THESIS

FINE PARTICLE SOURCES AND ADVERSE EVENTS IN INFANTS USING HOME CARDIORESPIRATORY MONITORS

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ABSTRACT

FINE PARTICLE SOURCES AND ADVERSE EVENTS IN INFANTS USING HOME CARDIORESPIRATORY MONITORS

Background: Recent research has provided a wealth of knowledge of the contributions of air pollution to adverse cardiovascular and respiratory events in sensitive populations. Source apportionment methods can be used to apportion and identify ambient sources of air pollution, which can then be used to estimate health effects of air pollution sources. Infants are thought to be particularly susceptible to air pollutant sources; however, little research has been conducted. The objective of this study was to examine the associations of ambient source apportioned fine particulate matter with bradycardia (low heart rate) and apnea (cessation of respiration) events in a cohort of infants prescribed home cardiorespiratory monitors.

Methods: We utilized data from 3,629 infants within the Atlanta metropolitan statistical area who used home cardiorespiratory monitors between November 19, 1998 and December 31, 2002. Home monitors were used to record respiratory effort and heart rate to detect bradycardia and apnea events. Chemical mass balance (CMB) and positive matrix factorization (PMF) source apportionment methods for fine particulate matter ($PM_{2.5}$) were used to produce 14 source profiles. Repeated-measures unconditional logistic regression using generalized estimating equations (GEEs) was used to associate

cardiorespiratory events with air pollution sources. A stationary 45-dependent correlation structure was used to account for the correlation of multiple event-days for a patient. The model included age of the infant, the squared age of the infant, average daily temperature, the square of average daily temperature and indicator variables for weekend and federal holiday. Our analysis used a day, day-squared and day-cubed set of variables for the full term/normal birth weight apnea analysis to adjust for time. Cubic splines with seasonal knots for time were used to adjust for long term temporal trends in the remainder of the presented final results for apnea analyses and all of the bradycardia analyses. We performed separate analyses for zero and one-day lags of pollution. We used odds ratios (ORs) and 95% confidence intervals (CI's) as our measure of effect size to describe the odds of an event occurring. ORs from the analysis were calculated for an inter-quartile range (IQR) increase in each of the single pollutant source models. Apnea and bradycardia were evaluated separately.

Results: We observed a pattern of suggestive positive odds ratios, especially in the primary analysis, such as in the woodsmoke source, which were consistent across source apportionment method and lag structure. We observed positive associations in the positive matrix factorization models for the woodsmoke source in the apnea zero-day lag for the primary analysis with an odds ratio of 1.031 (95% CI: 1.001-1.061; IQR: 0.93 $\mu g/m^3$ increase). We also observed positive associations in the positive matrix factorization models for the woodsmoke source in the apnea one-day lag analysis for primary and premature/normal birth weight with an odds ratio of 1.048 (95% CI: 1.017-1.080; IQR: 0.93 $\mu g/m^3$ increase) and 1.041 (95% CI: 1.006-1.077; IQR: 0.93 $\mu g/m^3$

increase), respectively. The results for the full term/normal birth weight strata had stronger odds ratios than for both the primary and premature/low birth weight strata.

Conclusions: Although we did observe wide confidence intervals and some protective odds ratios, we also observed stronger odds ratios in the one-day lag models compared to the zero-day lag models for the apnea events across both source apportionment methods. We observed some suggestive associations between cardiorespiratory events and source apportioned fine particulate matter that contributes to the body of air pollution literature. The access to such a large cohort of infants with the apnea and bradycardia data made this study a contribution to the understanding of the associations between cardiorespiratory events and source apportioned fine particulate matter in infants at high risk for cardiorespiratory events.

TABLE OF CONTENTS

Chapter 1: Introduction

Introduction

Since the occurrence of major air pollution incidents, such as the Meuse Valley incident of 1930 and the Great Smog of London in 1952, air pollution has become an important public health concern (Andersen et al. 2007; Logan 1953; Loomis et al. 1999). Research since then has provided evidence of adverse health effects of air pollution (American Lung Association 2008; Brook et al. 2010; Chow et al. 2006; Pope and Dockery 2006; US-EPA 2009b). Studies using air quality measurements and longitudinal patient follow-up data have further shown associations of ambient air pollution with at-risk populations, such as the elderly, children and infants being exposed to ambient air pollution (Sarnat et al. 2008). More recent research has provided a wealth of knowledge of the contributions to adverse cardiovascular and respiratory events in especially sensitive populations. Premature, low birth weight and neonatal infants have documented adverse events being associated with increased ambient air pollution with the primary associations being with particulate matter (Andersen et al. 2007; Concericao et al. 2001; Dales et al. 2006; Ha et al. 2003; Lin et al. 2004; Loomis et al. 1999; Moore et al. 2008; Pierse et al. 2006; Triche et al. 2006; Woodruff et al. 2006).

Hypotheses are moving toward the idea that specific components of pollution may be positively associated with immune inflammatory responses for which an over-reaction may lead to wheezing and coughing which can then lead to cardiorespiratory events, such as apnea, bradycardia, and dysrhythmia as well as hampering lung growth/development in children, as summarized in Table 1.1 (American Lung Association 2008; Brook et al. 2010; Chow et al. 2006; Firket 1931; Logan 1953; Pope and Dockery 2006). Infants and children are more vulnerable to the effects of air pollution than adults because of a number of factors, such as the following: (1) infants have a higher respiratory rate coupled with a larger lung surface area per kilogram of body weight, (2) approximately 80% of the alveoli in the lungs are formed postnatally and continue to develop through adolescence, and (3) an infant's immune system is not yet fully developed (Kim 2004; Schwartz 2004). It appears that one of the mechanisms by which air pollution, including particulate matter with average aerodynamic diameter less than 10 microns (PM_{10}) and particulate matter with average aerodynamic diameter less than 2.5 microns ($PM_{2.5}$), are having an impact on cardiorespiratory health is by depressing the function and development of epithelial cells, macrophages and respiratory extra-cellular lining fluid in the lungs as described in Fig 1.1 (Gilliland et al. 1999), by increasing blood pressure by instigating acute autonomic imbalance (Brook et al. 2010) and by increasing systemic inflammation (Delfino et al. 2009).

Source apportionment methods are used to apportion and identify ambient concentrations from specific sources by analyzing the chemical composition, size, concentration and co-presence of certain pollutants in sampled air. The concept that differing levels of toxicity may lend itself to the idea that these more toxic particles

would help identify the sources that produced them, thereby driving the focus of research from a wide range of sources toward those most likely to be associated with adverse health events. Researchers may then identify the main sources that lead to these more toxic particles, which contribute to triggering health effects. This would point toward the possibility of more specific control regulations and strategies which could be aimed to address the sources responsible for the majority of the health conditions (Hopke et al. 2005; Hwang and Hopke 2006; Katsouyanni et al. 2001; Kim et al. 2003). Our work here addresses the challenge of which air pollution sources may cause cardiorespiratory events by investigating the association of cardiorespiratory events with source apportioned air pollution.

In this project we used data from 3,629 infants within the Atlanta metropolitan statistical area followed by the Apnea Center of Children's Healthcare of Atlanta at Egleston from November 19, 1998 to December 31, 2002. Patients were prescribed a home monitor for prematurity, gastroesophageal reflux disease, previous apnea events, for having a sibling who suffered from Sudden Infant Death Syndrome (SIDS) or due to an apparent life threatening event. Cardiorespiratory event data (including apnea and bradycardia) were collected by the Apnea Center. A previous investigation of this population reported associations between bradycardia and ozone (OR: 1.049 per 25ppb; 95% CI: 1.021, 1.087) and nitrogen dioxide (OR: 1.025 per 20 ppb; 95% CI: 1.000-1.050) (Peel et al. 2003). The results of the analysis by Peel et al. revealed attenuated odds ratios among the premature/low birth weight group compared to those among the full term and normal birth weight group (Peel et al. 2003). The abnormal development of an immune response, increased respiratory rate (and therefore increased tidal flow) along

with under-developed anatomy and physiology was thought to contribute to a lack of association between ambient air pollutants and cardiorespiratory events in preterm infants in the previous investigation (Peel et al. 2003).

Temperature, chemical composition, gaseous pollutants and particle size fractions were measured by the Study of Particles and Health in Atlanta (SOPHIA) project at the Aerosol Research and Inhalation Epidemiology Study (ARIES) monitoring station in downtown Atlanta. Measurements included ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, volatile organic carbon, elemental carbon, organic carbon, water-soluble transition metals, PM_{10} and $PM_{2.5}$ (Sarnat et al. 2008). Investigators from Georgia Tech have performed two methods of source apportionment, chemical mass balance (CMB) and positive matrix factorization method (PMF), which were used for this project (Marmur et al. 2007; Sarnat et al. 2008). The sources resulting from the chemical mass balance and positive matrix factorization methods include mobile sources (both gasoline and diesel), biomass burning or woodsmoke, soil, sulfate rich secondary aerosols, and nitrate-rich secondary aerosols (Marmur et al. 2007). In this investigation, we evaluated the association of sources of $PM_{2.5}$ with the cardiorespiratory events (apnea and bradycardia) among infants using home monitors. Repeated-measures unconditional logistic regression was utilized to account for potential autocorrelation of the outcome within subject. The analysis was performed using these methods because the data are longitudinal in nature, and the events being measured represent dichotomous, repeated-measurements on each subject. Additionally, generalized estimating equations (GEEs) were utilized as multivariate generalization of quasi likelihood using observed variability to generate usable standard errors (Agresti 2002; Sarnat et al. 2008).

Statement of Problem

The development of the cardiorespiratory system has been shown to be sensitive to increased levels of air pollution (American Lung Association 2008). It is possible that both the immune development and the anatomy/physiology unique to infants at risk of apnea and bradycardia leave this population at increased risk to the effects of ambient air pollution. Research by a group at Emory University has shown that infants on home cardiorespiratory monitors appear to have adverse health events associated with $PM_{2.5}$ components (Peel et al. 2003). Their analysis further showed interesting differences in odds ratios, in that the analysis of the data on full term and normal birth weight infants revealed stronger associations with air pollution than that for premature/low birth weight infants. The investigators theorized that this may be due to the underdevelopment of an immune response of the premature infants (Peel et al.2003). In this project, we further examine this population by evaluating associations between sources of fine particulate matter and cardiorespiratory events in the population of premature infants.

Specific Aims

We examined associations of fine particulate matter sources with apnea and bradycardia events in infants using home respiratory monitors. Based on the source profiles of particulate matter in Atlanta and previous research (Andersen et al. 2007; Bates 1995; Pierse et al. 2006; Sarnat et al. 2008; Triche et al. 2006), as well as published work on this population (Peel et al. 2003), we hypothesized that apnea and bradycardia events were positively associated with air pollution sources.

In analysis of both apnea and bradycardia events our sub-aims were to examine the particulate matter source associations with apnea and bradycardia events in full term

infants compared to the premature infants. This aim is justified based on prior analysis done on this population (Peel et al. 2003). The hypothesis driving these sub-aims is the research by Peel et al. showing evidence that suggests that normal/full term infants were more sensitive to pollutants than were the premature infants. Here we expected to observe similar associations between apnea and bradycardia with fine particulate matter sources among premature infants represented by lower odds ratios, thereby both supporting the hypothesis that the under-developed respiratory system of the premature infant lacks appropriate immune responses and shedding more light on the differences and similarities of how normal/full term infant and premature/low birth weight infants respond to ambient air pollutant sources.

1. Specific Aim 1: Examine the association of fine particulate matter sources with apnea events in infants using home monitors.
    a. Sub-Aim: Examine particulate matter associations with apnea in full term/ normal birth weight infants compared to the premature/low birth weight infants.
2. Specific Aim 2: Examine the association of fine particulate matter sources with bradycardia events in infants using home monitors.
    a. Sub-Aim: Examine particulate matter associations with bradycardia in full term/ normal birth weight infants compared to the premature/low birth weight infants.

Table 1.1: Acute and Chronic effects of ambient air pollution on children's health; adapted from Gilliland et al. (1999).

Acute Effects	*Chronic Effects (putative)*
Increased respiratory symptoms	Impaired functional lung growth
Increased respiratory illness	Earlier onset and increased rate of decline in lung function with aging
Asthma exacerbations	Increased lifetime risk for chronic respiratory diseases including chronic obstructive pulmonary disease, asthma and lung cancer
Increased health care utilization	Altered lung structure including metaplasia of the respiratory epithelium in respiratory bronchioles, mononuclear peribronchiolar inflammation, localized deposition and alteration in collagen, and remodeling of the peribronchiolar airspace.
Excess cardiorespiratory mortality	
Respiratory tract inflammation	
Increased airway reactivity	
Altered host defenses including oxidant defenses, mucociliary clearance, macrophage function, and immune response	

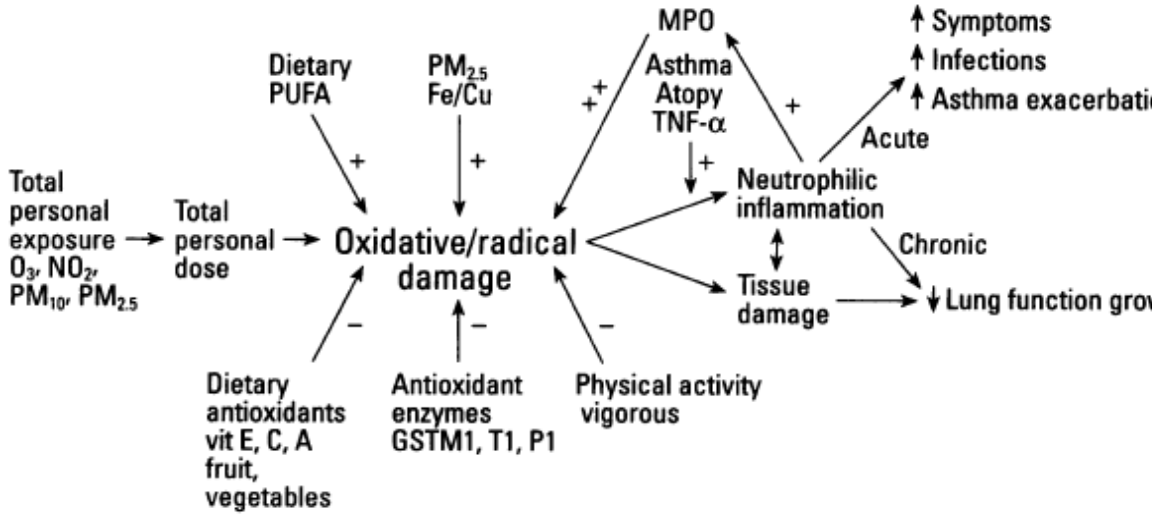

Fig 1.1 Biologic impact pathways of ozone, nitrogen dioxide, particulates on acute and chronic respiratory effects ands susceptibility factors. Cu, copper; F, iron; GST, glutathione S-transferase (M1 T1 polymorphic); MPO, myeloperoxidase (polumorphic); PA, physical activity; PUFA, polyunsaturated fatty acids; TNF-alpha, tumor necrosis facto alpha; vit E,C, A, vitamins E, C, A. Adapted from Gilliland et al (1999)

Chapter 2: Background and Literature Review

Clean Air Act, US-EPA and Air Pollution

The Clean Air Act is a federal law that covers the United States (Peel et al. 2003; US-EPA 2007). The United States Environmental Protection Agency sets the allowable limits on certain types of air pollutants that can be in ambient air. Through the Clean Air Act, the agency also has the authority to limit the emissions from chemical plants, utilities and steel mills sources (US-EPA 2007). The Clean Air Act was born from the Air Pollution Control Act of 1955, which was the first federal legislation involving air pollution, and provided funds for federal research in pollution (US-EPA 2007, 2008c). The Clean Air Act of 1963 became the nation's first federal legislation on the control of air pollution and a federal program within the U.S. Public Health Service (US-EPA 2008b). Four years later, in 1967, the Air Quality Act was put in place to expand the federal government's activities in enforcement proceedings in regions subject to interstate air pollution transport, studies of air pollutant emission inventories, ambient monitoring techniques, control techniques, and for the first time extensive ambient monitoring studies and stationary source w (US-EPA 2008b, c).

The Clean Air Act of 1970 authorized the development of comprehensive federal and state regulations limiting industrial and mobile sources. From the 1970 Clean Air Act, the National Ambient Air Quality Standards (NAAQS), State Implementation Plans, National Emission Standards for Hazardous Air Pollutants and New Source Performance

Standards became the major regulatory programs for stationary sources. The US-EPA was then created in 1971 to implement the requirements mandated by the Clean Air Act of 1970 (US-EPA 2008c). The creation of the Air Pollution Control Act of 1955, the Air Quality Act of 1967, the Clean Air Acts of 1963 and 1970, and the amendments that followed, which resulted in the creation of the US-EPA, came out of the global concern that air pollution was affecting public health and the environment. Major examples of air pollution events include the 63 deaths and thousands sick, which were recorded in the Meuse Valley Fog of 1930 (Firket 1931) and the Great London Smog of 1952 in which more than 3,000 deaths were recorded (Logan 1953). Domestically, the health implications of air pollution were also demonstrated within the United States in the Donora, Pennsylvania incident of 1948 where 20 deaths with upwards of 6,000 illnesses were recorded (Schrenk et al. 1949).

Of great interest to health research is the effect of fine particulate matter ($PM_{2.5}$) air pollution. Fine particulate matter, one of the six ambient criteria air pollutants regulated by the EPA, is a mixture of liquid and solid particles that can vary in solubility, chemical composition, shape, size, and origin. Particulate matter is characterized by size distribution of: coarse PM ($PM_{2.5\text{-}10\ \mu m}$), fine PM ($PM_{< 2.5\ \mu m}$) and ultrafine particles ($PM_{< 100\ nm}$) (Brook et al. 2010; Canada 2004; Dockery and Pope 1994; Künzli and Tager 2005; Osunsanya et al. 2001; Pope et al. 2002; Pope and Dockery 2006; Pope 2000; Seaton et al. 1995; Seaton et al. 1999). Particulate matter is produced in two primary ways depending upon the size. The coarse particles are created from the residual of the mechanical breakdown of larger particles, and the smaller particles are formed from gases and nucleation from condensation, combustion reactions and chemical reactions

forming new particles in the atmosphere (Brunekreef and Holgate 2002). Research studies from around the world reviewing the health effects of air pollution and the cardiovascular and respiratory effects of particulate matter have built a body of knowledge documenting the adverse health effects of ambient particulate matter in general populations (Brook et al. 2010; Brunekreef and Holgate 2002; Canada 2004; Dockery and Pope 1994; Künzli and Tager 2005; Nel 2005; Osunsanya et al. 2001; Pope et al. 2002; Pope and Dockery 2006; Pope 2000; Seaton et al. 1995; Seaton et al. 1999). These and many other studies may be given credit for the ongoing revisions of the US-EPA's NAAQS limiting the amount of each criteria pollutant (Table 2.1).

An important component of ambient pollution is fine particulate matter, $PM_{2.5}$. Fine particulate matter is a heterogeneous mixture of many components from various sources (Cherrie 2002). Fine PM is of particular concern as compared to larger size fractions because of its ability to penetrate deep into the respiratory and the circulatory system and deposit into the blood stream and potentially reach the cardiac system (Seaton et al. 1999). As these fine particles are released into the air and interact with the atmosphere, the amount of fine particulate matter can be measured. Source apportionment addresses where these different components of particulate matter are coming from. For example, particles containing relatively high amounts of arsenic and selenium may be more likely to have come from coal combustion, whereas nickel and vanadium may be due to oil combustion (Grahame and Hidy 2004). To study appropriately the health effects of particulate matter it is vital that we understand this make up since the agents it contains (e.g., nickel, arsenic, selenium, aluminum, nitrates, sulfates, etc.) may have differing toxicity levels. More recent research has begun to

address the effect of fine particulate matter on public health. Research studies have shown positive associations between visits to emergency rooms for upper respiratory infections (URI) and PM_{10}, nitrogen dioxide, ozone and carbon monoxide among infants and children (National Research Council 2004; Peel et al. 2005).

Whose health is most affected by particulate matter appears to be dependent upon the health end point evaluated and levels and lengths of exposures. In the case of acute exposures to moderately elevated particulate matter, in their review of the over 100 published research articles since the early 1990's, Pope and Dockery concluded that persons with influenza, asthma and chronic cardiopulmonary disease are most susceptible, with the elderly and the very young being most at risk (Dockery and Pope 1994; Pope and Dockery 2006). The progression of air pollution research has led to studying the associations of adverse health effects in these high risk populations (Atkinson and Lewis 1974; Dockery et al. 1993; Harley et al. 1989; Schauer et al. 1996).

Source Apportionment

Source Apportionment - Introduction

The number of mathematical models to apportion the aerosols that receptor measures at a site to its sources are numerous. Over the past 30 years receptor-based models have seen substantial development (Henry et al. 1984). Source apportionment can be applied to existing samples from air quality compliance networks; however, it has been documented that compliance monitoring sites may not provide the contrast needed between varying times of day and proximity to suspected contributors (Watson et al. 2002). Watson et al. in 2002 outlined eight generally accepted steps in conducting a

source apportionment study: (1) formulate conceptual model, (2) compile emissions inventory, (3) characterize source emissions, (4) analyze ambient samples for mass, elements, ions, carbon, and other components from sources, (5) confirm source types with multivariate model, (6) quantify source contribution, (7) estimate profile changes and limiting precursors, and (8) reconcile source contributions with other data analysis and source models (Watson et al. 2002).

The estimation of emissions from air pollution sources is often supported by emissions factors, which are values that attempt to represent the amount of a pollutant in the atmosphere to an activity associated with the pollutant's release (US-EPA 2009a). Emissions factors are published by the US-EPA in the AP-42 Emissions Factors for use in formulating national inventories; however, these may be of limited use for specific air-sheds. Hence, locally obtained emissions factors should be utilized wherever possible (Watson et al. 2002).

Source apportionment methods have gained in utility and advancement in recent times. To better investigate the association between health outcomes and sources of pollutants, epidemiological studies are making use of source apportionment models and are now beginning to increase in frequency. The two methods we utilize in our study, which we will now describe, are chemical mass balance and positive matrix factorization methods.

Chemical Mass Balance

In chemical mass balance (CMB) modeling and analysis, ambient chemical concentrations are expressed as the sum of products of species abundances and source

contributions. These equations are solved for the source contributions when ambient concentrations and source profiles are supplied as input. Several methods for solving these equations have been applied; however, the effective variance least squares estimation method is most commonly used because it incorporates precision estimates for all of the input data into the solution and propagates these errors to the model outputs (Watson et al. 2002).

The chemical mass balance equations have been used to apportion observed pollutant concentrations to their various pollution sources. The model is based on the principle of conservation of mass; the amount of a chemical species observed in ambient air is a sum of the pollutant contributions released from a finite number of pollution sources in the region (Miller et al. 1972; Winchester and Nifong 1971). Hence, the mass concentration of the i^{th} species (y_i) is a linear combination of contributions from k pollution sources:

$$y_i = \sum_{j=1}^{k} x_{ij} * B_j + e_i;$$

where i = 1, …, p, B_j is the mass contribution of source j to the atmosphere at the receptor, e_i is the measurement error at the receptor for the i^{th} species and $x_{(j)} = (x_{1j}, \ldots, x_{pj})'$, j = 1, …, k, represents the composition or "profile" of the j^{th} source (Christensen and Gunst 2004; Hopke 1991; Watson et al. 2002).

The chemical mass balance model is utilized with respect to the assumptions that (1) source emission compositions are constant over time, chemical species do not react with each other (they add linearly), (3) all influential sources are speciated, (4) source compositions are linearly independent, (5) the number of sources does not exceed the

number of chemical species and (6) measurement uncertainties are random, uncorrelated and normally distributed (Christensen and Gunst 2004; Henry et al. 1984; Watson et al. 2002). These assumptions are essentially addressing the issue of analysis simplicity; that is, that modeling emissions which do not change, species are not reacting (they add linearly), we have all the species, the sources have the possibility to be assigned a 'unique signature' and the residual-errors not be correlated with one another. Of particular concern can be the violations of assumptions which researchers should be keeping an eye out for:

> Assumption One: Constant source compositions – this assumption tends to be violated simply due to the heterogeneity of operating conditions. It is quite obvious that source compositions may vary somewhat depending upon operational, environmental and atmospheric factors; however, the mathematics used for this type of analysis is complex and continues to improve to account for these variations (Watson et al. 2002).
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> Assumption Four and Assumption Six: Correlation of source compositions, non-zero measurement error correlations and non-zero correlations within a profile across species and within species across profiles. The violations of these assumptions challenge epidemiologists attempting to elucidate the associations between health endpoints and pollutant sources as problems of collinearity arise in source apportionment research. Careful and knowledgeable decision-making during analysis by the investigator is the primary defense for this challenge (Watson et al. 2002).

Hildemann (2002) summarizes chemical mass balance by pointing out that chemical mass balance must have complete emissions composition information for each source and cannot operate with missing sources or missing data (Hildemann 2002). Chemical mass balance can analyze single receptor samples and can identify specific, well-known sources. Although in using chemical mass balance, researchers must recognize that chemical mass balance cannot resolve collinear sources and learn to spot problems in model output such as missing sources (Christensen and Gunst 2004).

Positive Matrix Factorization

Positive matrix factorization (PMF) has been applied to a wide range of data (Engel-Cox and Weber 2007; Hopke et al. 2005; Hwang and Hopke 2006; Kim et al. 2004; Reff et al. 2007; Thurston et al. 2005). The goal of a multivariate receptor model, such as the positive matrix factorization method, is to identify a number of factors and specie profiles for each source and the amount of mass contributed by each factor to each individual sample. Positive matrix factorization is a multivariate factor analysis tool that is used to decompose a matrix of speciated sample data into two matrices. These two matrices have to then be interpreted as to which source types are represented using measured source profile information. A speciated data set is viewed as a data matrix. The results are constrained so that no sample can have a negative source contribution – each of the data points are individually weighted. Similar to chemical mass balance, a mass balance equation can be written to account for the species in the samples as contributions from independent sources (Hildemann 2002; Hopke 2000).

Just as in the case of the chemical mass balance method, positive matrix factorization method has assumptions of its own: (1) the original data must be reproduced

by the model, (2) the predicted source compositions must be non-negative, (3) predicted source contributions to the aerosol must all be non-negative and (4) the sum of the predicted elemental mass contributions for each source must be less than or equal to total measured mass for each element (Hopke 2000). These constraints essentially address that the model needs to replicate the actual observed data, which would never apply a negative value to a measurement or percentage and the model should not predict mass that exceeds total mass.

A disadvantage of the least squares approach in the positive matrix factorization method is that it can yield multiple solutions depending on the initial starting point. Hence, it is usually advised to perform the analysis several times to be certain that there is replication in the solution (Hopke 2000; Reff et al. 2007; US-EPA 2008a). Although collinearity is still an issue, the added conveniences of the positive matrix factorization method are that it does not require source compositions as inputs, accounts for uncertainties in the input measurements and can handle missing and below detection limit input data (Hildemann 2002; Hopke 2000; US-EPA 2008a). The positive matrix factorization method side steps the problem presented in standard principle component analysis (PCA) of distorted scaling, or non-optimal scaling from column/row scaling (Hopke 2000).

Comparison of Chemical Mass Balance and Positive Matrix Factorization

Receptor models are tools based on the same scientific principles as source models that are explanatory rather than predictive of source contributions. The utility of

chemical mass balance has been well established and widely used to develop pollution control strategies (Watson et al. 2002). Both source apportionment models, chemical mass balance and positive matrix factorization methods, have similar aims and provide quantitative estimates of the source contributions. Also, each method utilizes least squares fitting; however, they have different essential mechanisms and methods for how error structures are modeled (Engel-Cox and Weber 2007; Hildemann 2002; US-EPA 2008a).

With chemical mass balance, source profiles must be provided by the analyst. The model then uses this information to apportion mass. Chemical mass balance also allows for the assignment of error estimates to each source contribution value. The positive matrix factorization model estimates the source profiles and may utilize source profiles (if they are known) to decrease the rotational indeterminacy. A limitation of the positive matrix factorization method is that one cannot assign errors to the source profile or contributions (Kim et al. 2003; US-EPA 2008a), and it also uses estimates of the average source profiles over the time period of sample collection.

Chemical mass balance and positive matrix factorization methods have already been applied to epidemiological studies in the Atlanta air-shed where our sample of infants resides (Sarnat et al. 2008). Additionally, work has been done on source identification of Atlanta aerosol (Kim et al. 2003), as well as on improving the source identification of Atlanta aerosol (Kim et al. 2004).

Infant Physiology and Growth

Premature and Low Birth Weight Infants

The development of the fetus is an important aspect of how an infant's body and organs respond to the environment around them after birth (Kenner and McGrath 2004) . Disruption of the delicate developmental process, such as premature and/or low weight at birth, can greatly and adversely affect an infant's ability to survive (Kenner and McGrath 2004). The National Center for Health Statistics Division of the Centers for Disease Control and Prevention observed that, from data on births in 2007, premature and low birth weight births held steady at 12.7% from 2006 estimates of 12.8% (Martin et al. 2010). During the period of our study, the 2002 final birth report indicated two primary population-level predictors of infant health whose indices rose 1 - 2 % from 2001 (Martin et al. 2010): (1) percent of births born premature (under 37 completed weeks of gestation) and (2) the percent of births born low birth weight (under 2,500 grams). Increases in premature and low birth weight rates of 3% and 1%, respectively, were noted between 2000 and 2001. Figure 2.1 by Kochaneck and Martin (2005) show that since 1990 premature and low birth weight rates have risen steadily. Moderately premature (32-36 weeks of gestation) and moderately low birth weight (1,500-2,499 grams) infants appear to account for the main portion of the increase. From 1990 to 2002, the moderately premature rate rose from 8.7% to 10.1% and the moderately low birth weight rate increased from 5.7% to 6.4%, while the rate for very premature (under 32 gestational weeks) rose from 1.92% to 1.96% and the very low birth weight (less than 1,500 grams) from 1.27% to 1.46%. There appears to be evidence of increased risk of early death

associated with the low the birth weight or gestational classification (Mathews et al. 2003).

A number of documented health consequences have been associated with premature and low birth weight infants. The designation of being premature means that the infant has not fully developed and thus is at a higher risk than full term infants for a suite of health challenges including hearing and vision problems, longer-term motor, cognitive, behavioral, social issues and gastrointestinal, immunologic, and acute respiratory and growth problems (Behrman and Butler 2007; Moster et al. 2008). Similarly, low birth weight infants tend to experience more challenges with health issues, such as respiratory distress syndrome, retinopathy, underdeveloped lungs and, heart problems, immature liver growth anemia or polycythemia or regulating and maintaining a normal body temperature (Stevens 2002).

Cardiovascular and Respiratory Development

At approximately the 27th through 29th days, the chambers of the heart can be filled with blood cells and plasma (Kenner and McGrath 2004) . During the sixth through eighth weeks post-fertilization, the embryo will begin to develop pharyngeal arches, which will develop into the maxillary and mandibular prominences. At the same time the esophagus will continue to grow and the flow of blood through the atrioventricular canal will begin to divide into a left and a right stream (Kenner and McGrath 2004) . During this period of time, the heart will grow, better defining the ventricles. The heart will show signs of dividing into its four chambers at approximately 41 days (postovulation) (Jirasek 2004; Kenner and McGrath 2004; Thorburn and Harding 1994; Yagel et al. 2006). In the 9th through 15th weeks, the heart beat can begin to be detected and the lungs continue to

develop. The fetus may then respire the amniotic fluid that is necessary for the developing alveoli inside the lungs to function properly (Kenner and McGrath 2004).

As the respiratory system begins to mature to the point that the lungs have reached the canalicular stage, the bronchioles divide into two or more respiratory bronchioles, which will eventually develop into the alveolar ducts. Nearing 24 weeks conceptional age, extrauterine respiration is possible. However, surfactant production will not reach the optimal levels in the fetus until closer to 28 weeks conceptional age, rendering unassisted respiration insufficient. From 24 weeks to birth, the lung development is completing its terminal stage marked by the rapid growth of the sacs that are the site of gas exchange in the lungs, thinning of epithelium and bulging of capillaries into the sacs for gas exchange (Kenner and McGrath 2004; Thorburn and Harding 1994). By approximately 28 weeks, the lining of the sacs in the lungs undergoes a shedding in which type I alveolar cells (squamous epithelial cells) are replaced by pulmonary surfactant secreting type II alveolar cells. It is important to note here that at weeks 28 to 32 the fetus begins to develop an immune system. Yet, it will take until weeks 38 to 40 conceptional age that full surfactant production is achieved (Jirasek 2004; Kenner and McGrath 2004).

From week 37 the birth of a fetus is considered to be full term even though a normal human pregnancy is noted to be 40 weeks in length (Kenner and McGrath 2004). The lung development is considered to be capable of supporting life from 37 weeks forward (Kenner and McGrath 2004). The premature infant is defined as <37 weeks gestation, moderate prematurity 31-36 weeks and severe prematurity 24-30 weeks (Kenner and McGrath 2004; Swamy 2004). Low and very low birth weight are

documented at < 2500 grams and <1500 grams, respectively. Premature infants are often also low birth weight; however, a full term infant may be born low birth weight and present different complications (Kenner and McGrath 2004).

The premature infant is at a respiratory disadvantage in part due to the proportionately larger head and tongue and smaller, narrower nasal passages, an anterior and cephalad larynx, long epiglottis and short trachea and neck as seen in Figures 2.2 and 2.3 (Swamy and Mallikarjun 2004). Furthermore, the narrow cricoid cartilage and narrow trachea increase the ease and likelihood of both a mechanically blocked airway, as well as immune induced closure of the airway in comparison to even a five-year-old (Loughlin 2000; American Heart Assoc 2006; Matthew 2003; Kelmanson 2006).

The mortality rates for premature infants reported by the Center for Disease Control and Prevention reflect the challenges to survival of a premature fetus with 68.6% of all infant deaths in 2005 occurring among premature infants (MacDorman and Mathews 2008). These data are biologically understandable given that independent life is not viable until gestational age is 24-26 weeks due to development of the airway system, alveolar growth and surface active proteins (Kelmanson 2006; Kenner and McGrath 2004). Premature infants may suffer from a lack of breathing control due to the immature hypoxic and hypercapnic ventilatory drives that depress respiration (Kenner and McGrath 2004). This lack of control combined with susceptibility to fatigue of the respiratory muscles may be responsible for increased rates of apnea in premature infants (Kenner and McGrath 2004). Thus, we find that infants are at an increased risk of inhalative exposure since their oxygen consumption, with a respiratory and heart rate of 40 breaths and 140

beats per minute, is nearly double that of an adult (American Heart Assoc 2006; Kelmanson 2006; Loughlin 2000; Matthew 2003; Swamy and Mallikarjun 2004).

Apnea and Bradycardia

The cardiorespiratory system of the infant is not a uniform entity; it covers vast ranges of heterogeneity that make managing the airway a complex task (American Heart Assoc 2006; Kelmanson 2006; Loughlin 2000; Matthew 2003; Swamy and Mallikarjun 2004). Apnea (cessation of breathing for more than 20 seconds) and bradycardia (low heart rate) are two health events of concern

Matthew et al. (2003) present analysis in which they show approximately 97% of bradycardias are preceded by apnea events. Apnea is understood as the brief cessation in breathing. Healthy, normal infants have been recorded to cease respiration for up to 15-20 seconds (Kenner and McGrath 2004). Apnea is defined as the cessation of breathing for more than 20 seconds (Loughlin 2000). The causes of apnea are still being investigated and have been linked with other infant mortality risk factors, including sleep apnea and Sudden Infant Death Syndrome (SIDS) (Spitzer 2005). In infants these short disruptions in breathing patterns (less than 20 seconds) are said to be normal; however, the termination of breathing for more the 20 seconds is considered worthy of seeking medical attention (Kelmanson 2006). Symptoms of obstructive apnea are snoring, restless sleep, labored breathing and changes in color (Matthew 2003).

The literature reports three types of apnea. The first type is obstructive apnea in which an obstruction causes the apnea. An example of an obstruction would be food, toys or even enlarged tonsils and adenoids (Matthew 2003). Prolonged apnea occurs in nearly

all premature infants < 28 weeks post-conceptional age, and has been found to occur in approximately half of infants at 31 weeks (Matthew 2003). Central apnea occurs when there is a malfunction in the section of the brain that controls the start or maintenance of breathing functions. This is especially common in very premature infants because the respiratory center in the brain is immature. Finally, mixed apnea is described as a combination of central and obstructive apnea and is mostly seen in infants and young children who have abnormal control of breathing.

Bradycardia is defined as a slower than normal heart rate (Kenner and McGrath 2004). A drop in heart rate can mean that the body's organs do not obtain as much oxygen as they should which can lead to dizziness, fatigue, and fainting, as well as chest pains and other problems (Kelmanson 2006). Bradycardia can be caused by a disturbance in the electrical impulses of the heart that control the rate of work. Other documented causes of bradycardia include the degeneration, infection or damage of tissues in the heart, an iron buildup in the organs and repeated disruptions of breathing or bouts of apnea which is cause for additional observation (Spitzer and Gibson 1992). In infants, especially premature and low birth weight infants, the incomplete development of the lungs and heart chambers can be a cause of bradycardia. Additionally, the under-development of the immune system may leave these infants at increased susceptibility of bradycardia episodes due to infection. The Children's Healthcare of Atlanta defines bradycardia for infants as: heart rate <100 beats per minute in a premature infant, <80 beats per minute in a full term infant and <60 beats per minute in an infant > 3 months (Kelmanson 2006; Kenner and McGrath 2004).

Cardiorespiratory Monitors

The physiology of infants, especially in the disrupted development of premature and low birth weight infants, has lead to the need for increased observation and monitoring of these infants. Premature and low birth weight infants are permitted to be taken home by the parent(s) under the aided care of a computerized home cardiorespiratory monitor. These monitors are portable machines to record the infant's heart rate and breathing (Erler and Peters 2006; Gibson et al. 1996; HealthCentral 2009; Medline Plus 2009; Spitzer 2005; Spitzer and Gibson 1992). In most cases the electrodes are secured by stick-on patches or a belt attached to the subject's chest or stomach (Medline Plus 2009). The measurement of respiration with most all of these monitors is accomplished through a surrogate measure of impedance typically using an elastic band around the chest of the infant. Thus, these monitors are measuring respiratory effort, or more accurately chest movement, as a surrogate measure of respiration. If the heart or breathing rate falls below the preset limit on the monitor, an alarm signals to alert the attention of a care provider or parent. Since the early 1970's, home monitors have been used to care for infants thought to be at risk of illnesses, such as Sudden Infant Death Syndrome (SIDS), by recording heart rate and breathing (Halbower 2008). Some notable debate has occurred over the years of the utility of these monitors as no randomized or controlled trials were performed on the efficacy of monitor use prior to public distribution. Thus, although many studies have looked at compliance, access to and quality of life with monitor use; there have not been a large number of studies which address the actual life-saving role of monitor use (Halbower 2008). Although researchers also debate the utility and efficacy of home monitor therapies due to false alarms,

monitors have continued to be utilized and credited with successful cardiorespiratory recording (Erler and Peters 2006; Gibson et al. 1996; HealthCentral 2009; Medline Plus 2009; Spitzer 2005; Spitzer and Gibson 1992).

Health Effects of Ambient Air Pollution in Child/Infant Populations

Identifying populations, such as infants, that are susceptible to the acute adverse health effects of ambient pollutants, and providing insight regarding biological mechanisms are both priorities in air pollution research (National Research Council 2004). A large body of research from around the world investigating associations between air pollution and health effects of infants and children has been accumulated (Awasthi et al. 1996; Bates 1995; Bayer-Oglesby et al. 2005; Bobak and Leon 1999a; Concericao et al. 2001; Dales et al. 2006; Gilliland et al. 1999; Ha et al. 2003; Heinrich and Slama 2007; Kaiser et al. 2004; Kim 2004; Lin et al. 2004; Loomis et al. 1999; Moore et al. 2008; Morgenstern et al. 2008; Moshammer et al. 2006; Nicolai et al. 2003; Peel et al. 2003; Pierse et al. 2006; Pope and Dockery 1992; Schwartz 2004; Sunyer et al. 2004; Triche et al. 2006; Wang and Pinkerton 2007; Ward and Ayres 2004; Wong et al. 2004; Woodruff et al. 1997). Air pollution can be especially dangerous to infants and children due to the increased heart rate and respirations, which lead to high volumes of air exchange and thus increased potential for exposure to pollutants (Gilliland et al. 1999; Kim 2004). Additionally, infants are more susceptible to disease due to the underdevelopment of the immune system. The consequences of air pollution are not balanced for all members of a population, and the literature is showing that infants and children are among the most vulnerable and sensitive of subgroups (Heinrich and Slama 2007). The effects of air pollutants on infants and children have included postnatal

development (Wang and Pinkerton 2007) and increased adverse pregnancy outcomes and infant mortality (Bobak and Leon 1999a, b; Loomis et al. 1999; Woodruff et al. 1997; Woodruff et al. 2006) and respiratory and lung function (Awasthi et al. 1996; Brunekreef et al. 1995; Pierse et al. 2006).

Fetal and Early Postnatal Development

A number of studies have investigated the effects of air pollution on fetal and early postnatal development has shown an increasing body of evidence that fine particle exposure has a measurable impact on birth outcomes (Heinrich and Slama 2007). In discussing their work reviewing birth outcomes and development, Heinrich found that intrauterine growth retardation was consistently associated with particulate matter and increased risk of prematurity with particulate matter levels (Heinrich and Slama 2007). Additionally, particulate matter exposure during pregnancy was associated with increases in birth defects, such as atrial septal defects (Heinrich and Slama 2007).

Wang and Pinkerton in 2007 observed that exposure to air pollutants during fetal development and early postnatal life is associated with abnormal development including low birth weight, premature birth, intrauterine growth restriction, congenital defects, decreased lung growth, and neurocognitive decrements(Wang and Pinkerton 2007). In another review, Moshammer et al. (2006) suggest that the heterogeneous nature of particulate matter containing heavy metals, persistent organic pollutants (POPs) and polycyclic aromatic hydrocarbons (PAHs) can impact fetal and early postnatal development (Moshammer et al. 2006). Research two years later by Bateson and Schwartz in 2008 corroborated the suggestions by Moshammer et al. in which they explained that considerable evidence of maternal exposure to air pollution during

pregnancy is associated with adverse birth outcomes. Bateson and Schwartz (2008) found in reviewing the literature that increases in prevailing level of air pollution are associated with early fetal loss, premature delivery, and lower birth weight.

Mortality

Researchers have also documented relationships between air pollution and infant mortality. Reviews by Pope and Dockery have addressed the susceptibility of infants and children to air pollution (Pope and Dockery 2006). The literature reveals an increasing body of evidence that fine particle exposure has a measurable impact on infant health (Heinrich and Slama 2007). In research by Lacasana et al. in 2005 the authors reviewed the literature and observed that an increase of $10\mu g/m^3$ in particle concentration PM_{10} is associated with a nearly 5% increase in post-neonatal mortality for all causes and nearly 22% for post-neonatal mortality for respiratory diseases (Lacasana et al. 2005).

Sram et al. reviewed the literature and observed there to be a near consensus of the association between infant and childhood mortality and exposure to particulate matter (Šrám et al. 2005). Sram et al. (2005)concluded their research by stating that the evidence is sufficient to believe there is a causal relationship between particulate air pollution and respiratory deaths in the postneonatal period. Wang and Pinkerton (2006) reviewed the relationship between infant mortality and outdoor air pollutants and concluded that carbon monoxide and PM_{10} were both observed to be associated across a number of studies. The research performed by Bateson and Schwartz (2008) cites separate work by Woodruff et al. (1997), Bobak et al. (1999), Loomis et al. (1999), Bateson et al. (2008) and Ritz et al. (2006) which identified particulate matter as associated with infant

mortality. The works by these researchers provide abundant evidence of the impact air pollution has on infant mortality.

Respiratory Illnesses/Events

Studies have shown evidence of associations between respiratory symptoms and air pollutants. Odds ratios for PM_{10} have been estimated at 1.62 (95% CI: 1.31-1.97) and 1.42 (95% CI: 1.02-1.97) for incident symptoms of cough without a cold and wheezing without a cold, respectively (Pierse et al. 2006). Bayer-Oglesby et al. (2005) observed moderate declines in air pollution levels in the 1990's in Switzerland to be associated with reduced respiratory symptoms and diseases in school children in a cross-sectional study of 9,951 participants(Bayer-Oglesby et al. 2005). In an 18-year study, work done by Moore et al. who studied the time trends in associations between child asthma hospitalizations observed that a 10-ppb mean increase in mean quarterly 1-hr maximum O_3 resulted in a 4.6% increase in the same quarterly outcome (Moore et al. 2008). Triche et al. (2006) concluded that levels of ozone exposure close to (or even below) the U.S. EPA standards, appear to place infants at increased risk of respiratory symptoms based upon their analysis that revealed a 37% (95% CI: 2-84%) increased likelihood of wheezing for every interquartile-range (11.8 parts per billion) increase in same-day 24-hour average ozone. This percent increased to 59% (95% CI: 1-154%) for infants of asthmatic mothers (Moore et al. 2008; Triche et al. 2006). Dales et al. (2006) observed multiple associations in their Canadian study testing the associations between daily concentrations of ambient gases and daily respiratory hospitalizations (asphyxia, respiratory failure, dyspnea and respiratory abnormalities, respiratory distress syndrome, unspecified birth asphyxia in live-born infant, other respiratory problems after birth and

pneumonia) in which O_3, NO_2, and CO were observed to be significant at the 0.05 level of significance with odds ratios of 3.35 (95% CI: 1.73-4.77 per 12.0 μg/m^3 increase), 2.85 (95% CI: 1.68-4.02 per 10.0 μg/m^3 increase), and 9.61 (95% CI: 4.53-14.7 per 0.5 μg/m^3 increase), respectively (Dales et al. 2006). Research by Peel et al. (2003) on the same cohort of 3,629 infants as included in our current study observed associations between bradycardia and ozone (OR: 1.049 per 25 ppb; 95% CI: 1.021-1.087) and nitrogen dioxide (OR: 1.025 per 20 ppb; 95% CI: 1.000-1.050). The infants were under six months in age at the beginning of the study within the Atlanta metropolitan statistical area and were patients of the Healthcare of Atlanta at Egleston Apnea Center from August 1, 1998 to December 31, 2002 (Peel et al. 2003). Patients were prescribed a home monitor for prematurity, gastroesophageal reflux disease, previous apnea events, apparent life threatening events or have a sibling who suffered from Sudden Infant Death Syndrome (SIDS).

Health Effects of Source Apportioned Air Pollution

The evaluation of the health effects of source apportioned air pollution is a field of study gaining in utility, yet is still in its early phases. As such, there are only limited publications from such studies. Prior studies have observed interesting associations which have helped to form the hypotheses of our work here. For instance, Larson et al. (1994) and Schreuder et al. (2008) observed consistent associations between a biomass burning source and a number of respiratory end points using a tracer method of source identification that matched well with other source apportionment methods (source apportionment comparisons not published) (Larson and Koenig 1994; Schreuder et al. 2008).

A 2009 study observed an association of hospital admissions for arrhythmia with Aitken mode particles and $PM_{2.5}$ from the traffic source in which a 3.1% increase (95% CI: 0.43–5.8 per 2,467 cm^{-3} increase) for pneumonia over the 5-day mean, and a 3.8% increase (95% CI: 1.3–6.3 per 2,467 cm^{-3} increase) for asthma-COPD at lag 0 was observed. They also observed an association of respiratory mortality mainly with accumulation Aitken mode particles (5.1%; 1.2–9.0 at lag 0 per 287 cm^{-3} increase) (Halonen et al. 2009). Research by Ito et al. (2005) used air pollution data from the city of Washington, D.C. and a Poisson generalized linear model (GLM) to estimate source-specific apportionment to estimate relative risks (RR) at lags 0–4 days for total non-accidental, cardiovascular, and cardiorespiratory mortality adjusting for weather, seasonal/temporal trends, and day-of-week. The results from this workshop on air sheds and health statistics data from Washington, DC estimated mean relative risks associating $PM_{2.5}$, soil, sulfates and traffic sources with cardiovascular and non-accidental mortalities. Ito et al. (2005) presented results from the workshop on particulate matter source apportionment and health effects for Washington, DC in which they observed that the percent excess deaths per 5^{th}-95^{th} percentile increment (values not provided) of apportioned $PM_{2.5}$ for total mortality was significantly associated with the secondary sulfate source at 6.7% increase (95% CI: 1.7-11.7) with a 3 day lag (three days following the event), 2.6% increase (95% CI: -1.6-6.9) for the traffic source related $PM_{2.5}$, 2.1% increase (95% CI: -0.8-4.9) for the soil source and 2.7% increase (95% CI: -1.1-6.5) for residual oil factor source on a 2 day lag (two days following the event) in the DC dataset (Ito et al. 2005).

A Copenhagen study observed that an increase in the 4-day PM_{10} average was associated with a 2.7% increase in cardiovascular disease hospital admissions the next day (95% confidence interval 1.3%–4.2%; per 14.0 $\mu g/m^3$ increase). For respiratory disease and asthma, one IQR increase in 5- and 6-day PM_{10} averages was associated with 3.7% (1.4%–6.0% per 14.0 $\mu g/m^3$ increase) and 7.7% (0.4%–15.5% per 14.0 $\mu g/m^3$ increase) increases in hospital admissions the next day, respectively (Andersen et al. 2007).

In their 2008 study, Sarnat et al. (2008) observed that their results using both CMB and PMF source apportionment methods were robust to the selection of source-apportionment method. They observed several significant, positive associations, such as between cardiovascular disease and same-day $PM_{2.5}$ source concentrations of diesel, gasoline and biomass combustion in both the PMF and CMB modeling estimates. They also observed secondary sulfate to be significant in the respiratory disease analysis (Sarnat et al. 2008). Their results show an important relationship between the two models which provides evidence that there may be little difference in associations observed in epidemiological studies when associating health events and source apportioned air pollution.

Mar et al. (2005) found small or no associations between the biomass burning source and cardiovascular disease (CVD), in a comparison of a suite of multivariate factor analytic based models target-transformation factor analysis, confirmatory factor analysis, unmix and positive matrix factorization method (Ito et al. 2005; Mar et al. 2005). Datasets presented by Mar et al. (2005) observed evidence that cardiovascular mortality was associated with the secondary sulfate source (16.0% per 5^{th}-95^{th} percentile,

actual values not provided) at lag zero-day was associated with cardiovascular mortality and the traffic source (13.2% per 5^{th}-95^{th} percentile [actual values not provided] at lag one-day in Phoenix. However, in their analysis, the investigators noted that an increase in the time between exposure and event observation showed a decreased association in the traffic related particulate matter. In an earlier 2000 study, Mar et al. (2000) observed significant associations between cardiovascular mortality and selected gaseous air pollutants with relative risks of: CO 1.05 (95% CI: 1.00-1.11; per 1.19 ppm increase) and 1.10 (95% CI: 1.04-1.15; per 1.19 ppm increase) in 0- and 1-day lags, respectively, and NO_2 with a relative risk of 1.10 (95% CI: 1.04-1.17; per 0.02 ppm increase) and 1.10 (95% CI: 1.04-1.15; per 0.02 ppm increase) at the 1-day lag. There was also an association with SO_2 at the 0 day lag. Cardiovascular mortality was positively associated with CO (0-4 days lag). The associations between PM_{10} and total mortality and between the coarse fraction of particulate matter ($PM_{10-2.5}$) and total mortality were marginal. Mar et al. (2000) observed the strongest associations with cardiovascular mortality with PM_{10} with a relative risk of 1.05 (95% CI: 1.01-1.09; 24.88 per $\mu g/m^3$ increase), the non-soil $PM_{2.5}$ source with a relative risk of 1.04 (95% CI: 1.00-1.08; 0.02 per $\mu g/m^3$ increase), and $PM_{10-2.5}$ with a relative risk of 1.05 (95% CI: 1.01-1.09; 18.39 per $\mu g/m^3$ increase).

Summary

Air pollution and its effects on human health have been the subject of a number of studies. Research has indicated a further need to explore the effects of the sources of air pollution and address the effects of air pollution, as well as source apportioned air pollution on vulnerable populations. The emerging methodology and technology to detect and to ascertain the sources of fine particles provides researchers with an expanded array

of tools, such as improved source apportionment models that may increase the precision and accuracy of effect estimations within certain populations. As presented above, the challenges and need to address at risk and highly susceptible populations, such as infants, is great. The amount of current research on specific respiratory and cardiac events in infants is lacking in quantity due in part to the technological and methodological challenges, such as the development of source apportionment standards and the conduct of longitudinal studies which require long term follow-up, patient commitment and compliance in order to obtain the large amount of data required by such studies. The public health concern and need to address the association between air pollution and health provide increased motivation to investigate the hypothesis of source associated health effects to improve our understanding of the relationship between infant health and air pollution sources. Fine particulate air pollution is becoming an increasing concern in the field of air pollution due to the effects shown in studies investigating respiratory outcomes, cardiovascular health, pregnancy outcomes, asthma, and SIDS. The work we present here can add to the growing body of literature in narrowing the constituent sources of air pollution which may be harmful to infants.

Table 2.1: United States National Ambient Air Quality Standards, adapted from the United States Environmental Protection Agency's National Ambient Air Quality Standards website (US-EPA 2009c).

NATIONAL AMBIENT AIR QUALITY STANDARDS

	Primary Standards		Secondary Standards	
Pollutant	Level	Averaging Time	Level	Averaging Time
Carbon Monoxide	9 ppm 35 ppm	8-hour 1-hour	None None	None None
Lead	0.15 µg/m^3 1.5 µg/m^3	Rolling 3-month average Quarterly average	Same as Primary Same as Primary	Same as Primary Same as Primary
Nitrogen Dioxide	0.053 ppm	Annual (Arithmetic Mean)	Same as Primary	Same as Primary
Particulate Matter (PM_{10})	10 µg/m^3	24-hour (3)	Same as Primary	Same as Primary
Particulate Matter ($PM_{2.5}$)	15.0 µg/m^3 35 µg/m^3	Annual(4) (Arithmetic Mean) 24-hours (5)	Same as Primary Same as Primary	Same as Primary Same as Primary
Ozone	0.075 ppm (2008 std) 0.08 ppm (1997 std) 0.12 ppm	8-hour 8-hour 1-hour(8) (Applies only in limited areas)	Same as Primary Same as Primary Same as Primary	Same as Primary Same as Primary Same as Primary
Sulfur Dioxide	0.03 ppm	Annual (Arithmetic mean)	0.5 ppm (1300 µg/m^3)	3-hour

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

(2) final rule signed October 15, 2008.

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

(4) to attain this standard, the 3-year average of the weighted annual mean $pm_{2.5}$ concentration from single or multiple community oriented monitors must not exceed 15.0 µg/m^3

(5) 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).

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.

(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.

(8) (a) the standard is attained when the expected number of days per calendar year with maximum hourly average concentration above 0.12 ppm is < 1.

(b) as of June 15, 2005 EPA revoked the 1-hour ozone standard in all areas exept the 8-hour ozone nonattainment Early Action Compact (EAC) Areas.

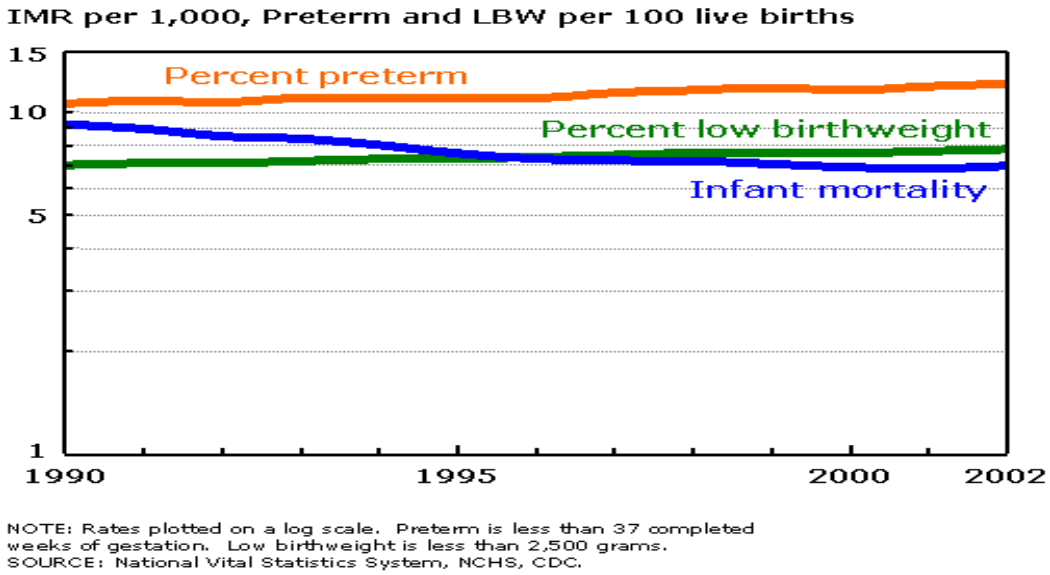


Figure 2.1 Infant Mortality Rate of Premature and Low Birth Weight live births adapted from Kochanek and Martin (2005).

Infant/Child Airway (A) – side view

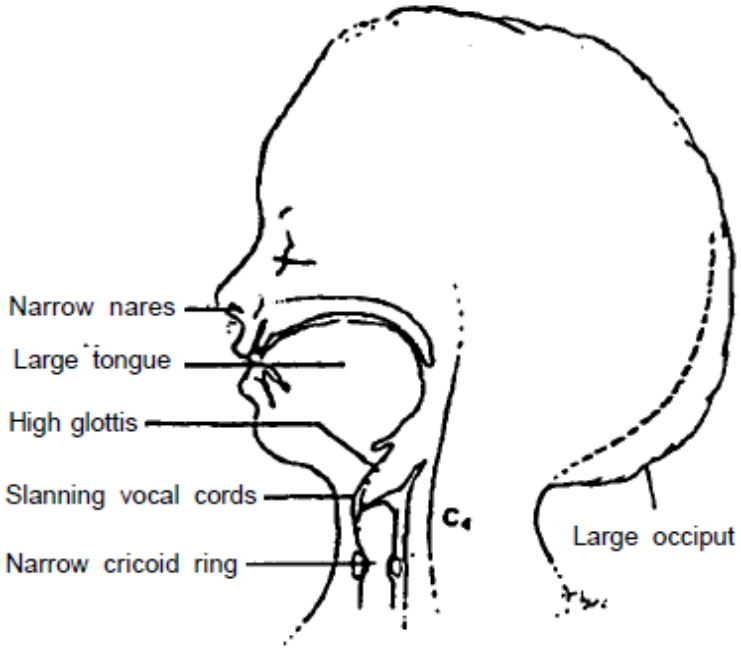


Figure 2.2: Anatomical challenges in infants, adapted from Swamy and Mallikarjun (2004).

Infant/Child Airway (B) – side view

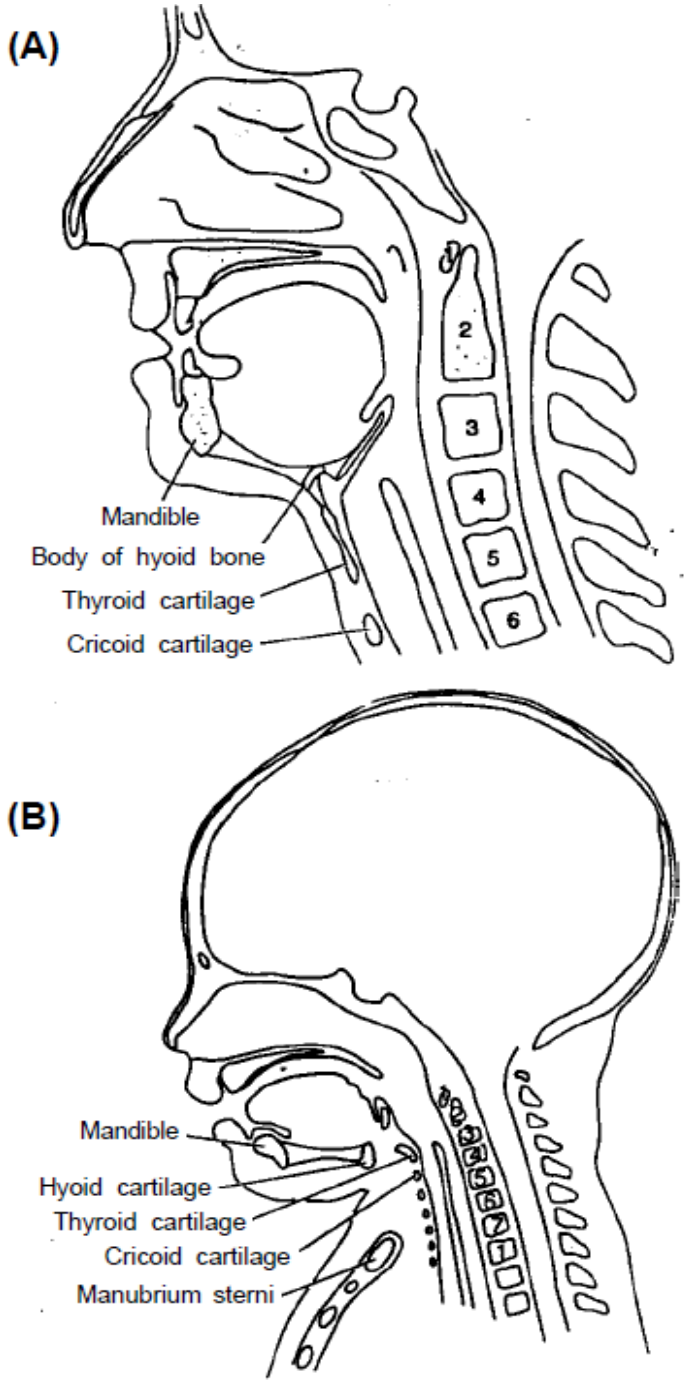


Figure 2.3: Sagittal section of the adult (A) and infant (B) airway, adapted from Swamy and Mallikarjun (2004).

Chapter 3: Methods

The analysis for this work used existing data from various sources. The source apportioned fine particulate matter data were merged with the patient clinical and event data into one database for analysis. We then utilized SAS 9.2 (SAS Inc; Cary, NC) to perform unconditional logistic regression (within a generalized estimating equation framework to account for autocorrelation within subject) to investigate the association between particulate matter sources and apnea and bradycardia events. Our analysis was performed using the sources identified from both chemical mass balance and positive matrix factorization source apportionment methods based on single source models (one source per model).

Study Population

The data from this research are part of a previous project that examined the relationship between ambient air pollution and cardiorespiratory events (apnea and bradycardia) in a population of primarily premature and low birth weight infants monitored with home devices (Peel et al. 2003). The event and patient data were obtained from the Apnea Center at Children's Healthcare of Atlanta at Egleston. Data collected included date of birth, gender, race, gestational age at birth, birth weight, payment method, reason for referral and residential zip code for all patients followed by the Apnea

Center. Data were collected from an electronic database and included patients whose residential zip codes

were within the 20-county Atlanta Metropolitan Statistical Area (MSA) (Peel et al. 2003). The 3,629 infants less than six months of age at the beginning of the study, were followed from November 19, 1998 to December 31, 2002, corresponding to the availability of the source data. Patients were prescribed a home monitor for various reasons including prematurity, gastroesophageal reflux disease, previous apnea events, apparent life threatening events, or having a sibling who had suffered from Sudden Infant Death Syndrome (SIDS).

Event Data

The monitors recorded heart rate, ECG, and a measure of chest impedance for apnea (when the infant briefly stops breathing) and bradycardia (low heart rate), using pre-set parameters to recognize the events. The apnea setting is usually set at 20-25 seconds to detect longer pauses in respirations, and heart rate is typically set to measure periods where the rhythm falls below 100 bpm, 80 bpm and 60 bpm for premature, full term and infants $\geq$ three months old, respectively. These settings are chosen based on the gestational age at birth and age of each infant. Normal birth weight and full term infants have been known to have short periods of apnea and the age of the infant determines what the normal heart rate should be (Halbower 2008; Kenner and McGrath 2004). Impedance is the method of measurement of respiration wherein expansion and contraction of the trunk and chest region are used to detect respiratory effort, typically using an elastic band around the circumference of the infant. Impedance is an indirect method of detecting apnea by monitoring the rise and fall of the chest, which means that only apneas that occur when there is no respiratory effort (central apneas) rather than obstructive apneas are detected. Bradycardias in our study may represent primary cardiac

events, as well as events which are secondary to obstructive apnea events that would not be documented apneas since they could be missed by the impedance method.

Approximately once a month or when events were being experienced by the infant, the monitor wave forms were collected and reviewed by the clinicians. Using these waveforms, clinicians assessed the type and validity of the event and summarized the information into a patient file which contained the unique patient identification number, event time, date, type and duration of the event, the lowest heart rate during a bradycardia, the time period the download covers, type of monitor, the monitor's low heart rate and apnea settings, and compliance for that download. If the monitors are incorrectly secured or the electrodes fell off the infant, a false event may be recorded. The clinicians were able to determine if a recorded event was a false event or a true apnea or bradycardia. The monitor is recommended to be used for about 20 hours per day, especially during sleep, car seat use, or when an adult is not present in the same room. It is the goal of the Apnea Center to collect 90 event-free days before the cessation of monitor use.

Patients included in the study were patients younger than six-months of age at the start of their follow-up and where patient cardiorespiratory monitor use was more than 66% compliant during a download period and only the download periods for which the infant used the monitor for more than 66% of the days. Follow-up time was censored at six-months of age or at the end of the study period – which ever was first.

Source Apportionment

The source apportionment methods were presented by Kim et al. (2004), Marmur et al. (2005) and Sarnat et al. (2008). Investigators utilized chemical mass balance and positive matrix factorization methods of source apportionment on $PM_{2.5}$ mass collected from November 19, 1998 to December 31, 2002 in the urban area of Atlanta monitored at the Jefferson Street site, four kilometers northwest of downtown Atlanta. This site is a primary measurement site for the Southeastern Aerosol Research and Characterization Study (SEARCH), the Aerosol Research Inhalation Epidemiology Study (ARIES) and other studies that are part of the Studies of Particles and Health in Atlanta (SOPHIA) . These two methods produced 14 source profiles (see Table 3.1). Of these profiles, six (gasoline, diesel, woodsmoke, soil, secondary sulfate I, and secondary nitrate) were identified by both source apportionment methods, while three (power plants, other OC and ammonium bisulfate) were identified only by the chemical mass balance method, and five (cement kiln, bus and highway, railroad, metal processing and secondary sulfate II) were identified only by the positive matrix factorization method.

The positive matrix factorization method (PMF) done by Kim et al. (2004) used daily integrated $PM_{2.5}$ composition data including eight individual carbon fractions collected at the Jefferson Street monitoring site in Atlanta (Kim et al. 2004; Sarnat et al. 2008). Particulate carbon was analyzed using the thermal optical reflectance method that divides carbon into four organic carbon (OC), pyrolized organic carbon (POC), and three elemental carbon (EC) fractions. A total of 529 samples and 28 variables were measured between August 1998 and August 2000. PMF identified 11 sources in this study: sulfate-rich secondary aerosol I (50% - average mass distribution), on-road diesel emissions

(11%), nitrate-rich secondary aerosol (9%), woodsmoke (7%), gasoline vehicle (6%), sulfate-rich secondary aerosol II (6%), metal processing (3%), airborne soil (3%), railroad traffic (3%), cement kiln/carbon-rich (2%), and bus maintenance facility/highway traffic (2%). This study indicated that the temperature-resolved fractional carbon data can be utilized to enhance source apportionment study, especially with respect to the separation of diesel emissions from gasoline vehicle sources (Kim et al. 2004).

The chemical mass balance done by Marmur et al. (2005), in addition to the commonly used particulate-phase source profiles, used a modified approach to $PM_{2.5}$ source apportionment, using source indicative sulfur dioxide/$PM_{2.5}$, carbon monoxide/$PM_{2.5}$, and nitrous oxides/$PM_{2.5}$ ratios as constraints to develop sources. Additional information from gas-to-particle ratios assisted in reducing collinearity between source profiles. The solution is based on a global optimization mechanism, minimizing the weighted error between apportioned and ambient levels of $PM_{2.5}$ components, while introducing constraints on calculated source contributions that ensure that the ambient gas-phase pollutants (sulfur dioxide, carbon monoxide, and nitrous oxide) are reasonable (Marmur et al. 2005).

Source apportionment is a developing technique with practitioners using their own personal knowledge to guide them in source naming and profile discrimination. Thus, the missing components of air pollution which may be needed to estimate pollution sources may prevent the estimation of a source in practitioner's technique. The lack of uniformity in the field of source apportionment means that there can be differences or misleading similarities in the naming, compound and component make-up of a source.

The challenge of non-uniformity in source identification conventions, along with estimating differences between the two source apportionment methods we used to estimate the sources, lead to inconsistency of the days for which each method was able to generate source data measurements. In order to help to reconcile these differences so that comparable days of data would be used, we censored the source data to include only days in which we obtained source contributions for similar sources from both positive matrix factorization and chemical mass balance methods. Missing values present in the source data occurred when data could not be obtained from the central monitor, in which case the source apportionment measurements cannot be estimated.

Statistical Methods

All statistical analysis was performed using SAS 9.2 (SAS Inc., Cary, NC). The clinical and demographic data were merged with event data for each of the patients to construct the database. Descriptive statistics for the air quality (mean, interquartile range, percentiles and standard deviation) and outcome data (apnea and bradycardia events) were calculated. Spearman correlation coefficients between the sources within and between the PMF and CMB methods were calculated. We examined the association between the apnea and bradycardia and source apportioned fine particulate matter (Aim 1 and 2, respectively) from the positive matrix factorization and chemical mass balance methods separately. We assigned the dependent variable as an event-day (apnea or bradycardia event evaluated separately on each day). We evaluated the association with the source data for the day of (zero-day lag) and the day before (one-day lag) the event utilizing one source per model.

Repeated-measures unconditional logistic regression within a generalized estimating equation (GEE) framework was used to address the possibility that multiple event-days for a patient may be correlated (Agresti 2002). Due to the availability of only a few models to handle the joint distribution of repeated observations for each subject, the analysis of longitudinal data is challenging and requires the use of GEEs, which are an extension of generalized linear models (Liang and Zeger 1986). The utility of GEEs is the ability to estimate the average response comprised of the sample population to create a population-averaged effect (Hardin and Hilbe 2003). One of the strengths of GEEs is the ability of the equations to be constructed when the joint distribution of the observations is unknown or not given. GEEs have become an increasingly important tool by providing a methodology for the statistical analysis of correlated data, such as those which are regularly seen in longitudinal data, as well as nested and repeated-measures designs wherein measurements taken have characteristics in common and are taken at different points in time (Ballinger 2004; Liang and Zeger 1986). GEEs are also able to generate more efficient and unbiased regression parameters as compared to the ordinary least-squares regression since they allow for the working correlation matrix, which dictates the structure of the within-subject correlation to be directly specified (Ballinger 2004).

We attempted to utilize a model, we call the 'preferred model', which included the fine particle source, age, age-squared, temperature splines with knots at the 25^{th} and 75^{th} percentiles, time splines with seasonal knots, and indicator for weekend and holidays. Later in this section, we describe problems in utilizing this 'preferred model' which lead to presenting the results of from two models. The first model was used for the

full term/normal birth weight strata was the same as the 'preferred model' but replaced the temperature splines with average daily temperature and the square of daily temperature variables to adjust for temperature and replaced time splines with day, day-squared and day-cubed variables to adjust for time. The second model used for the remainder of the analysis was identical to the 'preferred model' but replaced the temperature splines with average daily temperature and the square of daily temperature variables to adjust for temperature.

We used a stationary 45-dependent correlation structure; average daily temperature and the square of average daily temperature were used to adjust for daily average temperature as well as indicator variables for holidays and weekends. Age and a quadratic term for age of infant were included in the model so that we could adjust for the age of the infant since the probability of cardiorespiratory events, such as apnea and bradycardia, decrease with the increase in age of the infant (Peel et al. , 2003). The stationary 45-dependent correlation structure attempts to account for the possibility that multiple events recorded by a subject are correlated, by treating events occurring less than 45 days apart as a correlated event. Events which occur more than 45 days apart are treated as separate independent, uncorrelated events. We included the terms day, day-squared and day-cubed in the full term/normal birth weight apnea analysis to adjust for temporal trends and cubic splines with seasonal knots for adjustment for long term temporal trends in the remainder of the study. The quadratic age term is included to account for the decreased probability of an event (both bradycardia and apnea) with increasing age (Peel et al. 2003).

The odds ratio (OR) is a measure of effect size used to describe the strength of association between data values. All odds ratios (ORs) and 95% confidence intervals (CIs) from GEE unconditional logistic analysis using apportioned sources lagged zero and one-day were calculated for increase in each pollutant source equal to the inter-quartile range.

The analyses for apnea events and for bradycardia events were conducted separately (Aim 1 and 2, respectively). We evaluated the association between each of the sources with apnea or bradycardia events for the entire population and then stratified the subjects by birth weight and gestational age status to compare the odds ratios of the primary analysis utilizing all birth weights and gestational ages versus the low birth weight/premature infants (< 2500 g/<37 months) and those of normal birth weight/full term infants ($\geq$2500g/$\geq$37 months) (Sub-Aim i). These aims were justified based on prior analysis done on this population showing evidence that suggests that normal/full term infants were more sensitive to pollutants than were the premature infants (Peel et al. 2003).

Upon running the described 'preferred' model (fine PM source, age, age-squared, temperature splines with knots at the 25^{th} and 75^{th} percentiles, time splines with seasonal knots, and indicators for weekend and holidays), the Hessian matrices, constructed in order to produce the needed covariance matrices to calculate confidence intervals, would not converge, causing us to have to simplify the model (data not presented). We ran the analysis of all strata changing the correlation structure from stationary 45-dependent to independent, compound symmetry and autoregressive. Using the independent correlation structure, all of the off-diagonal correlations are zero. These off-diagonal zeros are

interpreted in our research as each cardiorespiratory event being completely uncorrelated. In the exchangeable correlation structure, the off-diagonal is assumed to be equally uniformly correlated in a manner such that every observation of an event an infant experiences is equally correlated with every other observation by that infant. Thus, the off-diagonal correlations in the correlation matrix of the exchangeable correlation structure are equal. Since the correlations between observations in our study are likely to diminish as the time between observations increases, we did not expect the exchangeable correlation structure to be fitting for our analysis. The autoregressive (AR) correlation structure assumes observations are related to their own past values. An autoregressive correlation structure indicates that two observations taken close in time within an individual tend to be more highly correlated than two observations taken far apart in time from the same individual. Utilizing an m-dependent correlation structure, the analysis assumes that the further apart to observations are, the less correlated they will be. The m-dependent correlation structure allows the analyst to specify a number (m), such that observations more than a distance m apart will have zero correlations.

In each case, the Hessian matrices would not converge (we compared the resulting point estimates to those of our results presented and observed little difference, data not presented). The similarity we observed is not surprising given that the GEE method is robust to changes in correlation structure (Twisk 2003).

We resorted to removing one variable at a time to see if we could find the variable that would allow the model to run. We left the splines for the last attempt only to find that removing the temperature splines solved the problem for all but the full term/normal birth weight infant apnea stratum constructing a model which included fine PM source, age,

age-squared, weekend, time splines with seasonal knots and holiday. We then re-attempted the changes in correlation structures without the temperature splines which did allow for convergence in all categories other than the full term/normal birth weight infant apnea analysis (data not presented).

We then replaced the temperature splines with temperature (24-hour average) and temperature-squared constructing a model which included fine PM source, age, age-squared, temperature, temperature-squared, weekend, time splines with seasonal knots and holiday, which still allowed the program to produce the estimates in all cases other than the full term/normal birth weight infant apnea sets. We removed the temporal splines, which did allow the estimates to be run (fine PM source, age, age-squared, temperature, temperature-squared, weekend and holiday, data not presented). This lead us to a model that included the fine PM source, indicator variables for holidays and weekends and linear and quadratic terms for temperature and age of infant with a stationary 45-dependent correlation structure for the full term/normal birth weight infant apnea analysis (fine PM source, age, age-squared, temperature, temperature-squared, weekend and holiday, data not presented) and the same variables with the addition of the temporal splines for the remainder of the strata (fine PM source, age, age-squared, temperature, temperature-squared, time splines with seasonal knots, weekend and holiday, data not presented).

Recognizing the importance of accounting for temporal trends, we calculated the estimates replacing the time splines with day of study, day of study squared and day of study cubed (fine PM source, age, age-squared, temperature, temperature-squared, day, day-squared, day-cubed, weekend and holiday; data not presented) in the hopes that this

simplification would allow the model to run. Another attempt involved creating indicator variables for year and indicator variables for season and the interaction between the indicator variables for season and year (age, age-squared, weekday, holiday, temperature, temperature-squared, indicator variables for year and indicator variables for season and the interaction between the indicator variables for season and year, data not presented) using 1999 and winter as referent year and season. Both of these methods were successful in producing convergent Hessian matrices that resulted in odds ratios and confidence intervals. However, these results were so similar (<10% difference) to those presented in the final model (age, age-squared, temperature, temperature-squared, time splines with seasonal knots, weekend and holiday, model 9; for full term/normal birth weight apnea analysis: fine PM source, age, age-squared, temperature, temperature-squared, weekend and holiday, model 8), we chose to use model 10 (fine PM source, age, age-squared, temperature, temperature-squared, day, day-squared, day-cubed, weekend and holiday) for the apnea full term/ normal birth weight analysis and model 9 (age, age-squared, temperature, temperature-squared, time splines with seasonal knots, weekend and holiday) for the remainder of the strata (all infants, premature and low birth weight).

In the interest of performing a sensitivity analysis, we compiled all of the point estimates from all of the described program output attempts. Using a 10% change in odds ratio point estimate values as a guide, the comparison observed only few minor discernible differences. We calculated differences between odds ratio point estimate values in the 'preferred' model (model 1: fine PM source, age, age-squared, temperature splines, time splines with seasonal knots, weekend and holiday) and the final model (fine PM source, age, age-squared, temperature, temperature-squared, time splines with

seasonal knots, weekend and holiday, model 9) and observed that there was only one instance of a difference greater than 10% (10.23%) which was in the apnea full term/normal birth weight section for the one-day lag in the diesel/gas PMF analysis. Four other instances showed a slightly more than 10% difference in the comparison between model 1 (preferred) and model 10 (using day, day squared and day cubed) among the apnea full term/normal birth weight in the diesel/gas PMF (10.8%), gas PMF (10.1%) and diesel CMB (10.1%). Lastly, the other instance which showed more than a 10% difference was the comparison between model 1 (preferred) and model 8 (age, age-squared, temperature, temperature-squared, weekend and holiday) in the apnea full term/normal birth weight section for the zero-day lag in the diesel/gas PMF analysis.

We observed these few differences above 10% to be tolerable given sensitivity analysis for GEE methods. Thus, we conclude that the results presented are robust to changes in correlation structure, as well as the method in adjusting for time and temperature. Thus, we chose to use model 10 (fine PM source, age, age-squared, temperature, temperature-squared, day, day-squared, day-cubed, weekend and holiday) for the apnea full term/ normal birth weight analysis and model 9 (age, age-squared, temperature, temperature-squared, time splines with seasonal knots, weekend and holiday) for the remainder of the analysis.

Table 3.1: Source apportionment names by category. Adapted from Sarnat et al. (2008)

Positive Matrix Factorization Factors	Chemical Mass Balance Sources
Gasoline	Gasoline
Diesel	Diesel
Woodsmoke	Biomass burning
Soil	Soil
Secondary sulfate I	Ammonium sulfate
Secondary nitrate	Ammonium nitrate
Secondary sulfate II	----
Metal processing	----
Railroad	----
Bus and highway	----
Cement kiln	----
----	Power plants
----	Other OC
----	Ammonium bisulfate

Chapter 4: Results

Descriptive Statistics

There were 1,891 infants out of 3,629 who experienced at least one apnea event (see table 4.1). These infants had 95,339 total follow-up days. Among infants with at least one apnea event we observed there were 821 males (56.9%), 1,683 were low birth weight (89.0%) and 1,766 were born prematurely (93.4%) with 1,178 infants (62.3%) being both low birth weight and premature. The mean follow-up time in days was 50.4 days with a mean age at the start of follow-up and mean gestational age at birth of 40.9 days and 31.2 weeks, respectively. There were 3,629 infants who experienced at least one bradycardia event (see table 4.1). These infants had 157,753 total follow-up days. We calculated that 53.5% of the infants were male (N=1,499), 85.1% were low birth weight (N=3,089) and 89.1% were born prematurely (N= 3,233) with 78.4% of infants (2,125) being both low birth weight and premature. The mean follow-up time at the start of follow-up was 43.5 days with a mean age and mean gestational age at birth of 46.0 days and 31.6 weeks, respectively.

Tables 4.2.A and 4.2.B present the descriptive statistics (N, mean, standard deviation, 25^{th}, median and 75^{th} percentiles, minimum and maximum) of the identified sources during the 1,502 day study period. The results of these calculations appeared to be within reason. We observed that comparable sources from the two methods had similar values. The gas and ammonium sulfate CMB sources were nearly identical to the

gas and ammonium sulfate PMF sources, respectively. The soil and ammonium nitrate CMB sources were very similar to the gas and ammonium nitrate PMF sources, respectively, although not quite as close as the gas and ammonium sulfate.

The Spearman correlation coefficients (r) demonstrated that the two source apportionment methods appeared to be well correlated where similar sources were identified (Tables 4.3, 4.5 and 4.6). The majority of the correlations were as would be expected, such as the similarly named sources between CMB and PMF Diesel (r= 0.84) and Woodsmoke (r= 0.76). However, it was surprising that the correlation between the two gas sources was relatively low (r= 0.37). Furthermore, the results reflected that various other sources were also highly correlated (see Tables 4.3, 4.5 and 4.6). For instance, comparing the CMB sources, we observed moderate correlations between the gas and woodsmoke source (r= 0.57), the ammonium nitrate sources (r= 0.51), and the diesel sources (r= 0.48), respectively. The diesel and other organic compound sources were strongly correlated (r= 0.69). The correlation for PMF sources demonstrated that the diesel source was highly correlated with the combined diesel/gas (r= 0.95), gas (r= 0.63) and woodsmoke (r= 0.57) sources. The combined diesel/gas source was highly correlated with the PMF gas source (r= 0.82) and moderately correlated with the woodsmoke source (r= 0.58).

Comparing the CMB gasoline sources to the PMF sources, we observed some expected moderate and strong correlations, such as with the diesel-PMF source (r= 0.66), the metal processing-PMF source (r= 0.64), the combined diesel/gas-PMF source (r= 0.61), the woodsmoke-PMF source (r= 0.57) and the cement kiln-PMF source (r= 0.44). The diesel (CMB) source observed positive matrix factorization source correlations to be

expectedly strong with the diesel source (PMF) (r= 0.84) and the combined diesel/gas (PMF) source (r= 0.76). The soil (CMB) source was highly correlated with the soil (PMF) source (r= 0.94). The woodsmoke source (CMB) also had a strong correlation with its positive matrix factorization method counterpart woodsmoke (PMF) source (r= 0.76), as well as with the combined diesel/gas (PMF) source (r= 0.73), the diesel (PMF) source (r= 0.68) and the gas (PMF) source (r= 0.65). The other organic carbon source (CMB) has a moderate to strong correlation to the gas (PMF) source (r= 0.69) and the combined diesel/gas (PMF) source (r= 0.77). The power plant (CMB) and cement (PMF) sources were also highly correlated (r= 0.71). The ammonium sulfate (CMB) source with the ammonium sulfate (PMF) source (r= 0.94) and the ammonium nitrate (CMB) source with the ammonium nitrate (PMF) source (r= 0.90) were also observed to be highly correlated. The gas (CMB) source has a moderate correlation with the woodsmoke (PMF) source (r= 0.57) and the combined diesel/gas (PMF) source (r= 0.61).

Figure 4.1presents a distribution of the proportion of the sources contributing to $PM_{2.5}$ showing that the secondary sulfate (38% in CMB) and ammonium sulfate (36% in PMF) sources make up a large proportion of the overall source apportioned pollution. For the PMF method diesel made up 13%, while in the CMB category the other organic carbon source (15%) and unspecified components (13%) were a larger proportion of the distribution than diesel (9%). The strong correlations between the like named sources across the PMF and CMB methods are not surprising given the similarities of the source profiles (see figures 4.2 and 4.3). We observe from the source profiles that in comparing the key elemental components (also known as tracers), the descriptive profiles of the PMF and CMB methods are very similar. For example, in both source apportionment

methods, the diesel source revealed a large proportion of elemental carbon and the gasoline sources both revealed high proportions of organic carbon and elemental carbon.

Statistical Analysis

Our study examined the relationship between cardiorespiratory events (apnea and bradycardia) in infants on home monitors in relation to daily source apportioned daily fine PM in Atlanta from November 19, 1998 through December 31, 2002. We calculated 252 odds ratio estimates (108 CMB figures 5.1, 5.2, 5.5 and 5.6 and 144 PMF figures 5.3, 5.4, 5.7 and 5.8). The sources used in this study are described by their names, as well as by their primary identifying elemental or compound constituent(s). However, there are a few sources that warrant some additional explanation: other organic carbon, secondary sulfate/ammonium sulfate, secondary nitrate/ammonium nitrate and ammonium bisulfate. As such, they have been labeled based on their primary elemental or compound constituent(s) (Kim et al. 2004; Marmur et al. 2006):

> Other organic carbon: is a source category for which the profile did not sufficiently fit other source categories that contain organic carbon.
>
> Ammonium sulfate/secondary sulfate/bisulfate: formed largely from photochemical reactions involving SO_2 from primary power plant emissions. Ammonium nitrate/secondary nitrate: aerosol is identified by its high concentration of NO_3.

Chemical Mass Balance

CMB: Apnea Zero-Day Lag

There were no significant associations in the zero-day lag in CMB models for apnea events.

CMB: Apnea One-Day Lag

We observed that, for the CMB models for full term/normal birth weight infants, airborne soil was significant at the 0.05 level of significance in the apnea one-day lag analysis with an odds ratio of 0.769 (95% CI: 0.668-0.885; IQR: 0.27 $\mu g/m^3$ increase, Table 4.6.A). Our analysis also observed a positive association between apnea and ammonium nitrate (one-day lag) among the full term/normal birth weight infants in the chemical mass balance analysis with an odds ratio of 1.159 (95% CI: 1.000-1.343; IQR: 1.29 $\mu g/m^3$ increase, Table 4.6.A.).

CMB: *Bradycardia Zero-Day Lag*

We observed significant negative associations between bradycardia events and coal fired power plants in the zero-day lag with an odds ratio of 0.972 (95% CI: 0.950-0.995; IQR: 0.13 $\mu g/m^3$ increase, Table 4.6.B) and ammonium nitrate with an odds ratio of 1.025 (95% CI: 1.001-1.049; IQR: 1.29 $\mu g/m^3$ increase, Table 4.6.B) among low birth weight/premature of the chemical mass balance model (Table 4.6.B).

CMB: *Bradycardia One-Day Lag*

We did not observe any significant associations in the one-day lag for the CMB models in the bradycardia analysis.

<u>CMB Suggestive Patterns</u>

CMB: Apnea Zero-Day Lag

We observed suggestively strong odds ratios in the CMB primary apnea analysis among the zero-day lag for the woodsmoke source with an odds ratio of 1.024 (95% CI: 0.982-1.068; IQR: 0.72 μg/m^3 increase) and the ammonium nitrate source with an odds ratio of 1.051 (95% CI: 0.995-1.109; IQR: 5.05 μg/m^3 increase).

CMB: Apnea One-Day Lag

Strong odds ratios were also observed in the one-day lag for the full term/normal birth weight analysis in the ammonium nitrate and soil sources with an odds ratio of 1.054 (95% CI: 0.890-1.250; IQR: 1.29 μg/m^3 increase) and 1.034 (95% CI: 0.959-1.155; IQR: 0.27 μg/m^3 increase), respectively.

In the one-day lag of the gas source we observed these suggestively strong odds ratios in all strata with odds ratios for the primary analysis, premature/low birth weight and full term/normal birth weight of 1.032 (95% CI: 0.997-1.069; IQR: 0.94 μg/m^3 increase), 1.029 (95% CI: 0.990-1.069; IQR: 0.94 μg/m^3 increase) and 1.039 (95% CI: 0.884-1.221; IQR: 0.94 μg/m^3 increase), respectively. Similarly, we observed strong odds ratios in all strata for diesel with odds ratios for the primary analysis, premature/low birth weight and full term/normal birth weight of 1.029 (95% CI: 0.991-1.068; IQR: 1.17 μg/m^3 increase), 1.029 (95% CI: 0.987-1.073; IQR: 1.17 μg/m^3 increase) and 1.039 (95% CI: 0.837-1.073; IQR: 1.17μg/m^3 increase), respectively.

In the one-day lag of the other organic carbon source we observed strong odds ratios in the primary and full term/normal birth weight analysis with odds ratios of 1.027 (95% CI: 0.991-1.064; IQR: 1.79 μg/m^3 increase) and 1.095 (95% CI: 0.962-1.247; IQR: 1.79 μg/m^3 increase), respectively.

CMB: Bradycardia Zero-Day Lag

Suggestively strong odds ratios were observed in the zero-day lag among the full term/normal birth weight strata of the coal-fired power plant source with an odds ratio of 1.085 (95% CI: 0.990-1.188; IQR: 0.13 μg/m^3 increase).

CMB: Bradycardia Zero-Day Lag

We observed suggestively strong odds ratios in the bradycardia analysis mostly in the full term/normal birth weight strata. In the CMB models, suggestively strong odds ratios in the one-day lag were observed among the full term/normal birth weight in the gas source 1.029 (95% CI: 0.944-1.122; IQR: 0.94 μg/m^3 increase), the diesel source 1.062 (95% CI: 0.972-1.162; IQR: 1.17 μg/m^3 increase), woodsmoke 1.051 (95% CI: 0.943-1.173; IQR: 0.72 μg/m^3 increase), and the other organic carbon source 1.049 (95% CI: 0.962-1.144; IQR: 1.79 μg/m^3 increase).

Positive Matrix Factorization

PMF: Apnea Zero-Day Lag

In the PMF analysis we observed a number of associations between apnea events between stationary-type sources. We also observed the woodsmoke source was significant in the apnea zero-day lag for the primary analysis with an odds ratio of 1.031 (95% CI: 1.001-1.061; IQR: 0.93 μg/m^3 increase, Table 4.7.A).

We also observed associations with apnea in the positive matrix factorization method models for the ammonium sulfate source with an odds ratio of 1.054 (95% CI: 1.003-1.108; IQR: 5.78 μg/m^3 increase) in the primary analysis in the zero-day lag

We also observed negative associations with apnea in the positive matrix factorization method models for the cement kiln source among the primary analysis with an odds ratio of 0.970 (95% CI: 0.945-0.995; IQR: 0.33 μg/m^3 increase, Table 4.7.A) and among the premature/low birth weight with an odds ratio of 0.968 (95% CI: 0.940-0.9996; IQR: 0.33 μg/m^3 increase).

PMF: Apnea One-Day Lag

We observed, in the positive matrix factorization models, that woodsmoke was significant at the 0.05 level of significance in the apnea one-day lag analysis for premature/normal birth weight infants with an odds ratio of 1.041 (95% CI: 1.006-1.077; IQR: 0.93 μg/m^3 increase, Table 4.7.A). The woodsmoke source was statistically significant in the one-day lag analysis with an odds ratio of 1.048 (95% CI: 1.017-1.080; IQR: 0.93 μg/m^3 increase) in the primary strata.

We also observed associations with apnea events and the diesel/gas source in the one-day lag for the primary analysis with an odds ratio of 1.037 (95% CI: 1.000-1.076; IQR: 3.27 μg/m^3 increase; Table 4.7.A). Additionally, the positive matrix factorization method one-day lag model observed the airborne soil source was associated with apnea events with an odds ratio of 0.757 (95% CI: 0.650-0.883; IQR: 0.48 μg/m^3 increase).

PMF Bradycardia Zero-Day Lag

We observed one association in the zero-day lag for the bradycardia analysis, which was in the premature/low birth weight strata of the cement kiln source with an odds ratio of 0.983 (95% CI: 0.967-0.999; IQR: 0.33 μg/m^3 increase, Table 4.7.B).

PMF Bradycardia One-Day Lag

All three of the associations observed in the one-day lag in the bradycardia analysis were among the full term/normal birth weight infants and the sources bus/highway, woodsmoke and cement kiln with odds ratios of 0.978 (95% CI: 0.959-0.997; IQR: 0.11 μg/m^3 increase), 1.106 (95% CI: 1.031-1.186; IQR: 0.93 μg/m^3 increase) and 0.979 (95% CI: 0.963-0.995; IQR: 0.33 μg/m^3 increase), respectively.

We also observed an association for the one-day woodsmoke in the bradycardia analysis of the full term/normal birth weight strata with an odds ratio of 1.106 (95% CI: 1.031-1.186; IQR: 0.93 μg/m^3 increase).

Suggestive Patterns

PMF: Apnea Zero-Day Lag

We observed a pattern of suggestively strong odds ratios in the analysis with the pattern being most pronounced across the study in the primary analysis. Suggestively strong odds ratios were also observed in the zero-day lags for full term/normal birth weight infants in the secondary sulfate, ammonium sulfate, gas and soil sources with odds ratios of 1.059 (95% CI: 0.901-1.244; IQR: 1.31 μg/m^3 increase), 1.097 (95% CI: 0.920-1.1.308; IQR: 5.78 μg/m^3 increase) and 1.040 (95% CI: 0.958-1.128; IQR: 0.48 μg/m^3 increase), respectively.

PMF: Apnea Zero-Day Lag

In the apnea models, primary analysis (using the entire population) exhibited some strong, although not statistically significant, odds ratios in the gas source 1.030 (95% CI: 0.995-1.067; IQR: 1.23 μg/m^3 increase) and diesel with an odds ratio of 1.036 (95% CI: 0.999-1.075; IQR: 2.26 μg/m^3 increase) in the one-day lag for PMF and the gas source with an odds ratio of 1.032 (95% CI: 0.997-1.069; IQR: 0.94 μg/m^3 increase). We observed these stronger odds ratios in the PMF method for one-day lags in the railroad source with an odds ratio of 1.041 (95% CI: 0.995-1.090; IQR: 0.51 μg/m^3 increase). The ammonium sulfate source also showed a suggestively strong odds ratio in the one-day lags with an odds ratio 1.035 (95% CI: 0.985-1.087; IQR: 5.78 μg/m^3 increase), respectively.

Strong odds ratios were observed in the one-day lag of 1.112 (95% CI: 0.923-1.341; IQR: 0.91 μg/m^3 increase), 1.087 (95% CI: 0.954-1.239; IQR: 2.26μg/m^3 increase), 1.067 (95% CI: 0.921-1.235; IQR: 0.51 μg/m^3 increase) and 1.064 (95% CI: 0.937-1.210; IQR: 1.23 μg/m^3 increase) for apnea in the full term/normal birth weight strata for the ammonium nitrate, diesel, railroad and gas sources, respectively.

PMF: Bradycardia Zero-Day Lag

In the PMF bradycardia analysis of the full term/normal birth weight strata, we observed suggestive odds ratios in the diesel source 1.034 (95% CI: 0.950-1.126; IQR: 2.26 μg/m^3 increase), the gas source 1.042 (95% CI: 0.967-1.123; IQR: 1.23 μg/m^3 increase), and the diesel/gas source 1.040 (95% CI: 0.957-1.130; IQR: 3.27 μg/m^3 increase) in the zero-day and one-day lags.

We also observed a suggestively strong odds ratio of 1.069 (95% CI: 0.997-1.145; IQR: 0.93 μg/m^3 increase) in the zero-day lag among the full term/normal birth weight infants in the woodsmoke source model.

PMF: Bradycardia Zero-Day Lag

In the PMF bradycardia analysis of the full term/normal birth weight strata, we observed suggestive odds ratios in the diesel source 1.067 (95% CI: 0.978-1.164; IQR: 2.26 μg/m^3 increase), the gas source 1.054 (95% CI: 0.973-1.143; IQR: 1.23 μg/m^3 increase), and the diesel/gas source 1.067 (95% CI: 0.980-1.163; IQR: 3.27 μg/m^3 increase) in the zero-day and one-day lags, respectively. The railroad source observed a suggestively strong odds ratio of 1.055 (95% CI: 0.939-1.185; IQR: 0.51 μg/m^3 increase) in the full term/normal birth weight strata in the one-day lag.

Table 4.1 Characteristics of 3,629 infants with follow-up on monitors between 11/19/1998 – 12/31/2002.

	Infants with at least 1 apnea event	Infants with at least 1 bradycardia event
Number of patients, N	1,891	3,629
Mean (SD) follow-up time (days)	50.4 (32.6)	43.5 (31.0)
Mean (SD) age (days)	40.9 (30.6)	46.0 (34.7)
Male, N (%)	821 (56.9)	1,499 (53.5)
Mean (SD) age at date of follow-up (days)	41.1 (30.4)	45.9 (34.4)
Mean (SD) gestational age at birth (weeks)	31.2 (3.8)	31.6 (4.3)
Birth weight <2,500 grams, N (%)	1683 (89.0)	3089 (85.1)
Gestational age < 37 weeks, N (%)	1766 (93.4)	3233 (89.1)
Method of payment, N (%)		
Insurance	784 (57.7)	1,479 (56.1)
Medicaid	531 (39.0)	1,071 (40.6
Not Insured	45 (3.3)	86 (3.3)
Total number of apnea-days	8,605	-
Total number of bradycardia days	-	27,246
Total number of follow-up days	95,339	157,753
Mean (SD) compliance per patient (percent of days used of the total follow-up days)	96.8 (7.2)	96.8 (7.1)

SD = Standard Deviation

Table 4.2.A: Descriptive statistics for 24-hour average source results in µg/m^3 out of 1,502 days for chemical mass balance (CMB), November 19, 1998 – December 31, 2002; Atlanta

	N	Mean	Std Dev	25th Percentile	Median	75th Percentile	Minimum	Maximum
$PM_{2.5}$ Mass	1459	17.31	8.42	11.10	15.89	22.18	1.74	65.81
Gas	1018	1.25	0.95	0.64	1.03	1.58	0.06	8.99
Diesel	1018	1.46	1.07	0.73	1.18	1.90	0.00	8.69
Soil	1018	0.30	0.36	0.11	0.21	0.38	0.00	4.76
Woodsmoke	1018	1.03	0.60	0.60	0.90	1.32	0.08	4.55
Power Plant	1085	0.13	0.11	0.05	0.10	0.18	0.00	0.81
Ammonium Sulfate	1018	6.27	4.18	3.27	5.26	8.32	0.00	24.90
Ammonium Bisulfate	1085	0.47	1.17	0.00	0.00	0.25	0.00	11.40
Ammonium Nitrate	1009	1.43	1.25	0.60	1.01	1.89	0.02	9.66
Other Organic Carbon	1085	2.52	1.67	1.45	2.17	3.24	0.00	20.00

Table 4.2.B: Descriptive statistics for 24-hour source average results in µg/m^3 out of 1,502 days for positive matrix factorization (PMF), November 19, 1998 – December 31, 2002; Atlanta

	N	Mean	Std Dev	25th Percentile	Median	75th Percentile	Minimum	Maximum
$PM_{2.5}$ Mass	1459	17.31	8.42	11.10	15.89	22.18	1.74	65.81
Ammonium Nitrate	1009	0.98	0.89	0.38	0.68	1.29	0.00	8.03
Diesel	1018	2.24	2.12	0.80	1.62	3.06	0.00	18.89
Metal Processing	1147	0.78	0.75	0.27	0.60	1.09	0.00	8.20
Railroad	1147	0.63	0.39	0.35	0.58	0.85	0.00	2.35
Secondary Sulfate	1147	1.54	1.10	0.78	1.39	2.10	0.00	7.89
Ammonium Sulfate	1018	6.63	4.99	3.01	5.29	8.79	0.00	31.00
Bus/Highway	1147	0.14	0.46	0.01	0.03	0.13	0.00	9.32
Gas	1018	1.39	1.29	0.57	1.03	1.80	0.00	13.70
Woodsmoke	1018	1.15	1.04	0.51	0.91	1.44	0.00	9.40
Cement Kiln	1147	0.40	0.42	0.15	0.28	0.49	0.00	5.10
Soil	1018	0.55	0.74	0.20	0.38	0.67	0.00	10.70
Diesel/Gas	1018	3.63	3.14	1.58	2.69	4.84	0.00	31.00

Table 4.3: Spearman correlation coefficients between chemical mass balance sources, November 19, 1998 – December 31, 2002; Atlanta

	Gas	Diesel	Soil	Woodsmoke	Power Plant	Ammonium Sulfate	Ammonium Bisulfate	Ammonium Nitrate
Gas	1.00							
Diesel	0.48	1.00						
Soil	-0.01	0.29	1.00					
Woodsmoke	0.57	0.43	0.28	1.00				
Power Plant	0.08	0.22	0.28	0.12	1.00			
Ammonium Sulfate	0.09	0.29	0.41	0.19	0.18	1.00		
Ammonium Bisulfate	-0.02	-0.11	-0.15	0.05	0.03	-0.18	1.00	
Ammonium Nitrate	0.51	0.26	-0.28	0.38	0.05	-0.13	0.26	1.00
Other Organic Carbon	0.28	0.69	0.30	0.45	0.14	0.34	-0.05	0.12

Table 4.4: Spearman correlation coefficients between positive matrix factorization sources, November 19, 1998 – December 31, 2002; Atlanta

	Ammonium Nitrate	Diesel	Metal Processing	Railroad	Secondary Sulfate
Ammonium Nitrate	1.00				
Diesel	0.13	1.00			
Metal Processing	0.18	0.40	1.00		
Railroad	-0.14	-0.14	-0.13	1.00	
Secondary Sulfate	0.01	0.08	-0.07	0.25	1.00
Ammonium Sulfate	-0.09	0.20	0.09	0.12	0.24
Bus/Highway	0.08	0.38	0.33	-0.02	-0.15
Gas	0.03	0.63	0.19	-0.40	-0.03
Woodsmoke	0.33	0.57	0.24	-0.32	0.06
Cement Kiln	0.07	0.35	0.31	0.09	0.23
Soil	-0.31	0.13	0.10	0.14	0.11
Diesel/Gas	0.10	0.95	0.36	-0.26	0.05

	Ammonium Sulfate	Bus/ Highway	Gas	Wood smoke	Cement Kiln	Soil
Ammonium Nitrate						
Diesel						
Metal Processing						
Railroad						
Secondary Sulfate						
Ammonium Sulfate	1.00					
Bus/Highway	-0.08	1.00				
Gas	0.05	0.13	1.00			
Woodsmoke	0.03	0.18	0.47	1.00		
Cement Kiln	0.11	0.16	0.07	0.26	1.00	
Soil	0.30	0.03	0.08	-0.01	0.34	1.00
Diesel/Gas	0.16	0.32	0.82	0.58	0.28	0.12

Table 4.5: Spearman correlation coefficients between chemical mass balance (CMB) and positive matrix factorization sources (PMF), November 19, 1998 – December 31, 2002; Atlanta

CMB / PMF	Ammonium Nitrate	Diesel	Metal Processing	Railroad	Secondary Sulfate	Ammonium Sulfate
Gas	0.40	0.66	0.64	-0.13	0.05	0.05
Diesel	0.06	0.84	0.37	0.20	0.13	0.24
Soil	-0.37	0.24	0.11	0.17	0.13	0.34
Woodsmoke	0.22	0.68	0.31	-0.30	0.12	0.16
Power Plant	-0.03	0.14	0.08	0.11	0.20	0.15
Ammonium Sulfate	-0.13	0.23	0.14	0.17	0.34	0.94
Ammonium Bisulfate	0.20	-0.03	-0.07	-0.15	0.00	0.05
Ammonium Nitrate	0.90	0.37	0.26	-0.20	0.03	-0.08
Other Organic Carbon	-0.09	0.71	0.15	0.04	0.32	0.30
PM 2.5	0.12	0.63	0.40	0.01	0.30	0.72

CMB / PMF	Bus/ Highway	Gas	Woodsmoke	Cement Kiln	Soil	Diesel/Gas	$PM_{2.5}$
Gas	0.35	0.37	0.57	0.44	-0.02	0.61	0.46
Diesel	0.37	0.42	0.33	0.33	0.64	0.76	0.59
Soil	0.10	0.14	-0.02	0.32	0.94	0.23	0.19
Woodsmoke	0.18	0.65	0.76	0.33	0.26	0.73	0.58
Power Plant	0.05	0.01	0.10	0.71	0.37	0.11	0.29
Ammonium Sulfate	-0.07	0.06	0.03	0.18	0.36	0.19	0.71
Ammonium Bisulfate	-0.01	0.00	0.08	-0.06	-0.11	-0.02	0.22
Ammonium Nitrate	0.20	0.20	0.47	0.18	-0.27	0.34	0.23
Other Organic Carbon	0.20	0.69	0.30	0.16	0.15	0.77	0.61
PM 2.5	0.13	0.47	0.46	0.28	0.12	0.61	1.00

Table 4.6.A: Odds Ratios and 95% confidence intervals (per µg/m^3 IQR increase) from GEE unconditional repeated-measures logistic regression models examining the association of daily ambient source apportioned (chemical mass balance analysis) air pollution level (of lag 0 and lag 1) and apnea evening in infants on home cardiorespiratory monitors, 11/19/1998-12/31/2002.

Chemical Mass Balance Source	Source IQR	Analysis	Apnea (lag 0) OR	Apnea (lag 0) 95% CI	Apnea (lag 1) OR	Apnea (lag 1) 95% CI
$PM_{2.5}$	11.08	Primary	0.990	0.951,1.031	1.009	0.967,1.052
		Full term and NBW	1.042	0.932,1.165	1.017	0.911,1.136
		Premature and LBW	0.988	0.945,1.032	1.000	0.957,1.044
Gas	0.94	Primary	1.011	0.977, 1.046	1.032	0.997, 1.069
		Full term and NBW	1.010	0.849,1.202	1.039	0.884, 1.221
		Premature and LBW	1.003	0.967, 1.041	1.029	0.990, 1.069
Diesel	1.17	Primary	1.010	0.973, 1.050	1.029	0.991, 1.068
		Full term and NBW	0.991	0.851,1.151	1.039	0.837, 1.160
		Premature and LBW	1.011	0.968, 1.055	1.029	0.987, 1.073
Soil	0.27	Primary	0.986	0.959, 1.014	0.980	0.952, 1.008
		Full term and NBW	1.034	0.925,1.155	0.769	0.668, 0.885
		Premature and LBW	0.980	0.952, 1.009	0.978	0.948, 1.008
Woodsmoke	0.72	Primary	1.024	0.982, 1.068	1.039	0.995, 1.085
		Full term and NBW	1.044	0.881, 1.236	1.144	0.987, 1.325
		Premature and LBW	1.016	0.971, 1.064	1.026	0.978, 1.076
Coal-fired Power plant	0.13	Primary	0.987	0.951, 1.024	1.027	0.988, 1.066
		Full term and NBW	0.942	0.749, 1.187	0.873	0.720, 1.058
		Premature and LBW	0.985	0.946, 1.025	1.018	0.976, 1.061
Ammonium Sulfate	5.05	Primary	1.051	0.995, 1.109	1.013	0.962, 1.068
		Full term and NBW	1.038	0.871, 1.237	0.926	0.737, 1.164
		Premature and LBW	1.050	0.989, 1.115	1.007	0.951, 1.066
Ammonium Bisulfate	0.25	Primary	1.000	0.994, 1.007	1.006	0.999, 1.012
		Full term and NBW	1.021	0.998, 1.044	1.018	0.997, 1.040
		Premature and LBW	0.998	0.991, 1.006	1.005	0.998, 1.012
Ammonium Nitrate	1.29	Primary	1.008	0.969, 1.049	0.999	0.961, 1.038
		Full term and NBW	1.054	0.890, 1.250	1.159	1.000, 1.343
		Premature and LBW	1.008	0.965, 1.052	0.985	0.944, 1.027
Other Organic Carbon	1.79	Primary	1.010	0.975, 1.046	1.027	0.991, 1.064
		Full term and NBW	1.002	0.855, 1.174	1.095	0.962, 1.247
		Premature and LBW	1.010	0.971, 1.050	1.020	0.980, 1.061

[*] OR – Odds Ratio; IQR – Interquartile Range; CI – Confidence Interval; NBW – Normal Birth Weight; LBW – Low Birth Weight; GEE – Generalize Estimating Equation; Primary – Entire Population

[**] The model includes the source variable and age, age-squared, average daily temperature, average daily temperature squared, indicator variables for holiday amd weekday, and temporal splines with seasonal knots(temporal splines with seasonal knots are replaced with the variable combination day, day-squared and day-cubed for normal birth weight/full term apnea analysis)

Table 4.6.B: Odds Ratios and 95% confidence intervals (per μg/m^3 IQR increase) from GEE unconditional repeated-measures logistic regression models examining the association of daily ambient source apportioned (chemical mass balance analysis) air pollution level (of lag 0 and lag 1) and bradycardia evening in infants on home cardiorespiratory monitors, 11/19/1998-12/31/2002.

Chemical Mass Balance Source	Source IQR	Analysis	Bradycardia Lag 0 OR	Bradycardia Lag 0 95% CI	Bradycardia Lag 1 OR	Bradycardia Lag 1 95% CI
$PM_{2.5}$	11.08	Primary	0.999	0.975, 1.024	0.999	0.975,1.024
		Full term and NBW	1.065	0.955, 1.188	1.053	0.943,1.175
		Premature and LBW	0.994	0.968, 1.021	0.995	0.969,1.023
Gas	0.94	Primary	0.993	0.973, 1.013	0.996	0.976, 1.017
		Full term and NBW	1.022	0.930, 1.122	1.029	0.944, 1.122
		Premature and LBW	0.988	0.967, 1.010	0.989	0.967, 1.011
Diesel	1.17	Primary	1.000	0.978, 1.023	1.007	0.986, 1.029
		Full term and NBW	1.021	0.929, 1.123	1.062	0.972, 1.162
		Premature and LBW	0.999	0.976, 1.023	1.005	0.981, 1.029
Soil	0.27	Primary	0.996	0.981, 1.011	0.993	0.978, 1.008
		Full term and NBW	1.007	0.950, 1.068	1.005	0.950, 1.063
		Premature and LBW	0.994	0.977, 1.010	0.988	0.971, 1.004
Woodsmoke	0.72	Primary	0.986	0.961, 1.011	0.990	0.965, 1.015
		Full term and NBW	1.012	0.915, 1.118	1.051	0.943, 1.173
		Premature and LBW	0.984	0.957, 1.012	0.984	0.957, 1.011
Coal-fired Power plant	0.13	Primary	0.985	0.964, 1.006	0.999	0.978, 1.021
		Full term and NBW	1.085	0.990, 1.188	1.003	0.921, 1.091
		Premature and LBW	0.972	0.950, 0.995	0.991	0.968, 1.014
Ammonium Sulfate	5.05	Primary	1.001	0.970, 1.032	0.982	0.955, 1.010
		Full term and NBW	1.016	0.893, 1.156	1.009	0.891, 1.143
		Premature and LBW	0.992	0.959, 1.026	0.987	0.957, 1.018
Ammonium Bisulfate	0.25	Primary	0.999	0.995, 1.002	1.002	0.999, 1.006
		Full term and NBW	1.001	0.983, 1.019	0.994	0.976, 1.011
		Premature and LBW	0.997	0.993, 1.002	1.003	0.999, 1.006
Ammonium Nitrate	1.29	Primary	1.020	0.998, 1.042	0.993	0.971, 1.015
		Full term and NBW	0.978	0.880, 1.087	0.961	0.860, 1.075
		Premature and LBW	1.025	1.001, 1.049	0.989	0.965, 1.014
Other Organic Carbon	1.79	Primary	1.005	0.985, 1.026	0.998	0.977, 1.019
		Full term and NBW	1.021	0.941, 1.108	1.049	0.962, 1.144
		Premature and LBW	0.998	0.976, 1.021	0.998	0.976, 1.021

* OR – Odds Ratio; IQR – Interquartile Range; CI – Confidence Interval; NBW – Normal Birth Weight; LBW – Low Birth Weight; GEE – Generalize Estimating Equation; Primary – Entire Population

** The model includes the source variable and age, age-squared, average daily temperature, average daily temperature squared, indicator variables for holiday and weekday, and temporal splines with seasonal knots(temporal splines with seasonal knots are replaced with the variable combination day, day-squared and day-cubed for normal birth weight/full term apnea analysis)

Table 4.7.A: Odds ratios and 95% confidence intervals (per µg/m^3 IQR increase) from GEE unconditional repeated-measures logistic regression models examining the association of daily ambient source apportioned (positive matrix factorization) air pollution level (of lag 0 and lag 1) and apnea evening in infants on home cardiorespiratory monitors, 11/19/1998-12/31/2002.

Positive Matrix	Source		Apnea Lag 0		Apnea Lag 1	
Factorization	IQR	Analysis	OR	95% CI	OR	95% CI
$PM_{2.5}$	11.08	Primary	0.990	0.951, 1.031	1.009	0.967, 1.052
		Full-term and NBW	1.042	0.932, 1.165	1.017	0.911, 1.136
		Pre-term and LBW	0.988	0.945, 1.032	1.000	0.957, 1.044
Ammonium Nitrate	0.91	Primary	1.012	0.972, 1.054	0.999	0.960, 1.040
		Full term and NBW	1.009	0.818, 1.244	1.112	0.923, 1.341
		Premature and LBW	1.020	0.975, 1.067	0.993	0.951, 1.038
Diesel	2.26	Primary	1.009	0.974, 1.046	1.036	0.999, 1.075
		Full term and NBW	1.020	0.878, 1.185	1.087	0.954, 1.239
		Premature and LBW	1.006	0.967, 1.048	1.031	0.989, 1.075
Metal processing Plants	0.82	Primary	0.988	0.956, 1.020	1.002	0.970, 1.035
		Full term and NBW	0.938	0.786, 1.120	0.811	0.645, 1.020
		Premature and LBW	0.989	0.954, 1.026	1.018	0.982, 1.056
Railroads	0.51	Primary	1.018	0.973, 1.064	1.041	0.995, 1.090
		Full term and NBW	0.949	0.791, 1.139	1.067	0.921, 1.235
		Premature and LBW	1.021	0.973, 1.071	1.025	0.975, 1.078
Secondary Sulfate	1.31	Primary	0.997	0.957, 1.039	0.969	0.928, 1.012
		Full term and NBW	1.059	0.901, 1.244	0.937	0.747, 1.176
		Premature and LBW	0.994	0.950, 1.040	0.957	0.913, 1.003
Ammonium Sulfate	5.78	Primary	1.054	1.003, 1.108	1.035	0.985, 1.087
		Full term and NBW	1.097	0.920, 1.308	0.951	0.775, 1.165
		Premature and LBW	1.048	0.993, 1.107	1.028	0.975, 1.085
Bus and Highway	0.11	Primary	1.000	0.992, 1.008	1.003	0.995, 1.010
		Full term and NBW	0.964	0.929, 1.001	0.998	0.981, 1.015
		Premature and LBW	0.997	0.988, 1.006	1.003	0.994, 1.011
Gas	1.23	Primary	1.015	0.981, 1.050	1.030	0.995, 1.067
		Full term and NBW	1.024	0.891, 1.177	1.064	0.937, 1.210
		Premature and LBW	1.012	0.975, 1.052	1.027	0.988, 1.067
Wood-Smoke	0.93	Primary	1.031	1.001, 1.061	1.048	1.017, 1.080
		Full term and NBW	1.017	0.878, 1.180	1.112	0.993, 1.246
		Premature and LBW	1.024	0.991, 1.059	1.041	1.006, 1.077
Cement Kiln	0.33	Primary	0.970	0.945, 0.995	1.016	0.991, 1.042
		Full term and NBW	0.933	0.833, 1.045	0.937	0.813, 1.079
		Premature and LBW	0.968	0.940, 0.996	1.019	0.990, 1.048
Soil	0.48	Primary	0.985	0.962, 1.008	0.983	0.960, 1.007
		Full term and NBW	1.040	0.958, 1.128	0.757	0.650, 0.883
		Premature and LBW	0.978	0.955, 1.002	0.980	0.955, 1.006
Diesel/Gas	3.27	Primary	1.013	0.978, 1.049	1.037	1.000, 1.076
		Full term and NBW	1.024	0.883, 1.186	1.084	0.955, 1.231
		Premature and LBW	1.009	0.970, 1.050	1.032	0.991, 1.075

[*] OR – Odds Ratio; IQR – Interquartile Range; CI – Confidence Interval; NBW – Normal Birth Weight; LBW – Low Birth Weight; GEE – Generalize Estimating Equation; Primary – Entire Population

[**] The model includes the source variable and age, age-squared, average daily temperature, average daily temperature squared, indicator variables for holiday and weekday, and temporal splines with seasonal knots(temporal splines with seasonal knots are replaced with the variable combination day, day-squared and day-cubed for normal birth weight/full term apnea analysis)

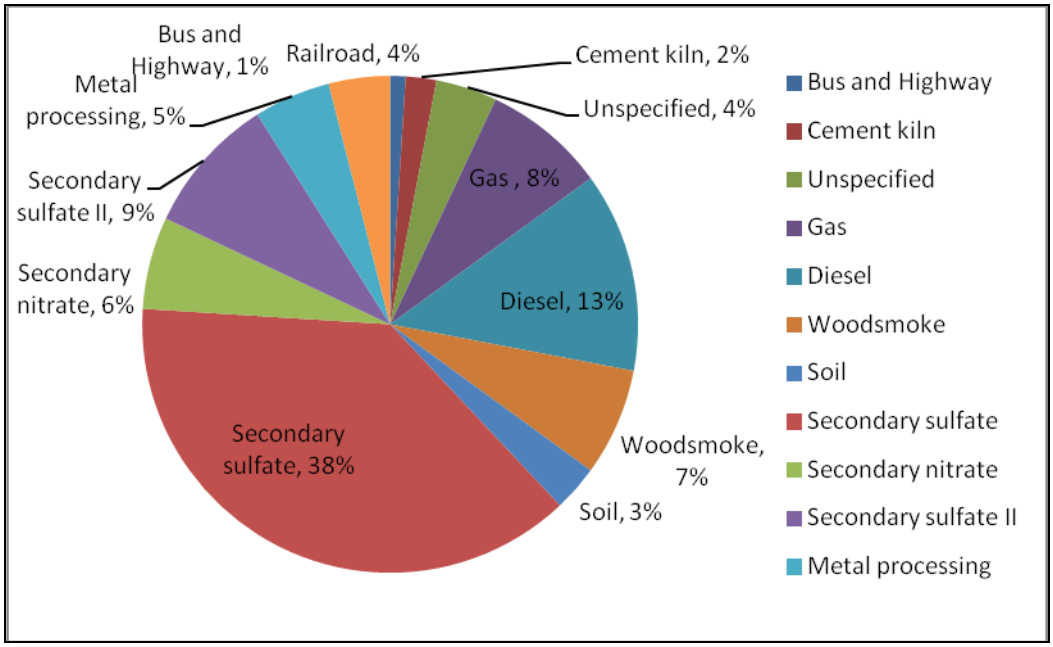
Table 4.7.B: Odds ratios and 95% confidence intervals (per μg/m^3 IQR increase) from GEE unconditional repeated-measures logistic regression models examining the association of daily ambient source apportioned (positive matrix factorization) air pollution level (of lag 0 and lag 1) and bradycardia evening in infants on home cardiorespiratory monitors, 11/19/1998-12/31/2002.

Positive Matrix	Source		Bradycardia Lag 0		Bradycardia Lag 1	
Factorization	IQR	Analysis	OR	95% CI	OR	95% CI
$PM_{2.5}$	11.08	Primary	0.999	0.975, 1.024	0.999	0.975,1.024
		Full term and NBW	1.065	0.955, 1.188	1.053	0.943,1.175
		Premature and LBW	0.994	0.968, 1.021	0.995	0.969,1.023
Ammonium Nitrate	0.91	Primary	1.018	0.994, 1.042	0.991	0.969, 1.014
		Full term and NBW	0.983	0.883, 1.094	0.951	0.853, 1.059
		Premature and LBW	1.023	0.997, 1.049	0.989	0.964, 1.013
Diesel	2.26	Primary	0.995	0.974, 1.017	1.001	0.979, 1.023
		Full term and NBW	1.034	0.950, 1.126	1.067	0.978, 1.164
		Premature and LBW	0.992	0.969, 1.015	0.993	0.970, 1.018
Metal processing Plants	0.82	Primary	0.989	0.971, 1.008	0.986	0.966, 1.007
		Full term and NBW	1.015	0.937, 1.100	0.988	0.900, 1.086
		Premature and LBW	0.984	0.964, 1.004	0.984	0.963, 1.006
Railroads	0.51	Primary	1.001	0.975, 1.027	1.020	0.993, 1.047
		Full term and NBW	0.900	0.795, 1.018	1.055	0.939, 1.185
		Premature and LBW	1.005	0.977, 1.033	1.020	0.991, 1.050
Secondary Sulfate	1.31	Primary	1.018	0.995, 1.042	1.005	0.983, 1.028
		Full term and NBW	0.971	0.873, 1.082	0.978	0.878, 1.089
		Premature and LBW	1.022	0.996, 1.048	1.006	0.982, 1.031
Ammonium Sulfate	5.78	Primary	0.991	0.963, 1.020	0.986	0.960, 1.012
		Full term and NBW	1.007	0.894, 1.134	0.993	0.890, 1.109
		Premature and LBW	0.982	0.952, 1.012	0.992	0.963, 1.021
Bus and Highway	0.11	Primary	0.998	0.994, 1.002	0.997	0.992, 1.001
		Full term and NBW	1.000	0.987, 1.013	0.978	0.959, 0.997
		Premature and LBW	0.997	0.993, 1.001	0.997	0.993, 1.002
Gas	1.23	Primary	0.997	0.977, 1.017	1.002	0.982, 1.022
		Full term and NBW	1.042	0.967, 1.123	1.054	0.973, 1.143
		Premature and LBW	0.989	0.967, 1.011	1.002	0.980, 1.024
Wood-Smoke	0.93	Primary	1.007	0.989, 1.026	1.009	0.990, 1.028
		Full term and NBW	1.069	0.997, 1.145	1.106	1.031, 1.186
		Premature and LBW	1.001	0.981, 1.021	1.001	0.981, 1.022
Cement Kiln	0.33	Primary	0.986	0.972, 1.000	0.986	0.972, 1.000
		Full term and NBW	0.995	0.933, 1.060	0.998	0.935, 1.065
		Premature and LBW	0.983	0.967, 0.999	0.979	0.963, 0.995
Soil	0.48	Primary	0.993	0.980, 1.006	0.997	0.985, 1.010
		Full term and NBW	1.008	0.961, 1.057	1.005	0.961, 1.051
		Premature and LBW	0.990	0.976, 1.005	0.993	0.979, 1.007
Diesel/Gas	3.27	Primary	0.995	0.974, 1.017	1.001	0.980, 1.023
		Full term and NBW	1.040	0.957, 1.130	1.067	0.980, 1.163
		Premature and LBW	0.990	0.967, 1.013	0.996	0.973, 1.020

* OR – Odds Ratio; IQR – Interquartile Range; CI – Confidence Interval; NBW – Normal Birth Weight; LBW – Low Birth Weight; GEE – Generalize Estimating Equation; Primary – Entire Population

** The model includes the source variable and age, age-squared, average daily temperature, average daily temperature squared, indicator variables for holiday and weekday, and temporal splines with seasonal knots(temporal splines with seasonal knots are replaced with the variable combination day, day-squared and day-cubed for normal birth weight/full term apnea analysis)

A.



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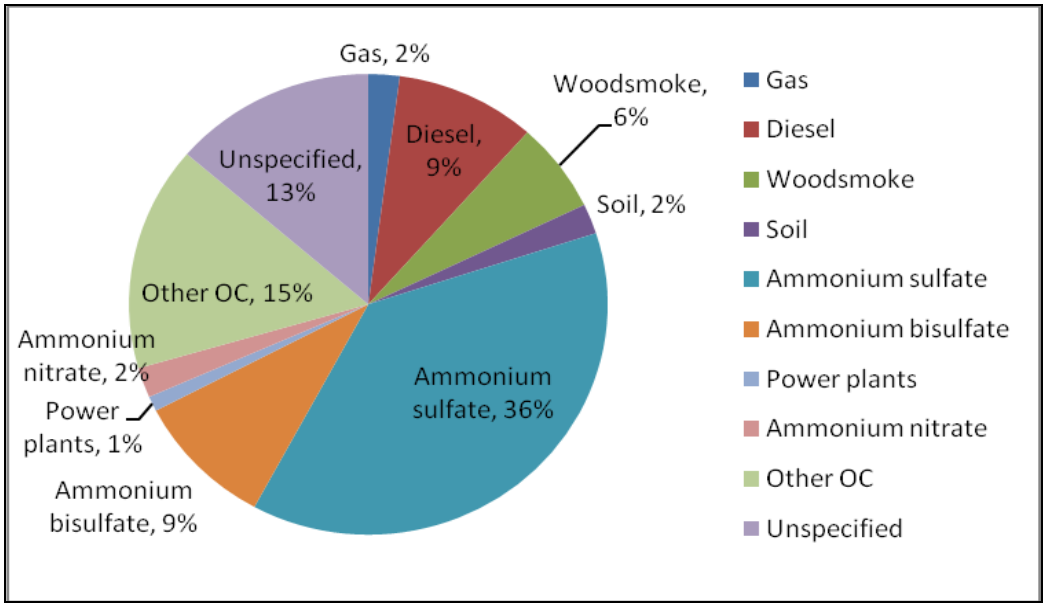

Figure 4.1: Fractional contribution to $PM_{2.5}$ source categories from (A) positive matrix factorization and (B) chemical mass balance.

Species	Gasoline	Diesel	Soil	Woodsmoke	Coalfired Power Plant	Cement Kiln	Ammonium Sulfate*	Ammonium Bisulfate*	Ammonium Nitrate*	Other Organic Carbon*
SO_{4-2}	0.013	0.005	0.001	0.024	0.287	0.314	0.727	0.835	0.000	0.000
NO_{3-}	0.000	0.002	0.001	0.002	0.007	0.089	0.000	0.000	0.775	0.000
Cl-	0.000	0.001	0.001	0.076	0.009	0.071	0.000	0.000	0.000	0.000
NH_{4+}	0.000	0.000	0.000	0.017	0.018	0.024	0.273	0.156	0.225	0.000
EC	0.236	0.735	0.006	0.158	0.014	0.030	0.000	0.000	0.000	0.000
OC	0.549	0.198	0.044	0.644	0.272	0.128	0.000	0.000	0.000	1.000
Al	0.002	0.000	0.095	0.001	0.053	0.011	0.000	0.000	0.000	0.000
As	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Ba	0.000	0.000	0.000	0.000	0.011	0.000	0.000	0.000	0.000	0.000
Br	0.000	0.000	0.000	0.001	0.000	0.001	0.000	0.000	0.000	0.000
Ca	0.012	0.001	0.018	0.004	0.166	0.175	0.000	0.000	0.000	0.000
Cu	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000
Fe	0.012	0.000	0.053	0.001	0.036	0.013	0.000	0.000	0.000	0.000
K	0.000	0.000	0.009	0.057	0.005	0.116	0.000	0.000	0.000	0.000
Mn	0.000	0.000	0.002	0.000	0.001	0.001	0.000	0.000	0.000	0.000
Pb	0.002	0.000	0.000	0.000	0.001	0.001	0.000	0.000	0.000	0.000
Sb	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Se	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000
Si	0.012	0.000	0.266	0.003	0.107	0.043	0.000	0.000	0.000	0.000
Sn	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Ti	0.000	0.000	0.010	0.000	0.009	0.002	0.000	0.000	0.000	0.000
Zn	0.009	0.001	0.000	0.000	0.003	0.004	0.000	0.000	0.000	0.000

Figure 4.2 CMB particulate source profiles used in the apportionment process (Fraction of total $PM_{2.5}$ emissions and standard deviations over multiple measurements. * Based on molecular-weight fractions. Adapted from Marmur et al. (2005).

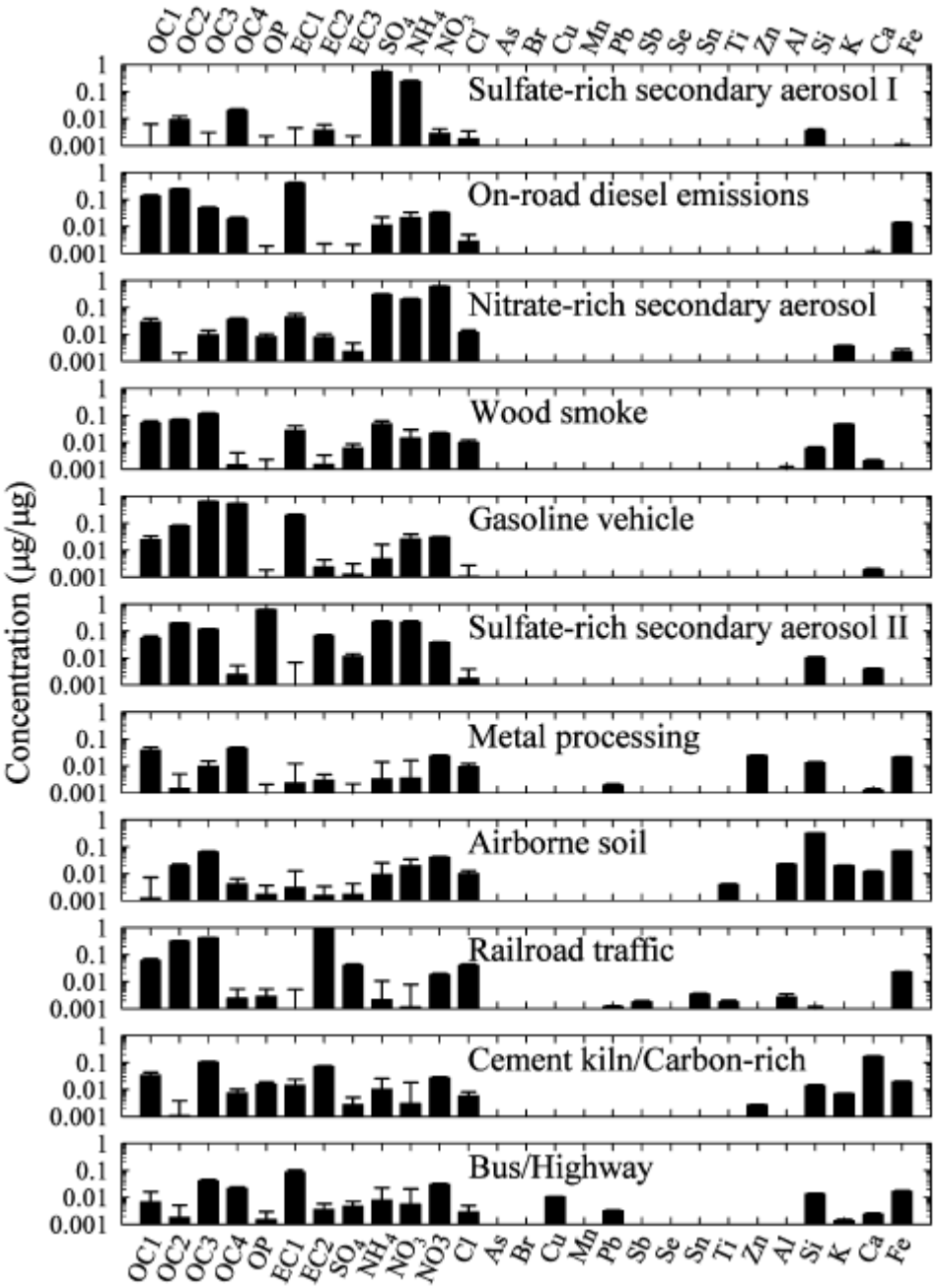

Figure 4.3. PMF source profiles resolved from $PM_{2.5}$ samples (prediction $\pm$ standard deviation). Adapted from Kim et al. (2004).

Chapter 5: Discussion

In general, results from this study were null. We did observe a pattern of suggestive positive odds ratios, especially in the primary analysis, such as for woodsmoke source, which were consistent across source apportionment method and lag structure. We observed positive associations in the positive matrix factorization models for the woodsmoke source in the apnea zero-day lag for the primary. We also observed positive associations in the positive matrix factorization models for the woodsmoke source in the apnea one-day lag analysis for primary and premature/normal birth weight. The results for the full term/normal birth weight strata had stronger odds ratios than for both the primary and premature/low birth weight strata.

Overall in our analysis, we observed a similar pattern across apnea and bradycardia analysis for both positive matrix factorization method and chemical mass balance leading to evidence that possibly supports the proposed suggestion by Peel et al. (2003) that premature infants may not be able to launch an appropriate immune response to the pollutants (Figures 5.1-5.8). This may be interpreted to corroborate prior work by Peel et al. (2003) in that these infants may have had an underdeveloped response to the pollutants and pollutant sources. This study directly addresses previous research by Bates et al. (1995), Bateson et al. (2008) and Brook et al. (2010) who have speculated that infants and children may be more at risk of adverse health effects of air pollution.

Overall, the results were robust to changes in specified correlation structure as we saw minimal changes in point estimates and confidence intervals across stationary 45-

dependent, autoregressive, compound symmetric and independent correlation structures. Across the two source apportionment methods we observed that the odds ratios for the mobile sources corresponded well, as did those of the woodsmoke, cement kiln, metal processing plant and coal-fired power plant sources.

We observed interesting associations between cardiorespiratory events and source apportioned fine particulate matter reflected in patterns of significant and suggestively strong odds ratios across the PMF and CMB analysis. The stronger and consistent pattern in the woodsmoke source made its association with cardiorespiratory events stand out more than other sources. It appeared in our study that the most evidence of suggestively strong odds ratios came from the results of the primary analysis in the woodsmoke source. The woodsmoke source results in the primary analysis appeared to maintain these stronger odds ratios across both source apportionment methods. These suggestively strong odds ratio were also observed to remain strong in both lag structures and in the apnea and bradycardia analysis. The main component of woodsmoke was organic carbon (OC) and elemental carbon (EC), which made it somewhat surprising that we did not see as many significant associations between the cardiorespiratory events and the sources containing OC such as diesel, gas and other organic carbon. Although, across the study, these OC containing sources did not show statistically significant results as consistently as woodsmoke, they did fall into the pattern of suggestively strong odds ratios.

The metal processing, cement kiln, secondary sulfate, soil, bus/highway and coal-fired power plant sources were all consistently observed to have odds ratios below the null. We are unsure as to why these sources would result in 'protective' odds ratios. It could be that the wind may be related to the appearance of a protective effect of these

sources since the wind may be lowering the impact of these other sources by dispersion. The dispersion of pollutant sources would decrease the infants' exposure to the pollutant sources. The hypothesis being that when the wind comes up infants are not exposed at as high levels as the air pollution monitors recorded resulting in the observation of protective odds ratios.

Overall in the CMB, we did not observe any clear patterns in the data, although, it appeared that the point estimates were stronger in the one-day lags in comparison to the zero-day lags among the apnea events. However, no discernable pattern was observed in the results among the lag periods for the bradycardia events. Across the gestational age and birth weight strata in the CMB method, it was evident that the infants in the full term/normal birth weight strata had stronger odds ratios compared to those of the primary or the premature/low birth weight strata. By event, the apnea events showed a stronger pattern than bradycardia. Most of these suggestive apnea odds ratios were in the zero-day lag analysis and the full term/normal birth weight strata.

Similar to the CMB lag analysis, in the analysis of the PMF method we did observe that apnea odds ratio estimates being stronger for one-day lags than for zero-day lags. Among the suggestively stronger odds ratios, the pattern of apnea odds ratio point estimates for one-day lags were stronger than zero-day lags was clearer. The pattern of stronger odds ratios among the bradycardia odds ratio point estimates was only apparent across the suggestively strong estimates.

By grouping what could be considered the PMF mobile sources diesel, gas and diesel/gas together, we observed very similar odds ratio estimates and confidence

intervals. Among the mobile sources in the CMB method gas and diesel we also observed very similar estimates. While the railroad and bus/highway sources seemed to follow similar patterns with each other within the apnea analysis, they did not appear to fit a pattern within the bradycardia or the other mobile sources. Although they were primarily skeptical protective odds ratios, the cement kiln and the metal processing plant sources, we observed strikingly similar point estimates and confidence intervals. These similarities across the study lead us to believe there is a strength and consistency in our results. When taking the presence of the suggestively strong odds ratios, it is our interpretation that further research is worthwhile in investigating the associations of cardiorespiratory events in infants of the Atlanta area with mobile source pollution.

Our results were similar to those highlighted in the work by Peel et al. (2003), in that Peel et al. recognized that full term/normal birth weight infants appeared to have stronger odds ratios than premature/low birth weight infants. The investigation by Peel et al. (2003) estimated associations between cardiorespiratory events and daily ambient air pollution on the same cohort of infants from August 1, 1998 to December 31, 2002. Similar to the results by Peel et al. (2003), we observed mostly non-significant associations, yet some suggestively strong odds ratios.

The results of this study also contribute evidence that supports the findings of work by Larson et al. (1994) who observed consistent associations between biomass burning and respiratory events. Thurston and Ito et al. (2005) observed associations between secondary sulfates and traffic related fine particulate matter ($PM_{2.5}$) and cardiovascular/non-accidental mortality in the D.C. and Phoenix cohorts, which match with our findings of secondary sulfates and combined diesel/gasoline mobile sources.

The strength of the associations is consistent with the odds ratios and relative risks seen in other similar studies. For example, a six year study observed that crustal and secondary sources were associated with cardiovascular admissions, biomass sources were associated with respiratory admissions, and vehicle sources were associated with asthma admissions (Andersen et al. 2007). Sarnat et al. (2008) observed significant, positive associations between cardiovascular-related emergency department visits with same-day $PM_{2.5}$ concentrations attributed to mobile sources with relative risks ranging from 1.018 to 1.025 (per IQR increase) and biomass combustion with relative risks ranging from source categories 1.024 to 1.033 (per IQR increase). Sarnat et al. (2008) also observed associations between source categories containing sulfate-rich secondary $PM_{2.5}$ with relative risks ranging from 1.012 to 1.020 (per IQR increase).

Limitations

Information Bias

This research has a number of limitations. One limitation is the cardiorespiratory monitor use and the failure to capture all events due to the infant not always being connected to the monitor. Missing these events can lead to a potential for event days to be misclassified as non-event days resulting in false negatives and reducing sensitivity of monitor data. Misclassification of event days as non-event days would likely result in a bias toward the null and would likely decrease the power of our analysis. Clinicians verified recorded cardiorespiratory events. This clinician verification confirmed the validity of recorded events assuring there were no false positive events. Clinician verification and using only patient data from infants who had download periods with

more than 66% compliance during a download period and only the download periods for which the infant used the monitor for 66% of the days reduced our concern of further bias due to misclassification of events.

Exposure estimation is often considered the most challenging aspect of environmental epidemiological studies. Error in assessing environmental exposure in this study may have resulted in systematic error resulting in a bias towards null. The error may have occurred due to the use of a centralized air monitor for collecting the air pollution data which could have lead to non-differential misclassification.

Selection Bias

Selection bias is especially of concern in case control studies in selection of cases and controls in epidemiological studies because of the possibility that participants might have been selected differently based on disease and exposure status. Selection bias can also be of concern in cohort studies when there is loss to follow-up. Since the patients in our study were selected without knowledge of their exposure status to the ambient air pollution sources and the nature of our study did not allow for the possibility of loss to follow-up, we do not believe there to be a concern for selection bias.

Confounding and Effect Modification

We attempted to adjust for time, season, age and temperature in the statistical models. The complication of the model resulting in the inability to use the preferred model, which included splines for temperature, was partially rectified by using the 24-hour average for temperature and temperature-squared. This change was less than ideal for accounting for the influence of temperature in our analysis; however, we did find the

results to be robust to changes in temperature adjustment (data not presented). In the additional models we ran, we did not observe much evidence of confounding by the time and temperature variables. Some factors, such as smoking status of family members/caretakers, smoking status in the household, indoor allergens such as, molds, pollens, dust, rodents or other local or household exposures, amount of time outside, neonatal exposures to endocrine disrupting compounds, maternal consumption of alcohol and cigarettes are less of a concern as confounders in our study since they are unlikely to be associated with the day-to-day change in pollution. However, these could be potential effect modifiers of interest, which future studies may consider addressing.

Other Limitations

It was surprising that both the CMB coal fired power plant source and the PMF cement kiln source resulted in 'protective' odds ratios since we observed no evidence in the literature to support this. In our study we estimated odds ratios and 95% confidence intervals for 22 sources, two lag periods, two health outcome measures, and three strata of gestation and birth weight status totaling 252 estimates. With this number of statistical tests, (if each of these tests were independent, which they were not) we would expect that approximately 13 estimates would result in significance at the 5% level of significance (both positive and protective). The challenge of these associations presents a substantial limitation since we cannot differentiate between the significant results observed that are true from those which are statistical anomalies. Furthermore, the inability to utilize the same covariates in the analysis of the full term/normal birth weight infant in the apnea analysis due to failure of convergence of the Hessian matrices resulted in a lack of

comparability of the full term/normal birth weight infant in the apnea results across the analysis.

Another limitation to this study is one of temporal sequence in the zero-day lag. Since events in our study are presented as event-days, we cannot be sure that the exposure came before the event. An example is the situation in which an infant has a cardiorespiratory event in the early hours of the morning, say 3 a.m. When we are analyzing the data using the zero-day lag, we might falsely assume that the event occurred after the exposure. However, the temporal sequence cannot be verified.

The incorporation of source apportionment is a relatively new tool to epidemiological studies. As few epidemiological studies have utilized source apportionment in their studies, the standardization of methods and protocols for utilizing this tool are still being developed. Three key issues arise from the novelty of source apportionment in epidemiological studies. The first is that the 'art' of source apportionment means that different practitioners may make different decisions along the series of decisions that lead them to discriminate between sources. Second, the naming of the sources may lead to different practitioners using the same name to describe sources whose sources are actually the not the same. Lastly, the naming of sources may not actually be what the name implies. These three issues mean that there may be a lack of repeatability and consistency in the source apportionment of air pollution which leads to a challenge in interpreting the results of epidemiological studies. However, studies by Thurston et al. (2005), Ito et al. (2006) and Hopke et al. (2006) have shown in work with the United States Environmental Protection Agency there to be reliability in the

consistency across methods such that there is less concern about issues which may arise due to source naming and practitioner techniques.

The exposure assessment is also complicated by the fact that the majority of our cohort was low birth weight and premature infants who likely spent very little time out of doors. Furthermore, approximately 83% of homes in Atlanta are equipped with central air conditioning, which can change the actual exposure to ambient outdoor air pollution sources (US Census Bureau 1997). Thus, the presence of air conditioning in the home may have an unknown impact on the actual exposure of the infants to pollution sources, resulting change in the exposure of the participants than what was measured at the air pollution monitor (Metzger et al. 2004; Peel et al. 2005).

Strengths

The clinician verification of the events decreased the potential for systematic error by limiting measurement error. Furthermore, this study adds to the body of source apportionment and health effect literature utilizing two methods of source apportionment and novel health outcomes. Additionally, a notable strength in our study is the large sample size. The access to such a large cohort of infants with the apnea and bradycardia data made this study a unique and important contribution to the understanding of the associations between cardiorespiratory events and source apportioned fine particulate matter in infants on cardiorespiratory monitors.Our study also provides information on a sensitive and susceptible population of research.

Conclusion

We examined the associations of ambient source apportioned air pollutants with bradycardia and apnea events in a cohort of infants prescribed home cardiorespiratory monitors. Our results were primarily null. We observed a pattern of suggestively strong odds ratios, especially in the primary analysis, such as in the woodsmoke source results, which were consistent across source apportionment method and lag. We observed positive associations in the positive matrix factorization models for the woodsmoke source in the apnea zero-day lag for the primary as well as in the one-day lag analysis for primary and premature/normal birth weight. Our analysis also observed a positive association between apnea and the ammonium nitrate source (one-day lag) among the full term/normal birth weight infants in the chemical mass balance in the zero-day lag model among low birth weight/premature of the chemical mass balance model for bradycardia. We observed some suggestive associations between apnea and bradycardia events and source apportioned fine particulate matter, which contributes to the body of air pollution literature.

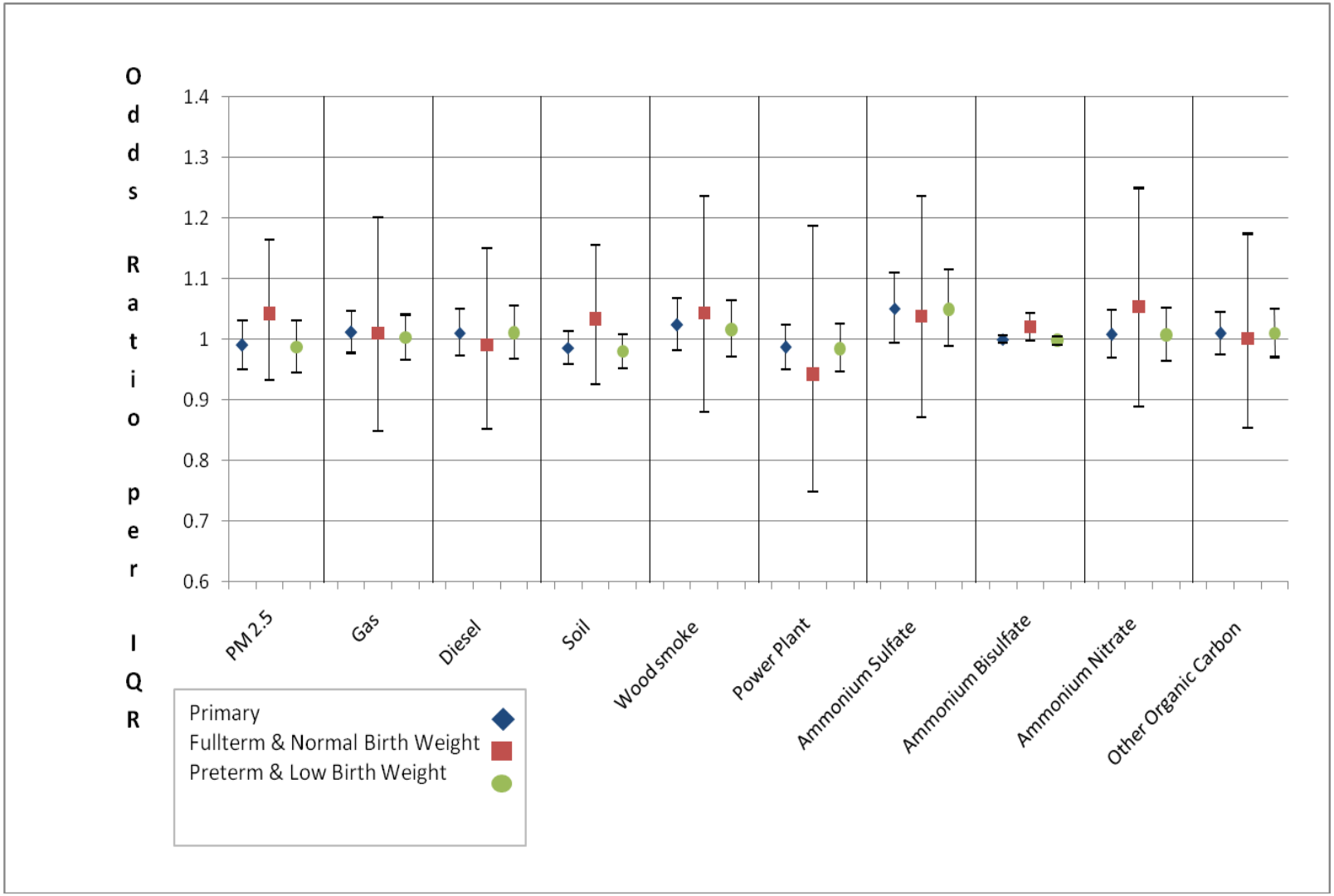

Figure 5.1 Chemical Mass Balance Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 0-day Lag Apnea Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

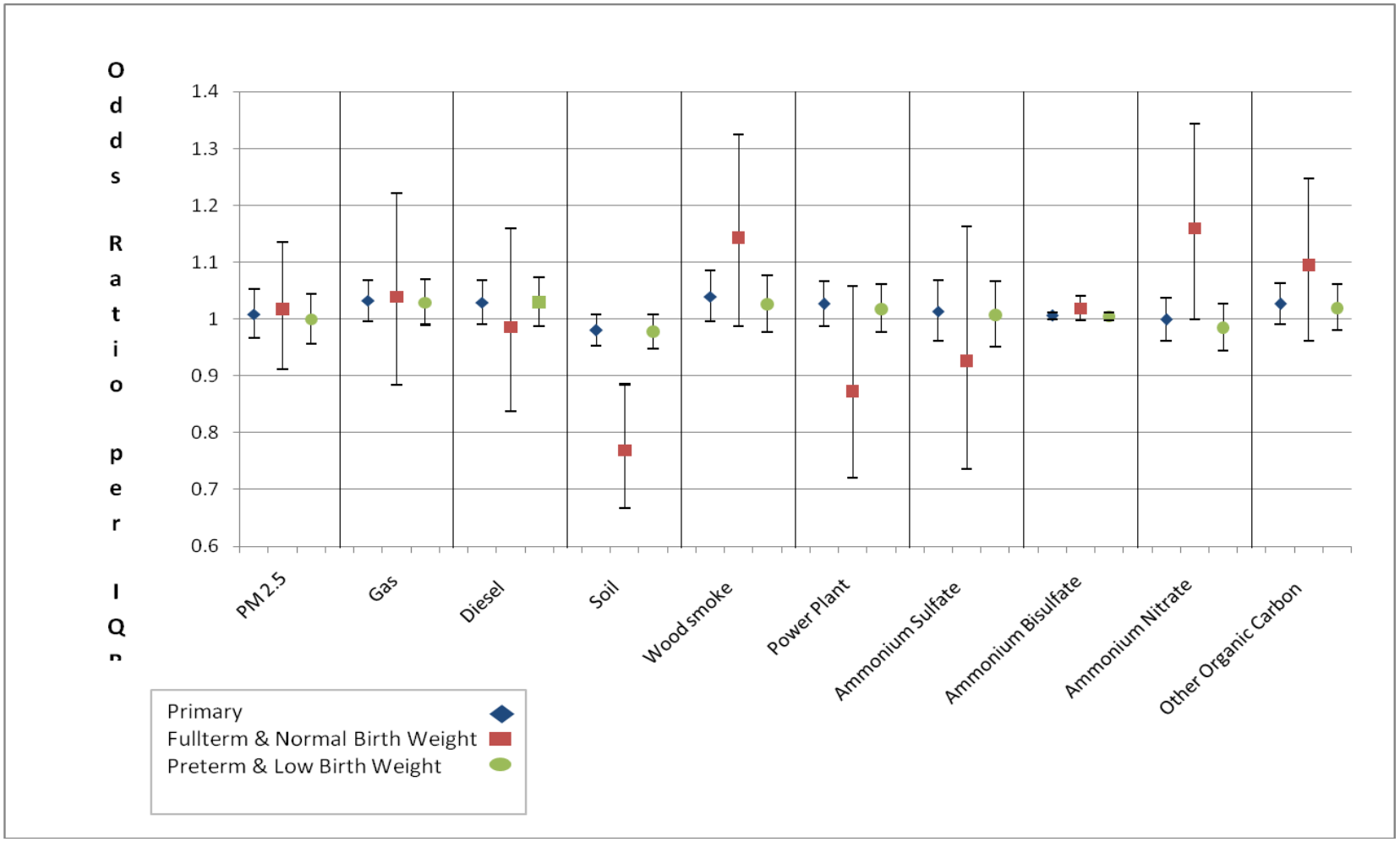

Figure 5.2 Chemical Mass Balance Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 1-day Lag Apnea Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

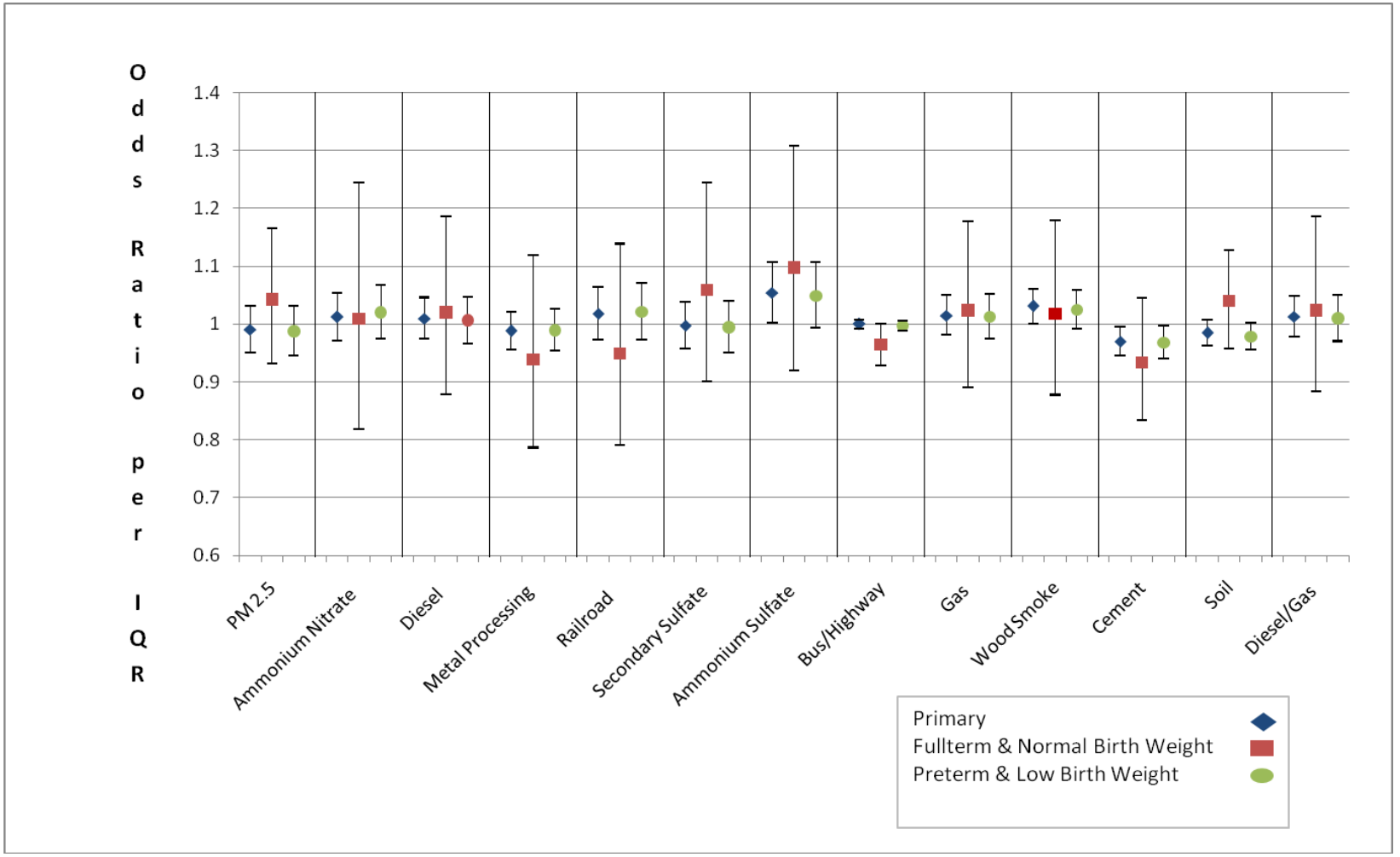

Figure 5.3 Positive Matrix Factorization Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 0-day Lag Apnea Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

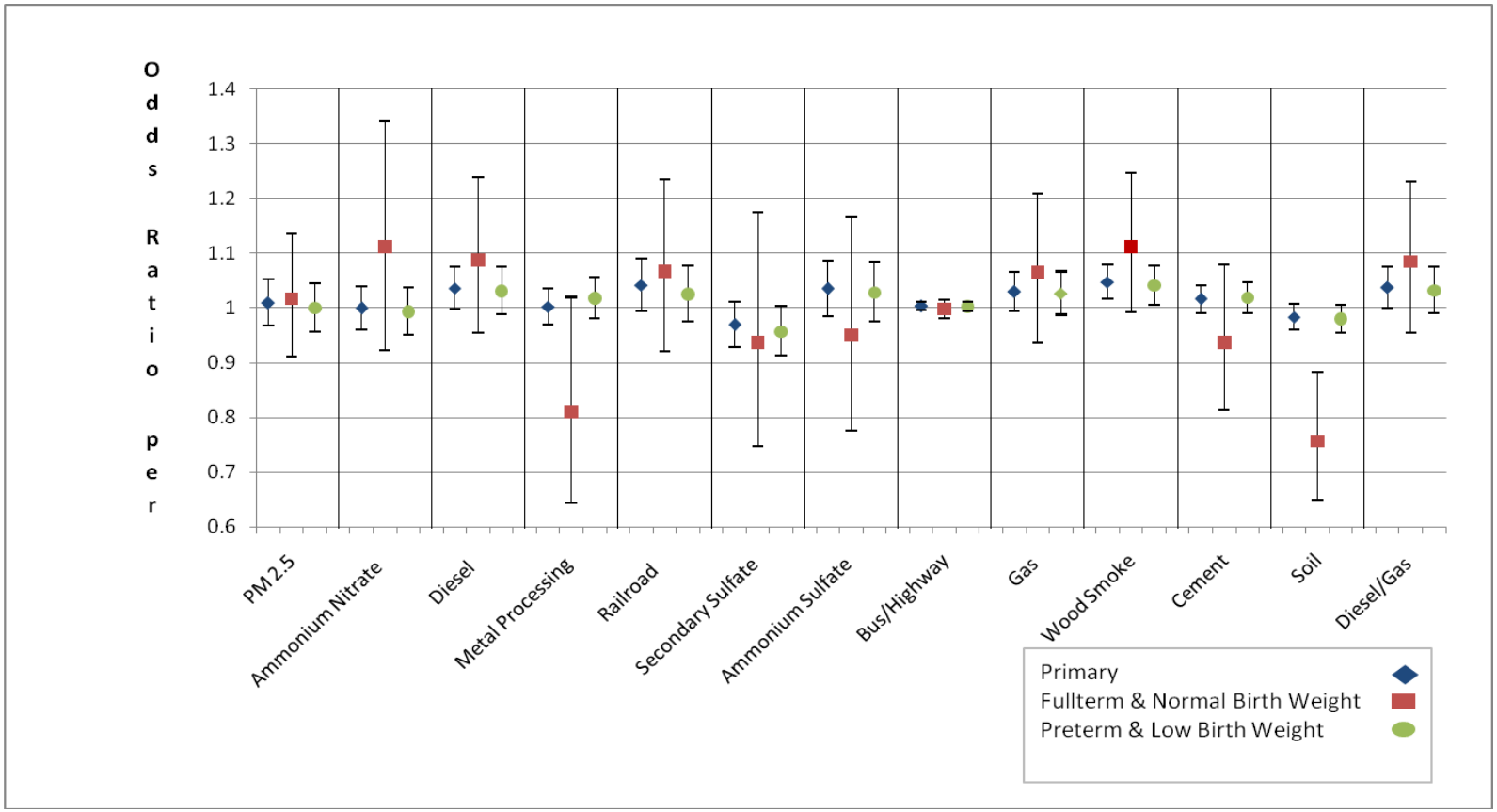

Figure 5.4 Positive Matrix Factorization Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 1-day Lag Apnea Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

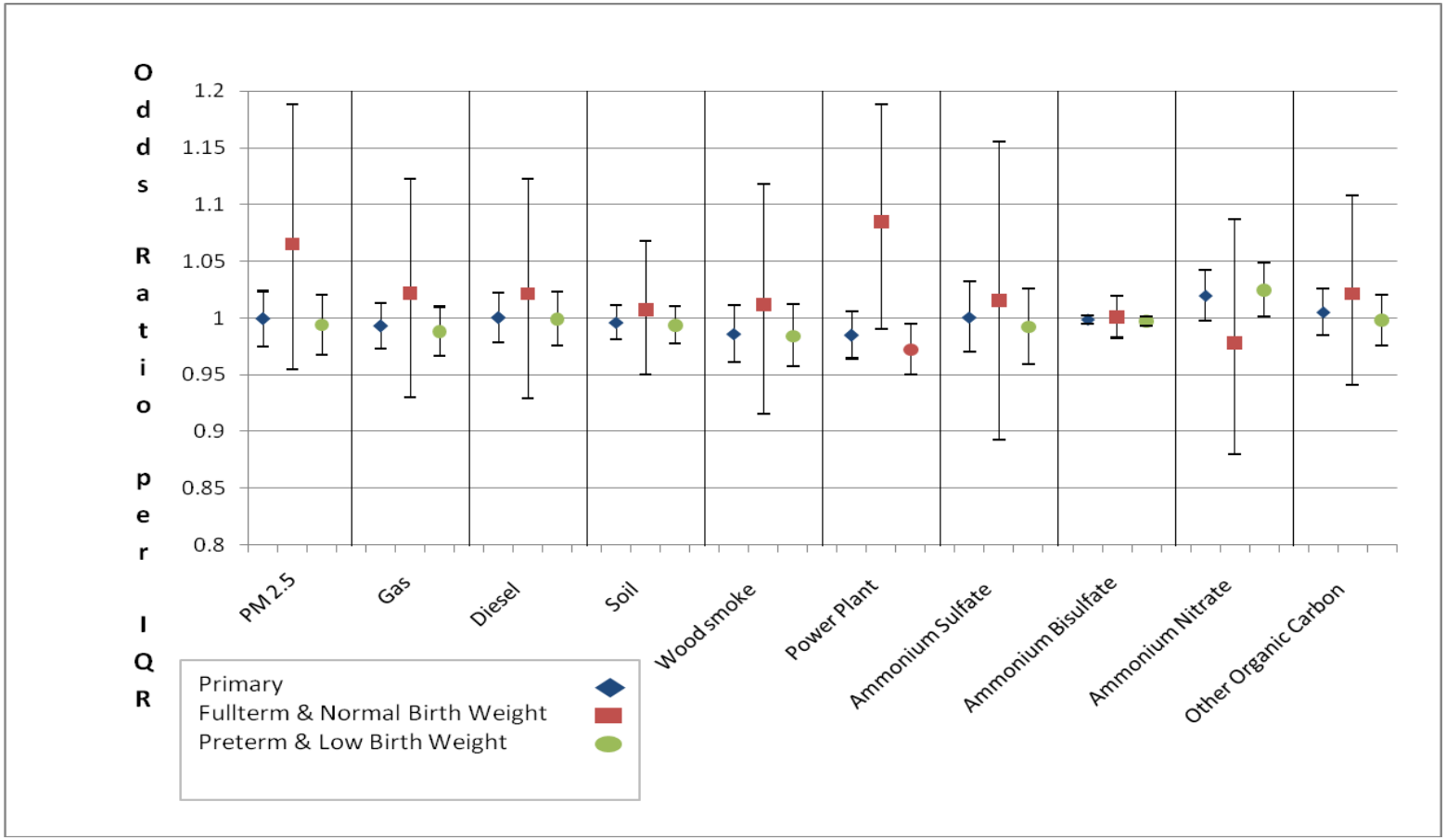

Figure 5.5 Chemical Mass Balance Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 0-day Lag Bradycardia Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

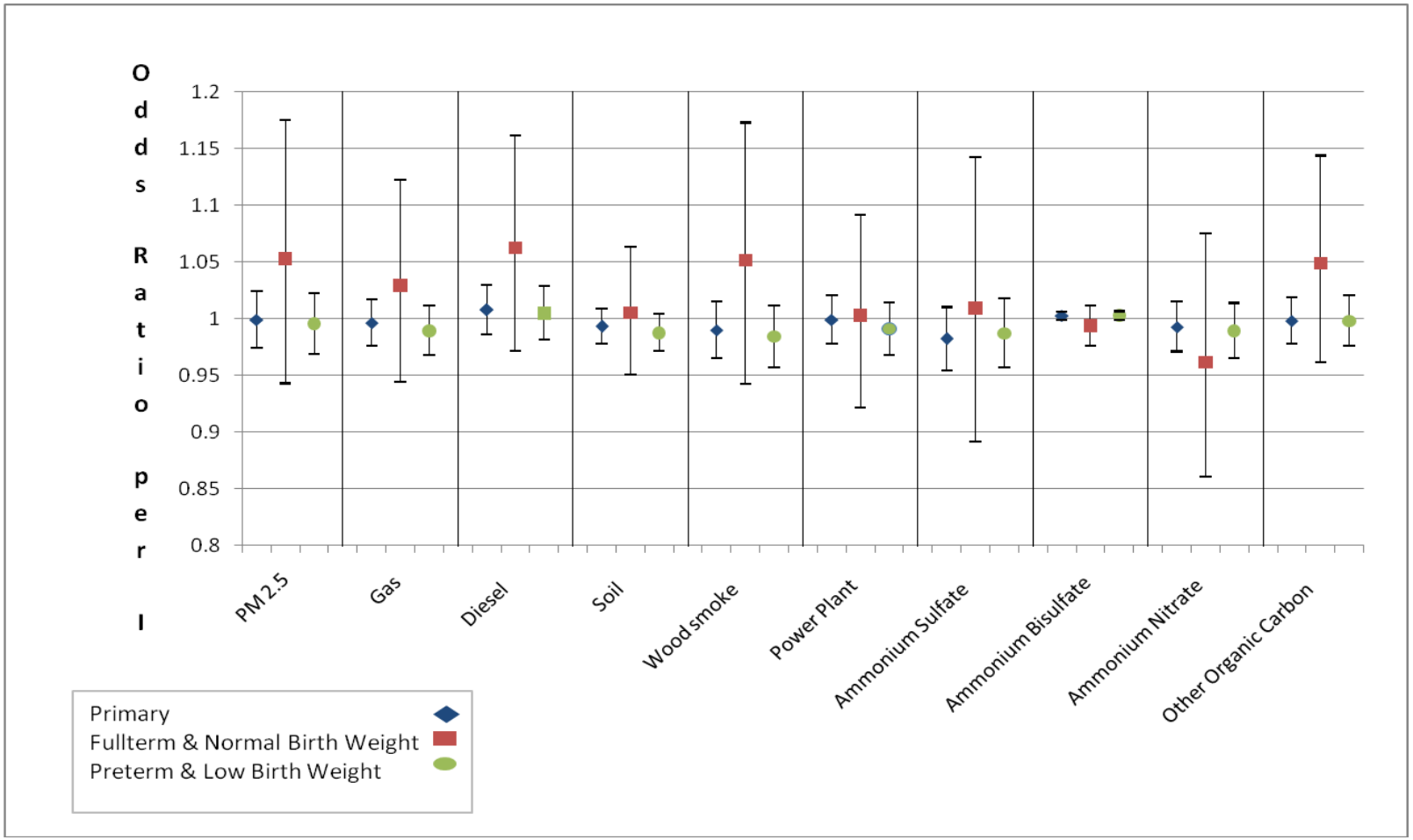

Figure 5.6 Chemical Mass Balance Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 1-day Lag Bradycardia Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

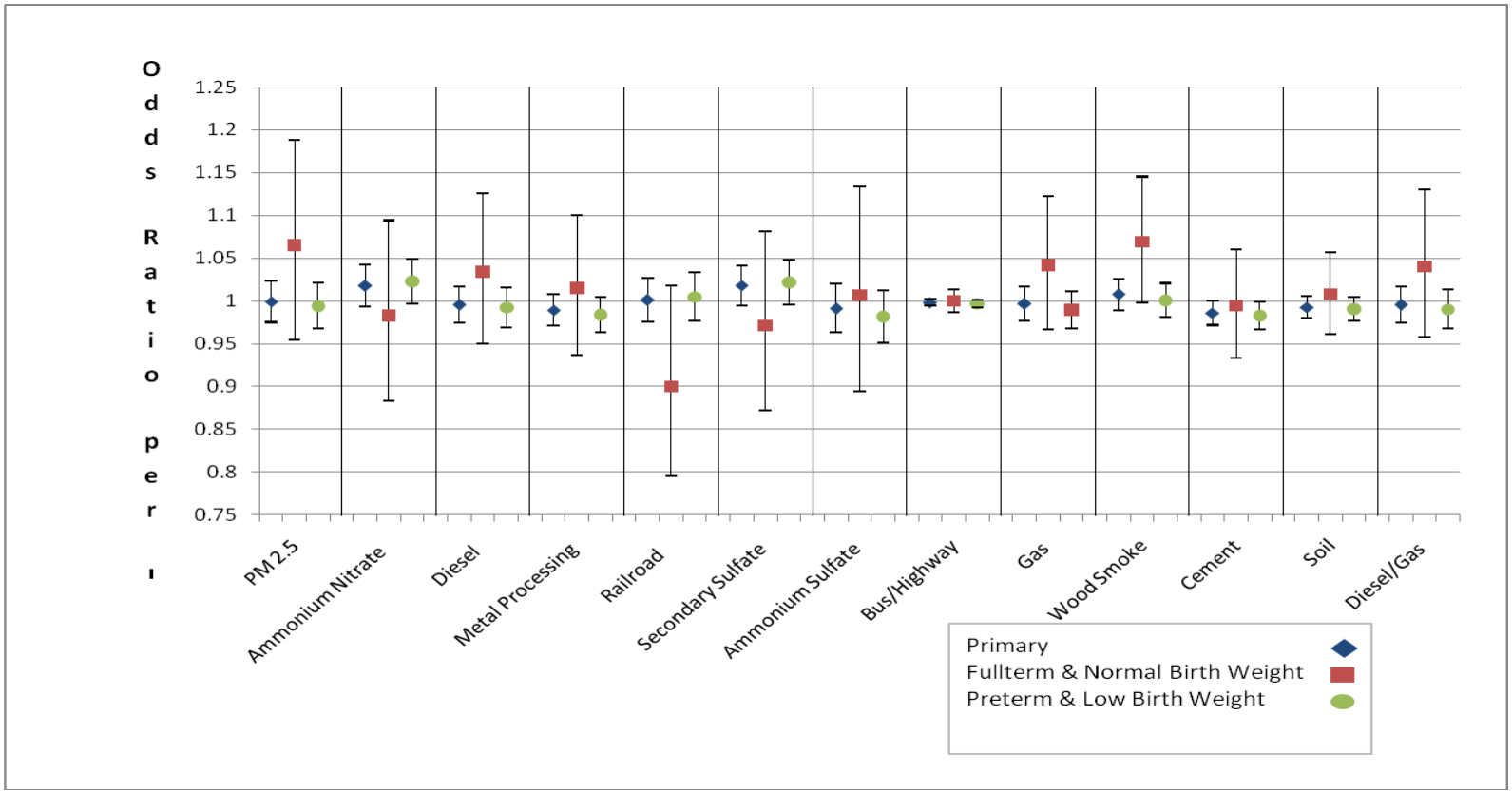

Figure 5.7 Positive Matrix Factorization Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 0-day Lag Bradycardia Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

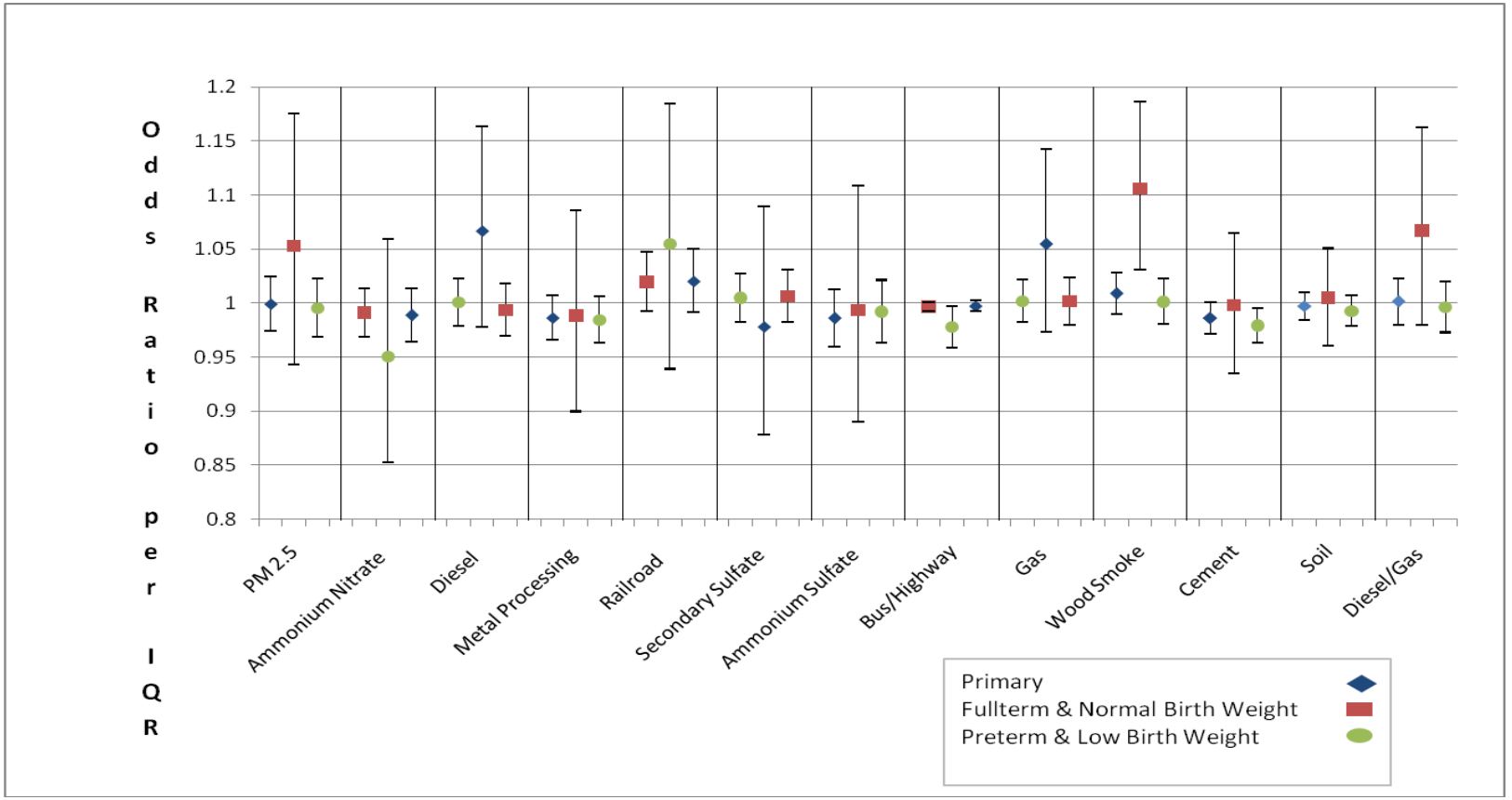

Figure 5.8 Positive Matrix Factorization Results (with 95% Confidence Intervals) for GEE Unconditional Logistic Regression Analyses Examining the Association of Daily Source apportioned Air Pollution Levels (per Interquartile-Range) for 1-day Lag Bradycardia Events in Infants on Home Cardiorespiratory Monitors, 11/19/1998 - 12/31/2002, Atlanta

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