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An Analysis of the American Cancer Society Cohort Linking Specific Chemical Constituents of Air Pollution to Mortality

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AN ANALYSIS OF THE AMERICAN CANCER SOCIETY COHORT LINKING SPECIFIC CHEMICAL CONSTITUENTS OF AIR POLLUTION TO MORTALITY

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the degree of Master of Science in Epidemiology

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ABSTRACT

Air pollution is an important determinant of population health. The World Health Organization estimates that air pollution is responsible for nearly 2% of all deaths globally. The current research is aimed at determining the specific components of air pollution that are most likely linked to increased risk of mortality. Since one air pollutant is unlikely to be emitted by itself, various mixtures of air pollutants must be investigated. It is possible that the health effects of one pollutant in the mixture might be larger than the health effects of another. The current research focuses on the relationship between multiple air pollutants and mortality in the general population. By examining combinations of pollutants, it is possible to isolate, to a certain extent, the effects of individual pollutants.

The population health outcomes investigated include mortality from cardiopulmonary conditions, lung cancer, and all causes combined. Air pollution data from various metropolitan regions in the U.S. were linked to the health outcomes of individuals living in these areas. Characteristics of individuals that may affect the relationship between air pollution and mortality, such as age, sex, smoking history, alcohol use, were obtained from the American Cancer Society Cancer Prevention Study II cohort. Nearly 1.2 million adults were enrolled in this study in 1982, and have been followed up on an on-going basis. This study suggests that sulfate and, more broadly, fine particulate matter may be the most important contributors to excess risk of all-cause, cardiopulmonary, and lung cancer mortality.

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C. LIST OF ACRONYMS, ABBREVIATIONS, AND OTHER TERMS

ACS	American Cancer Society
AIRS	Aerometric Information Retrieval System
APHEA	Air pollution and Health: a European Approach
AQS	Air Quality System
BMI	Body mass index
CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic Obstructive Pulmonary Disease
CPS-II	Cancer Prevention Study II
DNA	Deoxyribonucleic acid
EPA	U.S. Environmental Protection Agency
HNO_3	Nitric acid
H_2SO_4	Sulfuric acid
H_2O_2	Hydrogen peroxide
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD-9	International Classification of Diseases, Ninth Revision
IPMN	Inhalable Particle Monitoring Network
MSA	Metropolitan statistical area
NAAQS	National Ambient Air Quality Standards
NAD	National Aeromatic Database
NAD(P)	Nicotinamide adenine dinucleotide phosphate
NERAM	Network for Environmental Risk Assessment and Management
NH_3	Ammonia
NH_4^+	Ammonium
NH_4HSO_4	Ammonium bisulfate
NMMAPS	National Mortality, Morbidity, and Air Pollution Study
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
O_3	Ozone
OHREB	Ottawa Hospital Research Ethics Board
$PM_{(n)}$	Particulate matter (< n micrometers in mean aerodynamic diameter)
ppb	Parts per billion
ppm	Parts per million
RR	Relative risk
SAS	Statistical Application Software
SO_2	Sulfur dioxide
SO_4^{2-}	Sulfate
SO_x	Sulfur oxides
TNF	Tumor necrosis factor
UV	Ultraviolet
WHO	World Health Organization
ZCA	Zip code area

1. INTRODUCTION

The current study is a further examination of the effect of long-term exposure of individual chemical constituents of ambient air pollution on mortality based on longitudinal data from the American Cancer Society (ACS) Cancer Prevention Study (CPS) II cohort (Krewski et al., 2000; Pope et al., 2002; Krewski et al., 2008). The majority of previous epidemiological research has centered on the effects of short-term exposures to air pollution. However, it has been suggested that long-term exposure may be more important in terms of public health (Pope & Dockery, 1999). The estimated effect of particulate air pollution increases with length of exposure periods (Schwartz, 2000; Zanobetti et al., 2002).

In the past, relevant studies generally separate the air pollution mixture's components in analyzing their adverse effects. Individual components of air pollution have been measured and then regression techniques have been used to characterize the independent effects of the components on population health. Results of single pollutant analyses may be difficult to interpret since the sum of the "impact" of each pollutant grossly overestimates the contribution of air pollution to mortality (Kunzli, 2002). Even though the air pollution/mortality relationship has been extensively studied using epidemiologic methods, there is still a need to characterize the independent and synergistic effects of the components of the complex mixture of air pollutants to which we are exposed on mortality. When considering the potential effects of mixtures, it is possible that certain agents within the mixture interact, potentially introducing synergism.

This synergism may lead to mortality outcomes that could not be predicted solely by the effects of individual components (Samet, 1995).

This study seeks to further our understanding of the specific causes of increased mortality associated with ambient air pollution. Air pollution continues to be an important environmental health issue (Craig et al., 2008). The World Health Organization (2002) estimates that particulate air pollution is responsible for nearly 2% of all deaths worldwide. A need to "advance understanding of the toxicity-determining characteristics of particulate matter as well as the role of gaseous co-pollutants [in air pollution]" and to "characterize the health effects of complex mixtures in the atmosphere" was addressed in the most recent Network for Environmental Risk Assessment and Management (NERAM V) colloquium (Craig et al., 2008).

A previous study by Krewski et al. (2000) used fine particulate matter ($PM_{2.5}$) as the primary measure of ambient pollution, relating $PM_{2.5}$ to various mortality outcomes in the general population using a random effects version of the Cox survival model. In fact, the great majority of recent studies linking air pollution to mortality concentrate on fine particles as the major contributor to mortality. However, the question remains as to what are the specific effects of the other major air pollution constituents on mortality, especially in combination with multiple major air pollutants. Rather than focus exclusively on $PM_{2.5}$, the current study considers the effects of six major air pollutants - $PM_{2.5}$, O_3, SO_2, SO_4^{2-}, NO_2, and CO_2 - separately and in combination on mortality. (These pollutants represent the so-called 'criteria pollutants', for which National Ambient Air Quality Standards have been established in the United States (EPA, 2008).) In the current study, we examine all-cause, cardiopulmonary and lung cancer mortality as the

population health outcomes of primary concern in relation to exposure to ambient air pollution.

The results of the current study could have important implications for air quality risk management policy (Craig et al., 2008). Even though air pollution is a well-known population health issue, further and more precise assessment of the constituents associated with health effects leads to more effective air quality management policies and strategies. The current research addresses pressing knowledge gaps in the current scientific literature and provides further guidance as to which pollution controls can most effectively address air pollution health risks.

This study focuses on the contribution of six important air pollution constituents ($PM_{2.5}$, SO_4^{2-}, O_3, NO_2, CO, and SO_2) to all-cause, lung cancer, and cardiopulmonary mortality based on data from the ACS CPS II cohort. The major objectives of the proposed study are:

1) to determine the relationships between the combined exposures to six major air pollutants and mortality with an adjustment for confounding effects, and
2) to evaluate the effect of previously unused ecological covariates available for the year 1990 on pollutant exposure/mortality relationships.

In addition, secondary objectives of the study were:

3) to assess effect modification by education level; and
4) to consider spatial autocorrelation by performing a sensitivity analysis using random effect Cox models.

This study begins with a literature review (Chapter 2). The literature review begins with an overview of the major studies on air pollution and health, which is

followed by a summary of the sources and biological effects associated with each pollutant investigated. The methods are presented next in Chapter 3. In this chapter, background information is provided on the study population, metropolitan areas under study, air pollution exposure measurements, ecological covariates, methodology behind individual covariate selection, and finally, the approaches taken for the statistical analysis. Results of the statistical analyses are presented in detail in the following section (Chapter 4). An interpretation of the findings, including further literature analysis, is provided in Chapter 5 - the discussion. Included in the discussion are the in-depth analyses of the results for each of the multiple pollutants (5.1), the study limitations, including limitations related to air pollution mixtures (5.2a), exposure data (5.2b), individual covariates (5.2c), and ecological covariates (5.2d). A separate section outlining the effect of educational attainment on air pollution and mortality is included subsequently (5.3). Hill's causal criteria in relation to air pollution and mortality are used to summarize the findings of the current study and are discussed in section 5.4. The overall conclusions of the present study are detailed in section 5.5. Finally, the references are listed (Chapter 6) and the original questionnaires used to obtain information on individual confounders are included in the appendix (Chapter 7).

2. LITERATURE REVIEW

Air pollution has a significant impact on population health. It is estimated that ambient air pollution causes about 3 % of mortality worldwide from cardiopulmonary disease, about 5 % of mortality from cancer of the trachea, bronchus, and lung, and nearly 1 % of acute respiratory infections in children under 5 years of age. Air pollution is estimated to responsible for 0.8 million premature deaths and 6.4 million years of life lost around the globe (Cohen et al., 2005). The Ontario Medical Association estimates that in Toronto alone, air pollution accounts for 1,700 premature deaths annually (Penegelly & Sommerfreund, 2004).

The notion that air pollution may be related to health and premature mortality was introduced in 1952 with the occurrence of the great London fog event in London, England. Stagnant weather conditions caused the concentration of air pollutants in the area to increase sharply. As a result, over three times as many people died than expected over a period of several days of intense fog. The excess death toll was estimated to be over 4000 people (Ministry of Health, 1954). The maximum concentration of smoke recorded was 4.46 mg/m^3 and sulfur dioxide reached a maximum of 1.34 ppm (Wilkins, 1952). These daily average values were approximately 10 and 12 times the normal averages expected for this period, respectively (Wilkins, 1952). The original 1954 report on the London fog event suggested that deaths occurred mostly in individuals who were already in a state of compromised health. However, the death rate in London remained high for several months following the event, and a more recent reanalysis of the data suggested that the excess death toll was more likely around 12,000 (Bell & Davis, 2001).

Historical air pollution events have also been recorded in the Meuse Valley, Belgium, in 1930 (Firket, 1931), and in Donora, Pennsylvania, in 1948 (Ciocco & Thompson, 1961). Fortunately, air quality has improved from the levels seen in the 1950s, due to legislation that established more stringent air quality standards (Brunekreef & Holgate, 2002).

In the late 1970s, it was considered unlikely that the low concentrations of pollutants present in ambient air in developed countries would result in adverse health effects in the general population (Brunekreef & Holgate, 2002). However, air pollution has since re-emerged as a population health risk issue at levels previously thought to be safe, such as those found in typical North American urban areas. Even so, the question remains as to what is the extent of long-term exposure to lower levels of air pollution on life expectancy and health. Further, photochemical air pollution, characterized by high ozone concentrations during warm and sunny weather, has been recently observed in areas where it had not been found previously at such increased levels. Emission patterns have also changed in North America over the past few decades. Because mixtures of airborne particles have changed with respect to both their size distribution and composition, their toxicity may be altered (Brunekreef & Holgate, 2002). Air pollution continues to be a threat to the health and well-being of populations around the world.

In 2004, the National Research Council identified 10 priorities for airborne particulate matter (Committee on Research Priorities for Airborne Particulate Matter, 2004). Of the 10 priorities, 3 are directly addressed by the proposed study. The addressed priorities are as follows:

- *Combined Effects of Particulate Matter and Gaseous Pollutants:* How can the effects of particulate matter be disentangled from the effects of other pollutants? How can the effects of long-term exposure to particulate matter and other pollutants be better understood?
- *Assessment of Hazardous Particulate Matter Components:* What is the role of physiochemical characteristics of particulate matter in eliciting adverse health effects?
- *Exposures of Susceptible Subpopulations to Toxic Particulate Matter Components:* What are the exposures to biologically important constituents and specific characteristics of particulate matter that cause responses in potentially susceptible subpopulations and the general population?

Short-term studies have found a relationship between variations in air pollution and health. Similar associations have also been found in long-term studies, which followed cohorts of exposed individuals over time (Brunekreef & Holgate, 2002). Short-term exposure to particulate air pollution resulted in increased morbidity and mortality in the general population (Burnett et al., 2000; Lin et al., 2002; Villeneuve et al., 2003). Most of these short–term studies were time-series studies. The time-series approach investigates the association between short-term changes, such as changes in pollution levels with short-term changes in acute health outcomes (Bell et al., 2004). Time-series studies have previously indicated that particulate air pollution is associated with declines in lung function, increased respiratory symptoms, respiratory hospitalizations, restricted activity due to respiratory illness, and increased mortality, particularly cardiovascular and respiratory mortality (Pope et al., 1995a).

Two major multi-centre time-series studies of daily levels of air pollution are the National Mortality, Morbidity, and Air Pollution Study (NMMAPS) (Samet et al., 2000b; Samet et al., 2000c) and Air Pollution and Health: a European Approach (APHEA) (Katsouyanni et al., 1995; Katsouyanni et al., 2001). The NMMAPS study focused on the effects of PM_{10} on mortality from 1987 to 1994 in the 90 large cities in the U.S., with a more detailed focus on the 20 largest cities and the effects of PM_{10} on emergency hospital admissions in 14 of the cities. The findings of this study for the 20-city and 90-city analyses strongly supported the evidence for the effect of particulate matter on mortality. Further, the analysis of hospitalization in persons aged 65 years or older in 14 cities provided additional evidence for the adverse health effects of particulate air pollution.

The APHEA study investigated the short-term effects of air pollution on mortality and hospital admissions within and across selected European cities. One project, APHEA1, analyzed the link between sulfur dioxide and particulate matter in relation to mortality in 12 European cities while another project, APHEA2, assessed the short-term effects of ambient particulate matter on total non-accidental mortality in 29 European cities. The results of APHEA1 indicated that daily mortality significantly increased with both sulfur dioxide and PM_{10} exposures. Cumulative effects of prolonged exposure to the pollutants (two to four day average exposure) resulted in estimates similar to those obtained with single day exposures. Further, the effects of the pollutants were stronger during the summer months and were mutually independent (Katsouyanni et al., 1997). Ambient particulate matter mortality was associated with an increase in daily mortality

even after considering other pollutants as well as meterologic and chronologic variables (Katsouyanni et al., 2001).

Currently, the Air Pollution and Health: a European American Approach (APHENA) project, is being undertaken to build on the findings of APHEA (Samoli et al., 2001; Atkinson et al., 2001; Sunyer et al., 2003; Samoli et al., 2003). This project is a collaborative effort between leading investigators from Europe and North America to conduct joint time-series analyses on separate and combined databases, evaluate and strengthen methods used in time-series analysis, and better estimate short-term effects of air pollution on morbidity and mortality using the increased power of joint data sets (Health Effects Institute, 2005).

Direct comparisons between short-term time-series studies and long-term cohort studies are difficult to make. While time-series studies attempt to answer whether the individuals with preexisting cardiorespiratory illness die because of short-term increases in air pollution, prospective cohort studies address whether long-term exposure of mainly healthy individuals to air pollution increases the risk of mortality (Gamble, 1998). For example, Dockery et al. (1993) stated, "because the daily time-series studies evaluated only the effect of short-term changes in pollutions whereas [the Six Cities study] evaluated associations with long-term exposure..., quantitative comparisons with these investigations are difficult to make". However, both short-term and long-term studies show strong evidence of a relationship between air pollution exposure and adverse health events.

In the 1990s, two large cohort studies documented that long-term exposure to fine particulate matter is significantly associated with annual average all-cause mortality. The

Harvard Six Cities Study (Dockery et al., 1993), published in *The New England Journal of Medicine,* was a prospective cohort study aimed at estimating the effects of air pollution on mortality while controlling for individual confounding factors. The study population consisted of 8111 adults in six U.S. cities: Portage, Wisconsin; Topeka, Kansas; Watertown, Massachusetts; Harriman, Tennessee; St. Louis, Missouri; and Steubenville, Ohio. Study participants began enrollment at varying times between 1974 and 1977. Air pollution data collection for the Six-Cities Study extended from the late 1970s to the mid 1980s. Mortality follow-up of the cohort extended to between 14 to 16 years. The statistical analyses of all-cause mortality and cause-specific mortality were derived from Cox proportional hazards regression models. The results were stratified by gender and 5 year age groups. They were also adjusted for potential confounders such as cigarette smoking, level of income, body mass index, and occupational exposures to dusts, gases and fumes. Results from the Six-Cities Study indicated that both all-cause mortality and cardiopulmonary disease mortality increased with concentrations of inhalable particles, fine particles, and sulfate.

The ACS Study (Pope et al., 1995b) was a larger retrospective cohort study involving 156 cities, based on data from the ACS Cancer Prevention Study II. The analysis was restricted to adults who lived in the 48 contiguous states of the United States for which data on sulfate and fine particle air pollution were available. Risk ratios for all-cause and cardiopulmonary diseases in relation to air pollution levels were estimated after adjusting for certain individual risk factors (for example, smoking, education, body mass index, alcohol consumption, and self-reported occupational exposure to a number of substances). Results from the ACS study showed that higher mean levels of sulfate were

significantly associated with increased mortality from all-causes, lung cancer, and cardiopulmonary disease in both men and women. However, the association for women with lung cancer, although elevated and similar in magnitude to the association in men, was not significant at the 95% level of confidence. Also, fine particles were associated with all-cause, lung cancer, and cardiopulmonary mortality. An increase of 10 $\mu g/m^3$ of fine particles corresponded to a 4%, 6%, and 8% increase in all-cause, cardiopulmonary, and lung cancer mortality, respectively.

Both of these studies were used by the U.S. Environmental Protection Agency (EPA) to determine new National Ambient Air Quality Standards (NAAQS) for fine particles and to confirm current standards for particles less than 10 μm in median aerodynamic diameter (PM_{10}). These studies led to an update of previous standards for fine particulate matter, which were first introduced in 1997 by the EPA (Greenbaum et al., 2001). However, both studies were criticized for the potential residual confounding by individual risk factors (such as sedentary lifestyle, active or passive cigarette smoking) or ecological risk factors (such as climate or social milieu). In addition, the studies evoked controversy over the adequacy of the characterization of the long-term exposure of study subjects and potential bias resulting from the allocation of exposure to separate cities. An additional criticism included the lack of robustness in the results upon changes in the specification of statistical models (Lipfert & Wyzga, 1995; Gamble, 1998). It should be noted that the number of metropolitan areas with available pollution data differed by pollutant, time period, and quality control criteria used to assemble the data.

Since the findings of the Harvard Six Cities Study and the ACS cohort mortality study played such a key role in air pollution regulatory policy development in the United

States, Krewski et al. (2000) conducted an independent reanalysis of the data from these two critical studies to 1) validate the original findings; and 2) test the robustness of the findings to alternative analytic approaches. This reanalysis of the ACS cohort found that original and alternative risk estimates for both fine-particle and sulfate air pollution were highly robust against alternative statistical techniques and spatial modeling approaches. That is, particulate air pollution was significantly associated with cardiopulmonary and lung cancer mortality, but was not associated with mortality due to other causes. However, though the increase in risk was not likely the result of confounding by smoking, the effect of other unmeasured potential confounders could not be ruled out with certainty (Krewski et al., 2000).

Following the reanalysis, Pope et al. (2002) undertook a second analysis incorporating an additional 10 years of data through December 31, 1998. Exposure data were expanded to incorporate gaseous co-pollutants and additional fine particle information from the period following the enactment of the new air quality standards. Results of the study suggested that fine particle and sulfur oxide-related pollution were associated with all-cause, cardiopulmonary, and lung cancer mortality. This study lends the most evidence to date of the association between lung cancer and cardiopulmonary mortality and long-term exposure to fine particulate matter in air pollution.

Another major cohort study linking air-pollution and health found a significant association of PM_{10} with non-malignant respiratory deaths in men and women, and with lung cancer mortality in men, in a cohort of non-smoking Seventh Day Adventists (Abbey et al., 1999). As well, ozone showed a strong association with lung cancer mortality for males and sulfur dioxide showed strong associations with lung cancer

mortality for both sexes. The study included a follow-up extending between 1977 and 1992 in a cohort of 6,338 participants. The study adjusted for a wide range of potentially confounding factors, including occupational exposures and indoor sources of air pollutants. However, recent reviews by the EPA criticized the study on account of the small number of cases and lack of statistical precision in the estimates as well as the usefulness of these findings for regulatory action (EPA, 2007f).

There currently exists some debate within the scientific literature regarding which specific constituents of air pollution contribute most significantly to mortality. For example, Samet et al. (2000a) showed that mixtures of pollutants other than fine particles (that is, mixtures of SO_2, NO_2, CO and O_3) were not significantly associated with mortality rates in the 20 cities that were studied. Further, it has been argued that since only a few excess deaths and hospitalizations occurred when the concentrations of particulate air pollution were low, previous studies lacked enough statistical power to precisely estimate the effects of particles at these levels (Kaiser, 1997). However, both the U.S. Environmental Protection Agency (EPA) and the American Heart Association recognize the additional constituents of air pollution, namely CO, NO_2, SO_2, O_3 and Pb, as important air pollutants in terms of human health (EPA, 2006a; American Heart Association, 2007). The U.S. EPA collectively calls this set of air pollutants the "criteria pollutants".

In addition to the statistical association of air pollution with mortality, there are possible explanations for the existence of such an association from an etiological perspective. First, it is possible that air pollution may increase mortality in the general population by exacerbating existing health conditions in individuals. For example, one

study found consistent increases in mortality across most types of ambient particles for persons who had cancer, acute lower respiratory diseases, any form of cardiovascular disease, chronic coronary artery diseases, and congestive heart failure (Goldberg et al., 2000). As well, an association for individuals who did not have any cardiovascular disease, lower respiratory diseases, and cancer was seen in those who had no interactions with the health care system one year before death (12%) and individuals with a wide variety of potentially fatal diseases (52%), including neurological conditions (12%), diabetes (8%), cardiac dysrhythmias (8%), dementia (6%), organic psychotic disorders (6%), and anemias (4%) (Goldberg et al., 2000). It is also possible that long-term exposure to air pollution could be directly associated with morbidity and later, mortality, through a common toxicity pathway.

Most evidence linking air pollutants with adverse health effects is derived from population-based, observational research. However, understanding the biological mechanisms of the air pollutants on physiology can lead to a greater understanding of the potentially causal relationship between air pollution and morbidity and mortality. It is important to understand the biological and chemical plausibility of the pollutants in order to properly interpret the statistical findings.

Further, understanding the sources of the pollutants is important in order to be able to target risk management. One must consider the susceptible subpopulations. Being at risk for health effects of air pollution depends on the specific health endpoint in question and the level and duration of exposure (Pope, 2000b). Children may be particularly susceptible to the health risks of air pollution because they differ from adults in many toxico-kinetic processes (Heinrich & Slama, 2007). Children usually have a

lower body weight, higher ratio between surface and body weight, smaller lung capacity, higher particle deposition in the respiratory tract, and lungs that are not completely developed, all of which can result in more severe effects following exposure to air pollution (Polgar & Weng, 1979; Zeltner et al., 1987; Schultz et al., 1997). Furthermore, children breathe 50% more air per kilogram of body weight than adults (Zeltner et al., 1987; Schwartz, 2004). Other characteristics that may influence susceptibility to the health effects of ambient air pollution include genetic and social factors, age, gender, ethnicity, pre-existing respiratory or cardiovascular diseases, diabetes, medication, health care availability, and housing characteristics, among others (Pope & Dockery, 2006).

The following section provides an overall summary (Table 1), followed by a more detailed summary, of the sources of the six selected air pollutants and their major biological effects and clinical presentations.

Table 1. Major sources, clinical presentations, and possible biological effects of the major air pollutants.

Pollutant	Major Sources[a]	Possible Biological Effects
Fine particulate matter ($PM_{2.5}$)	Combustion processes in vehicles and industrial facilities, road dust	Inflammation, oxidative stress, development of atherosclerosis and cardiovascular disease, declines in lung function, increases in respiratory symptoms such as coughing, shortness of breath and asthma attacks, ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest
Sulfate particulate matter (SO_4^{2-})	Derived mainly from SO_2 oxidation in the atmosphere, metal smelters (e.g., copper) are major source	Acidic ultrafine particles may provoke alveolar inflammation, the impairment of lung defenses and physiological disturbances of gas transfer
Ozone – ground level (O_3)	Formed by the reaction of nitrogen oxides and volatile organic compounds (mainly from vehicle exhaust and industrial emissions) in the presence of sunlight	Powerful oxidant, exacerbates pulmonary disease, results in shortness of breath, chest pain when inhaling deeply, wheezing and coughing, increased susceptibility to respiratory infections, inflammation of the lungs and airways, increased asthma attacks
Sulfur dioxide (SO_2)	Combustion of coal (e.g., in power plants or metal smelting) and other fuels (e.g., diesel) containing sulfur	Respiratory tract irritant with acute effects such as coughing and decreased lung function at high concentrations. Effects of chronic exposure to lower concentrations are less defined.
Nitrogen dioxide (NO_2)	Vehicle emissions, combustion of other fuels (e.g., power-generating industries)	Oxidant, leads to irritation of lungs and lower resistance to respiratory infections
Carbon monoxide (CO)	Incomplete combustion of fuels such as those in vehicle emissions	Increased CO decreases the amount of O_2 the blood can carry, can lead to serious respiratory disease at chronic low-levels of exposure

[a] (Abelsohn et al., 2002)

Fine Particulate Matter ($PM_{2.5}$)

Sources of Fine Particles

Particulate air pollution is the general term used for a mixture of solid, liquid, or solid and liquid particles suspended in air. It includes aerosols, smoke, fumes, dust, ash and pollen (MOE, 2007). Components of particulate matter include acids (such as nitrates and sulfates), organic chemicals, metals, soil and dust particles, and carbon particles with various chemicals adsorbed onto their surfaces. Fine particulate matter is a major constituent of ambient air pollution and is defined as particles that are less than 2.5 μm in median aerodynamic diameter, or $PM_{2.5}$. More specific classifications of particulate matter are shown below (Table 2).

Table 2. Classification and description of particulate matter size ranges.

Particulate Matter Classification	Particle Size
Total suspended particulates (TSP)	< 15 μm (in median aerodynamic diameter)
Coarse particles	2.5 to 10 μm
Inhalable particulate matter (PM_{10})	< 10 μm
Respirable particles or fine particles ($PM_{2.5}$)	< 2.5 μm
Ultrafine particles	< 0.1 μm

Fine particulate matter is derived mainly from high-temperature combustion processes directly as particles or through gas-to-particle conversion (Swietlicki et al.,

1996). They may also be derived from natural sources through geological disturbances, biological debris, forest fires, and oxidation of biogenic reactive gasses, for example (Schlesinger, 2007). Fine particles, as opposed to coarse particles, have an atmospheric residence time of several days or weeks and can be transported over long distances (Jaenicke, 1982; Baird & Cann, 2004). Coarse particles are mainly the result of the breakup of larger particles, but fine particles are mainly formed from chemical reactions between gases and by the coagulation of smaller species (Baird & Cann, 2004).

Primary particles are those emitted directly from a source. Sources of primary particles include construction sites, unpaved roads, fields, smokestacks, or fires (EPA, 2007e). A significant source of carbon-based primary particles is the exhaust from vehicles, especially those with diesel engines (Baird & Cann, 2004). These particles include complex mixtures of metals, for example. Other particles, such as sulfur oxides and nitrogen oxides, are formed as by-products of reactions occurring in power plants, industries, and automobiles. These particles, or *secondary particles*, make up most of fine particulate matter pollution in the United States (EPA, 2007e). Secondary fine particulate matter includes compounds such as ammonium sulfate and sulfuric acid derived from the oxidation of sulfur dioxide, sodium and ammonium nitrate derived from the oxidation of nitrogen oxides and secondary organic matter derived from the oxidation of hydrocarbons (Malcolm et al., 2000). The composition of fine particulate matter is depicted in Figure 1.

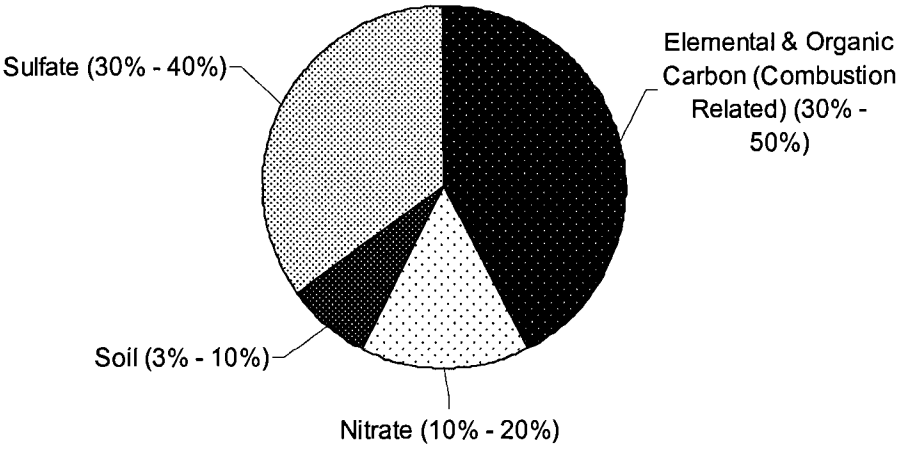


Figure 1. Fine particulate matter composition (MOE, 2007).

Biological Activity of Fine Particles

There currently exist multiple proposed mechanisms by which fine particles may cause or exacerbate vascular disease. One such mechanism supposes fine particulate matter deposes into the lungs inciting low-grade alveolar inflammation with a secondary systemic inflammatory response. The result of the inflammation is downstream cardiovascular exacerbations in susceptible individuals (Seaton et al., 1995). Fine particles, as opposed to larger particulate matter (for example, PM_{10}), penetrate farther into the lower respiratory system and enter the bloodstream, leading to systemic inflammatory changes which may affect blood coagulability (Brunekreef & Holgate, 2002). The inflammatory response may trigger the release of potentially harmful

cytokines trigger other physiological responses such as an increased risk of cardiovascular events and the accelerated development of atherosclerosis and cardiovascular disease (Libby et al., 2002; Suwa et al., 2002). Sun et al. (2005) confirmed these results stating that in an $apoE^{-/-}$ mouse model, long-term exposure to low concentrations of fine particulate matter altered vasomotor tone, induced vascular inflammation, and potentiated atherosclerosis. Furthermore, endothelial dysfunction induced by the soluble and/or particulate components of particulate matter or by mediators of the systemic inflammatory response, and central nervous system treatment of cardiovascular function upon particulate matter exposure may be associated with extra-pulmonary translocation of fine particles that activates vasculature (Bai et al., 2007).

Another mechanism of fine particle action involves oxidative stress mediated by the particles, resulting in cardiovascular dysfunction. Oxidative stress may be generally defined as an unbalance in favor of pro-oxidants and disfavor of antioxidants, potentially leading to damage of biomolecules (Sies, 1993). This scenario might arise from the generation of reactive oxygen species on the surface of particles, for example. Oxidative stress can arise from mitochondrial respiration, ischemia, inflammation, and metabolism of foreign compounds (Risom et al., 2005). Oxidative DNA damage that results might play a role in cancer initiation or progression and may serve as a marker for other health effects of air pollution (Risom et al., 2005).

Pope et al. (2004) examined potential pathways by which particulate matter may increase cardiopulmonary mortality. Their analysis suggested that relevant physiological pathways include pulmonary and systemic inflammation, accelerated atherosclerosis, and

altered cardiac autonomic function. Particulate matter particles mobilize monocytes, band cells, and neutrophils from bone marrow, increase serum IL-1ß and IL-6, and upregulate endothelial adhesion molecules that are important in leukocyte recruitment into atherosclerotic plaques (van Eeden et al., 2005). Under this hypothesis, proximate exposures to particulate matter may be more strongly associated with cardiopulmonary mortality than distal exposures, because subjects with advanced cardiovascular degeneration are at the greatest risk of mortality (Pope et al., 2004). Further, chronic vascular response to respiratory and systemic effects of long-term particulate matter exposure were supported by a study by Künzli et al. (2005).

According to Alessandrini et al. (2006), those who are sensitized to allergens may be more susceptible to the health effects of ultrafine particles. Exposure of sensitized mice to ultrafine carbon particles before the allergen challenge exerted a strong adjuvant effect on the manifestation of allergic airway inflammation. The result of inhalation of ultrafine particles 24 hours before allergen challenge was a significant increase in bronchoalveolar lavage inflammatory cell infiltrate, protein, IL-4, IL-5, and IL-13 when compared to control mice. Increased mucus production, peribronchiolar and perivascular inflammation, and enhanced airway hyperresponsiveness also resulted upon exposure of the sensitized mice to ultrafine particles. Further, ultrafine ambient particles produced pulmonary inflammation in CD1 mice (Dick et al., 2003). Also, increasing the antioxidant capacity of the lung reduced the particle-induced cytokine and cellular responses.

Animal studies have further shown that exposure to particulate matter leads to a reduction in heart rate variability, which may be a result of alterations in cardiac

autonomic function which is a risk factor for death from arrhythmia and sudden death (Watkinson et al., 1998; Godleski et al., 2000; Campen et al., 2000). Animal studies have also been critical in demonstrating a link between the degree of lung inflammation and the extent of thrombosis following injury, such as that induced by air pollution (Nemmar et al., 2003).

Elevated levels of particulate air pollution have previously been linked with declines in lung function, and increases in respiratory symptoms such as coughing, shortness of breath, and asthma attacks (Dockery et al., 1989; Schwartz, 1989; Xu et al., 1991). There is also an association between air pollution and hospitalization rates, chronic obstructive pulmonary disease, and restricted activity due to illness (Euler et al., 1987; Pope, 1989; Ostro, 1990). Long-term exposure to particulate matter has been linked to mortality due to ischemic heart disease, dysrhythmias, heart failure and cardiac arrest (Pope et al., 2004; Zanobetti & Schwartz, 2007). Further, particulate matter has been found to increase the progression of atherosclerosis (Suwa et al., 2002; Kunzli et al., 2005), impair endothelial function (Brook et al., 2004) and automatic function (Liao et al., 1999; O'Neill et al., 2005). Potential additional pathways by which particulate matter exposure could increase mortality risk are by arrhythmias (Peters et al., 2000), pneumonia (Zanobetti et al., 2000), and COPD (Schwartz, 1993). Fine particles are also important with respect to health effects because of their high fraction of alveolar deposition, large surface area, and chemical composition (Donaldson et al., 2001).

Sulfate (SO_4^{2-})

Sources of Sulfate

Fine particulate matter includes most sulfate (SO_4^{2-}) particles. Sulfate is generally not emitted directly from specific sources, but is formed in the atmosphere from reactions of "precursor" pollutants. Sulfate is derived mainly from sulfur dioxide (SO_2) oxidation in the atmosphere (Harrison & Yin, 2000). This reaction may be catalyzed by certain transition metals in ambient air pollution (Schlesinger, 2007). For example, catalysis may occur with iron and manganese, which are commonly found within the fine fraction of ambient particulate matter (Costa, 2001). Primary metal sulfates may be emitted directly from local sources such as smelters and diesel engines (Schlesinger, 2007).

Copper smelters may account for a large portion of emissions related to sulfate particulate air pollution. For example, in the 1960s, copper smelters accounted for nearly 90% of all sulfate emissions in the Southwest states of New Mexico, Arizona, Utah, and Nevada (Pope et al., 2007). Sulfate is also a useful indicator for air pollution in regions where coal is the major source of energy (Zhang et al., 2000).

Biological Activity of Sulfate

Sulfate particulate matter has previously been positively associated with cardiorespiratory acute care hospital admissions (Burnett et al., 1994; Burnett et al., 1995; Gwynn et al., 2000). Burnett et al. (1994; 1995) found a significant relation between

increased admission rates and elevated levels of both ozone and sulfate aerosols in areas near 168 hospitals over the days before admission. Burnett et al. (1994) also speculated that the sulfate's effect is intensified by an excess of positive ions in the air. Increased levels of ambient sulfate have also been speculated to increase the risk of supraventricular arrhythmia in the elderly (Sarnat et al., 2006). According to the American Heart Association (2007), fine particulate matter and sulfate may lead to an increase in heart rate, or changes in heart rate variability, suggesting a possible link between these pollutants and sudden death.

The biological mechanism of sulfate action is not yet well understood. However, acidic ultrafine particles are hypothesized to provoke alveolar inflammation which results in acute changes in blood coagulability as well as the release of mediators that may provoke acute respiratory illnesses in susceptible individuals (Seaton et al., 1995). Additional mechanisms may include the impairment of lung defenses and physiological disturbances of gas transfer (Katsouyanni et al., 1997).

Ozone (O_3)

Sources of Ozone

Ozone (O_3) is a strong oxidizing agent that is formed by a complex series of reactions involving sunlight, nitrogen dioxide, and hydrocarbons (WHO, 2000). Stratospheric ozone – the "good" ozone – extends in a layer from about 6 to 30 miles into the atmosphere. This ozone is beneficial since it protects life on Earth from the sun's

harmful ultraviolet (UV) rays. However, ground-level ozone – the "bad" ozone – is found close to the earth's surface (0 to 7 miles above the Earth's surface) and may be harmful to inhale and damages crops, trees, and other vegetation. Ground-level ozone is also the main ingredient in urban smog (EPA, 2003).

Ozone is formed when nitrogen oxides (NO_x) and volatile organic compounds (VOCs), emitted from motor vehicle exhaust and industrial emissions, gasoline vapors, and chemical solvents as well as natural sources, react in the presence of heat and sunlight. A simplified reaction scheme of anthropogenic ground-level ozone formation is depicted as follows:

$$\text{VOCs} + \text{NO} + O_2 + \text{sunlight} \rightarrow \rightarrow \text{mixture of } O_3, HNO_3, \text{ and organics}$$

where VOCs denote volatile organic compounds, NO is nitric oxide, O_2 is oxygen, and HNO_3 is nitric acid

Here, the reactants – nitric oxide and volatile organic compounds – are relatively innocuous, while the products – ozone, nitric acid, and partially oxidized organic compounds – are much more toxic. Nitric oxide is emitted into the air mainly from internal combustion engines and electric power plants. Volatile organic compounds are present in urban air mainly as a result of the evaporation of solvents, liquid fuels, other organic compounds, and internal combustion engines (Baird & Cann, 2004). The reaction of nitrogen dioxide to produce ozone can further be summarized as follows:

$$NO_2 + h\nu \text{ (UV radiation)} \rightarrow NO\cdot + O\cdot$$

$$O_2 + O\cdot \rightarrow O_3$$

According to the EPA (2004), over 100 million people in the U.S. live in areas in which ozone concentrations exceed the 8 hour regulatory standard. Concentrations of ozone in city centres are generally lower than those in suburbs because ozone is scavenged by nitric oxide originating from traffic (WHO, 2000).

Biological Activity of Ozone

Ozone may cause harmful effects to lung and other tissues. While ozone does not penetrate lung tissue, ozone attacks the tissue through chemical reactions, thereby 'oxidizing' the tissue. This oxidative stress can exacerbate pulmonary disease (Chen et al., 2007b). The combination of oxidative stress, inflammation, and blood lipid levels, may lead to the development of atherosclerosis and ischemic cardiovascular disease (Libby et al., 2002). Effects on clinical chemistry, white and red blood cells, the circulatory system, the liver, endocrine organs, and the central nervous system have also been observed (EPA, 2006b). Animal and human in-vitro and in-vivo studies of ozone exposure have shown that the powerful oxidant may activate stress signaling pathways in epithelial cells (Bayram et al., 2001) and resident alveolar inflammatory cells (Mochiate et al., 2001).

The mechanism of action involves activation of the nuclear factor-kappaB (NF-kappaB) and its translocation to the nucleus. In the nucleus, it then binds to DNA

consensus sequences in the promoters of pro inflammatory genes that code for cytokines, chemokines that attract neutrophils, and adhesion molecules (Nichols et al., 2001). These molecules then increase netruophil recruitment into airways and alveoli thus activating them for mediator secretion and the capability of damaging tissue (Jorres et al., 1996; Bassett et al., 2001).

Large interindividual differences in the response to inhaled ozone can be explained largely by genetics. Genes important in the responsiveness to ozone may include TNFα, manganese, superoxide dismutase, glutathione peroxidase, NAD(P), quinine oxidoreductase, and glutathione S transferases (Rahman & MacNee, 2000). Aside from genetics, factors such as the distribution of ventilation in the different lung compartments and differences in the regional deposition of particles in the lungs could also play a role in interindividual variability in the response to ozone inhalation (Brunekreef & Holgate, 2002).

The inflammatory response of the lung upon exposure to ozone in addition to the increasing neuropeptide release from sensory neurons plays a factor in the acute broncho-constrictor response and hyper-responsiveness seen in asthma upon exposure to ozone (Holz et al., 1999; Schelegle et al., 2001). These responses in the lung also contribute to the tolerance induced by repeated short-term ozone exposure (Jorres et al., 2000). The main mechanism causing changes in spirometry after exposure to ozone involves limiting deep inspiration which leads to decreased vital capacity (Silverman et al., 1976; Hazucha et al., 1989)

Clinical presentations of the health effects of ozone include shortness of breath (dyspnea), chest pain when inhaling deeply, wheezing and coughing, increased

susceptibility to respiratory infections, inflammation of the lungs and airways, increased asthma attacks, and increased need for medical treatment and hospital admission for those with existing lung diseases, such as asthma or chronic obstructive pulmonary disease (COPD) (Moolgavkar et al., 1997; Burnett et al., 1997a; Gent et al., 2003; Medina-Ramon et al., 2006). Further, ozone has been linked with school absenteeism, emergency room visits, and restricted activity days (EPA, 1999).

Sulfur Dioxide (SO_2)

Sources of Sulfur Dioxide

Sulfur dioxide (SO_2) is a major precursor to fine particulate matter and is one of the broader class of sulfur oxide gases (SO_x). Sulfur oxide gases are formed when fuel containing sulfur, such as coal, diesel, and oil, is burned. The gases are also formed when gasoline is extracted from oil, or metals are extracted from ore (Schlesinger, 2007). Large point sources of sulfur dioxide are those associated with nonferrous smelting; that is, the conversion of ores to free metals (Baird & Cann, 2004). When ores are converted to free metals, they are usually first roasted in air to remove any sulfur such as in the following example with nickel (Ni):

$$2\ NiS(s) + 3\ O_2(g) \rightarrow 2\ NiO(s) + 2\ SO_2(g).$$

Natural sources also include sulfur-containing gases emitted from oceans, wetlands, and volcanic emissions (Schlesinger, 2007). Sulfur dioxide dissolves in water vapor to form acid, and then reacts with other gases and particles in the ambient air to

form sulfates and other chemicals that are potentially harmful to human health and the environment (EPA, 2007g).

Sulfur dioxide is a widespread air pollutant in areas neighboring coal-fired electric generating plants, smelters, sulfuric acid factories, and other industries (Petruzzi et al., 1994). Most of the sulfur dioxide in the air (67%) comes from fuel combustion and electrical utilities, particularly those that burn coal (Figure 2).

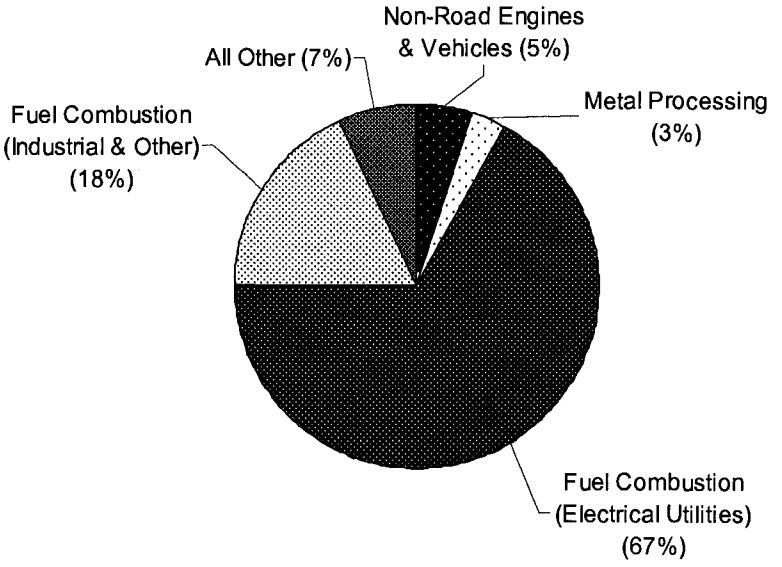


Figure 2. Main sources of anthropogenic sulfur dioxide in the U.S. (EPA, 2007g)

Other sources of sulfur dioxide include industrial facilities that obtain their products from raw materials such as metallic ore, coal, and crude oil. Industrial facilities that burn coal or oil to produce process heat also produce sulfur dioxide waste. Examples of these facilities include petroleum refineries, cement manufacturing, and metal processing facilities. Further, large sulfur dioxide emissions result from locomotives,

large ships, and some non-road diesel equipment that burn fuel containing high levels of sulfur (EPA, 2007g). Additionally, sulfur dioxide dissolves in water vapor to form acid that can then interact with other gases and particles to form sulfates and other respirable particles.

Biological Activity of Sulfur Dioxide

Some of the major health concerns associated with exposure to high concentrations of sulfur dioxide include respiratory illness, alterations in lung defense capability, aggravation of existing cardiovascular disease, and effects on breathing. Sulfur dioxide acts as an irritant and promotes the constriction of small airways and may consequently reduce the threshold of asthma patients to other stimulants (Orehek et al., 1976; Dockery et al., 1982). Previous studies have shown positive associations between sulfur dioxide and emergency room and hospital admissions (Sunyer et al., 1993; Gwynn et al., 2000), asthma attacks (Bates et al., 1990), COPD exacerbations (Sunyer et al., 1991), and death from cardiorespiratory conditions (Dockery & Pope, III, 1994). Asthmatics and those with existing cardiovascular disease or chronic lung disease, children, and the elderly are particularly sensitive to the health effects of sulfur dioxide (American Lung Association, 2000). Animal studies have shown that expiratory and or inspiratory times increase after exposure to sulfur dioxide at 5 ppm (Kitabatake et al., 1995). Conversely, several large studies have failed to detect an association between sulfur dioxide and mortality, including a cohort study of 20 U.S. cities with a follow up between 1987 and 1994 (Samet et al., 2000a), a large cohort study of 7445 Seventh-Day

Adventist adults in California (Euler et al., 1987), and another cohort study in Helsinki, Finland, between 1988 and 1996 (Penttinen et al., 2004).

To produce pathological changes in the pulmonary function of experimental animals, very high concentrations of sulfur dioxide are needed. As a result of sulfur dioxide inhalation, bronchial narrowing may result as suggested by an increase in airflow resistance. This effect occurs within minutes and is readily reversible which indicates that it is likely the result of an increase in bronchial smooth muscle tone (National Air Pollution Control Administration, 1969). The effect has been seen in guinea pigs, dogs, and cats in addition to human subjects.

In summary, sulfur dioxide may be a respiratory tract irritant showing acute respiratory health effects such as coughing and decreased lung function at higher concentrations. However, the effects of chronic exposure to lower concentrations of ambient sulfur dioxide have less defined human health effects (Chen et al., 2007a).

Nitrogen Dioxide (NO_2)

Sources of Nitrogen Dioxide

Nitrogen dioxide (NO_2) is the main precursor to ozone formation. Because of this, it is a major component of oxidant air pollution. Nitrogen dioxide is responsible for the reddish-brown layer that is often seen over many urban areas. Nitrogen oxides (NO_x) form when fuel is burned at high temperatures such as those in combustion processes

(EPA, 2007d). In ambient conditions, nitric oxide is transformed to nitrogen dioxide by atmospheric oxidants like ozone:

$$NO + O_3 \rightarrow NO_2 + O_2.$$

Most anthropogenic emissions of nitrogen oxides result from the combustion of fossil fuels from stationary sources such as heating and power generation and from motor vehicles (WHO, 2000). The main anthropogenic sources of nitrogen oxides are motor vehicles, electric utilities, and other industrial, commercial, and residential sources that burn fuels. However, nitrogen oxides can also be formed naturally (EPA, 2007d). The percentage of anthropogenic sources of nitrogen oxides in the U.S. in 2003 are shown in Figure 3.

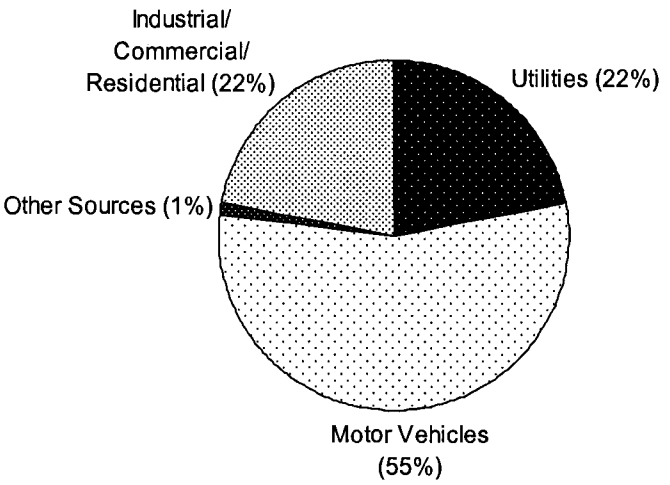


Figure 3. Contribution of anthropogenic sources to overall nitrogen oxides in the U.S., 2003 (EPA, 2007d).

Biological Activity of Nitrogen Dioxide

Little is known about the effects of nitrogen dioxide on normal and diseased lung. Epidemiologic studies produce inconsistent results. Vedal et al. (2003) reported that nitrogen dioxide showed an association with mortality only during the winter in Vancouver, Canada. In 2006, an analysis on Air pollution and Health: a European Approach-2 (APHEA2) found that nitrogen dioxide exposure resulted in a small, but statistically significant association with total and cardiovascular mortality (Samoli et al., 2006). However, other studies have failed to detect an association between nitrogen dioxide and adverse health effects. Samet et al. (2000a) found that PM_{10}, but not nitrogen dioxide, was associated with mortality based on a study of 20 U.S. cities between 1987 and 1994. Pollutants emitted from a coal-burning plant, including nitrogen dioxide, did not have significant effects on respiratory symptoms on nearby subjects with chronic obstructive pulmonary disorder and hypersensitivity to airborne allergens (Pershagen et al., 1984). Euler et al. (1987) reported no association between ambient nitrogen dioxide exposure and chronic respiratory symptoms in a cohort of 7445 Seventh-Day Adventist adults in California.

However, nitrogen dioxide has been linked to an increase in respiratory (Burnett et al., 1997b) and cardiac (Burnett et al., 1997b; Morgan et al., 1998; Moolgavkar, 2000) hospital admissions. Nitrogen dioxide has also shown associations with both incidence and exacerbation of asthma. For example, in a cohort of 842 children in 7 different Japanese communities, outdoor nitrogen dioxide was associated with wheezing and asthma (Shima & Adachi, 2000). Smith et al.(2000) also reported an association between

daily nitrogen dioxide exposure and asthma symptoms in children younger than 14 years of age.

In contrast, animal studies have shown that nitrogen dioxide may be implicated in airway inflammation and the development of respiratory symptoms. Animal and human in-vitro studies both show that nitrogen dioxide activates oxidant pathways. However, nitrogen dioxide is a less powerful oxidant than ozone (Blomberg et al., 1997). Furthermore, animal studies tend to use levels of nitrogen dioxide that are much higher than those found under ambient conditions (Chen et al., 2007a). The inflammatory response that follows exposure to nitrogen dioxide is different from that of ozone based on the enhancement of the recruitment of T lymphocytes and macrophages after nitrogen dioxide exposure (Sandstrom et al., 1992). Continued or frequent exposure to concentrations of nitrogen dioxide higher than normally found in ambient air may cause an increase in acute respiratory disease incidence in children (American Lung Association, 2000). Children and those with asthma appear to be especially susceptible to the effects of nitrogen dioxide exposure (Folinsbee, 1993). Sensitive individuals show detectable changes in lung function (American Heart Association, 2007).

The small airways are the most affected site of nitrogen dioxide-induced damage (Folinsbee, 1993). Nitrogen dioxide can irritate the lungs and lower resistance to respiratory infections, for example, influenza. One important feature of nitrogen dioxide that may exacerbate respiratory disease is its potential to impair alveolar macrophage and epithelial cell function, thus rendering the lungs more susceptible to infection (Frampton et al., 1989; Chauhan et al., 1998). In-vitro exposure to concentrations of nitrogen dioxide from 400 to 800 ppb was associated to the synthesis of various cytokines active

in cellular inflammation (Devalia et al., 1993). Exposure to high levels of nitrogen dioxide (20 ppm) for a few weeks or longer has been shown to cause emphysema-like changes in the lungs of animals (American Heart Association, 2007).

Animal studies have also supported a role of nitrogen dioxide in airway inflammation and development of respiratory symptoms. However, nitrogen dioxide levels used in these studies were much higher than those found in the environment. Also, high levels of nitrogen dioxide administered endotracheally to sheep resulted in increased airway resistance and significant parenchymal damage in sheep (Januszkiewicz & Mayorga, 1994). However, a suite of controlled studies have also failed to demonstrate consistent respiratory effects after exposure of both healthy and asthmatic subjects to varying concentrations of nitrogen dioxide (Adams et al., 1987; Koenig et al., 1987; Roger et al., 1990; Rubinstein et al., 1991).

Carbon Monoxide (CO)

Sources of Carbon Monoxide

Carbon monoxide (CO) is a colorless, odorless, and poisonous gas commonly associated with vehicle emissions, cigarette smoke and combustion reactions. It is formed when carbon in organic matter is not burned completely. Motor vehicle exhaust contributes nearly 56% of all carbon monoxide emissions in the United States (Figure 4).

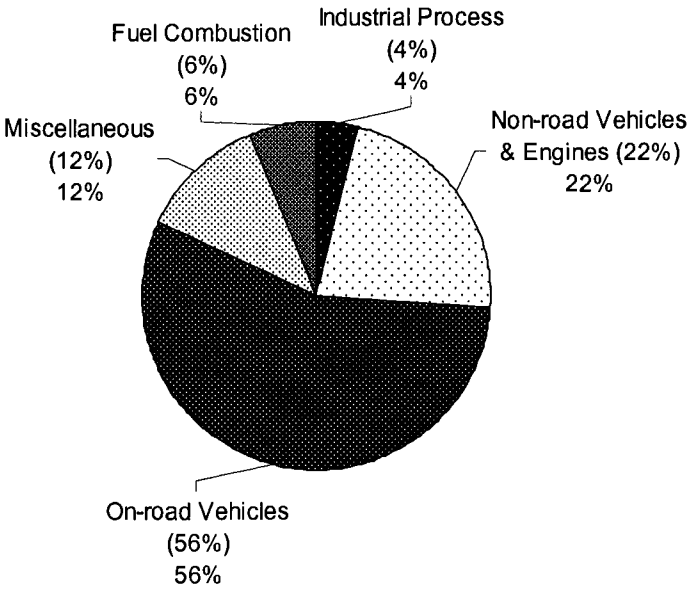


Figure 4. Sources of carbon monoxide (EPA, 2007c).

In urban areas, between 85% and 95% of carbon monoxide emissions result from motor vehicle exhaust. Other non-road engines and vehicles, for example construction equipment and boats, contribute to approximately 22% of all carbon monoxide emissions in the U.S. Outdoor carbon monoxide exposure occurs mainly in urban areas near roadways, and other poorly ventilated areas such as parking garages and traffic tunnels. Areas with heavy traffic are subject to higher levels of carbon monoxide. Industrial processes, residential wood burning, and natural sources such as forest fires may also increase ambient carbon monoxide levels. Carbon monoxide levels are usually highest in colder seasons when inversion conditions are common. Under these conditions, air pollution becomes trapped near the ground under a layer of warm air (EPA, 2007c). The average ambient concentration of carbon monoxide in the U.S. decreased from 10 to 6 ppm from 1975 to 1991 (Baird & Cann, 2004). Mexico City currently has the highest

levels of ambient carbon monoxide among the largest cities in the world (Baird & Cann, 2004).

Biological Activity of Carbon Monoxide

Carbon monoxide has been significantly associated with cardiac hospital admissions for congestive heart failure (Schwartz, 1997; Burnett et al., 1997a). At low concentrations of carbon monoxide, healthy individuals may experience fatigue, while those with heart disease may experience chest pain. Long-term, low-level exposure to carbon monoxide can been speculated to lead to serious respiratory diseases (American Heart Association, 2007). Carbon monoxide is especially dangerous to those who suffer from heart disease. Moderate concentrations of carbon monoxide can lead to angina, impaired vision, and reduced brain function (EPA, 2007a). High levels of carbon monoxide are poisonous and can cause death (EPA, 2007b). Such levels are higher than experienced with episodes of air pollution. However, carbon monoxide can accumulate in the blood from chronic exposure to low concentrations (10-30 ppm) or acute exposure to higher levels (> 100 ppm).

Inhalation of carbon monoxide results in the formation of carboxyhemoglobin in the blood, which inhibits the intake of oxygen. It follows that increased carbon monoxide levels in the blood leads to a decrease in the amount of oxygen blood can carry and thus reduces the amount of oxygen delivered to the body's organs and tissues. Carbon monoxide has a high affinity for hemoglobin. In fact, the relative affinity of carbon

monoxide for hemoglobin is roughly 245 times that of oxygen (Roughton & Darling, 1944).

Relatively little is actually known about the effects of chronic exposure to carbon monoxide on cardiopulmonary health. One study indicated that chronic exposure of rats to moderate amounts of carbon monoxide resulted in the stimulation of erythropoietin production and erythropoiesis (Sherpa et al., 1989). Another study showed that chronic carbon monoxide exposure of hypoxic rats increased in vitro sensitivity of pulmonary artery smooth muscle (Dubuis et al., 2003). In this study, exogenous carbon monoxide induced pulmonary vasodilation by acting directly on pulmonary artery smooth muscle cells. Allred et al. (1991) found that a significant dose-response relationship for individual differences in the time to angina for pre- versus post-exercise tests at three carboxyhemoglobin levels. That is, low doses of carbon monoxide produced significant effects on cardiac function during exercise in patients with existing coronary artery disease. It has also been suggested that carbon monoxide may increase mortality risk by interfering with homeostasis through alterations in the NO-cGMP signaling pathway (Burnett et al., 1998).

3. METHODS

In the current section, information is provided regarding the study population, metropolitan areas under study, air pollution exposure measurements, ecological covariates, methodology behind individual covariate selection, and finally the approaches taken for the statistical analysis. This section describes how individual mortality and potential confounder information will be combined with and ecological and air pollution

data in order to determine the relationships between the pollutants and mortality, and similarly the ecological covariates and mortality. This section also outlines the statistical approaches taken to analyze pollutant and ecological covariate associations with mortality. Thus, the analytical approach seeks to achieve the major objectives of the study – the determination of the relationships between the combined exposures to six major air pollutants and mortality with an adjustment for confounding effects, and the evaluation of the effect of previously unused ecological covariates on pollutant exposure/mortality relationships. In addition, approaches taken to address secondary objectives of the study – to assess effect modification by education level; and to consider spatial autocorrelation by performing a sensitivity analysis using random effect Cox models – are outlined in the current section.

Study Population

The analysis was carried out using mortality data from the American Cancer Society Cancer Prevention Study II cohort linked to air pollution data for major metropolitan areas throughout the United States. The ACS CPS II cohort was used to empirically estimate all-cause, cardiopulmonary, and lung cancer mortality. The ACS CPS-II is an ongoing prospective mortality study of nearly 1.2 million adults. Participants residing in 50 states, the District of Columbia, and Puerto Rico were enrolled by ACS volunteers in the fall of 1982. Participants were mostly friends, neighbors, or acquaintances of the ACS volunteers. Members who were at least 30 years of age and who were members of households with at least one individual aged 45 years older were permitted for enrollment into the study. Study participants completed a confidential

questionnaire that included questions on age, sex, weight, height, smoking history, alcohol use, occupational exposures, diet, education, marital status, and other relevant characteristics (ACS, 2007) (Appendix A). The analysis incorporated information from up to 172 different U.S. metropolitan areas.

Vital status information was determined by personal inquiries by the ACS volunteers in September 1984, 1986, and 1988. Automatic linkage of the CPS-II study with the National Death Index was also performed to ascertain vital status up to 1998. Ascertainment of deaths was over 98% complete for the period of 1982 to 1988 and nearly 93% complete following 1988. Death certificates or codes for cause of death were obtained for over 98% of known deaths (Calle & Terrell, 1993). A nosologist coded the cause-of-death according to the International Classification of diseases (ICD), 9th revision (WHO, 1975) with no knowledge of air pollution levels. An independent audit using a sample of 240 death certificates and an independent nosologist determined there was a 93.7% agreement in cause-of-death coding (Krewski et al., 2000).

The data for the current study was based on ongoing data collection that included vital status data for the CPS-II cohort with multiple cause of death codes updated on a continual basis. The cohort under study was limited to include only residents in U.S. metropolitan areas for which air pollution data were collected within the 48 contiguous states (including the District of Columbia).

Use of the American Cancer Society Cancer Prevention Study-II data was critical in allowing for a direct comparison of the proposed study with existing literature. The cohort nature of this data also allows for the most current and extensive data to be used for the study together with ongoing air pollution exposure data. The large nature of the

data set and the comprehensive information on individual confounders made the ACS CPS-II data preferable.

Definition of Metropolitan Areas

Data are usually compiled for areas that are defined by political borders. However, these borders do not always correspond to areas at which spatial processes of interest operate. In the study, an approximation was made by linking the last three digits of the study participant's zip code to the corresponding metropolitan area. According to the U.S. Census Bureau, a metropolitan statistical area (MSA) refers to an area with at least with 50,000 or more inhabitants and a metropolitan region that contains at least 100,000 inhabitants. MSAs are made up of the county that includes the most populated city, in addition to any adjacent counties where at least half of the population is in an urbanized region adjoining with that city. An MSA may be broken down into smaller component areas if it contains a minimum of 1 million inhabitants (OMB, 2005). In the current study, air pollution exposure data were linked to the cohort study participants by MSA of residence.

Air Pollution Exposure Measurements

Air pollution data were collected from air pollution monitoring sites in metropolitan areas throughout the United States. The data were retrieved from the Aerometric Information Retrieval System (AIRS) database, now called the Air Quality System (AQS), maintained by the U.S. EPA (EPA, 2007h). Information on ambient air

pollution data from the U.S. collected by EPA, state, local, and tribal air pollution control agencies from thousands of monitoring stations was obtained from AQS. Meteorological data, descriptive information about each monitoring station including its geographic location and its operator, and data quality assurance/quality control information was also retrieved from AQS. The information provided came from source reports by various stationary sources of air pollution, such as electric power plants, steel mills, factories, and universities. AQS provides information about specific air pollutants that the sources produce. Information on all major pollutant (CO, NO_2, SO_2 O_3, $PM_{2.5}$ and PM_{10}) trends, emissions, and air quality indexes from geographical areas, both metropolitan and county, are readily accessible online at www.epa.gov/ttn/airs/airsaqs. Data were also be retrieved from the Inhalable Particle Monitoring Network (IPMN) and the National Aeromatic Database (NAD).

In order to process exposure data for the current study, mean concentrations of air pollution for the corresponding metropolitan areas were compiled from the previously described data sources (Table 3). Information for particulate air pollution was available from the IPMN for the years 1979 to 1983 and from NAD for 1980 to 1981. This exposure data corresponded to the period just prior to or at the start of the follow up period of the ACS CPS II cohort (Pope et al., 2002). Mean concentrations of each pollutant were calculated from data available during the 1 to 2 year period before study enrollment from the AIRS database (Krewski et al., 2000). Fine particulate matter data were only collected for 61 metropolitan areas from 1979 to 1983; however, with the implementation of new fine particulate matter standards in the U.S., more sites began collecting data in 1999. Beginning in 1999 and ending after the first 3 quarters of 2000,

daily $PM_{2.5}$ measurements were compiled from the AIRS database. Quarterly averages for each monitoring site were then computed and measured first by site, then by metropolitan area. Mean sulfate concentrations for a total of 149 metropolitan areas were compiled from the IPMN and the NAD databases for the 1980-1981 period. Because glass fiber filters used to collect sulfate measurements for this period would have likely overestimated the actual ambient amount of sulfate, adjustments were made for both season and geographic region (Krewski et al., 2000).

Table 3. Air pollution data summary information.

Pollutant	Units	Years of Data Collection	Database	Data Compilation*	No. of Metropolitan Areas	Mean (SD)
$PM_{2.5}$	$\mu g/m^3$	1979 - 1983	IPMN	HEI	61	19.8 (4.7)
		1999 - 2000	AIRS	NYU	116	13.1 (3.3)
O_3	ppb	1980	AIRS	HEI	122	23.3 (5.2)
SO_4^{2-}	$\mu g/m^3$	1980 - 1981	IPMN / NAD	HEI	149	6.4 (3.0)
SO_2	ppb	1980	AIRS	HEI	118	9.2 (5.2)
NO_2	ppb	1980	AIRS	HEI	78	25.6 (8.6)
CO	ppm	1980	AIRS	HEI	113	1.6 (0.7)

* HEI refers to Health Effects Institute reanalysis team (Krewski et al., 2000), NYU refers to New York University School of Medicine, Nelson Institute of Environmental Medicine.

Ecological Covariates

Instead of being measured at the individual level, air pollution was measured at the ecological level. Thus, associations observed between air pollution exposure and mortality could have been partly due to other city-level characteristics that are correlated with both the exposures and outcomes. An analysis of the ecological covariates was performed in order to control for confounding at the same scale as air pollution exposure measurements.

Previous studies relating air pollution exposure to mortality based on data from the ACS CPS II cohort have focused solely on the effects of ecological covariates at the MSA level from 1980. In the current study, MSA-level ecological covariates from 1990 were obtained from the U.S. Census Bureau (2007) for the MSA areas for which air pollution data were available. Data from 1990 is representative of the approximate median of this follow-up period, which extends from 1982 to 2000. .

The selected ecological covariates represented well-defined attributes of each city and were thought to have a plausible biological or social mechanism that could affect mortality. In 1990, Evans and Stoddart identified three categories of integral and contextual health risk factors: the social environment, the biophysical environment, and the healthcare system. These categories influenced the decision of which ecological covariates to include in the study to control for potential confounding, based on previous work by Willis et al. (2003b). That is, for variables which the literature indicated a possible health risk, census data based on counties and metropolitan areas was used to control for ecological confounders. In the current study, ecological covariates from 1990

were used in place of the previously-used covariates from 1980 to investigate potential MSA-level characteristics that affect the air pollution-mortality relationship.

The ecological covariates controlled for in this analysis include percentage of adults with at least grade 12 education, percentage of unemployed persons of 16 years, income inequality (measured by the GINI coefficient), % below the poverty line, median household income, per capita income, percentage of residents that are white, percentage of residents that are black, percent population change from 1980, and finally, the percentage of residents over the age of 25 years. Information on neighborhood social confounders corresponding to zip code areas was obtained readily from the U.S. Census Bureau (http://censtats.census.gov/usa/usa.shtml).

Individual Covariate Selection

Potential individual confounders of the exposure/outcome relationship included those identified in previous analyses of the ACS CPS II cohort (Krewski et al., 2000; Pope et al., 2002). Information on individual confounders was supplied by study subjects via the original questionnaire administered to the ACS CPS II cohort. The individual covariates used include smoking history, education, marital status, body mass index, alcohol consumption, occupational exposures, and diet. Square terms of continuous variables, such as number of cigarettes smoked, years of smoking, and BMI, were included in order to account for nonlinear effects on mortality. Further, the models were stratified by 1-year age groups, ethnicity, and gender. In total, 44 individual-level

covariates were used. More specifically, variables represented individual characteristics as follows: eight variables for active smoking habits, seven variables for former smoking habits, one variable for passive smoke exposure, two variables for marital status, two variables for BMI (a linear and square term), six variables for alcohol consumption, seven variables for occupational exposure, one variable for self-reported workplace exposures, eight variables for diet, and variables for education.

Potential confounding by occupational exposure was addressed by using exposure indices that approximated exposures on the job. Occupational exposure may be an important potential confounder since individuals who live in heavily polluted regions might also work in more polluted workplaces. One index, the "dirtiness indicator", was developed by Siemiatycki et al. (1991) and used in a large community-based cancer case-control study in Montréal. This index is aimed at encompassing and integrating all exposures in the workplace, including exposure to pathogenic pollutants. It captures an aspect of social class that is correlated, but separate from, educational attainment. During the baseline interview in the ACS study, study subjects responded to questions concerning the current or last occupation and the occupation of longest duration. Occupations were coded based on 68 categories and employing these codes, Krewski et al. (2000) allocated two new variables to each study subject. Occupational exposures to asbestos, chemicals/acids/solvents, coal or stone dust, coal tar/pitch/asphalt, diesel engine exhaust, and formaldehyde were considered.

It is important to note that the original dataset excluded subjects with the following: unclassifiable or missing zip code, death rate before September 1982 (before interview), missing ethnicity, missing educational level, missing BMI, missing initial

sulfate/fine particulate measurements, resident in Hawaii, unclassifiable smoking status, missing or unclassifiable data for amount and duration of smoking for both current and former smokers, and missing data for all three measures of passive smoking.

Statistical Analysis

The association between ambient concentrations of air pollution and mortality on a national scale was examined using Cox proportional hazards models. Adjusted mortality hazard risk ratios and 95% confidence intervals (CIs) associated with each pollutant were estimated. Subjects were assigned initially to metropolitan areas based on the three first digits of their zip code at the time at which they completed the initial questionnaire of the ACS CPS II study. Each of six selected pollutants ($PM_{2.5}$, SO_4^{2-}, O_3, NO_2, CO, and SO_2) was entered into survival models (singly and in combinations) to test whether certain pollutants were more closely associated than others with mortality risks including all-cause, cardiopulmonary (composed of both respiratory and cardiovascular mortality, ICD9: 400-440, 460-519), and lung cancer (ICD9: 162) mortality (WHO, 1975) in 172 large U.S. metropolitan areas.

Using Statistical Analysis Software (SAS version 9.1, SAS Institute, Cary, NC), individual covariates derived from the original ACS questionnaires (Appendix A) were combined for all study participants. Information on age, gender, ethnicity, education, smoking history, alcohol consumption, and diet were obtained from these questionnaires. Indicator variables for missing data on alcohol consumption were used because of the large fraction of missing observations (approximately 70%). Since nearly 70% of study

participants did not respond to the question on alcohol consumption, it is likely that study participants were reluctant to respond to this question and thus form a separate group worth studying as a whole. Variables were included that accounted for the age at which a subject started smoking and marital status. Information on occupational exposures, in the form of a "dirtiness index" derived from previous work by Siemiatycki (1991) was also included. Upon collating individual confounder information, mortality data were linked to ACS data during the specified follow-up (from 1982 through 2000). Finally, air pollution data for each MSA were then linked to individual-level data based on location of residence at the time of the initial questionnaire.

Cox proportional-hazards modeling was performed by using the procedure 'PROC PHREG' in SAS. Initially, "base" models that included each air pollutant without any additional determinants of mortality were considered for all-cause, cardiopulmonary, and lung cancer mortality. The baseline hazard function was stratified by 1-year age intervals, ethnicity, and gender. The previously identified set of 44 individual covariates (Krewski et al., 2000; Pope et al., 2002; Krewski et al., 2005) were then included into models for each individual pollutant, thus forming the "adjusted" models for all three mortality outcomes. Pollutant reference levels were selected based on previous study by Krewski et al. (2008). Then, each possible combination of 2 pollutants was added into adjusted models. Finally, a full model, including all pollutants, was analyzed for all-cause, cardiopulmonary, and lung cancer mortality. These models were analyzed based on the largest available full set of pollutants in each case.

A second analysis identical to the above pollutant analysis was performed using the set of MSAs which contained pollutant exposures for all six pollutants under

investigation. This set of MSAs provides a more statistically sound comparison between pollutants which are correlated. However, such a strategy also lessens the statistical power of the results due to the decreased number of MSAs used in the analysis. As a sensitivity analysis, hazard ratios from both analysis strategies were compared.

Next, the log-likelihood estimates from the set of results based on a fixed set of MSAs were analyzed to assess the validity of adding the additional pollutant covariates into the models. For this, the values of the log-likelihood from the multiple pollutant models were subtracted from the values of the corresponding single pollutant models. The difference between the two values was assumed to have an approximately chi-squared distribution. Thus, from the resulting chi-square value, a p-value based on 1 degree of freedom at the 95% level of confidence was calculated.

Aikake's information criterion (AIC) values were then calculated between single and multiple pollutant models to assess the goodness of fit of the models to select the most parsimonious model. For this, the magnitude of the difference between the AICs for the single and multiple pollutant models based on the fixed site of MSAs described previously was assessed.

Upon consideration of the results from the multiple pollutant analyses, a "parsimonious" model including all 44 individual covariates and only those pollutants that seemed significantly related to each type of mortality was analyzed. This importance was judged based on a change of at least a 3 percent change in the hazard ratios upon the addition of additional pollutants into the model. The addition of none of the pollutants resulted in a change in the hazard ratio of more than 10 percent. For mortality due to all causes, fine particles, sulfate, and sulfur dioxide were included in the model. The model

for cardiopulmonary mortality included fine particles, sulfate, sulfur dioxide, and ozone. Finally, the model for lung cancer mortality included fine particles and sulfate.

Another sensitivity analysis was performed to identify the possible differences between local and regional activity of fine particles. Sulfate concentrations are fairly constant over a large regional scale and represent a large fraction of fine particles. Because of this, sulfate measurements were subtracted from fine particle measurements to represent a greater proportion of locally active fine particles. Though, there are still residual regional components present in the remaining fraction of particulate matter. Here, "$PM_{2.5}$ regional" represented the total fraction of $PM_{2.5}$ while "$PM_{2.5}$ local" represented the portion of $PM_{2.5}$ remaining after subtracting SO_4^{2-} measurements from the same time period (1980). Multiple pollutant models containing $PM_{2.5}$ and SO_4^{2-} in both the regionally- and locally- adjusted models were analyzed in an attempt to further disentangle the effects of $PM_{2.5}$ and SO_4^{2-} on all-cause, cardiopulmonary, and lung cancer mortality.

Because of potential complex spatial patterns in the data may have resulted in a variation in the health determinants of the study subjects by city of residence, a sensitivity analysis considering intracity correlation was performed in order to rule out potential spatial autocorrelation. For this, a random effects Cox proportional-hazards model was used to represent the unique characteristics of each city (Krewski et al., 2000; Ma et al., 2003). The random effects Cox proportional hazards model allowed individual measurements to be clustered at various geographical scales. Here, the random effects at the metropolitan level were included to capture differences in survival due to potential variation between metropolitan areas. Through the incorporation of one level of spatial

clustering, the statistical error structure of the survival data was characterized. That is, if the variation among cities is relatively large, then the weights assigned to each city will be similar and the larger cities were assigned less weight. In this random effects model, the variation in weight among clusters is positively associated with the cluster variance. Statistical methodology and computational software has previously been developed to take into account one (e.g. MSA) or two (e.g. MSA and zip code) levels of spatial clustering.

Finally, a sensitivity analysis comparing results using fine particle data in 1980 to that from 1999-2000 was performed, since all other pollutant exposures in the analyses were based on data from 1980. In the analyses, fine particle data from 1999-2000 were used because of the much larger number of MSAs with available data (N = 116 vs. 61). The validity of using a different year for exposure measurements was tested by comparing hazard ratios for all-cause, cardiopulmonary, and lung cancer mortality for single and multi-pollutant models.

Ecological data from 1990 was analyzed in a similar fashion for each pollutant. First, covariates derived from the 1990 U.S. Census were linked to air pollution exposures and individual data by MSA. Ecological covariates investigated included education, race, unemployment, per capita and median household income, poverty, income disparity (as measured by the GINI coefficient), population change from 1980, and percent residents over age 25. All-cause, cardiopulmonary, and lung cancer mortality hazard ratios for each ecological covariate were analyzed again using 'PROC PHREG' while adjusting for 44 individual covariates and stratifying the baseline hazard function by 1-year age intervals, ethnicity, and gender. Next, mortality hazard ratios for

all six pollutants were investigated while controlling for each ecological covariate separately. Again, these analyses controlled for 44 individual covariates and the baseline hazard functions were stratified by 1-year age intervals, ethnicity, and gender.

An identical analysis strategy was used to assess the effect of educational attainment on mortality hazard. The effect of attaining less than, equal to, or more than a high school education was assessed by stratifying the hazard ratios into three levels of educational attainment at the individual level. Another analysis involved the assessment of the effect of educational attainment at the MSA level by controlling for the percentage of those who had attained less than, equal to, or more than a high school education. For the models examining educational attainment at the individual level, 42 covariates were used with an exclusion of two variables representing educational status. The models used to assess educational attainment at the MSA level still controlled for education at the individual level. That is, the previously described set of 44 individual covariates was used in these analyses. The purpose of the educational level analysis at the MSA level was to determine related but independent community-level effects of educational attainment existing over those at the individual level.

Pearson correlation coefficients within and between pollutants and ecological covariates were calculated using the procedure 'PROC CORR' in SAS. The same procedure was also used to assess the correlation between individual covariates (from the ACS CPS II cohort) and ecological covariates (from the U.S. Census Bureau). The covariates similar between the ecological and individual covariates were education level and ethnicity.

4. RESULTS

Multiple Pollutants. Six major air pollutants ($PM_{2.5}$, O_3, SO_4^{2-}, SO_2, NO_2, and CO) were analyzed with respect to their association with all-cause, cardiopulmonary, and lung cancer mortality using standard Cox proportional hazards regression models. All models were stratified by 1-year age groups, gender, and ethnicity.

First, the relationship between each pollutants and mortality without the addition of any additional covariates were analyzed ("base" models, Tables 4, 5, and 6). Next, each pollutant in combination with 44 individual covariates controlling for confounding of smoking, alcohol use, diet, occupational exposures, education, income, marital status, and other relevant characteristics, was analyzed for its relationship with mortality ("adjusted" models, Tables 4, 5, and 6). These numbers were derived from models which considered the full set of MSAs for which pollutants were available for each separate model.

Table 4. Hazard ratios for all-cause mortality (1982-2000) based on single and multiple pollutant standard Cox survival model adjusting for 44 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis). Results for both maximum and restricted numbers of MSAs are shown.

Pollutant (increase)	Model	No. of MSAs	HR (95% CI)	Model	No. of MSAs	HR (95% CI)
$PM_{2.5}$	Base	116	1.051 (1.032, 1.070)	Base	50	1.041 (1.019, 1.063)
(10 $\mu g/m^3$)	Adjusted	116	1.033 (1.014, 1.052)	Adjusted	50	1.015 (0.993, 1.038)
(1999-	+ O_3	98	1.032 (1.012, 1.053)	+ O_3	50	1.017 (0.994, 1.041)
2000)	+ SO_4^{2-}	110	0.994 (0.972, 1.016)	+ SO_4^{2-}	50	0.985 (0.961, 1.011)
	+ SO_2	96	1.024 (1.004, 1.045)	+ SO_2	50	1.010 (0.987, 1.033)
	+ NO_2	65	1.027 (1.002, 1.052)	+ NO_2	50	1.027 (1.002, 1.052)
	+ CO	89	1.034 (1.014, 1.054)	+ CO	50	1.020 (0.997, 1.044)
	Full Pollutant	50	1.000 (0.968, 1.033)	Full Pollutant	50	1.000 (0.968, 1.033)
O_3	Base	122	0.999 (0.988, 1.010)	Base	50	0.984 (0.970, 0.998)
(10 ppb)	Adjusted	122	1.003 (0.992, 1.015)	Adjusted	50	0.997 (0.982, 1.011)
(1980)	+ $PM_{2.5}$	98	0.999 (0.987, 1.012)	+ $PM_{2.5}$	50	0.994 (0.980, 1.009)
	+ SO_4^{2-}	119	1.008 (0.996, 1.020)	+ SO_4^{2-}	50	1.005 (0.990, 1.020)
	+ SO_2	105	1.003 (0.992, 1.015)	+ SO_2	50	0.997 (0.983, 1.012)
	+ NO_2	76	0.997 (0.983, 1.011)	+ NO_2	50	1.000 (0.985, 1.015)
	+ CO	104	1.006 (0.994, 1.019)	+ CO	50	0.999 (0.984, 1.013)
	Full Pollutant	50	1.008 (0.992, 1.025)	Full Pollutant	50	1.008 (0.992, 1.025)
SO_4^{2-}	Base	149	1.078 (1.068, 1.088)	Base	50	1.095 (1.081, 1.108)
(5 $\mu g/m^3$)	Adjusted	149	1.038 (1.028, 1.048)	Adjusted	50	1.037 (1.023, 1.051)
(1980)	+ $PM_{2.5}$	110	1.048 (1.035, 1.062)	+ $PM_{2.5}$	50	1.041 (1.025, 1.056)
	+ O_3	119	1.038 (1.028, 1.049)	+ O_3	50	1.038 (1.024, 1.052)
	+ SO_2	114	1.033 (1.021, 1.046)	+ SO_2	50	1.029 (1.013, 1.045)
	+ NO_2	74	1.032 (1.021, 1.044)	+ NO_2	50	1.037 (1.023, 1.050)
	+ CO	109	1.035 (1.025, 1.046)	+ CO	50	1.036 (1.022, 1.050)
	Full Pollutant	50	1.029 (1.008, 1.051)	Full Pollutant	50	1.029 (1.008, 1.051)
SO_2	Base	118	1.030 (1.024, 1.036)	Base	50	1.030 (1.023, 1.037)
(5 ppb)	Adjusted	118	1.018 (1.012, 1.024)	Adjusted	50	1.015 (1.008, 1.023)
(1980)	+ $PM_{2.5}$	96	1.017 (1.011, 1.023)	+ $PM_{2.5}$	50	1.015 (1.008, 1.022)
	+ O_3	105	1.017 (1.011, 1.023)	+ O_3	50	1.015 (1.008, 1.023)
	+ SO_4^{2-}	114	1.009 (1.003, 1.016)	+ SO_4^{2-}	50	1.008 (1.000, 1.016)
	+ NO_2	71	1.017 (1.010, 1.024)	+ NO_2	50	1.017 (1.010, 1.024)
	+ CO	97	1.019 (1.013, 1.025)	+ CO	50	1.017 (1.010, 1.024)
	Full Pollutant	50	1.009 (1.000, 1.018)	Full Pollutant	50	1.009 (1.000, 1.018)

Table 4. Continued

Pollutant (increase)	Model	No. of MSAs	HR (95% CI)	Model	No. of MSAs	HR (95% CI)
NO_2	Base	78	0.987 (0.981, 0.994)	Base	50	0.986 (0.979, 0.993)
(10 ppb)	Adjusted	78	0.995 (0.988, 1.002)	Adjusted	50	0.994 (0.987, 1.002)
(1980)	+ $PM_{2.5}$	65	0.990 (0.982, 0.998)	+ $PM_{2.5}$	50	0.989 (0.981, 0.998)
	+ O_3	76	0.994 (0.987, 1.002)	+ O_3	50	0.994 (0.986, 1.002)
	+ SO_4^{2-}	74	0.995 (0.988, 1.002)	+ SO_4^{2-}	50	0.994 (0.987, 1.002)
	+ SO_2	71	0.991 (0.984, 0.999)	+ SO_2	50	0.991 (0.983, 0.998)
	+ CO	70	0.995 (0.985, 1.004)	+ CO	50	0.996 (0.986, 1.005)
	Full Pollutant	50	0.991 (0.980, 1.002)	Full Pollutant	50	0.991 (0.980, 1.002)
CO	Base	113	0.984 (0.976, 0.993)	Base	50	0.981 (0.970, 0.992)
(1 ppm)	Adjusted	113	0.994 (0.985, 1.003)	Adjusted	50	0.992 (0.980, 1.003)
(1980)	+ $PM_{2.5}$	89	0.991 (0.981, 1.000)	+ $PM_{2.5}$	50	0.989 (0.978, 1.001)
	+ O_3	104	0.994 (0.985, 1.003)	+ O_3	50	0.992 (0.980,1.004)
	+ SO_4^{2-}	109	0.997 (0.988, 1.006)	+ SO_4^{2-}	50	0.997 (0.986, 1.009)
	+ SO_2	97	0.991 (0.982, 1.000)	+ SO_2	50	0.987 (0.976, 0.999)
	+ NO_2	70	1.000 (0.986, 1.014)	+ NO_2	50	0.996 (0.981, 1.010)
	Full Pollutant	50	1.001 (0.986, 1.017)	Full Pollutant	50	1.001 (0.986, 1.017)

Table 5. Hazard ratios for cardiopulmonary mortality (1982-2000) based on single and multiple pollutant standard Cox survival model adjusting for 44 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis). Results for both maximum and restricted numbers of MSAs are shown.

Pollutant (increase)	Model	No. of MSAs	HR (95% CI)	Model	No. of MSAs	HR (95% CI)
$PM_{2.5}$	Base	116	1.115 (1.087, 1.144)	Base	50	1.134 (1.100, 1.168)
(10 $\mu g/m^3$)	Adjusted	116	1.097 (1.068, 1.126)	Adjusted	50	1.108 (1.073, 1.144)
(1999-	+ O_3	98	1.095 (1.065, 1.125)	+ O_3	50	1.108 (1.072, 1.145)
2000)	+ SO_4^{2-}	110	1.062 (1.030, 1.095)	+ SO_4^{2-}	50	1.085 (1.047, 1.124)
	+ SO_2	96	1.104 (1.073, 1.135)	+ SO_2	50	1.105 (1.070, 1.141)
	+ NO_2	65	1.109 (1.071, 1.148)	+ NO_2	50	1.124 (1.084, 1.166)
	+ CO	89	1.101 (1.071, 1.131)	+ CO	50	1.107 (1.071, 1.144)
	Full Pollutant	50	1.087 (1.037, 1.139)	Full Pollutant	50	1.087 (1.037, 1.139)
O_3	Base	122	1.013 (0.997, 1.029)	Base	50	1.003 (0.983, 1.023)
(10 ppb)	Adjusted	122	1.018 (1.002, 1.035)	Adjusted	50	1.016 (0.995, 1.037)
(1980)	+ $PM_{2.5}$	98	1.009 (0.992, 1.026)	+ $PM_{2.5}$	50	1.001 (0.980, 1.022)
	+ SO_4^{2-}	119	1.023 (1.007, 1.040)	+ SO_4^{2-}	50	1.029 (1.007, 1.051)
	+ SO_2	105	1.018 (1.001, 1.035)	+ SO_2	50	1.017 (0.996, 1.038)
	+ NO_2	76	1.011 (0.991, 1.032)	+ NO_2	50	1.013 (0.991, 1.035)
	+ CO	104	1.024 (1.007, 1.042)	+ CO	50	1.013 (0.992, 1.035)
	Full Pollutant	50	1.015 (0.992, 1.039)	Full Pollutant	50	1.015 (0.992, 1.039)
SO_4^{2-}	Base	149	1.087 (1.073, 1.101)	Base	50	1.119 (1.100, 1.139)
(5 $\mu g/m^3$)	Adjusted	149	1.041 (1.027, 1.056)	Adjusted	50	1.051 (1.031, 1.071)
(1980)	+ $PM_{2.5}$	110	1.042 (1.023, 1.060)	+ $PM_{2.5}$	50	1.029 (1.008, 1.051)
	+ O_3	119	1.043 (1.028, 1.058)	+ O_3	50	1.057 (1.037, 1.077)
	+ SO_2	114	1.039 (1.021, 1.056)	+ SO_2	50	1.053 (1.031, 1.077)
	+ NO_2	74	1.036 (1.019, 1.053)	+ NO_2	50	1.051 (1.032, 1.071)
	+ CO	109	1.039 (1.024, 1.054)	+ CO	50	1.056 (1.036, 1.076)
	Full Pollutant	50	1.036 (1.005, 1.068)	Full Pollutant	50	1.036 (1.005, 1.068)
SO_2	Base	118	1.035 (1.027, 1.043)	Base	50	1.033 (1.024, 1.043)
(5 ppb)	Adjusted	118	1.018 (1.010, 1.026)	Adjusted	50	1.012 (1.002, 1.022)
(1980)	+ $PM_{2.5}$	96	1.012 (1.004, 1.021)	+ $PM_{2.5}$	50	1.009 (0.999, 1.019)
	+ O_3	105	1.016 (1.008, 1.025)	+ O_3	50	1.012 (1.002, 1.022)
	+ SO_4^{2-}	114	1.008 (0.999, 1.018)	+ SO_4^{2-}	50	0.998 (0.986, 1.009)
	+ NO_2	71	1.011 (1.002, 1.021)	+ NO_2	50	1.011 (1.001, 1.021)
	+ CO	97	1.017 (1.008, 1.025)	+ CO	50	1.011 (1.002, 1.021)
	Full Pollutant	50	1.000 (0.987, 1.013)	Full Pollutant	50	1.000 (0.987, 1.013)

Table 5. Continued

Pollutant (increase)	Model	No. of MSAs	HR (95% CI)	Model	No. of MSAs	HR (95% CI)
NO_2	Base	78	1.000 (0.990, 1.009)	Base	50	0.999 (0.989, 1.010)
(10 ppb)	Adjusted	78	1.008 (0.998, 1.018)	Adjusted	50	1.009 (0.998, 1.019)
(1980)	+ $PM_{2.5}$	65	0.992 (0.981, 1.003)	+ $PM_{2.5}$	50	0.990 (0.978, 1.002)
	+ O_3	76	1.006 (0.996, 1.016)	+ O_3	50	1.007 (0.996, 1.018)
	+ SO_4^{2-}	74	1.009 (0.999, 1.019)	+ SO_4^{2-}	50	1.009 (0.998, 1.020)
	+ SO_2	71	1.007 (0.996, 1.017)	+ SO_2	50	1.007 (0.996, 1.018)
	+ CO	70	1.004 (0.991, 1.017)	+ CO	50	1.004 (0.991, 1.018)
	Full Pollutant	50	0.985 (0.970, 1.000)	Full Pollutant	50	0.985 (0.970, 1.000)
CO	Base	113	0.990 (0.978, 1.002)	Base	50	1.002 (0.987, 1.018)
(1 ppm)	Adjusted	113	1.001 (0.988, 1.013)	Adjusted	50	1.015 (0.998, 1.031)
(1980)	+ $PM_{2.5}$	89	1.000 (0.986, 1.014)	+ $PM_{2.5}$	50	1.002 (0.985, 1.019)
	+ O_3	104	1.000 (0.987, 1.013)	+ O_3	50	1.013 (0.996, 1.030)
	+ SO_4^{2-}	109	1.005 (0.992, 1.018)	+ SO_4^{2-}	50	1.023 (1.006, 1.040)
	+ SO_2	97	0.998 (0.985, 1.011)	+ SO_2	50	1.012 (0.995, 1.029)
	+ NO_2	70	1.011 (0.991, 1.031)	+ NO_2	50	1.010 (0.990, 1.032)
	Full Pollutant	50	1.022 (1.000, 1.045)	Full Pollutant	50	1.022 (1.000, 1.045)

Table 6. Hazard ratios for lung cancer mortality (1982-2000) based on single and multiple pollutant standard Cox survival model adjusting for 44 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis). Results for both maximum and restricted numbers of MSAs are shown.

Pollutant (increase)	Model	No. of MSAs	HR (95% CI)	Model	No. of MSAs	HR (95% CI)
$PM_{2.5}$	Base	116	1.167 (1.093, 1.246)	Base	50	1.172 (1.083, 1.267)
(10 $\mu g/m^3$)	Adjusted	116	1.118 (1.043, 1.197)	Adjusted	50	1.091 (1.004, 1.185)
(1999-	+ O_3	98	1.128 (1.050, 1.212)	+ O_3	50	1.110 (1.019, 1.208)
2000)	+ SO_4^{2-}	110	1.075 (0.993, 1.165)	+ SO_4^{2-}	50	1.055 (0.962, 1.157)
	+ SO_2	96	1.106 (1.028, 1.190)	+ SO_2	50	1.097 (1.009, 1.193)
	+ NO_2	65	1.121 (1.026, 1.224)	+ NO_2	50	1.116 (1.016, 1.225)
	+ CO	89	1.120 (1.043, 1.202)	+ CO	50	1.108 (1.017, 1.207)
	Full Pollutant	50	1.052 (0.935, 1.183)	Full Pollutant	50	1.052 (0.935, 1.183)
O_3	Base	122	0.986 (0.947, 1.027)	Base	50	0.950 (0.902, 1.000)
(10 ppb)	Adjusted	122	0.984 (0.944, 1.026)	Adjusted	50	0.965 (0.915, 1.018)
(1980)	+ $PM_{2.5}$	98	0.974 (0.931, 1.017)	+ $PM_{2.5}$	50	0.951 (0.901, 1.005)
	+ SO_4^{2-}	119	0.992 (0.951, 1.035)	+ SO_4^{2-}	50	0.977 (0.925, 1.032)
	+ SO_2	105	0.988 (0.947, 1.031)	+ SO_2	50	0.964 (0.914, 1.017)
	+ NO_2	76	0.952 (0.904, 1.002)	+ NO_2	50	0.962 (0.911, 1.017)
	+ CO	104	0.990 (0.947, 1.004)	+ CO	50	0.969 (0.917, 1.023)
	Full Pollutant	50	0.971 (0.916, 1.030)	Full Pollutant	50	0.971 (0.916, 1.030)
SO_4^{2-}	Base	149	1.131 (1.094, 1.169)	Base	50	1.148 (1.097, 1.201)
(5 $\mu g/m^3$)	Adjusted	149	1.066 (1.029, 1.104)	Adjusted	50	1.061 (1.011, 1.114)
(1980)	+ $PM_{2.5}$	110	1.045 (0.998, 1.093)	+ $PM_{2.5}$	50	1.047 (0.993, 1.105)
	+ O_3	119	1.062 (1.025, 1.102)	+ O_3	50	1.057 (1.006, 1.110)
	+ SO_2	114	1.103 (1.056, 1.151)	+ SO_2	50	1.104 (1.043, 1.169)
	+ NO_2	74	1.074 (1.030, 1.119)	+ NO_2	50	1.061 (1.011, 1.114)
	+ CO	109	1.057 (1.019, 1.097)	+ CO	50	1.059 (1.008, 1.112)
	Full Pollutant	50	1.078 (0.998, 1.164)	Full Pollutant	50	1.078 (0.998, 1.164)
SO_2	Base	118	0.986 (0.966, 1.006)	Base	50	0.980 (0.956, 1.004)
(5 ppb)	Adjusted	118	0.993 (0.973, 1.015)	Adjusted	50	0.990 (0.965, 1.015)
(1980)	+ $PM_{2.5}$	96	0.989 (0.967, 1.011)	+ $PM_{2.5}$	50	0.986 (0.961, 1.012)
	+ O_3	105	0.993 (0.971, 1.014)	+ O_3	50	0.989 (0.964, 1.015)
	+ SO_4^{2-}	114	0.965 (0.941, 0.989)	+ SO_4^{2-}	50	0.962 (0.933, 0.992)
	+ NO_2	71	0.989 (0.965, 1.014)	+ NO_2	50	0.989 (0.964, 1.015)
	+ CO	97	0.996 (0.975, 1.018)	+ CO	50	0.992 (0.966, 1.018)
	Full Pollutant	50	0.966 (0.933, 0.999)	Full Pollutant	50	0.966 (0.933, 0.999)

Table 6. Continued

Pollutant (increase)	Model	No. of MSAs	HR (95% CI)	Model	No. of MSAs	HR (95% CI)
NO_2	Base	78	0.984 (0.960, 1.009)	Base	50	0.992 (0.968, 1.019)
(10 ppb)	Adjusted	78	1.002 (0.977, 1.028)	Adjusted	50	1.000 (0.973, 1.028)
(1980)	+ $PM_{2.5}$	65	0.987 (0.958, 1.016)	+ $PM_{2.5}$	50	0.984 (0.954, 1.015)
	+ O_3	76	1.005 (0.979, 1.031)	+ O_3	50	1.006 (0.977, 1.035)
	+ SO_4^{2-}	74	1.002 (0.976, 1.029)	+ SO_4^{2-}	50	1.001 (0.973, 1.029)
	+ SO_2	71	1.004 (0.977, 1.031)	+ SO_2	50	1.003 (0.975, 1.031)
	+ CO	70	1.013 (0.979, 1.048)	+ CO	50	1.015 (0.980, 1.051)
	Full Pollutant	50	1.008 (0.969, 1.049)	Full Pollutant	50	1.008 (0.969, 1.049)
CO	Base	113	0.957 (0.928, 0.988)	Base	50	0.950 (0.922, 0.982)
(1 ppm)	Adjusted	113	0.973 (0.942, 1.005)	Adjusted	50	0.979 (0.938, 1.021)
(1980)	+ $PM_{2.5}$	89	0.972 (0.939, 1.007)	+ $PM_{2.5}$	50	0.967 (0.927, 1.010)
	+ O_3	104	0.971 (0.940, 1.004)	+ O_3	50	0.983 (0.942, 1.026)
	+ SO_4^{2-}	109	0.978 (0.946, 1.011)	+ SO_4^{2-}	50	0.987 (0.946, 1.030)
	+ SO_2	97	0.977 (0.945, 1.010)	+ SO_2	50	0.981 (0.940, 1.024)
	+ NO_2	70	0.969 (0.921, 1.019)	+ NO_2	50	0.966 (0.915, 1.018)
	Full Pollutant	50	0.990 (0.936, 1.048)	Full Pollutant	50	0.990 (0.936, 1.048)

These results showed significant, positive associations of fine particles with all-cause mortality (HR = 1.033, 95% CI: 1.014-1.052), cardiopulmonary mortality (HR = 1.097, 95% CI: 1.068-1.126), and lung cancer mortality (HR = 1.118, 95% CI: 1.043-1.197). Similarly, sulfate was significantly associated with all-cause (HR = 1.038, 95% CI: 1.028-1.048), cardiopulmonary (HR = 1.041, 95% CI: 1.027-1.056), and lung cancer (HR = 1.066, 95% CI: 1.029-1.104) mortality. There were also significant positive associations of sulfur dioxide with all-cause (HR = 1.018, 95% CI: 1.012-1.024) and cardiopulmonary (HR = 1.018, 95% CI: 1.010-1.026) mortality.

For fine particles in relation to all-cause mortality, the effect was nullified when sulfate was entered into the model (HR = 0.994, 95% CI: 0.972-1.016). Sulfate also

reduced the hazard ratio for fine particulate matter associated with cardiopulmonary mortality by 0.03 to 1.062 (95% CI = 1.030-1.095). Similarly, for lung cancer mortality, the fine particle hazard ratio was reduced from 1.118 to 1.075 when sulfate was entered into the model. Not surprisingly, fine particles and sulfate were highly positively correlated (r = 0.57) (Table 7). Contrarily, controlling for fine particulate matter resulted in the virtual elimination of the association between ozone and cardiopulmonary mortality (HR = 1.009, 95% CI: 0.992-1.026).

Table 7. Pearson correlations (x100) between pollutants recorded at the MSA levels.

Ecological Covariate	$PM_{2.5}$ (1999-2000)	O_3 (1980)	SO_4^{2-} (1980)	SO_2 (1980)	NO_2 (1980)	CO (1980)
$PM_{2.5}$ (1999-2000)	100	5	57	22	8	-17
O_3 (1980)		100	-12	-6	10	2
SO_4^{2-} (1980)			100	51	-6	-16
SO_2 (1980)				100	24	12
NO_2 (1980)					100	62
CO (1980)						100

The other pollutants did not significantly affect the sulfate hazard ratios when entered into survival models with the exception of sulfur dioxide associated with lung cancer mortality. The sulfate hazard ratio was increased from 1.066 to 1.103. However, the inclusion of sulfate into the Cox regression model significantly lessened the association between sulfur dioxide and all-cause (HR = 1.009, 95% CI: 1.003-1.016) and cardiopulmonary (HR = 1.008, 95% CI: 0.999-1.018) mortality.

When controlling for all six pollutants at a time, the only significant associations remaining appeared to be between sulfate and all-cause mortality, and both sulfate and fine particulate matter and cardiopulmonary mortality (based on "full pollutant" models).

None of the pollutants were significantly associated with lung cancer mortality overall, with the exception of sulfur dioxide, which was significantly inversely associated with lung cancer mortality (HR = 0.966, 95% CI: 0.933-0.999).

Ozone, nitrogen dioxide, and carbon monoxide were not significantly positively associated with all-cause or lung cancer mortality. Ozone had a significant positive association with cardiopulmonary mortality (adjusted HR = 1.018, 95% CI: 1.002-1.035) when considering potential individual confounders. However, nitrogen dioxide and carbon monoxide, in addition to sulfur dioxide, did not have a significant association with cardiopulmonary mortality.

A sensitivity analysis was performed comparing the set of multiple pollutant model results as described above using the maximum number of MSAs available for each pollutant or combination of pollutants to the multiple pollutant model results based on a fixed set of cities which had data available for all pollutants (N = 50) (Tables 4, 5, and 6). This sensitivity analysis revealed that the hazard ratio estimates did not differ by more than 2.2% upon selecting a different set of MSAs for exposure data. However, this change was indicated that $PM_{2.5}$ was no longer significantly associated with all-cause mortality and O_3 was no longer significantly associated with cardiopulmonary mortality. In both cases, the estimates are still very close to being significant at the 95% level of confidence.

Next, the validity of adding in multiple pollutants to single pollutant models and the goodness of fit of the models were assessed by comparing log-likelihoods and AIC values respectively (Tables 8, 9, and 10).

Table 8. Results of log-likelihood and AIC analyses for multiple pollutant analyses based on restricted MSA (N=50) conditions and all-cause mortality.

Pollutant (increase)	Model	HR (95% CI)	Log Likelihood (-2log L)	P-value	AIC	Δ AIC
$PM_{2.5}$	Base	1.041 (1.019, 1.063)				
(10 $\mu g/m^3$)	Adjusted	1.015 (0.993, 1.038)	1163150.0		1163240.0	
(1999-	+ O_3	1.017 (0.994, 1.041)	1163149.5	0.48	1163241.5	-1.5
2000)	+ SO_4^{2-}	0.985 (0.961, 1.011)	1163121.9	< 0.0001	1163213.9	26.1
	+ SO_2	1.010 (0.987, 1.033)	1163132.1	< 0.0001	1163224.1	15.9
	+ NO_2	1.027 (1.002, 1.052)	1163144.0	0.014	1163236.0	4
	+ CO	1.020 (0.997, 1.044)	1163146.9	0.078	1163238.9	1.1
	Full	1.000 (0.968, 1.033)	1163115.0	< 0.0001	1163215.0	25
O_3	Base	0.984 (0.970, 0.998)				
(10 ppb)	Adjusted	0.997 (0.982, 1.011)	1163151.6		1163241.6	
(1980)	+ $PM_{2.5}$	0.994 (0.980, 1.009)	1163149.5	0.15	1163241.5	0.1
	+ SO_4^{2-}	1.005 (0.990, 1.020)	1163122.8	< 0.0001	1163214.8	26.8
	+ SO_2	0.997 (0.983, 1.012)	1163132.7	< 0.0001	1163224.7	16.9
	+ NO_2	1.000 (0.985, 1.015)	1163149.3	0.13	1163241.3	0.3
	+ CO	0.999 (0.984, 1.013)	1163149.7	0.17	1163241.7	-0.1
	Full	1.008 (0.992, 1.025)	1163115.0	< 0.0001	1163215.0	26.6
SO_4^{2-}	Base	1.095 (1.081, 1.108)				
(5 $\mu g/m^3$)	Adjusted	1.037 (1.023, 1.051)	1163123.2		1163213.2	
(1980)	+ $PM_{2.5}$	1.041 (1.025, 1.056)	1163121.9	0.25	1163213.9	-0.7
	+ O_3	1.038 (1.024, 1.052)	1163122.8	0.53	1163214.8	-1.6
	+ SO_2	1.029 (1.013, 1.045)	1163119.8	0.065	1163211.8	1.4
	+ NO_2	1.037 (1.023, 1.050)	1163120.9	0.13	1163212.9	0.3
	+ CO	1.036 (1.022, 1.050)	1163123.0	0.65	1163215.0	-1.8
	Full	1.029 (1.008, 1.051)	1163115.0	0.0042	1163215.0	-1.8
SO_2	Base	1.030 (1.023, 1.037)				
(5 ppb)	Adjusted	1.015 (1.008, 1.023)	1163132.8		1163222.8	
(1980)	+ $PM_{2.5}$	1.015 (1.008, 1.022)	1163132.1	0.40	1163224.1	-1.3
	+ O_3	1.015 (1.008, 1.023)	1163132.7	0.75	1163224.7	-1.9
	+ SO_4^{2-}	1.008 (1.000, 1.016)	1163119.8	0.0003	1163211.8	11
	+ NO_2	1.017 (1.010, 1.024)	1163127.3	0.019	1163219.3	3.5
	+ CO	1.017 (1.010, 1.024)	1163128.3	0.034	1163220.3	2.5
	Full	1.009 (1.000, 1.018)	1163115.0	< 0.0001	1163215.0	7.8

Table 8. Continued

Pollutant (increase)	Model	HR (95% CI)	Log Likelihood (-2log L)	p-value	AIC	Δ AIC
NO_2	Base	0.986 (0.979, 0.993)				
(10 ppb)	Adjusted	0.994 (0.987, 1.002)	1163149.3		1163239.3	
(1980)	+ $PM_{2.5}$	0.989 (0.981, 0.998)	1163144.0	0.021	1163236.0	3.3
	+ O_3	0.994 (0.986, 1.002)	1163149.3	1.0	1163241.3	-2
	+ SO_4^{2-}	0.994 (0.987, 1.002)	1163120.9	< 0.0001	1163212.9	26.4
	+ SO_2	0.991 (0.983, 0.998)	1163127.3	< 0.0001	1163219.3	20
	+ CO	0.996 (0.986, 1.005)	1163149.0	0.6	1163241.0	-1.7
	Full	0.991 (0.980, 1.002)	1163115.0	< 0.0001	1163215.0	24.3
CO	Base	0.981 (0.970, 0.992)				
(1 ppm)	Adjusted	0.992 (0.980, 1.003)	1163149.8		1163239.8	
(1980)	+ $PM_{2.5}$	0.989 (0.978, 1.001)	1163146.9	0.89	1163238.9	0.9
	+ O_3	0.992 (0.980,1.004)	1163149.7	0.75	1163241.7	-1.9
	+ SO_4^{2-}	0.997 (0.986, 1.009)	1163123.0	< 0.0001	1163215.0	24.8
	+ SO_2	0.987 (0.976, 0.999)	1163128.3	< 0.0001	1163220.3	19.5
	+ NO_2	0.996 (0.981, 1.010)	1163149.0	0.37	1163241.0	-1.2
	Full	1.001 (0.986, 1.017)	1163115.0	< 0.0001	1163215.0	24.8

Table 9. Results of log-likelihood and AIC analyses for multiple pollutant analyses based on restricted MSA (N=50) conditions and cardiopulmonary mortality.

Pollutant (increase)	Model	HR (95% CI)	Log Likelihood (-2log L)	p-value	AIC	Δ AIC
$PM_{2.5}$	Base	1.134 (1.100, 1.168)				
(10 $\mu g/m^3$)	Adjusted	1.108 (1.073, 1.144)	557636.41		557726.41	
(1999-	+ O_3	1.108 (1.072, 1.145)	557636.40	0.92	557728.40	-1.99
2000)	+ SO_4^{2-}	1.085 (1.047, 1.124)	557628.93	0.0062	557720.93	5.48
	+ SO_2	1.105 (1.070, 1.141)	557633.41	0.083	557725.41	1
	+ NO_2	1.124 (1.084, 1.166)	557633.73	0.10	557725.73	0.68
	+ CO	1.107 (1.071, 1.144)	557636.36	0.82	557728.36	-1.95
	Full	1.087 (1.037, 1.139)	557622.48	0.00019	557722.48	3.93
O_3	Base	1.003 (0.983, 1.023)				
(10 ppb)	Adjusted	1.016 (0.995, 1.037)	557673.67		557763.67	
(1980)	+ $PM_{2.5}$	1.001 (0.980, 1.022)	557636.40	< 0.0001	557728.40	35.27
	+ SO_4^{2-}	1.029 (1.007, 1.051)	557642.24	< 0.0001	557734.24	29.43
	+ SO_2	1.017 (0.996, 1.038)	557668.19	0.019	557760.19	3.48
	+ NO_2	1.013 (0.991, 1.035)	557672.23	0.23	557764.23	-0.56
	+ CO	1.013 (0.992, 1.035)	557671.45	0.14	557763.45	0.22
	Full	1.015 (0.992, 1.039)	557622.48	< 0.0001	557722.48	41.19
SO_4^{2-}	Base	1.119 (1.100, 1.139)				
(5 $\mu g/m^3$)	Adjusted	1.051 (1.031, 1.071)	557649.24		557739.24	
(1980)	+ $PM_{2.5}$	1.029 (1.008, 1.051)	557628.93	< 0.0001	557720.93	18.31
	+ O_3	1.057 (1.037, 1.077)	557642.24	0.0082	557734.24	5
	+ SO_2	1.053 (1.031, 1.077)	557649.08	0.69	557741.08	-1.84
	+ NO_2	1.051 (1.032, 1.071)	557646.66	0.11	557738.66	0.58
	+ CO	1.056 (1.036, 1.076)	557642.11	0.0076	557734.11	5.13
	Full	1.036 (1.005, 1.068)	557622.48	< 0.0001	557722.48	16.76
SO_2	Base	1.033 (1.024, 1.043)				
(5 ppb)	Adjusted	1.012 (1.002, 1.022)	557670.63		557760.63	
(1980)	+ $PM_{2.5}$	1.009 (0.999, 1.019)	557633.41	< 0.0001	557725.41	35.22
	+ O_3	1.012 (1.002, 1.022)	557668.19	0.12	557760.19	0.44
	+ SO_4^{2-}	0.998 (0.986, 1.009)	557649.08	< 0.0001	557741.08	19.55
	+ NO_2	1.011 (1.001, 1.021)	557669.23	0.24	557761.23	-0.6
	+ CO	1.011 (1.002, 1.021)	557668.69	0.16	557760.69	-0.06
	Full	1.000 (0.987, 1.013)	557622.48	< 0.0001	557722.48	38.15

Table 9. Continued

Pollutant (increase)	Model	HR (95% CI)	Log Likelihood (-2log L)	p-value	AIC	Δ AIC
NO_2	Base	0.999 (0.989, 1.010)				
(10 ppb)	Adjusted	1.009 (0.998, 1.019)	557673.53		557763.53	
(1980)	+ $PM_{2.5}$	0.990 (0.978, 1.002)	557633.73	< 0.0001	557725.73	37.8
	+ O_3	1.007 (0.996, 1.018)	557672.23	0.25	557764.23	-0.7
	+ SO_4^{2-}	1.009 (0.998, 1.020)	557646.66	< 0.0001	557738.66	24.87
	+ SO_2	1.007 (0.996, 1.018)	557669.23	0.038	557761.23	2.3
	+ CO	1.004 (0.991, 1.018)	557672.57	0.33	557764.57	-1.04
	Full	0.985 (0.970, 1.000)	557622.48	< 0.0001	557722.48	41.05
CO	Base	1.002 (0.987, 1.018)				
(1 ppm)	Adjusted	1.015 (0.998, 1.031)	557672.97		557762.97	
(1980)	+ $PM_{2.5}$	1.002 (0.985, 1.019)	557636.36	< 0.0001	557728.36	34.61
	+ O_3	1.013 (0.996, 1.030)	557671.45	0.23	557763.45	-0.48
	+ SO_4^{2-}	1.023 (1.006, 1.040)	557642.11	< 0.0001	557734.11	28.86
	+ SO_2	1.012 (0.995, 1.029)	557668.69	0.039	557760.69	2.28
	+ NO_2	1.010 (0.990, 1.032)	557672.57	0.53	557764.57	-1.6
	Full	1.022 (1.000, 1.045)	557622.48	< 0.0001	557722.48	40.49

Table 10. Results of log-likelihood and AIC analyses for multiple pollutant analyses based on restricted MSA (N=50) conditions and lung cancer mortality.

Pollutant (increase)	Model	HR (95% CI)	Log Likelihood (-2log L)	p-value	AIC	Δ AIC
$PM_{2.5}$	Base	1.172 (1.083, 1.267)				
(10 $\mu g/m^3$)	Adjusted	1.091 (1.004, 1.185)	86221.098		86311.098	
(1999-	+ O_3	1.110 (1.019, 1.208)	86217.872	0.072	86309.872	1.226
2000)	+ SO_4^{2-}	1.055 (0.962, 1.157)	86218.250	0.091	86310.250	0.848
	+ SO_2	1.097 (1.009, 1.193)	86219.952	0.28	86311.952	-0.854
	+ NO_2	1.116 (1.016, 1.225)	86220.058	0.31	86312.058	-0.96
	+ CO	1.108 (1.017, 1.207)	86218.820	0.13	86310.820	0.278
	Full	1.052 (0.935, 1.183)	86211.550	0.0021	86311.550	-0.452
O_3	Base	0.950 (0.902, 1.000)				
(10 ppb)	Adjusted	0.965 (0.915, 1.018)	86223.606		86313.606	
(1980)	+ $PM_{2.5}$	0.951 (0.901, 1.005)	86217.872	0.017	86309.872	3.734
	+ SO_4^{2-}	0.977 (0.925, 1.032)	86218.852	0.029	86310.852	2.754
	+ SO_2	0.964 (0.914, 1.017)	86222.918	0.41	86314.918	-1.312
	+ NO_2	0.962 (0.911, 1.017)	86223.460	0.71	86315.460	-1.854
	+ CO	0.969 (0.917, 1.023)	86222.984	0.43	86314.984	-1.378
	Full	0.971 (0.916, 1.030)	86211.550	0.00052	86311.550	2.056
SO_4^{2-}	Base	1.148 (1.097, 1.201)				
(5 $\mu g/m^3$)	Adjusted	1.061 (1.011, 1.114)	86219.537		86309.537	
(1980)	+ $PM_{2.5}$	1.047 (0.993, 1.105)	86218.250	0.26	86310.250	-0.713
	+ O_3	1.057 (1.006, 1.110)	86218.852	0.41	86310.852	-1.315
	+ SO_2	1.104 (1.043, 1.169)	86213.321	0.13	86305.321	4.216
	+ NO_2	1.061 (1.011, 1.114)	86219.533	0.95	86311.533	-1.996
	+ CO	1.059 (1.008, 1.112)	86219.178	0.55	86311.178	-1.641
	Full	1.078 (0.998, 1.164)	86211.550	0.0047	86311.550	-2.013
SO_2	Base	0.980 (0.956, 1.004)				
(5 ppb)	Adjusted	0.990 (0.965, 1.015)	86224.697		86314.697	
(1980)	+ $PM_{2.5}$	0.986 (0.961, 1.012)	86219.952	0.029	86311.952	2.745
	+ O_3	0.989 (0.964, 1.015)	86222.918	0.18	86314.918	-0.221
	+ SO_4^{2-}	0.962 (0.933, 0.992)	86213.321	0.00074	86305.321	9.376
	+ NO_2	0.989 (0.964, 1.015)	86224.665	0.86	86316.665	-1.968
	+ CO	0.992 (0.966, 1.018)	86223.926	0.38	86315.926	-1.229
	Full	0.966 (0.933, 0.999)	86211.550	0.00029	86311.550	3.147

Table 10. Continued

Pollutant (increase)	Model	HR (95% CI)	Log Likelihood (-2log L)	p-value	AIC	Δ AIC
NO_2	Base	0.992 (0.968, 1.019)				
(10 ppb)	Adjusted	1.000 (0.973, 1.028)	86225.322		86315.322	
(1980)	+ $PM_{2.5}$	0.984 (0.954, 1.015)	86220.058	0.022	86312.058	3.264
	+ O_3	1.006 (0.977, 1.035)	86223.460	0.17	86315.460	-0.138
	+ SO_4^{2-}	1.001 (0.973, 1.029)	86219.533	0.016	86311.533	3.789
	+ SO_2	1.003 (0.975, 1.031)	86224.665	0.42	86316.665	-1.343
	+ CO	1.015 (0.980, 1.051)	86223.657	0.19	86315.657	-0.335
	Full	1.008 (0.969, 1.049)	86211.550	0.00021	86311.550	3.772
CO	Base	0.950 (0.922, 0.982)				
(1 ppm)	Adjusted	0.979 (0.938, 1.021)	86224.322		86314.322	
(1980)	+ $PM_{2.5}$	0.967 (0.927, 1.010)	86218.820	0.019	86310.820	3.502
	+ O_3	0.983 (0.942, 1.026)	86222.984	0.25	86314.984	-0.662
	+ SO_4^{2-}	0.987 (0.946, 1.030)	86219.178	0.023	86311.178	3.144
	+ SO_2	0.981 (0.940, 1.024)	86223.926	0.53	86315.926	-1.604
	+ NO_2	0.966 (0.915, 1.018)	86223.657	0.41	86315.657	-1.335
	Full	0.990 (0.936, 1.048)	86211.550	0.00035	86311.550	2.772

It is generally accepted that the best model fit is the one with the lowest AIC value. Here (Tables 8, 9, and 10), negative values reported in the ΔAIC column represent declines in model fit, while positive values represent improvements in fit of the model to the data. The AIC value for the all models of all-cause mortality is most improved upon adding SO_4^{2-} into the model. The models are also improved, but to a lesser extent, by adding SO_2 into the model. Additionally, the SO_4^{2-} model shows a slight decline in model predictive power upon the addition of $PM_{2.5}$ and only a very slight improvement upon adding SO_2. The model for SO_2 and all-cause mortality demonstrates a moderately large improvement in predictive power upon adding SO_4^{2-}. Furthermore, all models show relatively large decreases in AIC value upon adding all six pollutants, with the exception of SO_4^{2-} and SO_2: the model for SO_4^{2-} shows an increase in AIC value, or a decrease in model fit to the data upon adding in all six pollutants and the model for SO_2

shows only a modest reduction in the AIC value upon adding in all six pollutants. AIC values indicate that SO_4^{2-} followed by SO_2 may be the most important indicators of all-cause mortality.

For cardiopulmonary mortality, all models showed an improvement in model fit upon adding $PM_{2.5}$, followed by SO_4^{2-}, as demonstrated by reductions in AIC values. The model for $PM_{2.5}$ shows a modest reduction in AIC value upon the addition of SO_4^{2-} while the SO_4^{2-} model shows a larger reduction upon the addition of $PM_{2.5}$ as a covariate. The model for SO_2 shows much larger improvements upon the addition of both $PM_{2.5}$ and SO_4^{2-} as covariates. All models show significant reductions in the AIC upon the addition of all six pollutants. However, the reduction in the AIC value for $PM_{2.5}$ is only slight in comparison, and in the model including $PM_{2.5}$ and SO_4^{2-} shows a lower AIC value than when considering all six pollutants. Again, for the SO_4^{2-} model, the AIC value reduction is modest and the lowest AIC value is the one for the model containing both $PM_{2.5}$ and SO_4^{2-}. Based on AIC values, it appears that a model containing both $PM_{2.5}$ and SO_4^{2-} may be the best predictor of cardiopulmonary mortality.

Models for lung cancer mortality did not show much variation in AIC value. However, $PM_{2.5}$ and SO_4^{2-} showed the most consistent reductions in AIC value upon their addition as covariates into the pollutant models. Overall, NO_2 and CO were not generally associated with mortality, thus limiting the validity of the interpretation of AIC values.

Upon consideration of the results from the previous multiple pollutant analyses, "parsimonious" models including all 44 individual covariates and only those pollutants that seemed significantly associated with each type of mortality were assessed (Table 11).

Table 11. Parsimonious multiple pollutant models for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000). Hazard ratios based on standard Cox survival model controlling for 44 individual covariates, adjusting for significant pollutants and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Mortality	Pollutant	Model	HR (95% CI)	Variance ($/10^{-4}$)	Log Likelihood (-2log L)	P-value	AIC	Δ AIC
All-Cause	**$PM_{2.5}$**	Adjusted	1.015 (0.993, 1.038)	1.3	1163150.0		1163240.0	
	(1999-2000)	+ SO_4^{2-} + SO_2	0.989 (0.964, 1.014)	1.7	1163119.0	< 0.0001	1163213.0	27
	SO_4^{2-}	Adjusted	1.037 (1.023, 1.051)	0.45	1163123.2		1163213.2	
	(1980)	+ $PM_{2.5}$ + SO_2	1.033 (1.015, 1.051)	0.78	1163119.0	0.041	1163213.0	0.2
	SO_2	Adjusted	1.015 (1.008, 1.023)	0.12	1163132.8		1163222.8	
	(1980)	+ $PM_{2.5}$ + SO_4^{2-}	1.007 (0.999, 1.015)	0.18	1163119.0	0.00020	1163213.0	9.8
Cardio-pulmonary	**$PM_{2.5}$**	Adjusted	1.108 (1.073, 1.144)	2.7	557636.41		557726.41	
	(1999-2000)	+ O_3 + SO_4^{2-} + SO_2	1.077 (1.036, 1.120)	3.8	557627.69	0.0031	557723.69	2.72
	O_3	Adjusted	1.016 (0.995, 1.037)	1.1	557673.67		557763.67	
	(1980)	+ $PM_{2.5}$ + SO_4^{2-} + SO_2	1.013 (0.990, 1.036)	1.4	557627.69	< 0.0001	557723.69	39.98
	SO_4^{2-}	Adjusted	1.051 (1.031, 1.071)	0.92	557649.24		557739.24	
	(1980)	+ $PM_{2.5}$ + O_3 + SO_2	1.033 (1.006, 1.061)	1.7	557627.69	< 0.0001	557723.69	15.55
	SO_2	Adjusted	1.012 (1.002, 1.022)	0.25	557670.63		557760.63	
	(1980)	+ $PM_{2.5}$ + O_3 + SO_4^{2-}	1.001 (0.989, 1.013)	0..37	557627.69	< 0.0001	557723.69	36.94
Lung Cancer	**$PM_{2.5}$**	Adjusted	1.091 (1.004, 1.185)	17.9	86221.098		86311.098	
	(1999-2000)	+ SO_4^{2-}	1.055 (0.962, 1.157)	22.2	86218.250	0.091	86310.250	0.85
	SO_4^{2-}	Adjusted	1.061 (1.011, 1.114)	6.1	86219.537		86309.537	
	(1980)	+ $PM_{2.5}$	1.047 (0.993, 1.105)	7.5	86218.250	0.26	86310.250	-0.71

For all-cause mortality, it appears that adding both $PM_{2.5}$ and SO_2 into a model already containing SO_4^{2-} does not improve model fit to the data as evidenced by the insignificant p-value for the log-likelihood (0.65). This is further supported by the almost-null change in the AIC value. Contrarily, adding in SO_4^{2-} and SO_2 to the model with $PM_{2.5}$ and SO_4^{2-} and $PM_{2.5}$ to the model with SO_2 seemed to significantly improve the fit of the model to the data ($p < 0.0001$). Again, the AIC value is significantly lowered upon the addition of the extra covariates as described to the models of $PM_{2.5}$ and SO_2.

For cardiopulmonary mortality, $PM_{2.5}$, SO_4^{2-}, SO_2, and O_3 significantly improves the fit of the model when initially considering sulfate, sulfur dioxide, and ozone, as evidenced by the AIC values and the p-values based on the log-likelihood value differences between the single and multiple pollutant models. In the case of $PM_{2.5}$, adding in the other covariates does significantly change the log-likelihood and lower the AIC value. However, these changes are much smaller in comparison to the differences observed with the other three pollutants.

For lung cancer mortality, it appears that sulfate as a single pollutant may be the best predictor of this type of mortality. The p-value is insignificant and the AIC value increases upon adding $PM_{2.5}$ to the model. However, when initially considering the $PM_{2.5}$ single pollutant model, the AIC value is lowered upon the addition of SO_4^{2-}. The change in the log-likelihood value is insignificant in this case.

Another sensitivity analysis was performed to identify the possible differences between local and regional activity of fine particles on mortality (Table 12).

Table 12. Local and regional fine particle multiple pollutant models for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000). Hazard ratios for $PM_{2.5}$ are based on standard Cox survival model controlling for 44 individual covariates, adjusting for significant pollutants and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Morality	Pollutant (1980)	Model	HR (95% CI)
All-Cause	**$PM_{2.5}$ Regional**	Adjusted	1.026 (1.012, 1.041)
		+ SO_4^{2-}	0.998 (0.980, 1.016)
	$PM_{2.5}$ Local	Adjusted	1.004 (0.984, 1.024)
		+ SO_4^{2-}	1.009 (0.989, 1.029)
Cardio-pulmonary	**$PM_{2.5}$ Regional**	Adjusted	1.067 (1.045, 1.090)
		+ SO_4^{2-}	1.050 (1.023, 1.077)
	$PM_{2.5}$ Local	Adjusted	1.070 (1.040, 1.101)
		+ SO_4^{2-}	1.078 (1.048, 1.109)
Lung Cancer	**$PM_{2.5}$ Regional**	Adjusted	1.072 (1.017, 1.131)
		+ SO_4^{2-}	1.009 (0.945, 1.078)
	$PM_{2.5}$ Local	Adjusted	1.018 (0.947, 1.095)
		+ SO_4^{2-}	1.037 (0.964, 1.115)

It appears that for both all-cause and lung cancer mortality, attempting to adjust for $PM_{2.5}$ on a local scale renders the $PM_{2.5}$ estimate for both the single and two-pollutant model (including SO_4^{2-}) insignificant at the 95% level of confidence. This indicates that the regional component of fine particulate matter, largely sulfate, is most likely associated with mortality from all-causes and lung cancer. Though insignificant at the 95% level of confidence, the HR for local $PM_{2.5}$ adjusted for SO_4^{2-} is slightly increased. This indicates that there is potentially residual confounding present in the results. However, for cardiopulmonary mortality, the HR estimate for local $PM_{2.5}$ does not significantly change from that at the regional scale. Additionally, the HR estimates

remain significant. The inclusion of SO_4^{2-} into the locally- adjusted model also does not substantially change the $PM_{2.5}$ estimate. This suggests that local pollution may primarily be associated with cardiopulmonary mortality.

In order to determine the potential effect of spatial autocorrelation on resulting mortality hazard ratio estimates, a Random Effects survival model taking into account clustering at the MSA level was used to perform a sensitivity analysis (Table 13).

Table 13. Sensitivity analysis of spatial autocorrelation clustered at the MSA level using the Random Effects Survival Model with 44 individual covariates, stratifying the baseline hazard function by age (1-year groupings), gender, and race for all-cause, cardiopulmonary, and lung cancer mortality and based on the set of MSAs for which all pollutants were available (N=50) (95% confidence intervals given in parentheses).

Cause of Death	Model	HR (95% CI) Standard Cox	HR (95% CI) Random Effects
All-Cause	$PM_{2.5}$	1.034 (1.014, 1.055)	1.052 (1.011, 1.095)
	O_3	1.006 (0.994, 1.019)	1.008 (0.985, 1.033)
	SO_4^{2-}	1.044 (1.032, 1.057)	1.047 (1.026, 1.069)
	SO_2	1.018 (1.012, 1.025)	1.020 (1.008, 1.032)
	NO_2	0.994 (0.987, 1.002)	0.996 (0.978, 1.013)
	CO	0.993 (0.983, 1.003)	1.002 (0.982, 1.023)
	$PM_{2.5} + SO_4^{2-} + SO_2$*	1.001 (0.978, 1.024)	1.011 (0.968 1.056)
Cardiopulmonary	$PM_{2.5}$	1.111 (1.080, 1.143)	1.101 (1.044, 1.162)
	O_3	1.027 (1.009, 1.045)	1.028 (0.994, 1.063)
	SO_4^{2-}	1.059 (1.041, 1.077)	1.057 (1.026, 1.089)
	SO_2	1.017 (1.008, 1.026)	1.020 (1.003, 1.038)
	NO_2	1.009 (0.998, 1.019)	0.999 (0.971, 1.023)
	CO	1.007 (0.993, 1.021)	1.005 (0.976, 1.034)
	$PM_{2.5} + O_3 + SO_4^{2-} + SO_2$*	1.066 (1.030, 1.104)	1.047 (0.983, 1.115)
Lung Cancer	$PM_{2.5}$	1.098 (1.020, 1.183)	1.133 (1.018, 1.255)
	O_3	0.991 (0.946, 1.037)	0.988 (0.930, 1.049)
	SO_4^{2-}	1.067 (1.022, 1.114)	1.075 (1.018, 1.137)
	SO_2	0.996 (0.973, 1.020)	0.995 (0.965, 1.026)
	NO_2	1.000 (0.973, 1.028)	0.998 (0.954, 1.044)
	CO	0.982 (0.947, 1.018)	0.981 (0.933, 1.031)
	$PM_{2.5} + SO_4^{2-}$*	1.055 (0.970, 1.148)	1.079 (0.961, 1.212)

*Note that the hazard ratio reported refers to that of $PM_{2.5}$.

The results of this sensitivity analysis indicate that the parameters demonstrate only a slight increase upon considering random effects at the MSA level. Additionally,

the 95% confidence intervals become wider lowering the precision of the HR estimate upon consideration of random effects at the MSA level.

Finally, fine particulate matter exposure data from 1999-2000 instead of 1980 was used due to the much larger number of MSAs with available data for this time period (N = 116 vs. N = 60). The use of data from 1999-2000 instead of 1980 was validated by sensitivity analysis (Table 14).

Table 14. Sensitivity analysis for $PM_{2.5}$ covariates from 1999-2000 and 1980 for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000). Hazard ratios based on standard Cox survival model controlling for 44 individual covariates, adjusting for significant pollutants and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Cause of Mortality	Model	$PM_{2.5}$ (1999-2000) HR (95% CI)	$PM_{2.5}$ (1980) HR (95% CI)
All-Cause	Adjusted	1.033 (1.014, 1.052)	1.026 (1.012, 1.041)
	+ O_3	1.032 (1.012, 1.053)	1.028 (1.013, 1.043)
	+ SO_4^{2-}	0.994 (0.972, 1.016)	0.998 (0.980, 1.016)
	+ SO_2	1.024 (1.004, 1.045)	1.012 (0.995, 1.030)
	+ NO_2	1.027 (1.002, 1.052)	1.037 (1.019, 1.056)
	+ CO	1.034 (1.014, 1.054)	1.032 (1.017, 1.047)
Cardiopulmonary	Adjusted	1.097 (1.068, 1.126)	1.067 (1.045, 1.090)
	+ O_3	1.095 (1.065, 1.125)	1.070 (1.048, 1.093)
	+ SO_4^{2-}	1.062 (1.030, 1.095)	1.050 (1.023, 1.077)
	+ SO_2	1.104 (1.073, 1.135)	1.068 (1.042, 1.095)
	+ NO_2	1.109 (1.071, 1.148)	1.082 (1.055, 1.110)
	+ CO	1.101 (1.071, 1.131)	1.071 (1.049, 1.094)
Lung Cancer	Adjusted	1.118 (1.043, 1.197)	1.072 (1.017, 1.131)
	+ O_3	1.128 (1.050, 1.212)	1.080 (1.023, 1.139)
	+ SO_4^{2-}	1.075 (0.993, 1.165)	1.009 (0.945, 1.078)
	+ SO_2	1.106 (1.028, 1.190)	1.117 (1.046, 1.191)
	+ NO_2	1.121 (1.026, 1.224)	1.104 (1.035, 1.177)
	+ CO	1.120 (1.043, 1.202)	1.081 (1.024, 1.141)

A sensitivity analysis comparing single pollutant hazard ratios for fine particles associated with all-cause, cardiopulmonary, and lung cancer death, after controlling for important individual confounders and stratifying the baseline hazard function by age, gender and ethnicity, revealed that the percent increase from 1980 to 1999-2000 was 0.7%, 2.8%, and 4.3% respectively. Estimates from 1980 to 1999-2000 did not differ by more than 6%, with the majority of hazard ratio estimates only changing between 0 and 2.5%.

Ecological Covariates. The effect of ecological covariates on the association between air pollution exposure and morality was analyzed in the same way that air pollution exposure itself was analyzed using Cox proportional hazards regression models. It is important to note that since some of the ecological covariates were not available for all cities used in the study, the mortality hazard ratios associated with pollutant exposures may vary.

The relationship between ecological covariates and mortality while controlling for individual confounding was analyzed first without air pollutants as covariates (Table 15).

Table 15. Ecological covariate (at MSA-level) hazard ratios for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000) based on standard Cox survival model controlling for 44 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Ecological Covariate	Level of HR	HR (95% CI) for Cause of Mortality		
		All-Cause	Cardiopulmonary	Lung Cancer
Grade 12 (%)	10 %	0.989 (0.980, 0.999)	0.968 (0.955, 0.982)	0.943 (0.910, 0.977)
Unemployed (%)	5 %	1.027 (1.008, 1.046)	1.083 (1.056, 1.112)	0.974 (0.913, 1.040)
Income Disparity (GINI)	0.05	0.970 (0.953, 0.988)	0.988 (0.963, 1.013)	0.999 (0.935, 1.067)
Poverty (%)	5 %	1.005 (0.999, 1.011)	1.017 (1.008, 1.025)	1.011 (0.990, 1.033)
Household Income ($000s)	$10,000	0.988 (0.979, 0.997)	0.979 (0.967, 0.991)	0.994 (0.964, 1.026)
Per Capita Income ($000s)	$10,000	0.955 (0.935, 0.974)	0.918 (0.892, 0.945)	1.013 (0.941, 1.091)
White (%)	10 %	1.003 (0.998, 1.008)	0.996 (0.990, 1.003)	0.984 (0.967, 1.001)
Black (%)	10 %	1.005 (0.999, 1.011)	1.005 (0.997, 1.014)	1.038 (1.016, 1.059)
Population Change (%)	5 %	0.996 (0.994, 0.998)	0.997 (0.994, 1.000)	0.991 (0.983, 0.998)
Over 25 (%)	10 %	0.985 (0.970, 0.999)	0.960 (0.941, 0.979)	1.126 (1.059, 1.198)

Based on these results, significant reductions in all-cause (HR = 0.989, 95% CI: 0.980-0.999), cardiopulmonary (HR = 0.968, 95% CI: 0.955-0.982), and lung cancer (HR = 0.943, 95% CI: 0.910-0.977) mortality risk were seen for every 10% increase in the percentage of residents aged 25 and over in an MSA that have completed high school. That is, the risk of death from all causes, cardiopulmonary causes, and lung cancer decreased by 1.1%, 3.2%, and 5.7% respectively. A similar effect was also seen with income disparity (as measured by the GINI coefficient) and all-cause mortality: for every 0.05 unit increase in GINI coefficient, the risk of mortality from all causes decreased by 3%. Also, as both household and per capita income increased, the risks of both all-cause (HR = 0.988, 95% CI: 0.979-0.997 and HR = 0.955, 95% CI: 0.935-0.974 respectively)

and cardiopulmonary (HR = 0.979, 95% CI: 0.967-0.991 and HR = 0.918, 95% CI: 0.892-0.945 respectively) mortality decreased. These decreases in risk corresponded to a $10,000 increase in income.

In contrast, all-cause (HR = 1.027, 95% CI: 1.008-1.046) and cardiopulmonary (HR = 1.083, 95% CI: 1.056-1.112) mortality risk was increased for every 5% increase in unemployed persons over age 25 in an MSA. Furthermore, increased percentages of those of African American ethnicity at the MSA-level led to a significant increase in the risk of lung cancer mortality: for every 10% increase in percentage of African American residents in an MSA, the risk of lung cancer mortality was increased by 3.8% (HR = 1.038, 95% CI: 1.016-1.059). Lung cancer mortality also seemed to be greatly increased by the percentage of residents over age 25 in an MSA, even after stratifying the Cox models by 1-year age intervals for individuals (HR = 1.126, 95% CI: 1.059-1.198).

In summary, mortality risk decreased with increasing educational attainment, household, and per capita income, and decreasing income disparity. Increased levels unemployment and percentages of African Americans within an MSA were associated with increased mortality risk.

The effect of ecological covariates on the air pollution-mortality relationship was analyzed next (Tables 16, 17, and 18).

Table 16. Hazard ratios for all-cause mortality (1982-2000) based on standard Cox survival model controlling for 44 individual covariates, adjusting for a single ecological covariate at the MSA-level, and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Pollutant (increase)	Model	HR (95% CI)	Pollutant	Model	HR (95% CI)
$PM_{2.5}$	Adjusted	1.033 (1.014, 1.052)	**SO_2**	Adjusted	1.018 (1.012, 1.024)
(10 $\mu g/m^3$)	+ Grade 12 (1%)	1.030 (1.006, 1.054)	(5 ppb)	+ Grade 12 (%)	1.017 (1.011, 1.023)
(1999 – 2000)	+ Unemployed (%)	1.028 (1.008, 1.048)	**(1980)**	+ Unemployed (%)	1.017 (1.012, 1.023)
	+ Income Disparity (GINI)	1.047 (1.026, 1.068)		+ Income Disparity (GINI)	1.018 (1.012, 1.024)
	+ Poverty (%)	1.033 (1.013, 1.053)		+ Poverty (%)	1.018 (1.012, 1.024)
	+ Household Income ($000s)	1.033 (1.014, 1.053)		+ Household Income ($000s)	1.018 (1.012, 1.024)
	+ Per Capita Income ($000s)	1.033 (1.013, 1.052)		+ Per Capita Income ($000s)	1.017 (1.012, 1.023)
	+ White (%)	1.055 (1.032, 1.078)		+ White (%)	1.018 (1.012, 1.024)
	+ Black (%)	1.031 (1.010, 1.052)		+ Black (%)	1.018 (1.012, 1.024)
	+ Population Change (%)	1.029 (1.010, 1.049)		+ Population Change (%)	1.017 (1.010, 1.024)
	+ Over 25 (%)	1.032 (1.013, 1.052)		+ Over 25 (%)	1.018 (1.012, 1.024)
	Full Ecological	1.045 (1.017, 1.074)		Full Ecological	1.018 (1.010, 1.025)
O_3	Adjusted	1.003 (0.992, 1.015)	**NO_2**	Adjusted	0.995 (0.988, 1.002)
(10 ppb)	+ Grade 12 (%)	1.002 (0.991, 1.014)	(10 ppb)	+ Grade 12 (%)	0.992 (0.985, 0.999)
	+ Unemployed (%)	1.004 (0.992, 1.015)	**(1980)**	+ Unemployed (%)	0.994 (0.987, 1.002)
(1980)	+ Income Disparity (GINI)	1.004 (0.992, 1.015)		+ Income Disparity (GINI)	0.998 (0.991, 1.006)
	+ Poverty (%)	1.003 (0.992, 1.015)		+ Poverty (%)	0.995 (0.988, 1.002)
	+ Household Income ($000s)	1.003 (0.992, 1.015)		+ Household Income ($000s)	0.997 (0.990, 1.004)
	+ Per Capita Income ($000s)	1.000 (0.988, 1.011)		+ Per Capita Income ($000s)	0.998 (0.990, 1.005)
	+ White (%)	1.004 (0.993, 1.016)		+ White (%)	1.000 (0.992, 1.008)
	+ Black (%)	1.003 (0.992, 1.015)		+ Black (%)	0.995 (0.988, 1.002)
	+ Population Change (%)	1.012 (1.000, 1.024)		+ Population Change (%)	0.993 (0.986, 1.000)
	+ Over 25 (%)	1.000 (0.988, 1.013)		+ Over 25 (%)	0.995 (0.988, 1.002)
	Full Ecological	1.003 (0.988, 1.017)		Full Ecological	1.001 (0.990, 1.013)

Table 16. Continued

Pollutant (increase)	Model	HR (95% CI)	Pollutant (increase)	Model	HR (95% CI)
SO_4^{2-}	Adjusted	1.038 (1.028, 1.048)	**CO**	Adjusted	0.994 (0.985, 1.003)
($5\ \mu g/m^3$)	+ Grade 12 (%)	1.038 (1.027, 1.049)	(1 ppm)	+ Grade 12 (%)	0.992 (0.983, 1.001)
(1980)	+ Unemployed (%)	1.036 (1.026, 1.046)	**(1980)**	+ Unemployed (%)	0.992 (0.983, 1.001)
	+ Income Disparity (GINI)	1.038 (1.028, 1.048)		+ Income Disparity (GINI)	0.998 (0.988, 1.007)
	+ Poverty (%)	1.037 (1.027, 1.048)		+ Poverty (%)	0.994 (0.985, 1.002)
	+ Household Income ($000s)	1.037 (1.027, 1.047)		+ Household Income ($000s)	0.993 (0.985, 1.002)
	+ Per Capita Income ($000s)	1.036 (1.025, 1.046)		+ Per Capita Income ($000s)	0.994 (0.986, 1.003)
	+ White (%)	1.039 (1.029, 1.049)		+ White (%)	0.995 (0.986, 1.004)
	+ Black (%)	1.043 (1.031, 1.054)		+ Black (%)	0.994 (0.985, 1.003)
	+ Population Change (%)	1.037 (1.025, 1.048)		+ Population Change (%)	0.993 (0.985, 1.002)
	+ Over 25 (%)	1.040 (1.029, 1.050)		+ Over 25 (%)	0.994 (0.985, 1.003)
	Full Ecological	1.036 (1.021, 1.051)		Full Ecological	1.000 (0.990, 1.010)

Table 17. Hazard ratios for cardiopulmonary mortality (1982-2000) based on standard Cox survival model controlling for 44 individual covariates, adjusting for a single ecological covariate at the MSA-level, and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Pollutant (increase)	Model	HR (95% CI)	Pollutant (increase)	Model	HR (95% CI)
$PM_{2.5}$	Adjusted	1.097 (1.068, 1.126)	**SO_2**	Adjusted	1.018 (1.010, 1.026)
(10 $\mu g/m^3$)	+ Grade 12 (%)	1.077 (1.043, 1.113)	(5 ppb)	+ Grade 12 (%)	1.015 (1.007, 1.024)
(1999 – 2000)	+ Unemployed (%)	1.078 (1.048, 1.109)	**(1980)**	+ Unemployed (%)	1.015 (1.007, 1.024)
	+ Income Disparity (GINI)	1.108 (1.078, 1.140)		+ Income Disparity (GINI)	1.018 (1.010, 1.026)
	+ Poverty (%)	1.090 (1.060, 1.120)		+ Poverty (%)	1.019 (1.011, 1.027)
	+ Household Income ($000s)	1.098 (1.069, 1.128)		+ Household Income ($000s)	1.018 (1.010, 1.026)
	+ Per Capita Income ($000s)	1.096 (1.068, 1.126)		+ Per Capita Income ($000s)	1.017 (1.008, 1.025)
	+ White (%)	1.122 (1.087, 1.157)		+ White (%)	1.019 (1.010, 1.027)
	+ Black (%)	1.103 (1.071, 1.135)		+ Black (%)	1.017 (1.009, 1.026)
	+ Population Change (%)	1.095 (1.066, 1.125)		+ Population Change (%)	1.019 (1.010, 1.029)
	+ Over 25 (%)	1.094 (1.065, 1.123)		+ Over 25 (%)	1.019 (1.010, 1.027)
	Full Ecological	1.085 (1.044, 1.128)		Full Ecological	1.013 (1.002, 1.023)
O_3	Adjusted	1.018 (1.002, 1.035)	**NO_2**	Adjusted	1.008 (0.998, 1.018)
(10 ppb)	+ Grade 12 (%)	1.015 (0.998, 1.032)	(10 ppb)	+ Grade 12 (%)	1.007 (0.996, 1.018)
(1980)	+ Unemployed (%)	1.020 (1.003, 1.037)	**(1980)**	+ Unemployed (%)	1.002 (0.992, 1.013)
	+ Income Disparity (GINI)	1.018 (1.002, 1.035)		+ Income Disparity (GINI)	1.009 (0.999, 1.020)
	+ Poverty (%)	1.017 (1.001, 1.034)		+ Poverty (%)	1.007 (0.997, 1.017)
	+ Household Income ($000s)	1.018 (1.002, 1.035)		+ Household Income ($000s)	1.012 (1.002, 1.023)
	+ Per Capita Income ($000s)	1.012 (0.996, 1.029)		+ Per Capita Income ($000s)	1.014 (1.003, 1.024)
	+ White (%)	1.018 (1.001, 1.034)		+ White (%)	1.011 (1.000, 1.022)
	+ Black (%)	1.018 (1.002, 1.035)		+ Black (%)	1.008 (0.998, 1.018)
	+ Population Change (%)	1.026 (1.008, 1.044)		+ Population Change (%)	1.007 (0.997, 1.017)
	+ Over 25 (%)	1.009 (0.992, 1.027)		+ Over 25 (%)	1.007 (0.997, 1.017)
	Full Ecological	0.994 (0.974, 1.014)		Full Ecological	0.994 (0.977, 1.010)

Table 17. Continued

Pollutant	Model	HR (95% CI)	Pollutant	Model	HR (95% CI)
SO_4^{2-}	Adjusted	1.041 (1.027, 1.056)	**CO**	Adjusted	1.001 (0.988, 1.013)
(5 $\mu g/m^3$)	+ Grade 12 (%)	1.041 (1.027, 1.055)	(1 ppm)	+ Grade 12 (%)	0.996 (0.983, 1.009)
(1980)	+ Unemployed (%)	1.031 (1.015, 1.046)	**(1980)**	+ Unemployed (%)	0.995 (0.982, 1.008)
	+ Income Disparity (GINI)	1.034 (1.020, 1.049)		+ Income Disparity (GINI)	1.001 (0.988, 1.014)
	+ Poverty (%)	1.041 (1.027, 1.056)		+ Poverty (%)	0.998 (0.985, 1.011)
	+ Household Income ($000s)	1.040 (1.025, 1.054)		+ Household Income ($000s)	1.000 (0.988, 1.013)
	+ Per Capita Income ($000s)	1.039 (1.025, 1.054)		+ Per Capita Income ($000s)	1.002 (0.989, 1.015)
	+ White (%)	1.037 (1.023, 1.052)		+ White (%)	0.999 (0.986, 1.012)
	+ Black (%)	1.041 (1.027, 1.055)		+ Black (%)	1.031 (1.018, 1.044)
	+ Population Change (%)	1.046 (1.030, 1.062)		+ Population Change (%)	1.000 (0.988, 1.013)
	+ Over 25 (%)	1.045 (1.028, 1.061)		+ Over 25 (%)	1.001 (0.989, 1.014)
	Full Ecological	1.033 (1.011, 1.055)		Full Ecological	0.999 (0.985, 1.014)

Table 18. Hazard ratios for lung cancer mortality (1982-2000) based on standard Cox survival model controlling for 44 individual covariates, adjusting for a single ecological covariate at the MSA-level, and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Pollutant	Model	HR (95% CI)	Pollutant	Model	HR (95% CI)
$PM_{2.5}$	Adjusted	1.118 (1.043, 1.197)	**SO_2**	Adjusted	0.993 (0.973, 1.015)
(10 $\mu g/m^3$)	+ Grade 12 (%)	1.111 (1.021, 1.207)	(5 ppb)	+ Grade 12 (%)	0.989 (0.969, 1.011)
(1999 – 2000)	+ Unemployed (%)	1.141 (1.061, 1.226)	**(1980)**	+ Unemployed (%)	0.995 (0.974, 1.017)
	+ Income Disparity (GINI)	1.134 (1.055, 1.219)		+ Income Disparity (GINI)	0.994 (0.973, 1.015)
	+ Poverty (%)	1.130 (1.052, 1.215)		+ Poverty (%)	0.993 (0.972, 1.015)
	+ Household Income ($000s)	1.118 (1.043, 1.197)		+ Household Income ($000s)	0.993 (0.973, 1.015)
	+ Per Capita Income ($000s)	1.119 (1.045, 1.199)		+ Per Capita Income ($000s)	0.994 (0.973, 1.015)
	+ White (%)	1.121 (1.036, 1.213)		+ White (%)	0.994 (0.973, 1.015)
	+ Black (%)	1.095 (1.017, 1.180)		+ Black (%)	0.988 (0.967, 1.010)
	+ Population Change (%)	1.110 (1.036, 1.190)		+ Population Change (%)	0.978 (0.954, 1.002)
	+ Over 25 (%)	1.141 (1.064, 1.225)		+ Over 25 (%)	0.990 (0.969, 1.011)
	Full Ecological	1.189 (1.077, 1.313)		Full Ecological	0.987 (0.960, 1.014)
O_3	Adjusted	0.984 (0.944, 1.026)	**NO_2**	Adjusted	1.002 (0.977, 1.028)
(10 ppb)	+ Grade 12 (%)	0.981 (0.940, 1.023)	(10 ppb)	+ Grade 12 (%)	0.995 (0.969, 1.022)
(1980)	+ Unemployed (%)	0.983 (0.942, 1.025)	**(1980)**	+ Unemployed (%)	1.007 (0.981, 1.034)
	+ Income Disparity (GINI)	0.985 (0.944, 1.027)		+ Income Disparity (GINI)	1.006 (0.979, 1.033)
	+ Poverty (%)	0.984 (0.944, 1.026)		+ Poverty (%)	1.002 (0.977, 1.028)
	+ Household Income ($000s)	0.984 (0.944, 1.026)		+ Household Income ($000s)	0.999 (0.973, 1.026)
	+ Per Capita Income ($000s)	0.985 (0.945, 1.028)		+ Per Capita Income ($000s)	0.997 (0.971, 1.024)
	+ White (%)	0.982 (0.942, 1.024)		+ White (%)	0.995 (0.968, 1.024)
	+ Black (%)	0.983 (0.943, 1.025)		+ Black (%)	1.000 (0.974, 1.026)
	+ Population Change (%)	0.998 (0.955, 1.044)		+ Population Change (%)	0.998 (0.972, 1.024)
	+ Over 25 (%)	1.001 (0.958, 1.046)		+ Over 25 (%)	1.005 (0.979, 1.031)
	Full Ecological	1.013 (0.962, 1.066)		Full Ecological	1.026 (0.984, 1.070)

Table 18. Continued

Pollutant (increase)	Model	HR (95% CI)	Pollutant (increase)	Model	HR (95% CI)
SO_4^{2-}	Adjusted	1.066 (1.029, 1.104)	**CO**	Adjusted	0.973 (0.942, 1.005)
(5 $\mu g/m^3$)	+ Grade 12 (%)	1.051 (1.012, 1.091)	(1 ppm)	+ Grade 12 (%)	0.968 (0.937, 1.000)
(1980)	+ Unemployed (%)	1.071 (1.033, 1.109)	**(1980)**	+ Unemployed (%)	0.977 (0.946, 1.010)
	+ Income Disparity (GINI)	1.066 (1.029, 1.104)		+ Income Disparity (GINI)	0.973 (0.941, 1.007)
	+ Poverty (%)	1.065 (1.029, 1.103)		+ Poverty (%)	0.974 (0.943, 1.006)
	+ Household Income ($000s)	1.065 (1.029, 1.104)		+ Household Income ($000s)	0.973 (0.942, 1.005)
	+ Per Capita Income ($000s)	1.066 (1.029, 1.105)		+ Per Capita Income ($000s)	0.972 (0.941, 1.004)
	+ White (%)	1.064 (1.028, 1.102)		+ White (%)	0.969 (0.938, 1.001)
	+ Black (%)	1.051 (1.011, 1.093)		+ Black (%)	0.977 (0.945, 1.009)
	+ Population Change (%)	1.057 (1.016, 1.100)		+ Population Change (%)	0.972 (0.941, 1.004)
	+ Over 25 (%)	1.062 (1.025, 1.100)		+ Over 25 (%)	0.970 (0.939, 1.002)
	Full Ecological	1.038 (0.985, 1.093)		Full Ecological	0.982 (0.947, 1.018)

When added into Cox models individually with single pollutants, hazard ratios for all-cause, cardiopulmonary, and lung cancer mortality did not change by more than 3%. Even upon controlling for all selected ecological covariates simultaneously, no significant effects on the air pollution-mortality relationships were seen.

The mortality relationship between educational attainment at 3 different levels (less than high school, equal to high school, and greater than high school) was assessed at the MSA and level (Table 19).

Table 19. Education level attained (at MSA-level) hazard ratios for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000) based on standard Cox survival model controlling for 44 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Education Level Attained	HR (95% CI) for Cause of Mortality		
	All-Cause	Cardiopulmonary	Lung Cancer
< High School	1.001 (1.000, 1.003)	1.004 (1.002, 1.006)	1.011 (1.005, 1.016)
= High School	1.003 (1.002, 1.005)	1.003 (1.001, 1.005)	1.007 (1.002, 1.012)
> High School	0.997 (0.996, 0.998)	0.994 (0.993, 0.996)	0.996 (0.992, 1.000)

Mortality risk for all-cause, cardiopulmonary, and lung cancer was consistently lowest when associated with increased educational attainment of the population at the MSA level (as indicated by the percentage having completed more than high school). In all three cases, without the inclusion of pollutants, higher educational attainment at the MSA level was associated with a preventative effect on mortality. Mortality risk was higher among with completion of high school or less, but the actual trend between the two lower levels of educational attainment was unclear.

The effect of education both at the MSA and individual level on the air pollutant exposure/mortality relationship was also investigated (Tables 20 and 21).

Table 20. Hazard ratios for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000) by education level attainment at the MSA level based on single pollutant standard Cox survival model adjusting for 44 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Pollutant	Education Level	Level of HR	HR (95% CI) for Cause of Mortality		
			All-Cause	Cardiopulmonary	Lung Cancer
$PM_{2.5}$ (1999-2000)	< High School	10 $\mu g/m^3$	1.030 (1.007, 1.053)	1.083 (1.049, 1.118)	1.097 (1.011, 1.189)
	= High School		1.037 (1.017, 1.057)	1.101 (1.072, 1.131)	1.127 (1.051, 1.208)
	> High school		1.015 (0.995, 1.036)	1.070 (1.040, 1.101)	1.113 (1.034, 1.198)
	All Education		1.040 (1.015, 1.064)	1.084 (1.048, 1.121)	1.150 (1.055, 1.253)
O_3 (1980)	< High School	10 ppb	1.003 (0.992, 1.015)	1.018 (1.001, 1.035)	0.983 (0.943, 1.025)
	= High School		1.006 (0.994, 1.017)	1.020 (1.004, 1.037)	0.987 (0.946, 1.029)
	> High school		0.997 (0.986, 1.009)	1.009 (0.992, 1.026)	0.980 (0.939, 1.022)
	All Education		0.995 (0.983, 1.007)	1.003 (0.985, 1.020)	0.997 (0.954, 1.043)
SO_4^{2-} (1980)	< High School	5 $\mu g/m^3$	1.039 (1.028, 1.051)	1.033 (1.017, 1.049)	1.047 (1.007, 1.088)
	= High School		1.032 (1.021, 1.043)	1.037 (1.020, 1.054)	1.061 (1.021, 1.103)
	> High school		1.029 (1.018, 1.041)	1.018 (1.002, 1.035)	1.058 (1.016, 1.101)
	All Education		1.032 (1.020, 1.044)	1.025 (1.008 1.043)	1.045 (1.002, 1.090)
SO_2 (1980)	< High School	5 ppb	1.017 (1.011, 1.023)	1.015 (1.007, 1.024)	0.988 (0.967, 1.009)
	= High School		1.016 (1.009, 1.022)	1.017 (1.008, 1.026)	0.983 (0.960, 1.006)
	> High school		1.014 (1.008, 1.020)	1.009 (1.000, 1.018)	0.986 (0.964, 1.008)
	All Education		1.014 (1.007, 1.020)	1.012 (1.003, 1.021)	0.980 (0.957, 1.003)
NO_2 (1980)	< High School	10 ppb	0.992 (0.985, 0.999)	1.001 (0.991, 1.012)	0.993 (0.967, 1.020)
	= High School		0.999 (0.992, 1.007)	1.012 (1.002, 1.023)	1.008 (0.982, 1.035)
	> High school		0.994 (0.987, 1.001)	1.006 (0.996, 1.016)	1.002 (0.976, 1.028)
	All Education		0.998 (0.991, 1.006)	1.006 (0.995, 1.017)	0.995 (0.968, 1.024)
CO (1980)	< High School	1 ppm	0.992 (0.983, 1.001)	0.996 (0.984, 1.009)	0.966 (0.935, 0.999)
	= High School		0.996 (0.987, 1.005)	1.003 (0.990, 1.015)	0.975 (0.944, 1.007)
	> High school		0.994 (0.985, 1.003)	1.001 (0.988, 1.014)	0.973 (0.942, 1.005)
	All Education		0.997 (0.987, 1.006)	1.001 (0.988, 1.015)	0.963 (0.932, 0.996)

Table 21. Hazard ratios for all-cause, cardiopulmonary, and lung cancer mortality (1982-2000) by education level attainment at the individual level based on single pollutant standard Cox survival model adjusting for 42 individual covariates and stratifying the baseline hazard function by age (1-year groupings), gender, and ethnicity (95% confidence intervals given in parenthesis).

Pollutant	Education Level	Level of HR	HR (95% CI) for Cause of Mortality		
			All-Cause	Cardiopulmonary	Lung Cancer
$PM_{2.5}$ (1999-2000)	< High School	10 $\mu g/m^3$	1.031 (0.988, 1.077)	1.102 (1.040, 1.168)	1.248 (1.062, 1.467)
	= High School		1.060 (1.024, 1.097)	1.104 (1.051, 1.161)	1.227 (1.085, 1.388)
	> High school		1.018 (0.991, 1.045)	1.090 (1.049, 1.132)	1.014 (0.919, 1.117)
O_3 (1980)	< High School	10 ppb	0.995 (0.969, 1.022)	1.013 (0.978, 1.050)	0.949 (0.860, 1.048)
	= High School		1.002 (0.980, 1.024)	0.999 (0.969, 1.031)	1.031 (0.957, 1.111)
	> High school		1.005 (0.990, 1.021)	1.027 (1.004, 1.051)	0.973 (0.918, 1.032)
SO_4^{2-} (1980)	< High School	5 $\mu g/m^3$	1.044 (1.023, 1.067)	1.044 (1.015, 1.073)	1.145 (1.061, 1.237)
	= High School		1.052 (1.033, 1.070)	1.051 (1.025, 1.078)	1.070 (1.007, 1.137)
	> High school		1.022 (1.008, 1.037)	1.027 (1.006, 1.048)	1.031 (0.979, 1.086)
SO_2 (1980)	< High School	5 ppb	1.023 (1.011, 1.036)	1.024 (1.007, 1.041)	1.008 (0.962, 1.057)
	= High School		1.025 (1.014, 1.036)	1.026 (1.011, 1.041)	1.001 (0.966, 1.038)
	> High school		1.010 (1.001, 1.018)	1.007 (0.995, 1.020)	0.981 (0.950, 1.012)
NO_2 (1980)	< High School	10 ppb	0.984 (0.968, 1.001)	1.003 (0.981, 1.027)	1.005 (0.943, 1.072)
	= High School		0.998 (0.985, 1.011)	1.006 (0.987, 1.025)	0.975 (0.930, 1.021)
	> High school		0.998 (0.988, 1.007)	1.012 (0.999, 1.026)	1.018 (0.983, 1.055)
CO (1980)	< High School	1 ppm	0.984 (0.964, 1.004)	0.982 (0.955, 1.009)	0.966 (0.895, 1.043)
	= High School		0.991 (0.975, 1.007)	0.999 (0.975, 1.023)	0.953 (0.900, 1.009)
	> High school		0.999 (0.987, 1.012)	1.010 (0.992, 1.028)	0.991 (0.946, 1.037)

Upon controlling for each pollutant/mortality relationship by the three categories of educational attainment at the MSA level (Table 20, Figure 5), having completed more than high school was associated with the lowest hazard of mortality when the relationship between exposure and mortality was significant (all-cause mortality: SO_4^{2-} (HR = 1.029, 95% CI: 1.018-1.041) and SO_2 (HR = 1.014, 95% CI: 1.008-1.020), cardiopulmonary

mortality: $PM_{2.5}$ (HR = 1.070, 95% CI: 1.048-1.121), SO_4^{2-} (HR = 1.018, 95% CI: 1.002-1.035), and SO_2 (HR = 1.009, 95% CI: 1.000-1.018). This trend was also seen with fine particles and all-cause mortality, even though the relationship between having more than high school education and mortality was not significant at the 95% level of confidence (HR = 1.015, 95% CI: 0.995-1.036). In the case of fine particles and all-cause mortality, the relationships for having completed less than or equal to high school were significant while the association seemed to disappear upon having completed more than high school. The same was true for ozone and cardiopulmonary mortality. Again, even though the mortality hazards associated with ozone were not significant, having more than a high school education was consistently associated with having the lowest mortality hazard: all-cause mortality: HR = 0.997, 95% CI: 0.986-1.009, cardiopulmonary mortality: HR = 1.009, 95% CI: 0.992-1.026, and lung cancer mortality: HR = 0.980, 95% CI: 0.939-1.022. For all three mortality outcomes, nitrogen dioxide, and carbon monoxide did not show the expected trend of having the lowest hazard of mortality related to air pollution exposure. However, the resulting hazard ratios for these associations were not significant at the 95% level of confidence. The same was true for lung cancer mortality related to sulfur dioxide. The trend for mortality of those having less than a high school or equal to a high school education was not clearly defined.

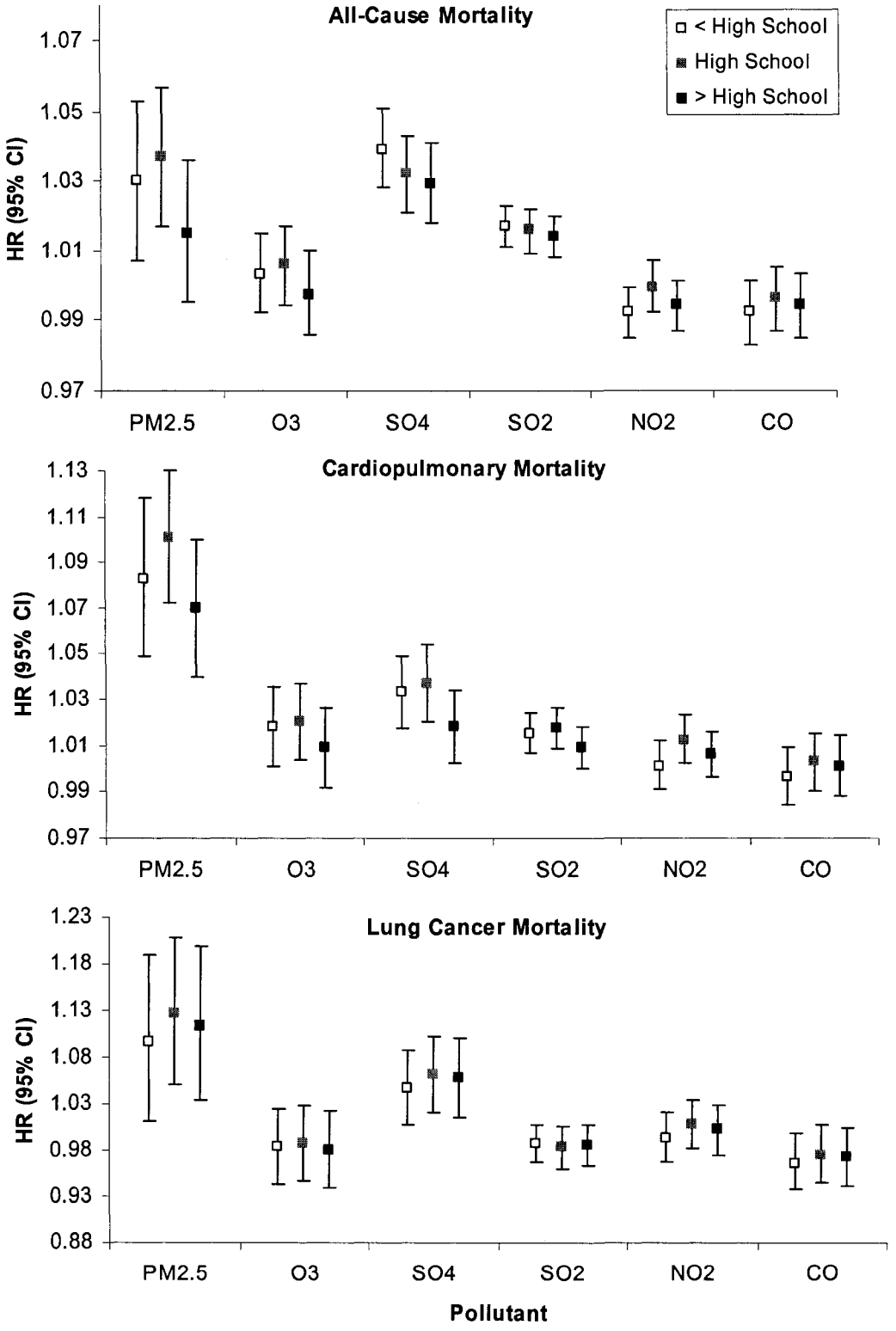


Figure 5. Hazard ratios and 95% confidence intervals of all-cause, cardiopulmonary, and lung cancer mortality associated with fine particles, ozone, sulfate, sulfur dioxide, nitrogen dioxide, and carbon monoxide controlling for educational attainment at the MSA level.

Again, where relationships between air pollution exposure and mortality were significant at the 95% level of confidence, those with more than high school had the lowest hazard of mortality from air pollution (Table 21, Figure 6).

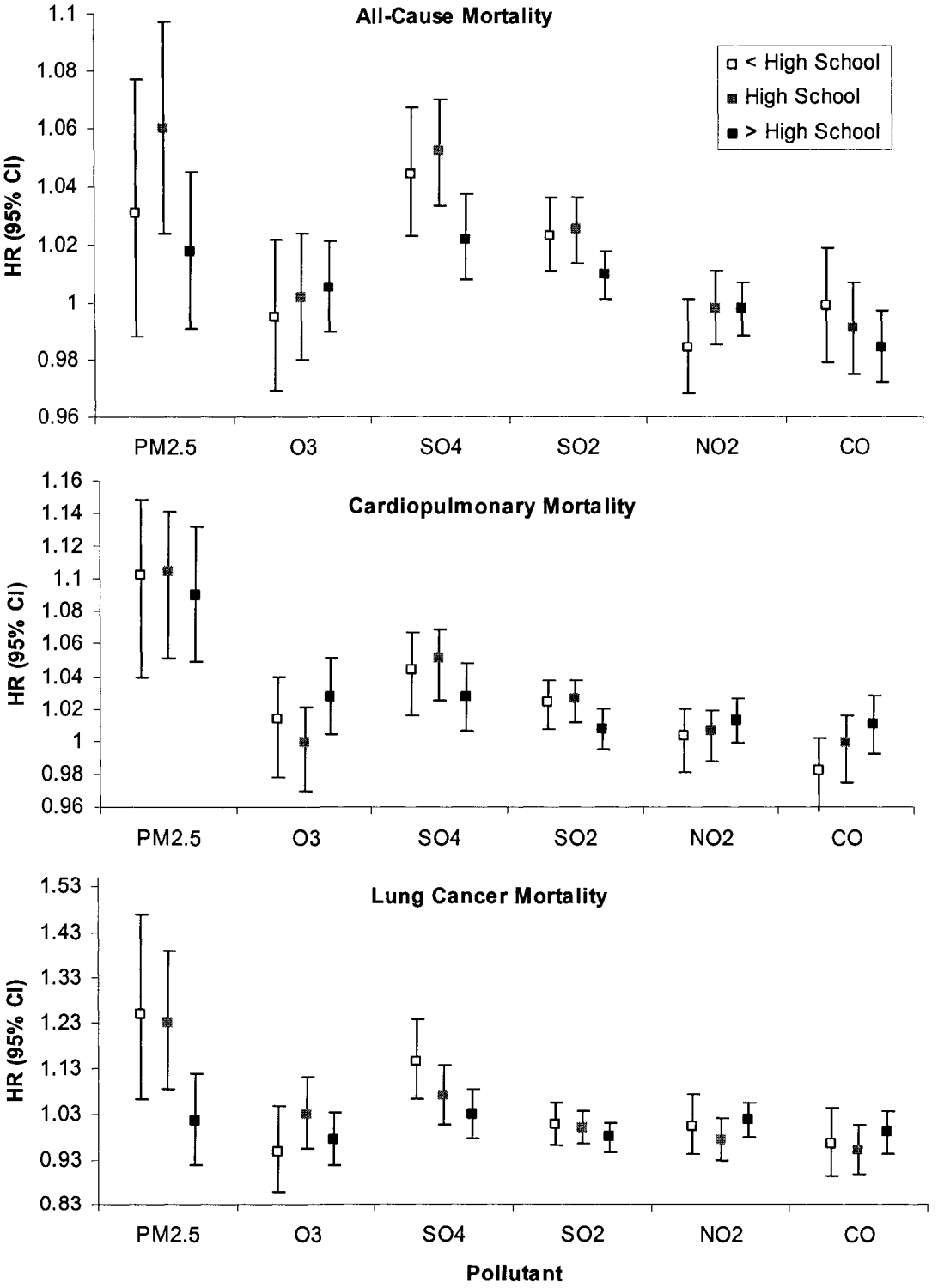


Figure 6. Hazard ratios and 95% confidence intervals of all-cause, cardiopulmonary, and lung cancer mortality associated with fine particles, ozone, sulfate, sulfur dioxide, nitrogen dioxide, and carbon monoxide controlling for educational attainment at the individual level.

Significant associations for having more than high school education were seen as follows: all-cause mortality: SO_4^{2-} (HR = 1.022, 95% CI: 1.008-1.037) and SO_2 (HR = 1.010, 95% CI: 1.001-1.018), and cardiopulmonary mortality: $PM_{2.5}$ (HR = 1.090, 95% CI: 1.049-1.132), SO_4^{2-} (HR = 1.027, 95% CI: 1.006-1.048). This trend was also present with fine particles and both all-cause mortality (HR = 1.018, 95% CI: 0.991-1.045) and lung cancer mortality (HR = 1.014, 95% CI: 0.919-1.117), despite an insignificant HR estimate at the 95% level of confidence. Even though the relationship between exposure to sulfate and lung cancer upon completing more than high school was not significant, it was associated with the lowest mortality risk (HR = 1.031, 95% CI: 0.979-1.086). The same was seen with sulfur dioxide and cardiopulmonary mortality (HR: 1.007, 95% CI = 0.995-1.020) and lung cancer mortality (HR = 0.981, 95% CI: 0.950-1.012). For fine particles and all-cause and lung cancer mortality, sulfate and lung cancer, and sulfur dioxide and cardiopulmonary mortality, the associations for having less than or equal to high school education were significant. However, significance, and likely the association, disappeared upon completing more than high school. For all three mortality outcomes, ozone, nitrogen dioxide, and carbon monoxide did not show the expected trend of having the lowest hazard of mortality related to air pollution exposure. However, the resulting hazard ratios for these associations were not significant at the 95% level of confidence. The trend for mortality of those having less than a high school or equal to a high school education was again not clearly defined.

Correlations: Pearson correlation coefficients were investigated for possible correlations between air pollutants and ecological covariates (Table 22).

Table 22. Pearson correlations (x100) between pollutants and ecological covariates recorded at the MSA level.

Ecological Covariate	$PM_{2.5}$ (1999-2000)	O_3 (1980)	SO_4 (1980)	SO_2 (1980)	NO_2 (1980)	CO (1980)
Grade 12	-49	4	-40	-21	2	10
Unemployed	10	-9	11	12	-2	-8
Income Disparity (GINI)	17	1	-4	-15	15	9
Poverty	10	-9	5	-11	-24	-15
Household Income	8	12	-9	-3	38	15
Per Capita Income	5	2	-13	-8	39	22
White	-37	-7	0	22	-23	-1
Black	41	2	26	-2	-1	-5
Population Change	-19	27	-40	-42	16	12
Over 25	6	-19	15	19	11	15

Completion of a grade 12 level of education at the MSA level was moderately negatively correlated with both fine particles (r = -0.49) and sulfate (r = -0.40). The percentage of white residents in an MSA was also fairly negatively correlated with fine particulate matter (r = -0.37) while the African American portion of the population was fairly highly correlated with fine particulate matter (r = 0.41). However, neither the white nor African American portions of the populations were highly correlated with sulfate exposure (r = 0 and 0.26 respectively). It appeared that percent population change from 1980 to 1990 was moderately negatively correlated with fine particulate matter (r = -0.19), sulfate (r = -0.40), and sulfur dioxide (r = -0.42). Finally, per capita and household income at the MSA level were positively correlated with nitrogen dioxide exposure (r = 0.38 and 0.39 respectively).

Pearson correlation coefficients were also analyzed in order to identify possible correlations between ecological covariates at the MSA level (Table 23).

Table 23. Pearson correlations (x100) between ecological covariates recorded at the MSA.

Ecological Covariate	Grade 12	Unemployed	Income Disparity (GINI)	Poverty	Household Income	Per Capita Income	White	Black	Population Change	Over 25
Grade 12	100	-48	-21	-31	38	38	29	-89	22	-17
Unemployed		100	28	45	-39	-41	-23	-10	-28	-11
Income Disparity (GINI)			100	29	2	21	-54	37	16	9
Poverty				100	-48	-41	-20	21	-12	-14
Household Income					100	93	-18	4	24	28
Per Capita Income						100	-21	8	26	47
White							100	-80	-24	5
Black								100	0	5
Population Change									100	-18
Over 25										100

It appeared that traditional indicators of low socioeconomic status were correlated as expected. For example, percent completion of more than grade 12 was positively associated with the household income (r = 0.38) and per capita income (r = 0.38) at the MSA level and was negatively associated with unemployment (r = -0.48) and poverty (r = -0.31). Unemployment was positively associated with poverty (r = 0.45) and negatively associated with household income (r = -0.39) and per capita income (r = -0.41). The percentage of residents over 25 years of age in an MSA demonstrated a moderate correlation with per capita income (r = 0.47). Household and per capita income were negatively associated with poverty (r = -0.48 and r = -0.41 respectively). Furthermore, per capita and household were almost completely correlated (r = 0.93), as may be expected.

Differing socioeconomic indicators were also apparent across ethnicity. For example, the white fraction of the population was moderately positively associated with the completion of grade 12 (r = 29) while the African American fraction was strongly negatively correlated with the completion of grade 12 (r = -0.89). Income disparity was negatively correlated with the white portion of the population (r = -0.54) but was positively associated with the African American portion (r = 0.37).

5. DISCUSSION

5.1 Multiple Pollutants

This study suggests that sulfate and, more broadly, fine particulate matter may be the most important contributors to excess risk of mortality. The resulting mortality hazard ratios were robust across MSA and exposure selection. Sulfate appeared to account for a significant portion of mortality attributed to fine particles and sulfur dioxide. It is possible that sulfate may be one of the most important contributors to air pollution-related mortality or it may be a better marker for the fraction of fine particles most likely linked to adverse health effects than are fine particles (as measured by $PM_{2.5}$) themselves.

The current study used data from the ACS CPS-II cohort to characterize mortality and potential individual confounders while air pollution data compiled from various monitors throughout the U.S. was used to quantify exposures. The prospective cohort design of this study allows for the use of individual level data on (such as age, sex, smoking habits, body mass index, and education), and ecological data on air pollution exposure and certain other confounders measured on a community scale (such as percent unemployment over age 16 and income disparity). Using a cohort of nearly 1.2 million study subjects with a follow-up time of 18 years, overall positive associations of sulfate exposure with all-cause and cardiopulmonary mortality were observed even after controlling for potential individual confounders. While fine particles and sulfur dioxide exposure were also significantly associated with all-cause and cardiopulmonary mortality, it can be argued that sulfate is the most appropriate surrogate for the active

component of fine particulate matter since it largely accounted for the apparent fine particle and sulfur dioxide associations. Overall, sulfate was most robustly and significantly associated with all-cause and lung cancer mortality while the combination of fine particles and sulfate were most highly associated with cardiopulmonary mortality.

Fine particles.

Regional fine particles. Particulate matter is significantly associated with all three mortality outcomes investigated in the current study. However, for all-cause and lung cancer mortality, the influence of fine particles seems to be largely accounted for by sulfate. Fine particles retain significant and fairly robust associations, however, upon the inclusion of sulfate into hazard models for cardiopulmonary mortality.

Sulfate is the chemical species that accounts for the largest single fraction of fine particulate matter in eastern North America. In eastern areas of the U.S., sulfates dominate the inorganic fraction of ambient fine particles, while in western U.S. nitrates are the dominant inorganic fine particle species (Davidson et al., 2005). In the U.S., sulfate concentrations generally range from 4 to 7 $\mu g/m^3$ while nitrate is typically found at concentrations lower than 1 $\mu g/m^3$ from northern Florida through the Midwest (EPA, 2001). Sulfate and nitrate particles are usually generated by conversion from primary sulfur and nitrogen oxide emissions and generally have short residence times in the atmosphere where they often coagulate to form larger fine particles. These secondary sources of particulate matter form a large part of the regional sources of airborne fine particulate matter (Malcolm et al., 2000).

A varying proportion of these species are acidic (Pope, 2000a). In fact, it has been argued that sulfates and strong aerosol acidity (H_3O^+) may be among the particulate matter components that elicit the most harmful toxicologic responses (Lippmann, 1989; Spengler et al., 1990; Seaton et al., 1995; EPA, 1996; Lippmann & Thurston, 1996; Stieb et al., 1998). Lippmann and Thurston (1996) instead indicated that sulfate itself is not likely the cause of morbidity or mortality. The authors proposed that sulfate is closely correlated with variations in the species ($PM_{2.5}$ and its acidic component) which are more likely associated with adverse outcomes. Contrarily, Abbey et al. (1993) indicated that through multiple pollutant analysis, the correlation was not the result of a surrogate relationship with other air pollutants. A 2004 report by the National Research Council Committee on Research Priorities for Airborne Particulate Matter states that the "health impacts of sulfate *per se* may not be proportional to their contribution to ambient PM mass" (NRC, 2004).

Nevertheless, it has previously been suggested that sulfate can be used as a useful surrogate for ambient concentrations of fine particles and the strong acidic component (H_3O^+) of particulate matter (Lippmann, 1985; Abbey et al., 1993; Lippmann & Thurston, 1996). Sulfuric acid is a dominant source of aerosol acidity (Lippmann, 1989). However, the sulfate in concentration measurement can represent the sum of multiple forms of airborne sulfate as follows in decreasing order of acidity: sulfuric acid [H_2SO_4] (pH ~ 1.0), ammonium bisulfate [NH_4HSO_4] (pH ~ 1.0 – 2.0), and ammonium sulfate [$(NH_4)_2SO_4$] (pH > 5.0) (Thurston et al., 1994a). The species containing ammonium (NH_4^+) result from the reaction between sulfuric acid and ambient ammonia (NH_3) (Schlesinger & Chen, 1994). As the distribution of each sulfate component in a particular

fine particle sample varies, the acidity of the sample also varies based on meteorological conditions and local concentrations of ammonia (Lioy & Waldman, 1989). In fact, the acidity of particulate ambient aerosols is a function of the rate at which sulfuric acid is added (either by primary emission or by atmospheric oxidation of sulfur dioxide) and the rate by which the acid is neutralized (for example, by ambient ammonia) (Thurston et al., 1994a). Ammonia gas is released in to the air largely from livestock and fertilizer use. For these reasons, the precipitation over central U.S. is not acidic (Baird & Cann, 2004).

While sulfate is not a perfect surrogate for acid aerosol, it is suggested as a better surrogate for the active component of fine particulate matter than fine particulate matter itself (Lippmann, 1985). Further, high sulfate levels are generally well-correlated with high levels of acidic aerosols (Bates & Sizto, 1987; Thurston et al., 1994a). A more representative measure of the aerosol acidity in the particulate matter sample would be the concentration of the hydronium ion [H_3O^+]. However, at concentrations such as those common in ambient exposures, the measurement of acidity in the form of H_3O^+ is more difficult to quantify. For example, several studies attempting to identify an association between acidic aerosol and health outcomes were unable to detect such an association (Dockery et al., 1992; Schwartz et al., 1996; Lippmann et al., 2000). It is possible that the insignificant results from these studies were the result of inaccurate acidity measurements. Analytical techniques around the time of the pollutant measurements were relatively well-standardized and believed to be reasonably accurate for sulfur dioxide. However, less information about ambient suspended sulfate was available and the assay systems used had a number of difficulties. Most notably, a portion of sulfates detected on the particle traps could have resulted from the reaction of sulfur dioxide with

the trapping material (Rall, 1974). Thus, these measurements would have been unrepresentative of actual atmospheric sulfate concentrations.

A further issue driven by acidic aerosols is the extent to which metals are made more bioavailable by secondary sulfates. That is, sulfates may also affect health indirectly. Sulfuric acid coatings on particles may lead to the solubilization of metals such as iron and aluminum that result in lung injury upon inhalation (Winchester, 1990; Dreher et al., 1997). It has been suggested that primary sulfate emissions contain metals which may induce adverse health effects principally related to the metals, rather than the sulfate component of the aerosol (Grahame & Hidy, 2004). For example, when a steel plant in Utah shut down for a year, the reduction in metal content of fine particles correlated significantly with a reduction in respiratory hospital admissions (Frampton et al., 1999). Also, a decreased inflammatory response to particulate matter resulted when the steel mill was not in operation (Ghio & Devlin, 2001). It is possible that acidic sulfate aerosols may potentiate the effects of other constituents of particulate matter (Stieb et al., 1998). Acid precipitation can affect the mobilization, transport, and speciation of toxic metals thereby inducing health effects of the metals in particulate matter (Lippmann, 1989). For example, the core of ultrafine particulates consists of the oxides of metals such as iron (Fe), calcium (Ca), and magnesium (Mg), and may be covered by a layer containing sodium (Na), arsenic (As), antimony (Sb), and zinc (Zn). Zinc is generally found at the highest concentration on the surface of particulate matter. Furthermore, as the particles cool, surface formation and/or condensation of a layer of sulfuric acid may occur (Lippmann, 1985).

Animal studies have supported the suggestion that sulfate-coated particles may carry an adverse health risk that is higher than sulfates alone. For example, studies with guinea pigs have shown that up to an order of magnitude higher level of exposure to aqueous sulfuric acid may be required to produce similar results as seen with solid particle cores coated with acid (Amdur & Chen, 1989). Exposures to acid coated particles at concentrations as low as 20 $\mu g/m^3$ were shown to result in adverse health effects. Another study by Jakab et al. (1996) showed adverse effects in mice exposed to cogenerated carbon black particles and sulfur dioxide, which were converted to acidic sulfates on the carbon in some cases. In cases where sulfur dioxide was oxidized to sulfate, phagocytosis by lavaged macrophages was significantly suppressed.

The hypothesis that sulfate may be indirectly associated with mortality via mechanisms described above is supported by the results of the current study if associations between sulfate and mortality were actually due to other correlated, but unmeasured, components of fine particulate matter, such as metals.

Local fine particles. Fine particulate matter is usually dominated by regional influences (mostly in the form of sulfate) rather than local sources (Wolff et al., 1985; Thurston et al., 1992; Suh et al., 1997). The long range transport of sulfate is of global importance (Forsberg et al., 2005) yet the influence of local sources is more difficult to estimate on account of the large uncertainties surrounding linking exposure data to health outcomes (Forsberg et al., 2005). Furthermore, local fine particle sources are difficult to measure in comparison to elevated background levels of regional sulfate when using a combined particulate measurement such as $PM_{2.5}$ (Kinney et al., 2000).

Transportation, wood burning, and dust form a large portion of local fine particle emissions (Cheng et al., 1998; Forsberg et al., 2005). Local sources of fine particles are mostly dominated by traffic sources (Nitta et al., 1993; Brunekreef et al., 1997). However, there is some suggestion that engine exhaust particles may comprise the fraction of local fine particles that are responsible for the most damaging health effects (Forsberg et al., 2005). For example, more than 90 percent of the total species concentration in diesel exhaust is formed of nanoparticles less than 50 nm composed of metals, elemental carbon, and semivolatile organic compounds formed during dilution and cooling after exiting exhaust pipes (Kittelson et al., 2000). Diesel exhaust particles are composed of roughly spherical nuclei composed of elemental carbon (WHO, 1996). These species have large surface areas (30-100 m^2/g) upon which a variety of organic compounds may be adsorbed (WHO, 1996).

Diesel engines produce a higher mass of particles in the exhaust than traditional gasoline because of "dirtier" fuel with no catalytic treatment of exhaust gases (Kittelson et al., 2000). In addition, diesel engines emit approximately ten times more particles per mile than traditional gasoline engines, as well as 30 to 70 times more than engines equipped with a catalytic converter (Godlee, 1991). The finest particles from these local fractions are dominated by volatile organic (carbon) compounds (Forsberg et al., 2005).

Earlier studies on the health effects of vehicular exhaust focused primarily on cancerous outcomes (Mauderly, 1994; eg. Bhatia et al., 1998). For example, it is known that polycyclic aromatic hydrocarbons emitted from exhaust can easily pass through epithelial cell membranes and bind to cytosolic receptors that affect cell growth and differentiation (Mazzarella et al., 2007). However, more recent research, the current

study included, has found that important effects may also be seen on the respiratory system. Recent experimental evidence suggests diesel exhaust may act as an irritant and/or may promote immunological effects on the respiratory system (Kobayashi et al., 1997; Bayram et al., 1998; Diaz-Sanchez et al., 2000). Other experimental evidence from chronic diesel exhaust exposure suggests respiratory function impairment (Moorman et al., 1985) with a histopathology that includes peribronchiolar fibrosis and epithelial metaplasia in terminal and respiratory bronchioles (Plopper et al., 1983). Additionally, six months after the exposure had ended, the epithelial changes lessened but fibrosis worsened. Diesel exhaust particles have also been shown to increase the hyperresponsiveness of airways in animal models of asthma (Mazzarella et al., 2007). A major experimental study on the effects of chronic exposure to gasoline fumes showed that induced functional and structural changes in airways and alveoli persisted after exposures ceased (Mauderly, 1994).

Epidemiologic studies suggest that residential proximity to traffic sources and adverse respiratory outcomes such as asthma increased respiratory symptoms (Wjst et al., 1993; vanVliet et al., 1997) and diminished lung function (Nitta et al., 1993; Brunekreef et al., 1997). These outcomes may result from exposure to diesel exhaust. Furthermore, hospitalizations among children may increase with diesel exhaust exposure (Edwards et al., 1994).

In summary, experimental and epidemiological evidence suggest that higher exposures to exhaust, a large fraction of local fine particles, likely affect respiratory function and contribute to the development of chronic respiratory disease (Mauderly, 1994). Single exposures to exhaust can cause lung inflammation and other cellular

changes, suggesting that chronic exposures may affect lung function. Further, chronic exposure to exhaust may affect particle clearance, and significant noncancer histopathology is demonstrated by respiratory function impairment (Mauderly, 1994).

Sulfate. Sulfate, as described above for fine particles, composes a large fraction of fine particulate matter in the United States. In the current study, sulfate also seems to be the pollutant that is most robustly associated with mortality from all-causes and lung cancer. Sulfate is also significantly associated with cardiopulmonary mortality; however, particulate matter also seems to have a robust association with this specific cause of mortality. As described in the section regarding fine particles, it is unlikely that sulfate itself is responsible for mortality. Rather, sulfate may be a more specific marker for the acidic component of fine particles than fine particles are themselves or sulfate may be a marker for other components of particulate matter, such as metals, that are coated with sulfate and are associated with harmful human health implications.

Several previous studies were able to detect associations between exposure to acidic sulfate aerosols and adverse pulmonary heath effects seemingly related to the acidity of sulfate aerosols or the ammonium ion, if present (Utell et al., 1982; Schlesinger, 1984; Dockery et al., 1989; Lippmann, 1989; Schlesinger, 1989; Koenig et al., 1989; Schlesinger et al., 1990a; Schlesinger et al., 1990b; Gwynn et al., 2000). However, results of these studies indicated that inhaled sulfuric acid had a disproportionately higher potency than ammonium bisulfate across several biological endpoints (Utell et al., 1982; Schlesinger, 1989; Schlesinger et al., 1990b).

Historical events have shown industrial pollution from steel mills and sulfuric acid plants were implicated in excess death and respiratory illness among the elderly, for example in the Meuse Valley, Belgium, in December, 1930, and in Donora, Pennsylvania, in October 1948. Additionally, coal smoke containing sulfuric acid played a direct role in the excess mortality during the London fog event from 1952 to 1962 (Lippmann, 1989). Furthermore, Kitagawa (1984) identified sulfuric acid as the causal agent for nearly 600 cases of respiratory disease in the Yokkaichi region of Japan from 1960 to 1969. Affected patients resided within 5 km of a titanium dioxide plant that emitted between 100 and 300 tons of sulfuric acid per month from 1961 to 1967. Upon installation of electrostatic precipitators in 1967 to control aerosol emissions, the number of patients diagnosed with allergic asthmatic bronchitis gradually decreased. This study greatly supported evidence for sulfuric acid as a causal agent of respiratory disease due to a lack of confounding pollutant factors (Lippmann, 1985).

Further, a strong association was noted between total respiratory and asthma hospital admissions in relation to H_3O^+ and sulfate (Thurston et al., 1992; Thurston et al., 1994b). Daily hospital admissions for respiratory causes in Toronto, ON, during the summers of 1986 to 1988 also showed significant associations with both H_3O^+ and sulfate; the acid component showing the strongest association (Thurston et al., 1994b). Additionally, total, circulatory-related, and respiratory-related mortality in Buffalo, NY, from 1988-1990 were significantly associated total mortality (Gwynn et al., 2000).

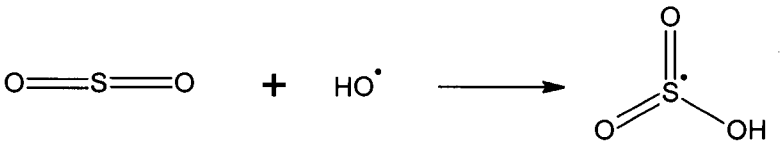
The suggestion that given the same concentration of protons, sulfuric acid is more biologically potent than ammonium bisulfate indicates that simply the acidic portion of these species may not be responsible in full for adverse biological effects. For example,

in rabbits, sulfuric acid is at least twice as effective per mole as ammonium bisulfate (Lippmann, 1985). One theory is that since sulfate particles are hygroscopic, they increase in size through the absorption of water from the respiratory tract following inhalation (Larson, 1989). It is possible that the growth in size between sulfuric acid and ammonium bisulfate differs. That is, the dose delivered to the target sites from each acid species may be different (Schlesinger & Chen, 1994). An alternative explanation for the difference could be that inhaled acidic sulfates are neutralized by endogenous ammonia within the respiratory tract (Larson et al., 1977; Schlesinger, 1984). Following exposure to an identical concentration of ammonia for a duration similar to that which would occur in the upper respiratory tract, more [H_3O^+] remained available from sulfuric acid than from ammonium bisulfate (Schlesinger & Chen, 1994). This has important implications because if it is assumed that all ambient acidity results from sulfuric acid, then observed health effects from epidemiological studies would be overestimated if, in fact, they are due at least in part to ammonium resulting from ammonium bisulfate (which is usually in mixture with sulfuric acid) (Thurston et al., 1994a).

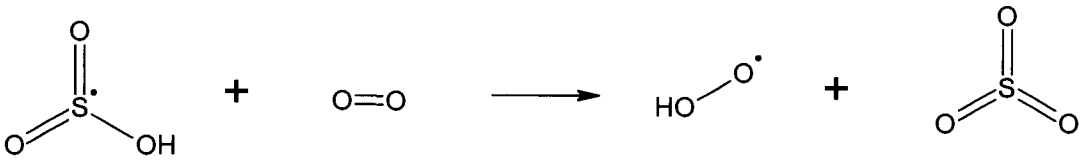
The amount of available protons deposited on airway surfaces may involve a threshold relationship with the amount of endogenous ammonia in the respiratory tract. It is possible that only after neutralization a certain concentration of ammonia may protons alter localized airway surface or cellular pH (Schlesinger & Cassee, 2003). It is possible that inconsistencies noted in human studies involving low acid exposure concentrations may be the result of such a threshold (Schlesinger & Cassee, 2003).

Sulfuric acid and other acid sulfates are known to be particularly toxic (Rall, 1974). Sulfuric acid is the hydrated form of sulfur trioxide (SO_3^{2-}) which is formed

through the oxidation of sulfur dioxide. Because sulfur trioxide is extremely hygroscopic, it is almost immediately converted to sulfuric acid in the atmosphere. One of the main ambient mechanisms of sulfuric acid formation is through a homogenous gas-phase reaction that occurs by several sequential steps. This gas-phase, homogeneous mechanism predominates under clear sky conditions. The hydroxyl radical (•OH) initiates the process. The hydroxyl radical adds to sulfur dioxide as follows (Baird & Cann, 2004):



Then, sulfur trioxide is formed from the resulting radical by the removal of the hydrogen atom, abstracted by oxygen (O_2) molecule:



Once sulfur trioxide is formed, it combines rapidly with a gaseous water molecule to form sulfuric acid. Gaseous sulfuric acid then reacts with water vapor to form an aerosol of droplets, each being an aqueous solution of sulfuric acid. The entire process is summarized as follows:

$$SO_2 + HO\cdot \longrightarrow HSO_3^{\bullet}$$

$$HSO_3^{\bullet} + O_2 \longrightarrow SO_3 + HOO\cdot$$

$$SO_3 + H_2O \longrightarrow H_2SO_4(g)$$

$$H_2SO_4 + \text{many } H_2O \longrightarrow H_2SO_4(aq).$$

Because sulfur dioxide is somewhat soluble in water, a fraction of ambient sulfur dioxide exists in the dissolved aqueous form, especially under cloudy or misty conditions. Sulfur dioxide dissolved in the aqueous phase forms sulfurous acid (H_2SO_3) according to the following process (Baird & Cann, 2004):

$$SO_2(g) + H_2O(aq) \rightleftharpoons H_2SO_3(aq).$$

Dissolved sulfur dioxide is then oxidized to sulfate by trace amounts of oxidizing agent such as hydrogen peroxide, H_2O_2, and ozone that are present in airborne droplets. Oxidation may be catalyzed by metals commonly found within the fine particulate matter fraction such as iron or manganese (Costa, 2001).

Almost all of the sulfur dioxide produced by the combustion of fossil fuel is eventually converted into sulfate (Rall, 1974). While only a third of the sulfur in the atmosphere is estimated to be derived from pollutant sources, this observation is not important in terms of local respirable ground levels of sulfur oxides (SO_x) which is almost completely derived from fossil fuel combustion in urban areas (Rall, 1974).

Sulfates formed from sulfur dioxide in the atmosphere are formed through two potentially related chemical processes: 1) sulfur dioxide may be oxidized to sulfuric acid, and 2) sulfuric acid may react with other cations to form sulfates. What is important in areas with mixtures of air pollution is that the catalytic oxidation of sulfur dioxide will occur in the absence of sunlight in aerosols upon which sulfur dioxide has been adsorbed. That is, metallic compounds found in aersols such as manganese, iron, vanadium, aluminum, lead, and copper, play a role in the catalytic conversion of sulfur dioxide to sulfates (Rall, 1974).

It is biologically plausible that the acidic component of sulfate is responsible for the adverse effects of air pollution. For example, animal studies have shown that exposure to acid aerosols results in adverse effects such as changes in pulmonary function (Amdur & Chen, 1989; Raizenne et al., 1996), airway hyperresponsiveness and secretory cell hyperplasia (Gearhart & Schlesinger, 1989; el-Fawal & Schlesinger, 1994), and clearance abnormalities (Chen & Schlesinger, 1983; Schlesinger, 1989; Spektor et al., 1989). In humans, short-term sulfuric acid exposures between 0.1 and 1.0 mg/m^3 resulted in lung clearance function and pulmonary mechanical effects through alveolar inflammation, causing the release of mediators that might induce acute respiratory illness attacks (Koenig et al., 1983; Leikauf et al., 1984). Furthermore, sulfates and sulfuric acid seem directly implicated in chronic respiratory disease (Abbey et al., 1993). Clearance abnormalities that may arise from the increased viscosity upon mucous acidification (Holma et al., 1977) may be an important study endpoint since mucociliary clearance is potentially linked to chronic bronchitis and because reduced clearance may increase susceptibility to infection (Wyzga & Folinsbee, 1995). Alternatively, the interference with the normal contractile/dilatory homeostatic process through the alteration of airway receptors may result in changes in airway responsiveness (el-Fawal & Schlesinger, 1994). However, the exact mechanism of acidic aerosol toxicity remains unclear.

Arguments can also be made against the direct biological action of acidic sulfate aerosols. For example, the concentration of acidic aerosol that actually enters the body may be different than the concentration present in the air due to neutralization of the acid within the airway. The lung has two main defenses against damage from acid aerosols: 1) neutralization by oral or nasal airway ammonia, and 2) buffering by the mucus lining

in the airway (Sarangapani & Wexler, 1996). It has been suggested that small particles (< 0.1 micron) undergo extensive neutralization, whereas larger particles (> 1.0 micron) experience negligible neutralization (Sarangapani & Wexler, 1996). Additionally, since these acidic aerosols are extremely hygroscopic, many acidic gases and particles may become incorporated into droplets that are part of ambient humidity. These droplets may then increase in size while still in the upper respiratory tract which would lower their chance of penetrating lower into the airway (Wyzga & Folinsbee, 1995).

In the current study, sulfate appears to be significantly associated with all-cause, cardiopulmonary, and lung cancer mortality. Sulfur dioxide and fine particles also show significant associations with mortality. However, these results seem to be largely accounted for by sulfate, especially in the case of all-cause and lung cancer mortality.

Sulfur dioxide. In addition to the statistical results of the epidemiological study, it is important to consider the biological plausibility of adverse events resulting from exposure to air pollutants. For example, the deposition of the pollutants depends on their reactivity and whether they are freely gaseous or are adsorbed onto particles, and whether they are inhaled through the mouth or the nose. For example, sulfur dioxide is a highly reactive hydroscopic gas that is almost completely absorbed into the nasal cavity during normal inhalation (Lebowitz, 1996). Furthermore, sulfate is generated from sulfur dioxide oxidation. Thus, it can be difficult to disentangle the health effects due to sulfate and sulfur dioxide on airway diseases since the occurrence of sulfur dioxide is proceeded by the formation of sulfate particles (Herbarth et al., 2001). However, given its high reactivity and low likelihood of penetrating the respiratory system coupled with current

statistical results that seem to be largely accounted for by sulfate, the argument against sulfur dioxide as a causal agent in air pollution-related mortality seems strong. Sulfur dioxide alone is of relatively low toxicity and is generally used as an index of pollution (Rall, 1974).

In the current study, sulfur dioxide shows significant but relatively small associations with all-cause and cardiopulmonary mortality. The association between sulfur dioxide and mortality seems to be largely explained by sulfates and fine particles. This, combined with what is known about the biological mechanisms of sulfur dioxide action, suggests that sulfur dioxide may act as a marker for sulfate and fine particulate matter pollution rather than being a causal agent itself.

Nitrogen dioxide. Nitrogen dioxide is less water soluble than sulfur dioxide, but is more insoluble than ozone. Therefore, nitrogen dioxide is expected to be taken up into the nasal passage more readily than ozone. Most particulate oxides of nitrogen actually consist primarily of nitrate (NO_3) salts (Schlesinger & Cassee, 2003). Nitrate salts do not seem directly implicated in adverse health events upon their exposure (Charles & Menzel, 1975; Ehrlich, 1979; Ziegler et al., 1994).

Under daytime ambient conditions, nitrogen dioxide can be converted to gaseous nitric acid (HNO_3) through reaction with hydroxyl radicals. At night, nitrogen oxides are oxidized to gaseous nitric acid by a sequence of reactions initiated by ozone (Schlesinger & Cassee, 2003). Due to its elevated saturation vapor pressure, nitric acid usually exists as a vapor under ambient conditions (Ellestad & Knapp, 1988). However, in acidic fogs, nitric acid maybe found within the coarse particulate mode (Jacob et al., 1985).

Upon inhalation, nitrogen dioxide is likely converted to nitrate or nitrite in the blood (Koenig, 2000). Nitric acid (HNO_3) is the final product of oxidation of atmospheric gases such as ammonia, nitric oxide, and nitrogen dioxide (Baird & Cann, 2004). This acid is also neutralized with ammonia gas in the air to form the salt ammonium nitrate, which is a solid that occurs in the particulate phase (Baird & Cann, 2004). Ammonium nitrate (NH_4NO_3) exists in equilibrium with its gas phase constituents, ammonia and nitric acid as follows (Lunden et al., 2003):

$$NH_4NO_3(s) \rightleftharpoons HNO_3(g) + NH_3(g)$$

$$NH_4^+(aq) + NO_3^- \rightleftharpoons NH_3(g) + HNO_3(g).$$

The reaction equilibria depend on ambient temperature and relative humidity.

The majority of studies on nitric acid were designed to investigate the histological response to nebulized acid, through procedures having no relevance to ambient exposures (Greenberg et al., 1971; Mink et al., 1984; Peters & Hyatt, 1986; Schlesinger & Cassee, 2003). Also, the collection toxicological studies are not as robust for nitrate as they are for sulfate (Schlesinger, 2007). However, in controlled clinical studies conducted with nitrates in concentrations from 200 to 7000 $\mu g/m^3$ using pulmonary function as an endpoint did not find significant results (Utell et al., 1979; Kleinman et al., 1980; Stacy et al., 1983). Both nitric acid and nitrates were not associated with respiratory symptoms in asthmatics in a study by Ostro et al (1991).

Most previous study also suggests that adverse health effects are unlikely to occur from current levels of nitrate, even in more sensitive subpopulations such as asthmatics (Schlesinger, 2007; Chen et al., 2007a). Overall, secondary nitrates have not been found to significantly contribute to adverse health outcomes (Schlesinger, 2007).

The lack of correlation between nitrogen dioxide and ozone (r = 10) in the current study is consistent with the tropospheric formation of these two species. As nitrogen dioxide is a major precursor and catalyst in ground level ozone formation (Fowler et al., 1998; Baird & Cann, 2004), one would expect a low correlation between the two chemicals since they do not appear simultaneously in high concentrations under ambient conditions. During the day, nitrogen dioxide undergoes photolysis with sunlight energy ($h\nu$) at wavelengths (λ) less than 400 nm as in via the following reaction:

$$NO_2 + h\nu \rightarrow NO + O\cdot.$$

Then ozone is formed through the reaction of the ground state oxygen, O, and tropospheric oxygen (O_2) with the energy of an active body (M^*), which may be molecular nitrogen (N_2) for example, to carry out energy from the reaction:

$$O_2 + O\cdot + M^* \rightarrow O_3 + M.$$

At night, ozone can then recombine with nitric oxide to form nitrogen dioxide and oxygen.

$$O_3 + NO \rightarrow O_2 + NO_2.$$

Overall, the cycle can be depicted as follows:

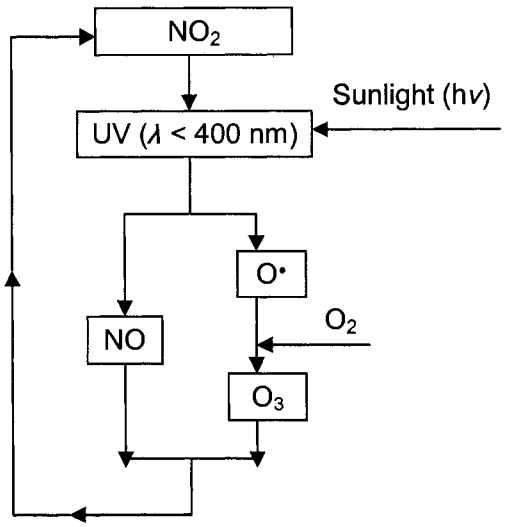


Figure 7. The formation and breakdown cycle between nitrogen dioxide and ozone.

Because this is the major mechanism of tropospheric ozone formation, with very small amounts brought down by vertical atmospheric mixing from the stratosphere, ozone formation takes place during the day in the presence of energy from the sun. Contrarily, nitrogen dioxide is present in its largest amounts at night.

The current study does not support an association of nitrogen dioxide with all-cause, cardiopulmonary, or lung cancer mortality. This finding also seems consistent with biological mechanisms involving nitrogen dioxide that mostly do not support chronic health effects of nitrogen dioxide. Further, though nitrogen dioxide may be a marker for ozone or nitrate air pollution, these related species also do not seem to be highly significantly associated with long-term mortality.

Ozone. A major mechanism of ozone toxicity is through oxidant damage. This may be achieved through the oxidation of biomolecules to form radical species such as the hydroxyl radical (•OH) or by driving radical-dependent production of cytotoxic, non-

radical species such as aldehydes (Mudway & Kelly, 2000). Under in vitro conditions, ozone reacts with polyunsaturated fatty acids to form free radicals (Pryor & Church, 1991; Menzel, 1992). However, the actual amount of ozone that actually reaches pulmonary cell membranes under ambient conditions, if any, remains under scrutiny.

Upon inhalation, ozone first encounters the lung epithelial lining fluid which is a bi-layer structure compsed of a lower aqueous sol phase and an upper mucus gel-phase (Mudway & Kelly, 2000). This upper layer is particularly good at trapping microorganisms and large particles that enter the airway (Quinton, 1979). Upon encounter with the epithelial lining, ozone reacts with water soluble antioxidants, glycoproteins, and unsaturated fatty acids (Koenig, 2000). However, ozone reacts preferentially with antioxidants (Mudway & Kelly, 2000). The uptake of ozone is directly related to its reactions with substrates that are present in the pulmonary lining fluid (Langford et al., 1995). Since these substrates are numerous, ozone does not actually transit the pulmonary lining fluid and therefore does not interact directly with pulmonary epithelium. Instead, it is consumed during reactions with substrates found in this compartment (Mudway & Kelly, 2000). It has further been suggested that mucus and phagocytic sinks can irreversibly neutralize reactive gases such as ozone and nitrogen oxides thereby providing effective protection against the oxidative effects on respiratory cells (Vostal, 1994). Thus, cellular responses to ozone inhalation are the result of a cascade of secondary free radical-derived ozonation products (Pryor, 1991; Kelly et al., 1995).

In other words, ozone is generally too reactive to reach the surface of the lung (Mudway & Kelly, 2000). However, certain individuals show a range of responses even

upon exposure relatively low oxygen levels. In general, at low levels of ambient ozone such as the exposures in the current study (< 75 ppb), most of the ozone will be neutralized through reactions with uric acid in the nasal passages and the upper airways. When ozone exposure occurs at higher levels, or when concentrations of pulmonary lining fluid antioxidant defense are low or compromised, ozone may react with macromolecule targets such as proteins and lipids. The products of these reactions can then go on to cause a certain amount of damage to underlying pulmonary epithelium (Mudway & Kelly, 2000).

Previous studies suggest that the impact of ozone on mortality is a contributing factor to the 'hastening of death' at best (Mudway & Kelly, 2000). Mortality may occur sooner than expected upon exposure to ozone, but this in itself is unlikely a cause of death. Nearly 10% of deaths in industrialized countries are accounted for by diseases of the respiratory tract. Anything that exacerbates an already weakened respiratory system is likely to impact the current condition and hasten mortality (Kinney & Ozkaynak, 1991). Ozone may initiate a range of pulmonary responses in only about 10-15% of the healthy population (Mudway & Kelly, 2000). Based on the findings of this study and what is known of ozone mechanistically, it appears likely that ozone might have specific implications for cardiopulmonary mortality, but in comparison, does not have as great effects on overall mortality as fine particulate matter or sulfate, especially given the relatively low exposure concentrations.

Carbon monoxide. Carbon monoxide was not responsible for any significant mortality associations in the current study. Relatively few studies have focused on the

chronic biological effects of chronic, low dose carbon monoxide exposure. However, low doses of carbon monoxide may have significant implications on cardiac function during exercise in patients with existing coronary artery disease (Allred et al., 1991). Another study looked at carbon monoxide exposure and hospitalization for congestive heart failure among the elderly in seven large U.S. cities (Morris et al., 1995). Ambient carbon monoxide levels were positively associated with hospital admissions for congestive heart failure in both single and multi-pollutant models for each of the cities. While carbon monoxide is known to induce hypoxia, there is also evidence that chronic exposure may result in local mediation in both endothelial and smooth muscle cells (Loennechen et al., 1999). It appears that chronic carbon monoxide exposure may be important in a select subgroup of individuals; namely, the elderly with existing cardiopulmonary conditions. It is possible that if the current study was restricted to those individuals, that a more significant association between carbon monoxide air pollution and mortality, especially cardiopulmonary, would be seen.

5.2 Study Limitations

a. Air Pollution Mixtures

A major problem with studying health effects of exposure to air pollution is that the ambient air is a complex mixture of several gaseous and particulate pollutants that may vary greatly from one location to the other from day to day. The difficulty in

studying the effects of air pollutants lies in the inherent inability to isolate and study the impact of single air pollutant on the population health due to co-emission of air pollutants. Furthermore, the proportions and concentrations of each individual pollutant are not static in the mixtures over time. Changes in the individual components of the mixtures may alter the overall toxicity of the mixture. By attempting to isolate the effect of an individual pollutant, the synergistic effects of multiple pollutants might be lost.

Since air pollution is generally a mixture of pollutants, it is likely that one or more of the pollutants are correlated and that one pollutant may simply be a marker for another. The same may be true for ecological covariates. If covariates are highly correlated, the validity of the results may be undermined and a loss in accuracy may result.

One early study reported an interactive effect of ozone and sulfur dioxide exposure in combination. In this study, pulmonary function responses to ozone were increased upon the addition of sulfur dioxide exposure (Hazucha & Bates, 1975). However, subsequent attempts failed at replicating these results (Bedi et al., 1979; Bedi et al., 1982). Mixtures of nitrogen dioxide and ozone in controlled human exposures have generally showed similar responses in pulmonary function as those seen with ozone alone (Folinsbee et al., 1981; Adams et al., 1987).

A complex chemical mixture, such as the one presented by fine particulate matter, can affect various cell populations, including epithelial and endothelial cells. Solubilized fractions of fine particles like metals and organic compounds may diffuse into the parenchyma. The mixture may then circulate in the bloodstream. Nanomolar concentrations of xenobiotics and metals may then transiently up-regulate or down-regulate metabolic activities taking place within the lung endothelium thus having an

indirect effect on coronary circulation or a direct effect on coronary vasculature (Burnett et al., 1995).

Associations between fine particle and sulfate pollution in ambient air and cardio-respiratory morbidity and mortality are well-established in epidemiologic literature. Both time-series and cohort studies have previously shown positive associations between fine particulate matter exposure, sulfate exposure and mortality. However, the association between mortality and exposure to other constituents of air pollution has not been as thoroughly investigated.

Caution must be taken in the interpretation of the multiple pollutant results, mainly due to the potential for overadjustment and the moderately high correlation among pollutants (and other ecological covariates). The correlation of the multiple pollutants means that epidemiological studies cannot simply assign observed effects to single pollutants since single pollutant assessments may greatly overestimate the impact. A high level of covariance among pollutants makes the disentanglement of their effects difficult and can lead to results that deviate from the truth. However, even though fine particles are likely a major marker of the component of air pollution responsible for adverse health events, restriction of analyses to fine particles may underestimate independent effect of air pollution that cannot be explained by or correlated with particulate matter fractions (Kunzli et al., 2000).

In fact, due to a lack of data on how particulate matter components act within a mixture, experts have previously doubted the possibility of precisely quantifying the contributions from the main air pollutant sources and components on the effects on human health (WHO, 2003; WHO, 2004). While we acknowledge these difficulties, an

attempt is still made to validate the evaluation of the robustness of selected co-emitted and correlated air pollutants in the current study by means of sensitivity analyses.

Pearson correlation coefficients were used to assess the extent of the correlation between variables. The Pearson correlation coefficient measures the strength and direction of the linear relationship between the two variables in question. That is, the Pearson correlation coefficient is a marker of the extent to which you can guess the value of one variable given the value of the other. As expected, sulfate is moderately correlated with both sulfur dioxide and fine particulate matter. Because sulfate forms such a large component of fine particulate matter and is also generated from sulfur dioxide oxidation, it is possible that when one models either fine particles, sulfate, or sulfur dioxide, the same thing is actually being modeled, thus introducing collinearity. Collinearity can be problematic in studies such as the current study because socioeconomic and environmental risk factors may be more correlated with each other between groups than they are at the individual level (Morgenstern, 1998). The effects of these covariates may be indistinguishable if they are not sufficiently controlled for in the design of the study.

Because sulfate, sulfur dioxide, and fine particulate matter are chemically related, it follows that sulfate and fine particles are also moderately statistically correlated ($r = 0.51$). Given that sulfate seemed to significantly lessen the apparent relationship between both fine particles and sulfur dioxide and mortality, it seems as though sulfate may have been the major contributor to both all-cause and lung cancer mortality.

Nitrogen dioxide and ozone had a low correlation ($r = 0.10$). Ozone is derived from chemical processes in which nitrogen dioxide is a precursor. Both ozone and nitrogen dioxide were not significantly associated with all-cause and lung cancer

mortality. However, when ozone showed significant effects with cardiopulmonary mortality, the effect was significantly lessened by nitrogen dioxide (HR = 1.013, 95% CI: 0.991-1.035). This supports the idea that both may be markers of the same phenomenon, since they are linked in the chemical formation-breakdown cycle.

Having a high degree of correlation between variables may affect the stability of risk estimates. However, the addition of multiple, somewhat correlated pollutants into the same model can be somewhat justified in the current study since none of the correlation coefficients are high enough to assume collinearity affects the model. Also, the pollutants were not perfectly correlated because each model properly converged. To further validate the use of multiple somewhat correlated pollutants within the same model, the set of MSAs that contained data for all six pollutants was selected and both single and multiple pollutant models were then analyzed using this set of MSAs. The hazard ratios resulting from this "restricted MSA" analysis were then compared to the hazard ratios resulting from the "maximum MSA" analysis. This sensitivity analysis indicated that hazard ratios obtained with both the restricted and maximum MSA analyses were nearly identical. Where possible, following analyses used the maximum number of MSAs possible since these results are closer to the true estimate given their higher statistical power.

To further examine the limitations of using statistical modeling techniques on correlated pollutants, the multiple pollutant models were assessed based on log-likelihood and AIC comparisons between the relevant single and multiple pollutant models. The resulting significance between the difference of single and multiple pollutant model log-likelihoods was based on p-values assessed at the 95% level of confidence resulting from

the assumption that the difference in log-likelihood produced an approximately chi-square distribution. The goodness-of-fit of the models were assessed using AIC values. That is, AIC values give an indication of how well the model relating exposure to outcome fits the available data, while considering the complexity of the model. Both models of fine particles and sulfur dioxide had lower AIC values upon the addition of sulfate to the model, thus indicating a better fit of the model to the data. These results were further supported by the analysis of log-likelihood values, which indicated that adding sulfate as a covariate to fine particle or sulfur dioxide models significantly added to the existing model, but not vice versa. These values support the conclusion that fine particles, sulfur dioxide, and sulfate, as well as ozone and nitrogen dioxide, are strongly correlated.

By adding extra covariates into the model, the log-likelihood value will always show an improvement. However, the improvement may not prove to be significant. In fact, adding in extra unnecessary covariates may lessen the predictive power of the model. For these reasons, a "parsimonious" model containing only those pollutants seemingly significantly associated with all-cause, cardiopulmonary, and lung cancer mortality respectively were included into multiple pollutant models. Given that the log-likelihood values showed significance and AIC values generally decreased upon adding in sulfate to the models, it may be inferred that this phenomenon also supports the idea that sulfate may be important in modeling air pollution-related mortality. The results of the log-likelihood and AIC value analyses lend further evidence towards the assumption that sulfate is the greatest indicator of air pollution-related all-cause and lung cancer mortality amongst the pollutants investigated. Based on the current study, fine particles

may be most associated with cardiopulmonary mortality. However, sulfate still plays a significant role in cardiopulmonary mortality along with fine particles. Further, the analysis suggests that even though sulfate forms a significant portion of fine particulate matter, both species represent related but still independent effects on mortality.

Because sulfate may form a large component of fine particulate matter and sulfate concentrations are fairly constant over a large regional scale, an analysis was performed to disentangle the effects between local and regional fine particles. This was done by subtracting sulfate measurements from fine particle measurements (both in 1980, since sulfate data from 1999-2000 was unavailable) to represent more consistently the local activity of fine particles. However, it should be noted that there are still residual regionally active particles remaining in the examined "local" particulate matter fraction. Upon inspection of the results, it appears that regional pollution is most closely associated with mortality from all causes and lung cancer, while cardiopulmonary mortality may be more closely linked with the approximated local fraction of particulate matter. This suggests that sulfate is an indicator for the most harmful agent with respect to mortality from all causes and lung cancer, whether from an acidic species or perhaps metals coated with sulfate, while cardiopulmonary mortality may be more closely linked to the mixture of both regional and local sources of particulate matter pollution, resulting from vehicular emissions, for example.

b. Exposure Data

Exposure measurement error is likely present in this study because the data used to evaluate individual exposures to ambient air pollutants was collected from fixed-site monitors rather than personal dosimeters. In addition, these fixed-site monitors provided data that was established for purposes other than health-related research as surrogates of exposure. However, the variation in pollution levels within a large metropolitan area may be larger than the measurement error. Inter-individual differences could also potentially be greater than intercity differences, but the exposure measurements are only intended to serve as crude predictors of exposure. It should be noted that secondary sulfates are generally more homogeneous spatially than many other components of particulate matter and thus are associated with comparatively less measurement error (Schlesinger, 2007).

All pollutant exposures used in the current study were representative of ambient air pollution exposures in the year 1980, with the exception of fine particles, for which exposure data from 1999-2000 was used. Because fine particles were measured in far fewer metropolitan areas in 1980 than in 1999-2000 (N = 60 vs. N = 116), it was preferable to use data from 1999-2000 in order to assure the highest possible statistical power, especially during restricted MSA multiple pollutant analyses. A sensitivity analysis revealed that hazard ratios changed by less than 5% upon using exposure data from 1980 instead of 1999-2000.

An interesting trend to note was that resulting hazard ratios were consistently increased for 1999-2000 exposure in comparison to 1980 exposure estimates. A possible

explanation for this phenomenon is that given the larger number of MSAs available in the latter exposure period, the estimate is more representative of the true fine particle effect on mortality. The larger number of available MSAs allows for an increased precision in the results, as evidenced by a lower standard deviation for fine particle estimates from 1999-2000 when compared with the standard deviation from 1980 (3.3 vs. 4.7 respectively).

Certain limitations of using ecological variables for air pollution exposure is that there may be variations within and between cities during follow-up, levels of ambient particles are generally declining over time, and the chemical makeup of air pollution is constantly changing. It has been noted by Zidek et al. (1996) that when fixed-site monitors are used and other internal sources of particles are excluded, measurement error should bias estimates towards the null hypothesis and decrease statistical precision. Previous studies have also shown that using community-level exposure to represent individual-level exposure tends to bias exposure effects towards the null (Dominici et al., 2000; Zeger et al., 2000).

The cohort nature of the current study also implies that the exposure estimates used reflect long-term relatively constant air pollution concentrations. However, it is likely that ambient air pollution concentrations were changing and were higher in the past. For example, Darlington et al. (1997) noted that there were significant reductions in PM_{10} in the United States from 1988 through 1995. Over the country as a whole, the weighted annual average concentration of PM_{10} was reduced from 34 $\mu g/m^3$ to 26 $\mu g/m^3$ during this time. The average reduction of the anthropogenic fraction of PM_{10} (mainly $PM_{2.5}$) was between 27 and 33%. In addition, ozone levels have generally declined in the

US since the enactment of the Clean Air Act in 1970. Emission control programs have been largely successful in reducing anthropogenic concentrations of ozone. However, higher concentrations of ozone remain in many areas, which have levels above the health-based National Ambient Air Quality Standards (NAAQS). Levels of nitrogen dioxide in the United States have also been decreasing. Since 1983, 90% of 125 monitoring sites across the U.S. consistently record concentrations lower than 0.055 ppm (Chen et al., 2007a). At these concentrations, pulmonary function is generally not affected. Carbon monoxide emissions have declined significantly since catalytic converters were introduced for motor vehicles. The introduction of catalytic converters in 1975 resulted in a 76.3% reduction in carbon monoxide emissions (Mott et al., 2002). However, carbon monoxide concentrations can briefly increase in times of higher automobile volume.

Using mean concentrations of ambient air pollution to estimate cumulative long-term exposure is valid if ambient air pollution concentrations are an adequate proxy for individual exposure. Ecological, or group-level, exposure data can lead to error in estimating individual risk, especially since ambient exposure is poorly correlated with personal exposure. In fact, ambient concentrations of air pollutants might not reflect personal exposure on a day-to-day basis or lifetime exposure. It is also possible that differences between individuals within the same city are larger than differences between cities themselves. Exposure estimates might not necessarily be representative of long-term air pollution concentrations and do not take into account changes in the pollution levels. It is also possible that air pollution exposure measurements were collected too close to the time of death to be causally linked to chronic mortality (Gamble, 1998).

There is the possibility that an individual living in an area of low ambient levels of air pollution might personally be exposed to higher levels of air pollution (based on lifestyle and occupational characteristics) than an individual living in a more polluted air, but who spends more time indoors. For example, it has been estimated that Canadians spend nearly 88.6% of their time indoors, 6.1% outdoors, and 5.3% in vehicles (Leech et al., 1996). Similarly, it has been estimated that in the United States as well as most other industrialized nations, people spend more than 80% of their time indoors. A study on national human activity patterns estimated that United States residents spend 87% of their time in enclosed buildings and about 6% of their time in enclosed vehicles (Klepeis et al., 2001).

This phenomenon is made more difficult by the fact that data from other cities show that outdoor concentrations may be poor surrogates for personal exposure (Mage & Buckley, 1995; Ozkaynak et al., 1995; Brown et al., 1997). Yet, it is still possible to estimate indoor air pollution concentrations from outdoor particulate matter concentrations. The ratio of ambient particulate matter indoor to outdoor concentration, or the infiltration factor, depends on the rate of air exchange, penetration efficiency, deposition, and removal rates between these two environments and is also a function of particle size. Fine particles may have an infiltration factor as high as 0.4 to 0.7 (Costa, 2001).

Physical activity status may be an important confounder in the current study, especially if individuals choose to exercise outdoors. The level of physical activity may also depend on health status. That is, healthier individuals may be able to perform more intense exercise. However, exposure to ambient air pollution may also increase the risk

of developing disease, with disease responsible for a lower physical activity level. Physical activity level may be part of the path of causation between exposure to air pollution and mortality. In the ACS CPS II cohort, 28% reported no or a slight amount of exercise, 64% of the study participants reported moderate exercise, and 8% reported heavy exercise (Krewski et al., 2000). In a recent study, habitual exercise was found to prevent premature death attributable to air pollution (Wong et al., 2007).

Another potentially major limitation of the current study is that the analysis did not consider time-varying covariates. It is important to bear in mind that particulate matter is a mixture that varies in composition both temporally and spatially. Temporal information on covariates was also not available for the study. An ideal analysis includes time-dependent exposure profiles for each individual in the study (Murdoch et al., 1992). However, in the reanalysis of the Harvard Six Cities study by Krewski et al. (2000), incorporating information on changes over time in cigarette smoking and BMI had little effect on the association between fine particles and mortality. By extension, it is therefore possible that while the incorporation of time-varying covariates may be preferred, the current results may still afford an appropriate approximation.

c. Individual Covariates

Perhaps the most obvious limitation of this data set is that it was not designed specifically to address the relation between air pollution constituents and mortality. The original goal of the study was to examine the impact of environmental and lifestyle factors on cancer etiology in a large group of men and women in the United States. Also,

participants in the ACS study were enlisted in a highly selective cohort that is not necessarily representative of the general population. The ACS CPS II cohort is composed of mainly white (94%), upper middle class volunteers. The percentage of high school graduates was also much higher among study participants than in the general population of each community, according to 1990 Census Bureau data. If the study subjects were not representative of their communities, then the generalizability of the study findings is likely compromised. The differences may have led to significant selection bias. It can be argued that biological processes relating to air pollution and mortality may be identical across racial groups. However, it is also possible that differences across racial groups might be present (Krewski et al., 2000).

Since study subjects were recruited by ACS volunteers without the use of standard statistical and epidemiological methods from well-defined sampling frames, recruitment may have varied by community. The result of this may be that study subjects may vary by community based on potential recruitment differences in each area. Thus, study participants in different cities may have varied in their demographic, social, economic, and lifestyle characteristics based on differences in recruitment. Selection bias may be present in the estimates of mortality effects resulting from air pollution exposure because of the recruitment differences if the reasons for inclusion or exclusion in the study differed in each city, and if these reasons correlated with mortality.

A potential methodological issue presented in the current study is that standard Cox regression models commonly used in the analysis of mortality in cohort studies are based on the assumption that individual observations are independent. However, complex spatial patterns may exist in the ACS data, leading to spatial autocorrelation. It

is possible that survival experience clusters by community or neighborhood. Longevity might be more similar among subjects within the same community or neighborhood when compared to those from different geographic areas even when potential individual confounders are considered. Furthermore, nearby cities may have similar demographic characteristics and are more likely to have similar economic and environmental climates (Higgins et al., 2000). If this spatial autocorrelation is not taken into consideration, bias and a loss of precision in the estimates are possible.

Previous study found no evidence of statistically significant spatial autocorrelation in the survival data after controlling for fine particulate air pollution and other individual risk factors (Krewski et al., 2000; Pope et al., 2002; Krewski et al., 2005). In the current study, a sensitivity analysis was performed comparing results from the random effects Cox regression model, which controlled for spatial patterns in the data, to the traditional Cox regression model, which assumed that individual observations were independent. That is, the standard Cox model assumed a fixed collection of locations with fixed variance between the cities whereas the random effects model assumed a random sample of cities with random variance in relationships between cities counted towards the total variation (Higgins et al., 2003). The random effects model is based on the assumption that individual mortality risks carry more variation than can be explained by the standard Cox model. The differences in individual mortality risk in different cities is assumed to be independent of the proximity of those cities, indicating that mortality may be spatially clustered beyond the spatial association of specific MSAs (Krewski et al., 2000). The random effects model assumes that unmeasured risk factors do not confound the effects resulting from the pollutant of interest (Higgins et al., 2003).

In the current study, a random effects survival model was used to estimate hazard ratios with one level of clustering at the MSA level. Inclusion of random effects into the Cox proportional hazards regression models inflated the uncertainty in the resulting estimates, as demonstrated by the wider confidence intervals. The results indicated no statistical difference when both models were compared. That is, the estimates obtained in the current study relating air pollution to mortality were robust to control for clustering at the MSA level for random effects.

The long follow-up period of the ACS CPS II cohort is ideal in that it allows for the detection of effects that may occur at a low frequency. However, the longer the follow-up period, the more exposure misclassification may be present. With a long follow-up period, there is a greater chance that population mobility has occurred and the results may be biased towards the null. The results of the current study show competing factors of bias to the null from exposure misclassification and more accurate risks due to more complete follow-up.

Another limitation of the ACS cohort in the context of the current study is the lack of information on population mobility. Population mobility is important to consider because when cohort members change residences, their exposure may change as well since level of exposure can vary substantially with geographic location. In addition, population change is considered to be an indicator of the economic climate in a particular area. That is, healthy individuals generally move out of areas that are experiencing recession to areas of increased economic prosperity. For example, areas in which heavy manufacturing was common during the 1980s were more likely to have experienced a recession at this time as well as being areas high in levels of fine particles and sulfate

(Krewski et al., 2000). Short-term mobility, as in working in a location different from one's residence and not working on weekends, is also important to consider. Unfortunately, since residential addresses were only available at the time of recruitment into the ACS CPS-II cohort in 1982 (and at the time of death for subjects who died during the follow-up period), population mobility of the cohort could not be evaluated.

A further problem with the data is that there was no defined target population and response rates to the ACS questionnaire were not defined. It is possible that error also arose from inaccuracy of mortality data. It has been suggested that cancer deaths are usually coded with more than 80% accuracy (Percy et al., 1981). However, respiratory and cardiovascular deaths might not have such a high rate of accuracy in the coding due to confusion between the two. For example, if persons had these conditions concurrently, there may be some uncertainty about the primary cause of death. Also, it may be difficult to select the cause of death in the event of a complex chain of health events. For example, acute bronchiolitis may be confused with pulmonary edema or can increase the likelihood of heart failure. However, pulmonary edema may be caused by increased lung permeability that results from air pollution exposure (Schwartz, 1994). Due to these difficulties potentially resulting in cross-coding, cardiovascular and respiratory deaths were combined in this study.

In the original ACS questionnaire, information was collected on occupational exposures. Occupational exposure is an important potential confounder in the air pollution exposure/mortality relationship since individuals who live in highly polluted areas might also work in more polluted environments. The occupational "dirtiness index" used in this study is a variable designed to encompass and integrate exposures in the

workplace. It may also be conceptualized as a variable that captures an aspect of social class that is correlate with, but different from, educational attainment (Krewski et al., 2000). Certain limitations are presented with using the occupational dirtiness index. First, occupational information collected from study participants was not a detailed history of lifetime work. Second, the indices are only simplifications of complex exposure circumstances. Third, the validity of the occupational coding has not been established for the extent to which it reflects actual jobs and occupations (Krewski et al., 2000). These limitations may lessen the ability to control for confounding occupational exposures in the study.

All Cox proportional hazard models were stratified by 1-year age groups, gender, and ethnicity. This has previously been suggested to be adequate to control for the effects of age on survival (Krewski et al., 2000). Socioeconomic inequalities in health are well-documented. Furthermore, inequalities in cardiovascular (Huisman et al., 2005; Picciotto et al., 2006) and respiratory diseases (Prescott et al., 2003; Power et al., 2005) are especially well-documented. It is suspected that socioeconomic circumstances may account for the complex unequal distribution of health status. For example, poor diet, smoking, and excessive drinking (Blakely & Wilson, 2005; Ness et al., 2005), psychosocial stress (Metcalfe et al., 2005) and genetic differences (Davis et al., 2005) could account, in part, for the socioeconomic differences. It is also been suggested that inadequate access to health care services heavily influences health inequality (Fiscella & Williams, 2004). Both individual and ecological covariates are used in the current study to control for these socioeconomic factors that may confound the air pollution-mortality relationship.

d. Ecological Covariates

Ecological confounders do not have to be associated with the exposure in every group. However, they must be "ecologically" associated with the exposure across groups (Morgenstern, 1998). Confounding arises when the spatial pattern of the covariate and of the exposure are such that the covariate confounds the exposure/outcome relationship (Willis et al., 2003a). A problem with air pollution exposure estimates is that exposure might follow a similar geographic pattern as another ecological covariate. This complicates the distinction between the covariate and the exposure and the effect on mortality. Air pollution is partially determined by the same economic factors that influence other mortality risk factors (Willis et al., 2003b). As an example, particulate air pollution is largely generated from heavy industry. However, areas where this type of industry is present have previously been associated with other risk factors such as a depressed economy and a blue-collar culture which is linked to higher smoking and alcohol consumption, less exercise, and a poorer diet (Garrison et al., 1993). Control of confounding limits this to a certain extent; however, residual confounding is possible.

Ecological covariates were used in order to more fully account for sociodemographic risk factors present at the metropolitan level, thus in an effort to reduce bias. In the current study, ecological covariates from 1990 were used to represent the median values for the duration of the 1982-2000 follow-up period of the study. According to this study, African Americans seem to live in areas having a greater risk of mortality from lung cancer. Furthermore, the greater the proportion of the population

over the age of 25, the greater the lung cancer mortality risk, even after controlling for individual age. This is to be expected since the major risk factor for lung cancer is smoking and the older the population, the greater the chance that smoking (either active or passive) occurred. The analyses controlled for smoking and age at the individual level; however, residual confounding is likely present.

In general, controlling for ecological covariates did not significantly change the relationship between the individual pollutants and mortality. Ecological covariates did not appear to exert a significant confounding influence on the relationship between pollutant exposure and mortality. It is unlikely that these ecological covariates exert a significant confounding influence. In this study, it appears that controlling for confounders at the individual level is sufficient to account for any related MSA-level characteristics that might affect the air pollution-mortality relationship. This notion is further supported by the fact that when mortality hazard ratios were stratified by education level at both the MSA and individual level, resulting estimates were nearly identical.

Information bias is possibly present in the analysis since air pollution data was available for counties in which air pollution levels were most likely to be high. Also, the effect of ecological confounders differs in analyses that use smaller geographic units. At the MSA scale, ecological variables might show too much intraurban variation to represent the socioeconomic or environmental conditions of interest without significant measurement error (Krewski et al., 2005). To minimize aggregation problems, certain researchers suggest the smallest available unit of analysis should be used unless there is sufficient reason to believe that using larger units will reveal more about the effect in

question (Bailey & Gatrell, 1995). Because of this, it may be assumed that results of the current study underestimate the true mortality hazards.

An ideal study would measure long-term individual-level exposure air pollution (Abbey & Burchette, 1996). The EPA (1996) highlighted that individual exposure is "important in itself, because the body may react differently to ambient and non-ambient particles". It has previously been stated that trends in air pollution exposure and mortality are more likely to be confounded at the national scale than at the local scale (Janes et al., 2007). Individual-level covariates are also generally preferred in epidemiologic analysis. Any resulting causal inferences suggested from ecological studies fail to demonstrate the true effect at the individual level (Morgenstern & Thomas, 1993). However, certain variables inherently represent community-level effects such as unemployment. Further, since income data was not available at the individual level, ecological information was used in its place.

Even though individual-level covariates are generally preferred in epidemiologic analysis, certain variables inherently represent community-level effects, such as median household income. Since income data was not available at the individual level, ecological information was used in its place. In addition to exposure data, ecological information was used for certain population-based variables such as income disparity. The limitation of adjusting for place-specific ecological covariates is that the data used may not be representative of the exposures of the study subjects, resulting in misclassification (Willis et al., 2003a). Non-differential misclassification has previously been speculated to always lead to an overestimation of effects in ecological studies when compared to effects derived from individual studies, even if no other sources of bias exist

(Brenner et al., 1992). However, it is possible that misclassification in this study is differential because smaller metropolitan areas may be more internally homogeneous for these factors than larger ones (Willis et al., 2003b). Differential misclassification may bias the results either towards or away from the null, depending on the situation. However, according to previous analysis, using smaller county units of geographical area (i.e. zip code level) results in significantly increased risk estimates over estimates using MSA analytic units (Krewski et al., 2000). This means that differential misclassification in the current study may have biased the results to the null. Abrahamowicz et al. (2004) showed that inclusion of ecological covariates in the models results in a downward bias in estimates of relative risk. Even though this bias may be minimal, it persists regardless of the strength of association between the ecological covariate and mortality.

5.3 The Effect of Educational Attainment on Air Pollution and Mortality

Based on previous indication that education significantly modified the relationship between mortality associated with fine particulate matter, relative risk of mortality associated with air pollutants in this study was assessed by level of educational attainment (Krewski et al., 2000). The explanation for the modifying effect of education is unknown. O'Neill et al.(2003) postulated three hypotheses to explain the educational effect on air pollution-related health outcomes: 1) groups with lower socioeconomic status may be more susceptible to the health effects of air pollution since they already have compromised health status resulting from deprivation; 2) they may receive higher

exposure to air pollution; and 3) they are likely to suffer greater health effects from exposure to air pollution due to the combination of greater exposure and enhanced susceptibility. These ideas are supported in numerous other reviews. For example, Reynolds et al. (2001) state that those with lower socioeconomic status may be exposed to up to an order of magnitude more traffic near their homes. Jerrett et al. (2001) agree that these individuals might also live nearer to large industrial sites that emit industrial air pollution. In the U.S. and Canada, disadvantaged groups who live in low-cost housing are generally subjected to higher potential exposure to air pollution (Jerrett et al., 2001). The U.S. Institute of Medicine (1999) further indicated that poor and minority groups may suffer higher burdens of sociobehavioural health risks as well as greater exposure to pollution. While impoverished and minority groups already generally suffer from poor nutrition, higher occupational exposure to pollutants, and psychosocial stress, they might also face greater exposure to environmental pollutants than the general population. Disadvantaged and minority groups are generally exposed to disproportionately high levels of ambient air pollution.

Because these groups are already associated with other risk factors of disease and mortality, such exposures to higher levels of air pollution might exacerbate existing conditions and psychosocial stress of relatively low status individuals. The risk factors might combine multiplicatively with other determinants of health (Birch et al., 2000). If these individuals already face complex and significant burdens on their health due to social inequalities, they may be more susceptible to the health effects of other risk factors (Jerrett et al., 2003). Due to disproportionately high health risks faced by disadvantaged and minority groups, it is important to control for confounders in order to achieve an

appropriate estimate of the risk of air pollution on mortality. Lack of control for any of these variables could result in a false attribution of the health effects of air pollution.

However, it is also possible that educational attainment is an indication of socioeconomic status, which known to be correlated with health status (Willis et al., 2003b; Huisman et al., 2005; Lynch et al., 2005). That is, education may be a marker for a more complex mixture of socioeconomic variables that impact the level of mortality risk (Krewski et al., 2000). These socioeconomic variables that are associated with inequalities in education level attained as well as health status may be represented by certain behavioral and material factors. Among the relevant behavioral factors are smoking, drinking, exercise, and dietary habits. Material factors may include environmental quality and psychosocial stress of living with a lack of wealth (Schrijvers et al., 1999). The educational effect might also be the result of differential exposure. That is, those who are less educated may be less likely to avoid the risks of ambient air pollution (Hamilton, 1995), and other risks that influence health (Link & Phelan, 1996). Another explanation for the effect of education on the air pollution/mortality relationship is that within better-educated communities, there is a tendency towards a healthier lifestyle since those in close proximity are likely to imitate the behavior of those around them (Krewski et al., 2000). Finally, the higher the socioeconomic status, the more likely that the individual has access to air conditioning in their home or work (Higgins et al., 2003). Though indoor concentrations of fine particles infiltrating from the outside is nearly 70% of the outdoor value, air conditioning can reduce this concentration to about 30% (Dockery & Spengler, 1981).

In the current study, it appears that mortality risk differs by education level attainment. When assessing the air pollution-mortality relationship by educational attainment at both the MSA and individual levels, having completed more than high school was consistently associated with a lower risk of all-cause, cardiopulmonary, and lung cancer mortality when the relationships between air pollution exposure and mortality were significant in the first place (e.g. $PM_{2.5}$, SO_4^{2-}, SO_2). As the percentage of residents over age 25 who have completed high school and income increases and income disparity is reduced, mortality risk decreases. Education and income appear to be markers of socioeconomic status and the higher the level of socioeconomic status in an MSA, the lower the mortality risk. The distinction between having completed less than high school and equal to high school was more ambiguous. Possible reasons for this ambiguity may include lower statistical power (in the case of those with less than high school due to smaller sample size) and exposure misclassification due to population mobility. However, it follows that a higher level of educational attainment seems to be associated with a lower risk of mortality. It is unlikely that education itself provides a protection factor for mortality but it may serve as a marker for complex processes associated with higher socioeconomic status and improved health outcomes.

5.4 Hill's Causal Criteria in Relation to Air Pollution and Mortality

An obvious question concerning the air pollution-mortality relationship is "what is the likelihood that the relationship is causal?" In response to this question, Hill's 1965

causal criteria may be used to examine the extent of causality in the air pollution-mortality relationship. These criteria have been popular in previous assessment of causal relationships (Rothman & Greenland, 1998). Hill suggested the following criteria in attempting to distinguish causal and noncausal associations: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biologic gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy.

The first criterion, the strength of the association, may be used to determine causality to a certain extent. However, a weak association does not necessarily rule out causality nor does a strong association necessarily mean causality. A strong association may rule out hypotheses that the association is entirely due to one weak unmeasured confounder or another source of bias (Rothman & Greenland, 1998). The strength of the association was assessed in terms of the level of statistical significance, based on 95% confidence intervals for the relevant hazard ratios in this study.

Consistency refers to the constant repetitions of observations of an association in different populations, under different conditions and times. That is, consistent results should be seen across independent studies. Upon routine statistical tests of significance, certain relationships will appear to be unlikely due to chance. To determine consistency, a repetition of the circumstances and the observations must occur to rule out chance (Hill, 1965). Previous cohort studies have generally consistently linked chronic exposure to fine particles and sulfate, and to a lesser extent ozone and sulfur dioxide to morality, whereas carbon monoxide and nitrogen dioxide have previously failed to show such an association. For the current study, the consistency of the results were weighed against previous findings.

Specificity is achieved when a cause leads to a specific effect. Because air pollution has previously been linked to a myriad of respiratory and cardiovascular conditions, this criterion does not add much information in determining the causality of the relationship. Even though the respiratory tract is the initial target of air pollution, a multitude of health effects may result upon exposure. Rothman and Greenland (1998) agree that specificity does not give greater validity to any causal inference regarding the exposure effect. Thus, specificity was not examined as a potential indicator of causality in this study.

The next Hill criterion is temporality. Temporality is important because we need to know that exposure precedes disease in order to hypothesize causality. For chronic diseases with long latent periods, such as lung cancer or cardiorespiratory conditions, exposure must take place years or decades before the disease arises. In this study, it can be generally assumed that exposure to air pollution began at birth and so exposure preceded disease. However, exposure estimates in this study were collected for only a few years before vital status ascertainment. For example, fine particle data were collected from 1979 to 1983 and mortality was assessed from 1982 through 2000. Thus, exposure estimates were collected no more than 3 years before chronic disease, which takes decades to develop, may have presented itself. However, it can also be argued that this relatively acute exposure is a proxy for lifetime exposure and thus the temporality criterion of exposure preceding disease was met (Gamble, 1998).

The biological gradient refers to the existence of a uni-directional dose-response curve. Hill (1965) suggested that a clear dose-response pattern implies a simple explanation of the cause-effect relationship. However, associations that show a uni-

directional trend in dose and response are not necessarily causal. It is possible that confounding can result in the appearance of such a trend between a noncausal risk factor and the anticipated response. It is also possible that a threshold relationship exists. When there is a threshold, no adverse effects are seen below a certain concentration (Rothman & Greenland, 1998). For these reasons, the existence of a uni-directional dose-response trend is neither necessary nor enough to claim a causal relationship and biological gradients was not considered in this study.

The next criterion, plausibility, refers to the biological plausibility of the hypothesized relationship. Hill (1965) described this criterion as helpful, but not necessary since what is biologically plausible depends on the state of biological knowledge at the time. However, in this study, key potential biological mechanisms previously described in the literature review were summarized.

Coherence is suggested as the next criterion. This criterion recommends that cause-and-effect interpretation of the data should not seriously conflict with generally accepted facts concerning the history and biology of the conditions in question (Hill, 1965). For this study, coherence was assessed based on the following: knowledge of tropospheric chemistry and biological mechanisms (as previously discussed), in addition to statistical results of the current study. Coherence represents the overall strength of the link between the pollutant and mortality outcomes.

Experimental evidence may also be used to test a hypothesis of a causal effect. Experimental tests have certain strengths: the conditions can be well-controlled and the effects of the specific risk in question may be unambiguously monitored. However, animal studies have certain limitations because they generally consider concentrations of

pollutants that are much higher than those that would be observed at ambient conditions, animals may metabolize the pollutants in a different manner than humans, and it is unlikely that the pollutants the animals are exposed to mirror the compositions of actual ambient air pollution mixtures. Because it is unethical to purposely expose humans to large and prolonged quantities of air pollutants, we have to rely on evidence from laboratory experiments, often in the form of animal studies. Another way to interpret Hill's experimental evidence criterion is that the observance (in humans) of a preventative association if the risk in question is reduced can serve as experimental evidence. However, because in this study it is difficult to explicitly assume that the individuals in areas with lower levels of air pollution were less exposed than individuals in areas with higher pollution and individual exposures are not controlled or measured, experimental evidence was given in terms of animal toxicological studies despite their limitations.

The final hypothesized criterion is analogy. Rothman and Greenland (1998) suggested that because scientists can generally find analogies everywhere, whatever insight may be gained from an analogy is lost due to the sheer number of possible analogies. An analogy may provide an elaborate hypothesis about the association in question at best.

A summary of the major Hill criteria and supporting evidence for each pollutant is summarized in Table 24.

Table 24. Strength of Causality in Air Pollution-Mortality Relationship Using Hill's 1965 Causation Criteria

Hill's Criteria[a]	$PM_{2.5}$	SO_4^{2-}	O_3
Strength of Association	High	High	Medium
Consistency with Previous Results	High	Medium	Medium
Plausibility	• Can penetrate deep into lower respiratory system, enter the bloodstream and lead to systemic inflammatory changes which may affect blood coagulability and may trigger faster development of cardiovascular disease and atherosclerosis. • May mediate oxidative stress resulting in cardiovascular dysfunction.	• Health effects possibly due to acidic component. • Acidic ultrafine particles may provoke alveolar inflammation resulting in acute changes in blood coagulability and the release of mediators that may provoke acute respiratory illnesses. • May cause clearance abnormalities from the increased viscosity upon mucous acidification. • May act indirectly through solubilization of metals resulting in lung injury upon inhalation.	• Oxidant • Leads to activation of nuclear factor-κB and its translocation to the nucleus where it binds to DNA consensus sequences in promoters of pro- inflammatory genes that code for cytokines, chemokines, and adhesion molecules • These molecules then increase netruophil recruitment into airways and alveoli, activating them for mediator secretion and damaging tissue.
Experimental Evidence	• Long-term exposure of mice to low [$PM_{2.5}$] altered vasomotor tone, and induced vascular inflammation and atherosclerosis. • Exposure of sensitized mice to $PM_{2.5}$ before allergen exerted strong adjuvant effect on expression of allergic airway inflammation. • $PM_{2.5}$ produced lung inflammation in mice.	• Animal studies showed acid aerosols may cause lung function changes, airway hyperresponsiveness, secretory cell hyperplasia, and clearance abnormalities. • In humans, short-term H_2SO_4 exposures [0.1 - 1.0 mg/m^3] resulted in lung clearance function and pulmonary mechanical effects through alveolar inflammation.	• O_3 may activate stress signaling pathways in resident alveolar inflammatory cells in rats and in human epithelial cells
Coherence (Chemistry, Biology & Data)	High	Medium	Medium
Overall Association with Mortality	High	High	Medium

[a] The additional Hill criteria: specificity, temporality, biological gradient, and analogy, are not included for reasons discussed above.

Table 24. Continued

Hill's Criteria[a]	SO_2	NO_2	CO
Strength of Association	Medium	Low	Low
Consistency with Previous Results	Medium	High	High
Plausibility	• May act as an irritant, promotes constriction of small airways, and may then reduce the threshold of asthma patients to other stimulants. • SO_2 is a highly reactive hydroscopic gas that is almost completely absorbed into the nasal cavity during normal inhalation	• Oxidant (less powerful than O_3) • May exacerbate respiratory disease by impairing function of alveolar macrophages and epithelial cells, increasing risk of lung infection. • Inhalation may lead to the synthesis of various cytokines active in cellular inflammation.	• Increased levels in blood lead to a decrease in the amount of oxygen blood can carry and thus reduces the amount of oxygen delivered to the body's organs and tissues. • Inhalation of CO results in the formation of carboxyhemoglobin in the blood, which inhibits the intake of oxygen.
Experimental Evidence	• Pathological changes in lung function of experimental animals required very high concentrations of SO_2. • SO_2 inhalation caused bronchial narrowing which occurred within minutes and was readily reversible, indicating it was likely the result of an increase in bronchial smooth muscle tone (effect h seen in guinea pigs, dogs, and cats and humans).	• Human and in-vitro studies showed that NO_2 activates oxidant pathways • Exposure to high levels of NO_2 (20 ppm) for a few weeks or longer has been shown to cause emphysema-like changes in the lungs of animals.	• Chronic exposure of rats resulted in stimulation of erythropoietin production • Chronic exposure of hypoxic rats induced pulmonary vasodilation by acting directly on lung artery smooth muscle cells. • CO may interfere with homeostasis through alterations in the NO-cGMP signaling pathway.
Coherence (Chemistry, Biology & Data)	Medium	High	High
Overall Association with Mortality	Medium	Low	Low

[a] The additional Hill criteria: specificity, temporality, biological gradient, and analogy, are not included for reasons discussed above.

5.5 Conclusions

Even though individual health risks of air pollution are relatively small, the public health impacts of air pollution exposure are significant. However, uncertainties still remain regarding the role of chemistry versus size of the particles and the use of fixed-site monitors to estimate effects on individuals who spend the majority of their time indoors. Biological mechanisms, most importantly for sulfate and fine particle mixtures, also require additional investigation. A major assumption in the current study is that risk factors for mortality, such as smoking habits, education, and air pollution, remained constant over the follow-up period. This is likely untrue, but may still provide a reasonable approximation. The results of this study also require caution in their interpretation both because of potential over-adjustment of covariates and a moderate correlation among some pollutants as well as ecological covariates.

Despite using such crude measurements of air pollution exposure, we are able to detect differences in mortality that, when controlled for confounding, show small but significant and robust associations between air pollution and mortality. The current study provides robust evidence of a significant association between fine particles and more specifically, sulfates, and mortality. While risk estimates may not be exact due to some slight instability resulting from moderate correlation between pollutants, results consistently indicate that sulfate may be the most important pollutant involved in air pollution-related mortality from all causes and lung cancer, while the combination of sulfate and fine particles may be most important for cardiopulmonary mortality.

Sulfate most likely acts as a marker of aerosol acidity, or the acidic component of particulate matter, generated predominately from sulfuric acid and ammonium bisulfate. Previous studies likely underestimated the effect of aerosol acidity due to inaccurate chemical

analysis tools available at the time. Further underestimation may have resulted upon assuming that all sulfate aerosol acidity resulted solely from the more potent sulfuric acid in epidemiologic studies. It is likely that a portion of sulfate aerosol acidity is in the partially neutralized form, ammonium bisulfate, which is less likely to result in adverse health effects. In reality, a lower concentration of aerosol acidity in the form of ammonium bisulfate would be required to generate the adverse health effects seen.

Alternatively, sulfate may also be a marker for other compounds, such as metals, which may be coated with sulfate. Thus, aerosol sulfate acidity may cause adverse health outcomes via two main mechanisms: 1) directly, through clearance abnormalities, changes in lung function, airway hyperresponsiveness and secretory cell hyperplasia, for example, or 2) indirectly, by acting as markers for other components of particulate matter, such as metals. Sulfate may act as a more accurate marker of the adverse fraction of fine particulate matter than fine particles themselves. The findings of the current study suggest that while sulfate is a component of fine particulate matter, the two overall pollutants exert related but independent effects on mortality.

This study implies that sulfur dioxide is not likely implicated in mortality, but may be a marker of sulfate and fine particle pollution. The study further suggests that ozone may be important to a sensitive subpopulation with existing cardiopulmonary conditions. Nitrogen dioxide and carbon monoxide do not appear to be significantly implicated in excess mortality. However, carbon monoxide may be likely more of a health threat in acute high exposures or to those with chronic cardiopulmonary conditions.

Particulate air pollution is an ongoing, international population health issue (Cohen et al., 2005). Even though air pollution levels have decreased in many Western countries over the past few decades, many parts of the world are still largely affected by air pollution. For example,

areas such as southern Poland, the Czech Republic, and eastern Germany, until very recently burned large amounts of coal with high sulfur content (up to 15%) (Baird & Cann, 2004). Both sulfur dioxide and particulate matter levels regularly exceed WHO recommendations in Beijing, Seoul, and Mexico City. Particulate matter levels also consistently surpass guidelines in Bangkok, Mumbai, Cairo, Calcutta, Delhi, Jakarta, Karachi, Manila, and Shanghai. In many of these places, coal is still used as the predominant fuel. If countries like India and China do not attempt to reduce levels of sulfur dioxide, by 2020 the concentration of this gas in cities such as Mumbai, Shanghai, and Chongqing will be nearly four times the WHO maximum safe limit (Baird & Cann, 2004). Outdoor air pollution harms more than 1.1 billion people each year (UNEP and C4, 2002). The United Nations Environment Programme estimated that 2.7 to 3.0 million deaths worldwide in 2001 were attributed to air pollution. Ninety percent of the deaths occurred in those living in developing countries (UNEP and C4, 2002). This number is estimated to rise to 8 million by 2020 (Baird & Cann, 2004).

It is also important to consider that air pollution may be transported over long distances, therefore affecting countries that would otherwise emit or be exposed to less air pollution. This long-range air pollution may have important effects on mortality, as demonstrated in the current study by sulfate.

Because most fine particles in urban air are secondary, they must be controlled by reducing emissions of primary pollutant gases such as nitrogen oxide, volatile organic compounds, and sulfur dioxide, from which they are formed. Furthermore, the drive to decrease fine particle levels will be counterproductive if, in the process, the concentration of ultrafine particles is increased; for example, through the conversion of diesel fuel to natural gas use in vehicles (Baird & Cann, 2004). Although acute sulfur-based smog episodes no longer occur in

the West, exposure to measurable levels of suspended particles containing sulfates and sulfuric acid still occur due to long-range transport of these substances from regions that still emit sulfur dioxide.

Though the empirical results of the current study are subject to great uncertainty, consideration of each of the pollutants may help to further refine the effects of each agent. Analyses of additional statistical measures such as AIC and log-likelihood values further support the importance of sulfate and fine particles overall to mortality. The combination of results from AIC and log-likelihood values as well as the sensitivity analysis considering fine particle fractions approximated at the local and regional scale are all consistent in suggesting that sulfate, or the regional component of fine particulate matter, is most likely implicated in mortality from all causes and lung cancer while the combination of the regional and local fraction of fine particulate matter is more closely linked to cardiopulmonary mortality. The large attribution of air pollutant exposure to cardiopulmonary mortality seems consistent with biological mechanisms of air pollution action on the respiratory system.

The results of this study are of public health interest since afflictions of the respiratory tract account for a significant proportion of total acute illness in the population at large. Such adverse events result in lost time from school and work and increased doctor visits and hospital admissions (Lebowitz, 1996). While air pollution has been associated with a wide range of health effects, its effects on mortality are debatably the most important. The results of this study alone are insufficient to conclude a causal relationship between air pollution and mortality. However, the results from the current study strongly indicate that particulate matter and, more specifically, sulfate are either direct contributors to excess mortality or are markers of the causal agent. The results from the current study add to existing literature that strongly suggests that air

pollution is implicated in excess mortality. Expanding exposures to include metals and volatile organic compounds as well as conducting a source apportionment analysis would further disentangle the effects of particulate matter components on mortality.

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7. APPENDICES

Appendix A : ACS Questionnaires

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II QUESTIONNAIRE FOR MEN	Division No.	Unit No.	Group No.
	Researcher No.	Family No.	Person No.

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother or Sister)	IS THIS PERSON? (Circle One)	IF ALIVE, GIVE AGE	IF DEAD, GIVE AGE AT DEATH	DID THIS PERSON EVER HAVE CANCER? (Circle One)	IF "YES," SPECIFY TYPE OF CANCER	AT WHAT AGE?
Father	Alive Dead			Yes No		
Mother	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes," a) What type? _____ b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Prostate Trouble
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No If "yes," specify type and date(s) of operation(s): _____
4. How **many** x-ray or fluoroscopic **examinations** (GI series, barium enema, etc.) have you **ever** had of:

	0	1-5	6 or More		0	1-5	6 or More
Stomach	☐	☐	☐	Chest	☐	☐	☐
Intestine	☐	☐	☐	Arms/Legs	☐	☐	☐
Back	☐	☐	☐	Head/Neck	☐	☐	☐

5. Have you ever been **treated** with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   What part of your body? _____
6. How many times have you had colds or flu in the past twelve months? _____

CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night? _____
3. On the average, how many times a month do you have insomnia? _____ ☐ None
4. Within the last month, have you noticed:
   a) Painful or frequent urination? ☐ Yes ☐ No
   b) An unusual discharge from your penis? ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains? _____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition? _____

HABITS:

1. **Whether or not you smoke,** on the average, how many **hours a day** are you exposed to cigarette smoke of others:
   At home_____, At work_____, In other areas_____.
2. Do you now or have you ever smoked cigarettes, cigars or pipes, at least one a day for one year's time? ☐ Yes ☐ No
   If never smoked, skip to question 8.
3. If you **currently** smoke cigarettes, cigars or pipes, fill in the information below:

Current Smokers	Cigarettes	Cigars	Pipes
Average number smoked per day			
Age began smoking			
INHALATION:			
Do not inhale			
Inhale slightly			
Inhale moderately			
Inhale deeply			
Total years of smoking			
Years smoked **filtered** cigarettes			
Years smoked **non-filtered** cigarettes			

4. Current brand of cigarette: _____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand: _____

5. If you have **quit** smoking cigarettes, cigars or pipes, fill in the information below:

Ex-Smokers	Cigarettes	Cigars	Pipes
Average number smoked per day			
Age began smoking			
Age quit			
INHALATION:			
Did not inhale			
Inhaled slightly			
Inhaled moderately			
Inhaled deeply			
Total years smoked			
Years smoked **filtered** cigarettes			
Years smoked **non-filtered** cigarettes			

6. Last brand of cigarette smoked: _____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand: _____

7. Current **and** ex-cigarette smokers, fill in the following information for:
   1) The **first** brand smoked regularly; and
   2) The brand of cigarette smoked for the **longest** period of time.

Brand Name	Size	Filter		Menthol		Number Per Day	Years
		Yes	No	Yes	No		
1.							
2.							

8. Have you ever chewed tobacco at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to question 9.
   a) Age began chewing tobacco: _____
   b) How many times a week? _____
   c) For how many years? _____
   d) Do you still chew tobacco? ☐ Yes ☐ No
9. Have you ever used snuff at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to "Diet."
   a) Age began using snuff: _____
   b) How many times a week? _____
   c) For how many years? _____
   d) Do you still use snuff? ☐ Yes ☐ No

DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

Beef		Raw vegetables	
Pork		Carrots	
Chicken		Squash/Corn	
Liver		Citrus fruits/Juices	
Ham		Spaghetti/Macaroni/ White rice	
Fish		White bread/Rolls/ Biscuits	
Smoked meats		Brown rice/Whole wheat/Barley	
Frankfurters/ Sausage		Bran/Corn muffins	
Butter		Potatoes	
Margarine		Oatmeal/Shredded wheat/Bran cereals	
Cheese		Cold (Dry) cereals	
Eggs		Ice cream	
Green leafy vegetables		Chocolate	
Tomatoes			
Cabbage/Broccoli/ Brussels sprouts			

2. How many days a week do you eat the following fried foods?

Fried eggs		Fried hamburgers or beef	
Fried bacon		Other fried foods	
Fried chicken/fish			
French fries			

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
If "yes," what type and for how many years? _____

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
If "yes," what was the change? _____

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
☐ Yes, currently ☐ Formerly ☐ Never
b) If ever used artificial sweeteners, indicate amount per day and for how long.
Packets: No. per day _____ Years _____
Drops: No. per day _____ Years _____
Tablets: No. per day _____ Years _____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify) _____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2.)

Beverages	Currently		Previously	
	Amount	Years	Amount	Years
Whole milk (not skim milk)				
Caffeinated coffee				
Decaffeinated coffee				
Tea				
Diet soda or diet iced tea				
Non-diet colas				
Other non-diet soft drinks				
Beer				
Wine				
Hard liquor				

MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

Medications and Vitamins	Times	Years
Aspirin, Bufferin, Anacin		
Tylenol		
Vitamin A		
Vitamin C		
Vitamin E		
Multi-Vitamins		
Blood Pressure pills		
Diuretics (water pills)		
Thyroid medications		
Heart medications		
Anti-Acid medications		
Valium		
Librium		
Prescription sleeping pills		
Tagamet (for ulcers)		
Other: _____		
_____		

OCCUPATIONS:

1. What is your current occupation and what are your duties? _____
   _____
   _____ How many years: _____
2. If retired, what was your last occupation? _____
   _____
   _____
   _____ Year retired: _____
3. What other job have you held for the longest period of time? _____
   _____
   _____ How many years: _____
4. What time of day do you start working? _____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____, volunteer work _____,
   housework _____.
6. In your work or daily life, are (were) you **regularly** exposed to any of the following? If "yes," indicate the number of years exposed.

Exposure to:	Check One		Number of Years
	Yes	No	
Asbestos			
Chemicals/Acids/Solvents			
Coal or Stone Dusts			
Coal Tar/Pitch/Asphalt			
Diesel Engine Exhaust			
Dyes			
Formaldehyde			
Gasoline Exhaust			
Pesticides/Herbicides			
Textile Fibers/Dusts			
Wood Dust			
X-rays/Radioactive Materials			

REMARKS:

MISCELLANEOUS:

1. Where were you born? _____ (city) _____ (state/country)
2. Where were your parents born?
   Father: _____
   Mother: _____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination? _____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood? _____
6. How many friends or relatives do you feel close to? _____
7. How many times a month do you:
   a) Go to church or temple? _____
   b) Attend club meetings? _____
   c) Participate in group activities? _____
8. Were you in the U.S. Armed Services? ☐ Yes ☐ No
   If "yes,"
   a) What branch of the service were you in? _____
   _____
   b) What were your dates of service?
   _____ to _____,
   _____ to _____.
   c) Where did you serve? _____
   _____
9. What is the most upsetting event that happened to you in about the last five years? _____
   _____
   _____ ☐ None
10. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) How many times a week is it used? _____
    c) For how many years have you used it? _____

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II QUESTIONNAIRE FOR WOMEN 	Division No.	Unit No.	Group No.
	Researcher No.	Family No.	Person No.

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother or Sister)	IS THIS PERSON? (Circle One)	IF ALIVE, GIVE AGE	IF DEAD, GIVE AGE AT DEATH	DID THIS PERSON EVER HAVE CANCER? (Circle One)	IF "YES," SPECIFY TYPE OF CANCER	AT WHAT AGE?
Father	Alive Dead			Yes No		
Mother	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes,"
   a) What type? _____
   b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Breast Cysts
   - ☐ Gynecological Problems
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No
   If "yes," specify type and date(s) of operation(s):
   _____
   _____
   _____
   _____
4. How **many** x-ray or fluoroscopic **examinations** (GI series, barium enema, etc.) have you **ever** had of:

	0	1-5	6 or More		0	1-5	6 or More
Stomach	☐	☐	☐	Chest	☐	☐	☐
Intestine	☐	☐	☐	Breast	☐	☐	☐
Back	☐	☐	☐	Head/Neck	☐	☐	☐

5. Have you ever been **treated** with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   _____
   What part of your body? _____
   _____
6. How many times have you had colds or flu in the past twelve months? _____

CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night?_____
3. On the average, how many times a month do you have insomnia?_____ ☐ None
4. Within the last twelve months, have you noticed:
   a) A lump or thickening in your breast?
   ☐ Yes ☐ No
   b) An unusual discharge from your breast?
   ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains?_____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition?_____
   _____
   _____

MENSTRUAL AND REPRODUCTIVE HISTORY:

1. How old were you when menstruation began?_____
2. What is your current menopausal status?
   ☐ Still regularly menstruating
   ☐ In menopause ☐ Past menopause
3. During your menstrual history:
   a) Are (were) your periods: ☐ Regular ☐ Irregular
   b) What is (was) the usual number of days of flow?_____
4. **If past menopause:**
   a) Was your menopause: ☐ Natural ☐ Artificial
   b) Age when periods stopped completely?_____
   c) Did you have excessive bleeding during menopause? ☐ Yes ☐ No
5. Have you ever had or tried to have children?
   ☐ Yes ☐ No
   If "no," skip to question 9.
6. Have you ever had difficulty becoming pregnant?
   ☐ Yes ☐ No
   If "yes," what was the reason?_____
   _____
   _____
7. How many times have you been pregnant?_____
   a) Your age at your first pregnancy?_____
   b) Your age at your first live birth?_____
   c) Number of children born alive?_____
   d) Number of stillbirths (carried 5 months or more)?_____
   e) Number of miscarriages (carried less than 5 months)?_____
8. Were you ever given DES (Diethylstilbestrol) to prevent miscarriage? ☐ Yes ☐ No
   If "yes,"
   a) At what age did you take it?_____
   b) For how many months did you take it?_____
9. Birth control methods: Indicate your age when **first used** and number of years of use.

Method Used	Age	Years
Rhythm		
Diaphragm		
Cream/Foam/Jelly		
Tubal Ligation		
Intrauterine Device (IUD)		
Condom (partner)		
Vasectomy (partner)		
NONE OF THE ABOVE ☐		

10. Have you **ever** taken oral contraceptives (birth control pills)? ☐ Yes ☐ No
    If "no," skip to question 11.
    a) Age when you first took them?_____
    b) How many years did you take them?_____
    c) What brand(s) do (did) you take?_____
    _____
    d) If you stopped taking them, what was the reason?_____
    e) Did you have irregular or painful periods when you stopped? ☐ Yes ☐ No
11. Have you **ever** used female hormones (estrogens) other than oral contraceptives? ☐ Yes ☐ No
    a) Why do (did) you take estrogens?
    ☐ Menopausal symptoms ☐ Hysterectomy
    ☐ Bone problems ☐ Cancer
    ☐ Other (specify)_____
    b) Age first took estrogens?_____
    c) For how many years did you take them?_____
    d) How did you take them? ☐ Injection ☐ Cream
    ☐ Pill (brand):_____

HABITS:

1. **Whether or not you smoke,** on the average, how many **hours a day** are you exposed to cigarette smoke of others:
   At home_____, At work_____, In other areas_____.
2. Do you now or have you ever smoked cigarettes, at least one a day for one year's time? ☐ Yes ☐ No

Smoking History	Current Smokers	Ex-Smokers
Number smoked a day		
Age began smoking		
Age quit smoking		
Most recent (last) brand		
Years smoked **this** brand		
Total years smoked **filtered** cigarettes		
Total years smoked **non-filtered** cigarettes		
Total years of smoking (filtered + non-filtered)		

3. Current and ex-smokers:
   a) Do (did) you inhale? ☐ No, never
   ☐ Slightly ☐ Moderately ☐ Deeply
   b) Fill in the following information for:
   1) The **first** brand smoked regularly; and
   2) The brand of cigarette smoked for the **longest** period of time.

Brand Name	Size	Filter		Menthol		Number Per Day	Years
		Yes	No	Yes	No		
1.							
2.							

DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

Beef	Raw vegetables
Pork	Carrots
Chicken	Squash/Corn
Liver	Citrus fruits/Juices
Ham	Spaghetti/Macaroni/ White rice
Fish	
Smoked meats	White bread/Rolls/ Biscuits
Frankfurters/ Sausage	Brown rice/Whole wheat/Barley
Butter	Bran/Corn muffins
Margarine	Potatoes
Cheese	Oatmeal/Shredded wheat/Bran cereals
Eggs	
Green leafy vegetables	Cold (Dry) cereals
Tomatoes	Ice cream
Cabbage/Broccoli/ Brussels sprouts	Chocolate

2. How many days a week do you eat the following **fried** foods?

Fried eggs	Fried hamburgers or beef
Fried bacon	Other fried foods
Fried chicken/fish	
French fries	

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
   If "yes," what type and for how many years?

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
   If "yes," what was the change?

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
   ☐ Yes, currently ☐ Formerly ☐ Never
   b) If **ever** used artificial sweeteners, indicate amount per day and for how long.
   Packets: No. per day____ Years____
   Drops: No. per day____ Years____
   Tablets: No. per day____ Years____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify)____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2).

Beverages	Currently		Previously	
	Amount	Years	Amount	Years
Whole milk (not skim milk)				
Caffeinated coffee				
Decaffeinated coffee				
Tea				
Diet soda or diet iced tea				
Non-diet colas				
Other non-diet soft drinks				
Beer				
Wine				
Hard liquor				

MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

Medications and Vitamins	Times	Years
Aspirin, Bufferin, Anacin		
Tylenol		
Vitamin A		
Vitamin C		
Vitamin E		
Multi-Vitamins		
Blood Pressure pills		
Diuretics (water pills)		
Thyroid medications		
Heart medications		
Anti-Acid medications		
Valium		
Librium		
Prescription sleeping pills		
Tagamet (for ulcers)		
Other:		