MATERNAL EXPOSURE TO CRITERIA AIR POLLUTANTS DURING EARLY PREGNANCY AND CONGENITAL HEART DEFECTS IN OFFPSRING

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ABSTRACT

JEANETTE ANNE STINGONE: Maternal exposure to criteria air pollutants during pregnancy and congenital heart defects in offspring
(Under the direction of Andrew F. Olshan, PhD)

Toxicological and epidemiological literature suggests that maternal exposure to air pollutants during pregnancy has the potential to disrupt fetal development, resulting in adverse pregnancy outcomes in offspring. The goal of this dissertation was to explore the relationship between maternal exposure to carbon dioxide, nitrogen dioxide, ozone, coarse and fine particulate matter and sulfur dioxide during the window of fetal cardiac development, weeks 2 through 8 of pregnancy, and congenital heart defects (CHDs) in offspring within the context of the National Birth Defects Prevention Study (NBDPS), a large population-based case-control study. Specific Aim 1 sought to explore the relationships between pollutants and individual CHDs in a novel way, by assessing individual weeks of exposure in addition to a seven-week summary measure and utilizing hierarchical regression models to address the issue of multiple inference. These relationships were also explored in a multipollutant context by using principal components analysis to construct source-factor models. Positive associations were observed for several pollutants and CHDs in both single-pollutant and source-factor analyses. Assessing individual weeks of fine particulate matter exposure revealed potential windows of greater susceptibility, including week 2 for tetralogy of Fallot (odds ratio, OR 1.98 95% confidence interval, CI 1.11,3.46) and week 5 for pulmonary valve stenosis (OR 1.83 95% CI 1.08,3.12) when contrasting women in the highest and lowest deciles of exposure. Women who used supplements containing folic-acid, a methyl donor involved in the regulation of DNA methylation processes, had lower odds of offspring with CHDs associated with fine particulate

matter exposure than women who did not report taking supplements, suggesting a potential mechanism underlying these associations. Specific Aim 2 sought to compare the monitor-derived estimates of fine particulate matter and ozone exposure to model-derived estimates with greater temporal and spatial resolution. This comparison revealed little effect of the greater temporal resolution and found observed differences in results using monitor-based versus model-based exposure estimates potentially attributable to the spatial differences in the composition of particulate matter. The findings of this dissertation support further avenues of research including how risk of CHDs varies by the composition of fine particulates and the quality of maternal nutrition.

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LIST OF ABBREVIATIONS

APVR: anomalous pulmonary venous return

AQS: air quality system

ASD: atrial septal defect

ATSDR: Agency for Toxic Substances and Disease Registry

AVSD: atrioventricular septal defect

CATI: computer assisted telephone interview

CDC: Centers of Disease Control

CHD: congenital heart defect

CI: confidence interval

CMAQ: community multiscale air quality

CO: carbon monoxide

COA: coarctation of the aorta

DAG: directed acyclic graph

DFE: dietary folate equivalents

DORV: double outlet right ventricle

d-TGA: d-Transposition of the Great Arteries

EDD: estimated date of delivery

EMM: effect measure modification

EPA: Environmental Protection Agency

HLHS: hypoplastic left heart syndrome

IAA: interrupted aortic arch

ICD: international classification of diseases

IRB: institutional review board

LUR: land use regression model

LVOTO: left ventricular outflow tract obstructions

NBDPS: National Birth Defects Prevention Study

NO: nitrogen oxide

NO_2: nitrogen dioxide

OR: odds ratio

PAH: polycyclic aromatic hydrocarbon

PCA: principal component analysis

$PM_{2.5}$: particulate matter 2.5 micrometers or less in diameter

PM_{10}: particulate matter 10 micrometers or less in diameter

PVS: pulmonary valve stenosis

RVOTO: right ventricular outflow tract obstructions

SLAMS: state and local air monitoring systems

SMOKE: sparse matrix operator kernel emissions model

SO_2: sulfur dioxide

STS: Society of Thoracic Surgeons

TAPVR: total anomalous pulmonary venous return

TOF: tetralogy of Fallot

UV: ultra-violet

VSD: ventricular septal defect

CHAPTER 1

1. INTRODUCTION AND SPECIFIC AIMS

Over the past few decades, the availability of ambient air pollutant monitoring data has led to extensive research investigating the health effects of exposure to air pollution on adults and children.[1,2] In the last decade, a growing number of studies have examined prenatal exposure to air pollutants and a variety of adverse birth outcomes.[3-27] The pollutants most often examined are the criteria air pollutants identified by the Clean Air Act: carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) and less than 2.5 μm in diameter ($PM_{2.5}$), ozone (O_3), and sulfur dioxide (SO_2).

Epidemiologic studies provide some evidence of an association between congenital heart defects (CHDs), the most common class of birth defects, and exposure to criteria air pollutants. However, results have been inconsistent, with observed associations between pollutants and specific defects not replicated in subsequent studies.[5,8,16,18,22-25] Because the observed effect estimates are small, exposure misclassification and confounding can have a large impact on results, potentially contributing to these discrepancies. One potential source of misclassification is the use of ambient measurements taken at a single stationary monitor to assign exposure, regardless of the distance from the maternal residence. Spatiotemporal prediction models, which predict a gridded air pollutant surface from multiple sources of data, including emissions and meteorological data, may provide a better estimation of exposure in areas with low monitoring density.[28]

Misclassification can also arise from assigning exposure using residence at delivery, instead of complete residential histories.[29,30] Important associations may be masked when individual CHDs are aggregated into etiologically heterogeneous groupings, when pollutants are examined individually, without adjusting for other copollutants, or by residual confounding from the incomplete or inaccurate information on confounders contained in administrative data sources used for many studies.[31,32] Additionally, analytic methods often do not easily allow for exploring multiple windows of exposure through the course of pregnancy, nor do they account for the underlying spatial and temporal correlation in the data which can impact precision of estimates.[33]

Although mechanisms behind the associations between air pollutants and birth defects are not well elucidated, Baccarelli et al has shown exposure to particulate air pollution was associated with decreased DNA methylation.[34] Considered in conjunction with previous research which found associations between measures of maternal DNA methylation during pregnancy and birth defects, there may be potential for altered DNA methylation mechanisms to play a role in the association between particulate matter and CHDs.[35] Because folate acts as a methyl donor that is necessary to initiate and regulate DNA methylation processes, it is possible that a woman's folate status during pregnancy may modify impacts from particulate matter, and that women with low folate levels may be especially vulnerable to the impacts of air pollutants.[36] To date, no studies have examined the role of folate as a potential modifier in the relationship between particulate matter and birth defects, as most studies utilizing administrative databases lack detailed nutrition information.

The goal of this dissertation is to utilize the National Birth Defects Prevention Study (NBDPS), a large population-based national case-control study of birth defects with detailed residential history, nutrition and other covariate information in order to investigate the relationships between maternal exposure to criteria air pollutants during pregnancy and CHDs. The specific aims are:

Specific Aim 1: To determine whether exposure during pregnancy to individual criteria air pollutants, assessed using measurements from stationary air monitors, is associated with CHDs

Subaim 1a: To determine if the relationship between exposure to $PM_{2.5}$ and CHDs is modified by use of folic-acid supplements early in pregnancy

Subaim 1b: To explore the effect of multiple pollutants on CHDs using principal components analysis (PCA)

Specific Aim 2: To utilize the greater spatial and temporal resolution of exposure estimates derived from deterministic pollutant simulation models to investigate the association between select criteria air pollutants and CHDs

Subaim 2a: To compare effect estimates and model fit when using monitoring data and output from a statistical model which combines the two in order to assign women's exposure during pregnancy

Subaim 2b: To determine if the addition of rural populations, who are often excluded from studies due to large distance from monitoring sites, affects the observed relationship between exposure to criteria air pollutants and CHDs

Specific Aim 1 will be accomplished by linking data from the NBDPS to measured ambient levels of criteria air pollutants obtained from EPA's repository of air quality monitoring data, known as the air quality system (AQS). Specific Aim 2 will focus on $PM_{2.5}$ and ozone and will utilize modeled exposure estimates derived from the EPA's community multiscale air quality (CMAQ) model, a deterministic pollutant simulation model, as well as a downscaler spatiotemporal statistical model which combines the gridded cell predictions of CMAQ with monitoring data to point locations.[28]

CHAPTER 2

2. BACKGROUND

2.1 Ambient Air Pollution

Ambient air pollutants are any solid, liquid, or gaseous substance found in the outdoor air, resulting from either natural or man-made processes. For centuries, there has been concern over the impact of contaminants in the air on the health of exposed populations. As far back as the 18th century, Bernardo Ramazzini discussed in his treatise *De Morbis Artificum* the case of a manufacturing plant in a small town outside of Modena where "fumes given off by the vitriol which so tainted the air nearby that it was rendered unhealthy and dangerous for the lungs".[37] In 1931, the New York Academy of Medicine published its first report on the effect of air pollution on health, concluding that the air pollution problem in New York City and other cities was a "serious menace to health".[38] Two decades later, following the Great Smog of London in 1952, the U.S. federal government began to address the issue by passing the Air Pollution Control Act of 1955, which provided federal monies for air pollution research.[39] In 1963, the first Clean Air Act was passed, which provided funds and authorization for federal research into air pollution monitoring and control. A few years later, the Air Quality Act of 1967 expanded monitoring studies and began to regulate interstate air pollution transport. However, it was the Clean Air Act of 1970 that created specific federal and state regulations designed to limit pollutant emissions and to expand enforcement of these regulations.[39] The Clean Air Act focused on the monitoring and regulation of six ubiquitous pollutants which were linked to harmful effects on human health. These pollutants

known as the criteria air pollutants are: carbon monoxide (CO), lead, nitrogen oxides (NO_x) with a particular focus on nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM) of different sizes, and sulfur dioxide (SO_2). The National Ambient Air Quality Standards (NAAQS) for these pollutants are provided in Table 1.[40]

Table 2.1: Current National Ambient Air Quality Standards for the Criteria Air Pollutants

	Primary Standard		Secondary Standard	
Pollutant	Level	Averaging Time	Level	Averaging Time
Carbon Monoxide	9 ppm (10 mg/m^3)	8-hour┼	None	
	35 ppm (40 mg/m^3)	1-hour┼		
Lead	0.15 µg/m^3	Rolling 3-Month Average	Same as Primary	
Nitrogen Dioxide	53 ppb	Annual	Same as Primary	
	100 ppb	1-hour±	None	
PM_{10}	150 µg/m^3	24-hour€	Same as Primary	
$PM_{2.5}$	12.0 µg/m^3	Annual (averaged over 3 years)	Same as Primary	
	35 µg/m^3	24-hour±	Same as Primary	
Ozone	0.075 ppm (2008 std)	8-hour ¥	Same as Primary	
	0.08 ppm (1997 std)	8-hour¥	Same as Primary	
	0.12 ppm	1-hour	Same as Primary	
Sulfur Dioxide	0.03 ppm	Annual	0.5 ppm	3-hour┼
	0.14 ppm	24-hour┼		
	75 ppb	1-hour	None	

*reproduced from http://www.epa.gov/air/criteria.html; primary standards are defined as limits to protect public health, while secondary standards set limits to protect public welfare, which includes protecting damage to animals, crops, vegetation, and buildings

┼ cannot be exceeded more than once per year

±the 3-year average of the 98th percentile at each monitor within an area cannot exceed the limit

€ cannot be exceeded on average more than once per year over a 3 –year period

¥3-year average of the fourth-highest daily maximum 8-hour average

As a result of increased monitoring and regulation mandated by the Clean Air Act of 1970 and its subsequent amendments, the concentration of pollutants in air has greatly diminished.[41] Despite these improvements, there are many areas of the US which remain in non-attainment of the NAAQS standards. Additionally, research indicates that these pollutants may have health effects

below current regulatory levels, particularly among vulnerable populations such as the elderly, children, asthmatics, people with preexisting heart conditions, pregnant women and developing fetuses.[42,43] The extensive monitoring system begun to oversee compliance with the Clean Air Act provides a valuable resource for air pollution epidemiology and public health research, as the availability of exposure estimates for the entire United States greatly facilitates human health studies into the effects of the criteria air pollutants.

2.1.1 Criteria Air Pollutants

As a result of the Clean Air Act and changes in motor vehicle and industrial technologies, the ambient air concentration of all of the criteria air pollutants has decreased. However, since the reduction and eventual removal of lead from gasoline, the concentration of lead in the air has dropped more than any other pollutant. From 1980-2009, the amount of lead found in ambient air has dropped, on average, 93%.[44] Subsequently, the primary route of exposure to lead is through dust and soils, and not inhalation of ambient air. Therefore, lead will not be included in this study of criteria air pollutants and birth outcomes. Below is a brief description of each of the criteria air pollutants, including information about sources, variability, and general toxicity. More detailed information on potential mechanisms for their action on reproductive and birth outcomes are included in Section 2.1.1.6.

2.1.1.1 Carbon Monoxide (CO)

Description and Sources

Carbon monoxide is a colorless, odorless gas emitted from incomplete combustion of organic materials. The EPA estimates that 95% of CO emissions in the US are from man-made sources, with more than two-thirds resulting from motor vehicle emissions.[45] Since the late 1970s when motor vehicles became equipped with catalytic convertors, which convert CO into carbon dioxide, the levels of CO in ambient air have been greatly reduced, approximately 80% since 1980. Subsequently, the ability for ambient CO to be used as a marker for exposure to

motor vehicle traffic has been diminished. People are also exposed to CO through use of tobacco products and exposure to environmental tobacco smoke.

Temporal and geographic variability

CO is highest in late winter, when weather inversions trap ambient air pollutants closer to the earth's surface. Daily patterns in CO levels follow the use of motor vehicles, with highest levels corresponding to morning and early evening rush hours. Ambient levels tend to be greater at higher altitude, and are also greater in urban areas, corresponding to greater amounts of motor vehicle use.[45]

Toxicity

CO primarily acts by displacing oxygen and binding with hemoglobin in the blood to form carboxyhemoglobin. This reduces the oxygen-carrying ability of the blood and the amount of oxygen transported to tissues and organs, with the degree dependent upon the amount of CO exposure. High exposures of CO can lead to severe tissue hypoxia. Exposures to CO from the ambient air and/or exposure to tobacco smoke are generally lower than the level associated with severe toxicity, but have been shown to cause more subtle hypoxic effects. Additionally, CO can bind with heme in proteins in other areas of the body, including myoglobin in muscle tissue, certain transcription factors, and in proteins involved in physiological regulatory processes that may utilize endogenous CO. It is hypothesized that exposure to exogenous CO may disrupt these regulatory processes, which include nitric oxide cell-signaling pathways, energy metabolism, and mitochondrial respiration.[45]

2.1.1.2 Nitrogen Dioxides (NO_2)

Description and Sources

Nitrogen dioxide is also a gaseous pollutant produced through combustion processes, often with nitrogen oxide (NO) and other oxidized nitrogen compounds. In conjunction with

volatile organic compounds and hydrocarbons, NO_2 is a precursor for ozone formation, as well as other air toxics including nitro-PAHs, which are formed either directly through combustion of fuels or in the atmosphere. NO_2 also contributes to the acidification of particulate matter in the ambient air. While the relative contribution of sources can vary by local area, the primary sources of NO_2 are motor vehicles and electricity generation.[46]

Temporal and Geographic Variability

Similar to other air pollutants, NO_2 is higher in winter due to weather inversions and tends to fluctuate according to periods of high motor vehicle use. Ambient levels of NO_2 often peak during morning rush hour and tends to be higher in urban areas, particularly in the Northeastern United States.[46]

Toxicity

NO_2 is highly water soluble, and when inhaled, reacts with moisture in the airways to produce nitric acids, which irritate the airways. Further, NO_2 can react with unsaturated fatty acids in the body, initiating the production of free radicals, which can cause protein oxidation, lipid peroxidation, and cell membrane damage. At high exposures, NO_2 will displace oxygen and bind with hemoglobin in the blood stream to form methemoglobin, which can lead to hypoxia.[46]

2.1.1.3 Ozone (O_3)

Description and Sources

Ozone is a secondary pollutant. It is formed from atmospheric reactions involving sunlight and other air pollutants and is not directly emitted from a mobile or fixed source. The two primary classes of ozone precursors are NO_x and VOCs. As discussed above, the primary source of atmospheric NO_x is motor vehicle exhaust, while the primary source of VOCs is solvent use, followed closely by on-road vehicles.[47]

Temporal and Geographic Variability

Because ozone forms as a result of photochemical reactions in the atmosphere, ambient levels tend to be higher in summer when sunlight is greater and in the mid-afternoon, when enough time as passed for the reactions to take place. In many areas of the United States, ozone isn't monitored in the winter months. Similar to other pollutants, ambient ozone levels are higher in urban areas, but geographically tend to be greater in the warm areas of the West and Southwest, as opposed to the Northeast.[47]

Toxicity

Ozone is a highly reactive gas and, similar to NO_2, its main method of action is through oxidation, particularly of unsaturated fatty acids in the extracellular lining fluid of the respiratory tract. Ozone-mediated oxidation reactions generate free radicals, which can then react to form cytotoxic nonradicals. The byproducts of these reactions may provide the mechanism for non-pulmonary health effects by initiating/propagating inflammatory effects or increasing oxidative stress.[47]

2.1.1.4 Particulate Matter (PM)

Description and Sources

Particulate matter (PM) refers to a heterogeneous mixture of solid and liquid particles that can vary in size, shape and composition based on their source. Classified by particle diameter, the most commonly monitored and investigated classes are PM_{10} and $PM_{2.5}$. The subscript refers to the diameter size of the particles included in the grouping. Often PM_{10} is used to refer to $PM_{10-2.5}$ which includes particles with diameters between 2.5 and 10 microns in diameter. This is often referred to as coarse PM. $PM_{2.5}$ is referred to as fine PM, while particulates with diameter less than 0.1 microns are designated as ultrafine. Primary particulates result from a specific source, while secondary particles are created through the

oxidation of pollutant gases. Coarse PM is more likely to consist of primary particulates. The predominant source of primary PM_{10} is road dust, while the predominant source of primary $PM_{2.5}$ is wild fires, followed by road dust and electricity generation. The majority of $PM_{2.5}$ is secondary particles, formed through processes such as coagulation, where two small particles combine to form one, condensation, when gases combine to form a single particle or through nucleation where gases react to form products with very low vapor pressure and then undergo a phase change to create an ultrafine particle. In addition to size, PM can be further classified by its primary chemical constituents. The primary chemical species of $PM_{2.5}$ investigated are sulfate, nitrate, organic carbon, elemental carbon, total carbon, and water-soluble metals.[48]

Temporal and geographic variability

In general, PM peaks during cooler temperatures, although this varies based on geography and composition of the particles. Certain chemical species of $PM_{2.5}$ exhibit more seasonality than others. For example, organic carbon particulates peak during the fall and winter in the western United States and between spring and fall in the southeastern United States, while elemental carbon is relatively stable. Concentrations of sulfate in particulates peak during warmer temperatures when more oxidation of SO_2 occurs. In contrast, nitrate species peak during cooler temperatures when there is more temperature-driven partitioning and volatilization. Both PM_{10} and $PM_{2.5}$ peak twice during the day, once in the morning, corresponding to rush hour and the breakup of the overnight inversion layer and again starting during the evening rush hour and extending into the later evening hours corresponding to changes in atmospheric layers.

Geographically, coarse PM is found in warmer, drier climates such as the West and Southwest while $PM_{2.5}$ has higher ambient levels in the northeastern areas of the United States, particularly in urban areas. There is also geographic variability among the different chemical

species of $PM_{2.5}$. In the eastern United States, sulfate is the most common component followed by organic carbon, while in the western part of the country, organic carbon is most prevalent.[48]

Toxicity

Both its chemical composition and the surface characteristics of the particulate are thought to give PM oxidative potential, causing injury and inflammation within the respiratory cells. It is also suggested that exposure to PM can indirectly cause inflammation by triggering a release of reactive oxidative species from respiratory cells. These oxidative species can impact intracellular signaling pathway at low levels, while higher levels can lead to DNA damage and cellular toxicity. It is hypothesized that pulmonary inflammation can lead to systemic inflammation through the release of cytokines, potentially explaining associations between PM and non-respiratory health effects.[48] Additionally, previous research suggests that exposure to PM can change plasma viscosity and endothelial function.[49] Recently, it has been hypothesized that PM may also play a role in promoting epigenetic changes, by reducing DNA methylation, which is involved in regulating cellular processes such as gene transcription, genomic imprinting, and chromosome stability.[34]

2.1.1.5 Sulfur Dioxide (SO_2)

Description and sources

SO_2 is a gaseous pollutant whose primary source is electricity generation, followed by fossil fuel combustion and industrial processes. Because of these sources, SO_2 is generally thought of as a marker of regional pollution, as opposed to a pollutant like NO_2 which is more a marker for local, motor vehicle pollution. Volcanoes and wildfires can also contribute to SO_2 in the ambient air, but to a much lower amount than processes related to human activity.[50]

Temporal and Geographic Variability

There is no strong, seasonal trend for SO_2 that is consistent across the United Dates. Levels are highly dependent upon prevailing winds. Oxidation of SO_2 is greater at higher temperatures, sometimes causing lower measured levels in the warmer months. SO_2 levels in the ambient air tend to peak mid-day, and reach their lowest levels overnight. SO_2 levels are higher in the Eastern United States, particularly the Mid-Atlantic and Northeastern sections.[50] Approximately 80% of SO_2 emissions in the US come from the 31 states bordering or east of the Mississippi River.[51]

Toxicity

Highly water-soluble, SO_2 is absorbed by moisture in the nasal and respiratory tracts and can be broken down into bisulfites and sulfites, which get distributed throughout the body via the bloodstream. Bisulfites can react with a number of biomolecules, including nucleic acids which can lead to mutational events. Additionally, through autoxidation, bisulfites can generate free radicals which can be distributed systemically and are hypothesized to contribute to observed associations between SO_2 exposure and cardiac events.[52]

2.1.1.6 Toxicity Specific to the Pre-and Perinatal Time Period

General toxicity of the individual criteria air pollutants was summarized above. The potential for developmental toxicity of these pollutants is not well characterized, but it is hypothesized that the developing organs and body systems of a fetus are particularly vulnerable to environmental insult.[53] It is also possible that the relative dose received by the fetus may be different than what is received by maternal tissues following exposure. For example, differences in maternal and fetal kinetics and hemoglobin binding affinity are thought to cause the measured concentration of carboxyhemoglobin to be 10-15% higher in the fetus than in the mother, following CO exposure.[54]

As described by Slama *et al*, air pollutants could directly impact the fetus, as they readily pass through the placenta, or the effects could be indirect, mediated by effects on the mother and/or the placenta.[13] Some of these mechanisms include triggering epigenetic changes in the mother or the fetus, affecting maternal-fetal nutrient exchange through changes in plasma viscosity, endocrine disruption through alteration of the mother's progesterone production (e.g. activation of the hypothalamic-pituitary-adrenal axis), direct disruption of organogenesis, and release of cytokines and induction of oxidative stress in the mother contributing to systemic inflammation in the fetus. There is also the possibility that air pollutants could impact the germ cells of either the mother or the father. Proposed biological mechanisms are further discussed in Section 2.2.6 and 2.3.5.

2.1.2 Methods of Exposure Assessment

Exposure to ambient air pollution can be assessed in multiple ways. Personal air monitoring, where an individual wears a sampling device for a specified period of time, is the only method which directly measures an individual's exposure to ambient air pollutants. However, due to the cost and infeasibility of having large numbers of pregnant women reliably wear bulky air monitors, most large-scale studies do not utilize this technology. All other exposure assessment methods use some other measurement as a proxy for direct personal exposure. Some methods directly measure ambient levels of pollutants at centralized locations and use that as a proxy of individual exposure, while others use sophisticated mathematical prediction models to estimate pollutant concentrations using knowledge of emissions and atmospheric chemistry. Below, the different methods are briefly discussed, listed from the most crude method of assessment to the most complex.

2.1.2.1 Proximity-based

Proximity-based measures use the distance from an individual's location to a source of exposure as a proxy for an individual's exposure to air pollution. There is no direct measurement or estimation of air pollutant concentrations in the ambient air. This method is often utilized in studies examining motor vehicle traffic, with exposure assessed as distance to a primary roadway. It has also been used in studies which examine fixed sources of pollutants such as industrial operations or power plants. This method is easy to implement, but is subject to high levels of misclassification.[55] It is grounded in the assumption of isotropic dispersion, that pollutants will disperse from the emission source equally in all directions. This assumption often does not hold for air pollutants due to wind direction and atmospheric reactions between pollutants from different sources. While there are techniques to deal with incorporating distance to multiple sources, they are often not complete, leaving the potential for unaccounted sources of exposure. Additionally, interpreting findings based on these proximity measures can be difficult since it is often unclear how much of each pollutant were emitted by the source.[55]

2.1.2.2 Emissions Inventories

Emissions inventories are source-specific, comprehensive listings of air pollutant emissions for a defined geographic area, during a specified period of time. In the United States, they are often compiled at the state and/or local level and then submitted to the Environmental Protection Agency for inclusion in the National Emissions Inventory database.[56] Again, pollutant concentrations are not directly measured, but emissions of specific pollutants are reported for different pollution sources. Currently, the EPA mandates reporting the emissions of criteria air pollutants, while emissions of hazardous air pollutants and greenhouse gases can be submitted on a voluntary basis by the states and local agencies. The pollutant sources which are inventoried fit into the following categories:

Facility/point sources: large, fixed sources of pollutants that are mandated to report their emissions of individual pollutants directly to the state/local agencies. These often include large industrial facilities, power plants, etc.

Area/Non-point sources: smaller, fixed sources of pollutants that are either too numerous, too small, or to impractical to mandate individual reporting of emissions. Instead, emissions from these sources are reported in the aggregate. Non-point sources could include dry cleaners, commercial solvent use within a specified county, etc.

Onroad/Non-road : motor vehicles and off-road vehicles, engines and equipment used for construction and other activities. The emissions from these sources are estimated, often at the county level by a local or state agency, and reported in aggregate.

Events: sudden or unexpected events that emit pollutants into the atmosphere. Examples would be wildfires, natural disasters, etc. These are reported as necessary by the state and local agencies.

Biogenic: naturally occurring emissions. These are not reported, but are directly estimated by the EPA and then included in the NEI.

Data from the NEI are publicly available, and relatively consistent for all regions of the United States. Additionally, these emissions have been reported and recorded for many years allowing for historical examination of emission trends. The smallest level of aggregation though is often the county level. This can make obtaining a proxy for individual exposure difficult, as all people within the same county would have the same assigned exposure. It can also be difficult to assess temporal differences in exposure as the emissions are usually reported as an annual average.[56]

2.1.2.3 Measurements at Centralized Ambient Air Monitors

This method directly measures concentrations of air pollutants in samples of the ambient air. Air monitors are often stationary as part of a fixed monitoring network, but they can be mobile or set up by an individual investigator or agency for a specific purpose. Because the Clean Air Act mandated that every state establish a network of air monitoring stations for criteria air pollutants, measurements from these centralized, stationary air monitors are often utilized in air pollution epidemiology. The monitors in this network are called the State and Local Air Monitoring Stations (SLAMS) and the data from these stations is reported to and compiled by EPA. There are other national air-monitoring networks including the National Air Monitoring Stations , the Special Purpose Monitors , and the Photochemical Assessment Monitoring Stations which supplement the SLAMS network.[57] To ensure that measurements taken in different states and local areas are consistent across the United States, the EPA has published detailed reference and equivalent methods to measure the concentrations of specific air pollutants in the ambient air that must be used by the SLAMS.[58] General descriptions of the most commonly used methods for each criteria pollutant are briefly described below:

Carbon Monoxide: A sample of ambient air is drawn into a chamber where it is exposed to a beam of infrared light while a chamber with no ambient air contains another beam of infrared light. Because CO absorbs infrared radiation, measuring the decrease in intensity of the beam exposed to the ambient air corresponds to the CO concentration of the sampled air.[59]

Nitrogen Dioxide: Nitric oxide (NO) reacts with ozone to produce light at wavelengths greater than 600nm. NO_2 is measured by comparing the intensity of light produced when NO_2 in ambient air is first converted into NO and then reacted with ozone to the intensity of light produced when ambient air is reacted with ozone, without converting the NO_2 to NO.[60]

Ozone: Ozone absorbs UV light at wavelengths of 254nm. Using this knowledge, a photometric method to measure ozone concentration is utilized by comparing the absorption of an ambient air sample to an ambient air sample where the ozone has been reduced to molecular oxygen.[61]

Particulate Matter: Air samplers draw ambient air into a specially-shaped inlet and through a particle size separator, after which particles of the specified size are deposited onto a filter. The filter is then weighed and the mass of the particles is the difference between that weight and the weight of the filter alone. The concentration is expressed as the measured mass of the particles divided by the total amount of air that was sampled. Special monitors with three separate filters are used to measure the different chemical species of $PM_{2.5}$. The filters are sent to a centralized laboratory and particles on the Teflon filter are used to assess total mass and the presence of elements/metals. The nylon filter is analyzed using filter extraction and ion chromatography for anions (e.g. sulfate, nitrate) and cations (e.g. potassium, sodium), while the quartz filter is analyzed for organic and elemental carbon using a thermal optical transmittance method.[62]

Sulfur Dioxide: When SO_2 reacts with ultraviolet (UV) energy, it emits light of a specific wavelength. SO_2 in air is measured by passing a sample of ambient air into a chamber where it reacts with UV energy and the light emitted is measured and used to calculate the SO_2 concentration.[63]

Often, the measurements taken at the air monitor closest to an individual's location, usually the location of residence at a specified point in time, will be used to assign exposure. This may provide a good exposure proxy where individuals live close to a monitor, but may be less appropriate in rural areas where monitors may be very far from an individual's location. Additionally, using the single closest monitor does not account for wind, topography, and other

factors that may influence air concentrations at the individual's location, nor does it account for measurements taken at other monitors that may also be in close proximity or in a more relevant geographical position (i.e. upwind as opposed to downwind of an individual's location).

2.1.2.4 Geostatistical Models using Monitoring Data

Using measurements taken at centralized air monitors, geostatistical models estimate ambient levels of pollutants at locations between monitors using interpolation techniques. The most common technique is called kriging and it examines spatial patterns in the measurements taken at multiple monitoring stations in order to model the variation and estimate pollutant levels, with corresponding standard errors, at other locations of interest. These models are most effective when there is a dense, evenly-distributed network of monitors, which is often not in the case in suburban and rural areas. Additionally, these methods may not reflect local sources of pollutants since they are dependent upon the available monitoring data at distant points. Similar to measurements taken at the closest monitor, exposure estimates obtained by kriging do not incorporate wind, topography, secondary atmospheric reactions, and other factors that could influence ambient levels of pollutants at an individual's location.[55,64]

2.1.2.5 Land Use Regression Models

Land use regression models (LURs) utilize topography and land use characteristics in their estimation of ambient pollutant levels at non-measured locations. An LUR uses measurements obtained from a network of air monitoring stations as a dependent variable and land use variables such as traffic counts, road networks, topography, meteorology, and proximity to industrial sources as the independent variables in order to estimate parameters that can be applied to locations without monitoring stations, in order to predict pollutant concentrations. While generally successful in studying intraurban pollutant levels, these models

are often limited to studies of smaller geographic areas, due to the density of the air monitoring network and level of detailed information on other factors needed for its implementation. Additionally, the model often has limited generalizability and cannot be applied to areas with different land characteristics or pollutant sources, restricting its use to small areas very similar to where the model was originally developed.[65]

2.1.2.6 Deterministic Prediction Models

Rather than using measurements taken at centralized fixed monitors as the basis for interpolating or predicting ambient pollutant levels at non-monitored locations, deterministic prediction models utilize information on emissions, fate-transport of pollutants, atmospheric chemistry and production of secondary pollutants, and meteorology in order to predict a pollutant concentration surface for a specified geographic area. The simplest form of this model, a dispersion model, is based on Gaussian plume equations which are used to represent how pollutants are generated and transported in the ambient air.[64] Integrated meteorological-emissions models, another deterministic numerical-based model, utilizes those same multiple sources of data but then mathematically simulates the dynamic processes that occur in the atmosphere in order to predict pollutant concentration surfaces.[55] The EPA's Community Multi-scale Air Quality (CMAQ) model is an example of an integration meteorological-emissions model and will be discussed in more detail in Section 3.2.2.2.[66] In order to improve pollutant prediction, models which combine the numerical output from the simulation models with monitoring data through hierarchical Bayesian techniques have also been developed.[67] One example of this hierarchical, spatiotemporal model which utilizes output from the EPA's CMAQ model is discussed in more detail in Section 3.2.2.2. Although deterministic prediction models are computationally more intensive, they utilize much more available information to model how

pollutants are distributed in the ambient air, providing a more accurate proxy estimation of exposure at an individual's location.

2.1.2.7 Probabilistic Exposure Models

While the deterministic models described above utilize large amounts of data to predict ambient levels of pollutants in the ambient air, they do not account for human activity, time-spent indoors, and other factors that can lead to misclassification when ambient estimates are used as proxy exposures for an individual. Probabilistic exposure models attempt to incorporate human activity into pollutant exposure models by simulating the population's exposure as they move through multiple microenvironments during their daily life.[68] Data on individual activities that are incorporated into the models comes from detailed diaries kept my people living within the area the model is being developed. Because they are estimating population exposures on an aggregate level such as census block or block group, the outputs from these models yield a range of exposures or an estimated percentage of residents in a given area who are above a certain exposure.[69] Because they do not output a single exposure estimate that can be applied to an individual, their utility in epidemiologic studies of etiologic disease-exposure relationships are somewhat limited.

It should be noted that in addition to the measured and/or predicted ambient levels of pollutants described above, there are biological measures which reflect exposure to air pollutants. Previous studies have utilized urinary measurements of gasoline additives, concentrations of polycyclic aromatic hydrocarbons (PAH) DNA-adducts in plasma, and other biological markers of exposure measured in sputum, urine, and/or blood in order to investigate the impact of air pollution on health outcomes.[12,70-72] However, for many of these markers, multiple collections would be necessary, as it is unclear how reflective of exposure during pregnancy a single measurement might be. Additionally, due

to the large expense of collecting and analyzing biospecimens, they have not been utilized in large-scale studies.

2.2 Congenital heart defects

2.2.1 Definition and Diagnosis

Congenital heart defects (CHDs), also referred to as cardiac birth defects or congenital heart disease, are generally defined as any abnormality in the structure and/or function of the heart or great vessels, which is present at birth. This definition results in a heterogeneous group of defects that vary anatomically, embryologically, in severity, and, potentially in etiologic risk factors.[73] Depending upon the classification system used, there can be over 30 distinct groups of CHDs, with each group potentially containing defects of slightly varying phenotype and/or combinations of multiple defects. CHDs can be diagnosed prenatally using a fetal echocardiogram or after the infant is born using other imaging and diagnostic technologies, such as echocardiograms, electrocardiograms, chest X-rays, MRIs and CT scans. If a defect is not detected during prenatal screening, usually only defects that cause symptoms in the infant will be detected and diagnosed. These symptoms include irregular heartbeats, irregular breathing, poor weight gain, swelling of the extremities, and cyanosis.[73]

2.2.2 Prevalence, Morbidity and Mortality

Birth defects occur in 1 in 33 live-births in the United States annually. Of these, CHDs are the most common group, with birth prevalence estimates ranging from 4 to 14 per 1,000 live-births.[73] Reviewing 44 studies of the prevalence of CHDs, Hoffman et al estimated the median birth prevalence of CHDs to be approximately 7.7 per 1000 live-births.[74] The authors concluded that variability in estimates tended to be dependent upon how the birth defect cases were ascertained (i.e. intensive active-monitoring programs vs. use of defect reporting in administrative databases) and the inclusion of more prevalent, but minor defects, such as small ventricular septal defects (VSDs), in later studies which have been more

easily diagnosed with newer technologies. They noted that the birth-prevalence of more severe forms of CHDs was relatively stable at 1.3 per 1000 live-births.[74] Studies published since the Hoffman review have been consistent with these findings. Two studies in the US, one in Atlanta[75] and one in California[76], had differing overall prevalence of CHDs, 6.2 vs. 3.2 per 1000 live-births respectively, but found the same prevalence of severe defects at 1.3 per 1000 live births. The study in Atlanta had similar findings to a consortium study in Europe, which observed an overall prevalence of 6.6 per 1000 live-births and a prevalence of 1.3 per 1000 live births for severe defects.[77] Other studies in France, Sweden, and Taiwan had similar prevalence estimates for severe CHDs.[73]

It should be noted that birth-prevalence is defined as the number of infants with diagnosed CHDs divided by the total number of live-births during a given time period. Because CHDs can cause spontaneous abortions, stillbirths or lead to elective terminations, some studies include fetal deaths after 20 weeks due to a cardiac birth defect and elective terminations due to a cardiac birth defect in the calculation. But elective termination data are sometimes not available. Some studies have tried to quantify the impact of missing data on elective terminations, but have found considerable variability in the effect on estimates.[78,79] Differences in these impacts are dependent upon the utilization of prenatal diagnosis and elective terminations of fetuses with defects.[80] It can be difficult to estimate the impact of elective terminations for single, isolated CHDs. A study in Atlanta found that 8% of pregnancies with fetuses with prenatally diagnosed defects were electively terminated.[81] However, that figure included all CHDs. CHDs are more prevalent in fetuses with chromosomal abnormalities like trisomy, and the termination rate among those fetuses has been increasing and tends to vary by population.[82,83] The termination rate among single, isolated CHDs is likely lower.

The contribution of CHDs to early, spontaneous fetal loss, before 20 weeks, is not well understood and thus calculations of incidence are not feasible due to difficulty in determining total number of pregnancies at risk and ascertainment of defects at early stages of pregnancy. It is hypothesized that

severe CHDs may be more prevalent among early fetal losses, causing an underestimation of the true incidence of defects when examining only late fetal loss and live-births.[73] Although all defects are present at birth, the majority of CHDs are not diagnosed prenatally and some diagnoses are delayed until many months after birth, when they begin to affect the infant's breathing and growth. This delayed diagnosis is more common among defects such as ASDs and VSDs, which may result in minor or no symptoms. Rarely, minor defects can be undiagnosed well into adulthood.

Table 2.2: Typical fetal cardiac development by week of pregnancy, measured from conception

Week	Cardiac Developmental Events
3	Endocardial tubes form from cells in the cardiogenic plate and move toward each other, eventually fusing to form a single heart tube with separate "sections" that will form the chambers of the heart. The heart tube than moves into the thoracic region.
4	Fusion of the endocardial tubes is complete, and the heart begins to beat. Pericardial cavity is formed. Heart tube begins to grow and fold upon itself, creating the positions and early structures of the fetal heart. Ventricles begin to dilate. The pulmonary artery begins to form on the left wall of the atrium. The endocardial cushions appear/form the atrioventricular canal.
5	The truncal swellings, which will eventually form the septum in the outflow tract that contributes to the formation of the aorta and pulmonary trunk, begin to form. The partitioning of the atrium begins. The ostium (foramen) secundum, forms.
6	The foramen ovale forms and establishes the primary path of the fetal circulatory system. Endocardial cushions begin fuse to partition the atrioventricular canal and eventually form the mitral and tricuspid valves.
7	The growth of the ventricles is completed, and the ventricular septum, which divides the two ventricles, stops growing. The coronary sinus is formed.
8	The aorta and pulmonary trunk are completely separated.

In addition to being the most common group of birth defects, CHDs are also the leading cause of birth-defect related death. The age-standardized mortality rate for cardiac birth defect related deaths in the US from 1999-2006 was 1.78 per 100,000.[84] There have not been very many long-term follow-up studies among infants born with birth defects to examine long-term prognosis and mortality. Within the Texas Birth Defects Registry from 1996-2003, it was observed that 8% of infants born with a cardiac birth defect died within the first year of life.[85] Nationally, it is estimated that about half of cardiac-defect related deaths occur during the first-year of life, with approximately 70% of those occurring

during the neonatal period (<28 days post-birth). In the US, 4.2% of all neonatal deaths have a cardiac birth defect listed as the underlying cause.[86] Among infants who survive the first year of life, 76% of birth-defect related mortality occurs in adulthood.[84] Improvements in surgical interventions and treatments have greatly improved prognosis, and the mortality rates of CHDs have been decreasing among all age-groups.[84,87] Currently there are 1.4 million children and adults living in the US who were diagnosed with a cardiac birth defect. Even after corrective surgery and/or medication regimens, many people born with a CHD will have physical limitations and ongoing complications throughout their lifetime. Some of these complications include infectious endocarditis, arrhythmias, reoperations on their defects, heart failure, and in rare cases pulmonary hypertension.[73] Additionally, women with CHDs are more likely to have pregnancy complications, including having a child with a CHD.[88]

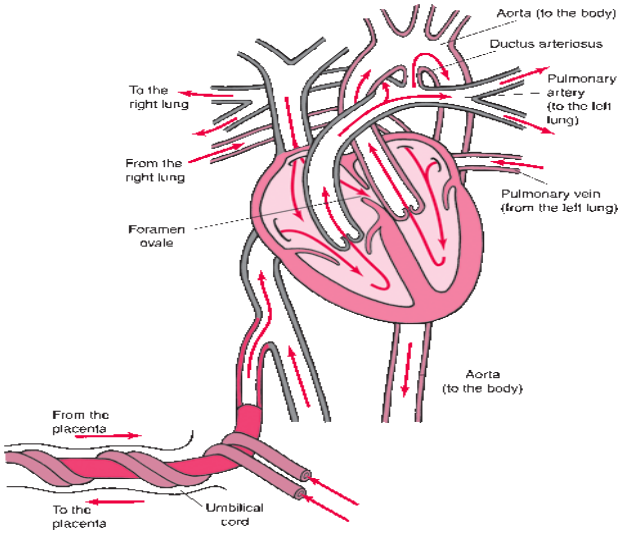

Figure 2.1: Fetal Heart Circulation
http://www.merckmanuals.com/home/sec23/ch265/ch265b.html

2.2.3 Cardiac Development and Relevant Time Periods of Exposure

CHDs result from alterations from normal heart development, which occurs during weeks 3 through 8 of pregnancy. Cardiac development in a typically developing embryo is summarized, by week of pregnancy, in Table 2.2.[89]

Following week 8, the heart's development is mainly complete, and it continues to grow in size along with the fetus. However, fetal circulation is different than circulation following birth (Figure 2.1). In typical human circulation, blood enters the heart from the body through the right atrium, travels into the right ventricle and then into the pulmonary artery where it receives oxygen from the lungs. The pulmonary vein carries oxygen-rich blood to the left atrium, where it enters the left ventricle and is then pumped out to the tissues of the body. During fetal life, oxygen is delivered from the mother to the

fetus through the placenta and umbilical cord. Because the fetal lungs are not in use, temporary fetal structures, the foramen ovale and the ductus arteriousus, shunt blood away from the pulmonary circulatory system. The foramen ovale allows blood to pass directly from the right atrium to the left atrium, bypassing the right ventricle where it would normally be sent to the pulmonary artery. The ductus arteriousus connects the pulmonary artery directly to the aorta, shunting any blood that didn't pass through the foramen ovale away from the lungs. Once the fetus is born and takes his/her first breath, pressure changes cause these two structures to close and blood to flow through the pulmonary circulatory system, ensuring oxygen-carbon dioxide exchange. Many CHDs impact the infant by shunting blood within the heart in a way that reduces oxygenation of the body organs and tissues.[90]

Most studies of CHDs focus on exposures only during the first 2 months of pregnancy, when the structure of the fetal heart is developing. However, because of the potential for epigenetic changes in either the mother and/or the germ cells to contribute to the development of CHDs, exposures prior to pregnancy may also be relevant.[13] Additionally, insults in late pregnancy can impact the normal closure of remnants of the fetal circulation system. For example, ibuprofen taken in the 3rd trimester has been shown to cause premature closure of the ductus arteriousus.[73] Whether certain late-pregnancy insults can prevent closure has not been examined.

As stated above, defects occur when these developmental events fail to proceed and/or complete properly. In the following section, details on individual defects, including formation and resulting morbidity are described.

2.2.4 Classification and Description of CHDs

As written above, CHDs are a heterogeneous group of defects. Recently, an international collaborative committee, led by the Society for Thoracic Surgeons (STS), created a standard nomenclature of congenital heart surgery, which included 150 individual diagnoses, the majority of which were individual structural defects.[91] In the clinical setting, CHDs are described using these

individual diagnoses. On the population level, because there are so many different individual phenotypes, aggregation is required to ensure consistency for surveillance and research purposes, as well as to avoid extremely small sample sizes. While there are classification schemes based on the clinical severity of the defects[73] or on the pathogenetic mechanisms underlying the defects[92], most are based on anatomical location of the defect.[31,93,94] The International Classification for Diseases (ICD) codes have been used to classify CHDs[94], although most surveillance programs in the US utilize the classification system developed by the British Pediatric Association[93], which was subsequently modified by the Centers of Disease Control. These BPA/CDC codes are more detailed than the ICD codes. Recently, the STS has developed a classification scheme based on the standardized nomenclature mentioned above.[95] Although there are some differences between these classification schemes, they all utilize multiple levels of aggregation starting with categories broadly based on anatomy and/or developmental considerations, which are then further broken down into specific individual defects.

Below, the broadest groupings of CHDs used by the STS classification system are listed and described.[91,96] More detailed descriptions of some of the more common defects within those groups are also included.[96] The National Birth Defects Prevention Study (NBDPS), the source of the data for this proposal, utilizes a different classification scheme that was created explicitly for the purposes of that study.[97] Because the NBDPS excludes certain classes of defects, the STS groupings are more comprehensive for a general overview. The NBDPS classification scheme will be described in detail in Section 3.2.1.3.

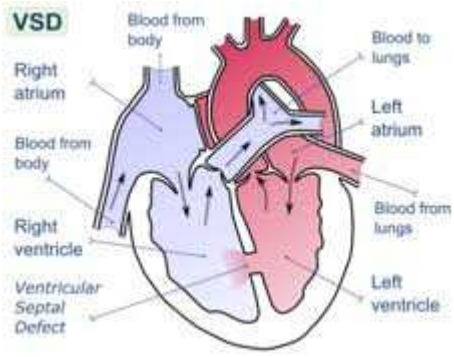

Figure 2.2: Ventricular Septal Defect

http://www.merckmanuals.com/home/sec23/ch265/ch265b.html#v815583

2.2.4.1 Ventricular Septal Defects

The most prevalent of the CHDs, ventricular septal defects (VSDs) are defects

located in the wall, or septum, which separates the left and right ventricle. VSDs are hypothesized to arise from abnormal folding of the heart during development. As shown in Figure 2.2, this enables left-to-right shunting of blood within the heart, disrupting normal ventricular volume and pressure. These defects range in size and severity, with smaller VSDs causing no symptoms and often closing on their own as the heart grows. Larger VSDs can cause pulmonary hypertension and may require surgery. VSDs can be further classified by where in the septum they are located: in the membranous section (the most common of the defects), in the muscle, in the subpulmonary outlet or in the inlet/atrioventricular section. Only membranous and muscular VSDs are included in the VSD group heading. VSDs in the outlet are classified under the heading of conotruncal defects, and VSDs in the atrioventricular section are classified under the heading of atrioventricular septal defects.

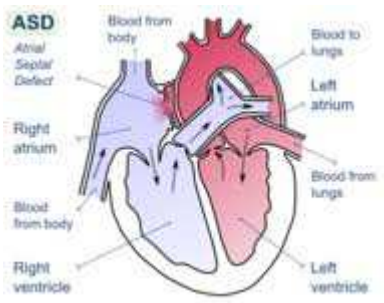

Figure 2.3: Atrial Septal Defects

http://www.merckmanuals.com/home/sec23/ch265/ch265b.html#v815583

2.2.4.2 Atrial Septal Defects

Atrial septal defects (ASDs) are another common defect, which are located in the septum which separates the left and right atrium (Figure 2.3). Similar to VSDs, ASDs, can cause left-to-right shunting of blood. They vary by size and severity, and small ASDs are often asymptomatic. There are 3 types of ASDs: ASD secundum (ASD2), ASD primum (ASD1), and ASD sinus venous. ASD, primum is categorized as an atrioventricular septal defects since it involves the endocardial cushions. ASD, sinus venous are included in the cell growth grouping of defects. ASD, secundum is the most prevalent ASD and is a defect within the middle of the septum, where the foramen ovale was located. They result from inadequate growth of the septum secundum or too much reabsorption of the septum primum during development. ASD,

secundums are not foramen ovales that failed to close after birth. Those defects, called patent foramen ovale, are not generally considered an ASD, but a separate defect.

2.2.4.3 Atrioventricular Septal Defects

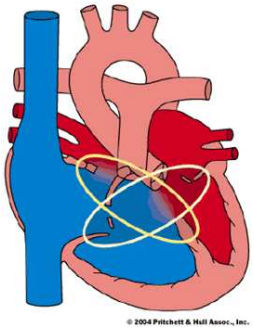

Figure 2.4: Complete Atrioventricular Septal Defect

http://www.childrensmn.org/web/cardiovas/115292.asp

Previously known as endocardial cushion defects, atrioventricular septal defects arise when the two endocardial cushions fail to fuse properly with the atrial septum and/or ventricular septum during development. These defects are actually a combination of multiple defects that involve the atrial and ventricular septums and the valves at their junctions. AVSDs are further classified as partial, intermediate (or transitional), or complete depending mostly upon the degree of ventricular malformation. A partial AVSD is an ASD primum, described above as a defect in the anterior section of the atrial septum, either with or without a cleft located in the mitral valve. The transitional AVSD also has a minor defect in the ventricular septum, while a complete AVSD has an ASD1, a VSD in the inlet, and abnormalities in the valves that separate the atria and ventricles. The combination of an ASD1 and a VSD in the ventricular inlet results in a large, centralized defect which causes shunting of the blood that disrupts volume and pressure in all 4 chambers of the heart, causing the heart to become enlarged (Figure 2.4). Due to abnormalities in the valves, blood can also flow "backwards" through the valves, also known as valve regurgitation. These defects can be corrected with surgery.

2.2.4.4 Conotruncal Defects

Conotruncal defects are malformations concerning the outflow tracts of the heart, the portion of the ventricles that connect to the great arteries. The most common conotruncal defect is Tetralogy of Fallot (TOF), a collection of 4 distinct malformations. As shown in Figure 2.5, TOF consists of a narrowing of the pulmonary valve, known as pulmonary stenosis, a

thickening of the wall of the right ventricle, a displaced aorta that overlaps the right ventricle, and a VSD. The pulmonary stenosis restricts the amount of blood that can flow out of the right ventricle, causing this blood to go into the left ventricle and into the displaced aorta. In essence, the blood bypasses the pulmonary circulation and fails to become oxygenated. This leads to cyanosis. TOF requires surgical correction. Transposition of the Great Arteries (TGA) is another common conotruncal defect where the placement of the aorta and the pulmonary artery are reversed, so oxygenated blood travels back and forth between the lungs and the heart, but is never pumped to the body tissues. TGA must be surgically corrected within the first few days of life. In a Double Outlet Right Ventricle (DORV) defect, the aorta is connected to the right ventricle, instead of the left ventricle. DORV defects always occur with a VSD, which allows some oxygenated blood to enter the aorta, but still limits the oxygenation of body tissues. Isolated VSDs of the outlet are also classified as conotruncal defects.

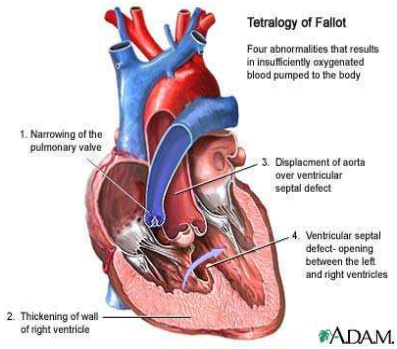

Figure 2.5: Tetralogy of Fallot

http://www.bluebabysyndrome.org/93/blue-baby-syndrome-treatmenttetralogy-of-fallot/

2.2.4.5 Right Ventricle Outflow Tract Obstructions (RVOTO)

This grouping contains defects which block or obstruct the boundary between the right ventricle and the pulmonary artery. The defect can occur in the pulmonary valve, the supravalvar region, the upper part of the ventricle from which the pulmonary artery arises (the conus arteriousus), or in the pulmonary artery. Described above, valvular pulmonary stenosis (PVS), the narrowing of the pulmonary valve, is the most common RVOTO defect.

2.2.4.6 Left Ventricle Outflow Tract Obstructions (LVOTO)

Similar to RVOTOS, LVOTOS block or obstruct the movement of blood through the left ventricle into the aorta, potentially reducing the oxygenation of the body's organs and tissues.

These defects occur in the aortic valve, or in the sub- or supravalvar region. The most common LVOTO is coarctation of the aorta, a narrowing of the aorta at the ductus arteriousus (the fetal structure which connected the pulmonary artery to the aorta to bypass pulmonary circulation). Severity of this defect depends upon where the narrowing occurs, before or after the ductus arteriousus. Hypoplastic left heart syndrome (HLHS) is a severe LVOTO defect where, because the ventricular region of the endocardial tube gets "pinched" during development, the left side of the heart is underdeveloped, including the aorta, the aortic valve, the left ventricle, and the mitral valve. This defect causes the right side of the heart to be overworked. Surgery is eventually required or it results in heart failure. Similar to pulmonary stenosis, aortic stenosis is a narrowing of the aortic valve.

2.2.4.7 Ebstein's

Ebstein's anomaly is given its own category, even though it is one of the more rare defects. Named after the German physician who first described the defect, Ebstein's anomaly is a malformation in the tricuspid valve, the valve that separates the right atrium from the right ventricle. When the valve is open in a normal heart, blood flows from the atrium into the ventricle. The valve closes when the ventricle contracts to pump blood to the rest of the body. In Ebstein's anomaly, the leaflets of the valve are located further in the ventricle, causing the atrium to be larger than normal and the ventricle to be smaller. The malformed leaflets also allow blood to travel back from the ventricle into the atrium. This defect can cause blood/fluid build-up in the left atrium and affects oxygenation of the blood and subsequently the body's organs and tissues. Less severe forms of this defect can be treated with medication, but more severe forms require surgery to repair the malformed valve.

2.2.4.8 Patent Ductus Arteriousus

As described in a previous section, the ductus arteriousus is a fetal structure that allows the fetal circulation to bypass the lungs by connecting the pulmonary artery directly to the aorta. Once an infant is born and the lungs fill with air, pressure changes cause the ductus arteriousus to close, usually within the first few days. If it fails to close, the defect is known as patent ductus arteriousus (PDA) and, depending upon its size, can reduce the amount of blood that travels to the lungs to be oxygenated. PDA is more common among infants born preterm, and usually will close on its own within 2 years in these infants. Among term babies, a PDA that fails to close within a few days likely will require intervention if it causes symptoms. Medications, such as a specific form of ibuprofen, can cause the PDA to close. Otherwise, catheterization and sometimes surgery are required. PDA that occurs in isolation in preterm babies is often excluded from structural defect studies, as it is hypothesized to be a result of being born preterm and not a developmental or structural defect in the heart.

2.2.4.9 Cardiac Looping

In the initial stages of cardiac development, the heart consists of endocardial tubes which fuse and form a single tube which then loops and folds on itself in order to create the cardiac structure and the position of the four chambers. Defects that form as a result of an incorrect looping process are grouped together in this category. The disruptions in looping can cause atrioventricular discordance defects, where the right ventricle is on the left side of the septum and the left ventricle is on the right. Incorrect looping can also cause single ventricle defects, where only one ventricle is developed correctly. These defects are rare and very complex, almost always requiring surgery.

2.2.4.10 Heterotaxy

These defects arise as part of the failure during development to establish typical left-right differences in anatomy. For example, one defect in this grouping, dextrocardia, is when the heart is located in the right side of the thorax. The defects in this group are often complex, consisting of multiple malformations within the heart.

2.2.4.11 Abnormal Cell-growth Defects

Another grouping of rare defects, this group consists primarily of defects in the connections between the pulmonary veins and the left atrium. If all four pulmonary veins are connected somewhere besides the left atrium, the defect is referred to as total anomalous pulmonary venous return (TAPVR). If only some of the veins are connected into the wrong section of the heart, the defect is known as partial anomalous pulmonary venous return (PAPVR). The result of this defect is a lack of oxygenated blood being distributed to the body.

2.2.4.12 Cardiomyopathy

Cardiomyopathy encompasses diseases of the muscle tissue in the heart. Because it is not a structural defect, even though it can be present at birth, it is often not included in studies of CHDs.

There are some individual defects and congenital heart diagnoses which do not fit into the above categories. These defects are either very rare, usually occur in the presence of other defects and have little clinical significance when present alone, or include diagnoses, such as arrhythmias or aneurisms, that are not typically included in birth defect surveillance and research.

Infants with CHDs can be further classified according to whether they are found in the presence of chromosomal abnormalities, or other non-cardiac defects. Cases of birth defects can be referred to as “multiple” or “isolated” depending on the presence of other defects. The proportions of infants that

fall into these different categories tend to vary by study population. A recent review of metropolitan Atlanta's birth defects surveillance system from 1968-2005 found that, within their system, the majority of infants with a cardiac birth defect (71.3%) had no other congenital anomalies, while 13.5% had both cardiac and non-cardiac defects.[98] Approximately 13% of CHDs occurred in conjunction with either a chromosomal abnormality or a recognized syndrome of defects, while 2% occurred in the presence of laterality defects, when the left-right orientation of the body is disrupted.[98] Additionally, previous population-based studies found that even among infants with only CHDs, approximately 22% have more than one defect present.[97] It should be noted some phenotypes, such as Tetralogy of Fallot or Hypoplastic Left Heart Syndrome, are classified as a single phenotype, even though they are a collection of different structural anomalies. These different levels of complexity must be addressed in research of CHDs, since the etiology of a single, CHD is probably not the same as the etiology of that same defect, if it is accompanied by multiple other cardiac and non-cardiac defects within an infant.

2.2.5 Risk Factors

Approximately 8-10% of all cases of CHDs are associated with a chromosomal abnormality.[73] It is estimated that almost half of all children with Down syndrome, trisomy 21, have a CHD.[99] Additionally, another 3-5% of cases have single-gene disorders and syndromes.[73] The remaining majority of cases have an unclear etiology, but previous research has identified certain risk factors for having a CHD, although most are not well-established. Much of the previous research within the US is from state surveillance programs, the Baltimore-Washington Infant Study, a case-control study of birth defects conducted in the 1980s[100], and the National Birth Defects Prevention Study[101] (NBDPS), an ongoing population-based case-control study that is the source of the data for this proposal. The risk factors examined in previous research are summarized in Table 2.3. Research on exposure to air pollutants and CHDs will be described in detail in Section 2.4. Currently, maternal diabetes mellitus, maternal phenylketonuria, thalidomide exposure, exposure to retinoic acids, and maternal rubella are

the only well-established risk factors.[73] For all other risk factors listed, the results from previous research have either been mixed, with some studies observing associations that are not replicated in subsequent studies, or have only been examined in one or two studies.

In addition to the risk factors listed below, there has been research into the genetic contributors to non-syndromic CHDs. Single gene mutations have been linked to ASDs, TOF, TGS, VSDs, and bicuspid aortic valves.[73] Researchers have also observed associations between common variants in the epidermal growth factor receptor signaling pathway and LVOTO[102] defects and genes in the folate-metabolizing pathway and conotruncal defects.[103]

Table 2.3: Summary of Potential Risk Factors for Congenital Heart Defects

Risk Factors	Description of Association
Demographic Factors	
Infant Sex[104]	Males more likely to have severe defects such as HLHS, TGA
Maternal Race/Ethnicity[104,105]	African-American mothers more likely than Whites to have TOF, PS, but lower VSD; Hispanic mothers less likely to have TOF, HLHS, ASD
Maternal Age[106,107]	Mothers greater than 39 years more likely to have Ebstein anomaly, VSD, ASD, TOF, PS, LVOTO, RVOTO
Paternal Age[108]	Older fathers (greater than 35 years) more likely to have RVOTO; among younger fathers, increasing risk of APVR, coarctation of the aorta that plateaus at older ages
Socioeconomic Factors[109]	Measured via education and income; Lower SES associated with multiple defects; not many studies
Maternal Diseases and Illnesses	
Diabetes[110,111]	Type 1 diabetes linked to multiple CHDs, strong associations with conotruncal defects; type1 or type2 linked with multiple defects
Phenylketonuria[112]	Uncontrolled phenylketonuria associated with all defects, but most commonly with TOF, VSDs, PDA, and SV
Rubella[73]	Associated with PDA, pulmonary valve abnormalities, VSDs and peripheral pulmonary stenosis
Fever/Influenza[113]	Associations with PS, RVOTO, LVOTO, coarctation of the aorta, conotruncal defects, VSDs, and pulmonary atresia
Epilepsy[114]	Associated with any heart defect; Unclear if it is epilepsy or medications used
Obesity[115]	Increasing BMI associated with conotruncal and RVOTO
Medications and Substance Use	
Thalidomide[73]	Known cardiac teratogen; associated with broad spectrum of defects
Retinoids[116]	Associated with Outflow Tract Defects
Ibuprofen[117]	Associations with VSDs
Multivitamin w/folic acid[118-120]	Association between using multivitamin containing folic acid and lower prevalence of all CHDs; Also shown to reduce risk of CHDs in the presence of other risk factors
Lithium[121,122]	Associated with Ebstein's anomaly
SSRIs[123]	Associations with septal defects

Table 2.3 (cont.)

Risk Factors	Description of Association
Tobacco Use[124-126]	Maternal Associated with multiple defects, but larger studies have observed no associations
Marijuana Use[127]	Associated with VSDs
Alcohol Use[127,128]	Very high levels of drinking associated with VSDs and ASDs
Environmental Factors	
Maternal Exposure to Solvents[129]	Associated with multiple defects including conotruncal, HLHS, PS, aortic coarctation, TOF, ASD, TAPVR, Ebstein's anomaly
Maternal Exposure to Herbicides/Pesticides[103,129]	Associated with conotruncals, TGA, TAPVR, and VSDs
Air Pollution[5,8,16,22-24]	Associated with multiple defects, sometimes not replicated in subsequent studies; See Section 2.4 for more details

2.2.6 Potential Biological Pathways for Air Pollutants to Contribute to CHDs

Weeks 3 through 8 of pregnancy are hypothesized to be the relevant time periods of exposure for CHDs. The mechanisms for how exposure to air pollutants during this critical time is not well understood. Animal studies suggest that exposure to pollutants such as ozone, NO_2 and CO can be embryotoxic, but they haven't been associated directly with CHDs.[23] It is possible that pathways which are hypothesized to impact fetal growth, such as pollutants causing increased viscosity of blood plasma and affecting maternal/fetal nutrition through the umbilical, could have a role in disrupting the growth and development of the cardiac structure.[13]

Another potential biological pathway is through epigenetic changes. Recent research by Chowdhury et al found associations between measures of maternal global DNA hypomethylation and CHDs.[35] DNA methylation refers to the addition of a methyl group to the cytosine base on DNA. Cells have a specific methylation pattern that encodes protein expression and is maintained during cell replication. DNA methylation is associated with repressed gene expression, potentially by blocking promoters were transcription factors can bind. Previous research has found that DNA hypomethylation contributes to chromosomal instability, altered gene expression, cellular differentiation, and apoptosis during embryogenesis.[130] In a mouse model, disruption of DNA methylation was shown to cause exencephaly in treated mice[131], and a recent epidemiologic study found associations between lower levels of DNA methylation and neural tube defects.[132] Baccarelli et al have observed DNA hypomethylation after

exposure to particulate matter and black carbon, a measure of traffic pollutants.[34] Thus, it is possible that exposure to pollutants early in pregnancy, may trigger DNA hypomethylation which disrupts normal cardiac development. Because folate acts as a methyl donor, necessary to initiate and regulate DNA methylation processes, it is possible that a woman's folate status at the beginning of her pregnancy may modify impacts from air pollution, and that women with low folate levels may be especially vulnerable to the impacts of air pollutants if this mechanism is true.[36]

2.3 Previous Epidemiological Research on Ambient Air Pollutants and CHDs

To date, there have been eight previously published studies on exposure to ambient air pollutants during pregnancy and CHDs.[5,8,16-18,22,24,25] For the purpose of this proposal, only studies which directly measured or estimated ambient levels of at least one of the criteria air pollutants were included (i.e., proximity studies, biomarker studies, studies of non-criteria pollutants were not included). These studies are presented in Table 2.4.

2.3.1 Summary of Study Characteristics and Findings

Study Design and Population: Six of the studies have been case-control designs[5,8,16,17,24,25], while two were cohorts[18,22], analyzed as a time-series design. Four were within the United Kingdom or England, three were conducted in the United States, and one was conducted in Australia. All but the study in Australia utilized population-based birth defect registries and vital records/birth certificates as their source of data. The study in Australia used hospital-based records. The four studies conducted in the UK/England included elective terminations at any gestational age as cases; all other studies included only live births and fetal deaths after 20 weeks.

Outcome Assessment: There was some heterogeneity in how studies aggregated the CHDs into groupings. The three earlier studies used the same six groupings of CHDs which were not based on a specific classification scheme. The four studies in England used ICD-10 codes to group the CHDs,

although the Rankin study had a total of six groups, while the others had 10 groups. Strickland et al used 12 distinct groupings, based on the STS cardiac codes described in section 2.2.4. Many of the studies examined groups and individual defects, so the groupings were not mutually exclusive. Thus, there wasn't much of an improvement in the classification from the original studies that examined 6 groups, except for studies of more prevalent individual defects such as TOF and TGA. Two studies, Gilboa et al and Hansen et al, did not exclude or stratify by presence of chromosomal anomalies.

Exposure Assessment: None of the studies have examined $PM_{2.5}$. All other criteria pollutants have been examined, although not in every study. All studies used either local area code (e.g. ZIP Code or municipal code) or residential address at the time of delivery to assign exposure. All but 2 studies used an average or weighted average of exposure over weeks 3-8 of pregnancy. One study used a single average over the entire first trimester, while the Ritz et al study calculated averages for each of the first 3 months of pregnancy, as well as the subsequent two trimesters, and the 3 month period prior to pregnancy. Four studies assigned exposure using the closest, stationary air monitor. One averaged all of the monitors within a specific radius. One study, Strickland et al, used a single, centralized monitor to assign the same exposure to all women who conceived on the same day. Dolk et al assigned women the average exposure from 1996 determined by a prediction model which used monitoring and emissions data. Another study in the UK conducted by Dadvand et al utilized output from a spatiotemporal prediction model to assign exposure. That model was constructed similar to a land-use regression model, described in Section 2.1.2.5 as covariates such as traffic, population density, and other land use variables were used to predict pollutant levels at maternal postal areas. The first stage of the model utilized meteorological data to quantify the regional, temporal trend in air pollutant concentrations, and then used that as an offset in the second stage of the model which used land-use variables at the different monitoring sites as predictors of the air pollutant concentrations for the different postal areas.

Covariate Assessment: All studies were limited to data from vital records, birth defects registries or hospital records for the covariates. Each study utilized a different adjustment set, except for the two studies by Dadvand et al which had the same adjustment set, as seen in Table 2.4. Almost all studies included adjustment for season of conception, and in non-time series analyses, demographic factors related to socioeconomic status. Only one study examined alcohol use. The Rankin et al study adjusted for birth weight. A number of studies adjusted for infant sex.

Findings: Each study examined multiple pollutants and multiple windows of exposure, so there were many effect estimates reported for each study. In general, results were inconsistent between studies. There was a general lack of precision, which made drawing conclusions about many of the estimates difficult. There were some common associations observed. Two studies which utilized the same outcome classification found elevated odds of pulmonary artery and valve defects with ozone exposure. A few studies found associations between SO_2 and conotruncal defects, such as TOF, and COA. The analysis in Atlanta which used a time-series analysis did not observe any statistically significant findings, except for PM and PDA. But, they did observe elevated effect estimates for some associations that did not reach statistical significance, even though they were greater than effects observed in other studies. For example, the rate ratio for TGA and ozone was 1.70, but imprecise with a confidence interval of 0.83, 3.48. A recent review and meta-analysis of all the studies above found that relationships between SO_2 and tetralogy of Fallot and coarctation of the aorta, NO_2 and tetralogy of Fallot and coarctation of the aorta and PM_{10} and ASDs were statistically significant although had small effects, with summary effect estimates all less than 1.20.[23] No other significant associations emerged from their analyses. However, because all studies did not examine all pollutants and due to heterogeneity in the defect classification, not all relationships could be examined.

Table 2.4: Summary of Previous Epidemiological Research on Exposure to Air Pollutants and Congenital Heart Defects

Author, Year	Geographic Area, Years	Design and Analysis method	Outcome Classification	Exposure Assessment	Adjustment Set	Findings (ORs/RRs, CIs)	Misc.
Ritz et al, 2002[5]	California, 4 counties 1987-1993	case-control: cases include live-born and fetal deaths from birth defects registry, diagnosis up to 1 year old controls randomly selected from birth certificates must live within 10km of a monitor Analysis: logistic regression	Six groups: aortic defects, defects of the atrium and atrium septum, endocardial and mitral valve defects, pulmonary artery and valve defects, conotruncal defects, and ventricular septal defects (not in conotruncal)	Pollutants Examined: CO, NO_2, O_3, PM_{10} Data Source Closest stationary monitor Exposure Window Monthly avg. for first 3 months of pregnancy; averages over 2nd trimester, 3rd trimester, and 3 months prior to conception	maternal age, maternal race/ethnicity, maternal education, access to prenatal care, infant gender, decade of birth, parity, birth type, time since last pregnancy, season of conception, and other air pollutants	2nd month CO VSDs 2.84 (1.15, 6.99) 2nd month ozone aortic artery and valve defects 2.68 (1.19, 6.05), pulmonary artery and valve 2.94 (1.00, 8.67), conotruncal 2.63 (0.75, 9.24) Inverse associations between 1st month and 3rd month ozone and pulmonary artery and valve and 3rd month ozone and aortic artery and valve	No evidence of EMM by race or age
Gilboa et al, 2005[8]	Texas, 7 counties 1997-2000	case-control: cases include live-born and fetal deaths from birth defects registry; controls selected from vital records,frequency-matched on vital status, year and maternal county of residence at delivery restricted to parents > 18 Analysis: logistic and polytomous logistic regression	Six groups: similar to Ritz et al	Pollutants Examined: CO, NO_2, O_3, PM_{10}, SO_2 Data Source Closest stationary monitor Exposure Window Average over weeks 3-8 of pregnancy	Varied by pollutant-defect combination; included maternal education, race/ethnicity, season of conception, plurality,parity, infant sex, maternal age, marital status, prenatal care, maternal illness, gravidity, tobacco use	CO and conotruncals 1.46 (1.03, 2.08) CO and TOF 2.04 (1.26, 3.29) SO_2 and VSDs 2.16 (1.51, 3.09) PM_{10} and ASDs 2.27 (1.43, 3.60) Inverse associations between CO and ASD, O_3 and VSD, SO_2 and ASD and conotruncals, PM_{10} and endocardial cushion defects	didn't report controlling for matching factors No evidence of EMM by sex, plurality, education, race, season of conception

Table 2.4 (cont.)							
Author, Year	Geographic Area, Years	Design and Analysis method	Outcome Classification	Exposure Assessment	Adjustment Set	Findings (ORs/RRs, CIs)	Misc.
Hansen et al, 2009[16]	Brisbane, Australia, 1998-2004	case-control cases and controls selected from vital records;singleton live-births and fetal deaths matched on maternal age, marital status, indigenous status, number of previous pregnancies, month of LMP, area-level SES, distance to air pollution monitor Analysis: Conditional logistic regression in Bayesian framework	Six groups similar to Ritz et al and Gilboa et al	Pollutants Examined CO, NO_2, O_3, PM_{10}, SO_2 Data Source Closest stationary monitor Exposure Window Average over weeks 3-8 of pregnancy	Infant sex	Examining all births Inverse associations between CO and VSDs and conotruncals Births within 6km of a monitor O_3 and pulmonary artery and valve 2.96 (1.34, 7.52) SO_2 aortic artery and valve defects 10.76 (1.50, 179.8) NO_2 and endocardial cushion defects 6.93 (0.93, 114.8) Inverse between SO_2 and conotruncals	Small number of cases in each group
Rankin et al, 2009[17]	Northern United Kingdom, 1985-2000	case-control: population-based congenital defect registry includes livebirths, fetal deaths (>20 weeks), elective terminations; controls randomly selected from birth records Analysis: logistic regression	Six groups based on ICD-10 codes	Pollutants Examined Black Smoke (BS), SO_2 Data Source Average of all monitors within 10km of maternal residence Exposure Window Average over first trimester	birth weight, infant sex, material deprivation	BS ORs range from 0.90-1.03; nothing statistically significant SO_2 All CHDs 0.82 (0.68, 0.98) AVSD 1.35 (0.60, 3.05) PDA 0.36 (0.19, 0.69) VSD 0.78 (0.58, 1.04)	

Table 2.4 (cont.)							
Author, Year	Geographic Area, Years	Design and Analysis method	Outcome Classification	Exposure Assessment	Adjustment Set	Findings (ORs/RRs, CIs)	Misc.
Strickland et al, 2009[18]	Atlanta, GA, 5 counties, 1986-2003	cohort, time series includes all live-births and fetal-deaths > 20 weeks gestation from vital records linked to birth defects registry Analysis: Poisson regression	12 groups, some individual defects, some groupings so not mutually exclusive	Pollutants Examined CO, PM_{10}, O_3, NO_2 Data Source Stationary monitor in Central Atlanta Exposure Window Weighted average of Weeks 3-7 of pregnancy; greater weight in center weeks	week of year and day of follow-up-modeled as cubic spline with knot every year	PDA and PM_{10} 1.60 (1.11, 2.31) Only sig. result O_3: ranged from 0.78-1.29 (3 below 1.0, 9 above) PM_{10}: ranges from 0.85, 1.60 (6 below 1.0, 6 above) NO_2: ranges from 0.80-1.27 (4 below, 8 above) CO: ranges from 0.80-1.16 (7 below, 5 above) SO_2: 0.70-1.22 (7 below, 5 above)	
Dolk et al, 2010[22]	England, 4 regions, 1991-1999	Cohort cases from population-based congenital defect registry includes livebirths, fetal deaths (>20 weeks), elective terminations; controls randomly selected from birth records Analysis: Poisson Regression	10 groups based on ICD-10 codes; some individual defects, some groupings so not mutually exclusive	Pollutants Examined PM_{10}, NO_2, SO_2 Data Source Estimates for local areas from prediction models which include monitoring data and emissions data Exposure Window Annual average for 1996	maternal age, neighborhood socioeconomic deprivation, hospital catchment area	SO_2 and TOF 1.38 (1.07,1.79) NO_2 and TOF 1.44 (0.71, 2.93) PM_{10} and TOF 1.48 (0.57,3.84) SO_2 ranged from 0.94, 1.15 for other defects NO_2 ranged from 0.62, 1.50 for other defects PM_{10} ranged from 0.49, 1.22 for other defects	

Table 2.4 (cont.)							
Author, Year	Geographic Area, Years	Design and Analysis method	Outcome Classification	Exposure Assessment	Adjustment Set	Findings (ORs/RRs, CIs)	Misc.
Dadvand et al, 2011[24]	Northeast England, 1985-1996	case-control: cases from population-based congenital defect registry includes livebirths, fetal deaths (>20 weeks), elective terminations; controls randomly selected from birth records Analysis: logistic regression	10 based on ICD-10 codes; some individual defects, some groupings so not mutually exclusive	Pollutants Examined BS, SO_2 Data Source Spatiotemporal Model Exposure Window Average of weeks 3-8 of pregnancy	birth year, socioeconomic status, infant sex, season of conception, and degree of urbanity	BS malformations of cardiac chambers and connections 2.00 (1.27, 3.17) VSD 0.73 (0.58, 0.91) Others range from 0.83-1.43; SO_2 Malformations of great arteries and veins 0.58 (0.40,0.86) COA 0.39 (0.22, 0.70) Others range from 0.75-1.18	
Dadvand et al, 2011b[25]	Northeast England, 1993-2003	Case-control cases from population-based congenital defect registry includes livebirths, fetal deaths (>20 weeks), elective terminations; controls randomly selected from birth records frequency-matched on birth year Analysis: logistic regression	10 based on ICD-10 codes; some individual defects, some groupings so not mutually exclusive	Pollutants Examined O_3, CO, PM_{10}, NO_2, NO, SO_2 Data Source Stationary air monitor closest to maternal residence at delivery Exposure Window Average over weeks 3-8	birth year, socioeconomic status, infant sex, season of conception, and degree of urbanity	Malformations of cardiac chambers and connections 1.47 (0.48, 4.37) Malformations of cardiac septa 2.33 (1.75, 3.10) COA:2.17 (0.54, 8.70) PS:2.68 (1.30, 5.53) TOF:1.98 (0.53, 7.31) VSD:2.63 (1.87, 3.71) Malformations of great arteries and veins 0.76 (0.32, 1.80) All other comparisons around 1	

2.3.2 Methodological Limitations of Previous Studies

Although there were differences in study design, exposure and outcome assessment and subsequent findings from the previous investigations into exposure to air pollutants and CHDs, there were some consistent limitations and methodological challenges. CHDs are an extremely heterogeneous outcome, and associations with particular defects may be masked when lumped with other CHDs into a single group for analysis. This is difficult challenge since CHDs are a rare occurrence and stratification reduces an already small sample size. However, more consistent findings between the studies were for the larger, individual defects that are relatively homogeneous such as TOF and COA. It is possible that further refinement in outcome aggregations within a larger study of birth defects would have an enhanced ability to explore etiologic relationships.[31,97] Additionally, not all studies excluded or stratified by the presence of chromosomal anomalies. CHDs in the presence of chromosomal anomalies may have a different etiology. This is also true for CHDs which are found in combination with other CHDs. Many of the studies, including Strickland et al[18], included cases with more than one CHD, and either classified them according to the more severe defect or counted them twice if the defects were hypothesized to be developmentally independent.

Misclassification of exposure is another consistent challenge.[133] The majority of studies used one exposure metric, the average ambient concentration during weeks 3 through 8 of pregnancy. Because of the timing of the development of the cardiac structure, we know that exposure during week 8 is not equivalent to exposure in week 3. Yet, most analytic methods cannot handle the correlation in exposure between the different weeks of development if entered simultaneously into a standard logistic model like those used in the studies described. Additionally, identifying this relevant time period is highly dependent upon obtaining a correct gestational age. Because most studies utilize records from birth certificates, LMP is used to calculate gestational age.

Previous research has shown some misclassification in gestational age based on LMP recorded on the birth certificate, which could impact identifying the relevant time period.[134]

As stated previously, these studies are measuring a proxy for exposure, the ambient concentrations of pollutants in the air at the monitor closest to the woman's residential location, often at the time of delivery. While having personal air monitors to collect exposure is not feasible, there needs to be an attempt to minimize the misclassification based on using this proxy for exposure.[133] Most of the studies relied primarily on monitoring data from stationary monitors, but as discussed in Section 2.1.2, there are deterministic models that utilize additional types of data, including atmospheric and meteorological data, knowledge about atmospheric chemistry and transport, and reported emissions to predict pollutant surfaces over a geographic area that can be used to assign exposure at maternal locations. These models can be also be combined with monitoring data using statistical methods to improve estimation of pollutant concentrations.[67]

Tracking residential mobility during pregnancy is another way to minimize exposure misclassification. Recent studies on residential mobility during pregnancy within the individual sites of the National Birth Defects Prevention Study revealed geographic differences in mobility. Approximately 30% of women in Texas moved during pregnancy[30], compared to 22% in Atlanta[135], and 17% in upstate New York[29]. Two of these studies found that using residence at delivery did not cause considerable misclassification of exposure to ozone and PM_{10} or benzene due to the relatively short distance of the move. Kappa statistics calculated in these studies ranged from 0.69 to 0.99, suggesting agreement between exposures determined using address at delivery and using address at birth.[29,30] However, it is unclear if these patterns on pregnancy mobility are generalizable to other locations. Additionally, in Texas, cases were more likely to move earlier in pregnancy, which could suggest differential misclassification, particularly when the relevant time window of exposure for birth defects is limited to the first 8 weeks of pregnancy.[30]

Residual confounding is another limitation of these studies.[133] Available covariates are limited to data collected as part of vital records or birth defects registries, excluding factors such as illegal substance use, medication use and other variables associated with CHDs that may vary spatially like air pollutants. Additionally, the quality of data collected on administrative forms can be highly variable. Having access to a larger number, and more standardized collection of covariate information would be able to reduce some of this confounding.[133] Utilizing time-series study designs, such as those employed by Strickland et al[18] could also reduce the need to collect data on spatial confounders, since the relationship is explored within the temporal domain only. However, using a single, central stationary monitor to reflect the exposure at a given time points for an entire population may introduce exposure misclassification, particularly for pollutants with considerable local spatial variation.

CHAPTER 3

3. METHODOLOGY

3.1 Study Overview

The study was conducted by linking ambient air pollutant data from different EPA exposure assessment methods to birth outcomes and covariate data from the National Birth Defects Prevention Study using geocoded maternal residential history during pregnancy. For Specific Aim 1, exposure to the individual criteria air pollutants, except lead, will be assessed using the EPA's Air Quality Systems (AQS) data which is composed of actual monitoring data of ambient concentrations of the pollutants collected from stationary air monitors located across the United States, as described in Section 2.1.2.3. In Specific Aim 2, exposure to $PM_{2.5}$ and ozone will also be assessed using output from an EPA product, referred to as downscaler CMAQ, which combines numerical output from a deterministic prediction model that predicts air pollutant surfaces based on emissions inventories, meteorological factors, atmospheric reactions, and pollutant transport information with actual monitoring data.[28] Because downscaler CMAQ only started producing these predicted surfaces in 2001 and only produced estimates for the eastern US, only births in those geographic areas with estimated conception dates after January 1, 2001 will be included in those analyses.

3.2 Data Sources

3.2.1 Study Population, the National Birth Defects Prevention Study

The National Birth Def Defects Prevention Study (NBDPS) is the largest, ongoing, population-based site case-control study of birth defects within the US.[101] Directed by the Centers for Disease

Control (CDC), the NBDPS began in 1996 through the establishment of 7 collaborative Centers for Birth Defects Research and Prevention. These centers were based in the CDC's Metropolitan Atlanta Congenital Defects Program, and existing birth defects surveillance programs in Arkansas, California, Iowa, Massachusetts, New Jersey, New York, and Texas. While some centers cover births in the entire state, others only monitor specific counties/catchment areas. In 2002, two additional centers were added, North Carolina and Utah, while New Jersey's site ceased data collection activities. Using the infrastructure of their existing surveillance programs, each center aims to contribute 300 eligible birth defect cases annually to the NBDPS. Cases include livebirths and stillbirths greater than 20 weeks gestation or at least 500 grams, as well as elective terminations of prenatally-diagnosed defects at any gestational age, where available. Each center also aims to recruit 100 controls annually. Controls are live-births who are randomly selected from either vital records (IA, MA, NC, NJ, UT, CDC-MACDP) or hospital records (AR, CA, NY, TX). The records for controls that are randomly selected for participation are also reviewed to ensure the infant was not a stillbirth and the infant does not have any congenital defects. At each center, clinicians review the medical records of cases using standardized criteria to ensure eligibility and review and appropriately classify or reclassify defects. Working together by using a clinical database shared between the centers, clinicians make individual notes on each case and collectively resolve any questions about a case's classification.[136] Overall, there is a 69% participation rate among cases and a 65% participation rate among controls. To date, the NBDPS has recruited over 27,000 cases and over 10,000 controls.

As part of the NBDPS protocol, mothers complete a detailed, one-hour computer assisted telephone interview (CATI) on a wide range of questions on demographics, pregnancy history, maternal conditions and illnesses, family history, lifestyle and behavioral factors, maternal nutrition, medication use, multivitamin use before and during pregnancy, environmental exposures,

occupational history and physical activity. Participants are also asked to provide complete residential history during pregnancy. The NBDPS also collects biological specimens, in the form of buccal cells, for DNA extraction and genetic analysis. The study has the ability to link participation information with the clinical records used to classify defects. Some centers also link NBDPS participants with their original birth certificate information from vital records. Analytic databases are created from the pooled data from each center and made available to all centers periodically.

3.2.1.1 Assessing Gestational Age within the NBDPS

The NBDPS has a standardized protocol for assessing gestational age at birth of participants in the study. During the maternal interview, mothers are asked about the estimated date of delivery (EDD) that was given to them by their clinician while pregnant with the enrolled child. If a mother was given more than one EDD during her pregnancy, she is asked to give the last estimate given to her. This date is used to calculate her estimated date of conception (DOC) which in conjunction with the infant's date of birth, is used to calculate gestational age. If a mother cannot recall the estimated delivery date she was given, NBDPS staff can refer to her medical records and use an ultrasound given before 14 weeks to estimate the EDD. If no early ultrasound is available, then the NBDPS will look at the LMP and if available ultrasound given before 27 weeks or a neonatal exam. If 2 of the 3 agree, are within 7 days of each other if assessed during the first trimester and 14 days if assessed in the 2nd trimester, that EDD will be used. If the different sources don't agree, then the NBDPS will use LMP, and if that is not available then ultrasound < 27 weeks, and if nothing else is available, neonatal estimate.

3.2.1.2 Residential History and Geocoding within the NBDPS

As part of the maternal interview, participants are asked to provide the addresses of all of their residential locations from 3 months prior to the estimated DOC through the

infant's date of birth or date of stillbirth/termination. The addresses are recorded along with the dates the participant resided at each location. Due to the highly identifiable nature of addresses, this data is stored locally at each center. Periodically, the NBDPS compiles the address information from all of the centers and utilizes the Geospatial Research, Analysis and Services Program of the Agency for Toxic Substances and Disease Registry (ATSDR) to geocode the data using a standardized protocol. Once geocoded, the data for each center is sent back only to that center for storage; a centralized database is not maintained. Centers wishing to utilize geocodes for research studies must obtain each center's geocodes directly from them. The dates of residence for each geocoded address, as well as the total number of addresses for each participant, are maintained in the centralized analytic database. For this study, we will be using geocoded data for participants with EDDs through 12/31/2006.

3.2.1.3 CHDs within the NBDPS: Exclusion Criteria and Classification

Not all CHDs are eligible for inclusion in the NBDPS. Because of the implicit known etiology, all defects, cardiac and non-cardiac, associated with chromosomal/microdeletion disorders and single-gene deletion disorders are excluded. Additionally, certain CHDs are also excluded, either because they are extremely rare, they are difficult to ascertain during infancy, they deal mainly with the vascular system and likely have a different etiology, or they are not generally considered a structural defect of clinical importance. These defects are listed in Table 3.1. It should be noted that the recruitment of VSDs, muscular and not specified is no longer being pursued since the higher prevalence of that defect led to a sufficient number of cases within the NBDPS.[97]

Table 3.1: Congenital heart defects excluded from the National Birth Defects Prevention Study

Patent Ductus Arteriosus	Bicuspid Aortic Valve
Patent Foramen Ovale	Aortic Dilatation
Cor Triatrium	Right Aortic Arch
Aortopulmonary windeo	Aberrant Subclavian Artery
Double Outlet Left Ventricle	Double Aortic Arch
Isolated Congenitally Corrected TGA	Vascular Ring
Mitral Stenosis	Isolated Valve Dysplasias
Isolated Congenital Arrhythmias	Cardiomyopathy
Coronary Anomalies	

Because specific CHDs are both rare and heterogeneous, the NBDPS developed a unique classification scheme, with the specific purpose of balancing the needs between aggregation and maintaining relatively homogeneous outcome groups to facilitate etiologic research. Cases are classified according to three axes: cardiac phenotype, cardiac complexity, and the presence of other defects.[97] Cardiac phenotype refers to the specific CHD, or defects a case has had diagnosed. There are three levels of aggregation for cardiac phenotypes: the first is a detailed description of the phenotype, for example transposition of the great arteries, atrial septal defect, secundum, and pulmonary stenosis. The NBDPS contains over 85 unique phenotypes, known as Level-1 groups (Table A1). Level-2 consists of 28 cardiac categories, which are relatively homogeneous but still provide adequate sample size. These 28 categories can be collapsed into a third level of aggregation, Level-3, which consists of eight heterogeneous groupings with larger sample size. The 28 categories, with their corresponding 8 higher aggregations, are listed in Table 3.2 with estimated sample sizes in the most recent analytic database which includes births with estimated delivery dates from the start of the study in 1997 through 12/31/2007.

Cardiac complexity refers to whether there are one or more CHDs present. If only a single defect, or well-established condition treated like a single defect (such as Tetralogy of Fallot), the case is classified as simple. If the case has two or three fairly simple defects,

which are observed together, the case is classified as association. If there are multiple, independent defects, the case is classified as complex. The third axis refers to whether any non-CHDs are present. If there are no other defects present, the case is classified as isolated.

Table 3.2: Classification of Congenital Heart Defects, using 2-level of Aggregations and Corresponding Sample Size within the NBDPS most recent analytic database

Left Ventricular Outflow Tract Obstruction (LVOTO)		**Right Ventricular Outflow Tract Obstruction (RVOTO)**	
Hypoplastic Left Heart Syndrome (HLHS)	475	Pulmonary Atresia	188
Interrupted Aortic Arch, Type A (IAA-A)	14	Tricuspid Atresia	128
Coarctation of the Aorta (COA)	839	Ebstein's Malformation	124
Aortic Stenosis (AS)	356	Pulmonary Valve Stenosis	1112
Conotruncal		**Septals**	
Truncus	90	VSDs, perimembranous	1547
Interrupted Aortic Arch, Type B (IAA-B)	30	VSDs, muscular	743
Interrupted Aortic Arch, NOS (IAA-NOS)	8	VSDs, OS/NOS	90
D-Transposition of the Great Arteries (TGA)	591	Atrial Septal Defect (ASD), secundum	1856
Tetralogy of Fallot (TOF)	886	ASD, OS/NOS	572
Double Outlet Right Ventricle (DORV)-TGA	127	**Complex**	
Double Outlet Right Ventricle (DORV)-other	90	Single Ventricle	265
Ventricular Septal Defect VSD, conoventricular	126	L-TGA	42
Atrioventricular Septal Defect (AVSD)	260	Other Association	112
Anomalous Pulmonary Venous Return (APVR)		**Laterality Defects**	325
Total APVR (TAPVR)	224		
Partial APVR (PAPVR)	48		

3.2.2 Sources of Air Pollution Data from the Environmental Protection Agency

3.2.2.1 Ambient Air Monitoring Data

As described in Section 2.1.2.3, states, local agencies, and tribal agencies within the United States maintain a broad network of stationary air monitors in order to comply with regulations in the Clean Air Act. Measurement data from these monitors are provided to the Environmental Program Agency, where it is compiled and housed in a repository known as the Air Quality System (AQS). Through collaboration with researchers at the EPA, AQS data were obtained for all monitors within the nine states where NBDPS centers are located.

The daily average of pollutant concentrations were provided for each pollutant measured at each monitoring station, except for ozone where an 8-hour average is used. Not all monitors record measurements on all days. For example, $PM_{2.5}$ can be measured daily, every 3rd day, or every 6th day depending on the monitor location.

3.2.2.2 Downscaler Community Multiscale Air Quality (downscaler CMAQ) Model

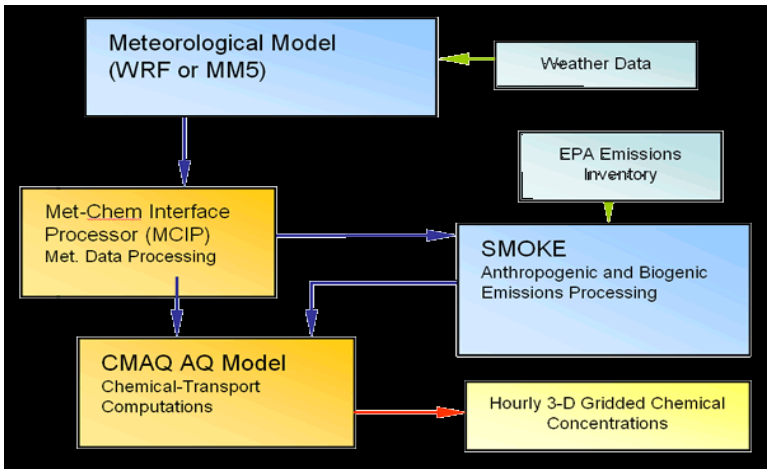

Figure 3.1: Data Inputs into the Community Multiscale Air Quality (CMAQ) Model
http://www.epa.gov/AMD/ModelDevelopment/index.html

As described above, the EPA's Community Multiscale Air Quality (CMAQ) is a deterministic prediction model that utilizes multiple inputs to predict air pollutant concentrations for $PM_{2.5}$ and ozone across the United States.[137] As illustrated in Figure 3.1, weather data is input into the meteorological model which simulates atmospheric circulation. The output of this model is then used as the input to MCIP, the meteorological-chemical interface processor, that formats/translates the meteorological data so it can be linked to the chemical/emissions data and used for air quality simulations. Separately, data from the EPA Emissions Inventory, described in Section 2.1.2.2, is input into the Sparse Matrix Operator Kernel Emissions Model (SMOKE), which processes the emissions data in order to create gridded, speciated, hourly emissions data that can be input into the CMAQ model. SMOKE also receives inputs from MCIP, in order to use atmospheric data to model emissions. Both the meteorological data and the emissions data is then input into the CMAQ Air Quality model,

which contains the chemical-transport processors that simulate chemical transformation and fate within the atmosphere. Processes simulated in this model include gas-phase chemical reactions, deposition, horizontal and vertical diffusion, aerosol dynamics and thermodynamics, and plume chemistry effects, among others.[137] From this model, predicted concentrations of pollutants are output as a gridded surface, in grids that vary in size. For the eastern part of the United States, the gridded outputs are 12 km x 12 km. For the west, the output grids are 36 km x 36 km. Thus, pollutant estimates are obtained for the many areas which lack monitoring stations.

Downscaler CMAQ takes the numerical output from this model and combines it with EPA monitoring data using linear regression with spatially- and temporally-varying bias coefficients in a Bayesian framework.[138] The numerical output is combined with monitoring data to improve spatial predication, as output from CMAQ can be biased due to the varying quality of the underlying emissions inventories and the many assumptions made throughout the modeling process. The resulting model, referred to as downscaler CMAQ because it scales gridded CMAQ output down to the point-level monitoring data, provides bias-corrected, daily predictions of concentrations of 24-hour $PM_{2.5}$ and 8-hour maximum ozone at the centroid of every census tract in the United States.

Both sources of exposure data will provide daily estimates of ambient concentrations of the pollutants. However, based on previous work utilizing this data, it was determined that daily estimates of pollutant concentrations possess a great amount of random variation that negatively impacts estimation and precision of the etiologic relationships of interest from subsequent modeling processes. Using monthly or trimester-specific averages, while reducing the random variation, also smoothes over important temporal variation in pollutant concentrations that may lead to misclassification of exposure. It was observed that weekly averages were able to minimize the

random variation, while still maintaining the ability to observe relevant trends in air pollutant concentrations.[139] Therefore, using both data sources, weekly averages will be constructed for each pollutant, for every calendar week during the study period 1997-2006.

3.2.3 Supplemental Sources for Covariate Information

Road Networks from ESRI StreetMap North America: Some of the pollutants, such as SO_2, measured by the EPA monitors are a marker of regional pollution. These pollutants may interact with more local sources of pollution, such as living close to a major roadway. Proximity to a roadway will be quantified by calculating the shortest straight-line distance to a major roadway. The source of the roadway network that will be used is the ESRI StreetMap North America dataset. Using the participant's residential location as the starting point, the distance to the closest major road, defined as a highway or major arterial road, will be calculated geodesic distance measurements, which avoids distortion due to projection of geographic coordinates. This was performed in ArcGIS. The continuous value of the shortest distance was stored as the exposure metric, although distance to a major road will also be examined categorically in the analysis.

3.3 Methodology for Specific Aim 1

Specific Aim 1: To determine whether exposure during pregnancy to individual criteria air pollutants, assessed using measurements from stationary air monitors, is associated with CHDs

Subaim 1a: To determine if the relationship between exposure to $PM_{2.5}$ and CHDs is modified by use of folic-acid supplements early in pregnancy

Subaim 1b: To explore the effect of multiple pollutants on CHDs using principal components analysis (PCA)

Eight sets of analyses will be performed in order to address Specific Aim 1. They are summarized in Table 3.3 and the methodology is described in more detail below.

Table 3.3: Summary of Analyses to Address Specific Aim 1

Specific Aim	Population	Outcome Grouping	Exposure Source	Pollutants Examined	EMM/Confounders	Model
1	All	6 categories	Monitoring Data	All	Identified through DAG/Prelim Analysis	Hierarchical Regression
1	All	28 categories	Monitoring Data	All	Identified through DAG/Prelim Analysis	Hierarchical Regression
1	<10km to a monitor	6 categories	Monitoring Data	All	Identified through DAG/Prelim Analysis	Polytomous Logistic
1	<10km to a monitor	28 categories	Monitoring Data	All	Identified through DAG/Prelim Analysis	Polytomous Logistic
1a	<50km to PM monitor	6 categories	Monitoring Data	$PM_{2.5}$	Use of Folic Acid and Identified through DAG/Prelim Analysis	Polytomous Logistic
1a	<50km to PM monitor	28 categories	Monitoring Data	$PM_{2.5}$	Use of Folic Acid and Identified through DAG/Prelim Analysis	Polytomous Logistic
1b	Near all monitors	6 categories	Monitoring Data	All	Identified through DAG/Prelim Analysis	PCA and Hierarchical Regression
1b	Near all monitors	28 categories	Monitoring Data	All	Identified through DAG/Prelim Analysis	PCA and Hierarchical Regression

3.3.1 Study Population

For this aim, the study population consists of all participants in the NBDPS with at least one diagnosed CHD and all controls who are included in the most recent version of the NBDPS analytic database who have estimated date of delivery (EDDs) from the start of the study in 1997 through 12/31/2006. These dates were selected because geocoded residential addresses are not yet available for participants with EDDs after 12/31/2006. Additionally, women who reported having non-gestational diabetes during their pregnancy will be excluded from this aim because of the strong association between maternal diabetes and CHDs.[110] For specific aim 1a, the analysis will be restricted to women who live within 50 km of an air pollution monitor measuring $PM_{2.5}$. Due to changes in pollutant monitoring, this effectively limits the population to women with EDDs from 1/1/1999-12/31/2006. For specific aim 1b, the analysis is limited to women who live within 50 km of each type of air pollutant monitor. Again, due to the monitoring of $PM_{2.5}$, this limits to women with EDDs from 1/1/1999-12/31/2006.

3.3.2 Outcome Assessment

The classification scheme for CHDs utilized by the NBDPS was described above in Section 3.2.1. For the primary analyses of this specific aim, cases will be limited to participants who have a simple, isolated defect. This translates to each having a single CHD or well-defined pattern of CHDs without any concurrent non-CHDs. In a previous version of the data, it was calculated that 65% of cardiac cases were simple and isolated. These groupings are considered to be the most etiologically pure and are able to be classified into mutually exclusive groups. Subsequent analyses may include cases classified as association and isolated, those who have two or three simple CHDs only. Before these analyses are pursued, we will consult with the collaborating NBDPS cardiologist to determine appropriate classification.

Among the simple, isolated cases, the cases will be aggregated into groups using the 28 categories defined in the Level-2 aggregation and the 8 Level-3 aggregations as recommended by NBDPS cardiologists. Because we are limiting to simple, isolated CHDs, only six of the level-3 aggregations are represented in our sample. The Level-3 aggregations will be for instances when the sample size of the Level-2 aggregation is too small for analytic purposes. Additionally, some Level-2 categories within the same Level-3 heading may be collapsed to improve sample size, for example Truncus, Interrupted Aortic Arch, Type B and Interrupted Aortic Arch, NOS could be collapsed into an Other Conotruncals category, which would maintain the homogeneity of larger conotruncal categories, such as d-TOF and TGA.

3.3.3 Exposure Assessment

Specific aim 1 will utilize monitoring data to assign exposure for the individual criteria air pollutants. As written in section 3.2.2, weekly averages for all pollutants will be constructed for the entire study period, 1997-2006. Using ArcGIS, for each case and control, all residential locations throughout pregnancy will be linked to the closest air monitor. Additionally, the distance to the

closest air monitor will be stored in order to calculate an indicator for women who live within 10 km of a monitor. Subsequent subanalyses will be restricted to those women as it is expected that the exposure classification will be better for women who live closer to the air monitors. Once the cases and controls are linked to a source of pollutant data, exposure metrics will be constructed for weeks 2 through 8, to correspond to the critical period of exposure for cardiac development. In addition to assigning average exposures for the individual weeks, each participant will be assigned a single average of weeks 2 through 8, in order to compare to previous studies which utilized a single metric.

3.3.3.1 Constructing source-factors for Specific Aim 1b

In order to obtain the source factors used to assess the relationship between air pollutants and CHDs in a multipollutant context, principal component analysis (PCA) was conducted among the subset of participants who lived within 50 km of each type of pollutant and had pollutant concentrations for all six pollutants. PCA is a dimension-reduction technique that is used to reduce the number of correlated variables, which you believe may be measuring the same construct, into a smaller number of artificial variables that capture most of the variance of the original variables while being uncorrelated with each other.[140] Using this method, we avoid the issue of multicollinearity that would arise if we tried to simultaneously enter each pollutant in a regression model.[141] We standardized the exposure data to prepare the data for PCA. Using SAS v9.2 to run the PCA, we retained components with an eigenvalue at or greater than 1, which indicates that the component accounts for at least the same or more variance than one of the original pollutant variables. We then applied a varimax rotation and calculated factor scores for each participant.

3.3.4 Covariate Selection

The directed acyclic graph (DAG) describing the potential relationship between exposure to air pollutants during pregnancy, CHDs and potential confounders and effect measure modifiers is illustrated in Figure 3.2. DAGs graphically describe the relationships between variables and provide a systematic method to assess a variable's potential for confounding. Based on the previous literature, there are a number of variables that could confound the association between air pollutants and birth defects. It should be noted that this DAG is meant to be a general representation of the relationship between air pollutants and CHDs. It is possible that some aspects could be different for specific pollutants and/or specific defects.

Exposure to air pollution is assessed by residential exposure. "Choice" of geographic residence is affected by many demographic factors, which in turn can be associated with behaviors that could increase the risk for CHDs. For example, behavioral risk factors for CHDs, such as tobacco and alcohol use during pregnancy[124,128], are also associated with exposure to air pollution through demographic variables and socioeconomic status.[142] There are also direct pathways from race/ethnicity, paternal/maternal age and socioeconomic status to both CHDs and choice of geographic residence. These paths suggest that controlling for the demographic factors would block both sets of pathways. Maternal fever/influenza during pregnancy is also not a direct cause of air pollution, but it does vary by season, which is associated with air pollution through temperature and other weather conditions. This suggests that controlling for season would block the entire pathway. Living near a roadway is also included in this DAG, as they represent a much more local exposure to air pollutants. The exposure being assessed in this study is over a considerable amount of space and it is possible that living near a roadway has an effect on CHDs, separate from the air pollutant exposures we are measuring. However, it is possible that controlling for this variable will adjust away some of the relationship between exposure to air pollution and CHDs. Use of folic-acid

supplements is another behavioral factor that is affected by SES and associated with CHDs.[118] However, due to the previous research on DNA methylation[34,36], folic-acid supplementation will be assessed for effect measure modification as the primary analysis of Specific Aim 1a.

The DAG doesn't show family history because while having a family history of CHDs is a risk factor for having an infant with a CHD, but there is not clear association with exposure to air pollution. However, it is possible that family history may be associated with increased susceptibility

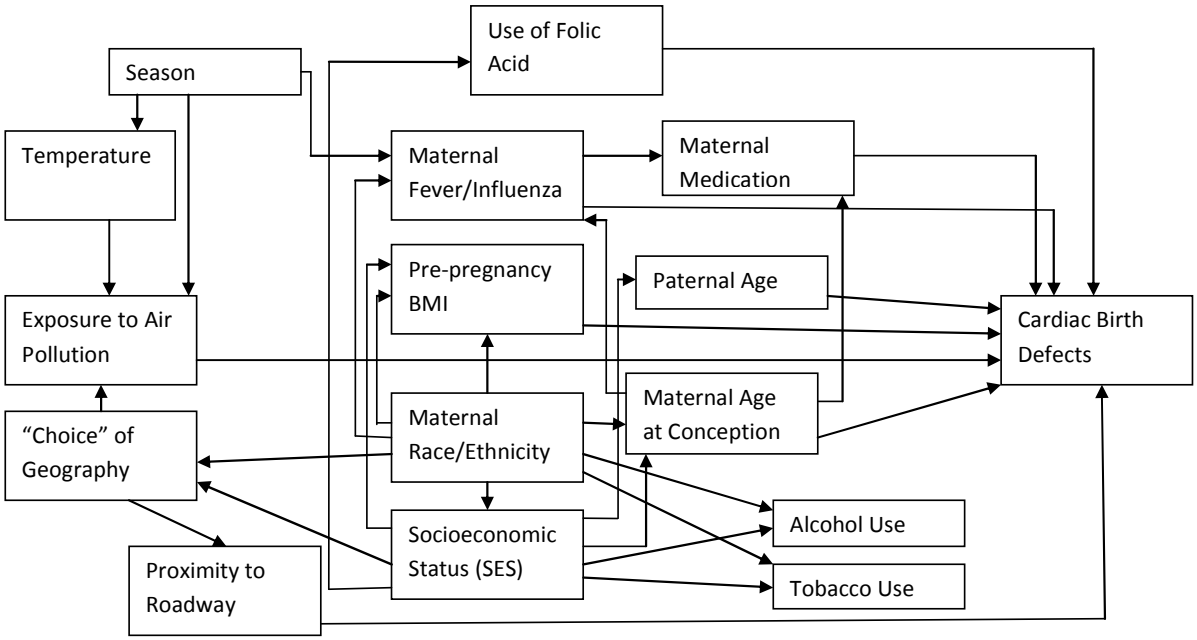

Figure 3.2: Directed Acyclic Graph (DAG) of the relationship between Exposure to Air Pollutants and Congenital Heart Defects

to insults to cardiac development.[73] Therefore, we will assess family history for effect measure modification (EMM). Previous studies have also adjusted for infant sex, but there isn't a direct path connecting it to air pollution and CHDs. Previous research suggests that exposure to some environmental toxins could be able to affect the sex ratio[143], although this is not well established for air pollutants. That would put infant sex on the causal pathway, and thus it should not be controlled for in the analysis. It's also possible that infant sex could impact susceptibility to air pollution, and therefore it could be assessed for EMM. A summary of the variables described above are presented

in Table 3.4, including whether the DAG suggests it should be controlled for, the source of data, and how it is originally coded. There are a number of variables within the NBDPS dataset that could reflect socioeconomic status. They will be examined individually and in combination to see the impact they have on the estimates. Some variables listed have more detailed coding available within the CATI. This may be examined if deemed appropriate during analyses.

Table 3.4: Summary of Potential Confounders and Effect Measure Modifiers for Specific Aim 1

Variable	Data Source	Original Coding	Identified by DAG as Needing Adjustment
Maternal Age	CATI	Continuous, years	Yes
Paternal Age	CATI	Continuous, years	Yes
Maternal Race/Ethnicity	CATI	Non-Hispanic White Non-Hispanic Black Hispanic Asian/Pacific Islander Native American/ Alaskan Native Other	Yes
Alcohol Use	CATI	Yes/No OR Binge drinking/Non-binge drinking/ No drinking OR Yes/No by each of the first 3 months of pregnancy, each trimester, and 3 mos. Prior to conception	No
Tobacco Use	CATI	Yes/No Ever OR Yes/No by each of the first 3 months of pregnancy, each trimester, and 3 mos. Prior to conception	No
Infant Sex	CATI	Male/Female	No
Proximity to a Roadway	Calculated using geocoded residence and road networks	Continuous distance	Yes
Use of Folic-Acid Supplementation	CATI	Yes/No by month from 3 mos. Before conception to birth	No
Season of Conception	CATI	Four seasons	Yes
Fever/Influenza	CATI	Yes/No and month during pregnancy if Yes	No
Maternal Medication Use	CATI	Yes/No, type of medication and month during pregnancy	No
Socioeconomic Status			

Table 3.4 (cont.) Variable	Data Source	Original Coding	Identified by DAG as Needing Adjustment
Maternal Education	CATI	No formal schooling 1-6 years 7-8 years 9-11 years 12 years, completed high school or equivalent 1-3 years of college Completed technical college 4 years college/bachelor's degree Master's degree Advanced degree (MD, PhD, JD)	Yes
Paternal Education	CATI	Same as above	
Household Income	CATI	Categorical: 10,000-50,000 in 10,000 increments	
Pre-pregnancy BMI	CATI	Continuous and Categorical	No
Family History of Birth Defects	CATI	Yes/No for each parent and Y/N for extended family	No/ Potential EMM

3.3.5 Data Exploration and Coding

Descriptive, univariate analysis on the variables discussed above using the original coding will be performed and outliers and prevalence of missing data will be identified. We will also examine the number of geocoded cases within each of the 28 categories of CHDs and collapse as necessary to ensure that each analytic group has a minimum of 100 cases. Following univariate analysis, we will conduct bivariate analysis between each pollutant and any CHD as an outcome to explore the general shape of the relationship between exposure and outcome. This will be examined using both continuous measures of exposure and multiple categorizations to best capture the relationship. We will start by examining exposure contrasts that were used in previous research. The choice of exposure coding will also be reassessed during the modeling process. As illustrated in the DAG, there are complex relationships between the multiple demographic and socioeconomic factors. In order to prevent collinearity in our models, we will assess associations between the demographic and various measures of socioeconomic status. Additionally, we will explore the distribution of covariates between cases and controls and explore the distributions of exposure at

the different levels of each of the covariates. At this point, we will explore different coding options for the covariates. For continuous variables such as age, we will determine if the relationship with the odds of having a defect is approximately linear, or if we need to construct indicator variables to accommodate a non-linear relationship. For categorical variables, we will explore collapsing levels within variables if sample size is small. As shown in the table above, use of folic-acid supplementation was originally collected for each month of pregnancy and the 3 months prior to conception. Because we are interested in early folic-acid supplementation use for specific aim 1a, we will focus on use during the month prior and two months after conception. We will explore different combinations, such as only examining one month prior (as a proxy for the very beginning of pregnancy), one month after conception and two months after conception separately, combining one month prior and one month after, and then aggregating all three.

After exploring variable coding, we will explore preliminary EMM and confounding by all of the covariates by constructing simple, logistic regression models of the disease-exposure relationship. This will be done since exposure will be assessed continuously or with multiple categorical indicators, and tabular analyses are not feasible. In order to assess EMM by each covariate, likelihood ratio tests will compare models which include interaction terms between the exposure and covariate of interest and those that do not, using an α-level of 0.2 to indicate the potential for EMM. If a variable is not determined to be a potential modifier, it will then be assessed for confounding by comparing the change-in-estimate from models which do and do not contain the individual covariates . If the change-in-estimate is greater than 0.05, it will be considered a potential confounder. Because the effect estimates from these models tend to be small, I have chosen to use a smaller change-in-estimate criterion than typical. These analyses will be done individually for the 6 larger aggregations.

The results from these analyses will be examined, in combination with the DAG and information on potential biological mechanisms and relationships to make a decision about which covariates will be assessed for EMM and confounding in the final modeling strategy. In general, if a covariate is identified as a potential modifier by the preliminary data analysis, it will be explored as a modifier in the multivariable analysis. For variables not identified as modifiers, if the DAG indicates a need for adjustment, the covariate will be considered a potential confounder and assessed during modeling, in the presence of other covariates. If the DAG doesn't indicate a need for adjustment, but analysis of the data indicate the potential for EMM or confounding, it will also be assessed in the presence of other covariates. Otherwise, the variable will not be assessed in the final strategy.

3.3.6 Modeling Strategy

A two-stage hierarchical regression model will be utilized for the primary analyses and for aim 1b. For sensitivity analyses and aim 1a, only the first-stage model, the polytomous logistic regression model will be used due to reduced sample size.

3.3.6.1 Polytomous Logistic Regression

As shown in Table 3.3, there will be eight sets of models using a polytomous logistic regression model. The outcome will be defined using either the 6 level-3 groupings or the individual CHDs. Exposure will be a single average for weeks 2 through 8 or simultaneously modeling each week of exposure. Exposure will be examined both continuously and categorically, based on results from the data exploration analyses described above. For specific aim 1b, the factor scores will be used to assign exposure.

The models will be constructed using a backward elimination strategy, starting with a full model that contains all covariates that were identified as potential modifiers and confounders in the data exploration analyses. EMM will be assessed first, by comparing the

full model which includes the interaction term(s) to a model that does not. This will be done for each potential modifier, and if one drops out, the new full model will not contain that interaction term. Likelihood ratio tests will be performed to determine which modifiers will remain using an α-level of 0.20. Any variables not identified as modifiers will be assessed for confounding by individually removing covariates and comparing stratum-specific estimates (if modifiers are present) for all cardiac levels back to the full model. We will examine the change-in-estimate and change-in-precision for each calculated estimate. Because we are using polytomous models, the models result in multiple estimates, one for each CHD grouping (i.e. outcome level). Therefore, there is only one adjustment set for all of the different categories of defects. If the change-in-estimate for at least one defect category is greater than 0.05, the covariate being examined will be retained in the model. If the change-in-estimate for some defect categories caused by adjusting for a variable corresponds to a greater loss of precision in others, we will evaluate running separate models for the different cardiac outcomes as opposed to running polytomous models. This will be done for all covariates. The order of removal will be covariates that were identified through data exploration and then covariates that were identified by the DAG only and then covariates that were identified by the DAG and through data exploration. The final determination of the model will consider the results of this strategy along with the DAG and the adjustment sets in previous research.

As a sensitivity analysis, the models will be conducted by restricting to women who live within 10 km of a monitor. We hypothesize that we may reduce exposure misclassification by limiting the population to women whose assigned exposure may be more reliable. For aim 1a, if folic acid-containing supplement use was not determined to be

a modifier through the modeling building process, it will be put back in to the final model and reassessed using likelihood ratio tests.

3.3.6.2 Hierarchical Model

Because we simultaneously assessed multiple weeks of exposure and multiple defects/groupings, we constructed two-stage hierarchical regression models, using a software program adapted from Witte et al, to account for the correlation between estimates and partially address multiple inference. For the primary analyses and aim 1b, the polytomous logistic regression described above represents the first-stage model. Equation 1 represents the unconditional, polytomous logistic regression model containing all individual weeks of exposure, or the single 7-week average, and the full adjustment set determined by the process described above.

$$\Pr(Y = d|x, w) = \frac{\exp(\alpha_d + \boldsymbol{x\beta}_d + \boldsymbol{w\gamma}_d)}{1 + \sum_{k=1}^{m} \exp(\alpha_k + \boldsymbol{x\beta}_k + \boldsymbol{w\gamma}_k)} \quad (1)$$

x represents either the seven-week average or the vector of weekly pollutant concentrations, β_d is the vector of regression coefficients corresponding to pollutant exposure for a specific CHD (*d*), *w* represents the covariates and γ_d is the vector of regression coefficients corresponding to the covariates for that specific CHD. The second-stage model is given in equation 2

$$\boldsymbol{\beta}_i = \boldsymbol{Z}_i\boldsymbol{\pi} + \boldsymbol{\delta}_i \quad (2)$$

where Z_i is a row in the design matrix that includes an intercept term and then indicator variables for type of defect, broader defect grouping, and exposure week/level for the i-th β, π is the vector of coefficients estimated from the data and δ_i are independent normal random variables with a mean of zero and a variance of τ^2 that describe the residual variation in β_i, not captured by the design matrix. The obtained second-stage coefficients

are used to estimate the means toward which the first-stage coefficients will be shrunk towards, with the magnitude of the shrinkage depending upon the precision of the maximum likelihood estimate obtained in stage 1 and the value of the second stage variance, τ^2.[144,145] We fixed τ^2 at 0.5, corresponding to a prior belief with 95% certainty that the residual odds ratio will fall within a 16-fold span.

This model was implemented using Proc IML in SAS v9.2. To assess whether our results were robust to changes in model specification we explored setting the value of τ^2 to 0.25, corresponding to a 7-fold odds ratio span as well as to a value of 1, corresponding to a 50-fold span. Additionally, we explored different specifications for the design matrix which would define the prior mean as either a common mean for all defects, a common mean for each defect, or a common mean for each exposure week/level, across defects.

3.3.7 Minimum Effect Size Analysis

The minimum effect size is calculated based on a previous version of the analytic dataset. We will gain additional cases by using the new dataset for this proposed study which will add an extra year of data. Based on a previous study by Gilboa et al, we estimated that 86% of cases and 80% of controls, across all study centers, would be successfully geocoded.[8] Based on this, analyses would be conducted using 5,445 controls. The table below lists the minimum detectable effect estimate for all of the 28 CHD groupings with more than 100 geocoded cases. For this analysis, we consider those who have exposure greater than the 75th percentile of each pollutant distribution in the controls as "exposed". Using that definition of exposed and assuming unadjusted logistic regression and 80% power, the effect estimate detectable for a subgroup of 100 would be 1.83. The proposed analysis will be more complex than the assumptions of this effect size analysis. This will impact the minimum detectable estimate that our study will be able to detect. However, if we

conclude that there not enough cases within a subgroup to obtain a reliable estimate, we will use the greater level aggregations for the analysis.

Table 3.5: Minimum Effect Size Analysis for Different Congenital Heart Defects

CHD Groupings	Total Geocoded Cases (estimated)	Minimum Detectable Effect Estimate
Hypoplastic Left Heart Syndrome (HLHS)	475	1.35
Coarctation of the Aorta (COA)	839	1.27
Aortic Stenosis (AS)	356	1.41
D-Transposition of the Great Arteries (TGA)	591	1.31
Tetralogy of Fallot (TOF)	886	1.26
Double Outlet Right Ventricle (DORV)-TGA	127	1.75
Ventricular Septal Defect VSD, conoventricular	126	1.75
Atrioventricular Septal Defect (AVSD)	260	1.50
Total APVR (TAPVR)	224	1.53
Pulmonary Atresia	188	1.60
Tricuspid Atresia	128	1.75
Ebstein's Malformation	124	1.76
Pulmonary Valve Stenosis	1112	1.23
VSDs, perimembranous	1547	1.20
VSDs, muscular	743	1.29
Atrial Septal Defect (ASD), secundum	1856	1.19
ASD, OS/NOS	572	1.32
Single Ventricle	265	1.49
Other Association	112	1.78
Laterality Defects	325	1.43

3.4 Methodology for Specific Aim 2

Specific Aim 2: To utilize the greater spatial and temporal resolution of exposure estimates derived from deterministic pollutant simulation models to investigate the association between select criteria air pollutants and CHDs

Subaim 2a: To compare effect estimates and model fit when using monitoring data and output from a statistical model which combines the two in order to assign women's exposure during pregnancy

Subaim 2b: To determine if the addition of rural populations, who are often excluded from studies due to large distance from monitoring sites, affects the observed relationship between exposure to criteria air pollutants and CHDs

3.4.1 Study Population

For this aim, the study population consists of all participants in the NBDPS with at least one diagnosed CHD and all controls who are included in the most recent version of the NBDPS analytic database who have EDDs from the start of downscaler CMAQ predictions in 1/1/2001 through 12/31/2006. This effectively excludes women from the California and Utah sites as no predictions were made for the western United States until 2007. It also excludes women from the Texas site with EDDs prior to 1/1/2002, when downscaler CMAQ predictions began for that state. As for specific aim 1, women who reported having non-gestational diabetes during their pregnancy will be excluded from this aim because of the strong association between maternal diabetes and CHDs.[110] To address subaim 2a, the population will be limited to women who have AQS measurements available, i.e. live within 50 km of an air pollutant monitor for $PM_{2.5}$ or ozone. For subaim 2b, the full population will be compared to the population used in subaim 2a.

3.4.2 Outcome Assessment

Outcome assessment for this aim is the same as for Specific Aim 1. Due to smaller sample sizes, some individual defects will only be able to be analyzed as part of the larger defect-groupings.

3.4.3 Exposure Assessment

Specific aim 2 will utilize model-based data from the downscaler CMAQ model to assign exposure for $PM_{2.5}$ and ozone. Using ArcGIS, for each case and control, all residential locations throughout pregnancy will be linked to the closest centroid of a census tract, where downscaler CMAQ predictions were made. Once the cases and controls are linked to a census-tract centroid, exposure metrics will be constructed for weeks 2 through 8, to correspond to the critical period of exposure for cardiac development. In addition to assigning average exposures for the individual

weeks, each participant will be assigned a single average of weeks 2 through 8, in order to compare to previous studies which utilized a single metric.

3.4.4 Covariate Assessment

Covariate assessment and DAG analysis were the same as for specific aim 1. Because of limited sample size, effect measure modification of folic-acid will not be assessed in this aim.

3.4.5 Data Exploration and Coding

Data exploration and coding will be the same as outlined for specific aim 1. In addition, to compare pollutant concentrations obtained from the downscaler CMAQ model to those obtained from AQS air monitors, distributions of pollutant concentrations from each source for the population that lived within 50 km of an air monitor were compared. Then, distributions of downscaler CMAQ values among those who do and do not live within 50 km of a stationary air monitor were compared to determine the impact of including populations that do not live near regulatory monitors as detailed in subaim 2b. The pollutant concentrations were also compared categorically, as these types of metrics are often utilized in epidemiologic studies.

3.4.6 Modeling Strategy

For this aim, two-stage hierarchical regression models, as detailed for specific aim 1, were constructed. The procedure for constructing the first-stage polytomous models was also the same. Three sets of models were constructed for comparison purposes. For aim 2a, models using AQS measurements to assign exposure for those living within 50 km of an air monitor were compared to those using CMAQ predictions to assign exposure for those living within 50 km of an air monitor. For aim 2b, the models using downscaler CMAQ predictions constructed above were compared to a model using downscaler CMAQ predictions for the full population. Both the seven-week summary measure and individual weekly averages were assessed.

CHAPTER 4

4. MATERNAL EXPOSURE TO CRITERIA AIR POLLUTANTS DURING EARLY PREGNANCY AND CONGENITAL HEART DEFECTS IN OFFSPRING: RESULTS FROM THE NATIONAL BIRTH DEFECTS PREVENTION STUDY

4.1 Introduction

Epidemiologic studies provide inconsistent evidence of an association between exposure to air pollutants and CHDs. [5,8,16-18,22-25] A recent meta-analysis identified two associations: nitrogen dioxide (NO_2) exposure and tetralogy of Fallot (TOF) and sulfur dioxide (SO_2) exposure and coarctation of the aorta (COA).[23] However, each meta-analysis was based on only four studies and only able to explore five defects/defect groupings. Moreover, to date, no studies have explored the relationship between particulate matter with aerodynamic diameter less than 2.5 micrometers ($PM_{2.5}$) and CHDs.

Most previous studies utilized monitoring data and assigned exposure by averaging daily pollutant averages over post-conception weeks three through eight. This method misses short-term temporal variability in pollutant concentrations and higher, acute exposures. Consequently, it does not capture the temporal variability in exposure across windows with greater impact on cardiac development, which could mask or attenuate associations. Utilizing daily maximum concentrations, as opposed to averages, to calculate exposure would better capture daily exposure peaks and more closely parallel regulatory standards issued by the Environmental Protection Agency (EPA). [40] Separating a single overall average into weekly averages would also allow for the exploration of specific windows of susceptibility and reduce potential misclassification of exposure.

This study utilizes data from the National Birth Defects Prevention Study (NBDPS), a large population-based case-control study of birth defects to investigate the association between CHDs in offspring and maximum ambient levels of the following criteria air pollutants during early pregnancy: carbon monoxide (CO), NO_2, ozone, particulate matter with aerodynamic diameter less than 10 micrometers (PM_{10}), $PM_{2.5}$, and SO_2. Although a criteria air pollutant, lead was not included in this study as the primary route of exposure to lead is through dust and soils, and not inhalation of ambient air.

4.2 Methodology

4.2.1 Study Population

The NBDPS has been approved by the institutional review boards (IRBs) of all participating centers. These analyses were reviewed and approved by the University of North Carolina IRB. The design of the NBDPS has been described previously. [101] Cases include livebirths and stillbirths greater than 20 weeks gestation or at least 500 grams, as well as elective terminations of prenatally-diagnosed defects when available, at nine US study sites. The NBDPS excludes cases with chromosomal/microdeletion disorders and disorders of known single-gene deletion causation. Controls are unaffected livebirths who are randomly selected from either vital records or hospital records, depending upon study center. The participation response was 69% among all cases and 65% for controls.

For this analysis, the study population consisted of all controls and eligible cases with a simple, isolated CHD (ie a single CHD with no extra-cardiac birth defects present) and had an estimated date of delivery (EDD) from the start of the study in 1997 through 12/31/2006. Women who reported having pregestational diabetes (Types I and II) during their pregnancy were excluded owing to the established association with CHD. [110] The NBDPS classification methodology called for a team of clinicians with expertise in pediatric cardiology to assign a single, detailed cardiac

phenotype to each case based on a review of information abstracted from the medical record and then aggregate them into individual CHDs and defect-groupings. [97] Our isolated CHD cases fell into 24 individual defects and six broader groupings (Table 4.1). The following additional groups were created due to limited sample size of individual defects: 1)other conotruncal defects, which included common truncus, interrupted aortic arch-type b, interrupted aortic arch-not otherwise specified (iaa-typeb, iaa-nos), double outlet right ventricle associated with transposition of the great arteries (DORV-TGA) and not associated with TGA (DORV-other) and conoventricular septal defects (VSD-conoventricular); and 2) atresias that included both pulmonary and tricuspid atresia.

As part of the NBDPS protocol, mothers completed a computer assisted telephone interview, which included a residential history during the pregnancy. These addresses were centrally geocoded to ensure consistency across study centers. Each geocoded residential address during the first eight weeks of pregnancy was matched to the closest stationary air monitor with more than 50% of data available, for each pollutant using ArcGISv10 and monitor locations obtained using data from EPA's Air Quality System. If a woman lived more than 50 km away from the closest pollutant-specific air monitor, she was excluded from that analysis. $PM_{2.5}$ measurements first became available in 1999, so participants from 1996-1998 were excluded from that analysis.

4.2.2 Exposure Assignment and Covariates

Pollutant concentrations from the closest monitor were assigned to the woman's corresponding pregnancy period for each address reported during the first eight weeks of pregnancy. For CO, NO_2, and SO_2, we used the daily maximum hourly measurement, while we used the daily maximum 8-hour average for ozone to parallel the EPA regulatory standards and capture daily variability in ambient concentrations. [40] Concentrations of $PM_{2.5}$ and PM_{10} are based on 24-hour measurements, but were often measured only on every 3rd or 6th day. For the present analysis, we averaged over the daily maximum or 24-hour measurements for weeks two through eight of

pregnancy, measured from the estimated date of conception, to assign a seven-week and also one-week averages of the maximum daily values. Per NBDPS protocols, estimated date of conception was obtained by calculating backwards from the estimated date of delivery each woman reported being given by her clinician during pregnancy. We included week two in addition to the standard window of cardiac development, as previous literature suggests the potential for lag effects of air pollution. [3,146] Ambient levels of each pollutant except ozone were categorized using the distribution of pollutant concentration among the controls into the following categories: less than the 10th centile (referent), 10th centile to the median, median to the 90th centile and greater than or equal to the 90th centile. These categories captured the departure from linearity observed in initial, exploratory analyses. Ozone was categorized into quartiles for the same reason. Centiles were calculated separately for the seven-week and one-week measures of exposure, although the values were very similar.

Potential confounders were identified through review of the literature and directed acyclic graph analysis.[147] The following variables obtained from the maternal interview were included in the final adjustment set for all statistical models: age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, alcohol consumption during the first trimester, and maternal birth outside of the US. Educational attainment was collapsed into the following categories: 0-6 years, 7-11 years, completed high school or equivalency, 1-3 years college or completed technical school, bachelor's degree, and masters or advanced degree. In order to account for potential differences in case ascertainment by study center, final models were also adjusted for the center-specific ratio of septal defects to total heart defects. This adjustment for center was chosen to account for differences in the types of cardiac cases that were recruited at each site, without controlling away effects due to spatial variability in pollutant concentrations that could occur when using a crude indicator for site. Distance to the closest major road, defined as an

interstate, US highway, state or larger county highway was constructed using ArcGISv10 and then dichotomized first at 200 meters and then at 50 meters, consistent with previous research which suggests that pollutant levels drop-off more than 200 meters from a roadway. [148] All potential confounders, as well as pre-pregnancy body mass index, maternal occupation status during pregnancy (defined dichotomously), and distance to a major roadway were assessed for effect measure modification using likelihood ratio tests with an *a priori* alpha level of 0.1.

4.2.3 Statistical Analysis

For each pollutant, models were constructed to explore individual defects and defect-groupings. Because we simultaneously assessed multiple weeks of exposure and multiple defects/groupings, we constructed two-stage hierarchical regression models, using a SAS/IML software program adapted from Witte et al, to account for the correlation between estimates and partially address multiple inference. [144,149] The first-stage, represented in Equation 1, was an unconditional, polytomous logistic regression model of individual CHDs on exposure (*X)* defined as either all one-week averages of maximum or 24-hour pollutant values or the single 7-week average, and the full adjustment set (*w)* detailed above.

$$\Pr(Y = d|x, w) = \frac{\exp(\alpha_d + \boldsymbol{x\beta}_d + \boldsymbol{w\gamma}_d)}{1 + \sum_{k=1}^{m} \exp(\alpha_k + \boldsymbol{x\beta}_k + \boldsymbol{w\gamma}_k)} \quad (1)$$

β_d is the vector of regression coefficients corresponding to pollutant exposure for an individual CHD (*d*), while γ_d is the vector of regression coefficients corresponding to the covariates for a given defect, and *m* is the total number of individual types of CHDs. The second-stage model is given in Equation 2

$$\boldsymbol{\beta}_i = \boldsymbol{Z}_i\boldsymbol{\pi} + \boldsymbol{\delta}_i \quad (2)$$

where Z_i is a row in the design matrix that includes an intercept term and then indicator variables for type of defect, broader defect grouping, and exposure week/level for the i-th β, π is the vector of

coefficients corresponding to the variables included in the design matrix and δ_i are independent normal random variables with a mean of zero and a variance of τ^2 that describe the residual variation in β_i. The obtained second-stage coefficients,π, are used to estimate the means toward which the first-stage coefficients will be shrunk, with the magnitude of the shrinkage depending upon the precision of the maximum likelihood estimate obtained in stage 1 and the value of the second stage variance, τ^2. [144,145] We fixed τ^2 at 0.5, corresponding to a prior belief with 95% certainty that the residual odds ratio will fall within a 16-fold span.

To assess whether our results were robust to changes in model specification we conducted sensitivity analyses by setting the value of τ^2 to 0.25, corresponding to a 7-fold odds ratio span, as well as to a value of 1, corresponding to a 50-fold span. We also explored different specifications for the design matrix, in turn defining the prior mean as a common mean for all defects, a common mean for each defect, or a common mean for each exposure week/level, across defects. Defects with fewer than 100 cases were excluded from hierarchical models and explored using Firth's penalized maximum likelihood method to address the quasi-complete separation that occurred due to small sample size. [150]

In order to explore associations with CHDs within a multipollutant context, a principal component analysis (PCA) was conducted among the subset of participants who lived within 50 km of each type of monitor and had pollutant concentrations for all six pollutants. PCA is used to reduce the number of correlated variables, which are believed to be measuring the same construct or source, into a smaller number of artificial variables that capture most of the variance of the original variables while being uncorrelated with each other. [140] This allows the resulting source-factors to be included within the same model, reducing issues of multicollinearity. From this analysis, we retained components with an eigenvalue at or greater than 1, which indicates that the component accounts for at least the same or more variance than one of the original pollutant

variables. We then applied a varimax rotation and calculated factor scores for each participant. These factor-scores were subsequently categorized using the 10^{th}, 50^{th} and 90^{th} centiles and used to assign exposure in hierarchical models.

4.3 Results

Characteristics of the study population are detailed in Table 4.1. Approximately 90% of both cases and controls had a successfully geocoded residential address during the first 8 weeks of pregnancy. Women with successfully geocoded addresses delivered infants with a similar case phenotype and had a racial, educational, and behavioral profile similar to the full study population. There were site-related differences in both geocoding success and proximity to pollutant monitors with more rural sites making up a smaller percentage of the analytic samples. Additionally, women who lived within 50 km of a SO_2 monitor were slightly older, more likely to be White or African-American, work outside the home, have higher household income and report alcohol consumption during pregnancy. The majority of women had daily exposure levels below EPA's regulatory standards.

4.3.1 Exposure assigned as a single 7-week average of daily maximums or 24-hour measurements

Figure 4.1 shows the estimated adjusted odds ratios (OR) and 95% confidence intervals (CI) resulting from the hierarchical regression models of the 7-week average exposure to individual pollutants and CHDs. Crude estimates were similar to estimates adjusted for confounders, so only adjusted estimates are shown. Larger ORs were observed for both left and right ventricular outflow tract obstruction defects (LVOTO, RVOTO) than other defect groups. For example, women with the highest average daily maximum exposure to NO_2 (greater than 45.5 ppb) had more than two times the odds of both COA (OR 2.5 95% CI 1.21, 5.18) and PVS (OR 2.03 95%CI 1.23, 3.33) as women with the lowest exposure (less than 18.9 ppb). We observed a similar relationship between SO_2 exposure and PVS, although it was attenuated at the highest exposure level (OR 10-50/10 centile contrast

2.34 95% CI 1.33, 4.14; OR 50-90/10 centile contrast 2.06 95% CI 1.16, 3.67; OR 90/10 centile contrast 1.48 95% CI 0.74, 2.97). The odds of the conotruncal and septal groups were elevated with exposure to NO_2 and PM_{10} although to a lesser magnitude than observed for the outflow tract defects. There was some evidence of heterogeneity within the LVOTO defects as hypoplastic left heart syndrome (HLHS) was associated with exposure to $PM_{2.5}$ (90/10 centile contrast: OR 2.04 95% CI 1.07, 3.89) but not NO_2. There was also some evidence of heterogeneity within septals related to SO_2 exposure, as we observed increased odds of VSDs (OR 90/10 centile contrast 1.48 95% CI 0.91 2.42) and reduced odds of atrial septal defects (ASD) (OR 90/10 centile contrast 0.67 95% CI 0.41, 1.09). Although imprecise, the effect estimates for anomalous pulmonary venous return (APVR) and CO and NO_2 exposures indicated lower odds with greater exposure, although this was somewhat attenuated at the highest level of exposure. Complete estimated ORs and 95% CIs are listed in Table A2.1. For both PM_{10} and NO_2, we found evidence of effect measure modification by distance to a major road in first-stage maximum likelihood models (PM_{10} likelihood ratio test: χ^2 =30.5, p=0.03; NO_2 likelihood ratio test: χ^2=34.5, p=0.01). In both cases, odds ratios were generally greater for women who lived within 50 meters of a roadway (Table A2.2).

4.3.2 Exposure assigned as one-week average of daily maximums or 24-hour measurements

Examining the individual weeks of exposure did not identify periods of susceptibility that were consistent across pollutants. For example, Figure 4.2 shows the weekly odds of PVS, a defect where elevated effect estimates were observed when using the seven-week summary measure of exposure. As illustrated in the figure, there was no consistent window across pollutants, but both CO and ozone have individual weeks where the estimates were larger in magnitude than estimates obtained using the summary exposure and where the other weeks were closer to null, suggesting a period of greater susceptibility (CO-week 2: 90/10 centile comparison: OR 0.37 95% CI 0.19,0.7; ozone-week 3 75/25 centile comparison: OR 2.15 95% CI 1.22, 3.78). Additionally, when exploring

$PM_{2.5}$, a pollutant that had no association with PVS when using a summary measure of exposure, there was an almost doubling of odds in week 5 when comparing women with exposure greater than the 90th centile to women with exposure less than the 10th centile (OR 1.83 95% CI 1.08, 3.12) that was similarly observed in week 8.

Weekly analysis of $PM_{2.5}$ revealed more potential windows of susceptibility, particularly week 2 of pregnancy. For example, women having a child with TOF have almost twice the odds of being above the 90th centile versus below the 10th centile for $PM_{2.5}$ exposure in week 2 of pregnancy as controls (OR 1.96, 95% CI 1.11, 3.46) while women with a baby with atrioventricular septal defect (AVSD) have more than three times the odds (OR 3.43 95% CI 1.36,8.66). Women with offspring with other septal defects, such as ASDs and perimembranous VSDs were less likely to have higher exposure during this time (OR 0.6, 95% CI 0.4, 0.9). Another potential window was observed when exploring SO_2 and VSDs, where the summary exposure revealed a slightly elevated odds ratio among women with exposure greater than the 90th centile, but weekly analysis revealed this effect was limited to week 3 and the magnitude increased (OR 1.98 95% CI 1.1, 3.56). Drastic weekly fluctuations in odds were also observed, for example reduced odds for women with $PM_{2.5}$ exposure above the 90th centile observed for aortic stenosis, COA, and dTGA in week 3 followed by elevated odds in week 4. Full results for the weekly exposure analyses are provided in Tables A2.3 and A2.4.

4.3.3 Principal Component Analysis

Only 26% of the geocoded population lived within 50km of each type of pollutant monitor and had exposure data for all pollutants (Table 4.1). These women were primarily from the Massachusetts and Atlanta sites, African-American, living in a higher income household, and non-smokers during pregnancy, and they were more likely to be born outside the US. Using this subsample, three source-factors emerged from the principal component analysis. The factor that explained the largest amount of total variance was loaded primarily by CO and NO_2 and is likely

related to motor vehicle traffic. The second factor, driven by PM_{10}, $PM_{2.5}$ and ozone likely represents multiple sources as PM is a mixture itself and both $PM_{2.5}$ and ozone are secondary pollutants. The third factor was loaded by SO_2 and most likely represents pollution from coal combustion. Within this multipollutant context, we again observed elevated odds of multiple types of defects with greater exposure (Table 4.2). Findings were less precise due to the reduced sample size, but elevated effect estimates between the NO_2 loaded factor and LVOTO defects, as well as TOF, were seen although there was greater attenuation of odds at the highest exposure level in the source factor model than we observed in the single pollutant models. In contrast, we did not observe a strong relationship between the NO_2-loaded factor and PVS, although we did observe greater odds of PVS among women exposed to higher levels of the PM_{10}/$PM_{2.5}$/ozone factor. Within the multipollutant context, the SO_2 source factor was no longer associated with elevated odds of defects, and we observed an inverse relationship between that factor and septal defects.

We did not observe a considerable difference in results obtained when using different values of second-stage variance or different design matrices. In order to explore our choice of including all women living within 50 km of a monitor, we reran our first-stage maximum likelihood single-pollutant analyses limiting subjects to women who lived within 10 km of a monitor. This reduced the sample to 27.5-48.1% of the original study population depending upon pollutant. Despite the greater imprecision, we observed that estimates were generally similar or larger in magnitude in this subpopulation when examining the larger defect-groupings. The exception to this was for SO_2, where estimates were lower although very imprecise (Table A2.5).

Table 4.1: Demographic comparison of NBDPS congenital heart cases and controls, 1997-2006, for full study and each pollutant examined [a]

	Full Sample of Controls and Simple		Population with Geocoded		Population living within 50km from a		Population living within 50km from an		Population living within 50km from an		Population living within 50km from a		Population living within 50km from a		Population living within 50km from an		Population living within 50km from all	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL POPULATION	12383		11144		7458		6849		7636		8077		7827		6205			
Excluded Diabetes	185	1.5	170	1.5	98	1.3	89	1.3	126	1.7	117	1.4	113	1.4	85	1.4		
ANALYTIC POPULATION	12198		10974		7360		6760		7510		7960		7714		6120		2914	
CONTROLS	7056	57.9	6328	57.7	4349	59.1	3968	58.7	4422	58.9	4632	58.2	4407	57.1	3508	57.3	1652	56.7
TOTAL CASES	5142	42.2	4646	42.3	3011	40.9	2792	41.3	3088	41.1	3328	41.8	3307	42.9	2612	42.7	1262	43.3
Left Ventricular Outflow Tract Obstructions	902	7.4	829	7.6	580	7.9	545	8.1	566	7.5	611	7.7	596	7.7	462	7.5	233	8
Aortic Stenosis	200	1.6	182	1.7	117	1.6	110	1.6	112	1.5	137	1.7	135	1.8	87	1.4	47	1.6
Coarctation of the Aorta	338	2.8	312	2.8	229	3.1	215	3.2	223	3	231	2.9	233	3	195	3.2	97	3.3
Interrupted Aortic Arch-Type A	11	0.1	9	0.1	6	0.1	6	0.1	7	0.1	7	0.1	8	0.1	6	0.1	3	0.1
Hypoplastic Left Heart Syndrome	353	2.9	326	3	228	3.1	214	3.2	224	3	236	3	220	2.9	174	2.8	86	3
Conotruncals	1099	9	1004	9.2	753	10.2	691	10.2	736	9.8	757	9.5	736	9.5	587	9.6	315	10.8
Common Truncus	46	0.4	44	0.4	33	0.5	30	0.4	24	0.3	32	0.4	32	0.4	26	0.4	16	0.5
Interrupted Aortic Arch – Type B/NOS	14	0.1	14	0.1	10	0.1	9	0.1	9	0.1	8	0.1	9	0.1	6	0.1	2	0.1
d-Transposition of the Great Arteries	368	3	339	3.1	247	3.4	238	3.5	254	3.4	252	3.2	235	3.1	200	3.3	100	3.4
Tetralogy of Fallot	571	4.7	520	4.7	399	5.4	355	5.3	386	5.1	401	5	396	5.1	307	5	168	5.8
Double Outlet Right Ventricle	50	0.4	41	0.4	32	0.4	28	0.4	30	0.4	34	0.4	30	0.4	22	0.4	12	0.4
Conoventricular septal defect	50	0.4	46	0.4	32	0.4	31	0.5	33	0.4	30	0.4	34	0.4	26	0.4	17	0.6
Atrioventricular Septal Defects	97	0.8	82	0.8	53	0.7	53	0.8	49	0.7	55	0.7	62	0.8	46	0.8	20	0.7
Anomalous Pulmonary Venous Return	171	1.4	155	1.4	105	1.4	100	1.5	112	1.5	118	1.5	114	1.5	84	1.4	46	1.6
Total	147	1.2	135	1.2	96	1.3	93	1.4	104	1.4	105	1.3	101	1.3	74	1.2	42	1.4
Partial	24	0.2	20	0.2	9	0.1	7	0.1	8	0.1	13	0.2	13	0.2	10	0.2	4	0.1

TABLE 4.1: (cont.)

	Full Sample of Controls and Simple		Population with Geocoded		Population living within 50km from a		Population living within 50km from an		Population living within 50km from an		Population living within 50km from a		Population living within 50km from a		Population living within 50km from an		Population living within 50km from all	
Right Ventricular Outflow Tract Obstructions	811	6.7	728	6.6	502	6.8	459	6.8	487	6.5	522	6.6	540	7	443	7.2	211	7.2
Pulmonary Atresia	100	0.8	92	0.8	69	0.9	60	0.9	65	0.9	72	0.9	71	0.9	59	1	29	1
Tricuspid Atresia	45	0.4	41	0.4	32	0.4	30	0.4	33	0.4	36	0.5	34	0.4	26	0.4	15	0.5
Ebstein's Anomaly	58	0.5	53	0.5	34	0.5	33	0.5	37	0.5	35	0.4	38	0.5	31	0.5	12	0.4
Pulmonary Valve Stenosis	606	5	540	4.9	365	5	334	4.9	350	4.7	377	4.7	395	5.1	327	5.3	155	5.3
Septals	2062	16.9	1848	16.8	1018	13.8	944	14	1138	15.2	1265	15.9	1259	16.3	990	16.2	437	15
Perimembranous ventricular septal defects	846	6.9	765	7	501	6.8	461	6.8	495	6.6	522	6.6	538	7	438	7.2	230	7.9
Muscular ventricular septal defects[b]	130	1.1	123	1.1	85	1.2	74	1.1	79	1.1	109	1.4	0	0	86	1.4	0	0
Ventricular septal defects,NOS	26	0.2	24	0.2	16	0.2	14	0.2	14	0.2	17	0.2	12	0.2	14	0.2	3	0.1
Atrial septal defects	1057	8.7	936	8.5	416	5.7	395	5.8	550	7.3	617	7.8	709	9.2	452	7.4	204	7
BIRTH OUTCOME																		
Live Birth	12153	99.6	10935	99.6	7331	99.6	6735	99.6	7480	99.6	7930	99.6	7684	99.6	6096	99.6	2899	99.5
Fetal Death	31	0.3	26	0.2	18	0.2	17	0.3	19	0.3	21	0.3	18	0.2	18	0.3	11	0.4
Induced Abortion	7	0.1	7	0.1	5	0.1	3	<0.1	5	0.1	5	0.1	6	0.1	4	0.1	2	0.1
STUDY SITE																		
Arkansas	1835	15	1225	11.2	328	4.5	337	5	406	5.4	401	5	650	8.4	388	6.3	217	7.5
California	1471	12.1	1343	12.2	1237	16.8	1299	19.2	1302	17.3	1281	16.1	1068	13.8	253	4.1	209	7.2
Iowa	1390	11.4	1333	12.2	502	6.8	236	3.5	532	7.1	857	10.8	734	9.5	430	7	42	1.4
Massachusetts	1673	13.7	1624	14.8	1459	19.8	1485	22	1412	18.8	1398	17.6	1190	15.4	1479	24.2	858	29.4
New York	1095	9	1046	9.5	715	9.7	686	10.2	956	12.7	565	7.1	681	8.8	884	14.4	250	8.6
Texas	1665	13.7	1550	14.1	598	8.1	484	7.2	966	12.9	841	10.6	917	11.9	385	6.3	170	5.8
Metropolitan Atlanta	1460	12	1342	12.2	1314	17.9	1326	19.6	980	13.1	1329	16.7	1076	14	1276	20.9	790	27.1
North Carolina	715	5.9	654	6	495	6.7	177	2.6	507	6.8	513	6.4	633	8.2	448	7.3	68	2.3
Utah	894	7.3	857	7.8	712	9.7	730	10.8	449	6	775	9.7	765	9.9	577	9.4	310	10.6
MATERNAL AGE(avg,sd)	26.9 (6.18)		27.1 (6.16)		27.8 (6.08)		27.7 (6.12)		27.5 (6.22)		27.5 (6.1)		27.5 (6.11)		28.2 (6.05)		28.4 (6.18)	
MATERNAL NATIVITY																		
Born Outside United States	2212	18.5	1972	18	1546	21.1	1411	20.9	1558	20.9	1616	20.4	1514	19.7	1117	18.3	620	21.4

TABLE 4.1: (cont.)

	Full Sample of Controls and Simple		Population with Geocoded		Population living within 50km from a		Population living within 50km from an		Population living within 50km from an		Population living within 50km from a		Population living within 50km from a		Population living within 50km from an		Population living within 50km from all	
MATERNAL RACE																		
White, non-Latino	7331	60.1	6658	60.7	4263	57.9	3896	57.7	4227	56.3	4625	58.1	4507	58.4	3855	63	1668	57.3
Black, non-Latino	1380	11.3	1189	10.8	913	12.4	864	12.8	861	11.5	931	11.7	886	11.5	905	14.8	506	17.4
Latino	2755	22.6	2471	22.5	1659	22.6	1523	22.5	1909	25.4	1851	23.3	1783	23.1	924	15.1	502	17.2
Asian/ Pacific Islander	324	2.7	292	2.7	262	3.6	246	3.6	238	3.2	265	3.3	229	3	216	3.5	130	4.5
Other	405	3.3	362	3.3	261	3.6	229	3.4	273	3.6	286	3.6	307	4	219	3.6	107	3.7
PATERNAL RACE																		
White, non-Latino	6986	59	6424	59.5	4155	57.4	3796	57	4089	55.4	4493	57.4	4338	57.3	3757	62.3	1634	57.1
Black, non-Latino	1483	12.5	1305	12.1	982	13.6	920	13.8	940	12.7	1009	12.9	972	12.8	972	16.1	523	18.3
Latino	2714	22.9	2459	22.8	1635	22.6	1504	22.6	1885	25.5	1829	23.4	1774	23.4	924	15.3	495	17.3
Asian/ Pacific Islander	282	2.4	263	2.4	235	3.2	220	3.3	214	2.9	237	3	204	2.7	189	3.1	111	3.9
Other	370	3.1	342	3.2	236	3.3	218	3.3	252	3.4	261	3.3	282	3.7	193	3.2	101	3.5
MATERAL EDUCATION																		
0-6 years	422	3.5	362	3.3	249	3.4	228	3.4	270	3.6	267	3.4	264	3.4	140	2.3	78	2.7
7-8 years	228	1.9	206	1.9	128	1.8	110	1.6	145	1.9	146	1.8	141	1.8	96	1.6	45	1.6
9-11 years	1427	11.9	1263	11.6	767	10.5	716	10.6	852	11.4	851	10.7	865	11.3	542	8.9	259	8.9
Completed HS/Equiv.	2959	24.7	2646	24.2	1574	21.5	1468	21.8	1681	22.5	1769	22.3	1721	22.4	1263	20.7	575	19.8
1-3 years College	2925	24.4	2671	24.4	1745	23.8	1613	24	1748	23.4	1913	24.1	1853	24.1	1453	23.8	632	21.8
Completed Technical School	410	3.4	376	3.4	225	3.1	214	3.2	245	3.3	239	3	250	3.3	198	3.2	69	2.4
4 Years College/Bachelor's Degree	2610	21.8	2457	22.5	1869	25.5	1690	25.1	1774	23.7	1966	24.8	1844	24	1662	27.2	830	28.6
Master's Degree	779	6.5	732	6.7	591	8.1	539	8	587	7.9	589	7.4	577	7.5	581	9.5	317	10.9
Advanced Degree	226	1.9	216	2	181	2.5	157	2.3	171	2.3	185	2.3	165	2.2	167	2.7	97	3.3
PATERNAL EDUCATION																		
0-6 years	471	4.1	411	3.9	290	4.1	266	4.1	314	4.3	315	4.1	307	4.1	163	2.7	81	2.9
7-8 years	221	1.9	196	1.8	122	1.7	113	1.7	138	1.9	130	1.7	133	1.8	85	1.4	39	1.4
9-11 years	1300	11.2	1162	10.9	680	9.5	637	9.7	765	10.5	775	10	804	10.8	494	8.3	221	7.8
Completed HS/Equiv.	3568	30.7	3203	30.1	1928	27	1786	27.2	2076	28.6	2121	27.5	2115	28.3	1617	27.1	748	26.4
1-3 years College	2241	19.3	2044	19.2	1349	18.9	1246	19	1339	18.5	1471	19.1	1425	19.1	1084	18.2	503	17.7
Completed Technical School	369	3.2	338	3.2	215	3	187	2.9	224	3.1	238	3.1	229	3.1	198	3.3	82	2.9
4 Years College/Bachelor's Degree	2414	20.8	2271	21.4	1721	24.1	1577	24	1621	22.3	1814	23.5	1688	22.6	1545	25.9	757	26.7
Master's Degree	689	5.9	654	6.1	536	7.5	490	7.5	504	6.9	543	7	506	6.8	509	8.5	249	8.8
Advanced Degree	363	3.1	350	3.3	300	4.2	258	3.9	277	3.8	309	4	269	3.6	277	4.6	159	5.6

TABLE 4.1 (cont)

	Full Sample of Controls and Simple		Population with Geocoded		Population living within 50km from a		Population living within 50km from an		Population living within 50km from an		Population living within 50km from a		Population living within 50km from a		Population living within 50km from an		Population living within 50km from all	
MATERNAL HOUSEHOLD INCOME																		
<10,000	2146	19.4	1837	18.2	1118	16.5	1028	16.5	1282	18.6	1249	17.2	1289	17.6	805	14.3	391	14.1
>50,000	3671	33.3	3513	34.8	2756	40.7	2513	40.4	2630	38.2	2811	38.7	2796	38.1	2506	44.5	1312	47.3
In Between	5223	47.3	4757	47.1	2899	42.8	2685	43.1	2964	43.1	3213	44.2	3258	44.4	2321	41.2	1072	38.6
MATERNAL BODY MASS INDEX																		
Underweight	613	5.3	534	5	339	4.8	313	4.8	356	4.9	362	4.7	364	4.9	278	4.7	142	5
Normal Weight	6234	53.5	5683	53.8	3951	55.7	3635	55.8	3923	54.4	4234	55.2	3945	53.2	3340	56.3	1592	56.4
Overweight	2717	23.3	2471	23.4	1610	22.7	1469	22.6	1680	23.3	1761	23	1764	23.8	1330	22.4	634	22.4
Obese	2091	17.9	1877	17.8	1188	16.8	1097	16.8	1251	17.4	1309	17.1	1347	18.2	989	16.7	457	16.2
MATERNAL SMOKING																		
Reported Ever Smoking	4044	33.6	3637	33.2	2299	31.3	2097	31.1	2426	32.4	2508	31.6	2419	31.4	2031	33.2	901	31
Reported Smoking in 1st month of pregnancy	2012	16.7	1768	16.2	976	13.3	904	13.4	1082	14.5	1115	14	1104	14.4	886	14.5	372	12.8
MATERNAL ALCOHOL CONSUMPTION																		
Reported month prior through first trimester																		
None	7709	64.7	6968	64.2	4593	63	4243	63.2	4666	62.8	4991	63.3	4944	64.8	3708	61.1	1782	61.7
Less than 4 drinks per week	2749	23.1	2544	23.4	1858	25.5	1700	25.3	1885	25.4	1946	24.7	1822	23.9	1651	27.2	828	28.7
Binge drinking (4+ drinks per week)	1459	12.2	1345	12.4	844	11.6	766	11.4	879	11.8	947	12	869	11.4	710	11.7	277	9.6
MATERNAL OCCUPATIONAL STATUS																		
Did not work outside home	3416	28.5	3059	28	2024	27.6	1883	27.9	2147	28.7	2207	27.8	2208	28.7	1567	25.7	803	27.6
PROXIMITY OF MATERNAL RESIDENCE TO MAJOR ROADWAY																		
Within 50 km	n/a		2012	18.3	1330	18.1	1232	18.2	1397	18.6	1449	18.2	1412	18.3	1155	18.9	570	19.6
MONITOR-RELATED CHARACTERISTICS																		
Median distance to monitor (km)					14.8		13.7		12.8		13.5		10.4		18.8			
EPA Regulatory Standard, averaging time					35ppm,1hr		100 ppb,1hr		75 ppb,8hr		150 µg/m^3,24hı		35 µg/m^3,24hr		75 ppb,1hr			
At least one day of exposure greater than regulatory standard					0	0	251	3.7	2908	38.7	76	1	1735	22.5	803	13.1		

[a] Does not include missing data so not all variables will sum to the total sample size

[b] PM2.5 data was only available after 1999 and NBDPS stopped recruiting simple, isolated muscular VSDs after the first year of data collection.

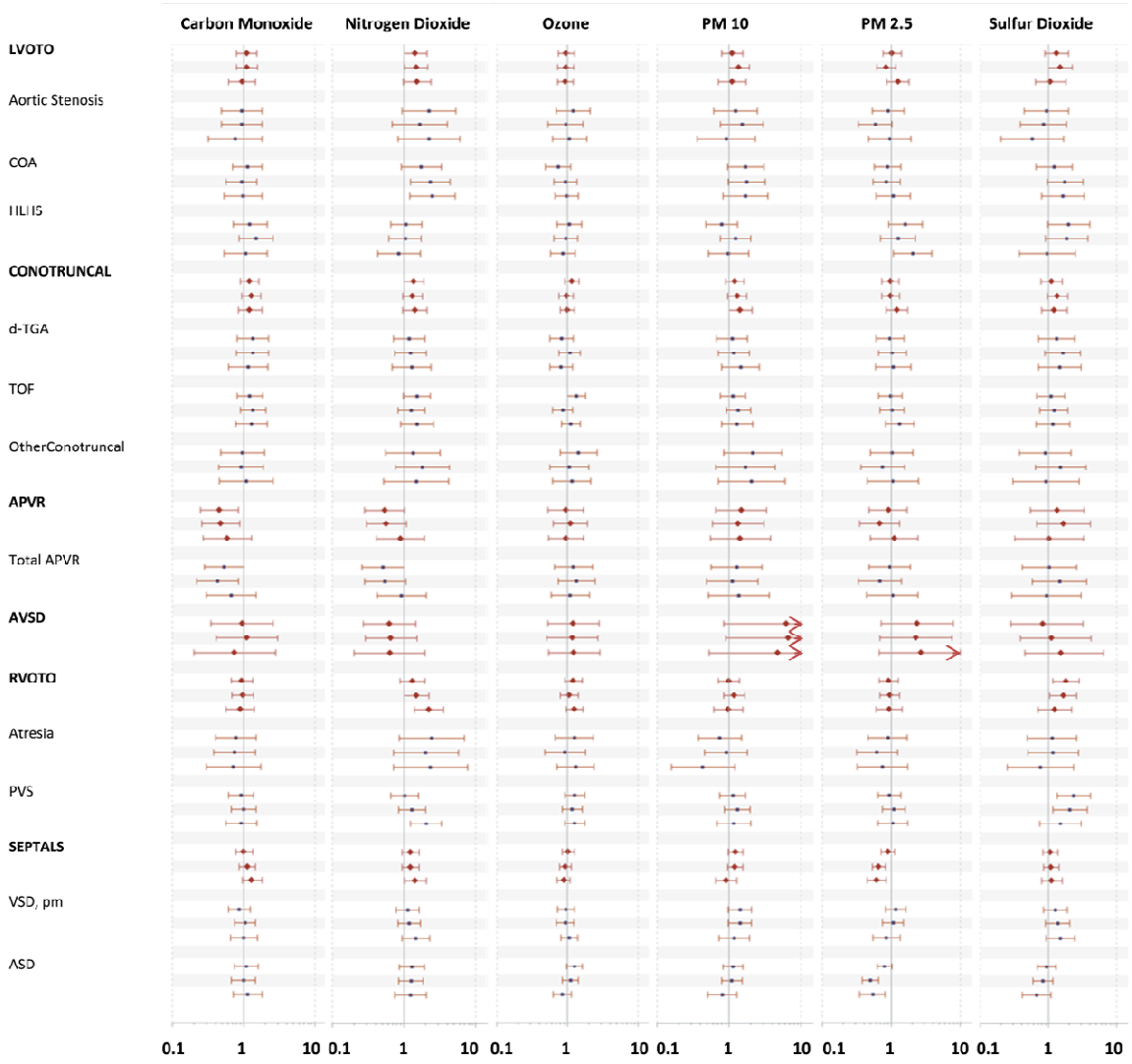

Figure 4.1: Estimated adjusted odds ratios and 95% confidence intervals between congenital heart defects and 7-week average of daily maximums/24 hour measures of criteria air pollutants, NBDPS 1997-2006

For all pollutants except ozone, the three categories of exposure are: 10th centile to 50th centile, 50th centile to 90th centile, at or greater than the 90th centile, with the referent level being less than the 10th centile among controls. For ozone, the three categories of exposure were 25th to 50th centile, 50th centile to 75th centile, at or greater than the 75th centile, with the referent grouping being below the 25th centile. Diamond markers indicate defect groupings, while squares indicate individual defects. A double arrow indicates the confidence interval went beyond the boundary of the figure.

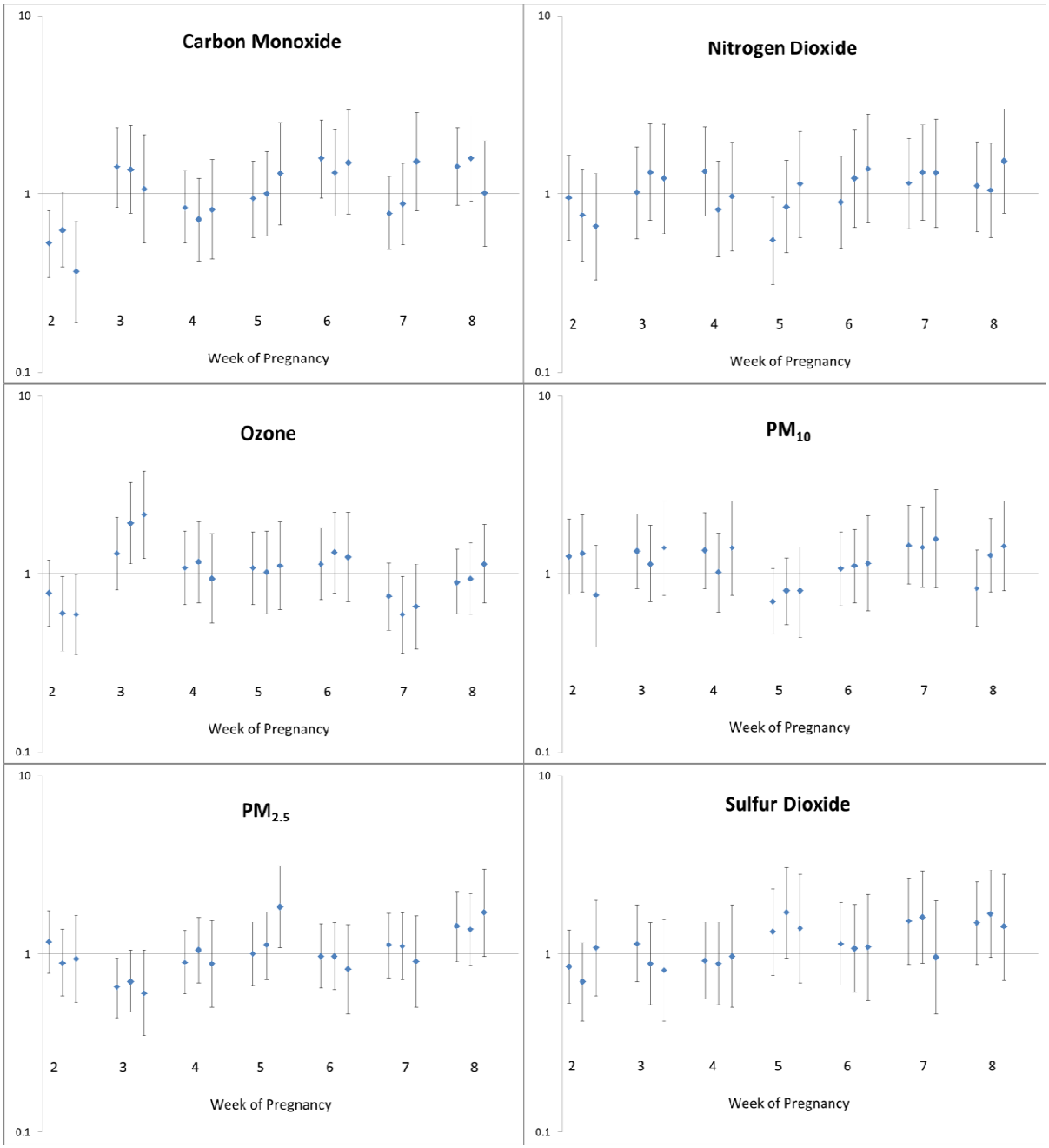

Figure 4.2: Estimated adjusted odds ratios and 95% confidence intervals of pulmonary valve stenosis (PVS) for categorical measures of one-week averages of daily maximums/24 hour measures of criteria air pollutants, plotted for weeks 2 through 8 of pregnancy NBDPS 1997-2006.

Table 4.2: Estimated adjusted odds ratios and 95% confidence intervals between pollutant factors identified through principal components analysis and cardiac birth defects within NBDPS 1999-2006

Loadings	Factor 1 **CO: 85** PM10: 40	**NO2: 71** PM2.5: 21	OZ:-39 SO2:5	
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
LVOTO[a]	1	1.57 (0.93,2.63)	1.62 (0.96,2.74)	1.04 (0.51,2.1)
Aortic Stenosis[b]	1	2.31 (0.76,6.98)	2.34 (0.76,7.15)	1.88 (0.31,11.21)
Coarctation of the Aorta[b]	1	1.25 (0.61,2.57)	1.47 (0.71,3.03)	1.22 (0.49,3.02)
Hypoplastic Left Heart Syndrome[b]	1	1.59 (0.77,3.28)	1.58 (0.75,3.3)	1.21 (0.46,3.22)
CONOTRUNCALS[a]	1	1.18 (0.75,1.84)	1.35 (0.86,2.12)	1.24 (0.71,2.17)
d-TGA[b]	1	1.09 (0.57,2.1)	1.17 (0.6,2.27)	1.17 (0.52,2.66)
Tetralogy of Fallot[b]	1	1.33 (0.74,2.4)	1.64 (0.91,2.97)	1.27 (0.6,2.69)
Other Conotruncals[b]	1	1.08 (0.44,2.63)	1.08 (0.43,2.69)	1.23 (0.41,3.65)
APVR[a]	1	0.52 (0.23,1.2)	0.66 (0.29,1.5)	0.83 (0.3,2.3)
AVSD[c]	1	0.40 (0.13, 1.36)	0.87 (0.28, 2.68)	0.51 (0.10, 2.70)
RVOTO[a]	1	1.13 (0.68,1.86)	1.27 (0.77,2.11)	1.4 (0.75,2.62)
Pulmonary/Tricuspid Atresia[b]	1	1.37 (0.59,3.21)	0.85 (0.34,2.14)	1.26 (0.43,3.68)
Pulmonary Valve Stenosis[b]	1	1.06 (0.6,1.85)	1.41 (0.8,2.48)	1.41 (0.69,2.89)
SEPTALS[a]	1	1.03 (0.69,1.52)	1.2 (0.81,1.78)	1.12 (0.69,1.81)
VSD-perimembranous[b]	1	0.8 (0.5,1.27)	0.97 (0.6,1.56)	0.95 (0.53,1.71)
ASDs[b]	1	1.36 (0.77,2.39)	1.49 (0.84,2.64)	1.32 (0.67,2.62)

[a]Estimates results from a hierarchical regression model. First stage was polytomous logistic model with defect groupings as outcomes and adjusted for maternal race, maternal age, maternal educational attainment, maternal household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio. Second stage was a linear model with indicator variables for defect grouping and level of exposure.

[b]Estimates result from a hierarchical regression model, same as above but with individual defects as outcomes.

[c]Estimates result from model utilizing Firth's penalized maximum likelihood regression to deal with quasi-separation of points due to small sample size in certain cells. Model adjusted for variables listed above.

Table 4.2 (cont.)

Loadings	Factor 2 CO: 11 **PM10: 68** <10th percentile (Referent)	NO2: 6 **PM2.5: 71** 10th percentile to median	**OZ: 66** SO2: -3 median to 90th percentile	>90th percentile
LVOTO[a]	1	1.42 (0.86,2.36)	1.26 (0.75,2.12)	1.33 (0.69,2.53)
Aortic Stenosis[b]	1	2.15 (0.72,6.45)	1.89 (0.62,5.72)	1.93 (0.5,7.36)
Coarctation of the Aorta[b]	1	0.99 (0.52,1.87)	0.82 (0.42,1.59)	1.37 (0.62,3)
Hypoplastic Left Heart Syndrome[b]	1	2.04 (0.88,4.73)	1.94 (0.82,4.56)	1.26 (0.44,3.63)
CONOTRUNCALS[a]	1	1.11 (0.72,1.69)	1.15 (0.74,1.77)	1.19 (0.69,2.04)
d-TGA[b]	1	1.04 (0.55,1.96)	1.03 (0.54,1.99)	1.29 (0.58,2.86)
Tetralogy of Fallot[b]	1	1.15 (0.66,2)	1.33 (0.76,2.33)	1.27 (0.63,2.55)
Other Conotruncals[b]	1	1.23 (0.5,3.02)	0.96 (0.38,2.44)	0.99 (0.32,3.06)
APVR[a]	1	0.84 (0.37,1.91)	0.72 (0.3,1.69)	0.59 (0.19,1.85)
AVSD[c]	1	1.32 (0.38, 4.59)	0.67 (0.17, 2.62)	1.20 (0.25, 5.91)
RVOTO[a]	1	1.32 (0.78,2.24)	1.24 (0.72,2.14)	1.85 (0.99,3.46)
Pulmonary/Tricuspid Atresia[b]	1	1.49 (0.57,3.87)	0.99 (0.36,2.73)	1.7 (0.56,5.13)
Pulmonary Valve Stenosis[b]	1	1.2 (0.66,2.18)	1.28 (0.7,2.34)	1.89 (0.94,3.79)
SEPTALS[a]	1	1.06 (0.74,1.52)	0.89 (0.61,1.3)	0.73 (0.44,1.19)
VSD-perimembranous[b]	1	1.47 (0.89,2.43)	1.09 (0.65,1.84)	0.95 (0.5,1.83)
ASDs[b]	1	0.8 (0.51,1.27)	0.78 (0.49,1.25)	0.62 (0.32,1.17)

Table 4.2 (cont.)

Loadings	Factor 3 CO: -11 PM10: -18	NO2:25 PM2.5: 32	OZ: -20 **SO2: 94**	
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
LVOTO[a]	1	1.02 (0.58,1.77)	1.01 (0.58,1.77)	0.86 (0.44,1.7)
Aortic Stenosis[b]	1	1.58 (0.56,4.52)	1 (0.35,2.9)	0.69 (0.16,3.1)
Coarctation of the Aorta[b]	1	0.81 (0.38,1.73)	1.28 (0.61,2.67)	0.67 (0.26,1.72)
Hypoplastic Left Heart Syndrome[b]	1	1.1 (0.5,2.43)	0.88 (0.4,1.96)	1.15 (0.46,2.86)
CONOTRUNCALS[a]	1	0.79 (0.48,1.28)	1.05 (0.64,1.7)	0.8 (0.44,1.44)
d-TGA[b]	1	0.68 (0.32,1.44)	1.15 (0.55,2.39)	1.05 (0.45,2.43)
Tetralogy of Fallot[b]	1	0.85 (0.45,1.61)	1.01 (0.54,1.89)	0.72 (0.34,1.56)
Other Conotruncals[b]	1	0.78 (0.31,1.94)	0.97 (0.39,2.39)	0.48 (0.14,1.7)
APVR[a]	1	0.58 (0.23,1.49)	0.92 (0.37,2.3)	0.47 (0.14,1.53)
AVSD[c]	1	2.84 (0.28, 28.9)	2.18 (0.21, 22.7)	2.59 (0.21, 32.7)
RVOTO[a]	1	1.35 (0.74,2.45)	1.1 (0.6,2.02)	1.18 (0.58,2.38)
Pulmonary/Tricuspid Atresia[b]	1	0.97 (0.36,2.63)	1.05 (0.39,2.82)	0.87 (0.27,2.81)
Pulmonary Valve Stenosis[b]	1	1.51 (0.76,3)	1.08 (0.54,2.18)	1.03 (0.46,2.31)
SEPTALS[a]	1	0.69 (0.47,1.03)	0.64 (0.43,0.97)	0.54 (0.32,0.9)
VSD-perimembranous[b]	1	0.65 (0.4,1.07)	0.59 (0.36,0.98)	0.67 (0.37,1.23)
ASDs[b]	1	0.76 (0.45,1.29)	0.7 (0.41,1.19)	0.4 (0.19,0.83)

4.4 Discussion

In this analysis, we found the odds of several CHDs were higher among women with greater exposures to criteria air pollutants. Evaluating individual weeks of exposure revealed some potential windows of susceptibility for individual defect-pollutant relationships. This is the first study to examine $PM_{2.5}$ exposure and CHDs, and we found elevated odds of AVSD, HLHS, PVS, and TOF within the period of cardiac development. The toxicology of the criteria pollutants suggest that maternal exposure early in pregnancy may play a role in altered cardiac development, potentially through mechanisms such as inflammatory processes in the mother, altered DNA methylation, and increased viscosity of blood plasma affecting blood flow and maternal/fetal nutrition.[13,151]

Utilizing one-week averages, we observed temporal variability in odds of certain CHDs within the window of cardiac development, including elevated odds of COA with week 3 ozone exposure and elevated odds of TOF and AVSD, but reduced odds of septal defects, with greater exposure to $PM_{2.5}$ during week 2 of pregnancy. It is possible that environmental insults early in cardiac development could result in more complex defects, thus reducing the risk of a single, isolated septal defect associated with $PM_{2,5}$ exposure. One limitation of using multiple weeks of exposure in a single model is the multicollinearity which arises due to the high correlation between individual weeks of exposure. Although utilizing hierarchical regression partially addressed multiple inference and accounted for some of the correlation between effect estimates, more sophisticated models which utilize Bayesian shrinkage to a greater degree may better account for the correlation between time periods of exposure and improve. [33]

Our main analysis explored each pollutant individually, potentially confounding effects of the different pollutants. The PCA-based analysis that we used to explore the odds of defects in a multipollutant context continued to show greater odds of certain CHDs with increasing pollutant exposure. Many of the associations with SO_2 found in the single-pollutant analysis, however, were not observed when the SO_2 loaded component was examined simultaneously with other pollutant components. These differences could be due to co-pollutants not accounted for in the single-pollutant models or to the smaller size and different demographics of the subsample of women with data on all pollutants. In single-pollutant analyses, we observed greater odds ratios among women living close to major roadways for both exposure to NO_2 and PM_{10}. As these pollutants are known to arise from motor vehicle traffic and distance to a monitor was highly correlated to distance to a major roadway, it seems likely that living near a roadway was a marker for more accurate exposure classification rather than an interaction between different sources of pollutants.

When using the single 7-week summary exposure, we observed the primary associations reported in the previous meta-analysis, NO_2 and TOF and SO_2 exposure and COA. [23] The meta-analysis also suggested associations between NO_2 and COA, SO_2 and TOF, and PM_{10} and ASDs, although these were no longer significant once the largest study was excluded. Of these, we only observed the association between NO_2 and COA. Our results were consistent with some of the findings from individual studies that were not identified in the meta-analysis. We observed the association between SO_2 and VSDs observed in Gilboa et al. (2005) and, had we collapsed the different VSD categories, we would have seen the increased odds of VSDs with CO exposure observed by Ritz et al. (2002). We did not observe the inverse associations between SO_2 and conotruncal defects reported by both Gilboa et al and Hansen et al [8,16] but in our source-factor analysis, there was a suggestion of an inverse relationship between conotruncal defects and the factor driven by SO_2.

As the largest, ongoing case-control study of birth defects in the United States, the NBDPS has a large sample size that allows analysis of systematically classified CHDs. We limited our analyses to simple, isolated defects to avoid heterogeneity from etiologies of multiple defects. The variation observed within larger groupings of CHDs illustrates the importance of examining individual CHDs, as aggregations based on different classification schemes would impact observed estimates. We had complete residential history, avoiding the misclassification of exposure that occurs when using residence at delivery. [135] We also explored how timing of exposure within the critical window of heart development impacted the odds of different defects and utilized daily maximums so as not to smooth over potentially relevant variability in exposure. Utilizing hierarchical regression allowed us to improve estimation and partially address the issue of multiple testing. Finally, this was the first study to explore associations between $PM_{2.5}$ and CHDs and to

utilize principal component analysis to assess the relationship between air pollutants and CHDs in a multipollutant context.

Assigning ambient concentrations of pollutants at their residential location as an individual's exposure does not account for time-activity patterns such as time spent indoors and pollutant concentrations at other relevant locations. This potential for exposure misclassification could impact our effect estimates if there are differences in these factors between cases and controls, which could occur if women of case offspring had more difficult pregnancies, limiting their outdoor movement.

The NBDPS had a response slightly lower than 70% and like many studies is subject to potential selection bias based on who agrees to participate. Additionally, there is the potential for selection bias if the factors that contribute to women living near a pollutant monitor are also associated with pollutant exposure and CHDs. While monitors are often sited based on population density and suspected pollutant exposure [152], we did not observe strong associations between maternal demographic factors that could influence residential location and the presence of CHDs within our full population. However, our results may not be generalizable to rural populations that live more than 50 km from an air monitor. Our source-factor analysis was based on small numbers of a highly select population who live near multiple pollutant monitors and may not be generalizable to the larger population. We conducted many analytic contrasts, and although hierarchical regression partially addresses multiple comparisons, it is possible that some of our findings are due to chance.

In this study, we observed associations between several CHDs and greater pollutant exposure, even at ambient levels below current EPA regulatory standards. Some of these elevated effects were observed only during specific weeks within the window of cardiac development, suggesting that accounting for temporal variability in pollutant concentrations and developmental

susceptibility can improve effect estimation. Future research should focus on further exploration of temporal windows of susceptibility and examining the risk of CHDs within a multipollutant context, in order to gain understanding of the contribution of the different air pollutants and their sources.

CHAPTER 5

5. COMPARING THE IMPACT OF MONITOR-BASED VERSUS MODEL-BASED ESTIMATES OF POLLUTANT EXPOSURE ON THE RELATIONSHIP BETWEEN MATERNAL EXPOSURE TO $PM_{2.5}$ AND OZONE URING PREGNANCY AND CONGENITAL HEART DEFECTS IN OFFSPRING

5.1 Introduction

Epidemiologic studies of the health effects of air pollutants often take advantage of existing stationary air monitoring networks to provide air pollutant information over large spatial areas.[13,153] Measurements from these networks, intended to assure compliance with the Environmental Protection Agency's (EPA) regulatory standards, are compiled into a publicly available, repository known as the Air Quality System (AQS).[57] The AQS can then be used to provide historical measurements of multiple air pollutants in order to assign exposure at a relatively low-cost to researchers. However, the density of these air monitoring networks is not consistent across space or time, as most monitors are located in urban areas and for some pollutants, including fine particulate matter ($PM_{2.5}$), measurements are not taken daily or in the case of ozone, are not measured during colder months. This lack of spatial and temporal resolution can impact the effect estimates of epidemiologic studies by excluding rural populations who do not live in proximity to air monitors as well as excluding those individuals whose period of exposure occurs when monitors are non-operational.

Spatiotemporal deterministic air pollutant prediction models, such as the EPA's Community Multiscale Air Quality (CMAQ) model have the capability of predicting air pollutant concentrations consistently across large spatial areas, by utilizing multiple sources of data, including emissions and meteorological data, to simulate chemical transformation and fate within the atmosphere.[137] The resulting output, a 12 km x 12 km gridded pollutant surface, can be used to assign daily exposures for the entire population, including those living far from air monitoring networks. However, these outputs can be subject to some bias due to the varying quality of the underlying emissions inventories and the many assumptions made throughout the modeling process. For example, a recent study by Bravo et al compared estimates from AQS and CMAQ and found that for short-term metrics of exposure (i.e. daily or weekly) there were seasonal, as well as spatial variations in how well the CMAQ predictions matched AQS measurements.[154]

Methods have been developed which calibrate the CMAQ predictions using monitoring measurements where they are available, to take advantage of the greater temporal and spatial resolution of predictive models, while improving these predictions by incorporating information from the presumably unbiased measurements. One such method, described by Berrocal et al, combines these two sources of data using linear regression with spatially- and temporally-varying bias coefficients in a Bayesian framework.[138] The resulting model, referred to as downscaler CMAQ because it scales gridded CMAQ output down to the point-level monitoring data, provides bias-corrected, daily concentrations of 24-hour $PM_{2.5}$ and 8-hour maximum ozone at the centroid of every census tract in the United States. One previous study has compared estimates obtained using output from the downscaler CMAQ numerical model to those obtained from AQS measurements, but the study focused only on ozone and was limited to a single state.[155] Exploring a larger geographic area could provide details on how agreement between AQS measurements and downscaler CMAQ model estimates vary spatially.

The goal of this analysis was to compare the use of pollutant concentration measurements from the AQS monitoring network to calibrated pollutant predictions from the downscaler CMAQ model to assign exposure in a study of the relationship between maternal air pollutant exposure during pregnancy and congenital heart defects (CHDs) in offspring. We explored whether there were differences in the magnitude of the assigned exposure, as well as whether differences in study population due to the greater spatial and temporal resolution of the downscaler CMAQ model impacted effect estimates.

5.2 Methodology

This study was reviewed and approved by the University of North Carolina, Chapel Hill Institutional Review Board.

5.2.1 Study Population

The National Birth Defects Prevention Study, a large multisite, population-based case-control study begun in 1997, has been described previously.[101] Cases include livebirths and stillbirths greater than 20 weeks gestation or at least 500 grams, as well as elective terminations of prenatally-diagnosed defects at any gestational age. Because of their known etiology, cases with chromosomal/microdeletion disorders and single-gene deletion disorders are excluded. Controls are livebirths who are randomly selected from either vital records or hospital records, depending upon study center. There is a 69% response among cases and a 65% response for controls. Because downscaler CMAQ predictions were only available starting in 2001, we restricted to participants who had estimated dates of conception from 2001 through 2006, the last year for which geocoded residential information was available for NBDPS participants at the time of this study. Additionally because downscaler CMAQ predictions were not available for the entire US during this time period, if a woman resided in a geographic location where downscaler predictions were not created, she

was excluded from this analysis. This restriction resulted in excluding women from the California and Utah study centers, and women from the Texas study center with estimated dates of conception prior to 2002.

The NBDPS case-classification scheme for CHDs has been described previously [97]. A team of reviewers assign a single, detailed cardiac phenotype to each case based on medical record review. These phenotypes are then aggregated into 27 main individual defects and then again into eight broader groupings of defects. To create a homogeneous case group, cases with multiple CHDs or a simultaneous non-CHD were excluded from this analysis, as were cases with mothers who had non-gestational diabetes due to its strong association with CHDs in offspring.[110] The resulting single, isolated CHDs fell into 23 individual defects and six broader groupings (Table 5.1). Due to sample size limitations, only aortic stenosis, coarctation of the aorta (COA), hypoplastic left heart syndrome (HLHS), tetralogy of Fallot (TOF), transposition of the great arteries (dTGA), pulmonary valve stenosis (PVS), perimembranous ventricular septal defects(VSD_{pm}) and atrial septal defects (ASD) were examined as individual defects. Common truncus, interrupted aortic arch-type b, interrupted aortic arch-not otherwise specified (iaa-typeb, iaa-nos), double outlet right ventricle associated with transposition of the great arteries (DORV-TGA) and not (DORV-other) and conoventricular septal defects (VSD_{cono}) were aggregated into a new category, 'Other Conotruncals'. All other individual defects were explored only as part of the larger, broader categories.

5.2.2 Exposure Assignment and Confounder Selection

NBDPS participants complete a computer-assisted telephone interview and provide their complete residential history during pregnancy. Because the downscaler CMAQ predicts pollutant concentrations at the centroid of every census tract, women were matched to the closest centroid of a census tract, using ArcGIS v10, starting with their residence at conception. In some cases, the closest centroid was not the centroid of the census tract the woman lived within. If a woman had

additional residences during the first eight weeks of pregnancy, she was matched to the centroids closest to those residences as well, corresponding to the time of pregnancy that she lived there. For both $PM_{2.5}$ and ozone, daily predictions at that centroid from the downscaler CMAQ model were assigned to each woman and then averaged over weeks two through eight of pregnancy, the window of cardiac development, to create a single 7-week measure of exposure. Individual weekly averages were also constructed to explore the effects of the greater temporal resolution of downscaler CMAQ predictions. In order to compare the downscaler CMAQ predictions to measurements from AQS monitors, women whose residential addresses were within 50 km of a stationary air monitor were assigned exposure from that source in the same manner as above. At many monitoring sites, $PM_{2.5}$ measurements were only taken every 3rd or 6th day.

To compare pollutant predictions obtained from the downscaler CMAQ model to concentrations obtained from AQS air monitors, we compared the distributions of pollutant predictions and concentrations from each source for the population that lived within 50 km of an air monitor. We then compared the distributions of downscaler CMAQ predictions among those who do and do not live within 50 km of a stationary air monitor to determine the impact of including populations that do not live near regulatory monitors. We also explored the pollutant predictions and concentrations categorically, as this form of an exposure metric is often utilized in epidemiologic studies. Accounting for departures of linearity observed in exploratory analyses, we categorized $PM_{2.5}$ using the pollutant prediction or concentration among the controls into the following categories: Low- less than the 10th percentile (referent), Low-middle-10th percentile to the median, Middle-high median to the 90th percentile and High- greater than or equal to the 90th percentile. These percentile cut-offs were calculated separately for the following three measures: CMAQ predictions for the full population, AQS concentrations for the population within 50 km of a monitor and CMAQ predictions for the population within 50 km of a monitor. Percentiles were

calculated separately for the seven-week average and the individual weeks of exposure, although the values were very similar. Ozone was categorized into quartiles in a similar manner. We used percentile based cut-offs to accommodate the differences in distribution between the different exposure metrics. We also explored using constant numeric cutoffs to create our categories but did not observe substantial difference in the resulting categorizations and continued to use the percentile-based cut-offs. In addition, we explored factors which we hypothesized could impact agreement between the two metrics constructed for the same population (i.e. those living within 50 km of a monitor), including season of exposure and closer proximity to the stationary air monitor.

Potential confounders were identified through review of the literature and directed acyclic graph analysis. The following variables obtained from the maternal interview were included in the final adjustment set: age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, and alcohol consumption during the first 3 months of pregnancy. Additionally, in order to account for potential differences in case ascertainment by study center, final models were adjusted for the center-specific ratio of septal defects to total CHDs. This adjustment for center was chosen to account for differences in the types of cardiac cases that were recruited at each site, as single-isolated setpal defects are often the most sensitive markers of differences in case ascertainment. Maternal birth outside the US was identified as a potential confounder through review of the literature but did not affect the estimates obtained upon adjustment, and was not included in the final model. A potential effect measure modifier, distance to the closest major road, defined as an interstate, US highway, state or larger county highway (FCC code A10-A39), was constructed using ArcGISv10 and then dichotomized at 50 meters. That distance variable, as well as pre-pregnancy body mass index, maternal occupation status, and the confounders listed above were assessed for effect measure modification using likelihood ratio tests with an *a priori* alpha level of 0.1.

5.2.3 Statistical Analysis

In order to contrast how changing the source of exposure assignment and/or changing the population included impacts the estimate of the relationship between each pollutant and CHDs, we constructed the following three sets of models: 1) using CMAQ predictions to assign exposure for the full population 2) using AQS measurements to assign exposure for those living within 50 km of an air monitor 3) using CMAQ predictions to assign exposure for those living within 50 km of an air monitor. Because each model simultaneously assessed multiple weeks of exposure and multiple defects/groupings, we constructed two-stage hierarchical regression models, using a software program adapted from Witte et al, to account for the correlation between estimates and partially address multiple inference. [144,149] The first-stage was an unconditional, polytomous logistic regression model containing all individual weeks of exposure, or the single 7-week average, and the full adjustment set detailed above. The resulting coefficients for the pollutant-defect relationships from that model were then regressed on a linear combination of indicator variables that defined the exposure week/level, the type of individual defect, and the broader defect-grouping of each coefficient in a second-stage model. The obtained second-stage coefficients are used to estimate the values toward which the first-stage coefficients will be shrunk towards, with the magnitude of the shrinkage depending upon the precision of the maximum likelihood estimate obtained in stage 1 and the value of the second stage variance, τ^2. [144,145] We fixed τ^2 at 0.5, corresponding to a prior belief with 95% certainty that the residual odds ratio (i.e. not defined by the second stage) will fall within a 16-fold span. To assess whether our results were robust to changes in model specification we explored setting the value of τ^2 to 0.25, corresponding to a 7-fold odds ratio span as well as to a value of 1, corresponding to a 50-fold span. Since there were fewer than 50 cases, the defect grouping of atrioventricular septal defects (AVSD) was explored separately using Firth's penalized

maximum likelihood method to address the quasi-complete separation that occurred due to small sample size. [150]

5.3 Results

After the study exclusions, 2,051 cases and 2,791 controls were included in our full study population (Table 5.1). Approximately 88.1% of these women lived within 50 km of an operational stationary air monitor for $PM_{2.5}$ and 69.5% lived within 50 km of an operational stationary air monitor for ozone. The lower percentage of women with ozone measurements from an AQS monitor is partly due to location and partly due to the lack of monitoring in many locations during the fall/winter months. As shown in Table 5.1, despite reducing sample size, the profile of different CHDs does not vary greatly in the limited populations, although women whose offspring had septal defects made up a slightly lower percentage of women living near an ozone monitor. There was a considerable difference in the breakdown of study sites as women from Arkansas and Iowa were less likely to live near either type of AQS monitor. Demographically, women living near AQS monitors were slightly older, more likely to be Black or Latino, have an advanced educational degree, have a household income greater than $50,000 and be born outside of the United States. These women were slightly less likely to smoke during pregnancy and more likely to work outside the home. While many of these differences were more pronounced for women living near ozone monitors, there was not a considerable difference in the make-up of the populations.

Figure 5.1a shows the population distribution of the seven-week average $PM_{2.5}$ concentration when using downscaler CMAQ predictions to assign exposure for the full population, downscaler CMAQ predictions for the population living within 50 km of an air monitor and the AQS measurements for the population living within 50 km of an air monitor. Comparing the distributions of AQS measurements and downscaler CMAQ predictions for the population living within 50 km of an air monitor, we observe that using the AQS measurements yields a distribution with a slightly

larger range and slightly greater density in the tails of the distribution than when using the downscaler CMAQ predictions, although the mean is slightly lower. The Spearman correlation coefficient between the AQS measurements and the downscaler predictions for the population with both measurements is 0.88. When contrasting the distributions of downscaler CMAQ predictions for the full population vs. the population that lives within 50 km of an air monitor, it appears that including the full population shifts the curve slightly to the left, but the shape doesn't change considerably. All three distributions have a relatively similar shape. Figure 5.1b shows similar results for the population distributions of the seven-week average ozone concentration. Again, using the AQS measurements provides a distribution with a lower mean, greater range and heavier tails, particularly the lower tail, although the Spearman correlation coefficient between the AQS measurements and the downscaler predictions is higher at 0.95. However, the AQS and downscaler CMAQ distributions for the limited populations still have a relatively similar shape. Including the full population does not just shift the curve left, as it did for $PM_{2.5}$, but instead increases the proportion of lower-middle values, changing the shape of the distribution from the other two.

The categorical exposure metrics based on these distributions also revealed differences that could impact the estimates obtained from epidemiologic studies. Because the AQS and downscaler CMAQ distributions are different, the percentile cut-off values used to create the categorical exposure metrics, as described in the methods, vary slightly, although we observed similar results when using constant numeric cutoffs. Approximately 72.2% of participants maintained the same exposure classification for both exposure metrics for PM2.5 and 79.5% of participants maintained consistent classification for ozone. For $PM_{2.5}$, the remaining 27.8% were split in half as to whether their categorization increased or decreased when using the downscaler CMAQ predictions as opposed to AQS measurements. Similarly, equal percentages of participants saw their categorization of ozone exposure increase or decrease. When restricting to participants who lived

within 10 km of a stationary air monitor, the percentages of agreement increased very slightly, to 74.6% for $PM_{2.5}$ and 81.1% for ozone.

These findings did not change considerably based on case/control status. However, agreement between AQS-derived and downscaler CMAQ-derived $PM_{2.5}$ exposure categorizations varied considerably by site, with Texas, Massachusetts and New York having lower levels of agreement than other sites. There was less variability by site for agreement in ozone exposure, although Massachusetts had lower agreement than other sites. When dichotomizing the exposure metrics by season of conception (winter/fall vs. spring/summer), we did not observe differences in categorization for $PM_{2.5}$ when compared to the full sample, but we did for ozone. While the amount of agreement was consistent for both seasons (78.9% spring/summer vs. 80% winter/fall), in spring/summer months, a larger percentage of participants had higher categorization based on the downscaler CMAQ predictions than the categorization obtained using AQS measurements (14.3% vs. 6.7%). This was reversed in winter months (4.9% vs. 14.8%).

Figures 5.2 and 5.3 compare adjusted estimates obtained from the hierarchical analysis when using the three different exposure metrics. Estimates and 95% CIs are presented in Table A3.1. Comparing estimates obtained using AQS vs. downscaler CMAQ for the population living within 50 km of a stationary air monitor, we observed that for some defects there are considerable differences in estimates obtained. For example, using AQS measurements to assign exposure, the odds of left ventricular outflow tract obstruction (LVOTO) defects are 1.57 times as high in the highest decile of $PM_{2.5}$ exposure compared to the lowest decile (95% CI 0.88, 2.78). When using the downscaler CMAQ to assign exposure, the odds ratio is 0.86 (95% CI 0.46, 1.6). A similar discrepancy was observed for COA, an individual LVOTO defect. Other smaller differences between the two are observed for individual defects TOF and PVS. When we compare to the estimates obtained from using downscaler CMAQ predictions for the full population, we see that adding in the additional

participants didn't considerably alter estimates from what was obtained for the limited population, although there are still considerable differences from the AQS-based estimates.

For ozone, there are stronger similarities between the three different estimates across defects, with greater precision of the protective effect of the highest quartile of ozone exposure on ASDs and a greater magnitude of the relationship between the highest level of exposure and PVS when using downscaler CMAQ estimates on the full population as the notable exceptions. We reran the models using constant numeric cutoffs across the three different metrics to create the categorical values and continued to find differences in the resulting effect estimates, although in some cases these differences were attenuated (Table A3. 2). When examining $PM_{2.5}$ and ozone among the population living within 50 km of an air monitor, the AIC values from the first-stage logistic models were slightly lower when using AQS-derived estimates of exposure than when using downscaler CMAQ-derived estimates, suggesting slightly better model fit ($PM_{2.5}$: 11635 vs. 11647; ozone: 9052 v 9057).

Generally, adjusted estimates were closer to the null than crude estimates and only adjusted estimates are presented. Adjusting for site-related differences in case phenotypes, as represented by the percent of cases that were septal defects, in models using AQS-based exposures and CMAQ-based exposures of ozone had little effect beyond moving the estimates of ASDs closer to the null, after simultaneous adjustment of demographic factors. However, adjusting for this factor in the models of downscaler-CMAQ based estimates of $PM_{2.5}$ resulted in larger movement toward the null for multiple defects and movement away from the null for PVS. When comparing estimates unadjusted for site-related case ascertainment differences, the odds of PVS with greater $PM_{2.5}$ exposure obtained from the downscaler CMAQ-based models were similar to those from the AQS-based models. Differences in other defect estimates persisted.

Assessing the odds of CHDs by weekly averages revealed elevated odds ratios that were not observed when utilizing the seven-week average. This was true across all three metrics. In some cases, estimates from the three metrics were in agreement, for example elevated odds of PVS with greater exposure to $PM_{2.5}$ during week 8 of pregnancy (Table A3.3). There were also examples of discrepancies in estimates obtained using the different exposure metrics. For example, using AQS-derived measurements to assign exposure, there is more than a doubling of the odds of PVS when comparing the highest to lowest quartiles of ozone exposure (OR 2.22 95% CI 1.06, 4.67). When this is explored in the full population using the downscaler CMAQ predictions to assign exposure, the odds ratio is only equal to 1.21 (95% CI 0.68, 2.17). Often, when the difference between estimates was greater than expected given the precision of the estimates, the AQS-derived estimate was greater in magnitude. Full weekly results are provided in Tables A3.3 and A3.4.

Because we observed slight differences in classification of ozone by season of conception/exposure, we reran the first-stage, maximum likelihood models with an interaction term between seven-week exposure and season to obtain season-specific estimates and observed the differences between the AQS-based and downscaler CMAQ-based estimates were relatively consistent given the reduced precision. Additionally, we reran the hierarchical models using different values of tau-squared and found our results were robust to these changes in model specification.

Table 5.1: Case phenotypes, demographic and behavioral characteristics of NBDPS participants with single, isolated congenital heart defects and controls with estimated dates of delivery from 2001-2006[a]

	Full Population		Population living within 50km of a PM2.5 air monitor		Population living within 50km of an ozone air monitor	
	N	%	N	%	N	%
Total N	4842		4264		3364	
Case Phenotypes						
Controls	2791	57.6	2451	57.5	1970	58.6
LVOTO	327	6.8	284	6.7	225	6.7
Aortic Stenosis	74	1.5	60	1.4	44	1.31
Coarctation of the Aorta	134	2.8	121	2.8	90	2.68
IAA-Type A	4	0.1	4	0.1	3	0.09
Hypoplastic Left Heart Syndrome	115	2.4	99	2.3	88	2.62
CONOTRUNCAL	437	9	393	9.2	311	9.2
Common Truncus	20	0.4	17	0.4	10	0.3
IAA-Type B/NOS	6	0.1	6	0.1	6	0.2
d-TGA	143	3	131	3.1	104	3.1
Tetralogy of Fallot	237	4.9	213	5	171	5.1
DORV-TGA/DORV-Other	14	0.3	11	0.3	9	0.3
VSD-conoventricular	18	0.4	15	0.4	11	0.3
AVSD	39	0.8	36	0.8	26	0.8
APVR	71	1.5	64	1.5	55	1.6
Total-APVR (TAPVR)	61	1.3	56	1.3	49	1.5
Partial APVR (PAPVR)	10	0.2	8	0.2	6	0.2
RVOTO	313	6.5	280	6.6	209	6.2
Pulmonary Atresia	36	0.7	34	0.8	28	0.8
Tricuspid Atresia	17	0.4	17	0.4	13	0.4
Ebstein's Anomaly	26	0.5	22	0.5	17	0.5
Pulmonary Valve Stenosis	234	4.8	207	4.9	151	4.5
SEPTALS	864	17.8	756	17.7	568	16.9
VSD-perimembranous	361	7.5	313	7.3	234	7
VSD-NOS/OS/multiple	6	0.1	6	0.1	3	0.1
ASDs, all	497	10.3	437	10.3	331	9.8
Birth Outcome						
Live Birth	4825	99.7	4248	99.6	3350	99.6
Fetal Death	8	0.2	7	0.2	6	0.2
Induced Abortion	4	0.1	4	0.1	3	0.1
Study Site						
Arkansas	567	11.7	447	10.5	197	5.9
Iowa	751	15.5	543	12.7	308	9.2
Massachusetts	940	19.4	912	21.4	807	24
New York	476	9.9	443	10.4	435	12.9
Texas	686	14.2	526	12.3	516	15.3
Metropolitan Atlanta	755	15.6	752	17.6	589	17.5
North Carolina	649	13.4	628	14.7	502	14.9
Utah	18	0.4	13	0.3	10	0.3
Maternal Age at conception, avg (sd)	27.7 (6.2)		28.0 (6.2)		28.2 (6.3)	
Maternal Race						
NH White	2911	60.1	2533	59.4	1888	56.1
NH Black	652	13.5	615	14.4	505	15
Latino	940	19.4	791	18.6	710	21.1
Other	338	7	324	7.6	260	7.7

TABLE 5.1 (cont.)

	Full Population		Population living		Population living	
	N	%	N	%	N	%
Maternal Education						
0-8 years	245	5.1	210	5	172	5.1
9-11 years	528	11	456	10.7	360	10.8
12 years, Completed High School or Equivalent	1078	22.4	889	21	671	20.1
Some College/Completed Trade School	1205	25	1034	24.4	792	23.7
4 Years College or Bachelors Degree	1218	25.3	1140	26.9	909	27.2
Masters Degree/Advanced Degree	541	11.2	515	12.1	440	13.2
Maternal Household Income						
<=50,000	2768	60.3	2329	57.5	1804	56.6
>50,000	1822	39.7	1720	42.5	1384	43.4
Maternal BMI						
Underweight	206	4.4	177	4.3	142	4.4
Normal Weight	2431	52.3	2170	53	1712	53.2
Overweight	1146	24.7	1004	24.5	790	24.5
Obese	867	18.7	745	18.2	577	17.9
Maternal Birth in the United States						
No	920	19.1	845	19.9	721	21.6
Maternal Smoking first month of pregnancy						
Yes	786	16.3	658	15.5	498	14
Alcohol Consumption anytime in the month before to 3rd month of pregnancy						
None	2939	61.5	2553	60.6	2011	60.6
Less than 4 drinks per week	1270	26.6	1170	27.8	939	28.3
Binge drinking (4+ drinks per week)	568	11.9	493	11.7	368	11.1
Maternal Occupational Status						
Did not work outside the home	1343	27.9	1175	27.7	979	29.3

[a] Does not include missing data so not all variables will sum to the total sample size

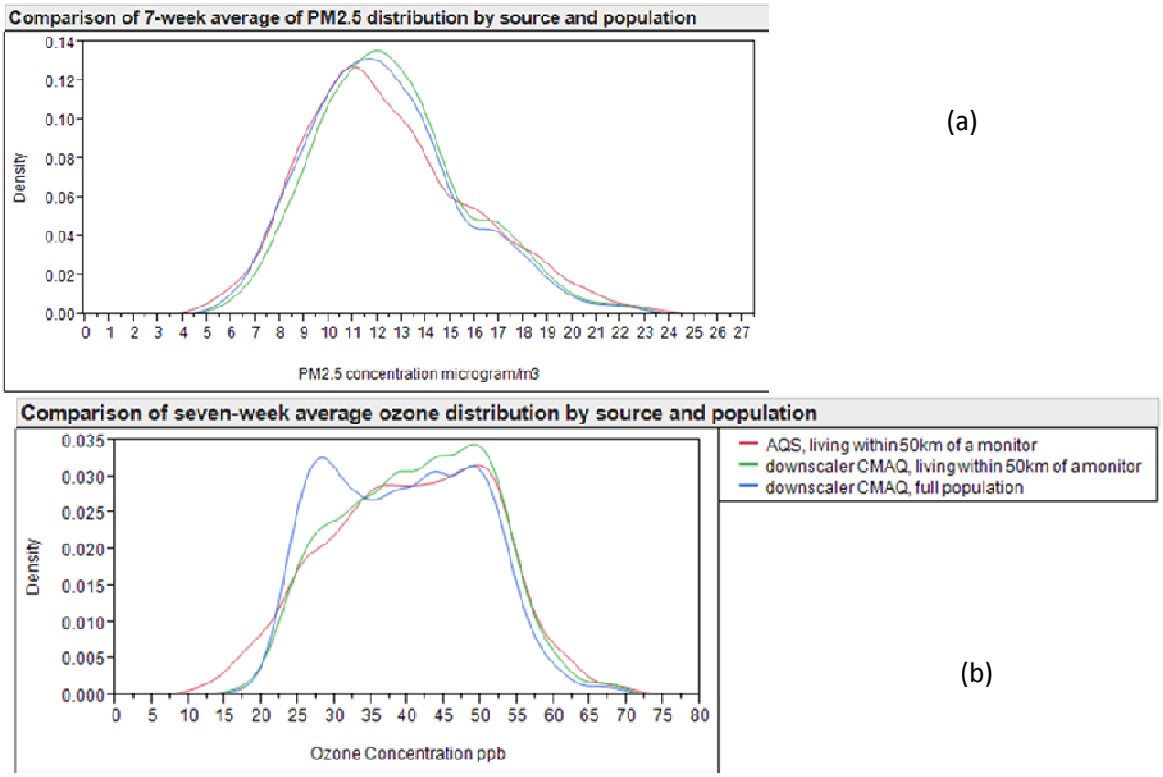

Figure 5.1: Population distribution of 7-week average of 24-hr measurements or 8 hour maximums, by source of exposure metric; Red line indicates AQS-derived exposure, Green line indicates downscaler-CMAQ for population living within 50 km of a monitor, Blue line indicates downscaler-CMAQ for full population (a): $PM_{2.5}$ (b): ozone

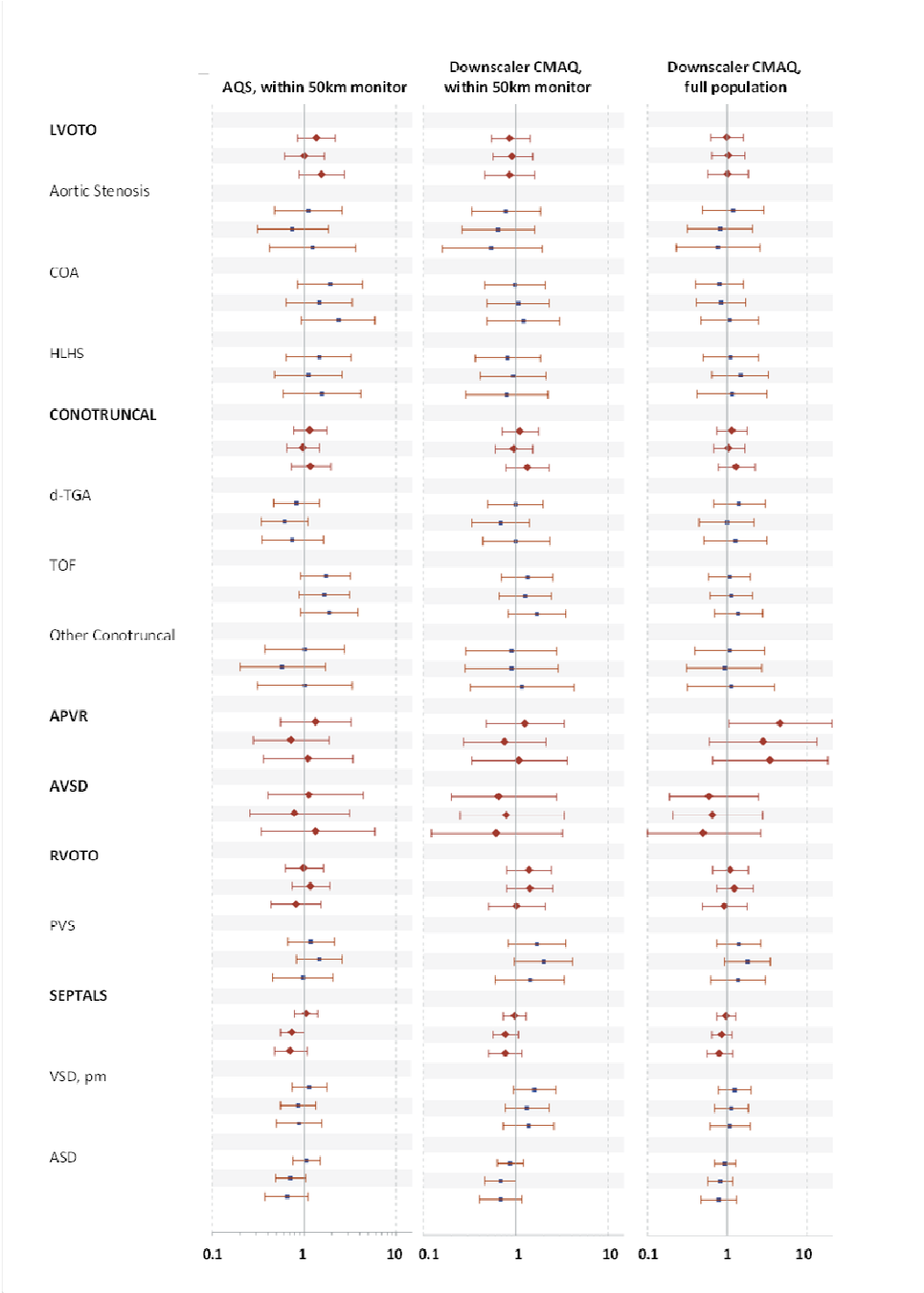

Figure 5.2: Adjusted odds ratios and 95% confidence intervals for the relationship between maternal exposure to $PM_{2.5}$ and congenital heart defects, by source of exposure metric

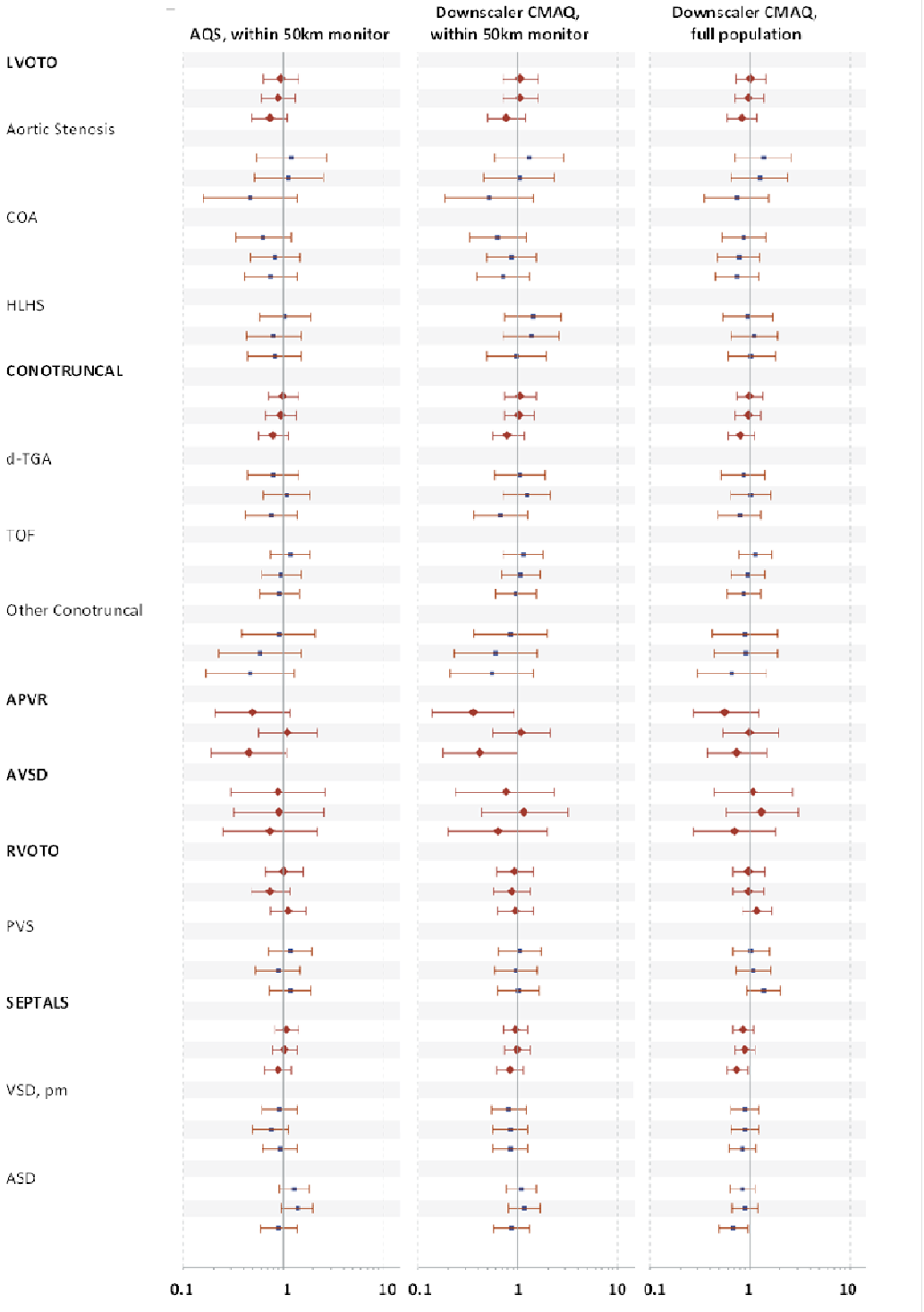

Figure 5.3: Adjusted odds ratios and 95% confidence intervals for the relationship between maternal exposure to ozone and congenital heart defects, by source of exposure metric

5.4 Discussion

In summary, we observed differences in both the population included and the magnitude of the pollutant concentrations assigned when using AQS-derived and downscaler CMAQ-derived exposure estimates. These differences contributed to slightly differing estimates of the effect of pollutant exposure during pregnancy and CHDs in offspring, whether using a seven-week average measure of exposure or individual weekly averages. For example, based on AQS-derived estimates of exposure, we observed greater odds of LVOTO defects, particularly COA, with greater exposure to $PM_{2.5}$ and greater odds of PVS with exposure to ozone in week 3 of pregnancy. These associations were not observed when using downscaler CMAQ-derived estimates of exposure. Other observed associations, such as between $PM_{2.5}$ and TOF, were observed for the three different metrics with differing magnitudes. In general, differences between estimates using the different metrics were more pronounced in models of $PM_{2.5}$ when compared to ozone, and the $PM_{2.5}$-related differences were most notable when comparing AQS-derived estimates among populations living within 50 km of an air monitor to downscaler-CMAQ derived estimates among the full population.

Previous research on the CMAQ model found spatial differences in agreement with AQS measurements for both $PM_{2.5}$ and ozone.[154] Our study also found spatial differences in agreement, particularly for $PM_{2.5}$. In the previous study examining differences in estimates obtained from the different exposure metrics for ozone, there did not appear to be a large difference in estimates obtained from AQS measurements versus those obtained from downscaler CMAQ, beyond greater precision due to increased sample size.[155] Yet, we observed greater spatial variability in agreement for $PM_{2.5}$ and composition of $PM_{2.5}$ varies spatially, while ozone does not.[156] When exploring the association between $PM_{2.5}$ and CHDs across a large spatial gradient, the resulting effect estimate mixes the effects of the different components. Previous research suggests that the different components of particulate matter can impact different biological systems.[157,158] Therefore, it is

possible that the relationship between exposure to $PM_{2.5}$ and risk of CHDs may vary by composition. Thus not only can inclusion of rural populations, where the composition may be different from those who live close to monitoring networks impact effect estimates related to $PM_{2.5}$ exposure, but if the agreement between AQS and downscaler CMAQ varies in a spatial process that coincides with differences in composition, the resulting effect estimates related to $PM_{2.5}$ exposure would be different between the two models. This could also explain why adjusting for site-related characteristics had a larger impact on models using downscaler-CMAQ derived estimates of exposure to $PM_{2.5}$ than either models using AQS-derived estimates or models exploring ozone exposure. Given the agreement between estimates from models using downscaler-CMAQ derived exposures for the full and limited populations, it does not appear that adding in the rural populations has much of an impact, aside from spatial differences in agreement between downscaler-CMAQ and AQS measurements and increase in sample size.

Limiting to women within 10 km of a monitor did not greatly improve the agreement between the AQS and downscaler CMAQ exposure distributions, suggesting that it is not a matter of misclassification of exposure due to distance from the monitor. Because we assigned downscaler-CMAQ exposures by matching to the closest census tract centroid in the same process as matching to the closest air monitor, both metrics were subject to misclassification due to topography, wind direction etc. although the distance to a census tract centroid are generally shorter than to an air monitor. Some differences in effect estimates were attenuated when using constant numeric cut-offs to create the categorical variables. This could be because the distribution of downscaler CMAQ predictions had lighter tails than the AQS distribution, causing discrepancies in percentile-based cutoffs.

We observed seasonal differences in agreement between monitor-based and model-based estimates of ozone exposure. This did not have an impact on our estimates because CHDs do not

vary seasonally, nor do the relationships between ozone exposure and CHDs. However, in a study of a seasonally-varying outcome, such as preterm birth, these differences could have a large impact on study results and should be accounted for in the analysis.

Using a multisite study, such as the NBDPS, provided a favorable study population with large spatial and temporal variability in order to compare the different exposure metrics as well as examine the impact of inclusion of more rural populations. We observed that agreement between AQS concentrations and downscaler-CMAQ predictions vary spatially. Due to the time period of the study, we were limited to participants who lived in the eastern and central US. Agreement between AQS measurements and downscaler CMAQ predictions may be different in Western states. Additionally, we tried to control for site-related differences in case ascertainment using the variable containing the percentage of septal cases at each site. It is unclear what is driving these site-related differences in case phenotype. If these differences are due to spatial variability in pollutant concentrations, we are overadjusting our models and true effect estimates would be further from the null. However, as stated previously, the impact of site-adjustment was not very large for the AQS-derived model estimates apart from attenuating the protective effect of pollutant exposure on ASDs.

Differences in effect estimates obtained from using downscaler CMAQ predictions to assign exposure versus AQS measurements were larger when investigating $PM_{2.5}$ compared to ozone, potentially due to the spatially varying composition of the particles causing spatial variability in the effect of $PM_{2.5}$ on risk of CHDs. The seasonal variation in agreement between AQS and downscaler CMAQ ozone predictions could have had a larger impact on effect estimates if our outcome of interest had also varied seasonally. Further application of using downscaler CMAQ predictions to assign exposure in epidemiologic studies should carefully assess the spatial and seasonal variability

in both the outcome itself and the relationship of interest to determine if there is a potential for biased estimates.

CHAPTER 6

6. INVESTIGATING THE IMPACT OF FOLIC-ACID SUPPLEMENT USE ON THE RELATIONSHIP BETWEEN EXPOSURE TO $PM_{2.5}$ DURING PREGNANCY AND CONGENITAL HEART DEFECTS

6.1 Introduction

One of the potential biological pathways through which air pollutants could cause congenital heart defects (CHDs) is through epigenetic changes.[36] Research by Chowdhury et al found associations between measures of maternal global DNA hypomethylation and CHDs, while research by Sheng et al found lower levels of methylation in children with tetralogy of Fallot, a conotruncal CHD.[35,159] DNA methylation refers to the addition of a methyl group to the cytosine base on DNA. Cells have a specific methylation pattern that encodes protein expression and is maintained during cell replication. DNA methylation is associated with repressed gene expression, potentially by blocking promoters were transcription factors can bind. Previous research has found that DNA hypomethylation contributes to chromosomal instability, altered gene expression, cellular differentiation, and apoptosis during embryogenesis.[130] In a mouse model, disruption of DNA methylation was shown to cause exencephaly in treated mice[131], and a recent epidemiologic study found associations between lower levels of DNA methylation and neural tube defects.[132] Baccarelli et al have observed DNA hypomethylation after exposure to particulate matter and black carbon, a measure of traffic pollutants.[34] Thus, it is possible that exposure to pollutants early in pregnancy, may trigger DNA hypomethylation which disrupts normal cardiac development. Because folate acts as a methyl donor, necessary to initiate and regulate DNA methylation processes, it is possible that a woman's folate status at the beginning of her pregnancy may modify impacts from air pollution, and

that women with low folate levels may be especially vulnerable to the impacts of air pollutants if this mechanism is true.[36] The goal of this subanalysis was to investigate whether use of folic-acid supplements modifies the relationship between exposure to fine particulate matter ($PM_{2.5}$) during pregnancy and CHDs within the National Birth Defects Prevention Study (NBDPS).

6.2 Methods

The population for this subanalysis were all controls and cases with a single, isolated CHD, with no non-CHDs present who had an estimated date of delivery (EDD) from 1999, when $PM_{2.5}$ monitoring began through 12/31/2006 and lived within 50 kilometers of a $PM_{2.5}$ stationary air monitor. Women with non-gestational diabetes were excluded. Cases were classified according to standardized NBDPS criteria.[97]

Pollutant concentrations from the closest monitor were assigned to the woman's corresponding pregnancy period. If a woman had more than one residential address, daily exposures were assigned using the monitors closest to the residence that corresponded to that day of pregnancy. Concentrations of $PM_{2.5}$ are based on 24-hour measurements, but were often measured only on every 3rd or 6th day. For the present analysis, we explored exposure using individual weekly averages. We included week two in addition to the standard window of cardiac development, as previous literature suggests the potential for lag effects of air pollution [3,146]. Ambient levels were categorized using the distribution of pollutant concentration among the controls into the following categories: less than the 10th percentile (referent), 10th percentile to the median, median to the 90th percentile and greater than or equal to the 90th percentile. These categories captured the departure from linearity observed in initial, exploratory analyses.

Folic-acid use was categorized in two ways: as a dichotomous ever/never variable and a multilevel variable incorporating information on both supplement use and dietary intake of folate and folic-acid. Because the use of folic-acid supplements varies during pregnancy, women reported

their supplement use on a monthly basis for the duration of pregnancy. Because defects are triggered very early in pregnancy, we explored supplement use in the month prior to conception and then explored supplement use in the first month of pregnancy. Dietary folate was assessed using a shorted version of the Willett food frequency questionnaire and transformed into dietary folate equivalents (DFE) which allows for the combination of naturally occurring folate in foods and folic-acid supplementation of foods, such as grains.[160] Because it is semi-quantitative, the food frequency questionnaire often does not provide an exact intake of DFE, but instead provides a relative measure that can be used to accurately rank women's intake. Therefore, we dichotomized women at the median level of DFE's among controls. This measure was then combined with supplement use in the month prior to conception to form a multilevel variable with the following categories: 1-No supplementation and dietary folate less than the median, 2- No supplementation and dietary folate greater than or equal to the median , 3- Supplementation and dietary folate less than the median, 4- Supplementation and dietary folate greater than or equal to the median. We also created a similar variable using supplement use in the first month of pregnancy.

Potential confounders were identified through review of the literature and directed acyclic graph analysis. The following variables obtained from the maternal interview were included in the final adjustment set: age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, alcohol consumption during the first 3 months of pregnancy, and maternal birth outside of the US. Additionally, in order to account for potential differences in case ascertainment by study center, final models were adjusted for the center-specific ratio of septal defects to total CHDs. This adjustment for center was chosen to account for differences in the types of cardiac cases that were recruited at each site, controlling away effects due to spatial variability in pollutant concentrations.

Main effects of use of folic-acid supplements, dietary intake of DFEs, and $PM_{2.5}$ exposure were assessed using polytomous logistic regression models adjusted for the set of confounders defined above. Effect measure modification was assessed by using likelihood ratio tests comparing logistic regression models with and without interaction terms between $PM_{2.5}$ exposure and supplement use, defined dichotomously or as the multi-level variable. An *a priori* α-level was set at 0.2 to indicate the presence of effect measure modification, given the small sample size for individual defects. When we explored $PM_{2.5}$ exposure during weeks 5-8, we only explored folic-acid supplement use in the first month of pregnancy, and not the month prior to conception, due to the short amount of time folate is available in the body.

6.3 Results

Demographics of the study population are provided in Table 6.1. Approximately 35% of women reported taking a folic-acid containing supplement one month prior to pregnancy, while 53.9% reported taking supplements by the first month of pregnancy. Approximately 32% of women had lower dietary intake of folate and did not report taking a folic-acid supplement while 16% had high dietary intake and reported taking a supplement in the month prior to conception.

6.3.1 Main Effects

Results from the main effect analyses of folic-acid use are shown in Table 6.2. Generally, odds of CHDs associated with not taking a folic-acid supplement were slightly greater when exploring use in the month prior to conception than when exploring use in the first month of pregnancy. Greater odds of ASDs were observed among the offspring of women who did not report taking supplements in the month prior to pregnancy as well as among women with lower dietary intake of folate. Women with lower dietary intake also had greater odds of offspring with d-transposition of the great arteries and total anomalous pulmonary venous return. Women with higher dietary intake who also reported taking a supplement had lower odds of many individual

defects when compared to women with lower intake who did not take a supplement. In previous analyses of the main effects of $PM_{2.5}$, we observed elevated odds of tetralogy of fallot (TOF) with greater exposure in week 2 of pregnancy and elevated odds of pulmonary valve stenosis were observed in weeks 5 and 8.

6.3.2 Effect Measure Modification

We found evidence that the odds of TOF with greater exposure to week 2 exposure of $PM_{2.5}$ were modified by use of folic-acid supplements in the month prior to pregnancy. Looking at the stratum-specific estimates, we observed that women who did not take supplements had larger odds ratios, but this became attenuated at the higher pollutant levels (Table 6.3). We observed a similar pattern when using the combination folic-acid variable (Table 6.4). Women who had higher amounts of dietary intake and took a folic-acid supplement before pregnancy had lower odds of offspring with TOF until the highest decile of $PM_{2.5}$ exposure. Unlike for TOF, there was no evidence of modification of the relationship between $PM_{2.5}$ exposure and coarctation of the aorta using the likelihood ratio test, although the stratums-specific estiamtes were on opposite sides of the null. When we examined supplement use in the first month of pregnancy, the likelihood ratio test gave a p-value of 0.08, suggesting the presence of modification. The stratum-specific estimates remained on opposite sides of the null, through imprecise. In contrast with the findings observed for TOF, when we examined the combination variable, women who took a supplement but had low dietary folate intake had the lowest odds ratios describing the association between $PM_{2.5}$ exposure and COA.

Table 6.1: Demographic characteristics of NBDPS study population living within 50km of a PM2.5 monitor

Characteristic	N	%	Characteristic	N	%
Maternal Age (avg, sd)	27.5 (6.11)		Maternal Race		
			White, non-Latino	4507	58.4
Controls	4407	57.1	Black, non-Latino	886	11.5
Cases			Latino	1784	23.1
LVOTO	596	7.7	Asian/ Pacific Islander	229	3
Aortic Stenosis	135	1.8	Other	307	4
Coarctation of the Aorta	233	3			
IAA-Type A	8	0.1	Maternal Education		
Hypoplastic Left Heart Syn.	220	2.9	0-6 years	264	3.4
CONOTRUNCAL	736	9.5	7-8 years	141	1.8
Common Truncus	32	0.4	9-11 years	865	11.3
IAA-Type B/NOS	9	0.1	12 Years, Completed HS or Equiv.	1721	22.4
d-TGA	235	3	1-3 years College	1854	24.1
Tetralogy of Fallot	397	5.1	Completed Technical School	250	3.3
DORV-TGA/DORV-Other	30	0.4	4 Years College/Bachelor's Degree	1844	24
VSD-conoventricular	34	0.4	Master's Degree	577	7.5
AVSD	63	0.8	Advanced Degree	165	2.2
APVR	114	1.5			
Total-APVR (TAPVR)	101	1.3	Maternal Household Income		
Partial APVR (PAPVR)	13	0.2	<10,000	1289	17.6
RVOTO	540	7	>50,000	2796	38.1
Pulmonary Atresia	71	0.9	In Between	3259	44.4
Tricuspid Atresia	34	0.4			
Ebstein's Anomaly	38	0.5	Maternal BMI		
Pulmonary Valve Stenosis	395	5.1	Underweight	364	4.9
SEPTALS	1259	16.3	Normal Weight	3946	53.2
VSD-perimembranous	538	7	Overweight	1764	23.8
VSD-NOS/OS	12	0.2	Obese	1347	18.2
ASDs, all	709	9.2			
			Maternal Smoking first month of pregnancy		
Study Site			Yes	1104	14.4
Arkansas	650	8.4			
California	1069	13.9	Alcohol Consumption, month prior-first trimester		
Iowa	734	9.5	None	4945	64.8
Massachusetts	1190	15.4	Less than 4 drinks per week	1822	23.9
New York	681	8.8	Binge drinking (4+ drinks per week	869	11.4
Texas	917	11.9			
Metropolitan Atlanta	1076	14	Use of Folic Acid Supplements		
North Carolina	633	8.2	One month prior to conception	2697	35.3
Utah	765	9.9	First month of pregnancy	4118	53.9
			No Supplement and low DFE[a]	2473	32.4
			Supplement and low DFE	1461	19.2
			No Supplement and high DFE	2461	32.3
			Supplement and high DFE	1236	16.2

[a]DFE, dietary folate equivalents-categories created by dichotomizing at the median

Table 6.2: Adjusted[a] main effects of folic-acid supplement use and dietary folate on congenital heart defects

	Use of Folic Acid Supplement			Dietary Folate Equivalents, DFE	
	Used Supplement (referent)[b]	No use one month prior to pregnancy	No use during first month of pregnancy	At or above the median	Below the median
LVOTO	1	1.06 (0.87, 1.30)	0.89 (0.73, 1.09)	1	1.15 (0.96, 1.37)
Aortic Stenosis	1	1.05 (0.71, 1.56)	1.00 (0.67, 1.48)	1	1.06 (0.74, 1.52)
Coarctation of the Aorta	1	1.18 (0.86, 1.61)	0.88 (0.64, 1.20)	1	1.16 (0.88, 1.53)
Hypoplastic Left Heart Syn.	1	0.96 (0.69, 1.33)	0.83 (0.61, 1.15)	1	1.20 (0.90, 1.60)
CONOTRUNCALS	1	0.93 (0.77, 1.12)	0.90 (0.75, 1.08)	1	1.12 (0.95, 1.32)
d-TGA	1	0.98 (0.72, 1.34)	0.91 (0.67, 1.23)	1	1.32 (1.00, 1.74)
Tetralogy of Fallot	1	0.85 (0.66, 1.08)	0.87 (0.68, 1.11)	1	1.11 (0.90, 1.38)
Other Conotruncals	1	1.19 (0.73, 1.95)	1.04 (0.66, 1.63)	1	0.81 (0.54, 1.22)
APVR	1	1.20 (0.74, 1.94)	1.02 (0.66, 1.58)	1	1.51 (1.00, 2.27)
AVSD	1	0.87 (0.49, 1.54)	0.78 (0.45, 1.37)	1	1.45 (0.86, 2.45)
RVOTO	1	1.07 (0.86, 1.33)	0.96 (0.78, 1.18)	1	1.02 (0.85, 1.24)
Pulmonary/Tricuspid Atresia	1	1.03 (0.63, 1.67)	0.93 (0.59, 1.46)	1	1.12 (0.74, 1.69)
Pulmonary Valve Stenosis	1	1.02 (0.79, 1.30)	0.95 (0.74, 1.20)	1	1.02 (0.82, 1.26)
SEPTALS	1	1.19 (1.01, 1.39)	1.07 (0.93, 1.24)	1	1.16 (1.02, 1.33)
VSD-perimembranous	1	1.11 (0.89, 1.38)	1.07 (0.87, 1.32)	1	1.09 (0.91, 1.32)
ASD-all	1	1.23 (1.00, 1.51)	1.04 (0.87, 1.26)	1	1.23 (1.03, 1.45)

[a] Models adjusted for maternal race, age, educational attainment, birth outside the US, tobacco, alcohol use, and site-specific septal case ratio.

[b] Referent group changes depeding upon time period explored; when comparing to no use one month prior to pregnancy, it consists of women who used a supplment one month prior to pregnancy; when comparing to women with no use in the first month of pregnancy, it consists of women who used a supplement during the first month of pregnancy

Table 6.3: Adjusted[a] odds ratios and 95% confidence intervals of PM 2.5 and selected CHDs, by folic acid supplement use

	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile	X^2 from likelihood ratio test	p-value
Tetralogy of Fallot, week 2 exposure						
Supplement use month prior to conce	1	1.36 (0.64, 2.91)	1.63 (0.76, 3.47)	2.11 (0.86, 5.14)	4.83	0.18
No supplement use month prior to cor	1	2.37 (1.11, 5.02)	1.60 (0.73, 3.50)	2.57 (1.09, 6.10)		
Supplement use first month of pregan	1	1.66 (0.85, 3.24)	1.78 (0.90, 3.52)	2.07 (0.93, 4.61)	4.83	0.18
No supplement use first month of preg	1	2.14 (0.90, 5.11)	1.33 (0.54, 3.28)	2.68 (1.01, 7.12)		
Coarctation of the aorta, week 2 exposure						
Supplement use month prior to conce	1	0.80 (0.37, 1.72)	0.83 (0.38, 1.83)	0.89 (0.30, 2.70)	1.86	0.6
No supplement use month prior to cor	1	1.55 (0.71, 3.41)	1.60 (0.71, 3.63)	2.10 (0.78, 5.60)		
Supplement use first month of pregan	1	0.84 (0.46, 1.56)	0.78 (0.41, 1.49)	0.89 (0.36, 2.17)	6.833	0.08
No supplement use first month of preg	1	3.47 (0.80, 15.0)	4.28 (0.98, 18.7)	5.75 (1.17, 28.4)		

[a] Models adjusted for maternal race, age, educational attainment, birth outside the US, tobacco, alcohol use, and site-specific septal case ratio.

Table 6.4: Adjusted[a] odds ratios and 95% confidence intervals of week 2 exposure to PM 2.5 and tetralogy of Fallot and coarctation of the aorta, by folic-acid supplement use

	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Tetralogy of Fallot				
No supplement use, Low DFE	1	2.38 (0.83, 6.85)	1.71 (0.58, 5.04)	3.06 (0.95, 9.88)
Supplement use, Low DFE	1	2.75 (0.80, 9.40)	2.71 (0.80, 9.26)	2.34 (0.56, 9.72)
No supplement use, High DFE	1	1.91 (0.73, 5.00)	1.37 (0.51, 3.68)	1.74 (0.57, 5.29)
Supplement use, High DFE	1	0.73 (0.27, 1.96)	1.28 (0.50, 3.27)	2.31 (0.75, 7.10)
Coarctation of the aorta				
No supplement use, Low DFE	1	2.80 (0.35, 22.0)	4.71 (0.60, 37)	7.56 (0.84, 68)
Supplement use, Low DFE	1	0.5 (0.24, 1.04)	0.6 (0.29, 1.26)	0.56 (0.19, 1.64)
No supplement use, High DFE	1	4.30 (0.55, 33.5)	3.67 (0.46, 29)	3.74 (0.39, 36)
Supplement use, High DFE	1	2.43 (0.71, 8.36)	1.56 (0.43, 5.65)	2.17 (0.44, 10.6)

[a] Models adjusted for maternal race, age, educational attainment, birth outside the US, tobacco, alcohol use, and site-specific septal case ratio.

6.4 Discussion

Our findings suggest use of a folic-acid supplement may reduce the risk of CHDs associated with $PM_{2.5}$ exposure during early pregnancy. These findings were primarily limited to $PM_{2.5}$ exposure very early in pregnancy and were observed for only TOF and COA. It is well established that folic-acid intake reduces the odds of neural tube defects[161], and literature suggests that it also reduces the odds of other birth defects, including CHDs, although mechanisms are unclear.[162,163] However, to our knowledge, this is the first study to show that folic-acid supplement use modifies the odds of CHDs associated with maternal exposure to $PM_{2.5}$ in early pregnancy. The differences in results when incorporating dietary folate intake could be a result of the imprecision of the estimates given the small sample size, or it could suggest the potential for hypermethylation to play a role in the development of COA from too much folic-acid.[164]

A recent study found lower methylation levels in the cardiac tissue of infants with TOF.[159] In conjunction with previous research associating maternal levels of DNA methylation with CHDs in offspring[35], this suggests that altered DNA methylation processes could play a role in the

development of CHDs. Toxiciological and epidemiologic literature suggest that exposure to $PM_{2.5}$ can impact methylation processes[34,36], suggesting a potential pathway between associations observed between maternal exposure to air pollutants and CHDs in offspring. It is possible that folic-acid taken very early in pregnancy counteracts the detrimental effects of particulates on methylation processes during development. Our findings for TOF suggest that there could be a threshold of particulate exposure, after which folic-acid can no longer prevent disruption of the DNA methylation processes. This did not appear to be the case for COA, however, and further research is necessary to determine not only if our findings can be replicated, but if there are different mechanisms at play for the different defects.

This study relied on maternal report of folic acid supplement use and maternal reports of food intake to calculate dietary folate intake, and so is subject to the same potential for recall bias as other case-control studies with retrospective exposure ascertainment. Additionally, the food frequency questionnaire used was only semi-quantitiative, and we could only account for dietary intake using a crude dichotomy at the median level. Similarly, although we were able to explore folic-acid use monthly, we used an ever/never categorization within that time period and did not differentiate by when during the month a woman initiated use, how often she took the supplement, and what other nutrients were contained in the supplement. More refined categorizations could potentially improve effect estimation and help determine at what point folic-acid may modify the effects of $PM_{2.5}$. It is possible that unmeasured characteristics of women who are more likely to take folic-acid supplements early in pregnancy are confounding this observed interaction. For example, women who report taking folic-acid in the month prior to conception may have healthier habits or may have been more likely to have planned the pregnancy. We adjusted our models for many demographic factors that are associated with choosing to use folic-acid supplements but residual confounding is a possibility. It is also possible that other nutrients within supplements or

within foods that contain folate are responsible for our results. This could potentially explain why women who didn't take a supplement but had higher dietary folate levels showed a larger effect of $PM_{2.5}$ on COA. Finally, this study did not have any information on genetic factors that could influence this relationship, for example an individual's ability to metabolize folate and other methyl donors. This lack of information would potentially attenuate the true modification by folic-acid, as it would allow us to get a better measure of the amount of methyl groups truly available for the methylation processes within the body.

In summary, we found that use of a folic-acid supplement reduced the association between maternal $PM_{2.5}$ exposure and CHDs in offspring. Future research could focus on better characterization of folic-acid use and dietary intake of folate and other nutrients, as well as incorporating measures of maternal DNA methylation within analyses.

CHAPTER 7

7. CONCLUSIONS

7.1 Summary of Findings

The purpose of this dissertation was to utilize the NBDPS, a large population-based multi-site case-control study of birth defects with large geographic variability, complete residential history during pregnancy and detailed nutrition and other covariate information in order to investigate the relationships between maternal exposure to criteria air pollutants during pregnancy and CHDs. The detailed covariate information allowed for the exploration of potential effect measure modification by use of folic-acid during pregnancy, and the large geographic extent of the study population allowed for a meaningful comparison of monitor-based versus model-based estimates of exposure to air pollutants.

This study found greater odds of multiple types of CHDs with greater exposure to criteria air pollutants. Consistent with a previous meta-analysis, the main analyses revealed a greater risk of COA and TOF with greater exposure to NO_2 and greater risk of COA with exposure to SO_2.[23] The odds of outflow tract obstruction defects, both left and right, were elevated with greater exposure to multiple individual air pollutants, with odds ratios often around 2 when comparing the highest to lowest decile of exposure. The similarity in findings for the outflow tract defects across different pollutants suggests the potential for outflow tract development to be particularly susceptible to environmental insult.

This study also revealed evidence of both temporal and spatial variability in these relationships, which had not been examined in previous studies. Utilizing hierarchical regression to account for the association between individual weeks of exposure, this study identified potential temporal windows of susceptibility within the typical window of cardiac development, for example week 3 ozone exposure and PVS and week 2 $PM_{2.5}$ exposure and TOF. Findings in week 2 support the occurrence of lagged effects of air pollutants, suggested in previous studies[146], as cardiac development doesn't typically begin until week 3 of pregnancy.

The potential for spatial differences were revealed by comparing the findings reported in Chapter 4 which used AQS measurements to assign exposure to the NBDPS population to Chapter 5 which used different exposure metrics to assign exposure to the subpopulation that had downscaler CMAQ data available. The primary difference between these two populations was the exclusion of western states from analyses reported in Chapter 5. The results for ozone between the two AQS-based analyses are consistent, even showing similar temporal variability and elevated odds of PVS in week 3. However, the $PM_{2.5}$ analyses were not consistent, most notably the elevated odds of HLHS are only observed when the western states are included. It is known that the composition of $PM_{2.5}$ varies spatially, as previous research suggests $PM_{2.5}$ in the western states is more likely to be composed of organic carbon and nitrates as opposed to greater sulfate composition in the eastern states. [156] Thus, it is possible the discrepancy in the findings between the two analyses suggests that the relationship between particulates and CHDs varies by the composition of $PM_{2.5}$. The lack of difference in the ozone results makes it unlikely that a difference in model construction or temporal differences in the population (i.e. excluding women from 1999-2001 when downscaler CMAQ estimates became available) are responsible for the discrepancy.

This study also explored the variability in effect by maternal use of folic-acid very early in pregnancy. Although estimates were imprecise, there was evidence of effect measure modification as assessed by likelihood ratio tests and when examining estimates of the odds of TOF and COA with increasing $PM_{2.5}$ exposure stratified by maternal use of folic-acid supplements. This suggests that folic-acid may modify the air pollutant-CHD association, potentially by disrupting DNA methylation processes. The differences in results when incorporating dietary folate intake could be a result of the imprecision of the estimates given the small sample size, or it could suggest the potential for hypermethylation to modify the relationship between air pollutants and CHDs.[164]

In addition to investigating the etiologic relationship between maternal air pollutant exposure and CHDs in offspring, this study also explored how differences in exposure assessment can impact the observed relationships. By comparing the distribution of monitor-based exposure estimates to model-based estimates for the same population, it was observed that, for both $PM_{2.5}$ and ozone, the magnitude of the estimate assigned to an individual, although highly correlated, changes, resulting in a model-based distribution that has thinner tails and a slightly narrower range than the monitor-based distribution. The statistical analyses using the model-based exposure estimates resulted in lower effect estimates for some defects when comparing the highest and lowest deciles of exposure and slightly worse model fit than the models which used monitor-based measurements. Including the population living far from monitors that would typically be excluded from these analyses caused estimates to be even more divergent from the AQS findings. Differences were greater for $PM_{2.5}$ than ozone. Again, this potentially suggests that the relationship between $PM_{2.5}$ exposure and CHDs varies by the composition of the particulate. If different components of PM drive the relationship with CHD development and using model-based estimates allows for the inclusion of populations from a greater spatial area, it is possible that those additional populations are exposed to a particulate with a different composition, mixing effects of the different

components and causing the effect estimate to vary from that obtained when using the monitor based measure for a more narrowly-defined geographic population.

7.2 Strengths and Limitations

This was the first study to explore the relationship between exposure to $PM_{2.5}$ and CHDs and how this relationship may be modified by use of folic-acid early in pregnancy. This was also the first study to explore temporal variability in the associations between criteria air pollutants and CHDs within the window of cardiac development and the first to use PCA to explore how source-factors of pollutants are associated with CHDs in a multipollutant context.

One of the most prominent strengths of this dissertation is the use of the study population from the NBDPS. As the largest, ongoing case-control study of birth defects in the United States, it has a large sample size that allows analysis of systematically classified CHDs within etiologically relevant subgroups as opposed to larger, more heterogeneous aggregations. The study collected a large amount of information on relevant covariates, including nutritional factors, which allowed the exploration of biologically-relevant interactions between air pollution and use of folic-acid, as well as reduce residual confounding that may have affected previous research in this field that depended upon administrative data sources. As a multi-site study, the NBDPS has a large amount of geographic diversity in the study population, which provided a greater exposure gradient than previous single-site studies may have been able to observe. The large geographic extent of the study participants also allowed for a meaningful comparison of two different sources of exposure data and how agreement varies in time and space for each pollutant. Additionally, the hierarchical models we propose using will enable us to investigate multiple windows of exposure simultaneously, rather than having to average over multiple weeks, potentially smoothing over relevant temporal fluctuations. We also had complete residential history for the 3 months prior to conception and throughout pregnancy. This reduced exposure misclassification that can occur when

only residence at delivery is used to assign exposure. Additionally, we averaged over daily maximums to assign exposure, the metric used by the EPA to regulate these pollutants, as opposed to daily averages. This reduced the possibility that we would smoother over potentially important temporal variability in ambient pollutant concentrations.

Despite the large sample size, some defects are so rare that estimates were very imprecise and often could only be studied as part of a larger defect-grouping. Additionally, the subsample that lived within 50 km of all types of air pollutant monitors was small, and may not be generalizable to the larger population. Although this study compared two different sources of data to estimate exposure during pregnancy, they are both proxies for an individual woman's actual exposure to air pollutants. We also don't have any measures of time spent outdoors, time spent at locations other than the primary residence, or physical activity performed outdoors, which would all impact an individual's exposure to the ambient air. It is possible that the attenuated odds we observed at the highest exposure levels for certain pollutants was due to women avoiding the outdoors in highly polluted areas. Additionally, in our models which utilize air monitoring data, we are simply matching women to the closest monitor within 50 km, which is a rather large distance. Our sensitivity analysis restricting to women who lived within 10kilometers of an air monitor found that most estimates were larger in magnitude when compared to the primary analyses, but this subsample was much smaller causing imprecise estimates. It is also possible that the closest monitor is not the most relevant, for example if the monitor is down-wind from the home. The participation rates of the NBDPS are relatively high, but they do vary slightly by racial group. There may be other difference between those who agree to participate and those who do not. This potential selection bias could impact our study results. There is the possibility of recall bias affecting our estimates for the folic-acid subanalysis, as mothers of case births might be more likely to recall their supplement and diet information than a control mother.

7.3 Public Health Impact and Avenues for Further Research

This study further adds to the literature on exposure to air pollutants during pregnancy and CHDs by providing evidence suggesting that these relationships can vary in time, space and by maternal nutrition factors. It also helps advance risk assessment, by identifying potentially susceptible windows during cardiac development when the fetus is more susceptible to environmental insult. These more refined effect estimates can be used when determining the risk to a population that accompanies an increase in ambient air pollutant concentrations. This is facilitated by the use of daily maximums to assign exposure, as that is the metric used by the EPA to regulate pollutants. Exploring the source-factors of the pollutants in a multipollutant context also advances risk assessment, as populations are rarely exposed to one pollutant at a time. Identifying the potential modification of the relationship between $PM_{2.5}$ exposure and CHDs by use of folic-acid could inform mechanistic research aimed at investigating the role of DNA methylation in these associations. Additionally, it points to the possibility of a potential future intervention aimed at increasing supplement use among women of reproductive age, particularly in developing countries which are just now beginning to see increases in air pollutants due to increased industrialization but lack the dietary supplementation programs for folic-acid.

There are multiple avenues for further research. First, as these individual pollutants are highly correlated with each other and other hazardous air pollutants, continuing to explore their relationship with CHDs in a multipollutant context will help to determine which pollutants and which sources may be driving the associations with CHDs. There are multiple statistical techniques to explore multipollutant contexts[165], but it will also require finding populations where multiple types of monitors are co-located or taking advantage of model-based estimates to fill in the gaps of the monitoring networks.

As many of the findings in this study pointed toward the potential for the relationship between $PM_{2.5}$ and CHDs to vary by the composition of $PM_{2.5}$, future studies should explore the speciated components of $PM_{2.5}$ as different, correlated measure of exposure. This can be done using the hierarchical regression methods utilized in the current study. Exploring these components, including how they vary geographically, could further refine some of the effect estimates we observed between particulate exposure and CHDs.

Finally, it is possible that other maternal dietary factors could modify the relationship between pollutant exposure and disrupted fetal development.[166] For example, DNA methylation is only one potential mechanism which could underly the relationship between air pollutant exposure and CHDs. Oxidative stress is another potential mechanism, which has been discussed with respect to other adverse birth outcomes resulting from pollutant exposure such as preterm birth.[13] Exploring whether a mother's antioxidant intake modifies the impact of pollutant exposure could provide evidence supporting a hypothesis of that mechanism.

In conclusion, this study was able to determine that the odds of multiple individual CHDs are associated with greater pollutant exposure, in both single-pollutant and source-factor models. There is some evidence that these relationships vary within the window of cardiac development, suggesting potential windows of increased susceptibility. These estimates can be used to enhance risk assessment and determine how changes in ambient air pollutant concentrations can impact human health. Future research should focus on further exploring the simultaneous effects of multiple pollutants, refining exposure assessment to focus on individual components of $PM_{2.5}$ to improve effect estimation and continuing to explore the potential for maternal dietary factors to modify the relationship between pollutant exposure and CHDs in offspring.

APPENDIX 1

LIST OF CONGENITAL HEART DEFECT CLASSIFICATIONS IN NATIONAL BIRTH DEFECTS PREVENTION STUDY

Conotruncal

Truncus Truncus arteriosus with or without atrial septal defect

IAA, B Interrupted aortic arch type B, with or without atrial septal defect

IAA, nos Interrupted aortic arch, type not specified but presumed to be type B, with or without atrial septal defect

d-TGA-IVS d-transposition of the great arteries with intact ventricular septum, with or without atrial septal defect

d-TGA-IVS 1 LVOTO (PS) d-transposition of the great arteries with intact ventricular septum, plus pulmonary stenosis or other left ventricular outflow tract obstruction

d-TGA-IVS 1 RVOTO (AS, COA) d-transposition of the great arteries with intact ventricular septum, plus aortic stenosis or coarctation or other right ventricular outflow tract obstruction

TGA nos d-transposition of the great arteries, not otherwise specified, but presumed to be with intact ventricular septum, with or without atrial septal defect

TGA os d-transposition of the great arteries, otherwise specified. Usually with other defects

d-TGA-VSD d-transposition of the great arteries with noninlet ventricular septal defect, with or without atrial septal defect

d-TGA-VSD 1 LVOTO (PS) d-transposition of the great arteries with noninlet ventricular septal defect, plus pulmonary stenosis or other left ventricular outflow tract obstruction

d-TGA-VSD 1 RVOTO (AS, COA) d-transposition of the great arteries with noninlet ventricular septal defect, plus aortic stenosis or coarctation or other right ventricular outflow tract obstruction

TOF Tetralogy of Fallot with or without atrial septal defect; NOT pulmonary atresia with ventricular septal defect

TOF, absent pulmonary valve Tetralogy of Fallot with absent pulmonary valve

PA-VSD (TOF anatomy) Pulmonary atresia with ventricular septal defect, tetralogy of Fallot variant, with or without atrial septal defect

DORV-TOF type Double outlet right ventricle (tetralogy of Fallot type anatomy) with normally positioned great arteries, with or without atrial septal defect

DORV-TGA type Double outlet right ventricle with malposed great vessels or d-transposed great artery type, with or without atrial septal defect

DORV, os Double outlet right ventricle, other specified type (NOT tetralogy type or malposed great arteries), with or without atrial septal defect

DORV, nos Double outlet right ventricle, type not otherwise specified, with or without atrial septal defect

VSD conov Ventricular septal defect reported as conoventricular, malalignment-type, or subaortic (not otherwise specified)

IAA, B 1 Truncus Interrupted aortic arch, Type B plus truncus arteriosus, with or without atrial septal defect

Atrioventricular Septal Defect (AVSD)

AVSD, unspecified Unspecified type of atrioventricular septal defect, with or without other atrial or ventricular septal defects

ASD-1 Primum type atrial septal defect (isolated atrial component of atrioventricular septal defect)

VSD, inlet-type Inlet type ventricular septal defect (isolated ventricular component of atrioventricular septal defect)

AVSD, complete Complete atrioventricular septal defect, with both atrial and ventricular septal defects

AVSD, transitional Transitional type atrioventricular defect (endocardial cushion defect, otherwise specified)

AVSD 1 LVOTO Atrioventricular septal defect plus left ventricular outflow tract obstruction (includes unbalanced defects with left ventricular dominance)

AVSD 1 RVOTO Atrioventricular septal defect plus right ventricular outflow tract obstruction (includes

unbalanced defects with right ventricular dominance)

Anomalous-Pulmonary Venous Return (APVR)

TAPVR Total anomalous pulmonary venous return

TAPVR 1 RVOTO Total anomalous pulmonary venous return, plus pulmonary stenosis

TAPVR 1 LVOTO Total anomalous pulmonary venous return, plus aortic stenosis or coarctation

PAPVR Partial anomalous pulmonary venous return

PAPVR 1 RVOTO Partial anomalous pulmonary venous return, plus pulmonary stenosis

PAPVR 1 LVOTO Partial anomalous pulmonary venous return, plus aortic stenosis or coarctation

Left Ventricular Outflow Tract Obstruction (LVOTO)

HLHS, IVS Hypoplastic left heart syndrome with intact ventricular septum, with or without atrial septal defect

HLHS 1 VSD Hypoplastic left heart syndrome with ventricular septal defect, with or without atrial septal defect

HLHS 1 APVR Hypoplastic left heart syndrome plus total or partial anomalous pulmonary venous return

IAA, A Interrupted aortic arch type A, with or without atrial septal defect

COA-IVS Coarctation of aorta with intact ventricular septum, with or without atrial septal defect

AS Aortic stenosis with or without atrial septal defect

AS 1 COA Aortic stenosis with or without atrial septal defect, plus coarctation

Right Ventricular Outflow Tract Obstruction (RVOTO)

PVS Pulmonary valve stenosis

PVS, nos Pulmonary stenosis not otherwise specified but presumed to be valvar

Tricuspid atresia, IVS Tricuspid atresia with intact ventricular septum, with or without atrial septal defect

Tricuspid atresia 1 VSD Tricuspid atresia with ventricular septal defect, with or without atrial septal defect

Ebstein Ebstein malformation or anomaly

PA-IVS Pulmonary atresia with intact ventricular septum, with or without atrial septal defect

PA, nos Pulmonary atresia not otherwise specified but presumed to be with intact ventricular septum

PA-VSD (not TOF anatomy) Pulmonary atresia with ventricular septal defect, not tetralogy of Fallot variant, with or without atrial septal defect

PA-VSD, nos Pulmonary atresia with ventricular septal defect, not stated if tetralogy variant

PA-IVS 1 Ebstein Pulmonary atresia with intact ventricular septum, plus Ebstein's malformation

Tricuspid atresia 1 PA-IVS Pulmonary atresia with intact ventricular septum, plus tricuspid atresia

Septal Defects

VSD pm Perimembranous ventricular septal defect

VSD musc Muscular ventricular septal defect

VSD nos Ventricular septal defect, type not specified

VSD os Ventricular septal defect, otherwise specified

ASD2 Secundum atrial septal defect

ASD, nos Atrial septal defect, not otherwise specified, but presumed secundum type

ASD, os Other specified type atrial septal defect (i.e., sinus venosus, coronary sinus)

VSDs multiple (pm, musc, or nos) Combination of perimembranous, muscular, or not otherwise specified types of ventricular septal defects

VSD (non-inlet) 1 ASD2/ASD nos Any non-inlet ventricular septal defect plus atrial septal defect

Heterotaxy

Heterotaxy or S.I.totalis: simple CVM Laterality defects (heterotaxy, situs inversus totalis) with simple cardiovascular malformation

Heterotaxy or S.I.totalis: complex CVM Laterality defects (heterotaxy, situs inversus totalis) with complex cardiovascular malformation

Heterotaxy or S.I.totalis: no CVM Laterality defects (heterotaxy, situs inversus totalis) with no cardiac malformations

Single Ventricle/Complex

Multiple, complex heart anomaly In general, three or more defects (in addition to simple atrial septal

defect, ventricular septal defect)
SV Single (univentricular) heart, excludes functional single ventricle such as HLHS, DORV with malaligned AVSD. Typically associated with several other defects
SV, DILV, nos Single ventricle, double-inlet left ventricle type with great artery position not specified
SV, DILV, l-malposition Single ventricle, double-inlet left ventricle type with l-malposed great arteries
SV, DILV, d-malposition Single ventricle, double-inlet left ventricle type with d-malposed great arteries
SV, DIRV Single ventricle, double-inlet right ventricle
SV, os Single ventricle, other specified type
SV, nos Single ventricle, not otherwise specified type
L-TGA L-transposition of the great arteries with or without atrial or ventricular septal defects
L-TGA 1 RVOTO (AS, COA) L-transposition of the great arteries plus aortic stenosis or coarctation (morphological right ventricular outflow obstruction)
L-TGA 1 LVOTO (PS) L-transposition of the great arteries plus pulmonic stenosis (morphological left ventricular outflow obstruction)

ASSOCIATIONS

Conotruncal + AVSD
d-TGA-IVS + AVSD d-Transposition of the great arteries with intact ventricular septum, plus atrioventricular septal defect
d-TGA-VSD + AVSD d-Transposition of the great arteries with noninlet of ventricular septal defect plus atrioventricular septal defect
TOF + AVSD Tetralogy of Fallot plus atrioventricular septal defect
PA-VSD (TOF anatomy) + AVSD Pulmonary atresia with ventricular septal defect, tetralogy of Fallot variant, plus atrioventricular septal defect
APVR + AVSD
TAVPR + AVSD Total anomalous pulmonary venous return, plus atrioventricular septal defect
PAVPR + AVSD Partial anomalous pulmonary venous return, plus atrioventricular septal defect
Septal + LVOTO
VSD (non-inlet) + COA Coarctation of aorta with noninlet ventricular septal defect, with or without atrial septal defect
VSD (non-inlet) + ASD2/nos + AS Any non-inlet ventricular septal defect plus atrial septal defect plus aortic valve stenosis
VSD (non-inlet) + ASD2/nos + COA Any non-inlet ventricular septal defect plus atrial septal defect plus coarctation
Septal + RVOTO
ASD + PVS Pulmonary valve stenosis plus atrial septal defect
VSD (non-inlet) + PVS Pulmonic valve stenosis plus noninlet ventricular septal defect, with or without atrial septal defect
VSD (non-inlet) + ASD2/nos + PVS Any non-inlet ventricular septal defect plus atrial septal defect plus pulmonary valve stenosis
Other Associations Two (occasionally three) major defects not specified elsewhere

APPENDIX 2

SUPPLEMENTARY TABLES FOR CHAPTER 4

Table A2.1: Odds Ratios and 95% Confidence Intervals between CHDs and 7-week average exposure to air pollutants

	Carbon Monoxide, ppm			
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	< 0.58	0.58-1.16	1.16-2.13	>2.13
LVOTO[a]	1	1.11 (0.8,1.53)	1.11 (0.8,1.55)	0.95 (0.62,1.45)
Aortic Stenosis[b]	1	0.93 (0.49,1.79)	0.94 (0.49,1.81)	0.76 (0.32,1.79)
Coarctation of the Aorta[b]	1	1.13 (0.7,1.82)	0.93 (0.57,1.52)	0.98 (0.53,1.82)
Hypoplastic Left Heart Syndrome[b]	1	1.22 (0.71,2.12)	1.5 (0.87,2.6)	1.07 (0.53,2.14)
CONOTRUNCALS[a]	1	1.21 (0.9,1.64)	1.28 (0.94,1.73)	1.22 (0.84,1.79)
d-TGA[b]	1	1.34 (0.81,2.22)	1.34 (0.8,2.23)	1.15 (0.61,2.19)
Tetralogy of Fallot[b]	1	1.22 (0.81,1.83)	1.35 (0.9,2.03)	1.29 (0.78,2.14)
Other Conotruncals[b]	1	0.96 (0.48,1.95)	0.92 (0.45,1.88)	1.08 (0.46,2.56)
Common Truncus[c]	1	1.03 (0.35,3.99)	0.7 (0.22,2.82)	0.33 (0.03,2.06)
DORV-TGA and DORV-Other[c]	1	1.03 (0.3,5.35)	0.88 (0.25,4.6)	1.34 (0.29,7.82)
IAA TypeB/NOS[c]	1	0.34 (0.07,2.03)	0.17 (0.02,1.27)	1.72 (0.32,10.56)
VSD-Conoventricular[c]	1	0.8 (0.26,3.18)	1.33 (0.45,5.15)	1.32 (0.28,6.33)
APVR[a]	1	0.46 (0.25,0.84)	0.48 (0.26,0.88)	0.59 (0.27,1.28)
TAPVR[b]	1	0.53 (0.28,1)	0.43 (0.22,0.84)	0.67 (0.3,1.5)
AVSD[a]	1	0.95 (0.35,2.56)	1.11 (0.41,2.98)	0.75 (0.2,2.83)
RVOTO[a]	1	0.94 (0.67,1.33)	0.97 (0.69,1.37)	0.89 (0.57,1.39)
Pulmonary/Tricuspid Atresia[b]	1	0.77 (0.4,1.5)	0.75 (0.38,1.47)	0.72 (0.3,1.73)
Pulmonary Atresia[c]	1	0.68 (0.33,1.53)	0.55 (0.26,1.27)	0.68 (0.24,1.87)
Tricuspid Atresia[c]	1	0.81 (0.26,3.25)	1.12 (0.38,4.4)	0.79 (0.13,4.11)
Pulmonary Valve Stenosis[b]	1	0.92 (0.61,1.37)	1 (0.67,1.49)	0.92 (0.56,1.53)
Ebstein's Anomaly[c]	1	8.46 (1.15,1081)	5.25 (0.67,678)	4.4 (0.35,612)
SEPTALS[a]	1	1.01 (0.78,1.33)	1.13 (0.86,1.47)	1.3 (0.95,1.8)
VSD-perimembranous[b]	1	0.87 (0.62,1.23)	1.04 (0.74,1.47)	1.01 (0.66,1.56)
VSD-muscular[c]	1	2.13 (0.22,272)	2.37 (0.27,297)	2.78 (0.3,354)
ASD-all[b]	1	1.08 (0.74,1.59)	0.99 (0.67,1.46)	1.13 (0.71,1.8)

[a]Estimates results from a hierarchical regression model. First stage was polytomous logistic model with defect groupings and adjusted for maternal race, maternal age, maternal educational attainment, maternal household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio. Second stage was a linear model with indicator variables for defect grouping and level of exposure.

[b]Estimates result from a hierarchical regression model, same as above but used individual defects as outcomes.

[c]Estimates result from model utilizing Firth's penalized maximum likelihood regression to deal with quasi-separation of points due to small sample size in certain cells. Model adjusted for same variables as above.

Table A2.1 (cont.)

	Nitrogen Dioxide, ppb			
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<18.9	18.9-33.3	33.3-45.5	>45.5
LVOTO[a]	1	1.44 (1,2.08)	1.49 (1.03,2.15)	1.53 (0.98,2.39)
Aortic Stenosis[b]	1	2.22 (0.94,5.26)	1.66 (0.69,3.99)	2.22 (0.83,5.97)
Coarctation of the Aorta[b]	1	1.74 (0.91,3.32)	2.34 (1.24,4.42)	2.5 (1.21,5.18)
Hypoplastic Left Heart Syndrome[b]	1	1.07 (0.65,1.78)	1.04 (0.62,1.72)	0.85 (0.43,1.68)
CONOTRUNCALS[a]	1	1.36 (0.99,1.88)	1.32 (0.96,1.82)	1.42 (0.96,2.11)
d-TGA[b]	1	1.18 (0.71,1.95)	1.24 (0.75,2.04)	1.29 (0.69,2.38)
Tetralogy of Fallot[b]	1	1.51 (0.98,2.34)	1.27 (0.82,1.97)	1.51 (0.89,2.57)
Other Conotruncals[b]	1	1.33 (0.55,3.22)	1.81 (0.76,4.31)	1.49 (0.52,4.24)
Common Truncus[c]	1	5.6 (0.7,724.31)	9.65 (1.29,1233.7)	3.46 (0.18,507.59)
DORV-TGA and DORV-Other[c]	1	1.1 (0.24,10.38)	1.57 (0.37,14.56)	1.25 (0.16,13.91)
IAA TypeB/NOS[c]	1	0.68 (0.12,6.89)	0.21 (0.02,2.61)	1.36 (0.16,15.75)
VSD-Conoventricular[c]	1	0.6 (0.21,2.05)	0.76 (0.28,2.54)	0.87 (0.19,3.65)
APVR[a]	1	0.54 (0.28,1.03)	0.57 (0.3,1.09)	0.89 (0.41,1.94)
TAPVR[b]	1	0.51 (0.26,1.01)	0.54 (0.28,1.06)	0.92 (0.42,2.03)
AVSD[a]	1	0.63 (0.27,1.47)	0.66 (0.29,1.54)	0.64 (0.2,1.98)
RVOTO[a]	1	1.32 (0.88,1.97)	1.5 (1.01,2.24)	2.22 (1.4,3.52)
Pulmonary/Tricuspid Atresia[b]	1	2.45 (0.86,6.95)	2.02 (0.71,5.79)	2.33 (0.71,7.68)
Pulmonary Atresia[c]	1	1.76 (0.64,6.64)	1.58 (0.57,5.96)	2.1 (0.59,8.97)
Tricuspid Atresia[c]	1	2.81 (0.68,25.85)	1.88 (0.43,17.67)	2.07 (0.27,22.91)
Pulmonary Valve Stenosis[b]	1	1.02 (0.66,1.59)	1.3 (0.85,2)	2.03 (1.23,3.33)
Ebstein's Anomaly[c]	1	6.17 (0.79,795)	8.39 (1.12,1075)	11.88 (1.25,1582
SEPTALS[a]	1	1.24 (0.94,1.64)	1.23 (0.94,1.63)	1.44 (1.02,2.03)
VSD-perimembranous[b]	1	1.13 (0.78,1.64)	1.18 (0.82,1.71)	1.47 (0.94,2.3)
VSD-muscular[c]	1	0.75 (0.17,3.7)	0.56 (0.13,2.84)	0.46 (0.08,2.85)
ASD-all[b]	1	1.29 (0.87,1.91)	1.25 (0.84,1.86)	1.23 (0.74,2.04)

Table A2.1 (cont.)

	Ozone, ppb			
	<25th percentile (Referent)	25th percentile to median	median to 75th percentile	>75th percentile
Pollutant concentrations	<32.2	32.2-42.9	42.9-51.8	>51.8
LVOTO[a]	1	0.96 (0.74,1.25)	0.95 (0.73,1.23)	0.94 (0.73,1.22)
Aortic Stenosis[b]	1	1.21 (0.7,2.11)	0.95 (0.53,1.67)	1.07 (0.61,1.87)
Coarctation of the Aorta[b]	1	0.74 (0.49,1.11)	0.94 (0.64,1.38)	0.97 (0.67,1.42)
Hypoplastic Left Heart Syndrome[b]	1	1.07 (0.72,1.58)	0.95 (0.64,1.41)	0.86 (0.58,1.29)
CONOTRUNCALS[a]	1	1.16 (0.92,1.45)	0.97 (0.76,1.22)	1 (0.79,1.26)
d-TGA[b]	1	0.82 (0.56,1.21)	1.08 (0.76,1.53)	0.81 (0.56,1.19)
Tetralogy of Fallot[b]	1	1.34 (0.99,1.81)	0.86 (0.62,1.19)	1.11 (0.82,1.51)
Other Conotruncals[b]	1	1.44 (0.79,2.62)	1.07 (0.56,2.02)	1.15 (0.62,2.13)
Common Truncus[c]	1	1.73 (0.48,7.32)	1.64(0.43,7.12)	2.40 (0.70, 9.98)
DORV-TGA and DORV-Other[c]	1	1.26 (0.41,4.09)	1.34 (0.44,4.32)	0.97 (0.31,3.23)
IAA TypeB/NOS[c]	1	1.10 (0.23,5.25)	0.15 (0.01,1.58)	0.85 (0.14,4.40)
VSD-Conoventricular[c]	1	1.53 (0.61,3.95)	0.98 (0.35,2.67)	0.89 (0.32,2.42)
APVR[a]	1	0.95 (0.53,1.71)	1.11 (0.63,1.94)	0.95 (0.54,1.7)
TAPVR[b]	1	1.22 (0.65,2.27)	1.35 (0.74,2.46)	1.09 (0.59,2.04)
AVSD[a]	1	1.22 (0.53,2.81)	1.18 (0.51,2.72)	1.24 (0.54,2.85)
RVOTO[a]	1	1.21 (0.91,1.61)	1.07 (0.8,1.44)	1.26 (0.95,1.67)
Pulmonary/Tricuspid Atresia[b]	1	1.25 (0.67,2.32)	0.92 (0.48,1.79)	1.31 (0.72,2.39)
Pulmonary Atresia[c]	1	1.23 (0.55,2.78)	1.06 (0.46,2.45)	1.87 (0.91,4.01)
Tricuspid Atresia[c]	1	1.27 (0.49,3.34)	0.71 (0.22,2.06)	0.59 (0.19,1.72)
Pulmonary Valve Stenosis[b]	1	1.27 (0.91,1.78)	1.17 (0.84,1.64)	1.27 (0.91,1.77)
Ebstein's Anomaly[c]	1	0.74 (0.29,1.85)	0.68 (0.25,1.74)	0.88 (0.34,2.22)
SEPTALS[a]	1	1.03 (0.85,1.25)	0.94 (0.77,1.14)	0.89 (0.72,1.09)
VSD-perimembranous[b]	1	0.96 (0.73,1.26)	0.93 (0.7,1.23)	1.06 (0.81,1.39)
VSD-muscular[c]	1	0.91 (0.36,2.19)	1.28 (0.45,3.41)	1.08 (0.47,2.42)
ASD-all[b]	1	1.25 (0.97,1.61)	1.1 (0.84,1.44)	0.85 (0.63,1.14)

Table A2.1 (cont.)

	PM10, micrometers/cubic meter			
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<14.9	14.9-24.2	24.2-40.6	>40.6
LVOTO[a]	1	1.1 (0.79,1.55)	1.37 (0.99,1.91)	1.12 (0.72,1.72)
Aortic Stenosis[b]	1	1.24 (0.62,2.46)	1.51 (0.76,2.98)	0.92 (0.36,2.32)
Coarctation of the Aorta[b]	1	1.71 (0.95,3.09)	1.77 (0.98,3.2)	1.68 (0.82,3.45)
Hypoplastic Left Heart Syndrome[b]	1	0.79 (0.48,1.31)	1.24 (0.76,2.01)	0.98 (0.52,1.87)
CONOTRUNCALS[a]	1	1.21 (0.89,1.64)	1.31 (0.96,1.78)	1.44 (0.99,2.1)
d-TGA[b]	1	1.1 (0.67,1.81)	1.16 (0.71,1.92)	1.45 (0.8,2.64)
Tetralogy of Fallot[b]	1	1.14 (0.76,1.7)	1.35 (0.91,2.02)	1.3 (0.79,2.16)
Other Conotruncals[b]	1	2.12 (0.84,5.39)	1.68 (0.65,4.34)	2.07 (0.71,6.02)
Common Truncus[c]	1	2.79 (0.68,25.68)	2.34 (0.55,21.79)	1.75 (0.22,19.95)
DORV-TGA and DORV-Other[c]	1	1.21 (0.36,6.2)	0.94 (0.27,4.93)	1.41 (0.29,8.49)
IAA TypeB/NOS[c]	1	2.58 (0.27,341.64)	1.01 (0.05,147.07)	8.75 (0.6,1249.69)
VSD-Conoventricular[c]	1	1.29 (0.38,6.6)	1.12 (0.32,5.82)	1.25 (0.25,7.71)
APVR[a]	1	1.49 (0.66,3.33)	1.34 (0.59,3.03)	1.44 (0.55,3.79)
TAPVR[b]	1	1.28 (0.57,2.89)	1.12 (0.49,2.55)	1.36 (0.52,3.6)
AVSD[a]	1	6.25 (0.84,46.26)	6.7 (0.9,49.66)	4.8 (0.53,43.41)
RVOTO[a]	1	1 (0.71,1.41)	1.18 (0.84,1.66)	0.98 (0.62,1.55)
Pulmonary/Tricuspid Atresia[b]	1	0.75 (0.38,1.49)	0.91 (0.46,1.8)	0.43 (0.16,1.21)
Pulmonary Atresia[c]	1	0.68 (0.32,1.59)	0.82 (0.39,1.9)	0.48 (0.13,1.51)
Tricuspid Atresia[c]	1	0.84 (0.28,3.32)	1.04 (0.35,4.02)	0.32 (0.03,2.07)
Pulmonary Valve Stenosis[b]	1	1.13 (0.75,1.7)	1.31 (0.87,1.98)	1.17 (0.68,2)
Ebstein's Anomaly[c]	1	0.6 (0.21,2.01)	0.73 (0.26,2.43)	1.26 (0.31,5.07)
SEPTALS[a]	1	1.23 (0.97,1.57)	1.21 (0.95,1.55)	0.91 (0.65,1.28)
VSD-perimembranous[b]	1	1.42 (0.98,2.05)	1.42 (0.98,2.05)	1.18 (0.73,1.92)
VSD-muscular[c]	1	1.18 (0.52,2.88)	1.68 (0.73,4.13)	0.69 (0.12,3.06)
ASD-all[b]	1	1.14 (0.83,1.57)	1.09 (0.79,1.51)	0.81 (0.51,1.28)

Table A2.1 (cont.)

	PM2.5 micrometers/cubic meter			
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<7.77	7.77-12.1	12.1-19.7	>19.7
LVOTO[a]	1	1.03 (0.76,1.39)	0.85 (0.62,1.15)	1.25 (0.86,1.82)
Aortic Stenosis[b]	1	0.9 (0.53,1.51)	0.59 (0.33,1.03)	0.96 (0.47,1.94)
Coarctation of the Aorta[b]	1	0.88 (0.56,1.37)	0.85 (0.54,1.35)	1.06 (0.6,1.87)
Hypoplastic Left Heart Syndrome[b]	1	1.59 (0.91,2.79)	1.25 (0.7,2.21)	2.04 (1.07,3.89)
CONOTRUNCALS[a]	1	0.97 (0.73,1.29)	0.98 (0.73,1.31)	1.2 (0.84,1.72)
d-TGA[b]	1	0.96 (0.6,1.53)	1.03 (0.65,1.65)	1.07 (0.59,1.93)
Tetralogy of Fallot[b]	1	0.97 (0.66,1.44)	1.02 (0.69,1.51)	1.32 (0.83,2.12)
Other Conotruncals[b]	1	1.02 (0.5,2.05)	0.75 (0.36,1.57)	1.05 (0.45,2.49)
Common Truncus[c]	1	1.2 (0.35,6.16)	0.97 (0.27,5.13)	2.54 (0.58,14.64)
DORV-TGA and DORV-Other[c]	1	0.54 (0.2,1.64)	0.4 (0.13,1.31)	0.22 (0.02,1.22)
IAA TypeB/NOS[c]	1	0.56 (0.09,5.69)	0.32 (0.04,3.53)	2.35 (0.36,25.05)
VSD-Conoventricular[c]	1	1.52 (0.47,7.7)	1.03 (0.3,5.35)	0.97 (0.18,6)
APVR[a]	1	0.91 (0.48,1.71)	0.68 (0.35,1.32)	1.1 (0.5,2.44)
TAPVR[b]	1	0.95 (0.48,1.87)	0.68 (0.33,1.39)	1.04 (0.44,2.44)
AVSD[a]	1	2.36 (0.71,7.85)	2.27 (0.68,7.59)	2.67 (0.67,10.53)
RVOTO[a]	1	0.92 (0.67,1.27)	0.96 (0.69,1.32)	0.93 (0.6,1.42)
Pulmonary/Tricuspid Atresia[b]	1	0.89 (0.46,1.7)	0.62 (0.31,1.23)	0.74 (0.32,1.73)
Pulmonary Atresia[c]	1	0.68 (0.33,1.52)	0.61 (0.29,1.4)	0.69 (0.25,1.86)
Tricuspid Atresia[c]	1	1.37 (0.49,5.21)	0.53 (0.15,2.27)	0.9 (0.18,4.45)
Pulmonary Valve Stenosis[b]	1	0.93 (0.64,1.36)	1.09 (0.74,1.58)	1.05 (0.64,1.72)
Ebstein's Anomaly[c]	1	0.8 (0.32,2.36)	0.7 (0.27,2.13)	0.45 (0.04,2.34)
SEPTALS[a]	1	0.89 (0.72,1.1)	0.66 (0.53,0.83)	0.62 (0.45,0.85)
VSD-perimembranous[b]	1	1.17 (0.83,1.64)	1.06 (0.75,1.5)	0.85 (0.54,1.35)
VSD-muscular[c]	1	n/a	n/a	n/a
ASD-all[b]	1	0.8 (0.63,1.03)	0.5 (0.38,0.65)	0.54 (0.35,0.81)

Table A2.1 (cont.)

	Sulfur Dioxide, ppb			
	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<3.45	3.45-9.70	9.70-19.9	>19.9
LVOTO[a]	1	1.32 (0.88,1.98)	1.49 (0.99,2.24)	1.07 (0.64,1.79)
Aortic Stenosis[b]	1	0.93 (0.44,1.97)	0.84 (0.39,1.83)	0.58 (0.2,1.65)
Coarctation of the Aorta[b]	1	1.21 (0.65,2.24)	1.74 (0.95,3.2)	1.62 (0.79,3.3)
Hypoplastic Left Heart Syndrome[b]	1	1.98 (0.97,4.04)	1.84 (0.89,3.78)	0.96 (0.37,2.47)
CONOTRUNCALS[a]	1	1.12 (0.78,1.6)	1.35 (0.95,1.92)	1.22 (0.79,1.88)
d-TGA[b]	1	1.32 (0.72,2.43)	1.61 (0.88,2.96)	1.46 (0.71,2.98)
Tetralogy of Fallot[b]	1	1.08 (0.67,1.73)	1.2 (0.74,1.92)	1.17 (0.66,2.07)
Other Conotruncals[b]	1	0.9 (0.37,2.16)	1.5 (0.64,3.53)	0.91 (0.3,2.79)
Common Truncus[c]	1	0.74 (0.21,3.17)	1.19 (0.35,5.14)	1.58 (0.31,8.16)
DORV-TGA and DORV-Other[c]	1	0.79 (0.18,4.66)	1.71 (0.42,10.11)	0.41 (0,5.48)
IAA TypeB/NOS[c]	1	n/a	n/a	n/a
VSD-Conoventricular[c]	1	0.82 (0.22,4.4)	1.27 (0.35,6.91)	0.5 (0.04,3.88)
APVR[a]	1	1.33 (0.54,3.3)	1.65 (0.67,4.09)	1.02 (0.32,3.28)
TAPVR[b]	1	1.03 (0.41,2.61)	1.46 (0.58,3.62)	0.93 (0.29,2.99)
AVSD[a]	1	0.82 (0.28,3.2)	1.1 (0.39,4.23)	1.54 (0.45,6.46)
RVOTO[a]	1	1.81 (1.15,2.83)	1.65 (1.04,2.6)	1.24 (0.7,2.18)
Pulmonary/Tricuspid Atresia[b]	1	1.13 (0.49,2.61)	1.17 (0.5,2.73)	0.76 (0.25,2.31)
Pulmonary Atresia[c]	1	1.22 (0.47,3.94)	1.31 (0.5,4.23)	0.74 (0.16,3.09)
Tricuspid Atresia[c]	1	0.81 (0.25,3.34)	0.66 (0.19,2.82)	0.78 (0.13,4.17)
Pulmonary Valve Stenosis[b]	1	2.34 (1.33,4.14)	2.06 (1.16,3.67)	1.48 (0.74,2.97)
Ebstein's Anomaly[c]	1	0.75 (0.24,3.01)	0.76 (0.23,3.15)	1.45 (0.34,6.72)
SEPTALS[a]	1	1.06 (0.82,1.38)	1.09 (0.84,1.43)	1.12 (0.8,1.58)
VSD-perimembranous[b]	1	1.26 (0.84,1.89)	1.36 (0.9,2.05)	1.48 (0.91,2.42)
VSD-muscular[c]	1	n/a	n/a	n/a
ASD-all[b]	1	0.93 (0.68,1.28)	0.83 (0.59,1.16)	0.67 (0.41,1.09)

Table A2.2: Adjusted Odds Ratios and 95% Confidence Intervals between Cardiac Birth Defects and 7-week average exposure to nitrogen dioxide andPM10, by distance to major road[a]

	Living within 50 meters of a major roadway			
	Nitrogen Dioxide, ppb			
	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<18.9	18.9-33.3	33.3-45.5	>45.5
LVOTO	1	1.01 (0.45,2.26)	1.31 (0.6,2.85)	2.11 (0.82,5.45)
Aortic Stenosis	1	3.29 (0.4,26.86)	1.42 (0.16,13.01)	7.52 (0.81,69.88)
Coarctation of the Aorta	1	0.23 (0.05,0.98)	1.22 (0.44,3.4)	1.69 (0.47,6.16)
Hypoplastic Left Heart Syndrome	1	1.6 (0.44,5.78)	1.41 (0.39,5.14)	1.12 (0.18,6.97)
CONOTRUNCALS	1	3.17 (1.21,8.26)	3.8 (1.47,9.8)	7.12 (2.53,19.99)
d-TGA	1	2.68 (0.59,12.04)	3.54 (0.81,15.57)	6.23 (1.24,31.19)
Tetralogy of Fallot	1	4.66 (1.08,20.11)	4.53 (1.05,19.47)	11.05 (2.39,51)
Other Conotruncals	1	1.34 (0.15,12.2)	3.06 (0.38,24.63)	1.49 (0.09,24.47)
APVR	1	1.01 (0.26,3.92)	1.18 (0.31,4.42)	1.1 (0.18,6.85)
RVOTO	1	1.56 (0.62,3.95)	1.14 (0.44,2.97)	3.55 (1.25,10.06)
Pulmonary/Tricuspid Atresia	1	1.4 (0.28,6.92)	0.96 (0.18,5.1)	1.83 (0.25,13.43)
Pulmonary Valve Stenosis	1	1.48 (0.48,4.58)	1.09 (0.34,3.47)	3.11 (0.86,11.18)
SEPTALS	1	1.74 (0.93,3.26)	1.41 (0.74,2.66)	1.8 (0.8,4.03)
VSD-perimembranous	1	2.68 (1.02,7.05)	1.98 (0.74,5.27)	2.87 (0.91,9.06)
ASD-all	1	1.07 (0.48,2.38)	0.96 (0.43,2.17)	0.97 (0.31,3.05)
	PM10, micrometers/cubic meter			
	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<14.9	14.9-24.2	24.2-40.6	>40.6
LVOTO	1	1.21 (0.56,2.6)	1.33 (0.62,2.86)	2.2 (0.85,5.71)
Aortic Stenosis	1	1.49 (0.32,6.98)	1.15 (0.23,5.69)	3.9 (0.68,22.49)
Coarctation of the Aorta	1	0.56 (0.16,1.9)	1.34 (0.44,4.09)	1.76 (0.42,7.42)
Hypoplastic Left Heart Syndrome	1	1.89 (0.55,6.5)	1.43 (0.4,5.11)	1.76 (0.34,9.13)
CONOTRUNCALS	1	1.19 (0.59,2.4)	1.55 (0.78,3.09)	2.63 (1.14,6.06)
d-TGA	1	0.97 (0.31,3.06)	1.46 (0.48,4.44)	2.04 (0.52,8)
Tetralogy of Fallot	1	1.14 (0.45,2.89)	1.61 (0.65,4)	2.86 (0.98,8.42)
Other Conotruncals	1	2.34 (0.29,18.99)	1.54 (0.18,13.38)	3.13 (0.27,35.94)
APVR	1	b	b	b
RVOTO	1	1.74 (0.66,4.63)	1.99 (0.75,5.28)	3.59 (1.14,11.38)
Pulmonary/Tricuspid Atresia	1	2.72 (0.34,21.81)	2.49 (0.31,20.25)	1.49 (0.09,24.62)
Pulmonary Valve Stenosis	1	1.29 (0.43,3.93)	1.71 (0.57,5.12)	3.25 (0.87,12.15)
SEPTALS	1	1.51 (0.86,2.64)	1.43 (0.81,2.52)	1.36 (0.6,3.1)
VSD-perimembranous	1	1.68 (0.73,3.89)	1.59 (0.68,3.7)	1.77 (0.56,5.57)
ASD-all	1	1.37 (0.66,2.83)	1.24 (0.59,2.61)	0.96 (0.3,3.06)

[a]Estimates result from maximum-likelihood, polytomous logistic model includes an interaction term between exposure and distance to roadway and adjusted for maternal race, maternal age, maternal educational attainment, maternal household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio.

[b] Could not be estimated due to small sample size

Table A2.2 (cont.)

		Living beyond 50 meters of a major roadway		
		Nitrogen Dioxide, ppb		
	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<18.9	18.9-33.3	33.3-45.5	>45.5
LVOTO	1	1.54 (1.01,2.33)	1.53 (1.01,2.33)	1.41 (0.85,2.34)
Aortic Stenosis	1	2.03 (0.79,5.25)	1.63 (0.63,4.25)	1.57 (0.5,4.93)
Coarctation of the Aorta	1	2.79 (1.19,6.52)	3.28 (1.41,7.61)	3.32 (1.3,8.43)
Hypoplastic Left Heart Syndrome	1	0.97 (0.56,1.7)	0.95 (0.55,1.66)	0.76 (0.36,1.6)
CONOTRUNCALS	1	1.16 (0.82,1.64)	1.07 (0.76,1.52)	0.96 (0.62,1.5)
d-TGA	1	1 (0.58,1.71)	1 (0.58,1.71)	0.88 (0.43,1.77)
Tetralogy of Fallot	1	1.26 (0.79,1.99)	1.01 (0.63,1.61)	0.92 (0.5,1.69)
Other Conotruncals	1	1.28 (0.49,3.38)	1.6 (0.62,4.17)	1.4 (0.43,4.5)
APVR	1	0.45 (0.21,0.95)	0.45 (0.21,0.95)	0.88 (0.36,2.14)
RVOTO	1	1.25 (0.8,1.95)	1.53 (0.99,2.38)	1.98 (1.19,3.31)
Pulmonary/Tricuspid Atresia	1	3.6 (0.85,15.26)	3.04 (0.71,12.97)	3.07 (0.61,15.48)
Pulmonary Valve Stenosis	1	0.93 (0.58,1.5)	1.28 (0.8,2.04)	1.85 (1.08,3.18)
SEPTALS	1	1.14 (0.84,1.55)	1.18 (0.87,1.61)	1.35 (0.93,1.98)
VSD-perimembranous	1	0.93 (0.62,1.4)	1.05 (0.71,1.57)	1.28 (0.78,2.09)
ASD-all	1	1.36 (0.87,2.14)	1.34 (0.85,2.11)	1.3 (0.73,2.3)
		PM10, micrometers/cubic meter		
	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentrations	<14.9	14.9-24.2	24.2-40.6	>40.6
LVOTO	1	1.08 (0.74,1.57)	1.37 (0.95,1.98)	0.96 (0.59,1.57)
Aortic Stenosis	1	1.18 (0.54,2.55)	1.57 (0.73,3.35)	0.49 (0.14,1.67)
Coarctation of the Aorta	1	2.18 (1.08,4.39)	1.97 (0.97,3.98)	1.78 (0.76,4.12)
Hypoplastic Left Heart Syndrome	1	0.63 (0.36,1.09)	1.19 (0.71,2.01)	0.88 (0.44,1.78)
CONOTRUNCALS	1	1.2 (0.85,1.69)	1.25 (0.89,1.76)	1.27 (0.84,1.94)
d-TGA	1	1.12 (0.64,1.94)	1.1 (0.63,1.92)	1.38 (0.71,2.68)
Tetralogy of Fallot	1	1.13 (0.72,1.77)	1.3 (0.83,2.04)	1.08 (0.61,1.92)
Other Conotruncals	1	2.07 (0.73,5.88)	1.67 (0.58,4.81)	1.96 (0.59,6.5)
APVR	1	b	b	b
RVOTO	1	0.9 (0.62,1.3)	1.07 (0.74,1.54)	0.75 (0.45,1.25)
Pulmonary/Tricuspid Atresia	1	0.58 (0.27,1.22)	0.77 (0.37,1.58)	0.29 (0.09,0.96)
Pulmonary Valve Stenosis	1	1.09 (0.7,1.69)	1.24 (0.8,1.93)	0.95 (0.52,1.72)
SEPTALS	1	1.17 (0.89,1.53)	1.16 (0.88,1.52)	0.83 (0.57,1.21)
VSD-perimembranous	1	1.36 (0.9,2.04)	1.38 (0.91,2.08)	1.08 (0.63,1.86)
ASD-all	1	1.1 (0.77,1.56)	1.06 (0.74,1.51)	0.77 (0.47,1.28)

Table A2.3: Adjusted Odds Ratios and 95% Confidence Intervals between cardiac defect-groupings and weekly exposure to criteria air pollutants from hierarchical models

Week of Pregnancy		Week 2			
		<10th	10th percentile	median to 90th	
Cardiac Defect	Pollutant	percentile	to median	percentile	>90th percentile
LVOTO	Carbon Monoxide	1	0.99 (0.67,1.47)	0.99 (0.63,1.55)	0.98 (0.56,1.7)
	Nitrogen Dioxide	1	0.92 (0.57,1.47)	0.94 (0.56,1.56)	1.1 (0.62,1.97)
	Ozone[a]	1	0.83 (0.59,1.18)	0.96 (0.65,1.44)	0.88 (0.57,1.37)
	PM 10	1	0.98 (0.66,1.43)	1.1 (0.74,1.63)	0.91 (0.55,1.51)
	PM 2.5	1	1.11 (0.79,1.55)	1.1 (0.77,1.57)	1.48 (0.94,2.33)
	Sulfur Dioxide	1	0.79 (0.52,1.2)	0.65 (0.41,1.02)	0.7 (0.4,1.24)
CONOTRUNCALS	Carbon Monoxide	1	1.17 (0.81,1.69)	1.04 (0.69,1.57)	0.93 (0.56,1.56)
	Nitrogen Dioxide	1	0.95 (0.61,1.46)	1.11 (0.7,1.77)	1.15 (0.67,1.96)
	Ozone[a]	1	1.03 (0.76,1.39)	0.73 (0.51,1.05)	0.99 (0.67,1.46)
	PM 10	1	1.01 (0.7,1.46)	1.12 (0.77,1.62)	1 (0.63,1.59)
	PM 2.5	1	1.39 (0.98,1.97)	1.29 (0.9,1.86)	1.5 (0.96,2.35)
	Sulfur Dioxide	1	0.83 (0.55,1.25)	1.12 (0.72,1.73)	1 (0.58,1.72)
APVR	Carbon Monoxide	1	0.67 (0.35,1.3)	0.84 (0.4,1.77)	1.16 (0.47,2.87)
	Nitrogen Dioxide	1	0.77 (0.36,1.66)	0.65 (0.29,1.47)	1.5 (0.61,3.71)
	Ozone[a]	1	0.77 (0.38,1.56)	1.01 (0.48,2.1)	1.19 (0.54,2.59)
	PM 10	1	1.19 (0.51,2.77)	1.77 (0.78,4.05)	0.93 (0.34,2.54)
	PM 2.5	1	1.57 (0.79,3.16)	1.14 (0.55,2.35)	1.79 (0.76,4.22)
	Sulfur Dioxide	1	0.87 (0.42,1.83)	0.81 (0.38,1.77)	0.66 (0.24,1.82)
AVSD	Carbon Monoxide	1	0.73 (0.31,1.7)	0.76 (0.31,1.86)	2 (0.74,5.45)
	Nitrogen Dioxide	1	0.64 (0.26,1.52)	0.8 (0.33,1.95)	1.35 (0.49,3.71)
	Ozone[a]	1	1.17 (0.51,2.68)	1.03 (0.42,2.51)	1.36 (0.53,3.49)
	PM 10	1	0.98 (0.38,2.53)	0.97 (0.38,2.51)	1.76 (0.61,5.08)
	PM 2.5	1	1.27 (0.54,2.98)	0.82 (0.34,1.99)	3.43 (1.36,8.66)
RVOTO	Carbon Monoxide	1	0.61 (0.42,0.91)	0.64 (0.41,1)	0.45 (0.25,0.8)
	Nitrogen Dioxide	1	1.02 (0.62,1.7)	0.85 (0.49,1.48)	0.71 (0.38,1.34)
	Ozone[a]	1	0.87 (0.59,1.28)	0.61 (0.39,0.95)	0.72 (0.45,1.14)
	PM 10	1	1.1 (0.72,1.67)	1.16 (0.76,1.79)	0.83 (0.47,1.45)
	PM 2.5	1	1.2 (0.84,1.71)	0.92 (0.63,1.35)	0.95 (0.57,1.57)
	Sulfur Dioxide	1	0.81 (0.53,1.25)	0.78 (0.49,1.24)	1.05 (0.59,1.87)
SEPTALS	Carbon Monoxide	1	1.07 (0.76,1.5)	1.03 (0.7,1.5)	0.9 (0.57,1.42)
	Nitrogen Dioxide	1	0.99 (0.67,1.44)	0.92 (0.61,1.39)	0.8 (0.49,1.3)
	Ozone[a]	1	1.02 (0.79,1.31)	0.72 (0.53,0.97)	0.83 (0.6,1.16)
	PM 10	1	0.87 (0.66,1.16)	0.9 (0.67,1.21)	0.75 (0.5,1.12)
	PM 2.5	1	1.02 (0.8,1.31)	0.92 (0.71,1.2)	0.6 (0.4,0.9)
	Sulfur Dioxide	1	0.75 (0.55,1.01)	0.63 (0.45,0.88)	0.79 (0.52,1.2)

[a]Ozone exposure was categorized as follows: Less than the 25th percentile (referent), 25th percentile to median, median to 75th percentile and 75th percentile and greater

Table A2.3 (cont.)

Week of Pregnancy		Week 3 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Cardiac Defect	Pollutant				
LVOTO	Carbon Monoxide	1	1.06 (0.69,1.62)	1.21 (0.75,1.95)	1.15 (0.64,2.08)
	Nitrogen Dioxide	1	1.22 (0.74,2.03)	1.37 (0.8,2.36)	0.79 (0.41,1.52)
	Ozone[a]	1	1.13 (0.79,1.63)	0.99 (0.64,1.52)	1.12 (0.69,1.8)
	PM 10	1	0.89 (0.61,1.28)	0.89 (0.61,1.3)	0.85 (0.52,1.39)
	PM 2.5	1	0.69 (0.51,0.94)	0.54 (0.38,0.75)	0.52 (0.33,0.83)
	Sulfur Dioxide	1	1.11 (0.69,1.78)	1.42 (0.86,2.36)	1.66 (0.91,3.05)
CONOTRUNCALS	Carbon Monoxide	1	0.93 (0.63,1.36)	0.95 (0.62,1.47)	0.75 (0.43,1.29)
	Nitrogen Dioxide	1	1.87 (1.14,3.08)	1.63 (0.96,2.79)	1.6 (0.88,2.93)
	Ozone[a]	1	1.26 (0.91,1.75)	1.27 (0.87,1.86)	1.19 (0.77,1.82)
	PM 10	1	1.02 (0.71,1.46)	1 (0.69,1.44)	1.11 (0.7,1.75)
	PM 2.5	1	0.8 (0.59,1.09)	0.72 (0.52,0.99)	0.58 (0.38,0.9)
	Sulfur Dioxide	1	0.89 (0.58,1.35)	0.99 (0.63,1.55)	1.1 (0.64,1.89)
APVR	Carbon Monoxide	1	1.03 (0.52,2.04)	1.23 (0.56,2.67)	1.12 (0.43,2.92)
	Nitrogen Dioxide	1	1.33 (0.6,2.95)	0.98 (0.42,2.31)	1.02 (0.38,2.72)
	Ozone[a]	1	0.97 (0.48,1.96)	1.44 (0.69,3.02)	0.94 (0.41,2.17)
	PM 10	1	0.97 (0.45,2.07)	1.02 (0.48,2.18)	1.56 (0.64,3.77)
	PM 2.5	1	0.61 (0.34,1.09)	0.65 (0.35,1.22)	0.77 (0.34,1.74)
	Sulfur Dioxide	1	1.35 (0.6,3.02)	1.34 (0.58,3.1)	1.08 (0.38,3.04)
AVSD	Carbon Monoxide	1	1.14 (0.48,2.74)	1.43 (0.57,3.56)	0.77 (0.23,2.58)
	Nitrogen Dioxide	1	0.98 (0.39,2.43)	1.33 (0.53,3.37)	1.22 (0.41,3.57)
	Ozone[a]	1	1.03 (0.45,2.37)	0.92 (0.37,2.28)	1.34 (0.51,3.5)
	PM 10	1	0.74 (0.28,1.95)	1.83 (0.73,4.55)	1.19 (0.23,6.12)
	PM 2.5	1	0.71 (0.31,1.65)	1.44 (0.65,3.22)	0.69 (0.24,2)
RVOTO	Carbon Monoxide	1	1.33 (0.85,2.1)	1.15 (0.69,1.92)	1.03 (0.55,1.93)
	Nitrogen Dioxide	1	0.94 (0.55,1.6)	1.29 (0.73,2.29)	1.23 (0.64,2.36)
	Ozone[a]	1	1.18 (0.78,1.8)	1.86 (1.16,2.98)	2.01 (1.21,3.36)
	PM 10	1	1.48 (0.95,2.3)	1.28 (0.81,2.02)	1.46 (0.83,2.55)
	PM 2.5	1	0.74 (0.53,1.04)	0.76 (0.53,1.09)	0.71 (0.43,1.16)
	Sulfur Dioxide	1	1.31 (0.82,2.1)	1.07 (0.65,1.77)	0.96 (0.51,1.79)
SEPTALS	Carbon Monoxide	1	0.93 (0.65,1.33)	1.07 (0.72,1.61)	1.2 (0.74,1.95)
	Nitrogen Dioxide	1	1.11 (0.74,1.67)	1.05 (0.67,1.63)	0.84 (0.5,1.41)
	Ozone[a]	1	1 (0.77,1.3)	0.9 (0.66,1.24)	0.95 (0.67,1.36)
	PM 10	1	1.18 (0.88,1.57)	1.03 (0.76,1.39)	1 (0.66,1.49)
	PM 2.5	1	0.86 (0.68,1.1)	0.78 (0.6,1.02)	0.84 (0.58,1.23)
	Sulfur Dioxide	1	0.9 (0.66,1.23)	1.05 (0.74,1.49)	1.24 (0.8,1.91)

Table A2.3 (cont.)

Week of Pregnancy		Week 4			
		<10th	10th percentile to	median to 90th	>90th
Cardiac Defect	Pollutant	percentile	median	percentile	percentile
LVOTO	Carbon Monoxide	1	0.76 (0.51,1.13)	0.6 (0.38,0.95)	0.76 (0.43,1.34)
	Nitrogen Dioxide	1	1.34 (0.82,2.21)	1.1 (0.64,1.89)	1.2 (0.64,2.23)
	Ozone[a]	1	0.98 (0.68,1.42)	0.95 (0.61,1.47)	0.85 (0.52,1.38)
	PM 10	1	0.95 (0.65,1.39)	1 (0.68,1.48)	1.09 (0.66,1.77)
	PM 2.5	1	1.37 (0.96,1.96)	1.28 (0.87,1.87)	1.56 (0.97,2.51)
	Sulfur Dioxide	1	1.01 (0.63,1.61)	1.36 (0.82,2.24)	0.71 (0.37,1.35)
CONOTRUNCALS	Carbon Monoxide	1	1.12 (0.76,1.65)	1.27 (0.82,1.95)	0.96 (0.56,1.65)
	Nitrogen Dioxide	1	1.57 (0.98,2.5)	1.39 (0.84,2.3)	1.45 (0.81,2.59)
	Ozone[a]	1	1.13 (0.81,1.57)	0.85 (0.58,1.26)	0.86 (0.56,1.33)
	PM 10	1	0.76 (0.54,1.08)	0.83 (0.58,1.18)	0.98 (0.63,1.53)
	PM 2.5	1	0.95 (0.69,1.32)	1.1 (0.78,1.55)	1.11 (0.71,1.71)
	Sulfur Dioxide	1	1.33 (0.86,2.05)	1.06 (0.66,1.69)	0.97 (0.55,1.72)
APVR	Carbon Monoxide	1	0.79 (0.4,1.55)	0.88 (0.41,1.9)	0.96 (0.37,2.48)
	Nitrogen Dioxide	1	1.01 (0.47,2.16)	0.9 (0.39,2.06)	1.15 (0.44,3)
	Ozone[a]	1	1.04 (0.52,2.1)	0.9 (0.41,1.95)	0.99 (0.43,2.31)
	PM 10	1	1.01 (0.49,2.11)	1.09 (0.53,2.24)	0.65 (0.25,1.68)
	PM 2.5	1	1.32 (0.67,2.59)	1.28 (0.63,2.58)	1.28 (0.53,3.08)
	Sulfur Dioxide	1	1.4 (0.59,3.29)	1.52 (0.64,3.63)	1.05 (0.36,3.04)
AVSD	Carbon Monoxide	1	1.24 (0.51,3.04)	1.13 (0.44,2.87)	0.94 (0.3,2.98)
	Nitrogen Dioxide	1	0.94 (0.39,2.24)	1 (0.4,2.51)	0.95 (0.32,2.84)
	Ozone[a]	1	1.38 (0.6,3.17)	0.91 (0.35,2.37)	1.6 (0.6,4.23)
	PM 10	1	1.52 (0.52,4.39)	1.3 (0.46,3.69)	0.75 (0.19,2.96)
	PM 2.5	1	1.56 (0.67,3.64)	1.23 (0.52,2.92)	1.19 (0.42,3.36)
RVOTO	Carbon Monoxide	1	0.92 (0.6,1.42)	0.81 (0.49,1.31)	0.94 (0.52,1.71)
	Nitrogen Dioxide	1	1.29 (0.76,2.2)	0.9 (0.5,1.6)	1.02 (0.53,1.95)
	Ozone[a]	1	0.91 (0.59,1.38)	1.06 (0.66,1.71)	0.84 (0.5,1.42)
	PM 10	1	1.12 (0.75,1.69)	0.8 (0.52,1.22)	1.04 (0.61,1.76)
	PM 2.5	1	0.96 (0.68,1.37)	0.98 (0.67,1.43)	0.94 (0.57,1.54)
	Sulfur Dioxide	1	0.98 (0.62,1.55)	0.87 (0.53,1.43)	0.95 (0.52,1.76)
SEPTALS	Carbon Monoxide	1	1.16 (0.81,1.65)	1.16 (0.78,1.74)	1.1 (0.68,1.78)
	Nitrogen Dioxide	1	1.52 (1,2.32)	1.51 (0.96,2.39)	1.48 (0.88,2.51)
	Ozone[a]	1	1.1 (0.84,1.45)	1.07 (0.77,1.49)	1 (0.69,1.45)
	PM 10	1	1.02 (0.76,1.35)	0.98 (0.73,1.33)	0.86 (0.57,1.29)
	PM 2.5	1	1 (0.78,1.3)	0.92 (0.7,1.22)	0.95 (0.65,1.39)
	Sulfur Dioxide	1	1.19 (0.86,1.64)	1.03 (0.71,1.48)	0.87 (0.55,1.38)

Table A2.3 (cont.)

Week of Pregnancy		Week 5			
Cardiac Defect	Pollutant	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
LVOTO	Carbon Monoxide	1	1.13 (0.75,1.73)	1.07 (0.67,1.72)	0.79 (0.43,1.44)
	Nitrogen Dioxide	1	1.03 (0.62,1.7)	1.08 (0.63,1.86)	0.98 (0.52,1.85)
	Ozone[a]	1	0.65 (0.46,0.94)	0.69 (0.45,1.06)	0.73 (0.45,1.17)
	PM 10	1	1.1 (0.75,1.63)	1.25 (0.84,1.86)	0.88 (0.52,1.49)
	PM 2.5	1	1.01 (0.73,1.41)	0.95 (0.67,1.36)	1.12 (0.7,1.79)
	Sulfur Dioxide	1	1.02 (0.64,1.63)	1.04 (0.63,1.72)	1.16 (0.64,2.12)
CONOTRUNCALS	Carbon Monoxide	1	0.83 (0.57,1.22)	0.85 (0.55,1.31)	0.91 (0.53,1.55)
	Nitrogen Dioxide	1	0.51 (0.34,0.76)	0.49 (0.31,0.77)	0.48 (0.28,0.83)
	Ozone[a]	1	1.14 (0.82,1.58)	1.36 (0.92,2.01)	1.38 (0.89,2.15)
	PM 10	1	1.12 (0.78,1.62)	1.19 (0.82,1.74)	1.22 (0.76,1.95)
	PM 2.5	1	1.01 (0.73,1.39)	0.91 (0.65,1.28)	0.91 (0.58,1.42)
	Sulfur Dioxide	1	0.8 (0.54,1.2)	0.77 (0.49,1.19)	0.77 (0.45,1.31)
APVR	Carbon Monoxide	1	1.27 (0.64,2.51)	0.81 (0.37,1.81)	1.17 (0.45,3.05)
	Nitrogen Dioxide	1	0.53 (0.24,1.16)	0.94 (0.42,2.15)	1.53 (0.59,3.97)
	Ozone[a]	1	1.18 (0.59,2.36)	1.19 (0.55,2.58)	0.96 (0.41,2.25)
	PM 10	1	0.73 (0.34,1.55)	1.23 (0.6,2.52)	1.58 (0.66,3.78)
	PM 2.5	1	1.46 (0.7,3.04)	1.78 (0.85,3.75)	1.6 (0.64,3.98)
	Sulfur Dioxide	1	1.25 (0.55,2.83)	1.66 (0.72,3.83)	0.76 (0.25,2.36)
AVSD	Carbon Monoxide	1	1.05 (0.45,2.46)	1.07 (0.43,2.69)	0.57 (0.15,2.13)
	Nitrogen Dioxide	1	0.63 (0.27,1.48)	0.67 (0.27,1.66)	0.64 (0.2,1.98)
	Ozone[a]	1	0.61 (0.27,1.39)	0.62 (0.25,1.55)	0.81 (0.31,2.16)
	PM 10	1	0.75 (0.29,1.95)	1.63 (0.65,4.05)	1.18 (0.23,6.11)
	PM 2.5	1	1.37 (0.61,3.07)	1.19 (0.52,2.72)	1.29 (0.47,3.57)
RVOTO	Carbon Monoxide	1	1.11 (0.71,1.74)	1.26 (0.76,2.09)	1.37 (0.73,2.55)
	Nitrogen Dioxide	1	0.72 (0.43,1.21)	1.04 (0.59,1.82)	1.13 (0.59,2.16)
	Ozone[a]	1	1.01 (0.67,1.52)	1.02 (0.63,1.64)	1.07 (0.64,1.8)
	PM 10	1	0.81 (0.55,1.18)	0.84 (0.56,1.24)	0.86 (0.51,1.45)
	PM 2.5	1	1.09 (0.75,1.56)	1.17 (0.79,1.72)	1.74 (1.07,2.83)
	Sulfur Dioxide	1	1.19 (0.73,1.94)	1.45 (0.86,2.44)	1.34 (0.71,2.51)
SEPTALS	Carbon Monoxide	1	0.99 (0.69,1.42)	1.04 (0.69,1.57)	1.23 (0.75,2)
	Nitrogen Dioxide	1	0.99 (0.66,1.49)	1.15 (0.74,1.8)	1.56 (0.93,2.6)
	Ozone[a]	1	1.16 (0.88,1.53)	1.4 (1.01,1.95)	1.58 (1.09,2.29)
	PM 10	1	1.2 (0.88,1.61)	1.31 (0.96,1.78)	1.46 (0.98,2.19)
	PM 2.5	1	1.12 (0.87,1.45)	0.95 (0.72,1.26)	1.2 (0.82,1.75)
	Sulfur Dioxide	1	1.2 (0.86,1.68)	1.3 (0.9,1.88)	1.34 (0.86,2.1)

Table A2.3 (cont.)

Week of Pregnancy		Week 6			
		<10th	10th percentile	median to 90th	>90th
Cardiac Defect	Pollutant	percentile	to median	percentile	percentile
LVOTO	Carbon Monoxide	1	1.16 (0.76,1.76)	1.28 (0.8,2.05)	0.88 (0.48,1.6)
	Nitrogen Dioxide	1	1.03 (0.63,1.69)	1.08 (0.63,1.85)	1 (0.53,1.87)
	Ozone[a]	1	1.52 (1.05,2.2)	1.34 (0.86,2.1)	1.22 (0.74,2.01)
	PM 10	1	0.98 (0.67,1.43)	0.98 (0.66,1.44)	0.86 (0.51,1.45)
	PM 2.5	1	1.04 (0.74,1.47)	1.09 (0.75,1.57)	0.95 (0.58,1.55)
	Sulfur Dioxide	1	1.3 (0.79,2.13)	1.03 (0.61,1.74)	1.02 (0.54,1.91)
CONOTRUNCALS	Carbon Monoxide	1	1.26 (0.85,1.87)	1.32 (0.85,2.05)	1.53 (0.9,2.61)
	Nitrogen Dioxide	1	1.14 (0.72,1.8)	1.4 (0.85,2.29)	1.21 (0.68,2.17)
	Ozone[a]	1	1 (0.73,1.38)	1.04 (0.71,1.52)	0.83 (0.53,1.29)
	PM 10	1	0.89 (0.63,1.26)	0.72 (0.5,1.03)	0.9 (0.57,1.42)
	PM 2.5	1	1.02 (0.73,1.42)	1 (0.7,1.42)	0.89 (0.57,1.41)
	Sulfur Dioxide	1	1.03 (0.66,1.59)	1.17 (0.73,1.88)	1.15 (0.65,2.02)
APVR	Carbon Monoxide	1	1.09 (0.56,2.13)	0.93 (0.43,2.03)	0.49 (0.18,1.34)
	Nitrogen Dioxide	1	0.94 (0.44,2.03)	0.85 (0.37,1.96)	0.64 (0.23,1.75)
	Ozone[a]	1	0.9 (0.45,1.78)	0.91 (0.42,1.96)	1.07 (0.46,2.48)
	PM 10	1	1.19 (0.56,2.54)	0.96 (0.45,2.04)	0.89 (0.35,2.31)
	PM 2.5	1	0.79 (0.44,1.42)	0.48 (0.25,0.94)	1 (0.45,2.24)
	Sulfur Dioxide	1	1.28 (0.55,3.01)	1.06 (0.45,2.54)	2.34 (0.89,6.17)
AVSD	Carbon Monoxide	1	1.05 (0.45,2.4)	0.97 (0.39,2.36)	0.87 (0.28,2.72)
	Nitrogen Dioxide	1	1.43 (0.58,3.54)	1.11 (0.43,2.9)	0.59 (0.17,1.99)
	Ozone[a]	1	1.69 (0.77,3.71)	0.88 (0.36,2.18)	0.41 (0.14,1.17)
	PM 10	1	1.46 (0.56,3.79)	0.95 (0.36,2.5)	0.85 (0.25,2.91)
	PM 2.5	1	1.23 (0.57,2.67)	0.89 (0.4,1.99)	0.48 (0.15,1.57)
RVOTO	Carbon Monoxide	1	1.45 (0.93,2.28)	1.18 (0.71,1.95)	1.46 (0.79,2.7)
	Nitrogen Dioxide	1	0.74 (0.44,1.23)	0.96 (0.55,1.68)	1.02 (0.54,1.93)
	Ozone[a]	1	1.07 (0.71,1.6)	1.22 (0.76,1.95)	1.13 (0.67,1.89)
	PM 10	1	0.97 (0.65,1.45)	0.98 (0.65,1.48)	0.94 (0.54,1.63)
	PM 2.5	1	0.82 (0.58,1.17)	0.84 (0.58,1.22)	0.76 (0.46,1.26)
	Sulfur Dioxide	1	1.16 (0.71,1.89)	1.06 (0.63,1.78)	1.09 (0.58,2.06)
SEPTALS	Carbon Monoxide	1	1 (0.71,1.42)	0.84 (0.56,1.24)	0.92 (0.57,1.48)
	Nitrogen Dioxide	1	0.68 (0.46,0.99)	0.74 (0.49,1.13)	0.63 (0.38,1.05)
	Ozone[a]	1	1.09 (0.83,1.42)	1.09 (0.79,1.51)	0.87 (0.6,1.26)
	PM 10	1	0.98 (0.74,1.29)	0.9 (0.67,1.2)	0.92 (0.62,1.38)
	PM 2.5	1	0.97 (0.76,1.26)	0.89 (0.68,1.18)	0.81 (0.55,1.2)
	Sulfur Dioxide	1	0.97 (0.7,1.34)	1.11 (0.77,1.59)	1.12 (0.71,1.75)

Table A2.3 (cont.)

Week of Pregnancy		Week 7			
Cardiac Defect	Pollutant	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
LVOTO	Carbon Monoxide	1	1.03 (0.69,1.56)	1.25 (0.79,1.99)	1.45 (0.82,2.59)
	Nitrogen Dioxide	1	1.24 (0.75,2.02)	1.34 (0.78,2.29)	1.58 (0.86,2.92)
	Ozone[a]	1	1.18 (0.82,1.69)	1.03 (0.67,1.58)	1.24 (0.78,1.99)
	PM 10	1	1.43 (0.94,2.18)	1.38 (0.9,2.12)	1.53 (0.9,2.6)
	PM 2.5	1	1.16 (0.82,1.64)	1.2 (0.84,1.73)	1.23 (0.75,2.01)
	Sulfur Dioxide	1	1.28 (0.78,2.09)	1.38 (0.82,2.33)	0.94 (0.5,1.8)
CONOTRUNCALS	Carbon Monoxide	1	1.13 (0.77,1.67)	1.16 (0.75,1.78)	1.59 (0.94,2.69)
	Nitrogen Dioxide	1	1.06 (0.69,1.63)	0.83 (0.51,1.33)	0.91 (0.52,1.58)
	Ozone[a]	1	0.84 (0.61,1.15)	0.75 (0.52,1.09)	0.75 (0.49,1.14)
	PM 10	1	1.04 (0.73,1.5)	1.11 (0.77,1.62)	1.14 (0.72,1.82)
	PM 2.5	1	1.28 (0.91,1.82)	1.4 (0.97,2.01)	1.52 (0.97,2.4)
	Sulfur Dioxide	1	1.09 (0.71,1.67)	1.18 (0.74,1.88)	0.94 (0.53,1.67)
APVR	Carbon Monoxide	1	0.51 (0.27,0.98)	0.47 (0.22,0.99)	0.93 (0.37,2.35)
	Nitrogen Dioxide	1	1.37 (0.63,3.02)	1.26 (0.54,2.93)	0.63 (0.22,1.81)
	Ozone[a]	1	0.98 (0.5,1.91)	0.71 (0.33,1.53)	0.87 (0.38,1.99)
	PM 10	1	1.78 (0.78,4.08)	1.22 (0.53,2.82)	1.28 (0.49,3.38)
	PM 2.5	1	1.27 (0.68,2.39)	0.97 (0.49,1.9)	1.02 (0.42,2.49)
	Sulfur Dioxide	1	1.29 (0.58,2.89)	0.9 (0.39,2.1)	1.38 (0.52,3.64)
AVSD	Carbon Monoxide	1	0.88 (0.38,2.05)	1.02 (0.42,2.49)	1 (0.32,3.12)
	Nitrogen Dioxide	1	0.96 (0.41,2.26)	0.76 (0.3,1.89)	1.05 (0.37,3.02)
	Ozone[a]	1	0.92 (0.42,2.03)	0.53 (0.21,1.34)	0.85 (0.33,2.2)
	PM 10	1	1.25 (0.54,2.9)	0.58 (0.23,1.46)	1.92 (0.71,5.24)
	PM 2.5	1	1.14 (0.48,2.71)	1.32 (0.56,3.1)	2.45 (0.92,6.5)
RVOTO	Carbon Monoxide	1	0.83 (0.54,1.28)	0.95 (0.59,1.55)	1.48 (0.83,2.67)
	Nitrogen Dioxide	1	1.38 (0.81,2.37)	1.33 (0.74,2.39)	1.27 (0.66,2.45)
	Ozone[a]	1	0.74 (0.5,1.1)	0.64 (0.41,1)	0.67 (0.41,1.09)
	PM 10	1	1.34 (0.86,2.1)	1.49 (0.94,2.34)	1.6 (0.92,2.81)
	PM 2.5	1	1.05 (0.74,1.5)	1 (0.69,1.45)	0.81 (0.48,1.37)
	Sulfur Dioxide	1	1.27 (0.78,2.07)	1.31 (0.78,2.21)	0.81 (0.42,1.56)
SEPTALS	Carbon Monoxide	1	1.24 (0.87,1.77)	1.25 (0.84,1.87)	1.31 (0.81,2.13)
	Nitrogen Dioxide	1	1.15 (0.78,1.69)	0.88 (0.57,1.35)	0.92 (0.56,1.52)
	Ozone[a]	1	0.73 (0.56,0.95)	0.57 (0.42,0.77)	0.68 (0.48,0.96)
	PM 10	1	0.94 (0.71,1.24)	0.95 (0.71,1.27)	0.88 (0.59,1.31)
	PM 2.5	1	1.17 (0.9,1.51)	1.14 (0.86,1.51)	0.98 (0.65,1.47)
	Sulfur Dioxide	1	1.1 (0.8,1.52)	1.01 (0.7,1.46)	0.89 (0.56,1.4)

Table A2.3 (cont.)

Week of Pregnancy		Week 8			
Cardiac Defect	Pollutant	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
LVOTO	Carbon Monoxide	1	1.13 (0.76,1.69)	1.09 (0.7,1.71)	0.91 (0.52,1.62)
	Nitrogen Dioxide	1	0.68 (0.44,1.06)	0.68 (0.42,1.09)	0.76 (0.43,1.33)
	Ozone[a]	1	0.99 (0.7,1.38)	1.1 (0.75,1.62)	1.08 (0.7,1.67)
	PM 10	1	0.63 (0.44,0.91)	0.81 (0.56,1.16)	1.05 (0.66,1.65)
	PM 2.5	1	1.18 (0.85,1.64)	1.01 (0.71,1.44)	0.95 (0.59,1.53)
	Sulfur Dioxide	1	1.57 (0.98,2.53)	1.39 (0.84,2.32)	1.7 (0.93,3.1)
CONOTRUNCALS	Carbon Monoxide	1	0.96 (0.67,1.38)	0.94 (0.63,1.41)	0.84 (0.51,1.4)
	Nitrogen Dioxide	1	0.9 (0.59,1.37)	1.13 (0.71,1.77)	1.19 (0.7,2.03)
	Ozone[a]	1	1.05 (0.78,1.41)	1.01 (0.71,1.42)	1.11 (0.75,1.63)
	PM 10	1	0.71 (0.5,1.01)	1.01 (0.71,1.43)	1.06 (0.69,1.65)
	PM 2.5	1	0.9 (0.65,1.25)	1.19 (0.85,1.66)	1.23 (0.8,1.87)
	Sulfur Dioxide	1	1.23 (0.81,1.86)	1.24 (0.79,1.94)	1.14 (0.66,1.96)
APVR	Carbon Monoxide	1	0.81 (0.42,1.56)	0.83 (0.39,1.77)	0.97 (0.39,2.45)
	Nitrogen Dioxide	1	0.93 (0.44,1.96)	0.53 (0.23,1.22)	1.51 (0.61,3.71)
	Ozone[a]	1	1.05 (0.55,2)	0.95 (0.46,1.95)	1.04 (0.47,2.28)
	PM 10	1	0.45 (0.23,0.85)	0.46 (0.25,0.88)	0.93 (0.43,2.02)
	PM 2.5	1	1.36 (0.7,2.66)	1.03 (0.51,2.1)	1.33 (0.56,3.16)
	Sulfur Dioxide	1	1.96 (0.79,4.85)	2.16 (0.87,5.37)	1.39 (0.47,4.1)
AVSD	Carbon Monoxide	1	0.97 (0.43,2.2)	0.77 (0.32,1.86)	0.75 (0.24,2.3)
	Nitrogen Dioxide	1	0.8 (0.34,1.91)	1 (0.41,2.45)	0.68 (0.21,2.24)
	Ozone[a]	1	0.85 (0.36,2)	1.61 (0.69,3.72)	1.39 (0.54,3.57)
	PM 10	1	0.52 (0.23,1.2)	0.79 (0.36,1.72)	0.6 (0.18,1.94)
	PM 2.5	1	0.96 (0.47,1.98)	0.67 (0.31,1.44)	1.07 (0.41,2.75)
RVOTO	Carbon Monoxide	1	1.15 (0.75,1.77)	1.31 (0.81,2.12)	0.81 (0.44,1.5)
	Nitrogen Dioxide	1	1.04 (0.62,1.75)	0.97 (0.55,1.68)	1.53 (0.83,2.83)
	Ozone[a]	1	1.17 (0.81,1.69)	1.08 (0.71,1.65)	1.24 (0.78,1.96)
	PM 10	1	0.86 (0.56,1.31)	1.19 (0.78,1.82)	1.27 (0.75,2.15)
	PM 2.5	1	1.15 (0.8,1.65)	1.06 (0.72,1.56)	1.38 (0.85,2.24)
	Sulfur Dioxide	1	1.29 (0.81,2.04)	1.4 (0.86,2.3)	1.31 (0.71,2.41)
SEPTALS	Carbon Monoxide	1	0.75 (0.54,1.03)	0.85 (0.59,1.22)	0.79 (0.5,1.25)
	Nitrogen Dioxide	1	1.06 (0.72,1.56)	1.18 (0.77,1.8)	1.82 (1.13,2.94)
	Ozone[a]	1	1.17 (0.91,1.51)	1.13 (0.84,1.52)	1.33 (0.95,1.86)
	PM 10	1	0.96 (0.72,1.28)	1.05 (0.78,1.41)	1.05 (0.71,1.55)
	PM 2.5	1	0.88 (0.69,1.13)	0.99 (0.76,1.29)	1.02 (0.71,1.48)
	Sulfur Dioxide	1	0.99 (0.72,1.34)	1.07 (0.76,1.51)	1.09 (0.71,1.68)

Table A2.4: Odds Ratios and 95% Confidence Intervals between individual cardiac birth defects and weekly exposure to criteria air pollutants from hierarchical models

Cardiac Defect	Pollutant	Week 2 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxide	1	0.88 (0.46,1.68)	0.95 (0.46,1.93)	0.9 (0.37,2.18)
	Nitrogen Dioxide	1	0.89 (0.44,1.8)	0.72 (0.34,1.53)	1.14 (0.48,2.72)
	Ozone[a]	1	0.96 (0.52,1.78)	1.3 (0.68,2.52)	0.98 (0.46,2.06)
	PM 10	1	1.02 (0.51,2.05)	1.54 (0.77,3.07)	1 (0.41,2.41)
	PM 2.5	1	1.09 (0.61,1.94)	1.18 (0.65,2.16)	1.7 (0.78,3.69)
	Sulfur Dioxide	1	0.37 (0.19,0.74)	0.74 (0.37,1.5)	0.68 (0.27,1.73)
Coarctation of the Aorta					
	Carbon Monoxide	1	0.9 (0.54,1.52)	0.93 (0.52,1.65)	0.83 (0.4,1.74)
	Nitrogen Dioxide	1	1.1 (0.57,2.13)	0.92 (0.46,1.84)	1.35 (0.63,2.89)
	Ozone[a]	1	0.64 (0.38,1.07)	0.79 (0.45,1.4)	0.81 (0.44,1.49)
	PM 10	1	1.24 (0.7,2.19)	1.19 (0.67,2.12)	0.81 (0.38,1.73)
	PM 2.5	1	1.18 (0.73,1.92)	1.19 (0.71,1.98)	1.4 (0.73,2.69)
	Sulfur Dioxide	1	1.03 (0.57,1.85)	0.68 (0.37,1.27)	0.72 (0.34,1.52)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxide	1	1.13 (0.64,1.99)	1.01 (0.54,1.89)	1.01 (0.48,2.15)
	Nitrogen Dioxide	1	0.87 (0.47,1.6)	1.17 (0.61,2.23)	0.85 (0.38,1.86)
	Ozone[a]	1	0.89 (0.55,1.43)	0.85 (0.49,1.47)	0.78 (0.43,1.44)
	PM 10	1	0.76 (0.45,1.29)	0.84 (0.5,1.43)	0.91 (0.47,1.77)
	PM 2.5	1	1.01 (0.62,1.64)	0.87 (0.52,1.46)	1.18 (0.62,2.25)
	Sulfur Dioxide	1	0.96 (0.53,1.73)	0.71 (0.38,1.33)	0.95 (0.44,2.07)
d-TGA					
	Carbon Monoxide	1	0.98 (0.59,1.64)	0.73 (0.41,1.29)	0.64 (0.31,1.33)
	Nitrogen Dioxide	1	0.88 (0.49,1.56)	0.97 (0.52,1.8)	0.87 (0.41,1.82)
	Ozone[a]	1	0.92 (0.58,1.47)	1.01 (0.6,1.71)	0.89 (0.5,1.59)
	PM 10	1	1.04 (0.61,1.8)	0.93 (0.53,1.64)	1 (0.5,1.97)
	PM 2.5	1	1.2 (0.73,1.97)	1.09 (0.65,1.83)	0.96 (0.49,1.89)
	Sulfur Dioxide	1	0.81 (0.44,1.47)	1.25 (0.67,2.32)	0.86 (0.4,1.86)
Tetralogy of Fallot					
	Carbon Monoxide	1	1.3 (0.8,2.09)	1.36 (0.81,2.31)	1.29 (0.68,2.44)
	Nitrogen Dioxide	1	0.97 (0.57,1.65)	1.11 (0.63,1.94)	1.37 (0.72,2.6)
	Ozone[a]	1	1.11 (0.76,1.63)	0.6 (0.37,0.96)	1.13 (0.7,1.84)
	PM 10	1	1.09 (0.68,1.74)	1.26 (0.78,2.04)	1.14 (0.63,2.05)
	PM 2.5	1	1.64 (1.02,2.63)	1.41 (0.87,2.31)	1.96 (1.11,3.46)
	Sulfur Dioxide	1	0.84 (0.51,1.39)	0.95 (0.56,1.62)	0.99 (0.51,1.91)

[a]Ozone exposure was categorized using the following categories: Less than the 25th percentile (referent), 25th percentile to median, median to 75th percentile and 75th percentile and greater

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 2 <10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxide	1	1.15 (0.58,2.29)	0.84 (0.4,1.76)	0.7 (0.28,1.76)
	Nitrogen Dioxide	1	0.99 (0.43,2.24)	1.43 (0.63,3.27)	1 (0.38,2.64)
	Ozone[a]	1	1.03 (0.55,1.93)	0.62 (0.3,1.29)	0.89 (0.42,1.91)
	PM 10	1	0.7 (0.35,1.4)	1.03 (0.53,2.02)	0.63 (0.25,1.57)
	PM 2.5	1	0.99 (0.5,1.95)	1.23 (0.62,2.45)	1.13 (0.46,2.8)
	Sulfur Dioxide	1	0.56 (0.26,1.21)	1 (0.46,2.14)	0.96 (0.38,2.44)
TAPVR					
	Carbon Monoxide	1	0.71 (0.37,1.38)	0.91 (0.43,1.92)	1.02 (0.4,2.58)
	Nitrogen Dioxide	1	0.71 (0.34,1.52)	0.6 (0.26,1.36)	1.43 (0.58,3.53)
	Ozone[a]	1	0.71 (0.34,1.5)	1.18 (0.56,2.48)	1.36 (0.62,2.97)
	PM 10	1	1.05 (0.46,2.42)	1.57 (0.7,3.53)	0.88 (0.33,2.36)
	PM 2.5	1	1.43 (0.72,2.86)	0.98 (0.47,2.04)	1.67 (0.71,3.95)
	Sulfur Dioxide	1	0.89 (0.42,1.9)	0.87 (0.4,1.91)	0.76 (0.28,2.07)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxide	1	0.92 (0.48,1.78)	0.78 (0.37,1.62)	0.92 (0.37,2.31)
	Nitrogen Dioxide	1	0.93 (0.43,1.99)	0.98 (0.44,2.18)	1.03 (0.4,2.63)
	Ozone[a]	1	1.05 (0.52,2.08)	0.63 (0.29,1.36)	1.15 (0.53,2.49)
	PM 10	1	0.88 (0.44,1.75)	0.9 (0.45,1.81)	1.08 (0.46,2.57)
	PM 2.5	1	1.6 (0.83,3.09)	0.99 (0.48,2)	1.12 (0.46,2.7)
	Sulfur Dioxide	1	0.79 (0.37,1.67)	1.32 (0.61,2.87)	0.59 (0.2,1.74)
Pulmonary Valve Stenosis					
	Carbon Monoxide	1	0.53 (0.34,0.81)	0.63 (0.39,1.02)	0.37 (0.19,0.7)
	Nitrogen Dioxide	1	0.95 (0.55,1.65)	0.76 (0.42,1.37)	0.66 (0.33,1.29)
	Ozone[a]	1	0.78 (0.51,1.2)	0.6 (0.37,0.97)	0.59 (0.35,0.99)
	PM 10	1	1.25 (0.77,2.04)	1.3 (0.79,2.14)	0.76 (0.39,1.46)
	PM 2.5	1	1.17 (0.78,1.75)	0.89 (0.58,1.37)	0.94 (0.54,1.65)
	Sulfur Dioxide	1	0.85 (0.53,1.36)	0.7 (0.42,1.16)	1.08 (0.58,2.01)
VSD-perimembranous					
	Carbon Monoxide	1	1.08 (0.71,1.65)	1.05 (0.65,1.68)	0.95 (0.54,1.69)
	Nitrogen Dioxide	1	1.09 (0.67,1.78)	0.95 (0.56,1.61)	0.94 (0.51,1.73)
	Ozone[a]	1	0.92 (0.64,1.32)	0.86 (0.57,1.31)	0.97 (0.61,1.52)
	PM 10	1	0.84 (0.57,1.24)	0.92 (0.62,1.36)	0.87 (0.52,1.47)
	PM 2.5	1	0.97 (0.68,1.38)	1.05 (0.72,1.51)	0.6 (0.34,1.04)
	Sulfur Dioxide	1	0.76 (0.5,1.15)	0.65 (0.41,1.02)	1.08 (0.63,1.85)
ASD-all					
	Carbon Monoxide	1	1.07 (0.69,1.67)	0.94 (0.57,1.54)	0.67 (0.36,1.25)
	Nitrogen Dioxide	1	0.94 (0.58,1.52)	0.9 (0.54,1.52)	0.65 (0.34,1.22)
	Ozone[a]	1	1.18 (0.87,1.61)	0.64 (0.44,0.94)	0.77 (0.5,1.18)
	PM 10	1	0.98 (0.67,1.41)	0.98 (0.67,1.44)	0.66 (0.38,1.15)
	PM 2.5	1	1.07 (0.8,1.45)	0.84 (0.6,1.17)	0.66 (0.4,1.11)
	Sulfur Dioxide	1	0.7 (0.48,1)	0.63 (0.41,0.95)	0.64 (0.37,1.12)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 3 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxide	1	0.93 (0.47,1.82)	1.06 (0.51,2.2)	0.66 (0.25,1.74)
	Nitrogen Dioxide	1	1.73 (0.78,3.88)	2.38 (1.03,5.46)	0.63 (0.21,1.89)
	Ozone[a]	1	1.58 (0.85,2.96)	1.13 (0.55,2.32)	1.45 (0.66,3.16)
	PM 10	1	1.35 (0.71,2.57)	1.03 (0.53,2)	0.51 (0.18,1.42)
	PM 2.5	1	0.55 (0.33,0.89)	0.42 (0.24,0.73)	0.39 (0.17,0.88)
	Sulfur Dioxide	1	1.49 (0.7,3.18)	1.23 (0.55,2.76)	1.18 (0.45,3.15)
Coarctation of the Aorta					
	Carbon Monoxide	1	1.2 (0.68,2.12)	1.21 (0.65,2.27)	1.11 (0.5,2.42)
	Nitrogen Dioxide	1	1.16 (0.6,2.24)	1.36 (0.68,2.7)	0.74 (0.33,1.68)
	Ozone[a]	1	1.1 (0.64,1.87)	1.16 (0.63,2.11)	1.22 (0.63,2.36)
	PM 10	1	0.91 (0.54,1.53)	0.87 (0.51,1.49)	1.12 (0.57,2.22)
	PM 2.5	1	0.82 (0.53,1.27)	0.59 (0.36,0.95)	0.52 (0.27,1.01)
	Sulfur Dioxide	1	0.97 (0.51,1.86)	1.74 (0.9,3.39)	1.96 (0.9,4.25)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxide	1	0.94 (0.52,1.7)	1.13 (0.59,2.14)	1.27 (0.58,2.76)
	Nitrogen Dioxide	1	1.09 (0.58,2.05)	1.09 (0.55,2.15)	1.07 (0.48,2.38)
	Ozone[a]	1	1.07 (0.65,1.77)	0.85 (0.47,1.52)	0.97 (0.51,1.84)
	PM 10	1	0.66 (0.39,1.1)	0.91 (0.54,1.51)	0.9 (0.47,1.75)
	PM 2.5	1	0.79 (0.49,1.27)	0.71 (0.43,1.18)	0.79 (0.41,1.51)
	Sulfur Dioxide	1	1.05 (0.57,1.95)	1.09 (0.57,2.08)	1.35 (0.6,3.02)
d-TGA					
	Carbon Monoxide	1	1.07 (0.61,1.86)	1 (0.54,1.84)	0.94 (0.44,2.01)
	Nitrogen Dioxide	1	1.73 (0.91,3.31)	1.23 (0.62,2.47)	1.24 (0.56,2.73)
	Ozone[a]	1	1.33 (0.82,2.16)	1.25 (0.72,2.18)	1.18 (0.64,2.2)
	PM 10	1	0.79 (0.47,1.32)	0.76 (0.45,1.29)	1.05 (0.55,2.01)
	PM 2.5	1	0.79 (0.5,1.26)	0.77 (0.47,1.26)	0.47 (0.23,0.95)
	Sulfur Dioxide	1	1.21 (0.67,2.22)	0.94 (0.5,1.79)	0.96 (0.45,2.06)
Tetralogy of Fallot					
	Carbon Monoxide	1	0.84 (0.53,1.35)	0.82 (0.48,1.38)	0.56 (0.29,1.09)
	Nitrogen Dioxide	1	1.65 (0.91,2.99)	1.6 (0.85,2.99)	1.4 (0.68,2.86)
	Ozone[a]	1	1.25 (0.83,1.89)	1.26 (0.78,2.02)	1.13 (0.66,1.94)
	PM 10	1	1.18 (0.74,1.88)	1.1 (0.68,1.76)	1.1 (0.61,1.98)
	PM 2.5	1	0.78 (0.53,1.16)	0.7 (0.46,1.06)	0.73 (0.43,1.24)
	Sulfur Dioxide	1	0.76 (0.46,1.26)	1.06 (0.63,1.81)	1.14 (0.59,2.2)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 3 <10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxide	1	0.94 (0.45,1.96)	1.49 (0.69,3.21)	1.31 (0.51,3.34)
	Nitrogen Dioxide	1	1.45 (0.61,3.45)	1.33 (0.55,3.19)	1.58 (0.6,4.16)
	Ozone[a]	1	1.12 (0.57,2.18)	1.27 (0.61,2.64)	1.32 (0.59,2.99)
	PM 10	1	0.99 (0.47,2.1)	1.19 (0.57,2.48)	1.12 (0.46,2.74)
	PM 2.5	1	0.95 (0.5,1.79)	0.73 (0.37,1.43)	0.36 (0.13,1.01)
	Sulfur Dioxide	1	0.99 (0.45,2.19)	1.16 (0.52,2.61)	1.74 (0.68,4.42)
TAPVR					
	Carbon Monoxide	1	1.05 (0.52,2.11)	1.06 (0.48,2.33)	1.16 (0.44,3.05)
	Nitrogen Dioxide	1	1.3 (0.59,2.87)	0.79 (0.34,1.86)	1.01 (0.38,2.64)
	Ozone[a]	1	0.95 (0.46,1.97)	1.42 (0.68,2.97)	0.85 (0.37,1.96)
	PM 10	1	0.82 (0.38,1.76)	0.92 (0.43,1.95)	1.52 (0.64,3.63)
	PM 2.5	1	0.5 (0.27,0.91)	0.62 (0.33,1.16)	0.72 (0.31,1.64)
	Sulfur Dioxide	1	1.34 (0.6,2.99)	1.34 (0.59,3.05)	0.99 (0.35,2.84)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxide	1	0.91 (0.47,1.78)	0.58 (0.27,1.24)	0.81 (0.32,2.09)
	Nitrogen Dioxide	1	0.72 (0.34,1.52)	1.08 (0.49,2.36)	0.96 (0.36,2.53)
	Ozone[a]	1	1.06 (0.51,2.19)	1.66 (0.78,3.52)	1.27 (0.55,2.91)
	PM 10	1	1.5 (0.69,3.23)	1.35 (0.62,2.93)	0.79 (0.28,2.2)
	PM 2.5	1	0.97 (0.52,1.83)	0.73 (0.37,1.44)	0.83 (0.35,1.95)
	Sulfur Dioxide	1	1.61 (0.66,3.91)	1.6 (0.65,3.91)	1.48 (0.53,4.17)
Pulmonary Valve Stenosis					
	Carbon Monoxide	1	1.42 (0.86,2.37)	1.38 (0.78,2.42)	1.07 (0.54,2.14)
	Nitrogen Dioxide	1	1.02 (0.56,1.85)	1.33 (0.71,2.49)	1.22 (0.6,2.48)
	Ozone[a]	1	1.3 (0.81,2.08)	1.93 (1.15,3.25)	2.15 (1.22,3.78)
	PM 10	1	1.34 (0.82,2.17)	1.14 (0.7,1.88)	1.4 (0.76,2.58)
	PM 2.5	1	0.65 (0.44,0.95)	0.7 (0.47,1.05)	0.6 (0.35,1.05)
	Sulfur Dioxide	1	1.14 (0.7,1.87)	0.88 (0.52,1.49)	0.81 (0.42,1.57)
VSD-perimembranous					
	Carbon Monoxide	1	0.93 (0.6,1.46)	1.09 (0.67,1.8)	1.07 (0.59,1.96)
	Nitrogen Dioxide	1	1.14 (0.68,1.91)	1.18 (0.68,2.06)	0.89 (0.47,1.71)
	Ozone[a]	1	1.11 (0.76,1.62)	1.07 (0.69,1.66)	1.02 (0.63,1.66)
	PM 10	1	1.3 (0.86,1.96)	1.16 (0.76,1.77)	0.86 (0.48,1.52)
	PM 2.5	1	1.06 (0.74,1.51)	0.88 (0.6,1.3)	0.73 (0.43,1.24)
	Sulfur Dioxide	1	1.32 (0.82,2.11)	1.5 (0.91,2.48)	1.98 (1.1,3.56)
ASD-all					
	Carbon Monoxide	1	0.88 (0.55,1.41)	1 (0.59,1.69)	1.04 (0.55,1.98)
	Nitrogen Dioxide	1	1.06 (0.63,1.77)	0.99 (0.57,1.73)	0.8 (0.41,1.55)
	Ozone[a]	1	0.94 (0.68,1.29)	0.82 (0.56,1.21)	0.92 (0.59,1.43)
	PM 10	1	1.16 (0.8,1.68)	1.02 (0.69,1.5)	1.13 (0.67,1.91)
	PM 2.5	1	0.74 (0.55,0.98)	0.72 (0.52,0.99)	0.95 (0.6,1.49)
	Sulfur Dioxide	1	0.75 (0.52,1.1)	0.84 (0.55,1.28)	0.79 (0.44,1.39)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 4 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxide	1	0.65 (0.34,1.22)	0.59 (0.29,1.2)	0.68 (0.27,1.7)
	Nitrogen Dioxide	1	1.27 (0.59,2.71)	1.11 (0.5,2.48)	1.94 (0.78,4.81)
	Ozone[a]	1	1.16 (0.62,2.15)	0.91 (0.44,1.85)	1.16 (0.53,2.54)
	PM 10	1	0.94 (0.49,1.81)	1.12 (0.58,2.14)	0.96 (0.41,2.23)
	PM 2.5	1	1.42 (0.77,2.62)	1.3 (0.68,2.48)	1.67 (0.75,3.72)
	Sulfur Dioxide	1	0.84 (0.4,1.77)	1.43 (0.66,3.1)	0.73 (0.27,2.02)
Coarctation of the Aorta					
	Carbon Monoxide	1	0.81 (0.48,1.37)	0.62 (0.34,1.12)	0.91 (0.43,1.9)
	Nitrogen Dioxide	1	1.65 (0.82,3.32)	1.53 (0.74,3.19)	1.48 (0.65,3.37)
	Ozone[a]	1	1.03 (0.6,1.77)	1.07 (0.58,1.97)	0.85 (0.43,1.66)
	PM 10	1	1.02 (0.58,1.78)	1.07 (0.61,1.87)	1.1 (0.54,2.22)
	PM 2.5	1	1.37 (0.82,2.29)	1.45 (0.85,2.48)	1.61 (0.82,3.14)
	Sulfur Dioxide	1	1.38 (0.71,2.67)	1.63 (0.82,3.23)	0.93 (0.41,2.14)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxide	1	1.12 (0.63,2)	0.91 (0.48,1.72)	1.05 (0.49,2.27)
	Nitrogen Dioxide	1	1.27 (0.69,2.36)	0.9 (0.46,1.77)	0.83 (0.37,1.88)
	Ozone[a]	1	0.86 (0.52,1.42)	0.89 (0.5,1.59)	0.77 (0.4,1.47)
	PM 10	1	0.92 (0.54,1.58)	0.89 (0.52,1.54)	1.01 (0.52,1.98)
	PM 2.5	1	1.11 (0.67,1.84)	0.92 (0.54,1.56)	1.13 (0.58,2.21)
	Sulfur Dioxide	1	0.83 (0.46,1.51)	1.14 (0.61,2.15)	0.6 (0.25,1.44)
d-TGA					
	Carbon Monoxide	1	1.15 (0.65,2.03)	1.65 (0.89,3.07)	1.01 (0.46,2.2)
	Nitrogen Dioxide	1	1.56 (0.82,2.94)	1.37 (0.69,2.72)	1.67 (0.76,3.64)
	Ozone[a]	1	0.88 (0.54,1.43)	0.76 (0.44,1.34)	0.83 (0.45,1.54)
	PM 10	1	0.78 (0.46,1.31)	0.84 (0.49,1.43)	1.07 (0.56,2.06)
	PM 2.5	1	1.04 (0.62,1.73)	1.43 (0.85,2.43)	1.31 (0.67,2.57)
	Sulfur Dioxide	1	0.9 (0.49,1.66)	1.09 (0.57,2.07)	1.16 (0.54,2.5)
Tetralogy of Fallot					
	Carbon Monoxide	1	0.94 (0.59,1.51)	0.95 (0.57,1.6)	0.73 (0.38,1.4)
	Nitrogen Dioxide	1	1.77 (0.99,3.14)	1.51 (0.81,2.8)	1.46 (0.72,2.96)
	Ozone[a]	1	1.21 (0.8,1.83)	0.88 (0.54,1.45)	0.81 (0.47,1.4)
	PM 10	1	0.69 (0.45,1.05)	0.82 (0.53,1.26)	0.87 (0.5,1.51)
	PM 2.5	1	0.87 (0.58,1.31)	0.96 (0.63,1.46)	1.06 (0.63,1.81)
	Sulfur Dioxide	1	1.43 (0.84,2.44)	0.91 (0.51,1.61)	0.94 (0.47,1.87)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 4 <10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxide	1	1.31 (0.63,2.74)	1.15 (0.53,2.54)	1.32 (0.52,3.32)
	Nitrogen Dioxide	1	1.01 (0.47,2.16)	1.02 (0.46,2.28)	1.01 (0.39,2.61)
	Ozone[a]	1	1.63 (0.83,3.21)	1.01 (0.46,2.21)	1.2 (0.52,2.78)
	PM 10	1	1.1 (0.53,2.28)	0.82 (0.39,1.73)	1.12 (0.47,2.68)
	PM 2.5	1	1.17 (0.59,2.29)	1.09 (0.54,2.19)	0.83 (0.32,2.14)
	Sulfur Dioxide	1	1.82 (0.8,4.14)	1.4 (0.6,3.29)	0.53 (0.16,1.69)
TAPVR					
	Carbon Monoxide	1	0.84 (0.42,1.65)	0.79 (0.36,1.73)	1.04 (0.4,2.7)
	Nitrogen Dioxide	1	0.98 (0.46,2.1)	0.85 (0.37,1.95)	1.1 (0.42,2.88)
	Ozone[a]	1	0.98 (0.48,2)	0.8 (0.37,1.75)	0.98 (0.43,2.24)
	PM 10	1	0.85 (0.41,1.78)	1.06 (0.52,2.17)	0.65 (0.25,1.67)
	PM 2.5	1	1.11 (0.56,2.18)	1.17 (0.58,2.35)	1.39 (0.59,3.3)
	Sulfur Dioxide	1	1.32 (0.57,3.06)	1.39 (0.59,3.28)	1.06 (0.38,3)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxide	1	1.47 (0.71,3.02)	0.99 (0.45,2.17)	0.99 (0.38,2.6)
	Nitrogen Dioxide	1	1.43 (0.65,3.15)	1.52 (0.66,3.51)	0.94 (0.33,2.69)
	Ozone[a]	1	0.88 (0.42,1.81)	1.02 (0.48,2.18)	0.83 (0.36,1.92)
	PM 10	1	0.98 (0.53,1.83)	0.5 (0.25,0.99)	0.45 (0.17,1.21)
	PM 2.5	1	1.09 (0.59,2.02)	0.8 (0.41,1.57)	1.06 (0.45,2.49)
	Sulfur Dioxide	1	1.59 (0.72,3.52)	0.87 (0.38,2.02)	0.96 (0.35,2.62)
Pulmonary Valve Stenosis					
	Carbon Monoxide	1	0.84 (0.53,1.35)	0.72 (0.42,1.22)	0.82 (0.43,1.56)
	Nitrogen Dioxide	1	1.34 (0.75,2.39)	0.82 (0.44,1.53)	0.97 (0.48,1.95)
	Ozone[a]	1	1.08 (0.67,1.73)	1.16 (0.69,1.98)	0.94 (0.53,1.68)
	PM 10	1	1.35 (0.82,2.2)	1.02 (0.61,1.69)	1.4 (0.76,2.56)
	PM 2.5	1	0.9 (0.6,1.35)	1.05 (0.69,1.61)	0.88 (0.5,1.54)
	Sulfur Dioxide	1	0.92 (0.56,1.51)	0.88 (0.52,1.51)	0.97 (0.5,1.87)
VSD-perimembranous					
	Carbon Monoxide	1	0.91 (0.59,1.4)	0.98 (0.6,1.59)	0.9 (0.5,1.62)
	Nitrogen Dioxide	1	1.24 (0.74,2.06)	1.31 (0.75,2.28)	1.09 (0.57,2.09)
	Ozone[a]	1	1.15 (0.78,1.71)	1.05 (0.66,1.66)	1.15 (0.7,1.9)
	PM 10	1	1.13 (0.75,1.71)	1.06 (0.7,1.62)	0.9 (0.52,1.57)
	PM 2.5	1	1.02 (0.7,1.47)	1.06 (0.72,1.56)	1.14 (0.68,1.89)
	Sulfur Dioxide	1	1.36 (0.86,2.15)	0.94 (0.57,1.55)	0.77 (0.42,1.42)
ASD-all					
	Carbon Monoxide	1	1.42 (0.88,2.3)	1.3 (0.76,2.21)	1.19 (0.62,2.29)
	Nitrogen Dioxide	1	1.6 (0.93,2.77)	1.52 (0.85,2.75)	1.6 (0.81,3.14)
	Ozone[a]	1	1.17 (0.83,1.63)	1.16 (0.78,1.72)	0.9 (0.56,1.44)
	PM 10	1	0.99 (0.68,1.42)	0.95 (0.65,1.39)	0.8 (0.48,1.36)
	PM 2.5	1	1.01 (0.75,1.37)	0.83 (0.59,1.16)	0.83 (0.51,1.35)
	Sulfur Dioxide	1	1.01 (0.68,1.49)	1.11 (0.71,1.73)	0.9 (0.49,1.63)

Table A2.4 (cont.)

		Week 5			
Cardiac Defect	Pollutant	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxid	1	1.48 (0.73,2.99)	1.38 (0.64,2.96)	0.95 (0.36,2.5)
	Nitrogen Dioxide	1	0.96 (0.46,1.98)	0.79 (0.36,1.72)	0.67 (0.26,1.75)
	Ozone[a]	1	0.97 (0.53,1.78)	0.72 (0.35,1.46)	0.77 (0.35,1.71)
	PM 10	1	0.9 (0.49,1.64)	0.88 (0.47,1.63)	0.72 (0.3,1.73)
	PM 2.5	1	0.83 (0.48,1.45)	1.28 (0.72,2.26)	1 (0.43,2.31)
	Sulfur Dioxide	1	0.69 (0.34,1.39)	0.63 (0.29,1.34)	1.11 (0.45,2.72)
Coarctation of the Aorta					
	Carbon Monoxid	1	0.94 (0.55,1.62)	0.88 (0.48,1.62)	0.78 (0.35,1.71)
	Nitrogen Dioxide	1	1.22 (0.58,2.54)	1.28 (0.6,2.73)	1.55 (0.68,3.58)
	Ozone[a]	1	0.55 (0.32,0.94)	0.72 (0.39,1.31)	0.94 (0.49,1.8)
	PM 10	1	1.78 (0.94,3.38)	1.71 (0.9,3.26)	1.13 (0.51,2.54)
	PM 2.5	1	0.99 (0.63,1.57)	0.9 (0.55,1.46)	0.98 (0.51,1.89)
	Sulfur Dioxide	1	1.06 (0.57,1.97)	1.01 (0.53,1.94)	1.08 (0.5,2.32)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxid	1	1.09 (0.6,1.97)	1.13 (0.59,2.15)	0.79 (0.35,1.78)
	Nitrogen Dioxide	1	0.86 (0.46,1.61)	0.99 (0.51,1.94)	0.63 (0.27,1.47)
	Ozone[a]	1	0.76 (0.46,1.26)	0.93 (0.52,1.66)	0.79 (0.41,1.52)
	PM 10	1	0.89 (0.51,1.55)	1.32 (0.77,2.29)	0.97 (0.47,1.98)
	PM 2.5	1	1.24 (0.75,2.05)	0.87 (0.5,1.51)	1.52 (0.79,2.94)
	Sulfur Dioxide	1	1.35 (0.68,2.66)	1.53 (0.75,3.1)	1.29 (0.55,3.04)
d-TGA					
	Carbon Monoxid	1	0.83 (0.48,1.43)	0.99 (0.54,1.82)	0.87 (0.4,1.85)
	Nitrogen Dioxide	1	0.6 (0.34,1.04)	0.54 (0.29,0.99)	0.64 (0.3,1.34)
	Ozone[a]	1	1.29 (0.8,2.09)	1.53 (0.86,2.69)	1.27 (0.67,2.41)
	PM 10	1	0.81 (0.48,1.35)	0.88 (0.52,1.49)	0.92 (0.47,1.8)
	PM 2.5	1	0.92 (0.57,1.47)	0.92 (0.56,1.51)	0.97 (0.5,1.87)
	Sulfur Dioxide	1	0.86 (0.48,1.54)	0.74 (0.4,1.39)	0.95 (0.45,1.98)
Tetralogy of Fallot					
	Carbon Monoxid	1	1.09 (0.67,1.77)	0.94 (0.55,1.63)	1.24 (0.64,2.39)
	Nitrogen Dioxide	1	0.53 (0.33,0.86)	0.55 (0.32,0.93)	0.47 (0.24,0.92)
	Ozone[a]	1	1.03 (0.68,1.56)	1.16 (0.71,1.9)	1.31 (0.76,2.26)
	PM 10	1	1.62 (0.96,2.74)	1.66 (0.97,2.83)	1.62 (0.86,3.05)
	PM 2.5	1	1.11 (0.73,1.68)	1.05 (0.68,1.63)	0.9 (0.51,1.58)
	Sulfur Dioxide	1	0.93 (0.56,1.53)	0.86 (0.5,1.48)	0.76 (0.39,1.49)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 5 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxid	1	0.57 (0.29,1.13)	0.81 (0.39,1.69)	0.68 (0.27,1.74)
	Nitrogen Dioxide	1	0.72 (0.33,1.56)	0.78 (0.35,1.76)	0.86 (0.34,2.21)
	Ozone[a]	1	0.89 (0.45,1.74)	1.16 (0.55,2.44)	1.36 (0.59,3.11)
	PM 10	1	0.76 (0.38,1.49)	0.86 (0.43,1.69)	1.02 (0.43,2.39)
	PM 2.5	1	1.13 (0.59,2.16)	0.65 (0.32,1.31)	1.29 (0.55,3.02)
	Sulfur Dioxide	1	0.62 (0.29,1.29)	0.91 (0.42,1.94)	0.87 (0.34,2.27)
TAPVR					
	Carbon Monoxid	1	1.36 (0.68,2.72)	0.8 (0.36,1.8)	1.15 (0.44,3.04)
	Nitrogen Dioxide	1	0.54 (0.24,1.2)	1.09 (0.48,2.49)	1.38 (0.52,3.62)
	Ozone[a]	1	1.55 (0.77,3.14)	1.38 (0.63,3.02)	1 (0.42,2.38)
	PM 10	1	0.69 (0.33,1.47)	1.07 (0.52,2.2)	1.58 (0.67,3.74)
	PM 2.5	1	1.53 (0.68,3.4)	1.7 (0.76,3.79)	1.91 (0.75,4.84)
	Sulfur Dioxide	1	1.25 (0.54,2.93)	1.74 (0.74,4.11)	0.86 (0.28,2.61)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxid	1	1.39 (0.66,2.93)	1.56 (0.7,3.46)	1.1 (0.4,2.97)
	Nitrogen Dioxide	1	1.16 (0.51,2.64)	1.32 (0.56,3.1)	0.76 (0.26,2.2)
	Ozone[a]	1	0.78 (0.38,1.62)	1.24 (0.58,2.62)	1.02 (0.44,2.33)
	PM 10	1	1.27 (0.61,2.64)	1.07 (0.5,2.25)	1.23 (0.49,3.1)
	PM 2.5	1	1.23 (0.64,2.35)	1.2 (0.6,2.39)	1.53 (0.65,3.6)
	Sulfur Dioxide	1	0.77 (0.37,1.59)	0.8 (0.37,1.73)	1.23 (0.49,3.12)
Pulmonary Valve Stenosis					
	Carbon Monoxid	1	0.94 (0.57,1.53)	1 (0.58,1.72)	1.3 (0.67,2.53)
	Nitrogen Dioxide	1	0.55 (0.31,0.96)	0.85 (0.47,1.54)	1.14 (0.57,2.24)
	Ozone[a]	1	1.08 (0.68,1.71)	1.02 (0.6,1.73)	1.11 (0.63,1.98)
	PM 10	1	0.7 (0.46,1.07)	0.8 (0.52,1.23)	0.8 (0.44,1.42)
	PM 2.5	1	1 (0.66,1.51)	1.12 (0.72,1.72)	1.83 (1.08,3.12)
	Sulfur Dioxide	1	1.33 (0.76,2.31)	1.71 (0.95,3.06)	1.39 (0.69,2.81)
VSD-perimembranous					
	Carbon Monoxid	1	0.87 (0.56,1.36)	0.99 (0.6,1.64)	0.97 (0.53,1.77)
	Nitrogen Dioxide	1	1.03 (0.61,1.75)	1.23 (0.7,2.16)	1.75 (0.92,3.33)
	Ozone[a]	1	1.21 (0.82,1.78)	1.22 (0.77,1.93)	1.33 (0.8,2.2)
	PM 10	1	1.3 (0.84,2)	1.3 (0.84,2.03)	1.76 (1.02,3.03)
	PM 2.5	1	1.34 (0.92,1.95)	1 (0.67,1.5)	1.34 (0.8,2.23)
	Sulfur Dioxide	1	0.97 (0.61,1.53)	1.23 (0.75,2.02)	1.13 (0.62,2.04)
ASD-all					
	Carbon Monoxid	1	1.14 (0.71,1.85)	1.03 (0.6,1.77)	1.58 (0.83,3.02)
	Nitrogen Dioxide	1	0.74 (0.45,1.22)	0.87 (0.5,1.5)	1.05 (0.55,2.01)
	Ozone[a]	1	1.09 (0.78,1.54)	1.4 (0.93,2.1)	1.76 (1.11,2.8)
	PM 10	1	1.04 (0.71,1.51)	1.18 (0.8,1.73)	1.13 (0.67,1.91)
	PM 2.5	1	0.97 (0.71,1.31)	0.93 (0.67,1.31)	1.13 (0.71,1.82)
	Sulfur Dioxide	1	1.37 (0.92,2.05)	1.23 (0.78,1.95)	1.37 (0.77,2.44)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 6 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxide	1	1.14 (0.58,2.24)	1.18 (0.57,2.47)	0.74 (0.28,1.94)
	Nitrogen Dioxide	1	0.95 (0.47,1.92)	0.68 (0.32,1.48)	0.57 (0.22,1.47)
	Ozone[a]	1	1.38 (0.75,2.54)	0.9 (0.44,1.84)	0.74 (0.33,1.66)
	PM 10	1	0.73 (0.41,1.31)	0.64 (0.35,1.17)	0.77 (0.34,1.76)
	PM 2.5	1	1.59 (0.86,2.93)	1.06 (0.55,2.05)	0.81 (0.33,2)
	Sulfur Dioxide	1	1.43 (0.67,3.07)	0.78 (0.35,1.76)	1.3 (0.51,3.33)
Coarctation of the Aorta					
	Carbon Monoxide	1	1.48 (0.83,2.64)	1.39 (0.74,2.61)	1.19 (0.54,2.62)
	Nitrogen Dioxide	1	0.92 (0.47,1.8)	1.23 (0.61,2.48)	1.32 (0.6,2.91)
	Ozone[a]	1	1.38 (0.82,2.33)	1.34 (0.72,2.49)	1.37 (0.7,2.7)
	PM 10	1	1.03 (0.59,1.77)	0.93 (0.53,1.63)	0.99 (0.48,2.04)
	PM 2.5	1	0.71 (0.45,1.13)	0.92 (0.57,1.49)	0.96 (0.5,1.82)
	Sulfur Dioxide	1	1.39 (0.72,2.69)	1.05 (0.53,2.08)	1.32 (0.6,2.9)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxide	1	0.97 (0.55,1.71)	1.3 (0.7,2.43)	0.82 (0.36,1.83)
	Nitrogen Dioxide	1	1.1 (0.58,2.09)	1.11 (0.56,2.2)	0.89 (0.39,2.04)
	Ozone[a]	1	1.57 (0.94,2.62)	1.47 (0.81,2.68)	1.3 (0.66,2.54)
	PM 10	1	1.12 (0.63,1.98)	1.31 (0.74,2.34)	0.89 (0.42,1.88)
	PM 2.5	1	1.11 (0.65,1.88)	1.22 (0.71,2.12)	0.91 (0.44,1.85)
	Sulfur Dioxide	1	1.24 (0.65,2.37)	1.27 (0.65,2.5)	0.68 (0.27,1.71)
d-TGA					
	Carbon Monoxide	1	1.12 (0.64,1.94)	1.16 (0.63,2.14)	1.34 (0.63,2.81)
	Nitrogen Dioxide	1	0.97 (0.52,1.82)	1.21 (0.62,2.36)	1.55 (0.72,3.34)
	Ozone[a]	1	0.86 (0.53,1.39)	1.13 (0.65,1.95)	0.91 (0.48,1.7)
	PM 10	1	1.25 (0.71,2.21)	0.89 (0.5,1.61)	1.1 (0.54,2.24)
	PM 2.5	1	0.82 (0.5,1.34)	0.88 (0.53,1.46)	1.15 (0.61,2.17)
	Sulfur Dioxide	1	1 (0.54,1.87)	1.08 (0.56,2.07)	1.31 (0.61,2.81)
Tetralogy of Fallot					
	Carbon Monoxide	1	1.24 (0.76,2.03)	1.39 (0.81,2.39)	1.6 (0.83,3.1)
	Nitrogen Dioxide	1	1.22 (0.7,2.14)	1.42 (0.78,2.58)	0.97 (0.47,1.98)
	Ozone[a]	1	1.09 (0.72,1.65)	1.09 (0.67,1.77)	0.88 (0.5,1.52)
	PM 10	1	0.84 (0.55,1.28)	0.71 (0.46,1.1)	0.81 (0.46,1.43)
	PM 2.5	1	1.19 (0.77,1.84)	1.09 (0.69,1.72)	0.79 (0.44,1.41)
	Sulfur Dioxide	1	1 (0.59,1.71)	1.15 (0.66,2.03)	0.91 (0.45,1.84)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 6 <10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxide	1	1.39 (0.68,2.85)	1.07 (0.49,2.33)	1.18 (0.47,2.99)
	Nitrogen Dioxide	1	0.79 (0.36,1.71)	1.02 (0.46,2.28)	0.69 (0.26,1.86)
	Ozone[a]	1	1.28 (0.67,2.47)	0.9 (0.43,1.91)	0.72 (0.31,1.7)
	PM 10	1	0.65 (0.34,1.27)	0.61 (0.31,1.2)	1 (0.44,2.29)
	PM 2.5	1	0.93 (0.47,1.83)	0.97 (0.48,1.94)	0.82 (0.33,2.03)
	Sulfur Dioxide	1	1.05 (0.47,2.32)	1.19 (0.53,2.68)	1.3 (0.5,3.42)
TAPVR					
	Carbon Monoxide	1	1.15 (0.59,2.27)	0.94 (0.43,2.07)	0.53 (0.19,1.45)
	Nitrogen Dioxide	1	1.09 (0.5,2.39)	0.79 (0.34,1.82)	0.57 (0.21,1.59)
	Ozone[a]	1	0.8 (0.39,1.62)	0.95 (0.44,2.04)	1.05 (0.45,2.42)
	PM 10	1	1.19 (0.57,2.52)	0.84 (0.39,1.8)	0.76 (0.29,1.99)
	PM 2.5	1	0.88 (0.47,1.62)	0.54 (0.27,1.07)	0.93 (0.4,2.15)
	Sulfur Dioxide	1	1.19 (0.51,2.75)	1.1 (0.47,2.58)	1.95 (0.74,5.11)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxide	1	0.97 (0.48,1.93)	0.97 (0.45,2.08)	1.61 (0.64,4.06)
	Nitrogen Dioxide	1	0.62 (0.3,1.27)	0.7 (0.32,1.52)	0.59 (0.22,1.59)
	Ozone[a]	1	1.06 (0.53,2.15)	1.17 (0.55,2.51)	1.17 (0.51,2.69)
	PM 10	1	1.09 (0.52,2.29)	1.11 (0.53,2.33)	0.88 (0.34,2.27)
	PM 2.5	1	0.73 (0.4,1.31)	0.66 (0.35,1.25)	0.95 (0.41,2.18)
	Sulfur Dioxide	1	1.21 (0.55,2.67)	1 (0.44,2.27)	1.12 (0.42,3.02)
Pulmonary Valve Stenosis					
	Carbon Monoxide	1	1.57 (0.95,2.6)	1.31 (0.75,2.29)	1.5 (0.77,2.94)
	Nitrogen Dioxide	1	0.9 (0.5,1.63)	1.22 (0.65,2.28)	1.38 (0.69,2.8)
	Ozone[a]	1	1.14 (0.73,1.81)	1.32 (0.78,2.22)	1.24 (0.7,2.22)
	PM 10	1	1.07 (0.67,1.71)	1.11 (0.69,1.78)	1.15 (0.62,2.12)
	PM 2.5	1	0.97 (0.64,1.47)	0.97 (0.63,1.49)	0.82 (0.46,1.46)
	Sulfur Dioxide	1	1.14 (0.67,1.95)	1.07 (0.61,1.88)	1.09 (0.55,2.17)
VSD-perimembranous					
	Carbon Monoxide	1	1.04 (0.68,1.61)	0.86 (0.53,1.4)	0.76 (0.42,1.38)
	Nitrogen Dioxide	1	0.7 (0.43,1.12)	0.79 (0.47,1.34)	0.63 (0.34,1.18)
	Ozone[a]	1	1.09 (0.75,1.6)	1.16 (0.74,1.81)	1.08 (0.65,1.79)
	PM 10	1	0.87 (0.59,1.27)	0.81 (0.55,1.2)	0.75 (0.44,1.29)
	PM 2.5	1	0.88 (0.61,1.26)	0.95 (0.65,1.38)	0.72 (0.42,1.23)
	Sulfur Dioxide	1	0.95 (0.6,1.51)	1.13 (0.69,1.85)	1.02 (0.56,1.86)
ASD-all					
	Carbon Monoxide	1	0.97 (0.61,1.52)	0.9 (0.54,1.49)	1.13 (0.6,2.13)
	Nitrogen Dioxide	1	0.77 (0.47,1.26)	0.81 (0.47,1.39)	0.76 (0.4,1.45)
	Ozone[a]	1	1.04 (0.75,1.45)	1.02 (0.69,1.52)	0.72 (0.45,1.16)
	PM 10	1	1.21 (0.83,1.76)	1.03 (0.7,1.53)	1.23 (0.73,2.08)
	PM 2.5	1	1.05 (0.78,1.43)	0.84 (0.6,1.18)	0.87 (0.53,1.42)
	Sulfur Dioxide	1	0.95 (0.64,1.4)	1.1 (0.71,1.71)	1.07 (0.6,1.92)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 7 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxide	1	0.77 (0.4,1.5)	1.11 (0.54,2.28)	1.35 (0.55,3.29)
	Nitrogen Dioxide	1	0.96 (0.47,1.95)	0.9 (0.42,1.94)	0.98 (0.4,2.43)
	Ozone[a]	1	0.89 (0.49,1.63)	0.71 (0.36,1.44)	1.27 (0.6,2.69)
	PM 10	1	0.89 (0.48,1.66)	1.06 (0.57,1.98)	0.82 (0.35,1.96)
	PM 2.5	1	1.03 (0.6,1.76)	0.87 (0.48,1.56)	0.95 (0.41,2.21)
	Sulfur Dioxide	1	1.23 (0.59,2.53)	0.98 (0.45,2.14)	0.52 (0.18,1.46)
Coarctation of the Aorta					
	Carbon Monoxide	1	1.44 (0.81,2.58)	1.6 (0.85,3.01)	1.7 (0.78,3.71)
	Nitrogen Dioxide	1	1.31 (0.66,2.6)	1.4 (0.68,2.86)	1.79 (0.81,3.96)
	Ozone[a]	1	1.11 (0.66,1.87)	0.97 (0.53,1.77)	1.27 (0.66,2.44)
	PM 10	1	1.4 (0.75,2.6)	1.54 (0.83,2.87)	1.82 (0.86,3.82)
	PM 2.5	1	1.23 (0.76,2.01)	1.2 (0.72,2)	1.15 (0.58,2.28)
	Sulfur Dioxide	1	1.37 (0.69,2.72)	1.49 (0.74,3.02)	1.3 (0.57,2.93)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxide	1	0.79 (0.45,1.37)	0.96 (0.52,1.77)	1.26 (0.59,2.67)
	Nitrogen Dioxide	1	1.21 (0.64,2.28)	1.37 (0.69,2.7)	1.34 (0.6,2.98)
	Ozone[a]	1	1.2 (0.73,1.99)	1.03 (0.58,1.83)	0.9 (0.47,1.72)
	PM 10	1	1.97 (1.02,3.82)	1.46 (0.75,2.86)	1.69 (0.78,3.64)
	PM 2.5	1	1.25 (0.73,2.15)	1.51 (0.86,2.63)	1.62 (0.81,3.27)
	Sulfur Dioxide	1	1.31 (0.67,2.53)	1.53 (0.77,3.04)	0.87 (0.36,2.13)
d-TGA					
	Carbon Monoxide	1	1.12 (0.64,1.94)	1.08 (0.59,1.99)	1.42 (0.68,2.97)
	Nitrogen Dioxide	1	1.15 (0.64,2.06)	0.94 (0.49,1.77)	0.74 (0.34,1.61)
	Ozone[a]	1	0.59 (0.37,0.95)	0.66 (0.39,1.12)	0.64 (0.35,1.17)
	PM 10	1	1.16 (0.66,2.04)	1.3 (0.74,2.3)	1.07 (0.53,2.19)
	PM 2.5	1	1.18 (0.71,1.95)	1.19 (0.7,2.01)	1.32 (0.68,2.58)
	Sulfur Dioxide	1	0.93 (0.5,1.71)	1.19 (0.63,2.27)	0.98 (0.45,2.12)
Tetralogy of Fallot					
	Carbon Monoxide	1	1.24 (0.76,2.01)	1.32 (0.77,2.25)	1.73 (0.91,3.32)
	Nitrogen Dioxide	1	1 (0.6,1.68)	0.79 (0.45,1.39)	1.19 (0.62,2.27)
	Ozone[a]	1	1.02 (0.68,1.53)	0.84 (0.52,1.35)	0.89 (0.53,1.51)
	PM 10	1	0.92 (0.59,1.43)	0.93 (0.59,1.46)	1.09 (0.62,1.92)
	PM 2.5	1	1.16 (0.75,1.8)	1.41 (0.9,2.2)	1.37 (0.79,2.4)
	Sulfur Dioxide	1	1.35 (0.78,2.33)	1.4 (0.78,2.51)	1.13 (0.56,2.31)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 7 <10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxide	1	0.88 (0.44,1.75)	0.88 (0.42,1.87)	1.61 (0.66,3.93)
	Nitrogen Dioxide	1	1.67 (0.73,3.81)	1.21 (0.52,2.83)	0.88 (0.32,2.41)
	Ozone[a]	1	0.98 (0.52,1.88)	0.74 (0.36,1.53)	0.64 (0.28,1.46)
	PM 10	1	1.17 (0.54,2.54)	1.31 (0.61,2.83)	1.41 (0.57,3.49)
	PM 2.5	1	1.54 (0.7,3.41)	1.27 (0.57,2.84)	1.96 (0.78,4.9)
	Sulfur Dioxide	1	0.89 (0.43,1.86)	0.78 (0.36,1.68)	0.55 (0.2,1.54)
TAPVR					
	Carbon Monoxide	1	0.57 (0.3,1.1)	0.53 (0.25,1.15)	1.25 (0.49,3.16)
	Nitrogen Dioxide	1	1.37 (0.61,3.04)	1.44 (0.62,3.34)	0.72 (0.25,2.05)
	Ozone[a]	1	1.07 (0.54,2.11)	0.72 (0.33,1.57)	0.85 (0.37,1.93)
	PM 10	1	1.64 (0.72,3.7)	1.17 (0.51,2.67)	1.12 (0.42,2.93)
	PM 2.5	1	1.47 (0.75,2.87)	1.14 (0.56,2.31)	0.87 (0.33,2.27)
	Sulfur Dioxide	1	1.39 (0.6,3.21)	0.99 (0.42,2.34)	1.37 (0.51,3.66)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxide	1	0.99 (0.49,1.97)	1.14 (0.54,2.44)	1.45 (0.57,3.73)
	Nitrogen Dioxide	1	1.77 (0.81,3.87)	0.93 (0.4,2.16)	0.93 (0.35,2.52)
	Ozone[a]	1	0.69 (0.35,1.37)	0.71 (0.34,1.49)	0.76 (0.34,1.7)
	PM 10	1	0.82 (0.4,1.65)	1.24 (0.62,2.46)	1.25 (0.52,3.01)
	PM 2.5	1	0.95 (0.52,1.73)	1.02 (0.54,1.92)	0.83 (0.34,2.03)
	Sulfur Dioxide	1	0.83 (0.4,1.71)	1.02 (0.47,2.2)	0.52 (0.18,1.55)
Pulmonary Valve Stenosis					
	Carbon Monoxide	1	0.78 (0.49,1.25)	0.88 (0.52,1.49)	1.52 (0.81,2.87)
	Nitrogen Dioxide	1	1.15 (0.64,2.05)	1.32 (0.71,2.46)	1.31 (0.65,2.63)
	Ozone[a]	1	0.75 (0.48,1.16)	0.59 (0.36,0.97)	0.66 (0.38,1.14)
	PM 10	1	1.45 (0.88,2.41)	1.41 (0.85,2.37)	1.57 (0.84,2.95)
	PM 2.5	1	1.12 (0.74,1.69)	1.1 (0.72,1.7)	0.91 (0.5,1.64)
	Sulfur Dioxide	1	1.53 (0.87,2.69)	1.61 (0.89,2.91)	0.96 (0.46,2)
VSD-perimembranous					
	Carbon Monoxide	1	1.2 (0.77,1.88)	1.35 (0.82,2.21)	1.79 (0.99,3.23)
	Nitrogen Dioxide	1	1.23 (0.75,2.01)	0.77 (0.45,1.32)	0.95 (0.51,1.77)
	Ozone[a]	1	0.74 (0.51,1.06)	0.49 (0.32,0.75)	0.56 (0.35,0.89)
	PM 10	1	0.96 (0.65,1.42)	0.91 (0.61,1.35)	0.98 (0.58,1.66)
	PM 2.5	1	1.21 (0.83,1.75)	1.13 (0.77,1.68)	0.9 (0.52,1.56)
	Sulfur Dioxide	1	1.22 (0.77,1.93)	1.03 (0.62,1.69)	0.98 (0.54,1.78)
ASD-all					
	Carbon Monoxide	1	1.26 (0.79,2.01)	1.13 (0.67,1.91)	0.99 (0.52,1.9)
	Nitrogen Dioxide	1	1.26 (0.75,2.11)	1.18 (0.67,2.07)	1.12 (0.58,2.16)
	Ozone[a]	1	0.79 (0.57,1.09)	0.71 (0.48,1.05)	0.94 (0.6,1.45)
	PM 10	1	1 (0.7,1.44)	1.02 (0.7,1.49)	0.91 (0.53,1.54)
	PM 2.5	1	1.19 (0.87,1.64)	1.19 (0.84,1.68)	1.12 (0.67,1.86)
	Sulfur Dioxide	1	1.04 (0.7,1.53)	1.05 (0.67,1.64)	0.79 (0.43,1.43)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 8 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis					
	Carbon Monoxide	1	0.93 (0.48,1.79)	0.94 (0.46,1.92)	0.9 (0.37,2.18)
	Nitrogen Dioxide	1	0.72 (0.35,1.48)	0.96 (0.45,2.03)	1.72 (0.73,4.04)
	Ozone[a]	1	1.29 (0.72,2.34)	1.48 (0.77,2.84)	1 (0.47,2.13)
	PM 10	1	0.46 (0.25,0.85)	0.82 (0.46,1.46)	1.02 (0.48,2.17)
	PM 2.5	1	1.18 (0.67,2.06)	0.95 (0.52,1.73)	1.04 (0.46,2.35)
	Sulfur Dioxide	1	1.45 (0.67,3.11)	1.26 (0.56,2.82)	1.83 (0.71,4.71)
Coarctation of the Aorta					
	Carbon Monoxide	1	1.13 (0.65,1.94)	1.12 (0.62,2.03)	1.06 (0.5,2.25)
	Nitrogen Dioxide	1	0.74 (0.41,1.34)	0.67 (0.36,1.25)	0.62 (0.3,1.31)
	Ozone[a]	1	0.81 (0.5,1.31)	0.83 (0.48,1.42)	0.75 (0.41,1.36)
	PM 10	1	1.05 (0.58,1.89)	1.22 (0.68,2.18)	1.44 (0.71,2.9)
	PM 2.5	1	1.47 (0.9,2.4)	1.09 (0.64,1.83)	1.15 (0.59,2.24)
	Sulfur Dioxide	1	1.08 (0.59,1.97)	1.35 (0.72,2.51)	1.31 (0.62,2.78)
Hypoplastic Left Heart Syndrome					
	Carbon Monoxide	1	1.11 (0.63,1.93)	0.98 (0.53,1.81)	0.6 (0.27,1.33)
	Nitrogen Dioxide	1	0.67 (0.38,1.18)	0.67 (0.37,1.24)	0.76 (0.36,1.61)
	Ozone[a]	1	1.1 (0.68,1.79)	1.25 (0.73,2.14)	1.65 (0.91,2.99)
	PM 10	1	0.62 (0.37,1.03)	0.72 (0.43,1.19)	0.98 (0.52,1.85)
	PM 2.5	1	0.85 (0.53,1.37)	0.93 (0.57,1.54)	0.72 (0.36,1.42)
	Sulfur Dioxide	1	1.99 (1.01,3.95)	1.18 (0.57,2.42)	1.74 (0.76,3.98)
d-TGA					
	Carbon Monoxide	1	1 (0.59,1.71)	0.94 (0.52,1.69)	1.08 (0.53,2.21)
	Nitrogen Dioxide	1	0.9 (0.5,1.62)	1.21 (0.65,2.26)	1.23 (0.59,2.59)
	Ozone[a]	1	1.48 (0.96,2.29)	0.91 (0.53,1.54)	1.18 (0.67,2.09)
	PM 10	1	0.92 (0.5,1.66)	1.44 (0.8,2.58)	1.52 (0.76,3.03)
	PM 2.5	1	1.28 (0.76,2.16)	1.33 (0.77,2.28)	1.17 (0.59,2.3)
	Sulfur Dioxide	1	1.13 (0.63,2.03)	1.15 (0.62,2.13)	0.86 (0.4,1.86)
Tetralogy of Fallot					
	Carbon Monoxide	1	0.91 (0.58,1.43)	0.92 (0.56,1.52)	0.71 (0.38,1.35)
	Nitrogen Dioxide	1	0.91 (0.55,1.52)	1.04 (0.6,1.8)	1.1 (0.58,2.11)
	Ozone[a]	1	0.9 (0.61,1.32)	1.01 (0.66,1.56)	1.03 (0.63,1.68)
	PM 10	1	0.58 (0.38,0.89)	0.87 (0.57,1.31)	0.95 (0.56,1.62)
	PM 2.5	1	0.82 (0.54,1.23)	1.14 (0.75,1.74)	1.42 (0.85,2.37)
	Sulfur Dioxide	1	1.17 (0.71,1.95)	1.15 (0.67,1.98)	1.29 (0.67,2.5)

Table A2.4 (cont.)

Cardiac Defect	Pollutant	Week 8 <10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Other Conotruncals					
	Carbon Monoxide	1	0.96 (0.49,1.91)	0.91 (0.43,1.9)	0.74 (0.29,1.85)
	Nitrogen Dioxide	1	0.71 (0.33,1.51)	0.99 (0.45,2.17)	1.17 (0.47,2.92)
	Ozone[a]	1	0.71 (0.37,1.39)	1.23 (0.63,2.4)	1.19 (0.56,2.57)
	PM 10	1	0.86 (0.43,1.72)	0.83 (0.42,1.66)	0.77 (0.32,1.84)
	PM 2.5	1	0.6 (0.32,1.14)	1.07 (0.57,1.99)	0.63 (0.25,1.59)
	Sulfur Dioxide	1	1.49 (0.66,3.35)	1.54 (0.67,3.51)	1.15 (0.42,3.15)
TAPVR					
	Carbon Monoxide	1	0.82 (0.43,1.59)	0.76 (0.36,1.63)	1.04 (0.41,2.63)
	Nitrogen Dioxide	1	0.77 (0.37,1.62)	0.5 (0.22,1.14)	1.65 (0.68,4.01)
	Ozone[a]	1	1.09 (0.56,2.11)	1 (0.48,2.09)	1.14 (0.52,2.53)
	PM 10	1	0.48 (0.25,0.92)	0.47 (0.24,0.91)	0.99 (0.45,2.17)
	PM 2.5	1	1.54 (0.75,3.15)	1.05 (0.5,2.23)	1.27 (0.51,3.14)
	Sulfur Dioxide	1	1.72 (0.71,4.2)	1.88 (0.77,4.57)	1.38 (0.48,3.97)
Pulmonary/Tricuspid Atresia					
	Carbon Monoxide	1	0.72 (0.38,1.38)	0.89 (0.44,1.82)	0.51 (0.19,1.36)
	Nitrogen Dioxide	1	0.68 (0.33,1.4)	0.68 (0.31,1.47)	1.19 (0.48,2.92)
	Ozone[a]	1	1.98 (1.03,3.82)	1.29 (0.61,2.72)	1.22 (0.55,2.7)
	PM 10	1	0.9 (0.44,1.84)	0.83 (0.41,1.7)	1.16 (0.49,2.74)
	PM 2.5	1	0.59 (0.34,1.01)	0.45 (0.24,0.83)	0.7 (0.31,1.57)
	Sulfur Dioxide	1	0.84 (0.42,1.66)	0.74 (0.35,1.56)	0.93 (0.36,2.38)
Pulmonary Valve Stenosis					
	Carbon Monoxide	1	1.43 (0.87,2.35)	1.58 (0.91,2.73)	1.01 (0.51,1.98)
	Nitrogen Dioxide	1	1.1 (0.62,1.96)	1.05 (0.57,1.93)	1.53 (0.78,3)
	Ozone[a]	1	0.9 (0.6,1.37)	0.94 (0.59,1.5)	1.14 (0.69,1.9)
	PM 10	1	0.83 (0.51,1.36)	1.27 (0.79,2.05)	1.43 (0.8,2.57)
	PM 2.5	1	1.43 (0.91,2.24)	1.37 (0.86,2.19)	1.71 (0.97,3)
	Sulfur Dioxide	1	1.49 (0.87,2.53)	1.68 (0.96,2.95)	1.42 (0.71,2.81)
VSD-perimembranous					
	Carbon Monoxide	1	0.84 (0.55,1.27)	0.83 (0.53,1.32)	0.87 (0.49,1.53)
	Nitrogen Dioxide	1	0.94 (0.58,1.53)	1.05 (0.62,1.78)	1.88 (1.04,3.4)
	Ozone[a]	1	1.13 (0.79,1.6)	0.98 (0.65,1.48)	1.43 (0.91,2.24)
	PM 10	1	1.01 (0.66,1.56)	1.48 (0.96,2.28)	1.24 (0.72,2.16)
	PM 2.5	1	0.93 (0.65,1.32)	1.08 (0.74,1.56)	1.25 (0.77,2.04)
	Sulfur Dioxide	1	0.82 (0.54,1.25)	1 (0.63,1.57)	0.93 (0.53,1.63)
ASD-all					
	Carbon Monoxide	1	0.68 (0.44,1.04)	0.83 (0.52,1.33)	0.6 (0.33,1.12)
	Nitrogen Dioxide	1	1.14 (0.68,1.9)	1.24 (0.71,2.14)	1.49 (0.79,2.81)
	Ozone[a]	1	1.27 (0.92,1.74)	1.24 (0.86,1.8)	1.17 (0.76,1.81)
	PM 10	1	0.99 (0.69,1.43)	0.9 (0.62,1.32)	0.99 (0.6,1.64)
	PM 2.5	1	0.87 (0.65,1.18)	0.96 (0.69,1.33)	0.87 (0.54,1.4)
	Sulfur Dioxide	1	1.13 (0.78,1.66)	1.03 (0.67,1.59)	1.1 (0.62,1.93)

Table A2.5: Adjusted Odds Ratios and 95% Confidence Intervals between Cardiac Birth Defects and 7-week average exposure to criteria air pollutants among participants who lived within 10 km of a stationary air monitor[a]

	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Carbon Monoxide, ppm				
LVOTO	1	1.38 (0.78,2.45)	1.39 (0.78,2.47)	1.25 (0.62,2.53)
CONOTRUNCALS	1	1.19 (0.74,1.94)	1.13 (0.69,1.85)	1.43 (0.8,2.57)
APVR	1	0.51 (0.18,1.42)	0.56 (0.2,1.57)	0.59 (0.16,2.18)
RVOTO	1	0.99 (0.57,1.74)	0.89 (0.5,1.57)	0.7 (0.33,1.47)
SEPTALS	1	0.89 (0.59,1.36)	1.03 (0.68,1.56)	1.1 (0.66,1.82)
Nitrogen Dioxide, ppb				
LVOTO	1	1.25 (0.54,2.88)	1.37 (0.6,3.13)	1.44 (0.58,3.61)
CONOTRUNCALS	1	1 (0.49,2.04)	1.2 (0.59,2.43)	1.1 (0.49,2.48)
APVR	1	0.22 (0.07,0.69)	0.27 (0.09,0.81)	0.56 (0.16,1.99)
RVOTO	1	1.5 (0.52,4.34)	1.39 (0.48,4)	2.33 (0.75,7.22)
SEPTALS	1	1.01 (0.55,1.86)	0.91 (0.5,1.67)	1.12 (0.56,2.24)
Ozone, ppb				
LVOTO	1	1.47 (0.81,2.67)	1.41 (0.78,2.56)	1.62 (0.84,3.13)
CONOTRUNCALS	1	1.18 (0.76,1.84)	1.04 (0.67,1.63)	0.88 (0.51,1.52)
APVR	1	0.65 (0.21,2.02)	1.2 (0.43,3.39)	1.13 (0.33,3.84)
RVOTO	1	1.61 (0.81,3.21)	2 (1.02,3.91)	1.52 (0.7,3.31)
SEPTALS	1	1.35 (0.87,2.09)	1.25 (0.81,1.95)	1.07 (0.63,1.85)
PM10, micrometers/cubic meter				
LVOTO	1	0.87 (0.48,1.57)	1.13 (0.63,2.03)	1.02 (0.51,2.03)
CONOTRUNCALS	1	0.95 (0.54,1.66)	1.09 (0.63,1.89)	1.05 (0.56,1.97)
APVR	1	1.37 (0.31,6.08)	1.26 (0.28,5.57)	1.2 (0.23,6.31)
RVOTO	1	1.12 (0.72,1.76)	1.01 (0.65,1.58)	0.89 (0.52,1.53)
SEPTALS	1	1.26 (0.28,5.57)	1.2 (0.23,6.31)	1.2 (0.23,6.15)
PM2.5 micrometers/cubic meter				
LVOTO	1	1.18 (0.78,1.78)	1.1 (0.71,1.68)	1.57 (0.93,2.66)
CONOTRUNCALS	1	0.95 (0.65,1.4)	0.96 (0.65,1.43)	1.43 (0.88,2.3)
APVR	1	0.95 (0.41,2.19)	0.87 (0.36,2.09)	1.55 (0.54,4.46)
RVOTO	1	1.17 (0.72,1.88)	1.35 (0.84,2.18)	1.21 (0.65,2.28)
SEPTALS	1	0.91 (0.68,1.22)	0.67 (0.49,0.91)	0.71 (0.45,1.1)
Sulfur Dioxide, ppb				
LVOTO	1	1.18 (0.58,2.4)	1.29 (0.63,2.65)	0.74 (0.3,1.83)
CONOTRUNCALS	1	0.75 (0.4,1.42)	0.75 (0.4,1.42)	0.61 (0.29,1.31)
APVR	1	1.95 (0.21,17.97)	4.01 (0.45,35.46)	1 (0.05,18.29)
RVOTO	1	1.46 (0.7,3.04)	0.93 (0.43,1.99)	0.69 (0.27,1.74)
SEPTALS	1	1.75 (1.07,2.85)	1.34 (0.8,2.25)	1.52 (0.83,2.76)

[a]Estimates result from first stage maximum-likelihood, polytomous logistic model with defect groupings as outcomes and adjusted for maternal race, maternal age, maternal educational attainment, maternal household income, maternal smoking status and alcohol consumption during early pregnancy, nativity, and site-specific heart defect ratio.

APPENDIX 3

SUPPLEMENTARY TABLES FOR CHAPTER 5

Table A3.1: Adjusted odds ratios and 95% confidence intervals for CHDs and 7-week average exposure to $PM_{2.5}$ and ozone

	AQS , population within 50km of an air monitor			
PM2.5	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentration cut-off values	<8.47 µg/m3	8.47-12.2 µg/m3	12.2-17.5 µg/m3	>=17.5 µg/m3
LVOTO[a]	1	1.37 (0.85,2.19)	1.02 (0.62,1.66)	1.57 (0.88,2.78)
Aortic Stenosis[b]	1	1.11 (0.48,2.59)	0.75 (0.31,1.84)	1.24 (0.42,3.61)
Coarctation of the Aorta[b]	1	1.91 (0.85,4.26)	1.45 (0.64,3.31)	2.37 (0.94,5.93)
Hypoplastic Left Heart Syndrome[b]	1	1.45 (0.64,3.29)	1.11 (0.48,2.58)	1.55 (0.59,4.08)
CONOTRUNCALS[a]	1	1.17 (0.78,1.75)	0.98 (0.65,1.47)	1.19 (0.73,1.96)
d-TGA[b]	1	0.83 (0.47,1.47)	0.62 (0.34,1.12)	0.75 (0.35,1.63)
Tetralogy of Fallot[b]	1	1.72 (0.92,3.21)	1.65 (0.88,3.1)	1.87 (0.91,3.85)
Other Conotruncals[b]	1	1.03 (0.38,2.76)	0.58 (0.2,1.69)	1.02 (0.31,3.36)
APVR[a]	1	1.34 (0.55,3.25)	0.73 (0.28,1.9)	1.11 (0.36,3.41)
AVSD[c]	1	1.13 (0.40, 4.36)	0.79 (0.26, 3.10)	1.33 (0.34, 5.88)
RVOTO[a]	1	1.01 (0.63,1.61)	1.19 (0.74,1.91)	0.82 (0.44,1.54)
Pulmonary Valve Stenosis[b]	1	1.19 (0.67,2.13)	1.46 (0.82,2.59)	0.97 (0.46,2.04)
SEPTALS[a]	1	1.06 (0.8,1.4)	0.74 (0.55,0.99)	0.72 (0.48,1.08)
VSD-perimembranous[b]	1	1.14 (0.74,1.75)	0.86 (0.55,1.35)	0.88 (0.5,1.55)
ASD-all[b]	1	1.06 (0.76,1.48)	0.72 (0.49,1.04)	0.65 (0.38,1.12)
Ozone	<25th percentile	25th percentile to median	median to 75th percentile	>75th percentile
Pollutant concentration cut-off values	<32.4 ppb	32.4-41.4 ppb	41.4-49.8 ppb	>=49.8 ppb
LVOTO[a]	1	0.95 (0.64,1.42)	0.89 (0.6,1.32)	0.74 (0.49,1.12)
Aortic Stenosis[b]	1	1.22 (0.54,2.76)	1.14 (0.52,2.53)	0.47 (0.16,1.36)
Coarctation of the Aorta[b]	1	0.63 (0.33,1.2)	0.83 (0.47,1.48)	0.75 (0.41,1.36)
Hypoplastic Left Heart Syndrome[b]	1	1.05 (0.58,1.92)	0.8 (0.43,1.51)	0.82 (0.44,1.53)
CONOTRUNCALS[a]	1	1.01 (0.72,1.43)	0.95 (0.67,1.34)	0.8 (0.56,1.14)
d-TGA[b]	1	0.79 (0.44,1.44)	1.09 (0.64,1.86)	0.76 (0.42,1.36)
Tetralogy of Fallot[b]	1	1.19 (0.75,1.86)	0.96 (0.61,1.52)	0.92 (0.58,1.47)
Other Conotruncals[b]	1	0.91 (0.39,2.1)	0.59 (0.23,1.53)	0.47 (0.17,1.29)
APVR[a]	1	0.5 (0.21,1.19)	1.11 (0.57,2.19)	0.46 (0.19,1.09)
AVSD[a]	1	0.90 (0.30, 2.64)	0.91 (0.32, 2.57)	0.75 (0.25, 2.20)
RVOTO[a]	1	1.03 (0.67,1.58)	0.75 (0.48,1.18)	1.13 (0.75,1.7)
Pulmonary Valve Stenosis[b]	1	1.19 (0.72,1.95)	0.89 (0.53,1.48)	1.18 (0.73,1.91)
SEPTALS[a]	1	1.09 (0.83,1.43)	1.04 (0.78,1.38)	0.9 (0.66,1.21)
VSD-perimembranous[b]	1	0.91 (0.62,1.36)	0.76 (0.5,1.14)	0.93 (0.63,1.37)
ASD-all[b]	1	1.29 (0.92,1.82)	1.4 (0.96,2.02)	0.89 (0.59,1.36)

a Models constructed using two-stage hierarchical regression models of defect-groupings, adjusted for maternal age, race, educational level, household income, tobacco use during the first month of pregnancy, alcohol consumption during the first three months of pregnancy, and site-specific percentage of septal defects

b Models constructed using two-stage hierarchical regression models of individual defects, adjusted for maternal age, race, educational level, household income, tobacco use during the first month of pregnancy, alcohol consumption during the first three months of pregnancy, and site-specific percentage of septal defects

c Models constructed using Firth-adjusted logistic regression model, adjusted for maternal age, race, educational level, household income, tobacco use during the first month of pregnancy, alcohol consumption during the first three months of pregnancy, and site-specific percentage of septal defects

Table A3.1 (cont.)

	downscaler CMAQ , population within 50km of an air monitor			
PM2.5	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentration cut-off values	< 9.03 µg/m3	9.03-12.4 µg/m3	12.4-17.1 µg/m3	>= 17.1 µg/m3
LVOTO[a]	1	0.87 (0.54,1.42)	0.92 (0.56,1.51)	0.86 (0.46,1.6)
Aortic Stenosis[b]	1	0.77 (0.33,1.84)	0.64 (0.26,1.59)	0.54 (0.16,1.91)
Coarctation of the Aorta[b]	1	0.98 (0.46,2.1)	1.06 (0.49,2.29)	1.21 (0.49,2.97)
Hypoplastic Left Heart Syndrome[b]	1	0.81 (0.36,1.83)	0.93 (0.41,2.13)	0.8 (0.29,2.21)
CONOTRUNCALS[a]	1	1.12 (0.71,1.75)	0.96 (0.6,1.52)	1.33 (0.78,2.26)
d-TGA[b]	1	0.99 (0.5,1.95)	0.68 (0.33,1.39)	1.01 (0.44,2.31)
Tetralogy of Fallot[b]	1	1.34 (0.7,2.55)	1.26 (0.66,2.44)	1.69 (0.82,3.5)
Other Conotruncals[b]	1	0.9 (0.29,2.77)	0.9 (0.28,2.88)	1.17 (0.32,4.32)
APVR[a]	1	1.27 (0.48,3.35)	0.76 (0.27,2.16)	1.09 (0.33,3.59)
AVSD[c]	1	0.65 (0.20, 2.73)	0.79 (0.25, 3.33)	0.62 (0.12, 3.22)
RVOTO[a]	1	1.39 (0.79,2.44)	1.42 (0.8,2.52)	1.03 (0.51,2.08)
Pulmonary Valve Stenosis[b]	1	1.69 (0.82,3.46)	2 (0.96,4.13)	1.42 (0.6,3.34)
SEPTALS[a]	1	0.98 (0.73,1.3)	0.78 (0.57,1.07)	0.77 (0.51,1.16)
VSD-perimembranous[b]	1	1.59 (0.94,2.7)	1.31 (0.76,2.26)	1.38 (0.73,2.6)
ASD-all[b]	1	0.87 (0.63,1.2)	0.68 (0.46,1)	0.68 (0.4,1.15)
Ozone	<25th percentile	25th percentile to median	median to 75th percentile	>75th percentile
Pollutant concentration cut-off values	<33.4 ppb	33.4-42.1 ppb	42.1-49.6 ppb	>= 49.6 ppb
LVOTO[a]	1	1.07 (0.72,1.6)	1.07 (0.72,1.58)	0.77 (0.5,1.18)
Aortic Stenosis[b]	1	1.32 (0.59,2.93)	1.04 (0.46,2.35)	0.52 (0.19,1.43)
Coarctation of the Aorta[b]	1	0.63 (0.33,1.2)	0.87 (0.49,1.54)	0.72 (0.39,1.31)
Hypoplastic Left Heart Syndrome[b]	1	1.42 (0.75,2.68)	1.36 (0.72,2.57)	0.97 (0.49,1.92)
CONOTRUNCALS[a]	1	1.06 (0.75,1.51)	1.05 (0.74,1.47)	0.8 (0.56,1.15)
d-TGA[b]	1	1.05 (0.59,1.88)	1.23 (0.72,2.09)	0.67 (0.36,1.26)
Tetralogy of Fallot[b]	1	1.13 (0.71,1.8)	1.07 (0.68,1.68)	0.96 (0.6,1.53)
Other Conotruncals[b]	1	0.84 (0.36,1.98)	0.6 (0.23,1.56)	0.55 (0.21,1.44)
APVR[a]	1	0.36 (0.14,0.92)	1.08 (0.56,2.08)	0.42 (0.18,1)
AVSD[a]	1	0.77 (0.24, 2.33)	1.16 (0.44, 3.17)	0.64 (0.20, 1.95)
RVOTO[a]	1	0.94 (0.61,1.44)	0.88 (0.58,1.34)	0.95 (0.63,1.44)
Pulmonary Valve Stenosis[b]	1	1.05 (0.64,1.73)	0.96 (0.59,1.57)	1.03 (0.63,1.66)
SEPTALS[a]	1	0.95 (0.73,1.25)	1 (0.75,1.33)	0.84 (0.62,1.13)
VSD-perimembranous[b]	1	0.81 (0.55,1.22)	0.84 (0.57,1.25)	0.84 (0.57,1.25)
ASD-all[b]	1	1.09 (0.78,1.53)	1.17 (0.81,1.7)	0.87 (0.58,1.31)

Table A3.1 (cont.)

	downscaler CMAQ, full population			
PM2.5	<10th percentile	10th percentile to median	median to 90th percentile	>90th percentile
Pollutant concentration cut-off values	< 8.61 µg/m3	8.61-12.1 µg/m3	12.1-16.9 µg/m3	>= 16.9 µg/m3
LVOTO[a]	1	1 (0.63,1.61)	1.04 (0.64,1.69)	1.03 (0.57,1.86)
Aortic Stenosis[b]	1	1.18 (0.49,2.85)	0.82 (0.32,2.1)	0.77 (0.23,2.59)
Coarctation of the Aorta[b]	1	0.8 (0.4,1.61)	0.84 (0.41,1.72)	1.09 (0.47,2.5)
Hypoplastic Left Heart Syndrome[b]	1	1.11 (0.5,2.48)	1.47 (0.65,3.35)	1.15 (0.42,3.13)
CONOTRUNCALS[a]	1	1.17 (0.75,1.82)	1.06 (0.67,1.68)	1.32 (0.78,2.24)
d-TGA[b]	1	1.42 (0.67,3.03)	0.99 (0.45,2.19)	1.29 (0.52,3.19)
Tetralogy of Fallot[b]	1	1.08 (0.59,1.95)	1.14 (0.62,2.11)	1.39 (0.7,2.78)
Other Conotruncals[b]	1	1.07 (0.39,2.95)	0.93 (0.31,2.73)	1.12 (0.32,3.9)
APVR[a]	1	4.71 (1.06,20.91)	2.84 (0.6,13.34)	3.5 (0.66,18.44)
AVSD[c]	1	0.60 (0.19, 2.49)	0.66 (0.21, 2.81)	0.50 (0.10, 2.64)
RVOTO[a]	1	1.1 (0.66,1.83)	1.25 (0.74,2.12)	0.93 (0.49,1.78)
Pulmonary Valve Stenosis[b]	1	1.41 (0.74,2.69)	1.81 (0.94,3.5)	1.38 (0.63,3)
SEPTALS[a]	1	0.98 (0.75,1.28)	0.86 (0.64,1.16)	0.81 (0.55,1.2)
VSD-perimembranous[b]	1	1.26 (0.79,2.01)	1.14 (0.7,1.86)	1.09 (0.61,1.96)
ASD-all[b]	1	0.94 (0.69,1.27)	0.83 (0.57,1.19)	0.79 (0.47,1.31)
Ozone	<25th percentile	25th percentile to median	median to 75th percentile	>75th percentile
Pollutant concentration cut-off values	<30.5 ppb	30.5-39.6 ppb	39.6-48.2 ppb	>= 48.2 ppb
LVOTO[a]	1	1.02 (0.73,1.42)	0.98 (0.71,1.36)	0.84 (0.59,1.18)
Aortic Stenosis[b]	1	1.36 (0.71,2.61)	1.26 (0.66,2.4)	0.74 (0.35,1.56)
Coarctation of the Aorta[b]	1	0.86 (0.53,1.42)	0.77 (0.47,1.26)	0.74 (0.45,1.23)
Hypoplastic Left Heart Syndrome[b]	1	0.95 (0.54,1.68)	1.11 (0.65,1.9)	1.03 (0.6,1.79)
CONOTRUNCALS[a]	1	1 (0.75,1.35)	0.97 (0.72,1.29)	0.81 (0.6,1.1)
d-TGA[b]	1	0.86 (0.52,1.41)	1.02 (0.64,1.63)	0.79 (0.48,1.3)
Tetralogy of Fallot[b]	1	1.13 (0.77,1.65)	0.96 (0.66,1.41)	0.87 (0.59,1.29)
Other Conotruncals[b]	1	0.89 (0.42,1.87)	0.91 (0.44,1.89)	0.66 (0.3,1.46)
APVR[a]	1	0.57 (0.27,1.23)	1.01 (0.54,1.92)	0.75 (0.38,1.5)
AVSD[a]	1	1.09 (0.44, 2.68)	1.31 (0.58, 3.04)	0.71 (0.27, 1.82)
RVOTO[a]	1	0.98 (0.68,1.41)	0.97 (0.68,1.38)	1.19 (0.85,1.67)
Pulmonary Valve Stenosis[b]	1	1.03 (0.68,1.58)	1.09 (0.73,1.64)	1.38 (0.94,2.03)
SEPTALS[a]	1	0.86 (0.68,1.09)	0.9 (0.72,1.14)	0.75 (0.59,0.95)
VSD-perimembranous[b]	1	0.89 (0.64,1.23)	0.9 (0.66,1.24)	0.84 (0.61,1.17)
ASD-all[b]	1	0.84 (0.63,1.14)	0.9 (0.67,1.22)	0.69 (0.5,0.95)

Table A3.2: Adjusted odds ratios and 95% confidence intervals between CHDs and 7-week average exposure to $PM_{2.5}$ and Ozone using constant numeric cutoffs

PM2.5	AQS , population within 50km of an air monitor			
Pollutant concentration cut-off values	<8.47 µg/m3	8.47-12.2 µg/m3	12.2-17.5 µg/m3	>=17.5 µg/m3
LVOTO[a]	1	1.37 (0.85,2.19)	1.02 (0.62,1.66)	1.57 (0.88,2.78)
Aortic Stenosis[b]	1	1.11 (0.48,2.59)	0.75 (0.31,1.84)	1.24 (0.42,3.61)
Coarctation of the Aorta[b]	1	1.91 (0.85,4.26)	1.45 (0.64,3.31)	2.37 (0.94,5.93)
Hypoplastic Left Heart Syndrome[b]	1	1.45 (0.64,3.29)	1.11 (0.48,2.58)	1.55 (0.59,4.08)
CONOTRUNCALS[a]	1	1.17 (0.78,1.75)	0.98 (0.65,1.47)	1.19 (0.73,1.96)
d-TGA[b]	1	0.83 (0.47,1.47)	0.62 (0.34,1.12)	0.75 (0.35,1.63)
Tetralogy of Fallot[b]	1	1.72 (0.92,3.21)	1.65 (0.88,3.1)	1.87 (0.91,3.85)
Other Conotruncals[b]	1	1.03 (0.38,2.76)	0.58 (0.2,1.69)	1.02 (0.31,3.36)
APVR[a]	1	1.34 (0.55,3.25)	0.73 (0.28,1.9)	1.11 (0.36,3.41)
AVSD[c]	1	1.13 (0.40, 4.36)	0.79 (0.26, 3.10)	1.33 (0.34, 5.88)
RVOTO[a]	1	1.01 (0.63,1.61)	1.19 (0.74,1.91)	0.82 (0.44,1.54)
Pulmonary Valve Stenosis[b]	1	1.19 (0.67,2.13)	1.46 (0.82,2.59)	0.97 (0.46,2.04)
SEPTALS[a]	1	1.06 (0.8,1.4)	0.74 (0.55,0.99)	0.72 (0.48,1.08)
VSD-perimembranous[b]	1	1.14 (0.74,1.75)	0.86 (0.55,1.35)	0.88 (0.5,1.55)
ASD-all[b]	1	1.06 (0.76,1.48)	0.72 (0.49,1.04)	0.65 (0.38,1.12)
Ozone	AQS , population within 50km of an air monitor			
Pollutant concentration cut-off values	<32.4 ppb	32.4-41.4 ppb	41.4-49.8 ppb	>=49.8 ppb
LVOTO[a]	1	0.95 (0.64,1.42)	0.89 (0.6,1.32)	0.74 (0.49,1.12)
Aortic Stenosis[b]	1	1.22 (0.54,2.76)	1.14 (0.52,2.53)	0.47 (0.16,1.36)
Coarctation of the Aorta[b]	1	0.63 (0.33,1.2)	0.83 (0.47,1.48)	0.75 (0.41,1.36)
Hypoplastic Left Heart Syndrome[b]	1	1.05 (0.58,1.92)	0.8 (0.43,1.51)	0.82 (0.44,1.53)
CONOTRUNCALS[a]	1	1.01 (0.72,1.43)	0.95 (0.67,1.34)	0.8 (0.56,1.14)
d-TGA[b]	1	0.79 (0.44,1.44)	1.09 (0.64,1.86)	0.76 (0.42,1.36)
Tetralogy of Fallot[b]	1	1.19 (0.75,1.86)	0.96 (0.61,1.52)	0.92 (0.58,1.47)
Other Conotruncals[b]	1	0.91 (0.39,2.1)	0.59 (0.23,1.53)	0.47 (0.17,1.29)
APVR[a]	1	0.5 (0.21,1.19)	1.11 (0.57,2.19)	0.46 (0.19,1.09)
AVSD[a]	1	0.90 (0.30, 2.64)	0.91 (0.32, 2.57)	0.75 (0.25, 2.20)
RVOTO[a]	1	1.03 (0.67,1.58)	0.75 (0.48,1.18)	1.13 (0.75,1.7)
Pulmonary Valve Stenosis[b]	1	1.19 (0.72,1.95)	0.89 (0.53,1.48)	1.18 (0.73,1.91)
SEPTALS[a]	1	1.09 (0.83,1.43)	1.04 (0.78,1.38)	0.9 (0.66,1.21)
VSD-perimembranous[b]	1	0.91 (0.62,1.36)	0.76 (0.5,1.14)	0.93 (0.63,1.37)
ASD-all[b]	1	1.29 (0.92,1.82)	1.4 (0.96,2.02)	0.89 (0.59,1.36)

a Models constructed using two-stage hierarchical regression models of defect-groupings, adjusted for maternal age, race, educational level, household income, tobacco use during the first month of pregnancy, alcohol consumption during the first three months of pregnancy, and site-specific percentage of septal defects

b Models constructed using two-stage hierarchical regression models of individual defects, adjusted for maternal age, race, educational level, household income, tobacco use during the first month of pregnancy, alcohol consumption during the first three months of pregnancy, and site-specific percentage of septal defects

c Models constructed using Firth-adjusted logistic regression model, adjusted for maternal age, race, educational level, household income, tobacco use during the first month of pregnancy, alcohol consumption during the first three months of pregnancy, and site-specific percentage of septal defects

Table A3.2 (cont.)

PM2.5	downscaler CMAQ , population within 50km of an air monitor			
Pollutant concentration cut-off values	<8.47 µg/m3	8.47-12.2 µg/m3	12.2-17.5 µg/m3	>=17.5 µg/m3
LVOTO[a]	1	0.75 (0.43,1.34)	0.83 (0.46,1.48)	0.74 (0.36,1.51)
Aortic Stenosis[b]	1	0.56 (0.21,1.48)	0.48 (0.17,1.33)	0.35 (0.08,1.47)
Coarctation of the Aorta[b]	1	1 (0.4,2.52)	1.06 (0.41,2.7)	1.17 (0.4,3.42)
Hypoplastic Left Heart Syndrome[b]	1	0.67 (0.26,1.76)	0.9 (0.34,2.37)	0.74 (0.23,2.35)
CONOTRUNCALS[a]	1	1.03 (0.59,1.79)	0.96 (0.55,1.7)	1.15 (0.6,2.19)
d-TGA[b]	1	0.83 (0.37,1.86)	0.57 (0.25,1.31)	0.77 (0.29,2.04)
Tetralogy of Fallot[b]	1	1.58 (0.65,3.84)	1.72 (0.7,4.21)	2.08 (0.79,5.5)
Other Conotruncals[b]	1	0.65 (0.19,2.18)	0.72 (0.2,2.51)	0.55 (0.12,2.54)
APVR[a]	1	2.44 (0.54,11)	1.67 (0.35,7.87)	1.73 (0.31,9.77)
AVSD[c]	1	0.51 (0.14, 2.82)	0.57 (0.15, 3.22)	0.57 (0.10, 3.86)
RVOTO[a]	1	0.81 (0.44,1.51)	1.01 (0.54,1.89)	0.5 (0.22,1.14)
Pulmonary Valve Stenosis[b]	1	1.04 (0.47,2.32)	1.48 (0.66,3.31)	0.76 (0.28,2.04)
SEPTALS[a]	1	0.75 (0.55,1.03)	0.63 (0.44,0.88)	0.61 (0.39,0.95)
VSD-perimembranous[b]	1	1.44 (0.77,2.72)	1.3 (0.68,2.5)	1.34 (0.64,2.83)
ASD-all[b]	1	0.67 (0.48,0.95)	0.52 (0.35,0.78)	0.51 (0.29,0.91)
Ozone	downscaler CMAQ , population within 50km of an air monitor			
Pollutant concentration cut-off values	<32.4 ppb	32.4-41.4 ppb	41.4-49.8 ppb	>=49.8 ppb
LVOTO[a]	1	1.14 (0.75,1.72)	0.96 (0.65,1.43)	0.8 (0.52,1.24)
Aortic Stenosis[b]	1	1.11 (0.49,2.52)	0.88 (0.39,1.98)	0.49 (0.18,1.33)
Coarctation of the Aorta[b]	1	0.84 (0.45,1.58)	0.82 (0.46,1.48)	0.8 (0.43,1.49)
Hypoplastic Left Heart Syndrome[b]	1	1.38 (0.72,2.65)	1.19 (0.63,2.25)	0.97 (0.49,1.94)
CONOTRUNCALS[a]	1	1.02 (0.71,1.45)	0.93 (0.66,1.31)	0.75 (0.52,1.1)
d-TGA[b]	1	0.97 (0.54,1.74)	1.04 (0.61,1.78)	0.65 (0.35,1.23)
Tetralogy of Fallot[b]	1	1.1 (0.69,1.76)	0.94 (0.6,1.48)	0.9 (0.56,1.45)
Other Conotruncals[b]	1	0.81 (0.33,1.95)	0.65 (0.26,1.62)	0.49 (0.18,1.35)
APVR[a]	1	0.38 (0.15,0.94)	0.9 (0.46,1.76)	0.42 (0.18,0.99)
AVSD[a]	1	1.80 (0.58, 6.32)	1.53 (0.52, 5.25)	1.00 (0.28, 3.73)
RVOTO[a]	1	0.91 (0.58,1.42)	0.85 (0.56,1.3)	0.95 (0.62,1.46)
Pulmonary Valve Stenosis[b]	1	0.97 (0.58,1.62)	0.92 (0.57,1.5)	1.01 (0.62,1.65)
SEPTALS[a]	1	0.88 (0.66,1.17)	0.93 (0.7,1.23)	0.81 (0.6,1.1)
VSD-perimembranous[b]	1	0.75 (0.49,1.13)	0.77 (0.52,1.14)	0.84 (0.56,1.25)
ASD-all[b]	1	1.02 (0.72,1.46)	1.12 (0.77,1.62)	0.82 (0.53,1.25)

Table A3.2 (cont.)

PM2.5	downscaler CMAQ, full population			
Pollutant concentration cut-off values	<8.47 µg/m3	8.47-12.2 µg/m3	12.2-17.5 µg/m3	>=17.5 µg/m3
LVOTO[a]	1	0.86 (0.53,1.38)	0.92 (0.56,1.51)	0.8 (0.42,1.54)
Aortic Stenosis[b]	1	0.93 (0.38,2.24)	0.71 (0.28,1.81)	0.52 (0.13,2.07)
Coarctation of the Aorta[b]	1	0.74 (0.36,1.53)	0.83 (0.39,1.73)	0.89 (0.36,2.21)
Hypoplastic Left Heart Syndrome[b]	1	0.92 (0.42,2.05)	1.19 (0.52,2.7)	0.96 (0.34,2.73)
CONOTRUNCALS[a]	1	0.99 (0.63,1.55)	0.94 (0.59,1.5)	1.13 (0.64,1.98)
d-TGA[b]	1	1.16 (0.55,2.47)	0.82 (0.37,1.8)	1.11 (0.43,2.86)
Tetralogy of Fallot[b]	1	0.95 (0.51,1.75)	1.06 (0.56,1.98)	1.29 (0.62,2.68)
Other Conotruncals[b]	1	0.85 (0.31,2.35)	0.86 (0.29,2.52)	0.67 (0.17,2.69)
APVR[a]	1	3.75 (0.84,16.7)	2.5 (0.53,11.72)	2.63 (0.47,14.76)
AVSD[c]	1	0.48 (0.15, 1.97)	0.53 (0.16, 2.23)	0.57 (0.11, 2.98)
RVOTO[a]	1	0.87 (0.66,1.15)	0.79 (0.58,1.08)	0.75 (0.49,1.15)
Pulmonary Valve Stenosis[b]	1	1.27 (0.65,2.47)	1.71 (0.87,3.39)	0.87 (0.36,2.13)
SEPTALS[a]	1	0.94 (0.56,1.58)	1.14 (0.67,1.95)	0.56 (0.26,1.2)
VSD-perimembranous[b]	1	1.12 (0.69,1.81)	1.05 (0.63,1.74)	1.04 (0.55,1.94)
ASD-all[b]	1	0.84 (0.62,1.14)	0.76 (0.52,1.1)	0.74 (0.43,1.28)
Ozone	downscaler CMAQ, full population			
Pollutant concentration cut-off values	<32.4 ppb	32.4-41.4 ppb	41.4-49.8 ppb	>=49.8 ppb
LVOTO[a]	1	1.1 (0.8,1.52)	0.95 (0.7,1.3)	0.81 (0.57,1.17)
Aortic Stenosis[b]	1	1.09 (0.6,1.99)	0.87 (0.48,1.59)	0.51 (0.23,1.14)
Coarctation of the Aorta[b]	1	0.93 (0.57,1.51)	0.82 (0.51,1.32)	0.83 (0.49,1.39)
Hypoplastic Left Heart Syndrome[b]	1	1.26 (0.73,2.15)	1.22 (0.73,2.05)	1.04 (0.58,1.86)
CONOTRUNCALS[a]	1	1 (0.75,1.33)	0.95 (0.72,1.25)	0.78 (0.57,1.07)
d-TGA[b]	1	0.97 (0.6,1.57)	1.07 (0.69,1.66)	0.71 (0.41,1.24)
Tetralogy of Fallot[b]	1	1.07 (0.74,1.55)	0.93 (0.65,1.34)	0.86 (0.57,1.29)
Other Conotruncals[b]	1	0.8 (0.39,1.65)	0.8 (0.4,1.61)	0.65 (0.29,1.44)
APVR[a]	1	0.58 (0.27,1.26)	1.32 (0.73,2.38)	0.62 (0.28,1.38)
AVSD[a]	1	1.33 (0.56, 3.14)	1.24 (0.55, 2.83)	0.85 (0.31, 2.20)
RVOTO[a]	1	1.04 (0.74,1.47)	1.19 (0.87,1.65)	1.06 (0.74,1.52)
Pulmonary Valve Stenosis[b]	1	1.08 (0.72,1.63)	1.37 (0.95,1.97)	1.18 (0.78,1.77)
SEPTALS[a]	1	0.94 (0.75,1.17)	0.89 (0.72,1.11)	0.83 (0.65,1.06)
VSD-perimembranous[b]	1	0.91 (0.66,1.25)	0.86 (0.64,1.17)	0.94 (0.68,1.3)
ASD-all[b]	1	0.97 (0.73,1.27)	0.91 (0.69,1.21)	0.75 (0.54,1.05)

Table A3.3: Odds Ratios and 95% confidence intervals resulting from hierarchical analysis between cardiac birth defects and weekly exposure to $PM_{2.5}$

Cardiac Defect	Source	Week 2 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	1.46 (0.71,2.97)	1.14 (0.54,2.4)	1.41 (0.57,3.52)
	CMAQ, within 50km of monitor	1	1.47 (0.69,3.14)	1.04 (0.46,2.31)	1.42 (0.54,3.7)
	AQS	1	1.03 (0.45,2.35)	1.1 (0.48,2.49)	1.19 (0.44,3.22)
Coarctation of the Aorta	CMAQ, full population	1	1.3 (0.7,2.42)	1.48 (0.79,2.79)	1.01 (0.45,2.28)
	CMAQ, within 50km of monitor	1	1.5 (0.77,2.94)	1.8 (0.92,3.54)	1.08 (0.45,2.56)
	AQS	1	1.23 (0.64,2.37)	1.32 (0.68,2.55)	0.68 (0.27,1.72)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	1.33 (0.71,2.49)	1.08 (0.56,2.09)	1.18 (0.53,2.62)
	CMAQ, within 50km of monitor	1	1.24 (0.65,2.35)	0.97 (0.49,1.89)	0.95 (0.4,2.23)
	AQS	1	1.13 (0.57,2.24)	1.02 (0.51,2.06)	1.23 (0.52,2.88)
d-TGA	CMAQ, full population	1	1.03 (0.59,1.81)	1.1 (0.62,1.97)	0.95 (0.44,2.03)
	CMAQ, within 50km of monitor	1	1.1 (0.63,1.95)	1.02 (0.56,1.84)	1.02 (0.47,2.2)
	AQS	1	1.15 (0.64,2.05)	0.79 (0.43,1.46)	0.57 (0.24,1.36)
Tetralogy of Fallot	CMAQ, full population	1	1.33 (0.8,2.21)	1.15 (0.68,1.96)	1.31 (0.7,2.47)
	CMAQ, within 50km of monitor	1	1.33 (0.78,2.26)	1.13 (0.65,1.97)	1.49 (0.78,2.86)
	AQS	1	1.09 (0.64,1.87)	0.99 (0.57,1.71)	1.19 (0.61,2.29)
Other Conotruncals	CMAQ, full population	1	1.09 (0.53,2.25)	0.93 (0.44,2)	0.87 (0.32,2.37)
	CMAQ, within 50km of monitor	1	1.08 (0.49,2.39)	1.19 (0.53,2.67)	1.14 (0.41,3.22)
	AQS	1	0.84 (0.36,1.97)	1.12 (0.49,2.56)	0.58 (0.18,1.85)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.3 (0.78,2.17)	1.07 (0.63,1.82)	1.33 (0.71,2.51)
	CMAQ, within 50km of monitor	1	1.64 (0.92,2.95)	1.48 (0.81,2.7)	1.84 (0.92,3.68)
	AQS	1	1.24 (0.7,2.21)	0.87 (0.48,1.59)	1.6 (0.81,3.17)
VSD-perimembranous	CMAQ, full population	1	1.01 (0.67,1.52)	1.16 (0.76,1.77)	0.89 (0.51,1.56)
	CMAQ, within 50km of monitor	1	1.18 (0.76,1.82)	1.25 (0.79,1.97)	0.97 (0.53,1.77)
	AQS	1	0.92 (0.58,1.44)	1.09 (0.69,1.73)	0.64 (0.33,1.22)
ASD-all	CMAQ, full population	1	0.99 (0.73,1.36)	1.11 (0.78,1.59)	0.79 (0.46,1.35)
	CMAQ, within 50km of monitor	1	1.1 (0.79,1.54)	1.07 (0.73,1.57)	0.79 (0.45,1.41)
	AQS	1	1.12 (0.76,1.65)	1.05 (0.69,1.58)	0.56 (0.3,1.06)
Defect Groupings					
APVR	CMAQ, full population	1	1.83 (0.8,4.18)	1.3 (0.56,3.05)	2.09 (0.8,5.45)
	CMAQ, within 50km of monitor	1	1.73 (0.79,3.78)	1.08 (0.47,2.48)	1.81 (0.7,4.68)
	AQS	1	1.1 (0.49,2.45)	0.78 (0.34,1.8)	1.43 (0.56,3.67)
Conotruncals	CMAQ, full population	1	1.16 (0.79,1.69)	1.07 (0.72,1.6)	1.07 (0.65,1.77)
	CMAQ, within 50km of monitor	1	1.12 (0.75,1.66)	1.01 (0.66,1.54)	1.18 (0.7,1.99)
	AQS	1	1.06 (0.71,1.59)	0.93 (0.61,1.41)	0.86 (0.5,1.48)

Table A3.3 (cont.)

		Week 3			
Cardiac Defect	Source	<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	0.38 (0.21,0.69)	0.33 (0.18,0.64)	0.39 (0.16,0.97)
	CMAQ, within 50km of monitor	1	0.26 (0.13,0.49)	0.3 (0.15,0.58)	0.3 (0.11,0.83)
	AQS	1	0.47 (0.24,0.92)	0.36 (0.18,0.75)	0.42 (0.15,1.16)
Coarctation of the Aorta	CMAQ, full population	1	0.68 (0.39,1.2)	0.72 (0.4,1.3)	0.8 (0.38,1.67)
	CMAQ, within 50km of monitor	1	0.69 (0.38,1.24)	0.69 (0.37,1.27)	0.85 (0.4,1.82)
	AQS	1	1.03 (0.56,1.91)	0.89 (0.47,1.68)	0.6 (0.25,1.43)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.74 (0.4,1.37)	0.98 (0.52,1.85)	0.92 (0.41,2.04)
	CMAQ, within 50km of monitor	1	0.62 (0.32,1.18)	0.95 (0.49,1.83)	0.81 (0.35,1.88)
	AQS	1	1 (0.51,1.98)	0.83 (0.41,1.68)	1.07 (0.47,2.46)
d-TGA	CMAQ, full population	1	1.11 (0.6,2.05)	1.09 (0.58,2.06)	1.03 (0.47,2.24)
	CMAQ, within 50km of monitor	1	0.99 (0.54,1.81)	0.94 (0.5,1.77)	0.94 (0.43,2.06)
	AQS	1	0.77 (0.44,1.36)	0.72 (0.4,1.3)	0.68 (0.31,1.48)
Tetralogy of Fallot	CMAQ, full population	1	0.9 (0.55,1.47)	0.85 (0.5,1.42)	0.97 (0.52,1.82)
	CMAQ, within 50km of monitor	1	0.91 (0.55,1.53)	0.77 (0.45,1.32)	0.81 (0.42,1.56)
	AQS	1	0.78 (0.47,1.29)	0.76 (0.45,1.27)	0.69 (0.35,1.33)
Other Conotruncals	CMAQ, full population	1	0.51 (0.25,1.02)	0.61 (0.3,1.25)	0.66 (0.26,1.71)
	CMAQ, within 50km of monitor	1	0.86 (0.4,1.85)	0.64 (0.29,1.44)	0.54 (0.19,1.59)
	AQS	1	0.52 (0.25,1.12)	0.58 (0.27,1.26)	0.4 (0.13,1.25)
Pulmonary Valve Stenosis	CMAQ, full population	1	0.72 (0.44,1.18)	0.93 (0.56,1.55)	0.72 (0.37,1.38)
	CMAQ, within 50km of monitor	1	0.71 (0.42,1.2)	0.91 (0.53,1.55)	0.73 (0.37,1.44)
	AQS	1	0.75 (0.44,1.26)	0.79 (0.46,1.35)	0.62 (0.31,1.26)
VSD-perimembranous	CMAQ, full population	1	1.23 (0.79,1.91)	1.17 (0.73,1.87)	0.94 (0.52,1.69)
	CMAQ, within 50km of monitor	1	1.07 (0.69,1.68)	0.98 (0.61,1.58)	0.84 (0.46,1.54)
	AQS	1	1.3 (0.79,2.12)	1.02 (0.61,1.71)	0.97 (0.52,1.83)
ASD-all	CMAQ, full population	1	0.92 (0.66,1.27)	0.94 (0.65,1.38)	1.37 (0.83,2.27)
	CMAQ, within 50km of monitor	1	0.74 (0.53,1.03)	0.76 (0.52,1.12)	1.12 (0.66,1.88)
	AQS	1	0.82 (0.56,1.2)	0.76 (0.5,1.15)	1.28 (0.75,2.18)
Defect Groupings					
APVR	CMAQ, full population	1	0.48 (0.25,0.92)	0.61 (0.31,1.2)	0.75 (0.3,1.87)
	CMAQ, within 50km of monitor	1	0.47 (0.24,0.93)	0.68 (0.34,1.37)	0.83 (0.33,2.09)
	AQS	1	0.62 (0.3,1.29)	0.67 (0.31,1.42)	0.91 (0.36,2.29)
Conotruncals	CMAQ, full population	1	0.92 (0.63,1.34)	0.92 (0.61,1.37)	1.01 (0.62,1.66)
	CMAQ, within 50km of monitor	1	1 (0.67,1.5)	0.88 (0.58,1.34)	0.91 (0.54,1.53)
	AQS	1	0.75 (0.51,1.1)	0.73 (0.49,1.09)	0.66 (0.4,1.11)

Table A3.3 (cont.)

Cardiac Defect	Source	Week 4 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	1.04 (0.52,2.11)	1.09 (0.53,2.26)	1.9 (0.8,4.53)
	CMAQ, within 50km of monitor	1	0.93 (0.43,1.98)	1.24 (0.58,2.69)	2.18 (0.88,5.37)
	AQS	1	0.89 (0.39,2.03)	1.37 (0.61,3.08)	2.23 (0.88,5.64)
Coarctation of the Aorta	CMAQ, full population	1	1.39 (0.73,2.63)	1.24 (0.64,2.4)	1.06 (0.47,2.37)
	CMAQ, within 50km of monitor	1	1.54 (0.79,3.01)	1.44 (0.72,2.86)	1.06 (0.45,2.5)
	AQS	1	1.44 (0.74,2.83)	1.36 (0.69,2.69)	1.54 (0.68,3.49)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.99 (0.54,1.83)	1.02 (0.54,1.92)	0.82 (0.36,1.88)
	CMAQ, within 50km of monitor	1	1.07 (0.56,2.06)	1.04 (0.53,2.04)	1 (0.43,2.33)
	AQS	1	1.48 (0.75,2.92)	0.99 (0.49,2.02)	1.45 (0.63,3.36)
d-TGA	CMAQ, full population	1	1.09 (0.61,1.97)	0.97 (0.52,1.79)	1.24 (0.59,2.61)
	CMAQ, within 50km of monitor	1	1.08 (0.59,1.96)	1.04 (0.56,1.95)	1.47 (0.69,3.13)
	AQS	1	0.94 (0.52,1.7)	1.13 (0.62,2.08)	1.5 (0.71,3.17)
Tetralogy of Fallot	CMAQ, full population	1	0.89 (0.55,1.43)	0.91 (0.56,1.5)	0.66 (0.34,1.27)
	CMAQ, within 50km of monitor	1	1.16 (0.68,1.96)	1.22 (0.71,2.11)	0.84 (0.42,1.7)
	AQS	1	1.15 (0.67,1.97)	1.17 (0.68,2.03)	1.18 (0.61,2.31)
Other Conotruncals	CMAQ, full population	1	1.05 (0.47,2.35)	1.65 (0.73,3.73)	1.14 (0.4,3.22)
	CMAQ, within 50km of monitor	1	0.86 (0.37,2)	1.69 (0.74,3.87)	1.42 (0.5,4.04)
	AQS	1	0.95 (0.41,2.2)	1.11 (0.48,2.57)	0.88 (0.3,2.62)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.28 (0.75,2.2)	1.36 (0.78,2.37)	0.89 (0.44,1.81)
	CMAQ, within 50km of monitor	1	1.22 (0.7,2.1)	1.2 (0.68,2.11)	0.9 (0.44,1.84)
	AQS	1	0.98 (0.58,1.68)	1.07 (0.62,1.85)	0.94 (0.47,1.9)
VSD-perimembranous	CMAQ, full population	1	0.77 (0.52,1.16)	0.93 (0.6,1.42)	1.23 (0.72,2.09)
	CMAQ, within 50km of monitor	1	0.83 (0.54,1.28)	1.02 (0.65,1.61)	1.49 (0.86,2.6)
	AQS	1	1.16 (0.72,1.88)	1.3 (0.79,2.12)	1.59 (0.88,2.89)
ASD-all	CMAQ, full population	1	1.2 (0.86,1.67)	1.18 (0.8,1.73)	1.04 (0.6,1.79)
	CMAQ, within 50km of monitor	1	1.53 (1.07,2.17)	1.38 (0.91,2.08)	1.4 (0.79,2.46)
	AQS	1	1.4 (0.94,2.11)	1.21 (0.79,1.87)	1.17 (0.65,2.1)
Defect Groupings					
APVR	CMAQ, full population	1	1.54 (0.73,3.25)	1.02 (0.46,2.26)	1.09 (0.41,2.94)
	CMAQ, within 50km of monitor	1	1.12 (0.56,2.22)	0.8 (0.38,1.68)	0.86 (0.31,2.33)
	AQS	1	1.23 (0.55,2.76)	1.41 (0.62,3.2)	1 (0.34,2.95)
Conotruncals	CMAQ, full population	1	0.96 (0.66,1.4)	0.99 (0.67,1.46)	0.87 (0.52,1.43)
	CMAQ, within 50km of monitor	1	1.05 (0.71,1.57)	1.17 (0.77,1.77)	1.03 (0.61,1.74)
	AQS	1	0.99 (0.66,1.48)	1.08 (0.72,1.63)	1.13 (0.68,1.88)

Table A3.3 (cont.)

Cardiac Defect	Source	Week 5 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	0.95 (0.49,1.85)	1.13 (0.57,2.27)	0.91 (0.36,2.34)
	CMAQ, within 50km of monitor	1	0.99 (0.47,2.12)	1.4 (0.65,3.03)	0.93 (0.34,2.59)
	AQS	1	0.81 (0.36,1.82)	1.31 (0.6,2.85)	0.76 (0.26,2.22)
Coarctation of the Aorta	CMAQ, full population	1	1.18 (0.64,2.19)	1.13 (0.6,2.16)	1.58 (0.74,3.35)
	CMAQ, within 50km of monitor	1	1.26 (0.66,2.4)	1.15 (0.59,2.24)	1.3 (0.58,2.89)
	AQS	1	0.89 (0.49,1.63)	0.72 (0.38,1.34)	1.23 (0.59,2.57)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	1.15 (0.61,2.15)	1.18 (0.61,2.26)	1.2 (0.53,2.7)
	CMAQ, within 50km of monitor	1	1.02 (0.53,1.94)	1.03 (0.53,2.01)	0.88 (0.37,2.08)
	AQS	1	1.09 (0.56,2.1)	0.85 (0.43,1.69)	0.84 (0.35,2.01)
d-TGA	CMAQ, full population	1	1.03 (0.59,1.78)	0.67 (0.37,1.21)	1.18 (0.58,2.41)
	CMAQ, within 50km of monitor	1	1 (0.58,1.72)	0.71 (0.4,1.28)	0.67 (0.3,1.48)
	AQS	1	0.72 (0.41,1.27)	0.78 (0.44,1.38)	0.88 (0.42,1.86)
Tetralogy of Fallot	CMAQ, full population	1	1.04 (0.64,1.71)	1.12 (0.67,1.88)	1.19 (0.63,2.25)
	CMAQ, within 50km of monitor	1	1.09 (0.64,1.86)	1.27 (0.74,2.2)	1.2 (0.61,2.35)
	AQS	1	1.11 (0.64,1.93)	1.1 (0.63,1.93)	0.87 (0.43,1.75)
Other Conotruncals	CMAQ, full population	1	1.76 (0.76,4.04)	1.37 (0.58,3.24)	0.9 (0.3,2.69)
	CMAQ, within 50km of monitor	1	1.68 (0.72,3.95)	1.24 (0.51,2.98)	0.74 (0.23,2.42)
	AQS	1	0.86 (0.39,1.88)	0.57 (0.25,1.31)	0.7 (0.25,1.95)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.31 (0.77,2.23)	1.17 (0.67,2.03)	1.44 (0.75,2.76)
	CMAQ, within 50km of monitor	1	1.34 (0.77,2.32)	1.16 (0.65,2.05)	1.2 (0.61,2.38)
	AQS	1	0.81 (0.48,1.36)	0.88 (0.52,1.51)	0.69 (0.34,1.4)
VSD-perimembranous	CMAQ, full population	1	0.89 (0.6,1.33)	0.82 (0.54,1.26)	0.82 (0.47,1.41)
	CMAQ, within 50km of monitor	1	1.12 (0.73,1.73)	0.85 (0.54,1.35)	0.81 (0.45,1.48)
	AQS	1	1 (0.64,1.55)	0.67 (0.42,1.07)	0.8 (0.44,1.45)
ASD-all	CMAQ, full population	1	1.1 (0.8,1.53)	1 (0.68,1.47)	1.16 (0.7,1.94)
	CMAQ, within 50km of monitor	1	1.01 (0.72,1.41)	0.9 (0.6,1.34)	0.93 (0.53,1.61)
	AQS	1	0.92 (0.62,1.37)	0.94 (0.62,1.44)	0.98 (0.55,1.74)
Defect Groupings					
APVR	CMAQ, full population	1	1.72 (0.71,4.17)	1.82 (0.75,4.42)	1.54 (0.54,4.38)
	CMAQ, within 50km of monitor	1	1.72 (0.71,4.16)	1.58 (0.64,3.86)	1.19 (0.41,3.48)
	AQS	1	1.11 (0.42,2.96)	1.13 (0.43,2.99)	0.91 (0.3,2.76)
Conotruncals	CMAQ, full population	1	1.08 (0.75,1.57)	0.94 (0.64,1.4)	1.11 (0.68,1.81)
	CMAQ, within 50km of monitor	1	1.06 (0.72,1.56)	0.98 (0.65,1.47)	0.88 (0.52,1.48)
	AQS	1	0.95 (0.65,1.41)	0.93 (0.62,1.38)	0.89 (0.53,1.47)

Table A3.3 (cont.)

Cardiac Defect	Source	Week 6 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	0.88 (0.46,1.66)	0.88 (0.44,1.74)	0.43 (0.14,1.3)
	CMAQ, within 50km of monitor	1	0.92 (0.46,1.84)	0.85 (0.4,1.8)	0.41 (0.12,1.45)
	AQS	1	1.83 (0.78,4.29)	1.29 (0.54,3.1)	0.82 (0.26,2.67)
Coarctation of the Aorta	CMAQ, full population	1	0.97 (0.53,1.74)	0.86 (0.46,1.59)	1.07 (0.51,2.24)
	CMAQ, within 50km of monitor	1	1.15 (0.6,2.2)	1.13 (0.58,2.19)	1.24 (0.56,2.74)
	AQS	1	1.44 (0.7,2.97)	1.51 (0.73,3.12)	2.17 (0.95,4.93)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	1.25 (0.66,2.38)	1.02 (0.52,2.01)	1.02 (0.45,2.33)
	CMAQ, within 50km of monitor	1	1.31 (0.65,2.62)	1.01 (0.49,2.08)	1.08 (0.46,2.57)
	AQS	1	1.88 (0.83,4.24)	1.52 (0.67,3.44)	1.75 (0.69,4.45)
d-TGA	CMAQ, full population	1	0.95 (0.53,1.69)	0.99 (0.54,1.79)	0.93 (0.44,1.98)
	CMAQ, within 50km of monitor	1	0.86 (0.48,1.55)	1.04 (0.57,1.9)	1.05 (0.49,2.25)
	AQS	1	0.97 (0.53,1.78)	1.15 (0.62,2.15)	1.32 (0.62,2.84)
Tetralogy of Fallot	CMAQ, full population	1	0.75 (0.47,1.2)	0.93 (0.57,1.52)	0.51 (0.26,0.99)
	CMAQ, within 50km of monitor	1	0.72 (0.44,1.2)	1.01 (0.61,1.68)	0.55 (0.28,1.1)
	AQS	1	1.3 (0.74,2.29)	1.25 (0.71,2.22)	1.11 (0.55,2.23)
Other Conotruncals	CMAQ, full population	1	1.22 (0.56,2.69)	0.99 (0.43,2.25)	0.98 (0.36,2.66)
	CMAQ, within 50km of monitor	1	0.97 (0.43,2.21)	1.03 (0.45,2.38)	0.89 (0.31,2.52)
	AQS	1	1.23 (0.49,3.08)	0.92 (0.36,2.31)	1.36 (0.49,3.81)
Pulmonary Valve Stenosis	CMAQ, full population	1	1 (0.6,1.66)	1 (0.59,1.7)	0.94 (0.49,1.8)
	CMAQ, within 50km of monitor	1	0.97 (0.57,1.64)	1.05 (0.61,1.81)	0.79 (0.4,1.58)
	AQS	1	1 (0.58,1.74)	1.21 (0.69,2.12)	0.84 (0.4,1.75)
VSD-perimembranous	CMAQ, full population	1	1.1 (0.73,1.67)	0.94 (0.6,1.46)	0.78 (0.44,1.39)
	CMAQ, within 50km of monitor	1	1.08 (0.7,1.67)	0.95 (0.59,1.51)	0.81 (0.44,1.48)
	AQS	1	1.27 (0.79,2.06)	1.29 (0.79,2.12)	1.02 (0.54,1.94)
ASD-all	CMAQ, full population	1	1.04 (0.75,1.44)	1.01 (0.69,1.48)	0.71 (0.41,1.23)
	CMAQ, within 50km of monitor	1	1.03 (0.73,1.45)	0.88 (0.59,1.32)	0.64 (0.35,1.14)
	AQS	1	1.08 (0.73,1.59)	0.94 (0.62,1.43)	0.79 (0.44,1.43)
Defect Groupings					
APVR	CMAQ, full population	1	1.24 (0.59,2.59)	0.75 (0.34,1.66)	1.27 (0.5,3.22)
	CMAQ, within 50km of monitor	1	0.98 (0.49,1.96)	0.63 (0.29,1.35)	1.01 (0.4,2.55)
	AQS	1	0.75 (0.38,1.47)	0.47 (0.22,1.01)	0.62 (0.22,1.74)
Conotruncals	CMAQ, full population	1	0.91 (0.63,1.31)	1 (0.68,1.47)	0.72 (0.43,1.18)
	CMAQ, within 50km of monitor	1	0.82 (0.56,1.2)	1.06 (0.71,1.57)	0.75 (0.45,1.26)
	AQS	1	1.23 (0.81,1.87)	1.23 (0.8,1.89)	1.3 (0.77,2.19)

Table A3.3 (cont.)

Cardiac Defect	Source	Week 7 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	0.87 (0.47,1.64)	0.63 (0.32,1.27)	1.05 (0.44,2.51)
	CMAQ, within 50km of monitor	1	0.62 (0.32,1.19)	0.57 (0.28,1.15)	0.69 (0.26,1.84)
	AQS	1	1.11 (0.53,2.34)	0.8 (0.36,1.76)	1.07 (0.39,2.93)
Coarctation of the Aorta	CMAQ, full population	1	1.26 (0.67,2.38)	1.26 (0.65,2.42)	1.54 (0.71,3.33)
	CMAQ, within 50km of monitor	1	0.76 (0.42,1.37)	0.89 (0.48,1.63)	1.16 (0.55,2.46)
	AQS	1	1.75 (0.88,3.5)	1.33 (0.66,2.71)	1.48 (0.64,3.45)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.85 (0.47,1.55)	0.96 (0.52,1.79)	0.99 (0.45,2.19)
	CMAQ, within 50km of monitor	1	0.65 (0.35,1.21)	0.9 (0.48,1.69)	1.02 (0.45,2.27)
	AQS	1	1.14 (0.56,2.33)	1.42 (0.69,2.89)	1.7 (0.73,3.99)
d-TGA	CMAQ, full population	1	1.52 (0.77,2.99)	1.62 (0.82,3.23)	1.75 (0.78,3.93)
	CMAQ, within 50km of monitor	1	1.47 (0.74,2.9)	1.41 (0.7,2.83)	1.29 (0.56,2.99)
	AQS	1	1.09 (0.6,1.99)	1.19 (0.64,2.2)	0.97 (0.43,2.21)
Tetralogy of Fallot	CMAQ, full population	1	0.96 (0.6,1.55)	0.85 (0.51,1.41)	1.42 (0.78,2.59)
	CMAQ, within 50km of monitor	1	1.04 (0.62,1.74)	0.87 (0.51,1.51)	1.39 (0.74,2.62)
	AQS	1	1.21 (0.68,2.16)	1.5 (0.84,2.68)	1.74 (0.89,3.41)
Other Conotruncals	CMAQ, full population	1	1.53 (0.67,3.5)	0.98 (0.41,2.33)	1.67 (0.62,4.46)
	CMAQ, within 50km of monitor	1	1.45 (0.59,3.57)	0.76 (0.3,1.95)	1.62 (0.58,4.49)
	AQS	1	1.19 (0.44,3.23)	0.95 (0.35,2.55)	1.53 (0.52,4.47)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.06 (0.65,1.74)	0.93 (0.55,1.57)	0.92 (0.48,1.76)
	CMAQ, within 50km of monitor	1	0.81 (0.5,1.33)	0.72 (0.43,1.21)	0.78 (0.4,1.49)
	AQS	1	1 (0.59,1.71)	0.86 (0.49,1.51)	1.31 (0.68,2.54)
VSD-perimembranous	CMAQ, full population	1	1.16 (0.77,1.76)	1.04 (0.67,1.62)	0.98 (0.56,1.73)
	CMAQ, within 50km of monitor	1	0.95 (0.62,1.46)	0.91 (0.58,1.43)	0.85 (0.47,1.54)
	AQS	1	1.38 (0.86,2.22)	1.07 (0.65,1.76)	1.1 (0.59,2.06)
ASD-all	CMAQ, full population	1	1.01 (0.74,1.39)	0.94 (0.65,1.36)	0.95 (0.56,1.62)
	CMAQ, within 50km of monitor	1	0.84 (0.61,1.16)	0.74 (0.5,1.08)	0.87 (0.5,1.52)
	AQS	1	1.3 (0.86,1.97)	1.13 (0.73,1.75)	1.17 (0.64,2.12)
Defect Groupings					
APVR	CMAQ, full population	1	2.37 (0.98,5.75)	1.53 (0.62,3.76)	1.1 (0.36,3.39)
	CMAQ, within 50km of monitor	1	1.61 (0.74,3.53)	1.09 (0.48,2.48)	0.85 (0.29,2.51)
	AQS	1	1.17 (0.57,2.39)	0.7 (0.32,1.55)	0.7 (0.23,2.19)
Conotruncals	CMAQ, full population	1	1.25 (0.85,1.85)	1.15 (0.76,1.73)	1.72 (1.05,2.79)
	CMAQ, within 50km of monitor	1	1.43 (0.94,2.17)	1.2 (0.77,1.86)	1.72 (1.03,2.89)
	AQS	1	1.27 (0.82,1.94)	1.44 (0.93,2.22)	1.56 (0.92,2.62)

Table A3.3 (cont.)

Cardiac Defect	Source	Week 8 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
Aortic Stenosis	CMAQ, full population	1	1.13 (0.56,2.27)	1.65 (0.81,3.36)	0.81 (0.28,2.3)
	CMAQ, within 50km of monitor	1	1.23 (0.58,2.59)	1.57 (0.73,3.38)	0.78 (0.25,2.44)
	AQS	1	1.83 (0.74,4.54)	1.83 (0.74,4.56)	1.26 (0.41,3.86)
Coarctation of the Aorta	CMAQ, full population	1	1.4 (0.74,2.64)	1.29 (0.67,2.47)	1.51 (0.7,3.27)
	CMAQ, within 50km of monitor	1	1.24 (0.66,2.32)	1.24 (0.65,2.36)	1.49 (0.69,3.21)
	AQS	1	1.72 (0.86,3.44)	1.51 (0.74,3.06)	2.2 (0.98,4.91)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	1.01 (0.55,1.83)	1.03 (0.55,1.93)	1.29 (0.6,2.77)
	CMAQ, within 50km of monitor	1	1.63 (0.79,3.37)	1.32 (0.63,2.78)	1.76 (0.75,4.12)
	AQS	1	1.85 (0.85,4.01)	2.05 (0.95,4.44)	1.63 (0.64,4.15)
d-TGA	CMAQ, full population	1	1.28 (0.7,2.32)	1.22 (0.66,2.27)	1.03 (0.47,2.24)
	CMAQ, within 50km of monitor	1	1.07 (0.6,1.91)	1.11 (0.61,2.02)	1.05 (0.49,2.26)
	AQS	1	1.48 (0.79,2.76)	1.21 (0.63,2.32)	1.36 (0.62,2.99)
Tetralogy of Fallot	CMAQ, full population	1	1.17 (0.71,1.94)	1.21 (0.72,2.03)	1.65 (0.89,3.04)
	CMAQ, within 50km of monitor	1	1.07 (0.64,1.8)	1.13 (0.66,1.92)	1.76 (0.94,3.28)
	AQS	1	1.48 (0.81,2.72)	2 (1.09,3.67)	1.86 (0.92,3.76)
Other Conotruncals	CMAQ, full population	1	1.05 (0.51,2.19)	0.93 (0.43,2.01)	1.28 (0.5,3.31)
	CMAQ, within 50km of monitor	1	1.55 (0.63,3.82)	1.35 (0.54,3.36)	1.94 (0.69,5.45)
	AQS	1	0.7 (0.31,1.54)	0.99 (0.46,2.17)	0.98 (0.35,2.69)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.16 (0.67,2)	1.85 (1.06,3.21)	1.9 (0.99,3.63)
	CMAQ, within 50km of monitor	1	1.34 (0.74,2.43)	2 (1.1,3.64)	2.31 (1.16,4.61)
	AQS	1	1.58 (0.85,2.9)	1.68 (0.9,3.12)	1.72 (0.83,3.55)
VSD-perimembranous	CMAQ, full population	1	0.88 (0.59,1.33)	1.21 (0.79,1.85)	1.1 (0.64,1.89)
	CMAQ, within 50km of monitor	1	1.19 (0.75,1.87)	1.46 (0.91,2.35)	1.17 (0.64,2.15)
	AQS	1	1.21 (0.75,1.95)	1.43 (0.88,2.31)	1.29 (0.7,2.37)
ASD-all	CMAQ, full population	1	1.07 (0.78,1.48)	1.01 (0.7,1.46)	1.15 (0.69,1.91)
	CMAQ, within 50km of monitor	1	0.92 (0.66,1.28)	0.94 (0.64,1.37)	0.98 (0.57,1.68)
	AQS	1	0.91 (0.62,1.33)	1.02 (0.68,1.53)	0.99 (0.57,1.73)
Defect Groupings					
APVR	CMAQ, full population	1	1.75 (0.8,3.82)	1.48 (0.66,3.31)	1.27 (0.45,3.55)
	CMAQ, within 50km of monitor	1	1.19 (0.59,2.39)	1.04 (0.5,2.19)	1.08 (0.4,2.91)
	AQS	1	1.32 (0.61,2.84)	0.99 (0.44,2.24)	1.39 (0.52,3.7)
Conotruncals	CMAQ, full population	1	1.12 (0.77,1.63)	1.08 (0.73,1.61)	1.27 (0.79,2.05)
	CMAQ, within 50km of monitor	1	1.05 (0.7,1.56)	1.06 (0.7,1.6)	1.39 (0.85,2.27)
	AQS	1	1.19 (0.78,1.82)	1.37 (0.89,2.12)	1.33 (0.79,2.23)

Table A3.3 (cont.)

Defect Grouping	Source		Week 2 <10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
LVOTO	CMAQ, full population		1	1.45 (0.94,2.24)	1.37 (0.86,2.17)	1.24 (0.69,2.21)
	CMAQ, within 50km of monitor		1	1.43 (0.9,2.27)	1.36 (0.84,2.21)	1.11 (0.59,2.07)
	AQS		1	1.18 (0.73,1.89)	1.19 (0.73,1.95)	1 (0.53,1.88)
RVOTO	CMAQ, full population		1	1.3 (0.83,2.03)	1.16 (0.72,1.86)	1.47 (0.83,2.59)
	CMAQ, within 50km of monitor		1	1.39 (0.85,2.26)	1.4 (0.84,2.33)	1.74 (0.95,3.2)
	AQS		1	1.43 (0.86,2.36)	0.86 (0.51,1.48)	1.49 (0.8,2.78)
Septals	CMAQ, full population		1	0.97 (0.74,1.26)	1.08 (0.81,1.45)	0.79 (0.52,1.19)
	CMAQ, within 50km of monitor		1	1.08 (0.81,1.43)	1.08 (0.79,1.48)	0.8 (0.51,1.26)
	AQS		1	1 (0.73,1.36)	1.03 (0.74,1.43)	0.57 (0.35,0.93)
		Week 3				
LVOTO	CMAQ, full population		1	0.56 (0.38,0.82)	0.62 (0.41,0.93)	0.67 (0.4,1.13)
	CMAQ, within 50km of monitor		1	0.47 (0.31,0.71)	0.58 (0.38,0.89)	0.6 (0.35,1.04)
	AQS		1	0.82 (0.54,1.26)	0.69 (0.44,1.08)	0.66 (0.37,1.18)
RVOTO	CMAQ, full population		1	0.76 (0.49,1.16)	0.87 (0.56,1.35)	0.7 (0.39,1.24)
	CMAQ, within 50km of monitor		1	0.69 (0.45,1.08)	0.79 (0.5,1.25)	0.66 (0.36,1.19)
	AQS		1	0.87 (0.55,1.39)	0.88 (0.55,1.42)	0.71 (0.38,1.33)
Septals	CMAQ, full population		1	1.08 (0.82,1.43)	1.06 (0.77,1.45)	1.2 (0.81,1.79)
	CMAQ, within 50km of monitor		1	0.9 (0.67,1.19)	0.87 (0.63,1.19)	1 (0.66,1.52)
	AQS		1	1.05 (0.76,1.44)	0.9 (0.64,1.26)	1.21 (0.79,1.86)
		Week 4				
LVOTO	CMAQ, full population		1	1.22 (0.8,1.86)	1.19 (0.76,1.86)	1.17 (0.67,2.04)
	CMAQ, within 50km of monitor		1	1.26 (0.8,1.99)	1.27 (0.79,2.03)	1.25 (0.7,2.23)
	AQS		1	1.3 (0.81,2.08)	1.19 (0.73,1.93)	1.61 (0.91,2.86)
RVOTO	CMAQ, full population		1	1.3 (0.83,2.04)	1.29 (0.8,2.06)	0.76 (0.41,1.4)
	CMAQ, within 50km of monitor		1	1.39 (0.86,2.23)	1.26 (0.77,2.07)	0.83 (0.44,1.56)
	AQS		1	0.98 (0.63,1.53)	0.94 (0.59,1.5)	0.8 (0.44,1.47)
Septals	CMAQ, full population		1	1.01 (0.77,1.33)	1.1 (0.81,1.49)	1.23 (0.83,1.83)
	CMAQ, within 50km of monitor		1	1.17 (0.88,1.57)	1.24 (0.9,1.72)	1.56 (1.03,2.36)
	AQS		1	1.25 (0.9,1.73)	1.22 (0.87,1.71)	1.31 (0.84,2.02)

Table A3.3 (cont.)

Cardiac Defect	Source		<10th percentile (Referent)	10th percentile to median	median to 90th percentile	>90th percentile
		Week 5				
LVOTO	CMAQ, full population		1	1.1 (0.73,1.67)	1.16 (0.75,1.79)	1.27 (0.74,2.17)
	CMAQ, within 50km of monitor		1	1.15 (0.74,1.78)	1.2 (0.76,1.9)	1.12 (0.62,2)
	AQS		1	0.99 (0.64,1.53)	0.93 (0.59,1.46)	1.05 (0.6,1.85)
RVOTO	CMAQ, full population		1	1.08 (0.7,1.66)	0.99 (0.63,1.56)	1.28 (0.74,2.21)
	CMAQ, within 50km of monitor		1	1.24 (0.79,1.96)	1.09 (0.68,1.76)	1.29 (0.73,2.3)
	AQS		1	0.99 (0.62,1.57)	1.14 (0.71,1.82)	0.98 (0.54,1.8)
Septals	CMAQ, full population		1	1.01 (0.77,1.32)	0.91 (0.67,1.23)	0.94 (0.64,1.4)
	CMAQ, within 50km of monitor		1	1.02 (0.77,1.34)	0.83 (0.6,1.13)	0.81 (0.53,1.24)
	AQS		1	1 (0.73,1.36)	0.84 (0.6,1.17)	0.96 (0.62,1.47)
		Week 6				
LVOTO	CMAQ, full population		1	1.09 (0.73,1.64)	0.96 (0.63,1.48)	0.94 (0.55,1.62)
	CMAQ, within 50km of monitor		1	1.26 (0.81,1.96)	1.12 (0.7,1.78)	1.07 (0.6,1.91)
	AQS		1	1.89 (1.11,3.22)	1.66 (0.96,2.87)	1.94 (1.04,3.65)
RVOTO	CMAQ, full population		1	1.13 (0.73,1.74)	1.09 (0.69,1.71)	1.01 (0.57,1.78)
	CMAQ, within 50km of monitor		1	1.12 (0.71,1.75)	1.11 (0.7,1.78)	0.89 (0.49,1.62)
	AQS		1	0.86 (0.55,1.35)	1.04 (0.65,1.64)	0.75 (0.4,1.4)
Septals	CMAQ, full population		1	1.08 (0.82,1.41)	0.98 (0.72,1.32)	0.77 (0.51,1.16)
	CMAQ, within 50km of monitor		1	1.06 (0.8,1.4)	0.91 (0.67,1.25)	0.74 (0.48,1.14)
	AQS		1	1.15 (0.84,1.57)	1.07 (0.77,1.5)	0.89 (0.56,1.39)
		Week 7				
LVOTO	CMAQ, full population		1	0.94 (0.63,1.41)	0.91 (0.6,1.39)	1.11 (0.66,1.89)
	CMAQ, within 50km of monitor		1	0.64 (0.43,0.95)	0.76 (0.5,1.15)	0.92 (0.54,1.58)
	AQS		1	1.32 (0.82,2.1)	1.18 (0.73,1.92)	1.37 (0.76,2.47)
RVOTO	CMAQ, full population		1	0.95 (0.63,1.43)	0.8 (0.52,1.24)	0.85 (0.49,1.46)
	CMAQ, within 50km of monitor		1	0.81 (0.54,1.22)	0.67 (0.44,1.04)	0.79 (0.45,1.38)
	AQS		1	0.97 (0.62,1.52)	0.83 (0.52,1.32)	1.26 (0.72,2.22)
Septals	CMAQ, full population		1	1.02 (0.78,1.33)	0.95 (0.7,1.27)	0.92 (0.62,1.38)
	CMAQ, within 50km of monitor		1	0.87 (0.66,1.14)	0.82 (0.6,1.11)	0.85 (0.56,1.3)
	AQS		1	1.28 (0.93,1.78)	1.08 (0.76,1.52)	1.08 (0.69,1.7)
		Week 8				
LVOTO	CMAQ, full population		1	1.16 (0.77,1.76)	1.21 (0.79,1.87)	1.2 (0.7,2.07)
	CMAQ, within 50km of monitor		1	1.36 (0.86,2.15)	1.31 (0.82,2.1)	1.35 (0.76,2.4)
	AQS		1	1.71 (1.03,2.85)	1.64 (0.98,2.76)	1.65 (0.89,3.06)
RVOTO	CMAQ, full population		1	1.12 (0.71,1.76)	1.6 (1.01,2.54)	1.67 (0.96,2.91)
	CMAQ, within 50km of monitor		1	1.27 (0.78,2.07)	1.62 (0.98,2.65)	1.91 (1.07,3.41)
	AQS		1	1.14 (0.71,1.83)	1.2 (0.74,1.96)	1.36 (0.76,2.45)
Septals	CMAQ, full population		1	0.98 (0.75,1.28)	1.06 (0.79,1.42)	1.05 (0.71,1.55)
	CMAQ, within 50km of monitor		1	0.94 (0.71,1.25)	1.03 (0.76,1.39)	0.9 (0.6,1.37)
	AQS		1	0.93 (0.68,1.27)	1.06 (0.76,1.46)	0.95 (0.62,1.46)

Table A3.4: Odds Ratios and 95% Confidence Intervals resulting from hierarchical analysis between cardiac birth defects and weekly exposure to ozone

Cardiac Defect	Source	Week 2 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	1.08 (0.58,2.01)	0.86 (0.42,1.78)	1.06 (0.49,2.29)
	CMAQ, within 50km of monitor	1	0.96 (0.44,2.1)	0.8 (0.35,1.86)	1.24 (0.53,2.91)
	AQS	1	0.79 (0.35,1.81)	0.56 (0.22,1.41)	1.12 (0.46,2.74)
Coarctation of the Aorta	CMAQ, full population	1	0.62 (0.37,1.05)	0.61 (0.33,1.14)	0.65 (0.34,1.25)
	CMAQ, within 50km of monitor	1	0.88 (0.47,1.64)	0.69 (0.34,1.4)	0.78 (0.38,1.61)
	AQS	1	0.46 (0.22,0.97)	0.67 (0.32,1.39)	0.75 (0.35,1.62)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.8 (0.46,1.41)	0.65 (0.34,1.26)	1.02 (0.52,2)
	CMAQ, within 50km of monitor	1	0.87 (0.47,1.62)	0.66 (0.33,1.32)	0.82 (0.4,1.68)
	AQS	1	0.54 (0.27,1.06)	0.58 (0.29,1.2)	0.64 (0.3,1.36)
d-TGA	CMAQ, full population	1	1.08 (0.65,1.78)	0.8 (0.43,1.49)	1.28 (0.67,2.42)
	CMAQ, within 50km of monitor	1	1.21 (0.68,2.15)	0.68 (0.34,1.36)	1.1 (0.55,2.2)
	AQS	1	0.9 (0.47,1.72)	0.65 (0.31,1.37)	0.79 (0.37,1.7)
Tetralogy of Fallot	CMAQ, full population	1	1.03 (0.68,1.57)	1.26 (0.77,2.05)	1.07 (0.63,1.83)
	CMAQ, within 50km of monitor	1	1.03 (0.63,1.69)	0.88 (0.51,1.54)	0.91 (0.5,1.63)
	AQS	1	0.96 (0.56,1.66)	0.73 (0.39,1.34)	0.75 (0.39,1.44)
Other Conotruncals	CMAQ, full population	1	1.13 (0.58,2.23)	0.53 (0.23,1.22)	0.84 (0.37,1.92)
	CMAQ, within 50km of monitor	1	1.09 (0.5,2.37)	0.45 (0.16,1.27)	0.93 (0.37,2.31)
	AQS	1	1.02 (0.45,2.32)	0.34 (0.11,1.06)	0.87 (0.33,2.3)
Pulmonary Valve Stenosis	CMAQ, full population	1	0.88 (0.57,1.35)	0.73 (0.44,1.21)	0.56 (0.33,0.97)
	CMAQ, within 50km of monitor	1	0.82 (0.48,1.4)	0.59 (0.32,1.07)	0.66 (0.35,1.22)
	AQS	1	0.8 (0.44,1.42)	0.43 (0.22,0.84)	0.43 (0.22,0.85)
VSD-perimembranous	CMAQ, full population	1	0.78 (0.55,1.1)	0.68 (0.44,1.03)	0.67 (0.42,1.05)
	CMAQ, within 50km of monitor	1	0.76 (0.45,1.28)	0.67 (0.38,1.19)	0.81 (0.45,1.47)
	AQS	1	0.87 (0.56,1.34)	0.67 (0.41,1.11)	0.85 (0.5,1.42)
ASD-all	CMAQ, full population	1	0.97 (0.72,1.32)	0.77 (0.53,1.11)	0.73 (0.49,1.11)
	CMAQ, within 50km of monitor	1	1.08 (0.75,1.54)	0.76 (0.5,1.17)	0.68 (0.42,1.1)
	AQS	1	1.2 (0.81,1.78)	0.74 (0.47,1.18)	0.58 (0.34,0.98)
Defect Groupings					
APVR	CMAQ, full population	1	0.77 (0.38,1.54)	0.79 (0.36,1.7)	1.28 (0.59,2.78)
	CMAQ, within 50km of monitor	1	0.77 (0.35,1.69)	1.14 (0.52,2.48)	1.23 (0.54,2.84)
	AQS	1	0.8 (0.36,1.79)	0.53 (0.21,1.33)	0.93 (0.38,2.25)
Conotruncals	CMAQ, full population	1	1.12 (0.81,1.55)	1.04 (0.7,1.55)	1.18 (0.77,1.81)
	CMAQ, within 50km of monitor	1	1.12 (0.77,1.65)	0.77 (0.49,1.22)	1 (0.62,1.61)
	AQS	1	1.04 (0.68,1.58)	0.7 (0.42,1.15)	0.86 (0.51,1.45)

Table A3.4 (cont.)

		Week 3			
Cardiac Defect	Source	<25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	1.35 (0.71,2.54)	0.88 (0.41,1.89)	1.01 (0.45,2.28)
	CMAQ, within 50km of monitor	1	0.98 (0.45,2.15)	1.49 (0.65,3.38)	0.84 (0.32,2.17)
	AQS	1	1.24 (0.53,2.89)	1.82 (0.76,4.39)	1.62 (0.62,4.25)
Coarctation of the Aorta	CMAQ, full population	1	0.8 (0.47,1.38)	0.83 (0.43,1.59)	0.85 (0.42,1.72)
	CMAQ, within 50km of monitor	1	0.89 (0.45,1.74)	1.58 (0.79,3.18)	1.27 (0.58,2.76)
	AQS	1	1.63 (0.81,3.28)	1.49 (0.69,3.25)	1.16 (0.5,2.68)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.8 (0.44,1.46)	1.03 (0.53,2.01)	0.79 (0.38,1.66)
	CMAQ, within 50km of monitor	1	1.59 (0.85,2.98)	1.14 (0.56,2.34)	0.87 (0.39,1.91)
	AQS	1	1.59 (0.81,3.13)	1.23 (0.58,2.63)	1.07 (0.48,2.4)
d-TGA	CMAQ, full population	1	1.05 (0.62,1.77)	0.82 (0.43,1.57)	0.9 (0.45,1.8)
	CMAQ, within 50km of monitor	1	1.6 (0.87,2.93)	1.33 (0.66,2.66)	1.29 (0.61,2.75)
	AQS	1	1.58 (0.82,3.03)	1.2 (0.57,2.52)	1.09 (0.49,2.43)
Tetralogy of Fallot	CMAQ, full population	1	0.69 (0.44,1.08)	1.03 (0.62,1.73)	1.01 (0.57,1.79)
	CMAQ, within 50km of monitor	1	0.92 (0.55,1.55)	1.31 (0.74,2.31)	1.25 (0.67,2.33)
	AQS	1	1.48 (0.83,2.61)	1.5 (0.79,2.82)	1.49 (0.75,2.96)
Other Conotruncals	CMAQ, full population	1	0.67 (0.32,1.42)	1.19 (0.55,2.56)	0.69 (0.28,1.68)
	CMAQ, within 50km of monitor	1	0.92 (0.39,2.15)	1.79 (0.77,4.17)	0.81 (0.29,2.26)
	AQS	1	0.95 (0.38,2.36)	1.96 (0.81,4.71)	0.95 (0.33,2.72)
Pulmonary Valve Stenosis	CMAQ, full population	1	0.83 (0.52,1.34)	1.2 (0.7,2.05)	1.21 (0.68,2.17)
	CMAQ, within 50km of monitor	1	1.13 (0.64,2)	1.59 (0.86,2.97)	1.53 (0.79,2.98)
	AQS	1	1.87 (0.99,3.55)	2.04 (1.01,4.11)	2.22 (1.06,4.67)
VSD-perimembranous	CMAQ, full population	1	0.95 (0.66,1.39)	1.15 (0.73,1.81)	1.11 (0.67,1.83)
	CMAQ, within 50km of monitor	1	1.6 (0.94,2.75)	1.78 (0.98,3.23)	1.44 (0.76,2.74)
	AQS	1	1.46 (0.93,2.29)	1.52 (0.91,2.55)	1.21 (0.68,2.15)
ASD-all	CMAQ, full population	1	0.95 (0.68,1.31)	0.93 (0.63,1.38)	0.97 (0.62,1.52)
	CMAQ, within 50km of monitor	1	1.19 (0.82,1.73)	1.21 (0.77,1.89)	1.11 (0.67,1.85)
	AQS	1	1.14 (0.76,1.72)	1.19 (0.74,1.93)	1.34 (0.78,2.29)
Defect Groupings					
APVR	CMAQ, full population	1	1.47 (0.74,2.93)	0.99 (0.45,2.21)	0.88 (0.38,2.04)
	CMAQ, within 50km of monitor	1	1.35 (0.64,2.86)	1.22 (0.54,2.76)	0.84 (0.34,2.07)
	AQS	1	1.23 (0.55,2.74)	1.4 (0.6,3.29)	0.94 (0.36,2.46)
Conotruncals	CMAQ, full population	1	0.78 (0.55,1.1)	0.96 (0.63,1.46)	0.92 (0.58,1.45)
	CMAQ, within 50km of monitor	1	1.08 (0.72,1.62)	1.32 (0.84,2.08)	1.16 (0.71,1.91)
	AQS	1	1.3 (0.83,2.04)	1.3 (0.78,2.14)	1.11 (0.65,1.91)

Table A3.4 (cont.)

Cardiac Defect	Source	Week 4 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	1.1 (0.57,2.13)	1.41 (0.66,2.98)	1.55 (0.67,3.6)
	CMAQ, within 50km of monitor	1	0.93 (0.43,2.03)	0.82 (0.34,1.94)	0.94 (0.37,2.38)
	AQS	1	0.87 (0.38,1.98)	0.81 (0.32,2.02)	1.08 (0.42,2.8)
Coarctation of the Aorta	CMAQ, full population	1	1.4 (0.82,2.39)	1.07 (0.54,2.1)	0.9 (0.43,1.89)
	CMAQ, within 50km of monitor	1	0.69 (0.37,1.3)	0.61 (0.3,1.24)	0.43 (0.2,0.94)
	AQS	1	0.75 (0.37,1.52)	0.96 (0.45,2.02)	0.5 (0.22,1.15)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	1.16 (0.64,2.09)	0.92 (0.46,1.83)	1 (0.48,2.1)
	CMAQ, within 50km of monitor	1	0.83 (0.44,1.57)	0.53 (0.25,1.11)	0.96 (0.45,2.05)
	AQS	1	0.76 (0.38,1.51)	0.83 (0.39,1.74)	0.93 (0.42,2.06)
d-TGA	CMAQ, full population	1	1.15 (0.67,1.96)	1.25 (0.65,2.41)	1.34 (0.65,2.75)
	CMAQ, within 50km of monitor	1	0.85 (0.47,1.56)	0.78 (0.39,1.56)	0.84 (0.4,1.79)
	AQS	1	0.47 (0.23,0.95)	1.03 (0.51,2.06)	0.91 (0.41,2)
Tetralogy of Fallot	CMAQ, full population	1	1.51 (0.98,2.35)	1.17 (0.67,2.04)	0.96 (0.53,1.77)
	CMAQ, within 50km of monitor	1	1.11 (0.66,1.84)	0.76 (0.42,1.39)	0.65 (0.34,1.24)
	AQS	1	1.24 (0.71,2.18)	0.79 (0.41,1.53)	0.8 (0.4,1.6)
Other Conotruncals	CMAQ, full population	1	0.94 (0.44,2.01)	1.78 (0.79,4.02)	1.81 (0.73,4.48)
	CMAQ, within 50km of monitor	1	0.77 (0.33,1.79)	0.86 (0.35,2.15)	1.15 (0.44,3.02)
	AQS	1	0.97 (0.42,2.27)	0.56 (0.19,1.62)	1.18 (0.43,3.24)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.41 (0.88,2.27)	1.33 (0.75,2.36)	1.54 (0.83,2.83)
	CMAQ, within 50km of monitor	1	0.78 (0.44,1.36)	0.69 (0.36,1.29)	0.65 (0.33,1.28)
	AQS	1	0.75 (0.4,1.42)	0.75 (0.37,1.5)	1.11 (0.54,2.28)
VSD-perimembranous	CMAQ, full population	1	1.16 (0.8,1.69)	1.1 (0.68,1.77)	1.26 (0.75,2.12)
	CMAQ, within 50km of monitor	1	0.92 (0.54,1.58)	1.08 (0.59,1.98)	1.16 (0.61,2.2)
	AQS	1	0.92 (0.58,1.45)	0.89 (0.52,1.53)	0.96 (0.54,1.72)
ASD-all	CMAQ, full population	1	1.03 (0.74,1.44)	1.09 (0.72,1.64)	1.23 (0.78,1.95)
	CMAQ, within 50km of monitor	1	0.75 (0.51,1.08)	0.76 (0.49,1.18)	0.81 (0.49,1.34)
	AQS	1	0.92 (0.61,1.39)	1.06 (0.66,1.7)	0.89 (0.51,1.55)
Defect Groupings					
APVR	CMAQ, full population	1	0.91 (0.44,1.88)	1.36 (0.62,2.97)	1.06 (0.44,2.51)
	CMAQ, within 50km of monitor	1	0.57 (0.25,1.29)	1.13 (0.5,2.54)	0.75 (0.31,1.85)
	AQS	1	0.87 (0.39,1.96)	0.83 (0.34,2.04)	1.06 (0.42,2.71)
Conotruncals	CMAQ, full population	1	1.29 (0.92,1.81)	1.25 (0.82,1.93)	1.16 (0.72,1.86)
	CMAQ, within 50km of monitor	1	1.09 (0.73,1.62)	0.9 (0.56,1.43)	0.88 (0.53,1.46)
	AQS	1	0.91 (0.6,1.4)	0.85 (0.52,1.38)	0.87 (0.52,1.48)

Table A3.4 (cont.)

Cardiac Defect	Source	Week 5 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	0.87 (0.46,1.66)	1.04 (0.5,2.17)	1.02 (0.44,2.35)
	CMAQ, within 50km of monitor	1	0.87 (0.4,1.88)	0.98 (0.42,2.29)	0.93 (0.37,2.37)
	AQS	1	1 (0.46,2.15)	0.72 (0.29,1.8)	0.73 (0.27,1.97)
Coarctation of the Aorta	CMAQ, full population	1	0.78 (0.45,1.36)	0.68 (0.34,1.34)	1.37 (0.67,2.8)
	CMAQ, within 50km of monitor	1	0.84 (0.43,1.63)	0.97 (0.46,2.05)	1.8 (0.85,3.84)
	AQS	1	0.44 (0.2,0.96)	0.68 (0.31,1.49)	1.47 (0.67,3.2)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.82 (0.44,1.52)	1.86 (0.95,3.63)	1.1 (0.51,2.35)
	CMAQ, within 50km of monitor	1	0.71 (0.35,1.45)	2.25 (1.12,4.53)	1.11 (0.49,2.48)
	AQS	1	1.02 (0.52,2.01)	1.33 (0.64,2.77)	0.95 (0.42,2.13)
d-TGA	CMAQ, full population	1	1.02 (0.6,1.74)	1.26 (0.67,2.37)	0.84 (0.41,1.72)
	CMAQ, within 50km of monitor	1	1.12 (0.62,2.05)	1.14 (0.58,2.25)	0.71 (0.33,1.57)
	AQS	1	1.4 (0.74,2.65)	1.39 (0.66,2.89)	0.95 (0.42,2.17)
Tetralogy of Fallot	CMAQ, full population	1	0.83 (0.53,1.29)	0.78 (0.46,1.34)	0.92 (0.52,1.66)
	CMAQ, within 50km of monitor	1	1 (0.59,1.69)	1.15 (0.63,2.1)	1.4 (0.74,2.63)
	AQS	1	0.82 (0.47,1.45)	1.28 (0.69,2.38)	1.39 (0.71,2.73)
Other Conotruncals	CMAQ, full population	1	0.82 (0.39,1.71)	1.17 (0.52,2.59)	1 (0.41,2.42)
	CMAQ, within 50km of monitor	1	1.24 (0.55,2.8)	1.17 (0.47,2.95)	1.15 (0.43,3.08)
	AQS	1	0.9 (0.38,2.12)	1.02 (0.4,2.63)	1.09 (0.39,3.04)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.01 (0.63,1.61)	0.99 (0.57,1.73)	0.94 (0.52,1.71)
	CMAQ, within 50km of monitor	1	1.17 (0.66,2.06)	1.17 (0.61,2.24)	1.26 (0.64,2.49)
	AQS	1	1.03 (0.55,1.92)	1.24 (0.63,2.47)	1.17 (0.57,2.42)
VSD-perimembranous	CMAQ, full population	1	1.41 (0.96,2.06)	1.26 (0.79,2.03)	1.23 (0.73,2.07)
	CMAQ, within 50km of monitor	1	1.06 (0.63,1.76)	0.97 (0.54,1.73)	1 (0.54,1.85)
	AQS	1	1.35 (0.85,2.15)	1.38 (0.8,2.36)	1.24 (0.69,2.21)
ASD-all	CMAQ, full population	1	1.01 (0.72,1.42)	1.21 (0.81,1.81)	1.18 (0.75,1.86)
	CMAQ, within 50km of monitor	1	1.38 (0.93,2.06)	1.8 (1.13,2.86)	1.68 (1,2.83)
	AQS	1	1.06 (0.7,1.61)	1.14 (0.7,1.84)	1.48 (0.87,2.52)
Defect Groupings					
APVR	CMAQ, full population	1	0.65 (0.31,1.39)	1.14 (0.51,2.52)	1.48 (0.64,3.45)
	CMAQ, within 50km of monitor	1	1.24 (0.57,2.71)	1.79 (0.77,4.14)	1.59 (0.64,3.94)
	AQS	1	1.22 (0.56,2.69)	1.41 (0.6,3.33)	0.8 (0.3,2.14)
Conotruncals	CMAQ, full population	1	0.88 (0.63,1.24)	0.95 (0.63,1.44)	0.87 (0.55,1.37)
	CMAQ, within 50km of monitor	1	0.97 (0.65,1.44)	0.99 (0.63,1.57)	0.94 (0.57,1.55)
	AQS	1	1.02 (0.67,1.56)	1.32 (0.81,2.13)	1.23 (0.73,2.09)

Table A3.4 (cont.)

Cardiac Defect	Source	Week 6 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	1.81 (0.95,3.43)	1.6 (0.76,3.37)	0.73 (0.3,1.79)
	CMAQ, within 50km of monitor	1	1.54 (0.71,3.32)	1.54 (0.66,3.6)	0.54 (0.18,1.59)
	AQS	1	1.87 (0.86,4.09)	1.19 (0.48,2.94)	0.46 (0.14,1.46)
Coarctation of the Aorta	CMAQ, full population	1	1.49 (0.87,2.56)	1.25 (0.64,2.43)	1.01 (0.48,2.1)
	CMAQ, within 50km of monitor	1	1.86 (0.98,3.54)	1.03 (0.48,2.23)	1.04 (0.46,2.32)
	AQS	1	1.28 (0.64,2.55)	1.13 (0.52,2.48)	0.79 (0.34,1.83)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.71 (0.39,1.29)	0.88 (0.46,1.69)	0.76 (0.37,1.57)
	CMAQ, within 50km of monitor	1	1.1 (0.57,2.12)	1.09 (0.53,2.24)	1.08 (0.49,2.37)
	AQS	1	1.23 (0.61,2.46)	1.68 (0.79,3.56)	1.23 (0.53,2.81)
d-TGA	CMAQ, full population	1	0.78 (0.46,1.31)	0.62 (0.33,1.18)	0.7 (0.35,1.4)
	CMAQ, within 50km of monitor	1	0.96 (0.52,1.76)	0.93 (0.47,1.85)	0.8 (0.37,1.72)
	AQS	1	1.02 (0.54,1.93)	1.05 (0.51,2.17)	0.74 (0.33,1.66)
Tetralogy of Fallot	CMAQ, full population	1	1 (0.65,1.54)	0.87 (0.51,1.49)	0.71 (0.39,1.28)
	CMAQ, within 50km of monitor	1	1.21 (0.72,2.03)	1.11 (0.6,2.03)	0.89 (0.46,1.73)
	AQS	1	1.24 (0.72,2.12)	0.91 (0.48,1.71)	0.65 (0.33,1.31)
Other Conotruncals	CMAQ, full population	1	1.03 (0.51,2.08)	0.96 (0.43,2.12)	0.65 (0.26,1.6)
	CMAQ, within 50km of monitor	1	1.15 (0.52,2.56)	1.16 (0.48,2.83)	0.56 (0.19,1.66)
	AQS	1	1.23 (0.54,2.8)	0.95 (0.37,2.42)	0.52 (0.17,1.57)
Pulmonary Valve Stenosis	CMAQ, full population	1	0.98 (0.62,1.56)	0.92 (0.53,1.59)	1.07 (0.6,1.93)
	CMAQ, within 50km of monitor	1	0.94 (0.53,1.67)	1.04 (0.54,1.97)	1.12 (0.57,2.2)
	AQS	1	0.82 (0.44,1.54)	0.91 (0.46,1.81)	1.17 (0.57,2.42)
VSD-perimembranous	CMAQ, full population	1	1.05 (0.72,1.52)	0.85 (0.53,1.35)	1.03 (0.62,1.71)
	CMAQ, within 50km of monitor	1	1.13 (0.68,1.9)	1.05 (0.58,1.9)	1.24 (0.65,2.35)
	AQS	1	1.09 (0.69,1.73)	0.9 (0.52,1.57)	1.25 (0.7,2.24)
ASD-all	CMAQ, full population	1	1.08 (0.78,1.51)	1.24 (0.83,1.85)	0.95 (0.6,1.5)
	CMAQ, within 50km of monitor	1	1.08 (0.73,1.6)	1.18 (0.75,1.88)	0.85 (0.5,1.45)
	AQS	1	1.24 (0.82,1.88)	1.32 (0.82,2.11)	0.75 (0.43,1.34)
Defect Groupings					
APVR	CMAQ, full population	1	0.67 (0.33,1.38)	0.8 (0.37,1.73)	0.73 (0.32,1.69)
	CMAQ, within 50km of monitor	1	0.68 (0.31,1.49)	0.64 (0.27,1.5)	0.73 (0.3,1.77)
	AQS	1	0.74 (0.33,1.67)	0.92 (0.39,2.17)	0.89 (0.35,2.32)
Conotruncals	CMAQ, full population	1	0.92 (0.66,1.28)	0.78 (0.52,1.18)	0.68 (0.43,1.08)
	CMAQ, within 50km of monitor	1	1.09 (0.73,1.62)	1.04 (0.65,1.64)	0.8 (0.48,1.33)
	AQS	1	1.09 (0.72,1.65)	0.88 (0.54,1.43)	0.61 (0.35,1.04)

Table A3.4 (cont.)

Cardiac Defect	Source	Week 7 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	0.73 (0.39,1.38)	0.7 (0.34,1.45)	0.59 (0.26,1.34)
	CMAQ, within 50km of monitor	1	0.71 (0.33,1.53)	0.65 (0.28,1.5)	0.65 (0.26,1.62)
	AQS	1	0.8 (0.36,1.77)	0.72 (0.3,1.74)	0.76 (0.29,2.02)
Coarctation of the Aorta	CMAQ, full population	1	0.79 (0.45,1.37)	0.95 (0.5,1.82)	1.16 (0.58,2.32)
	CMAQ, within 50km of monitor	1	0.8 (0.42,1.54)	0.89 (0.44,1.83)	0.93 (0.43,1.99)
	AQS	1	0.94 (0.47,1.88)	0.82 (0.38,1.79)	0.91 (0.4,2.05)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	0.92 (0.51,1.64)	0.82 (0.42,1.61)	0.76 (0.37,1.57)
	CMAQ, within 50km of monitor	1	0.93 (0.49,1.76)	0.7 (0.35,1.43)	0.63 (0.29,1.35)
	AQS	1	1.11 (0.57,2.16)	0.74 (0.35,1.58)	0.8 (0.36,1.77)
d-TGA	CMAQ, full population	1	0.67 (0.39,1.15)	0.92 (0.49,1.71)	0.82 (0.41,1.63)
	CMAQ, within 50km of monitor	1	0.72 (0.38,1.35)	1.1 (0.57,2.16)	0.83 (0.39,1.76)
	AQS	1	0.58 (0.3,1.13)	0.83 (0.42,1.66)	0.63 (0.29,1.37)
Tetralogy of Fallot	CMAQ, full population	1	1.1 (0.71,1.71)	1.12 (0.66,1.9)	0.92 (0.51,1.65)
	CMAQ, within 50km of monitor	1	0.73 (0.44,1.24)	0.85 (0.48,1.51)	0.65 (0.35,1.22)
	AQS	1	0.77 (0.44,1.33)	0.76 (0.41,1.39)	0.68 (0.35,1.32)
Other Conotruncals	CMAQ, full population	1	0.91 (0.45,1.82)	0.75 (0.33,1.68)	0.76 (0.32,1.79)
	CMAQ, within 50km of monitor	1	0.68 (0.31,1.51)	0.47 (0.19,1.21)	0.59 (0.23,1.55)
	AQS	1	1.08 (0.48,2.44)	0.53 (0.2,1.45)	0.6 (0.22,1.68)
Pulmonary Valve Stenosis	CMAQ, full population	1	0.98 (0.61,1.56)	0.95 (0.55,1.63)	0.85 (0.47,1.51)
	CMAQ, within 50km of monitor	1	0.77 (0.43,1.37)	0.91 (0.49,1.7)	0.82 (0.42,1.59)
	AQS	1	0.69 (0.38,1.27)	0.53 (0.27,1.04)	0.62 (0.31,1.25)
VSD-perimembranous	CMAQ, full population	1	0.93 (0.64,1.36)	0.88 (0.56,1.39)	0.67 (0.41,1.1)
	CMAQ, within 50km of monitor	1	0.65 (0.4,1.06)	0.49 (0.28,0.87)	0.45 (0.24,0.82)
	AQS	1	0.57 (0.36,0.89)	0.56 (0.34,0.92)	0.46 (0.27,0.8)
ASD-all	CMAQ, full population	1	0.72 (0.52,1)	0.74 (0.5,1.09)	0.66 (0.43,1.03)
	CMAQ, within 50km of monitor	1	0.7 (0.48,1.05)	0.73 (0.47,1.14)	0.83 (0.51,1.38)
	AQS	1	0.59 (0.39,0.89)	0.54 (0.33,0.87)	0.81 (0.48,1.37)
Defect Groupings					
APVR	CMAQ, full population	1	0.82 (0.4,1.65)	1.03 (0.48,2.21)	0.69 (0.3,1.62)
	CMAQ, within 50km of monitor	1	0.65 (0.3,1.42)	0.73 (0.32,1.65)	0.6 (0.25,1.46)
	AQS	1	0.82 (0.38,1.78)	0.66 (0.28,1.56)	0.49 (0.19,1.29)
Conotruncals	CMAQ, full population	1	0.97 (0.69,1.35)	1.07 (0.72,1.61)	0.93 (0.59,1.46)
	CMAQ, within 50km of monitor	1	0.79 (0.53,1.18)	0.98 (0.63,1.52)	0.79 (0.48,1.28)
	AQS	1	0.84 (0.55,1.28)	0.9 (0.56,1.42)	0.78 (0.47,1.3)

Table A3.4 (cont.)

Cardiac Defect	Source	Week 8 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
Aortic Stenosis	CMAQ, full population	1	0.79 (0.42,1.49)	1.03 (0.52,2.03)	0.76 (0.34,1.69)
	CMAQ, within 50km of monitor	1	1.79 (0.85,3.79)	1.57 (0.69,3.6)	0.86 (0.32,2.28)
	AQS	1	1.54 (0.72,3.29)	1.5 (0.65,3.5)	0.75 (0.26,2.17)
Coarctation of the Aorta	CMAQ, full population	1	1.29 (0.76,2.19)	1.38 (0.74,2.56)	1.08 (0.54,2.16)
	CMAQ, within 50km of monitor	1	1.21 (0.65,2.23)	1.01 (0.5,2.03)	1.15 (0.55,2.4)
	AQS	1	0.91 (0.47,1.77)	1.3 (0.64,2.66)	0.99 (0.46,2.17)
Hypoplastic Left Heart Syndrome	CMAQ, full population	1	1.38 (0.77,2.47)	1.95 (1.02,3.75)	1.26 (0.61,2.61)
	CMAQ, within 50km of monitor	1	1.93 (1,3.73)	1.85 (0.89,3.82)	1.64 (0.75,3.58)
	AQS	1	1.47 (0.77,2.79)	1.3 (0.64,2.66)	1.23 (0.57,2.69)
d-TGA	CMAQ, full population	1	1.26 (0.76,2.11)	1.35 (0.73,2.47)	1.03 (0.52,2.03)
	CMAQ, within 50km of monitor	1	1.5 (0.84,2.7)	1.07 (0.54,2.1)	1.23 (0.59,2.54)
	AQS	1	1.88 (1.03,3.44)	1.17 (0.57,2.42)	1.55 (0.73,3.29)
Tetralogy of Fallot	CMAQ, full population	1	0.67 (0.43,1.03)	0.88 (0.53,1.44)	1.09 (0.63,1.87)
	CMAQ, within 50km of monitor	1	0.9 (0.54,1.49)	0.9 (0.51,1.59)	1.27 (0.7,2.29)
	AQS	1	1.04 (0.61,1.76)	1.02 (0.56,1.86)	1.62 (0.87,3)
Other Conotruncals	CMAQ, full population	1	1.09 (0.56,2.13)	0.8 (0.36,1.77)	0.87 (0.37,2.02)
	CMAQ, within 50km of monitor	1	1.05 (0.47,2.34)	1.14 (0.48,2.71)	0.87 (0.32,2.34)
	AQS	1	0.69 (0.28,1.68)	1.34 (0.56,3.18)	1.05 (0.39,2.87)
Pulmonary Valve Stenosis	CMAQ, full population	1	1.28 (0.8,2.02)	1.55 (0.92,2.63)	1.58 (0.9,2.79)
	CMAQ, within 50km of monitor	1	1.37 (0.79,2.37)	1.37 (0.74,2.54)	1.46 (0.76,2.79)
	AQS	1	1.46 (0.81,2.62)	1.58 (0.82,3.04)	1.5 (0.75,2.99)
VSD-perimembranous	CMAQ, full population	1	0.98 (0.68,1.42)	1.06 (0.69,1.63)	1.23 (0.77,1.97)
	CMAQ, within 50km of monitor	1	1.25 (0.78,2)	0.9 (0.51,1.59)	1.41 (0.79,2.51)
	AQS	1	1.23 (0.79,1.9)	1.03 (0.62,1.72)	1.25 (0.73,2.16)
ASD-all	CMAQ, full population	1	1.05 (0.76,1.44)	1.06 (0.73,1.54)	0.94 (0.62,1.43)
	CMAQ, within 50km of monitor	1	0.96 (0.66,1.4)	1.04 (0.68,1.6)	0.92 (0.56,1.52)
	AQS	1	1.46 (0.98,2.17)	1.54 (0.98,2.42)	1.2 (0.71,2.05)
Defect Groupings					
APVR	CMAQ, full population	1	0.91 (0.46,1.78)	0.91 (0.43,1.91)	0.76 (0.34,1.71)
	CMAQ, within 50km of monitor	1	0.67 (0.31,1.47)	0.75 (0.33,1.68)	0.75 (0.32,1.76)
	AQS	1	1.15 (0.54,2.43)	1.03 (0.44,2.43)	1.15 (0.46,2.88)
Conotruncals	CMAQ, full population	1	0.86 (0.62,1.19)	0.94 (0.64,1.39)	0.99 (0.65,1.52)
	CMAQ, within 50km of monitor	1	1.03 (0.7,1.5)	0.92 (0.59,1.42)	1.12 (0.7,1.79)
	AQS	1	1.12 (0.76,1.67)	1.01 (0.64,1.61)	1.4 (0.86,2.27)

Table A3.4 (cont.)

Defect Grouping	Source	Week 2 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
LVOTO	CMAQ, full population	1	0.8 (0.56,1.15)	0.7 (0.45,1.1)	0.9 (0.56,1.44)
	CMAQ, within 50km of monitor	1	0.96 (0.62,1.49)	0.75 (0.45,1.25)	0.96 (0.57,1.63)
	AQS	1	0.57 (0.35,0.92)	0.66 (0.39,1.14)	0.83 (0.47,1.46)
RVOTO	CMAQ, full population	1	1.03 (0.7,1.5)	0.81 (0.51,1.27)	0.68 (0.42,1.12)
	CMAQ, within 50km of monitor	1	0.87 (0.54,1.4)	0.67 (0.39,1.15)	0.85 (0.49,1.48)
	AQS	1	0.74 (0.44,1.24)	0.48 (0.27,0.87)	0.58 (0.32,1.05)
Septals	CMAQ, full population	1	0.88 (0.69,1.12)	0.73 (0.54,0.99)	0.7 (0.5,0.98)
	CMAQ, within 50km of monitor	1	0.98 (0.73,1.32)	0.74 (0.52,1.05)	0.77 (0.52,1.12)
	AQS	1	1.06 (0.76,1.48)	0.76 (0.51,1.12)	0.72 (0.47,1.09)
		Week 3			
LVOTO	CMAQ, full population	1	0.87 (0.59,1.27)	0.87 (0.54,1.38)	0.83 (0.5,1.37)
	CMAQ, within 50km of monitor	1	1.03 (0.65,1.63)	1.19 (0.71,1.99)	0.87 (0.49,1.52)
	AQS	1	1.39 (0.84,2.29)	1.27 (0.72,2.25)	1.05 (0.58,1.91)
RVOTO	CMAQ, full population	1	0.71 (0.47,1.07)	1.11 (0.69,1.79)	1.21 (0.73,2.02)
	CMAQ, within 50km of monitor	1	0.96 (0.58,1.59)	1.38 (0.8,2.4)	1.51 (0.85,2.7)
	AQS	1	1.62 (0.92,2.83)	1.87 (1.01,3.46)	1.97 (1.04,3.73)
Septals	CMAQ, full population	1	0.94 (0.72,1.23)	1.02 (0.74,1.41)	1.03 (0.72,1.47)
	CMAQ, within 50km of monitor	1	1.22 (0.9,1.67)	1.23 (0.86,1.77)	1.08 (0.72,1.61)
	AQS	1	1.16 (0.82,1.65)	1.2 (0.8,1.79)	1.19 (0.77,1.83)
		Week 4			
LVOTO	CMAQ, full population	1	1.23 (0.84,1.79)	1.02 (0.63,1.64)	1.01 (0.6,1.69)
	CMAQ, within 50km of monitor	1	0.87 (0.56,1.35)	0.67 (0.4,1.11)	0.78 (0.45,1.34)
	AQS	1	0.83 (0.51,1.33)	0.91 (0.54,1.56)	0.78 (0.44,1.39)
RVOTO	CMAQ, full population	1	1.32 (0.88,1.97)	1.21 (0.74,1.98)	1.22 (0.72,2.08)
	CMAQ, within 50km of monitor	1	0.72 (0.45,1.17)	0.72 (0.42,1.23)	0.59 (0.33,1.05)
	AQS	1	0.63 (0.37,1.08)	0.81 (0.46,1.43)	0.86 (0.47,1.58)
Septals	CMAQ, full population	1	1.07 (0.82,1.38)	1.05 (0.76,1.46)	1.18 (0.82,1.7)
	CMAQ, within 50km of monitor	1	0.85 (0.63,1.15)	0.87 (0.61,1.25)	0.93 (0.62,1.38)
	AQS	1	0.98 (0.7,1.38)	1.16 (0.79,1.72)	1.07 (0.69,1.65)

Table A3.4 (cont.)

Cardiac Defect	Source	Week 5 <25th percentile (referent)	25th percetile to median	median to 75th percentile	> 75th percentile
LVOTO	CMAQ, full population	1	0.81 (0.55,1.19)	1.08 (0.68,1.71)	1.15 (0.69,1.91)
	CMAQ, within 50km of monitor	1	0.69 (0.44,1.1)	1.17 (0.71,1.93)	1.11 (0.64,1.91)
	AQS	1	0.67 (0.42,1.08)	0.76 (0.45,1.29)	0.95 (0.54,1.66)
RVOTO	CMAQ, full population	1	0.82 (0.55,1.23)	0.93 (0.58,1.49)	0.88 (0.53,1.47)
	CMAQ, within 50km of monitor	1	0.93 (0.57,1.5)	0.97 (0.56,1.66)	1.04 (0.59,1.83)
	AQS	1	1.03 (0.61,1.73)	1.16 (0.65,2.06)	1.16 (0.63,2.12)
Septals	CMAQ, full population	1	1.19 (0.91,1.55)	1.24 (0.9,1.72)	1.2 (0.84,1.73)
	CMAQ, within 50km of monitor	1	1.33 (0.97,1.83)	1.52 (1.05,2.2)	1.37 (0.91,2.06)
	AQS	1	1.02 (0.73,1.43)	1.03 (0.7,1.52)	1.19 (0.78,1.81)
		Week 6			
LVOTO	CMAQ, full population	1	1.33 (0.91,1.94)	1.3 (0.82,2.06)	0.95 (0.57,1.59)
	CMAQ, within 50km of monitor	1	1.55 (0.99,2.43)	1.26 (0.75,2.13)	1.01 (0.57,1.79)
	AQS	1	1.42 (0.88,2.27)	1.42 (0.83,2.44)	0.89 (0.49,1.63)
RVOTO	CMAQ, full population	1	0.92 (0.62,1.36)	0.75 (0.47,1.21)	0.95 (0.58,1.57)
	CMAQ, within 50km of monitor	1	0.93 (0.58,1.51)	0.89 (0.52,1.54)	1.03 (0.58,1.81)
	AQS	1	0.82 (0.49,1.39)	0.88 (0.49,1.56)	1.14 (0.62,2.09)
Septals	CMAQ, full population	1	1.1 (0.85,1.43)	1.11 (0.81,1.52)	1.04 (0.73,1.49)
	CMAQ, within 50km of monitor	1	1.09 (0.8,1.49)	1.1 (0.76,1.6)	1.07 (0.71,1.61)
	AQS	1	1.19 (0.85,1.67)	1.23 (0.84,1.81)	0.99 (0.64,1.54)
		Week 7			
LVOTO	CMAQ, full population	1	0.85 (0.58,1.24)	0.9 (0.58,1.41)	0.91 (0.55,1.48)
	CMAQ, within 50km of monitor	1	0.93 (0.59,1.45)	0.89 (0.54,1.47)	0.86 (0.5,1.47)
	AQS	1	1.24 (0.77,1.98)	1.04 (0.61,1.78)	1.15 (0.65,2.03)
RVOTO	CMAQ, full population	1	1.12 (0.75,1.67)	1.12 (0.7,1.78)	0.93 (0.56,1.53)
	CMAQ, within 50km of monitor	1	0.95 (0.59,1.53)	1.06 (0.63,1.79)	0.95 (0.54,1.66)
	AQS	1	0.82 (0.5,1.37)	0.65 (0.37,1.15)	0.69 (0.38,1.24)
Septals	CMAQ, full population	1	0.82 (0.63,1.07)	0.82 (0.6,1.12)	0.69 (0.48,0.97)
	CMAQ, within 50km of monitor	1	0.67 (0.49,0.92)	0.69 (0.49,0.98)	0.68 (0.46,1)
	AQS	1	0.64 (0.46,0.89)	0.56 (0.39,0.82)	0.66 (0.44,1)
		Week 8			
LVOTO	CMAQ, full population	1	1.14 (0.79,1.65)	1.4 (0.91,2.15)	0.98 (0.61,1.59)
	CMAQ, within 50km of monitor	1	1.6 (1.03,2.47)	1.41 (0.86,2.32)	1.23 (0.72,2.11)
	AQS	1	1.1 (0.71,1.7)	1.16 (0.71,1.9)	0.84 (0.48,1.46)
RVOTO	CMAQ, full population	1	1.3 (0.88,1.93)	1.57 (1,2.47)	1.5 (0.92,2.46)
	CMAQ, within 50km of monitor	1	1.53 (0.97,2.43)	1.42 (0.84,2.39)	1.36 (0.78,2.38)
	AQS	1	1.44 (0.88,2.34)	1.41 (0.81,2.44)	1.26 (0.7,2.27)
Septals	CMAQ, full population	1	0.99 (0.77,1.28)	1.01 (0.75,1.36)	1.02 (0.73,1.42)
	CMAQ, within 50km of monitor	1	1 (0.74,1.36)	0.97 (0.69,1.37)	0.98 (0.67,1.44)
	AQS	1	1.3 (0.94,1.79)	1.17 (0.81,1.69)	1.2 (0.8,1.8)

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