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Maternal benzene exposure and low birth weight risk in the United States: A natural experiment in gasoline reformulation

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ABSTRACT

We investigate the relationship between maternal exposure to benzene and birth weight outcomes for resident births in the United States in 1996 and 1999, taking advantage of a natural experiment afforded by the regulation of benzene content of gasoline in various American cities. Regression results show that a unit increase ($\mu g/m^3$) in maternal exposure to benzene reduces birth weight by 16.5 g (95% CI, 17.6 to 15.4). A unit increase in benzene exposure increases the odds of a low birth weight event by 7%. Similarly, a 1 $\mu g/m^3$ increase in benzene concentration increases the odds of very low birth weight event by a multiplicative factor of 1.23 (95% CI, 1.19 to 1.28). Difference-in-differences analyses show that birth weight increased by 13.7 g (95% CI, 10.7 to 16.8) and the risk of low birth weight decreased by a factor of .95 (95% CI, .93 to .98) in counties experiencing a 25% decline in benzene concentrations from 1996 to 1999. Public health policy and economic implications of results are discussed.

1. Introduction

Low birth weight is a significant predictor of neonatal mortality and post-natal morbidity (Hack et al., 1995). The known risk factors for low birth weight include demographic variables like maternal age, maternal education, marital status, and infant sex (Kramer, 1987; Lin et al., 2007; Alexander et al., 2003; Khoshnood et al., 2005; Kleinman and Madans, 1985; Valero de Bernabe et al., 2004), gestation and obstetric variables like adequacy of prenatal care and history of prior preterm or small-for-gestational age infants (Shi et al., 2004), and toxic exposure and behavioral variables like maternal cigarette, alcohol use, and maternal weight gain and nutrition (Kramer, 1987; Seidman et al., 1989). Researchers also note that maternal exposure to criteria air pollutants like carbon monoxide and particulate matter significantly decrease infant birth weight (Parker et al., 2005; Bell et al., 2007a,b; Woodruff et al., 2003). Preliminary research indicates that other, non-criteria air pollutants like benzene may cause fetal harm (Šrám et al., 2005; Agency for Toxic Substances and Disease Registry (ATSDR), 1997, 2007; National Center for Environmental Assessment (NCEA), 1998, 2002; Duarte-Davidson et al., 2001).

Animal studies, for example, find that maternal benzene exposure is fetotoxic, resulting in lower birth weight, delayed bone formation, and stunted bone marrow growth (ATSDR, 2007; Laskin et al., 1995; Snyder and Hedli, 1996). Pregnant women exposed to benzene and other aromatic organic solvents in petrochemical work settings are known to have lower birth weight infants (Chen et al., 2000). Maternal residential proximity to hazardous waste landfills containing benzene and volatile organic compounds is associated with low birth weight risk (Berry and Bove, 1997). A prospective study of non-smoking pregnant women reports significant negative associations between benzene exposure, fetal head circumference, and birth weight (Slama et al., 2009).

The biological mechanisms by which benzene affects birth weight are not precisely understood. Intrauterine growth retardation seems the most plausible pathway. Benzene is known to produce several toxic metabolites that cause oxidative damage in cells and suppress cell growth (ATSDR, 2007; Laskin et al., 1995; Rao and Snyder, 2006). Exposed to low levels of benzene, both petrochemical industry workers and service station attendants present with significantly higher urine biomarkers t,t-muconic

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acid and S-phenylmercaturic acid as compared with control groups (Fracasso et al., 2009). Urinary S-phenylmercaturic acid is significantly related to DNA damage (Fracasso et al., 2009). Endocrine disruption is also recognized as a possible mechanism for interfering with intrauterine growth, and has been demonstrated for diesel exhaust but not specifically for benzene (Takeda et al., 2004; Slama et al., 2009).

Our paper extends this literature by analyzing spatial and temporal variation in birth weight outcomes as a function of local ambient concentrations of benzene. First, we analyze 1.6 million resident singleton births in the United States in 422 counties with varying levels of median county-level ambient concentrations of benzene in 1999. Specifically, we analyze birth weight in grams and the risk of both low birth weight (2500 g or less) and very low birth weight (1500 g or less) as a function of maternal benzene exposure, adjusting for known correlates.

Second, using a regression-based difference-in-differences procedure, we analyze variation in 3.1 million singleton birth outcomes across areas experiencing substantial decline in benzene concentrations from 1996 to 1999 resulting from the reformulation of gasoline. As part of the Clean Air Act (amended in 1990), the EPA's Office of Mobile Sources mandated the sale of reformulated gasoline in the worst polluted metropolitan areas in the country. The benzene content of reformulated gasoline was reduced from 5 vol% to 1 vol% (Fortin et al., 2005). Gasoline reformulation caused an estimated 30–40% reduction in vehicle emissions of benzene by 1999 (Kirchstetter et al., 1999). Insofar as a relationship between maternal benzene exposure and birth weight exists, the observed reduction in atmospheric benzene concentrations from 1996 to 1999 (as a function of gasoline reformulation) may have produced measurable changes in infant birth weight.

In Section 2 we describe data sources, variable operations and modeling procedures used to address the possible link between maternal benzene exposure and birth weight. After that in Section 3we present descriptive, geographic, and regression results, and end with remarks on the public health and environmental policy implications of our results, as wells as study limitations, and suggestions for future research in Section 4.

2. Materials and methods

2.1. Natality data

Birth data are from the Division of Vital Statistics, National Center for Health Statistics for registered births in the United States from and January 1st to December 31st in 1996 and in 1999. We restrict analysis to singleton births, mothers aged 15–49, and infants with plausible gestational ages (above 20 weeks). Information on maternal residence and birth location by county were used to spatially match benzene concentration data. Analyses that follow assume that the county of maternal residence is where a mother lived throughout the gestation period. To strengthen this assumption we limit analysis to mothers with matched birth occurrence and residential county codes.

Each birth record in natality files contains information on a suite of variables known to influence birth weight outcomes (Kramer, 1987; Boardman et al., 2002; Sastry and Hussey, 2003). Four demographic control variables are analyzed: *maternal age, education, marital status, and infant sex*. Our measure of *maternal age* is divided into three categories: *age 15–19, 20–34, and 35–49. Maternal education* is measured by four categories: *less than high school* (11 years of reported education or less), *high school* (12 years of education), *some college* (13–15 years of education), and *college educated* (16 years of education or more). In addition to individual-level demographic variables, we measure the *proportion of females aged 15–44 living at or below the poverty line* to control for county-level socio-economic conditions specific to women in the reproductive window. Four gestation variables are analyzed: *adequacy of prenatal care, gestation length*, *gestational weight gain*, and *prior history of pre-term or small-for-gestational-age infant births. Adequacy of prenatal care* is measured as a binary variable with 1=adequate, and 0=non-adequate. Adequacy of care is determined by the *Kessner Index*, a measure of timing and quantity of prenatal visits, adjusted for gestational length. *Gestation length* is a continuous variable measured in weeks. *Gestational weight gain* is an eight category measure: less than 16 lbs, 16–20 lbs, 21–25 lbs, 26–30 lbs, 31–35 lbs 36–40 lbs, 41–45 lbs, and 46+ lbs. *Prior history of pre-term* or small-for-gestational-age birth is measured dichotomously, 1=yes, 0=no. Two toxic exposure variables are measured: *maternal alcohol consumption* and *cigarette use. Alcohol consumption* is measured as the average number of alcohol drinks per week during pregnancy. *Cigarette use* is measured as the average number of cigarettes smoked per day. Overall, 3.1 million singleton births are analyzed, including n=1,514,841 in 1996, and n=1,601,703 in 1999.

2.2. Benzene data

Maternal exposure is measured as the average annual ambient concentration of benzene ($\mu g/m^3$) at the county scale. Benzene data are from the US Environmental Protection Agency's (EPA) National Air Toxics Assessment. The National Air Toxics Assessment system is a "state-of-the-science" screening tool used by the EPA to assess cancer risk and other adverse health outcomes from inhalation of air toxins. National Air Toxics Assessment data summarize outdoor air quality. Validity and reliability of data vary by pollutant. The EPA assigns confidence levels for each pollutant—*higher*, *medium*, *and lower*. Benzene (C_6H_6) is classified as a higher confidence pollutant. Ambient concentrations of benzene are derived by a dispersion model called the Assessment System for Population Exposure Nationwide. The Assessment System for Population Exposure Nationwide model integrates data from various sources including the National Toxics Inventory, the Emissions Modeling System for Hazardous Air Pollutants, and meteorological data. To evaluate the quality of Assessment System for Population Exposure Nationwide model estimates, the EPA compares model estimates at the exact geographic coordinates of ambient air quality monitor locations. A total of 115 locations monitor benzene levels. For each pollutant, the EPA calculates a "median of ratios." A median of 1 suggests that the Assessment System for Population Exposure Nationwide model overestimates monitor readings as often as it underestimates monitor readings. Of all pollutants examined, the agreement between model estimates and monitor readings is best for benzene, with a median ratio of .95. No major changes in Assessment System for Population Exposure Nationwide model formulation occurred between 1996 and 1999 assessments, except for updated emissions, meteorological, and more monitor input data. The main sources of benzene are chemical plants, petroleum refining operations, oil storage tanks, gasoline, auto exhaust (benzene is both a constituent of unburned gasoline and a product of incompletely combusted hydrocarbons), and tobacco smoke (Fortin et al., 2005; ATSDR, 2007). According to the EPA's 1999 National Air Toxics Assessment data, about 50% of total benzene emissions are from on-road mobile sources.

2.3. Analytic procedures and logic

As with previous birth weight and air pollution studies (e.g., Basu et al., 2004; Parker et al., 2005; Woodruff et al., 2003; Maisonet et al., 2001; Ritz and Yu, 1999; Wilhelm and Ritz, 2005), we use a linear linear regression procedure to analyze birth weight as a continuous variable (in grams), and logistic regression procedures to model low birth weight (1=2500 g or less and 0=more than 2500 g) and very low birth weight (1=less than 1500 g and 0=more than 2500 g) as discrete outcomes. In Section 1, we perform cross-sectional analyses of 1.6 million birth outcomes in 422 counties in 1999.

In Section 2, we perform time-sensitive analyses of 3.1 million singleton birth outcomes in the same counties in 1996 and 1999. This second section of analysis logically exploits a regulatory event that unfolded in the United States between 1996 and 1999. The EPA's Office of Mobile Sources required the worst polluted metropolitan areas in the country to sell reformulated gasoline. The benzene content of gasoline went from 5 vol% to 1 vol% (Fortin et al., 2005), resulting in substantial reduction in vehicle emissions of benzene (Kirchstetter et al., 1999). As the bulk of benzene emissions are from mobile sources, we observe analogous reductions in ambient concentrations of benzene across mandated areas. In the 104 mandated counties examined, the average reduction in ambient concentrations of benzene was 11.67%—about twice the reduction observed in non-mandated counties over the same time period. The gas reformulation program presents us with a natural experiment, where birth events in areas experiencing significant decline in benzene concentrations can be examined across time periods and compared with areas not experiencing such decline.

Our temporal analysis utilizes a regression-based difference-in-differences procedure, comparing birth weight outcomes in areas experiencing measurable decline in benzene concentrations from 1996 to 1999 as a result of gas formulation with areas not witnessing such a dramatic decline. The logic of difference-in-differences analysis is straightforward. Let t=0 denote the pre-gas reformulation period (1996) and t=1 denote the post-gas reformulation period, and y_{it} denote the birth outcome for infant i in period t. A regression-based estimator is modeled as

$$y_{it} = \beta_0 + \beta_1 x_i + \beta_2 \pi_t + \beta_3 x_i \pi_t + \varepsilon_{it}$$

where x_i is a dummy variable assuming a value of 1 if an infant is born in the gas formulation treatment group and 0 if in the non-gas reformulation group, and π_t is

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a dummy variable taking a value of 1 if an infant is born in the post-gas reformulation period and 0 if in the pre-gas reformulation period. The difference-in-differences estimator is β_3 (the coefficient of interaction between x_i and π_t) that assumes a value of 1 only for infants in the gas reformulation treatment group in the post-gas reformulation treatment period. All regression analyses adjust for control variables described above.

2.4. Cost analysis method

To illustrate how small effects over a large population can yield large impact, we use regression results produced by the methods outlined above to calculate the approximate health-care related costs of benzene exposure through the increased probability of low-birth weight events in our sample. This cost analysis is *not* a full inventory of societal losses by benzene pollution, but rather an order of magnitude estimate of health care costs related to low birth outcomes. To our knowledge, no *ex ante* benefit–cost analysis of gasoline reformulation considered this epidemiological dimension. We begin with a baseline probability for low birth weight outcomes across the entire unaffected sample population. Then, we estimate the impact of a unit increase in benzene exposure from the higher odds of such a low birth weight outcome. We monetize this impact by deriving the differential costs of health care of a low birth weight child as compared to a normal child over years of development, multiplying these additional costs by the greater odds of the low birth weight event. Dollar values are indexed to the year of observation. We evaluate *a representative child's* expected health costs in the baseline case against expected health costs in the high benzene context, extrapolating this differential over the entire study sample to arrive at a total cost estimate for high benzene exposure. Finally, we use the same logic to monetize the impact of atmospheric benzene reduction from gasoline reformulation.

3. Results

Mean birth weight and standard deviation by variables examined for our 1999 study population are presented in Table 1. Data show that 5.8% of infants born were 2500 g or less, and 1% of infants were born 1500 g or less. The average weight for singleton births examined was 3349 g. Average maternal exposure was 1.52 μg/m^3 of benzene. On our main variable of interest, maternal benzene exposure, descriptive statistics show that average birth weight is 41.1 g lower in the highest benzene exposure quintile as compared to the lowest benzene exposure quintile (3328.8 g vs. 3369.9 g). The range of atmospheric benzene by quintile is: I=.430 to 1.049 μg/m^3; II=1.050 to 1.306 μg/m^3; III=1.307 to 1.571 μg/m^3; IV=1.572 to 1.973 μg/m^3; and V=1.974 to 4.929 μg/m^3. Table 1 also shows that the proportion of infants born at 2500 g or less is 23.5% higher in the most polluted counties as compared to least polluted counties.

3.1. Cross-sectional analysis results

Table 2 reports linear and logistic regression results predicting birth weight in grams, low birth weight and very low birth weight. The coefficients reported in linear Models 1 and 2 represent expected changes in infant birth weight expressed in grams. Columns 3–6 report odds ratios corresponding to unit changes in predictors for low birth weight and very low birth weight events respectively. Beginning with the linear model in column 1, results show that a unit increase (μg/m^3) in benzene concentration decreases birth weight by 16.5 g (95% CI, −17.6 to −15.4). In marginal effect terms, a percent change in benzene concentration decreases average birth weight by half a percentage point. For comparative purposes, Model 1 also reports coefficients for reported maternal alcohol and cigarette use during pregnancy. Results show that a unit increase in the average number of cigarettes smoked per day decreases infant birth weight by 10.9 g (95% CI, −11.2 to −10.8). Similarly, a unit in the average number of alcoholic drinks had per week decreases birth weight by 11.9 g (95% CI, −14.8 to −11.4). In Model 2, we divide the distribution of atmospheric benzene into quintiles. The estimated reduction in birth weight over quintile I is 10.5 g for quintile II, 21.1 g for quintile III, 26.3 g for quintile IV, and 33.9 g for quintile V. Model residuals from the linear regression have a mean of 1.54e−07 and properties of Gaussianity and homoskedasticity.

In columns 3 and 4 of Table 2, odds ratios predicting low birth weight are reported. Results show that a 1 μg/m^3 increase in benzene exposure increases the odds of a low birth weight

Table 1
Cross-tabulation of birth weight outcomes by variables examined, 1999.

Variable	Average birth weight	Low birth weight	Very low birth weight
Demographic variables			
Maternal age			
15 to 19 yr	3210.9 ± 560.6	.081 ± .273	.013 ± .115
20 to 34 yr[a]	3366.1 ± 558.7	.053 ± .223	.009 ± .093
35 to 49 yr	3391.5 ± 602.8	.062 ± .242	.011 ± .106
Maternal education			
Less than high school	3270.5 ± 570.1	.073 ± .260	.011 ± .106
High school	3327.1 ± 573.3	.062 ± .242	.011 ± .102
Some college	3384.2 ± 564.7	.051 ± .221	.009 ± .095
College[a]	3439.1 ± 534.8	.038 ± .192	.006 ± .077
Maternal marital status			
Married	3409.5 ± 546.3	.044 ± .205	.007 ± .083
Non-married	3241.5 ± 587.8	.082 ± .274	.015 ± .120
Infant sex			
Male	3404.2 ± 579.1	.053 ± .225	.010 ± .098
Female	3291.7 ± 548.7	.062 ± .242	.010 ± . 097
Poverty county			
Low	3386.2 ± 560.0	.051 ± .220	.008 ± .088
Medium	3340.2 ± 577.0	.061 ± .240	.011 ± .105
High	3314.1 ± 579.9	.066 ± .248	.012 ± .111
Gestational variables			
Adequacy of care			
Adequate care	3382.3 ± 551.7	.049 ± .215	.008 ± .088
Non-adequate care	3270.5 ± 595.4	.079 ± .270	.014 ± .118
Gestation length			
Full term (> 38 weeks)	3451.0 ± 470.3	.019 ± .138	.000 ± .019
Premature (< 38 weeks)	2882.3 ± 716.7	.232 ± .422	.052 ± .221
Gestational weight gain			
< 16 lbs[a]	3150.9 ± 679.6	.118 ± .323	.033 ± .178
16 to 20 lbs	3222.0 ± 588.4	.088 ± .284	.015 ± .122
20 to 25 lbs	3283.0 ± 540.7	.065 ± .247	.007 ± .086
26 to 30 lbs	3341.4 ± 518.4	.050 ± .218	.005 ± .069
31 to 35 lbs	3395.8 ± 504.1	.039 ± .193	.003 ± .054
36 to 40 lbs	3442.7 ± 508.7	.033 ± .179	.003 ± .051
41 to 45 lbs	3478.3 ± 506.5	.029 ± .168	.002 ± .044
> 46 lbs	3535.7 ± 526.8	.027 ± .162	.002 ± .049
Prior preterm birth			
Yes	2986.2 ± 726.0	.208 ± .406	.041 ± .199
No	3353.7 ± 563.3	.056 ± .229	.009 ± .096
Toxic exposure variables			
Alcohol consumption			
Yes	3168.7 ± 655.2	.129 ± .335	.022 ± .148
No	3343.5 ± 567.4	.059 ± .235	.010 ± .098
Cigarette smoking			
Yes	3156.3 ± 562.9	.102 ± .303	.013 ± .115
No	3367.8 ± 563.5	.053 ± .225	.009 ± .096
Benzene concentration			
Quintile I[a]	3369.9 ± 547.5	.051 ± .219	.007 ± .083
Quintile II	3362.7 ± 568.2	.056 ± .230	.010 ± .098
Quintile III	3347.4 ± 579.9	.061 ± .240	.011 ± .105
Quintile IV	3326.9 ± 586.3	.065 ± .247	.013 ± .112
Quintile V	3328.8 ± 581.6	.063 ± .244	.013 ± .111
Response variables			
Infant birth weight	3349.3 ± 567.3		
Low birth weight status		.058 ± .233	
Very low birth weight status			.010 ± .098

Notes: the value following ± is the standard deviation.

[a] Reference group.

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Table 2
Linear and logistic regression models predicting birth Weight, low birth weight and very low birth weight (95% confidence interval) in 1999.

	Birth weight Model 1 Expected change in birth weight (95% CI)	Birth weight Model 2 Expected change in birth weight (95% CI)	Low birth weight Model 1 Odds ratios (95% CI)	Low birth weight Model 2 Odds ratios (95% CI)	Very low birth weight Model 1 Odds ratios (95% CI)	Very low birth weight Model 1 Odds ratios (95% CI)
Alcohol consumption (# per week)	−11.9 (−14.8 to −11.4)	−13.0 (−14.7 to −11.3)	1.05 (1.04 to 1.06)	1.05 (1.04 to 1.06)	1.06 (1.04 to 1.09)	1.06 (1.04 to 1.09)
Cigarette smoking (# per day)	−10.9 (−11.2 to −10.8)	−11.0 (−11.2 to −10.8)	1.05 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.02 (1.02 to 1.03)	1.02 (1.02 to 1.03)
Benzene concentration (μg/m^3)	−16.5 (−17.6 to −15.4)		1.07 (1.06 to 1.08)		1.23 (1.19 to 1.28)	
Benzene quintile II		−10.5 (−12.7 to −8.17)		1.10 (1.07 to 1.13)		1.44 (1.30 to 1.58)
Benzene quintile III		−21.1 (−23.3 to −18.9)		1.17 (1.14 to 1.20)		1.63 (1.48 to 1.79)
Benzene quintile IV		−26.3 (−28.4 to −24.1)		1.17 (1.14 to 1.19)		1.74 (1.59 to 1.90)
Benzene quintile V		−33.9 (−36.6 to −31.3)		1.21 (1.17 to 1.24)		1.82 (1.64 to 2.02)

Note: control variables include: maternal age, education, marital status, infant sex, local reproductive age female poverty, adequacy of prenatal care, gestation length, maternal weight gain, and prior history of pre-term or small-for-gestational-age infant births. The expected change in mean birth weight (in grams) or the odds ratios for low birth weight and very low birth weight are with respect to an increase of: 1 cigarette per week, 1 drink per week, and 1 μg/m^3 in the concentration of benzene.

outcome by a multiplicative factor of 1.07 (95% CI, 1.06 to 1.08). Column 4 shows the risk of low birth weight by benzene quintiles. Results show that odds of low birth weight increase incrementally from the second (OR=1.10) to the fifth quintile (OR=1.21) in atmospheric benzene levels. Columns 5 and 6 show odds ratios predicting very low birth weight (less than 1500 g=1). We find that a 1 μg/m^3 increase in atmospheric benzene increases the risk of very low birth weight by a multiplicative factor of 1.23 (95% CI, 1.19 to 1.28). Column 6 shows that mothers residing in the most polluted counties (Quintile V) are 1.82 times (95% CI, 1.64 to 2.02) as likely as comparable mothers in the least polluted counties to birth a very low weight infant.

Table 3 recapitulates analyses in Table 2, but restricts the pool of cases to full term infants (38–42 weeks of gestational age). The purpose here is to test whether intrauterine growth retardation is a plausible pathway of maternal benzene exposure to low birth weight. In column 1, reporting coefficients from our linear model of birth weight in grams, we find that a 1 μg/m^3 increase in benzene exposure decreases infant birth weight by 12.5 g (95% CI, −13.6 to −11.3). Results also indicate that infants born to mothers residing in the most benzene polluted counties are 21.7 g (95% CI, −24.4 to −18.9) smaller in birth weight than children born in the least polluted counties. In Column 3, results show that a 1 μg/m^3 increase in benzene levels increases the odds of a low birth weight event by a multiplicative factor of 1.04. Similarly, in Column 5, we observe that 1 μg/m^3 increase in atmospheric benzene raises the odds of a very low birth weight outcome by a multiplicative factor of 1.20–1.48. Overall, atmospheric benzene coefficients and odds ratios behave similarly in terms of direction (with modest reduction in magnitude) for full term infants as compared to models of all infants reported in Table 2.

3.2. Temporal analysis results

We begin our temporal analysis with an examination of birth weight and benzene concentration outcomes at the aggregate level. First, we calculate the correlation between the change in county-level ambient concentrations of benzene (μg/m^3) from 1996 to 1999 and the change in mean predicted birth weight in US counties from 1996 to 1999. We find a statistically significant negative association between the change in mean birth weight and the change in atmospheric benzene (r=.34, p=.001). Independent samples t-test results corroborate correlation analyses, showing that counties involved in the gas reformulation program witnessed both significantly greater decline in benzene levels (t=3.1009, $p<.001$) and, correspondingly, greater increase in average infant birth weight (.55% vs. .76%, t=3.0995, $p<.001$).

In Table 4 we report results of our difference-in-differences analyses comparing birth weight outcomes in gas reformulated counties experiencing at least a 25% reduction in benzene concentrations from 1996 to 1999 with counties not observing such decline. We also report results comparing counties experiencing at least a 10% reduction in benzene concentrations from 1996 to 1999 with areas not observing such decline, as well as results treating change in benzene concentration as a continuous variable. In Column 1, results show that infants born in counties that experienced a 25% reduction in atmospheric benzene were about 13.7 g (95% CI, 10.7 to 16.8 g) heavier than infants born in counties not experiencing such a decline. In Column 3, results indicate that average birth weight significantly decreased by up to 2/3rd of a gram for a 1% increase in atmospheric benzene. On the risk of low birth weight, in Column 4, we observe a 5% (95% CI .93 to .98) decline in the odds of low birth weight for children born in gas reformulated counties experiencing a 25% reduction in

Table 3
Linear and logistic regression models predicting birth Weight, low birth weight and very low birth weight (95% confidence interval) in 1999, restricted to full term births.

	Birth weight Model 1 Expected change in birth weight (95% CI)	Birth weight Model 2 Expected change in birth weight (95% CI)	Low birth weight Model 1 Odds ratios (95% CI)	Low birth weight Model 2 Odds ratios (95% CI)	Very low birth weight Model 1 Odds ratios (95% CI)	Very low birth weight Model 1 Odds ratios (95% CI)
Alcohol consumption (# per week)	−10.8 (−12.8 to −8.81)	−10.7 (−12.7 to −8.74)	1.05 (1.04 to 1.07)	1.05 (1.04 to 1.07)	1.00 (.84 to 1.19)	1.00 (.84 to 1.18)
Cigarette smoking (# per day)	−10.9 (−11.1 to −10.7)	−10.9 (−11.1 to −10.7)	1.05 (1.04 to 1.05)	1.05 (1.04 to 1.05)	1.02 (1.00 to 1.04)	1.02 (1.00 to 1.04)
Benzene concentration ($\mu g/m^3$)	−12.5 (−13.6 to −11.3)		1.04 (1.02 to 1.06)		1.33 (1.20 to 1.48)	
Benzene quintile II		−7.24 (−9.61 to −4.87)		1.05 (1.01 to 1.09)		1.72 (1.18 to 2.49)
Benzene quintile III		−15.1 (−17.5 to −12.8)		1.12 (1.07 to 1.16)		2.04 (1.43 to 2.91)
Benzene Quintile IV		−21.7 (−23.9 to −19.4)		1.14 (1.09 to 1.18)		1.99 (1.41 to 2.80)
Benzene quintile V		−21.7 (−24.4 to −18.9)		1.10 (1.05 to 1.15)		2.41 (1.69 to 3.42)

Note: control variables include: maternal age, education, marital status, infant sex, local reproductive age female poverty, adequacy of prenatal care, gestation length, maternal weight gain, and prior history of pre-term or small-for-gestational-age infant births. The expected change in mean birth weight (in grams) or the odds ratios for low birth weight and very low birth weight are with respect to an increase of: 1 cigarette per week, 1 drink per week, and 1 $\mu g/m^3$ in the concentration of benzene.

Table 4
Linear and logistic regression models predicting birth weight and low birth weight (95% confidence interval) in 1996 and 1999.

	Birth weight Model 1 Expected change in birth weight (95% CI)	Birth weight Model 2 Expected change in birth weight (95% CI)	Birth weight Model 3 Expected change in birth weight (95% CI)	Low birth weight Model 1 Odds ratios (95% CI)	Low birth weight Model 2 Odds ratios (95% CI)	Low birth weight Model 3 Odds ratios (95% CI)
Alcohol consumption (# per week)	−8.89 (−9.83 to −7.96)	−8.88 (−9.81 to −7.94)	−8.88 (−9.81 to −7.94)	1.04 (1.03 to 1.05)	1.04 (1.03 to 1.05)	1.04 (1.03 to 1.05)
Cigarette smoking (# per day)	−10.7 (−10.8 to −10.6)	−10.7 (−10.9 to −10.6)	−10.7 (−10.9 to −10.6)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)
Benzene reduction (25% or more)[a]	13.7 (10.7 to 16.8)			.95 (.93 to .98)		
Benzene reduction (10% or more)[a]		4.46 (2.31 to 6.61)			.97 (.95 to .99)	
Benzene change (%)[b]			−.13 (−.19 to −.65)			1.01 (1.00 to 1.01)

Notes: control variables include: maternal age, education, marital status, infant sex, local reproductive age female poverty, adequacy of prenatal care, gestation length, maternal weight gain, and prior history of pre-term or small-for-gestational-age infant births.

[a] Variables assume a value of 1 only for infants in gas reformulating counties experiencing a 25% or a 10% reduction of benzene concentration, and born in the post-gas reformulation treatment period.

[b] Reports the effect on birth weight for a 1% increase in benzene concentration between measurement periods. The expected change in mean birth weight (in grams) or the odds ratios for low birth weight and very low birth weight with are respect to an increase of: 1 cigarette per week, 1 drink per week, and 1 $\mu g/m^3$ in the concentration of benzene.

Table 5
Expected health care related costs of infant exposure to benzene (in utero) from birth to age 15.

Scenario	Baseline P(LBW)	Regression odds ratio (OR)	P(LBW)	P(NBW)	Costs of low birth weight (C_{lbw})	Costs of normal birth weight (C_{nbw})	Expected costs (EC) per live birth	Change from status quo (EC)
Status quo	.060	1.00	.060	.940	$89,974.76	$3432.07	$8624.63	
Upper 95% CI high benzene exposure	.060	1.24	.074	.926	$89,974.76	$3432.07	$9836.23	+$1211.60
High benzene exposure scenario	.060	1.21	.073	.927	$89,974.76	$3432.07	$9749.69	+1125.06
Lower 95% CI high benzene exposure	.060	1.17	.070	.930	$89,974.76	$3432.07	$9490.06	+865.43
Lower 95% CI benzene reduction	.060	.93	.056	.944	$89,974.76	$3432.07	$8278.46	−$346.17
Benzene reduction 25% scenario	.060	.95	.057	.943	$89,974.76	$3432.07	$8365.00	−$259.63
Upper 95% CI benzene reduction	.060	.98	.059	.941	$89,974.76	$3432.07	$8538.09	−86.54

atmospheric benzene as compared to children in non-gas reformulated counties.

3.3. Cost analysis results

Recall from Section 2 that our regression modeling allows for the estimation of the total health-care related costs of benzene exposure, where seemingly small individual changes in the odds of a low birth weight event can generate surprisingly large cost effects when considered over larger populations. We emphasize that the following cost estimation exercise is *not* a complete inventory of costs associated with benzene exposure. Instead, we perform an *ex post* cost analysis of ignored cost in *ex ante* analyses, namely the additional health care related costs associated with the observed increase in low birth weight events from benzene exposure.

From our logistic regression model of low birth weight in Table 2, we find that a unit increase in maternal benzene exposure increases the odds of a low birth weight event by a factor of 1.07. For singleton births, we observe a baseline probability of a low birth weight outcome of .060. Benzene exposure increases this probability to .064 ($.06 \times 1.07$). Similarly, an infant born to a mother exposed to atmospheric benzene levels higher than 1.973 $\mu g/m^3$ (our top quintile) is 1.21 times more likely to suffer a low birth weight outcome. For such infants, maternal benzene exposure increases our baseline probability to .073($.06 \times 1.21$).

Such small increases have significant cost ramifications, given the high cost of initial and ongoing care for low birth children. Average care costs for a normal birth-weight infant's (C_{nbw}) first year are approximately $3432 in 1999 dollars, adjusted for health cost inflation, vs. $27,095 for low birth weight babies (Lewit et al., 1995). In addition to these first year costs, an additional $62,879 of health-care related costs are typical over the first 15 years of life due to ongoing complications from low birth weight, totaling $89,974 of added health care costs (C_{lbw}). For our baseline case, the average expected health-care related cost per infant is (EC):

$$EC = P(\text{NBW}) \times C_{nbw} + P(\text{LBW}) \times C_{lbw}$$

$$EC = 0.94 \times \$3432 + 0.06 \times \$89{,}974 = \$8624.63$$

The expected health-care related costs per infant born in the most polluted counties:

$$EC = P(\text{NBW}) \times C_{nbw} + P(\text{LBW}) \times C_{lbw}$$

$$EC = 0.927 \times \$3432 + 0.073 \times \$89{,}974 = \$9749.69$$

The costs attributable to the increase in the probability of low birth weight in moving from the lowest to the highest quintile of benzene exposure is $1125.06 per child, rising from $8624.63 in the baseline case to $9749.69 in the higher benzene context. By multiplying the added health care cost of $1125.05 from high benzene exposure over the entire study population of 1.6 million live births, we estimate that the increase in low birth weight probability creates $1.8 billion of additional expected health-care related costs annually.

This extrapolation procedure can also be used to estimate the reduction in low birth weight health care related costs from policies that reduce benzene exposure, such as the gas reformulation program discussed above. In Table 3, for example, we observed that a 25% reduction in atmospheric benzene reduced the odds of low birth weight by 5% (95% CI 7% to 2%). The average health-care related cost per infant in our baseline case remains $8624.63. The expected health-care related costs per infant born in benzene reducing counties:

$$EC = 0.943 \times \$3432 + 0.057 \times \$89{,}974 = \$8635.00,$$

constituting a health care cost reduction of $259.63 per live birth. In Table 5, we report the range of estimated health care related costs associated with high benzene exposure, leveraging intervals of confidence reported in Table 2, and a range of cost estimates associated with reduction in atmospheric benzene, using confidence intervals reported in Table 4.

4. Discussion and conclusion

Environmental health and population scientists note that birth weight outcomes are importantly correlated with maternal exposure to pollutants. Known pollutants that affect birth weight and low birth weight risk include carbon monoxide and particulate matter, among others (Parker et al., 2009; Bell et al., 2007a,b; Woodruff et al., 2003). Prior research indicates that other, non-criteria air pollutants like benzene may cause fetal harm (ATSDR, 2007; Laskin et al., 1995; Snyder and Hedli, 1996; Chen et al., 2000; Berry and Bove 1997; Slama et al., 2009). Our study corroborates and extends previous research on the relationship between maternal exposure to benzene and low birth weight outcomes by cross-sectional analyses of 1.6 million resident singleton births in counties with varying levels of atmospheric benzene, and by temporal analyses exploiting a regulatory event involving the reformulation of the benzene content of gasoline in various American cities.

Our results show that maternal benzene exposure is a statistically significant and meaningful correlate of birth weight and the risks of low and very low birth outcomes. Adjusting for known correlates of birth weight, infants born to mothers residing in counties with the highest levels of atmospheric benzene are on average 33.6 g lighter than children in the least polluted counties. Cross-sectional analyses show that the risks of low and very low birth outcomes are 1.21 and 1.82 times higher, respectively, in the most benzene-polluted counties.

Temporal analyses performed corroborate cross-sectional results. At the aggregate level, we find a significant correlation

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between delta birth weight and delta atmospheric benzene, and observe that counties involved in the gas reformulation program experienced both significantly larger reductions in benzene levels and significantly greater increases in average infant birth weight. Individual-level analyses of 3.1 million singleton births in 1996 and 1999, show that counties experiencing a 25 or more percent decline in atmospheric benzene concentrations witnessed a gain of 13.7 g to the average birth weight of a child, and enjoyed about a 5% reduction in the risk of low birth weight. These gains are non-trivial, in effect, statistically offsetting the expected loss in birth weight from a mother smoking 1–2 cigarettes a day during pregnancy. From a policy standpoint, the decline in low birth weight risk is particularly meaningful when multiplied over large populations.

To illustrate how small effects over a large population can yield large impact, we used logistic regression results from Table 2 to approximate the health-care related costs associated with maternal benzene exposure. We found that health care related costs were from $856 to $1125.06 more per child born in counties in the highest quintile of atmospheric benzene as compared to children born in counties in the lowest quintile of benzene exposure. Using difference-in-differences regression results reported in Table 4, we found that expected health care costs were reduced from $85.64 to $346.17 per child in counties experiencing at least a 25% reduction in atmospheric benzene from 1996 to 1999. These dollar figures constitute *order of magnitude* estimates of what was potentially gained by gas reformulation in terms of lower health care related costs of live births. It should be noted that these calculations are specific to the US context, do not integrate other known costs of low birth weight including, learning deficits, employment prospects, and do not consider the suffering and distress experienced by parents following the birth of a low birth weight infant (Singer et al., 1999).

While our study usefully extends existing literature on the relationship between maternal benzene exposure and low birth weight risk, it is not without limitations. First, our atmospheric benzene measure is an estimate derived from a dispersion model integrating information from only 115 monitor locations. While agreement between monitor readings and dispersion model estimates is best for benzene among pollutants estimated in the National Air Toxics Assessment, the true amount of maternal benzene exposure is imperfectly measured. Therefore, observed changes from 1996 to 1999 likely contain measurement error and must be interpreted cautiously. Second, our estimates of atmospheric benzene are organized at the county scale. Because on-road mobile sources account for the bulk of benzene emissions, it is safe to assume that atmospheric benzene is not uniformly spatially distributed within counties. To roughly estimate the spatial uniformity of benzene within counties, we downloaded census tract benzene data from the EPA's National Toxic Assessment, 1999. The census tract is the finest spatial resolution available. A total of 66,300 census tracts were examined. We calculated a signal-to-noise ratio ($SNR=\mu/\sigma$) for each county for which benzene data are available, where μ is the mean census tract benzene level and σ is the standard deviation in benzene level. The average signal-to-noise ratio was 3.61 for the 422 counties examined, meaning that average census tract benzene is about three times larger than the standard deviation in atmospheric benzene across census tracts within counties. Clearly, atmospheric benzene levels are not perfectly spatially homogeneous within counties, but our signal-to-noise calculation indicates that census tracts are substantially more alike than not.

A third limitation, regarding the temporal feature of our study, is that observed changes in atmospheric benzene may be coincidental with changes in other toxins like particulate matter known to negatively affect birth weight outcomes. To address this limitation, we collected inhalable particle data, particulate matter with aerodynamic diameters less than or equal to 10 microns (PM_{10}), from the EPA. Data on PM_{10} from 1990 to 2008 show inhalable particles actually *increased* during our 1996–1999 study period (http://www.epa.gov/airtrends/pm.html), Insofar as fine particles are associated with gestational outcomes like birth weight and risk of low birth weight, our estimates showing an increase in birth weight as a function of gasoline formulation (that caused a decrease in atmospheric concentration of benzene) can be interpreted as conservative. Other toxins implicated in the gas reformulation program and estimated in the National Air Toxics Assessment like acetaldehyde and 1-3-butadiene (Fortin et al., 2005) are not independently correlated with birth weight outcomes. Given that both toxins are defined by the EPA as "lower confidence" pollutants (http://www.epa.gov/ttn/atw/nata1999/177poll.html), measurement error could account for this uncorrelated outcome.

Future studies will analytically profit from expected spatial and temporal improvements in the validity and reliability of atmospheric benzene data, allowing for more precise investigations of the relationship between maternal benzene exposure and birth weight outcomes. With information on date of birth and estimated gestational length, one can calculate the average or total or number of days that exceed normal levels of benzene pollution a mother is exposed to over the entire pregnancy period, or even assess the effects of maternal exposure to benzene during first, second and/or third trimester periods of gestation. Future studies can also take advantage of sudden (acute) changes in benzene levels to deepen understanding of the nature of the relationship between maternal benzene exposure and infant birth weight. With improvements in measurement of emissions, both in terms of quality and geographic scope, scholars can more precisely investigate the developmental mechanisms involved in the apparent increased risk of low birth weight from maternal exposure to benzene. Finally, future studies may consider a larger subset of risk factors, teasing out potentially meaningful interaction effects between maternal benzene exposure, prior maternal health conditions, and negative birth outcomes other than low birth weight.

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