Health Effects of Airborne Black Carbon Particles

Why Did it Take So Long to Find Out?

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Background for Presentation

- Particulate matter in air subject to regulation under initial Clean Air Act (1970)
- With increasing knowledge, EPA has regulated ever smaller sizes (TSP, then PM10, then PM2.5), but not, so far, different chemical species
- Presentation will review evidence for why PM2.5 black carbon (BC) only *lately* appears to pose significant health threat, likely most harmful of PM2.5 species

Outline of Talk

- What is black carbon (BC)? What are sources?
- *How* do we learn which atmospheric $PM_{2.5}$ species are harmful, which may not be?
  - *What are best methodologies?*
- Applying best methodologies, *which types of airborne tiny particles seem most likely to cause cardiovascular diseases, premature mortality, etc.?*
- What criteria can we use to judge causality?

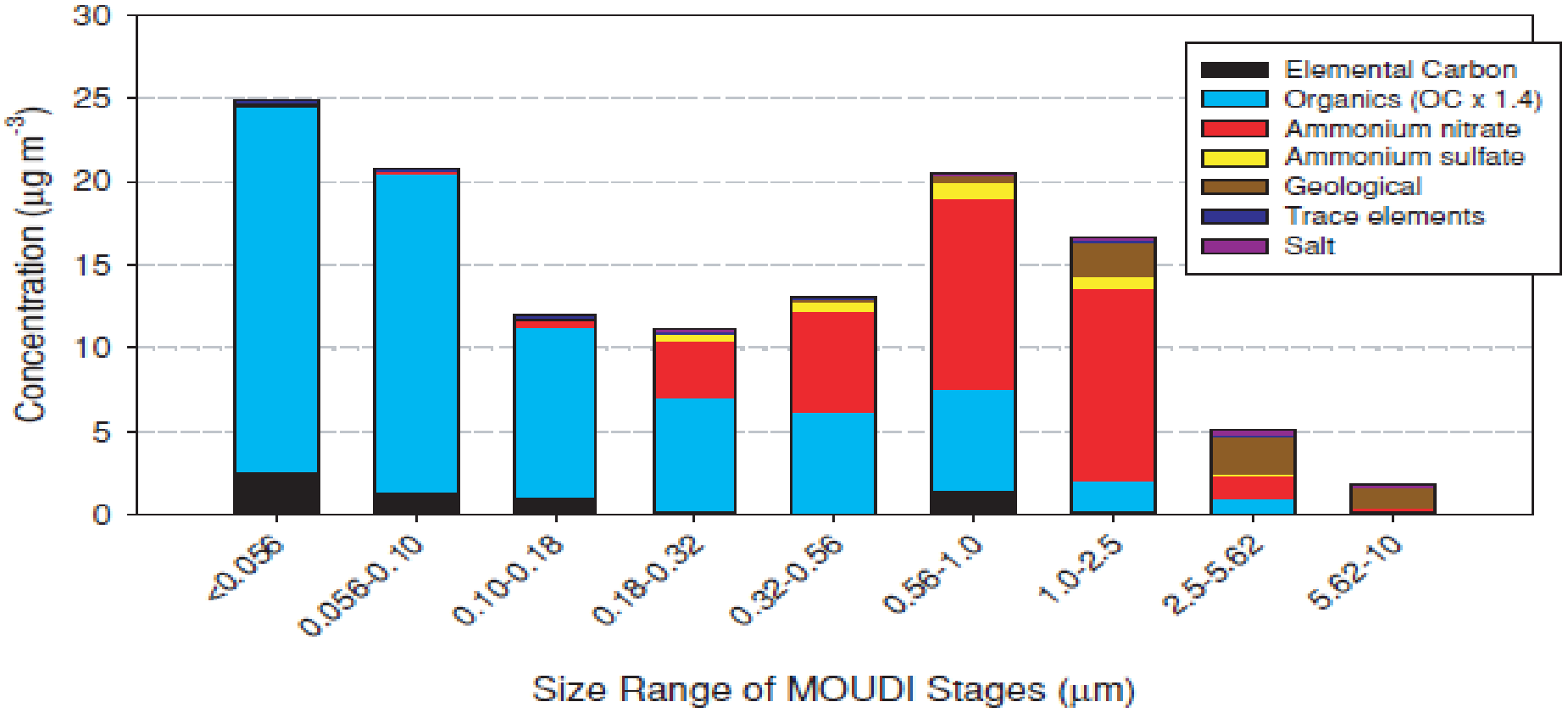
1. What is Black Carbon?

- BC is one of many types of tiny airborne particles 2.5 microns or smaller ($PM_{2.5}$)
  - BC is ~ 1/12th of total $PM_{2.5}$ mass
- BC has a core of elemental carbon (EC) with various co-emitted organic species adsorbed onto it (BC has ~ 20% more mass than its EC core)
- BC is produced by imperfect combustion of carbonaceous fuels such as diesel, coal, wood, agricultural wastes – in developed world, diesel is main source of BC

BC is in Tiniest Size Fractions

- BC is both a carrier of harmful species of $PM_{2.5}$, and a marker for other, co-emitted chemically reactive particulate organics not adsorbed, including Particulate Organ Carbon (POC) species, e.g., polycyclic aromatic hydrocarbons (PAHs)
- Almost all BC and POC is in smallest size fractions ("ultrafine PM"), which penetrate most deeply into lungs, into lung cells

Illustration of EC/BC Sizes (from Fresno Supersite)



Source: Mauderly and Chow, 2008

Sources and Amounts of BC

- Gigagrams/yr., 1996, worldwide:
- Open burning (all sources): 3281
- Contained combustion (all): 4669
  - Diesel (on road) 792
  - Diesel (off road): 579
  - Wood (residential) 880
  - Coal (industry) 642
  - Coal (residential) 480
  - **Coal (power) 7**
  - Other 1289

Source: Bond et al. (2004)

2. How Do We Learn Which PM2.5 Species are Most Harmful?

- Tools researchers use:
  - (A) ***Population based epidemiology*** uses monitors for air pollutants based in populated areas, then statistically relates air pollution levels to health endpoints
  - Endpoint comes from medical data, usually mortality (all-cause, cardiovascular disease (CVD); or hospital admissions, including CVD; or respiratory outcome
  - Time periods are often single or multi-day averages, but long term studies often compare annual pollution levels, mortality risks among different cities or counties

2. How Do We Learn Which PM2.5 Species are Most Harmful?

- Two Other Equally Important Methods
  - (B) ***Human Panel Studies***
    - Using a discrete number of individual subjects, monitor for CVD issues (blood pressure; biomarkers in blood of oxidative stress, inflammation, platelet activation; ST-segment depression (a measure of ischemia); defibrillator shocks and measures of arrhythmias; heart rate variability changes; etc.
  - (C) ***Toxicology*** (with cells [*in vitro*] and animals [*in vivo*]
    - Toxicology can examine biological mechanisms by which pollution might cause harm, generate hypotheses which can then be evaluated in studies with humans, ambient air

2. How Do We Learn Which PM2.5 Species are Most Harmful?

- These tools aren't enough *per se*, they must be used in a way most likely give reliable answers (best methods)
  - * Must investigate several PM2.5 species in same model, to test which are more influential
  - * Results of population based epidemiology should agree with human panel studies and toxicology
  - * Studies with good exposure to pollutants in question are more likely to give reliable answers than those w/o
  - * Need consistency of results across studies

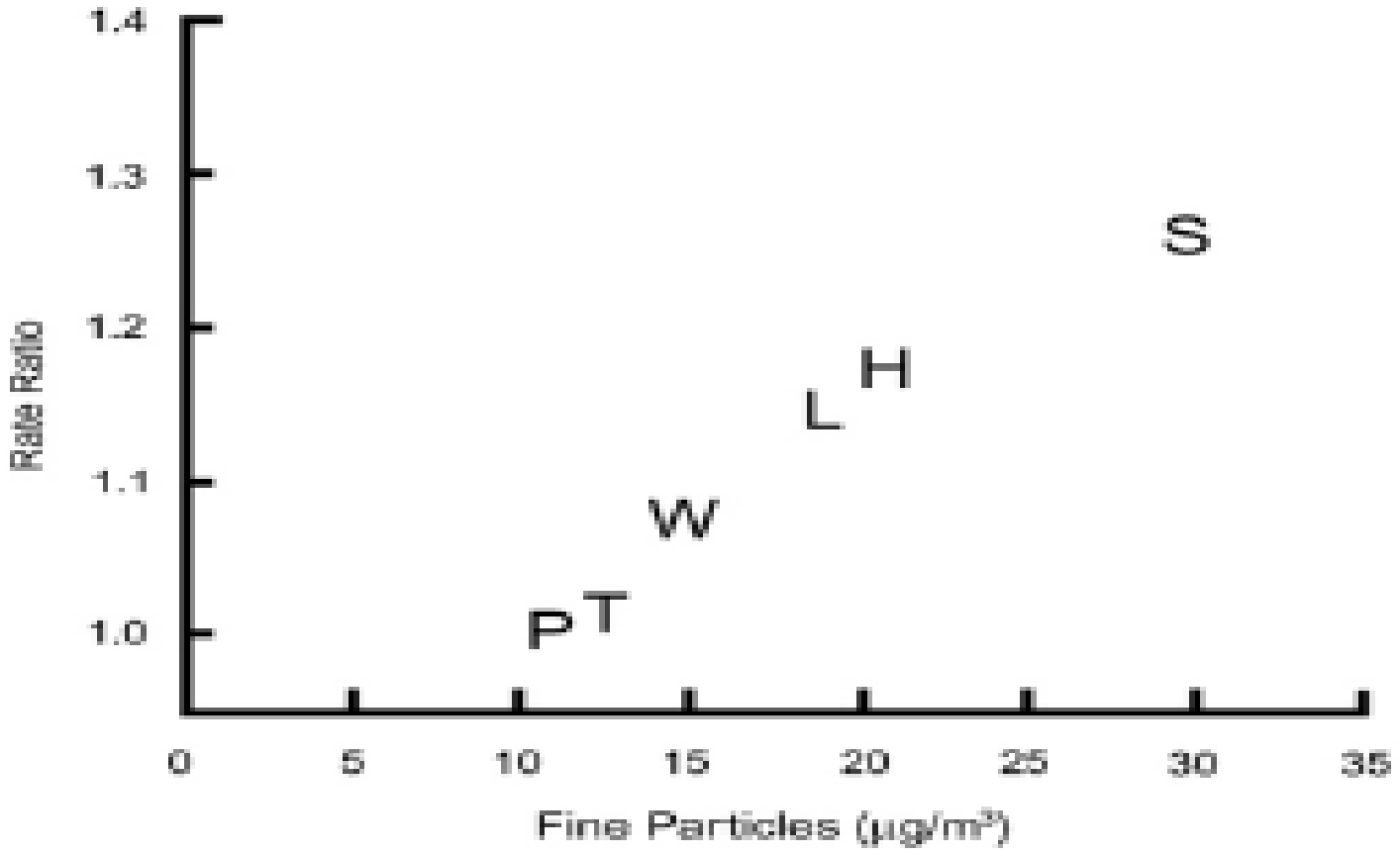
3. Applying the Methodologies

- We'll start from nearly the beginning

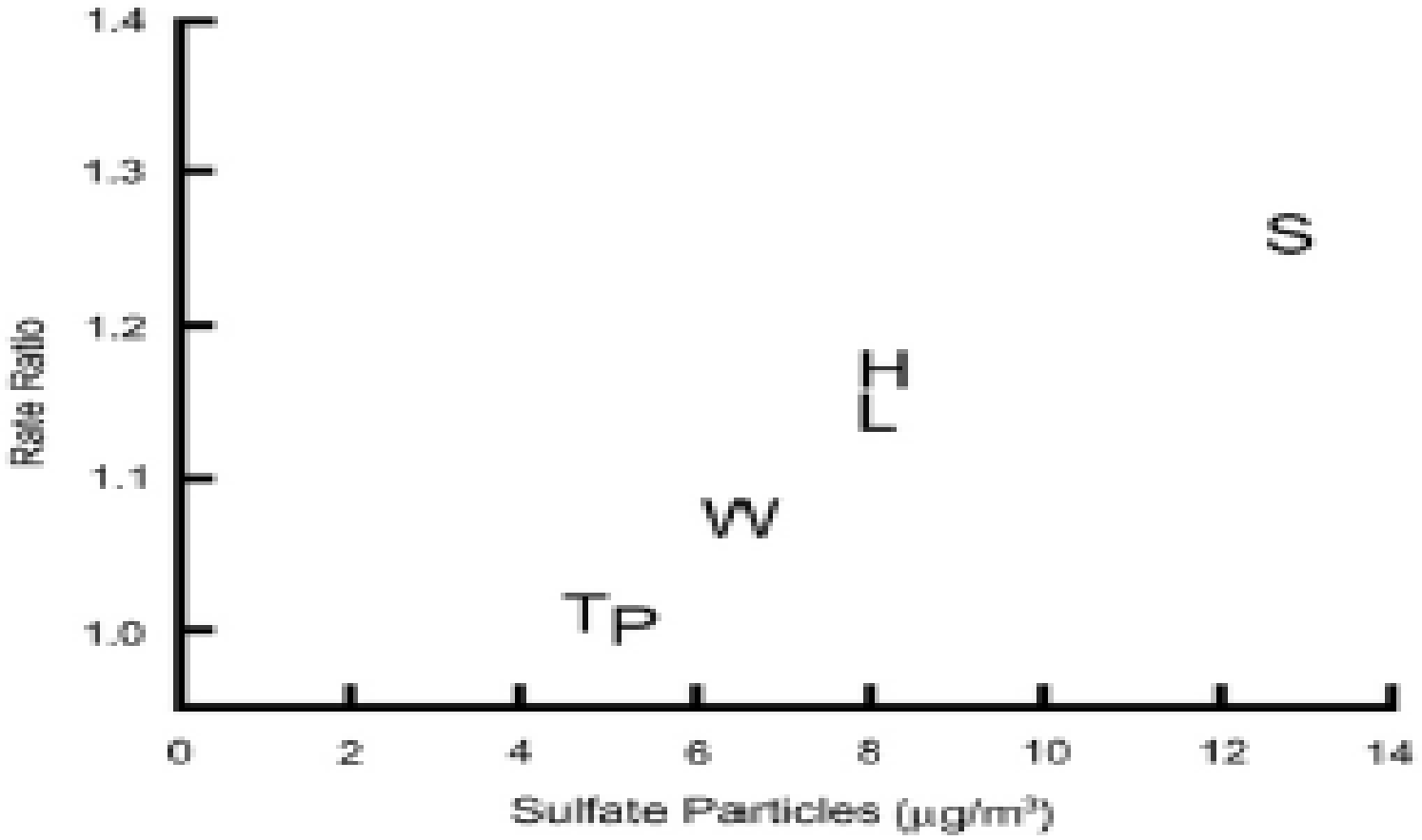
Six Cities and ACS Studies

- Early, influential) studies
  - ***Six Cities*** (1993)
  - ***American Cancer Society*** (ACS - 1995)
- Key features of these studies:
  - **Monitored only $PM_{2.5}$ mass, plus one $PM_{2.5}$ species (sulfate, only species for which widespread monitoring was available) -- BC, metals not included**
  - **Pollution from long ago, starting in 1979**

Six Cities Study: Key Figures (this slide [$PM_{2.5}$] and next)



Six Cities Figures (Sulfate)



ACS Study Findings

- Both $PM_{2.5}$ and sulfate were associated with elevated mortality:
  - All Cause
  - Cardiopulmonary
  - Lung Cancer

How to interpret these findings?

- One way, especially if you are in charge of protecting public health by regulating air pollution: both $PM_{2.5}$ and sulfate appear to be harmful, we need to regulate all $PM_{2.5}$
  - EPA's advisors (CASAC) at the time were divided, many said in writing there was a need to examine biological mechanisms by which PM or PM constituents might cause mortality

How to interpret these findings? (Cont.)

- Another way (how many of us were taught in graduate level statistics):
  - Correlation is not causation
  - Typical questions to ask regarding possible causation when adverse health findings are found:
    - Are there alternative explanations for associations in the graphs?
    - Toxicology: are there biological mechanisms by which **different** PM2.5 or PM2.5 components could cause various health effects?

Alternative Explanations

- In the late 1970s, 1980s, sulfate and SO_2 (which is chemically transformed in atmosphere to secondary sulfate) were emitted from:
  - ***High sulfur diesel fuels*** **of time, co-emitted with BC, PAHs, etc.**
  - ***Residual oil*****, co-emitted with metals such as nickel**
  - ***Steel mills*****, co-emitted with various metals**
  - ***Coke ovens*****, co-emitted with organics and PAHs**
- But none of these other $PM_{2.5}$ species, such as BC, were included in early assessments, such as Six Cities and ACS studies

Sources: Grahame and Hidy (2007), Grahame and Schlesinger (2005)

What About Toxicology?

- Sulfate causes cancer?
  - Not according to the Ames test
- How would sulfate cause harm in human body?
  - Generally accepted that sulfate isn't harmful *per se*
    - [Source: Schlesinger and Cassee, 2003)]
  - But, proponents say, epidemiology shows these associations, so there must be something happening in atmosphere to cause sulfate to in some way to become harmful – so we're back to epidemiology
  - Now, what about toxicology of co-emissions?

What About Toxicology?

- Toxicology of BC and diesel
  - Much work, from UCLA and USC, to University of Edinburgh and collaborators, to National Environmental Respiratory Center, show multitude of BC or diesel PM cardiovascular effects, in humans and in animals
- Toxicology of metals such as PM2.5 Nickel
  - Not yet as advanced as for BC and diesel , but Ni in particular looks to be harmful at elevated levels
  - Other PM2.5 metals might also be important (Cu, Zn, Fe)

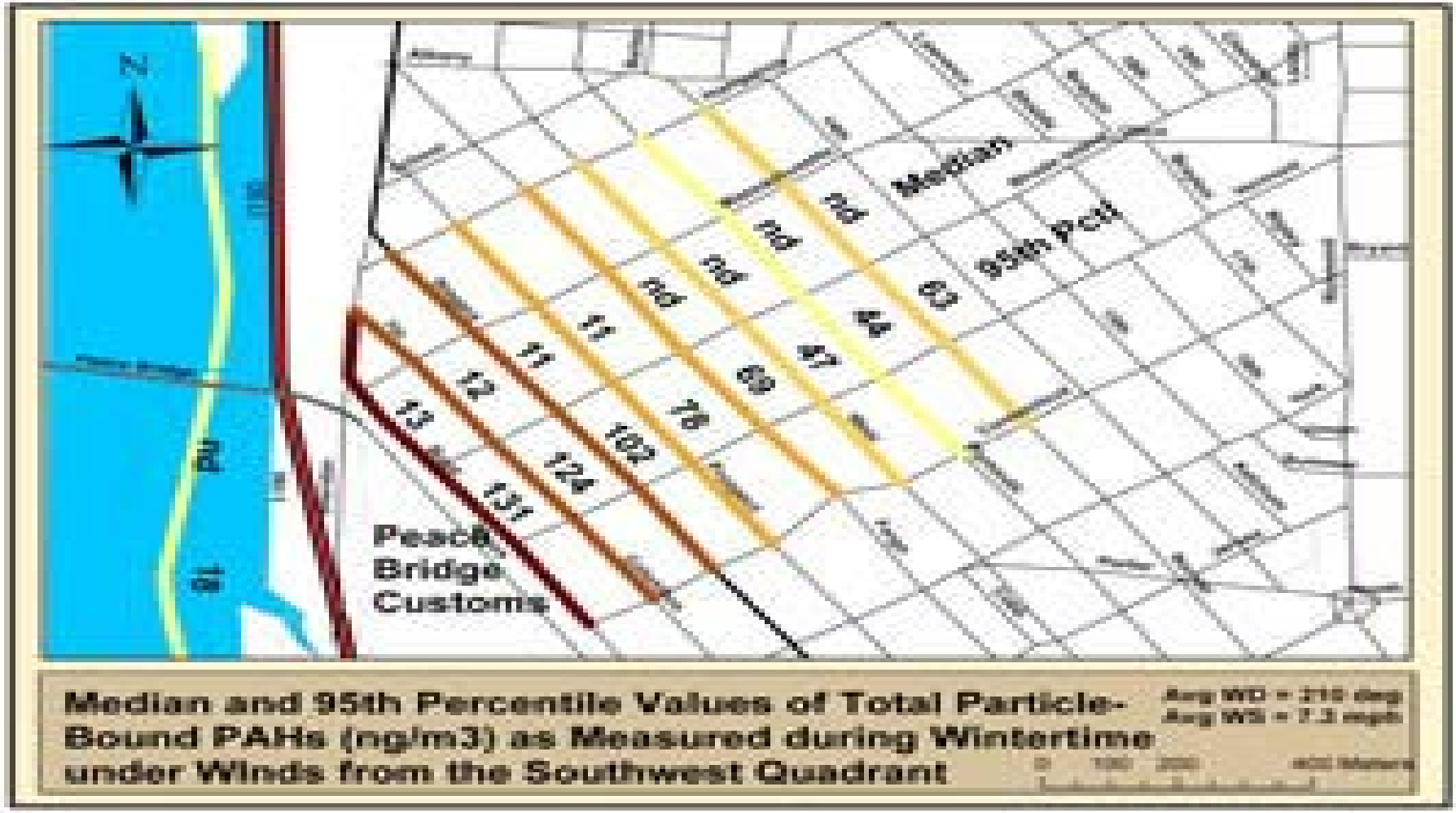
Human Panel Studies?

- Human panel studies use subjects (often elderly) about whom much is known (age, medications, prior conditions, etc.)
  - Associate PM species with various measurable health conditions noted earlier, taking into account this specific knowledge about subjects

Human Panel Studies: Importance of Good Exposure

- Why does good subject exposure information yields more reliable associations in human panel (and other) studies?
- Next 2 slides illustrate:
  - Large local spatial variation in PAHs (BC similar)
  - How health associations with BC differ, when a personal monitor is used to express subject exposure, vs. central monitor reading as a proxy for exposure for people over a large area

PAHs much higher near major bridge, connecting roads



For BC, All Associations with Personal Monitors are Significant

Association Between 24-hour Ambient and Personal EC Concentrations with Different HRV Measures (from Suh and Zanobetti, 2010)

	Ambient (Central Monitor)		Personal Monitor	
HRV Measure	*Change (%)*	*95% Confidence Interval*	*Change (%)*	*95% Confidence Interval*
SDNN	-1.0	-3.7 to 1.7	**-4.66**	**-7.99 to -1.22**
RMSSD	-3.6	-9.5 to 2.8	**-10.97**	**-18.00 to -3.34**
PNN50	-0.34	-10.55 to 11.04	**-15.16**	**-26.33 to -2.29**
HF	-2.36	-11.67 to 7.92	**-13.41**	**-23.95 to -1.41**
LF/HF ratio	2.60	-1.89 to 7.29	**6.22**	**0.15 to 12.64**

Results in boldface indicate statistical significance at the 95% confidence level.

Human Panel Studies including BC/EC: Results

- Delfino et al papers (5 papers)
  - All feature good subject exposure information
- Harvard School of Public Health (31 papers)
  - About 20% have good subject exposure information (including Suh and Zanobetti, 2010), the rest use central monitor reading as proxy for subject exposure
- We will then look at "highway proximity" studies, which in 2002 galvanized research into effects of highway emissions

Delfino et al. Studies (Summary of Methodologies)

- All in Los Angeles area, of seniors in community living quarters, all since 2008
- Exposure monitored inside and outside residences

Delfino et al. Studies (Summary of Results)

- **BC, EC, and primary organic carbon (POC)** significantly associated with biomarkers in blood of ***oxidative stress, inflammation, and platelet activation*** (all lead to cardiovascular disease), but secondary organic carbon (SOC) ***not*** associated (2 studies)
- In third study, **PAHs** significantly associated with inflammation endpoints (only biomarkers in study, BC/EC, POC not used)

Delfino et al. Studies (Summary of Results, Cont.)

- In fourth study, ST-segment depression associated with **BC, POC** but *not* with **SOC**
- Fifth study: SBP, DBP associated with **BC, POC, SOC**, with BC associations slightly more consistent
- Summary of Delfino et al studies:
  - **BC/EC and POC** (and **PAHs** when used) are consistently associated with a variety of cardiovascular disease (CVD) health effects

HSPH studies

- We'll summarize data from HSPH studies (most in last 5 years) separately, according to these criteria (many different health end points in each)
  - (A) Subjects with good exposure information, pollutants include BC/EC and at least one other measure of PM2.5
  - (B) Subjects without good exposure information, pollutants include BC/EC and at least one other measure of PM2.5
  - (C) Studies which include only BC/EC, all but one of which have good subject exposure

HSPH studies (A)

- ST-segment depression: BC associated, PM2.5 not associated
  - Gold et al., 2005
- Heart Rate Variability changes
  - Suh and Zanobetti (2010) : BC associated, PM2.5 and sulfate not associated, with good exposure; otherwise no associations
  - Schwartz et al. (2005): **BC strongly associated, PM2.5 less so** in initial results; then, when BC subtracted from PM2.5, remainder termed "secondary PM", **no** associations with secondary PM

Schwartz et al. (2005) HRV study

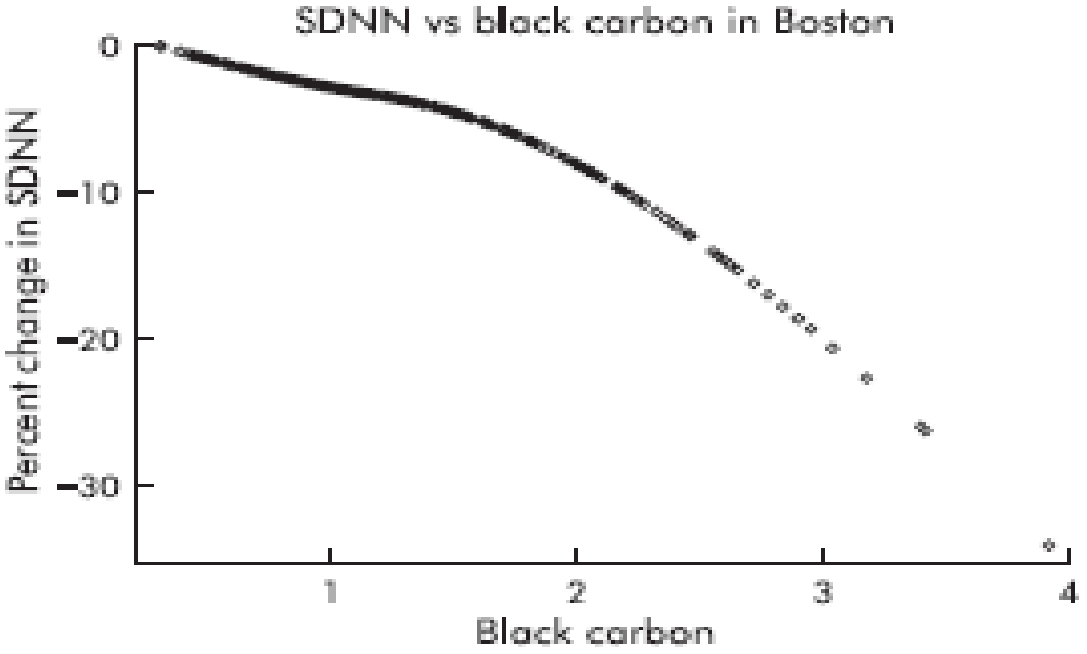


Figure 2 Smoothed plot of the percentage deviation from predicted SDNN (based on the model with all other covariates) versus black carbon concentrations in Boston. The association is nearly linear, despite being fit with about 3 degrees of freedom.

Schwartz et al. (2005) HRV study

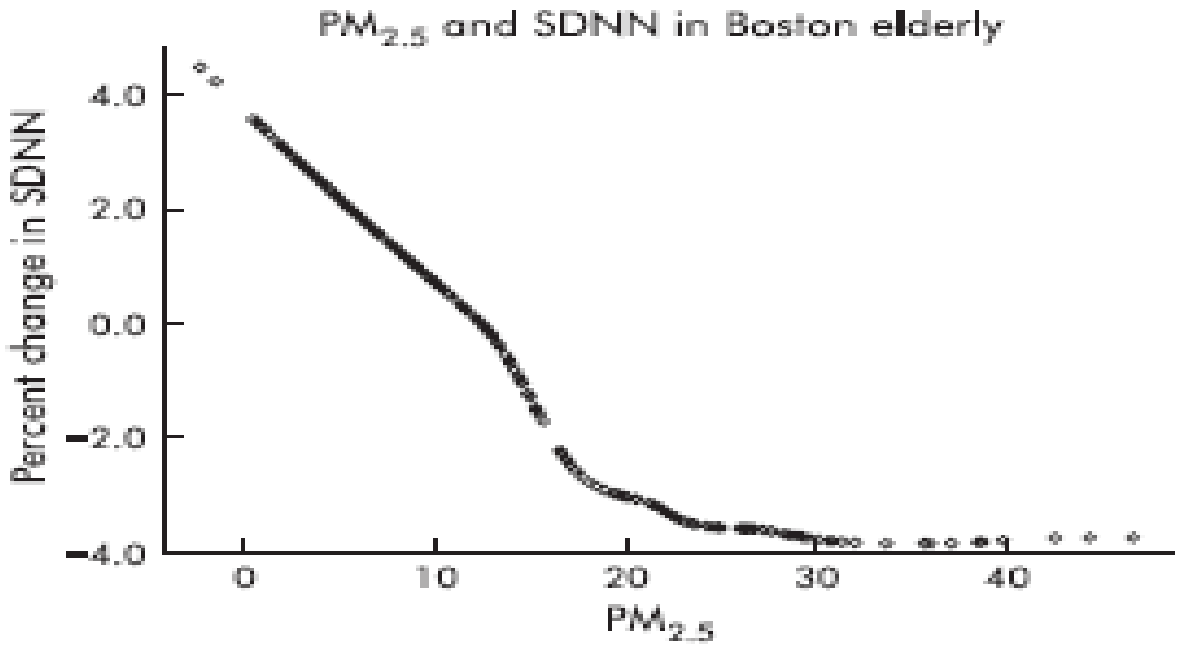


Figure 3 Smoothed plot of the percentage deviation from predicted SDNN (based on the model with all other covariates) versus $PM_{2.5}$ concentrations in Boston. The association flattens out at high concentrations where the correlation between $PM_{2.5}$ and black carbon disappears.

HSPH studies (A) (Cont.)

- Heart Rate Variability changes (cont.)
  - Adar et al. (2007), the St. Louis bus study: both BC and PM2.5 associated with changes in HRV; when subjects got on bus, with BC levels nearly 10 times higher, their HRV changes approximated the changes in BC – see next slide
  - Two other studies with similar outcomes

Adar et al. (2007) HRV study: BC and PM2.5 well correlated

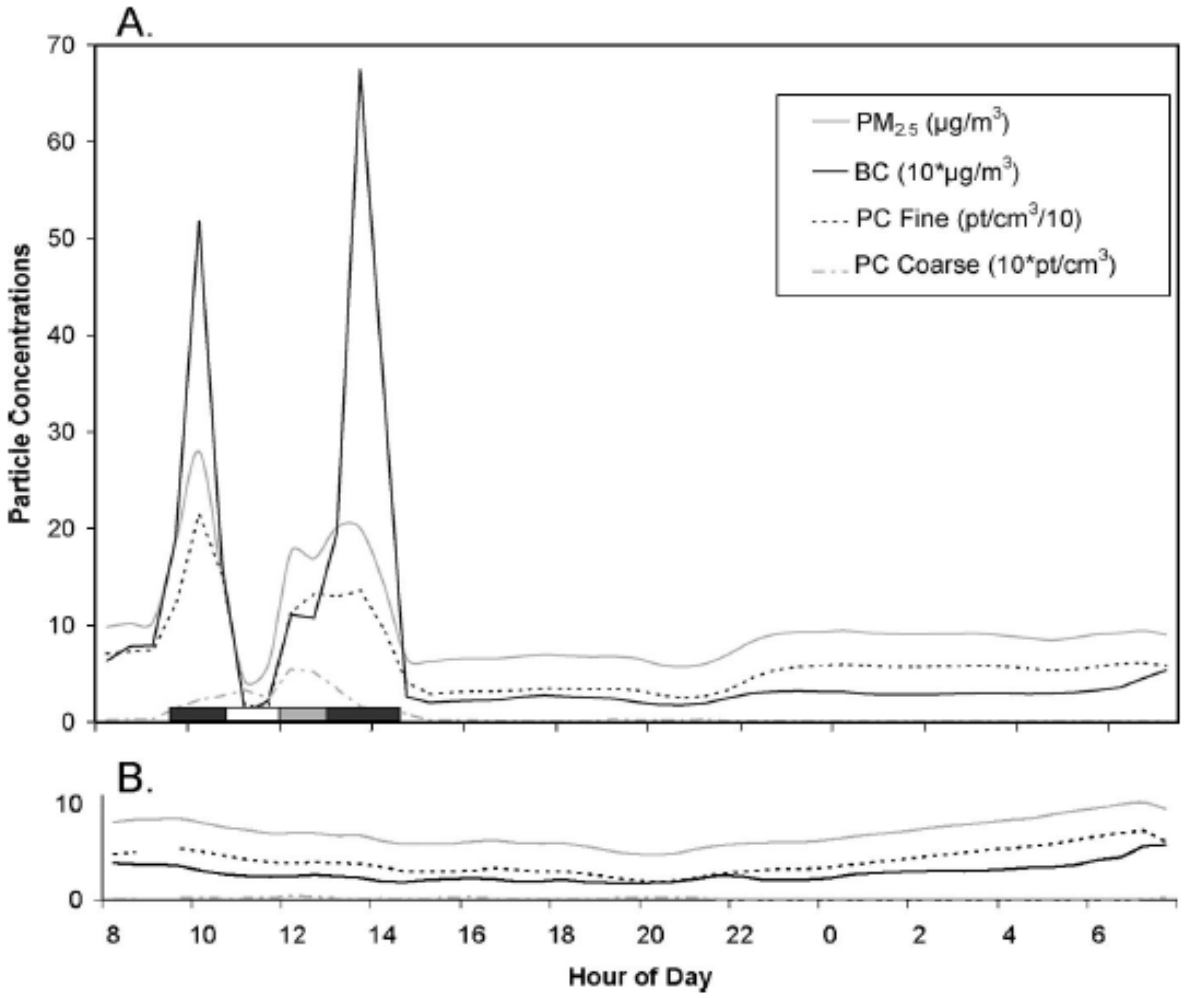


FIGURE 1. Particulate concentrations during (A) a sample trip day and (B) the previous nontrip day. Dark boxes at bottom of graph A represent any time periods during which the one-hour bus trips occurred. Lunch was demarcated using a light shaded box, whereas the activity (an Omni movie) was highlighted with the clear box.

HSPH studies (A): Summary

- Summary of five studies in (A) category: In all five, BC is associated with health endpoints, but other PM measures less so; PM associations appear to be driven by BC component

HSPH studies (B)

- Total of 20 studies of many different CVD-related endpoints
- Bottom line summary (don't have time for full review –obviously!):
  - Despite poor subject exposure, BC significantly associated with health endpoint in 15 of 20 studies; associations are more consistent with BC than with other PM2.5 measures (PM2.5 mass, sulfate)

HSPH studies (C)

- These six studies have good subject exposure but don't include other PM species, or PM2.5
  - Lack of other PM2.5 species is a weakness, as noted earlier, need many species in model, if possible
  - Nevertheless, BC/EC is associated with health endpoint in all six studies, including two of cognitive function

HSPH Studies: Summary

- BC is almost always associated with health endpoint studied (about a dozen), even when subject exposure wasn't good
- Other PM2.5 measures or species were less frequently associated
- In at least several cases, PM2.5 associations appeared to be driven by BC component of PM2.5

Now…"Highway Proximity" studies

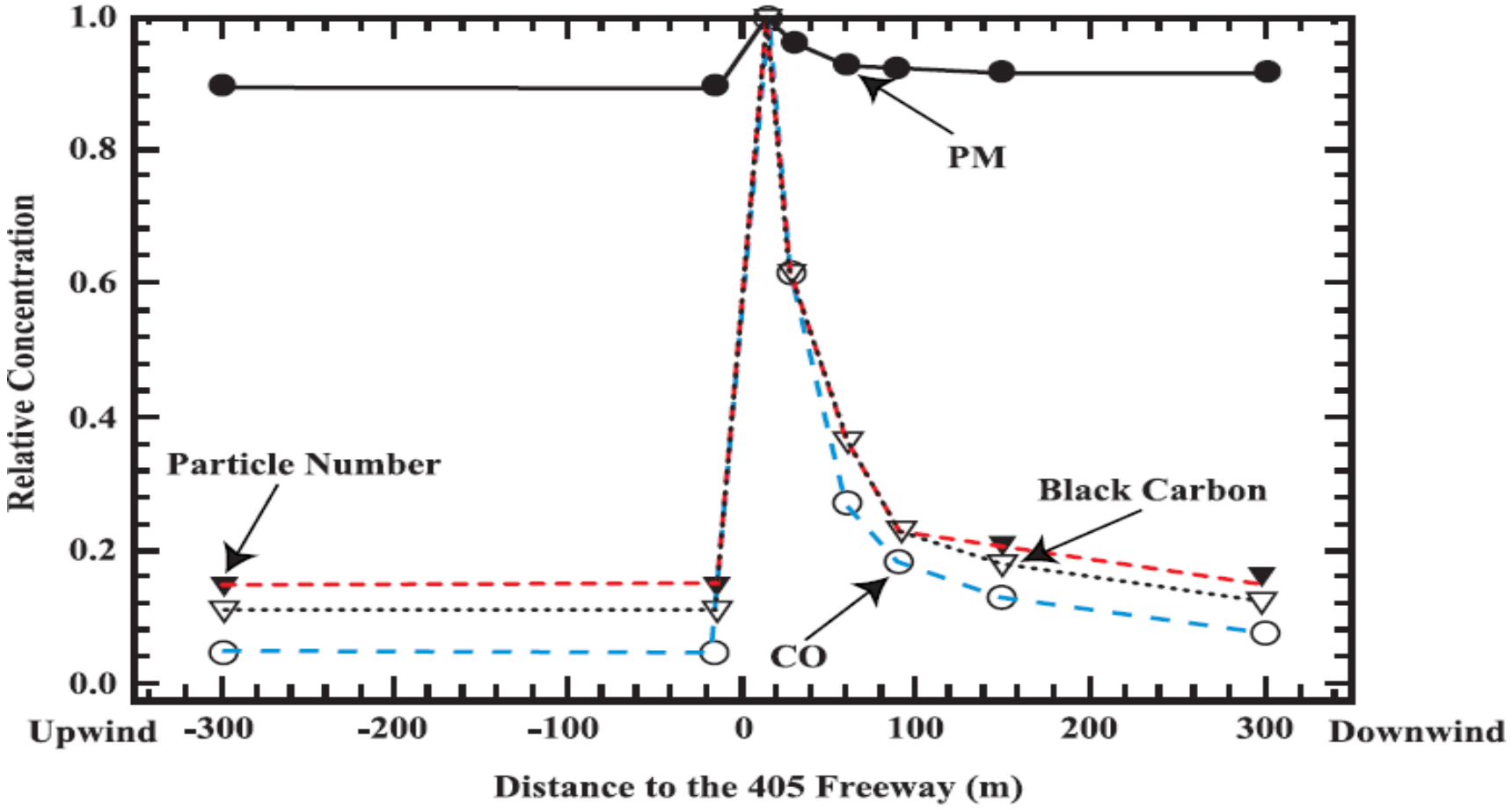
- Why did researchers focus on health associations with PM2.5 *per se* for so long?
  - ***Only very sporadic monitoring for BC, metals, other PM species until early 2000s*** (then needed several years to gather data, write studies)
  - Interest in health effects of vehicular emissions, BC was galvanized by publication of studies in ~ 2002 showing ***adverse mortality effects for those living near major roads***

Important Breakthroughs Regarding BC Health Effects

- Vehicular Emissions, such as BC, show a strong decline away from major roads….

- Picture turns out to be worth 1,000 words

Decline of Vehicular Emissions with Distance from Highway



Source: Zhu et al., 2002

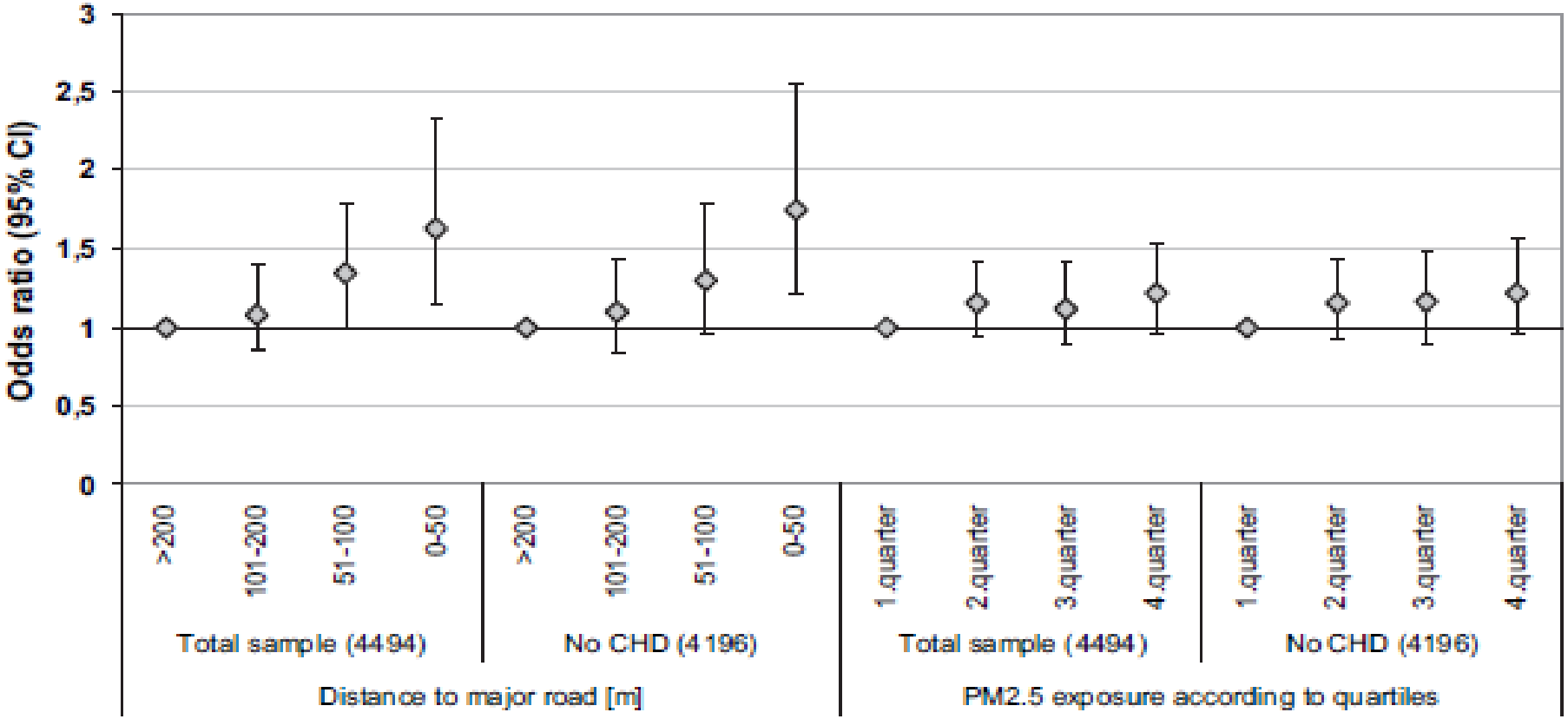
"Highway Proximity" Studies of Health Associations

- **Subjects living close to a major road had a significantly increased risk of mortality*** (RR = 1.18)
- **"Mortality rate advancement period" associated with residence near a major road was 2.5 years** (also statistically significant)
- By comparison, rate advancement periods attributable to **chronic pulmonary disease, chronic ischemic heart disease, diabetes were 3.4 years, 3.1 years, and 4.4 years**

  - * Close to a major road, in studies of health effects, is usually defined as 100 meters from freeway, or 50 meters from a major urban road
  - Source: Finkelstein et al., 2004

Coronary Artery Calcification

- Hoffmann et al., 2007:



Highway Proximity Health Studies: Summary

- These two studies are broadly representative of tens of such studies, virtually all of which show significant associations with various CVD and respiratory outcomes for those living close to major roads
- But….which vehicular emissions, including gases, are most likely to be causative?

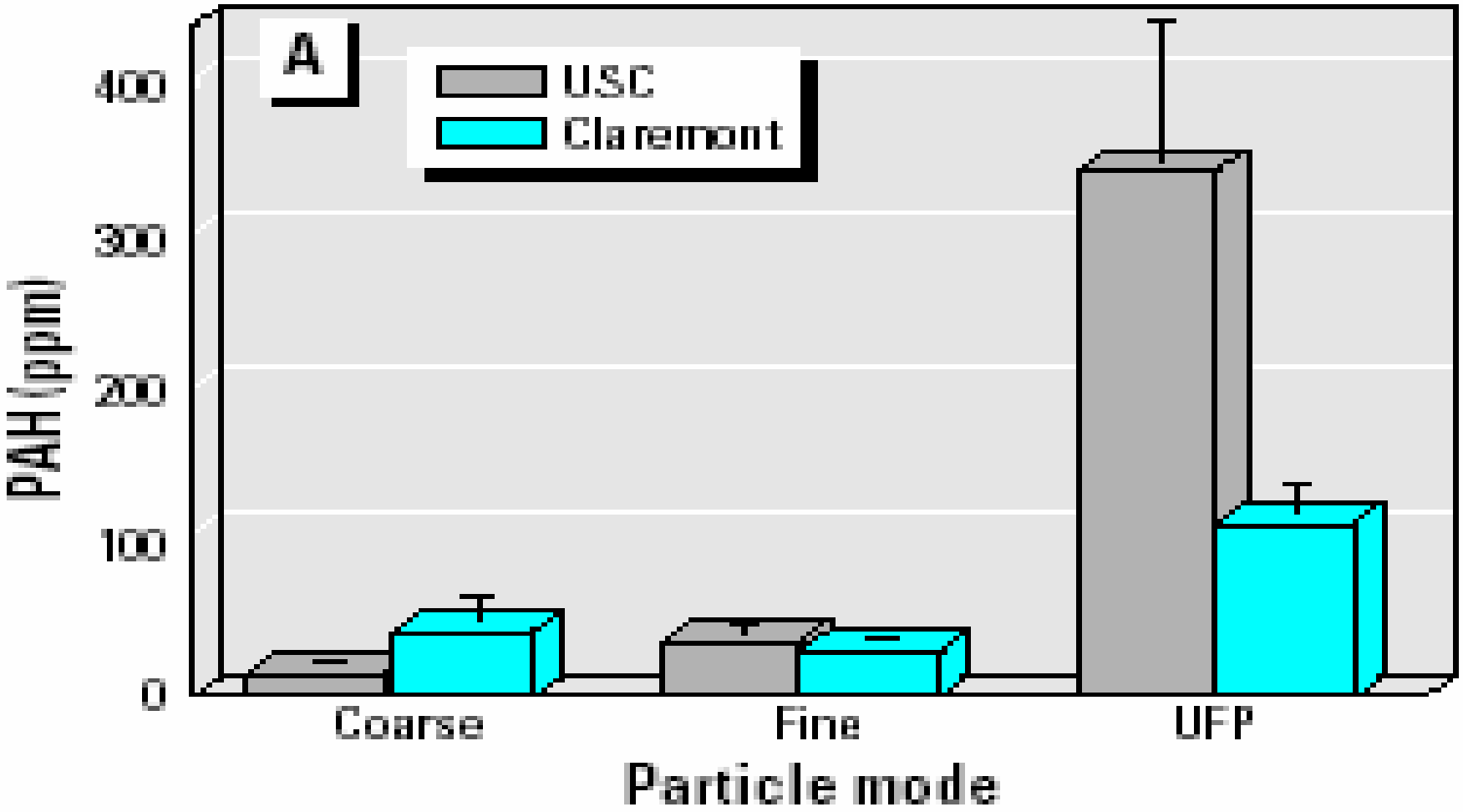
Which Vehicular Emissions are Harmful?

- First thing to know: particles, not gases, are most likely to be major cause of harm
- Two tests of subjects using face masks in Beijing showed that for both young and elderly subjects, all CVD endpoints examined were abrogated when a face mask was used, vs. not used (walked same route in each case)
  - Sources: Langrish et al., 2009, 2012

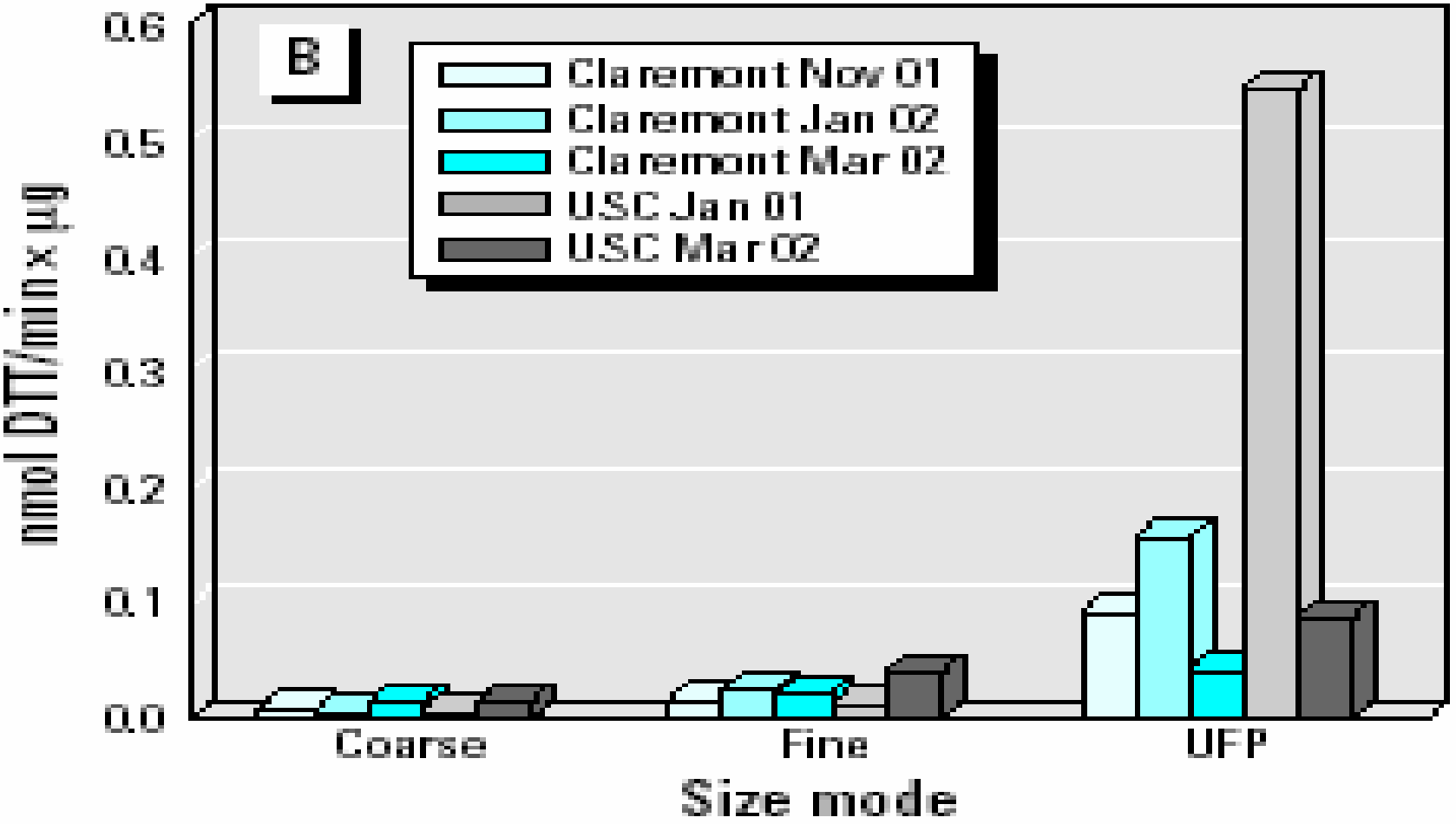
Zeroing in on BC

- Toxicology – next several slides from several publications from Ning Li (summarizing work in Andre Nel's lab at UCLA)

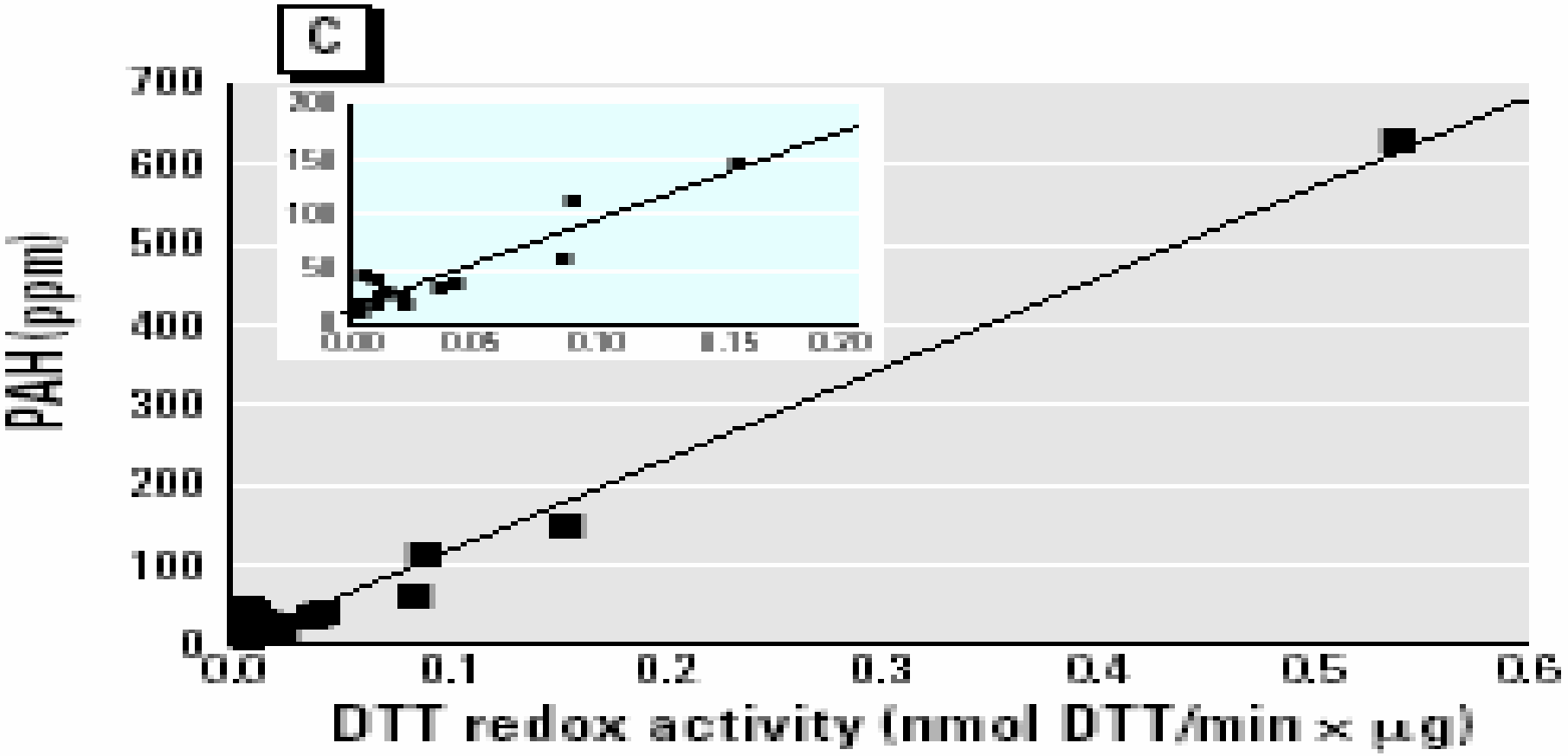
PAHs primarily in ultrafine PM in Los Angeles air



Greater oxidative stress in ultrafine PM than in larger PM fractions



PAH content correlated with oxidative stress



Connecting Toxicology, Human Panel Studies, Population-Based Epidemiology

- Review study links BC/EC effects found with *in vitro*, *in vivo*, human panel studies, highway proximity studies
- Linkages found for eight different CVD endpoints
- Such linkages suggests results of individual studies, or types of studies, may reflect causation, rather than chance
  - Source: Grahame and Schlesinger, 2010

Do BC/diesel emissions shorten life by shortening telomeres?

- Two separate literatures:
- (A) Biological health literature
  - In health literature, accelerated shortening of telomeres (caps on your chromosomes) increases biological aging, and
  - Oxidative stress accelerates shortening of telomeres
- (B) Vehicular emissions literature
  - Many studies suggest that exposure to diesel, or to BC/EC, or to POC, increases oxidative stress
    - Source: Grahame and Schlesinger (2012)

Purpose of Telomere

- From Wikipedia:
  - "Telomere…protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes"
  - When telomere gets too short, the cell can no longer divide (which protects against degradation of genetic information in the chromosome), but the cell then becomes senescent, over time no longer does its job properly

Examples of Oxidative Stress After Exposure to Diesel/BC

- Sauvain et al (2011)
  - Bus maintenance workers showed greater levels of oxidative stress (measured by chemicals in urine) after a shift, vs. before, with levels increasing as week went on
- Lee et al. (2011)
  - In diesel exhaust inspectors, vs. matched controls, inspectors had higher levels of marker for oxidative stress after two and three work days, oxidative stress markers significantly correlated with PAHs in diesel emissions

Assessing BC's Relative Mortality Effect vs. PM2.5

- Janssen et al. (2011) found that removing a unit of PM2.5 BC from urban air would increase life by 4 to 9 times longer than removing a unit of PM2.5
- First study to directly compare effect of PM2.5 BC vs. that of PM2.5

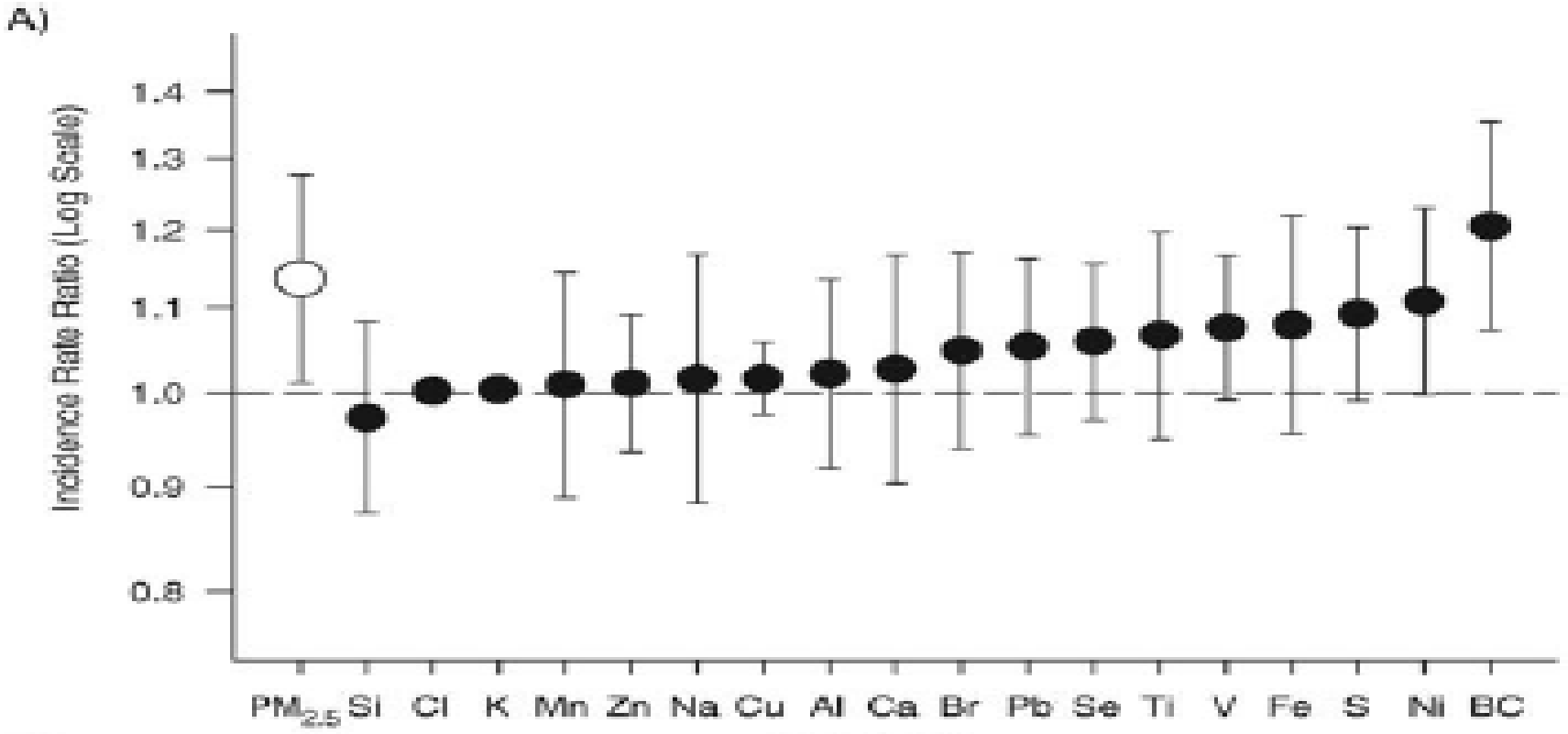
Mostofsky et al. (2012)

- Acknowledges issues when multiple PM2.5 species may be associated with health outcome:
  - Uses **18 PM2**.5 species in models (Alternative explanations…)
  - States that if a PM2.5 species is highly correlated with PM2.5, then associations may exist only because of correlation with PM2.5, not necessarily inherent toxicity
  - States **that more sophisticated models are required when multiple PM2.5 species are emitted from different sources**, need to know if a PM2.5 species is toxic, **or just a marker** for different co-emission
  - As with Janssen et al. (2011), this is new type of study needed

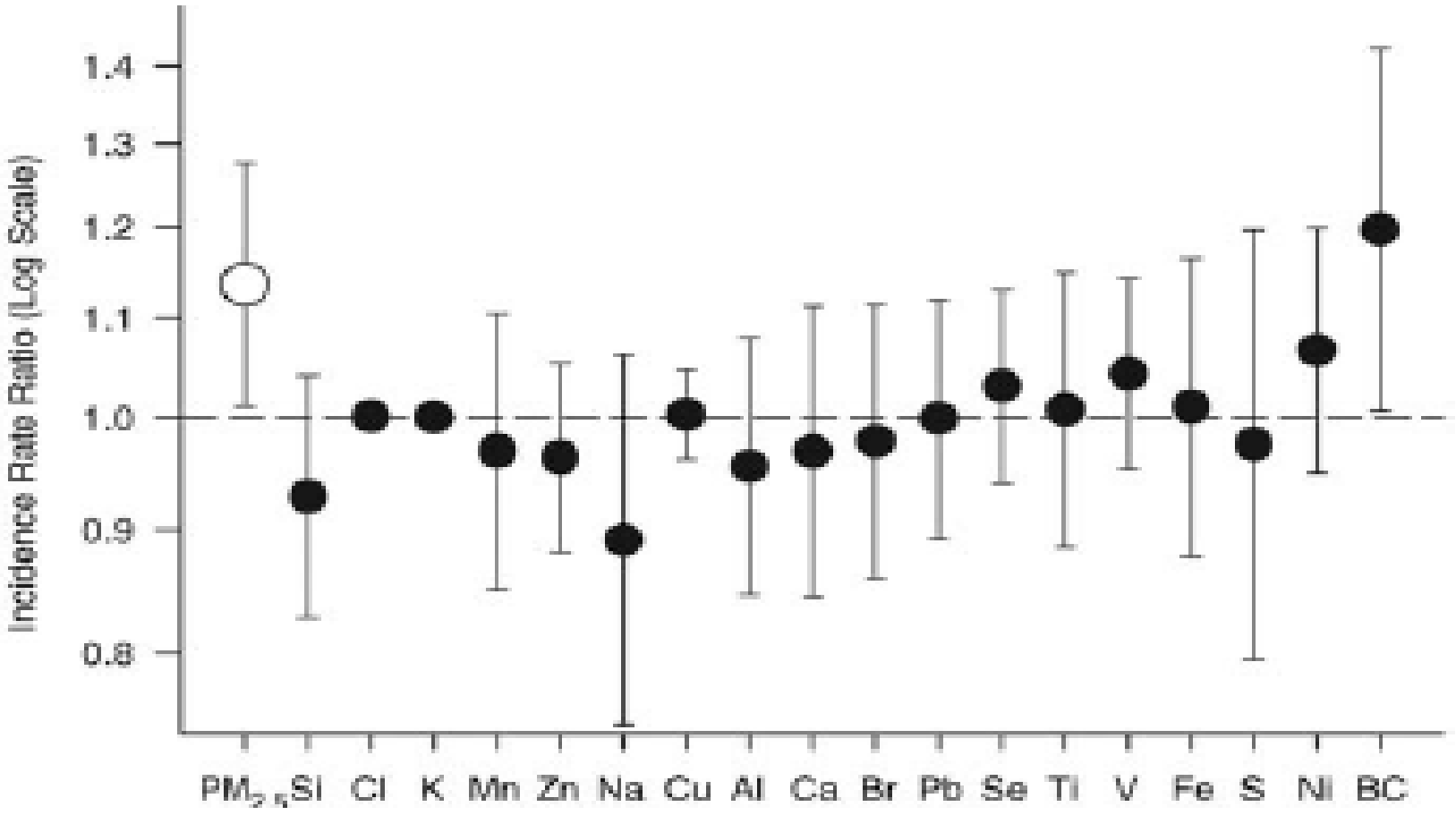
Mostofsky et al. (2012) Modeling Results

- Defined six modeling methods, last five more sophisticated that the first, which is broadly representative of most epidemiology until now
- Pursued two of the last five as being theoretically more attractive, built models, compared results to those of first model
- Here are results for first model (which doesn't deal with issues noted on previous slide) and other two, more advance models

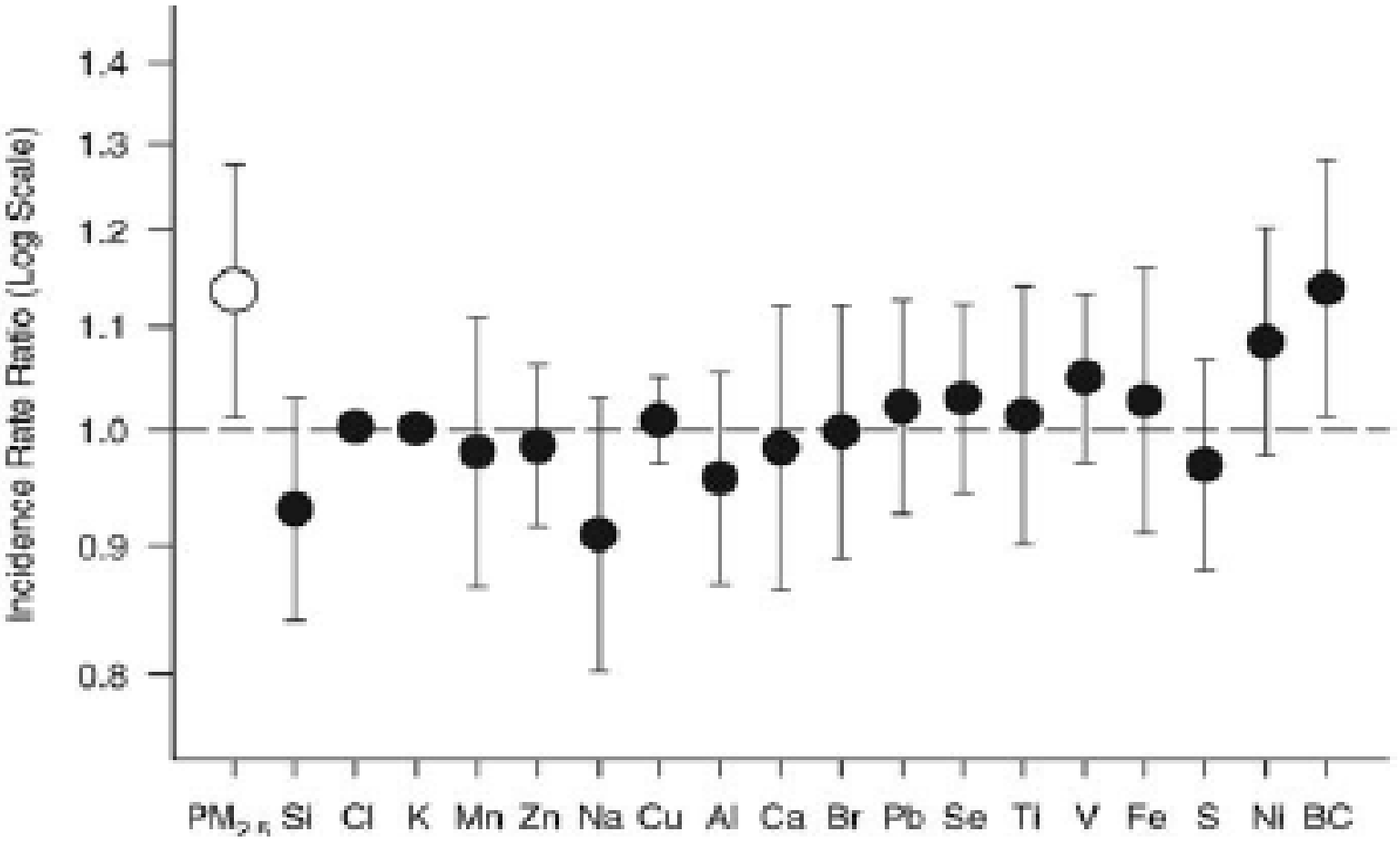
Mostofsky et al. (2012) Results (A)



Mostofsky et al. (2012) Results (B)



Mostofsky et al. (2012) Results (C)



EPA Criteria for Determining Causality of PM (but we are considering BC)

- Consistency:
  - "An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies, conducted in multiple locations by multiple investigators. The reproducibility of findings constitutes one of the strongest arguments for causality…"
  - From Integrated Science Assessment (ISA) for PM
  - **Check** – for BC/EC, consistent results by different researchers in different areas

EPA Criteria for Determining Causality of PM (BC)

- Coherence:
  - "An inference of causality from epidemiologic associations may be strengthened by other lines of evidence (e.g., controlled human exposure and animal toxicological studies) that support a cause-and-effect interpretation of the association."
  - **Check**

EPA Criteria for Determining Causality of PM (BC)

- Biological Plausibility:
  - "An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A proposed mechanistic linking between an effect, and exposure to the agent, is an important source of support for causality…"
  - **Check** - biological mechanisms found with in vivo, in vitro, and human panel studies

World Health Organization (2012) "Health Effects of Black Carbon"

- BC "may operate as a universal carrier of a wide variety of, especially, combustion-derived chemical constituents of varying toxicity to sensitive targets in the human body such as the lungs, the body's major defense cells and possibly the systemic blood circulation."
- Calls for consideration of a separate BC pollution indicator as a means of benefiting public health by reducing exposure to combustion PM from motorized traffic

Summary

- Why did it take us so long to understand the adverse health effects of BC?
  - We didn't have monitoring networks early on, so we didn't include many health relevant PM2.5 species, including BC/EC
  - Highway gradient studies needed to catalyze research
  - Until there were enough studies, we couldn't link *in vitro* and *in vivo* results, showing biological mechanisms, with effects in human panel studies and in population based epidemiology
  - We didn't have most sophisticated epidemiology models (e.g., Janssen et al., to distinguish effects of BC vs. PM2.5; Mostofsky et al. to distinguish among different PM2.5 species)

From Integrated Science Assessment

- Integrated Science Assessment on confounding by missing pollutants (pg. 1-16):
  - "The use of multi-pollutant regression models has been the prevailing approach for controlling potential confounding by co-pollutants in air pollution health effects studies. Finding the pollutant likely responsible for the health outcome from multi-pollutant regression models is made difficult by the possibility that *one or more air pollutants may be acting as a surrogate for an unmeasured or poorly-measured pollutant* or for a particular mixture of pollutants."

Schwartz et al. (2005) HRV study

Table 3 Percentage change in heart rate variability associated with an interquartile range increase in particle exposure

Variable	SDNN (ms)	r-MSSD (ms)	PNN_{50} (%)	LFHFR
BC*	−4.6 (−2.0 to −7.2)	−6.1 (0 to −11.9)	−9.4 (−0.1 to −17.8)	1.8 (−3.0 to 7.0)
BC†	−5.1 (−1.5 to −8.6)	−10.1 (−2.4 to −17.2)	−16.9 (−6.0 to −26.6)	7.2 (.7 to 14.1)
$PM_{2.5}$*	−3.4 (0.6 to −7.3)	−7.4 (1.6 to −15.5)	−12.9 (0 to −24.2)	1.4 (−5.5 to 8.8)
$PM_{2.5}$†	−2.6 (0.8 to −6.0)	−10.1 (−2.8 to −16.9)	−12.7 (−1.6 to −22.5)	0.2 (−4.6 to 5.2)
Secondary PM*	−0.5 (2.8 to −3.7)	−3.0 (4.8 to −10.3)	−6.6 (−16.9 to 5.0)	1.4 (−4.1 to 7.2)
Secondary PM†‡	−0.9 (2.5 to −4.1)	−6.4 (0.6 to −12.9)	−5.8 (−15.6 to 5.1)	−2.4 (−7.6 to 3.1)

All models control for subject, temperature, day of week, hour of day, medication use on that day, and time trend.

*1 hour average.

†24 hour average.

‡Residuals of $PM_{2.5}$ controlling for black carbon (BC).