The relationship between air pollution and low birth weight: effects by mother's age, infant sex, co-pollutants, and pre-term births

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The relationship between air pollution and low birth weight: effects by mother’s age, infant sex, co-pollutants, and pre-term births

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Received 15 July 2008
Accepted for publication 7 October 2008
Published 22 October 2008
Online at stacks.iop.org/ERL/3/044003

Abstract

Previously we identified associations between the mother’s air pollution exposure and birth weight for births in Connecticut and Massachusetts from 1999–2002. Other studies also found effects, though results are inconsistent. We explored potential uncertainties in earlier work and further explored associations between air pollution and birth weight for PM\textsubscript{10}, PM\textsubscript{2.5}, CO, NO\textsubscript{2}, and SO\textsubscript{2}. Specifically we investigated: (1) whether infants of younger (\(\leq 24\) years) and older (\(\geq 40\) years) mothers are particularly susceptible to air pollution’s effects on birth weight; (2) whether the relationship between air pollution and birth weight differed by infant sex; (3) confounding by co-pollutants and differences in pollutants’ measurement frequencies; and (4) whether observed associations were influenced by inclusion of pre-term births. Findings did not indicate higher susceptibility to the relationship between air pollution and birth weight based on the mother’s age or the infant’s sex. Results were robust to exclusion of pre-term infants and co-pollutant adjustment, although sample size decreased for some pollutant pairs. These findings provide additional evidence for the relationship between air pollution and birth weight, and do not identify susceptible sub-populations based on infant sex or mother’s age. We conclude with discussion of key challenges in research on air pollution and pregnancy outcomes.

Keywords: air pollution, birth weight, carbon monoxide, nitrogen dioxide, particulate matter, PM\textsubscript{10}, PM\textsubscript{2.5}, pregnancy, sensitivity analysis, sulfur dioxide

1. Introduction

Several studies have examined the relationship between mother’s exposure to air pollution and birth weight or risk of low birth weight infants (Glinianaia \textit{et al.} 2004, Maisonet \textit{et al.} 2004, Srám \textit{et al.} 2005, Triche and Hossain 2007). While results generally indicate that higher levels of air pollution are associated with lower birth weight, comparison across studies is hindered by variety in the study designs, the nature and quality of datasets, underlying populations, and pollution characteristics (Slama \textit{et al.} 2008). Our recent study of 358,504 births from 1999 to 2002 in Massachusetts and Connecticut identified associations between mother’s exposure over the gestational period to nitrogen dioxide (NO\textsubscript{2}), carbon monoxide (CO), and particulate matter with aerodynamic diameters <10 and 2.5 \(\mu\text{m}\) (PM\textsubscript{10} and PM\textsubscript{2.5}), and birth weight (Bell \textit{et al.} 2007b). We found differential impacts of pollution on birth weight by race, with higher impacts for infants of...
Black/African–American mothers, a group already at risk for lower birth weight compared to Caucasian infants.

While our findings provide evidence for an association between maternal exposure to air pollution and risk of low birth weight, several critical questions remain. In particular, although we accounted for gestational age, our dataset included some pre-term births. While we address co-pollutants, we did not account for the different measurement frequency of various pollutants (Bell et al. 2008, Salam 2008). A recent literature review summarized evidence on whether air pollution’s effect on pregnancy outcomes differ by gender (Ghosh et al. 2007). The authors concluded that the limited research available indicated differential effects of air pollution on low birth weight by gender, but noted that further research was needed as this issue has not been extensively studied.

These issues are key concerns for not only our study, but also raise broader issues that are critical to understanding the literature on air pollution and pregnancy outcomes more broadly and underscore some of the challenges of such studies. Here we present results of analyses performed to address these limitations and uncertainties in previous work regarding co-pollutants and the inclusion of pre-term births in the dataset. We also investigate whether infants of younger or older mothers, sub-populations already at risk of low birth weight, are particularly susceptible to the effects of air pollution on birth weight, and compare the relationship between air pollution and birth weight by sex of the infant.

2. Materials and methods

2.1. Data on health, weather, and air pollution

This analysis is based on 358,504 births in Massachusetts and Connecticut from 1999 to 2002, except where a subset of the data is specified. Birth data were obtained from birth certificate registries from the Division of Vital Statistics, Reproductive Statistics Branch of the National Center for Health Statistics. For each subject, the birth certificate included data on the counties of birth and residence; mother’s and father’s ages and races; mother’s marital status, educational attainment, smoking use during pregnancy, and alcohol use during pregnancy; gestational age in weeks; child’s sex; birth weight; type of birth; prenatal care; and birth order. Observations missing these data were excluded. The dataset was limited to single births, gestational length of 32–44 weeks, and weights of 1000–5500 g.

Exposure was estimated based on an average of air pollutant and meteorological data in the county of mother’s residence, including only births for which exposure data were available for ≥75% of the weeks in each trimester. Births in counties without air pollution monitors were excluded. Air pollution data were obtained from the US Environmental Protection Agency, and weather data were obtained from the National Climatic Data Center. Further information can be found elsewhere (Bell et al. 2007b).

2.2. Analytical approach

We applied a linear model incorporating birth weight as a continuous variable. All models included variables for child’s sex; mother’s education, tobacco use, marital status, age, and race; prenatal care; birth order; type of birth (e.g., vaginal, cesarean section); apparent temperature, which incorporates temperature and dew point temperature, at each trimester; year; and gestational length. Additional information on the methods and dataset are available elsewhere (Bell et al. 2007b).

In our initial study, results of the linear model indicate that higher mother’s exposure to NO2, CO, PM10, and PM2.5 were associated with lower birth weight. No association was observed between gestational exposure to sulfur dioxide (SO2) and birth weight. We conducted four sets of analysis to further investigate the relationship between air pollution and birth weight to consider the impact of: (1) differential effect based on mother’s age; (2) differential effect by infant’s sex; (3) adjustment by co-pollutants; and (4) exclusion of pre-term births in the analysis.

To investigate effects by mother’s age, we constructed a model with a variable for the pollutant of interest, an indicator for mother’s age by strata, and interaction terms for the pollutant and the indicators of mother’s age. The age strata were ≤24, 25–29, 30–39, and ≥40 years, with 30–39 years used as the reference category. Earlier work found that the risk of low birth weight was similar for infants of mothers ages 30–35 and 36–39 years or for infants of mothers ages <20 and 20–24 years (Bell et al. 2007b). We examined differential air pollution effects by mother’s age for the pollutants demonstrating an association with birth weight in the non-interaction gestational exposure model (PM10, PM2.5, NO2, and CO).

We examined whether the association between air pollution and birth weight differed by sex of infant by repeating analysis for the pollutants demonstrating a relationship in the total dataset (PM10, PM2.5, NO2, and CO) with a subset of data representing female infants only, and then with a dataset representing males only.

Earlier work included multivariate models to consider potential confounding by co-pollutants for pairs of co-pollutants that were not highly correlated (Bell et al. 2007b). These results indicated that the single pollutant model results were robust to adjustment by other pollutants. However, data for all pollutants were not available for all study subjects (Salam 2008). As a function of the distribution of monitoring networks, exposure estimates may be available for some pollutants but not others, raising challenges to the study of multiple pollutants simultaneously. We generated a new dataset for each pair of pollutants considered in co-pollutant adjustment by including only observations for which data are available for both pollutants. Potential confounding by co-pollutants was estimated by generating effect estimates for the relationship between exposure to a given air pollutant and birth weight based on three combinations of model structures and datasets, represented by the rows of table 1.

The first row represents a model including the pollutant of interest and no variables for other pollutants, for a dataset with all observations for which gestational exposure data were available for that specific pollutant. The second row also includes the pollutant of interest and no variables for other pollutants, but for the subset of observations for which...
gestational exposure data were available for that specific pollutant and the potential confounder of interest. The final model contains variables for both the pollutant and the co-pollutant and is based on observations with data for both those pollutants. For example, we calculated the association between PM$_{2.5}$ and birth weight for all births with PM$_{2.5}$ data without adjusting by co-pollutants, the association between PM$_{2.5}$ and birth weight without co-pollutant adjustment but considering only the subset of births with CO data available, and the association between PM$_{2.5}$ and birth weight adjusted by CO.

Our initial analysis addressed gestational length by omitting births with gestational length <32 weeks or >44 weeks, and by adjusting all models for gestational length at 2-week intervals (32–34, 35–36, 37–38, 39–40, 41–42, and 43–44 weeks) (Bell et al. 2007b). Sensitivity analyses concluded that the initial results identifying associations between gestational exposure and air pollution were robust to models with gestation specified at 1-week intervals (data not shown).

This original dataset included births that meet the clinical definition of pre-term (<37 weeks). We performed new analysis by restricting the observations to only those births with 37–44 weeks gestation and generated effect estimates for gestational exposure and each trimester. The inclusion of only births at gestations of 37–44 weeks is consistent with several previous studies (Basu et al. 2004, Maisonet et al. 2001, Ritz and Yu 1999, Salam et al. 2005). Trimesters were defined as 1–13 weeks, 14 to 26 weeks, and 27 weeks to birth. We applied a linear model with separate variables for each trimester’s exposure. As concentrations of pollutants can be correlated across trimesters, we also implemented a model that includes the exposure level for a specified trimester, and the exposure levels for the remaining two trimesters adjusted for the initially specified trimester’s exposure, repeated for each model as the specified trimester. Additional details on this modeling structure are provided elsewhere (Bell et al. 2007b). Effect estimates for trimester exposure were based on results that were consistent across all the trimester models.

### 3. Results

#### 3.1. Differential impact of air pollution on birth weight by mother’s age

Our results did not identify susceptibility to the association between air pollution and low birth weight based on mother’s age. The infants of the older mothers (≥40 years) or younger mothers (≤24 years or 25–29 years) did not exhibit relationships with air pollution and birth weight statistically different from those of the reference category (age 30–39 years). Figure 1 shows the change in birth weight in grams for an interquartile increase in gestational pollutant exposure for infants of the youngest and oldest age group, compared to the change in birth weight for the same increment in pollution for the reference age group (30–39 years). These results indicate the change in birth weight for infants of the mothers in the youngest and oldest age categories beyond the change in birth weight experienced by infants with mothers 30–39 years. Results do not indicate that infants of the older or younger mothers are particularly susceptible to the association between air pollution and birth weight, in that effects for these groups were not statistically different from the middle-age category.

#### 3.2. Differential impact of air pollution on birth weight by infant’s sex

In our dataset, 51.1% of subjects were male infants and 48.9% female. Males had higher birth weights. Results from stratified models with male only or female only infants revealed no differences in the relationship between air pollution and birth weight by infant sex. Table 2 shows the change in birth weight per interquartile (IQR) increase in pollutant over gestational exposure for the entire dataset and for male and female infants separately. The association between air pollutants and birth weight was statistically significant for either males or females alone (p < 0.001).
3.3. Co-pollutant adjustment

For pollutant pairs that were not highly correlated we performed co-pollutant adjustment with the multiple model structures listed above. For instance, for models analyzing the effects of PM$_{10}$ or PM$_{2.5}$, we adjusted for CO and SO$_2$. We did not adjust PM$_{10}$ by PM$_{2.5}$ or vice versa as PM$_{2.5}$ is a subset of PM$_{10}$ and their concentrations co-vary (correlation 0.77, p-value <0.001). As the monitoring networks differ by pollutant, inclusion of multiple pollutants reduced the sample size. For analysis of PM$_{10}$, adjusting by CO and SO$_2$ reduced the sample size by 4.4 and 3.5%, respectively. Figure 2 shows the sample size available for the single and two pollutant models. The largest reduction in sample size was for PM$_{2.5}$ with adjustment for CO or SO$_2$, for which 30% and 28% of the CO observations did not have co-pollutant exposure data.

Figure 3 shows the reduction in birth weight for an interquartile increase in mother’s exposure to pollutant over the gestational period, with and without co-pollutant adjustment. Results from three types of models are included: (1) single pollutant model, shown with boxes and solid lines; (2) single pollutant model based on the subset of data for which exposure data on the co-pollutant are available, shown with circles and solid lines; and (3) two pollutant model (i.e., the effect estimate for one pollutant, adjusted by another pollutant), shown as circles with dashed lines. Comparison of models with and without co-pollutant adjustment, based on the same dataset, can be made by examining model types 2 and 3. The association between air pollutant exposure and birth weight persists with adjustment by co-pollutants, and remains statistically significant in all cases. The magnitude of the effect is generally lower with co-pollutant adjustment, but not in all cases.

3.4. Impact of pre-term births

We performed sensitivity analysis by restricting observations to those with a gestational period of 37–44 weeks. Births with gestational length of 32–36 weeks accounted for 6.7% of the original observations; therefore the restricted dataset contained 334 305 births. Effects estimates based on gestational exposure from the subset analysis (37–44 weeks) were very similar to those from the original analysis (32–44 weeks), as shown in table 3, indicating that the original results are not an artifact of inclusion of pre-term births.

Figure 4 compares trimester results from the original analysis including births with gestational length of 32–44 weeks, to results from the sensitivity analysis with births with gestational length of 37–44 weeks. Each line plots the range of effect estimates across the trimester models. Results from the original and new analysis are similar; although there are differences in statistical significance. The new analysis finds statistically significant relationships between birth weight and PM$_{2.5}$ at the first trimester and PM$_{10}$ at the second trimester. The original analysis found similar effect estimates for these pollutants and trimesters (p < 0.06 for PM$_{2.5}$, p < 0.08

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### Table 2. Difference in birth weight (gm) per IQR increase in pollution for the gestational period (95% confidence interval), by infant sex (Note: the interquartile range (IQR) refers to the difference between the 75th and 25th percentile.)

<table>
<thead>
<tr>
<th>Pollutant (IQR)</th>
<th>All infants</th>
<th>Male infants only</th>
<th>Female infants only</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$ (4.8 ppb)</td>
<td>-8.9(-10.8, -7.0)</td>
<td>-8.7(-11.4, -6.0)</td>
<td>-9.0(-11.7, -6.4)</td>
</tr>
<tr>
<td>CO (303 ppb)</td>
<td>-16.2(-19.7, -12.6)</td>
<td>-16.6(-21.6, -11.7)</td>
<td>-15.6(-20.6, -10.6)</td>
</tr>
<tr>
<td>PM$_{10}$ (7.4 µg m$^{-3}$)</td>
<td>-8.2(-11.1, -5.3)</td>
<td>-7.2(-11.3, -3.1)</td>
<td>-9.3(-13.4, -5.2)</td>
</tr>
<tr>
<td>PM$_{2.5}$ (2.2 µg m$^{-3}$)</td>
<td>-14.7(-17.1, -12.3)</td>
<td>-15.4(-18.9, -11.9)</td>
<td>-14.4(-17.8, -10.9)</td>
</tr>
</tbody>
</table>

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### Table 3. Difference in birth weight (gm) per IQR increase in pollution for the gestational period (95% confidence interval), for different datasets based on gestational age. (Note: the interquartile range (IQR) refers to the difference between the 75th and 25th percentile.)

<table>
<thead>
<tr>
<th>Pollutant (IQR)</th>
<th>Observations with gestation</th>
<th>Observations with gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$ (4.8 ppb)</td>
<td>-8.9(-10.8, -7.0)$^a$</td>
<td>-9.0(-10.9, -7.0)$^a$</td>
</tr>
<tr>
<td>CO (303 ppb)</td>
<td>-16.2(-19.7, -12.6)$^a$</td>
<td>-14.7(-18.3, -11.1)$^a$</td>
</tr>
<tr>
<td>SO$_2$ (1.6 ppb)</td>
<td>-0.9(-4.4, 2.6)</td>
<td>-0.7(-4.3, 2.9)</td>
</tr>
<tr>
<td>PM$_{10}$ (7.4 µg m$^{-3}$)</td>
<td>-8.2(-11.1, -5.3)$^a$</td>
<td>-9.0(-11.9, -6.0)$^a$</td>
</tr>
<tr>
<td>PM$_{2.5}$ (2.2 µg m$^{-3}$)</td>
<td>-14.7(-17.1, -12.3)$^a$</td>
<td>-14.7(-17.2, -12.2)$^a$</td>
</tr>
</tbody>
</table>

$^a$p < 0.001.
Figure 3. Change in birth weight per IQR increase in gestational exposure to pollutant, for single and two pollutant linear models. (Note: the point reflects the central estimate; the vertical line represents the 95% confidence interval. Models without co-pollutant adjustment are shown with solid lines; models adjusted by co-pollutants are shown with dashed lines.)

for PM$_{10}$). Estimates for PM$_{10}$ in the third trimester under the new analysis had $p < 0.08$. Trimester results based on the sensitivity analysis (subset of births with 37–44 weeks gestation) were similar to original results (births with 32–44 weeks gestation).

4. Discussion

Findings indicate that while some populations are at higher risk of low birth weight (e.g., infants of younger or older mothers, female infants), the relationship between air pollution and low birth weight did not differ by mother’s age or infant’s sex. Although only limited research has been conducted on these topics, our results contrast earlier work indicating a higher association between air pollution and risk of low birth weight for males compared to females for a total suspended particles (TSP) and SO$_2$ pollutant indicator (Rogers et al 2000), TSP (Wang et al 1997), and PM$_{10}$ and NO$_2$ (Wilhelm and Ritz 2003). At term, male infants are typically not as developed as female infants, and this differential development could play a role in potential interaction between air pollution and birth weight (Ghosh et al 2007). Even with our new analysis, there exists limited findings on this issue and further investigation is warranted.

Analysis found that results were robust to co-pollutant adjustment, with analysis restricted to observations with data for multiple pollutants to allow a comparison across identical datasets. Results were further robust to exclusion of pre-term births, with models identifying the same suite of pollutants and similar effect estimates. While these sensitivity analyses provide confidence in our results, they also highlight challenges to research on air pollution and pregnancy outcomes, and in fact to the study of air pollution and human health effects more broadly. Exposure to air pollution in epidemiological settings typically is estimated from data based on existing regulatory monitors. Therefore, not all regions of interest may have monitoring data available for all pollutants. In our study, the reduction in sample size for two pollutant models did not greatly affect results, although the lack of exposure information did prevent us from analyzing some births, or from analyzing co-exposure in some locations. For Massachusetts and Connecticut, based on 2007 monitor locations, county-level exposures can be estimated for 56.7, 62.5, 47.9, 55.2, and 69.6% of the total population for NO$_2$, CO, SO$_2$, PM$_{10}$, and PM$_{2.5}$, respectively (US Census Bureau 2007, US EPA 2007). Only 29.4% of the population has data for all of these pollutants, and no monitors for any of these pollutants are located in the counties of 12.5% of the population. As research evolves to consider the health burden of the overall air pollutant mixture, the lack of co-located air pollutant measurements will become increasingly prohibitive.

An additional challenge in multi-pollutant analysis is the relationship between multiple pollutants, with some pollutants
functioning as precursors to others (e.g., NO₂ as a precursor to ozone); the heterogeneity in the chemical composition of particulate matter, which is in itself a complex air pollutant mixture (Bell et al. 2007a); and the high correlation of some pollutants due to similar sources (e.g., traffic as sources of CO and PM₁₀). By definition, PM₂.₅ is a subset of PM₁₀, making separation of the effects of these pollutants quite challenging. While our research indicates associations with birth weight and both PM₂.₅ and PM₁₀, information on which size distributions, chemical components, and sources of particles are most toxic is a necessary topic of further research. Another limitation to this work, and much air pollution human health research, is that pollution exposures were based on county-wide estimates, which do not account for within-county heterogeneity of pollutant levels or differences among individuals’ exposures, such as due to occupational exposure, housing structure, or indoor/outdoor activity patterns.

Exposure estimates are further hindered by the ‘snapshot’ nature of many data sources, such as the birth certificates used in this study. Studies of the residential mobility of pregnant women provide varying results, identifying 12% (Fell et al. 2004) to 33% (Canfield et al. 2006) of pregnant women moving during pregnancy, although other research found that most moves were within the same county and that exposure based on the residence at time of delivery is an appropriate measure for county-level exposures (Shaw and Malcoe 1992). Still measurement error is introduced by the assumption that exposure based on residence at time of birth is applicable to the entire gestational period. Such measurement error is larger for first trimester estimates than for third trimester estimates. Measurement error may also change throughout pregnancy if the indoor/outdoor activity patterns change. A recent study found that more time was spent indoors later into pregnancy (Nethery et al. 2008a).

A variety of techniques have been developed to address some of these concerns. Factor analysis and other source apportionment techniques have been used to separate particulate matter effects into the contribution from different sources (Duvall et al. 2008, Laden et al. 2000, Thurston et al. 2005), and some work has examined the impact of specific particulate chemical components on health (Ostro et al. 2007 and 2008). Air quality models can be used to estimate pollutant concentrations in areas or time periods for which monitoring data do not exist (Bell 2006, Sanhueza et al. 2003). Other exposure estimates such as proximity to traffic or land-use modeling have been used in exposure estimations (Gauderman et al. 2005, Nethery et al. 2008b, Ryan et al. 2007). These techniques could be applied to study of air pollution and birth outcomes. Brauer et al. (2008) found that residence within 50 m of a highway was associated with higher risk of small for gestational age and low birth weight infants. Slama et al. (2007) supplemented ambient pollution levels with data on land-use, population density, and features of the roadways in a study of birth weight.

While the analysis here provides additional evidence for the impact of air pollution on birth weight, several questions remain unanswered, such as a full understanding of the physiological mechanism by which a pollutant, or set of pollutants, could result in lower birth weight infants (Slama et al. 2008). Challenges inherent to the study of air pollution and pregnancy outcomes include the difficulties in estimating exposure as discussed above, as well as discrepancies of data characteristics across multiple studies (e.g., different data types for prenatal care), which hinder comparison and synthesis of results. Additional research is needed to gain a better understanding of the impacts of air pollution on pregnancy outcomes, including identification of susceptible

**Figure 4.** Change in birth weight per IQR increase in trimester exposure to pollutant, with and without inclusion of pre-term births. (Note: each line represents the range of results across the trimester models. The horizontal line reflects results based on births with gestational length 32–44 weeks; the vertical line reflects results based on births with gestational length of 37–44 weeks. Dotted lines indicate that results were not statistically significant across all trimester models. Results for a pollutant and trimester without statistically significant results are not shown.)
sub-populations, effects of multiple pollutants, and results in various locations and time periods with different study designs.

Acknowledgments

Funding for MLB and KE was provided by the Health Effects Institute through the Walter A Rosenblith New Investigator Award (4720-RFA04-2/04-16). Funding for MLB was also provided by the National Institute of Environmental Health Sciences (NIEHS) Outstanding New Environmental Scientist (ONES) Award (R01 ES015028). Funding for KB was provided by NIEHS (ES07456-07, ES11013).

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