Testimony

of

Joel Schwartz

Professor of Environmental Health and Epidemiology, Harvard School of Public Health and Director, Harvard Center for Risk Analysis

Before the Subcommittee on Regulatory Affairs, Stimulus Oversight, and Government Spending
Committee on Oversight & Government Reform

July 26, 2011

Qualifications

I am a Professor in the Departments of Environmental Health and Epidemiology at the Harvard School of Public Health, in the Department of Medicine at Harvard Medical School, Director of the Harvard Center for Risk Analysis, member of the faculty of the Environmental Biostatistics program, of the Cardiovascular Epidemiology program, and on the Steering Committee of the Harvard University Center for the Environment. I am also a former member of the Board of Councilors of the International Society for Environmental Epidemiology, and the Editorial Board of the American Journal of Respiratory and Critical Care Medicine. I have served on two National Academy of Sciences panels, and was a recipient of a John D. and Catherine T. MacArthur Fellowship. I am the most cited author in the field of air pollution research. I have over 454 peer-reviewed papers published or

in press, which have been cited over 23,000 times in other peer-reviewed publications.

Testimony

There is clear, convincing evidence that this particulate air pollution is not merely a nuisance darkening our skies. It kills people. And the number of people it kills each year in the United States is not small—it is larger than the number of deaths each year from AIDS, breast cancer, and prostate cancer put together. The difference is we do not know how to cure AIDS, breast cancer, or prostate cancer. But we do know how to dramatically reduce those particle levels. In particular, the technology to control particle-forming emissions from coal burning power plants has been commercially available since the 1970's. Over half the power plants in the U.S. already use this technology, but other plants have delayed installing it for decades. The Clean Air Transport Rule addresses the emissions from those plants, and will save **tens of thousands of lives per year**.

Another comparison that puts the rule in perspective is that in 2001, more people in New York City died from particulate air pollution than from the attack on the World Trade Center on September 11. And the largest single source of those particles was emissions from coal burning power plants.

In addition to killing people, particles trigger heart attacks, destabilize people with heart failure, driving them into the hospital, and exacerbate respiratory infections, leading to increased hospital admissions for those conditions.

THE SCIENTIFIC CONSENSUS

This conclusion is not just mine; it is the overwhelming consensus of the scientific and medical community. It is widely accepted that particles reduce life expectancy, trigger heart attacks, and have a wide range of other adverse effects on health, and that sufficient evidence exists to quantitatively estimate the impacts of reducing air pollution on avoided deaths, etc. Several of the most reputed health organizations have noted the consensus on the health effects of particulate matter. For example, the World Health Organization, in setting a global maximum PM_{10} standard of 20 $\mu g/m^3$ in 2005, roughly equivalent to the U.S. EPA standard of 15 $\mu g/m^3$ for $PM_{2.5}$, stated:

> By reducing particulate matter pollution from 70 to 20 micrograms per cubic metre as set out in the new Guidelines, we estimate that we can cut deaths by around 15%," said Dr. Maria Neira, WHO Director of Public Health and the Environment. "By reducing air pollution levels, we can help countries to reduce the global burden of disease from respiratory infections, heart disease, and lung cancer which they otherwise would be facing.

Their press release went on to say:

> These new guidelines have been established after a worldwide consultation with more than 80 leading scientists and are based on

> review of thousands of recent studies from all regions of the world. As such, they present the most widely agreed and up-to-date assessment of health effects of air pollution, recommending targets for air quality at which the health risks are significantly reduced. We look forward to working with all countries to ensure these Guidelines become part of national law

and,

"For example, in the European Union, the smallest particulate matter alone ($PM_{2.5}$) causes an estimated loss of statistical life expectancy of 8.6 months for the average European."

Hence the WHO concluded not merely that the association of particles with early deaths is causal, but that the evidence is strong enough to allow quantitative estimates of the mortality benefits of reducing particle concentrations. Earlier, in the 2002 World Health Report, WHO concluded "Particulate air pollution (i.e. particles small enough to be inhaled into the lung) is consistently and independently related to the most serious [acute and chronic health] effects, including lung cancer and other cardiopulmonary mortality."

In 2005 the European Union, after its own detailed evaluation of the scientific evidence, set standards for particulate air pollution, and developed strategies to reduce particle levels. In EU Clean Air For Europe (COM(2005) 446 final Communication From The Commission to the Council and the European Parliament) they state that the goal of the strategy is a "47% reduction in loss of life expectancy as a result of exposure to particulate matter; **To achieve these objectives, SO2 emissions will need to**

decrease by 82%." That is, they concluded SO2 emissions from coal burning power plants were responsible for substantial loss of life, and embarked in 2005 on the pollution control policies the EPA is only now proposing to start in 2012.

As part of the Clean Air Act, the U.S. EPA is required to regularly review the evidence on the health effects of criteria air pollutants, and have its summary review of the science about each pollutant reviewed by an external, statutory Clean Air Science Advisory Board (CASAC). In reviewing the EPA Staff Paper in 2006 the CASAC stated, "In summary, the epidemiologic evidence, supported by emerging mechanistic understanding, indicates adverse effects of $PM_{2.5}$ at current annual average levels below 15 $\mu g/m^3$." In its letter of 6/29/06, CASAC reiterated:

> The CASAC recommended changes in the annual fine-particle standard because *there is clear and convincing scientific evidence that significant adverse human-health effects occur in response to short-term and chronic particulate matter exposures at and below 15 μg/m3, the level of the current annual $PM_{2.5}$ standard.*
>
> It goes on to say:
>
> > Significantly, we wish to point out that the CASAC's recommendations were consistent with the mainstream scientific advice that EPA received from virtually every major medical association and public health organization that provided their input to the Agency, including the American Medical Association, the American Thoracic Society, the American Lung Association, the American Academy of Pediatrics, the American College of Cardiology, the American Heart Association, the American Cancer Society, the American Public Health Association, and the National Association of Local Boards of Health. Indeed, to our knowledge there is no science, medical or

> public health group that disagrees with this very important aspect of the CASAC's recommendations. EPA's recent "expert elicitation" study (Expanded Expert Judgment Assessment of the Concentration-Response Relationship Between $PM_{2.5}$ Exposure and Mortality, September 21, 2006) only lends additional support to our conclusions concerning the adverse human health effects of $PM_{2.5}$.

As noted above, these conclusions are supported by all the major associations of health professionals, which include as members almost all researchers on heart disease, lung disease, and cancer. In their letter to the EPA administrator on the $PM_{2.5}$ standard the health professional organizations stated:

> There is a robust and growing body of evidence linking PM to adverse health effects. PM has now been linked to a broad range of adverse health effects, both respiratory and cardiovascular, in epidemiological and toxicological research. Epidemiological research has shown an association between PM exposure and increased risk for mortality. Time-series studies reported in the early 1990s showed that day-to-day variation in PM concentration was associated with mortality counts. These studies in selected cities have now been followed by national-level time-series analyses in the United States and Europe that pool data from broad regions to produce national estimates of the effect of PM on daily mortality.
>
> For example, in 90 U.S. cities, the National Morbidity and Mortality Air Pollution Study (NMMAPS) estimated a 0.2% increase of all-cause mortality per 10 $\mu g/m^3$ increase in PM_{10}. Risk was highest in the northeast and for cardiovascular and respiratory causes of death. Findings of follow-up studies, including most notably the Harvard Six Cities Study and the American Cancer Society's Cancer Prevention (CPS) II Study, show that the resulting loss of life may be substantial. The time-series studies show a linear relationship between PM concentration and risk at concentrations measured routinely in many U.S. cities.
>
> There is a now a substantial, parallel literature on PM and morbidity. Studies have addressed PM and risk for hospitalization and other clinical outcomes and pre-clinical biomarkers. Since the 1997 PM NAAQS, there has been an explosion of research on cardiovascular

consequences of exposure to PM indicating short-term and long-term effects of PM on cardiovascular health.

A recent study, that includes data from over 11 million Medicare beneficiaries, shows that even small increases in exposure to PM results in increased admissions for cardiac and respiratory conditions, including heart and vascular diseases, heart failure, chronic obstructive pulmonary disease and respiratory infections. The effect was even greater in participants over 75 years old, in terms of heart problems and COPD than participants 65 – 74 years old.

In short, a significant body of research has described potential mechanisms for and the range of health effects caused by PM air pollution. The undersign physician organizations find the body of scientific evidence to be rigorous, comprehensive and compelling enough to justify a significant tightening of the existing NAAQS PM standards.

Sincerely,

American Thoracic Society

American Academy of Pediatrics

American College of Cardiology

American Association of Cardiovascular and Pulmonary Rehabilitation

National Association for the Medical Direction of Respiratory Care

In separate comments, the *American Medical Association* wrote:

The new evidence on harmful effects of PM is substantial. PM has been linked to a broad range of adverse health effects, both respiratory and cardiovascular, in epidemiologic and toxicologic research. Studies of daily variation in concentrations and national level time-series analyses have linked PM with increased morbidity and mortality. Many U.S. and Canadian studies are available that provide evidence of associations between $PM_{2.5}$ and serious health effects in areas with air quality at and above the level of the 1997 annual standard (15 μg/m3). Newer short term mortality studies provide evidence of statistically significant associations with $PM_{2.5}$ in areas with long-term average concentrations of 13 to 14 $\mu g/m^3$, concentrations that are below the 1997 standard. Short-term studies of emergency room visits and cardiovascular mortality suggest measurable health effects at $PM_{2.5}$ concentrations of ~12 $\mu g/m^3$. A recent study (Dominici F, Peng D, Bell ML et al. *JAMA*; 2006; 295:1127-1134) showed that $PM_{2.5}$ concentrations are associated with short-term increases in hospital admissions for cardiovascular and

> respiratory diseases among Medicare enrollees, arguing for setting a $PM_{2.5}$ standard that is adequate to protect the health of these individuals. The AMA supports the recommendations of EPA staff and the Clean Air Scientific Advisory Committee to EPA for more stringent air quality standards. In fact, several physician organizations, including the American Thoracic Society, American College of Cardiology, American College of Preventive Medicine, and the American Academy of Pediatrics, support a more stringent $PM_{2.5}$ standard of 12 $\mu g/m^3$ for the average annual standard; 25 $\mu g/m^3$ for the 24-hour standard; and use of the 99th percentile form for compliance determination. The AMA believes the Administrator should adopt these more stringent standards in order to provide adequate protection for the public from the adverse health effects of both long- and short-term exposures to fine particulate matter in the ambient air.

Hence by 2006 every major scientific body involved in either research or the evaluation of research relating to particulate air pollution has concluded that it is a major health hazard, whose consequences include early deaths.

Since 2006, the evidence has become even more convincing. The American Heart Association recently appointed a panel of scientific experts to review the new evidence on the risk posed by particles. That review was published in 2010 in Circulation, the world's leading peer reviewed journal on heart disease. The abstract of that peer-reviewed paper summarizes the conclusions as follows:

> In 2004, the first American Heart Association scientific statement on "Air Pollution and Cardiovascular Disease" concluded that exposure to particulate matter (PM) air pollution contributes to cardiovascular morbidity and mortality. In the interim, numerous studies have expanded our understanding of this association and further elucidated the physiological and molecular mechanisms involved. The main objective of this updated American Heart Association scientific statement is to provide a comprehensive review of the new evidence

> linking PM exposure with cardiovascular disease, with a specific focus on highlighting the clinical implications for researchers and healthcare providers. The writing group also sought to provide expert consensus opinions on many aspects of the current state of science and updated suggestions for areas of future research. On the basis of the findings of this review, several new conclusions were reached, including the following: Exposure to PM <2.5 μm in diameter (PM2.5) over a few hours to weeks can trigger cardiovascular disease–related mortality and nonfatal events; longer-term exposure (eg, a few years) increases the risk for cardiovascular mortality to an even greater extent than exposures over a few days and reduces life expectancy within more highly exposed segments of the population by several months to a few years; reductions in PM levels are associated with decreases in cardiovascular mortality within a time frame as short as a few years; and many credible pathological mechanisms have been elucidated that lend biological plausibility to these findings. It is the opinion of the writing group that the overall evidence is consistent with a causal relationship between PM2.5 exposure and cardiovascular morbidity and mortality. This body of evidence has grown and been strengthened substantially since the first American Heart Association scientific statement was published. Finally, PM2.5 exposure is deemed a modifiable factor that contributes to cardiovascular morbidity and mortality.

After extensive scientific review by the CASAC, the US EPA in 2009 published their new Integrated Science Assessment summarizing the state of the science about particulate air pollution. This new ISA was particularly focused on examining the evidence for causality of the relation of particles with various health effects, and drawing scientific consensus conclusions about that evidence. It is useful to summarize the rigorous and extensive review this process entails. The process begins with EPA using internal scientists and contracting with external, university scientists to write chapter of an Integrated Science Assessment (ISA), which summarizes the state of the science about the air pollutant, in our case particles. Draft chapters are

sent out to review by other external scientists, and discussed at public meetings with CASAC, where others are encouraged to provide comments. Based on the review by CASAC, EPA has the ISA revised, and brings it back for a second review. This process continues until the CASAC is satisfied, and approves the ISA, and its conclusions.

EPA then drafts a Risk Assessment and a Policy Document. The Risk Assessment's goal is to quantify risk to the extent consistent with the CASAC review of the ISA. This risk assessment is then put through the same review protocol as the ISA, and must be approved by CASAC to be used. The Policy Document, which summarizes the policy relevant science the in implications for potential standards, likewise goes through the same process. The ISA, as approved by the external Clean Air Scientific Advisory Board states:

> Epidemiologic studies that examined the effect of PM2.5 on cardiovascular emergency department (ED) visits and hospital admissions (HA) reported consistent positive associations (predominantly for ischemic heart disease [IHD] and congestive heart failure [CHF]), with the majority reporting increases ranging from 0.5 to 3.4% per 10 μg/m^3 increase in PM2.5. These effects were observed in study locations with mean1 24-h avg PM2.5 concentrations ranging from 7-18 μg/m^3 (Section 6.2.10), with effects becoming more precise and consistently positive in locations with mean PM2.5 concentrations of 13 μg/m^3 and above (Figure 2-1). Toxicological studies have provided biologically plausible mechanisms (e.g., increased right ventricular pressure and diminished cardiac contractility) for the associations observed between PM2.5 and CHF in epidemiologic studies. (p2-14)

and:

> There is also a growing body of evidence from controlled human exposure and toxicological studies demonstrating PM2.5-induced changes on markers of systemic oxidative stress and heart rate variability (HRV) (Section 6.2.1 and Section 6.2.9). Additional, but

> inconsistent effects of PM2.5 on BP, blood coagulation markers, and markers of systemic inflammation have also been reported across disciplines. Together, the collective evidence from epidemiologic, controlled human exposure, and toxicological studies is sufficient to conclude that a causal relationship exists between short- term exposures to PM and cardiovascular effects. (p 2-15)

and:

> Collectively, the studies evaluated demonstrate a wide range of respiratory responses, and although results are not fully consistent and coherent across studies the evidence is sufficient to conclude that a causal relationship is likely to exist between short-term exposures to PM2.5 and respiratory effects.

and:

> An evaluation of the epidemiologic literature indicates consistent positive associations between short-term exposure to PM2.5 and all-cause, cardiovascular-, and respiratory- related mortality (Section 6.5.2.2.). ....Collectively, the epidemiologic literature provides evidence that a causal relationship is likely to exist between short-term exposures to PM2.5 and mortality.

and:

> Evidence from toxicological studies provides biological plausibility and coherence with studies of short-term exposure and CVD morbidity and mortality, as well as with studies that examined long- term exposure to PM2.5 and CVD mortality. Taken together, the evidence from epidemiologic and toxicological studies is sufficient to conclude that **a causal relationship exists between long-term exposures to PM2.5 and cardiovascular effects.** (emphasis in original)

(Integrated Science Assessment for Particulate Matter. ISA: December 2009 EPA/600/R-08/139F).

Commenting on the ISA, the CASAC stated:

"CASAC also supports EPA's changes to the causal determinations for long-term exposure to PM2.5 and cardiovascular effects (from 'likely causal' to 'causal') and, "CASAC recommends 'upgrading' the causal classification for

PM2.5 and total mortality to 'causal' for both the short-term and long-term time frames" (EPA-CASAC-10-001 Letter to the Administrator).

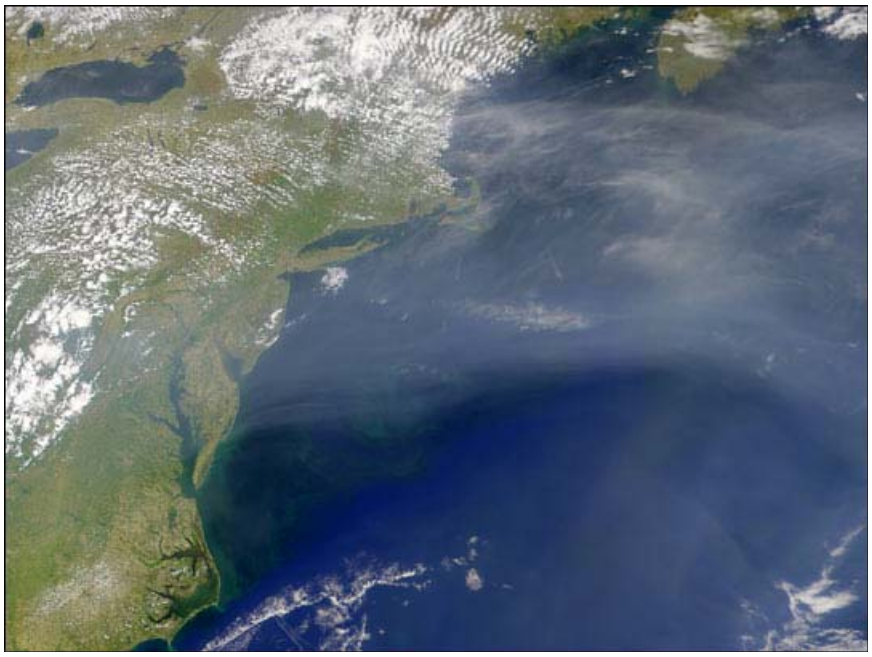
That is, CASAC has concluded that the association between PM2.5 and deaths is causal.

After reaching conclusions on the causality of the association of particles with early deaths, the US EPA presented the CASAC with a plan for doing a quantitative risk assessment, and after review, with a risk assessment for changing the ambient standard for particles, which was again approved by CASAC. As part of this process CASAC agreed that it was possible to quantify the early deaths that would be avoided by reducing particulate air pollution, a stance, as noted above, agreed by the European Union and the World Health Organization. In addition the U.S. National Academy of sciences report on Estimating the Public Health Benefit of Proposed Air Pollution Regulations supports that conclusion and specifically the use of the epidemiology studies to compute those estimates[1]. In summary, the scientific consensus is that particles cause early deaths, that reducing particle levels reduces early deaths, and that the association is strong enough to allow the reductions in early deaths to be quantified.

Particulate air pollution is not merely fatally dangerous, it is ubiquitous. The satellite picture below shows a particle haze obscuring the view of most of the eastern coast of the United States. In contrast, at the lower left of the image, one can see an area that has escaped the particle

haze, where the ground is clearly visible. Particulate air pollution is the only manmade object visible from space. And, especially in summer months, the largest single source is often sulfate particles from coal burning power plants.

The Only Manmade Object Visible from Space



Mortality

I find, as did the major scientific organizations, that there is clear, convincing evidence that exposure to particles shortens life expectancy by substantial amounts. I base this judgment on the extensive literature, as outlined below.

In 1970, Lave and Seskin published a paper regressing age standardized mortality rates in US cities against average particle

concentrations in those cities[2]. The advantage of that study was that the mortality experience of the entire population of each city was compared to the average particle concentration from the population- oriented monitors in the city. The difficulty was that no individual level covariates (i.e. other individual factors such as hypertension, diabetes, smoking, etc that may differ on average between the people in different cities, and might explain the differences between those cities in mortality rates) were controlled, raising questions about confounding (i.e. that another variable explains the observed association).

More recent studies have alleviated that problem by recruiting cohorts of individuals in various areas, and measuring those individual covariates. It is these new cohort studies, starting with the Harvard Six City Study, and including the American Cancer Society (ACS) study, the Women's Health Initiative study, the Nurses Health Study, etc, together with parallel findings for short term effects and in toxicology that lead CASAC to tell EPA to conclude that the association of particles with total mortality was causal. The EPA Integrated Science Assessment states:

"An evaluation of the epidemiologic literature indicates consistent positive associations between short-term exposure to $PM_{2.5}$ and all-cause, cardiovascular-, and respiratory-related mortality (Section 6.5.2.2.)…. Collectively, the epidemiologic literature provides evidence that **a causal relationship exists between short-term exposures to PM2.5 and mortality**. (p2-11, emphasis in original**)"**

and

"Collectively, the evidence is sufficient to conclude that **a causal relationship exists between long-term exposures to PM2.5 and mortality**.(p2-12, emphasis in original**).**

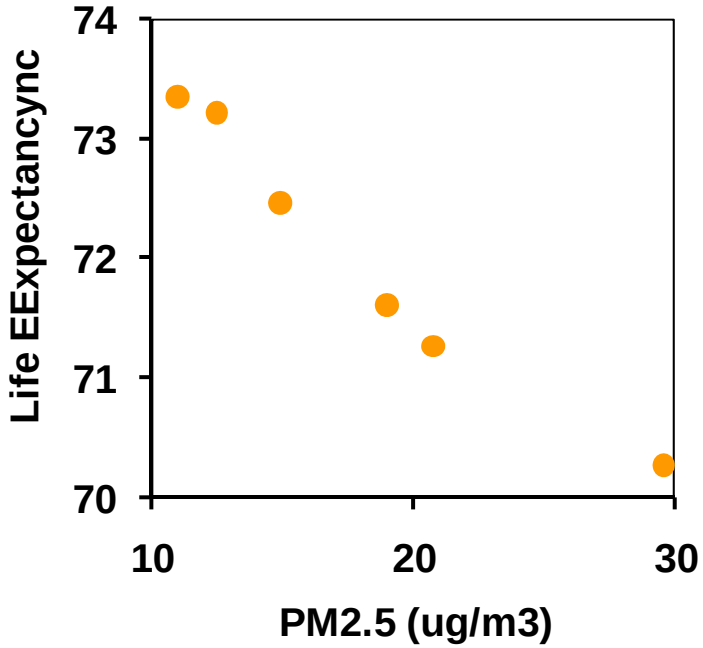
Below, I summarize the studies that supported that conclusion with emphasis on a set of issues, such as measurement error and confounding.

Measurement Error

An issue with most of those cohort studies is that they estimate community average pollution from monitors and assign the same exposure to everyone living in the same city. Because everyone's exposure in not, in fact identical, this is effectively error in assessing the exposure-health association, and likely to lead to an underestimate of the effect of exposure on mortality risk, which is the general result of such non-differential measurement error. In particular, in studies such as the American Cancer Society study some subjects could live as far as 100 miles from a monitor, adding considerable error to the exposure assignment for them.

These concerns apply to most of the cohort studies, with the obvious exception of the Six City Study[3]. The Six City Study chose a neighborhood within each city, recruited a **random** sample of that neighborhood, and put a population oriented particle monitor in the middle of each neighborhood. This means that the extra source of uncertainty, and extra downward bias, present in the other studies is reduced in the Six City Analysis, suggesting this study should be given greater consideration. The reduction in life expectancy with higher exposure to particles that the Six City Study found was substantial, as indicated in the figure below, which shows the life expectancy in each city, after adjusting for age, sex, cigarette smoking,

occupation, education, obesity, and chronic disease, plotted against the mean $PM_{2.5}$ in that city. To put this in perspective, between 1995 and 2005 life expectancy in the U.S. increased by 2 years. Hence, PM can obliterate the effects of one and a half decades of medical progress on life expectancy.



Further evidence that exposure error in the original ACS study and most cohort studies resulted in an underestimate of the effects of particles on deaths comes from a number of more recent studies. A reanalysis of the ACS study that only used monitors in the same county of residence of each subject to assign exposure (the original could assign subjects exposure from a monitor in a different county on the opposite side of the metropolitan area)[4].

That study found a substantially higher coefficient for the effects of sulfate particles on mortality than the original study. Even more intriguingly, another study examined only the 22,905 participants of the ACS study living in Southern California using a geographic information system based exposure model, which captures the local exposure gradient within Southern California, and reported even larger effect size estimates for $PM_{2.5}$[5]. Similarly, the Women's Health Initiative study found a larger effect on mortality when they used more local, within-city exposure estimates[6].

Another new cohort study examined over 66,000 nurses living in the Northeast and upper Midwest[7]. Unlike previous studies they used a spatial model that estimated individual exposures at the home address of each nurse, and found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ at the nurse's address was associated with a 26% increase in risk of dying in that year. As with other studies with better exposure estimates, this increase was considerably larger than that seen in studies that only looked at exposure differences across cities. Similar to my analysis of the Six City Study (see below), they found this increase was predominantly seen within a year of the change of exposure. This effect estimate is considerably higher than the Six City estimate, suggesting again the improved exposure results in higher estimates of the effects of particles on mortality.

Similarly, in the California Teachers Cohort study of Ostro results are reported using two exposure assignments. One analysis is restricted to

participants living within 8 km (5 miles) of the nearest monitor. The other used subjects living within 30 km (19 miles) of the nearest monitor. The extra measurement error entailed in using monitors farther away results in an reduction in the estimated effect of sulfate particles on mortality rates by 25%[8]. In that study, sulfate particles, the ones produced by coal burning power plants, were more statistically significant as predictors of mortality than $PM_{2.5}$.

Hence the use of more localized measures of exposure, with resultant lower exposure error, generally has resulted in larger effect estimates. That is, it is clear that the error in exposure by assigning air pollution in large areas to all subjects in that area is resulting in underestimates of the effects of particles. Consequently, estimates of early deaths avoided by reducing air pollution, using studies that relied on between city exposure differences, are almost certainly underestimates of the true health benefits.

Confounding

Studies that examine change in exposure play an important role in understanding the effects of particles for several reasons. First, if particle-induced changes in health are permanent, and we have to wait for a new generation before seeing public health improvements follow the exposure reductions, there are important public health implications. It certainly dramatically affects any cost-benefit analyses. Secondly, showing that a

change in exposure produces a change in response more directly addresses the causality of the association. If A causes B, then changing A will change B. Finally, cross-area comparisons between lung function, mortality rates, or any other response and cross-area variations in exposure across communities have the potential to be confounded by any unmeasured predictors of outcome that vary geographically (by confounder I mean another variable (e.g. smoking) that is causally related to the outcome, and correlated with exposure, which actually explains the observed association between, in our case, particles and outcome). That is, if we controlled for that other variable the association with particles would go away.

Naturally, epidemiology studies try to identify such variables and control for them. Equally importantly, the Six City Study went further, and showed the association of air pollution with life expectancy before and after controlling for each potential confounder, such as smoking, hypertension, diabetes, occupational exposures, obesity, etc. There was no evidence of confounding by any of the covariates examined except age. Another recent analysis, which extended the previous analyses of the ACS study to include more years and more data, included census tract level data on socioeconomic status based on where the participants lived. Importantly they also reported associations between sulfate particles, the type produced by coal burning power plants, and deaths from ischemic heart disease[9]. Interestingly, they

found that control for neighborhood socio-economic status increased the risk associated with sulfates, rather than decreasing it.

This provides some reassurance that confounding is unlikely. However, one cannot measure everything about a person's health, so it is always possible that such confounding exists. That is why it is important to look at multiple studies, and multiple study designs that have different potentials for such confounding.

For example, suppose there is an unmeasured health risk (say, smoking) in a cohort study that predicts mortality. For this to be a problem in the traditional analysis contrasting mortality rates across cities with air pollution across cities, smoking rates across cities would have to be correlated with particulate air pollution levels across cities. It is unclear why this would happen, but suppose this were also true in one study. Unless there is a *systematic process* that is inducing correlations between air pollution and smoking rates everywhere, another cohort study is unlikely to find the same problem. And why would the confounding remain if we only looked at differences in exposure and differences in mortality risk **within** a city, as in the new ACS analysis or the Nurse's Health Study or Women's Health Initiative analysis? And if there was something about the U.S. social structure that made that true in U.S. cities, why would that still be true in the Netherlands, with a very different social structure, where within city variations in particles were also associated with variations in the risk of

death? It is hard to see how those same unmeasured confounders could apply in all the cases above.

One other way to assure that the observed association is real is to conduct studies not merely in different locations, and across different scales of geography, but in different ways, including where exposure varies by time, and not geographic location. Examinations of year to year changes in exposure within location do not suffer the potential confounding that, as above, some unmeasured confounder may differ from one city to another or even from neighborhood to neighborhood within city. These cannot be correlated with exposure that only varies from year to year within city. Other variables, which do vary from year-to-year, might confound, but are unlikely to be the same as the potential confounders of the cross-sectional associations. Hence, if associations are seen using this very different study design as well, it provides greater confidence that the associations are causal.

Consequently a key finding for cohort studies of mortality has come from studies examining *changes* in exposure and *changes* in mortality rates. Most of the cohort studies, including the original Six City Study, have contrasted a measure of long-term exposure with long-term survival. They tell us that people live less long in more polluted cities. They do not, directly, tell us what mortality reduction accompanies a reduction in exposure. In a follow-up of the Harvard Six City Study, Laden and coworkers provide precisely that estimate[10]. They examined a further 10 years of follow-up and

mortality in the six cities. In some cities there was a substantial drop in pollution between the first and second follow-up periods, in some cities there was a moderate drop, and in some cities there was little or no change. The mortality rate ratios followed the same pattern: where there was a substantial drop in pollution there was a substantial improvement in life expectancy; where there was little change in pollution concentrations there was little change in life expectancy. The slope for *change* in exposure and *change* in death rate was similar to, but slightly higher, than the cross-sectional slope.

Again, if the mortality rates change within a town as the air pollution changes, and those changes fit on the same dose-response curve as the original cross-sectional association, this provides substantial assurance that the association is not confounded, because the factors that are likely to confound an association of temporal change are usually different from those that might confound a cross-sectional study, and there is no reason for the confounding of two different estimates by different confounders to produce similarly sized estimated effects for particles.

This conclusion is also supported by natural experiments. Pope and coworkers reported that mortality fell in the Utah Valley in the year a strike closed a steel mill, and returned to its previous level the next year when mill operations resumed[11].

The finding of a rapid change in mortality risk associated with change in particle exposure in the Six City Study fits nicely with the similar report for lung function from the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) study[12].

Another recent study examined changes in life expectancy across 51 metropolitan areas in the United States, between 1980 and 2000. They found that 15% of the *increase* in life expectancy during that period came from *decreases* in air pollution, and that in the more polluted cities that cleaned up, life expectancy was increased by 10 months[13].

Recently, the study of Zanobetti and Schwartz examined over 190,000 subjects discharged alive from hospitals following myocardial infarctions (heart attacks)[14]. They looked at year-to-year changes in exposure **within** cities related to the probability of surviving that year, given the participant was alive on January 1. They adjusted for long-term time trend, and did separate analyses within each of 21 cities. They then combined the results across cities. This approach does not allow any differences in exposure across a city to contribute to the association (which is only examined *within* the city), does not allow similarities in long term trends in mortality and air pollution to contribute to the association, and again focuses on year to year temporal changes in particles and mortality. Hence, as in the Six City analysis above, the set of potential confounders is quite different from those in a traditional cohort study. They reported a significant association with

PM_{10} in this susceptible subgroup; they also found larger coefficients (the slope between exposure and mortality risk) than were seen in the Six City Study. A follow-up study looking at people with chronic bronchitis and emphysema in the same manner found a similar result[15].

Another study in a similar vein was the work of Janke and coworkers[16]. They looked at 354 local governmental units in England. They look at annual mortality rates for multiple years in each location, controlling for *location and local time trend*. In effect they are looking at whether random deviations from year to year in air pollution around the local means and local time trend are correlated with random deviations in mortality rates around the local mean and local time trend. Such a design leaves little room for confounding. They found a strong association with particulate air pollution.

This approach of looking at year to year changes in mortality rates and air pollution fits in quite well with developing studies looking at shorter term exposure to air pollution (discussed in the section on acute effects below), that have extended their ambit from looking at immediate effects of the last few day's exposure to include months of exposure. I examined the association of daily deaths[17] and hospital admissions[18] with particles when averaged over different periods, from days to months, after filtering out seasonal and long term trends. I found that the size of the PM effect increased as one went from days to periods of up to two months. At that point, the effect size estimates

seemed intermediate between those reported in classical time series, which looked at yesterday's exposures, and those reported in the cohort studies.

A frequency domain regression approach by Zeger and coworkers showed similar results[19]. In several studies, Zanobetti and coworkers examined the time course of the mortality–death relationship directly, using distributed lag models[20, 21]. These models showed a pattern concordant with my hypothesis. There was an immediate increase in deaths following an increase in particle exposure, followed by a long tail of slightly increased deaths, stretching out for 40 days after the initial response. Time series studies by their nature have to control for season, and this makes it difficult to examine lags longer than a month or two, but the substantial increase in effect size reported by Zanobetti in these studies again suggests that the short term and long term responses to changes in airborne particles fall on a continuum.

Further support for this theory comes from recent studies looking at pregnancy outcomes and infant mortality. Both responses, by definition, involve exposures of less than a year. For example, Bobak and Leon examined the cross–sectional association between air pollution and infant mortality rates across towns in the Czech Republic[22, 23]. A significant association was seen with particle concentrations. Woodruff and coworkers compared infant death rates in US cities with their levels of PM in the air[24]. They excluded infant deaths in the first month after birth as likely to reflect

complications of pregnancy and delivery, and found that PM_{10} was associated with higher death rates in the next 11 months of life. This excess risk seemed to be principally from respiratory illness, although sudden infant death syndrome deaths were also elevated. Further studies in later years, and looking at $PM_{2.5}$ confirmed this association[25, 26].

Dose Response and Threshold

A critical issue is whether a threshold exists for the effects of particles, and more broadly, what is the shape of the dose response curve. After its recent reviews of the literature, EPA has concluded there is no evidence for a threshold. For example, the Regulatory Impact Analysis for the Transport Rule, states:

"Based on our review of the current body of scientific literature, EPA estimated PM related mortality without applying an assumed concentration threshold. EPA's Integrated Science Assessment for Particulate Matter (U.S. EPA, 2009b), which was recently reviewed by EPA's Clean Air Scientific Advisory Committee (U.S. EPA-SAB, 2009a; U.S. EPA-SAB,2009b), concluded that the scientific literature consistently finds that a no-threshold loglinear model most adequately portrays the PM-mortality concentration-response relationship while recognizing potential uncertainty about the exact shape of the concentration-response function." (EPA 2011, p 192).
This issue was extensively peer reviewed by the CASAC, which concurred with the conclusion that there is no evidence for a threshold.

"Although there is increasing uncertainty at lower levels, there is no evidence of a threshold (i.e., a level below which there is no risk for adverse health effects)."(EPA-CASAC-10-015, letter of 9/10/2010 to the Administrator of EPA).

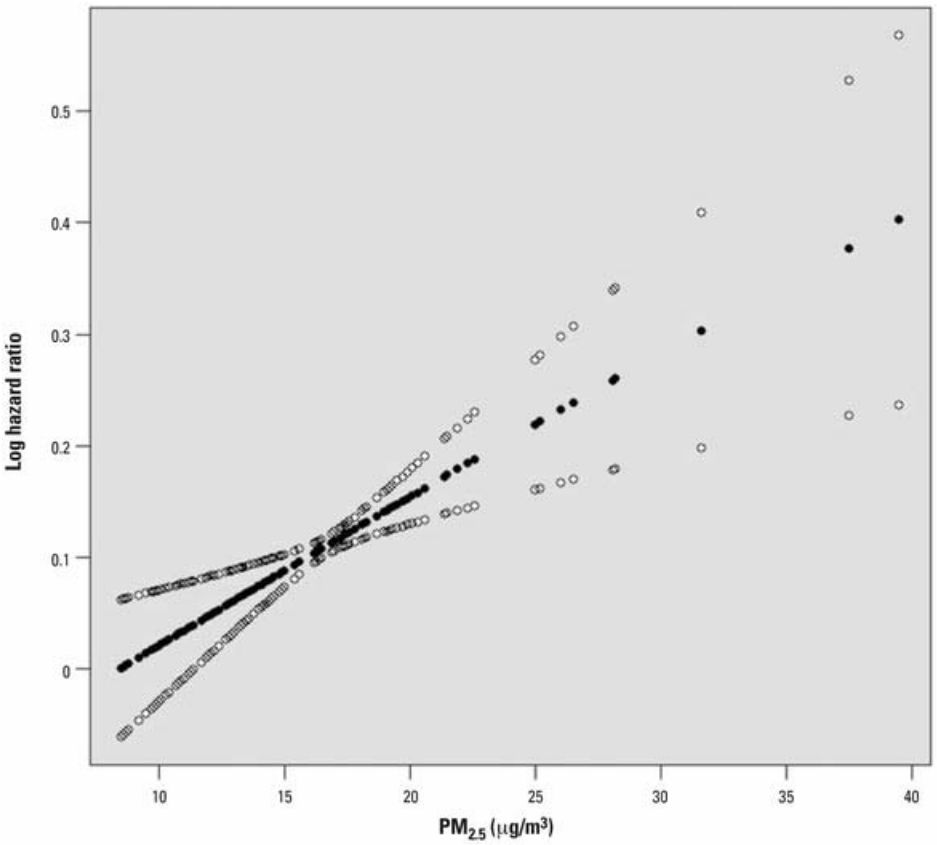
Similarly, the EPA Policy Assessment, also reviewed and approved by CASAC, stated:

"We note that no discernible thresholds have been identified for any health effects associated with long or short-term PM2.5 exposures." (p ES-1)

The National Academy of Sciences concurs, stating[27], "For pollutants such as PM_{10} and $PM_{2.5}$, there is no evidence for any departure of linearity in the observed range of exposure, nor any indication of a threshold". This is also the view of the World Health Organization.

The Office of Management and Budget asked EPA, as part of its risk assessment process, to conduct an expert elicitation on the dose-response relation between particles and deaths, and have it reviewed by EPA's external review body, the Science Advisory Board. This is a well-established process in Decision Science, and in this case involved having an outside contractor select experts in the field, obtain from them the studies each thought were most relevant to the issue and making sure all the experts had seen all the studies, and then conducting a structured 8 hour interview with each expert separately. In addition to review by the Science Advisory Board, this analysis was also published in a peer review journal. Part of this process addressed the question of a threshold. As noted in EPA's Expert Elicitation Report, 11 out of 12 reviewers believed there was neither evidence nor even a theoretical basis for a threshold. The remaining reviewer thought there was a

50% probability of a threshold, but that if it existed, there was an 80% probability that it was below 5 μg/m^3. There are no counties in the US with annual average concentrations that low, rendering such a threshold moot. It is easy to see why they reached this conclusion. For example, in another follow-up analysis of the Six City Study I looked at year-to-year changes in particle concentrations to examine two questions—does the dose-response continue below 15 μg/m^3; and what is the lag between change in exposure and change in mortality rate[28]. We used a penalized spline with up to 18 degrees of freedom (essentially, a polynomial with 18 terms to capture any deviation from linearity), showed that the association was essentially linear down to 8 μg/m^3, where the data becomes sparse, and that the effects of reduced particle exposure on mortality appear to be mostly seen within two years. The figure below shows that association.



Because the uncertainties around the dose-response curve from fitting a particular model do not reflect the uncertainty in model choice we also used model averaging, where 32 models are fit explicitly, and averaged, weighted by their probability of being correct given the data[28]. These models explicitly included the possibility of thresholds at multiple different particle concentrations. The association was again indistinguishable from linear with no evidence of a threshold down to the lowest measured level of 8 μg/m^3. Similarly, Pope and coworkers used nonparametric smoothing to look at the association of PM2.5 and mortality in the ACS cohort, and the association was linear from 15 μg/m^3 down to the lowest observed levels (which were also about 8 μg/m^3)[29].

Generalizability

Each cohort study selected people in different ways, an all were living in urban areas. This could raise questions about the generalizability to rural areas. More recently an innovative study modernized the Lave and Seskin approach to address this. They looked at over 2300 counties in the Eastern US, and used remote satellite sensing data to estimate $PM_{2.5}$ concentrations everywhere. The satellite data allows the incorporation of the many counties without monitoring. This allowed them to include thousands of counties, rather than hundreds. The examined the entire population of each county, avoiding any selection issues. They reported that standardized mortality rates for ischemic heart disease were associated with $PM_{2.5}$, in the Eastern US, a region of the country where sulfates from coal burning power plants are a major source of $PM_{2.5}$[30].

The association between airborne particles and mortality implies a very large public health impact. For example, the Laden paper suggests that an average 5 $\mu g/m^3$ decrease in $PM_{2.5}$ concentrations in the US would be associated with a 5-10% decrease in total mortality, which is 100,000-200,000 fewer deaths per year. **For comparison, the lower bound estimate is more deaths than from AIDS, breast cancer, and prostate cancer combined**.

While the association between exposure to particulate matter (PM) mass and mortality is well established, there remains uncertainty as to whether certain chemical components of PM are more harmful to human health than others. To date the evidence is not convincing that any form of fine combustion particles are more or less toxic than average, with different studies showing different results. It is important to understand that the conclusion (of the Clean Air Scientific Advisory Committee and others) that we cannot differentiate the toxicity of different types or sources of particles does not mean that we believe it likely that one type of source of particles will ultimately prove to be the "toxic agent". Rather, the consensus scientific opinion is that all fine combustion particles are toxic, although they may vary in their toxicity. There have been time series studies in locations, such as Santa Clara, CA, in the winter, where wood smoke is the dominant source of particles, that show significant associations with daily deaths[31, 32]. There are studies in locations such as Philadelphia where secondary sulfate particles are the major source, which again show day to day changes in air pollution are associated with day to day changes in deaths[33-36]. In Sao Paolo, Brazil, where traffic particles are the major sources, again, particles are associated with increased deaths[37, 38]. While we have not yet distinguished the relative effects of different sources of particles, it is clear that they all contribute to early deaths.

In the absence of good evidence that any source or type of particle had a *different* impact, CASAC recommended maintaining a standard for $PM_{2.5}$, that is, treating particles from all sources as having the *same* toxicity.

Sulfates are the principal particle type generated by coal burning power plants. Cohort studies such as the Six City Study and the ACS Cohort have reported that sulfates were associated with decreases in long term survival[3, 29].

Sulfates have also been associated with increases in mortality in time series studies of acute exposure, including Mar et al who found increased total and cardiovascular mortality associated with a regional sulfate factor in Phoenix[39], suggesting that the impact of sulfates is not only an east coast phenomenon.

While epidemiologic studies generally do not have the strength of an experimental design, the study of Pope and coworkers is an exception to that rule[40]. They looked at a natural experiment. A copper smelter strike in the Southwest between 15 July 1967 and early April 1968 shut down all the smelters in the region. During that period, smelters accounted for the large majority of the sulfate particles in these southwestern states. As reported by Trijonis and Yuan (1978) and Trijonis (1979) this strike led to significant reductions in sulfate particles in the Southwest, with an average decrease of 60% during the 8.5 month strike, which was equivalent to a reduction of approximately 2.5 $\mu g/m^3$ in mass concentration. This natural experiment

really is equivalent to a randomized trial. The population of the downwind states had no choice in the matter—they were exposed to higher, lower, and higher sulfate concentrations over time, just as in a crossover trial for a drug. Nor did they even have a perception that their exposure was changed, since sulfate concentrations are not a routinely monitored criteria air pollutant, and there was little public attention to air pollution in this period.

Pope and coworkers analyzed this natural experiment to see how mortality rates change in response to the change in sulfate concentrations. After controlling for time trends, mortality counts in bordering states, and influenza/pneumonia deaths; they found that the 2.5 $\mu g/m^3$ decrease in sulfate particle concentrations resulted in a 2.5% decrease in the number of deaths in the four-state region. This unambiguously establishes secondary sulfate particles as a cause of early death.

In comparison, a 2.5 $\mu g/m^3$ decrease in long term average $PM_{2.5}$ concentrations in the American Cancer Society Cohort study was associated with about a 1.5% decrease in deaths, whereas in the Harvard Six City Cohort, the same decrease was associated with a 4% reduction in deaths. Hence this natural experiment not only shows that sulfate particles kill people, its effect size is consistent with the long term studies of mortality from following cohorts. This has two implications. First, it again suggests that there is no reason to believe that sulfate particles are less toxic than average. Second, it shows that the reductions in mortality from reducing air

pollution do not take years to show up, they occur within the first year. If additional reductions would have occurred in subsequent years, then this study underestimates the health benefits of reducing sulfate particle levels.

O'Neill et al found an association between real outdoor sulfate particles and endothelial dysfunction[41,] and Chuang found sulfate increased oxidative stress and coagulation in a panel study[42]. Sulfate particles were also associated with disturbances in electrocardiogram patterns in studies of repeated measurements in two different populations of elderly adults[43, 44]. The positive sulfate effects observed in epidemiological studies may be attributable to the greater complexity of the sulfate particles in ambient air than the simple ammonium sulfate particles which are often used in toxicological studies, but are not often found in nature. For example, acid sulfate in the form of sulfuric acid or ammonium bisulfate can convert insoluble metal oxides (also present in ambient particulate pollution) to bio-available sulfate salts, and studies of particles collected in Washington DC have shown that much of the metal content was associated with sulfates. Metals on particles in turn have been linked to a wide variety of toxic responses. For example, toxicologic studies show Zinc sulfate to have cardiotoxicity.

Recently, Franklin and coworkers used data from the PM speciation network to examine this question further[45]. Because particle components, including sulfates, were only monitored 1 day in 3 or 1 day in 6, while $PM_{2.5}$

was monitored daily, they used a two stage approach. Taking advantage of the natural variation in PM components between cities, and between seasons within city, they fit season specific regressions in each of 25 cities with speciation monitors, in each season. In a second stage, they examined how the association between $PM_{2.5}$ and daily deaths was modified by the ratio of sulfate to particle mass, and similarly for the other measured components. If sulfates have a different toxicity than average for particles, then one would expect that a city where a high fraction of total particles were sulfate would have a different slope than a city with a low fraction. We found a significant overall effect of $PM_{2.5}$ with total mortality. Cities with high fractions of sulfate, arsenic (also a tracer of particles from coal burning power plants), silicon, and nickel had roughly twice the mortality slope as cities with low fractions. When multiple components were considered simultaneously, sulfate, nickel, and aluminum remained significant, and explained all of the apparent variation in effect estimates across cities and seasons.

A new analysis of the ACS study by Krewski and coworkers examined the extended follow-up period for the ACS, and looked at sulfate particles as well as all PM2.5.[9] Interestingly, they found a stronger effect for sulfates. They report that after controlling for the maximum number of individual and area based potential confounders that a 10 $\mu g/m^3$ increase in sulfate levels was associated with a 9% increase in death rate if they used as exposure sulfate levels two years before the cohort was recruited, and a 17% increase

in death rates when they used sulfate levels from 1990, roughly the midpoint of the follow-up of the cohort. These sulfate effects were larger than the effect for $PM_{2.5}$ in that study. Similarly, in the California Teachers Cohort study of Ostro, which was described before, sulfate particles were more statistically significant as predictors of mortality than $PM_{2.5}$.

Conclusions

The EPA Regulatory Impact Assessment for the Transport rule estimates that the pollution controls it requires will save 13,000 deaths per year based on the ACS study, and 34,000 deaths per year based on the Laden study. As noted above, recent studies have reported larger coefficients than either of these two studies, and the Laden study is not a high estimate, but rather a mid-range estimate. This conclusion is also endorsed by CASAC. In their review of the risk assessment for the new NAAQS for particles they stated:

> Based on quantifiable sensitivity analysis, the report generally clearly conveys that the "core" estimates appear to be at the low end of alternative "plausible" estimates.

Indeed using the sulfate coefficient from the most recent analysis of the ACS study would result in an estimate 50% larger than the estimate based on the Laden study. Hence is clear that this rule will save tens of thousands of lives each year, and probably many tens of thousands of lives

each year. There are very few government policies that have such a large public health impact, and the cost per life saved is quite low compared to most other policies. This policy should be implemented as soon as possible.

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