

**EPA CENTER FOR AMBIENT PARTICLE HEALTH EFFECTS
AT HARVARD SCHOOL OF PUBLIC HEALTH**

PROGRESS REPORT : YEAR FIVE

THEME I: ASSESSING PARTICLE EXPOSURES FOR HEALTH EFFECTS STUDIES

Project Ia: Assessing Human Exposures to Particulate and Gaseous Air Pollutants

A central research objective of this project has been the examination of relationships between ambient particles and gases and corresponding personal exposures. During the fifth year, we continued our analysis of data from the Boston and Baltimore panel studies. Pooling results from both locations, we assessed whether the contribution of ambient particles on personal exposures varied by city, season and cohort. No cohort effect was found on the attenuation factors, which suggests that subjects from each cohort (i.e., seniors, children, COPD patients) were exposed to the same fraction of ambient PM_{2.5}, given the same concentrations of ambient PM_{2.5}. A manuscript (Brown et al.) detailing these findings is currently being prepared for publication.

In a recent paper, we analyzed data from a Baltimore multiple pollutant exposure assessment to examine the role of ambient pollutant concentrations in PM_{2.5} epidemiologic models (Sarnat et al 2001). Since the Baltimore analysis was the first to examine relationships between personal exposures and ambient concentrations for PM_{2.5} and gaseous pollutants, it was important to conduct a similar analysis for other cities. During Year 5, we conducted an analysis including personal exposure and ambient concentration multi-pollutant data from the Boston panel study. Results from the Boston analysis, which includes both data from Baltimore and Boston (Figure 1 shows a summary of the results from both locations), provide further evidence that the ambient gaseous pollutant concentrations are better surrogates of personal PM_{2.5} exposures, especially personal exposures to PM_{2.5} of ambient origin, than their respective personal exposures. These findings suggest that using ambient gas concentrations in multiple-pollutant health effects models along with PM_{2.5} may not be appropriate, since both the ambient gaseous and PM_{2.5} concentrations are serving as surrogates for PM_{2.5} exposures. In addition, the robustness of these findings was demonstrated by using various analytical methods and model structures. A manuscript entitled, "Relationships among Personal Exposures and Ambient Concentrations of Particulate and Gaseous Pollutants and their Implications for Particle Health Effects Studies," is currently in press at Epidemiology.

Project Ib: Quantifying Exposure Error and its Effect on Epidemiological Studies

We have developed new methods to correct for measurement error in hierarchical models (Schwartz and Coull 2003). We showed that existing standard two-stage estimators will be biased in the presence of exposure measurement error, and that this bias can be away from the null hypothesis of no effect. We proposed two alternative methods for estimating the independent effects of two predictors in a hierarchical model. We applied the new methodology to show that the estimated effect of fine particles on daily deaths, independent of coarse particles, was downwardly biased by measurement error in an original analysis that did not correct for measurement error. We also used the methods to estimate the effect of gaseous air pollutants on daily deaths. The resulting effect size estimates were very small and the confidence intervals included zero. Finally, we have also applied this approach to a reanalysis of the NMMAPS mortality study conducted by Johns Hopkins. A paper reporting this NMMAPS re-analysis is now under review.

Also, using data from multi-pollutant exposure studies in Boston and Baltimore, simulations were conducted to assess the feasibility of health risks attributed to gases and particles (Schwartz et

al., in preparation). Results provided evidence that the gaseous pollutants are unlikely confounders of PM health risk estimates for these locations.

Spatial-Temporal Modeling of Exposure

We are currently developing spatial-temporal models of spatially-varying exposures, such as traffic pollution, in the Boston area. Given a good model for exposure, this approach yields more accurate measures of spatially heterogeneous exposures than central site monitoring, and allows examination of longer averaging times than the limited personal exposures. This approach can decrease the amount of measurement error associated with the central-site measurements and in turn yield more powerful tests of health effects. A paper (Gryparis et al.) describing the methodology and results of this analysis is currently under preparation.

Quantifying Model Uncertainty in Epidemiological Analyses

A criticism of existing PM epidemiologic analyses is the multiple sources of uncertainty involved in obtaining health effect estimates. One key uncertainty is the shape of the concentration-response relation. Another is estimating how long one would have to wait after lowering pollution before the health improvements arrive. That is, are the associations with twenty-year average exposures, which will change slowly, or are they with recent exposures?

We have examined the use of Bayesian model averaging as a way of addressing these two forms of model uncertainty in a reanalysis of the Six Cities study. This approach avoids relying on an effect estimates from a single "final" model, which ignores uncertainty associated with model choice and thus can underestimate the variability associated with these effect estimates, but rather takes a weighted average of estimates from a range of plausible models. We implemented this approach to average over plausible models for the dose-response relationship of PM, as well as the lag structure in the model. Preliminary results suggest that the dose-response curve is approximately linear and the strongest lagged effects occur during the current year (i.e. lag 0) and the immediately preceding year (i.e. lag 1). A paper describing the analysis (Schwartz et al.) is currently under preparation.

Project Ic: Differentiating Health Effects of Particles from Outdoor and Indoor Sources

We completed laboratory analysis and data processing of collected exposure and health data from three exposure and cardiovascular health studies conducted in Atlanta, GA, Steubenville, OH, and St. Louis, MO, all of which were co-sponsored by the Center. Analyses of the data are currently being finalized, with papers for these studies being drafted and revised. For the Atlanta and Steubenville studies, papers on the ability of ambient concentrations to reflect exposures are currently undergoing internal review. Similarly, a paper on the association between ambient pollutant exposures and heart rate variability is being prepared for the Atlanta study, while a paper on the association between ambient air pollution and arrhythmias is currently being prepared for the Steubenville cohort. For the St. Louis study, analysis of the effect of ambient and micro-environmental exposures on exhaled NO is currently underway. We expect these papers to be submitted to a peer-reviewed journal by the end of this summer.

We are repeating the analysis of indoor and outdoor particle toxicity performed by Long et al., (2001) using data collected inside and outside 16 homes located in Atlanta, GA. As before, toxicity was assessed using in vitro bioassays of TNF alpha production. Sample collection, laboratory analysis, and data processing have been completed, with data analysis currently underway.

THEME II: IDENTIFYING POPULATIONS SUSCEPTIBLE TO THE HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

Project IIa: Examining Conditions which Predispose Towards an Acute Adverse Effects of Particulate Exposures

Identification of populations that are especially susceptible to PM health effects can further our understanding of biologic mechanisms of heart and lung disease attributable to PM. Our previous research has shown that individuals with diabetes are at higher risk from exposure to PM. We have published several papers addressing this issue. A recent examined effect modification by concurrent diagnosis of diabetes overall and by age group in four US cities and found that individuals with diabetes have twice the risk of a PM10-associated cardiovascular admission compared to those without the disease. (Zanobetti & Schwartz, 2002)

To further examine susceptibility by diabetes observed in these population studies, we obtained clinical information to gain insights on potential biological mechanisms. With researchers at the Joslin Diabetes Center and Beth Israel/Deaconess Hospital, we analyzed the relationship between air pollution and both inflammation and vascular reactivity in over 200 greater-Boston residents participating in clinical trials. We used particle data (PM2.5, particle number (PN), black carbon (BC), and sulfate (SO₄²⁻)) measured at the HSPH site established by the PM center. Both black carbon and sulfate particles appeared to have effects on vascular reactivity and endothelial function, especially among people with diabetes. (O'Neill, M.S., Veves, A., Zanobetti, A., Sarnat, J.A., Gold, D.R., Economides, P.A., Horton, E., Schwartz, J. (2004) Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Submitted to *Circulation*.) Additional analyses have shown associations between increased particle levels and blood markers of inflammation, including ICAM-1, VCAM-1, and von Willibrand's factor, and manuscripts are in preparation.

We have continued to explore factors influencing vulnerability to temperature-related mortality.

Data on air pollution compiled for PM center projects have been used to control for confounding. In a study of seven U.S. cities, lower educational attainment, black race, and dying outside a hospital were markers of vulnerability to death on extreme temperature days, controlling for PM10 exposure. (O'Neill, M. S., et al., 2003). In a follow-up analysis, we found that air conditioning prevalence explained some of the observed racial disparities in heat-related mortality in four of these cities. (O'Neill, M.S., Zanobetti, A., Schwartz, J. Disparities by race in heat-related mortality in four U.S. cities: The role of air conditioning prevalence. In review at *Journal of Urban Health*). An additional analysis found that air pollution and epidemics were important confounders of temperature and mortality associations and suggested inclusion of PM10, ozone, and epidemic periods in future analyses which can be used in forecasting health impacts of climate change. (O'Neill, M.S., Hajat, S., Zanobetti, A., Ramirez-Aguilar, M., Schwartz, J. Impact of control for air pollution and respiratory epidemics on the estimated associations of temperature and daily mortality. Submitted to the *International Journal of Biometeorology*.)

The case-crossover approach was also used to examine the PM10-associated risk of emergency hospitalization for myocardial infarction during 1985-1999 among elderly residents of twenty-one US cities. Results from this study showed increased risk of hospitalization for myocardial infarction for diabetics. Effect sizes were roughly doubled in persons with COPD or concurrent pneumonia compared to those without (Zanobetti et al., 2004).

During the past year, we examined the association of PM2.5 and changes in blood markers of cardiovascular risk, including lipid profiles and markers of acute systemic inflammation, in the PRINCE study, a large, national randomized trial on the use of statins to lower such risk factors.

In the Placebo group we found associations between PM2.5 and CRP total cholesterol and LDL. For the same outcomes the associations were not significant in the group taking statins (Zanobetti et al 2004).

Project IIb: Assessing Life-Shortening Associated with Exposure to Particulate Matter

We continued analyses investigating harvesting in 10 European cities by examining all cause, respiratory, and cardiovascular deaths, for all ages and stratifying by age groups. Our study confirms that most of the effect of air pollution is not simply advanced by a few weeks, and that effects persist for over a month after exposure. We found that the effect size estimate for PM10 doubles when we considered longer term effects for all mortality and cardiovascular mortality and becomes 5 times higher for respiratory mortality. We found similar effects when stratifying by age groups (Zanobetti et al. 2003).

A great deal of work was due to the re-analysis of all previous studies that used Generalized Additive Models to assess PM health outcomes. In particular, recent work has shown that current approaches misestimate the standard errors of parametric terms when controlling for smooth functions, and this has raised questions about the entire approach. In addition to re-analyzing these data using different convergence criteria and natural splines, we have developed alternative approaches including the penalized spline method (Zanobetti & Schwartz 2003c). The results of the re-analysis didn't change substantially from previously reported results. (Schwartz et al. 2003, Zanobetti & Schwartz 2003b, Zanobetti & Schwartz 2003c)

Project IIc: Investigating Chronic Effects of Exposure to Particulate Matter

We have followed up the Six Cities Study cohort in an effort to assess the cumulative effect of long-term exposures on the incidence of lung cancer, nonmalignant respiratory disease, cardiovascular disease, and cause-specific mortality. More specifically, vital status was determined for the 8111 participants in the Harvard Six Cities adult cohort for an additional nine years of follow-up (1990-1998). We identified 1430 additional deaths bringing the total to 2737 deaths.

Survival analyses of all-cause mortality shows that life expectancy continues to be reduced in the more polluted cities, with the survival relative ranking being the same as that observed in the original study. Monitoring of PM2.5 and PM10 was included as part of the original study, but it was not continued in the more recent period of follow-up. Therefore, we have been modeling PM2.5 for this time period using data from nearby monitors in the EPA Air Quality System (AQS) monitoring network. A paper showing a decrease in the relative risk from mortality consistent with decreased air pollution levels in specific cities is under preparation by Laden et al. This paper, as well as one under preparation by Schwartz et al., also focuses on the effect of yearly changes in PM2.5.

THEME III: BIOLOGICAL MECHANISMS AND DOSIMETRY

Project IIIa: Differentiating the Roles of Particle Size, Particle Composition and Gaseous Co-Pollutants on Cardiac Ischemia.

The main aim of this project is to investigate the effects of concomitant gaseous co-pollutants, particle size, and particle composition. To date, a large number of animal exposure studies have been completed. These studies have been totally or partially funded by the Center. In this fifth year of the grant, our focus has been on completing experiments, data analysis, presenting results at meetings, and preparing manuscripts.

Over the last year, we have focused our efforts on completing a complex experiment on the effects of concentrated air particles (CAPs) and carbon monoxide (CO) on arrhythmia incidence in a rat model of myocardial infarction. These results were recently presented at the annual

meeting of the American Thoracic Society and a manuscript detailing the results has been accepted for publication in Toxicological Sciences. We have previously shown that inhalation exposure to combustion-derived PM increases the incidence of ventricular arrhythmias in rats with a recent myocardial infarction (Wellenius et al. 2002). However, it is unknown whether exposure to ambient PM would elicit the same response. Additionally, numerous studies have found an association between short-term increases in ambient CO levels and increased risk of cardiovascular morbidity (Burnett et al. 1997; Morris et al. 1995; Schwartz 1997; Schwartz and Morris 1995; Yang et al. 1998) and mortality (Hoek et al. 2001; Mar et al. 2000). Ambient levels of CO may confound or modify the PM-arrhythmia association observed in epidemiologic studies, but this hypothesis has not been evaluated in a controlled setting. Accordingly, the goal of this study was to examine the cardiac effects of exposure to ambient PM and CO, individually and in combination, in a rat model of myocardial infarction.

To evaluate these effects, left-ventricular myocardial infarction was induced in Sprague-Dawley rats by thermocoagulation. Diazepam-sedated rats were exposed (1h) to either filtered air (n=40), CO (35 ppm, n=19), concentrated air particles (CAPs, median concentration=350.5 $\mu\text{g}/\text{m}^3$, n=53), or CAPs and CO (CAPs median concentration=318.2 $\mu\text{g}/\text{m}^3$, n=23), 12-18h after surgery. Each exposure was immediately preceded and followed by a 1h exposure to filtered air (pre-exposure and post-exposure periods, respectively). The CO target dose of 35 ppm is related to the 1h US National Ambient Air Quality Standard. Surface electrocardiograms were recorded and heart rate and arrhythmia incidence were quantified. Contrary to our initial hypothesis, we found that CO exposure reduced ventricular premature beat (VPB) frequency by 60.4% ($p=0.012$) during the exposure period compared to control animals exposed to filtered air. This effect was modified by both the infarct type (transmural vs. subepicardial) and the number of pre-exposure VPBs (<4 vs ≥ 4), and was not mediated through changes in heart rate.

Overall, CAPs exposure increased VPB frequency during the exposure period, but this effect did not reach statistical significance. The increase in arrhythmia incidence was not significantly associated with CAPs mass concentration, CAPs number concentration, or the mass concentration of any specific component of CAPs that we measured. This effect was modified by the number of pre-exposure VPBs. Overall, CAPs had no effect on heart rate, but CAPs was associated with increased heart rate in specific subgroups. No significant interactions were observed between the effects of CO and CAPs. We conclude that in this animal model, the cardiac responses to CO and CAPs are distinctly different. In epidemiologic studies, it is often suggested that cardiac effects attributed to ambient PM actually represent effects of ambient CO instead. The results of this study suggest that it is unlikely that arrhythmogenic effects associated with ambient PM exposure are actually attributable to ambient CO instead.

Although less common, atrial arrhythmias were also observed in these experiments. Therefore, we have begun to evaluate the effects of CAPs and CO on atrial arrhythmias using these data. Preliminary results indicate that atrial responses to CAPs and CO are also distinctly different.

Additionally, we have begun collecting new experimental data to evaluate the effect of CAPs and ozone, individually and in combination, on cardiac arrhythmias. This new series of experiments overcomes some of the limitations of our past experiments by using radiotelemetry devices to monitor the electrocardiogram (as opposed to surface electrodes). This change in approach allows us to avoid the use of a sedative and provides for longer exposure times and pre- and post-exposure monitoring.

Project IIIb: Studies of Oxidant mechanisms of air particulate

Dr. González-Flecha and her colleagues have completed and published a study confirming the role of oxidants in the inflammatory response to CAPs in adult rats (Rhoden et al., 2003). The experimental protocol included exposures to filtered air (Sham) or CAPs aerosols (CAPs, 5 hours exposure, average mass concentration: $1100 \pm 300 \text{ g}/\text{m}^3$) in the presence or absence of 50 mg/Kg N-acetyl cysteine (NAC). BAL, tissue and blood samples were collected 24 hours after

exposure. The results of this study show a dramatic increase of PMN number in BAL as a result to CAPs exposures. This increase was mediated by oxidants, since pre-administration of NAC effectively prevented PMN influx into the lung. Additional recent data support our hypotheses that CAPs promotes oxidant-mediated cardiac dysfunction and that sympathetic activation after CAPs deposition in the lung is critical for CAPs cardiotoxicity. Adult Sprague-Dawley rats were treated with the 1-adrenoreceptor antagonist atenolol or saline prior to exposure to urban ambient particles (UAP, SRM 1649, 750 g/Kg). 30 min after UAP instillation the animals were anesthetized and assayed immediately for cardiac levels of oxidants (in situ chemiluminescence: CL). Tissue samples were collected and assayed for edema. Intratracheal instillation of UAP led to significant increases in heart oxidants and edema. -blockage by atenolol effectively prevented cardiac oxidative stress and damage. These observations were confirmed in a model of inhalation exposure to CAPs. Studies will continue in this important area in the coming year.

Project IIIc: Relating Changes in Blood Viscosity, Other Clotting Parameters, Heart Rate and Heart Rate Variability to Particulate and Criteria Gas Exposures

The Normative Aging Study (NAS) is a prospective cohort study of veterans living in the Boston area, enrolled between 1963 and 1968. Approximately 1200 active participants of this cohort are examined at the Boston Veterans Affairs (VA) Hospital on an every 3 to 5 year basis. During exams, height, weight blood pressure, cholesterol, fasting blood glucose, and standard blood parameters are measured. Cigarette smoking, alcohol consumption, medical history and conditions, and subjects' use of medications were assessed by questionnaire.

Since the year 2000, in collaboration with VA researchers, the PM Center has funded heart rate variability (HRV) measurements on the participants during their routine exams, as well as analysis of the inflammatory markers C-reactive protein (CRP) and the clotting factor fibrinogen in the blood. The CRP and fibrinogen analyses were conducted in addition to the standard blood analyses. Measurements of approximately 700 individuals have been completed to date.

Among 506 of the participants, we found an association between both PM_{2.5} and ozone and reduced HRV. Other pollutants showed few significant or consistent associations with HRV. The associations between both PM_{2.5} and reduced HRV were much stronger among participants with hypertension. Those with coronary heart disease also had stronger associations between HRV and PM_{2.5}. A manuscript (Park, S.K., et al., 2004) O'Neill, M.S., Vokonas, P.S., Sparrow, D., Schwartz, J. (2004)

In addition to pollutant associations with HRV, we were interested in examining associations by source region of the air. We used wind field model output from the National Oceanic and Atmospheric Administration (NOAA) and the Hybrid Single-Particle Lagrangian Integrated Trajectory (HYSPLIT) model to identify the sources of air over Boston on different days. The HYSPLIT model calculates 'back trajectories' showing the path of air parcels before they arrive in Boston during the 36 hours prior to the time of the subjects exam at the VA. In collaboration with Barbara Stunder of NOAA, we used factor analysis methods to cluster these trajectories by source region, and analyzed their association with heart rate variability. In preliminary analyses, we found that trajectories from the Northwest, which was associated with high concentrations of copper and zinc on PM filters, but not particularly high mass concentrations, was most strongly associated with decreases in heart rate variability. A manuscript, Park, S.K., et al. "Source location of air pollution and cardiac autonomic function," is currently in preparation.

In a preliminary analysis, we examined the effects of several pollutants (BC, PN, and PM_{2.5}) on the inflammatory markers and blood parameters measured among 701 subjects between 2000 and 2003. We examined the short term and latent effects of several pollutants (BC, PN, and PM_{2.5}) in intervals of time between 0 hour and one month before the blood measurement. C-reactive protein and fibrinogen were elevated in association with BC concentrations 48 hours, and a week before the measurement, and cholesterol increased with one month lagged exposures. A manuscript (Zeka, et al.) is currently in preparation.

Updated Harvard PM Center reference list - sorted by theme and project

THEME I: ASSESSING PARTICLE EXPOSURES FOR HEALTH EFFECTS STUDIES

Project Ia: Assessing Human Exposures to Particulate and Gaseous Air Pollutants

Janssen, N. A. H., Schwartz, J., Zanobetti, A., & Suh, H. (2002). Air Conditioning and Source-Specific Particles as Modifiers of the Effect of PM10 on Hospital Admissions for Heart and Lung Disease. *Environmental Health Perspectives*, 110, 43-49.

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Project Ib: Quantifying Exposure Error and its Effect on Epidemiological Studies

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Project Ic: Differentiating Health Effects of Particles from Outdoor and Indoor Sources

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THEME II: IDENTIFYING POPULATIONS SUSCEPTIBLE TO THE HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

Project IIa: Examining Conditions in the Elderly which Predispose Towards an Acute Adverse Effect of Particulate Exposures

Bateson, T., & Schwartz, J. (2001). Selection Bias and Confounding in Case-Crossover Analyses of Environmental Time Series Data. *Epidemiology*, 12, 654-661.

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Project IIb: Assessing Life-Shortening Associated with Exposure to Particulate Matter

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