EVALUATION OF THE RELATIONSHIP BETWEEN AMBIENT AIR POLLUTION AND HOSPITALIZATION FOR ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT TEMPLE UNIVERSITY HOSPITAL

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ABSTRACT

Background: Air pollution has been associated with adverse health effects for all-cause and specific respiratory morbidity and mortality outcomes. Acute exacerbations of COPD (AE-COPD) accelerate the decline in pulmonary function and are associated with greater mortality, morbidity, health care utilization, and reduced quality of life. Since the 1970 Clean Air Act was implemented, important reductions in air pollution have been achieved, but no safe threshold has been identified.

Objectives: The study was planned to evaluate associations between exposure to ambient concentrations of five criteria air pollutants (CO, SO_2, NO_2, ozone, $PM_{2.5}$) in Philadelphia, Pennsylvania, and visits to Temple University Hospital for AE-COPD, from January 1, 2005 through March 31, 2007. To identify subgroups with greater susceptibility to air pollution, associations were examined according to age, gender, race, residence, and antibiotic prescription.

Methods: Average daily air pollutant concentrations were obtained from the EPA's Air Quality Services Data Mart. Air pollutant exposures were evaluated for the day of the visit (lag0), one and two days preceding the visit (lag1 and lag2), and the average concentration over three days (lag012). Poisson regression provided rate ratios (RRs) to estimate associations between air pollution exposures and AE-COPD hospital visits.

Results: Of 1546 hospital visits for AE-COPD, 43% were from persons 65 years or older, 50% of each gender, and 90% from Philadelphia. In single pollutant models, increased RRs were present at all lags for NO_2 (e.g., RR = 2.27 [95%CI: 1.52, 3.38] at lag012) and SO_2 (e.g., RR = 1.70 [95%CI: 1.38, 2.08] at lag012). For $PM_{2.5}$, the direct effect was present only during the winter at lag1, lag2, and lag012 (RR = 1.79 [95%CI: 1.08, 2.96]). Inverse associations were present for ozone at all lags (e.g., RR = 0.64 [95%CI: 0.53, 0.76] at lag012).

Compared to the cohort as a whole, those ≥ 65 years of age were at greater risk of an AE-COPD hospital visit associated with $PM_{2.5}$ and CO at lag012, with NO_2 and SO_2 at lag0 and lag012, but there was no difference in ozone effect.

Conclusions: Primary gaseous air pollution exposures (SO_2, CO, NO_2) were associated with increased AE-COPD hospital visits among COPD patients at Temple University Hospital. The effects of SO_2, CO, NO_2, and $PM_{2.5}$ were greater for the subgroup ≥ 65 years of age compared to the cohort as a whole. Inverse association with ozone were consistent across subgroups. These results suggest that air quality during the study period was insufficient to protect the health of COPD patients, especially those ≥ 65 years old. Further study is needed to understand generalizability to other populations and to evaluate lower ranges of exposure from current levels of air pollution.

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Dr. Mamary was responsible for the collection of patient data for visits to Temple University Hospital because of acute exacerbations of COPD and was lead author of the analysis correlating Philadelphia air pollution data and hospital visits to Temple

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Gerard Criner, M.D., Department of Pulmonary and Critical Care Medicine

Dr. Criner was a contributor to the analysis correlating Philadelphia air pollution data and hospital visits to Temple University Hospital for acute exacerbation of COPD.

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CHAPTER 1
INTRODUCTION

Air pollution has been associated with adverse health effects in the United States and globally for all-cause and specific cardiovascular or respiratory morbidity and mortality outcomes. After the 1970 U.S. Clean Air Act was authorized, National Ambient Air Quality Standards (NAAQS) were defined for so-called criteria air pollutants, which include carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone, particulate matter (PM), and lead. The Environmental Protection Agency (U.S. EPA) monitors levels of the criteria air pollutants to protect the public from adverse health effects and to minimize negative effects on property and the environment.

Important reductions in air pollution have been achieved nationally and in Philadelphia. Nevertheless, the more recent lower air pollution concentrations have continued to be associated with adverse health effects, with no apparent safe threshold having been identified (Pope, 2000; Dominici, Peng, Bell, Pham, McDermott, Zeger, Samet, 2006). The objective of this dissertation was to evaluate further the relationship between short-term exposures to ambient air pollution in Philadelphia, Pennsylvania, and the frequency of hospital visits for acute exacerbation of chronic obstructive pulmonary disease (AE-COPD).

The lungs are the primary point of air pollutants' entry into the body, which provides the opportunity for an association with adverse respiratory effects. COPD is associated with an abnormal inflammatory response of the lung following exposure to noxious particles or gases. The most evident component is progressive airflow limitation, with symptoms of breathlessness, cough, and increased mucus production (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2008). AE-COPD is characterized by an acute change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal daily variation and may require a change in regular medication. Acute exacerbations accelerate the progressive loss of lung function and contribute to worsening COPD (GOLD, 2008). While mild AE-COPDs may be treated at home, moderate or severe exacerbations generally require hospitalization (Fein, Anzueto, Grossman, 2004). Approximately 70% of costs associated with COPD were related to AE-COPD hospitalizations, with a trend towards shorter lengths of stay but more frequent hospitalizations (Ramsey and Sullivan, 2003; Sullivan, Ramsey, and Lee (2000).

Because of the impact of AE-COPD on disease progression, with resulting reduction in quality of life, as well as the impact on heath care costs, this study focused specifically on the AE-COPD outcome. In addition, the acute nature of COPD exacerbations following inhalational insults suggests that this outcome is appropriate for evaluation of the effects of daily or short-term changes in air pollution concentrations on respiratory health.

Study Objectives

Following on a preliminary study by members of Temple University's Department of Pulmonary and Critical Care Medicine (Mamary, Permut, Halpin, Shenoy, Gaughan, Criner, 2008), the current study was planned to evaluate associations between exposure to daily ambient air concentrations of five criteria air pollutants (CO, SO_2, NO_2, ozone, or $PM_{2.5}$) and the outcome, hospital visits to Temple University Hospital (TUH) for AE-COPD, in Philadelphia, Pennsylvania, from January 1, 2005, through March 31, 2007. Air pollutant exposures were evaluated for the day of the visit (lag0), one and two days preceding the visit (lag1 and lag2), and the average concentration over these three days (lag012).

In addition to overall single pollutant (univariate) analyses, associations between AE-COPD hospital visits and daily concentrations of air pollutants were evaluated within seasons, with temperature as a covariate, and in multipollutant models.

A second objective was to identify groups with greater susceptibility to air pollution exposures. Associations were also examined for subgroups defined by age, gender, race, residence, or antibiotic use.

Rationale

In the United States, more than 12 million people are diagnosed with COPD, and another 12 million are thought to be unaware that subclinical disease is present (National Heart, Lung, and Blood Institute [NHLBI], 2006). COPD is a major cause of disability and the third leading cause of death in the US (NHLBI, 2010). As in the U.S. overall, air quality in Philadelphia has improved as a result of the U.S. EPA's implementation of regulations designed to protect the public health from impacts of air pollution. It is important to understand whether adverse health effects were associated with Philadelphia air quality during the current study (2005-2007).

Chronic Obstructive Pulmonary Disease

In most cases of COPD, both emphysema and chronic bronchitis are present. Symptoms of breathlessness at rest or on exertion usually lead to a diagnosis of COPD after a period of asymptomatic disease that typically lasts several decades (GOLD, 2008; Anto´, Vermeer, Vestboz, Sunyer, 2001).

Natural History of COPD

Lung function increases from childhood to a peak at 20 to 25 years of age, and then progressively declines (Anthonisen, Connett, Murray, 2002). Breathlessness at rest of on exertion is the usual symptom leading to diagnosis of COPD after an extended period of asymptomatic disease that is typically several decades long (GOLD, 2008; Anto´, Vermeer, Vestboz, Sunyer, 2001). COPD may involve one or both of two main conditions: emphysema and chronic obstructive bronchitis. With emphysema, the walls between air sacs are damaged, causing them to become inelastic and enlarge. If the walls are destroyed, the result is fewer and larger air sacs instead of many tiny ones, and this leads to reduced surface volume for oxygen exchange. With chronic obstructive bronchitis, the lining of the airways is constantly irritated and inflamed, which causes the lining to thicken and airway resistance to increase. Much thick mucus forms in the airways and increases breathing difficulty. In most cases of COPD, both emphysema and chronic bronchitis are present (MacNee, 2007).

AE-COPD

Based on patient diary data, reported AE-COPD frequencies ranged from 1.1 per patient per year (Anthonisen, Manfreda, Warren, Hershfield, Harding, Nelson, 1987) to 2.7 per patient per year (Wedzicha, 2002). A clinical phenotype of frequent AE-COPD has been proposed, although specific indicators of such a phenotype have not been agreed (Hurst, Vestbo, Anzueto, Locantore, Mullerova, Tal-Singer, et al. 2010).

AE-COPDs are believed to result from acute inflammatory events that occur in addition to the chronic inflammation present in COPD patients (Anzueto, Sethi, Martinez, 2007). The effects of AE-COPD can be long-lasting (Wedzicha, 2002), and AE-COPDs have significant negative impacts on lung function, and quality of life (Donaldson, Seemungal, Bhowmik, Wedzicha, 2002). AE-COPD also have important effects on mortality, with AE-COPD the most common cause of death (48%) among patients with severe COPD in Barcelona, Spain (Moreno, Montón, Belmonte, Gallego, Pomares, and Real, 2009).

Burden of Disease

In the U.S. in 1996, COPD was the eighth leading cause of disability for men and was responsible for 2.98% of total Disability Adjusted Life Years (DALYs). For women, COPD was the seventh leading cause of disability and responsible for 3.19% of total DALYs (Michaud, Murray, and Bloom, 2001).

In 2006, there were 670,000 first-listed hospital discharges for COPD, with an average length of stay of 4.4 days, and approximately 26.9 million physician visits for COPD (National Heart, Lung, and Blood Institute [NHLBI], 2010). Costs associated with COPD for 2010 were projected to total $49.9 billion, with $29.5 billion in direct costs, $8.0 billion in morbidity-related costs, and $12.4 billion in mortality-related costs (National Heart, Lung, and Blood Institute, 2010).

Ambient Air Pollution

Air Quality in Philadelphia

Beginning in 1990 and continuing to the present, the Philadelphia Department of Public Health's Air Management Services operated a network of air monitoring stations to measure concentrations of, to provide data used to demonstrate compliance with the U.S. EPA's NAAQS and monitor daily air quality. Monitoring stations were sited throughout the city so that measurements of the criteria air pollutants would provide the most relevant observations for each air pollutant (City of Philadelphia, Department of Public Health [DoPH], Air Management Services [AMS], 2007). Preliminary analyses suggested a relationship between air pollutants and hospitalizations for AE-COPD at TUH (Mamary, Permut, Halpin, Shenoy, Gaughan, Criner, 2008).

Adverse Effects of Air Pollution

Evidence of adverse effects of air pollution on health accumulated along with increasing industrialization and urbanization. A large-scale episode of cardiovascular and respiratory illnesses following extreme levels of air pollution occurred in Donora, Pennsylvania, (Bainbridge, 1948) and prompted the U.S. Public Health Service to investigate. Natural experiments such as the closure and re-opening of a steel mill in the Utah Valley (Pope, 1989) provided further evidence of the relationship between air pollution and health effects. With the availability of routinely collected data from air pollution monitoring, epidemiological studies have shown effects of air pollution on health. Prospective longitudinal cohort studies have related different levels of chronic ambient air pollution exposure to adverse health outcomes, including reduced pulmonary function, increased pulmonary disease, non-malignant respiratory mortality, and cardiopulmonary mortality (described in Chapter 2).

Time-Series Studies

Time-series studies are useful to evaluate associations between short-term exposures and acute outcomes, as in the current study. Several time series analyses reported in the late 1990's and early 2000's described associations between air pollution and "COPD-related" hospitalizations or "other respiratory-related outcomes" that included Emergency Department (ED) visits, a composite outcome (hospital admissions/ ED visits/ office visits for respiratory reasons), or "respiratory-related" mortality. In addition to different outcome definitions, these studies also differed in location, the air pollutants and covariates that were included, the definition of lags in exposure, and covariates included in analyses.

Criteria Air Pollutants

Of the seven defined criteria air pollutants, five were evaluated in this study. Two criteria air pollutants were excluded from evaluation because daily data were not available (particulate matter with an aerodynamic diameter of < 10 μm [PM_{10}]) or because the distribution of the pollutant was concentrated in one industrial area of the city (lead).

Particulate Matter: PM can be classified into three fractions based upon the mean aerodynamic diameter (mAD) of the particles, which determines the extent of entry into the tracheobronchial tree. The mAD is <0.1μm for ultrafine particles (UFP), 0.1 μm to < 2.5μm for fine particles, and 2.5μm to <10μm for coarse particles. Coarse particles include pollen, molds, sea salt, and dusts from roads, construction, demolition, and soil. Fine particles are derived mainly from gases or combustion processes, typically originating as UFP that coagulate into larger fine particles or from condensation of gas or vapor molecules onto existing particles.

Monitoring of PM is based on measures of PM_{10}, all particles with mAD < 10µm, or $PM_{2.5}$, all particles with mAD < 2.5µm. Although $PM_{2.5}$ is a component of the PM_{10} pollutant, the sources and proportion vary across the U.S., which means that measures of PM_{10} air pollution are not always good surrogate measures for $PM_{2.5}$ concentrations (Samet, Dominici, Curriero, Coursac, Zeger, 2000).

, *Carbon monoxide (CO)*: CO is a colorless and odorless gas formed from incomplete burning of the carbon in fuels. Motor vehicles are the largest source of ambient CO, estimated to contribute as much as 85 to 95% of CO in cities (U.S. EPA, 2011). Peak concentrations of CO typically occur in the winter months when home heating demands increased fossil fuel consumption and when atmospheric inversions may more often prevent dispersion of the CO (Comrie and Diem, 1999).

Nitrogen dioxide (NO_2) NO_2 is a strong oxidant that is rapidly formed when nitric oxide (NO) is exposed to air. Sources of NO may be natural or man-made combustion products from stationary sources (e.g., power generation, heating) or mobile sources (i.e., vehicles, ships). In addition, NO_2 can react with water to produce nitric acid (e.g., “acid rain”) and NO.

NO_2 is an important precursor for secondary pollutants, including ozone (as described below) and particulate matter. Solar radiation’s effects on NO_2 not only contribute to ozone formation but also to reactions that neutralize NO_2 by formation of ammonium salts, which are a type of particulate matter. Outdoor levels of NO_2 vary according to the time of day, season, and windspeed. In urban areas, a typical daily pattern includes peaks in concentrations that correspond to morning rush-hour traffic patterns, lower mid-day concentrations, with increasing concentrations in the evening resulting in peaks somewhat lower than those in the morning (Figure 2.4-17, U.S. EPA, 2008).

Ozone: Ozone is an oxidant that is not directly emitted by a primary source but instead is formed by atmospheric chemical reactions in which NO_2 is a central component. These reactions may occur in a photochemical equilibrium, or there may be imbalance due to increased consumption of NO (e.g., reaction with atmospheric peroxides produced by oxidation of volatile organic compounds [VOCs]) or due to increased production of NO_2 (e.g., combustion). Ozone is distributed by prevailing winds, which also distribute atmospheric peroxides that can re-convert to ozone. In addition to the dynamic state of ozone and related chemicals, the ambient concentration of ozone is affected by sunshine intensity, atmospheric convection, height of the thermal inversion layer, the concentrations of nitrogen oxides (NO_x) and VOCs, and the ratio of VOC:NO_x (Saldiva, Kűnzli, Lippmann, 2006).

Sulfur dioxide (SO_2) SO_2 is directly emitted into the atmosphere following combustion of sulfur-containing fuels used in home heating, power generation, and motor vehicles. SO_2 is readily soluble in water, resulting in one of two strong acids: sulfuric acid or ammonium bisulfate. Very small droplets of sulfuric acid have been observed in the atmosphere. SO_2 is distributed by prevailing winds, and the use of tall chimneys at power generating sites in order to dilute local SO_2 concentrations has resulted in wider dispersion, with similar concentrations in urban and rural locations (Lippmann and Ito, 2006).

Summary

This study was designed to evaluate the relationship between an acute health effect, AE-COPD, and daily exposure to ambient air pollution in Philadelphia. It is important to understand whether the optimal or near-optimal air pollutant concentrations in Philadelphia during the study period were associated with an important adverse effect on health, hospital visits.

CHAPTER 2
BACKGROUND AND SIGNIFICANCE

In the United States, as of June 2010, more than 12 million people were diagnosed with COPD, and many more were thought to be unaware that they had subclinical disease (National Heart Lung and Blood Institute, 2010). COPD is a major cause of disability, and it is the third leading cause of death in the United States (National Heart Lung and Blood Institute, 2010).

Natural History of COPD

COPD may include one or both of two main conditions: emphysema and chronic obstructive bronchitis. In emphysema, the walls between many of the air sacs are damaged, causing them to become inelastic and enlarge. If the walls of the air sacs are destroyed, the result is fewer and larger air sacs instead of many tiny ones, which results in less surface area for gas exchange. In chronic obstructive bronchitis, the lining of the airways is constantly irritated and inflamed, which causes the lining to thicken and thick mucus to form in the airways, making it hard to breathe. In most cases of COPD, both emphysema and chronic bronchitis are present. Undue breathlessness at rest or on exertion is the usual symptom that leads to a diagnosis of COPD after an extended period of asymptomatic disease that is typically several decades (GOLD, 2008; Anto´, Vermeer, Vestboz, Sunyer, 2001). Differences in diagnostic criteria have been proposed for various clinical settings, and these different criteria lead to varying estimates of prevalence. The definition recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) is based on the ratio of the FEV_1 to Forced Vital Capacity (FVC) being <70%, when measured after administration of a bronchodilator (Celli, MacNee, and the ATS/ERS committee members, 2004). This definition provides a uniform method that can be applied not only for diagnosis but also to measure the prevalence of COPD in populations. Using spirometric measures, the Global Initiative for Chronic Obstructive

Lung Disease (GOLD, 2008) defined four stages of the disease: mild (Stage 1), moderate (Stage 2), severe (Stage 3), and very severe (Stage 4). However, it was emphasized that these spirometric categories may not accurately reflect the extent of airflow limitation or the level of symptoms that may be due to processes other than airflow obstruction, such as infection and tissue remodeling.

Lung function increases from childhood to a peak at 20 to 25 years of age, and then progressively declines. Smoking is associated with a two- to four-fold acceleration of this age-related decline, as compared to non-smokers (Anto´, Vermeire, Vestboz, Sunyer, 2001). The U.S. Surgeon General attributed 80-90% of chronic obstructive lung disease in 1984 and 82% of COPD deaths in 1985 to cigarette smoking. Reports from 1964, 1984, 1989, 2001, and 2004 also described increased risks associated with greater amounts and durations of smoking, and a slowing of the age-related decline in pulmonary function following smoking cessation (U.S. Department of Health and Human Services, 2004).

However, approximately one-quarter of mild and moderate-to-severe COPD cases as staged by spirometry were identified as non-smokers in a case-control study based on the National Health and Nutrition Examination Survey III (NHANES-III), which was administered in 1988-1994. This study demonstrated a 6.6% prevalence rate of COPD among non-smokers. Among non-smokers with moderate-to-severe COPD, physician-diagnosed asthma was more common (45.1% ± 8.3 SE) than a previous diagnosis of chronic bronchitis (6.8% ± 3.3 SE) or emphysema (1.6% ± 1.1 SE). A diagnosis of asthma was associated with increased risks of mild COPD (odds ratio [OR] = 4.27, 95%CI: 2.59–7.04) and moderate-to-severe COPD (OR = 18.8, 95%CI: 8.6–40.8; Behrendt, 2005). Important risk factors for COPD other than cigarette smoking include occupational exposures to dust and fumes, history of chronic asthma, outdoor air pollution, and poor socioeconomic status (Salvi and Barnes, 2009).

AE-COPD

Over the natural history of COPD, acute exacerbations (AEs) have significant negative impacts on lung function, quality of life, and mortality. In a 4-year study of exacerbation frequency, the subjects with above the median frequency of AEs showed significantly greater decreases in FEV_1 and peak expiratory flow (PEF), with more hospital admissions and longer lengths of stay than those with below the median frequency of AEs (Donaldson, Seemungal, Bhowmik, Wedzicha, 2002).

AEs are believed to result from acute inflammatory events that occur in addition to the chronic inflammation present in COPD patients. AEs are most commonly associated with bacterial, viral, and atypical infectious agents, but acute inflammation may also be initiated by noninfectious causes such as exposure to airborne particles or noxious gases. Acute inflammation induces a complex series of responses and often leads to extended disability and permanent emphysematous changes (Anzueto, Sethi, Martinez, 2007). Following exposure to the inflammatory agent, a lag between exposure and an AE may reflect the time needed for inflammatory responses to become clinically evident (Curtis, Freeman, and Hogg, 2007).

The nonspecific, innate defense system in the lung is comprised of an intact epithelial barrier, the mucociliary clearance system, and rapid activation of the inflammatory response. Initial localized activation of the nonspecific inflammatory response may lead to mucosal edema, increased airway secretions; changes in mucociliary clearance, and stimulation of the coagulation and inflammation cascades. The inflammation cascade leads to migration into the inflamed tissue of polymorphonuclear neutrophils, macrophages, B-cell lymphocytes, dendritic cells, and natural killer. These acute responses may result in transient decreases in pulmonary function (Hogg, Chu, Utokaparch, Woods, Elliott, Buzatu, et al., 2004).

The adaptive immune response is specific with both cellular (T cells) and humoral components (B cells). The B cells exist in three forms: naive cells that have not yet encountered an antigen, antigen-presenting cells that are activated by the antigen and engaged in its elimination, and memory cells (long-term survivors responsible for "memory"). The following features have been observed among subjects with increasing levels of COPD severity (GOLD Stages 0-1 to GOLD Stage 4, very severe): an increased volume of tissue in the airway walls, resulting in narrowing of the airways; accumulation of inflammation-related mucus exudates within the airways; increased percentages of airways containing immune cells (polymorphonuclear neutrophils, macrophages, CD4 cells, CD8 cells, B cells, lymphoid aggregates containing follicles); and increased absolute volumes of B cells and CD8 cells (Hogg, Chu, Utokaparch, Woods, Elliott, Buzatu, et al., 2004).

These immune responses quickly lead to release of cytokines that control connective tissue deposition. Repair of damaged tissue restores the epithelium and microvasculature by adding connective-tissue matrix, but over-expression of cytokines may result in subepithelial and peribronchiolar fibrosis and has been associated with increased nonspecific airway responsiveness. Eventually, airflow limitation may result from excessive remodeling of small airways, and from loss of inelasticity within alveolar walls and enlargement of airspaces (Hogg, Chu, Utokaparch, Woods, Elliott, Buzatu, et al., 2004).

Based on patient diary data, reported AE-COPD frequencies ranged from 1.1 per patient per year (Anthonisen, Manfreda, Warren, Hershfield, Harding, Nelson, 1987) to 2.7 per patient per year (Wedzicha, 2002). A clinical phenotype of frequent AE-COPD has been proposed, although specific indicators of such a phenotype have not been agreed (Hurst, Vestbo, Anzueto, Locantore, Mullerova, Tal-Singer, et al. 2010). AE-COPDs have significant negative impacts on lung function and quality of life. In a 4-year study of exacerbation frequency, the group with above median frequency of exacerbations experienced greater decreases in forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) and more hospital admissions with longer lengths of stay (Donaldson, Seemungal, Bhowmik, Wedzicha, 2002).

The effects of AE-COPD can be long lasting. For example, 35 days after AE, peak flow had not returned to pre-AE level for 25% of patients, and at 91 days after AE, 7.1% of patients' peak flow was below pre-baseline ability (Wedzicha, 2002). AE-COPD also have important effects on mortality, with AE-COPD the most common cause of death (48%) among patients with severe COPD in Barcelona, Spain (Moreno, Montón, Belmonte, Gallego, Pomares, and Real, 2009).

Burden of Disease

Prevalence

Based on a representative sample of U.S. adults ≥ 18 years of age (Phase 2 of the NHANES-III in 1991-1994), the prevalence of COPD was estimated at 13.2% of the adult population using a spirometric measure of airway obstruction (Mannino, Ford, Redd, 2003). In comparison, the National Health Interview Survey (NHIS) conducted during the same time period used self-reported diagnoses of COPD, which provided a lower national estimate of approximately 10 million persons or 6.0% of the U.S. adult population (Mannino, Homa, Akinbami, Ford, and Redd, 2002). These different estimates indicate that, in the absence of spirometry-based screening, diagnosis of COPD is commonly delayed to later stages of disease and therefore prevalence may be underestimated. Underestimation of COPD prevalence most likely results from mild or "early" cases having little respiratory impairment and few symptoms that would prompt spirometry testing.

Among the NHANES III survey participants, the spirometric measure identified an estimated 2.4 million (1.4% of the 23.6 million total) as having severe or very severe COPD (Mannino, Ford, Redd, 2003). In the 2000 NHIS, self-reported prevalence rates had increased from the 1980 survey results (Table 1). The estimated U.S. prevalence rate of COPD (chronic bronchitis, emphysema, or both) was 60 per 1,000. Self-reported physician diagnoses of COPD increased with age, with the largest increase among ages 75 years and greater. There was an important increase of approximately 20 per 1,000 for women, which resulted in a statistically significant difference from the prevalence for men. There was also an important increase of approximately 20 per 1,000 for Blacks, although the prevalence rate remained approximately 13 per 1,000 lower than that for Whites (Mannino, Ford, Redd, 2003).

Table 1. Estimated annual prevalence rate per 1,000 of self-reported lifetime emphysema or chronic bronchitis in 12 months preceding 1980 survey or self-reported physician-diagnosed lifetime emphysema or chronic bronchitis in 12 months preceding the 2000 survey.

	U.S. National Health Interview Survey	
	1980	2000
Age (years)		
25-44	34.6	38.5
45-54	51.2	59.2
55-64	71.2	79.5
65-74	113.6	96.4
≥ 75	75.3	106.0
Sex[1]		
Male	58.0	45.5 [2]
Female	53.9	73.2
Race[1]		
White	58.9	63.6
Black	31.2	50.4
Other	46.3[3]	31.4
Total[1]	55.8	60.0

[1] Age-adjusted to the 2000 U.S. population.

[2] Difference between males and females is statistically significant (P <0.05).

[3] Estimate considered unreliable due to standard error of the estimate > 30%.

Source: Table 2, Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC (2002).

In 2004-2006, the percentage of U.S. adults (≥ 18 years old) with self-reported COPD remained greater for women (6.3% [SE = 0.1%]) than for men (4.3% [SE = 0.1%]) through ages up to 75 years (Akinbami, Liu, 2011). After age-adjustment to the

U.S. standard 2000 population, the age groups with the highest percentages reporting COPD were women 70 - 74 years of age (10.4% [SE = 0.5%]) and men 75 - 80 years of age (11.2% [SE = 1.0%]). This 75 - 80 year-old age group was the only age group in which there was a greater percentage of men reporting COPD. Across all income groups, the ethnic group with the greatest percentage reporting COPD was Puerto Rican (6.9% [SE = 1.0%]), followed by non-Hispanic whites (5.7% [SE = 0.1%]), non-Hispanic blacks (4.4% [SE = 0.1%]), and Mexican Americans (2.6% [SE = 0.3%]) as reported in the NHIS (Akinbami, Liu, 2011).

Mortality

COPD is the fourth leading cause of death in the U.S. (National Heart, Lung, and Blood Institute, 2006). However, measures of mortality due to COPD may be underestimates because of variability in reporting cause of death. Mannino, Brown, and Giovino (1997) evaluated mortality associated with obstructive lung disease (OLD) by reviewing death certificate information from 1979-1993. At the end of that period, the age-adjusted mortality rate was 77.5 per 100,000, which represented a 47.3% increase from the start of the period in 1979. Despite this increase in OLD-associated mortality, there was only a 6.0% increase in OLD as the underlying cause of death. Recently, overall age-adjusted COPD mortality rates among U.S. adults ≥ 25 years of age were stable, ranging from 65.2 per 100,000 in 2000 through 64.3 per 100,000 in 2005. Mortality rates for COPD increased markedly with age, from 7.9 per 100,000 for ages 45-54, to 40.1 per 100,000 at ages 55-64, to 157.2 per 100,000 among ages 65-74, and 444.2 per 100,000 among those ≥ 75 years of age (Centers for Disease Control and Prevention, 2008).

Over the same period, mortality rates were consistently greater for men (77.3 per 100,000 in 2005) than for women (56.0 per 100,000 in 2005). However, the absolute number of deaths was greater for women (65,193) compared to men (60,812) for the age-standardized 2000 U.S. population ≥ 25 years. Although the mortality rates for women were stable over the period from 2000-2005, from 1980 to 2000 there had been more than doubling of the COPD mortality rate among women: 20.1 per 100,000 in 1980 to 56.7 per 100,000 in 2000. During this time, the increase in COPD mortality among men was much smaller: from 73.0 to 82.6 per 100,000. Over the same period, mortality rates were consistently greater for Whites than for Blacks, which were greater than that for other races: 68.1, 42.4, and 24.0 per 100,000 for Whites, Blacks, and Other races, respectively (Center for Disease Control and Prevention, 2008).

Causes of death among COPD patients were recently described by Moreno, Montón, Belmonte, Gallego, Pomares, and Real (2009), who followed 203 patients with severe COPD in Barcelona, Spain. These patients had previously been admitted to the hospital or had two or more emergency room visits in one year. Mean duration of follow-up was 28 months (range, 6-60 months), with estimated survival of 80%, 53%, and 26% at 1, 3, and 5 years, respectively. Cause of death was determined from retrospective review of the medical record. The most common cause of death was COPD exacerbation (48%), followed by pneumonia (community-acquired, nosocomial, or invasive aspergillus; 24%), and out of hospital death (18%).

Morbidity

Using Disability Adjusted Life Years (DALYs), Michaud, Murray, and Bloom (2001) estimated that, in the U.S. in 1996, COPD was the eighth leading cause of disability for men and responsible for 2.98% of total DALYs. For women, COPD was the seventh leading cause of disability and responsible for 3.19% of total DALYs.

In 2006, there were 26,939,000 physician visits for COPD, and 670,000 first-listed hospital discharges for COPD, with an average length of stay of 4.4 days (National Heart, Lung, and Blood Institute, 2009b). Between 1992 and 2006, the overall hospital discharge rate with first-listed discharge diagnosis of COPD had increased by 33.1%

from 1.69 per 1,000 population to 2.25 per 1,000 population. In 2006, approximately two-thirds of these discharges were for patients 65 or more years of age. This represented a rate four times higher than that in the 45-64 age group (American Lung Association, 2009).

Costs

The National Heart Lung and Blood Institute estimated the national cost for COPD to be $42.6 billion in 2007. This included $26.7 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs, and $7.9 billion in indirect mortality costs. For 2010, costs associated with COPD are projected to total $49.9 billion, with $29.5 billion in direct costs, $8.0 billion in morbidity-related costs, and $12.4 billion in mortality-related costs (National Heart, Lung, and Blood Institute, 2009).

Summary

COPD is a term encompassing a group of chronic, progressive diseases that cause airflow limitation and are a significant cause of morbidity and mortality in the U.S. Because the prevalence of COPD increases markedly with age, the number of affected persons is expected to increase further as the population ages. AEs are responsible for increased intensity of health care utilization, including additional physician visits, emergency department (ED) visits, or hospitalizations, and they contribute to the progression of the disease. Infection may be the leading cause of AEs, but air pollution is thought to play an important additional role by causing or worsening inflammation. When the lungs are subject to repeated inflammatory responses, the results may include primarily airways obstruction or alveolar destruction leading to inelasticity of the lung and poor air exchange.

Characteristics of Criteria Air Pollutants

After passage of the Clean Air Act of 1970, National Ambient Air Quality Standards (NAAQS) were defined for six criteria air pollutants by the U.S. EPA in 1971 (U.S. EPA, 2011). Currently, the criteria air pollutants include suspended particulates, lead, and gaseous air pollutants. The primary gaseous air pollutants are carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), while ozone is considered a secondary air pollutant because it is formed from atmospheric interactions with other air pollutants. However, the processes that contribute to all of these air pollutants are interrelated, and therefore concentrations of air pollutants are likely to be interrelated. This interrelatedness of exposures increases the difficulty in assessing cause and effect of individual air pollutants.

Particulate Matter

NAAQS Values for PM.

Air quality monitoring of PM is based on measures of either PM_{10}, all particles with mAD <10μm, or $PM_{2.5}$, all particles with mAD <2.5μm. In North America, PM_{10} mass may include 10 to 60% particles with mAD from 2.5 to 10 μm and the remainder being particles with mAD <2.5μm. For fine particles, or PM with mean aerodynamic diameter (mAD) < 2.5μm ($PM_{2.5}$), the 24-hour standard is 35.0 μg/m^3, based on a three-year average of 98th percentiles of daily averages. The standard for the annual average (arithmetic mean) is 15.0 micrograms per cubic meter (μg/m^3), for a three-year average of annual $PM_{2.5}$ means. For PM with mAD < 10μg/m^3 (PM_{10}), the annual average (arithmetic mean) is 150 μg/m^3, not to be exceeded more than once per year and averaged over three years (U.S. EPA Air and Radiation Home, 2010).

Atmospheric PM

In urban areas, PM can be classified into three fractions based upon the mAD of the particles: <0.1µm for “ultrafine,” 0.1 µm to <2.5µm for “fine” particles, and 2.5µm to <10µm for “coarse” particles. Particle size is related to the source of the particles and thus to their chemical composition. PM_{10} may be composed of suspended soil particles, aerosols generated from industrial processes, pollen grains, bacterial fragments, other crustal elements from mining operations or unpaved roads, and sea spray. $PM_{2.5}$ is derived mainly from gases or combustion processes, typically originating as UFP (UFPs) that grow by coagulation into larger fine particles or by condensation of gas or vapor molecules onto existing particles. Because coagulation and condensation are less efficient at particle sizes > 1 µm, fine particles often accumulate in the range of 0.1 to 1 µm, which may be referred to as the “accumulation mode.” Common components of $PM_{2.5}$ include nitrogen oxides (NO_x), CO, SO_2, and ozone. Sources of these particles include fossil fuel combustion (mostly vehicular and power generation sources) and tobacco smoke.

In addition, a significant amount of $PM_{2.5}$ is composed of secondary particles that form in atmospheric chemical reactions. The gases NO_2, SO_2, ammonia, and volatile organic compounds (VOCs) are the main atmospheric precursors, and the resulting fine particulate fraction typically includes nitrates, sulfates, ammonium, elemental carbon, organic compounds, and trace metals. In addition, most of the acid component of PM is generally found in the fine particles as hydrogen ions, although under foggy conditions, there may be acid droplets suspended in the atmosphere. There is uncertainty whether PM effects are due to particle size or particle composition. In single pollutant models, similar effects are often seen for PM, SO_2, and NO_2.

The UFPs may result from condensation of metals or organic compounds that were vaporized in high-temperature combustion processes or condensation of low-vapor pressure gases resulting from atmospheric chemical reactions (Samet, Brauer, Schlesinger, 2006). Included in $PM_{2.5}$, UFPs account for more than half of particulate air pollution, have a high surface area-to-mass ratio (which may enhance biological toxicity), but are often short-lived because they tend to agglomerate and form larger particles (Brook, Franklin, Cascia, Hong, Howard, Lipsett, et al., 2004).

From 1990 through 2009, PM_{10} concentration decreased by 38% for the annual second maximum concentration averaged over 310 sites; the 2009 average (90^{th} percentile) for PM_{10} was 50.3 (77.5) µg/m^3. Monitoring of $PM_{2.5}$ began in 1999, and from 2000 through 2009, PM_{10} concentration decreased by 27%, based on a seasonally weighted annual average across 724 sites; the 2009 average (90^{th} percentile) for $PM_{2.5}$ was 9.9 (12.6) µg/m^3.

Although $PM_{2.5}$ is a component of the PM_{10} pollutant, the proportion varies across the U.S., which means that measures of PM_{10} air pollution are not always good surrogates for $PM_{2.5}$ concentrations (Samet, Dominici, Curriero, Coursac, Zeger, 2000). Carbonaceous matter is a major component of PM across North America, and sulfates comprise 20 to 50% of PM mass in the Eastern states. Outside of North America, concentrations of PM vary from comparable levels in Western Europe to much higher levels in developing countries.

Outdoor particulates can penetrate building structures and remain suspended in indoor air, thus contributing to total personal exposure in both indoor and outdoor environments. In a Seattle panel study performed from 1999 to 2002, $PM_{2.5}$ measures were obtained from three representative sites central to the subject's residential area, from inside and outside each subject's residence, and from a 24-hour personal monitor (Liu, Box, Kalman, Kaufman, Koenig, Larson, et al. 2003). The 24-hr $PM_{2.5}$ values were strongly correlated ($r = 0.70$) between those from the three representative central sites (median of 10.3 µg/m^3) and from outside the subjects' homes (median of 8.6 µg/ m^3). Therefore, ambient measures of PM were shown to provide relevant estimates of personal exposure. Among a subgroup of COPD patients, average personal exposures to $PM_{2.5}$ were similar to the average outdoor concentrations (Liu et al., 2002)

Biological Effects of PM Exposure.

Health effects of PM exposures may be influenced by size mode, mass concentration, number concentration, acidity, particle surface chemistry, particle core chemistry, metals, carbon, biogenic origin, secondary inorganic aerosols, materials associated with earth's crust, particle surface area, chemical reactivity, water solubility of chemical constituents, and geometric form (Samet, Brauer, Schlesinger, 2006). These different influences may result in variability among observed health effects associated with PM exposures.

The ability of particles to travel into the tracheobronchial tree is related to the mAD. Coarse particles are inhalable and usually settle in the upper airways and major air passages of the lungs. Fine particles are likely to be deposited in the smaller conducting airways and the alveoli, while UFPs may be able to cross the alveolar membrane and directly enter the circulation (Nemmar, Hoet, Vanquickenborne, et al, 2002).

PM exposure may produce direct effects on the respiratory tract through inflammation, increased airways hyperreactivity, and impaired pulmonary defenses associated with increased airways secretion and mucosal edema. The inflammatory response may be provoked by oxidative stress caused by the PM presence on tissue or by actions of the water-soluble chemical constituents. Experimental studies in animals have demonstrated that inhalation of concentrated ambient particles resulted in pulmonary inflammation as well as biomarker evidence of systemic inflammation, such as increased fibrinogen or leukocytosis (U.S. EPA, 1993 cited in Forastiere, Peters, Kelly, and Holgate. 2006).

Carbon Monoxide

NAAQS for CO

There are two standards for CO that are not to be exceeded more than once per year. The 1-hour standard is 35 ppm and the 8-hour standard is an average of 9 ppm (U.S. EPA, 2011).

Atmospheric CO

CO is a colorless and odorless gas that is formed from incomplete burning of the carbon in fuels. Motor vehicles are the largest source of CO, estimated to contribute to 56% of CO nationwide and as much as 85 to 95% in cities (U.S. EPA, 2009). Peak concentrations of CO typically occur in the winter months when home heating demands increase fossil fuel consumption and when atmospheric inversions may more often prevent dispersion of the CO (Comrie and Diem, 1999). Exposure may also be significant from indoor sources of incomplete combustion such as unvented kerosene and gas space heaters, leaking chimneys and furnaces, back-drafting from furnaces, gas water heaters, wood stoves, and fireplaces, gas stoves, and tobacco smoke.

In the U.S., the annual average of second maximum 8-hour concentrations across 187 monitoring sites decreased by 70% from 1990 through 2009. In 2009, the mean (90^{th} percentile) CO concentration was 1.775 (2.6) part per million (U.S. EPA, 2010a).

Biological Effects of CO

Interference with the oxygen-carrying capacity of the circulatory system is due to displacement of oxygen from the binding site on hemoglobin. The hemoglobin-CO bond is 200 to 300 times stronger than that between hemoglobin and oxygen. Therefore, CO is not easily displaced and carboxyhemoglobin can accumulate over time; thus, prolonged exposures to low concentrations can be as dangerous as shorter exposures to higher concentrations (Kurt, Mogielnicki, Chandler, Hirst, 1979).

Effects of oxygen deprivation due to CO exposure include tachycardia, reduced exercise capacity and impaired vigilance (decreased visual perception, manual dexterity, learning ability, and ability to perform complex sensorimotor tasks, such as driving). Persons with existing cardiovascular disease may also experience chest pain due to myocardial hypoxia as an early symptom in response to CO exposure. Symptoms of low-level exposures include fatigue, headache, dizziness, with higher exposures leading to impaired vision and coordination, nausea, convulsions, and death (Yassi, Kjellstrom, deKok, and Guidotti, 2001).

Nitrogen Dioxide

NAAQS Values for NO_2

The annual average (arithmetic mean) is 53 parts per billion (ppb) and 100 ppb for the 1-hour standard, defined as the 3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour average concentrations (U.S. EPA Nitrogen Dioxide Regulatory Actions, 2010).

Atmospheric NO_2

Nitric oxides (NO_x) may be produced from natural occurrences (e.g., volcanic activity, bacterial products, and lightning) or from man-made combustion products made by stationary (e.g., power generation, heating) or mobile sources (e.g., vehicles, ships). When nitric oxide (NO) is exposed to air, atmospheric oxidants rapidly convert NO to NO_2, which is also a strong atmospheric oxidant. The estimated time to convert 50% of NO to NO_2 is less than one minute at atmospheric concentrations of 0.1 ppm of NO and 0.1 ppm of ozone (Altshuller, 1956, cited in Forastiere, Peters, Kelly, and Holgate, 2006).

As NO_2 absorbs solar energy it becomes an important precursor for secondary pollutants, including ozone, SO_2, and particulate matter. NO_2 is the key initiator for photochemical formation of ozone. In a cyclical photolytic process, NO_2 dissociates and re-forms NO, along with a single molecule of oxygen (O); O combines with O_2 to form ozone (O_3); NO and O_3 then react to produce NO_2 and O_2. The reaction of NO_2 with water produces nitric acid (e.g., "acid rain") and nitric oxide (NO). A subsequent atmospheric transformation neutralizes nitric acid through formation of ammonium salts, which contribute to the PM_{10} and $PM_{2.5}$ fractions of particulate matter (Forastiere, Peters, Kelly, and Holgate, 2006). NO_x involvement in ozone formation is influenced by concentrations of volatile organic compounds (VOCs) as described in the ozone discussion, below.

Outdoor levels of NO_2 vary according to the time of day, season, and windspeed, and they have declined since the 1980s. In the U.S., the annual arithmetic mean across 154 monitoring sites decreased by 40% from 1990 through 2009, ranging from 19.8 ppb (90^{th} percentile of 34.4 ppb) in 1990 to 11.5 ppb (90^{th} percentile of 19.6) in 2009 (U.S. EPA, 2010a). In urban areas worldwide, a typical daily pattern includes peaks in concentrations that correspond to rush-hour traffic patterns. In these areas, annual mean concentrations commonly range from 10 to 50 ppb, but hourly averages near busy roads may be 500 ppb or 10 to 50 times greater (Forastiere, et al., 2006). In-vehicle concentrations of NO_2 may be 2 to 3 times higher than those at monitoring stations (U.S. EPA, 2010b).

Indoor sources of NO_2 include tobacco smoke and gas- or oil-fired appliances. Indoor concentrations may be greater than those outdoors, especially if appliances are being used as heat sources or if kerosene heaters are being used over several days (Forastiere, et al., 2006).

Biological Effects of NO_2 Exposure: A large portion (between 70% and 90%) of inhaled NO_2 may be absorbed in the nasopharynx (Wagner, 1970, cited in Forastiere, Peters, Kelly, and Holgate, 2006). Maximum tissue exposure is thought to occur at the junction between conducting airways (ending at terminal bronchioles) and gas-exchange airways (beginning with the respiratory bronchioles), which is where NO_2-induced lesions are typically observed in some species. However, exercise, by shifting to mouth breathing, increased minute ventilation, and increased tidal volume (i.e., volume of a breath), can increase the dose of NO_2 delivered to the gas-exchange region of the respiratory tract, i.e., respiratory bronchioles and alveolar ducts and sacs (Forastiere, Peters, Kelly, Holgate, 2006).

The results of NO_2 exposure in animal studies vary according to species, dose, and duration. In experimental studies with mice, rats, dogs, and monkeys, long-term exposure to NO_2 caused emphysema-like structural changes, thickening of the alveolar capillary membrane, loss of ciliated epithelium, and increases in lung collagen. In addition, several types of animal studies have shown that NO_2 increases susceptibility to bacterial and possibly viral infections, with acute exposures above 0.5 ppm causing decreased pulmonary bactericidal activity and alveolar macrophage function (Forastiere, et al., 2006).

In controlled clinical studies among healthy adults, the NO_2 concentration required to induce an acute effect on pulmonary function was 1.0 ppm, 20 or more times greater than typical background concentrations in urban ambient air but approximately two times greater than those near busy roads during peak traffic hours. Among subjects with COPD, low levels of NO_2 exposure (0.3 ppm) for up to 4 hours led to decreased FVC and FEV_1 (Morrow et al., 1992, cited in Forastiere, et al., 2006). Significantly, reduced mucociliary activity in healthy volunteers resulted from exposure to 1.5-3.5 ppm NO_2 for 20 minutes (Hellebore, Huberman, Blomberg, Stjernberg, Sandström , 1995).

Evidence suggests that observed effects of ambient NO_2 could be due to associated particulate matter (PM) rather than NO_2 itself. Exposure to diesel exhaust containing both NO_2 and PM_{10} resulted in neutrophil, mast cell, and lymphocyte infiltration of the airways, enhanced adhesion molecule expression in bronchial mucosa, and activation of bronchial epithelium to produce inflammatory cytokines (Rudell, Ledin, Hammarström, Stjernberg, Lundback, Sandström, 1996; Salvi, Nordenhall, Blomberg, Rudell, Pourazar, Kelly, et al., 2000). Without PM_{10}, none of these effects was observed after single or repeated exposure to NO_2 alone at doses up to 40 times greater (Blomberg, Krishna, Kelleday, Söderberg, Ledin, Kelly, et al. 1997; Blomberg, Krishna, Bocchino, Biscione, Shute, Kelly, et al., 1999).

Ozone

NAAQS Values for Ozone

The 8-hour average value for ozone is 0.075 ppm, based on the 3-year average of the fourth-highest daily maximum 8-hour average ozone concentrations measured at each monitor within an area over each year (U.S. EPA Air and Radiation Home, 2010).

Atmospheric Ozone

Ozone is a photochemical oxidant that is not directly emitted into the atmosphere but instead is formed by atmospheric chemical reactions in which NO_2 is a central component. Solar energy transferred to atmospheric NO_2 results in the dissociation of an oxygen atom, leaving nitric oxide (NO). The oxygen atom combines with atmospheric oxygen (O_2) to form ozone (O_3), which then reacts with the NO to re-form NO_2 and O_2 (Figure 1).

Nitrogen Cycle and the Photostationary-State Relationship for Ozone (O_3)

- $O + O_2 + M \rightarrow O_3 + M$, M = any body with mass which is required to absorb the heat produced by the reaction.
- $NO_2 + h\upsilon \rightarrow NO + O$, $h\upsilon$ = the ultraviolet portion of solar radiation.
- $O_3 + NO \rightarrow NO_2 + O_2$
  - Converts O_3 back to O_2 and NO back to NO_2, completing the "nitrogen cycle."

The VOC Oxidation Cycle

The key reaction in the VOC oxidation cycle is the conversion of NO to NO2. This takes place through the fast radical transfer reaction of the peroxy radical (RO2) with NO.

RO2 + NO → NO2 + RO, where R = hydrogen or any organic fragment

http://www.fraqmd.org/OzoneChemistry.htm, accessed October 19, 2011 from Feather River Air Quality Management District website.

Figure 1. Ozone Cycles Involving NO2 and VOCs

These reactions may occur in a photochemical equilibrium, or there may be imbalance either from increased consumption of NO (e.g., reaction with atmospheric peroxides produced by oxidation of volatile organic compounds [VOCs]) or from increased production of NO_2 (e.g., combustion). Atmospheric conditions may be NO_x sensitive, with lower NO_x and higher VOCs, when ozone *increases* with increased NO_x. Under other conditions, NO_x may be saturated, when ozone *decreases* with *increased* NO_x. The mixing ratio of NO*x* and VOC is dependent on the instantaneous rate of ozone production.

Ambient ozone concentrations reflect both photochemical production and atmospheric transport. Scavenging of ozone by NO in fresh vehicle exhaust can result in significantly lower ozone concentrations in areas of high traffic and building density (Lin, Young, and Wang, 2001). With air movement downwind from emission sources, NO_x is removed more rapidly than VOCs, resulting in a shift from a VOC-sensitive to an NO_x-sensitive condition. The effects of reducing NOx emissions vary by as much as 10-

fold between NOx-sensitive conditions and VOC-sensitive conditions (Sillman and He, 2003). In addition to the ozone distributed by prevailing winds, atmospheric peroxides that can re-convert to ozone are also distributed. In addition to the dynamic state of ozone and related chemicals, ambient concentrations of ozone are affected by sunshine intensity, atmospheric convection, and the height of the thermal inversion layer, (Saldiva, Kűnzli, Lippmann, 2006).

In the U.S., the annual fourth maximal 8-hour average ozone level across 523 monitoring sites decreased by 21% from 1990 through 2009. In 2009, the mean and 90th percentile ozone concentrations were 0.069 and 0.080 ppb, respectively (U.S. EPA, 2010a).

Personal exposures are better correlated with outdoor ozone concentrations in the summer than in other seasons. Because there are few indoor sources of ozone, indoor concentrations reflect the penetration of outdoor air, which differs with climate and the use of air conditioning. A study in central Pennsylvania demonstrated that ozone measures obtained from fixed site monitors did not provide accurate representations of personal exposures. For persons who spent the most time indoors at home, the best correlations of personal ozone exposure were based on a combination of indoor and outdoor microenvironment measurements. Because COPD patients with moderate or severe stages of disease may be likely to spend most of their time at home, ambient concentrations of ozone may underestimate actual exposure (Liu, Koutrakis, Suh, Mulik, and Burton, 1993).

Biological Effects of Ozone Exposure

Ozone effects occur mainly in the upper respiratory tract and the conducting intrathoracic airways. Inhalation of ozone causes diffuse inflammation of the respiratory tract, with the nasal cavity and transition zone between conducting and gas-exchange airways being most susceptible. Epithelial lining fluid (ELF) may minimize initial direct contact with the airway epithelium by oxidation of ELF substrates such as ascorbic acid, uric acid, glutathione, proteins and unsaturated lipids (Ballinger, Cueto, Squadrito, Coffin, Velsor, Pryor, Postlethwait, 2005). However, by-products of this oxidation, such as lipid hydroperoxides, cholesterol ozonization products, ozonides and aldehydes, may lead to inflammation and cell damage (Cross, van der Viiet, Louie, Thiele, Halliwell, 1998). Impaired pulmonary function and significant inflammation can be detected almost immediately after exposure as an increase in inflammatory biomarkers, followed by an increase in inflammatory cells a few hours after exposure and lasting for several days (Saldiva, Kűnzli, Lippmann, 2006). Aging-associated reduction of antioxidant capability in the ELF is one hypothesis for the greater effects of ozone among the elderly (Kelly, Dunster, Mudway, 2003).

Ozone-associated effects on morbidity have been demonstrated as increases in school absenteeism, severity of asthmatic symptoms, hospital admissions for respiratory diseases, and hospitalizations specifically for COPD, and short-term effects of ozone on mortality have been demonstrated in some observational studies (reviewed below).

Sulfur Dioxide

NAAQS for SO_2

The 1-hour standard was 75 parts per ***billion,*** based on 3-year average of the 99th percentile of the daily maximum 1-hour average at each monitor within an area. The 24-hour standard was 0.14 ppm (140 ppb), not to be exceeded more than once per year. The annual average (arithmetic mean) was 0.03 ppm (30 ppb; U.S. EPA Air and Radiation Home, 2008).

Atmospheric SO_2

Combustion of sulfur-containing fuels used in home heating, power generation, and motor vehicles (especially diesel fuel) results in direct emissions of SO_2 into the atmosphere. Another source of SO_2 is refining of sulfur-containing crude oil (“sour crude"). SO_2 is readily soluble in water, resulting in one of two strong acids: sulfuric acid or ammonium bisulfate. Very small droplets of sulfuric acid may be present in the atmosphere, formed either by condensation onto other fine particle nuclei or by de novo condensation and formation of nuclei. Another atmospheric transformation neutralizes sulfuric acid from SO2, by formation of ammonium salts, which contribute particles to the PM_{10} and $PM_{2.5}$ fractions of particulate matter (Samet, Brauer, and Schlesinger, 2006).

Volcanoes are natural sources of SO_2, but in urban areas, power generation, domestic heating, and transportation fuels are the largest sources. SO_2 is distributed by prevailing winds, and the use of tall chimneys at power generating sites in order to dilute SO_2 concentrations has resulted in wider dispersion to the point where urban and rural concentrations are similar in the economically developed countries. Indoor concentrations of SO_2 are usually lower than outdoor concentrations due to absorption onto walls, furniture, and clothing and in ventilating systems, except that some occupational exposures may still be excessive (Lippmann and Ito, 2006).

In the U.S., the annual arithmetic mean across 252 monitoring sites decreased by 65% from 1990 through 2009. In 2009, the mean (90th percentile) SO_2 concentration was 0.003 (0.005).ppb (U.S. EPA, 2010a).

Biological Effects of SO_2

Inhalation of SO_2 is the only significant route of exposure. Being water soluble, up to 99% may be absorbed in the mucus membranes of the nose and upper respiratory tract. Following hydration, inhaled SO_2 is converted to sulfite and bisulfite, which remain in the surface fluid in appreciable amounts. The sulfite ion is a reducing agent, which reacts with oxidized glutathione in the surface fluid of the airways to produce sulfate. In addition, a molybdenum-dependent sulfite oxidase enzyme converts bisulfite to sulfate, and ammonium found in the mouth as a bacterial by-product may help to neutralize inhaled SO_2 aerosols. Changing from nasal breathing to mouth breathing results in SO_2 delivery further into the lungs, (Lippmann and Ito, 2006).

Acute effects of short-term exposures to SO_2 include damage to airways epithelium, epithelial hyperplasia, dose-related increase in goblet cells (that secrete mucin), hypertrophy of submucosal glands, disruption of ciliary transport, and bronchoconstriction. In experiments with healthy humans, the maximum effect (reduced lung function) was observed within minutes, with gradual decline, and return to normal in minutes to hours after ending exposure. Volunteers with asthma responded similarly as healthy volunteers, but lower exposures were required for asthmatics to obtain a similar response (Lippmann and Ito, 2006).

Chamber studies of acute exposures in healthy volunteers have shown a range of sensitivity, with some volunteers unaffected by exposures that cause severe bronchoconstriction in others. The minimum exposure below which group means did not change significantly was 1,000 ppb, even with exercise. However, some individual subjects experienced increased airway resistance with deep breathing at that concentration. In short exposures (10 to 15 minutes) with exercise, the mean minimum concentration affecting lung function in asthmatics was 400 ppb, although two subjects experienced effects at 100 ppb (Linn, Avol, Peng, Shamoo, Hackney [1987] cited in Lippmann and Ito, 2006).

Exercise and mouth breathing increase the effect of SO_2, which delivers more SO_2 to the lower lung. SO_2 may also reach the lower lung in droplets formed around fine or UFP. In guinea pigs, the response to SO_2 was enhanced by simultaneous exposure to UFP, resulting in decreased lung volumes, decreased CO-diffusing capacity, edema, and damage to epithelial and endothelial cells (Amdur, 1986). Delivery of SO_2 in a chamber with cold dry air induced a greater response in asthmatic subjects than delivery of SO_2 at room temperature (Sheppard, Eschenbacher, Boushey, Bethel, 1984 cited in Lippmann and Ito, 2006).

Summary

In the U.S., air quality is characterized through monitoring concentrations of criteria air pollutants identified by the U.S. EPA for regulatory purposes against the NAAQS, which were set to provide thresholds below which human health effects could be prevented. PM, SO_2, and NO_2 are all products of combustion but also may be produced by atmospheric chemical reactions. As a result, the health effects of air pollution, including those demonstrated for CO, are often associated with high volumes of traffic and may increase during the heating season due to increased power generation. There is uncertainty whether PM effects are due to particle size or particle composition. In single pollutant models, similar effects are often seen for PM, SO_2, and NO_2. Ambient measures of PM have been shown, for the most part, to provide relevant estimates of personal exposure. Unlike the other criteria air pollutants, ozone is not emitted directly into the atmosphere but is produced in atmospheric photochemical reactions. A seasonal effect of greater ozone concentrations in summer is commonly observed due to the longer periods of sunlight, which contribute to its production. Ambient measures of ozone are thought to underestimate personal exposures, which may limit the ability to demonstrate health effects at ambient concentrations.

Health Effects of Air Pollution

The total burden of particulate exposure, including environmental tobacco smoke and indoor and outdoor air pollution, is considered to contribute to COPD risk. Only smoking and occupational exposure to certain aerosols and chemicals have been considered documented causes of COPD, while other exposures have been considered documented causes of exacerbations (GOLD, 2008).

The impact of non-smoking causes of COPD is suggested by the NHANES III survey, which showed that non-smokers accounted for 23% of the total number of participants with lung function criteria for limitation of expiratory flow, defined as the ratio between forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) less than 0.70 (Celli, Halbert, Nordyke, and Schau, 2005). A multicenter study in Spain showed similar results; i.e., 23.4% of COPD subjects were non-smokers (Pena, Miravitlles, Gabriel, Jiménez-Ruiz, Villasante, Masa, et al., 2000).

In the NHANES III, the rate of airway obstruction among lifelong non-smokers was 91.2 per 1000 (95% CI: 78.0, 104.3). Although 19% of these had a previous diagnosis of asthma and 12.5% had a previous diagnosis of COPD, the majority of participants had no previous diagnosis of respiratory disease, 68.5% or approximately 6% of participants (Celli, Halbert, Nordyke, and Schau, 2005). The suitability of the definition of airway obstruction, FEV_1:FVC <0.70 , is currently subject to debate (Quanjer, Enright, Miller, Stocks, Ruppel, Swanneye, et al., 2011; Mohamed Hoesein, Zanen, 2011; Vestbo, Rodriguez-Roisin, 2011). However, at minimum, the 31.5% of non-smokers with previously diagnosed respiratory disease would be considered true positives. These results suggest that non-smoking causes might have a substantial impact on the prevalence of disease.

Airborne particles and non-particulate gases have been associated with negative cardiopulmonary and respiratory health effects, including reduced lung function, increased ED visits, increased hospitalization for respiratory disease, and greater mortality due to cardiopulmonary causes, including COPD (studies reviewed below). A recent study found a direct association between first hospital admission for COPD and the 35-year mean NO_2 level as an indictor of long-term exposure to traffic-related air pollution in Denmark (Andersen, Hvidberg, Jensen, Ketzel, Loft, et al., 2011).

Historical Experience

Health effects due to visible air pollution have been observed on rare occasions since at least 1930, when the Meuse Valley in Belgium suffered more than 60 deaths during three days of “fog” (Nemery, Hoet, Nemmar, 2001). Subsequent dramatic episodes occurred in the Donora Valley of Pennsylvania, where 500 residents became ill and 19 died within a 24-hour period in 1948 (Bainbridge, 1948), and in London, where approximately 4,000 excess deaths were attributed to five days of smog in 1952 (Logan and Glasg, 1953). These three episodes occurred during temperature inversions, which prevented the usual dispersion of the air pollutants. In 1960s London, the health effects associated with high concentrations of sulfuric acid aerosol were greater compared to SO_2 or black smoke. Based on the association between high concentrations of SO_2, particles, and water vapor, researchers in the Advisory Group on the Medical Aspects of Air Pollution Episodes (1992) later suggested that the 1952 London health effects might have resulted from the delivery of sulfuric acid on the surface of fine and ultra fine particles.

Because of these episodes, efforts to decrease emissions from industrial sources were initiated, including passage of the U.S. Clean Air Act in 1970. This law also required that standards be set for six pollutants, referred to as "criteria air pollutants" (lead, SO_2, PM, CO, NO_2, and ozone), which was accomplished in 1971 (U.S. EPA History Home, 2007). The concentrations chosen to define the NAAQS were believed to be the upper limit of exposure that is free of any negative effect on health and so represent thresholds below which no health effects are expected. Monitoring of particulate matter was initiated with measurements of total suspended particulates (TSP), followed by measurement of particulate matter with an aerodynamic diameter of $\leq 10\mu m$ (PM_{10}).

In 1997, an additional criterion pollutant was added, that of particulate matter with an aerodynamic diameter of $\leq 2.5\mu m$ ($PM_{2.5}$). The exposure-response relationship for $PM_{2.5}$ appeared to be linear, with no clear evidence of a safe threshold (Pope, 2000), and measurable health effects from the other air pollutants at concentrations below the NAAQS thresholds continued to be demonstrated in the mid-1990's. Despite reductions in levels of air pollution over the two previous decades, continuing issues with acid rain and haze led to amendment of the Clean Air Act in 1990. Additional regulations were issued by the U.S. EPA in 2006. The Clean Air Interstate Rule targeted SO_2 and NO_2 emissions through permanent caps on emissions, the Clean Air Nonroad Diesel Rule targeted emissions leading to fine particle ($PM_{2.5}$) formation, and the $PM_{2.5}$ 24-hour standard was reduced from 65 to 35 $\mu g/m^3$ (U.S. EPA Air and Radiation Home, 2008).

More recently, the U.S. EPA revised the standards for NO2 and SO2 (U.S. EPA, 2010). A new one-hour standard for NO_2 was defined as the 3-year average of the 98th percentile of the annual distribution of daily maximum 1-hour average concentrations less than 100 ppb. The annual average NO_2 standard of 53 ppb was retained (U.S. EPA, 2010). A new 1-hour SO_2 standard at a level of 75 ppb, based on the 3-year average of the annual 99th percentile of 1-hour daily maximum concentrations. The EPA also revoked both the existing 24-hour and annual primary SO_2 standards.

Philadelphia Experience

Air pollution control measures were implemented in Philadelphia as early as 1904, with an ordinance that specified a color scale to assess the darkness of smoke emitted from chimneys, stacks, flues, or open spaces. From the mid-20th century, progressive efforts to improve the air quality in Philadelphia were implemented before the current study period. These included creation of the Air Pollution Control Board within the Department of Public Health (1949), prohibition of open burning and limits on smoke emissions (1954), creation of the Air Management Services laboratory (1964), creation of a city-wide network of air monitoring stations and detailed survey of city companies leading to schedules for compliance (1970), a ban on coal burning (1981), and implementation of provisions of the Clean Air Act Amendments of 1990.

Philadelphia Climate.

Philadelphia’s climate is affected by air masses and prevailing winds arriving from inland western locations. Generally, there is a pattern of alternating high and low pressure systems. Almost all of the low-pressure systems affecting weather in the United

States cross the country from the west to the Northeast closely enough to influence Philadelphia's weather. Stagnating high-pressure systems with winds of less than 7 mph lasting for seven or more days are uncommon due to the influence of alternating high and low pressure systems. In addition, diurnal variations in temperature contribute to mixing of the atmosphere (Davis, 1960). Because of this mixing of air, inversions that typically result in sustained air pollution episodes are rare in the Philadelphia area.

During the fall, winter, and spring, polar air masses cross the continent to the east, but they have generally been destabilized by heating from below before reaching Philadelphia. In the summer, Philadelphia weather is equally affected by inland and maritime tropical air masses. Night temperature inversions due to surface cooling are frequent, but they do not often persist because of turbulence produced by heating during the day. In the summer and early fall, high pressure areas may become stationary and result in periods of 4 or more days of atmospheric stability, but periods of stagnation lasting 10 or more days are infrequent, averaging approximately once per decade (Davis, 1960).

Geographic Features

Because of Philadelphia's location in the middle of the Atlantic Coastal Plain, there are no atmospheric effects from land-sea breezes and no mountain-valley effects on air circulation. There are also no marked geographic features that would contribute to temperature inversions. Elevation ranges from sea level in South and Southwest Philadelphia to approximately 450 feet in Northwest Philadelphia, about 10 miles away. One small area within the Northwestern section does experience marked changes in elevation along the Schuylkill River and Wissahickon Creek, which could contribute to local air quality problems (Davis, 1960). One of the city's air pollution monitors (ROX) has been located in that section (City of Philadelphia, Department of Public Health, Air Management Services, 2007). There are no obstacles to airflow to Philadelphia from neighboring western counties and no obstacles to airflow from Philadelphia to the neighboring eastern counties.

Philadelphia Air Quality

The city has met the NAAQS for NO_2 and SO_2 since 1987, for CO since 1990, for PM_{10} since 1999, and for lead since 2000 (City of Philadelphia, Department of Public Health, Air Management Services, 2007). Initially, Philadelphia had also met the daily standard for $PM_{2.5}$, but after the daily standard was revised in December 2006, the city was in nonattainment until 2008. In contrast, the city was in nonattainment with the annual standard for $PM_{2.5}$ (average of three consecutive years' 98th percentile) from 2000-2007, including the entire study period. Philadelphia was also in non-attainment for the 8-hour ozone standard throughout the study period. Therefore, evaluation of air pollutant effects in Philadelphia during this period will provide insight into the effectiveness of the NAAQS for the protection of public health and welfare.

Previous Studies of Philadelphia Air Pollution and Mortality

A series of eight studies described the relationship between air pollution and mortality in Philadelphia from 1973-1988 (Kelsall, Samet, Zeger, and Xu, 1997). In seven studies, estimates of single-pollutant effects of total suspended particulates (TSP) on mortality were significant and ranged from 1.2 to 3.1 percent change in mortality for each interquartile increase in TSP.

The most recent analysis of mortality data from 1974 through 1988 included five air pollutants: TSP, SO_2, NO_2, CO, and ozone. Over the 14-year study period, decreasing trends in air pollution concentrations were observed for all air pollutants except ozone, which increased. Median and 75th percentile air pollution concentrations were below the NAAQS for SO_2, NO_2, CO, and ozone. Air pollutant concentrations varied by season, but there was no evidence of differential effects of individual air pollutants by season. Single-pollutant analyses demonstrated significant effects of TSP, SO_2, CO averaged for 3 and 4 days before death, and ozone on daily mortality, excluding deaths from external causes (Kelsall et al., 1997). TSP was the only pollutant which showed modification of effect by age, with greater effects on total mortality among those 75 years or greater.

When TSP, NO_2, SO_2, and ozone were included in one multipollutant model, all individual pollutant effects were statistically significant for an increase in concentration of one interquartile range (IQR), with mean percent changes (MPC) in mortality ranging from 1.06% to 1.91% *increases* and with a *decrease* of 1.10% associated with one IQR increase in NO_2. The final model included all five air pollutants, season, and separate effects for TSP according to age group (Kelsall, Samet, Zeger, and Xu, 1997).

The Kelsall et al. analysis demonstrated increased mortality in the winter months, and this was more obvious among those aged 65 years or older. The current day's temperature and the three previous days' temperatures had different effects. Hot temperatures (> 80^{o}F) on the current day were associated with increased mortality, but lower temperatures (< 80^{o}F) averaged for the three previous days were also associated with increased mortality. There was a minimal effect of adding dew point temperature to the model (Kelsall, Samet, Zeger, and Xu, 1997).

In preliminary analyses, positive correlations were described between air pollution exposures for PM_{10}, NO_2, ozone, and cold weather in Philadelphia and hospital admissions for AE-COPD at Temple University Hospital from January 1, 2005, through March 31, 2007. The largest correlations were between AE-COPD hospital visits and six-day averages of PM_{10} at lags from 7 to 14 days (Mamary, Permut, Halpin, Shenoy, Gaughan, Criner, 2008).

Summary

Due to its geography, Philadelphia's air quality is influenced by air masses moving from the western inland regions of the continent, in addition to locally produced air pollutants from traffic on the roads, in its port, and from local industry. Weather conditions in the Philadelphia region contribute to atmospheric mixing throughout the year, so that air pollution episodes due to atmospheric inversions are rare. During the current period of study (January, 2005, through March, 2007), Philadelphia's air quality has been in compliance with the NAAQS for all of the criteria air pollutants except for the daily and annual $PM_{2.5}$ standard and the 8-hour ozone standard, suggesting that these two air pollutants could be candidates for exposures that would be associated with hospital visits for COPD AEs. Evidence of health effects occurring at concentrations below the NAAQS would also support consideration of an effect of the other air pollutants (NO_2, SO_2, and CO).

Epidemiologic Studies of Air Pollution and Respiratory Health Effects

The studies reviewed in this section focus on studies of adults with outcomes that could be relevant to understanding the relationship between air pollution and AE-COPD; therefore, studies of the relationship between air pollution and other outcomes such as childhood asthma, lung cancer, or acute myocardial infarction are not reviewed. Throughout this section, estimates of health effects will be presented as the *estimator = effect estimate (Lower limit of the 95% Confidence Interval, Upper limit of the 95% Confidence Interval),* unless otherwise specified. Statistically significant effects and important observations of non-significant effects are presented. Covariates, both those initially evaluated and those that were included in the final models, are also presented. The levels of air pollutants are described with reference to the NAAQS that were defined during the current study period.

Prospective Longitudinal Cohort Studies

Observations over time have related different levels of chronic exposure to ambient air pollution and health outcomes, including pulmonary function, pulmonary disease, non-malignant respiratory mortality, cardiopulmonary mortality, and all-cause mortality. COPD mortality was included in the cardiopulmonary mortality outcome

(Harvard Six Cities study, American Cancer Society-Cancer Prevention Study-2) and was reported separately in the Oslo, Norway cohort and in the NLCS-AIR study, as described below. Decreasing air pollution over time has also been associated with reductions in health effects. This supports public health efforts to reduce air pollution in order to improve population health.

Adventist Health Study of Smog (AHSMOG) and Respiratory Outcomes

In 1977, a cohort was formed to include 6,338 non-Hispanic, White, non-smoking California Seventh-Day Adventists who were residents of one of three metropolitan areas (San Francisco, the South Coast Air Basin, [i.e. Los Angeles and eastward], or San Diego) or else were part of a random sample of 862 individuals from other areas of California. The cohort subjects completed questionnaires in 1977, 1987, and 1992 during the low air pollution season in order to ascertain residence and work location histories, lifestyle and housing factors relevant to indoor and outdoor air pollutant exposures, and respiratory symptoms as measured by items that were subsequently included in the standardized American Thoracic Society questionnaire (American Thoracic Society, 1995).

Estimated exposures to ambient air pollution were determined for each subject based upon interpolation of monthly measurements at air monitoring stations, the subject's zip code of residence or work, cumulating exposures, and then averaged over time to the date of censoring. Average and maximum estimated exposures were below the NAAQS for $PM_{10,}$ SO_2, and ozone. The average estimated exposure for NO_2 was below the NAAQS, but the maximum estimated exposure and the 75th percentile were greater than the annual standard.

PM_{10} exposures were evaluated using two types of variables: average estimated PM_{10} concentration, and the exceedance frequency for the number of days per year when PM_{10} exceeded a threshold concentration [i.e., 100 µg/m^3 or PM(100)]. Similar results were obtained with both PM_{10} mean concentration and with PM(100). Increased relative risks were associated with 1,000 hours per year of exposure to PM(100) for development of airway obstructive disease (relative risk = 1.17 [1.02,1.33]), development of productive cough (relative risk = 1.21 [1.02,1.44]), and development of asthma (relative risk = 1.30 [0.97,1.73]; Abbey, Hwang, Burchette, Vancuren, and Mills, 1995).

Among these participants, a subgroup who were < 80 years old, had not smoked since 1977, and lived and worked within 20 miles of a California air-quality monitoring station was identified in 1993 (N = 1391). These subjects participated in lung function testing that included a spirometric measure of FEV_1 and FVC, and daily PEF measured 4 times per day for a week. Air pollution exposures to PM_{10}, ozone, and SO_2 for this subgroup were similar to those described for the full cohort (Abbey, Nishino, McDonnell, Burchette, Vancuren, and Mills, 1999). An IQR increase in PM(100) exceedance frequency of 54.2 days was associated with increased PEF lability of 0.8% for all females and 0.6% for all males and with a 7.2% decrease in FEV_1, as percent of predicted, in males whose parents had asthma, bronchitis, emphysema, or hay fever. An increase in the 8-hour average ozone of 23 ppb was associated with a 6.3% decrement in FEV_1, as percent of predicted in males whose parents had asthma, bronchitis, emphysema, or hay fever (Abbey, Burchette, Knutsen, McDonnell, Lebowitz, Enright, 1998).

In the main cohort, no association between air pollution and mortality was detected from 1977 to 1987. Mortality ascertainment and exposure data for PM_{10}, ozone, SO_2, and NO_2 were updated through 1992. The analyses were stratified by sex. Using these updated data, there was a significant association between non-malignant respiratory mortality and the number of days of PM_{10} exceeding 100 $\mu g/m^3$ (relative risk = 1.28, ([1.03, 1.57]), but not with average PM_{10} (relative risk = 1.23 [0.94, 1.61]). Increased mortality for mean was observed for 10 pack-years of past smoking (relative risk = 1.20[1.12, 1.29]).

Using information updated through 1992, for women, increased risk of mortality was observed for the lowest BMI category, < 21.0 kg/m^2, (relative risk = 1.98 [1.34, 2.94]) and for the highest BMI category, > 27.5 kg/m^2 (relative risk = 2.11 [1.44, 3.11]). Also among women, there was a statistically significant *decrease* in mortality relative risk for a one-unit increase in exercise level (i.e., from light/none to low, low to moderate, or moderate to high): relative risk = 0.86 [0.76, 0.98]). Additional models included medical history, diet, or other lifestyle factors but these showed no important impact on the estimates of air pollution effects (Abbey, Nishino, McDonnell, Burchette, Knutsen, Beeson, and Yang, 1999).

Harvard Six Cities Study of Mortality

From 1974-1991, a cohort of 8111 white adults from six U.S. cities was followed for mortality over 14 to 16 years. Average air pollution concentrations for each city were determined for the interval of 1979-1985 and used to identify the most and least polluted of the six cities, Steubenville, Ohio, and Portage, Wisconsin, respectively. Compared to Portage, average concentrations in Steubenville were more than twice as high for total particles, inhalable particles, fine particles, sulfate particles, and aerosol acidity and approximately four times as high for SO_2 and NO_2. Exposures above the annual average $PM_{2.5}$ standard of 15.0 μg/m^3 were present in three of the six cities, including Steubenville, with average exposures ranging from 19.0 to 29.6 μg/m^3. A fourth city experienced an average $PM_{2.5}$ of 14.9 μg/m^3. In all six cities, the average concentrations were below the NAAQS for daily standards of $PM_{2.5}$ and for all other air pollution exposures.

When the worst city (Steubenville) was compared to the best (Portage), the Mortality Rate Ratio (MRR) for all cause mortality was MRR = 1.26 (1.08, 1.47) with adjustment for age, sex, smoking, education, and body-mass index. There were 646 cardiovascular and 98 non-malignant respiratory causes of death, with an increased MRR for cardiopulmonary mortality (MRR = 1.37 [1.11, 1.68]). Increased MRRs were observed for current smokers compared to those who never smoked, for all-cause mortality (MRR = 2.00 [1.51, 2.65]) and for cardiopulmonary mortality (MRR = 2.30 [1.56, 3.41]). Increased MRRs were also observed for former smokers compared to those who never smoked, for all-cause mortality (MRR = 1.39 [1.10, 1.75]) and for cardiopulmonary mortality (MRR = 1.52 [1.10, 2.10]; Dockery, Pope, Xu, Spengler, Ware, Fay, et al., 2000).

Extended Follow-up of Mortality in the Six Cities Cohort

Between 1990 and 1998, an extension to the original cohort study was conducted (Period 2). This included 50% more person-years than Period 1 (the original study) during a time when particulate air pollution was decreasing. From Period 1 to Period 2, $PM_{2.5}$ concentrations decreased in five of the six cities. In addition, the number of deaths almost doubled from 13.1 per 1,000 person-years in Period 1 to 25.0 per 1,000 person-years in Period 2.

Over the combined periods, the adjusted proportional hazard MRR for all cause mortality was 1.16 (1.07, 1.26) for each 10 $\mu g/m^3$ increase in average ambient $PM_{2.5}$ over the combined follow-up periods. There were 195 deaths due to non-malignant respiratory causes out of 5,464 total deaths. The MRR for respiratory mortality was small (1.08 with 95%Confidence Interval [CI] 0.79, 1.49) and not statistically significant.

However, for each 10 $\mu g/m^3$ *decrease in $PM_{2.5}$ between periods*, there was a significant 27% reduction in all-cause mortality (MRR = 0.73, [0.57, 0.95]). The MRR for respiratory mortality decreased by 57%, but this was not statistically significant (MRR = 0.43 [0.16, 1.13]). These results support the expectation that reductions in air pollution can lead to reductions in mortality from cardiovascular and respiratory causes. Variables included in the model were current or former smoking, number of pack-years, education, and body-mass index (BMI). The analysis was based upon one-year strata defined by age and sex. Participants who moved were identified, but neither censoring at the time of starting follow-up nor excluding these “movers” affected the results (Laden. Schwartz, Speizer, and Dockery, 2006).

American Cancer Society - Cancer Prevention II (ACS-CPS II) Study of Mortality

In 1982, air pollution was monitored in more than 150 U.S. metropolitan areas with participants in The American Cancer Society - Cancer Prevention II Study. The ACS-CPS II study was a prospective cohort study of approximately 1.2 million adults from all states, the District of Columbia, and Puerto Rico. Subjects completed a confidential 44-item questionnaire that included smoking history, alcohol use, occupational exposures, diet, education, and marital status. A subgroup of the ACS-CPS II study cohort included more than 500,000 subjects with risk factor data who resided in the metropolitan areas that monitored air pollution when subjects enrolled in 1982. More than 93% of deaths were ascertained through December 1989.

Air pollution exposures for each metropolitan area were obtained from national databases. Mean exposures at the start of the study were below the NAAQS for all except that the $PM_{2.5}$ concentration (mean [sd] = 21.2 [4.6] $\mu g/m^3$) was above the annual standard (15.0 $\mu g/m^3$). Comparing the most polluted to the least polluted areas after adjustment for smoking, education, and other risk factors, all-cause mortality was increased with exposure to $PM_{2.5}$ (relative risk = 1.17 [1.09 to 1.26]) and sulfate particles (relative risk ratio = 1.15 [1.09 to 1.22]; Pope, Thun, Namboodiri, Dockery, Evans, Speizer, et al., 1995).

ACS-CPS II Extended Follow-up

In 1998, addition follow-up extended the period of observation to more than 16 years (Pope, Burnett, Thun, Calle, Krewski, Ito, et al., 2002). Levels of air pollution decreased from before enrollment through the follow-up period, but the rank ordering of cities was similar for the two periods. Mean (SD) values over the 1982-1998 period were below the NAAQS for PM_{10}, SO_2, NO_2, CO, and ozone. The authors estimated an integrated average $PM_{2.5}$ exposure using the pre-enrollment and 1999/2000 data (mean [sd] = 17.7 [3.7] μg/m^3), which was also below the NAAQS for the $PM_{2.5}$ daily standard (35.0 μg/m^3) but above the annual standard (15.0 μg/m^3). In addition, concentrations of sulfate particles were available for many cities during 1980-1981.

Reported results focused on the association between mortality and $PM_{2.5}$. For the period from 1979 - 2000, each 10 μg/m^3 increase in $PM_{2.5}$ was associated with increased all-cause mortality relative risk (relative risk = 1.06 [1.02 - 1.11]) and cardiopulmonary mortality (relative risk = 1.09 [1.03 - 1.16]). These relative risks were adjusted for age, sex, race, smoking, education, marital status, BMI, alcohol consumption, occupational exposure, and diet. In an alternative forward stepwise analysis, there was little effect of adding BMI, alcohol consumption, occupational exposure, or diet.

There were no effects associated with inhalable coarse particles (PM_{15}, $PM_{15\text{-}2.5}$, or PM_{10}) or total suspended particulates. Among the gaseous pollutants, there were no increased mortality risks for NO_2, CO, or ozone. SO_2 was associated with increased risks for all cause mortality, cardiopulmonary mortality, no increased risk of lung cancer mortality, and increased risk of mortality due to all other causes (relative risk approximately = 1.05 by extrapolation). Sulfate particles were associated with increased mortality risks from all-cause, cardiopulmonary, lung cancer, and all other causes (relative risk approximately = 1.05 to 1.10 by extrapolation; Pope, Burnett, Thun, Calle, Krewski, Ito, et al., 2002).

Data from the New York City and Los Angeles regions were evaluated for variations in intra-urban exposures by land use regression analysis (Krewski, Jerrett, Burnett, Ma, Hughes, Shi, et al., 2009). The method uses data for nearby traffic, land use, emissions from local sources, and population variables to predict accurate estimates for small areas without requiring monitors on or near the site (Briggs, de Hoogh, Gulliver, Wills, Elliott, Kingham, Smallbone, 2000).

After adjustment for the 44 individual-level variables, the analysis of data from the 28-county New York City region showed no increase in all-cause mortality associated with $PM_{2.5}$ concentrations (hazard ratio [HR] = 0.984 [0.948–1.020]). Ischemic heart disease was the only cause of death associated with $PM_{2.5}$ exposure (HR = 1.07 [1.00–1.15]). There were two important considerations with the New York City region. First, the variation in $PM_{2.5}$ exposure was small, with a difference between the highest and lowest exposures of only 1.5 μg/m^3 of $PM_{2.5}$. Second, there was an unexpected relationship between socioeconomic status and pollution severity, with the authors noting, "pollution appeared worst in areas where people seemed to be healthier and wealthier" (Krewski et al., 2009, p. 52). These observations highlight the need to understand how regional and local effects may differ from national effects.

Netherlands Cohort Study on Diet and Cancer (NLCS-AIR) Study of Mortality

In 1987, a cohort was formed with 120,842 participants from 204 municipalities in the Netherlands and followed until 1996 (Beelen, Hoek, van den Brandt, Goldbohm, Fischer, Schouten, et al., 2008). During the follow-up period, there were 17,610 deaths, with 1,016 deaths due to nonmalignant respiratory causes (ICD-9 codes 460-519). Overall exposures to NO_2, black smoke (BS), and PM_{10} were estimated as the sum of background exposures and traffic-related exposures at the subject's home address. $PM_{2.5}$ exposures were estimated from PM_{10} measures, using a fixed ratio that was established in the Netherlands at co-located monitoring sites. Overall exposures were below the NAAQS for the $PM_{2.5}$ daily standard, the NO_2 annual and 1-hour standards, and SO_2 daily and annual standards, but the overall exposure was greater than the annual standard for $PM_{2.5}$. Cause of death was ascertained from vital statistics.

With a 16 ppb (30 μg/m^3) increase in NO_2 concentration, there were increases in natural-cause mortality (relative risk = 1.08 [1.00, 1.16]) and respiratory mortality (relative risk = 1.37 [1.00, 1.87]). $PM_{2.5}$ and SO_2 concentrations were not associated with these causes of death.

The analysis was adjusted for age, sex, smoking status, and area level indicators of socioeconomic status. Geographic information system data were used to link the participant's home address to the Dutch network of roads in order to create three variables related to traffic exposures. Respiratory mortality increased with traffic intensity within 100 m of the residence (relative risk = 1.21 [1.02, 1.44]). There were no associations between respiratory mortality and traffic intensity on the nearest road or "living near a major road" or between natural-cause mortality and any of these traffic-related variables (Beelen, Hoek, van den Brandt, Goldbohm, Fischer, Schouten, et al., 2008).

Oslo, Norway Cohort Study of Mortality

In 1992, this cohort was formed to include all 143,842 residents of Oslo, Norway, who were 51 to 90 years old as of January 1, 1992 (Naess, Nafstad, Amodt, Claussen, and Rosland, 2006). Mortality status was followed through 1998. Maximum concentrations for $PM_{2.5}$ and PM_{10}, were less than the daily NAAQS, and for NO_2 were less than both annual and 1-hour standards. Relative to the annual average $PM_{2.5}$ standard (15.0 $\mu g/m^3$), concentrations were $\geq$ 14.26 $\mu g/m^3$ for 283 of 470 neighborhoods or approximately half of the population (quartiles 3 and 4 [Q3 and Q4]). Correlations between air pollutants were high, ranging from 0.88 to 0.95.

All cause mortality was increased with $PM_{2.5}$ exposure to concentrations in Q3 and Q4 for men 51-70 years of age (adjusted hazard ratio [HR] = 1.13 [1.03, 1.22]). Increased all-cause mortality was also observed with $PM_{2.5}$ exposure to Q4 concentrations for men 71-90 years of age (HR = 1.18, [1,10, 1.26]), for women of 51-70 years of age (HR = 1.41 [1.27, 1.57]), and for women of 71-90 years of age (HR = 1.11 [1.05, 1.17]).

Mortality due to COPD for men aged 51-70 years was associated with a quartile increase in concentrations of ambient NO_2 (HR = 1.21 [1.05, 1.39]), PM_{10} (HR = 1.29 [1.12, 1.48]), and $PM_{2.5}$ (HR = 1.27 [1.11, 1.47]). Similarly, mortality due to COPD for men aged 71-90 years was associated with a quartile increase in concentrations of ambient $PM_{2.5}$, (HR = 1.10 [1.00, 1.21]) but there were no increases associated with NO_2 or PM_{10}. Among women, there were no increases in HRs for COPD for either age group. These HRs were also adjusted for years of education and type of occupation, whether manual or not (Naess, Nafstad, Amodt, Claussen, and Rosland, 2006).

Swiss Cohort Study on Air Pollution and Lung Disease in Adults (SAPALDIA) Study

In 1990, a random sample of adults was selected from population registers in eight regions of Switzerland (Downs et al., 2007). Questionnaires, including smoking history and residential history, and spirometry were administered to 9,651 adults who had resided at the same address for at least three years. SO_2 was correlated with PM_{10} (r = 0.93) and NO_2 (r = 0.86). These cross-sectional data showed that mean values of SO_2, PM_{10}, and NO_2 were significantly associated with reduction in pulmonary function.

At a follow-up visit 11 years later, there were 4,792 subjects with complete information for PM_{10} exposure and pulmonary function outcome measures (FVC, FEV_1, and Forced Expiratory Flow from 25% to 75% [$FEF_{25\%-75\%}$]). Yearly estimates of PM_{10} exposure were made for each subject based upon the region of residence, using a dispersion model with 200m x 200m spatial resolution for 1990 and 2000 (PollluMap, version 2.0, European Environment Information and Observation Network [EIONET]). The sum of these exposures was the cumulative "interval exposure." In 1991, median PM_{10} concentrations by region ranged from 100 $\mu g/m^3$ in Davos to almost 400 $\mu g/m^3$ in Lugano (by interpolation from Figure 2.b.). Median values were above the PM_{10} NAAQS for six of the eight regions. By the end of the study period, overall PM_{10} concentrations declined by a median of 5.3 $\mu g/m^3$ (IQR: 3.3).

Expressed for a *decrease* in PM_{10} of 10 $\mu g/m^3$, the annual rates of decline were significantly reduced for FEV_1 by 3.1 mL (0.03, 6.2), for $FEF_{25\%-75\%}$ by 11.3 mL/sec (4.3,18.2). There was no significant effect on the annual rate of decline for FVC. Analysis of the subgroup of participants who never smoked showed a significant reduction in the annual rate of decline for $FEF_{25\%-75\%}$ by 11.3 mL/sec (1.4, 21.2). Estimates were made after controlling for the following variables: baseline PM_{10}, age, age squared, sex, height, parental smoking status, day of examination to control for seasonal effects, level of education in 1991, change in level of education, nationality, self-reported occupational exposure to dust or fumes in 1991 and in 2002, smoking status in 2002 (never smoked, former smoker, or current smoker), pack-years up to 1991, pack-years between 1991 and 2002, number of cigarettes per day in 1991 and in 2002, presence or absence of atopy, body-mass index in 1991, change in BMI between 1991 and 2002, and clustering within area (Downs et al., 2007).

Summary

Several large cohort studies followed participants over periods from the late 1970's through the late 1990's, with exposures to air pollutants that were generally lower than the NAAQS. These studies were carried out in different locations, evaluated different outcomes and exposures, and used study-specific approaches to controlling for covariates. Significant positive associations were observed between air pollutants (including PM_{10}, $PM_{2.5}$, NO_2, and ozone) and various outcomes, including mortality (all-cause, cardiopulmonary, non-malignant respiratory, or COPD mortality), indicators of respiratory morbidity (e.g., development of a productive cough), or pulmonary function tests. These findings support the hypothesis that health effects of air pollution may be present at concentrations below the standards set by the U.S. EPA, suggesting that an effect on AE-COPD hospital visits may be present in Philadelphia.

Importantly, the SAPALDIA study (Downs et al., 2007) and the extended follow-up of the Harvard Six Cities study (Laden. Schwartz, Speizer, and Dockery, 2006) showed that reductions in air pollution were beneficial, with reduction in pulmonary function decreases over time and reduction in all-cause mortality, respectively. In the ACS-CPSII extended follow-up period, the national findings associated with $PM_{2.5}$ were not observed for the New York City metropolitan area (Pope, Burnett, Thun, Calle, Krewski, Ito, et al., 2002), which reinforces the importance of understanding effects locally.

Time-Series Studies

Short-term changes in exposure may be linked to a health outcome using lag variables defined for same day exposure or exposure on specific days preceding the event. In this dissertation, exposure on the same day as the event will be defined as lag0, one day before the event will be lag1, etc. An alternative approach is to define a lag function that is fit to the data under analysis. Outcomes that have been evaluated with this approach include Emergency Department (ED) visits, hospitalizations for cardiovascular and respiratory diseases, emergency hospitalizations for COPD, and various definitions based on mortality. Unless specified as part of a multipollutant model, exposures described below were analyzed as single pollutants.

Montreal, Canada, Study of Daily Mortality

Associations between respiratory mortality and ambient $PM_{2.5}$, predicted $PM_{2.5}$, sulfate, and predicted sulfate from $PM_{2.5}$ were evaluated for the study interval (1984-1993). PM and sulfates were measured only once every six days, and measurements for $PM_{2.5}$ and PM_{10} were only available for 12% to 17% of the total number of days studied. Therefore, daily values of predicted $PM_{2.5}$ and predicted sulfate from $PM_{2.5}$ were estimated from regression of sulfate measures and the coefficient of haze. Daily mean concentrations were less than the 24-hour standard but greater than the annual standard for $PM_{2.5,}$ less than the daily and annual SO_2 standards; less than the standard for $PM_{10;}$ and less than both the 8-hour and 1-hour standards for ozone.

Among those ≥ 65 years, respiratory mortality increased with an IQR increase of 9.50 μg/m^3 in predicted $PM_{2.5}$ at lag0 (MPC = 4.24% [1.63, 6.92]) and at lag1 6.03% (3.41, 8.67). A greater effect was observed with the three-day mean of lag0, lag1, and lag2 (MPC = 9.03 [5.83, 12.33). However, lower effects for the three-day mean predicted $PM_{2.5}$ were observed after adjustment for SO_2 (MPC = 7.60%) or ozone (MPC = 6.86%). There were no associations between respiratory mortality among those ≥ 65 years and PM_{10} (Goldberg, Burnett, Bailar, Brook, Bonvalot, Tamblyn, et al., 2001).

Meta-analysis of Ten U.S. Cities for Cardiopulmonary Hospital Admissions

Based on daily monitoring of PM_{10} concentrations from 1986-1994, within-city associations between PM_{10} and hospital admissions for heart and lung disease among the population 65 years and older were evaluated and then combined in a meta-analysis (Zanobetti, Schwartz, and Dockery, 2000). Of the ten cities, New Haven, Connecticut, and Pittsburgh, Pennsylvania, were the two closest to Philadelphia. Among the ten cities, the median of daily maximum PM_{10} concentrations was well below (less than one-third) the NAAQS.

The authors stated that the multicity model averaged out noise due to multicollinearity among different lags within single city models. A model that simultaneously considered effects of a 10 μg/m^3 increase in PM_{10} for up to lag5 (i.e., an unconstrained distributed lag model) demonstrated increases in Mean Percent Change (SE) for COPD admissions (MPC [SE]= 2.54% [0.36]) and for pneumonia admissions (MPC [SE] = 1.95% [0.23]). In comparison, the model constrained at lag0 provided lower effects for COPD admissions (MPC [SE] =1.48 [0.23]) and for pneumonia admissions (MPC [SE] = 1.57 [0.15]). The authors suggested that use of single-day exposures could provide underestimates of these health effects.

An analysis restricted exposures to days with the 2-day mean $PM_{10} < 50\ \mu g/m^3$ (less than one-third the standard), and greater health effects were observed. Using these restricted data, effect sizes were larger than those observed for all exposures at lag0 for COPD admissions (MPC [SE] = 2.41% [0.47]) and for pneumonia admissions (MPC [SE] = 2.96% [0.33]). These effects were 20% or more greater than those observed using the 2-day mean of all data for COPD (MPC [SE] = 2.04% [0.25]) and for pneumonia admissions (MPC = 2.03% [0.17]). The authors suggested that stronger effects at lower concentrations of PM_{10} could indicate that the dose-response curve was steepest at low exposures and that the NAAQS concentration was not a true threshold for health effects.

Evaluation of effects of co-pollutants was improved by variation among cities. Of note, inclusion of ozone, SO_2, or both in the model did not lead to a meaningful change in the effect estimates for PM_{10}. Mean daily temperature, relative humidity, and barometric pressure were incorporated into the within-city models. Relative humidity was the only weather variable with an effect on COPD hospitalizations (MPC [SE] = 5.5% [1.2]). In addition, the models controlled for season and day of week of hospitalization. Similarly, variation among cities in poverty rates or minority status was useful for evaluation of effect modification by these conditions. No effect modification was demonstrated for minority status or poverty rates (Zanobetti, Schwartz, and Dockery, 2000).

Seven Canadian Cities Study of Cardiopulmonary Emergency Department Visits

Air pollution concentrations in seven Canadian cities were low compared to those observed in U.S. urban counties, and the $PM_{2.5}$ concentrations were below the NAAQS (Stieb, Szyszkowicz, Rowe, Leech, 2009). Among 12 hospitals, there were 389,856 total cardiopulmonary hospital admissions during the 1990’s to early 2000’s. The most common of these reasons for hospital admission was respiratory tract infection (125,145 admissions), with daily averages ranging from 2.2 to 24.8, while the total number of ED visits for COPD was 40,491, with daily averages ranging from 1.1 to 7.3.

There were no statistically significant increases in ED visits for COPD associated with any of the PM or gaseous air pollutants evaluated at lag0, lag1, or lag2. However, there were statistically significant *decreases* in ED visits of approximately 3% on lag1 for *increases in concentration* of 0.7 ppb CO and 18.2 ppb NO_2 (Stieb, Szyszkowicz, Rowe, and Leech, 2009).

Helsinki, Finland ED Visits for Respiratory Causes

In this metropolitan area (population = 1 million), the median (IQR) daily ED visit rates for asthma or COPD were 2 (2) for the age group 15-64 years and 3 (3) for the age group ≥ 65 years over the period from 1998-2004 (Halonen, Lanki, Yli-Tuomi, Kulmala, Tiittanen, and Pekkanen, 2008). Median and maximum concentrations were below the NAAQS for $PM_{2.5}$ (daily standard), CO (1-hour and 8-hour standards), and NO_2 (1-hour and annual standards); median and 75th percentile values were below the annual standard for $PM_{2.5}$, although the maximum value was above the annual $PM_{2.5}$ standard.

Interquartile increases of $PM_{2.5}$ were associated with increased MPC in hospital ER visits for asthma or COPD combined among the elderly (≥ 65 years of age) at lag0 (MPC = 3.09% [0.95, 5.27]) and lag1 (MPC = 2.26% [0.16. 4.41]). In addition, relative percent changes in hospital ER admissions for asthma or COPD combined were increased among the elderly for same day interquartile increases in $PM_{10-2.5}$ (coarse particles), CO, and $NO_{2.}$ No significant effects were observed for the overall adult population. Correlations among these three air pollutants were r = 0.07 between $PM_{10-2.5}$ and ozone, r = 0.030 between $PM_{10-2.5}$, and $NO_{2,}$ and r =0.42 between CO and NO_2 (Halonen et al., web only appendix, Table 1).

Two to three month intervals of time were modeled for time trend using spline smoothing. The final models were adjusted for time trend, weekday, holiday, influenza, and pollen epidemics, temperature, relative humidity and barometric pressure (Halonen, Lanki, Yli-Tuomi, Kulmala, Tiittanen, and Pekkanen, 2008).

Atlanta Metropolitan Area Study of ER visits for Respiratory Conditions

In this metropolitan area, increased risks of hospital ER visits for all respiratory conditions and for COPD specifically were observed with increased levels of $PM_{2.5}$ over the period from 1 August 1998 to 31 August 2000 (Peel, Tolbert, Klein, Metzger, Flanders, Todd, et al., 2005). There were 1,888,973 visits during this period, with daily mean (SD) numbers of ER visits of 241 (85.9) for respiratory conditions, including 12.2 (4.87) for COPD. The mean and 90th percentile concentrations were below the NAAQS for PM_{10} (annual standard), $PM_{2.5}$ (annual standard), CO (1-hour and 8-hour standards), and NO_2 (1-hour and annual standard), but the mean and 90th percentile were above the annual standard.

Increases in rate ratios (RR) of COPD ER visits were associated with a 1 ppm increase in 1-hour CO concentrations (RR = 1.026 [1.004, 1.048]) and a 20 ppb increase in 1-hour NO_2 concentrations (RR = 1.035 [1.006, 1.065]), averaged at lag0 - lag2. The basic and final models included day of week, season, hospital, holiday, time, temperature, and dew point temperature (Peel, Tolbert, Klein, Metzger, Flanders, Todd, et al., 2005).

Study of Hospital Admissions for Cardiovascular and Respiratory Diseases in the Medicare Population of 204 U.S. Urban Counties:

Among 11.5 million Medicare enrollees, the median (IQR) daily hospitalization rate for COPD was 2.6 (1.1) per 100,000 individuals (Dominici, Peng, Bell, Pham, McDermott, Zeger, Samet, 2006). The average of the county mean annual values for $PM_{2.5}$ from 1999-2002 was below the NAAQS daily and annual standards (mean = 13.4 $\mu g/m^3$, IQR = 11.3-15.2 μg/m3), with the 75th percentile just above the annual standard of 15.0 $\mu g/m^3$.

An increase of 10 μg/m^3 in $PM_{2.5}$ was associated with a national average relative rate of 0.91% increase (95% Posterior Interval [PI]: 0.18, 1.64) in daily hospitalization for COPD among the overall Medicare population and a relative rate of 1.47% increase (95%PI: 0.54 to 2.40) among the population ≥ 75 years old at lag0. The covariates that were evaluated and included in the model were county, day of week, calendar time, season, temperature, and dew point (Dominici, Peng, Bell, Pham, McDermott, Zeger, Samet, 2006).

Study of Hospital Admissions for Cardiovascular and Respiratory Diseases in the Medicare Population in 108 U.S. Urban Counties:

This study of coarse particulate matter ($PM_{10-2.5}$) and hospital admissions for cardiovascular and respiratory disease included approximately 12 million Medicare enrollees living within 9 miles of sites with co-located monitors for $PM_{2.5}$ and PM_{10} (Peng, Chang, Bell, McDermott, Zeger, Samet, and Dominici, 2008). The population of this study was similar to the one studied above (Dominici, Peng, Bell, Pham, McDermott, Zeger, Samet, 2006), except that fewer counties were included and the study period was three years longer. The median (IQR) daily hospitalization rate for respiratory tract admissions, including COPD and respiratory tract infections, was 7.3 (2.2) per 100,000 individuals. Median and 75th percentile concentrations of $PM_{2.5}$ and PM_{10} were below the 24-hour standards; the $PM_{2.5}$ median concentration was below the annual standard, but the 75th percentile was not.

An increase of 10 μg/m^3 in $PM_{2.5}$ was associated with a national average relative rate of 0.71% increase (95%PI: 0.45 to 0.96) in daily hospitalization rates for COPD among the overall Medicare population at lag0. An increase of 10 μg/m^3 in $PM_{10-2.5}$ was associated with a non-significant increase in the national average relative rate of 0.33% (95%PI: -0.32, 0.84) in daily hospitalization rates for COPD among the overall Medicare population at lag0. Covariates that were evaluated and included in the model were county, day of week, age, calendar time, season, temperature (lag0 through lag3), dew point (lag0 through lag3), indicator variable for age $\geq$ 75 years, time and age interaction term (Peng, Chang, Bell, McDermott, Zeger, Samet, and Dominici, 2008).

Nine California Counties Study of Mortality

This study included 65% of the state's population in evaluating the associations between daily $PM_{2.5}$ concentrations and hospital admissions for, including subcategories of respiratory, cardiovascular, ischemic heart disease, and diabetes during the period from 1999-2002 (Ostro, Broadwin, Green, Feng, and Lipsett, 2007). Data from nine counties were evaluated and then combined in a meta-analysis. Mean (range) $PM_{2.5}$ concentrations ranged from 14 (1-77) $\mu g/m^3$ in Contra Costa County to 29 (2-100) $\mu g/m^3$ in Riverside County, and all were below the NAAQS daily standard. However, six of the nine counties were above the NAAQS annual standard of 15.0 $\mu g/m^3$. Mean daily deaths from respiratory causes ranged from 1.4 in Kern County to 15.0 in Los Angeles County.

Overall, pooled estimates associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ were increased at lag0 and lag1 for all-cause, cardiovascular, respiratory, and subgroup (age > 65 years) mortality. In the cool months, $PM_{2.5}$ concentrations were higher, and pooled estimates of increased association with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ were present at lag0, lag1, lag2, and lag3 for all-cause, cardiovascular, respiratory, and subgroup (age > 65 years) mortality. In a model that included county, day of week, temperature at lag1, and humidity at lag 1, the adjustment for temperature and humidity provided slightly lower estimates than the unadjusted results (Ostro, Broadwin, Green, Feng, and Lipsett, 2007).

Hong Kong Study of AE-COPD Emergency Hospital Admissions

Among 15 hospitals in Hong Kong, the daily mean (SD) number of emergency hospital admissions for AE-COPD was 65.3 (18.9) from January, 2000, through December, 2005. Air pollution concentrations in Hong Kong were higher than those typical for studies in the U.S., but median and 75th percentile values were below the

NAAQS for PM_{10} (daily standard), SO_2 (daily and annual standards), NO_2 (1-hour and annual standards), and ozone (1-hour and 8-hour standards). For $PM_{2.5}$ concentrations, the median concentration was below the daily standard, but the 25th percentile was above the annual standard. Relative risk of emergency hospitalization for AE-COPD was evaluated at lag0, lag1, lag2, lag3, lag4, lag5, the average of lag0 and lag1 ("lag0-lag1"), and the average of lag0 through lag5 ("lag0-lag5") in single pollutant models.

For SO_2, there was only one marginally increased relative risk of hospital admission for AE-COPD (relative risk = 1.007 [1.001, 1.014]) at lag0. For the other air pollutants, increased relative risks were observed on most days and most averaged lags, with the largest increase being for ozone (relative risk = 1.034 [1.030, 1.040]) at the average of lag0-lag5. The best lag was identified by evaluating χ^2 values obtained from change in deviances (Hastie and Tibshirani, 1990), resulting in best choices of the average of lag0 through lag5 for $PM_{10,}$ $PM_{2.5}$, and ozone, the average of lag0 through lag3 for NO_2, and the same day (lag0) for SO_2.

Multipollutant models were constructed using $PM_{2.5}$ and other Hong Kong air pollution concentrations associated with the best lag. In a three-pollutant model, ozone, SO_2, and $PM_{2.5}$ were all associated with increased relative risk of emergency COPD admissions: for a 0.005 ppm increase in ozone, relative risk = 1.029 (1.022, 1.034) on lag0-lag5; for a 0.004 ppm increase in SO_2, relative risk = 1.008 (1.001, 1.015) on lag0; and, for a 10 $\mu g/m^3$ increase in $PM_{2.5}$, relative risk = 1.011 (1.004, 1.017) on lag0-lag5.

Seasonal effects were evaluated by comparing the cold period, when temperature was below 68°F, to the remainder of the study period (warm period). Temperatures below 68°F were associated with increased daily PM_{10}, $PM_{2.5}$, and NO2, decreased 8-hour ozone, and increased hospital admissions (Ko, Tam, Wong, Chan, Tung, Lai, and Hui, 2007).

Idaho Superfund Site Neighbors Study of Composite Outcome

The outcome was a composite of hospital admissions, ER visits, urgent care visits, and family practice visits among persons living near a superfund site comprised of former phosphate mines in or near Pocatello or Chubbock from November, 1994, through March, 2000. Outcomes were classified as respiratory, cardiovascular, or other based upon the International Classification of Disease, 9th revision (ICD-9) code assigned to the primary diagnosis. Air pollution data included PM_{10}, NO_2, and SO_2 measures from monitors located throughout this community. Mean and 90th percentile exposures were less than the standard (daily) for PM_{10}, less than the annual standard for NO_2, and less than the annual and daily standards for SO_2. The largest correlation coefficient between pollutants was $r = 0.47$ between PM_{10} and $NO_{2.}$

Single-pollutant models were evaluated for lags at days 0, 1, 2, 3, and 4, plus an average over lag0-lag4. The most robust results for respiratory outcomes were observed at lag0 for the overall population and for all age subgroups. For a PM_{10} increase of 50 µg/m^3 and the respiratory composite outcome, the overall MPC increased by 7.1% and the 65 years and more subgroup MPC increased by 15.4% in the single-pollutant model.

When NO_2 was added to the model, the overall MPC for a PM_{10} increase of 50 µg/m^3 increased to 17.5%. When SO_2 was added, the overall for MPC for a PM_{10} increase of 50 µg/m^3 increased to 16.3%. Inclusion of all three air pollutants resulted in an overall 21.7% MPC for a PM_{10} increase of 50 µg/m^3.

Daily weather data obtained from the National Weather Service station at the Pocatello airport included minimum and maximum temperatures and average relative humidity. The model included these weather variables, an indicator variable for day of week, and an indicator variable for influenza outbreak, defined as $\geq$ 10 influenza cases over 4 days (Ulirsch, Ball, Kaye, Shy, Lee, Crawford-Brown, et al., 2007).

Summary

Several time series analyses have been reported for air pollution data collected in the late 1990’s and early 2000’s. Exposures to air pollutants in these studies were generally lower than the NAAQS, including a study conducted in Hong Kong using air pollution concentrations obtained in 2000 - 2005 . By evaluating short-term differences in exposures and outcomes, these studies demonstrated significant positive associations between exposures to air pollutants and outcomes of ED visits, hospitalizations, mortality or a composite outcome of hospital admissions, ED visits, and office visits for respiratory causes. These findings provide further support for the conjecture that health effects of air pollution are present at concentrations below the thresholds set by the U.S. EPA. Therefore, an effect on AE-COPD hospital visits may be present in Philadelphia.

CHAPTER 3
METHODS

Data Acquisition

Study Setting

Temple University Hospital (TUH) is located in north central Philadelphia, Pennsylvania, at 3401 North Broad Street in zip code 19140. The Temple Lung Center is a large referral center for lung disease, treating more than 9,000 patients annually. The Lung Center has been nationally recognized for its specialized program for advanced COPD.

Hospital Visits for Acute Exacerbation of COPD

COPD hospital visits data were collected by members of the Department of Pulmonary and Critical Care Medicine, TUH, from 1546 total hospital visits for acute exacerbation of COPD (AE-COPD) over the period from January 1, 2005 through March 31, 2007. Hospital visit for AE-COPD was defined by a discharge diagnosis coded as 491.21 according to the International Classification of Diseases, 9th revision (ICD-9 code). A discharge diagnosis was available for all patients, including those who died in hospital. This series represents the complete population of patients who presented at a hospital visit for AE-COPD at TUH during the study's timeframe.

All hospital visits were included in this study's analyses, except those in a sensitivity analysis performed for first visits in the study period. The medical record number was used to identify patients with multiple visits. The first visit during the study period was then identified using the admission dates.

Covariates Associated with Hospital Visits

Additional covariates collected with the outcomes included medical record number, admission date, discharge date, age, sex, race (African American, White, Hispanic, Asian or Other), GOLD Stage score, results of pulmonary function testing, whether antibiotic therapy had been prescribed, and residence. Zip codes were used to determine residence within Philadelphia, from the surrounding suburbs, from more distant locations but within approximately 3 hours drive time, or from more distant locations. The numbers of visits in the latter two residence categories were very small, so these categories were not included in any analysis. Similarly, more than half of the visits were missing GOLD Stage scores or pulmonary function test results, and therefore these data were not analyzed in this study.

Protection of Human Subjects

Data were acquired after members of the TUH Department of Pulmonary and Critical Care Medicine obtained approval from the Temple University Institutional Review Board, and all relevant precautions were taken to de-identify the data. Any personally identifiable information was stored in a separate file in a secure location. The research for this dissertation was approved by the Temple University Institutional Review Board.

Air Pollution Exposures

Beginning in 1990 and continuing to the present, the Philadelphia Department of Public Health's Air Management Services operated a network of air monitoring stations to measure air quality, including concentrations of the seven criteria air pollutants. During the study period, the network included monitors identified as NAMS (National Air Monitoring Station) or SPLAMS (State/Local Air Monitoring Station), which were intended to provide data used to demonstrate compliance with the U.S. EPA's NAAQS. These monitoring stations were sited throughout the city so that measurements of the criteria air pollutants would provide the most relevant observations for each air pollutant (City of Philadelphia, [DoPH, AMS, 2007). Sample collection and analysis methods are described in Table 2.

Air quality in Philadelphia improved from 1990, when the annual Air Quality Index (AQI) identified 71 days rated good, 214 days rated moderate, and 80 days rated unhealthy. During the first two years of the study period, there were only 24 days rated unhealthy in each year, with 197 days rated good and 144 days rated moderate in 2005, and 200 days rated good, 141 days rated moderate in 2006 (City of Philadelphia, DoPH, AMS, 2010).

Philadelphia air quality during the study period was in compliance with the NAAQS defined for lead, CO, SO_2, NO_2, and out of compliance with particulate matter (PM) with mean aerodynamic diameter (mAD) of < 10 µm (PM_{10}), the annual standard for PM with mAD <2.5 µm ($PM_{2.5}$), and the 8-hour maximum ozone standard. For much of the study period, Philadelphia was in compliance with the $PM_{2.5}$ daily standard, but on December 18, 2006, the daily standard for $PM_{2.5}$ was lowered from 65 µg/m^3 to 35 µg/m^3 for the 3-year average of the 98th percentile of 24-hour concentrations at each population-oriented monitor. Afterwards, Philadelphia was out of compliance for the remainder of the study period (approximately 3.5 months) and until 2008. (City of Philadelphia, DoPH, AMS, 2010).

Methods of sample collection and analysis for measurement of the criteria air pollutants are described in Table 2. The location of monitors for determining compliance with NAAQS selected by Philadelphia Air Management Services to provide the most relevant measures for these pollutants (Table 3 and Figure 2).

Table 2. Methods of Sample Collection and Analysis for Air Pollutants by Philadelphia Air Management Services, 2005-2005

Air Pollutant	Sample Collection	Analysis Method
CO	Instrumental: Data from these instruments is telemetered to a central computer system and values are available in near "real time".	Carbon monoxide - Nondispersive infrared: A nondispersive infrared (NDIR) gas analyzer is an instrument that measures air samples for CO content.
NO_2	Instrumental: Data from these instruments is telemetered to a central computer system and values are available in near "real time".	Nitrogen Oxides - Chemiluminescence: Emission of light as a result of a chemical reaction at environmental temperatures. This analysis is used for NO, NOx, and Noy. NO2 is calculated as NOx- NO.
Oz.	Instrumental: Data from these instruments is telemetered to a central computer system and values are available in near "real time".	Ozone - Ultra Violet: A light, which supplies energy to a molecule being analyzed. Ozone is analyzed with UV.
SO2	Instrumental: Data from these instruments is telemetered to a central computer system and values are available in near "real time".	Sulfur dioxide - Pulsed Fluorescent: Pulsed fluorescence sulfur dioxide monitor where air is drawn from the outside and passes through the analysis cell, and a high intensity burst of UV light is emitted. The sulfur dioxide responds to the specific UV wavelength generated by absorbing the energy. When the flash lamp shuts off (in a fraction of a second) the SO2 fluoresces giving off an amount of photons directly proportional to the concentration of sulfur dioxide in the air.

Source: 2007-2008 Air Monitoring Network Plan, City of Philadelphia, Department of Public Health, Air Management Services (2007).

Table 2 Continued

Air Pollutant	Sample Collection	Analysis Method
PM	See below.	**Gravimetric:** The determination of the quantities of the constituents of a compound, describes a set of methods for the quantitative determination of an **a**nalyte based on the weight of a solid. **o BAM-Beta Attenuation** The principle of beta ray attenuation to provide a simple determination of mass concentration (mass density). Instrumental data is available in near real time.
$PM_{2.5}$	**R & P PM2.5:** Rupprecht & Patashnick PM2.5 monitors an air sample drawn through a Teflon filter for 24 hours.	
PM_{10}	**Hi-Vol-SA/GMW-321-B:** High Volume Sierra Anderson or General Metal Works (GMW) model 321-B PM10 is a high volume air sampler system that has a selective inlet 203 cm x 254 cm filter.	

Source: 2007-2008 Air Monitoring Network Plan, City of Philadelphia, Department of Public Health, Air Management Services (2007).

Table 3. Monitors that Provided Daily Averages for Air Pollutants in Philadelphia, PA, 2005-2007.

Monitor	**Address**	**CO**	**NO_2**	**Oz.**	**$PM_{2.5}$**	**PM_{10}**	**SO_2**
LAB	1501 E. Lycoming	✓	✓	✓		✓	✓
ROX	Eva & Dearnley			✓			
NEA	Grant & Ashton			✓	✓		
NBR	Broad & Butler	✓	✓			✓	✓
CHS	500 S. Broad Street*	✓	✓		✓	✓	✓
ELM	5917 Elmwood			✓	✓		

Source: 2007-2008 Air Monitoring Network Plan, City of Philadelphia, Department of Public Health, Air Management Services (2007).
*Broad Street at Lombard Street.

These measurements were provided to the EPA during the study period. Different monitors provided measurements for different air pollutants (Table 3; City of Philadelphia, Department of Public Health, Air Management Services, 2007). Concentrations of six criteria air pollutants ($PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and ozone) were obtained as 24-hour averages from the U.S. EPA's open access Air Quality Services Data Mart, which was last accessed on March 20, 2011, at the following internet address: http://www.epa.gov/ttn/airs/aqsdatamart/basic_info.htm. Data were retrieved as daily summary values representing the arithmetic mean of observations for a given monitor.

For each day in the study period, an air pollutant concentration was calculated as the arithmetic mean using all 24-hour values available from all relevant monitors. Days with missing values were uncommon except for PM_{10}, which was measured once every 6 days. Because of the large number of days with missing values, PM_{10} was excluded from analysis. For other air pollutant missing-values, an imputed value was calculated, using the average of the values one day before and one day after the missing value.

Weather Data

Daily values for average temperature, minimum temperature, maximum temperature, relative humidity, air pressure, and windspeed were obtained from the Pennsylvania State Climate Office at http://www.stateclimate.org/state.php?state_id=PA (accessed on February 19, 2011).

Seasons

Seasons were defined according to a meteorological definition based on the three coldest and three warmest months in the Northern Hemisphere. Therefore, winter included December, January, February; spring included March, April, May; summer included June, July, August; and fall included September, October, and November (National Weather Service Forecast Office, not dated). Each visit was assigned to a season based on the month of the visit.

Lagged Data

Lag periods were defined to represent the interval between exposure and effect. Lag0 represented an exposure on the same day as the hospital visit. Lag1 represented an exposure one day before hospital visit, and lag2 represented an exposure two days before hospital visit. In addition, exposures were evaluated using the average of air pollutant concentrations on the same day and one day earlier (lag01), the average of air pollutant concentrations on one and two preceding days (lag12), and the average of air pollutant concentrations on the same day and both preceding days (lag012). Lags for exposures at 7, 14, and 21 days were also evaluated and are reported in Appendix B. Interpretation of results for these longer lags is beyond the scope of this dissertation.

The possibility of a lagged effect of NO_2 concentrations on the concentrations of other air pollutants was evaluated with NO_2 concentrations at lag2, lag1, and lag0 correlated with the other air pollutants at lag0. Another possible lagged effect was evaluated using correlations between ozone concentrations at lag2, lag1, or lag0 and NO_2 concentrations at lag0.

Because the most common influence on Philadelphia weather conditions is related to the westerly winds, the possibility of a lagged effect of windspeed on other weather conditions was evaluated for correlations between lagged windspeed and temperature, relative humidity, and air pressure. Similarly, the possibility of a correlation between lagged temperature and on other weather conditions was evaluated.

Statistical Methods

Descriptive statistics were produced to characterize the visits during the study period and to describe the short-term exposure variables and weather covariates at lag0, lag1, lag2, lag01, lag12, and lag012. Because the descriptive statistics for lag01 and lag12 were very similar to those observed at lag012, the effects at lag01 and lag12 are not reported. Air pollution exposures and weather covariates were examined to determine whether they were normally distributed. Some of the air pollution exposures were positively skewed, and various transformations were evaluated. The $\log_{10}$ transformation provided the best approximation to normality for these exposure variables. Untransformed weather values were used throughout the analyses. Figures were produced using Microsoft® Office Excel® 2007.

The analysis was conducted using SAS Software for Windows, Version 9.1.3 (Statistical Analysis Systems Institute, Cary, North Carolina). Statistical significance was based upon a *P*-value < 0.05, with no adjustment for multiple comparisons. However, given the number of regression models constructed, small *P*-values are considered more reliable (e.g., $P \leq 0.0001$).

Correlations

Pearson correlation coefficients between air pollutants at lag0 and between weather conditions at lag0 were examined in preparation for multivariable modeling. In addition, some correlation coefficients were evaluated between variables at different lags, as described below.

Correlations among Air Pollutant Concentrations

Pearson correlation coefficients were evaluated for the five air pollutants on the same day (lag0) using data that had been $\log_{10}$-transformed to improve on the approximation to a normal distribution. Because NO_2 is a component of atmospheric reactions that produce other air pollutants, the correlation coefficients between NO_2 concentrations 1 or 2 days earlier (i.e., lag1 or lag2) and the other air pollutants at lag0 were evaluated.

Alternatively, NO_2 may be the product of a reaction between ozone and nitrous oxides, so the correlation coefficients between ozone concentrations 1 or 2 days earlier (lag1 or lag2) with NO_2 at lag0 were also examined. Because the atmospheric reaction involving ozone and NO_2 is photolytic and varies with the amount of sunshine, correlation coefficients between lagged ozone and NO_2 were also evaluated for each season.

Weather Conditions.

Pearson correlation coefficients were evaluated for the four weather conditions on the same day (lag0). Because of geographic characteristics of the Philadelphia region, winds from the northwest generally determine weather conditions. Therefore, correlation coefficients between windspeed on previous days (lag2 or lag1) and other weather conditions at lag0 were examined. Similarly, a lagged relationship between temperature at lag2, lag1, and lag0 and the other weather variables at lag0 was evaluated.

Associations between Air Pollutant Exposures and AE-COPD Hospital Visits

Single Pollutant Associations

Hospital visit for AE-COPD was first examined separately for each air pollutant (univariate analyses). Poisson regression models were used to evaluate the relationship between the independent variable of air pollution exposure and the dependent variable of the number of daily hospital visits for AE-COPD. The relationship between daily hospital visits for AE-COPD and weather conditions was also examined separately for each exposure by univariate Poisson regression at lag0, lag1, lag2, lag01, lag12, and lag012. Because the results of the univariate models at lag01 and lag12 generally did not differ from those observed at lag012, the effects at lag01 and lag12 are not reported.

Multipollutant Associations

Multivariable models were evaluated for air pollutants with correlation coefficients ≤ 0.55, an empirically based cutpoint, and statistically significant effects (*P*-value <0.05) in univariate models at the same lags. If both air pollutants had significant effects, then the pair was re-evaluated with inclusion of an interaction term to assess independence of effects.

Evaluation of the Effect of Weather Conditions

Temperature was the only weather condition with a statistically significant effect (*P*-value < 0.05) in univariate analysis of the relationship with AE-COPD hospital visits. The effect of temperature on associations between air pollutant exposures and hospital visit for AE-COPD was evaluated in a bivariate model for each air pollutant that had a statistically significant effect in the univariate analysis. The temperature effect was also included in models in which each of two air pollutants had a statistically significant effect in a bivariate model.

Evaluation of Subgroups

Seasonal analyses were performed for all air pollutants and temperature in univariate models. Multivariable models were evaluated for variables that were statistically significant (*P*-value <0.05) in the same season by univariate analyses.

Effect modification of the overall relationship between daily AE-COPD hospital visits and daily concentration of air pollutants was evaluated by stratified analysis of patient subgroups. These subgroups were defined according to age (< 65 or ≥ 65 years), gender (male or female), race (African American, White, Hispanic, or Asian or Other), residence (Philadelphia or surrounding suburban counties), or antibiotic-therapy (prescribed or not prescribed). Univariate models were evaluated for all of these subgroups, and multivariable models were evaluated for variables that were statistically significant (*P*-value <0.05) in the univariate analyses.

Sensitivity Analyses

Sensitivity analyses (described below) were performed to confirm the assumptions that underlie use of the Poisson model:

1. mean = variance
2. independence of outcomes
3. linearity of the relationship between exposures and outcomes

Pearson Scale.

In order to evaluate the final models for overdispersion, which occurs when the variance is greater than the mean, the fixed scale was changed to equal the Pearson Chi-square statistic divided by its degrees of freedom. Values close to 1.0 indicate that the model is not over- or under-dispersed.

Analysis of First Visits

A subset of 970 first visits within the study period was identified from the overall 1546 visits. An analysis of the association between air pollutant exposures at lag0 and hospital visits for AE-COPD was performed for the subset of first visits with subsequent visits excluded. The outputs of the main analysis and this subset analysis were compared to assess the consistency of results as an indicator of the independence of the outcomes.

Analysis of Quartile Indicator Variables.

For each date in the study period. the air pollutant exposure was assigned a quartile indicator based upon the quartiles from the overall distribution of air pollution concentrations at lag0. Regression was performed with these indicator variables as the independent variables. Consistent linear relationships for the quartile analysis and the continuous data analysis supports the appropriate use of the Poisson regression analyses.

CHAPTER 4
RESULTS

Hospital Visits for Acute Exacerbation of COPD

During the study period (January 1, 2005, through March 31, 2007), there were 1546 hospital visits to Temple University Hospital for acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) among 970 individual patients; 711 individuals presented once and 259 individuals presented two or more times. Daily numbers of visits ranged from 0 to 9 per day and were most commonly 1 per day. The mean (SD) was 1.9 (1.5), with similar median (IQR) of 2 (2) visits per day.

Demographic and Clinical Characteristics of Patients at Hospital Visits

Age at visit ranged from 28 to 96 years, with a mean (SD) of 62.8 (11.0) years. More than half of visits were for individuals less than 65 years of age (Table 4). Hospital visits were evenly divided between males and females. Approximately two-thirds (65%) were African American, and approximately one-fifth (22%) were White.

Table 4. Demographic Characteristics of Hospital Visits for AE-COPD

	Total Visits n = 1546	
	No.	%
Age (years)		
< 65 years	880	56.9%
≥ 65 years	666	43.1%
Gender		
Male	770	49.8%
Female	776	50.2%
Race*		
African American	995	64.5%
White	342	22.2%
Hispanic	182	11.8%
Asian/Other	23	1.5%

Note: n = number of admissions; No. = number; % = percentage.

* Race was missing for 4 admissions.

At more than half of hospital visits, the GOLD Stage score was missing (Table 5). Among the 643 visits with GOLD Stage scores, most were in the moderate (43%, 278/643) or severe (38%, 245/643) categories. Antibiotics were prescribed for almost half of the visits. Approximately 90% of hospital visits were for residents of Philadelphia and another 7% were for residents of surrounding counties.

Table 5. Distribution of Hospital Visits According to Clinical Characteristics and Residence

	Total Visits n = 1546 No.	%
GOLD Stage		
No Score	903	58.4%
All Scores	643	41.6%
Stage 2	120	8.2%
Stage 3	278	18.0%
Stage 4	245	15.8%
Antibiotic prescription		
No	788	51.0%
Yes	758	49.0%
Residence		
Philadelphia	1385	89.6%
Surrounding counties	105	6.8%
Within ~2 hour drive	48	3.1%
More distant	8	0.5%

Note: n = number of admissions; No. = number; % = percentage.

Seasonal Variation in Hospital Visits

Over the study period, seasonal variation in daily hospital visits was present, with more in the winter and spring months. The mean (SD) number of hospital visits ranged from 2.3 (1.7) in winter to 1.4 (1.3) in summer (Table 6). Every season had a minimum of 0 daily visits, while the maximum number of daily visits ranged from 6 in the summer and fall to 8 during the winter season.

Table 6. Daily Hospital Visits According to Season

	No. of Days	No. of Admissions	Mean	SD	Min.	Max.	Median
Winter	239	561	2.3	1.7	0	8	2
Spring	215	431	2.0	1.5	0	7	2
Summer	184	264	1.4	1.3	0	6	1
Fall	182	290	1.6	1.3	0	6	1
Total	820	1546	1.9	1.5	0	8	2

Note: No. = number; Max. = maximum; Min. = minimum.

Air Pollution and Weather Exposures during the Study Period

Air Pollution Concentrations during the Study Period

Distribution of Air Pollution Concentrations

The distributions of air pollution concentration are provided in Table 7. The air pollutant concentrations were not normally distributed, but $\log_{10}$ transformation resulted in closer approximation to normal.

During the study period, all values for PM_{10} were below the NAAQS limit for 24-hour values, 150 µg/m^3. For $PM_{2.5}$, the NAAQS limit for 24-hour values was reduced from 65 µg/m^3 to 35 µg/m^3 in December 2006; there were 14 days with $PM_{2.5}$ between 35 to 65 µg/m^3, with 12 of the 14 days in the summer season. For NO_2 the NAAQS limits were defined for an annual average of 53 ppb; only two days had values above this limit, with the maximum NO2 value of 59 ppb. All values of SO_2 were below the NAAQS limits whether defined for an annual average of 30 ppb or a 24-hour average of 14 ppm.

The NAAQS limits for CO and ozone were defined for both 1-hour and 8-hour maximums rather than daily or annual values. All values for the maximum 24-hour averages were less than the lower of the two limits, the 8-hour maximum, for both CO (9,000 ppb) and ozone (80 ppb).

Table 7. Daily Average Air Pollution Concentrations in Philadelphia, Pennsylvania, During the Study Period (January 1, 2005, through March 31, 2007)

	Units	n	Mean	SD	Q_1	Median	Q_3	Min.	Max.
$PM_{2.5}$	μg/m^3	820	13.4	7.9	7.4	11.4	17.6	1.5	48.2
PM_{10}	μg/m^3	114	25.0	16.3	15.0	22.3	31.5	2.0	133.0
CO	ppm	820	0.510	0.197	0.368	0.474	0.600	0.250	1.539
NO_2	ppm	820	0.024	0.009	0.018	0.024	0.029	0.006	0.059
SO_2	ppm	820	0.005	0.004	0.002	0.004	0.006	0.001	0.026
Ozone	ppb	820	0.022	0.012	0.013	0.022	0.032	0.002	0.055

Note: The data described in this table are original values (i.e., not log-transformed values). n = number of daily air pollution observations; Q1 - 1st quartile; Q3 = third quartile; Min. = minimum value; Max. = maximum value; $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; PM_{10} = particulate matter with mean aerodynamic diameter of 10 microns; μg/m^3 = microgram per cubic meter; CO = carbon dioxide; ppb = parts per billion; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

Seasonal Variation in Air Pollutants

Median air pollutant concentrations varied by season (Table 8). $PM_{2.5}$ concentrations were greatest in the summer and lowest in the spring and fall. Ozone concentrations were also greatest in the summer, slightly lower in spring, and approximately one-half to one-third of the summer median in the fall and winter. The greatest concentrations of CO and SO_2 were present during the winter, while NO_2 concentrations were similar over all seasons.

Table 8. Median and IQR of Air Pollutant Concentrations by Season and Overall

	Winter	Spring	Summer	Fall	Overall
No. of Days:	239	215	184	182	820
$PM_{2.5}$ ($\mu g/m^3$)					
Median	13	9	16	10	11
IQR	10	8	13	10	11
PM_{10} ($\mu g/m^3$)					
Median	23	22	33	16	22
IQR	8	7	19	11	17
CO (ppm)					
Median	0.541	0.438	0.451	0.477	0.474
IQR	0.506	0.203	0.249	0.214	0.232
NO_2 (ppm)					
Median	0.028	0.024	0.021	0.023	0.024
IQR	0.011	0.013	0.008	0.012	0.011
SO_2 (ppm)					
Median	0.006	0.003	0.003	0.003	0.005
IQR	0.005	0.003	0.003	0.003	0.004
Ozone (ppm)					
Median	0.011	0.030	0.033	0.016	0.022
IQR	0.012	0.010	0.013	0.011	0.019

Note: IQR = interquartile range; $PM_{2.5}$ = particulate matter with mean aerodynamic diameter < 2.5 microns; $\mu g/m^3$ = microgram per cubic meter; CO = carbon monoxide; ppm = parts per million; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

The greatest $PM_{2.5}$ concentrations were more than 40 µg/m^3 and occurred in summer in both 2005 and 2006 (Figure 2). Values greater than 20 µg/m^3 were more common in the summer and winter.

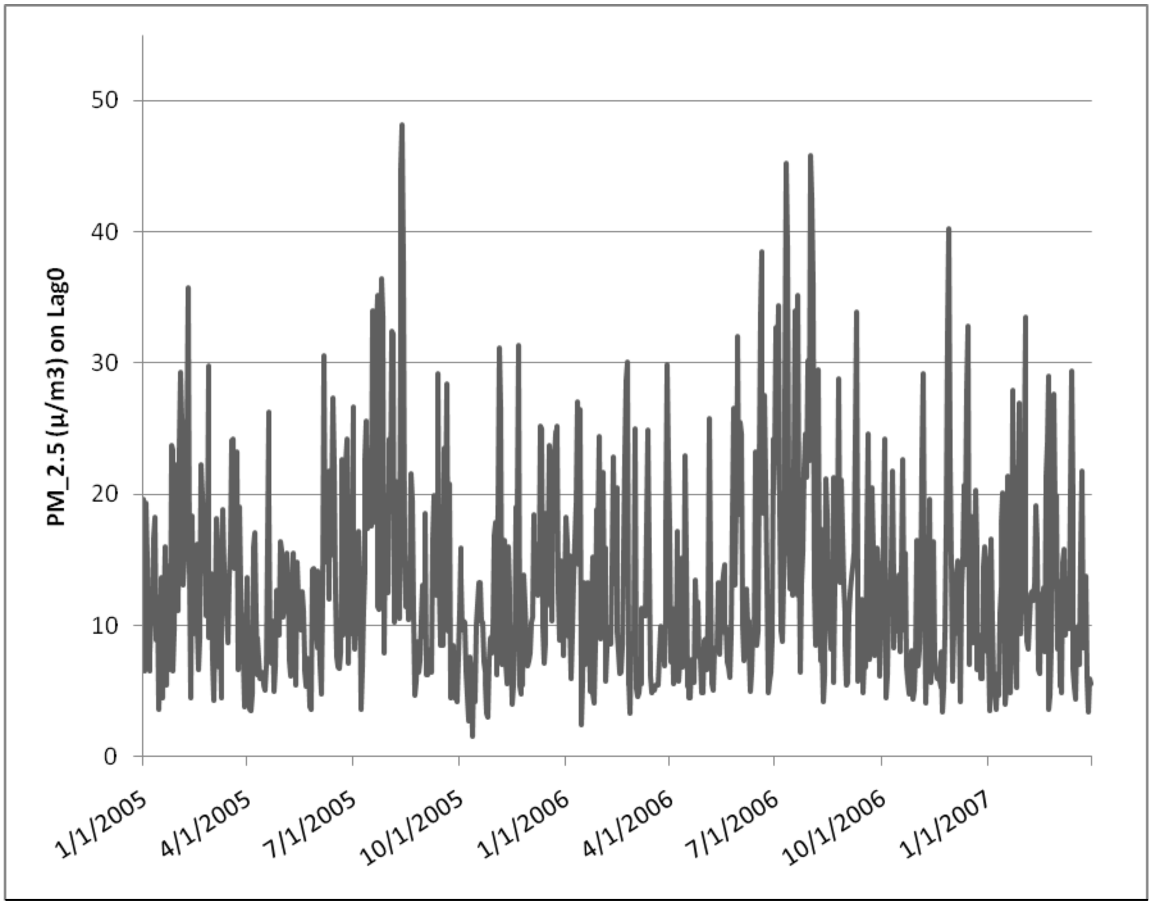

Figure 2. $PM_{2.5}$ Concentrations (µg/m^3) During Study Period

CO, NO_2, and SO_2 concentrations were highest in the fall and winter (Figure 3, Figure 4, and Figure 5).

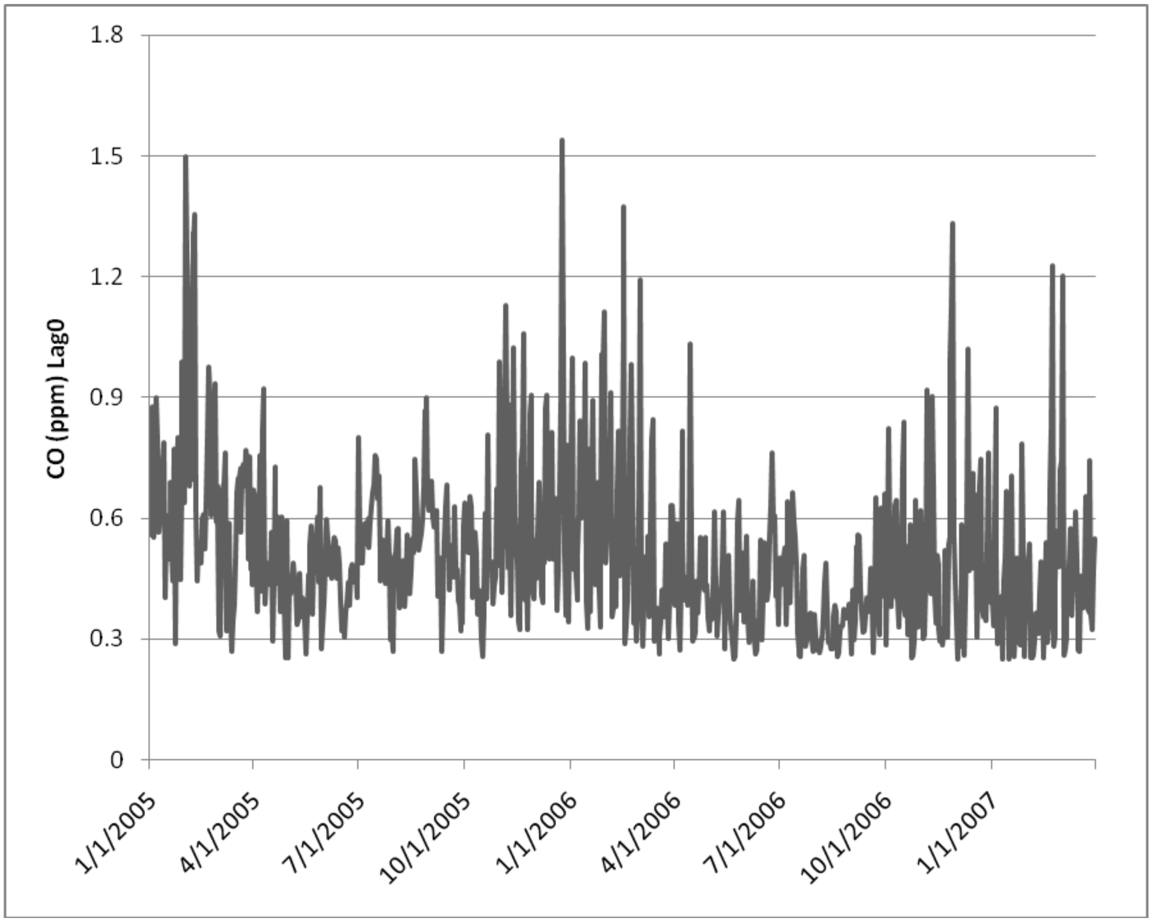

Figure 3. CO Concentrations (ppm) During Study Period

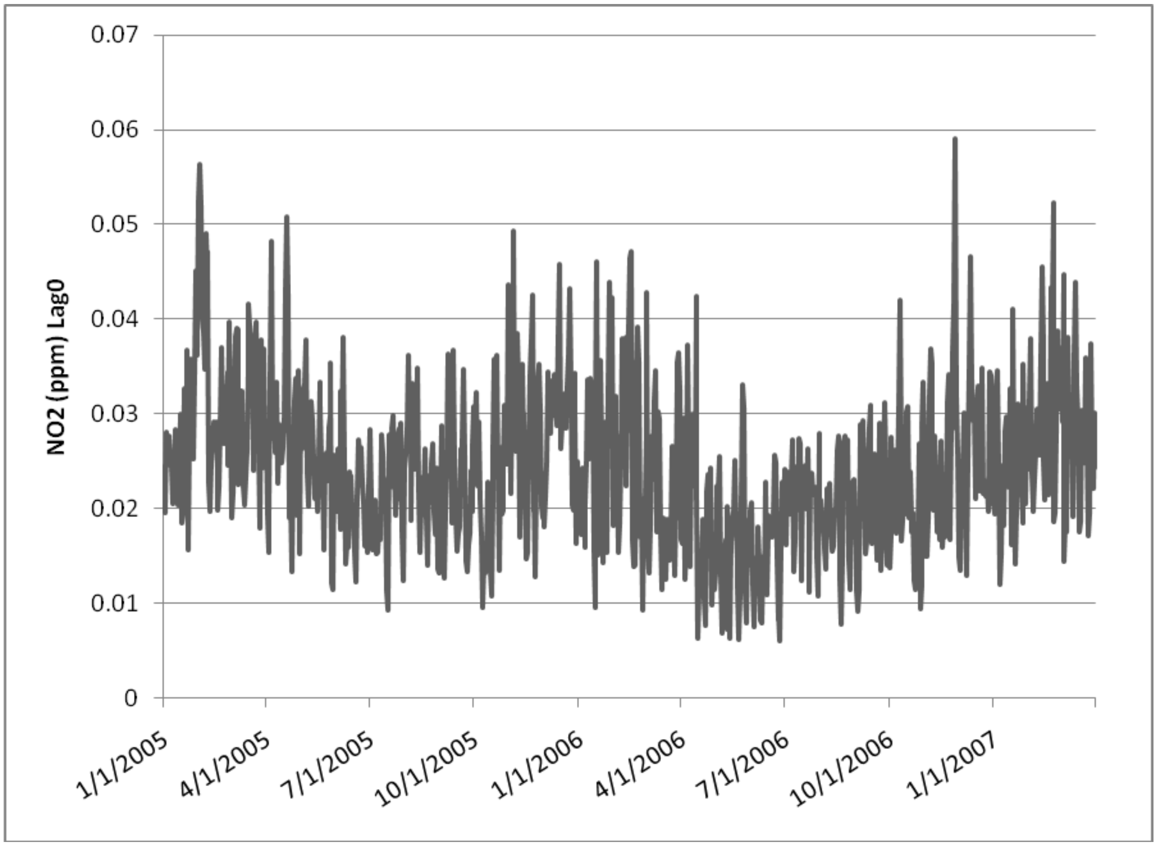

Figure 4. NO_2 Concentrations (ppm) During Study Period

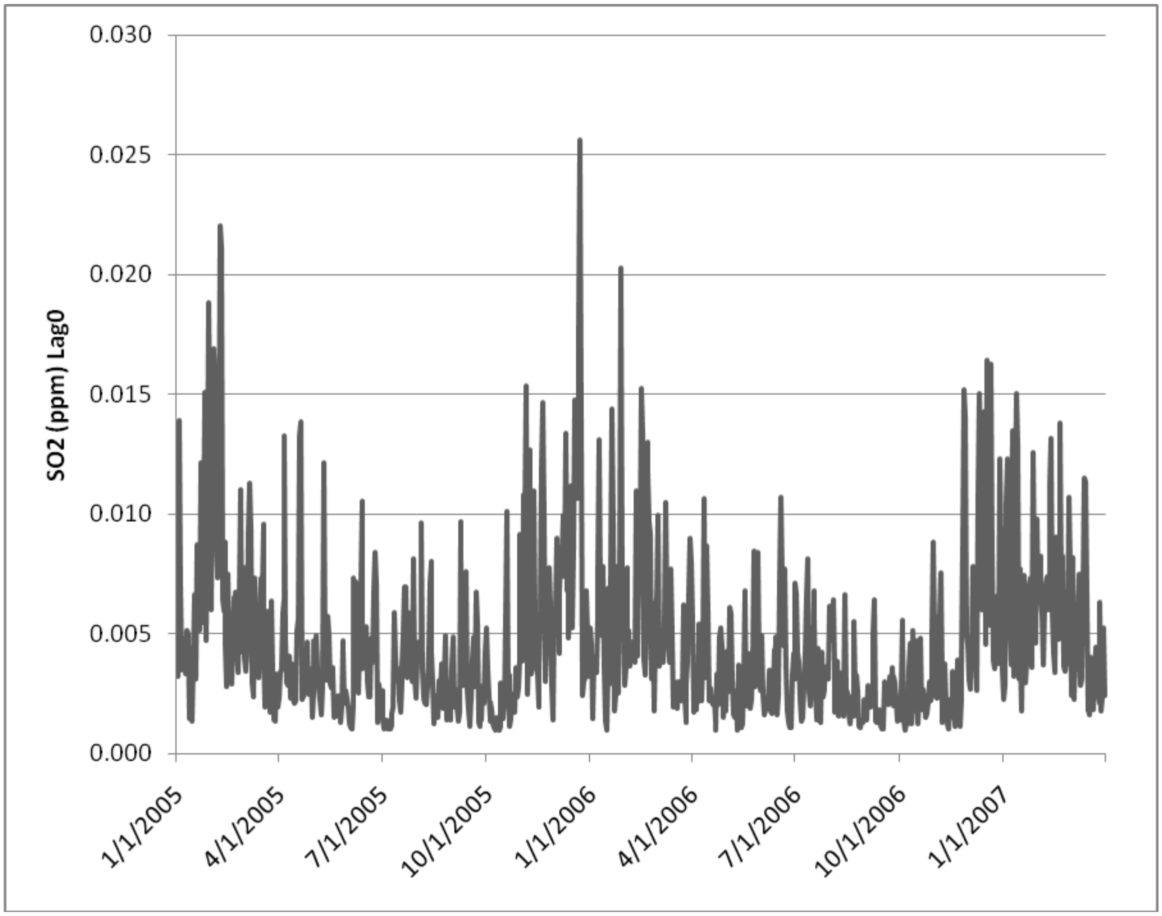

Figure 5. SO_2 Concentrations (ppm) During Study Period

Ozone had the highest median concentration in the summer, with a slightly lower median concentration in the spring (Figure 6) The NAAQS limits for CO and ozone were defined for both 1-hour and 8-hour maximums rather than daily or annual values. All values for the maximum 24-hour averages in the current study were less than the 8-hour maximum for both CO (0.009 ppm) and ozone (0.080 ppm), lower of the two limits (Table 7). The fall median concentration was less than that in spring, and it was greater than the median concentration in winter.

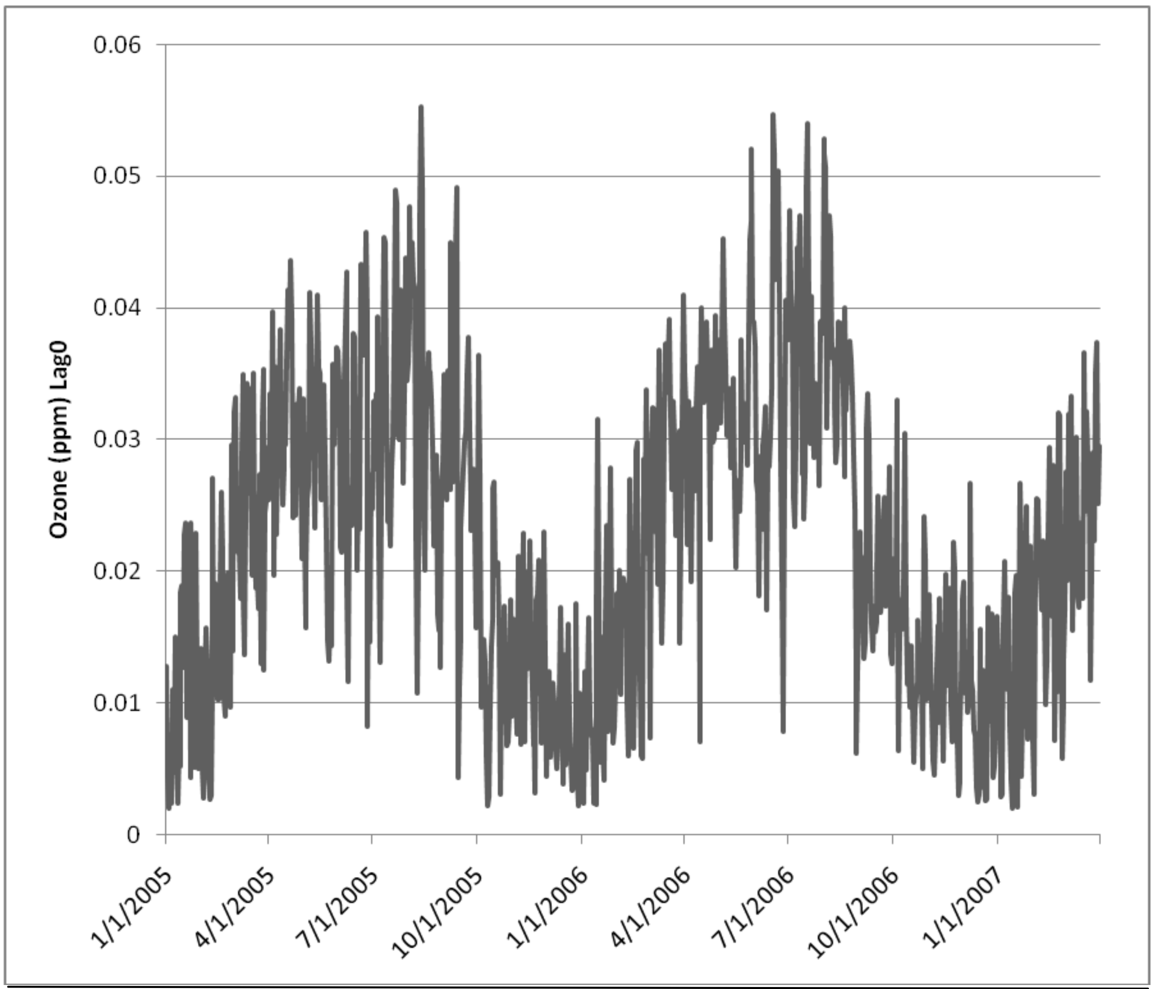

Figure 6. Ozone Concentrations (ppm) During the Study Period

Correlations among Air Pollutants

Correlations on the Same Day

Same-day Pearson correlation coefficients between air pollutants were all statistically significant (Table 9). The strongest were direct correlations of r = 0.64 between NO_2 and CO and between NO_2 and SO_2, followed by r = 0.55 between NO_2 and $PM_{2.5}$. Ozone was inversely correlated with all other air pollutants, with the strongest correlation between ozone and CO, r = -0.51. Similar correlations were observed using values averaged for lag0 and lag1, or lag1 and lag2, or averaged for lag0, lag1, and lag2.

Table 9. Pearson Correlations* Among Air Pollutants on the Same Day

	$PM_{2.5}$	CO	NO_2	SO_2	Ozone
$PM_{2.5}$		0.44	0.47	0.54	-0.11
CO			0.64	0.45	-0.51
NO_2				0.64	-0.37
SO_2					-0.34
Ozone					

Note: n = 820 observations; PM2.5 = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon monoxide; NO2 = nitrogen dioxide; SO_2 = sulfur dioxide.
* P-value 0 <0.0001 for all except P =0.0018 for correlation between $PM_{2.5}$ and ozone.

Lagged Correlations

The greatest absolute values for correlation coefficients were present between NO_2 and other air pollutants at the same day, lag0, and all were statistically significant (Table 10). Correlations between NO_2 concentrations at lag1 and other air pollutants at lag0 were approximately one-half as strong as those with lag0 NO_2 concentrations. With NO_2 concentrations from two days before (lag2), the correlations with other air pollutants at lag0 were even smaller and there was no significant correlation between NO_2 at lag2 and $PM_{2.5}$ at lag0. These results did not support a delayed relationship between NO_2 lagged by one or two days and other air pollutants at lag0.

Table 10. Pearson Correlations between NO_2 concentrations at Lag2, Lag1, or Lag0 and Other Air Pollutants at Lag0

	NO_2 lag2		NO_2 lag1		NO_2 lag0	
Lag0	*r*	*p*	*r*	*p*	*r*	*p*
$PM_{2.5}$	0.00002	0.9995	0.27	<.0001	0.47	<.0001
CO	0.15	<.0001	0.34	<.0001	0.64	<.0001
SO_2	0.16	<.0001	0.35	<.0001	0.64	<.0001
Ozone	-0.14	<.0001	-0.22	<.0001	-0.37	<.0001

Note: *r* = correlation coefficient; $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

Inverse correlations were present between ozone at lag2, lag1, and lag0 and NO_2 at lag0, with the greatest correlation between ozone and NO_2 at lag0 (Table 11). In every season, the largest absolute value of the correlation coefficient was also between ozone and NO_2 at lag0. Inverse correlations were present between ozone at lag0 and NO_2 at lag0 in winter, spring, and fall. However, in the summer, direct correlations were present between ozone at lag0 or lag1 and NO_2 at lag0. These results did not support a delayed correlation between ozone at lag2 or lag1 and NO_2 at lag0.

Table 11. Pearson Correlations between Ozone at Lag2, Lag1, or Lag0 and NO_2 at Lag0 Overall and by Season

	Ozone lag2		Ozone lag1		Ozone lag0	
NO_2 lag0	*r*	*p*	*r*	*p*	*r*	*p*
Overall	-0.11	0.0011	-0.20	<0.0001	-0.37	<0.0001
Winter	0.23	0.0004	-0.02	0.7068	-0.53	<0.0001
Spring	-0.11	0.1173	-0.25	0.0002	-0.50	<0.0001
Summer	0.10	0.1932	0.26	0.0003	0.30	<0.0001
Fall	0.05	0.4843	-0.11	0.1422	-0.23	0.0013

Note: *r* = correlation coefficient; NO_2 = nitrogen dioxide.

The differences in size and direction of correlation coefficients between NO_2 and ozone reflect the pronounced seasonal variation in ozone and the relatively constant concentrations of NO_2 over all seasons (Figure 4, Figure , and Table 8). The relationship between NO_2 and ozone over the study period is represented in Figure , which illustrates the seasonal relationship between concentrations of these two air pollutants and the effect on of the greater amount of sunlight that is available for ozone formation in the summer.

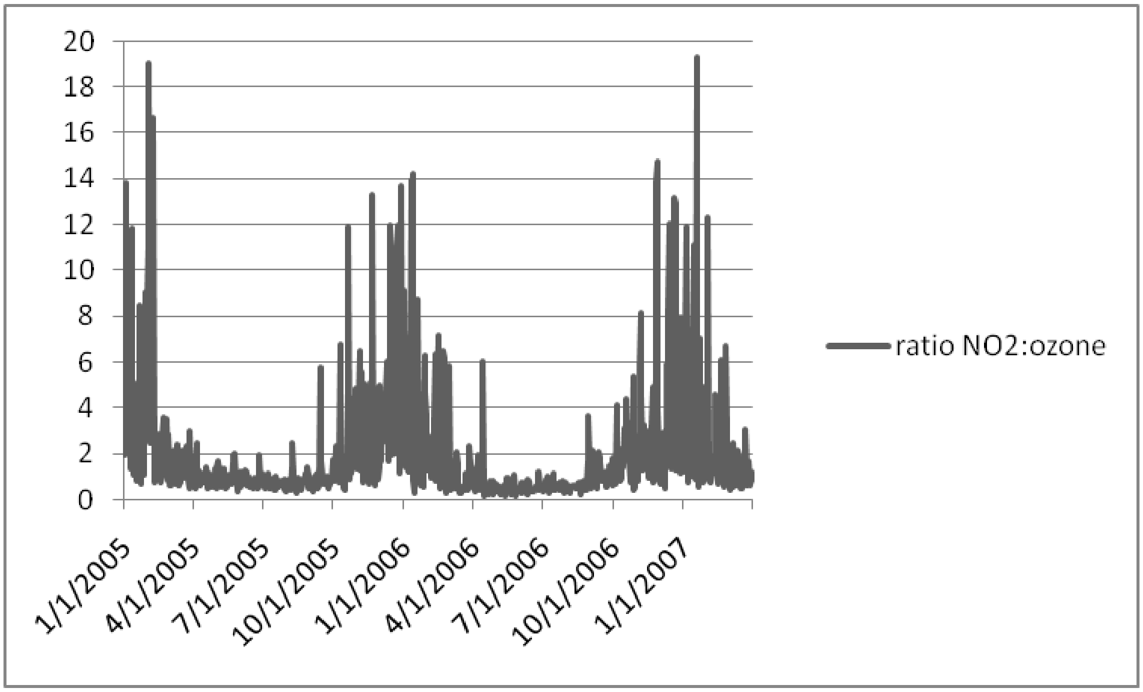

Figure 7. Ratio of NO_2 to Ozone Concentrations over the Study Period

Weather Conditions during the Study Period

Distribution of Weather Variables

During the study period, expected seasonal variations in temperature and relative humidity were present (Table 12). Average daily temperature was lowest in winter and highest in summer, ranging from a low of 13°F to a high of 90°F (Figure and Table 12). Actual minimum and maximum temperatures varied across seasons similarly to the pattern seen for average daily temperature, but the difference between daily minimum and maximum temperatures was less variable across the seasons.

Table 12. Summary Statistics for Temperature during the Study Period by Season and Overall

	Winter	Spring	Summer	Fall	Overall
Average Daily Temperature (°F)					
n	239	213	183	174	809
Mean	36	52	77	59	55
SD	10	12	6	12	18
Min	13	20	60	28	13
Max	65	81	90	82	90
Windspeed (mph)					
n	239	213	183	174	809
Mean	10	10	8	9	10
SD	4	4	2	4	4
Min	1	3	4	3	1
Max	24	22	16	23	24
Relative Humidity (%)					
n	239	213	167	174	793
Mean	60	53	65	65	60
SD	16	15	11	13	15
Min	31	18	38	37	18
Max	95	94	91	93	95

Note: °F = degrees Fahrenheit; n = number of observations; SD = standard deviation; Min = minimum; Max = maximum; mph = miles per hour; mbar = millibar.

Table 12. Continued

	Winter	Spring	Summer	Fall	Overall
Air pressure (mbar)					
n	239	213	167	174	793
Mean	1018	1014	1016	1017	1016
SD	9	11	4	8	9
Min	977	958	1003	990	958
Max	1042	1033	1023	1034	1042

Note: °F = degrees Fahrenheit; n = number of observations; SD = standard deviation; Min = minimum; Max = maximum; mph = miles per hour; mbar = millibar.

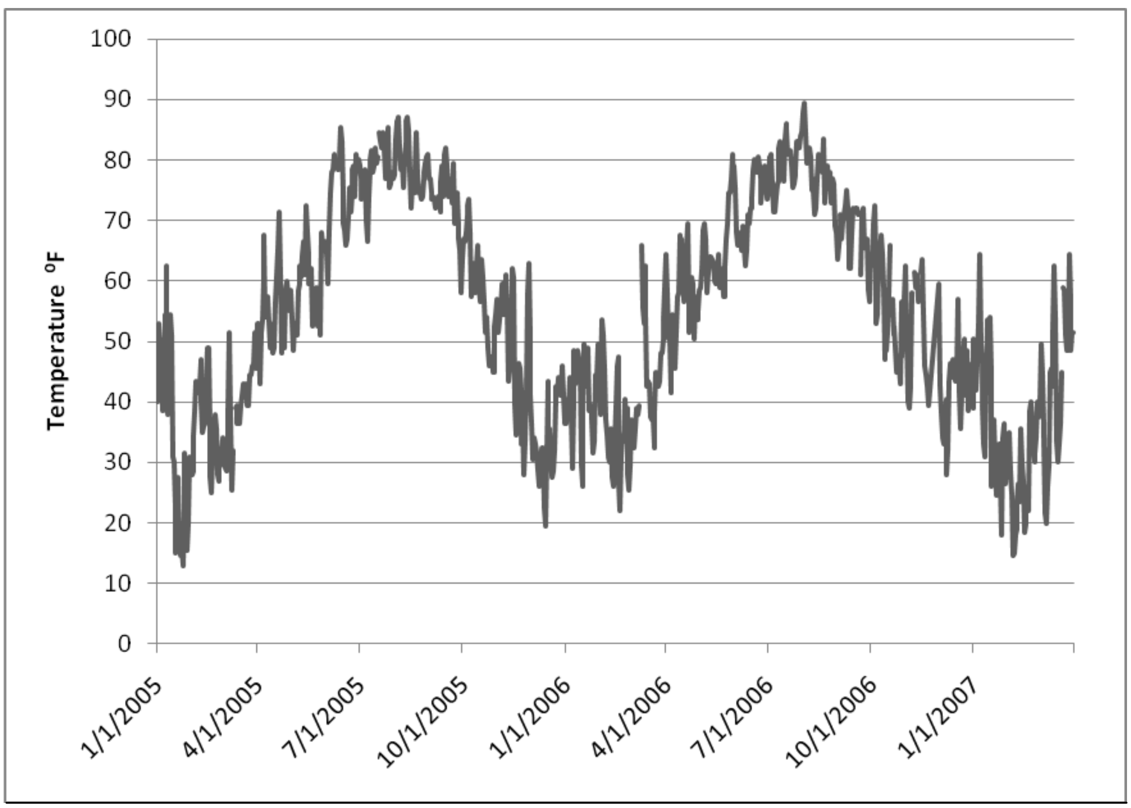

Figure 8. Average Daily Temperature (°F) Over the Study Period

Average windspeed varied little over most seasons with decreased variability and speed in the summer (Figure 9). The range of windspeed was lowest in the summer, from 4 to 16 mph, and highest in winter, from 1 to 24 mph (Table 12).

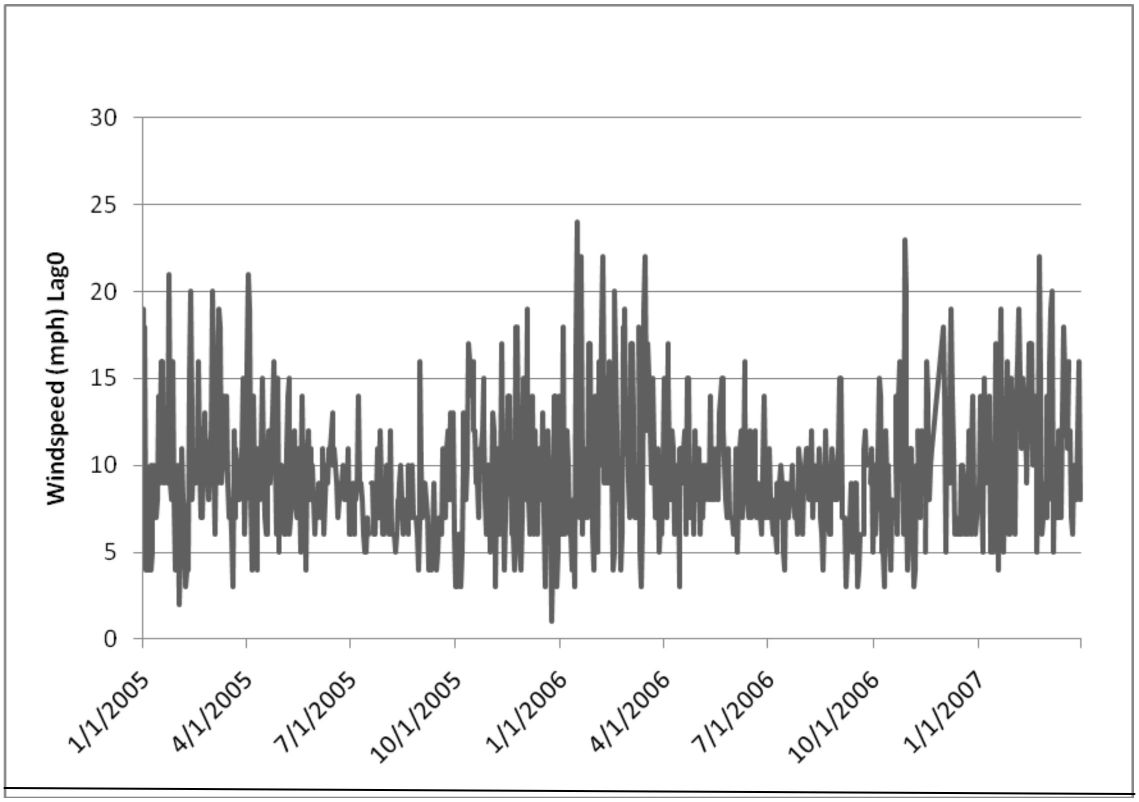

Figure 9. Windspeed (mph) Over the Study Period

Relative humidity varied from approximately 30% to approximately 90% over the study period, with highest values in summer and fall. The greatest range of relative humidity was in spring (Table 12 and Figure 10).

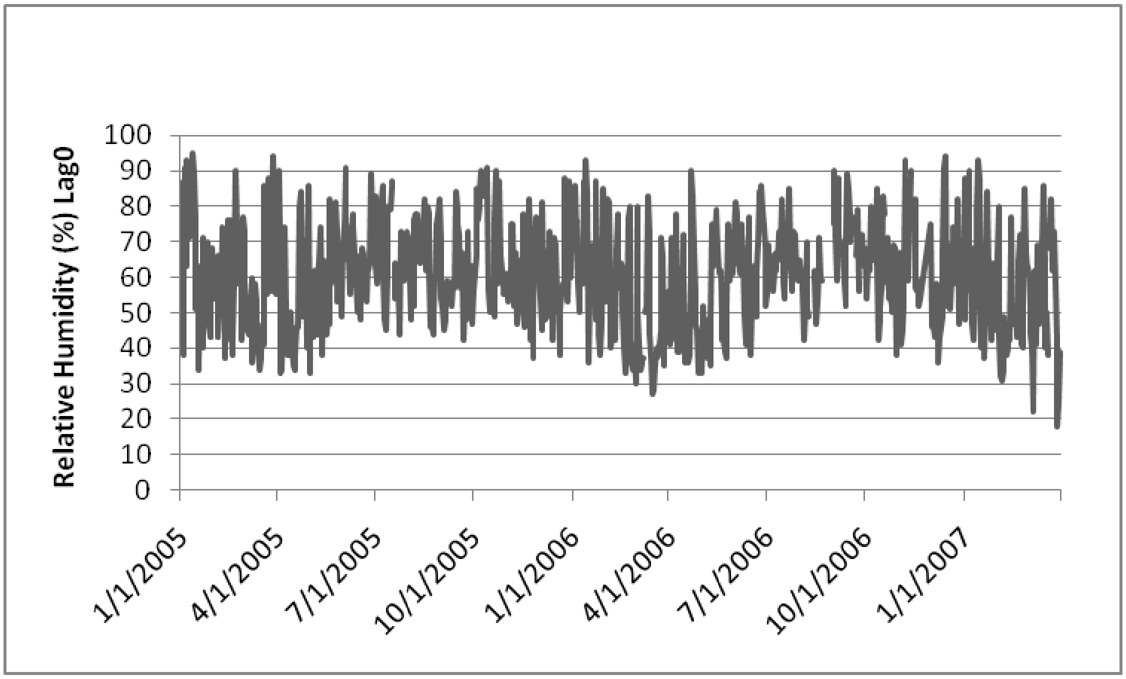

Figure 10. Relative Humidity (%) Over the Study Period

A number of low air pressure observations were apparent in the first half of 2005, but there was less variation for the remainder of the study period, with no apparent seasonal effect (Figure 11).

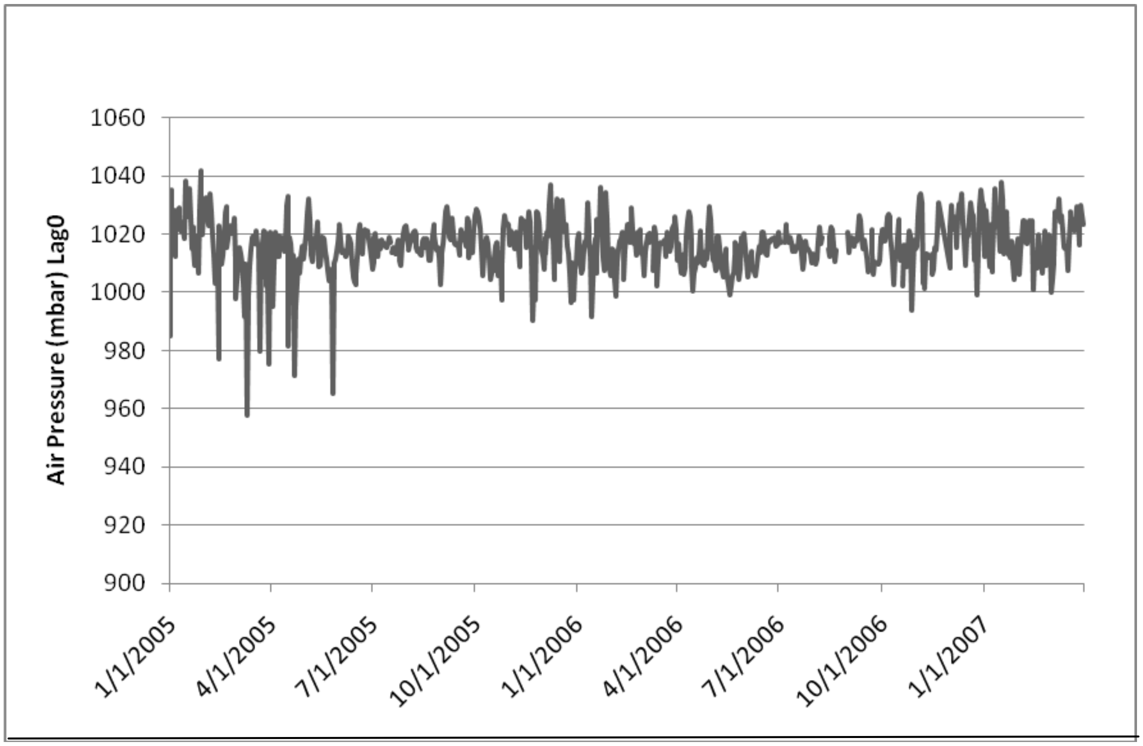

Figure 11. Air Pressure (mbar) Over the Study Period

Correlations Among Weather Variables

Correlations on the Same Day

Small ($r < 0.30$) direct correlations were present between average temperature and range of temperature or relative humidity (Table 13). Small ($|r| < 0.30$) inverse same-day correlations were present between average temperature and air pressure or windspeed, between daily range of temperature and relative humidity or windspeed, and between relative humidity and air pressure or windspeed. The absence of any strong correlation supports evaluation of each as a potentially important covariate.

Table 13. Same Day Pearson Correlations Between Weather Variables

		Average Temperature*	Daily Range*	Relative Humidity*	Air Pressure*	Windspeed*
Average Temperature*	*r*		0.24	0.27	-0.16	-0.29
	n		807	792	792	808
Daily Range of Temperature *				-0.23	0.01	-0.21
				792	792	808
Relative Humidity*	*r*				-0.18	-0.28
	n				793	793
Air Pressure*	*r*					-0.28
	n					793
Windspeed*	*r*					
	n					

Note: H_0 = null hypothesis; *r* = Pearson correlation coefficient.
* Probability > |r| under H0: Rho=0 <0.0001 for all except the correlation between daily range of temperature and air pressure, with p = 0.7485.

Lagged Correlations

Correlations between Lagged Windspeed and Other Weather Conditions

Small inverse correlations were present between windspeed at lag0 and all other weather variables at lag0 (Table 14). There was no indication of greater correlations between the other weather variables and windspeed on preceding days (lag2, lag1) than on the same day. Therefore, lag0 values for windspeed were used in further analysis.

Table 14. Pearson Correlation Between Windspeed at Lag2, Lag1, and Lag0 with Other Weather Variables at Lag0

	Windspeed lag2		Windspeed lag1		Windspeed lag0	
Lag0	*r*	*p*	*r*	*p*	*r*	*p*
Temperature	-0.20	<.0001	-0.21	<.0001	-0.29	<.0001
Daily range of temp.	-0.21	<.0001	-0.21	<.0001	-0.21	<.0001
Relative humidity	-0.28	<.0001	-0.28	<.0001	-0.28	<.0001
Air pressure	-0.28	<.0001	-0.28	<.0001	-0.28	<.0001

Note: *r* = Correlation coefficient; temp. = temperature.

Correlations Between Lagged Temperature and Other Weather Conditions.

Correlations between temperature at lag2, lag1, or lag0 and the other weather variables at lag0 were evaluated (Table 15). Small correlations between temperature and relative humidity or air pressure were greatest at lag0 and decreased at lag1 and lag2. A small inverse correlation between temperature at lag2, lag1, or lag0 and windspeed was consistent at all three lags. Therefore, lag0 values were used for temperature in further analysis.

Table 15. Pearson Correlation Between Average Daily Temperature at Lag0, Lag1, or Lag2 and Other Weather Variables at Lag0

	Temperature lag2		Temperature lag1		Temperature lag0	
Lag0	*r*	*p*	*r*	*p*	*r*	*p*
Daily range of temperature	0.08	0.0292	0.13	0.0002	0.24	<.0001
Relative humidity	0.19	<.0001	0.22	<.0001	0.27	<.0001
Air pressure	-0.10	0.0064	-0.14	0.0001	-0.16	<.0001
Windspeed	-0.29	<.0001	-0.29	<.0001	-0.29	<.0001

Note: *r* = Correlation coefficient.

Association Between Hospital Visits for AE-COPD and Air Pollution Exposures

Effects of Air Pollutant Exposures: Univariate Models

No association was present between $PM_{2.5}$ and hospital visits at lag0, lag1, lag2, or lag012 (Table 16). Increased RRs for AE-COPD hospital visit were present for NO_2 and SO_2 at all lags and for CO at lag1, lag2, and lag012. In contrast, decreased RRs for AE-COPD hospital visit were present for ozone at all lags.

Table 16. Effects of Air Pollution on Daily Hospital Visits for AE-COPD

						95% Wald CI		
Model	Exposure	Observation	Beta	SE	RR*	LL*	UL*	*p*
16.1	$PM_{2.5}$	lag0	0.0200	0.1000	1.02	0.83	1.24	0.8819
16.2		lag1	0.1834	0.1023	1.20	0.98	1.47	0.0731
16.3		lag2	0.1366	0.1024	1.15	0.94	1.40	0.1823
16.4		lag012	0.1840	0.1302	1.20	0.93	1.55	0.1576
16.5	CO	lag0	0.1300	0.1700	1.14	0.82	1.58	0.4319
16.6		lag1	0.3431	0.1653	1.41	1.02	1.95	0.0380
16.7		lag2	0.4078	0.1650	1.50	1.09	2.08	0.0135
16.8		lag012	0.4766	0.2100	1.61	1.07	2.43	0.0233
16.9	NO_2	lag0	0.5700	0.1600	1.77	1.29	2.42	0.0004
16.10		lag1	0.4814	0.1601	1.62	1.18	2.21	0.0026
16.11		lag2	0.4542	0.1599	1.57	1.15	2.15	0.0045
16.12		lag012	0.8181	0.2044	2.27	1.52	3.38	<.0001
16.13	SO_2	lag0	0.3000	0.0900	1.34	1.13	1.58	0.0006
16.14		lag1	0.3879	0.0860	1.47	1.25	1.74	<.0001
16.15		lag2	0.3919	0.0861	1.48	1.25	1.75	<.0001
16.16		lag012	0.5283	0.1044	1.70	1.38	2.08	<.0001

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

Table 16. Continued

Model	Exposure	Observation	Beta	SE	RR*	95% Wald CI LL*	UL*	*p*
16.17	Ozone	lag0	-0.2800	0.0800	0.76	0.65	0.89	0.0006
16.18		lag1	-0.3616	0.0798	0.70	0.60	0.81	<.0001
16.19		lag2	-0.3857	0.0795	0.68	0.58	0.79	<.0001
16.20		lag012	-0.4522	0.0923	0.64	0.53	0.76	<.0001

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

For the 24-hour NAAQS for SO_2 (0.14 ppm) at lag012, the model predicts 4.2776 as the number of daily hospital visits for AE-COPD. At a concentration of 0.15 ppm, the model predicts 4.3459 daily hospital visits. At a concentration of 0.13 ppm, the model predicts 4.0255 daily hospital visits.

For the 24-hour NAAQS for $PM_{2.5}$ (35 $\mu g/m^3$) at lag012, the model predicts 2.0604 as the number of daily hospital visits for AE-COPD. At a concentration of 36 ug/m^3, the model predicts 2.0651 daily hospital visits. At a concentration of 34 ug/m^3, the model predicts 2.0557 daily hospital visits.

Overall Effects of Weather Conditions

Small decreases in RRs for AE-COPD hospital visit were present for a 10ºF increase in temperature (Table 17). There were no other effects of weather conditions at the lags examined.

Table 17. Effects of Weather Conditions on Daily Hospital Visits for AE-COPD

						95% Wald CI		
Model	Parameter	Observation	Beta	SE	RR*	LL*	UL*	*p*
17.1	Temperature (10°F)	lag0	-0.0780	0.0140	0.93	0.90	0.95	<.0001
17.2		lag1	-0.0820	0.0140	0.92	0.90	0.95	<.0001
17.3		lag2	-0.0930	0.014	0.91	0.89	0.94	<.0001
17.4		lag012	-0.0890	0.0150	0.91	0.89	0.94	<.0001
17.5	Air pressure	lag0	-0.0029	0.0029	1.00	1.00	1.00	0.3234
17.6		lag1	-0.0009	0.0029	1.00	1.00	1.01	0.7622
17.7		lag2	0.0043	0.0030	1.00	1.00	1.01	0.1581
17.8		lag012	0.0004	0.0037	1.00	1.00	1.01	0.9150
17.9	Relative humidity (%)	lag0	-0.0004	0.0017	1.00	1.00	1.00	0.8230
17.10		lag1	0.0008	0.0017	1.00	1.00	1.00	0.6608
17.11		lag2	-0.0009	0.0017	1.00	1.00	1.00	0.6254
17.12		lag012	-0.0005	0.0022	1.00	1.00	1.00	0.8429
17.13	Windspeed	lag0	0.0087	0.0066	1.009	1.00	1.022	0.1884
17.14		lag1	-0.0023	0.0068	1.00	0.99	1.01	0.7355
17.15		lag2	-0.0005	0.0068	1.00	0.99	1.01	0.9413
17.16		lag012	0.0051	0.0096	1.005	0.99	1.024	0.5946

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL = lower limit(*exponentiated); UL = Upper Limit (*exponentiated); 10°F = effect is for each 10 degrees Fahrenheit.

Multivariable Models and Seasonal Effects

Multivariable Models at Lag0.

Independent effects of NO_2 and ozone and of SO_2 and ozone were evident (Table 18). The inverse association between ozone and hospital visits for AE-COPD was similar for univariate analysis (model 15.3) and with inclusion of NO_2 (model 15.6) or SO_2 (model 15.7). In contrast, the direct associations between NO_2 or SO_2 and hospital visit for AE-COPD were reduced with inclusion of ozone. Models with interaction terms for NO_2 and ozone or for SO_2 and ozone could not be constructed.

Table 18. Effects of Air Pollution on Hospital Visits for AE-COPD at Lag0

						95% Wald CI		
Model	Parameters	Exposure	Beta	SE	RR*	LL*	UL*	*p*
18.1	NO_2	NO_2 lag0	0.5700	0.1600	1.77	1.29	2.42	0.0004
18.2	SO_2	SO_2 lag0	0.3000	0.0900	1.34	1.13	1.58	0.0006
18.3	Ozone	Ozone lag0	-0.2800	0.0800	0.76	0.65	0.89	0.0006
18.4	NO_2 + Ozone	NO_2 lag0	0.4220	0.1731	1.53	1.09	2.14	0.0147
		Ozone lag0	-0.1932	0.0878	0.82	0.69	0.98	0.0278
18.5	SO_2 + Ozone	SO_2 lag0	0.2189	0.0918	1.24	1.04	1.49	0.0171
		Ozone lag0	-0.2010	0.0868	0.82	0.69	0.97	0.0205

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Seasonal Effects of Air Pollution Exposures or Temperature at Lag0

There were no significant effects of $PM_{2.5}$, CO, NO_2, or SO_2 by season (Table 19). For ozone, RRs decreased for AE-COPD hospital visit associated with the pollutant concentrations in spring, consistent with the overall study period. There were no effects of ozone in the summer, fall, or winter.

Average Daily Temperature Effects. Average daily temperature at lag0 in the winter was associated with a significant increase in RR for AE-COPD hospital visit. There were no significant effects of temperature in spring, summer, or fall.

Table 19. Seasonal Effects of Air Pollution Concentrations and Temperature on Hospital Visits for AE-COPD: Univariate Analyses at Lag0

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
$PM_{2.5}$ (lag0)								
Winter	239	n = 561	-0.0277	0.1793	0.97	0.68	1.38	0.8773
Spring	215	n = 431	-0.0155	0.2184	0.98	0.64	1.51	0.9433
Summer	184	n = 264	0.1012	0.2516	1.11	0.68	1.81	0.6876
Fall	182	n = 290	0.4328	0.238	1.54	0.97	2.46	0.0690
CO (lag0)								
Winter	239	n = 561	0.0158	0.2427	1.02	0.63	1.63	0.9479
Spring	215	n = 431	0.0116	0.3504	1.01	0.51	2.01	0.9737
Summer	184	n = 264	-0.7466	0.4945	0.47	0.18	1.25	0.1311
Fall	182	n = 290	-0.0273	0.4023	0.97	0.44	2.14	0.9459
NO_2 (lag0)								
Winter	239	n = 561	-0.032	0.3045	0.97	0.53	1.76	0.9164
Spring	215	n = 431	0.2964	0.2735	1.35	0.79	2.30	0.2786
Summer	184	n = 264	0.5516	0.4546	1.74	0.71	4.23	0.2250
Fall	182	n = 290	0.3421	0.3780	1.41	0.67	2.95	0.3655

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Table 19. Continued

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
SO_2 (lag0)								
Winter	239	n = 561	-0.0576	0.1669	0.94	0.68	1.31	0.7302
Spring	215	n = 431	0.2022	0.1962	1.22	0.83	1.80	0.3025
Summer	184	n = 264	-0.0027	0.2435	1.00	0.62	1.61	0.9912
Fall	182	n = 290	-0.0411	0.2029	0.96	0.64	1.43	0.8395
Ozone (lag0)								
Winter	239	n = 561	-0.0210	0.1384	0.98	0.75	1.28	0.8796
Spring	215	n = 431	-1.0706	0.3279	0.34	0.18	0.65	0.0011
Summer	184	n = 264	0.1375	0.3778	1.15	0.55	2.41	0.7160
Fall	182	n = 290	0.3141	0.2446	1.37	0.85	2.21	0.1991
Temp 10°F (lag0)								
Winter	239	n = 561	0.1470	0.0450	1.16	1.06	1.26	0.0010
Spring	215	n = 431	-0.0710	0.0420	0.93	0.86	1.01	0.0898
Summer	184	n = 264	-0.1510	0.1090	0.86	0.69	1.07	0.1657
Fall	182	n = 290	0.0520	0.0520	1.05	0.95	1.17	0.3200

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Multivariable Models at Lag1

Multipollutant models were constructed for NO_2 with ozone and for SO_2 with ozone (Table 20). The reduced effects of SO_2 with inclusion of temperature (model 17.4) or ozone with inclusion of temperature (model 17.5) suggested that temperature confounded the association of these exposures with hospital visits for AE-COPD.

Independent effects of SO_2 and ozone were both slightly reduced in the bivariate model (model 17.6).

Table 20. Effects of Air Pollution on Hospital Visits for AE-COPD at Lag1

						95% Wald CI		
Model	Parameters	Exposure	Beta	SE	RR*	LL*	UL*	*p*
17.1	SO_2	SO_2 lag1	0.3879	0.0860	1.47	1.25	1.74	<.0001
17.2	Ozone	Ozone lag1	-0.3616	0.0798	0.70	0.60	0.81	<.0001
17.3	Temp (10^oF)	Temp lag1	-0.0820	0.0140	0.92	0.90	0.95	<.0001
17.4	SO_2 +	SO2 lag1	0.2342	0.0931	1.26	1.05	1.52	0.0119
	Temp (10^oF)	Temp lag1	-0.0068	0.0015	0.93	0.91	0.96	<.0001
17.5	Ozone +	Ozone lag1	-0.2064	0.0902	0.81	0.68	0.97	0.0221
	Temp (10^oF)	Temp lag1	-0.0067	0.0016	0.94	0.91	0.96	<.0001
17.6	SO_2 + Ozone	SO_2 lag1	0.2827	0.0918	1.33	1.11	1.59	0.0021
		Ozone lag1	-0.2617	0.0860	0.77	0.65	0.91	0.0023

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); SO_2 = sulfur dioxide.; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Seasonal Effects of Air Pollution Exposures or Temperature at Lag1

There were no effects of NO_2 or SO_2 by season at lag1 (Table 21). Several other effects were present in winter. In contrast to the lack of effect of $PM_{2.5}$ year-round, there was an increased RR for AE-COPD hospital visit in winter: 1.59 (95%CI: 1.11, 2.28). In winter, an increased RR for AE-COPD hospital visit was associated with CO and a reduced RR for AE-COPD hospital visit was associated with ozone concentrations. There were no effects of CO or ozone in spring, summer, or fall.

Average Daily Temperature Effect. Average daily temperature in winter was associated with an increased RR for AE-COPD hospital visit at lag1. There were no effects of temperature in any other season.

Table 21. Seasonal Effects of Air Pollution Concentrations and Temperature on Hospital Visits for AE-COPD: Univariate Analyses at Lag1

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
$PM_{2.5}$ (lag1)								
Winter	239	n = 561	0.4643	0.1833	1.59	1.11	2.28	0.0113
Spring	215	n = 431	-0.0303	0.2187	0.97	0.63	1.49	0.8899
Summer	184	n = 264	0.3200	0.2533	1.38	0.84	2.26	0.2064
Fall	182	n = 290	0.3305	0.2383	1.39	0.87	2.22	0.1655
CO (lag1)								
Winter	239	n = 561	0.5318	0.2412	1.70	1.06	2.73	0.0275
Spring	215	n = 431	-0.4020	0.3543	0.67	0.33	1.34	0.2566
Summer	184	n = 264	-0.9702	0.4967	0.38	0.14	1.00	0.0508
Fall	182	n = 290	0.4642	0.3946	1.59	0.73	3.45	0.2394
NO2 (lag1)								
Winter	239	n = 561	0.4917	0.3092	1.64	0.89	3.00	0.1117
Spring	215	n = 431	0.0123	0.2675	1.01	0.60	1.71	0.9635
Summer	184	n = 264	-0.3326	0.4284	0.72	0.31	1.66	0.4376
Fall	182	n = 290	0.2814	0.3758	1.32	0.63	2.77	0.4541

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Table 21. Continued

Season	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
SO_2 (lag1)								
Winter	239	n = 561	0.0968	0.1675	1.10	0.79	1.53	0.5635
Spring	215	n = 431	0.2631	0.1950	1.30	0.89	1.91	0.1774
Summer	184	n = 264	0.2541	0.2433	1.29	0.80	2.08	0.2963
Fall	182	n = 290	-0.0145	0.2033	0.99	0.66	1.47	0.9433
Ozone (lag1)								
Winter	239	n = 561	-0.3564	0.1358	0.70	0.54	0.91	0.0087
Spring	215	n = 431	-0.3217	0.3453	0.72	0.37	1.43	0.3516
Summer	184	n = 264	0.6707	0.4074	1.96	0.88	4.35	0.0997
Fall	182	n = 290	0.0459	0.2381	1.05	0.66	1.67	0.8471
Temp 10°F (lag1)								
Winter	239	n = 561	0.1270	0.0440	1.14	1.04	1.24	0.0035
Spring	215	n = 431	-0.0730	0.0410	0.93	0.86	1.01	0.0768
Summer	184	n = 264	-0.0560	0.1100	0.95	0.76	1.17	0.6071
Fall	182	n = 290	-0.0260	0.0510	0.97	0.88	1.08	0.6062

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Multivariable Models in Winter at Lag1. Multipollutant models could not be constructed for the winter season (Table 22). Inclusion of temperature in the model resulted in only a slight reduction in the effect of $PM_{2.5}$ (model 19.3).

Table 22. Effects of Multivariable Models on Hospital Visits for AE-COPD in Winter at Lag1

						95%Wald CI		
Model	Parameters	Exposure	Beta	SE	RR*	LL*	UL*	*p*
22.1	$PM_{2.5}$	$PM_{2.5}$ lag1	0.4643	0.1833	1.59	1.11	2.28	0.0113
22.2	Temp (10^0F)	Temp lag1	0.1270	0.0440	1.14	1.04	1.24	0.0035
22.3	$PM_{2.5}$ +	$PM_{2.5}$ lag1	0.4175	0.1834	1.52	1.06	2.17	0.0229
	Temp (10^0F)	Temp lag1	0.1200	0.0440	1.13	1.03	1.23	0.0070

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter < 2.5 microns; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Multivariable Models at Lag2

A multipollutant model showed independent and opposing effects on AE-COPD hospital visit for SO_2 and ozone (Table 23). No models could be constructed for NO_2 and ozone at lag2. Although inclusion of temperature in the models with SO_2 or ozone resulted in reduced effects of SO_2 and ozone with inclusion of temperature (models 20.4 and 20.5), the association with AE-COPD hospital visits remained for both air pollution variables.

Table 23. Effects of Air Pollution on Hospital Visits for AE-COPD at Lag2

Model	Parameters	Exposure	Beta	SE	RR*	95% Wald CI LL*	UL*	*p*
23.1	SO_2	SO_2 lag2	0.3919	0.0861	1.48	1.25	1.75	<.0001
23.2	Ozone	Ozone lag2	-0.3857	0.0795	0.68	0.58	0.79	<.0001
23.3	Temp (10^0F)	Temp lag2	-0.0930	0.014	0.91	0.89	0.94	<.0001
23.4	SO_2 +	SO_2 lag2	0.2068	0.0935	1.23	1.02	1.48	0.0271
	Temp (10^0F)	Temp lag2	-0.0080	0.0015	0.92	0.90	0.95	<.0001
23.5	Ozone +	Ozone lag2	-0.2110	0.0901	0.81	0.68	0.97	0.0192
	Temp (10^0F)	Temp lag2	-0.0078	0.0016	0.92	0.90	0.96	<.0001
23.6	SO_2 + Ozone	SO_2 lag2	0.2756	0.0918	1.32	1.10	1.58	0.0027
		Ozone lag2	-0.2881	0.0858	0.75	0.63	0.89	0.0008

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); SO_2 = sulfur dioxide.; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Seasonal Effects of Air Pollution Exposures or Temperature at Lag2

$PM_{2.5}$ was associated with an increased RR for AE-COPD hospital visit in winter: RR = 1.53 (95%CI: 1.07, 2.19). There were no effects of CO, NO_2, SO_2, or temperature in any season (Table 24). A reduced RR for AE-COPD hospital visit was associated with ozone concentrations in spring, consistent with the year-round results, but there were no effects of ozone on AE-COPD hospital visits in the summer, fall, or winter.

Table 24. Seasonal Effects of Air Pollution Concentrations and Temperature on Hospital Visits for AE-COPD: Univariate Analyses at Lag2

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
$PM_{2.5}$ (lag2)								
Winter	239	n = 561	0.4248	0.1833	1.53	1.07	2.19	0.0204
Spring	215	n = 431	0.1594	0.2189	1.17	0.76	1.80	0.4666
Summer	184	n = 264	0.1448	0.2510	1.16	0.71	1.89	0.5640
Fall	182	n = 290	0.0839	0.2398	1.09	0.68	1.74	0.7266
CO (lag2)								
Winter	239	n = 561	0.4305	0.2414	1.54	0.96	2.47	0.0745
Spring	215	n = 431	0.0745	0.3501	1.22	0.61	2.42	0.5711
Summer	184	n = 264	-0.4176	0.4938	0.66	0.25	1.73	0.3978
Fall	182	n = 290	-0.0248	0.3997	0.98	0.45	2.14	0.9504
NO_2 (lag2)								
Winter	239	n = 561	0.4204	0.3086	1.52	0.83	2.79	0.1731
Spring	215	n = 431	0.0221	0.2695	1.02	0.60	1.73	0.9347
Summer	184	n = 264	0.1571	0.4412	1.17	0.49	2.78	0.7217
Fall	182	n = 290	-0.1779	0.3733	0.84	0.40	1.74	0.6336
SO_2 (lag2)								
Winter	239	n = 561	0.1843	0.1662	1.20	0.87	1.67	0.2674
Spring	215	n = 431	0.3077	0.1933	1.36	0.93	1.99	0.1113
Summer	184	n = 264	0.1906	0.2454	1.21	0.75	1.96	0.4374
Fall	182	n = 290	-0.1177	0.2047	0.89	0.60	1.33	0.5653

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit. ***Continued.***

Table 24. Continued

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
Ozone (lag2)								
Winter	239	n = 561	-0.2220	0.1375	0.80	0.61	1.05	0.1065
Spring	215	n = 431	-0.8489	0.3237	0.43	0.23	0.81	0.0087
Summer	184	n = 264	0.3917	0.4181	1.48	0.65	3.36	0.3488
Fall	182	n = 290	-0.1413	0.2334	0.87	0.55	1.37	0.5448
Temp 10°F (lag2)								
Winter	239	n = 561	0.0500	0.0430	1.05	0.97	1.14	0.2390
Spring	215	n = 431	-0.0680	0.0410	0.93	0.86	1.01	0.1015
Summer	184	n = 264	-0.0890	0.1090	0.91	0.74	1.13	0.4148
Fall	182	n = 290	-0.0520	0.0500	0.95	0.86	1.05	0.2968

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Multivariable Models at Lag012

Multipollutant models were constructed for NO_2 with ozone and for SO_2 with ozone (Table 25Table 25). A reduction in the effect of ozone was evident with inclusion of temperature (model 25.5). There were no interactions between SO_2 and ozone at lag012 (model 25.7), but there was an interaction between NO_2 and ozone (model 25.8). There were substantial reductions in the RR for AE-COPD hospital visit associated with NO_2 ozone, and the interaction (model 25.8).

Table 25. Effects of Air Pollution on Hospital Visits for AE-COPD at Lag012

Model	Parameters	Exposure	Beta	SE	RR*	95% Wald CI LL*	UL*	*p*
25.1	NO_2	NO2 lag012	0.8181	0.2044	2.27	1.52	3.38	<.0001
25.2	SO_2	SO2 lag012	0.5283	0.1044	1.70	1.38	2.08	<.0001
25.3	Ozone	Ozone lag012	-0.4522	0.0923	0.64	0.53	0.76	<.0001
25.4	Temp (10°F)	Temp lag012	-0.0890	0.0150	0.91	0.89	0.94	<.0001
25.5	Ozone +	Ozone lag012	-0.2158	0.1092	0.81	0.65	1.00	0.0480
	Temp (10°F)	Temp lag012	-0.0072	0.0017	0.93	0.90	0.96	<.0001
25.6	NO_2 + Ozone	NO_2 lag012	0.5251	0.2182	1.69	1.10	2.59	0.0161
		Ozone lag012	-0.3621	0.0997	0.70	0.57	0.85	0.0003
25.7	SO_2 + Ozone	SO_2 lag012	0.3868	0.1120	1.47	1.18	1.83	0.0006
		Ozone lag012	-0.3161	0.1003	0.73	0.60	0.89	0.0016
25.8	NO_2 + Ozone	NO_2 lag012	-2.6215	1.2679	0.07	0.01	0.87	0.0387
	+ NO_2*Ozone	Ozone lag012	-3.2210	1.1390	0.04	0.00	0.37	0.0047
		NO_2 lag012* Ozone lag012	-1.7900	0.7120	0.17	0.04	0.67	0.0119

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); NO_2 = nitrogen dioxide.; SO_2 = sulfur dioxide.; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

This ozone and NO_2 interaction was evaluated by analysis of AE-COPD hospital visits according to quartiles of ozone and NO_2 exposures (Table 26). Among the lowest quartile of ozone exposures, AE-COPD hospital visits increased markedly from 16 visits in the lowest NO_2 quartile (Q1) to almost half in the highest NO_2 quartile (Q4). The opposite was observed for the highest quartile of ozone exposures, for which AE-COPD hospital visits decreased from the NO_2 Q1, with 128 visits, to the NO_2 Q4, with 17 visits. Evaluation of NO_2 quartiles reflects a similar pattern of increased hospital visits as ozone exposures increase at low NO_2 exposures (Q1) and decreasing numbers of hospital visits as ozone exposures increase at high NO_2 exposures (Q4).

Table 26. Hospital Visits for AE-COPD according to Quartiles of NO_2 and Ozone

		NO_2 ppb				**Total**
Ozone	**ppb**	Q1 5.964 to ≤ 18.387	Q2 > 18.387 to ≤ 23.872	Q3 > 23.872 to ≤ 29.625	Q4 > 29.625 to 59.048	
Q1	2.00 to ≤ 12.698	16	64	149	217	446
Q2	> 12.698 to ≤ 22.267	87	90	88	135	400
Q3	> 22.267 to ≤ 31.500	112	111	97	72	392
Q4	> 31.500 to 55.292	128	77	86	17	308
Total		343	342	420	441	1546

Note: NO2 = nitrogen dioxide; ppb = parts per billion; Q1 = lowest 25% of values; Q2 = second lowest 25% of values; Q3 = second highest 25% of values; Q4 = highest 25% of values.

Seasonal Effects of Air Pollution Exposures or Temperature at Lag012

In the winter season $PM_{2.5}$was associated with an increased RR for AE-COPD hospital visit at lag012: 1.79 (95%CI: 1.08, 2.96) as shown in Table 27. Similar results in winter were observed for $PM_{2.5}$ models at lag1 and lag2.

There were no effects of CO, $NO_{2,}$ or SO_2 in any season at lag012 (Table 27). Consistent with the year-round results, a reduced RR for AE-COPD hospital visit was associated with ozone concentrations in winter and spring, but there were no effects of ozone in summer or fall.

Average Daily Temperature Effect. Average daily temperature in the winter was associated with an increased RR for AE-COPD hospital visit, unlike the year-round effect for which temperature was associated with a decreased RR for AE-COPD hospital visit. There were no effects of temperature in any other season.

Table 27. Seasonal Effects of Air Pollution Concentrations and Temperature on Hospital Visits for AE-COPD: Univariate Analyses at Lag012

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
$PM_{2.5}$ (lag012)								
Winter	239	n = 561	0.5795	0.258	1.79	1.08	2.96	0.0247
Spring	215	n = 431	0.0622	0.2812	1.06	0.61	1.85	0.8251
Summer	184	n = 264	0.3044	0.3203	1.36	0.72	2.54	0.3420
Fall	182	n = 290	0.4814	0.3112	1.62	0.88	2.98	0.1219
CO (lag012)								
Winter	239	n = 561	0.5513	0.3138	1.74	0.94	3.21	0.0790
Spring	215	n = 431	-0.1250	0.4953	0.88	0.33	2.33	0.8007
Summer	184	n = 264	-0.8967	0.5567	0.41	0.14	1.21	0.1072
Fall	182	n = 290	0.2448	0.5285	1.28	0.45	3.60	0.6432

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Table 27. Continued

	Days	Visits	Beta	SE	RR*	LL*	UL*	*p*
NO_2 (lag012)								
Winter	239	n = 561	0.5530	0.4217	1.74	0.76	3.97	0.1897
Spring	215	n = 431	0.1809	0.3479	1.20	0.61	2.37	0.6031
Summer	184	n = 264	0.2095	0.5916	1.23	0.39	3.93	0.7232
Fall	182	n = 290	0.2472	0.4873	1.28	0.49	3.33	0.6119
SO_2 (lag012)								
Winter	239	n = 561	0.1424	0.2286	1.15	0.74	1.80	0.5332
Spring	215	n = 431	0.4603	0.2599	1.58	0.95	2.64	0.0765
Summer	184	n = 264	0.2257	0.3029	1.25	0.69	2.27	0.4562
Fall	182	n = 290	-0.0899	0.2545	0.91	0.55	1.51	0.7238
Ozone (lag012)								
Winter	239	n = 561	-0.3680	0.1861	0.69	0.48	1.00	0.0480
Spring	215	n = 431	-1.5112	0.4785	0.22	0.09	0.56	0.0016
Summer	184	n = 264	0.6069	0.4975	1.83	0.69	4.86	0.2225
Fall	182	n = 290	0.1065	0.2963	1.11	0.62	1.99	0.7192
Temp 10°F (lag012)								
Winter	239	n = 561	0.1370	0.0490	1.15	1.04	1.26	0.0056
Spring	215	n = 431	-0.0079	0.0043	0.92	0.85	1.01	0.0680
Summer	184	n = 264	-0.1170	0.1200	0.89	0.70	1.12	0.3264
Fall	182	n = 290	-0.0120	0.0530	0.99	0.89	1.10	0.8199

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Multivariable Models in Winter at Lag012

Multivariable models were evaluated for variables that were significant in univariate analysis during the same season: ozone, $PM_{2.5}$, and temperature. There was no effect of ozone at lag012 in winter. Increased RR for AE-COPD hospital visit were associated with both $PM_{2.5}$ (model 25.1) and temperature (model 25.2) at lag012 in the winter (Table 28). Inclusion of temperature with $PM_{2.5}$ resulted in little change in these effects (model 24.3).

Table 28. Effects of Multivariable Models on Hospital Visit for AE-COPD in Winter at Lag012

						95%Wald CI		
Model	Parameters	Exposure	Beta	SE	RR*	LL*	UL*	*p*
28.1	$PM_{2.5}$	$PM_{2.5}$ lag012	0.5795	0.2580	1.79	1.08	2.96	0.0247
28.2	Temp (10^0F)	Temp lag012	0.1370	0.0490	1.15	1.04	1.26	0.0056
28.3	$PM_{2.5}$ +	$PM_{2.5}$ lag012	0.5811	0.2560	1.79	1.08	2.95	0.0232
	Temp (10^0F)	Temp lag012	0.1390	0.0500	1.15	1.04	1.27	0.0053

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter < 2.5 microns; Temp = Temperature; 10°F = effect is for each 10 degrees Fahrenheit.

Summary

SO_2 and ozone were the air pollutants with the most consistent effects on hospital visits for AE-COPD. Increased RRs were present in univariate analyses of SO_2 at all lags, decreased RRs were present in univariate analyses of ozone at all lags, and similar effects were present for SO_2 and ozone when put in the same model at all lags. The effects of both of these air pollutants were sometimes confounded by temperature (both at lag1and lag2, ozone at lag012). Positive correlations with SO_2 were present for NO_2 (r = 0.63), $PM_{2.5}$ (r = 0.55), and CO (r = 0.41.).

NO_2 was associated with increased RRs of AE-COPD hospital visit at all lags. RRs observed for NO_2 were numerically greater than those associated with SO_2. The associations between NO_2 and AE-COPD hospital visit were confounded at lag0 by ozone and temperature and at lag012 by ozone. An interaction between NO_2 and ozone was present at lag012.

$PM_{2.5}$ was not associated with AE-COPD hospital visit in the overall (i.e., non-seasonal) analyses. For CO, increased RR for AE-COPD hospital visit were present in univariate analyses at lag1, lag2, and lag012, but no multivariable models could be constructed with CO. Temperature was the only weather condition with statistically significant effects on RR of AE-COPD hospital visit in univariate analyses. Small reductions in RRs associated with temperature (7% to 9% reduction for each 10^{o}F increase) were present at all lags, and small effects of including temperature were present for SO_2 (lag1, lag2), NO_2 (lag0), and ozone (lag1, lag2, lag012) during the overall study period.

During the winter season, increased RR of AE-COPD hospital visit was associated with $PM_{2.5}$ (lag1, lag2, lag012) and temperature (lag0, lag2, lag012), unlike the lack of effect with $PM_{2.5}$ or the *reductions* in RRs observed with temperature over the whole study period. For CO at lag1 in the winter, the increased RR associated with AE-COPD hospital visit was greater than during all seasons combined.

Ozone's seasonal effects also differed from the reductions in RR of AE-COPD hospital visit that were observed over the whole study period. In the winter, the lag1 and lag012 reductions in association between AE-COPD and ozone were similar to the overall study period, while greater reductions in RR were present in the spring at lag0, lag2, and lag012. A directional change in ozone effect was suggested by *increased* RRs at all lags in the summer and at lag0, lag1, and lag012 in the fall, although these effects were not statistically significant ($p > 0.5$).

Effects of Air Pollution Exposures within Subgroups

Univariate Analyses for Subgroups

The relationships of hospital visits for AE-COPD are presented for each air pollutant exposure in Table 29 through Table 33.

Age. For those 65 years or greater, NO_2 and SO_2 were associated with an increased RR for AE-COPD hospital visit at lag0, and these RRs were greater than in the cohort as a whole. Also for those 65 years or greater, NO_2, SO_2, $PM_{2.5}$, and CO were associated with increased RR for AE-COPD hospital visit at lag012, and these RRs were greater than the effect of these pollutants on the cohort as a whole. In general, the RR observed at lag012 was greater than the RR observed at lag0. Age did not appear to modify the effect of ozone.

Gender. In both male and female subgroups, RRs for AE-COPD hospital visit at lag0 were similar to those of the overall cohort for all pollutants. In males, RRs at lag012 for AE-COPD hospital visit associated with CO and NO_2 were greater than in the cohort as a whole. Gender did not appear to modify the effects of $PM_{2.5}$, SO_2, or ozone at lag012.

Race. In African Americans, RR for AE-COPD hospital visit associated with NO_2 and SO_2 at lag0 and lag012 were similar to those for the cohort as a whole. In Whites RRs for AE-COPD hospital visit associated with NO_2 at lag0 and lag012 were greater than in the cohort as a whole. In the Hispanics or Latino subgroup, RRs for AE-COPD hospital visit associated with SO_2 at lag0 and lag012 were greater than in the cohort as a whole. Race did not appear to modify the effects of $PM_{2.5}$, CO, or ozone at lag0 or lag012.

Residence. In the subgroup of Philadelphia residents, the RR for AE-COPD hospital visit with $PM_{2.5}$ exposures at lag012 was greater than the RR for the overall sample.

Antibiotic Therapy. Among those not receiving antibiotic therapy, $PM_{2.5}$ and NO_2 at lag012 were associated with RRs for AE-COPD hospital visit that were greater than the RRs for the cohort as a whole. Receiving antibiotic therapy did not appear to modify the effects of any air pollutant at lag0 or lag012.

Table 29. Effects of $PM_{2.5}$ Exposures on Daily Hospital Visits for AE-COPD for Subgroups

$PM_{2.5}$	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	95% CI UL*	*p*
Overall	1546	lag0	0.0200	0.1000	1.02	0.83	1.24	0.8819
		lag012	0.1840	0.1302	1.20	0.93	1.55	0.1576
Age								
< 65	880	lag0	-0.1253	0.1353	0.88	0.68	1.15	0.3545
		lag012	-0.0292	0.1727	0.97	0.69	1.36	0.8659
≥ 65	666	lag0	0.2014	0.1559	1.22	0.90	1.66	0.1963
		lag012	0.4659	0.1984	1.59	1.08	2.35	0.0188
Gender								
Male	770	lag0	0.0285	0.1449	1.03	0.77	1.37	0.8441
		lag012	0.2516	0.1449	1.29	0.90	1.85	0.1731
Female	776	lag0	0.0020	0.144	1.00	0.76	1.33	0.9887
		lag012	0.1172	0.1836	1.12	0.78	1.61	0.5231
Race								
African American	995	lag0	-0.0225	0.1271	0.98	0.76	1.25	0.8596
		lag012	0.1872	0.1621	1.21	0.88	1.66	0.2480
White	342	lag0	0.1769	0.2173	1.19	0.78	1.83	0.4157
		lag012	0.1373	0.2769	1.15	0.67	1.97	0.6201
Hispanic	182	lag0	-0.1533	0.3002	0.86	0.48	1.54	0.6094
		lag012	0.2907	0.3825	1.34	0.63	2.83	0.4473
Asian or other	23	lag0	0.4455	0.8396	1.56	0.30	8.09	0.5957
		lag012	0.3113	1.0671	1.37	0.17	11.05	0.7705

Note: $PM_{2.5}$ = particulate matter with mean aerodynamic diameter < 2.5 microns; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

Table29. Continued

$PM_{2.5}$	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	0.0200	0.1000	1.02	0.83	1.24	0.8819
		lag012	0.1840	0.1302	1.20	0.93	1.55	0.1576
Residence[a]								
Philadelphia	1385	lag0	-0.039	0.1078	0.96	0.78	1.19	0.7175
		lag012	0.1053	0.1375	1.11	0.85	1.45	0.4438
Suburbs	105	lag0	0.74	0.3925	2.10	0.97	4.52	0.0594
		lag012	1.3065	0.4969	3.69	1.39	9.78	0.0086
Antibiotics								
Yes	761	lag0	-0.0689	0.1456	0.93	0.70	1.24	0.6358
		lag012	-0.0059	0.1858	0.99	0.69	1.43	0.9747
No	785	lag0	0.0967	0.1434	1.10	0.83	1.46	0.4998
		lag012	0.3678	0.1826	1.44	1.01	2.07	0.0440

Note: $PM_{2.5}$ = = particulate matter with mean aerodynamic diameter < 2.5 microns; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

[a] Excludes 56 visits with residence farther away than the counties bordering Philadelphia.

Table 30. Effects of Carbon Monoxide (CO) Exposures on Daily Hospital Visits for AE-COPD for Subgroups

CO	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	95% CI UL*	*p*
Overall	1546	lag0	0.1300	0.1700	1.14	0.82	1.58	0.4319
		lag012	0.3431	0.1653	1.61	1.07	2.43	0.0380
Age								
< 65	880	lag0	-0.0433	0.2216	0.96	0.62	1.48	0.8452
		lag012	0.2007	0.2799	1.22	0.71	2.12	0.4734
≥ 65	666	lag0	0.3585	0.2519	1.43	0.87	2.34	0.1547
		lag012	0.8371	0.3178	2.31	1.24	4.31	0.0084
Gender								
Male	770	lag0	0.1890	0.2356	1.21	0.76	1.92	0.4225
		lag012	0.7127	0.2965	2.04	1.14	3.65	0.0162
Female	776	lag0	0.0731	0.2349	1.08	0.68	1.70	0.7558
		lag012	0.2411	0.2976	1.27	0.71	2.28	0.7558
Race								
African American	995	lag0	0.0916	0.2073	1.10	0.73	1.65	0.6584
		lag012	0.3546	0.2621	1.43	0.85	2.38	0.1761
White	342	lag0	0.2738	0.3521	1.31	0.66	2.62	0.4369
		lag012	0.6235	0.4452	1.87	0.78	4.46	0.1614
Hispanic	182	lag0	0.0027	0.4908	1.00	0.38	2.62	0.9956
		lag012	0.8626	0.6122	2.37	0.71	7.87	0.1588
Asian or other	23	lag0	0.4315	1.3514	1.54	0.11	21.76	0.7495
		lag012	0.3344	1.7274	1.40	0.05	41.26	0.8465

Note: CO = carbon monoxide; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

Table30. Continued

CO	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	0.1300	0.1700	1.14	0.82	1.58	0.4319
		lag012	0.3431	0.1653	1.61	1.07	2.43	0.0380
Residence[a]								
Philadelphia	1385	lag0	0.2513	0.1749	1.29	0.91	1.81	0.1507
		lag012	0.5714	0.2212	1.77	1.15	2.73	0.0098
Suburbs	105	lag0	-0.4823	0.6478	0.62	0.17	2.20	0.4565
		lag012	0.8152	0.7963	2.26	0.47	10.76	0.3060
Antibiotics								
Yes	761	lag0	0.2407	0.2363	1.27	0.80	2.02	0.3083
		lag012	0.4234	0.2997	1.53	0.85	2.75	0.1578
No	785	lag0	0.0234	0.2342	1.02	0.65	1.62	0.9204
		lag012	0.5280	0.2944	1.70	0.95	3.02	0.0729

Note: CO = Carbon Monoxide; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

[a] Excludes 56 visits with residence farther away than the counties bordering Philadelphia.

Table 31. Effects of Nitrogen Dioxide (NO_2) Exposures on Daily Hospital Visits for AE-COPD for Subgroups

NO_2	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	0.5700	0.1600	1.77	1.29	2.42	0.0004
		lag012	0.8181	0.2044	2.27	1.52	3.38	<.0001
Age								
< 65	880	lag0	0.4000	0.2112	1.49	0.99	2.26	0.0583
		lag012	0.4641	0.2685	1.59	0.94	2.69	0.0838
≥ 65	666	lag0	0.7951	0.2471	2.21	1.36	3.59	0.0013
		lag012	1.2962	0.3150	3.66	1.97	6.78	<.0001
Gender								
Male	770	lag0	0.5469	0.2276	1.73	1.11	2.70	0.0163
		lag012	0.8755	0.2903	2.40	1.36	4.24	0.0026
Female	776	lag0	0.5896	0.2266	1.80	1.16	2.81	0.0093
		lag012	0.7615	0.2266	2.14	1.22	3.76	0.0093
Race								
African American	995	lag0	0.5097	0.1994	1.66	1.13	2.46	0.0106
		lag012	0.7229	0.2538	2.06	1.25	3.39	0.0044
White	342	lag0	0.7943	0.3446	2.21	1.13	4.35	0.0212
		lag012	0.8833	0.4352	2.42	1.03	5.68	0.0424
Hispanic	182	lag0	0.1827	0.4643	1.20	0.48	2.98	0.6940
		lag012	1.024	0.6035	2.78	0.85	9.09	0.0897
Asian or other	23	lag0	2.0417	1.3941	7.70	0.50	118.39	0.1430
		lag012	2.0485	1.7213	7.76	0.27	226.40	0.2340

Note: NO_2 = nitrogen dioxide; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

Table 31. Continued

NO_2	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	0.5700	0.1600	1.77	1.29	2.42	0.0004
		lag012	0.8181	0.2044	2.27	1.52	3.38	<.0001
Residence[a]								
Philadelphia	1385	lag0	0.5444	0.1693	1.72	1.24	2.40	0.0013
		lag012	0.8288	0.2157	2.29	1.50	3.50	0.0001
Suburbs	105	lag0	0.8952	0.6215	2.45	0.72	8.28	0.1497
		lag012	1.2724	0.7886	3.57	0.76	16.75	0.1066
Antibiotics								
Yes	761	lag0	0.6897	0.2300	1.99	1.27	3.13	0.0027
		lag012	0.6823	0.2904	1.98	1.12	3.50	0.0188
No	785	lag0	0.4518	0.2243	1.57	1.01	2.44	0.0439
		lag012	0.9505	0.2877	2.59	1.47	4.55	0.0010

Note: NO_2 = nitrogen dioxide; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

[a] Excludes 56 visits with residence farther away than the counties bordering Philadelphia.

Table 32. Effects of Sulfur Dioxide (SO_2) Exposures on Daily Hospital Visits for AE-COPD for Subgroups

SO_2	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	0.3000	0.0900	1.35	1.14	1.59	0.0006
		lag012	0.5283	0.1044	1.70	1.38	2.08	<.0001
Age								
< 65	880	lag0	0.1630	0.1143	1.18	0.94	1.47	0.1537
		lag012	0.3737	0.1383	1.45	1.11	1.91	0.0069
≥ 65	666	lag0	0.4746	0.1310	1.61	1.24	2.08	0.0003
		lag012	0.7331	0.1591	2.08	1.52	2.84	<.0001
Gender								
Male	770	lag0	0.3373	0.1221	1.40	1.10	1.78	0.0057
		lag012	0.5711	0.1481	1.77	1.32	2.37	0.0001
Female	776	lag0	0.2580	0.1214	1.29	1.02	1.64	0.0336
		lag012	0.4861	0.1471	1.63	1.22	2.17	0.0010
Race								
African American	995	lag0	0.2197	0.1073	1.25	1.01	1.54	0.0405
		lag012	0.5116	0.1299	1.67	1.29	2.15	<.0001
White	342	lag0	0.3167	0.1830	1.37	0.96	1.96	0.0834
		lag012	0.2371	0.2221	1.27	0.82	1.96	0.2858
Hispanic	182	lag0	0.6341	0.2522	1.80	1.15	3.09	0.0119
		lag012	1.1575	0.3073	3.18	1.74	5.81	0.0002
Asian or other	23	lag0	0.7110	0.7034	2.04	0.51	8.08	0.3121
		lag012	0.7834	0.8556	2.19	0.41	11.71	0.3599

Note: SO_2 = sulfur dioxide; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

Table 32. Continued

SO_2	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	0.3000	0.0900	1.35	1.14	1.59	0.0006
		lag012	0.5283	0.1044	1.70	1.38	2.08	<.0001
Residence[a]								
Philadelphia	1385	lag0	0.2998	0.0908	1.35	1.13	1.61	0.001
		lag012	0.5389	0.1101	1.71	1.38	2.13	<.0001
Suburbs	105	lag0	0.3225	0.3286	1.38	0.72	2.63	0.3264
		lag012	0.4849	0.3986	1.62	0.74	3.55	0.2238
Antibiotics								
Yes	761	lag0	0.3801	0.1226	1.46	1.15	1.86	0.0019
		lag012	0.5948	0.1487	1.81	1.35	2.43	<.0001
No	785	lag0	0.2170	0.1210	1.24	0.98	1.57	0.0728
		lag012	0.4639	0.1465	1.59	1.19	2.12	0.0015

Note: SO_2 = sulfur dioxide; AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

[a] Excludes 56 visits with residence farther away than the counties bordering Philadelphia.

Table 33. Effects of Ozone Exposures on Daily Hospital Visits for AE-COPD for Subgroups

Ozone	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	-0.2800	0.0800	0.76	0.65	0.89	0.0006
		lag012	-0.4522	0.0923	0.64	0.53	0.76	<.0001
Age								
< 65	880	lag0	-0.2342	0.1077	0.79	0.64	0.98	0.0296
		lag012	-0.4115	0.1228	0.66	0.52	0.84	0.0008
≥ 65	666	lag0	-0.3337	0.1221	0.72	0.56	0.91	0.0063
		lag012	-0.5056	0.1401	0.60	0.46	0.79	0.0003
Gender								
Male	770	lag0	-0.3567	0.1132	0.70	0.56	0.87	0.0016
		lag012	-0.5440	0.1299	0.58	0.45	0.75	<.0001
Female	776	lag0	-0.1971	0.1152	0.82	0.66	1.03	0.0870
		lag012	-0.3601	0.1312	0.70	0.54	0.90	0.0061
Race								
African American	995	lag0	-0.2802	0.1005	0.76	0.62	0.92	0.0053
		lag012	-0.4545	0.1149	0.63	0.51	0.80	<.0001
White	342	lag0	-0.3181	0.1706	0.73	0.52	1.02	0.0624
		lag012	-0.3804	0.1976	0.68	0.46	1.01	0.0542
Hispanic	182	lag0	-0.1970	0.2402	0.82	0.51	1.31	0.4121
		lag012	-0.5459	0.2691	0.58	0.34	0.98	0.0425
Asian or other	23	lag0	0.3497	0.7299	1.42	0.34	5.93	0.6319
		lag012	-0.4354	0.7581	0.65	0.15	2.86	0.5657

Note: AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

Table 33. Continued

Ozone	No. Adm.	Lag	Beta	SE	RR*	95% CI LL*	UL*	*p*
Overall	1546	lag0	-0.2800	0.0800	0.76	0.65	0.89	0.0006
		lag012	-0.4522	0.0923	0.64	0.53	0.76	<.0001
Residence[a]								
Philadelphia	1385	lag0	-0.2883	0.0851	0.75	0.63	0.89	0.0007
		lag012	-0.4802	0.0972	0.62	0.51	0.75	<.0001
Suburbs	105	lag0	-0.2213	0.311	0.80	0.44	1.47	0.4766
		lag012	-0.2759	0.3583	0.76	0.38	1.53	0.4414
Antibiotics								
Yes	761	lag0	-0.3308	0.1142	0.72	0.57	0.90	0.0038
		lag012	-0.4284	0.1319	0.65	0.50	0.84	0.0012
No	785	lag0	-0.2247	0.1142	0.80	0.64	1.00	0.0491
		lag012	-0.4751	0.1293	0.62	0.48	0.80	0.0002

Note: AE-COPD = acute exacerbation of COPD; No. Adm. = number of visits; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated).

[a] Excludes 56 visits with residence farther away than the counties bordering Philadelphia.

Multivariable Analyses for Subgroups

Multivariable models were evaluated for subgroups. Results are shown for age of 65 years or greater (Table 34), males and females (Table 35), and the presence or absence of antibiotic treatment (Table 36). Among those 65 years or more, there was evidence of confounding of NO_2 and SO_2 by ozone at lag012 and temperature at lag0 and lag012.

Table 34. Effects in Mutivariable Models on Daily Hospital Visits for AE-COPD for those 65 or More Years of Age at Lag0 or Lag012

						95% Wald CI		
Model	Parameters	Exposure	Beta	SE	RR*	LL*	UL*	*p*
34.1	NO_2 + Ozone	NO_2 lag012	1.0198	0.3375	2.77	1.43	5.37	0.0025
		Ozone lag012	-0.3309	0.1519	0.72	0.53	0.97	0.0293
34.2	SO_2 + Ozone	SO_2 lag012	0.5956	0.1724	1.81	1.29	2.54	0.0005
		Ozone lag012	-0.2921	0.1529	0.75	0.55	1.01	0.0561
34.3	NO_2 +	NO_2 lag0	0.5140	0.2573	1.67	1.01	2.77	0.0457
	Temp (10^o F)	Temp lag0	-0.0720	0.0230	0.93	0.89	0.97	0.0015
34.4	NO_2 +	NO_2 lag012	0.9110	0.3414	2.49	1.27	4.86	0.0076
	Temp (10^o F)	Temp lag012	-0.0680	0.0240	0.93	0.89	0.98	0.0047
34.5	SO_2 +	SO_2 lag0	0.3154	0.1426	1.37	1.04	1.81	0.0270
	Temp (10^o F)	Temp lag0	-0.0660	0.0230	0.94	0.89	0.98	0.0048
34.6	SO_2 +	SO_2 lag012	0.5293	0.1826	1.70	1.19	2.43	0.0037
	Temp (10^o F)	Temp lag012	-0.0580	0.0250	0.94	0.90	0.99	0.0230

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; SE = Standard Error; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated); NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp 10^{o}F = 10^{o}F change in temperature.

In the model for SO_2 and ozone, the RR for AE-COPD hospital visit associated with SO_2 for males and females was increased by the same amount as that for the cohort as a whole at lag012 (Table 35). Ozone was associated with a reduced RR for AE-COPD hospital visit among males but not among females at lag012.

Table 35. Effects in Mutivariable Models on Daily Hospital Visits for AE-COPD by Gender at Lag012

Sub-group	Model	Parameter	Beta	SE	RR*	95% Wald CI LL*	UL*	*p*
Male	SO_2 +	SO_2 lag012	0.3866	0.1584	1.47	1.08	2.01	0.0147
	Ozone	Ozone lag012	-0.4068	0.1415	0.67	0.50	0.88	0.0040
Female	SO_2 +	SO_2 lag012	0.3865	0.1584	1.47	1.08	2.01	0.0147
	Ozone	Ozone lag012	-0.2253	0.1422	0.80	0.60	1.05	0.1131

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated); NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp 10°F = 10°F change in temperature.

Among those not receiving antibiotic therapy, there were increased RR for AE-COPD hospital visit associated with NO_2 at lag012, with confounding by ozone or temperature. An increased RR for AE-COPD hospital visit was present for SO_2, with no effect of PM2.5 (Table 36).

Among those receiving antibiotic therapy, there were decreased RRs for AE-COPD hospital visit for ozone or temperature, with no effect of NO_2. SO_2 on RR for AE-COPD hospital visit, while $PM_{2.5}$ was associated with a decreased RR at lag012.

Table 36. Effects in Mutivariable Models on Daily Hospital Visits for AE-COPD for Subgroups according to Antibiotic Therapy at Lag012

Antibiotic	Model	Parameter	Beta	SE	RR*	95% Wald CI LL*	95% Wald CI UL*	*p*
No	NO_2 +	NO_2 lag012	0.6541	0.3074	1.92	1.05	3.51	0.0333
	Ozone	Ozone lag012	-0.3630	0.1398	0.70	0.53	0.91	0.0094
Yes	NO_2 +	NO_2 lag012	0.3931	0.3098	1.48	0.81	2.72	0.2045
	Ozone	Ozone lag012	-0.3610	0.1423	0.70	0.53	0.92	0.0112
No	NO_2 +	NO_2 lag012	0.6505	0.3120	1.92	1.04	3.53	0.0370
	Temp	Temp lag012	-0.0540	0.0220	0.95	0.91	0.99	0.0157
Yes	NO_2 +	NO_2 lag012	0.1124	0.3137	1.12	0.61	2.07	0.7202
	Temp	Temp lag012	-0.1039	0.02300	0.90	0.86	0.94	<.0001
No	$PM_{2.5}$ +	$PM_{2.5}$ lag012	0.1173	0.2089	1.12	0.75	1.69	0.5745
	SO_2	SO_2 lag012	0.4187	0.1671	1.52	1.10	2.11	0.0122
Yes	$PM_{2.5}$ +	$PM_{2.5}$ lag012	-0.4790	0.2139	0.62	0.41	0.94	0.0251
	SO_2	SO_2 lag012	0.7806	0.1706	2.18	1.56	3.05	<.0001

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*Exponentiated beta); LL = lower limit (*exponentiated); UL = upper limit (*exponentiated); NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide; Temp 10°F = 10°F change in temperature.

Summary

In general, effects were larger at lag012 than at lag0. RRs for AE-COPD hospital visit associated with ozone in all subgroups were similar to those associated with ozone in the overall cohort. Among the age group 65 years or older, RR of AE-COPD hospital visit were greater than the RRs for the cohort as a whole at lag0 for NO_2 and SO_2 and at lag012 for all air pollutants except ozone. Males had RRs of AE-COPD hospital visit that were greater than the RR for AE-COPD hospital visit for the cohort as a whole at lag012 for

CO and NO_2. In the Hispanics or Latino subgroup, RRs for AE-COPD hospital visit associated with SO_2 at lag0 and lag012 were greater than in the cohort as a whole.

Sensitivity Analyses

Pearson Scale

Use of the Pearson scale as a check for overdispersion confirmed the suitability of the Poisson model. After changing the scale of the main model (i.e., fixed scale) to the Pearson scale, the statistical significance of results (or lack thereof) was consistent with the models using the fixed scale with an exception in one univariate model. For the effect of SO_2 among African Americans, *P*-values were $P = 0.0405$ for the model with the fixed scale and $P = 0.0533$ for the model with the Pearson scale. Otherwise, *P*-values obtained with use of the Pearson scale were either the same or slightly larger but did not lead to any difference in statistical significance.

There was also one multivariable model in which the Pearson scale resulted in a non-significant effect for a component of the model that was significant with the fixed scale. In the model for ozone and temperature, the fixed scale provided $P = 0.0480$ for ozone, while the Pearson scale provided $P = 0.0636$.

Analysis of First Hospital Visits

The effect of CO was statistically significant among the first hospital visits although not for the overall sample of 1546 visits. Otherwise, significant effects were observed consistently with the overall sample, although the absolute effects were greater for the first visits subgroup (Table 37).

Table 37. Effects of Air Pollution and Temperature on Daily Hospital Visits for AE-COPD among First Visits (n=970) vs. All Visits (n=1546)

				95% Wald CI		
Dataset	Beta	SE	RR*	LL*	UL*	*p*
$PM_{2.5}$ All visits	0.0081	0.1017	1.01	0.83	1.23	0.9368
$PM_{2.5}$ 1^{st} visit	0.0955	0.1290	1.10	0.85	1.42	0.4591
CO All visits	0.1449	0.1655	1.16	0.84	1.60	0.3813
CO 1^{st} visit	0.4401	0.2080	1.55	1.03	2.33	0.0344
NO_2 All visits	0.5793	0.1599	1.78	1.30	2.44	0.0003
NO_2 1^{st} visit	0.7903	0.2046	2.20	1.48	3.29	0.0001
SO_2 All visits	0.2925	0.0857	1.34	1.13	1.58	0.0006
SO_2 1^{st}_visit	0.3792	0.1086	1.46	1.18	1.81	0.0005
Ozone All visits	-0.2788	0.0803	0.76	0.65	0.89	0.0005
Ozone 1^{st} visit	-0.3169	0.1013	0.73	0.60	0.89	0.0018
Temperature (10ºF) All visits	-0.0810	0.0140	0.92	0.90	0.95	<.0001
Temperature (10ºF) 1^{st} visit	-0.1070	0.0180	0.90	0.87	0.93	<.0001

Note: "First" visits were the first visit during the study period, but it was not determined if this was the "first ever" visit. AE-COPD = Acute Exacerbation of COPD; CI = confidence interval; RR = rate ratio (*Exponentiated beta); SE = Standard Error; LL = lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon monoxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

Analysis of Quartile Indicator Variables.

In terms of significance of effects and direction of effects, the results of the analysis of quartile indicators were consistent with the results obtained for lag0 exposures; however, the effect sizes were smaller with the categorical quartile analysis (Table 38).

Table 38. Effects of Air Pollution and Temperature by Lag0 Quartiles and Exposures on Daily Hospital Visits for AE-COPD

				95% Wald CI		
Parameter	Beta	SE	RR*	LL*	UL*	*p*
$PM_{2.5}$	0.0152	0.1021	1.02	0.83	1.24	0.8819
$PM_{2.5}$ Quartile	0.01560	0.0297	1.02	0.96	1.08	0.5980
CO	0.1308	0.1664	1.14	0.82	1.58	0.4319
CO Quartile	0.0450	0.0288	1.05	0.99	1.11	0.1178
NO_2	0.5684	0.1606	1.77	1.29	2.42	0.0004
NO_2 Quartile	0.1197	0.0294	1.13	1.06	1.19	<.0001
SO_2	0.2974	0.0861	1.35	1.14	1.59	0.0006
SO_2	0.0932	0.0299	1.10	1.04	1.16	0.0018
Ozone	-0.2774	0.0807	0.76	0.65	0.89	0.0006
Ozone Q	-0.1073	0.0289	0.90	0.85	0.95	0.0002
Temperature (10°F)	-0.0078	0.0014	0.92	0.90	0.95	<.0001
Temperature quartile	-0.1809	0.0294	0.83	0.79	0.88	<.0001

Note: AE-COPD = Acute Exacerbation of COPD; CI = confidence interval; RR = rate ratio (*Exponentiated beta); SE = standard error; LL = lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide;.

CHAPTER 5
DISCUSSION

Direct associations between hospital visits for AE-COPD at TUH and ambient concentrations of the primary gaseous air pollutants SO_2, NO_2, and CO in Philadelphia were found for the period of this study (January 1, 2005 - March 31, 2007). In addition, a direct association with $PM_{2.5}$ was present in the winter season. The association between AE-COPD hospital visits and ozone was inverse for the overall study period and for winter and spring; in the summer and fall, point estimates suggested direct associations, but these were not statistically significant. Levels of air pollution in Philadelphia were below or close to the NAAQS, indicating that adverse health effects were present while air quality was optimal or near-optimal according to U.S. EPA guidelines.

Results in Context

The results of this study demonstrate associations between an acute respiratory health effect, AE-COPD hospital visits, and ambient air pollution in Philadelphia. In the current study, identification of acute exacerbations requiring a hospital visit ensures that the outcome is well-defined and clinically important. Because an acute exacerbation is distinct from and may hasten disease progression, it is an appropriate outcome for study of short-term effects of air pollution. Previous research evaluated more broadly defined outcomes such as ED visits, hospitalizations, or mortality due to COPD (ICD codes 490 - 496) or due to all respiratory disease. The definition for respiratory disease in these studies included respiratory infections and asthma in addition to COPD (ICD codes 460-519). Lack of consistency among previous studies not only in outcome definitions but also in the exposures that were assessed and the covariates that were include may have contributed to the differences in study results.

Lagged exposure variables were created to allow for a latency period of up to three days. Related atmospheric processes contributing to air pollutant concentrations and consequent correlations among air pollutants were evidenced by positive correlations among PM, CO, NO_2, and SO_2 and by negative correlations between these pollutants and ozone. These relationships among primary air pollutants could also be seen in the limited number of multipollutant models that could be constructed. These models included SO_2 and ozone at lag0, lag1, lag2, lag012, and also NO_2 and ozone at lag0 and lag012. In these multipollutant models, effect sizes and directions were similar to those in single pollutant models, indicating separate and independent effects of SO_2 or NO_2 and ozone. Only one interaction was observed, which was between NO_2 and ozone.

SO_2

Acute effects of SO_2 exposure that could contribute to AE-COPD include increased bronchoconstriction (Lippmann and Ito, 2006), and decreased FEV_1 and FVC (Ackermann-Liebrich et al., 1997). Symptoms of respiratory distress leading to ED visits were directly associated with same-day (lag0) daily average SO_2 concentrations (mean = 1.2 ppm, sd = n.s.) during 2004 - 2007 in Palermo, where traffic is the main year-round source of air pollution (Tramuto, Cusimano, Cerame, Vultaggio, Calamusa, Maida, et al. (2011). There is an additional source of air pollution from ship traffic in the port during the warm season (April through September), when the effect of SO_2 on ED visits for respiratory distress was greater than the year-round effect (Tramuto, et al., 2011).

In the current study, increased AE-COPD hospital visits associated with SO_2 were found in single pollutant models (1.34 to 1.70 increase in hospital visits for each 1 logarithm increase in SO_2) at all lags. In comparison, hospitalizations for COPD were also increased with same-day short-term SO_2 exposure in single pollutant analyses reported from Barcelona at lag0 and lag1, but not lag2 (Sunyer, Antó, Murillo, and Saez, 1991) and Hong Kong at lag0 (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007).

Concentrations of SO_2 in the current study (mean=0.005 ppm, sd = 0.004 ppm) were much lower than those in the Hong Kong (mean = 5.3 ppm, sd = 4.1 ppm) or Barcelona (mean = 20 ppm, sd = 8 ppm) studies. In contrast, there was no association between SO_2 and hospitalization for COPD in Rome at lag0 through lag4, with a mean SO_2 concentration of 3.2 (sd = 2.1) ppm from January 1995 through October 1997 (Fusco, Forastiere, Michelozzi, Spadea, Ostro, Arca, et al., 2001). Fusco et al (2001) discuss differences between Europe and the US in pollutant sources, with ambient air in Rome having a mix of pollutants from long range transport and from local traffic. In Europe, more sulfur-containing diesel fuel was used than in the US, which may have contributed to the higher ambient SO_2 concentrations in Europe.

COPD hospitalizations were increased in a single-pollutant meta-analysis of maximum 1-hour SO_2 concentration in 6 European cities (APHEA, 1977-1992) at an average over lag0 through lag3 but not on the single best lag from 0 to 3 days (Anderson, Spix, Medina, Schouten, Castellsague, Rossi, et al., 1997). In the same study, similar-sized effects of 24-hour SO_2 concentrations were not significant, but both 1-hour and 24-hour SO_2 concentrations were associated with COPD hospitalizations in the warm season (April through September). Individual cities with direct associations between SO_2 and hospitalizations for COPD were Paris and Barcelona at lag0 and Milan at lag2 (Anderson,, et al., 1997). The evidence from the current study indicating an adverse effect of SO_2 air pollution on patients with COPD, is therefore consistent with most of the previous results describing increased COPD hospitalizations associated with SO_2 concentrations.

In the current study's two-pollutant model of SO_2 and ozone, smaller associations were present for SO_2 (range: 1.24 to1.47 increase for each 1 unit increase in SO_2) at all lags. In comparison, a multipollutant model showed direct associations between hospitalizations for COPD and SO_2, ozone, and $PM_{2.5}$ based on the data from Hong Kong

(Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007). The consistency of SO_2 effects in these two multipollutant analyses reinforces the importance of SO_2 air pollution in contributing to adverse effects on patients with COPD.

In the current study there were greater effects of SO_2 for those 65 years and older at lag0 and lag012 than for the cohort as a whole. In contrast, there was no association between SO_2 and COPD hospitalizations among those 65 years and older in Vancouver based on exposure periods from 1- to 7-day average concentrations during 1995-1998 (Yang, Chen, Krewski, Burnett, Shi, and McGrail, 2005). Compared to the current study's SO_2 concentration (mean=0.005 ppm, sd = 0.004 ppm), the lower concentrations in Vancouver (mean= 0.004 ppm, sd = 0.003 ppm; Yang, et al. 2005) may have been too low for an association to be apparent. In the next few years, it will be important to evaluate SO_2 effects at lower concentrations in U.S. locations, following the U.S. EPA's lowering of the SO_2 primary NAAQS in June 2010 (U.S. EPA, 2010a).

In the current study, effect modification was also present as greater effects of SO_2 for Hispanic subjects at lag0 and lag012. There is a lack of published information on the effect of air pollution on COPD-related health outcomes for U.S. patients of Hispanic or Latino ancestry. One paper from the metropolitan Los Angeles area reported CO, NO_2, and PM_{10} effects, but not SO_2 effects, among ethnic subgroups for cardiovascular hospitalizations, but not for respiratory-related hospitalizations (Linn, Szlachcic, Gong, Kinney, Berhane, 2000). In Philadelphia, the majority of the Latino population is of Puerto Rican origin (77%), with the others mainly from Colombia, Venezuela, the Dominican Republic, and Mexico (Congreso de Latinos Unidos, 2011). Diverse country of origin as well as unmeasured variations in environmental exposures, socioeconomic status, tobacco use, and access to health care among patients with Hispanic or Latino ancestry are limitations on interpretation of the current study's finding. In future COPD studies, the country of origin, duration of U.S. residency, and cultural ancestry should be collected to increase the understanding of the relationship between AE-COPD and air pollution in Hispanic or Latino patients.

There were no seasonal effects for SO_2 in the current study. In comparison, greater effects of SO_2 were reported for the cool season in Hong Kong, from October through March (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007). During this time, the Hong Kong climate is mild, and windows are commonly open for ventilation, which increases personal exposure to SO_2 (Ko, et al., 2007). This explanation is consistent with the lack of a seasonal effect for SO_2 in the current study, where Philadelphia winters are colder, requiring central heating, while air conditioning is common in the summer.

NO_2

Associations between AE-COPD hospital visits and NO_2 were found in the current study. Acute effects of NO_2 exposure that could contribute to AE-COPD, include inflammation (Blomberg, Krishna, Kelleday, Söderberg, Ledin, et al.,1997; Blomberg, Krishna, Bocchino, Biscione, Shute, Kelly, et al., 1999) and impaired host-defense leading to increased risk of bacterial or viral infection (Forastiere, Peters, Kelly, and Holgate, 2006). Reduced lung function has been reported among the Swiss participants in the SAPALDIA study (Ackermann-Liebrich et al., 1997) and among COPD subjects exposed to low levels of NO_2 (Morrow et al, 1992 cited in Forastiere, et al., 2006). A direct effect of same-day (lag0) daily average NO_2 concentrations on respiratory distress leading to ED Visits was reported in Palermo with a mean concentration of 20.5 ppm (sd = n.s.; Tramuto, Cusimano, Cerame, Vultaggio, Calamusa, Maida, et al., 2011).

In the current study, single-pollutant associations between overall AE-COPD hospital visits and NO_2 were observed at all lags and were somewhat larger (range: 1.57 to 2.27 increase for each 1 unit increase in NO_2) than those for SO_2. Same-day hospitalizations for COPD were also increased with short-term NO_2 exposure in single pollutant analyses reported from Hong Kong (Ko, Tam, Wong, Chang, Tung, Lai, and

Krewski D, Hui, 2007) and from metropolitan Los Angeles year-round and in the fall season (Linn, Szlachcic, Gong, Kinney, and Berhane, 2000). The NO_2 24-hour average concentrations in Hong Kong (mean = 25.3 sd = 10.8 ppb; Ko, et al., 2007) were similar to the 24 ppb daily average (sd = 8.6 ppm) in the current study, while higher values in the Los Angeles area ranged from 28 ppb in the spring to 41 ppb in fall (Linn,, et al., 2000). In contrast, there was no association between NO_2 and hospitalization for COPD in Rome at lag0 through lag4 with a mean NO_2 concentration of 42.8 ppb (sd = 8.0) from January, 1995, through October, 1997 (Fusco, Forastiere, Michelozzi, Spadea, Ostro, Arca, et al., 2001). As noted above, Fusco et al (2001) discuss differences in pollutant sources between Europe and U.S.

COPD hospitalizations were also increased in a single-pollutant meta-analysis of NO_2 in 6 European cities (APHEA, 1977-1992) at the single best lag (from lag0 through lag3) for both 24-hour and 1-hour exposures and also at an average of the same day and up to three previous days for the 24-hour exposure (Anderson, Spix, Medina, Schouten, Castellsague, Rossi, et al., 1997). London had the highest year-round 24-hr concentration of NO_2 (35.6 ppb, sd = n.s.) and was the only individual city with a direct association between NO_2 and hospitalizations for COPD at lag2. In the same study, both 24-hour and 1-hour NO_2 concentrations were associated with COPD hospitalizations in the warm season from April through September (Anderson, et al., 1997). The evidence from the current study indicating an adverse effect of NO_2 air pollution on patients with COPD is therefore consistent with most of the previous results describing increased COPD hospitalizations associated with NO_2 concentrations.

In the current study's two-pollutant models of NO_2 and ozone, there was a direct association between NO_2 and AE-COPD hospital visits at lag0 and lag012, with inverse associations between ozone and AE-COPD hospital visits. Reflecting the extent of correlation between NO_2 and the other primary gaseous pollutants, no model could be constructed to include NO_2 and SO_2 or NO_2 and CO. In Hong Kong, a multipollutant model also showed no effect of NO_2 when included with SO_2, ozone, and $PM_{2.5}$ (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007).

For those 65 years or older, a greater effect of NO_2 was present than for the cohort as a whole at lag012 in the current study (2.21 increase [lag0] to 3.66 [lag012] per each 1 unit increase in NO_2). As in the current study, associations between NO_2 and increased COPD hospitalizations among those ≥ 65 years were reported in Vancouver, based on exposure periods of one day or from 3- to 7-day average concentrations during 1995-1998 (Yang, Chen, Burnett , Shi, McGrail, 2005). In Helsinki, a direct association between NO_2 and COPD hospitalizations was present at lag0 among those ≥ 65 years, whereas the effect of NO_2 was not observed until lag5 for those 15-64 years of age (Halonen, Lanki, Yli-Tuomi, Kulmal, Tiittanen, and Pekkanen, 2008). Compared to the current study's NO_2 concentration (mean=24 ppb, sd=9 ppb), concentrations were lower in both Vancouver (range across seasons: 15.4 to 19.2 ppm) and Helsinki (median = 15 ppb). The current study's evidence of effect modification among those ≥ 65 years, along with the results observed in Vancouver and Helsinki in similar populations at even lower concentrations, supports the hypothesis of greater susceptibility to NO_2 air pollution among this older age group.

There were no seasonal effects for NO_2 in the current study. In comparison, greater effects of NO_2 were reported for the cool season in Hong Kong, from October through March (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007). During this time, the Hong Kong climate is mild**,** and windows are commonly open for ventilation, which increases personal exposure to NO_2 (Ko, et al., 2007). This explanation is consistent with the lack of a seasonal effect for NO_2 in the current study, where Philadelphia winters are colder, requiring central heating, while air conditioning is common in the summer. Linn, et al. (2000) suggested that similar increases in NO_2 effect during the fall and winter reflected the greater seasonal stagnation of the atmosphere in metropolitan Los Angeles, due to counterbalancing of winds from the ocean and the desert.

In the next few years, it will be important to evaluate NO_2 effects at lower concentrations in U.S. locations, following the U.S. EPA's lowering of the NO_2 primary NAAQS in June 2010 (U.S. EPA, 2010b).

CO

Acute effects of CO exposure that might contribute to AE-COPD include reduced oxygen-carrying capacity and impaired release of oxygen from hemoglobin. A direct association between CO 8-hour maximum concentrations and same-day hospitalization with symptoms of respiratory distress was reported in Palermo over the study period (2004-2007), with greater effects during the warm season, from April through September when the average concentration of CO was 0.892 ppm (sd = n.s.; Tramuto, Cusimano, Cerame, Vultaggio, Calamusa, Maida, et al., 2011).

In the current study, single-pollutant associations between overall AE-COPD hospital visits and CO (range: 1.41 to 1.61 increase for each 1 unit increase in CO) were slightly larger than those for SO_2, but they were observed only at lag1, lag2, or lag012. In contrast, direct associations were reported for CO concentration and COPD hospitalizations in Barcelona, lag not specified, (Sunyer, Antó, Murillo, and Saez, 1991), Rome, at lag4, (Fusco, Forastiere, Michelozzi, Spadea, Ostro, Arca,, et al., 2001), and in the Los Angeles metropolitan area at lag0 year-round, as well as in the fall and winter (Linn, Szlachcic, Gong, Kinney, and Berhane, 2000). However, in an earlier study of all-cause mortality in Philadelphia, there was also no effect at lag0, but there was a lagged effect of CO averaged between lag3 and lag4 (Kelsall, Samet, Zeger, and Xu, 1991). The CO 24-hour average concentrations in Barcelona were much higher than those in the current study (mean = 4.4, sd = 3.0 ppm compared to mean = 0.5 sd = 0.2 ppm); values in the Los Angeles area were higher than those in the current study, ranging from 1.0 ppm in the spring to 2.1 ppm in fall (Linn,, et al., 2000).

CO could not be incorporated into any multipollutant models in the current study, and multipollutant models were not reported for the studies in Barcelona (Sunyer, Antó, Murillo, and Saez, 1991) or Los Angeles (Linn, Szlachcic, Gong, Kinney, and Berhane, 2000). In Rome, only CO (mean = 2.9, sd = 1.0) was associated with COPD hospitalizations in the two-pollutant lag0 model with NO_2 (Fusco, Forastiere, Michelozzi, Spadea, Ostro, Arca,, et al., 2001). In contrast, effects of CO and lagged CO were present in two-pollutant models with TSP, SO_2, and ozone but only lagged CO was retained in additional multipollutant models for Philadelphia all-cause mortality (Kelsall, Samet, Zeger, and Xu, 1997).

In the current study, a greater effect of CO was present among those 65 years or more (2.3 increase in AE-COPD hospital visits for each 1 unit increase in CO at lag012) than among the cohort as a whole. Similarly, direct associations between CO and COPD hospitalizations among those 65 years or more were present in Vancouver, based on 7-day average daily concentrations during 1995-1998 (Yang, Chen, Burnett , Shi, McGrail, 2005), and in Helsinki based on the 8-hour maximum CO concentrations at lag0 and lag2 (Halonen, Lanki, Yli-Tuomi, Kulmala, Tiittanen, and Pekkanen, 2008). CO concentrations were similar between the current study (mean=0.5, sd =0.2 ppm daily average) and the Helsinki study's median of approximately 0.5 ppm (Halonen, et al., 2000), while the mean in Vancouver ranged from 0.56 ppm in the spring to 0.83 ppm in the winter (Yang, et al., 2005). The current study's evidence of effect modification among those $\geq$ 65 years, along with the results observed in Vancouver and Helsinki in similar populations at similar concentrations, supports the hypothesis of greater susceptibility to CO air pollution among this older age group.

Studies that evaluated effects of CO on COPD outcomes are less frequent than for other criteria air pollutants. For example, CO exposure was not analyzed in the Hong Kong data (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007) or in the APHEA meta-analysis of data from 6 European cities (Anderson, Spix, Medina, Schouten, Castellsague, Rossi, et al., 1997). Inclusion of CO in future studies may provide a clearer understanding of its relationship to adverse health effects for COPD patients, especially those 65 years or older.

$PM_{2.5}$

Acute effects of the deposition of inhaled particles on pulmonary epithelium include increases in oxidative stress and existing pulmonary inflammation (MacNee, Donaldson, 2000). In short-term exposure studies, PM produced exacerbation of respiratory symptoms and transient declines in lung function (Pope, Dockery, Spengler, Raizenne, 1991), including decreased FEV_1 and FVC (Ackermann-Liebrich et al., 1997), which are also observed with AE-COPD. In 2004-2007, symptoms of respiratory distress leading to ED visits were directly associated with same-day (lag0) daily average PM_{10} concentrations during 2004-2007 in Palermo (Tramuto, Cusimano, Cerame, Vultaggio, Calamusa, Maida,, et al. (2011). Compared to the coarse portion of inhalable PM (i.e., PM_{10}), fine particles ($PM_{2.5}$), are thought to be more toxic because they reach more deeply in the lungs, are suspended longer, are transported over longer distances, have greater indoors penetration, and are often composed of reactive materials such as nitrate, sulfate, ammonium, acids, or metals (Pope and Dockery, 2006).

In the current study, overall $PM_{2.5}$ concentrations were not associated with AE-COPD hospital visits. As with CO, there is little literature available describing the relationship between $PM_{2.5}$ and COPD hospitalizations in the general adult population. A study of Medicare recipients in 204 U.S. counties showed an overall association between $PM_{2.5}$ and hospitalizations for COPD. However, in regional analyses, the Southeast

Region was the only region where $PM_{2.5}$ was directly associated with increased COPD hospitalizations (Dominici, Peng, Bell, Pham, McDermott, Zeger et al., 2006). There was also no effect of $PM_{2.5}$ on mortality in the New York metropolitan region in the ACS-CPSII study. Lack of variability in regional $PM_{2.5}$ concentrations was suggested as a possible reason for that result (Pope, Thun, Namboodiri, Dockery, Evans, Speizer, et al., 1995). In the current study, daily $PM_{2.5}$ concentrations ranged from 2 to 48 µg/m^3, with mean (sd) of 13 (8) µg/m^3. Seasonal variation ranged from a median (IQR) of 9 (8) µg/m^3 in the spring to 16 (13) µg/m^3 in the summer.

Seasonal and geographic variation in $PM_{2.5}$ composition has been described based on a network of $PM_{2.5}$ speciation monitors in 187 U.S. mainland counties, including Philadelphia and several nearby counties (Bell, Dominici, Ebisu, Zeger, Samet, 2007). The overall highest $PM_{2.5}$ concentrations were observed for the Eastern states and California, with seasonal differences in occurrence of peak levels. In the Eastern states, the highest levels of $PM_{2.5}$ were in the summer as was also observed in the current study. Seven of 52 $PM_{2.5}$ components accounted for at least 1% of the total mass on a yearly or seasonal basis (Bell et al., 2007). Of these, the greatest yearly correlations with $PM_{2.5}$ total mass in the Eastern states were sulfate ($r = 0.84$), ammonium ($r = 0.75$), and organic carbonaceous material (OCM; $r = 0.69$). Analysis of respiratory hospital admissions of Medicare recipients in 119 urban U.S. counties showed no association with total $PM_{2.5,}$ but a small direct association with OCM (1.01% (95% PI, 0.04–1.98%) increase in risk per 1 IQR increase) at lag0. As discussed by the authors, a limitation of that study was the lack of specificity in the respiratory hospitalization outcome. Because there was no further breakdown of respiratory conditions, the association of $PM_{2.5}$ composition with COPD hospitalizations was not described (Peng, Bell, Geyh, McDermott, Zeger, Samet, et al., 2009).

A study of respiratory and cardiovascular (CV) hospitalizations in New York City showed that daily hospital admissions among Medicare recipients were differentially associated with source-apportioned $PM_{2.5}$ (Lall, Ito, and Thurston, 2011). In that study, total $PM_{2.5}$ mass was directly associated with hospitalization for respiratory conditions at lag2, but not at lag0, lag1, or lag3. "Steel-related" $PM_{2.5}$ exposures from routine construction and demolition were directly associated with hospitalizations for respiratory conditions at lag0 and lag3, including asthma (lag0) and pneumonia (lag3), but not for COPD hospitalizations. Traffic-related $PM_{2.5}$ exposures were not associated any respiratory admissions, but traffic-related $PM_{2.5}$ exposures were directly associated with CV hospitalizations. Neither respiratory nor cardiovascular admissions were associated with $PM_{2.5}$ apportioned to other sources such as soil, winter peaks in chlorine, or transported sulfates. Specifically for COPD hospitalizations, there was no association with any of the PM2.5 exposures, despite a total number of admissions and a daily average that were more than twice the values for asthma (Lall, et al. 2011).

A direct association between $PM_{2.5}$ and AE-COPD hospital visits was present in the current study during the winter at lag1, lag2, and lag012 in the single pollutant model. This may be influenced by seasonal variation in the chemical composition of $PM_{2.5}$, which has been shown to affect the association of $PM_{2.5}$ with health outcomes. Non-accidental mortality increased when the chemical composition of $PM_{2.5}$ included aluminum, sulfate, or nickel particles in a study of 25 U.S. counties with PM speciation data for a minimum of 2 years between 2000 and 2005 (Franklin, Koutrakis, and Schwartz, 2008). Seasonal variations in $PM_{2.5}$ concentrations reported for Philadelphia in the Franklin, et al. study (2008) and in the current study were similar, with the highest concentrations in summer, followed by winter, and then similar concentrations in the spring and fall. In winter, Philadelphia had the third highest seasonal concentrations of nickel in the winter and of sulfate in the summer, but concentrations for aluminum were consistent with most of the other counties (Franklin, et al., 1997, Figure 3).

Because the current study's only association between $PM_{2.5}$ and hospital visit for AE-COPD was in the winter, and nickel can produce an inflammatory response in human lung cells (Gao, Barchowsky, Nemec, and Fabisiak, 2004), a specific relationship between nickel-containing particulates and AE-COPD hospital visit should be considered in future research. However, unlike the winter association between total $PM_{2.5}$ mass and AE-COPD hospital visit in the current study, the association of total $PM_{2.5}$ mass with the broader outcome of non-accidental mortality in Philadelphia was present in the spring (Franklin, et al., 2008). Future studies of the effects of $PM_{2.5}$ should consider relevant source apportionment as well as chemical composition in addition to total mass of $PM_{2.5}$.

In the current study, there was a greater $PM_{2.5}$ effect for those $\geq$ 65 years of age (1.6 increase for 1 $\mu g/m^3$ increase in $PM_{2.5}$ at lag012) than for the cohort as a whole. As described above, data used in the large, national study were obtained from Medicare and so were limited to those $\geq$ 65 years of age. Similarly, in Helsinki, direct associations between $PM_{2.5}$ air pollution and COPD hospitalizations were observed for those 65 years or more, but were not observed among adults less than 65 years of age (Halonen, Lanki, Yli-Tuomi, Kulmala, Tiittanen, and Pekkanen, 2008). $PM_{2.5}$ concentrations were greater in the current study (mean=13 $\mu g/m^3$) than in the Helsinki study's median of 7.5 ppm (Halonen,, et al., 2000).

In the current study, there was a greater effect of $PM_{2.5}$ within the subgroup not receiving antibiotics than the overall study or within those not receiving antibiotics. This observation suggests a specific effect of $PM_{2.5}$ on AE-COPD that is separate from an infectious cause.

Ozone

Acute ozone exposure results in adverse effects on the respiratory tract that include diffuse inflammation detected as increases in inflammatory biomarkers almost immediately after exposure. This immediate effect is followed by increases in inflammatory cells beginning within hours of the exposure and lasting for several days (Saldiva, Künzli, Lippmann, 2006). Factors that influence ozone effects on pulmonary function include the ozone concentration, the respiratory minute volume (which increases with exercise), and the duration of exposure. Among subjects with COPD the combined effect of ozone plus exercise resulted in an 18% reduction in FEV_1, which was significantly greater than the 2% reduction observed for those without COPD (*P*-value <0.001, Gong, Shamdoo, Anderson, Linn, 1997). At 3 hours post-exposure, FEV_1 had recovered to just 3% below baseline, and subsequent FEV_1 responses were attenuated (Gong et al., 1997). However, airway reactivity remained increased for more than 24 hours, and it was not attenuated with subsequent exposures (Gong et al., 1997), which suggests a long-lasting effect of ozone exposures. In the AHSMOG study of Seventh Day Adventists in California metropolitan areas, reduction in FEV_1 was associated with increased levels of ozone during the "low ozone" season (Abbey, Hwang, Burchette, Vancuren, and Mills, 1995).

In the current study, there was an unexpected *indirect* association between ozone concentrations (median [IQR] = 22 [19] ppb) and AE-COPD hospital visits during the study period (0.64 to 0.76 *decrease* for each 1 unit increase in ozone) at all lags. In a study of 36 U.S. cities from 1986-1999, ozone concentrations were greater than those in the current study were (means [sd] = 27.6 [6.3] ppb in the cold season and 45.8 [9.2] ppb in the warm season). There was a similar inverse association between COPD hospitalizations and ozone concentrations at lag0, but there was a positive association at lag1, and no association at lag2 (Medina-Ramon, Zanobetti, Schwartz, 2006). Unlike the current study, there was no association between hospitalizations for COPD and ozone concentrations in the Los Angeles metropolitan area with mean concentrations ranging from 14 ppb in winter to 33 ppb in summer (Linn, Szlachcic, Gong, Kinney, Berhane, 2000). No association between hospital admissions for COPD and ozone concentrations (range of means: 10.3 to 22.1 ppb) was observed in a meta-analysis across 7 Canadian cities for varying time periods from 1992-2003 (Stieb, Szyszkowicz, Rowe, Leech, 2009). One of the seven cities, Montreal, was the only one with a city-specific increase in COPD hospital admissions that was directly associated with ozone concentrations (mean [sd] 18.3 [9.5] ppb) from 1997-2002 (Stieb, et al., 2009).

In contrast, increased hospitalizations for COPD were directly associated with daily ozone concentrations in two Hong Kong studies with median 6.3 ppm (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007) and median (11.4 ppm) concentrations that were somewhat lower than those in the current study (Wong, Lau, Yu, Neller, Wong, Tam, Pang, 1999). Direct associations between COPD hospitalizations and the maxiumum1-hour and 8-hour ozone concentrations were also reported in a meta-analysis of 5 (of 6) European cities participating in the APHEA project using the lag with the best association in each city and an average of lag0 with up to 3 additional days (Anderson, Spix, Medina, Schouten, Castellsague, Rossi, et al., 1997). Within these cities, median 8-hour ozone concentrations of 14 ppb in London (lag1), 10 ppb in Paris (lag0), and 28 ppb in Barcelona (lag1) were directly associated with hospitalizations for COPD, but higher concentrations in of 39.5 ppb in Amsterdam and 30.5 ppb in Rotterdam were not (Anderson, et al., 1997).

Inverse effects of ozone in multipollutant models with SO_2 or NO_2 were consistent in size and direction with those observed in the single pollutant models of the current study. In a multipollutant model from Hong Kong, direct associations between hospitalizations for COPD and ozone in combination with SO_2 and $PM_{2.5}$ were consistent with the direct effects observed in those single pollutant analyses (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007). Therefore, ozone effects were independent of the other air pollutants in both the current study and the study by Ko et al. (2007).

In the current study, the overall inverse ozone effects were consistent in direction (i.e., inverse effect) and size across subgroups of age, gender, race, residence, and antibiotic use. Unlike the current study, there was no association between ozone and COPD hospitalizations among those 65 years and older in Vancouver, based on exposure periods from 1- to 7-day average concentrations during 1995-1998 (Yang, Chen, Krewski, Burnett, Shi, and McGrail, 2005). Compared to the current study's ozone concentration (mean=22 ppb, sd = 12 ppb), lower concentrations in Vancouver (mean=14 ppb, sd = 7 ppb year-round; Yang, et al. 2005) may have been too low for an association to be apparent.

The seasonal analysis in the current study showed that associations between AE-COPD hospital visits and ozone concentrations in the winter (lag1, lag012) and spring (lag0, lag2, lag012) were similar in size and direction to the overall inverse effects. However, positive, nonsignificant effects of ozone were present during the summer (RR = 1.15 to 1.96, all lags) and fall (RR = 1.05 to 1.37, lag0, lag1, lag012). A somewhat similar seasonal pattern of ozone was present in the U.S. meta-analysis, with an inverse effect on COPD hospitalizations at lag0, a direct effect at lag1, and a direct cumulative effect (sum of lag0 and lag1 effect estimates) during the warm season. In contrast, COPD hospitalizations decreased with increasing ozone concentrations during the cold season (Medina-Ramon, Zanobetti, Schwartz, 2006). The proportion of city residents with air conditioning had an important effect on the warm season association between COPD hospitalizations and ozone concentrations, with lower effects reported when the proportion with air conditioning was greater in the U.S. meta-analysis. The authors suggested that this observation reflects the low penetrance of ambient ozone into indoor air when ventilation from the outdoors is minimized by closing windows in the winter and, with the presence of air conditioning, in the summer as well (Medina-Ramon, et al., 2006). According to the 2010 U.S. Census, 10.6% of Philadelphia housing units had a one-room air conditioner unit and 94.1% had units in one or more rooms or either central air conditioning (U.S. Census Bureau, 2011).

In the 7-city Canadian meta-analysis, there was no association between ozone and ED visits in the cool season, but in the warm season, the association between ozone and COPD visits was nearly twice as large as the year-round association (Stieb, Szyszkowicz, Rowe, Leech, 2009). As in the current study, the meta-analysis of 5 (of 6) European cities participating in the APHEA project, also reported a direct association between COPD hospitalizations and the maxiumum1-hour and 8-hour ozone concentrations in the warm season, but not in the cool season (Anderson, Spix, Medina, Schouten, Castellsague, Rossi, et al., 1997).

There were no seasonal effects of ozone on COPD hospitalizations in the Los Angeles metropolitan area, consistent with the overall lack of effect in this area (Linn, Szlachcic, Gong, Kinney, Berhane, 2000). In contrast, increased effects of ozone on COPD hospitalizations were observed in Hong Kong in the cold season (December through March). These results may also reflect the limited penetrance of ozone, but in a different season in Hong Kong, where opening windows for ventilation is more common during the mild winter months, while windows are generally closed in favor of air conditioning during the remaining months (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007).

The observation of a negative association with ozone in the winter months is consistent with a paradoxical ozone association (POA) as described by Joseph (2007). This paradoxical association is hypothesized as U-shaped, but the relationship may appear to have a negative slope if levels of ozone range between low and moderate concentrations from, i.e., up to 30 ppb (Joseph, 2007), as in the current study (median [IQR] = 22 [19] ppb). The POA is postulated to reflect the presence of ambient methyl nitrite (MN), a product of the combustion of reformulated gasoline that has had methyl tertiary butyl ether (MTBE) added. MN is a type of alkyl nitrite, and this class of chemicals has been shown to induce inflammation of the respiratory tract, inhibition of antibody responses, and sensitization with repeated inhalation. MN is rapidly destroyed by sunlight, with a half-life of approximately 10-15 minutes. Because of the opposite effects of sunlight, MN would be present at higher levels when ozone levels are lower and could be responsible for the increase in AE-COPD hospital visits observed with low ozone concentrations.

During the current study's data collection period, MTBE was an additive used in the reformulated gasoline that was mandated for use in the Philadelphia region to reduce severe or extreme ozone air pollution. Although it was banned in other states as early as 2000, it had not been banned in Pennsylvania (U.S. EPA, 2007). However, federal subsidies for MTBE production were discontinued in May 2006, and manufacturers removed MTBE from the gasoline supply. The current study's negative association between AE-COPD hospital visits and ozone concentrations may reflect a POA that could be attributed to this unmeasured exposure. The current study may be the first to demonstrate a POA for AE-COPD hospital visits, although studies have previously described the lack of an ozone effect consistent with a POA for outcomes of asthma and cardiovascular events (Linn, Szlachcic, Gong, Kinney, Berhane, 2000; Bhaskaran, Hajat, Haines, Herrett, Wilkinson, Smeeth, 2009).

Temperature

Temperature was associated with AE-COPD hospital visits in the current study. The effects of temperature for the overall study were consistently inverse, very small (0.91 to 0.93 for each 10°F increase in temperature), and takes up little of the variance in models with the air pollutants. Previously reported studies often demonstrated seasonal differences among air pollutants' effects using models that included average daily temperature as a covariate (Linn, Szlachcic, Gong, Kinney, Berhane, 2000; Medina-Ramón, Zanobetti, Schwartz, 2006). Most commonly, the temperature effect was greater in the "warm season," with little to no effect in the cool season. In the current study, seasonal analysis of temperature demonstrated a direct association with hospital visits for AE-COPD in the winter (at lag0, lag1, lag012) and no association between temperature and hospital visits for AE-COPD during any other season at any lag.

In the Philadelphia area, there is a marked seasonal change in temperatures, with the annual average temperature similar to the average temperatures in the spring and fall seasons. Minimum values in the spring and fall differ from winter values by approximately one standard deviation, indicating considerable overlap among these three seasons. The observation of an increase in AE-COPD hospital visits being directly associated with increases in temperature during the winter indicates that the effect observed in winter may be unlikely to be due to colder temperatures. A possible explanation could be an increased likelihood for patients to go outdoors and be exposed to ambient air pollution when the winter temperature is warmer.

Strengths and Limitations

Study Design

This case-only, ecologic study design is appropriate for investigating the effect of an exposure such as ambient air pollution to which all members of the population are exposed. Collection of individual-level covariates enabled stratification on individual-level characteristics in the analysis. Individual level data that were collected include demographic information, residence in Philadelphia or other locations, and prescription of antibiotic therapy, which was used as a surrogate for defining subgroups with or without possible bacterial causes of AE.

The current study's use of the outcome from one city hospital eliminates variation due to differences in patient populations among city hospitals or due to differences in medical diagnostic criteria, geographical location, weather, or air pollution sources. This results in reduced heterogeneity in outcomes and exposures, but a disadvantage may be that the smaller numbers of hospital visits results in practical limits to the complexity of analyses. For example, in comparison to this small study, the complex multilevel, hierarchical analyses conducted by Dominici, Peng, Bell, Pham, McDermott, Zeger, et al. (2006) and Peng, Chang, Bell, McDermott, Zeger, Samet, et al. (2005) were performed with datasets based on more than 100 urban counties with sample sizes of more than 11 million Medicare participants. However, the results of those studies did show heterogeneous effects according to region.

The relevance of the current study's outcomes to the population of Philadelphia is supported by the rates of hospital admissions in Philadelphia. During the study period, TUH was the hospital with the largest number of admissions (n = 65,436; 9.9%) of Philadelphia residents, with 79.8 average daily admissions (Pennsylvania Health Care Cost Containment Council, 2011). Over the period from 2003 through 2009, there was consistency in the percentage of Philadelphia hospital admissions admitted to TUH (range = 9.1% - 10.2%), percentage with respiratory diagnosis (range = 9.9% - 10.9%), and percentage that were age 65 or more years (range = 28.6% - 32.2%).

In addition, vital statistics for Philadelphia during 2005-2007 demonstrated consistency in mortality rates for chronic lower respiratory causes of death, ranging from 2.6% to 3.0% in the 45-64 year age group and from 4.5% to 4.8% for the 65 or more years age group (Philadelphia Department of Health, 2005, 2006, 2007). These data suggest that both morbidity and mortality associated with respiratory conditions have been stable in the Philadelphia patient population over the time period of the study.

AE-COPD Outcome

A strength of the outcome definition is that the hospital discharge diagnosis of AE-COPD was based on diagnosis by a limited number of pulmonologists in the TUH Department of Pulmonary and Critical Care Medicine, which minimizes the potential for misclassification error. A hospital visit is a definite event that can be associated with a specific calendar date, which avoids bias and minimizes variability in the time to event that might occur with a less clearly defined outcome.

The onset of an acute exacerbation occurs in a short timeframe, making this outcome suitable for evaluation of short-term variations in exposure. This is the first study in which AE-COPD was the specific outcome of interest (ICD-9 code 491.21). In comparison, earlier studies reported on broader outcomes defined as COPD (ICD-9 codes 490-492, 496) or respiratory disease (ICD-9 codes 460-519; Appendix D). Use of this more specific outcome may provide a more direct link between potential biological mechanisms of air pollution exposures as causes of the acute exacerbation. In addition, AE-COPD is a clinically important outcome because of the association between AE and progression of COPD.

Exposure

Exposure measurement is a critical issue in assessing health effects associated with ambient air pollution. In this study, ambient air pollution concentrations were obtained from the U.S. EPA’s Air Quality Services data mart, which is a federal repository for data acquired for air monitoring purposes, including those from the Philadelphia Air Monitoring Services department. At the time the data are loaded, a quality control process is applied. The advantage of using these data for the exposure variables is that they are the same data used to monitor air quality in Philadelphia, ensuring that any measurable health effect would be relevant to official indicators of air quality. Limitations in data acquisition included PM_{10} being measured only every six days and irregular $PM_{2.5}$ data availability due to start-up issues at monitoring sites.

Among the five air pollutants that were evaluated, common sources, involvement in the same chemical processes, or both are recognized as causing difficulties in isolating the effect of a single air pollutant in observational studies. In the current study, CO, NO_2, and SO_2 univariate models were directly associated with AE-COPD hospital visits and could not be included in multivariable models, but they were not put into multivariable models due to the correlations with each other (*r*-values from 0.45. to 0.64).

Multiple tests of statistical significance (“multiplicity”) is a related issue, leading to a potential to observe findings due to chance that would be greater than 0.05. Nevertheless, in the current study, most *P*-values were ≤ 0.0001, indicating that the results were not grossly inflated by multiple comparisons. An alternative concept to evaluating single pollutants or combinations of pollutant is the evaluation of the “exposure setting,” recognizing that the mix of exposures may vary and that a mix of exposures may reflect synergy between the individual exposures (Hertz-Piciotto, 1998). Application of this approach in the current study is limited by the single location, although with a larger data set, it might be considered for evaluating seasonal effects.

The time between exposure and onset of effect has been addressed in the current study by evaluating the association between outcome and exposure on the same day (lag0), on previous days (lag1 or lag2), and over exposures averaged from lag0, lag1, and lag2. Use of single day lags has been observed to produce lower effect estimates than use of distributed lags such as the 3-day averaged value (Kelsall, Samet, Zeger, and Xu, 1991). In the current study, variability (i.e., standard deviations) and spread of the distribution (e.g., 10^{th} to 90^{th} percentiles) were reduced with use of the lag012 values. Effects were generally consistent between lag0 and lag012, with somewhat smaller effect sizes for the lag0 measurement. Use of lags has been inconsistent, with some papers reporting lags as long as 6 days or averaged over 5 days (Ko, Tam, Wong, Chang, Tung, Lai, and Hui, 2007), and others using distributed lags determined by fitting the data to the best function (Dominici, Peng, Bell, Pham, McDermott, Zeger, et al., 2006). Application of the same lags to data from various studies might increase understanding of the best approaches for analyzing short-term effects of air pollution exposures.

In the current study, concentrations from all Philadelphia monitors were averaged for a single daily measurement, and there are several ways in which misclassification could be present. Use of 24-hour averages for CO, NO_2, ozone, or SO_2 may under-represent important shorter-term exposures such as the 1-hour or 8-hour maximum by averaging peak concentrations with lower concentrations. For example, ozone formation increases over the daylight hours, with maximal exposures in the late afternoon, while CO and NO_2 may follow the peaks of traffic patterns.

Possible unexamined heterogeneity in ambient air measurements could be present as increased variability in exposure measurements. For example, measurements were not always present from every monitoring station, and concentration measurements may differ among monitoring stations. Future studies could analyze both 24-hour and shorter time periods of exposure, as well as evaluate the variability among monitors, to ensure the best estimates of effects. For example, examination of each monitor's data when there is unusually high daily variability might lead to identification of outlier values that could be excluded.

In addition, the monitors are at fixed locations, while the actual sites (i.e., residence, work site) of exposure vary among patients. Personal exposures may also be affected by proximity of residence to traffic. This affects exposure to particulate matter, which decreases with increased distance from highways. In addition, ozone concentrations may be reduced by traffic-related sources of NO*x* and so increase with distance from highways (U.S. EPA, 2008). The extent of ventilation from the outdoors affects personal exposures to some air pollutants, such as NO_2, SO_2, and ozone, but it does not influence $PM_{2.5}$ exposures due to its ability to penetrate into indoor spaces. Other factors that could affect an individual's personal exposure include duration of commuting and resulting traffic exposure, occupational exposure, time spent indoors, and indoor sources of exposure.

Non-differential sources of variability or use of daily averages instead of more targeted measurements would tend to bias results towards the null. While these limitations have not prevented demonstration of associations in the current study, the associations might be less than those that would be observed with more individualized definitions of exposure variables.

Covariates

The current study is limited by the unavailability of covariates that have been included in other reported results. Stage of disease (GOLD Stage) and pulmonary function test results were available for only half of the visits. A greater response to air pollution exposures could be hypothesized for subjects with more advanced disease, but this could not be evaluated because of the incompleteness of these data.

Smoking status is another variable that is often considered in evaluating the occurrence of respiratory conditions. By adding to the burden of particulate matter, CO, and NO_2 concentrations, smoking may either obscure the effects of air pollution or add to the effects, but this information was unavailable for all of the visits. Although conflicting results have been reported (Kelsall, Samet, Zeger, Xu. 1997; Medina-Ramón, Zanobetti, Schwartz, 2006), socioeconomic status is another potential covariate that might impact response to air pollution but was not available for the current study. These unmeasured sources of variability might tend to bias results towards the null, therefore the current study's observed effects may be considered valid, although possibly lower than a more precise estimate might provide.

Implications

Policy Implication(s)

Following the initial definition of the NAAQS, periodic reviews were required according to the Clean Air Act (U.S.EPA, 2011c). Beginning with an Integrated Science Assessment (ISA) for $PM_{2.5}$ in 2008, the U.S. EPA completed ISAs for NO_2 (2008), SO_2 (2008), CO (2010), and ozone (first external re-review draft, 2011). Revisions to the NAAQS for NO_2 and SO_2 were implemented in 2010 (U.S. EPA, 2010b). In 2011, no revision was recommended for CO, and an ozone recommendation has been delayed until the next scheduled review. The existence of associations between AE-COPD and the low levels of air pollution in the current study highlight the importance of continued monitoring for adverse health effects of these criteria air pollutants. including the air pollutants for which no change was made (i.e., CO and ozone). In the next few years, it will be important to evaluate NO_2 and SO_2 effects at lower concentrations in U.S. locations as well as evaluation of the air pollutants for which no change was introduced (i.e. CO and ozone).

Public Health Implications

The current study supports other findings of adverse health-related effects for COPD patients due to exposures to ambient air pollution at concentrations lower than the regulatory-defined standards that were in place in 2005-2007. The observation of greater effects among COPD patients 65 years of age and older is especially important because the prevalence of COPD increases with age and the proportion of these age groups is increasing in the U.S. Public health measures to reduce the number of AE-COPDs could provide benefits of reduced morbidity and mortality from COPD, along with less impact of COPD on the quality of life and medical expenses.

COPD patients should be aware of actions that could minimize exposure to the identified air pollutants. These might include planning their day’s activities after considering the U.S. EPA's Air Now daily report of air quality (same day and predicted for the next day), understanding the effects of exercise on increasing exposure, using air conditioning on days with high ozone pollution, and minimizing exposures to air pollution in the winter.

Public health organizations could join efforts by governmental and non-governmental organizations to reduce air pollution from traffic or industrial sources of air pollution.

Suggestions for Future Research

The current study should be replicated using all Philadelphia hospitalizations for AE-COPD to provide a more complete estimate of the effects of air pollution on the health of Philadelphians with COPD. If the study period were defined to include data from before and after the change in NAAQS, the results would be useful to understand the impact of these revised standards on AE-COPD. Additional covariates (e.g., smoking status, socioeconomic status, availability of air conditioning) might provide valuable insights into the relationships between air pollution exposures and these covariates. As noted above, the definitions of lags should be standardized and evaluated across studies in order to understand the relative time to effect.

A better understanding of exposures could provide more specific assessments of associations with health effects. The paradoxical ozone effect, along with presence of an air pollutant that competes with ozone, e.g., MN, should be investigated. Characterization of PM according to chemical composition or source of the particles might improve understanding the presence or absence of health effects.

Conclusions

Evaluation of the effect of ambient air pollution on hospital visits for AE-COPD provided evidence that primary gaseous air pollution exposures (SO_2, CO, NO_2) contributed to increased AE-COPD hospital visits among COPD patients at TUH. The effects of SO_2, CO, NO_2, and $PM_{2.5}$ were greater for the subgroup $\geq$ 65 years of age compared to the cohort as a whole. These air pollutants were moderately intercorrelated and are known to share a common source, the incomplete combustion of fossil fuels associated with traffic and manufacturing. There was little evidence of an overall effect from $PM_{2.5}$, for which there are several possible explanations including homogeneous concentrations throughout the study period or a different composition for particulate matter compared to other locations where effect have been reported. An unexpected paradoxical effect of ozone was observed. This observation was consistent with a paradoxical ozone effect described in other research, which may suggest the presence of a competing effect from a gasoline additive (MTBE) or variation between personal exposures and ambient exposures.

In conclusion, the current study provides evidence of adverse effects of low levels of SO_2, CO, and NO_2 air pollution in Philadelphia on AE-COPD hospital visits, with greater effects among those 65 or more years of age, as well as evidence of a paradoxical effect of ozone.

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APPENDIXES

Appendix A. Glossary

μm	Micrometer or micron
$\mu g/m^3$	Microgram per cubic meter
AE	Acute Exacerbation
AE-COPD	Acute Exacerbation of COPD
ATS	American Thoracic Society
BMI	Body-Mass Index
CI	Confidence Interval
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability-Adjusted Life Year
ED	Emergency Department
EPA	Environmental Protection Agency
ER	Emergency Room
ERS	European Respiratory Society
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICD-9	International Classification of Diseases, 9^{th} Revision
IQR	Interquartile range
ISA	Integrated Science Assessment
mAD	Mean Aerodynamic Diameter
mbar	millibar
MPC	Mean Percent Change

Appendix A. Continued

MRR	Mortality Rate Ratio
NAAQS	National Ambient Air Quality Standards
NHANES-III	Third National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NO	Nitric oxide
NO*x*	Nitric oxides
NO_2	Nitrogen dioxide
OCM	Organic Carbonaceous Material
OLD	Obstructive Lung Disease
OR	Odds ratio
ppb	Parts per billion
ppm	Parts per million
PEF	Peak Expiratory Flow
PI	Posterior Interval
PM	Particulate Matter
$PM_{2.5}$	Particulate Matter with mean aerodynamic diameter <2.5 µg; also referred to as "fine particles"
PM_{10}	Particulate matter with mean aerodynamic diameter ≤ 10 µg; also referred to as "coarse particles"
Q3, Q4	Third Quartile, Fourth Quartile
r	Correlation coefficient
RR	Rate Ratio
sd	Standard Deviation
SO2	Sulfur dioxide

Appendix A. Continued

TUH	Temple University Hospital, which is located at 3401 N. Broad Street, Philadelphia, Pennsylvania, 19140
UFP	Ultrafine Particles
VOCs	Volatile organic compounds

Appendix B.

Effects of Air Pollution on Daily Hospital Admissions for AE-COPD at Lags of 0, 1, 2, 012, 7, 14, and 21

				95% Wald CI		
Exposure	Beta	SE	RR*	LL	UL	*P*-value
pm2_5log10_lag0	0.0152	0.1021	1.02	0.83	1.24	0.8819
pm2_5log10_lag1	0.1834	0.1023	1.20	0.98	1.47	0.0731
pm2_5log10_lag2	0.1366	0.1024	1.15	0.94	1.40	0.1823
pm2_5log10_lag012	0.184	0.1302	1.20	0.93	1.55	0.1576
pm2_5log10_lag7	0.0141	0.1031	1.01	0.83	1.24	0.8914
pm2_5log10_lag14	0.0473	0.104	1.05	0.86	1.29	0.6488
pm2_5log10_lag21	-0.1905	0.104	0.83	0.67	1.01	0.0670
colog10_lag0	0.1308	0.1664	1.14	0.82	1.58	0.4319
colog10_lag1	0.3431	0.1653	1.41	1.02	1.95	0.0380
colog10_lag2	0.4078	0.165	1.50	1.09	2.08	0.0135
colog10_lag012	0.4766	0.21	1.61	1.07	2.43	0.0233
colog10_lag7	0.2774	0.1679	1.32	0.95	1.83	0.0986
colog10_lag14	0.3128	0.1689	1.37	0.98	1.90	0.0640
colog10_lag21	-0.1753	0.1717	0.84	0.60	1.17	0.3071
no2log10_lag0	0.5684	0.1606	1.77	1.29	2.42	0.0004
no2log10_lag1	0.4814	0.1601	1.62	1.18	2.21	0.0026
no2log10_lag2	0.4542	0.1599	1.57	1.15	2.15	0.0045
no2log10_lag012	0.8181	0.2044	2.27	1.52	3.38	<.0001
no2log10_lag7	0.7503	0.1633	2.12	1.54	2.92	<.0001
no2log10_lag14	0.4008	0.1617	1.49	1.09	2.05	0.0132
no2log10_lag21	0.212	0.1603	1.24	0.90	1.69	0.1859

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

Appendix B. Continued

				95% Wald CI		
Exposure	Beta	SE	RR*	LL	UL	*P*-value
so2log10_lag0	0.2974	0.0861	1.35	1.14	1.59	0.0006
so2log10_lag1	0.3879	0.086	1.47	1.25	1.74	<.0001
so2log10_lag2	0.3919	0.0861	1.48	1.25	1.75	<.0001
so2log10_lag012	0.5283	0.1044	1.70	1.38	2.08	<.0001
so2log10_lag7	0.4636	0.0866	1.59	1.34	1.88	<.0001
so2log10_lag14	0.4668	0.0873	1.59	1.34	1.89	<.0001
so2log10_lag21	0.2366	0.0879	1.27	1.07	1.51	0.0071
ozonelog10_lag0	-0.2774	0.0807	0.76	0.65	0.89	0.0006
ozonelog10_lag1	-0.3616	0.0798	0.70	0.60	0.81	<.0001
ozonelog10_lag2	-0.3857	0.0795	0.68	0.58	0.79	<.0001
ozonelog10_lag012	-0.4522	0.0923	0.64	0.53	0.76	<.0001
ozonelog10_lag7	-0.2908	0.0815	0.75	0.64	0.88	0.0004
ozonelog10_lag14	-0.323	0.0814	0.72	0.62	0.85	<.0001
ozonelog10_lag21	-0.321	0.0815	0.73	0.62	0.85	<.0001

Note: AE-COPD = acute exacerbation of COPD; CI = confidence interval; RR = rate ratio (*exponentiated Beta coefficient); SE = Standard Error; LL - lower limit (*exponentiated); UL = upper limit (*exponentiated); $PM_{2.5}$ = particulate matter with mean aerodynamic diameter of 2.5 microns; CO = carbon dioxide; NO_2 = nitrogen dioxide; SO_2 = sulfur dioxide.

Appendix C. National Ambient Air Quality Standards (U.S. EPA)

		During Study Period	**Current***
		Primary Standards (for public health use)	**Primary Standards (for public health use)**
Pollutant	**Averaging Time**	**Concentration**	**Concentration**
CO	8-hour	9 ppm (10 mg/m^3) [1]	9 ppm (10 mg/m^3) [1]
	1-hour	35 ppm (40 mg/m^3) [1]	35 ppm (40 mg/m^3) [1]
Lead	---	1.5 µg/m^3 (Quarterly)	0.15 µg/m^3 (Rolling 3-month Average) [2]
NO_2	Annual	0.053 ppm (100 µg/m^3) [3]	53 ppb (100 µg/m^3) [3]
	1-hour	n.d.	100 ppb[4]
PM_{10}	24-hour	150 µg/m^3[5]	150 µg/m^3 [5]
$PM_{2.5}$	Annual	15 µg/m^3[6]	15 µg/m^3[6]
	24-hour	Reduced from 65 to 35 µg/m^3 [7] on December 18, 2006	35 µg/m^3[7]
Ozone	8-hour(	0.08 ppm (1997) [8]	0.075 ppm (100 µg/m^3; 2008) [9]
	1-hour	0.12 ppm [10]	Revoked [10]
SO_2	Annual	0.03 ppm [11](1971)	1971 continued until 1 year after designated for the 2010 standard
	24-hour[1]	0.14 ppm [11] (1971)	1971 continued until 1 year after designated for the 2010 standard
	1-hour	n.d.	75 ppb [12]

* Accessed at http://www.epa.gov/air/criteria.html , on October 22, 2011, when it was also last updated.

Appendix C. Continued

(1) Not to be exceeded more than once per year.

(2)Final rule signed October 15, 2008. The 1978 lead standard (1.5 µg/m^3 as a quarterly average) remains in effect until one year after an area is designated for the 2008 standard, except that in areas designated nonattainment for the 1978 standard, the 1978 standard remains in effect until implementation plans to attain or maintain the 2008 standard are approved.

(3) The official level of the annual NO_2 standard is 0.053 ppm, equal to 53 ppb, which is shown here for the purpose of clearer comparison to the 1-hour standard

(4) To attain this standard, the 3-year average of the 98th percentile of the daily maximum 1-hour average at each monitor within an area must not exceed 100 ppb (effective January 22, 2010).

(5) Not to be exceeded more than once per year on average over 3 years.

(6) To attain this standard, the 3-year average of the weighted annual mean PM2.5 concentrations from single or multiple community-oriented monitors must not exceed 15.0 µg/m^3.

(7) To attain this standard, the 3-year average of the 98th percentile of 24-hour concentrations at each population-oriented monitor within an area must not exceed 35 µg/m^3 (effective December 17, 2006).

(8) To attain this standard, the 3-year average of the fourth-highest daily maximum 8-hour average ozone concentrations measured at each monitor within an area over each year must not exceed 0.075 ppm. (effective May 27, 2008)

(9) (a) To attain this standard, the 3-year average of the fourth-highest daily maximum 8-hour average ozone concentrations measured at each monitor within an area over each year must not exceed 0.08 ppm.

(b) The 1997 standard—and the implementation rules for that standard—will remain in place for implementation purposes as EPA undertakes rulemaking to address the transition from the 1997 ozone standard to the 2008 ozone standard.

(c) EPA is in the process of reconsidering these standards (set in March 2008).

(10) (a) EPA revoked the 1-hour ozone standard in all areas, although some areas have continuing obligations under that standard ("anti-backsliding").

(b) The standard is attained when the expected number of days per calendar year with maximum hourly average concentrations above 0.12 ppm is ≤ 1.

(11) The 1971 sulfur dioxide standards remain in effect until one year after an area is designated for the 2010 standard, except that in areas designated nonattainment for the 1971 standards, the 1971 standards remain in effect until implementation plans to attain or maintain the 2010 standards are approved.

(12) Final rule signed June 2, 2010. To attain this standard, the 3-year average of the 99th percentile of the daily maximum 1-hour average at each monitor within an area must not exceed 75 ppb.

Appendix D. ICD-9 Codes for Respiratory Conditions

Acute respiratory infections (460–466)

- (460) Acute nasopharyngitis (common cold)
- (461) Acute sinusitis
    - (461.0) Sinusitis, acute, maxillary
    - (461.1) Sinusitis, acute, frontal
    - (461.9) Sinusitis, acute, NOS
- (462) Pharyngitis, acute
- (463) Tonsillitis, acute
- (464) Acute laryngitis and tracheitis
    - (464.0) Laryngitis, acute, no obstruction
    - (464.3) Epiglottitis, acute
    - (464.4) Croup
- (465) Acute upper respiratory infections of multiple or unspecified sites
    - (465.9) Upper respiratory infection, acute, NOS
- (466) Acute bronchitis and bronchiolitis
    - (466.0) Bronchitis, acute
        - (466.11) Bronchiolitis, acute, due to RSV

Other diseases of the upper respiratory tract (470–478)

- (470) Deviated nasal septum
- (471) Polyp, nasal cavity
- (472) Chronic pharyngitis and nasopharyngitis
  - (472.0) Rhinitis, chronic
- (473) Chronic sinusitis
  - (473.0) Sinusitis, chronic, maxillary
  - (473.1) Sinusitis, chronic, frontal
  - (473.9) Sinusitis, chronic, NOS
- (474) Chronic disease of tonsils and adenoids
  - (474.1) Hypertrophy of tonsils and adenoids
    - (474.11) Tonsillar hypertrophy alone
  - (474.9) Tonsil/adenoid disease, chronic, unspec.
- (475) Peritonsillar abscess
- (476) Chronic laryngitis and laryngotracheitis
  - (476.0) Laryngitis, chronic
- (477) Allergic rhinitis
  - (477.0) Rhinitis, allergic, due to pollen
  - (477.2) Rhinitis, allergic, due to animal dander
  - (477.9) Rhinitis, allergic, cause unspec.
- (478) Other diseases of upper respiratory tract
  - (478.1) Abscess/ulcer of nose

Pneumonia and influenza (480–488)

- (480) Viral pneumonia
    -
        - (480.31) Pneumonia, SARS associated coronavirus
    - (480.9) Pneumonia, viral, unspec.
- (481) Pneumococcal pneumonia
- (482) Other bacterial pneumonia
    - (482.9) Pneumonia, bacterial, unspec.
- (483) Pneumonia due to other specified organism
    - (483.0) Mycoplasma pneumoniae
- (485) Bronchopneumonia, organism unspecified
- (486) Pneumonia, organism unspecified
- (487) Influenza
    - (487.0) Influenza w/ pneumonia
    - (487.1) Influenza w/ other respiratory manifestations
- (488) Influenza due to identified Avian influenza virus
- (488.1) Influenza due to identified 2009 H1N1 virus

Chronic obstructive pulmonary disease and allied conditions (490–496)

- (490) Bronchitis, not specified as acute or chronic
- (491) Chronic bronchitis
  - (491.21) Obstructive chronic bronchitis; with acute exacerbation*
- (492) Emphysema
  - (492.0) Emphysematous bleb
  - (492.8) Other emphysema
- (493) Asthma
  - (493.0) Extrinsic asthma
  - (493.1) Intrinsic asthma
  - (493.2) Chronic obstructive asthma
- (494) Bronchiectasis
- (495) Extrinsic allergic alveolitis
- (496) Chronic airway obstruction, not elsewhere classified
  - (496.0) COPD, Not Otherwise Specified

Pneumoconioses and other lung diseases due to external agents (500–508)

- (500) Coal workers' pneumoconiosis
- (501) Asbestosis
- (502) Pneumoconiosis due to other silica or silicates
- (503) Pneumoconiosis due to other inorganic dust
- (504) Pneumonopathy due to inhalation of other dust
- (505) Pneumoconiosis, unspecified
- (506) Respiratory conditions due to chemical fumes and vapors
- (507) Pneumonitis due to solids and liquids
- (508) Respiratory conditions due to other and unspecified external agents

  - (508.0) Acute pulmonary manifestations due to radiation
  - (508.1) Chronic and other pulmonary manifestations due to radiation

Other diseases of respiratory system (510–519)

- (510) Empyema
- (511) Pleurisy
  - (511.0) Pleurisy without effusion or current tuberculosis
  - (511.1) Pleurisy with effusion with a bacterial cause other than tuberculosis
  - (511.8) Other specified forms of pleural effusion except tuberculous
    - (511.81) Malignant pleural effusion
    - (511.89) Other specified forms of effusion, except tuberculous
  - (511.9) Pleural effusion, NOS
- (512) Pneumothorax
  - (512.8) Pneumothorax, spontaneous
- (513) Abscess of lung and mediastinum
- (514) Pulmonary congestion and hypostasis
- (515) Postinflammatory pulmonary fibrosis
- (516) Other alveolar and parietoalveolar pneumonopathy
  - (516.3) Idiopathic fibrosing alveolitis
    - Hamman-Rich syndrome
- (517) Lung involvement in conditions classified elsewhere
  - (517.1) Rheumatic pneumonia
  - (517.2) Lung involvement in systemic sclerosis
  - (517.3) Acute chest syndrome
  - (517.8) Lung involvement in other diseases classified elsewhere

- (518) Other diseases of lung
  - (518.0) Atelectasis
  - (518.5) ARDS
    - (518.81) Respiratory failure, acute
- (519) Other diseases of respiratory system
  - (519.2) Mediastinitis

* http://www.icd9data.com/2012/Volume1/460-519/490-496/491/491.21.htm , accessed October 14, 2011