Air Pollution and Blood Markers of Cardiovascular Risk

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Recent studies have linked air pollution to tens of thousands of premature cardiovascular deaths per year. The mechanisms of such associations remain unclear. In this study we examine the association between blood markers of cardiovascular risk and air pollution in a national sample of the U.S. population. Air pollution concentrations were merged to subjects in the Third National Health and Nutrition Examination Survey (NHANES III) in the United States, and the association with fibrinogen levels and counts of platelets and white blood cells were examined. The subjects in NHANES III are a representative sample of the U.S. population. Regressions controlled for age, race, sex, body mass index, current smoking, and number of cigarettes per day. The complex survey design was dealt with using mixed models with a random sampling site effect. In single-pollutant models, PM$_{10}$ (particulate matter with a mass median aerodynamic diameter less than 10 µm) was associated with all three outcomes ($p < 0.05$): Sulfur dioxide (SO$_2$) was significantly associated only with white cell counts, nitrogen dioxide (NO$_2$) with platelet counts and fibrinogen, and ozone with none of the outcomes. In two-pollutant models, PM$_{10}$ remained a significant predictor of white cell counts controlling for SO$_2$ but not vice versa. PM$_{10}$ was marginally significant in a model for platelet counts with NO$_2$, and the sign of the NO$_2$ coefficient was reversed. These results were stable with control for indoor exposures (wood stoves, environmental tobacco smoke, gas stoves, fireplaces), dietary risk factors (saturated fat, alcohol, caffeine intake, n-3 fatty acids), and serum cholesterol. The magnitude of the effects are modest [e.g., 13 µg/dL fibrinogen for an interquartile range (IQR) change in PM$_{10}$, 95% confidence interval (CI) 4.6–22.1 mg/dL]. However, the odds ratio of being in the top 10% of fibrinogen for the same IQR change was 1.77 (95% CI 1.26–2.49). These effects provide considerable biologic plausibility to the mortality studies. PM$_{10}$, but not gaseous air pollutants, is associated with blood markers of cardiovascular risk, and this may explain epidemiologic associations with early deaths. Key words: air pollution, blood markers, cardiovascular disease, PM$_{10}$ — Environ Health Perspect 109(suppl 3):405–409 (2001).

The London smog episode of December 1952 resulted in approximately 4,000 excess deaths due to air pollution (1). Although the greatest relative increase in mortality was for respiratory causes, the majority of the excess deaths were from cardiovascular disease (1). However, most air pollution research in the next several decades focused on the respiratory effects of air pollution.

Beginning in the late 1980s, numerous studies reported associations between air pollution (principally particulate air pollution) and daily deaths in cities in the United States, Europe, Latin America, and Asia (2–4). The elevations in risk in these studies were much lower than in London in the 1950s, as were the particle concentrations, but because the exposures associated with the elevated risks occurred daily, the attributable number of early deaths appeared substantial. In addition, the majority of the excess deaths were cardiovascular (5,6). More recently, studies have reported that air pollution was associated with hospital admissions for heart disease (7–9), including myocardial infarctions. Another set of studies examined the location of deaths associated with air pollution. In 1994, Schwartz (10) reported that the greatest relative increase in pollution-associated deaths in Philadelphia, Pennsylvania, USA, was for “dead on arrival” deaths. In a more recent study, Schwartz examined the association between PM$_{10}$ (particulate matter with a mass median aerodynamic diameter less than 10 µm) and daily deaths in 10 U.S. cities and reported air pollution was primarily associated with deaths out of the hospital (11). These are mostly sudden deaths, many of which are due to arrhythmia and myocardial infarctions.

In the last 5 years, attention has focused on how air pollution can affect cardiovascular disease. One possibility is that pollution could induce arrhythmia. Animal studies have shown that urban combustion particles can produce reductions in heart rate variability that are risk factors for sudden death (12) and death from arrhythmia (13). Recently, three papers reported airborne particles were associated with decreases in heart rate variability (14–16). Another recent paper reported nitrogen dioxide (NO$_2$) and PM$_{2.5}$ (particulate matter with aerodynamic diameter less than 2.5 µm) were associated with defibrillator discharges due to ventricular arrhythmias in patients with implanted cardioverter defibrillators (17). Increased heart rate has also been associated with airborne particles (18,19). These findings suggest compromised autonomic control of the heart may play a role in the cardiovascular toxicity associated with particles.

Daily time-series studies have also indicated that particulate air pollution is associated with deaths (2) and hospital admissions for myocardial infarctions (7). Seaton et al. (20) have proposed that particles may increase pulmonary inflammation, possibly penetrate into the bloodstream, interact with platelets, and trigger systemic increases in coagulability and other risk factors for acute myocardial infarctions. Recently, Peters and co-workers reported an air pollution episode and daily variations in air pollution were associated with increased plasma viscosity (21). Gardner and colleagues reported increases in fibrinogen in animals exposed to urban particles (22). Human volunteers exposed to concentrated air particles also have increased levels of plasma fibrinogen (25). In addition, a recent controlled human exposure study found exposure to diesel particles for 1 hr at 300 µg/m$^3$ resulted in increased levels of peripheral neutrophils (24). Similar results were reported in rats exposed to concentrated air particles (25). In contrast, Seaton et al., in a longitudinal study of 131 subjects, have recently reported that PM$_{10}$ was negatively associated with plasma fibrinogen, and not associated with white blood cells (26). Increased levels of fibrinogen and neutrophil counts have been associated with coronary heart disease (27). This includes associations with sudden death (28) and myocardial infarction (29). In addition, elevations of fibrinogen are associated with inflammatory changes such as neutrophil activation (30). Studies of such intermediate end points are critical for better understanding how airborne particles might be affecting cardiovascular health. This article examines the association between air pollution and several such intermediate biomarkers of cardiovascular risk in a national sample of subjects chosen to be representative of the U.S. population.
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Data and Methods

Health Data

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted between 1989 and 1994. NHANES III is a stratified random sample of the U.S. population, with oversampling for minorities. Black Americans and Mexican Americans each separately represent 30% of the NHANES III sample. (Some sampled persons are members of both subgroups.) NHANES III also oversampled the elderly. Persons 60 years of age and older represent 20% of the sample but only 16% of the population. The NHANES III sample is equally split by gender. NHANES III was conducted in two phases, each sampling approximately 20,000 subjects in 44 communities. Each phase included individuals representative of the U.S. population. This analysis is restricted to subjects sampled in the first phase.

Subjects were seen in their homes by trained interviewers, and extensive medical history and demographic data were collected. The subjects then visited mobile medical examination centers, where they were examined. Blood specimens for a complete blood count, including platelets, were analyzed at the medical examination center using a Coulter S Plus Jr. The remaining blood was placed in appropriate vials stored under appropriate refrigerated (4–8°C) or frozen (–20°C) conditions until they were shipped to analytical laboratories for testing. Fibrinogen was stored in a 2-mL blue vial. The analytical methods used by each of the participating laboratories are described in Laboratory Procedures Used for NHANES III (31). The outcomes of interest in this study were fibrinogen levels, platelet counts, and white cell counts.

Air Pollution Data

Air pollution data was obtained from the Aerometric Information Retrieval System (AIRS) (http://www.epa.gov/air/data/databases.html) of the U.S. Environmental Protection Agency. AIRS contains information on all of the routine pollution monitoring in the United States. Pollution exposure was assigned to subjects on the basis of geocoding. Each participant in NHANES III was assigned the latitude and longitude of the population centroid of the census block group in which they lived. Block groups are collections of adjoining blocks with populations of 500–1,000 persons. The latitude and longitude of each monitor in the United States was obtained from AIRS. Persons were assigned exposure values equal to the weighted average of all monitors in their county of residence and adjoining counties, with weights proportional to the inverse of the square of the distance between their residence and the monitor. The use of all monitors in the county of residence and adjoining counties allowed geographic variability in exposure within area to be reflected in the exposure measures. This is more important for some pollutants (such as NO₂) more spatially heterogeneous than others (such as ozone). A recent study has shown that within-city variability in NO₂ is associated with pulmonary function (32). Exposure values were computed for the day of examination. Exposure the day before the examination was also considered. As subjects were examined for about 6 weeks in each study area, this provided considerable within-area spatial and temporal variability in exposure.

The air pollutants collected for this study were PM₁₀, sulfur dioxide (SO₂), NO₂, and ozone (O₃).

Statistical Analysis

The NHANES III was a not a simple random sample. Blacks and Hispanics were oversampled to provide sufficient numbers to allow separate analyses of health parameters in those groups. However, the exact probability of being selected was computed for each participant, and from that sampling, weights were computed. The use of weighted statistical analyses provides estimates representative of the U.S. noninstitutionalized population.

For sampling convenience the sampling strategy first selected 44 counties in the United States, then subjects within those counties. Because of regional differences in ethnicity, diet, and other factors, all of which may not be perfectly controlled for in a given analysis, the residuals of two persons chosen from the same county are likely to be more alike than the residuals from two persons randomly chosen from different locations. That is, there tends to be correlation with the sampling units. Mixed models, which allow for regression analyses with a covariance structure assuming a common correlation within these sampling units, provide proper standard error estimates for the regression parameters under these circumstances. This analysis used PROC MIXED in SAS (SAS Institute, Cary, NC, USA), with a random effect for each location in the survey, assuming a compound symmetry covariance structure. The final examination weights were also used. For estimates of the proportion of the population with high fibrinogen levels (or high white cell or platelet counts), I used PROC GENMOD to fit logistic regressions, with generalized estimating equations and an exchangeable covariance structure.

All regression analyses controlled for age, ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanics, and others), body mass index, a dummy variable for current smoker, cigarettes per day, and sex. PM₁₀, SO₂, NO₂, and O₃ were examined as potential predictors of the three outcome variables in single-pollutant models. If more than one pollutant was a significant predictor of an outcome in those models, multipollutant models were examined.

Sensitivity Analysis

To examine the potential of other variables to confound the association, I took two approaches. First, I examined the effect estimates for air pollution in models with and without all of the potential confounders added to the baseline model one at a time. Then, for each outcome, I identified all the covariates that were marginally significant (p < 0.10) when added singly to the baseline model. The pollution models were then reestimated with all of these covariates included simultaneously. The potential confounders fell into four categories: social risk factors, dietary risk factors, other indoor exposures, and other cardiovascular risk factors.

Social risk factors. One issue raised about previous reports of associations between particulate air pollution and daily deaths in two recent prospective cohort studies (33,34) was that they did not control for socioeconomic status or diet. If air pollution was correlated with these factors, they might have the potential to confound air pollution associations. I used the number of years of education of the subject, the poverty income ratio (the ratio of household income to the city specific poverty level), and their household size as indicators of social status, and examined their potential to confound the association.

Dietary risk factors. If persons in locations of high air pollution are more likely to eat an unhealthy diet, this might also confound the association. To examine whether diets that are potential risk factors for ischemic heart disease were confounders, I used dietary intake of saturated fat, alcohol consumption, and caffeine intake (defined as the sum of the average daily cups of caffeinated coffee plus half the number of daily cups of caffeinated tea). To examine dietary factors that might be protective for ischemic heart disease, I used dietary intake of fish and shellfish (as a proxy for n-3 fatty acid intake) and serum levels of vitamin C.

Other exposures. Recent studies have shown that outdoor concentrations of airborne particles are reasonable surrogates for personal exposure to particles of outdoor origin (34,35), but that there are substantial exposure to particles from indoor sources. As these particles have different chemical compositions as well as sources, they are best thought of as other exposures. If they are correlated with outdoor particle concentrations...
and with outcome, they may confound the association with the outdoor pollutant. We had variables that provided at least some assessment of many of the major indoor sources. For environmental tobacco smoke, we had an indicator variable for passive smoking in the home, as well as a serum cotinine measurement. We also had indicator variables for use of a wood stove, use of a gas stove, and use of a fireplace.

Other ischemic risk factors. The other major risk factors for ischemia we examined were systolic blood pressure, total serum cholesterol, and serum high-density lipoprotein cholesterol.

Results

Air pollution data were available only for subjects who resided in urban areas, and all pollutants were not monitored in each area of the United States during the study period. In addition, PM$_{10}$ was not measured every day in most locations, so the number of individuals with PM$_{10}$ measurements was substantially less than for the other pollutants. Table 1 shows, for each of the pollutants, the mean, standard deviation (SD), interquartile range (IQR), number of sampling locations for which measurements were available, and number of persons with measurements. Variation in exposure was due to three factors. First, persons were seen in each sampling location over about a 6-week period, providing temporal variation in exposure. Second, exposure levels differed across the 44 locations. Finally, the use of geocoding allowed different persons examined on the same day in the same city to be assigned different exposure values based on the estimated concentrations where they lived.

Table 2 shows the descriptive statistics for other data used in the analysis. Table 3 shows results of the initial analyses for air pollution. After controlling for age, race, sex, body mass index, and smoking, PM$_{10}$ was associated with all three outcomes. Platelet counts and plasma fibrinogen were associated with NO$_2$, and white cell counts with SO$_2$ in single-pollutant models. In two-pollutant models, only PM$_{10}$ continued to show a positive association with the three outcomes.

Table 4 shows the results of the sensitivity analyses for PM$_{2.5}$ that investigated a wide variety of potential confounders. The PM$_{10}$ results were quite robust to inclusion of these terms. In general, the effects of the potential confounders were not even consistent, raising the PM$_{10}$ effect estimates for some outcomes, but lowering them for others. The final model, using all covariates with even marginal associations with the outcomes simultaneously, further confirms the robustness of the results.

To put these results in context, Table 5 shows the relative odds of a high level of fibrinogen (426 mg/dL, the 90th percentile of the distribution for fibrinogen in this population), high platelet count (364, also the 90th percentile), and high white cell count (10, again the 90th percentile) associated with an IQR increase in PM$_{10}$.

Discussion

I found significant, consistent associations between PM$_{10}$ and the three cardiovascular risk factors examined. In contrast, no consistent associations were found for the gaseous pollutants. Unfortunately, carbon monoxide data were not matched to subjects in this study, so nothing can be said about that pollutant. Moreover, the odds ratios in Table 5 for the risk difference between the highest and lowest quartile of exposures in the United States were substantial.

These findings contrast with those of Seaton and co-workers (26), who reported a negative association between PM$_{2.5}$ concentrations and plasma fibrinogen in a panel study of 131 subjects in Edinburgh, Scotland. However, they are consistent with the results of a controlled human exposure study.
Table 4. Sensitivity analysis of effect of PM$_{10}$ on cardiovascular risk factors in blood: NHANES III.

| Covariate                  | Fibrogen | Platelets | White cells |
|----------------------------|----------|-----------|-------------|
| None (baseline)            | 0.514 (0.172) | 0.316 (0.111) | 0.0062 (0.0036) |
| Social factors             |          |           |             |
| Poverty ratio              | 0.387 (0.185) | 0.270 (0.119) | 0.0059 (0.0029) |
| Education (years)          | 0.481 (0.173) | 0.309 (0.114) | 0.0056 (0.0026) |
| Household size             | 0.516 (0.173) | 0.315 (0.113) | 0.0061 (0.0026) |
| Other exposures            |          |           |             |
| Wood stove                 | 0.518 (0.173) | 0.315 (0.115) | 0.0058 (0.0026) |
| Fireplace                  | 0.516 (0.173) | 0.317 (0.114) | 0.0062 (0.0026) |
| Gas stove                  | 0.532 (0.174) | 0.289 (0.118) | 0.0056 (0.0027) |
| Environmental tobacco smoke at home | 0.514 (0.172) | 0.312 (0.114) | 0.0062 (0.0026) |
| Serum cotinine             | 0.495 (0.174) | 0.365 (0.116) | 0.0064 (0.0023) |
| Dietary factors            |          |           |             |
| Serum vitamin C            | 0.500 (0.176) | 0.342 (0.115) | 0.0059 (0.0027) |
| Fish and shellfish         | 0.518 (0.172) | 0.320 (0.115) | 0.0062 (0.0026) |
| Saturated fat              | 0.508 (0.175) | 0.357 (0.117) | 0.0061 (0.0025) |
| Caffeine                   | 0.523 (0.173) | 0.306 (0.113) | 0.0062 (0.0026) |
| Alcohol                    | 0.505 (0.176) | 0.411 (0.115) | 0.0082 (0.0025) |
| Cardiovascular risk factors |          |           |             |
| Systolic blood pressure    | 0.540 (0.173) | 0.310 (0.113) | 0.0066 (0.0025) |
| Serum cholesterol (total)  | 0.502 (0.172) | 0.353 (0.115) | 0.0062 (0.0025) |
| Serum high density lipoprotein | 0.488 (0.172) | 0.356 (0.114) | 0.0063 (0.0025) |
| Final model$^a$            | 0.476 (0.173) | 0.383 (0.115) | 0.0074 (0.0025) |

$^a$Baseline model plus all covariates univariately associated with the outcome with $p < 0.10$.

Table 5. Relative odds for being above the 50th percentile for fibrogen, platelet count, and white cell count associated with an IQR increase in PM$_{10}$.

| Outcome                  | Odds ratio | 95% CI |
|--------------------------|------------|--------|
| High fibrogenogen        | 1.77       | 1.26, 2.49 |
| High platelet count       | 1.27       | 0.97, 1.67 |
| High white cell count     | 1.84       | 1.17, 2.39 |

study that reported increases in plasma fibrogenin (35), as well as with the animal study (22). While further results will be necessary to sort out the conflicting reports in epidemiologic studies, the weight of the evidence suggests that airborne particles are associated with increases in fibrogenin.

Likewise, Seaton and co-workers (26) did not find increases in white cell counts, whereas Salvi and colleagues (24) reported increases in peripheral neutrophils following controlled human exposures to particles. Our results confirm the report of Salvi and co-workers and extend it to the general population and substantially lower exposure levels.

One important result of this study is the examination of confounding by indoor sources of pollution. Some have criticized the use of outdoor air pollutants because they do not incorporate those indoor exposures. However, there are important differences between environmental tobacco smoke, for example, and particles of outdoor, ambient origin. No evidence has ever been presented to demonstrate that these pollutants are the same or have the same health effects. Hence, it is more appropriate to treat them as two pollutants and ask whether the indoor exposures are confounders for the outdoor exposures. This study, on a nationally representative sample of the U.S. population, suggests this is not the case. Neither measures of indoor particle sources (wood-burning stoves and fireplaces, environmental tobacco smoke), nor measures of indoor NO$_x$ exposures (gas stoves) appeared to confound the associations reported here. Given the representativeness of the sample, this suggests other large cross-sectional studies of the association between particle exposure and health effects, such as the American Cancer Societies CPS II study (29), are also unlikely to be confounded. These results are also consistent with the recent exposure work of Sarnat and co-workers (36). Using personal exposure monitors, they were able to estimate exposure to particles of ambient origin and of indoor origin in several cohorts. No correlation between the two measures was found.

Socioeconomic confounding has been posited as a possible explanation for some previous cross-sectional findings, such as the Six City Study reports (37) of associations between air pollution and life expectancy. The results from this study do not support that hypothesis. The NHANES III had detailed information on income, as well as social factors such as years of education, and these variables did not produce a major perturbation in the air pollution associations. Similarly, dietary risk factors do not seem to be important confounders of the association between air pollution and risk factors for ischemic events.

One important caveat for this study involves the implications of the outcome measures. Fibrogenin and white blood counts have been associated with increased risk of cardiovascular mortality in prospective cohort studies. In those studies a one-time measurement of these risk factors was taken as a measure (with error) of the longer-term levels in each subject and associated with longer-term risk. This study reports associations between short-term exposure to particles and fibrogenin and other risk factors. The extent to which short-term fluctuations in fibrogenin levels result in short-term fluctuations in cardiovascular risk is unclear.

What this study does provide, however, is evidence that particulate air pollution can influence important circulatory parameters that are risk factors for adverse events in some circumstances. Such changes could not occur if particles, constituents of particles, or chemical messengers resulting from particle exposures were not passed from the lung to the circulation. Such changes imply that important cardiovascular factors can be modified by airborne particles at commonly occurring concentrations. This provides considerable biologic plausibility for the associations reported in previous epidemiologic studies.

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