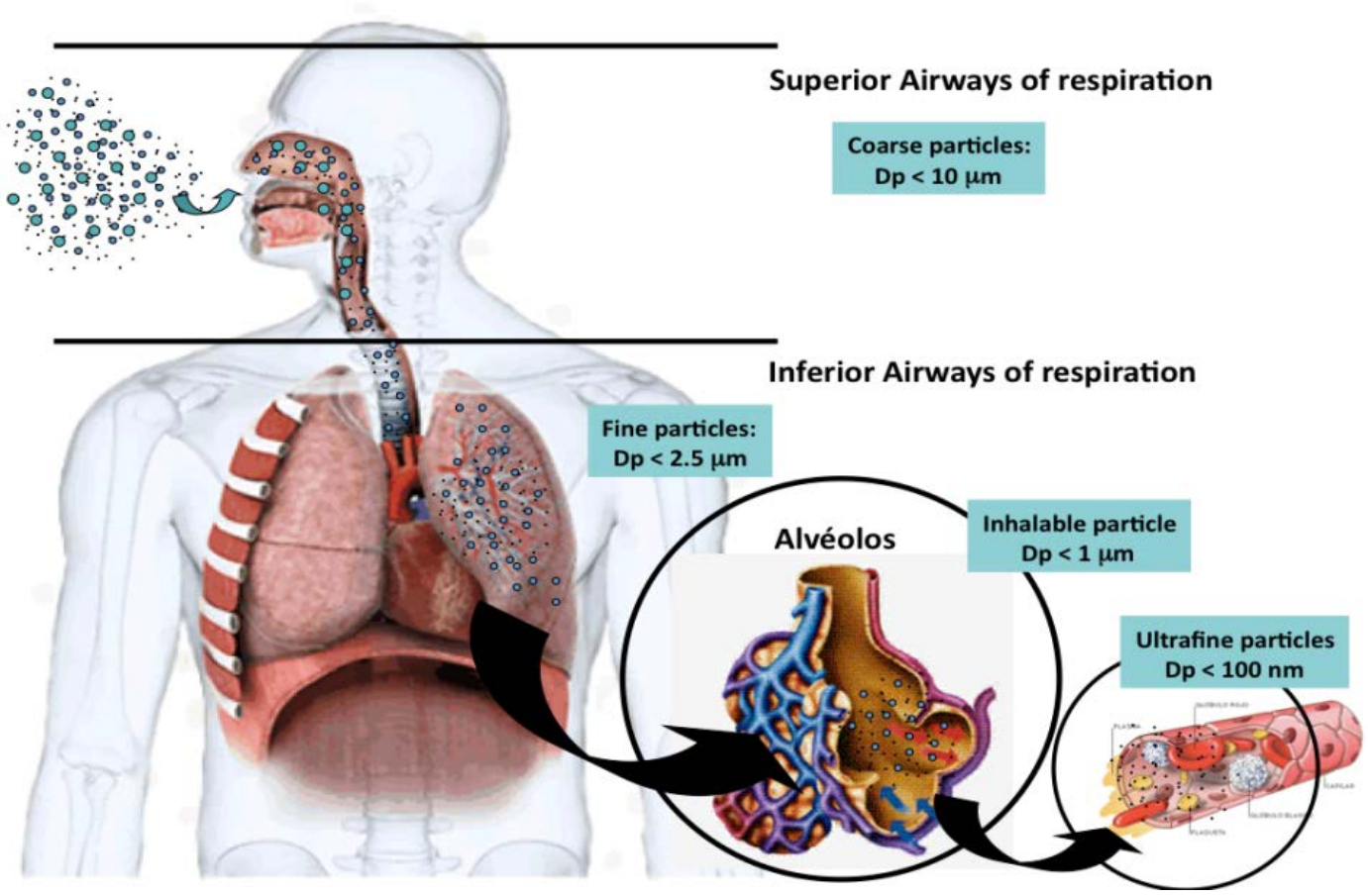


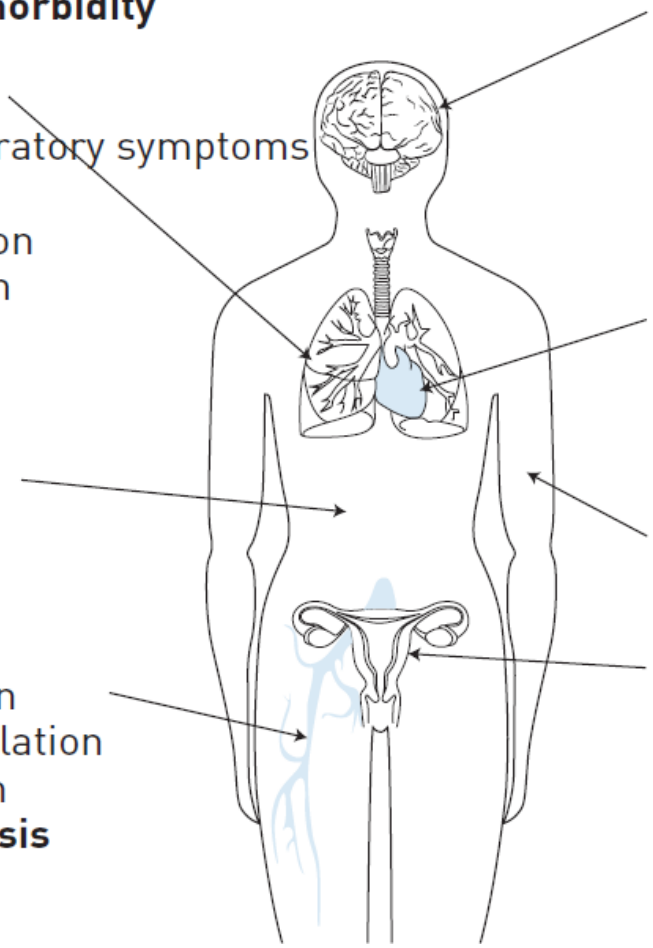
Image Source: http://www.reimaginegas.com/?p=2483

Multiple health effects on nearly every organ

Respiratory disease mortality
Respiratory disease morbidity
Lung cancer
Pneumonia
Upper and lower respiratory symptoms
Airway inflammation
Decreased lung function
Decreased lung growth

Insulin resistance
Type 2 diabetes
Type 1 diabetes
Bone metabolism

High blood pressure
Endothelial dysfunction
Increased blood coagulation
Systemic inflammation
Deep venous thrombosis



Stroke
Neurological development
Mental health
Neurodegenerative diseases

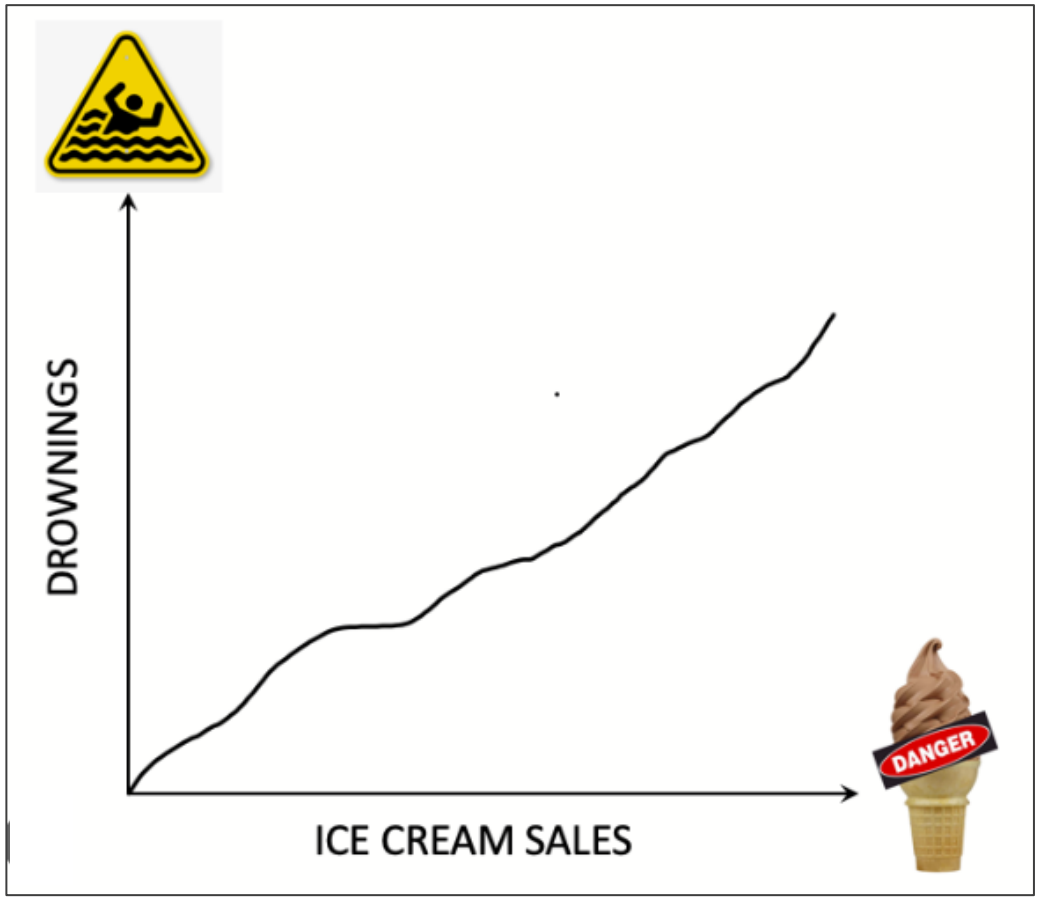
Cardiovascular disease mortality
Cardiovascular disease morbidity
Myocardial infarction
Arrhythmia
Congestive heart failure
Changes in heart rate variability
ST-segment depression

Skin ageing

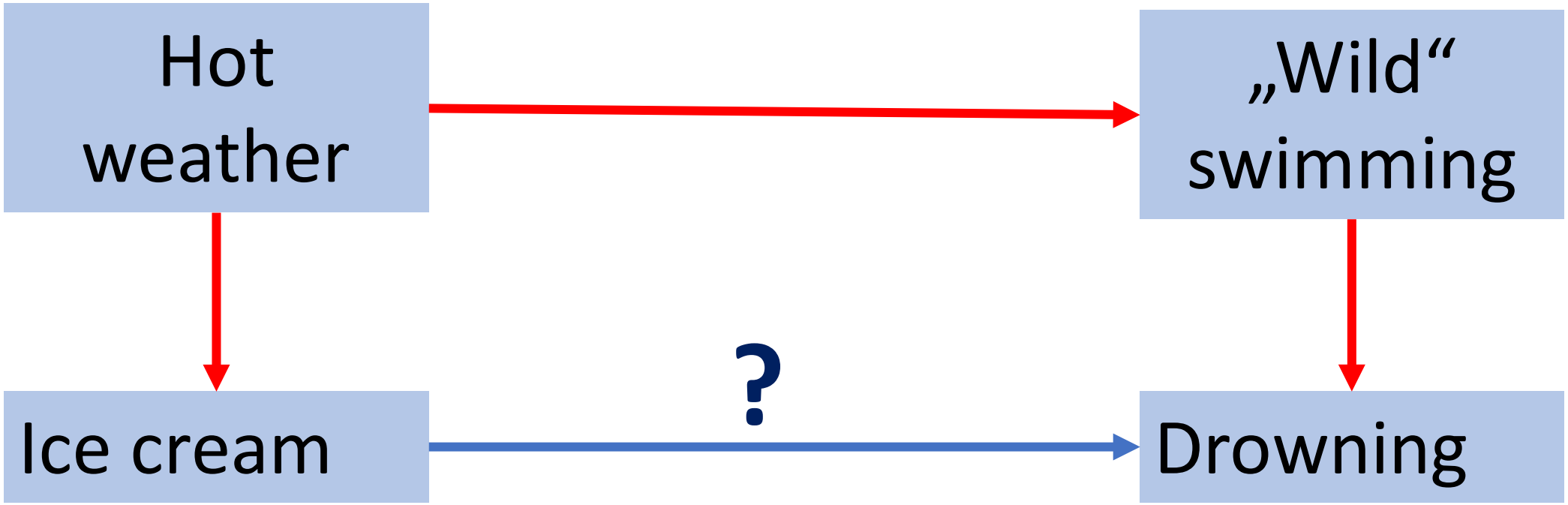
Premature birth
Decreased birthweight
Decreased fetal growth
Intrauterine growth retardation
Decreased sperm quality
Pre-eclampsia

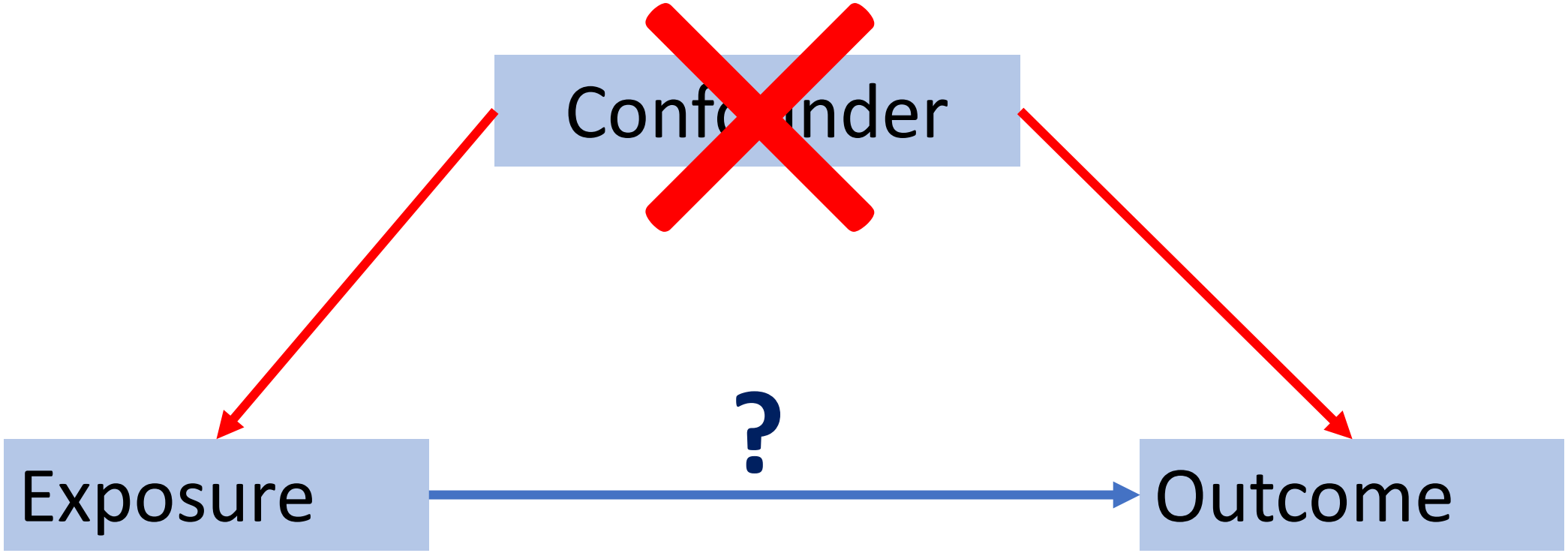
Thurston et al. ERJ 2017

The famous ice cream, that is killing people



Directed Acyclic Graph (DAG)



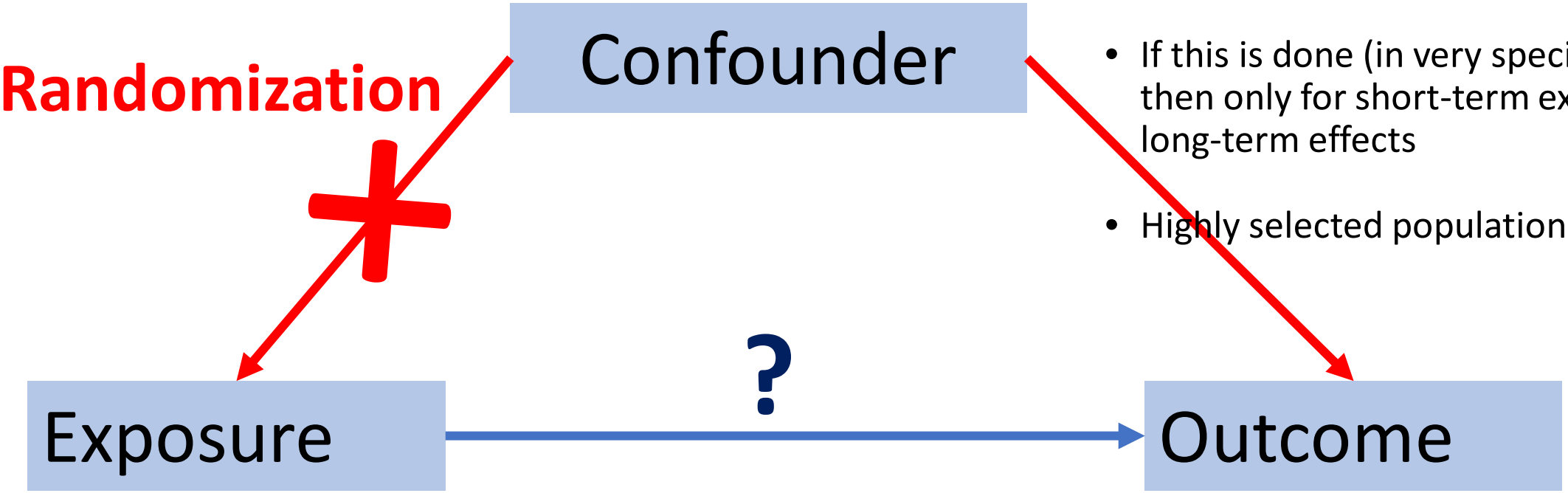

Confounder
?
Exposure
Outcome

Why we like randomized studies

- Equal distribution of potential confounders in exposed and unexposed group

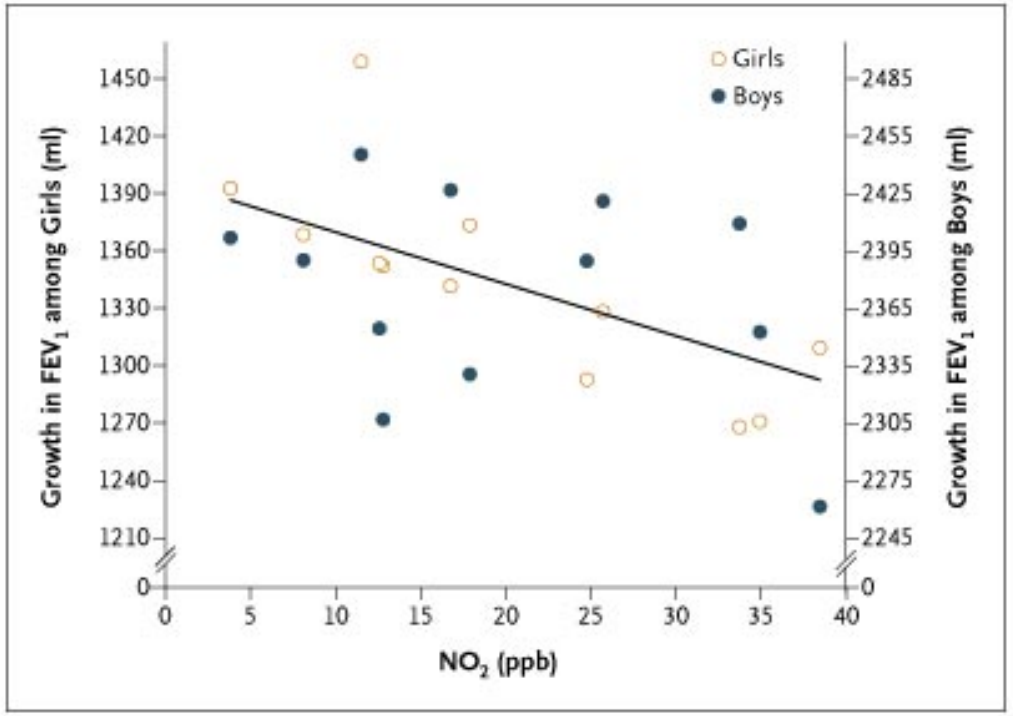
Why we do not like randomized studies

- In humans, we do not allow randomized assignment of potentially harmful exposures
- If this is done (in very specific cases), then only for short-term exposures, no long-term effects
- Highly selected populations



Get the best of two worlds –> make epi studies conceptually like randomized studies without the disadvantages of randomization

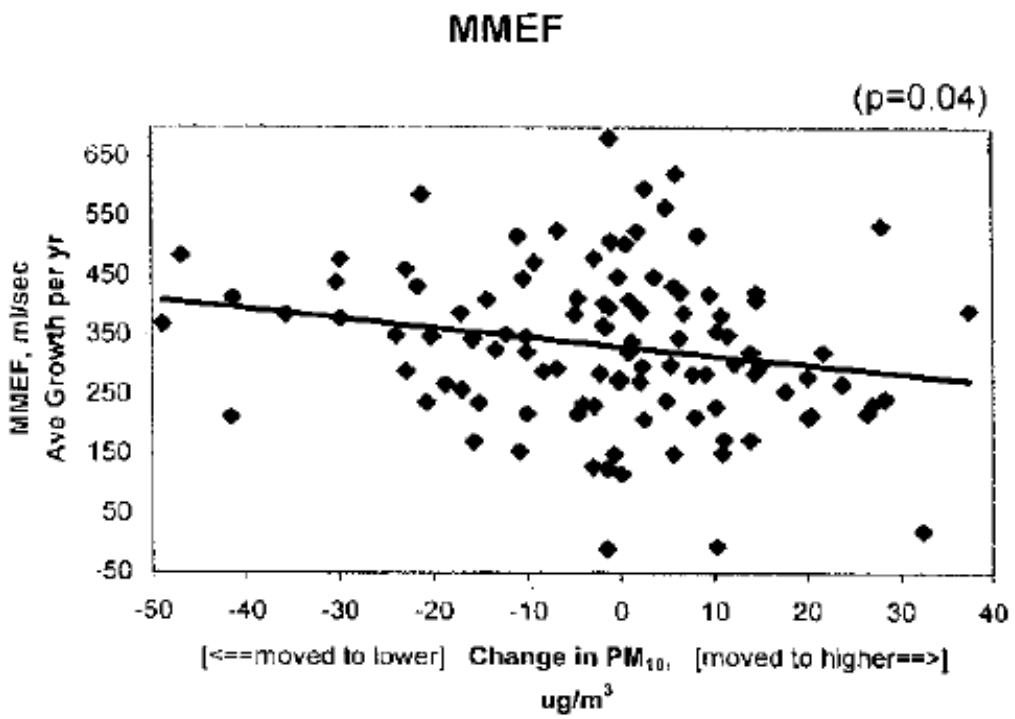
Children´s Health Study



Gauderman et al.2005

- Children relocating to other areas in the South-West
- Change in exposure purely related to parents´ jobs, living circumstances, etc., but unlikely related to potential confounders like smoking
- -> Pseudorandomization

Children´s Health Study



Avol et al. AJRCCM 2001

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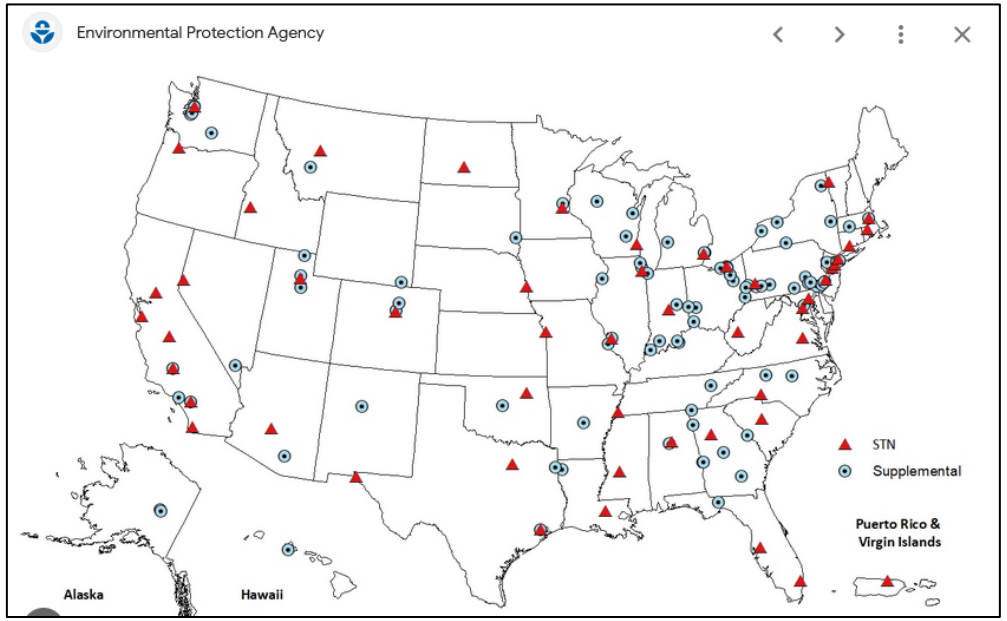
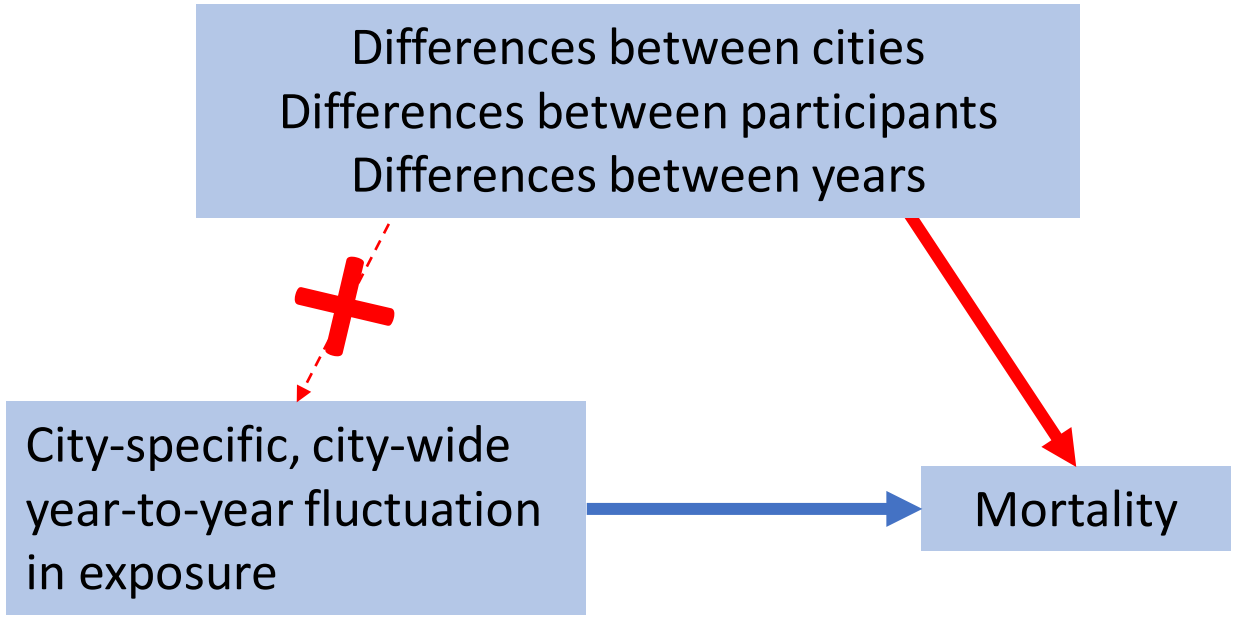
Long-term exposure and mortality in the Medicare Cohort

20 Mill subjects, 6 Mill deaths, 2000 - 2010

Measured exposure in each city and averaged to annual city-specific means

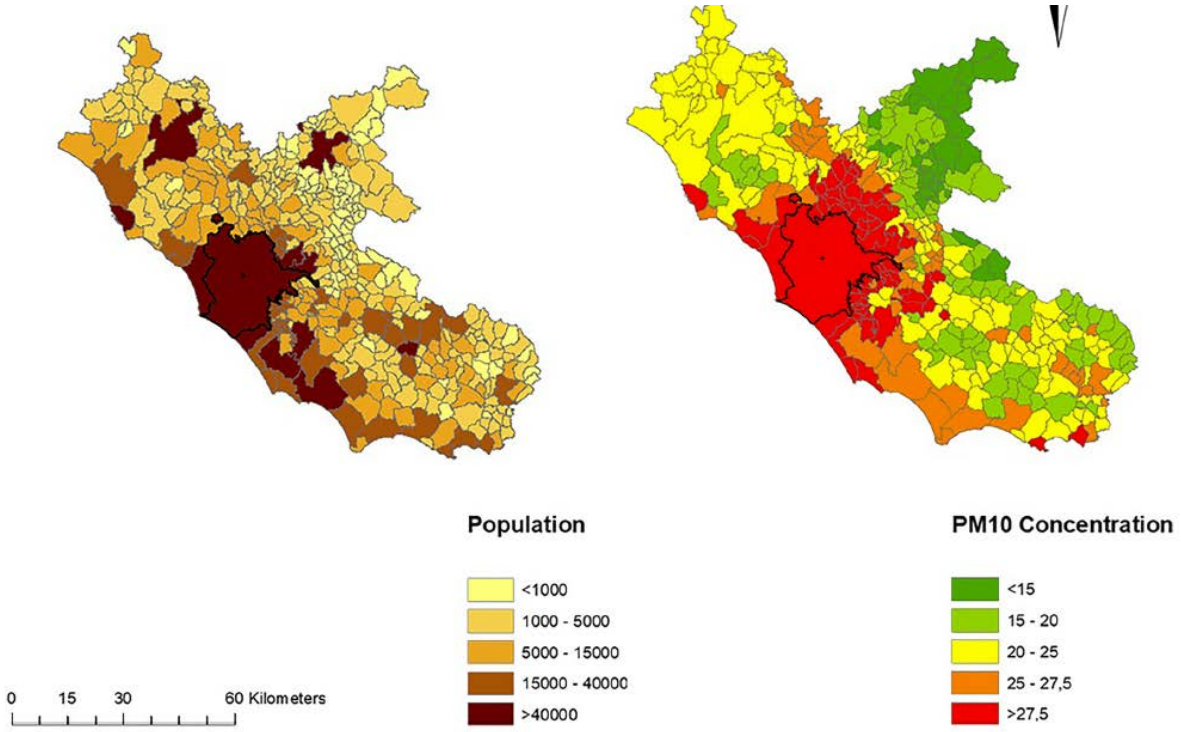
Assignment of yearly city-wide exposure fluctuations to each enrollee





Long-Term PM_{10} Exposure and Cause-Specific Mortality in the Latium Region (Italy): A Difference-in-Differences Approach

Matteo Renzi,[1] Francesco Forastiere,[2,3] Joel Schwartz,[4] Marina Davoli,[1] Paola Michelozzi,[1] and Massimo Stafoggia[1,5]



Modelled annual long-term exposure for each municipality

Annual counts of death for each municipality

Statistical analysis of fluctuations of exposure and fluctuations in outcome

Only potential plausible confounder is temperature, which was controlled for

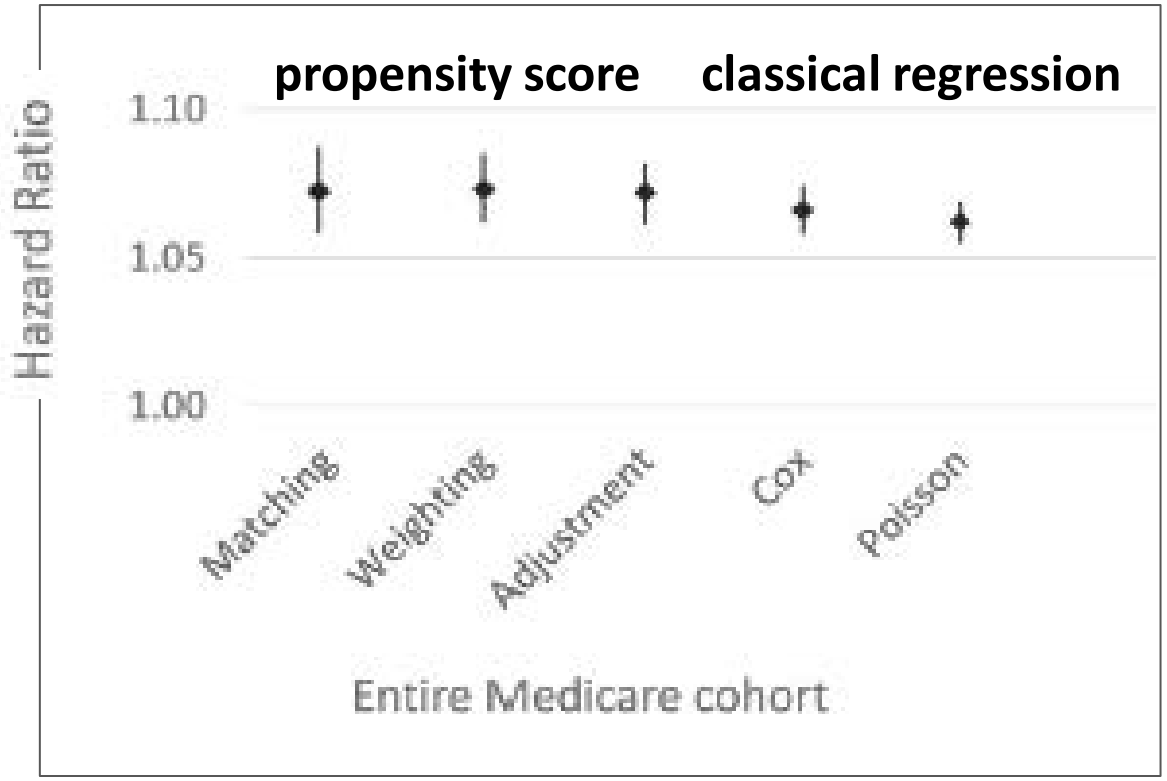
Results similar to other, more traditional approaches

Renzi et al.2019

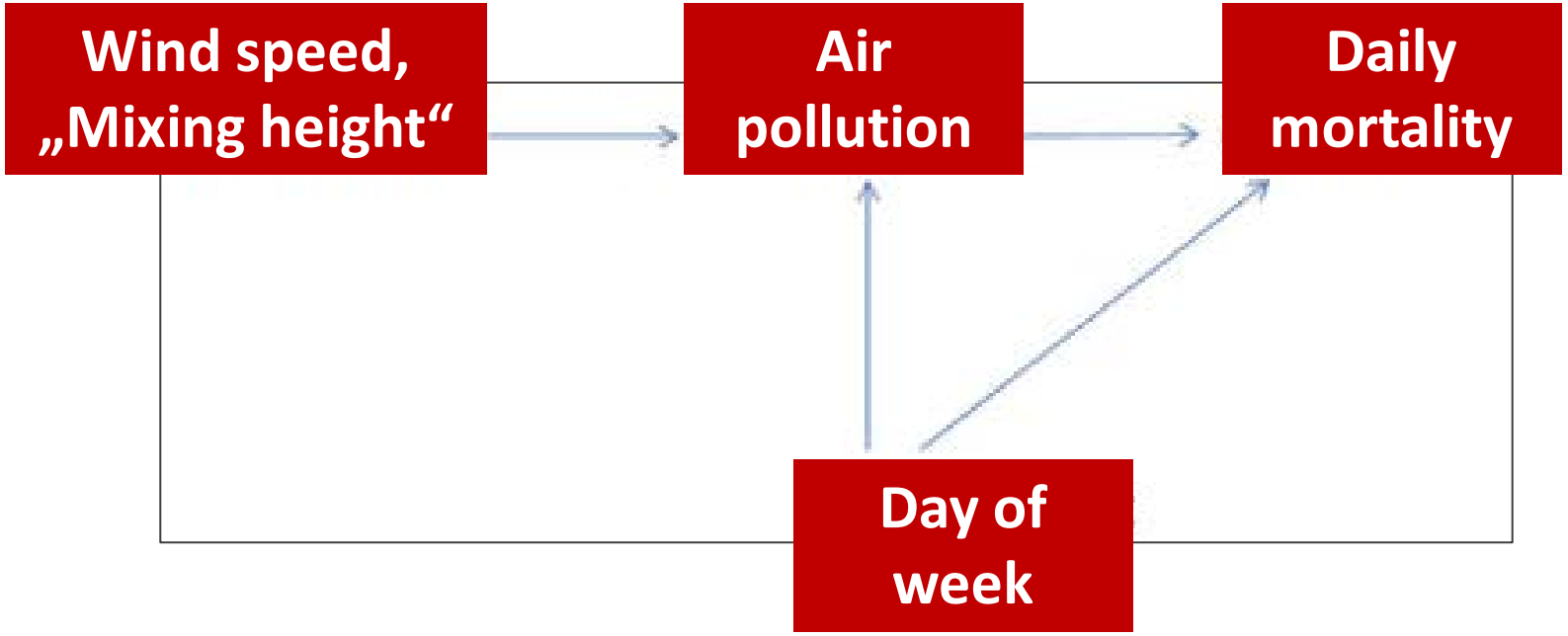
Other causal modeling approaches: Propensity score

Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Implementation of Causal Inference Methods

Francesca Dominici, Antonella Zanobetti, Joel Schwartz, Danielle Braun, Ben Sabath, and Xiao Wu



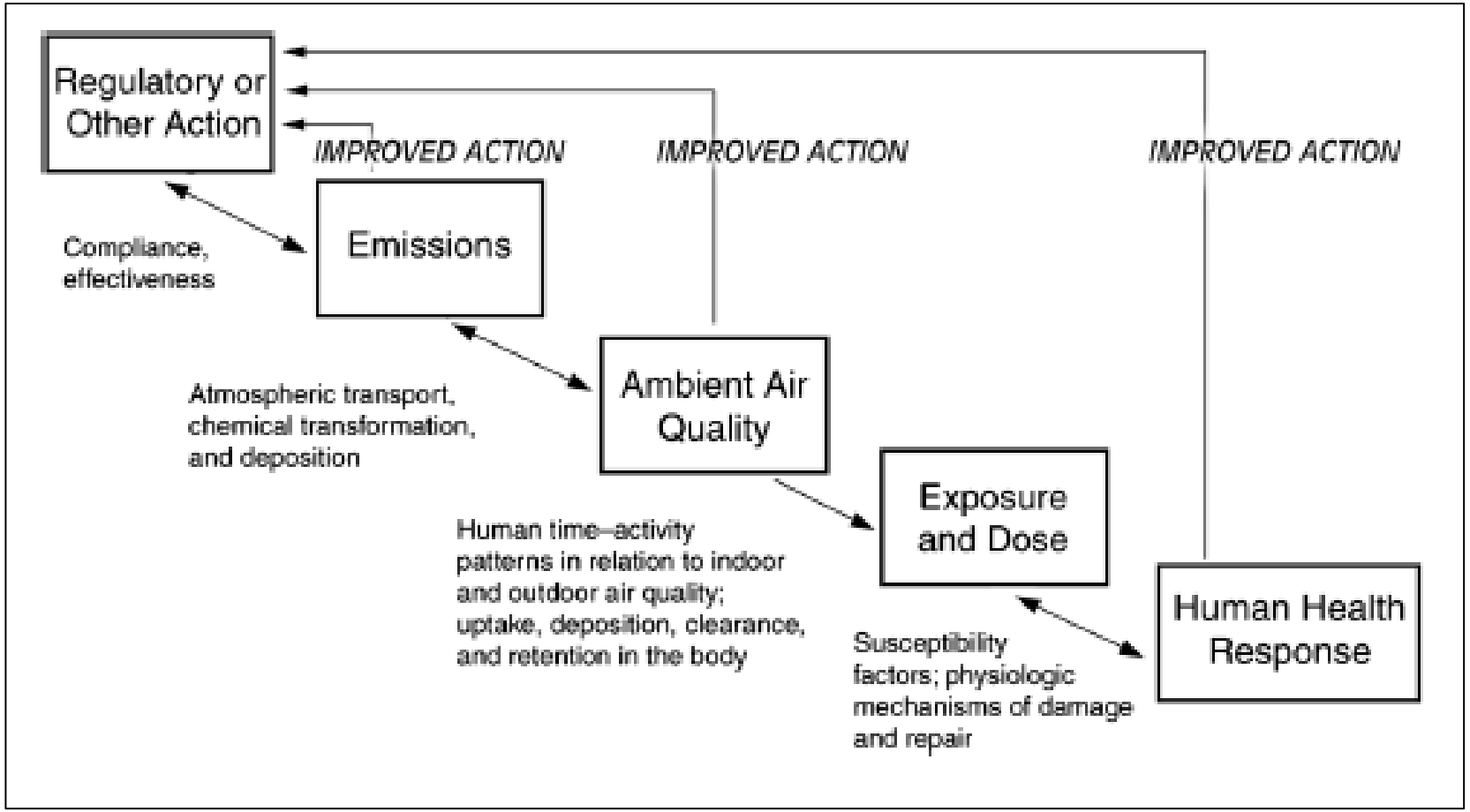
Instrumental variable



Accountability studies

- Empirical studies assessing the effects of regulatory actions or natural experiments

- Examples:
  - Dublin coal sale ban
  - Fuel sulfur content restrictions in Hong Kong
  - Traffic bans during Bejing Olympic Games

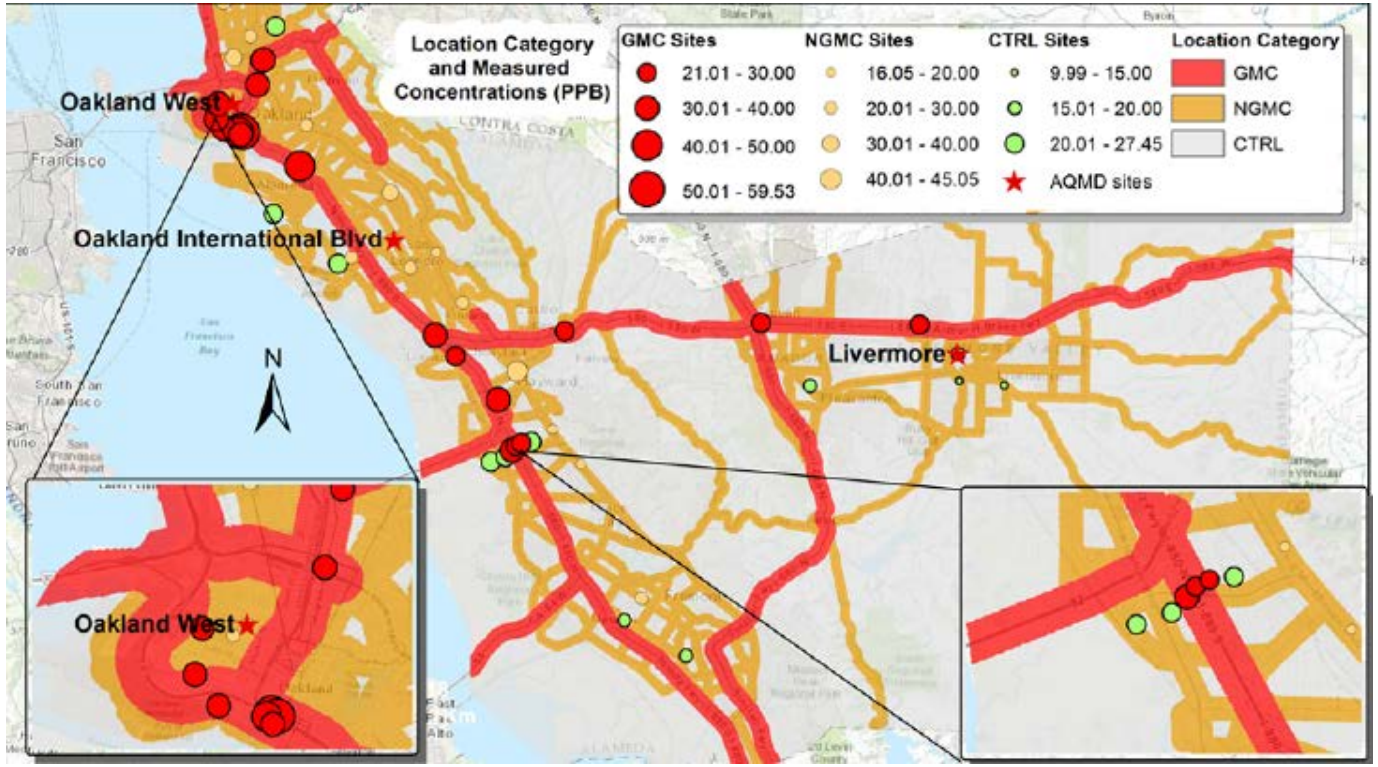


van Erp et al. HEI 2003

California Ports and Goods Movement Plan 2006

State program on reduction of traffic-related emissions

- 3 study areas with different level of intervention
- 23,000 Medi-Cal beneficiaries with chronic disease
- Change in exposure after regulation coming into effect
- Change in incidence of ER visits – DiD analysis



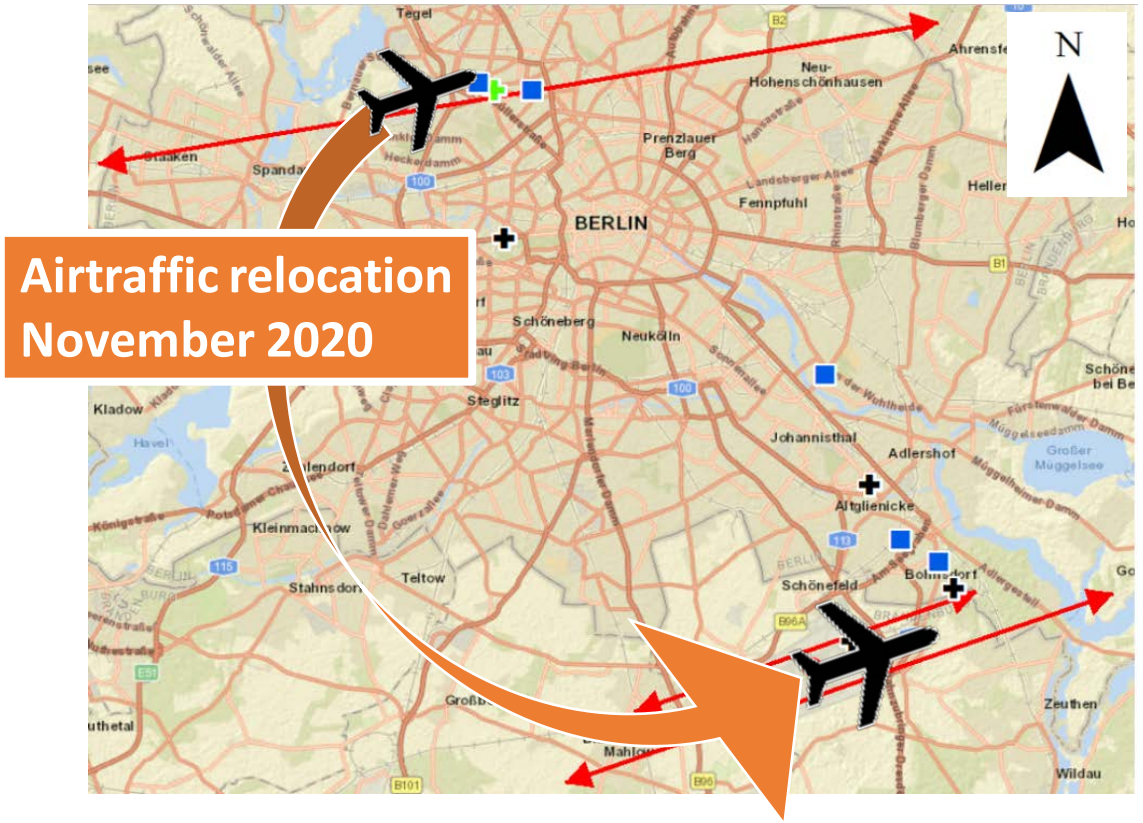
Largest exposure reductions of pollutant concentrations in GMC

Largest reductions in incidence of ER visits among asthma and COPD patients in GMC

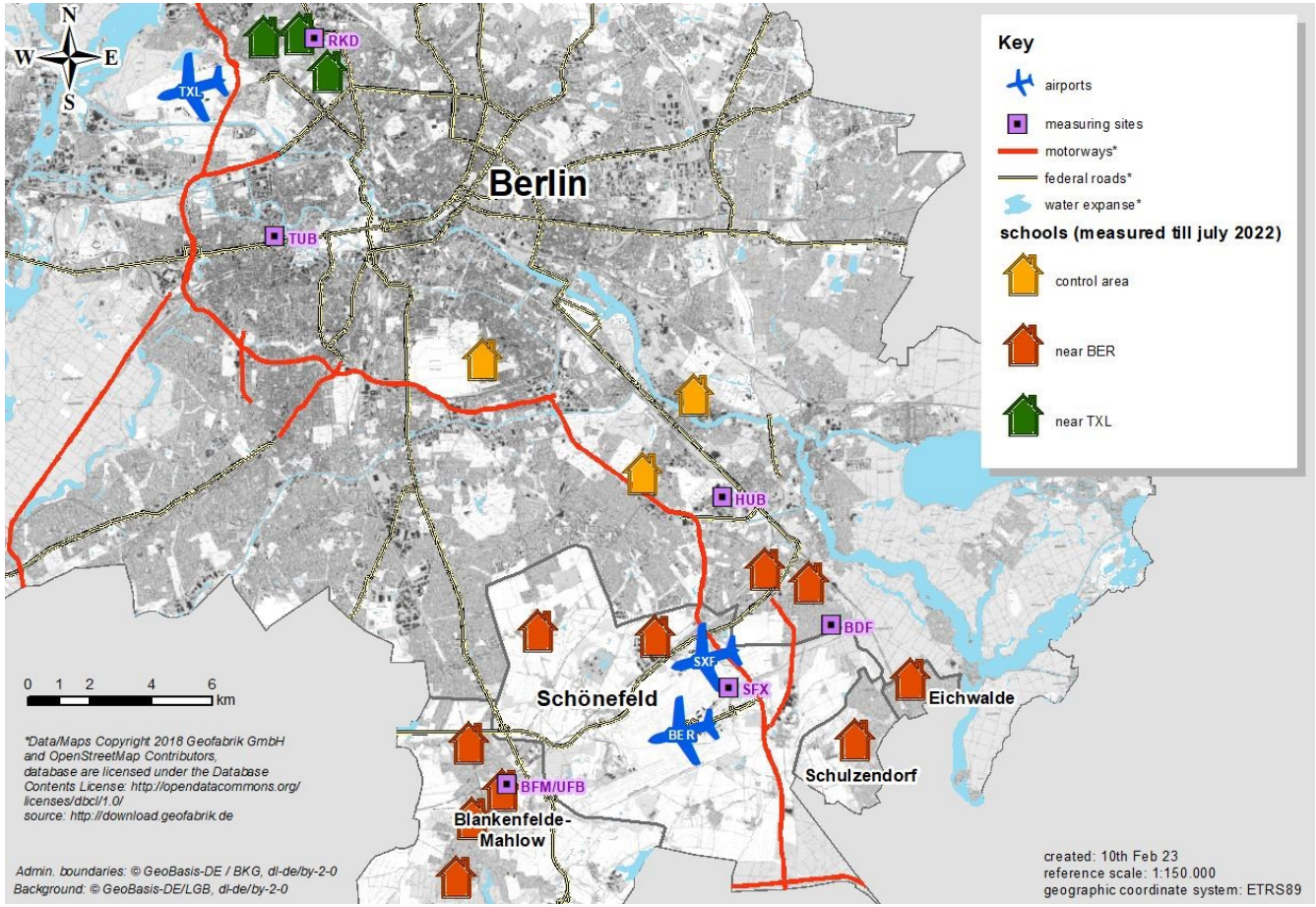
Meng et al. HEI 2021

BEAR-Study – a natural cross-over experiment

Airtraffic relocation from Berlin Tegel (TLX) to Berlin-Brandenburg (BER) in 2020



BEAR: Study aims and methods



Aims

1. To assess daily and long-term exposure to airtraffic-associated UFP before and after relocation in 3 areas of Berlin
2. To investigate short- and long-term effects from airtraffic-associated UFP on lung and cognitive growth in children

Methods

Crossover study of 1000 elementary school children

In 3 areas of the city (TXL, BER, control)

Repeated exams over follow-up of 4 years

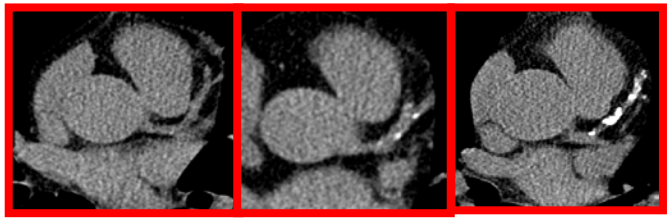
Effect estimation using DiD analysis

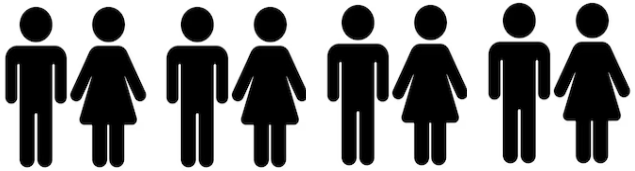
Air pollution epidemiology in risk assessment:

- Cause or correlation – evidence from epidemiological studies
- **Evidence synthesis**
- Getting the numbers right – how to get unbiased population-based health effect estimates

Chain of evidence

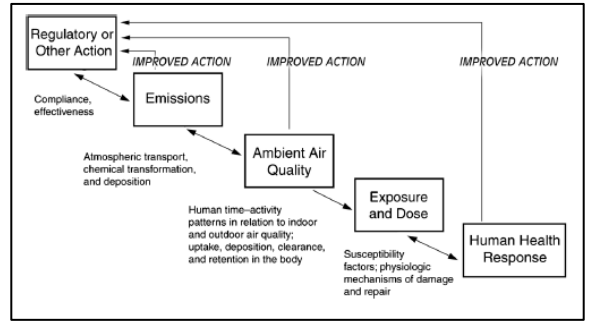
Classical cohort studies



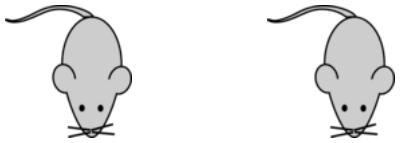


Long-term exposure and coronary atherosclerosis

Accountability studies



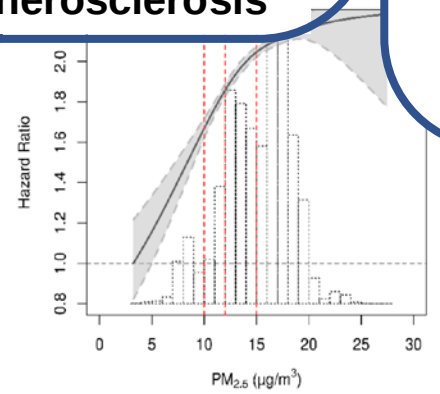
Hospital admissions after reduction of exposure



filtered AIR

concentrated particles

Disease processes, short-term exposures



Long-term exposure in large cohorts

Cell and animal toxicology

controlled exposure studies, epi panel studies

cohort and case-control studies

Air pollution epidemiology in risk assessment:

- Cause or correlation – evidence from epidemiological studies
- Evidence synthesis
- **Getting the numbers right – how to get unbiased population-based health effect estimates**

Need for supporting policy making

EUROPEAN COMMISSION

- Size of long-term effects in general population
- Burden of disease
- Cost-benefit analyses

Proposal for a

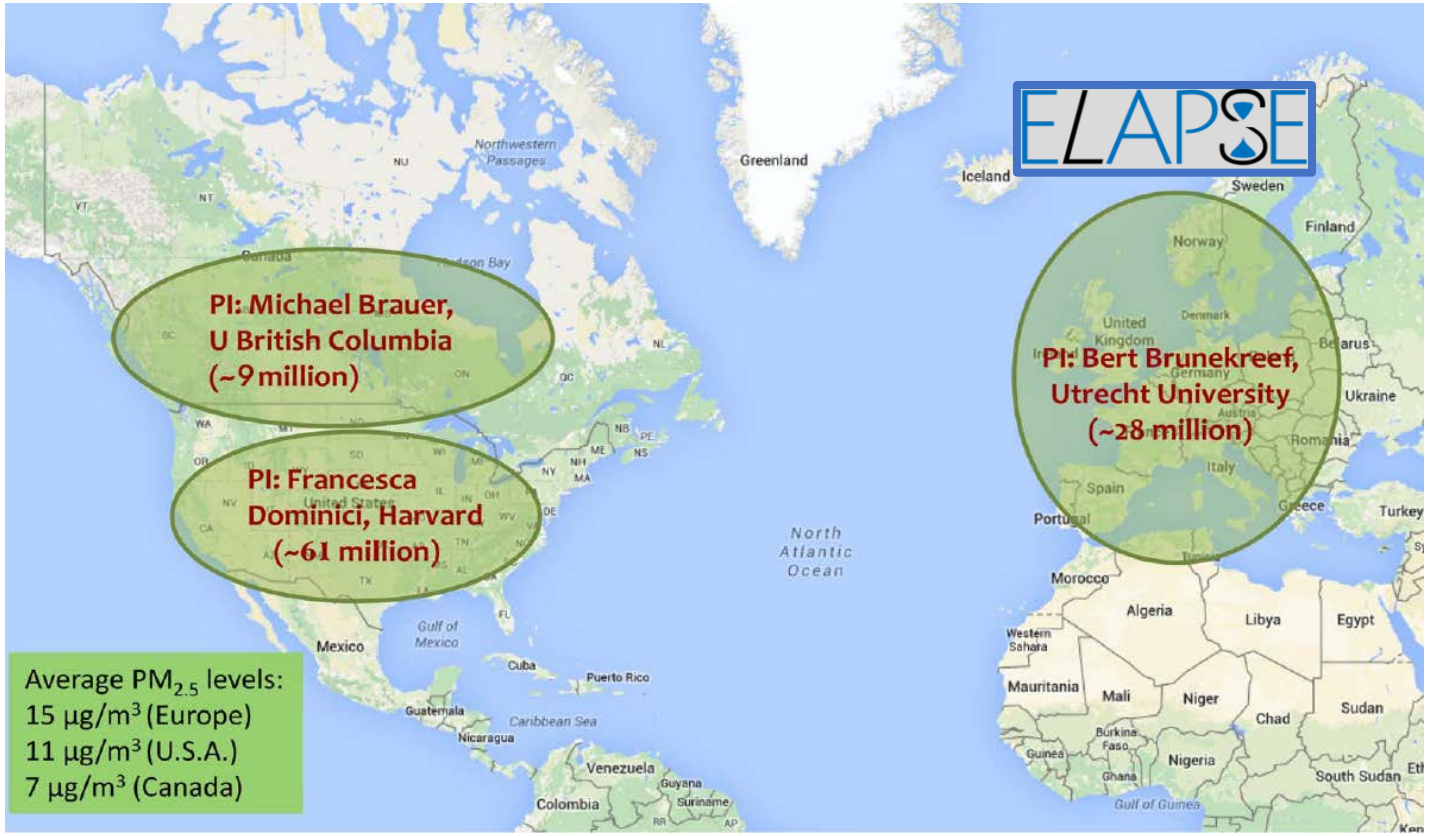
DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

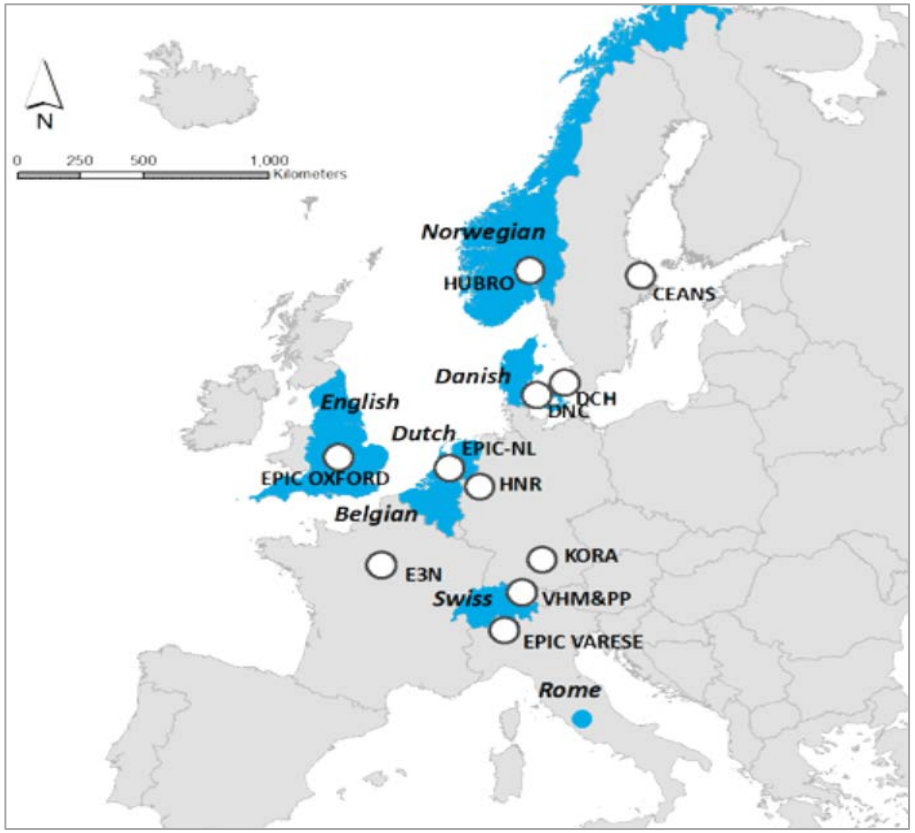
on ambient air quality and cleaner air for Europe

(recast)

„Administrative cohorts“

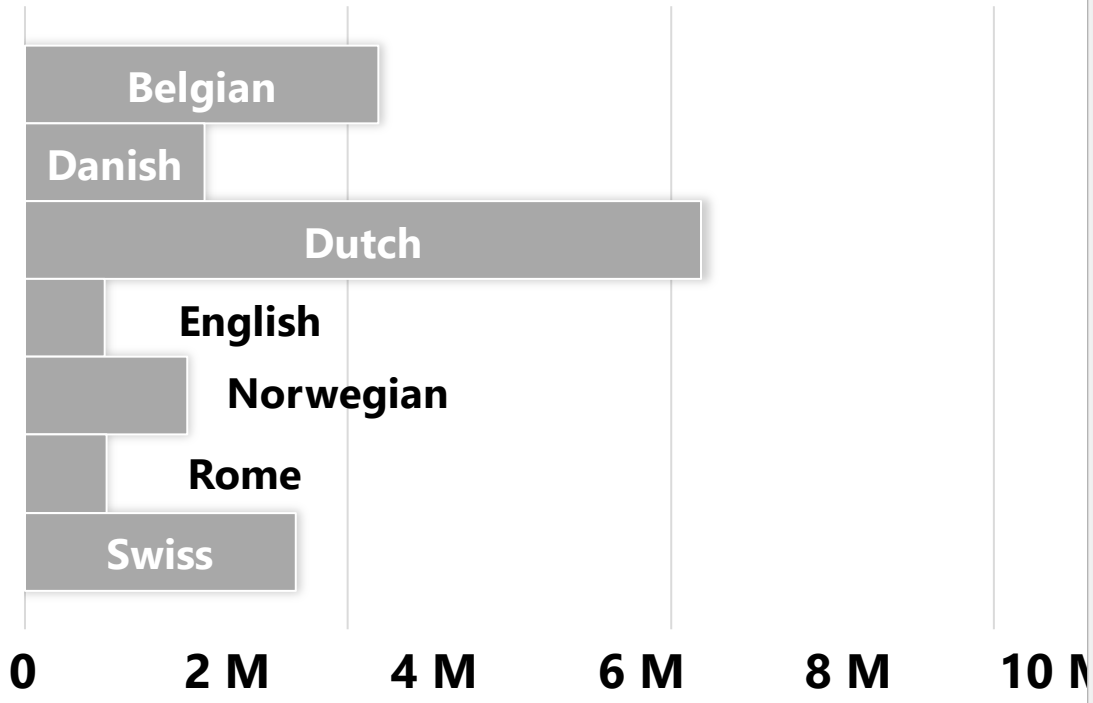
Effects of low levels of air pollution – a study in Europe

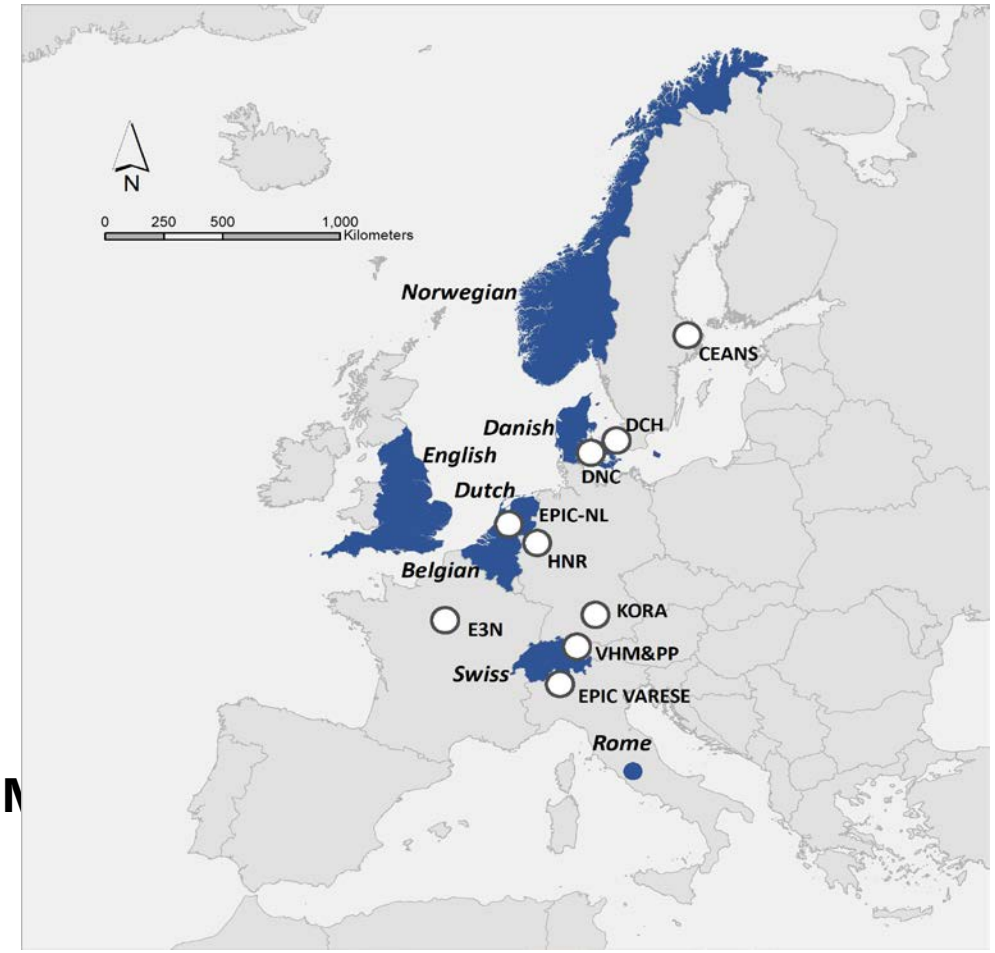




Administrative cohorts (N=28 Mill)

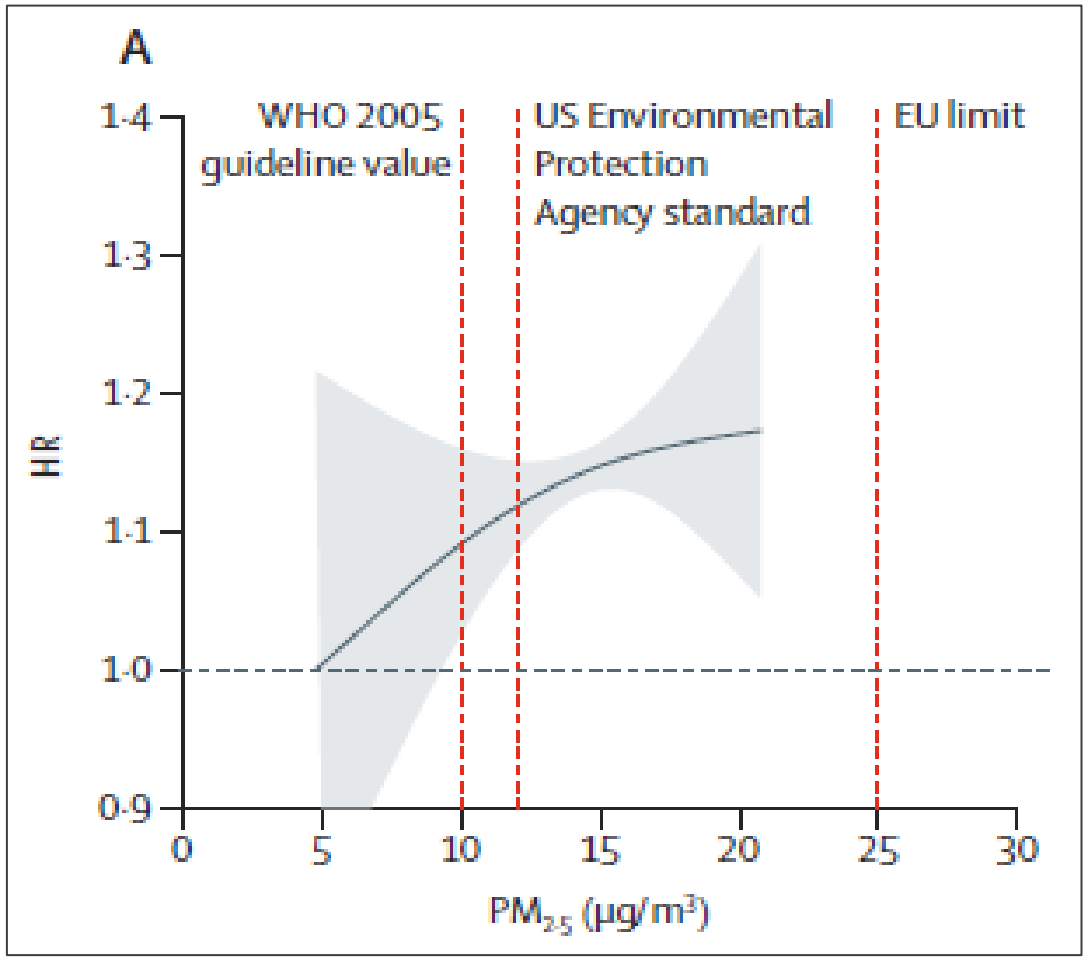
- From administrative data bases, e.g. population registers -> no selection bias
- Large numbers, vulnerable subgroups
- Exposure-response function
- Rich area-level confounder data
- Indirect adjustment





Brunekreef et al. 2021

Effects higher than known before



- **Effect sizes higher than previously estimated**
- **Effects down to lowest observed levels**
- **No threshold**
- **Effect sizes considerably higher at lower end of exposure**

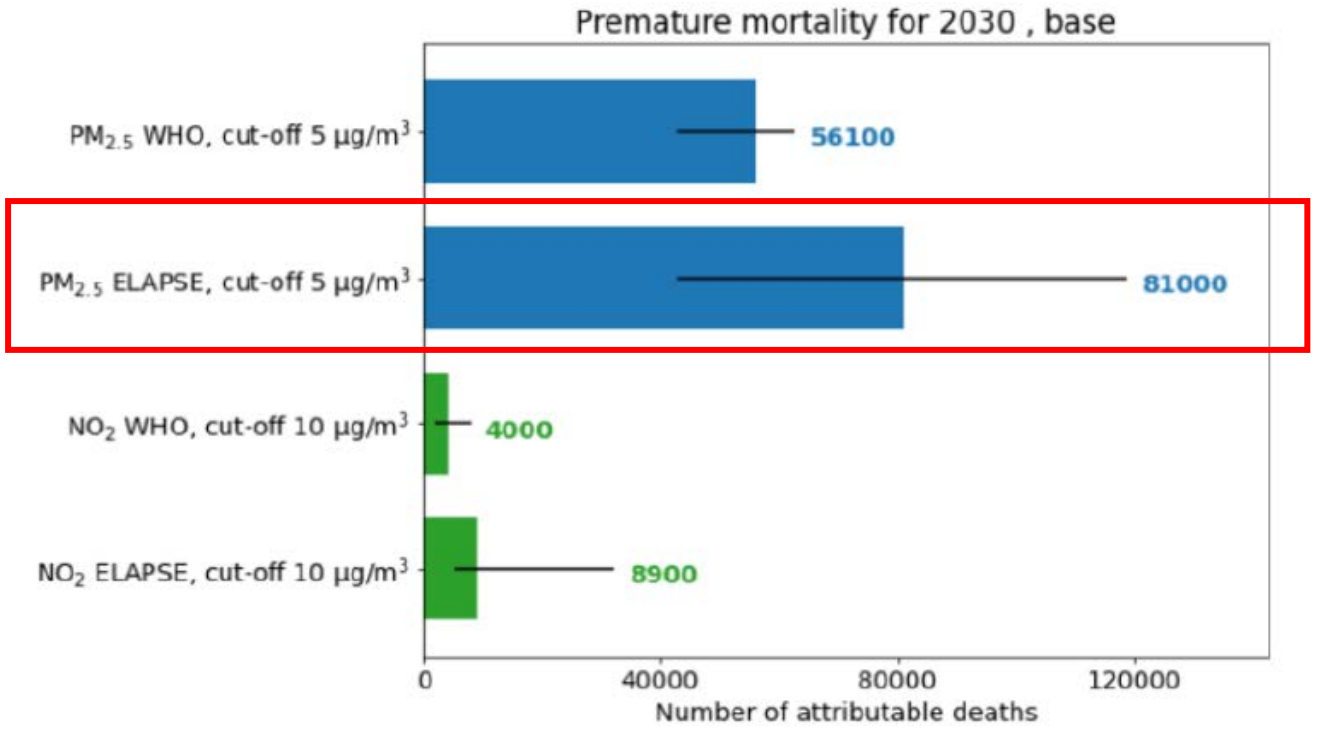
Stafoggia et al. 2022

EC Health Impact Assessment

Sensitivity analysis

EUROPEAN COMMISSION

Pollutant (per 10 µg/m3)	WHO 2021	ELAPSE 2022
PM2.5	1.08	1.118
NO2	1.02	1.045



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Hoffmann et al. 2022; EC 2022

7 Reasons why epi is so important for risk assessment

1. Long-term studies on potentially hazardous exposures possible
2. Evidence in unselected population
3. Size of effect in general population
4. Identification of susceptible population groups
5. Evidence of effectiveness of interventions
6. Basis for calculation of burden of disease
7. This is basis for political decisions on priorities

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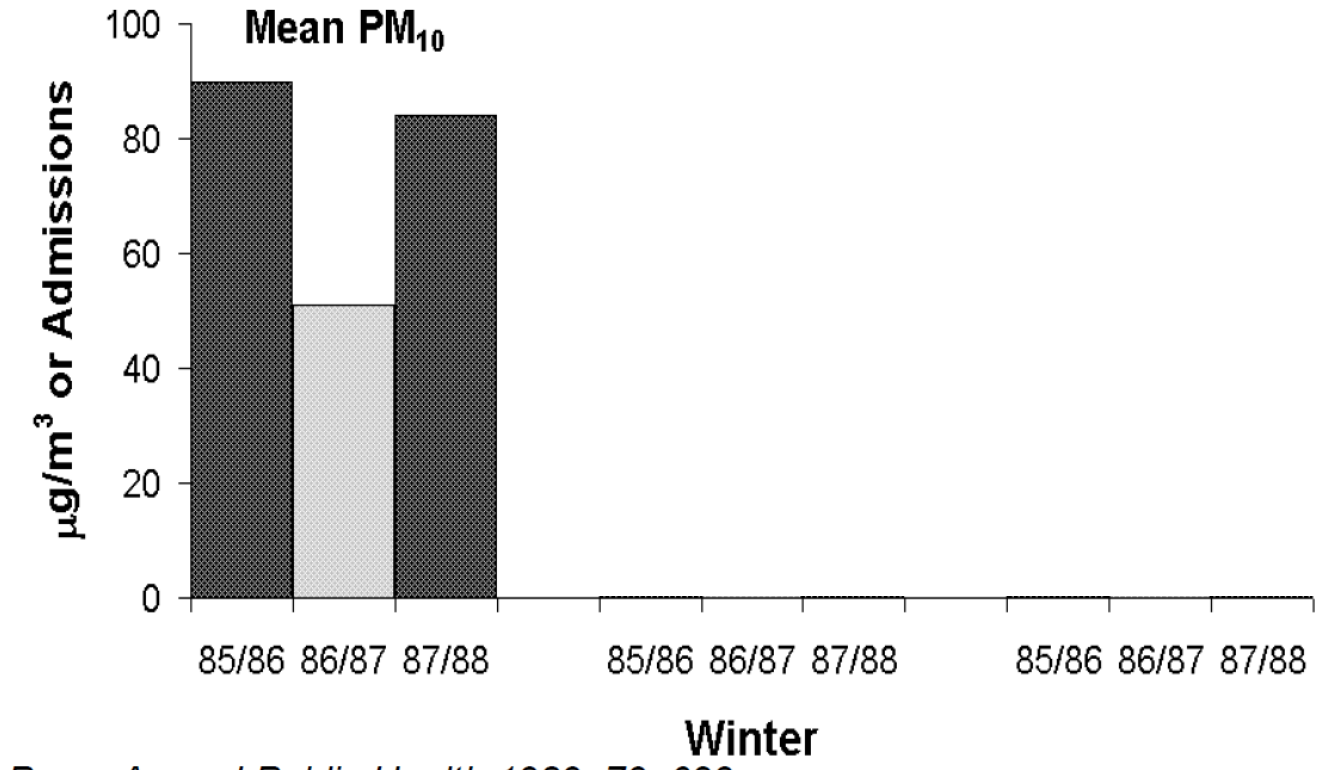
Conclusions

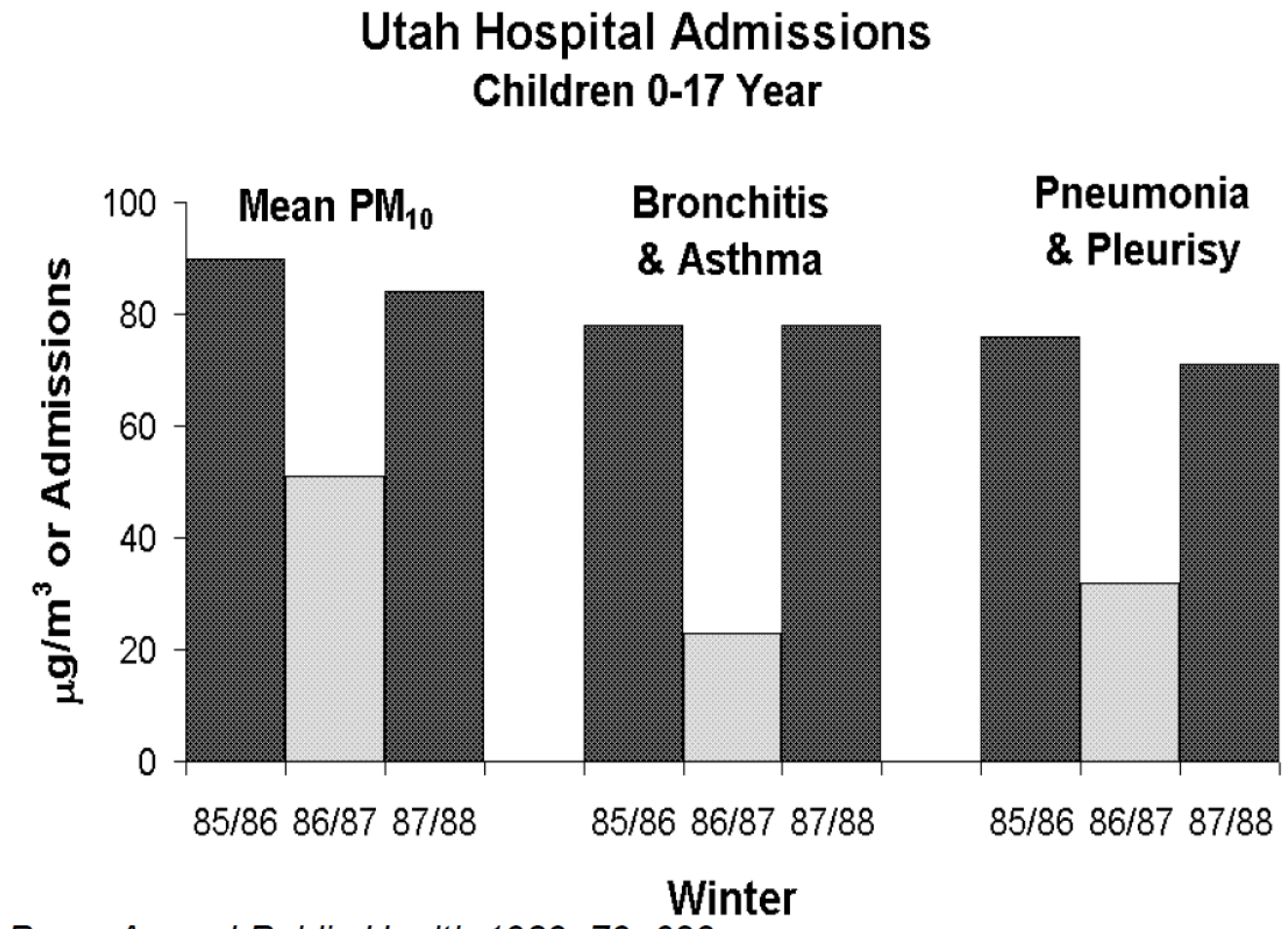
- Randomized controlled trials not always gold standard
- Selection bias can be avoided in administrative cohorts
- Chain of evidence is important „from cell to population“
- Epidemiological studies can inform about effect size in the general population and vulnerable subgroups
- Crucial function of epidemiological studies for informed plicy decision making in policy

History: Utah valley steel mill strike



Pope, Amer J Public Health 1989; 79: 623

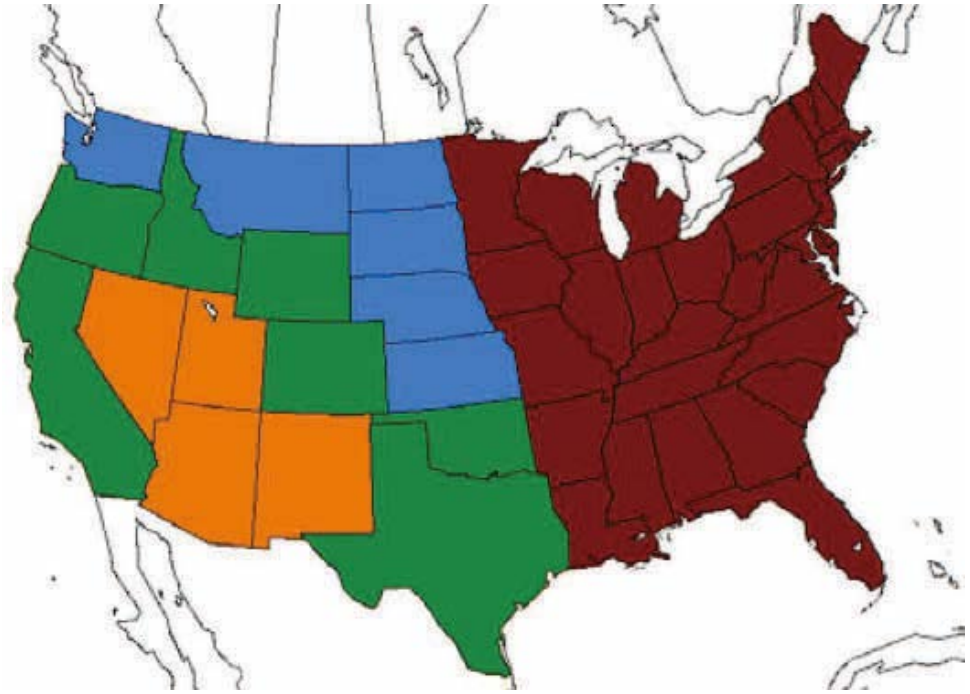
History: Utah valley steel mill strike



Pope, Amer J Public Health 1989; 79: 623

Copper smelter strike in the Southwest

Difference-in-Difference analysis in a natural experiment



- Strike: August 1967-March 1968
- 2.5 $\mu g/m^3$ decrease in sulfate particles
- Difference in mortality in strike area
- Difference in mortality in surrounding states not affected by strike, but underlying the same regional influences (wheather, influenza, etc.)

- **Result: 2.5% decrease in mortality**

Pope et al. | NUMBER 5 | May 2007 • Environmental Health Perspectives