Effects of prolonged exposure to ambient particulate and gaseous pollutants on cardiovascular and reproductive health

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Public Health

by

Jing Feng

Dr. Wei Yang/Dissertation Advisor

August, 2015
We recommend that the dissertation prepared under our supervision by

**JING FENG**

Entitled

**Effects Of Prolonged Exposure To Ambient Particulate And Gaseous Pollutants On Cardiovascular And Reproductive Health**

be accepted in partial fulfillment of the requirements for the degree of

**DOCTOR OF PHILOSOPHY**

Wei Yang, Ph.D., Advisor

Stanley Omaye, Ph.D., Committee Member

Lei Chen, Ph.D., Committee Member

Shawn Gerstenberger, Ph.D., Committee Member

Bernadette Longo, Ph.D., Graduate School Representative

David W. Zeh, Ph. D., Dean, Graduate School

August, 2015
Abstract

Whereas Particulate matter (PM) air pollution is increasingly recognized as an important and modifiable risk factor for cardiovascular disease (CVD), the association between CVD and PM has been established predominantly in acute exposure studies. There are still gaps regarding large population risk estimation of long-term exposures. Results from the nationwide Behavioral Risk Factor Surveillance System (BRFSS) were used along with air quality monitoring measurements to implement a systematic evaluation of PM-related CVD risks at the national and regional scales. CVD status and individual-level risk factors were available from more than 500,000 BRFSS respondents across 2,231 contiguous U.S. counties for 2007 and 2009. Chronic exposures to PM pollutants were estimated with spatial modeling from measurement data. CVD outcomes attributable to PM pollutants were assessed by mixed-effects logistic regression and latent class regression (LCR), with adjustment for multicausality. There were positive associations between CVD and PM after accounting for competing risk factors: the multivariable-adjusted odds for the multiplicity of CVD outcomes increased by 1.32 (95% confidence interval: 1.23-1.43) and 1.15 (1.07-1.22) times per 10 μg/m³ increase in PM$_{2.5}$ and PM$_{10}$ respectively in the LCR analyses. After controlling for spatial confounding, there were moderate estimated effects of PM exposure on multiple cardiovascular manifestations. These results suggest that chronic exposures to ambient particulates are important environmental risk factors for cardiovascular morbidity.

As well, there is increasing awareness of the cardiovascular effects associated with both air pollutants and asthma. However, population-based studies on their potentially synergistic relationship in cardiovascular morbidity are lacking. Epidemiological studies that support the formulation of plausible causal pathways are thus needed in order to better understand the link between air pollution and asthma in their effects on cardiovascular health. Using a hierarchical modeling approach that combined individual-level risk factors and local-scale air quality data, the second study evaluated the effects of PM and ozone pollution on ischaemic heart disease (IHD), adjusting for effect modification by asthma status. IHD status and co-risk factors including asthma were assessed in more than 600,000 BRFSS respondents across 2,318 contiguous U.S. counties for 2005, 2007 and 2009. Chronic
exposures to PM and ozone pollutants were estimated with kriging from measurement data. Overall, the study found elevated odds for IHD from long-term exposure to PM or ozone in adults with prior or current asthma, with effect modification more pronounced in regard to PM exposure. Further research is needed to clarify what conditions produce observable interactions between air pollutants and asthma, and to evaluate the biological mechanisms by which air pollution may engender an excess cardiovascular risk in asthmatics.

There is also expanding evidence that ambient air pollution is associated with adverse birth outcomes. The objective of the third study is thus to assess whether air pollution is associated with term low birth weight (LBW) among residents of Southern Nevada, and to provide empirical evidence that might help evaluate plausible biological explanations. The frequency of LBW was assessed from a retrospective cohort of singletons born alive in Clark County during the period 1995-2008. Stationary air sampling data were obtained from the U.S. EPA to estimate average trimester exposures to ambient air pollutants. The effects of pollutant exposure on LBW were estimated by logistic regression with adjustment for co-risk factors including gestational age, type of delivery, gender, period and season of birth, maternal age, education, race, marital status, parity, adequacy of prenatal care, and maternal tobacco and alcohol use. Birth weight was also analyzed as a continuous variable to estimate the reduction of birth weight associated with changes in mean exposure to air pollution during each trimester of pregnancy. Controlling for maternal and fetal covariates and average pollutant measurements in each trimester (trimester exposures assessed simultaneously), exposure to ambient CO during the third trimester was associated with a significantly increased risk for LBW (odds ratio per 1-ppm increment=1.25; 95% CI: 1.06-1.47). PM$_{10}$ also exhibited an inverse pattern with birth weight, although mean birth weight reductions associated with PM$_{10}$ were small and only significant for the last trimester exposure. These results suggest that fetuses in the late stages of development are particularly vulnerable to particulate and CO pollution. Further studies are necessary to validate fetal susceptibility to air pollutants in terms of critical exposure windows, magnitude of effects, and relevant toxic components.
# Table of Contents

Chapter 1  
Introduction .................................................................................................................. 1  
References .................................................................................................................... 5  

Chapter 2 Effects of Particulate Air Pollution on Cardiovascular Health: A Population Health Risk Assessment  
2.1 Abstract .................................................................................................................. 9  
2.2 Background ........................................................................................................... 10  
2.3 Methods ............................................................................................................... 11  
2.4 Results .................................................................................................................. 16  
2.5 Discussion ............................................................................................................ 23  
References ................................................................................................................... 31  
Supporting Information ................................................................................................ 36  

Chapter 3 Cardiovascular Risks among Asthmatic Populations in Relation to Ambient Particulate and Ozone Pollution  
3.1 Abstract ................................................................................................................ 41  
3.2 Background .......................................................................................................... 42  
3.3 Methods ............................................................................................................... 43  
3.4 Results .................................................................................................................. 47  
3.5 Discussion ............................................................................................................ 52  
References ................................................................................................................... 59  
Supporting Information ................................................................................................ 63  

Chapter 4 Association between Ambient Air Pollution and Low Birth Weight in Southern Nevada  
4.1 Abstract ................................................................................................................ 68  
4.2 Background .......................................................................................................... 69  
4.3 Methods ............................................................................................................... 71  
4.4 Results .................................................................................................................. 73  
4.5 Discussion ............................................................................................................ 78  
References ................................................................................................................... 84  

Chapter 5 Summary, Conclusions and Recommendations ......................................... 88  
References ................................................................................................................... 91  

Appendix A .................................................................................................................. 92  
References ................................................................................................................... 94
Chapter 1

Introduction

Ambient air is a heterogeneous mixture of gaseous and particulate matter. The main gaseous components of air pollution are nitrogen dioxide (NO₂), sulfur dioxide (SO₂), carbon monoxide (CO), ozone (O₃), carbonyl and organic compounds; particulate matter (PM) is made up of solid and liquid particles from several sources (e.g. industrial and domestic emissions, vehicle emissions, forest fires, cigarette smoke, natural environment and climate variations) and consists of inorganic and organic materials. PM is also subdivided into coarse particles (diameter 2.5–10 μm), fine particles (PM₂.₅, diameter <2.5 μm), and ultrafine particles (diameter <0.1 μm). Further, gaseous/particulate composition and concentrations are variable depending on many factors such as emission sources, seasonal changes, atmospheric and geographic variations.

It has long been known that air pollution can affect human health. Notwithstanding the lack of well-established mechanistic mode(s) of action, a wide variety of time-series analyses have associated recent exposure to pollution episodes with increased cardiovascular events. Across chronic exposure studies, evidence also accrued for an association between long-term PM exposure and cardiovascular mortality. In the U.S. Six Cities Study (which began in 1974), Dockery et al. estimated an adjusted cardiopulmonary mortality rate ratio of 1.26 for the most polluted versus the least polluted city using fine particles as measure of pollution. In the American Cancer Society (ACS) Cancer Prevention Study II (initiated in 1982), Pope et al. reported adjusted relative mortality risks from cardiopulmonary causes of 1.26 and 1.31 in the
most polluted areas versus the least polluted in terms of sulfates and fine particles levels respectively. The increased mortality risk was confirmed in extensive reanalyses and new analyses providing compelling evidence for a potential role of elevated PM concentrations in cardiovascular injury. The geographic area of investigation has also expanded, with several new studies from Japan and China supporting an association between long-term exposure to PM and cardiovascular mortality first identified in the U.S. Six Cities and ACS studies.

Regarding the adverse effects of PM, multiple chemical constituents have been implicated including iron, nickel, zinc, ammonium nitrate, elemental carbon, organic carbon, nitrates, and sulfates. Exposure to many of these toxic pollutant components has been demonstrated as entailing inflammatory and neurogenic responses with local and systemic consequences. Findings from animal studies for example, have provided evidence that acute exposure to particulate pollutants impairs cardiac function and augments ischemia-reperfusion injury, while long-term exposure may accelerate the development of atherosclerosis. Importantly, it should be noted that the health impact of ambient air pollution cannot be attributed to a single pollutant. A growing body of epidemiologic and experimental evidence supports the biological plausibility of pulmonary oxidant stress mediated by PM and ozone that can result in perturbations in the cardiovasculature.

There is also growing evidence for an association between asthma and CVD, although the biologic mechanisms underlying the relation between asthma and CVD have
not been fully established. Nevertheless, the epidemiological association has led to the hypothesis that inflammatory responses to inhaled exposures are actively involved in the pathogenesis of both conditions.\textsuperscript{35,38} However, little attention has been paid to the differential vulnerability of asthmatics to cardiovascular morbidity from exposure to air pollutants. Given that air pollutants may provoke cardiovascular events through proinflammatory pathways, it is possible that the chronic, inflammatory nature of asthma may enhance the atherothrombotic effects of acute and chronic exposure to air pollution.

Epidemiological studies that help formulate plausible causal pathways are thus needed in order to better understand the link between air pollution and asthma in their effects on cardiovascular health.

Despite general evidence for a link between air pollution and CVD, previous research has predominantly focused on investigating the temporal associations between short-term elevations in air pollutants and adverse cardiovascular outcomes. As such, the relationship between long-term exposure and the risk of CVD has a limited evidence base. As well, few studies have evaluated potential effect modification of asthma on the association between CVD and air pollution. To address these gaps, the present studies will examine whether long-term exposure to ambient particulates at regional and national scales contributes to cardiovascular morbidity (chapter 2), and determine whether cardiovascular effects related to particulates and ozone differ between asthmatics and healthy adults (chapter 3).
Additionally, there are indications that the adverse health effects of air pollution are higher for vulnerable subgroups such as the elderly population, children and fetuses. Indeed, air pollution has been implicated in adverse birth outcomes, particularly low birth weight (LBW) and short gestational duration, although results were inconclusive from different study locations/subjects. In the absence of definite biological mechanisms for the adverse effects of ambient air pollutants on birth outcomes, it is important to determine the consistency of the putative effects of specific pollutants by exploring the relation in different populations and sites. Thus, chapter 4 will assess the extent to which gaseous and particulate air pollution contributes to LBW outcomes at the local scale.

Overall, a large number of studies have provided a generally consistent picture substantiating the adverse health and reproductive effects of air pollutants. While the pathophysiologic consequences of air pollution have been extensively investigated in pulmonary systems, further studies are needed to confirm the cardiovascular and embryotoxic effects of air pollution and to support the biologic plausibility of these effects. To extend current research approaches, the current studies take advantage of geospatial modeling (see Appendix A for an exposure methodology description) and multilevel analyses to provide adequate exposure estimates, and to implement large population assessments of the putative effects of specific pollutants, with adjustment for various susceptibility factors and for spatial/temporal variability in the study outcomes. Although epidemiologic studies are not geared to definitive analyses of the biological pathways from exposure to response, they can provide empirical evidence to help evaluate plausible biological explanations, and to suggest priorities for future research.
References:


Chapter 2  
**Effects of Particulate Air Pollution on Cardiovascular Health: A Population Health Risk Assessment**

2.1 Abstract

Whereas Particulate matter (PM) air pollution is increasingly recognized as an important and modifiable risk factor for cardiovascular disease (CVD), the association between CVD and PM has been established predominantly in acute exposure studies. There are still gaps regarding large population risk estimation of long-term exposures. Results from the nationwide Behavioral Risk Factor Surveillance System (BRFSS) were used along with air quality monitoring measurements to implement a systematic evaluation of PM-related CVD risks at the national and regional scales. CVD status and individual-level risk factors were available from more than 500,000 BRFSS respondents across 2,231 contiguous U.S. counties for 2007 and 2009. Chronic exposures to PM pollutants were estimated with spatial modeling from measurement data. CVD outcomes attributable to PM pollutants were assessed by mixed-effects logistic regression and latent class regression (LCR), with adjustment for multicausality. There were positive associations between CVD and PM after accounting for competing risk factors: the multivariable-adjusted odds for the multiplicity of CVD outcomes increased by 1.32 (95% confidence interval: 1.23-1.43) and 1.15 (1.07-1.22) times per 10 $\mu$g/m$^3$ increase in PM$_{2.5}$ and PM$_{10}$ respectively in the LCR analyses. After controlling for spatial confounding, there were moderate estimated effects of PM exposure on multiple cardiovascular manifestations. These results suggest that chronic exposures to ambient particulates are important environmental risk factors for cardiovascular morbidity.
2.2 Background

The deleterious effects of air pollution on cardiac function have been well documented in animal studies: acute exposure to particulate air pollutants has been linked to ischemia-reperfusion injury [1]-[2], while long-term exposure has been demonstrated to augment the development of atherosclerosis [3]-[4]. A potential relation between air pollution and cardiovascular health has also been described in humans: a wide variety of time-series analyses have associated recent exposure to pollution episodes with increases in morbidity and mortality related to cardiovascular complications [5]-[13]; further, cohort studies such as the Harvard Six Cities Study and the American Cancer Society (ACS) Cancer Prevention Study II, have reported significant associations between long-term exposure to particulate matter (PM) air pollution and increased all-cause and cardio-respiratory mortality [14],[15]. The increased mortality risk was confirmed in extensive reanalyses and new analyses providing compelling evidence for a potential role of elevated PM concentrations in cardiovascular injury [16]-[19].

To extend previous analyses primarily concerned with cardiovascular deaths and hospitalization, this paper attempts to evaluate the long-term relationship between prevalent CVD and PM across the general population in the United States. In particular, lifestyle factors, socioeconomic attributes and comorbid conditions that are major CVD risk factors were considered together with ecologic air quality covariates to provide a broad context of risk assessment. Although epidemiologic studies are not geared to definitive analyses of the biological pathways from exposure to response, they can provide empirical evidence to help evaluate plausible biological explanations, and thus
enhance our understanding of the long-term cardiovascular health effects of PM pollution.

2.3 Methods

Individual-level data

Data on CVD status and individual covariates were obtained from the U.S. Behavioral Risk Factor Surveillance System (BRFSS) [20], a random digit-dialing cross-sectional household survey system which began to monitor CVD status among U.S. adults (18+ years old and non-institutionalized) since 2005. Developed by the Centers for Disease Control and Prevention, the BRFSS is the largest telephone health survey in the world and currently collects information on preventive health practices and risk behaviors as well as a wide range of health outcomes in 50 states, the District of Columbia (DC), and three territories. The BRFSS selected participants using probability sampling from all households with telephones in each state or territory at 1st stage and all adults per household at 2nd stage (1 adult selected per household) [21]-[23]. The survey questions pertaining to CVD were threefold, “Has a doctor, nurse, or other health professional ever told you that you had any of the following? (1) A heart attack, also called myocardial infarction (MI); (2) angina or coronary heart disease (CHD); and (3) stroke (STK).” Since data on relevant medical conditions (e.g. hypertension, high cholesterol) were only collected in odd-numbered years and to maintain coherence in survey protocols used to ascertain CVD status, the analysis was restricted to the BRFSS of 2007 (No. of valid responses [N-VR]=430,912; median interview completion rate among participating states [MICR-PS]=75.2%) and 2009 (N-VR =432,607; MICR-PS=77.6%). Most of the
respondents were non-Hispanic white (>85%), resulting in inadequate racial gradients and data sparseness after full adjustment for variations in race/ethnicity (the proportion of minority respondents of Asian, Native Hawaiian/ Pacific Islander, American Indian/Alaska Native, and/or multiracial origins was <5%). Study samples were thus restricted to non-Hispanic whites, African Americans and Hispanics to control data dimensionality and to accommodate potential biases arising from racial/ethnic distributions which may covary with the exposure of interest. The BRFSS data were deidentified and thus analyzed anonymously (survey instruments and data are available at www.cdc.gov/brfss; datasets compiled for this analysis are available upon request).

**Ambient air pollution data**

Concentration data available for estimating background levels of PM$_{10}$ (coarse/fine particle with diameter <10 μm) and PM$_{2.5}$ (fine particle with diameter <2.5 μm) were extracted from the U.S. Environmental Protection Agency’s Air Quality System [24]. Measurements from years 1999-2005 were obtained for PM$_{10}$ and PM$_{2.5}$ (no systematic sampling of PM$_{2.5}$ before 1999); for exposure assessment, data were further restricted to surveillance-type monitoring stations located throughout urban and rural areas in contiguous states, and to those with at least 50% of observations (percent of observations calculated as the ratio of valid days to scheduled days for the year). Yearly median value was the chosen measure of background particulate concentration. They were constructed from site-level PM concentrations computed as integrated averages of hourly samples collected in a 24-hour period. Table 1 shows the distributions of PM concentrations based on data from the selected period and monitoring sites. As a means of quantifying year
round exposure across region, median PM$_{10}$ and PM$_{2.5}$ concentrations obtained from the sampling sites had fairly strong temporal correlations for the study period (Table 1).

Table 1. Distributions of PM$_{10}$ and PM$_{2.5}$, 1999-2005, surveillance-oriented sites from contiguous U.S. region.

<table>
<thead>
<tr>
<th>Pollutant a</th>
<th>Study sites b</th>
<th>Median sampling days c</th>
<th>Yearly median levels (μg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per year total</td>
<td>Mean (SD)</td>
<td>25th percentile</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>853</td>
<td>60 384</td>
<td>19.7 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.0</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>734</td>
<td>112 656</td>
<td>10.7 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.9</td>
</tr>
</tbody>
</table>

Average correlation of yearly site-specific median measurements: PM$_{10}$ — 0.86  PM$_{2.5}$ — 0.81

a Following the promulgation of the National Ambient Air Quality Standard for PM$_{2.5}$ in 1997, routine collection of PM$_{2.5}$ was implemented in 1999. No attempt was made to convert PM$_{10}$ concentrations to PM$_{2.5}$, which requires a scaling factor based on a presumptive proportion of PM$_{2.5}$ in the PM$_{10}$ mass.

b Sites describe unique sampling points indicated by longitude/latitude. Those providing no geodetic datum information were not included.

c While PM was typically measured at a frequency of every six days or higher, many sites took daily sampling.

Geostatistical methods

Population exposures to PM for the available geographic unit of analysis (i.e. county) were assessed on the basis of long-term averaged yearly median concentrations by kriging in conjunction with block interpolation. County was the target interpolation block as the nationwide BRFSS does not record individuals’ residence at the city or town level currently. The kriging technique quantifies spatial dependence represented by available observations, and uses the estimated autocorrelation structure to form minimum variance estimators over the entire study domain [25],[26]. For this study, all sample points representing surveillance-type monitoring sites were used in model development for accurate spatial interpolation. Particulate concentrations were transformed to a logarithmic scale to better approximate a normal residual distribution and to constrain the modeled concentrations to be positive. Sampled data were first checked for autocorrelation and trends so as to determine the optimal parameters that characterize difference-squared values between each pairs of points at different distances lags (i.e. semivariogram); multiple semivariogram models were then fitted with different
specifications on distance lags and directional influences. The optimal kriging parameters were chosen based on leave-one-out cross-validated error statistics including the mean prediction error (ME), root-mean-squared-error (RMSE) and cross-validated $R^2$. A 44 x 44 km grid partition was used to convert point-kriged results to raster coverages at the continental scale. Area-based exposure assignment was subsequently made by computing block averages over discretized surfaces. All geostatistical analyses were implemented with ESRI ArcGIS (v9.3; ESRI Inc., Redlands, CA, USA).

**Statistical analysis**

Risks for individual CVD components (i.e. MI, CHD, STK) were estimated by standard mixed-effects logistic regression using the multilevel pseudo-maximum likelihood (MPML) method; MPML estimates of the overall CVD risks were obtained with multilevel latent class regression (LCR) [27]-[30]. This modeling approach posits that individuals form homogenous classes based on discrete observed variables (e.g. self-reports of CVD status), and class membership depends on a latent construct that serves as a summary of observed indicators. For the multilevel LCR analysis, a two-class or binary latent construct (denoted by C) was hypothesized (high vs. low CVD risks), with three categorical indicators obtained as item responses to the BRFSS CVD module enquiring the occurrence of MI, CHD, and STK. Class membership was characterized by both individual and group-level risk factors (denoted by X’s and Z’s respectively) for CVD, including age, gender, race, income, education, hypertension, hypercholesterolemia, diabetes, smoking, physical activity level, obesity, and ambient concentrations of PM.
spatially interpolated to each county. The multilevel LCR model is schematically depicted in Figure 1.

Figure 1. A schematic depiction of the multilevel latent class regression model

The conceptual equivalence between a latent class and random effects specifications has been demonstrated previously [31]-[33]. Per standard mixed-effects modeling, a random intercept deviation (for each county) was adopted to represent a covariance structure induced by county-to-county heterogeneity (i.e. interdependencies of individual observations within each county). The additional latent class specification is beneficial for synthesizing correlated item responses into an outcome that is easily interpretable while retaining latent heterogeneity in the data (i.e. unobserved but not strictly exogenous differences between individuals) as a means of controlling for unobserved influences that contribute to the relations between observed variables. Because there were empirical associations among the responses of interest (the three CVD indicators had a Fleiss Kappa coefficient of 0.3, implying a fair degree of agreement), and analyses stratified by CVD indicators unnecessarily attenuated the statistical relationship between them, the latent outcome formulation provided an improvement on bias control as it took into account the interdependency of reported cardiovascular symptoms in estimating the standard errors used in hypotheses testing.
The probability for a cardiovascular response in the form of MI, CHD or STK, or being a member of a high-risk class is defined in terms of binomial logit. Because of evidence of a curvilinear relationship between BMI and cardiovascular outcomes, linear and squared terms for BMI were used as continuous variables in model fitting. To allow for broad-scale regional effects, indicator variables representing the nine Census regions were employed; analyses were also stratified by the nine Census regions to explore the possibility of effect modification by region. Model evaluation consisted primarily of comparing hierarchically consistent candidate models on likelihood-based information criteria. Statistical programs SAS (v9.2; SAS Institute Inc., Cary, NC, USA) and Mplus (v6.1; Muthén & Muthén, Los Angeles, CA, USA) were used for the mixed-effects analyses.

2.4 Results

Spatial variations in background PM concentrations

Ordinary and universal kriging procedures were evaluated as methods to estimate the long-term averaged median PM concentrations. Table 2 summarizes the performance metrics for the preferred models with and without a spatial trend component. The models gave similar overall performance measures: incorporating a linear or quadratic trend component did not give a stronger basis for interpolation (as indicated by RMSE values).
Table 2. Modeled and observed pollutant levels and cross-validation summary statistics (μg/m³) for the exposure assessment methods.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Yearly median levels</th>
<th>Kriging method (log transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Estimated</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>PM₁₀ (N =853)</td>
<td>19.663</td>
<td>1.430</td>
</tr>
<tr>
<td>PM₂.₅ (N=734)</td>
<td>10.664</td>
<td>1.376</td>
</tr>
</tbody>
</table>

<sup>a</sup> N is the number of surveillance-oriented sites used for PM pollution modeling.

<sup>b</sup> A constant trend is implied by ordinary kriging.

<sup>c</sup> The optimal assessment method is indicated. When models rank similarly in terms of performance, the simpler specification that reproduces important features of the empirical variogram is deemed optimal.

Exposure estimation results showed that the chosen kriging models did not extrapolate much beyond the range of measured concentrations; however, estimated values have a markedly lower standard deviation (Table 2). Such discrepancies possibly arose from monitor placement bias as they tend to lie in urban, more polluted areas, whereas the modeled concentrations utilized measurements from neighboring samples to provide full coverages across measurement units. As such, they may give “smoothed” spatial patterns of pollution levels and underestimate exposure gradients. Figure 2 shows the median background PM concentrations across contiguous U.S. counties for the selected time window, based on the optimal modeling methods (defined as those with the lowest RMSE values). Interpolated PM surfaces were similar for the preferred kriging models, as indicated by the high correlations (>0.95) between estimates assessed with the different models. This suggests that the background PM pollution landscape for the study region and time frame was unlikely to change greatly depending on the choice of the optimal spatial interpolation model. Figure S1 in the Supporting Information provides graphical comparisons between measured concentrations at the study sites and predicted values by the chosen kriging methods.
Figure 2. Estimated background PM$_{10}$ and PM$_{2.5}$ concentrations ($\mu$g/m$^3$) across contiguous U.S. counties: A—PM$_{10}$ yearly median concentrations (averaging 1999-2005), assessed with ordinary kriging, exponential covariance, lag distance=125 km, nugget=0.037, range=1,538 km, partial sill=0.083; B—PM$_{2.5}$ yearly median concentrations (averaging 1999-2005), assessed with ordinary kriging, spherical covariance, lag distance=170 km, nugget=0.014, range=1,687 km, partial sill=0.066.

Cardiovascular risk estimation

For the assessment of cardiovascular health in relation to individual and ecologic co-risk factors, the 2007 and 2009 BRFSS data were linked to the estimated background PM concentrations by county of residence. Covariate missingness was analyzed with non-
response indicators constructed for items on which missing data may not occur randomly (e.g. income and education). Because of little evidence for associations of missingness indicators with CVD, the final study populations included only survey respondents with known responses on all individual covariates, and were limited to those residing in the 48 contiguous states and DC, of which 2,231 counties participated in the 2007 and 2009 BRFSS cardiovascular health survey module. The size of the samples ranged from 494,358 to 499,667, depending on the specific CVD components assessed separately or in combination as the outcome measure (taken together, a total of 500,715 responses were evaluated). The samples were approximately 39% men and 61% women, and the median age of participants 56 years. The age and sex characteristics of study subjects were comparable across levels of PM exposure (Supporting Information Table S1); the racial, socioeconomic and lifestyle traits were distributed somewhat unevenly across PM pollution ranges. The crude prevalence estimates were 6.2% (31,078) for MI, 6.6% (32,752) for CHD, and 3.9% (19,589) for STK. Estimated posterior probabilities indicated fairly homogeneous overall latent class patterns across all fitted models: around 11% of respondents constituted the high-risk class. Age, sex and race-adjusted prevalence was estimated for MI, CHD and STK (at mean values of individual-level covariates for the study population) in model building, with random effects adjustment of county-specific deviations in CVD outcomes. Overall, higher CVD rates occurred in the South and Midwest than in the Northeast and West (Supporting Information Figure S2); and higher-than-average particle concentrations occurred in the southern-central region (Supporting Information Table S2). Figures 3 and 4 show the PM pollution effect estimates from the final fitted models controlling for competing risk factors, with
adjustment for spatial and temporal trends in disease. All individual-level covariates were independently associated with CVD outcomes, and their effect estimates showed little change across models.

PM\textsubscript{10} or PM\textsubscript{2.5} alone were associated with MI, CHD and STK after accounting for effects attributable to age, sex, race, education, income, BMI, hypertension, hypercholesterolemia, diabetes, smoking status, physical activeness, and temporal patterns in CVD (year of interview used as the time index) (Figures 3 and 4). The multivariable-adjusted odds ratio (AOR) for MI was estimated at 1.12 (95% CI: 1.05-1.19), for CHD 1.08 (1.03-1.15), for STK 1.17 (1.09-1.27), and for overall susceptibility 1.15 (1.07-1.22) per 10 μg/m\textsuperscript{3} increase in yearly PM\textsubscript{10} median concentrations. PM\textsubscript{2.5} showed slightly stronger effects on overall cardiovascular morbidity, with an estimated AOR for MI of 1.17 (1.08-1.26), for CHD 1.28 (1.20-1.39), for STK 1.16 (1.06-1.27), and for overall susceptibility 1.32 (1.23-1.43) per 10 μg/m\textsuperscript{3} increase in yearly median concentrations. However, inclusion of geographic location indicators attenuated the PM-CVD associations, with significant effects only observed on MI (AOR=1.07; 95% CI: 1.01-1.15) and STK (1.08; 1.00-1.17) from PM\textsubscript{10} exposure, whereas CVD risks associated with PM\textsubscript{2.5} exposure remained elevated, if not significant. On considering possible effect modification by spatial location, region-specific models controlling for individual and temporal covariates were also assessed. Although the region-stratified approach does not provide a test of statistical significance of the differences between the stratified odds ratios, there was a mild indication of a region-PM interaction (Figure 5): PM showed strongest associations with MI in ENCen, with CHD in ESCen and Mid Atl,
and with STK in WNCen; the inverse PM associations with MI and STK estimated from SAatl and with CHD from NEng regions were likely due to discordance between morbidity and background PM across Central Florida and Maine counties respectively (Figure 2 and Figure S2).

Figure 3. Multivariable-adjusted odds ratios (AOR) and lower and upper 95% confidence limits (LCL & UCL) for CVD complications from PM10-fitted models — assessed with samples from the 2007 and 2009 Behavioral Risk Factor Surveillance System. Both regionally and non-regionally adjusted results were presented, with the former graphically displayed. BMI and (BMI-squared)/100 were included as continuous variables. PM10-related effects were associated with 10 μg/m³ increment in yearly median levels.
Figure 4. Multivariable-adjusted odds ratios (AOR) and lower and upper 95% confidence limits (LCL & UCL) for CVD complications from PM$_{2.5}$-fitted models — assessed with samples from the 2007 and 2009 Behavioral Risk Factor Surveillance System. Both regionally and non-regionally adjusted results were presented, with the former graphically displayed. BMI and (BMI-squared)/100 were included as continuous variables. PM$_{2.5}$-related effects were associated with 10 $\mu$g/m$^3$ increment in yearly median levels.
Figure 5. Region-specific multivariable-adjusted odds ratios (AOR) and lower and upper 95% confidence limits (LCL & UCL) per 10 μg/m³ increment in PM for CVD complications, controlling for age, gender, race, education, income, smoking status, physical activeness, BMI (linear and quadratic terms), hypertension, hypercholesteremia, diabetes, and year of interview.

<table>
<thead>
<tr>
<th>E N Cen</th>
<th>E S Cen</th>
<th>Mid Atl</th>
<th>Mtn</th>
<th>N Eng</th>
<th>Pacific</th>
<th>S Atl</th>
<th>W N Cen</th>
<th>W S Cen</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOR</td>
<td>LCL</td>
<td>UCL</td>
<td>AOR</td>
<td>LCL</td>
<td>UCL</td>
<td>AOR</td>
<td>LCL</td>
<td>UCL</td>
</tr>
<tr>
<td>1.19</td>
<td>0.96</td>
<td>1.44</td>
<td>1.05</td>
<td>0.91</td>
<td>1.16</td>
<td>1.08</td>
<td>0.91</td>
<td>1.16</td>
</tr>
<tr>
<td>1.05</td>
<td>0.87</td>
<td>1.24</td>
<td>1.06</td>
<td>0.87</td>
<td>1.18</td>
<td>1.06</td>
<td>0.87</td>
<td>1.18</td>
</tr>
<tr>
<td>1.39</td>
<td>0.96</td>
<td>1.60</td>
<td>1.13</td>
<td>1.20</td>
<td>1.50</td>
<td>1.13</td>
<td>1.20</td>
<td>1.50</td>
</tr>
<tr>
<td>1.07</td>
<td>0.70</td>
<td>1.44</td>
<td>1.03</td>
<td>0.91</td>
<td>1.06</td>
<td>1.03</td>
<td>0.91</td>
<td>1.06</td>
</tr>
<tr>
<td>1.69</td>
<td>1.10</td>
<td>2.42</td>
<td>1.75</td>
<td>2.17</td>
<td>2.54</td>
<td>2.08</td>
<td>2.12</td>
<td>2.50</td>
</tr>
</tbody>
</table>

2.5 Discussion

This study used time-averaged ambient air pollution data and a cross-sectional sample of 500,715 adults to assess CVD risks associated with background PM pollution across contiguous U.S.. There have been only a few previous studies that assessed long-term air pollution effects on CVD across large populations, partly due to the lack of direct exposure measurements at a broad scale. To address this limitation, reasonable spatial interpolation models were developed to enable population exposure assessment. On the basis of multilayered data, PM effects were evaluated on cardiovascular complications while directly adjusting for individual differences in major risk factors. There were moderate estimated effects of PM exposure on cardiovascular morbidity: multivariable-adjusted odds for the multiplicity of CVD outcomes increased by 1.32 and 1.15 times per 10 μg/m³ increase in PM$_{2.5}$ and PM$_{10}$ respectively in the LCR analyses; the estimated PM$_{2.5}$ effects diminished quite a bit following spatial adjustment with indicators distinguishing the nine Census regions, while the spatially adjusted PM$_{10}$ effects on MI...
and STK remained marginally significant (Figures 3 and 4). The effects of PM$_{10}$ cannot be independently quantified from those of PM$_{2.5}$ based on available data granularity however, since PM$_{2.5}$ is a key component of the total PM$_{10}$ mass.

Although differences in study design, endpoint/exposure assessment, and population or region covered limit the scope for direct comparison with earlier PM-related mortality studies, the moderate relative CVD risks associated with PM exposure found in the current study were roughly in line with previous findings. In the Six Cities Study, Dockery et al. estimated an adjusted cardiopulmonary mortality rate ratio of 1.26 for the most polluted versus the least polluted city using fine particles as measures of pollution [14]. In the ACS Study carried out by Pope et al., the adjusted relative mortality risks from cardiopulmonary causes were 1.26 and 1.31 times higher in the most polluted areas as in the least polluted in terms of sulfates and fine particles levels respectively [15]. A stronger correlation between fine particle pollution and cardiovascular mortality was found by Miller et al. in their Women’s Health Initiative observational study; they estimated a hazard ratio of 1.76 for death from CVD per 10 μg/m$^3$ increase in the mean PM$_{2.5}$ concentration [17]. In the reanalysis of the Six Cities Study and ACS Study data by the Health Effects Institute (HEI), inclusion of auxiliary socio-demographic and environmental variables at the areal level was shown to have little impact on the estimated associations between particulate pollution and cardiopulmonary mortality; however, risk estimates were somewhat sensitive to adjustment for spatial patterns in the ACS Study data [16]. This may reflect a spatial trend of disease burden which likely contributes to the observed PM-CVD relationship. In their Medicare Cohort Air Pollution
Study, Zeger et al. compared relative mortality risks associated with chronic PM$_{2.5}$ exposure across 250 counties; their results from applying different degrees of spatial smoothing (to adjust for potential spatial confounders) suggest that the evidence for PM$_{2.5}$-mortality association was stronger for larger spatial scale than more local scale comparisons [18]. The decrease in spatially adjusted relative risk with respect to PM is consistent with the findings reported here. Because the broad regional trends in CVD appeared to coincide with PM$_{2.5}$ formation shown by the exposure assessment map, regional adjustment may have over-adjusted the effect estimates for regional scale fine particle pollutants relative to more local scale coarse particle pollutants. Conversely, it might be conjectured that incorporating a state or county-based areal marker should induce greater uncertainty in the PM$_{10}$ effects. However, such local-level adjustment was not adopted as it depends on the usage of arbitrary administrative units which tend not to match PM distribution on a geographical or ecological scale. Consideration also needs to be given to the implications of using aggregate PM exposure data due to the lack of individual-level exposure data. Despite the inclusion of a relatively large set of personal characteristics measures, a strength of this study which helps remove the aggregation effects in analyzing geographically aggregated data, there is still the potential for ecological biases which introduce measurement errors and contribute to uncertainties in effect estimates. As with multilevel studies in general, this limitation needs to be recognized in risk estimation.

In separate analyses to characterize the spatial patterns of the PM effects on CVD, stronger PM-CVD correlations were detected in the eastern-central U.S. (Figure 5). The
geographical variations in PM effects may arise from heterogeneity in PM composition across regions, which cannot be adequately captured by concentration-based exposure metrics. A number of studies have reported regional differences in the acute or chronic effects of PM. Using daily time-series data of 1999-2002 on cause-specific hospitalization admissions for 204 U.S. counties, Dominici et al. investigated the short-term effects of PM$_{2.5}$ on cardiovascular and respiratory diseases and noted higher cardiovascular risks in the eastern region (including the Northeast, Southeast, Midwest and the South) [34]. More recently, Zeger et al. evaluated Medicare billing claims for 2000-2005 from urban areas within six miles of a PM$_{2.5}$ monitor; they found significantly elevated mortality risks in the eastern and central regions associated with PM$_{2.5}$ exposure after adjusting for smoking and socioeconomic status, but no PM$_{2.5}$-related effects in the western region [19]. Regarding the adverse effects of PM$_{2.5}$, multiple chemical constituents have been implicated including iron, nickel, zinc, ammonium nitrate, elemental carbon, organic carbon, nitrates, and sulfates [35]-[37]. In a study of the spatial and temporal variations in the PM$_{2.5}$ mixture across 187 U.S. counties for 2000-2005, Bell et al. observed higher sulfate levels in the eastern region, and higher nitrate levels in the western and northern regions [38]. As also noted in the study, a major obstacle to interpreting regional differences in the observed PM effects is that multiple sources of the PM mixture—often in complex interplay—complicate the identification of individual effects of various PM components on a regional or national scale. This suggests that the ability to distinguish and explain the spatial patterns of health risks associated with PM can be improved through localized compositional analyses of ambient PM where definitive source apportionment is feasible.
The present study used kriging for exposure classification, an approach also adopted by the HEI in their reanalysis of the Six Cities and ACS data. Kriging has the advantage of providing unbiased estimates of pollutant levels at unsampled locations with minimum estimated variance, and has been applied with success to model broad scale variations in background air pollution [39]-[41], where measurements are only made at designated sites. Nonetheless, important constraints on exposure modeling such as limitations in the spatial representativeness of the air sample data used need to be recognized. Because monitoring is costly, the density of monitoring networks is limited. Clustering of monitoring sites is also unavoidable due to monitor placement strategies favoring areas of high pollution levels. The uneven distribution of spatial observations could lead to a low degree of spatial autocorrelation, increased prediction uncertainty and potential exposure misclassification. These considerations suggest that the modeled concentrations should be interpreted as estimated background concentrations, rather than measurements of personal or microenvironmental exposures. In any case, reliance on monitored air pollution data alone provides only a partial picture of the air pollution situation in any area, and supplementing monitored air pollutant measurements with auxiliary factors (e.g. traffic volume, altitude, wind speed/direction, temperature, precipitation) would be worthwhile for more local scale exposure assessment.

Other limitations of the work reported here relate to the cross-sectional nature of the study and the resulting insufficiency of findings to demonstrate a cause-and-effect relationship between the studied air pollutants and CVD morbidity. Also, apart from
potential selection biases (e.g. non-coverage of cell phone only households or those with no phone at all) and the restriction of the study population to the selected racial groups, which limit generalizability of results to less-selective populations, a certain degree of inaccuracy in disease outcome and risk factors ascertainment is to be expected with self-reported data; however, it is probable that such inaccuracy would be non-differential, and any bias introduced would only obscure the effects found. In addition, misclassification may arise from exposure assignment according to residency at the time of survey data collection (the BRFSS questionnaires currently do not track migration activities or time spent in the area of residency). Such exposure misclassification is likely to be random and again its main consequence is the attenuation of the effects estimated.

Although the pathomechanisms responsible for the association between air pollution and CVD development or exacerbation have not been fully elucidated, previous observations suggest that exposure to air pollutants elicits morphological changes and systemic inflammatory processes, conditions that may lead to tissue damage and release of bioactive substances into the circulatory system, thus creating direct or indirect insults to the cardiovascular system. Results from air pollution studies show that a large proportion of the urban fine particle mass is made up of primary combustion products from mobile source emissions and includes organic compounds, elemental carbon, and metals [42],[43]. Exposure to many of these toxic pollutant components has been demonstrated as entailing inflammatory and neurogenic responses with local and systemic consequences. Greater toxicity has also been attributed to fine and ultrafine particles (PM with diameter <0.1 μm) due to their high pulmonary deposition efficiency,
higher particle number concentration than larger particles and a resulting higher surface area to carry toxic pollutants, as well as their translocation potential [44],[45]. The pathophysiologic consequences arising from PM exposure are both acute and chronic. Short-term exposure to fine particles has been linked to increased risks of myocardial infarction, vasoconstriction, reduced heart rate variability and arrhythmias [46]-[48]. The lifetime risks may be influenced by atherosclerotic and inflammatory responses as well as oxidative stress [45],[49],[50]. Importantly, the observed correlations between PM pollution and CVD evidence both acute and protracted mechanisms so a distinction between the short and long-term PM effects cannot be made easily.

While much remains to be discovered about the role of air pollution in cardiovascular pathologic manifestations, this study provides new evidence linking long-term PM exposure to cardiovascular impairment. Indeed, the associations between multiple CVD outcomes and PM remained robust after accounting for major risk factors including demographic characteristics, socioeconomic status, hypertension, hypercholesterolemia, diabetes, smoking, physical activity level and obesity. From a public health perspective, this study underlines the potentiality of air pollution abatement in reducing the morbidity and mortality associated with CVD.

In conclusion, geospatial modeling and multivariate techniques were used to implement a large population assessment of relative cardiovascular risks posed by airborne particulate matter across contiguous U.S.. The findings suggest that
improvements in air quality could imply a substantial reduction in the disease burden associated with CVD.

**Acknowledgments:**

The authors thank the U.S. Environmental Protection Agency for providing the air quality data and the Centers for Disease Control and Prevention for coordinating collection of the Behavioral Risk Factor Surveillance data used in the analysis. The authors would also like to thank the PLOS One academic editor and three anonymous reviewers for reviewing an earlier draft of this work and for their thoughtful comments and revision suggestions.
References:


Particulate air pollution as a predictor of mortality in a prospective study of U.S.

Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study
on particulate air pollution and mortality. Cambridge, MA: Health Effects Institute.

term exposure to air pollution and incidence of cardiovascular events in women. N

population and chronic exposure to fine particulate air pollution. Collection of

population and chronic exposure to fine particulate air pollution in urban centers

20. Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance

Surveillance System user’s guide. Atlanta, GA: U.S. Department of Health and
Human Services.

design of the Behavioral Risk Factor Surveillance System. Proceedings of the section


**Supporting Information Legends:**

Figure S1: Measured PM concentrations across study sites versus predicted values by the chosen kriging methods.

Figure S2: Age-Sex-Race (ASR) adjusted prevalence estimates across study counties—assessed with study samples from the ‘07 & ‘09 Behavioral Risk Factor Surveillance System: A—myocardial infarction (MI), B—coronary heart Disease (CHD), and C—stroke (STK).

Table S1: Characteristics of study subjects according to quartiles of PM$_{10}$ and PM$_{2.5}$ exposure across study counties.

Table S2: Modeled PM$_{10}$ and PM$_{2.5}$ yearly median concentrations (averaging 1999-2005) across study counties by regional strata.
Figure S1: Measured PM concentrations across study sites versus predicted values by the chosen kriging methods.

A

B

$R^2 = 0.453$

$R^2 = 0.734$
Figure S2: Age-Sex-Race (ASR) adjusted prevalence estimates across study counties—assessed with study samples from the ‘07 & ‘09 Behavioral Risk Factor Surveillance System: A—myocardial infarction (MI), B—coronary heart Disease (CHD), and C—stroke (STK).
Table S1: Characteristics of study subjects according to quartiles of PM$_{10}$ and PM$_{2.5}$ exposure across study counties.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$PM_{10}$ quartile (µg/m$^3$)</th>
<th>$PM_{2.5}$ quartile (µg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.73-18.38</td>
<td>20.18-21.21</td>
</tr>
<tr>
<td></td>
<td>18.39-20.17</td>
<td>21.22-33.96</td>
</tr>
<tr>
<td></td>
<td>21.22-33.96</td>
<td>4.68-9.14</td>
</tr>
<tr>
<td></td>
<td>9.15-11.37</td>
<td>11.38-12.83</td>
</tr>
<tr>
<td></td>
<td>12.84-15.56</td>
<td>15.56</td>
</tr>
<tr>
<td>N* (unweighted)</td>
<td>107,302</td>
<td>84,571</td>
</tr>
<tr>
<td>Age group (%)</td>
<td>85,511</td>
<td>223,331</td>
</tr>
<tr>
<td>18-24</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>25-34</td>
<td>6.8</td>
<td>7.0</td>
</tr>
<tr>
<td>35-44</td>
<td>14.7</td>
<td>15.0</td>
</tr>
<tr>
<td>45-54</td>
<td>23.0</td>
<td>21.9</td>
</tr>
<tr>
<td>55-64</td>
<td>24.2</td>
<td>23.9</td>
</tr>
<tr>
<td>65+</td>
<td>30.1</td>
<td>31.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>40.5</td>
<td>39.6</td>
</tr>
<tr>
<td>Race/Ethnicity (%)</td>
<td>39.2</td>
<td>39.2</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>93.2</td>
<td>88.8</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>2.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Education (%)</td>
<td>5.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Less than H.S. diploma</td>
<td>27.1</td>
<td>26.5</td>
</tr>
<tr>
<td>H.S. diploma or G.E.D.</td>
<td>26.2</td>
<td>26.9</td>
</tr>
<tr>
<td>Some post-H.S.</td>
<td>41.1</td>
<td>39.8</td>
</tr>
<tr>
<td>College degree or higher</td>
<td>8.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Household income per year (%)</td>
<td>14.7</td>
<td>15.6</td>
</tr>
<tr>
<td>Less than $15,000</td>
<td>11.6</td>
<td>11.7</td>
</tr>
<tr>
<td>$15,000 to 24,999</td>
<td>16.0</td>
<td>15.9</td>
</tr>
<tr>
<td>$25,000 to 34,999</td>
<td>49.4</td>
<td>48.1</td>
</tr>
<tr>
<td>$35,000 to 49,999</td>
<td>50.2</td>
<td>58.1</td>
</tr>
<tr>
<td>$50,000 or more</td>
<td>59.2</td>
<td>59.6</td>
</tr>
<tr>
<td>Married (%)</td>
<td>14.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>35.4</td>
<td>33.0</td>
</tr>
<tr>
<td>Current smoker†</td>
<td>49.8</td>
<td>51.7</td>
</tr>
<tr>
<td>Former smoker††</td>
<td>21.8</td>
<td>22.7</td>
</tr>
<tr>
<td>Never smoked</td>
<td>22.7</td>
<td>24.7</td>
</tr>
<tr>
<td>Leisure time exercise: none in past 30 days (%)#</td>
<td>24.7</td>
<td>26.0</td>
</tr>
</tbody>
</table>
Characteristic | PM$_{10}$ quartile (µg/m$^3$) | PM$_{2.5}$ quartile (µg/m$^3$) | Alcohol use: total no. of drinks in past 30 days (mean±SE) | Body Mass Index (mean±SE) | Hypertension (%) | Hypercholesterolemia (%) | Diabetes (excluding gestational diabetes) (%) | Cardiovascular complications including MI, CHD or STK (%) | * The unweighted BRFSS 2007 and 2009 samples were restricted to non-Hispanic whites/blacks and Hispanics with identified disease state pertaining to history of myocardial infarction (MI), coronary heart disease (CHD) and stroke (STK). Excluding incomplete respondents (those on whom at least one covariate or outcome measure had missing data), 494,358 participants were available for the LCR analysis, and the sample sizes for MI, CHD and STK risk assessments were 498,815, 496,909, and 499,667 respectively. Taken together, a total of 500,715 respondents were included in the data tabulation. † Respondents that reported having smoked at least 100 cigarettes (5 packs) in their lifetime and currently smoke some days or every day. †† Respondents that reported having smoked at least 100 cigarettes in their lifetime and currently do not smoke. # Leisure time exercise defined as doing physical activity or exercise during the past 30 days other than one’s regular job.

Table S2: Modeled PM$_{10}$ and PM$_{2.5}$ yearly median concentrations (averaging 1999-2005) across study counties by regional strata.
Chapter 3

Cardiovascular Risks among Asthmatic Populations in Relation to Ambient Particulate and Ozone Pollution

3.1 Abstract

Despite the increased awareness of the cardiovascular effects associated with both air pollutants and asthma, population-based studies on their potentially synergistic relationship in cardiovascular morbidity are lacking. Epidemiological studies that support the formulation of plausible causal pathways are thus needed in order to better understand the link between air pollution and asthma in their effects on cardiovascular health. Using a hierarchical modeling approach that combined individual-level risk factors and local-scale air quality data, this study evaluated the effects of particulate matter and ozone pollution on ischaemic heart disease (IHD), adjusting for effect modification by asthma status. IHD status and co-risk factors including asthma were assessed in more than 600,000 Behavioral Risk Factor Surveillance System respondents across 2,318 contiguous U.S. counties for 2005, 2007 and 2009. Chronic exposures to particulate matter (PM) and ozone pollutants were estimated with kriging from measurement data. Overall, the study found elevated odds for IHD from long-term exposure to PM or ozone in adults with prior or current asthma, with effect modification more pronounced in regard to PM exposure. Further research is needed to clarify what conditions produce observable interactions between air pollutants and asthma, and to evaluate the biological mechanisms by which air pollution may engender an excess cardiovascular risk in asthmatics.
3.2 Background

Previous research has suggested a potential link between asthma and ischaemic heart disease (IHD). Studies conducted in the U.S. and Italy for example, have documented excess mortality from IHD among asthmatics and elevated risks for coronary heart disease and atherosclerosis associated with asthma. A cross-link between asthma and vascular risk factors such as hypertension has also been reported, although results were inconclusive from different study locations/samples. The biologic mechanisms underlying the relation between asthma and IHD have not been fully established; nevertheless, the epidemiological association has led to the hypothesis that inflammatory responses to inhaled exposures are actively involved in the pathogenesis of both conditions. Indeed, substantial epidemiological and experimental evidence exists supporting the biological plausibility of pulmonary oxidative stress and proinflammatory pathways induced by exposures to environmental air pollution that can augment the development and progression of IHD. In particular, ambient particulate matter (PM) and ozone have been extensively investigated and implicated as environmental risk factors for IHD, adding to the burden of known lifestyle risk factors (e.g. tobacco use, physical inactivity).

Despite general evidence for a potential role of air pollution in cardiovascular injury, exposures to major components of air pollution (e.g. PM and ozone) have rarely been accounted for by researchers in their efforts to assess the asthma-IHD relationship. To address this gap, the present study attempts to investigate the effects of inhaled pollutant exposure with respect to the putative asthma-IHD comorbidity. Specifically, the
possibility of elevated risks for IHD among asthmatics from background exposures to air pollutants was investigated cross-sectionally, with adjustment for known vascular risk factors, lifestyle habits, demographic and socioeconomic attributes as well as spatial and temporal trends in disease. On the basis of suggested common inflammatory pathology, it is reasonable to hypothesize that the inflamed and hyperreactive airways of individuals with prior or current asthma enhances their vulnerability for IHD from environmental exposures promoting inflammation and oxidative stress.

3.3 Methods:

Air pollution and IHD morbidity data

This study used ambient air quality monitoring data from the U.S. Environmental Protection Agency’s Air Quality System to exploit exposure contrasts. Concentrations of PM$_{10}$ (coarse/fine particle with aerodynamic diameter $<10 \mu m$), PM$_{2.5}$ (fine particles with diameter $<2.5 \mu m$) and ozone were obtained for years 1999-2005 (no systematic sampling of PM$_{2.5}$ before 1999). To derive an overall estimate of PM exposure and to augment data coverage, PM$_{10}$ concentrations were converted to PM$_{2.5}$ using a scaling factor of 0.55, based on previously estimated percentages of PM$_{2.5}$ in PM$_{10}$ mass. Ecologic covariates, defined as long-term exposures to ambient PM and ozone at the target areal level, were assessed on the basis of yearly median measurements sampled from a restricted set of surveillance-type monitoring stations located throughout urban and rural areas in contiguous states. Table 1 shows the distributions of ozone and PM concentrations based on data from the selected period and monitoring sites. As a means of quantifying year round exposure across region, median ozone and PM concentrations
obtained from the sampling sites had fairly strong temporal correlations for the study period (Table 1).

Table 1. Distributions of O3 and PM2.5 (1999-2005) a, surveillance-oriented sites from contiguous U.S. region

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Median sampling frequency</th>
<th>Yearly median levels (O3—ppb; PM2.5—μg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per year</td>
<td>Period total</td>
</tr>
<tr>
<td>O3</td>
<td>899</td>
<td>5,735</td>
</tr>
<tr>
<td>PM2.5</td>
<td>1,203</td>
<td>105</td>
</tr>
</tbody>
</table>

Pairwise correlations of yearly median measurements averaged across monitors: O3 — 0.7 PM2.5 — 0.6

a Routine sampling of PM2.5 was implemented in 1999 following the promulgation of the National Ambient Air Quality Standard for PM2.5 in 1997. A scaling factor of 0.55 has been used to convert PM10 concentrations to PM2.5 in order to augment coverage. While PM was typically measured at a frequency of every six days or higher, many sites took daily sampling. Ozone was typically monitored at 1-hour or 8-hour interval.

b Sites describe unique sampling points indicated by longitude/latitude. Those providing no geodetic datum information were not included. Data reported here were based on monitor-specific sampling records (a site may host multiple monitors).

Individual-level data on IHD prevalence and co-risk factors were obtained from the Centers for Disease Control’s Behavioral Risk Factor Surveillance System (BRFSS) of 2005, 2007 and 2009 (data on known IHD risk factors such as hypertension and high cholesterol were only collected in odd-numbered years).20 The BRFSS is a random digit-dialing cross-sectional household survey system which collects information on preventive health practices and risk behaviors as well as a wide range of health outcomes in the 50 states, the District of Columbia (DC), and three territories. Participants were selected using probability sampling from all households with telephones in each state or territory at 1st stage and all adults per household at 2nd stage (1 adult selected per household). The survey questions pertaining to IHD were twofold, “Has a doctor, nurse, or other health professional ever told you that you had any of the following? (1) A heart attack, also called myocardial infarction (MI); and (2) angina or coronary heart disease (CHD).

Prevalence of asthma was assessed by asking all participants “Have you ever been told by
a doctor, nurse, or other health professional that you had asthma?” Currently, the nationwide BRFSS does not record individuals’ residence at the city or town level.

**Geostatistical methods**

Yearly median concentrations of PM and ozone from the selected time periods and monitoring sites were averaged for exposure estimation by kriging in conjunction with block interpolation. All sample points representing surveillance-type monitoring sites were used in model-based interpolation/prediction. Pollutant concentrations were transformed to a logarithmic scale to better approximate a normal residual distribution and to constrain the modeled concentrations to be positive. Sampled data were first checked for autocorrelation and trends so as to determine the optimal parameters that characterize difference-squared values between each pairs of points at different distances lags (i.e. semivariogram); multiple semivariogram models were then fitted with different specifications on distance lags and directional influences. The optimal kriging parameters were chosen based on cross-validated error statistics including the mean prediction error (ME), root-mean-squared-error (RMSE), and cross-validated $R^2$. Pollutant concentrations at unsampled locations were computed as the best liner unbiased estimator in the form of weighted moving averages of available sample observations modeled by variogram models. Block averages were then derived from point-kriged results to estimate long-term exposure to pollutants across contiguous counties. All geostatistical analyses were implemented with ESRI ArcGIS (v10.0; ESRI Inc., Redlands, CA, USA).
**Statistical analysis**

Multilevel mixed-effects logistic regression was used to estimate potential interactions for MI and CHD risks between asthma and long-term exposure to particulates and ozone. The probability for an IHD outcome is defined in terms of binomial logit, and characterized by both individual risk factors (e.g. age, gender, race, BMI, education, income, asthma, smoking, physical inactivity, diabetes, hypertension, high cholesterol) and ecologic covariates (ambient concentrations of PM$_{2.5}$ and ozone spatially interpolated to each county). To account for broad-scale regional effects, indicator variables representing the nine Census regions were adopted. Random county effects (deviations from the population intercept) were included to reflect the unmeasured influences of county-varying covariates on IHD, and this county-to-county heterogeneity was allowed to vary across time (year of interview). IHD risks were estimated for either PM$_{2.5}$ or ozone, where the potential interaction between lifetime asthma status and air pollution was investigated by nesting the ecologic covariates within asthma status in the fitted models. IHD odds ratios (OR) associated with PM$_{2.5}$ and ozone for asthmatics were then compared with those for non-asthmatics, with 95% confidence intervals computed for the ratios of pollutant effect measures among asthmatics to those at baseline (non-asthmatics). Model evaluation consisted primarily of comparing hierarchically consistent candidate models on likelihood-based information criteria. Sensitivity of associations reported from single-pollutant models were also tested with simultaneous adjustment for fine particle and ozone exposure as well as socio-demographic and comorbidity measures. The mixed-model analysis was conducted with SAS (v9.3; SAS Institute Inc., Cary, NC, USA).
3.4 Results:

Spatial variations in ambient air pollution

Ordinary and universal kriging procedures were evaluated as methods to estimate the long-term averaged median PM$_{2.5}$ and ozone concentrations. Table 2 summarizes the performance metrics for the preferred models with and without a spatial trend component. The models gave similar overall performance measures: incorporating a linear or quadratic trend component did not give a stronger basis for interpolation (as indicated by RMSE values).

Table 2. Modeled and observed pollutant levels and cross-validation summary statistics (O$_3$—ppb; PM$_{2.5}$—μg/m$^3$) for exposure assessment methods

<table>
<thead>
<tr>
<th>Pollutant Site-averaged yearly median levels</th>
<th>Kriging method (log transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Estimated Ordinary$^b$ Universal linear trend Universal quadratic trend</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>O$_3$ (N$^a$=899)</td>
<td>46.255</td>
</tr>
<tr>
<td>PM$_{2.5}$ (N=1,203)</td>
<td>10.984</td>
</tr>
</tbody>
</table>

$^a$ N is the number of surveillance-oriented sites used for pollutant exposure modeling.

$^b$ A constant trend is implied by ordinary kriging.

$^c$ The optimal assessment method is indicated. When models rank similarly in terms of performance, the simpler specification that reproduces important features of the empirical variogram is deemed optimal.

Exposure estimation results showed that the chosen kriging models did not extrapolate much beyond the range of measured concentrations; however, estimated values have a markedly lower standard deviation (Table 2). Such discrepancies possibly arose from monitor placement bias as they tend to lie in urban, more polluted areas, whereas the modeled concentrations utilized measurements from neighboring samples to provide full coverages across measurement units. As such, they may give “smoothed” spatial patterns of pollution levels and underestimate exposure gradients. Figure 1 shows the median
background ozone and PM$_{2.5}$ concentrations across contiguous U.S. counties for the selected time window, based on the optimal modeling methods (defined as those with the lowest RMSE values). Interpolated surfaces were similar for the preferred kriging models, as indicated by the high correlations (>0.98) between estimates assessed with the different models. This suggests that the background ozone and PM pollution landscape for the study region and time frame was unlikely to change greatly depending on the choice of the optimal spatial interpolation model. Figure S1 in the Supporting Information provides graphical comparisons between measured concentrations at the study sites and predicted values by the chosen kriging methods.

Figure 1. Estimated background O$_3$ (ppb) and PM$_{2.5}$ ($\mu$g/m$^3$) concentrations across contiguous U.S. counties: A—O$_3$ yearly median concentrations (averaging 1999-2005), assessed with ordinary kriging, exponential covariance, lag distance=14.1km, nugget=0.011, range=167.1km, partial sill=0.012; B—PM$_{2.5}$ yearly median concentrations (averaging 1999-2005), assessed with ordinary kriging, exponential covariance, lag distance=125km, nugget=0.036, range=1,000km, partial sill=0.049.
IHD risk estimation

There were 2,318 contiguous counties available for analysis in the linked BRFSS and pollutant concentration data. The study populations for the single-pollutant models comprised 683,576 to 686,137 adults with complete co-risk information for assessing either MI or CHD prevalence, and those for the two-pollutant models ranged from 682,306 (CHD) to 684,819 (MI). The samples were approximately 40% men and 60% women, the majority of which aged 55 years and over. The age and sex characteristics of study subjects were comparable across levels of ozone and PM exposure (Supporting Information Table S1); the racial and socioeconomic traits were distributed somewhat unevenly across pollution ranges. The crude prevalence estimates were 6.1% for MI and 6.5% for CHD. Age, sex and race-adjusted prevalence was also estimated at mean values of individual-level covariates for the study population, controlling for random county effects. Overall, higher IHD rates occurred in the South and Midwest than in the Northeast and West (Supporting Information Figure S2); and higher-than-average ozone and particle concentrations occurred in the southern-central region (Supporting Information Table S2). Figure 2 shows the exposure effect estimates for selected pollutants from the final fitted models controlling for competing risk factors, with adjustment for spatial and temporal trends in disease. All individual-level covariates were independently associated with IHD outcomes, and their effects showed little change across models.
Figure 2. Multivariable-adjusted odds ratios (AOR) and lower and upper 95% confidence limits (LCI & UCL) for IHD complications by multilevel risk factor (linear and quadratic terms of BMI were included as continuous variables; PM₂.₅ and ozone-related effects were associated with 10-μg/m³ and 10-ppb increment in yearly median levels respectively).

O₃ or PM₂.₅ alone was associated with MI and CHD after accounting for effects attributable to age, sex, education, income, BMI, hypertension, hypercholesterolemia, diabetes, smoking status, physical inactivity, and asthma, as well as regional and temporal variations in disease prevalence (Figure 2). The multivariable-
adjusted odds ratio (AOR) for MI was estimated at 1.07 for both asthmatics (95% CI: 1.02-1.14) and non-asthmatics (95% CI: 1.03-1.1) per 10 ppb increase in yearly O₃ median concentrations. O₃ showed similar associations with CHD, with AORs of 1.08 (95% CI: 1.02-1.14) and 1.05 (95% CI: 1.01-1.08) per 10 ppb O₃ increment among asthmatics and non-asthmatics respectively. There was no interaction observed for O₃ effects by asthma status on either MI or CHD morbidity. In the PM₂.₅ adjusted analysis, a 10 μg/m³ increase in yearly median concentrations conferred an AOR of 1.19 (95% CI: 1.04-1.36) for MI in asthmatics, compared to 1.06 (95% CI: 0.97-1.15) in non-asthmatics. The PM₂.₅ effect on CHD was slightly larger, especially among asthmatics, with an AOR per 10 μg/m³ PM₂.₅ increment of 1.25 (95% CI: 1.09-1.43) in asthmatics, versus 1.09 (95% CI: 1-1.2) in non-asthmatics. Likewise, the interaction for PM₂.₅ effects by asthma status was statistically significant for CHD (P-value for interaction=0.04), whereas that for MI did not reach significance (P-value=0.07). In two-pollutant models, O₃ was associated with MI risks among non-asthmatics (AOR of 1.08; 95% CI: 1.04-1.12), whereas PM₂.₅ was associated with CHD risks among asthmatics (AOR of 1.18; 95% CI: 1.01-1.37) (Figure 3). The interaction for PM₂.₅ effects by asthma status was somewhat sensitive to the adjustment for O₃: when O₃ concentrations were taken into account, the AORs for both MI and CHD were still elevated among asthmatics from PM₂.₅ exposure, although the rate ratios comparing AORs among asthmatics to those among non-asthmatics did not reach statistical significance (P-values of 0.05 and 0.08 for MI and CHD respectively).
Figure 3. Multivariable-adjusted odds ratios (AOR) and lower and upper 95% confidence limits (LCI & UCL) for IHD complications by multilevel risk factor with simultaneous adjustment for PM$_{2.5}$ and ozone (linear and quadratic terms of BMI were included as continuous variables; PM$_{2.5}$ and ozone-related effects were associated with 10-μg/m$^3$ and 10-ppb increment in yearly median levels respectively).

3.5 Discussion

A central finding of this large cross-sectional study is the association of O$_3$ and PM$_{2.5}$ with prevalent MI and CHD after adjustment for individual risk factors, including age, gender, race, income, education, physical inactivity, obesity, diabetes, hypertension, hypercholesteremia, and smoking, as well as geographic areas of exposure. The study further suggests an enhanced IHD risk among asthmatics from long-term exposure to background air pollution when compared to non-asthmatics.
The positive association between O₃ and PM₂.₅ with cardiovascular outcomes is consistent with findings in the Six Cities study⁸ and the American Cancer Society (ACS) Cancer Prevention Cohort studies.⁹-­¹⁰ The hazard ratio for cardiovascular mortality associated with a 10 μg/m³ increase in long-term PM₂.₅ exposure was 1.19 (95% CI: 1.05-1.34) in the Six Cities study by Dockery et al. and 1.13 (95% CI: 1.08-1.18) in the ACS study by Pope et al.. In the ACS study by Jerrett et al., increased concentrations of either PM₂.₅ or ozone were significantly associated with an increased risk of death from cardiovascular causes, although the effect of ozone on cardiovascular mortality was sensitive to the adjustment for PM₂.₅. Associations between elevated particulate matter levels and IHD hospitalization including the triggering of MI were also found in a few time-series studies, controlling for temperature, seasonal effects and other temporal trends.¹²,¹⁵,¹⁷ On the other hand, quantitative findings for the short-term effects of ozone on cardiovascular illness were rather limited.

While there is clear and continuing indication that increase in air pollution contribute to elevated cardiovascular health risks, little attention has been paid to the differential vulnerability of asthmatics to cardiovascular morbidity from long-term exposure to ambient particulate matter and ozone. The modeling approach used in this study enabled exploration of the interaction between asthma and air pollution in IHD pathogenesis. Overall, the study found elevated odds for IHD from long-term exposure to PM₂.₅ or ozone in adults with prior or current asthma, with effect modification more pronounced in regard to PM₂.₅ exposure. As well, asthma showed consistent associations with MI and CHD after accounting for relevant individual and ecologic covariates in both single and
two-pollutant models. This finding complements substantial evidence on asthma as an independent risk factor for cardiovascular disease.

The mechanisms of air pollutants-attributable cardiovascular health effects are believed to involve neurogenic and inflammatory processes as well as oxidative stress. The direct cardiovascular damages may occur via agents that readily cross the pulmonary epithelium into circulation and beyond, such as gases and smaller sized particles along with soluble constituents of PM. Effects of inhaled pollutants on autonomic nervous systems have been substantiated by clinical and experimental evidence, whereby activation of neural reflexes secondary to pollutant interactions with lung receptors may alter autonomic tone, contribute to plaque instability or thrombosis, and initiate cardiac arrhythmias. The altered cardiac autonomic function hypotheses represents a plausible explanation for acute cardiovascular responses such as the triggering of MI. Less acute and indirect effects may occur through pulmonary oxidative stress and inflammation induced by inhaled pollutants. The oxidative stress mediated by major components of air pollution such as PM and ozone may arise from generation of reactive oxygen species (ROS) from the surface of particles, soluble transitional metals or organic compounds, free radical components, altered function of mitochondria, and activation of inflammatory mediators. This subsequently may contribute to a thrombogenic and hypercoagulatory state, characterized by endothelial dysfunction, artery vasoconstriction, enhanced macrophage production of proinflammatory cytokines, blood viscosity, increased platelet activation and aggregation, and accelerated atherosclerosis. As such, PM and/or ozone-induced oxidative effects and
pulmonary/systemic inflammation promote the development and progression of ischemic events. Of note is that the increases in ischemic events with increasing exposure to air pollution may represent a combination of short-term effects of pollutants on susceptible individuals and the atherothrombotic consequences of chronic exposure. While this study lends support to the plausibility of adverse effects of long-term exposure to PM and/or ozone on the cardiovascular system, the effect estimates were attenuated when exposure to both pollutants were simultaneously controlled for.

The positive association between asthma and IHD fits well with prior studies that demonstrated a relationship between CVD risks and biomarkers of allergies. Furthermore, asthma was associated with atherosclerotic disease in several studies, with evidence of a common inflammatory pathology mediated by leukotrienes and the genes that regulate them. In addition, eosinophilic infiltration, a prominent feature of asthma, and poor pulmonary function have been shown to predict death from CHD and stroke. As well, it is increasingly recognized that the long-term airway remodeling from the inflammatory response and subsequent repair in asthmatics can contribute to irreversible airway obstruction and a decline in lung function over time. As such, it is possible that asthmatics’ greater vulnerability to CVD risk factors (e.g. obesity, hypertension) may be linked to their decreased lung function. Importantly, given that results of this study simultaneously adjusted for BMI, hypertension and other prominent CVD risks, the cross-link observed between asthma and IHD suggests that asthma may be associated with IHD risk independent of other biomedical risk factors.
This study found differential effects of PM on CHD according to asthma status, lending evidence to the notion that persons with hypersensitive airways and/or low lung function, including those with history of asthma, are more sensitive to the deleterious effects of air pollution on the cardiovasculature. Given that PM pollution provokes cardiovascular events through proinflammatory pathways, it is possible that the chronic, inflammatory nature of asthma may enhance the atherothrombotic effects of acute and chronic exposure to air pollution. The synergistic relationship between air pollutants and asthma that raises CHD risk may involve airway hyperactivity, decreased clearance of deposited particles, pulmonary macrophage function, stimulation of prothrombotic cytokines and systemic inflammation, and induction of cellular oxidative stress. The fact that effect modification by asthma between ozone pollution and coronary vulnerability was not detected was an unexpected finding, and likely reflects measurement imprecision of correlated ecologic covariates. In light of scavenging of ozone by nitrogen oxide near roadways, measurement at central monitors probably approximates population exposure to PM$_{2.5}$ more accurately than it represents exposure to ozone.$^{35}$ In addition, the effects of ozone could be confounded by the presence of PM$_{2.5}$ because of collinearity and the higher precision of measurements of PM$_{2.5}$. $^{36}$

A major limitation of this study is that asthma and IHD status was assessed by self-report, and therefore is prone to misclassification. However, misclassification with poor sensitivity and high specificity—as is often the case in self-reporting of acute-onset or potentially life-threatening conditions $^{37-38}$—should have little effect on the validity of the point estimates, as the number of subjects who didn’t report the exposure or endpoint of
interest in this study was large compared to those who did. As well, random
misclassification of exposure or outcome in self-reported data is likely to have attenuated,
rather than exaggerated, the effects found. A further limitation is that analysis was not
stratified according to asthma severity or lung function, as the BRFSS did not contain
such information. Since COPD is associated with systemic inflammation and
atherosclerosis, it is possible that the inclusion of subjects with decreased lung function,
such as COPD patients, may have impacted the association between asthma and
pollutant-induced IHD risk. Also, given the limited information on asthma subtypes—e.g.
by age of onset—in the BRFSS, the study was unable to assess the differential
vulnerability to IHD among adult- and child-onset asthmatics. To account for the distinct
inflammatory pathophysiology with these asthma subtypes, future research focusing on
their varying risk of CVD from exposure to air pollutants is needed. Other limitations of
the present study include geographic aggregation in exposure assignment and the
resulting ecological biases (attenuated by a large set of individual characteristics),
potential selection biases (e.g. non-coverage of cell phone only households or those with
no phone at all) and the restriction of the study population to the selected racial groups,
which limit generalizability of results to less-selective populations. Finally, given its
cross-sectional nature, the study was unable to exclude the possibility of reverse
causality.

The strengths of the present study include its large sample size, the availability of
traditional IHD risk factors, and the use of geospatial and multilevel modeling techniques
to investigate the differential IHD risks from exposure to air pollution across
heterogeneous populations. Despite the increased awareness of the cardiovascular effects associated with both air pollutants and asthma, population-based studies on their potentially synergistic relationship in IHD pathogenesis are lacking. Epidemiological studies that support the formulation of plausible causal pathways are thus needed in order to better understand the link between air pollution and asthma in their effects on cardiovascular health.

In conclusion, this study provides evidence for a greater susceptibility to cardiovascular injury among asthmatics from long-term exposure to ambient particles, after multivariate adjustment for major coronary risk factors. Further research is needed to clarify what conditions produce observable interactions between air pollutants and asthma, and to evaluate the biological mechanisms by which air pollution may engender an excess cardiovascular risk in asthmatics. Understanding the etiology of asthma-pollutant interactions in association with CVD would facilitate risk prognostication, improve preventive strategies and develop targeted interventions in high-risk populations.
References:


Supporting Information Legends:
Figure S1: Measured ozone and PM$_{2.5}$ concentrations across study sites versus predicted values by the chosen kriging methods.

Figure S2: Age-Sex-Race (ASR) adjusted prevalence estimates across study counties assessed with study samples from the 2005, 2007 and 2009 Behavioral Risk Factor Surveillance System: A—myocardial infarction (MI), B—coronary heart Disease (CHD).

Table S1: Characteristics of study subjects according to quartiles of ozone and PM$_{2.5}$ exposure across study counties.

Table S2: Modeled ozone and PM$_{2.5}$ yearly median concentrations (averaging 1999-2005) across study counties by regional strata.
Figure S1: Measured ozone and PM$_{2.5}$ concentrations across study sites versus predicted values by the chosen kriging methods.
Figure S2: Age-Sex-Race (ASR) adjusted prevalence estimates across study counties assessed with study samples from the 2005, 2007 and 2009 Behavioral Risk Factor Surveillance System: A—myocardial infarction (MI), B—coronary heart Disease (CHD).
Table S1: Characteristics of study subjects according to quartiles of ozone and PM$_{2.5}$ exposure across study counties.

<table>
<thead>
<tr>
<th>O$_3$ quartile (ppb)</th>
<th>PM$_{2.5}$ quartile (µg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.0-42.79</td>
<td>8.86-11.12</td>
</tr>
<tr>
<td>42.8-46.82</td>
<td>11.13-12.32</td>
</tr>
<tr>
<td>46.83-50.84</td>
<td>12.33-16.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group (%)</th>
<th>225,697</th>
<th>212,703</th>
<th>140,045</th>
<th>112,122</th>
<th>228,997</th>
<th>200,814</th>
<th>129,693</th>
<th>131,063</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>1.5</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>25-34</td>
<td>7.8</td>
<td>8.3</td>
<td>8.0</td>
<td>9.0</td>
<td>7.7</td>
<td>7.9</td>
<td>8.9</td>
<td>8.7</td>
</tr>
<tr>
<td>35-44</td>
<td>15.5</td>
<td>16.0</td>
<td>15.4</td>
<td>16.4</td>
<td>15.5</td>
<td>15.9</td>
<td>15.9</td>
<td>16.2</td>
</tr>
<tr>
<td>45-54</td>
<td>22.6</td>
<td>22.4</td>
<td>22.4</td>
<td>22.2</td>
<td>23.1</td>
<td>22.1</td>
<td>21.9</td>
<td>22.3</td>
</tr>
<tr>
<td>55-64</td>
<td>23.4</td>
<td>22.7</td>
<td>23.2</td>
<td>22.7</td>
<td>23.6</td>
<td>22.7</td>
<td>23.0</td>
<td>22.7</td>
</tr>
<tr>
<td>65+</td>
<td>29.2</td>
<td>28.9</td>
<td>29.4</td>
<td>28.1</td>
<td>28.7</td>
<td>29.9</td>
<td>28.6</td>
<td>28.4</td>
</tr>
</tbody>
</table>

| Male (%)             | 39.8    | 39.5    | 39.2    | 38.8    | 41.0    | 39.4    | 38.2    | 38.0    |

| Race/Ethnicity (%)   |         |         |         |         |         |         |         |         |
| White,Non-Hisp.      | 89.1    | 86.0    | 84.6    | 86.6    | 93.1    | 88.1    | 78.1    | 82.1    |
| Black,Non-Hisp.      | 5.0     | 9.3     | 10.6    | 9.8     | 1.2     | 6.1     | 17.7    | 14.3    |
| Hispanic             | 5.9     | 4.8     | 4.9     | 3.6     | 5.7     | 5.9     | 4.2     | 3.6     |

| Education (%)        |         |         |         |         |         |         |         |         |
| Less than H.S. diploma | 6.0    | 7.2     | 7.5     | 9.5     | 5.4     | 7.0     | 8.8     | 9.5     |
| H.S. diploma or G.E.D. | 25.8  | 27.8    | 29.5    | 30.3    | 26.2    | 27.6    | 29.2    | 29.9    |
| Some post-H.S.       | 27.6    | 26.4    | 27.0    | 26.7    | 28.8    | 26.5    | 25.7    | 25.8    |
| College graduate     | 40.6    | 38.6    | 35.9    | 33.5    | 39.5    | 38.9    | 36.4    | 34.8    |

| Household income per year (%) | 8.4 | 9.3 | 10.4 | 10.9 | 8.0 | 9.0 | 11.0 | 11.4 |
| Less than $15,000 | 15.4 | 15.6 | 16.3 | 17.1 | 15.1 | 15.4 | 16.6 | 17.4 |
| $15,000 to 24,999 | 12.2 | 11.9 | 12.4 | 12.4 | 12.4 | 11.9 | 11.9 | 12.4 |
| $25,000 to 34,999 | 16.6 | 15.7 | 16.3 | 16.1 | 17.3 | 15.7 | 15.3 | 15.7 |
| $35,000 to 49,999 | 47.5 | 47.5 | 44.7 | 43.4 | 47.2 | 48.0 | 45.1 | 43.0 |
| $50,000 or more   | 58.0 | 57.4 | 58.6 | 60.2 | 61.2 | 58.2 | 55.6 | 56.1 |

| Married (%)          | 9.6    | 9.3    | 10.4    | 10.9    | 8.0    | 9.0    | 11.0    | 11.4    |

| Smoking history (%)  |         |         |         |         |         |         |         |         |
| Current smoker†      | 15.4    | 16.6    | 17.1    | 17.6    | 14.6    | 16.5    | 17.8    | 18.3    |
| Former smoker†       | 33.6    | 31.9    | 31.1    | 29.2    | 33.0    | 32.8    | 30.1    | 30.0    |
| Never smoked         | 51.1    | 51.5    | 51.8    | 53.3    | 52.4    | 50.7    | 52.2    | 51.7    |

| No leisure time activity # in past 30 d (%) | 21.7 | 24.2 | 25.4 | 26.4 | 20.4 | 24.2 | 27.0 | 27.0 |

| Alcohol drinks in past 30 d (means(SE)) | 27.6±0.01 | 27.7±0.01 | 28.0±0.02 | 28.0±0.02 | 27.5±0.01 | 27.7±0.01 | 28.1±0.02 | 28.1±0.02 |
| Diabetes (excl. gestational diabetes) (%) | 10.6 | 11.5 | 12.4 | 12.9 | 10.0 | 11.6 | 13.0 | 13.2 |
| Hypertension (%)    | 36.2    | 38.0    | 39.6    | 39.8    | 35.3    | 37.9    | 40.6    | 40.5    |
| Life-time asthma (%) | 13.3 | 12.9 | 12.5 | 12.7 | 13.3 | 12.8 | 12.9 | 12.3 |
| MI complications (%) | 5.7    | 6.0     | 6.4     | 6.7     | 5.7     | 6.2     | 6.3     | 6.6     |
| CHD complications (%) | 6.2    | 6.4     | 6.7     | 7.0     | 5.9     | 6.6     | 6.8     | 7.0     |

* The BRFSS 2005, 2007 and 2009 samples were restricted to non-Hispanic whites/blacks and Hispanics with identified disease state pertaining to history of myocardial infarction (MI) or coronary heart disease (CHD). A total of 690,567 records were available for the analysis including incomplete respondents (those on whom at least one covariate or outcome measure had missing data).
† Respondents that reported having smoked at least 100 cigarettes (5 packs) in their lifetime and currently smoke some days or every day.
†† Respondents that reported having smoked at least 100 cigarettes in their lifetime and currently do not smoke.
# Leisure time exercise defined as doing physical activity or exercise during the past 30 days other than one’s regular job.
Table S2: Modeled ozone and PM$_{2.5}$ yearly median concentrations (averaging 1999-2005) across study counties by regional strata.

<table>
<thead>
<tr>
<th>Regional strata</th>
<th>No. of counties (No. of subjects)</th>
<th>O$_3$ concentrations (ppb)</th>
<th>PM$_{2.5}$ concentrations ($\mu$g/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Median Min Max</td>
<td>Mean (SD) Median Min Max</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>729 (140,774)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E N Cen</td>
<td>394 (66,929) 47.83 (4.29) 47.69 36 54.5 11.16 (2.09) 11.96 4.9 14.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W N Cen</td>
<td>335 (73,845) 44.43 (3.6) 43.63 36.97 52.19 9.06 (1.93) 9.37 4.49 14.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>212 (150,797)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid Atl</td>
<td>146 (57,040) 44.15 (4.32) 43.5 32.38 51.79 10.7 (1.64) 10.81 6.23 13.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Eng</td>
<td>66 (93,757) 43.22 (2) 42.5 39.19 47.47 7.88 (0.95) 7.59 6.45 10.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>1,078 (236,086)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E S Cen</td>
<td>296 (41,488) 50.16 (2.05) 50.41 44.31 54.33 12.37 (0.78) 12.35 10.25 14.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S Atl</td>
<td>471 (143,171) 49.9 (4.12) 51.48 34.43 57.05 12.14 (1.38) 12.43 8.33 15.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W S Cen</td>
<td>311 (51,427) 43.05 (3.02) 42.66 35.78 54.5 10.58 (1.34) 10.92 6.54 12.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>299 (162,910)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mtn</td>
<td>177 (86,613) 46.79 (3.57) 46.78 38.31 56.91 7.14 (1.46) 7.02 3.86 12.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>122 (76,297) 40.62 (5.47) 40.64 29.04 53.99 8.12 (1.54) 7.81 5.69 16.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4

Association between Ambient Air Pollution and Low Birth Weight in Southern Nevada

4.1 Abstract

There is expanding evidence that ambient air pollution is associated with adverse birth outcomes. In the absence of definite biological mechanisms for such an association, it is important to determine the consistency of the putative effects of specific pollutants by exploring the relation in different populations and sites. The objective of this study is to assess whether air pollution is associated with term low birth weight (LBW) among residents of Southern Nevada, and to provide empirical evidence that might help evaluate plausible biological explanations. The frequency of LBW was assessed from a retrospective cohort of singletons born alive in Clark County during the period 1995-2008. Stationary air sampling data were obtained from the U.S. EPA to estimate average trimester exposures to ambient air pollutants. The effects of pollutant exposure on LBW were estimated by logistic regression with adjustment for co-risk factors including gestational age, type of delivery, gender, period and season of birth, maternal age, education, race, marital status, parity, adequacy of prenatal care, and maternal tobacco and alcohol use. Birth weight was also analyzed as a continuous variable to estimate the reduction of birth weight associated with changes in mean exposure to air pollution during each trimester of pregnancy. Controlling for maternal and fetal covariates and average pollutant measurements in each trimester (trimester exposures assessed simultaneously), exposure to ambient CO during the third trimester was associated with a significantly increased risk for LBW (odds ratio per 1-ppm increment=1.25; 95% CI: 1.06-1.47). PM$_{10}$ also exhibited an inverse pattern with birth weight, although mean birth weight reductions associated with PM$_{10}$ were small and only significant for the last trimester exposure. These results suggest that fetuses in the late stages of development are particularly vulnerable to particulate and CO pollution. Further studies are necessary to validate fetal susceptibility to air pollutants in terms of critical exposure windows, magnitude of effects, and relevant toxic components.
4.2 Background

Ambient air pollution is associated with increased morbidity and mortality for multiple health indicators including lung cancer, acute respiratory infections, asthmatic attacks, chronic respiratory and heart diseases, and reduced life expectancy.\textsuperscript{1-8} There are also indications that the adverse health effects of air pollution are higher for vulnerable subgroups such as the elderly population, children and fetuses.\textsuperscript{9-11}

Indeed, there is now emerging evidence that air pollution is associated with adverse birth outcomes. In a study conducted in Los Angeles in the early 1970s, Williams et al. found that infants born to mothers who lived in the more polluted areas of the city weighed an average of 314 g less than those born to women living in the less polluted areas.\textsuperscript{12} More recently, Wang et al. assessed the effects of exposures to sulfur dioxide (SO\textsubscript{2}) and total suspended particles (TSP) among Chinese women living in Beijing, and reported an increase in risk for delivery of low-weight (<2,500 g) full-term neonates.\textsuperscript{13} Bobak and Leon conducted another study in the Czech Republic, and examined the relation between low birth weight (LBW) and maternal exposures to TSP, SO\textsubscript{2}, and nitrogen oxides (NO\textsubscript{x}). A small increase in risk was observed in administrative districts with increased exposures to SO\textsubscript{2}, but not to other contaminants.\textsuperscript{14} As well, Chen et al. reported a positive association between birth weight reduction of newborns and maternal exposure to particulate matter (PM) in Northern Nevada.\textsuperscript{15} No clear relationship was detected between ambient levels of ozone (O\textsubscript{3}) or carbon monoxide (CO) and LBW in the same study. In another study by Rogers et al., the association between the risk of very low birth weight (VLBW; <1,500 g) and maternal exposures to ambient SO\textsubscript{2} and TSP
was examined for mothers living in Georgia, United States, using the combined average concentrations of SO2 and TSP as the exposure measure. An increased risk of VLBW and maternal exposures above the 95th percentile of the exposure distribution was reported for the combined measure.16

Other evidence is less convincing. In a Swedish study by Landgren which looked at the independent effects of SO2 and NOx, no increase in risk for low birth weight was reported for these pollutants.17 In another study by Alderman et al. which examined the relation between LBW and maternal CO exposure in Denver, Colorado, no association was found between higher CO exposure and higher odds of LBW, after adjustment for the confounding effects of maternal race and education.18

Therefore the epidemiologic evidence for the relation between air pollution and LBW is not consistent. The etiologic mechanism by which these contaminants cause adverse pregnancy outcomes has not been fully understood either. Previous studies on maternal smoking habits and adverse reproductive outcomes suggest that increases in maternal carboxyhemoglobin levels may explain the relation between CO exposure and LBW.19-20 There is also molecular evidence that transplacental exposure to biologically active compounds in respirable particles (e.g. polycyclic aromatic hydrocarbons) may induce DNA damage and compromise fetal development.21

In the absence of definitive biological mechanisms for the potential associations between ambient air pollutants and fetal growth restriction, it is important to determine the consistency of the putative effects of specific pollutants by exploring the relation in different populations and sites. The objective of this study is to assess whether air
pollution is associated with term LBW among residents of Southern Nevada, and to provide empirical evidence that might help evaluate plausible biological explanations.

4.3 Methods

Population
The frequency of LBW was assessed from singletons born alive in Clark County during the period 1995-2008. De-identified birth certificates provided by the Nevada Department of Health and Human Services were used to ascertain birth weight and most covariates included in the analyses. For each birth, the exposure window comprising the first, second and third trimesters was determined using gestational age (based on clinical/obstetric estimates) and date of birth. In addition to excluding multiple births, the analyses also excluded those weighing below 1,000 or above 5,500 g at birth, those born before 37 or after 42 weeks of gestation, and those whose mothers suffered from hypertension, diabetes, or uterine bleeding prior to delivery. The exclusions of multiple, preterm and postterm births, those born at the extreme ends of the birth weight spectrum, and pregnancies presenting certain maternal complications were based on the assumption that any effect of ambient air pollution on such pregnancies would be far outweighed by the influence of the maternal risks or complications and/or the treatments for maternal conditions.

Exposure assessment
Infants with maternal residence in Clark County (as registered on the birth certificate) were used in exposure window-based linkage with air pollution data. Hourly monitor readings of CO, NO₂ and O₃ for each day, 24-hour monitor readings of PM₁₀ for every 6th day, and those of PM₂.₅ for every 3rd day were obtained from the U.S. Environmental
Protection Agency to estimate average countywide concentrations of pollutants for which routine sampling was conducted during the study period (measurements of PM$_{2.5}$ prior to 1999 and those of NO$_{2}$ prior to 2000 were not available due to lack of routine sampling). Levels of SO$_{2}$ were negligible, owing to the absence of SO$_{2}$-emitting industries in Clark County. Average exposure to ambient air pollutants was derived using available measurements during the potential exposure window for each study subject individually. For each birth therefore, average pollution concentrations were retrospectively calculated for the first, second, and third trimesters of pregnancy.

**Statistical analysis**

Logistic regression models were constructed to analyze the outcome of term LBW in relation to average exposures to air pollution constituents throughout the trimesters of pregnancy, as well as maternal and fetal covariates including gestational age (linear and quadratic terms), type of delivery, gender, birth cohort (period of 4 years) and season of birth, maternal age, education, race, marital status, parity, adequacy of prenatal care (adequate, intermediate/inadequate, no care), and maternal tobacco and alcohol use (yes, no). Individual models were constructed for each contaminant, with dose-response relationships assessed on the basis of 1-ppm increase in CO average trimester concentrations, 10-ppb increase in NO$_{2}$ and O$_{3}$ average trimester concentrations, and 10-µg/m$^3$ increase in PM$_{10}$ and PM$_{2.5}$ average trimester concentrations. Birth weight was also analyzed as a continuous variable to estimate the reduction of birth weight associated with changes in mean exposure to air pollution during each trimester of pregnancy, controlling for factors related to LBW. Model assessment tools such as the Hosmer and Lemeshow Test and regression diagnostics were examined for model fit and validity.
4.4 Results

There were 214,076 singleton infants whose birth certificates provided complete data on maternal and fetal covariates included in the analyses, after excluding multiple, preterm and postterm births, very LBW and very heavy babies, as well as pregnancies for which it was noted on the birth certificate that the mother had suffered from uterine bleeding, hypertension or diabetes prior to delivery. Of these live term births, 4,710 (2.2%) were low in birth weight (<2,500 g). The prevalence of LBW tended to be higher among female than male infants, and among infants whose mothers were younger than 20 years of age or older than 35 years, African American or Asian, unmarried, primiparous, had a lower level of education, had no or inadequate prenatal care, and consumed alcohol or smoked during the pregnancy (Table 1).

Table 1. Prevalence* of term LBW according to selected maternal and infant characteristics in Clark County, Nevada, 1995-2008

<table>
<thead>
<tr>
<th></th>
<th>No. of live births</th>
<th>%Col.</th>
<th>LBW (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>214,076</td>
<td>100.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Child gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108,873</td>
<td>50.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Female</td>
<td>105,203</td>
<td>49.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=19</td>
<td>24,425</td>
<td>11.4</td>
<td>3.0</td>
</tr>
<tr>
<td>20-24</td>
<td>57,557</td>
<td>26.9</td>
<td>2.3</td>
</tr>
<tr>
<td>25-29</td>
<td>61,156</td>
<td>28.6</td>
<td>1.9</td>
</tr>
<tr>
<td>30-34</td>
<td>46,431</td>
<td>21.7</td>
<td>1.8</td>
</tr>
<tr>
<td>35-39</td>
<td>20,534</td>
<td>9.6</td>
<td>2.5</td>
</tr>
<tr>
<td>40+</td>
<td>3,973</td>
<td>1.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Maternal race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>99,443</td>
<td>46.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Black</td>
<td>20,320</td>
<td>9.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Native</td>
<td>1,559</td>
<td>0.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Asian</td>
<td>16,201</td>
<td>7.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>76,553</td>
<td>35.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Maternal education (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8</td>
<td>15,745</td>
<td>7.4</td>
<td>1.8</td>
</tr>
<tr>
<td>9-11</td>
<td>42,398</td>
<td>19.8</td>
<td>2.6</td>
</tr>
<tr>
<td>12</td>
<td>68,914</td>
<td>32.7</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Table 2 outlines the sample characteristics of study pollutants pertaining to sampling days, percentile and extreme values during the study period. Concentrations of the study pollutants were well below the established standards. Table 3 presents the Pearson correlation coefficients among pollutant concentrations. CO, NO₂ and PM_{2.5} levels were positively correlated, due partly to the same vehicular sources. On the other hand, O₃ was
negatively correlated with CO, NO₂ and PM₂.₅, a reflection of the seasonal pattern of summer highs for O₃ and winter highs for the others (Figure 1).

Table 2. Summary statistics for daily average concentrations of selected air pollutants in Clark County, Nevada, 1994-2008*

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Sampling days (period)</th>
<th>Mean</th>
<th>5th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>95th</th>
<th>Highest value (date)</th>
<th>2nd highest (date)</th>
<th>3rd highest (date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO (ppm)</td>
<td>5,416 (94-08)</td>
<td>0.7</td>
<td>0.1</td>
<td>0.3</td>
<td>0.6</td>
<td>1.0</td>
<td>1.9</td>
<td>5.5 (01/21/94)</td>
<td>5.4 (01/04/94)</td>
<td>5.3 (01/19/94)</td>
</tr>
<tr>
<td>NO₂ (ppb)</td>
<td>3,196 (00-08)</td>
<td>11.0</td>
<td>3.2</td>
<td>7.1</td>
<td>10.5</td>
<td>14.2</td>
<td>20.5</td>
<td>35.0 (01/03/08)</td>
<td>32.5 (12/12/08)</td>
<td>31.1 (12/11/08)</td>
</tr>
<tr>
<td>O₃ (ppb)</td>
<td>5,479 (94-08)</td>
<td>30.9</td>
<td>10.0</td>
<td>21.1</td>
<td>31.5</td>
<td>40.6</td>
<td>51.3</td>
<td>81.6 (07/11/94)</td>
<td>73.8 (07/13/94)</td>
<td>72.0 (07/12/94)</td>
</tr>
<tr>
<td>PM₁₀ (µg/m³)</td>
<td>5,121 (94-08)</td>
<td>30.9</td>
<td>12.3</td>
<td>21.2</td>
<td>28.6</td>
<td>37.3</td>
<td>55.4</td>
<td>297.2 (04/15/02)</td>
<td>268.3 (07/26/08)</td>
<td>223.3 (01/16/96)</td>
</tr>
<tr>
<td>PM₂₅ (µg/m³)</td>
<td>3,065 (99-08)</td>
<td>9.2</td>
<td>3.1</td>
<td>5.7</td>
<td>7.8</td>
<td>10.8</td>
<td>20.6</td>
<td>84.6 (07/04/03)</td>
<td>56.1 (12/26/01)</td>
<td>46.2 (10/29/03)</td>
</tr>
</tbody>
</table>

*Routine sampling of PM₂₅ was implemented in 1999 in Clark County following the promulgation of the National Ambient Air Quality Standard for PM₂₅ in 1997. There was no systematic sampling of NO₂ in Clark County prior to 2000.

Table 3. Pearson correlation coefficients among daily average concentrations of study pollutants, Clark County, Nevada, 1994-2008

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>CO</th>
<th>NO₂</th>
<th>O₃</th>
<th>PM₁₀</th>
<th>PM₂₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO₂</td>
<td>0.78*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₃</td>
<td>-0.71*</td>
<td>-0.64*</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM₁₀</td>
<td>0.22</td>
<td>0.13</td>
<td>-0.02</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PM₂₅</td>
<td>0.66*</td>
<td>0.59*</td>
<td>-0.44*</td>
<td>0.4*</td>
<td>1</td>
</tr>
</tbody>
</table>

*p-value <0.0001.

Figure 1. Variations in monthly mean concentrations of selected air pollutants in Clark County, Nevada, 1994-2008.
Simultaneous adjustment for exposures to pollutants in the first, second and third trimesters as well as cohort effects and seasonal confounding showed that the odds for term LBW increased significantly with the following risk factors: younger or older maternal age (<20 or ≥35 years), maternal race (non-white), education (<12 years), and marital status (unmarried), primiparity, cesarean or operative delivery, no prenatal care, and female gender. After adjustment for maternal and fetal covariates (compiled from information reported on the birth certificate), exposure to ambient CO during the third trimester was associated with a significantly elevate odds ratio of 1.25 for LBW (95% CI: 1.06 to 1.47). Although the risks for LBW were also elevated from first and second trimester exposures to CO, they did not reach statistical significance (Figure 2). There was no indication of a robust association between term LBW and prenatal exposures to other criteria pollutants during the study period (Table 4).

Table 4. Covariates-adjusted odds ratios and 95% confidence intervals for term LBW at each trimester of pregnancy (trimester exposures included together; each pollutant separately fitted)

<table>
<thead>
<tr>
<th>Pollutant (increment)</th>
<th>Period of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st trimester</td>
</tr>
<tr>
<td>CO (1-ppm)</td>
<td>1.03 (0.88 to 1.21)</td>
</tr>
<tr>
<td>NO2 (10-ppb)</td>
<td>0.97 (0.95 to 0.99)</td>
</tr>
<tr>
<td>O3 (10-ppb)</td>
<td>1.01 (0.99 to 1.02)</td>
</tr>
<tr>
<td>PM10 (10-µg/m³)</td>
<td>1.00 (1.00 to 1.01)</td>
</tr>
<tr>
<td>PM2.5 (10-µg/m³)</td>
<td>1.00 (0.97 to 1.02)</td>
</tr>
</tbody>
</table>
Table 5 shows the coefficients obtained in linear regression models for changes in mean birth weight according to increments in air pollutant levels in each trimester of pregnancy. Inverse relations between CO levels and birth weight were statistically significant for first and third trimester exposures: a 1-ppm increase in first and third trimester exposures was associated with mean reductions in birth weight of 14.5 g (95% CI: -24.2 to -4.9) and 20.9 g (95% CI: -30.9 to -10.9) respectively. PM$_{10}$ also exhibited an
inverse pattern with birth weight, although mean birth weight reductions associated with PM$_{10}$ were small and only significant for third trimester exposure.

Table 5. Changes in birth weight (g) and 95% confidence intervals per increment in exposure to air pollutants at each trimester of pregnancy adjusted for covariates (trimester exposures included together; each pollutant separately fitted)

<table>
<thead>
<tr>
<th>Pollutant (increment)</th>
<th>1st trimester</th>
<th>Period of pregnancy</th>
<th>3rd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2nd trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (1-ppm)</td>
<td>-14.53 (24.16 to -4.89)</td>
<td>-4.58 (-15.06 to 5.90)</td>
<td>-20.93 (-30.93 to -10.93)</td>
</tr>
<tr>
<td>NO$_2$ (10-ppb)</td>
<td>13.71 (-0.02 to 27.44)</td>
<td>9.88 (-4.92 to 24.68)</td>
<td>-1.77 (-14.12 to 10.59)</td>
</tr>
<tr>
<td>O$_3$ (10-ppb)</td>
<td>-2.42 (-8.75 to 3.90)</td>
<td>-0.52 (-4.59 to 3.54)</td>
<td>0.78 (-5.69 to 7.26)</td>
</tr>
<tr>
<td>PM$_{10}$ (10-µg/m$^3$)</td>
<td>-0.55 (-4.17 to 3.06)</td>
<td>-1.14 (-5.38 to 3.11)</td>
<td>-7.63 (-11.43 to -3.82)</td>
</tr>
<tr>
<td>PM$_{2.5}$ (10-µg/m$^3$)</td>
<td>9.23 (-4.84 to 23.30)</td>
<td>10.81 (-5.65 to 27.27)</td>
<td>-13.24 (-26.96 to 0.47)</td>
</tr>
</tbody>
</table>

4.5 Discussion

The study of singleton term infants in Southern Nevada provided evidence of an increased risk for LBW and birth weight reduction in relation to maternal exposures to ambient CO and PM pollutants, especially during the third trimester of pregnancy.

Further, results of this population-based study suggest that ambient concentrations of CO confer risk of LBW even in the lower range of exposure. Exposures to NO$_2$ and O$_3$ were not associated with risks for LBW or birth weight reduction based on the analyses.

The elevated effect estimates for CO and particle pollution are consistent with findings from several studies on air pollution and adverse pregnancy outcomes. Ritz et al. reported a significantly increased risk for LBW from last trimester exposure to higher levels of ambient CO (>5.5 ppm) among women living in the Los Angeles area, while Ha et al. found significant associations between LBW and exposures to CO and TSP during the first trimester in Seoul, South Korea. In another study conducted in six northeastern cities of the United States, Maisonet et al. found an increased risk for LBW in relation to
increasing levels of CO >1.46 ppm during the third trimester. The investigation found no indication of a positive association between prenatal exposures to PM\textsubscript{10} and LBW.

While results from this study support a relation between CO and particle concentrations and birth weight, with CO presenting a more consistent effect, some methodological aspects of this study need to be discussed. First, as with previous epidemiological investigations, this study assessed birth weight at term to evaluate the impact of air pollution on fetal growth. The restriction to term births in fetal growth evaluation was based on the assumption that failure to reach 2,500 g after 37 weeks of gestation is indicative of intrauterine growth restriction (IUGR). This restriction was important because the pathophysiological mechanisms responsible for preterm birth, a prognostic of LBW, are quite different than those causing IUGR. However, excluding preterm births from the assessment of IUGR may impact the study findings if pollutant exposures exerted an effect on fetal growth in these births. Also, even with the exclusion of preterm births, term LBW is still a heterogeneous entity, and may include incorrectly classified preterm births. Nevertheless, measurement error regarding gestational age was likely nondifferential, and any bias introduced would probably attenuate effect estimates towards null.

Second, the study defined maternal exposure according to countywide levels of air pollution during each trimester of pregnancy. Limitations of this exposure estimation approach should be recognized. For example, while most studies that assessed pregnancy outcomes in relation to air pollution used trimester exposures, it could be argued that a smaller time window-based pollution indicator than trimester averages may better
represent maternal exposure. At present, few studies took into account the variability of air pollution levels during each trimester. A study in the Czech Republic found an increased risk of IUGR with exposures in the first month of pregnancy,\textsuperscript{29} while another reported a relation between birth defects and second-month exposures to outdoor air pollution in Southern California.\textsuperscript{30} The reporting of adverse birth outcomes associated with exposures early in pregnancy suggest a more chronic-type effect for air pollution. In contrast, this study reported results that are more consistent with the hypothesis that exposures in the third trimester or at the late stages of pregnancy are more likely to interfere with fetal growth.\textsuperscript{13,24,26} As such, critical time windows of exposure merit further investigation, and exposure measurements that differentiate cumulative effects from late effects are warranted to help elucidate potential mechanisms involved in the effects of air pollution on growth restriction.

Another limitation concerns the extrapolation from microenvironmental measurements to individual exposures, where daily air quality measures were averaged across available monitoring sites to obtain countywide means (across gestational trimesters), which do not necessarily represent exposures at the individual level. Indeed, evidence suggests that while PM levels are more homogeneously distributed across different areas of a city,\textsuperscript{31} and correlate well over time with individual monitoring data,\textsuperscript{32} CO concentrations can vary considerably over a region.\textsuperscript{30,33} The presence of larger spatial variations in CO when compared to PM suggests that the effects of CO assessed by this study were more obscured by nondifferential exposure misclassification than those of PM. To reduce ecological bias, Ritz et al. in their studies in the Los Angeles area assigned maternal
exposure according to the closest monitoring station to maternal residence.\textsuperscript{24,30} However, considering that pregnant women may spend substantial amounts of time outside the perimeter of a monitoring station for reasons such as working or shopping, it is not clear that their exposure is well represented by ambient air observed in one station. In fact, any approach that uses air quality registered at fixed sites to approximate personal exposures will be subject to measurement error, although this error is likely random and the impact would be to attenuate the effect estimates. As well, residential mobility presents another problem in exposure assessment. According to previous studies in Maryland and California, about 20% of pregnant women changed residence during pregnancy.\textsuperscript{34-35} Data were not available to assess the rate of residential mobility among the study subjects or the extent to which it may affect the results. Notwithstanding, the main consequence of such residential mobility would be nondifferential errors in exposure classification and decreased estimates for the effects of the air pollutants studied.

Finally, although the analyses controlled for a number of risk factors for LBW at the individual level, the records available to this study did not have information on socioeconomic status (maternal education adopted as a proxy indicator), maternal nutrition, occupational exposures, indoor sources of pollution, or behavioral risk factors (e.g. drug abuse). Therefore incomplete adjustment for potential confounders may have resulted in an overestimation of the magnitude of the LBW risks due to air pollution, if these uncontrolled variables covary with ambient pollutant levels.

Several biological mechanisms for the adverse effects of air pollutants on the fetus have been suggested. CO toxicity may occur through hypoxic stress as CO competes with
oxygen for hemoglobin binding sites, blocking oxygen transport to body tissues and possibly impairing electron transport. CO can also combine with fetal hemoglobin after crossing the placenta, and concentrate more in the fetus than in the mother, as its elimination is slower in fetal blood than in maternal circulation. As placental CO diffusing capacity increases with gestational age, the possibility of greater fetal vulnerability later in pregnancy with higher placental CO exchange cannot be excluded. In addition, oxidative stress pathways are possibly relevant for CO-mediated effects on fetal growth, since CO can affect leukocytes, platelets and the endothelium, inducing a cascade of effects resulting in oxidative injury.

With respect to the embryotoxic effects of PM, transplacental exposure to carcinogenic polycyclic aromatic hydrocarbons (PAHs) absorbed to respirable particles has been suggested as a potential mechanism. This hypothesis is consistent with the finding that infants with higher PAH-DNA adduct levels from umbilical cord leukocytes had decreased birth weight, length and head circumference compared to those with lower PAH-DNA adducts. Although the role of PAHs in fetal growth modulation is not well understood, disruptions to the endocrine system and DNA damages with resulting activation of apoptotic pathways are some possibilities. Another toxic mechanism of PM involves the hematologic effects of inhaled particles. It has been shown that PM can induce a broad polyclonal expression of proinflammatory mediators capable of changing blood viscosity and artery vasoconstriction. As such, the PM-mediated inflammatory processes contribute to enhanced blood coagulation and impaired efficiency of maternal circulation and placental functions including oxygen and nutrients exchange, thereby
restricting fetal growth. As well, given the heterogeneous chemical and physical nature of PM, there may be a plausible set of biological mechanisms through which particulate pollution interferes with fetal growth and development.

In conclusion, the present study provides evidence that ambient air pollution is associated with a modestly increased risk for LBW among women in Southern Nevada. The results suggest that fetuses in the late stages of development are particularly vulnerable to particulate and CO pollution. Further studies are necessary to validate fetal susceptibility to air pollutants in terms of critical exposure windows, magnitude of effects, and relevant toxic components. Further investigation is also needed to advance our understanding of the biologic mechanisms likely to explain the adverse effects of air pollutants on pregnancy and fetal outcomes.
References:


Chapter 5

Summary, Conclusions and Recommendations

In summary, geostatistical and multilevel analytic approaches were used to implement large scale, population-based epidemiological investigations of the relationship between ambient air pollution concentrations and adverse cardiovascular outcomes (chapters 2 and 3). The availability of individual level health outcome/covariate data from national scale surveillance systems and air quality measurements from a network of stationary monitors maintained by the U.S. EPA enabled the evaluation of cardiac risks related to long-term exposure to air pollution. Specifically, exposure modeling using kriging and monitoring station measurements provided contrasts in exposure due to spatial variations. This exposure assessment approach, combined with mixed-effects regression analyses, represents one of the best available methods for a large scale assessment of the adverse cardiovascular effects from long-term exposure to air pollution.

Results from the current studies lend evidence to the notion that that long-term exposure to PM has the potential to cause or exacerbate cardiovascular disorders independently of other commonly studied risk factors. PM-mediated effects likely arise from pulmonary and systemic oxidative stress and proinflammatory pathways, where prolonged exposure induces changes in plasma viscosity and endothelial functions with atherothrombotic consequences. Further, there was evidence for an elevated IHD risk in those with prior or current asthma, associated with prolonged exposure to PM or ozone, with PM presenting a more consistent effect. The synergistic or additive relationship between air pollutants and asthma that raises IHD risk may involve airway
hyperactivity, decreased clearance of deposited particles, pulmonary macrophage function, stimulation of prothrombotic cytokines and systemic inflammation, and induction of cellular oxidative stress.

To improve our understanding of the underlying biological mechanisms for PM-mediated cardiovascular effects, further studies are needed to clarify the link between short and long-term cardiovascular effects of PM on CVD. Because PM serves as a surrogate for a complex mixture of air pollutants, there is also a clear need to disentangle the influences of PM and other pollutants, and to identify the differential toxicity of various pollution constituents including toxic components of PM and other measured or unmeasured compounds that correlate with PM. To address some of the limitations of the current studies, improvement of exposure estimates and metrics (e.g. more local scale exposure data) and investigation of the roles of copollutants and confounders should be encouraged.

In the context of reproductive outcomes, improved estimation of the timing and intensity of exposure to particulate and gaseous pollutants during pregnancy would help evaluate the biological mechanisms by which adverse birth outcomes are induced. Whereas the retrospective cohort study (chapter 4) lends evidence to the fetotoxic effects of CO and PM exposures, especially during late pregnancy, investigating finer time scales (e.g. months rather than trimesters) and peaks in exposure (versus average exposures) might provide additional insights, since both air pollution levels and fetal sensitivity to pollutants may vary sharply over time, and different pathophysiological
mechanisms may be involved at different stages of pregnancy. Further, it is worth
considering whether effects are cumulative, and if so, what duration of pollutant exposure
is likely to cause cumulative effects. As well, future work should examine various
adverse reproductive outcomes (e.g. LBW, preterm birth, fetal death, birth defects) to
identify relevant biological mechanisms and critical windows of exposure.

Although it remains to be confirmed if the effects of air pollution on birth weight are
causal, the postulated mechanisms for the effects of CO and PM are consistent with
current knowledge on the etiology of IUGR. The altered fetal growth may arise from CO-
induced hypoxic injuries affecting metabolic and transport functions of the placenta,
which are key factors in fetal development. The pathophysiology of PM may be more
complex, given the different nature of the internal components of PM (across time and
space). In general, PM exposure has been associated with the production and release of
proinflammatory mediators capable of inducing hematologic effects,1-4 which in turn
influence maternal-placental exchange and hence fetal growth. Further, fetal toxicity may
be caused by DNA damage and endocrine disruption from exposure to toxic components
of PM (e.g. PAHs).6-7

On the whole, it is increasingly evident that relatively low concentrations of ambient
air pollution are associated with adverse health and reproductive outcomes in populations
with diverse risk profiles. Further work is warranted to corroborate the coherence of the
relation, and to help identify approaches to reduce the burden of morbidity and mortality
related to air pollution.
References:


Appendix A.

Air pollution surface estimation with kriging

Measurements of air pollutants sampled at stationary monitoring sites were compiled from the U.S. EPA’s Air Quality System, restricting to surveillance-type monitors located in contiguous states and to those with at least 50% data capture. This data capture threshold was adopted as a tradeoff between maintaining spatial data density and minimizing temporal variability. To prepare for kriging, monitor-specific measurements of the study period were temporally averaged, logarithm-transformed, linked to site-specific spatial coordinates, and reprojected to a common geodetic system (GCS_NAD_1983).

Kriging is a geostatistical method for predicting values of spatial phenomena in unsampled locations, based on the indices sampled spatially surrounding the unsampled ones. Kriging-based approaches to interpolating from sampled to unsampled locations and thus generating continuous representation of the spatial process (i.e. surface) require a mathematical model to represent the spatial autocorrelation or dependency in the data, commonly known as semivariogram. The input data are weighted for interpolation based on the semivariogram model so that the estimation variance is minimized under the unbiasedness condition. The most frequently used form of kriging is ordinary kriging (OK), which incorporates the local covariance structure via semivariogram fitting to improve the prediction, assuming that data come from a stationary stochastic process. OK can also be used in a generalized form (i.e. universal kriging) with a non-stationary mean,
where the long-range variation or broad scale trend is modeled as a deterministic function of the spatial coordinates.\textsuperscript{4}

Kriging was implemented with the Geostatistical Analyst extension of ArcGIS (version 9.3; ESRI Inc., Redlands, CA) to estimate background concentrations for the studied pollutants, on the basis of temporally averaged yearly median concentrations at each sampled location. The log-transformed observations were used for semivariogram determination and cross-validation. Semivariogram is operationally defined as half the expected squared difference between paired data points separated by similar distance lags.\textsuperscript{5} Three frequently referenced semivariogram models (spherical, exponential, Gaussian) were considered for the spatial structure of the data to obtain the optimal semivariogram parameters, i.e. range, partial sill, and nugget.\textsuperscript{6} (The height that the semivariogram reaches when it levels off is called the sill. It is composed of two parts: a discontinuity at the origin, called the nugget effect, and the partial sill, which added together give the sill. The nugget effect can be viewed as the sum of measurement error and microscale variation. The distance at which the semivariogram levels off to the sill is called the range.) The ‘goodness of fit’ of each semivariogram was assessed by standard leave-one-out cross-validation. Cross-validation parameters including mean prediction error (ME) and root-mean-squared-error (RMSE) were used to guide the model selection process (ME should be approximately zero and RMSE should be small). The non-constant mean assumption of universal kriging was also tested empirically by incorporating linear or quadratic trend components into the kriging estimations and calculating cross-validated error statistics. ME and RMSE as well as prediction surfaces
were comparable between ordinary and universal krigings, supporting the overall validity of using OK models to estimating background pollutant concentrations at the national scale. Based on the chosen OK models, county-level pollutant concentration predictions were derived from first grid-averaging point-kriged estimates, and then averaging the grids within each study county (implemented with the Areal Interpolation Layer to Polygons tool from the Geostatistical Analyst extension).

**References:**


