Low-Level Exposure to Air Pollution and Risk of Adverse Birth Outcomes in Hillsborough County, Florida

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Objective: In this retrospective cohort (1998 to 2007), 145,445 singleton live births in Hillsborough, Florida, were analyzed to elucidate the relationship between fetal morbidity and prenatal exposure to six criteria air pollutants. **Methods:** This study was based on three linked databases: Florida Hospital Discharge, vital statistics records, and air pollution meteorological data from the Environmental Protection Agency. The primary outcomes of interest were low birth weight, preterm births, and small for gestational age. This study used structural equation modeling and trimester groupings to evaluate the relationship between air pollution and birth outcomes of pregnant residents. **Results:** The latent variables of structural equation modeling yielded a significant *B* value of 0.35, indicating that exposure to the criteria pollutants in pregnancy may have a significant relationship to fetal morbidity. **Conclusion:** Exposure to criteria air pollutants in pregnancy is associated with fetal morbidity outcomes.

Learning Objectives

- Become familiar with previous studies on the potential impact of prenatal exposure to ambient air pollution, including their methodological limitations.
- Discuss the data sources and methods used in the new study, including the rationale for using structural equation modeling (SEM).
- Summarize the study findings, possible pathophysiologic mechanisms, and suggestions for further research.

Air pollution is common to all cities and exists in high concentrations in areas of high traffic or near industrial plants.[1] Air pollutants not only contribute to global warming but also have deleterious effects on the human health. In response, the US Environmental Protection Agency (EPA) instituted national standards under the Clean Air Act of 1970. After the Clean Air Act's first 20 years, more than 200,000 premature deaths were prevented, and almost 700,000 cases of chronic bronchitis were avoided.[2] Over the last 20 years, total emissions of the six principal air pollutants have decreased by more than 41%,[2] although in certain areas (eg, Hillsborough County where this study is being conducted), ozone (O_3) and lead (Pb) levels remain above the national standards.[1] Also, these standards were set in place to limit air pollution effects on adults and little is known about the acceptable ranges of ambient air pollutants on vulnerable populations such as pregnant women and their children. More research is needed because the limited published literature suggests that fetal morbidity and adverse birth outcomes are associated with exposure to poor air quality.

In recent years, there has been a growing interest in research focusing on the potential impact of prenatal exposure to ambient air pollutants. Studies have examined the association between exposure to air pollution and several birth outcomes, including low birth weight (LBW),[4,5] birth defects,[6,7] and infant morbidity and mortality.[8,9] These studies have produced inconsistent results. Methodological flaws seem to permeate most of these published results because of the challenge posed by the validity of modeling approaches. Current analyses that attempt to capture the association between exposure to these pollutants and birth outcomes depend on single multiple analyses.[10] A problem with such an approach is that the effect of multiple testing on the precision of estimates is ignored, and the final results may not be truly accurate.[10] Another problem with this one-to-one single multiple analysis is that it is assumed that all the responses reflect the same underlying variable, a notion that may be quite misleading in many instances.[9] And, although socioeconomic and racial disparities in infant health outcomes are well documented and disadvantaged groups may be exposed to higher levels of pollution, the potential confounding effects of demographic factors on the association between infant health and air pollution are not well understood. One noteworthy study by Salihu et al,[11] using the same data set, demonstrated that in women exposed (values more than median) to particulate matter 10 (PM_{10}) and particulate matter 2.5 ($PM_{2.5}$), there was an increased rate of LBW, very low-birth-weight and preterm birth (PTB) outcomes. African American women had the greatest odds for all morbidity outcomes, with the greatest relationship to very low-birth-weight infants.[11] Accordingly, we undertook this study to assess the impact of exposure to particulate matter (PM_{10} and $PM_{2.5}$, carbon monoxide [CO], sulfur dioxide [SO_2], nitrogen dioxide [NO_2], O_3 and Pb on fetal morbidity by using a more complex but accurate model that takes into account latent variables and multiple analysis.

Structural equation modeling (SEM) is a statistical analysis technique that permits simultaneous analysis of multiple factors whose true effects on an outcome cannot be assessed independently because of a lack of independent natural occurrence. Observed variables as well as latent variables are analyzed regarding their relationships with each other and, thus, how these interrelationships affect outcomes.[12] Numerous studies have emphasized the fact that people are simultaneously exposed to criteria and other ambient air pollutants, limiting the validity of the analysis that does not consider the possibility of combined effects.[3] The purpose of this study was to assess the impact of the exposure to the six criteria air pollutants (PM [PM_{10} and $PM_{2.5}$], CO, SO_2 NO_2, O_3, and Pb) on fetal morbidity outcomes (preterm delivery, LBW, and small for gestational age [SGA]), using SEM framework to assess the relationship(s).

MATERIALS AND METHODS

This retrospective cohort study included all live singleton births in Hillsborough County, Florida, from 1998 to 2007. Birth and delivery information were obtained through linked vital

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statistics birth-data file obtained from the Florida Department of Health and Hospital Inpatient Discharge data for Hillsborough County, provided by the Florida Agency for Health Care Administration. Maternal demographic information, including racial or ethnic status (white non-Hispanic, black non-Hispanic, Hispanic, and other), age, marital status, education, parity, obesity, cigarette smoking during pregnancy, and adequacy of prenatal care, was gathered from birth certificate data. Outcome information regarding birth weight and gestational age were also obtained from birth certificate data. Hospital discharge data provided pregnancy-complication information based on the *International Classification of Diseases, Ninth Revision*, diagnostic codes for anemia, gestational diabetes, diabetes mellitus, gestational hypertension and chronic hypertension, preeclampsia, eclampsia, placental abruption, and placenta previa.

Air-quality and meteorological data were obtained from the EPA's Air Quality System, which continuously collects pollutant-concentration data from monitoring stations throughout Hillsborough County, for the years *1998 to 2007*. Twenty-four–hour daily maximum concentrations were available for NO_2, while 6-day maximum concentrations were available for CO, O_3, Pb, PM_{10}, and $PM_{2.5}$. The pollution data, which were obtained from the Hillsborough Environmental Pollution Commission also, included latitudes and longitudes to which we assigned zip codes. Women were assigned air pollution concentration values from the nearest monitoring station, using Euclidean minimum distance from the station to the maternal residence at delivery. If the closest site was missing data for a particular day, data from the next closest site was assigned. In the case of missing data across all sites, exposure values were labeled as missing.

Primary outcomes of interest were LBW, PTB, and SGA. *Low birth weight* was defined as births weights less than 2500 g, while *very low birth weight* was defined as births weights less than 1500 g. *Preterm birth* was defined as live births before 37 weeks of gestation, and very preterm births were those occurring before 33 weeks of gestation. *Small for gestational age* was defined as births with a weight below the 10th percentile for gestational age, using sex- and race-specific population–based national reference curves.[13] Gestational age was calculated in weeks for the interval between the first day of the last menstrual period and the delivery date, when last menstrual period was available. If this estimate was inconsistent with the birth weight, clinical estimates of gestational age obtained from vital records were used instead.

TABLE 1. Demographic and Overall Pregnancy Complications of Women in Hillsborough County (1998–2007)

	n	%
Race/ethnicity		
White	80,003	55.01
Black	27,942	19.21
Hispanics	23,776	16.35
Other	13,724	9.44
Maternal age, yr		
<35	125,743	86.45
>35	19,700	13.54
Not reported	2	0.00
Maternal education		
Uneducated	28,253	19.43
Educated	116,275	79.94
Not reported	917	0.63
Marital status		
Not married	56,284	38.70
Married	89,142	61.29
Not reported	19	0.01
Smoking status		
Not smokers	132,925	91.39
Smokers	10,926	7.51
Not reported	1,594	1.10
Parity status		
Nulliparous	48,664	33.46
Multiparous	96,162	66.12
Not recorded	619	0.43
Adequacy of prenatal care		
Inadequate	48,086	33.06
Adequate	97,359	66.94
Overall complication		
No	113,129	77.78
Yes	32,316	22.22

Statistical Analysis

Demographic characteristics of the study sample were tabulated and recorded in Table 1. This study used SEM to simultaneously assess the relationship between multiple ambient air pollutants and fetal morbidity. The strength of this form of analysis lies in the ability to model relationships between direct and indirect latent variables while accounting for measurement error. The structural components of the analysis included the following variables: six continuous variables representing each of the six criteria pollutants, a continuous latent variable summarizing the relationship between them, three dichotomous variables for each of the three categories of outcomes (preterm delivery, LBW, and SGA), and a categorical latent variable summarizing the relationship between them. Measurement models were constructed to represent the relationship between the latent summary outcome variable and the latent exposure variable. *Racial or ethnic status (white non-Hispanic, black non-Hispanic, Hispanic, and other), maternal age, marital status, education, parity, obesity, cigarette smoking during pregnancy, and adequacy of prenatal care were controlled for within the modeling phase of analysis.*

Parameter estimation was completed in three stages by using the weighted least squares method, which is based on the work of Muthen.[14] Three indices were used to determine the goodness of fit for the final model: the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Tucker-Lewis Index (TLI).[15–17] From this analysis, a final model was obtained. Parameter estimates were used to obtain odds ratios (ORs; using method or description of calculation and standard error calculation) (Fig. 1). The RMSEA index, which incorporates a penalty function for poor model parsimony, assesses goodness of fit along a continuous scale, with values less than 0.06 indicating adequate fit and those more than 0.10 indicating poor fit.[18] The CFI and TLI are similar to the coefficient of determination used to assess the goodness of fit of linear models,[15,19] although these focus on incremental fit indices by contrasting the hypothesized model to a more restricted nested baseline or null model. Using a scale from 0 to 1, models with values more than 0.9 are indicative of an adequate fit.[15,20]

Parameter estimates were used to calculate the odds of fetal morbidity among exposed and unexposed women. Odds ratios were then calculated to quantify the nature of the relationship between criteria pollutant exposure and PTB, LBW, and small size for gestational age. *Subgroup analysis involving women in the study was additionally carried out by gestational age of the fetus (in weeks). Three separate analyses were performed on the basis of the period of exposure of study participants as follows: exposure during the first trimester, which included the period from conception to 12 weeks of gestation; exposure during the second trimester, which included*

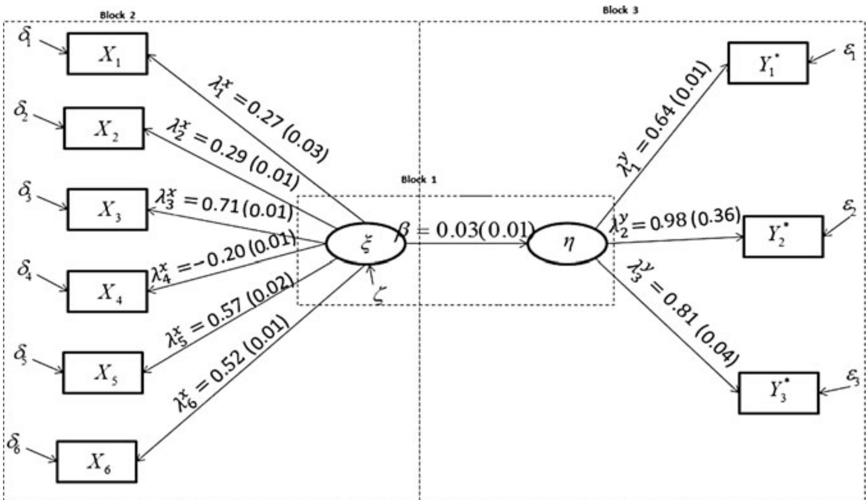

FIGURE 1. Path of the structural equation modeling, including parameter estimates (standard error) of the fitted model: the thresholds for $Y_1^* = 1.38$, $Y_2^* = 1.52$, $Y_3^* = 1.33$.

the period from conception to 29 weeks of gestation; and exposure during the third trimester, which included women who were exposed from the time of conception through 44 weeks of gestation.

RESULTS

The study sample consisted of 145,445 singleton births in Hillsborough County, Florida, from 1998 to 2007. Maternal demographic characteristics obtained from birth certificates and inpatient data are recorded in Table 1. In Hillsborough County, there were a total of 42 distinct monitoring stations distributed per pollutants as follows: 13 for PM_{10}, 4 monitors for $PM_{2.5}$, 6 for Pb, 6 for O_3, 3 for NO_2, 5 for CO, and 9 for SO_2. Summary statistics (mean [standard deviation], median, minimum, and maximum) for each pollutant is presented in Table 2. Hillsborough County's average annual pollutant concentrations were below EPA national standards for CO, nitrogen oxide, Pb, and PM_{10} during the study time frame of 1998 to 2007. The county-average O_3 concentration exceeded national standard ($\mu = 0.04$ parts per million), while the county range for $PM_{2.5}$ included the national standard (range, 7.5 to 35.8 $\mu g/m^3$).

The proposed structural model for this produced the following parameter estimates: The model created for parameter estimation had significant RMSEA, CFI, and TLI values, indicating adequacy of fit. The model's adequacy of fit persisted with the inclusion of observations with missing data by the CFI and TLI indexes, but had a RMSEA value slightly more than 0.06 (0.062) (Table 3). Odds ratios were obtained for the association between ambient air pollution exposure and preterm delivery, LBW, and small size for gestational age for the following temporal periods: the entire pregnancy period and first, second, and third trimesters (Table 4). Significant increases in odds of small size for gestational age and preterm delivery were seen for overall pregnancy exposure (SGA: OR = 1.11; 95% confidence interval [CI], 1.05 to 1.17; and PTB: OR = 1.23; 95% CI, 1.10 to 1.37) and second trimester exposure (SGA: OR = 1.27; 95% CI, 1.15 to 1.39; and PTB: OR = 1.62; 95% CI, 1.35 to 1.89). First trimester exposure did not result in significantly increased odds of any of the three fetal morbidity, while third trimester exposure presented a slightly protective but not significant trend in decreased odds of small size for gestational age, LBW, and preterm delivery.

DISCUSSION

Structural equation modeling was used to conduct analysis for this study to avoid statistical problems that arise with multiple testing (multiple exposures and multiple outcomes in this case). The use of SEM in ambient air pollution research has been gaining traction in the last decades in occupational and environmental epidemiology, where many environmental exposures cannot be assessed at an individual level and thus proxy variables (which tend to be correlated to each other) may have to be used.[12] In these cases, multicollinearity could substantially skew the results of the analysis by using a more traditional regression methodology.[1,12] Many studies have employed SEM to overcome multiple-testing limitations, as well as simultaneously assessing correlation among exogenic and endogenic variables. Budtz-Jørgensen[10] used SEM to overcome validity, measurement error, confounding and missing data limitation of multiple regression analysis when using biomarkers of prenatal mercury exposure to assess the relationship between mercury exposure and

TABLE 2. Summary Statistics of Criteria Pollutants in Hillsborough County (1998–2007)

Pollutants	Statistics* (*N* = 145,445)
PM	23.61 (4.42); 23.54; 10.70–41.13
Pb	1.32 (2.67); 0.24; 0.00–41.99
CO	0.90 (0.30); 0.99; 0.12–3.00
O_3	26.14 (3.58); 26.04; 0.02–48.77
SO_2	3.24 (1.68); 3.13; 0.00–10.21
NO_2	9.06 (2.13); 9.24; 0.00–21.86

*Values are indicated as mean (SD); median; minimum–maximum.
CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; Pb, lead; PM, particulate matter; SO_2, sulfur dioxide.

TABLE 3. Parameter Estimates From Structural Equation Modeling

	Without Missing Values			With Missing Values		
	Estimate	SE	*P*	Estimate	SE	*P*
B	0.42	0.1	<0.001	0.35	0.09	<0.001
RMSEA	0.058			0.062		
CFI	0.963			0.953		
TLI	0.949			0.935		

CFI, Comparative Fit Index; RMSEA, Root Mean Square Error of Approximation; SE, standard error; TLI, Tucker-Lewis Index.

TABLE 4. Association Between Criteria Pollutant Exposure and Fetal Morbidity in Hillsborough County (1998–2007)

	OR (95% CI)
Overall	
SGA	1.11 (1.05–1.17)
LBW	1.05 (0.85–1.24)
PTB	1.23 (1.10–1.37)
First trimester	
SGA	1.05 (0.99–1.12)
LBW	1.02 (0.79–1.24)
PTB	1.11 (0.97–1.25)
Second trimester	
SGA	1.27 (1.15–1.39)
LBW	1.08 (0.76–1.39)
PTB	1.62 (1.35–1.89)
Third trimester	
SGA	0.98 (0.91–1.05)
LBW	0.97 (0.79–1.15)
PTB	0.98 (0.89–1.07)

CI, confidence interval, LBW, low birth weight; OR, odds ratio; PTB, preterm birth; SGA, small for gestational age.

neurobehavioral outcomes in young children.[2,3] Lanphear and Roghmann used SEM to account for multiple source contributors to Pb exposure found to be correlated with each other, for children living in urban areas.[4] Sucharew et al also simultaneously assessed the role of traffic exhaust exposure, family, health, and home factors on recurrent dry night cough in children by using SEM, which allowed them to measure the true impact of traffic exhaust exposure by controlling for confounders and permitting the removal of multicollinearities, which could not be done with multivariate regression.[5] This study is unique in using SEM to assess the relationship between ambient air pollutants and fetal morbidity.

Sociodemographic data of this study demonstrated that no great deviation existed in the demographic or pregnancy complications in all exposure variables considered in the study. Pregnancy complications and morbidity outcomes were below the national percentages. Criteria pollutant ranges were also reported to be below the national standards. When exploratory factor analysis was performed, primary and secondary pollutants did have some correlation, but it could not be adequately modeled by our SEM approach. The significant B value from our latent regression model was 0.35. This indicates that exposure to the six criteria pollutant in pregnancy may have a significant relationship to all three birth outcomes if they are broken down into latent variables.

Some obvious strengths of this study include the study power and intrinsic temporality of the study. We had data for births from 1998 to 2007 and air pollution records for the same period. We controlled for several potential confounders, although we cannot rule out residual confounding due to unmeasured variables as well as the determination of exposure by residential zip code.

A limitation of this study included the exposure analysis. The exposed group was created on the basis of a population-level estimation of the values of the particulate pollutants, rather than the actual amount or concentration of the particulates detected in the individual's biological sample (eg, maternal blood). There is, therefore, a possibility of exposure misclassification because county-wide monitors were used to capture exposures at the individual level. This limitation is, however, not peculiar to this study, because other investigators have also had to manage this measurement error.[4,5,8,22] We were also unable to control for individual exposure variability induced by other factors, including distance from roads, traffic, place of work, seasonality, and period of time spent at the current address. Studies have also shown that 12% to 33% of women move from their initial address during pregnancy,[5] a potential source of nondifferential misclassification, which could have led to an underestimate of the association between the three pollutants and adverse birth outcomes examined in this study. Measurement error could also be present if mothers spent a considerable amount of time outside the perimeter of the residential air monitoring station.

The exploratory analysis data suggested that air pollutants could be possibly grouped together on the basis of primary and secondary status. Nevertheless, when further SEM analysis was performed, convergence was not obtained. This seems to suggest that the correct model takes into account that all pollutants simultaneously have the observed associated outcome and that, possibly, the pollutants taken as separate will not have as strong of an association. This may even contribute to the mixed results that prior studies demonstrated, using means and individually selecting relationships between exposures and birth outcomes.

CONCLUSION

Because these air pollutants continue to be a part of our daily life, the effects and pathophysiology should be made clear, because the outcomes can have long-lasting effects on our society and children. The suspected pathophysiology of morbidity and mortality from air pollution remains to be determined; however, scientists have suggested different theories. Some studies indicate that prenatal hazards that restrict fetal growth may be associated with small but measurable delays in motor and social development through childhood and reduced cognitive development.[24,25] An association between birth size and future development of adult-onset diseases such as type 2 diabetes and coronary artery disease has also been demonstrated.[26] Growth retardation, intellectual impairment, and poor health outcomes can follow the child into adulthood and decrease productivity in society, with potential for lifelong dependence, disability, or accommodations both in school and in the workplace. Society may bear the burden in either medical or disability cost.

An excellent epidemiological study to add to the body of knowledge of the cause of the disease would be a nested case–control study within a prospective cohort. Biological monitoring would be a potential important factor in this study to suggest causation. Blood samples, cord blood, DNA samples, or interval ultrasounds could be performed to monitor any changes in the size of the fetus or in various makers in the mother's blood.

Mothers and their babies are a vulnerable population who are more susceptible to lower levels of pollution. These air pollutants can possibly have long-term effects on children. Implantation of laws and regulations, warning system, or more strict EPA standards may be needed to adequately control the cost to our society and the environment.

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