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<http://dx.doi.org/10.1289/ehp.1510810>

Received: 28 September 2015

Accepted: 9 March 2016

Advance Publication: 29 March 2016

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Particulate Matter Exposure and Preterm Birth: Estimates of U.S. Attributable Burden and Economic Costs

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Running title: Particulate matter exposure and preterm birth

Acknowledgments: We are grateful to Gerard Carrino and Edward McCabe of the March of Dimes for insights regarding an earlier version of the manuscript.

Competing financial interests: The authors declare they have no actual or potential competing financial interests.

Abstract

Background: Preterm birth (PTB) rates (11.4% in 2013) in the United States (US) remain high and are a substantial cause of morbidity. Studies of prenatal exposure have associated particulate matter <2.5microns in diameter (PM_{2.5}) and other ambient air pollutants with adverse birth outcomes, yet, to our knowledge, burden and costs of PM_{2.5}-attributable PTB have not been estimated in the US.

Objectives: To estimate burden of PTB in the US and economic costs attributable to PM_{2.5} exposure in 2010.

Methods: Annual deciles of PM_{2.5} were obtained from US EPA. We converted PTB odds ratio (OR), identified in a previous meta-analysis (1.15 per 10µg/m³ for our base case, 1.07-1.16 for low- and high-end scenarios) to relative risk (RRs), to obtain an estimate that better represents the true relative risk. A reference level (RL) of 8.8µg/m³ was applied. We then used the RR estimates and county-level PTB prevalence to quantify PM_{2.5} attributable PTB. Direct medical costs were obtained from the 2007 Institute of Medicine report, and lost economic productivity (LEP) was estimated using a meta-analysis of PTB-associated IQ loss, and well-established relationships of IQ loss with LEP. All costs were calculated using 2010 dollars.

Results: An estimated 3.32% of PTBs nationally (corresponding to 15,808 PTBs) in 2010 could be attributed to PM_{2.5} (PM_{2.5}>8.8 µg/m³). Attributable PTBs cost were estimated at \$4.33 billion (SA: \$2.06-8.22B), of which \$760 million were spent for medical care (SA: \$362M-1.44B). The estimated PM_{2.5}-attributable fraction (AF) of PTB was highest in urban counties, with highest AFs in the Ohio valley and Southern US.

Conclusions: PM_{2.5} may contribute substantially to burden and costs of PTB in the US, and considerable health and economic benefits could be achieved through environmental regulatory interventions that reduce PM_{2.5} exposure in pregnancy.

Introduction

Preterm birth (PTB), defined as birth at <37 weeks gestation, remains a substantial cause of early life morbidity in the United States. In 2010, 35% of all infant deaths were due to preterm-related causes, with considerable disparities in rates across subpopulation (CDC 2014a). Preterm birth is recognized as a critical public health concern and, in addition, a reflection of persistent health disparities, being more prevalent among women of lower income status and from racial/ethnic minorities (Bryant et al. 2010). Although the national PTB rate in the US has declined from a peak of 12.8% in 2006 to 11.4% in 2013, the rate of decline is currently insufficient to meet the March of Dimes goal of 5.5% by 2030 (McCabe et al. 2014). Reducing rates of PTB is important not only to prevent neonatal complications such as respiratory distress syndrome, sepsis, and intraventricular hemorrhage, but also adverse psychological, behavioral, and educational outcomes in later life, mostly related to cerebral palsy and neurodevelopmental delay (Saigal and Doyle 2008). In addition, preterm babies are at higher risk of developing systemic hypertension, diabetes, and stroke later in life (Norman 2013).

While PTB, and the often associated low birth weight (LBW, <2,500 grams), are highly multifactorial (with risk factors including maternal age, prenatal care, race, socioeconomic status, and preeclampsia) (Woodruff et al. 2009), most of these risk factors are not amenable to modification or avoidance. However, environmental factors, such as outdoor air pollutants, are amenable to change, through reductions in vehicular emissions, filtration of emissions from coal-fired power plants and limits on residential use of coal and wood burning for heating and cooking (Trasande and Thurston 2005).

Though uncertainty remains about the contribution of specific outdoor air pollutants and windows of vulnerability, multiple observational studies of prenatal exposure have associated

particulate matter <2.5microns in diameter (PM_{2.5}) among other pollutants with adverse birth outcomes, most especially LBW and PTB (Darrow et al. 2009; Kloog et al. 2012; Laurent et al. 2016), although some studies did not report this association (Johnson et al. 2016). In addition, one quasi-experimental study identified reductions in PTB and LBW in association with electronic toll collection, which also reduced traffic congestion and vehicle emissions.

Further support for the notion that outdoor air pollution exposure may contribute to adverse birth outcomes is provided by laboratory experiments that document oxidant stress, inflammation and placental insufficiency as mechanisms by which air pollutants can contribute to early delivery (Institute of Medicine 2007; USEPA 2013; Woodruff et al. 2009).

A major barrier to reductions in outdoor air pollution is the perception that these reductions will undermine economic productivity (Trasande et al. 2011). As with outdoor air pollution-associated respiratory illnesses, the costs associated with adverse birth outcomes are born by society, rather than those who gain from industrial processes that emit pollutants. These include health care costs for treatment of prematurity-associated comorbidities and lost economic productivity due to PTB-associated reductions in cognitive potential. Yet, to our knowledge, estimates of the air pollution-attributable burden of preterm birth, and associated economic costs have not been made. Our primary objective was to provide an estimate of the economic costs associated with PTBs attributable to PM_{2.5} exposure (as a proxy for outdoor air pollution) in the US, estimates that could be used by decision-makers when regulatory interventions to reduce air pollution exposures are considered.

Methods

General approach

Outdoor air pollution is a complex mixture including, most notably, particulate matter <2.5 ($PM_{2.5}$) and <10 micron (PM_{10}), carbon monoxide, ozone, sulfur dioxide and nitrogen dioxide. Recognizing that each of these air pollutants may independently contribute and/or modify the effects of exposure at an individual level, this manuscript utilized $PM_{2.5}$ as a proxy for outdoor air pollution exposure, permitting use of a richer array of available measurements.

The present analysis adhered to the approach developed by the Institute of Medicine in assessing the "fractional contribution" of the environment to causation of illness, which is adapted below: (1981)

$$\text{Attributable Costs} = \text{Anthropogenic increment in preterm birth incidence} \times \text{Births} \times \text{Cost per preterm birth}$$

Because wildfires, dust storms and volcanoes contribute to outdoor air pollution, reference levels (RL) were applied. We adopted a RL of $8.8 \mu\text{g}/\text{m}^3$, and incorporated a scenario with a $5.8 \mu\text{g}/\text{m}^3$ threshold in sensitivity analyses. We chose this approach because this was the reference level applied for other health effects of $PM_{2.5}$ in the 2010 Global Burden of Disease estimates of $PM_{2.5}$ -attributable disease burden (i.e. the assumption was no health effects below this level) (Lim et al. 2012). Above the RL all $PM_{2.5}$ was considered of anthropogenic origin and an attributable fraction (AF) of 100% was applied against the increment in cases and social costs of PTBs that could specifically be attributed to $PM_{2.5}$.

Though studies have examined associations of outdoor air pollution with LBW (Woodruff et al. 2009), this also presents additional complexity in attribution in that it has two major origins

(PTB and intrauterine growth retardation, producing term-LBW), and therefore we limited our analysis to quantifying attributable PTB. In 2010, data from the US Environmental Protection Agency (US EPA) suggested that almost 124 million people in the US lived in areas in which levels of some air pollutants were higher than the limits set by the National Ambient Air Quality Standards (USEPA 2011). Specifically, for $PM_{2.5}$, the current limits set by the National Ambient Air Quality Standards are $12.0 \mu\text{g}/\text{m}^3$. This analysis estimates effects of prenatal $PM_{2.5}$ exposure on PTB occurring in the same year.

Subsequent sections describe approaches to estimating the $PM_{2.5}$ -attributable increment in PTB, the rate of prematurity, and costs.

$PM_{2.5}$ Attributable Fraction of Prematurity

We obtained daily averages of $PM_{2.5}$ in 2008 for all zip codes in the conterminous US as modeled by the EPA (USEPA 2014). Recognizing that many counties have multiple zip codes, and zip codes may cross county boundaries, we estimated daily average $PM_{2.5}$ for each county by averaging across all zip codes that comprise a portion of a given county. We then estimated deciles of $PM_{2.5}$ exposure for each county in 2008. We assumed that births were evenly distributed over the course of the year, with 10% of births experiencing pregnancy-wide exposure to $PM_{2.5}$ at the 90th percentile, and the next eight deciles of births exposed at the 80th, 70th, 60th, 50th, 40th, 30th, 20th and 10th percentiles of $PM_{2.5}$. The last decile of births was assumed to have no exposure or attributable PTB, whereas the other groups were assumed to have levels corresponding to the lowest extreme (e.g. 10th percentile for all exposure in the 10-19th percentile grouping)

The most recent meta-analysis of English-language studies (Sapkota et al. 2012) estimated an Odds Ratio (OR) for PTB of 1.15 (CI 1.14-1.16) per 10 $\mu\text{g}/\text{m}^3$ for pregnancy-wide exposure, and an OR of 1.07 (CI 1.00-1.15) per 10 $\mu\text{g}/\text{m}^3$ for third trimester exposure. In this meta-analysis, six studies contributed to the estimates for $\text{PM}_{2.5}$ and PTB; only studies that examined PTB (<37 weeks completed gestation) as the major endpoint and that reported results from single pollutant models were included. Combined estimates of the OR were calculated based on data from all studies selected using fixed and random effects models; unlike for PM_{10} , no significant heterogeneity was detected for studies that reported findings for $\text{PM}_{2.5}$. Another recent study also identified an OR of 1.16 per 10 $\mu\text{g}/\text{m}^3$ (Figure 11 of the supplementary material) for the entire pregnancy (Stieb et al. 2012). We used the OR for pregnancy-wide exposure from the most recent meta-analysis (1.15 per 10 $\mu\text{g}/\text{m}^3$) as the best estimate, but varied the OR from 1.07-1.16 in subsequent sensitivity analyses.

For each decile of births within each county, the OR from the meta-analysis was applied as a base with the exponent corresponding to the increment of the county-specific average $\text{PM}_{2.5}$ above the assumed RL (8.8 $\mu\text{g}/\text{m}^3$). The calculation is also depicted in the below formula:

$$\text{OR}_{\text{county-decile}} = \text{OR}_{\text{meta-analysis}}^{(\text{decile of county-averaged } \text{PM}_{2.5} - \text{RL})/10 \mu\text{g}/\text{m}^3}$$

Given that OR can overestimate relative risk and attributable fractions for common conditions such as PTB, we applied the formula described for estimating Relative Risk (RR) from OR and prevalence of PTB (Zhang and Yu 1998). For this calculation, county-level PTB rates for 2010 were obtained from the Centers for Disease Control and Prevention (CDC) WONDER database (CDC 2014b). Below is a numeric example to illustrate how RR was derived for Autauga county (Alabama):

First, we calculated the corresponding OR for each decile of exposure above the lowest decile. For example, using an OR of 1.15 (base case) for a $10 \mu\text{g}/\text{m}^3$ increase $\text{PM}_{2.5}$ and a RL of $8.8 \mu\text{g}/\text{m}^3$, the OR for the decile of births with the highest $\text{PM}_{2.5}$ exposure would be estimated as $\text{OR} = 1.15^{((19.35-8.8)/10)} = 1.16$, where $19.35 \mu\text{g}/\text{m}^3$ is the $\text{PM}_{2.5}$ concentration of the 90th percentile of the distribution for the county. Similarly, for the $\text{PM}_{2.5}$ concentration related to second lowest decile (20th) of average daily exposure for Autauga county ($8.06 \mu\text{g}/\text{m}^3$), $\text{OR} = 1.15^{((8.06-8.8)/10)} = 1.00$. Since this decile has $\text{PM}_{2.5}$ concentration less than the RL, the corresponding estimated OR of 1 indicates no increase in risk and, therefore, the corresponding decile of births is assumed to have no PTBs attributable to $\text{PM}_{2.5}$.

After deriving ORs for each decile, we use the formula by Zhang and Yu to estimate the RR for each decile, such that $\text{RR} = 1.16 / ((1 - 0.15) + (0.15 * 1.16)) = 1.13$, where 0.15 is the PTB rate in that specific county. The range of RRs derived using these calculations was 1.06 -1.18 (low-high scenarios).

Next, we compute the attributable fraction of PTB for outdoor air pollution for each decile, using the formula published by Levin, (Levin 1953):

$$\text{AF}_{\text{PM}_{2.5}, \text{county-decile}} = \text{Prevalence}_{\text{PM}_{2.5}\text{exposure}} \times (\text{RR}_{\text{county-decile}} - 1) / [1 + \text{Prevalence}_{\text{PM}_{2.5}\text{exposure}} \times (\text{RR}_{\text{county-decile}} - 1)]$$

Where the exposure prevalence is set to 10% for each decile. For example, for the highest decile of exposure in Autauga county (Alabama), $\text{AF} = (0.1 * (1.13 - 1)) / (1 + (0.1 * (1.13 - 1))) = 0.013$.

Finally, we sum the AF for each decile (e.g. for Autauga county, the sum was 0.04), and multiply the resulting value by estimated number of preterm births for each county, as shown below:

Cases of preterm births attributable to $PM_{2.5} = 0.04 * 99.6 = 3.96$, where 99.6 is the estimated number of preterm births in Autauga county. When aggregating AFs for each decile, a value of zero was assigned for AFs related to $PM_{2.5}$ deciles below the RL ($8.8 \mu\text{g}/\text{m}^3$), so that no cases of PTBs were attributed to those deciles of exposure.

Population at Risk

Births in each county were obtained from the CDC WONDER database, as were county-level PTB rates (CDC 2014b), and multiplied together to calculate the number of preterm births in a county in 2010. For counties with population <100,000 the number of births was estimated by taking the reported number of births across all these counties in each state and multiplying by the ratio of the county population to the total population of all counties with population <100,000 from US Census data. In addition, for these counties, the overall PTB rate of 0.15 was applied. The number of preterm births in each county was multiplied by the AF for each county to estimate the number of $PM_{2.5}$ -attributable premature births in 2010. Attributable PTBs in each county were aggregated to generate national estimates of attributable PTB.

Estimates of $PM_{2.5}$ -attributable social costs

Two direct costs of PTB were estimated: costs for treatment of PTB-associated medical conditions in the first five years of life, and costs after the first five years of life due to PTB-associated developmental disability. The direct health care costs in the first five years of life (estimated at \$31,920) were obtained from the 2007 Institute of Medicine report on premature birth (Institute of Medicine 2007). Costs were also updated to 2010 dollars using the Medical Care Consumer Price Index (US Department of Labor Bureau of Labor Statistics 2014), and discounted five years at 3%/year to account for the expenses' occurrence in the future. A similar approach was taken with health care costs after the first five years of life due to PTB-associated

developmental disability (estimated at \$1,920), except they were discounted by 3% for fifteen years due to their occurrence further in the future.

Lost economic productivity due to reduced cognitive potential was also measured as an indirect cost of PM_{2.5}-attributable PTB. PTB-associated IQ loss was calculated, using data from a systematic review that estimates a 11.9 point IQ decrement on average in PTB children (95% CI: 10.5–13.4) (Kerr-Wilson et al. 2012). The loss in IQ was estimated by multiplying attributable PTB by the 11.9 IQ decrement, and the lost lifetime economic productivity was estimated by multiplying the IQ loss by 2%, which corresponds to the base case (range 1.76 - 2.39%) described by Grosse et al. (Grosse et al. 2002), also used in previously published analyses (Trasande and Liu 2011), and the lifetime earnings estimate for a child born in 2010 (Max 2013). As with direct costs, all indirect costs are presented in 2010 dollars.

Sensitivity Analyses

Recognizing uncertainty in the exposure-outcome relationship and RL, we performed sensitivity analyses. A range of ORs corresponding to different pregnancy-wide and third-trimester specific ORs (1.07-1.16) identified by the meta-analyses examining air pollution-PTB associations (Sapkota et al. 2012; Stieb et al. 2012) was used to represent sensitivity of the model to the nature of the exposure-outcome relationship. An alternative scenario with RL of 5.8 µg/m³ was also examined.

Results

We examined 3,963,694 live births in the 48 contiguous United States, of which 475,368 (12%) were preterm births (Table 1). Applying the base case OR of 1.15 per 10 µg/m³ increment in PM_{2.5} and the reference level of 8.8 µg/m³, a median RR of 1.0031 was identified (IQR 1.000-

1.045; min 1.00, max 1.35) with 63.4% of births having $RR > 1$ (Table 2). We estimated that, across the 48 states, 3.32% of all preterm births in 2010 were attributable to $PM_{2.5}$ (15,808; sensitivity analysis using ORs of 1.07 and 1.16: 7,532-29,968). These estimated numbers of attributable preterm births cost \$760 million in medical care (sensitivity analysis: \$362 million-1.44 billion), and \$4.33 billion (sensitivity analysis: \$2.06-8.22 billion) in lost economic productivity was also identified (based on estimated reductions in IQ and estimated consequences for productivity over a lifetime). In total, we estimated that \$5.09 billion in preterm birth-related costs (medical care costs and lost economic productivity combined) could be attributed to $PM_{2.5}$, with the sensitivity analysis producing a range in those costs of \$2.43-9.66 billion.

Substantial variability in estimated attributable fraction and preterm births was identified at the state level in base case analyses. In Ohio, the attributable fraction was highest (5.44%), while only 0.12% of preterm births were attributable to $PM_{2.5}$ in New Mexico and Wyoming. California had the largest number of attributable preterm births (2,149) and costs (\$692 million) in base case analyses (Table 3).

At the county level, the variability in attributable preterm births was greater than at the state level, as presented in Figure 1 and detailed in Table 3, which indicates a range of 0.12% to 5.44%. The $PM_{2.5}$ - AF of PTB was generally higher in major urban regions. Consistent with the state level results, the highest AFs (>5%) were identified in the Ohio valley, the southern US, southern California, southeastern Pennsylvania, New York City and Chicago.

Discussion

The main finding of this analysis suggests that exposure to PM_{2.5} contributes significantly to preterm birth in the US and translates into substantial economic loss over a lifetime. To our knowledge, this is the first time that such economic estimates are reported, and suggest that considerable health and economic benefits can be gained through reductions in outdoor air pollution exposure in pregnancy.

Exposure to PM_{2.5} has been associated with PTB in a number of studies, although with variable results, as highlighted in the meta-analysis by Stieb and colleagues (Stieb et al. 2012). This meta-analysis included a total of 62 studies, and reported substantial heterogeneity between studies, as well as variability in risk by gestational period. Of note, one quasi-experimental (not observational) study identified reductions in PTB and LBW in association with electronic toll collection, which also reduced traffic congestion and vehicle emissions (Currie and Walker 2011). Studies to date have applied different methodological approaches to exposure and outcome assessment, and have been conducted in many regions of the world where air pollution composition may vary, accounting for differential effects (Woodruff et al. 2009). This is especially true for PM_{2.5}, which is a complex mixture of different chemicals, and may contribute to explaining the variable results obtained in these studies, with different mixtures leading to different outcomes (Harris et al. 2014), also depending on specific windows of exposure (Rappazzo et al. 2014). In addition, differences in population susceptibility most likely contribute to the observed variability.

We used 5.8-8.8 µg/m³ as reference levels, following the approach used by the 2010 Global Burden of Disease collaborators (Lim et al. 2012). These levels can be considered minimum achievable levels of PM_{2.5} insofar as anthropogenic sources can be limited, and no safe level of PM_{2.5} exposure has been identified. The estimated 15,808 preterm births can be considered

preventable through strategies to reduce PM_{2.5} exposure, though future work can model reductions due to changes in vehicular and other emissions insofar as the impact of regulatory and other interventions as counterfactuals, so as to inform cost-benefit and other regulatory impact analyses.

In our analysis we estimated loss of IQ related to preterm birth and its impact on earning potential, which can be considered the result of direct effects, such as lower cognitive capacities, and indirect effects due to diminished educational achievements and reduced ability to work (Grosse et al. 2002). Estimating and aggregating at national level the economic costs associated with PM_{2.5}-attributable preterm births provide a sense of the potential economic benefits that could be achieved by regulatory interventions aimed at reducing air pollution exposure during pregnancy. In addition, long-term health issues associated with preterm birth that prevent individuals from working translates into increased government expenditures for programs such as Supplemental Security Income, further adding to the economic costs shouldered by society as a whole (Perrin et al. 2007). Last but not least, it is important to consider that PTB also places an important emotional and psychological burden on parents and families, which, although non-financial, needs to be taken into account when considering the benefits that could be achieved by such regulatory interventions.

Limitations

There are important limitations to the interpretation of our findings. The specific components of outdoor air pollution that contribute to prematurity and other adverse birth outcomes remain elusive, as do the mechanisms by which they produce effects. While it is true that some studies to date have failed to find significant associations with adverse outcomes, exposure imprecision

may have biased those estimates (Fleiss and Shrouf 1977); others may have had modest statistical power to detect significant differences in prematurity. Therefore, some may argue that the scientific evidence for air pollution has not reached the threshold for causation. We take heed of Sir Austin Bradford Hill's landmark treatise on criteria for causation, in which he raises the need to consider the decision at hand in weighing the strength of the scientific evidence: "On fair evidence we might take action on what appears to be an occupational hazard...without too much injustice if we are wrong" (Hill 1965). More recently, we have developed methods to estimate probability of causation for diseases attributable to endocrine disrupting chemicals (Trasande et al. 2015). While the scope of the present analysis was limited and we did not formally evaluate the epidemiologic and toxicologic evidence, the evidence for air pollution and its effects on fetal growth are of similar strength to many of the exposure-outcome relationships considered in this more recent work. The evidence for causation of preterm births by outdoor air pollutants is strong, although not uniform, in that multiple observational studies have identified significant relationships, as evidenced in some of the most recent meta-analyses (Sapkota et al. 2012; Stieb et al. 2012). Though studies have not always yielded identical results, the findings in humans are consistent with those in the laboratory. These support the estimation of disease burden and costs as presented here, though we have not estimated a probability of causation as others have pursued in the presence of uncertainty (Trasande et al. 2015).

Models are also only as good as their inputs. Stationary monitor sites do not take into account variation in personal exposure levels, variations in $PM_{2.5}$ levels within the geographical area monitored by each site, or changes in residence during pregnancy. Data for ultrafine PM were not available, even though this form may pose a greater risk of adverse birth outcomes than $PM_{2.5}$. $PM_{2.5}$ measurements were estimated at the county level, and insofar as pregnancies are

not evenly distributed by outdoor air pollution, our approach introduces some imprecision. We also estimated attributable PTB assuming homogeneity in the PTB rate across small population counties, which may have added imprecision in county-level estimates. We did not consider effects on maternal health, or possible stillbirths and birth defects that are plausible although less supported by the literature (Woodruff et al. 2009).

Air pollution exposures over the period January-December 2008 can be expected to influence a broad period of pregnancies spanning at least nine months later, with birth dates spanning September 2008-August 2009 and most births in 2009. We acknowledge some imprecision in selecting the 2010 birth year to extrapolate disease burden. In part, the intention was to bring estimates in line with other environmentally related disease burden estimates which use 2010 year as a base (Trasande et al. 2015), and ensure comparability. Our decision was supported by the relative lack of changes between mean PM 2.5 between 2009 and 2010 (USEPA 2011).

We also note that we examine PTB as a categorical outcome, when shifts in gestational age are more likely to occur due to PM_{2.5}. Insofar as gestational age is not normally distributed, estimated PM_{2.5}-induced shifts in gestational age may potentially result in larger effects on PTB than the estimates we modeled here. PTB data from CDC are also based on last menstrual period, when the definition is changing to clinically-based obstetric estimates. A substantial literature suggests misclassification in both directions, with generally estimates based on last-menstrual period producing higher PTB rates (Hall et al. 2014; Qin et al. 2007), and so our methodology may have produced modestly higher estimates than that obtained using clinically-derived PTB data.

Conclusions

Our estimates suggest that PM_{2.5} may contribute substantially to burden and costs of PTB in the US. Because of the widespread exposure to PM_{2.5}, considerable health and economic benefits could be achieved through regulatory interventions that reduce such exposure in pregnancy. Furthermore, the differential impact of air pollution by socio-economic status and race/ethnicity, as suggested by current evidence (Bryant et al. 2010), underscores the importance of regulatory actions aimed at reducing exposure, since these may also reduce the well-known and long-standing disparities in preterm births.

References

1981. Institute of Medicine. Costs of Environment-Related Health Effects. Washington DC: National Academy Press.

Bryant AS, Worjloh A, Caughey AB, Washington AE. 2010. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *Am J Obstet Gynecol* 202:335-343.

CDC. 2014a. Preterm Birth. Available at <http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm> (Accessed 7 July 2015).

CDC. 2014b. Natality Information, Live Births. Available at <http://wonder.cdc.gov/natality.html> (Accessed 13 January 2015).

Currie J, Walker R. 2011. Traffic Congestion and Infant Health: Evidence from E-ZPass. *Am Econ J-Appl Econ* 3:65-90. Available at <http://www.nber.org/papers/w15413.pdf>.

Darrow LA, Klein M, Flanders WD, Waller LA, Correa A, Marcus M, et al. 2009. Ambient air pollution and preterm birth: a time-series analysis. *Epidemiology* 20:689-698.

Fleiss JL, Shrout PE. 1977. The effects of measurement errors on some multivariate procedures. *American journal of public health* 67:1188-1191.

Grosse SD, Matte TD, Schwartz J, Jackson RJ. 2002. Economic Gains Resulting from the Reduction in Children's Exposure to Lead in the United States. *Environmental Health Perspectives* 110:563-569.

Hall ES, Folger AT, Kelly EA, Kamath-Rayne BD. 2014. Evaluation of gestational age estimate method on the calculation of preterm birth rates. *Matern Child Health J* 18:755-762.

Harris G, Thompson WD, Fitzgerald E, Wartenberg D. 2014. The association of PM(2.5) with full term low birth weight at different spatial scales. *Environ Res* 134:427-434.

Hill A. 1965. The Environment and Disease: Association or Causation? *Proc R Soc Med* 58:295-300.

Institute of Medicine. 2007. *Preterm Birth: Causes, Consequences, and Prevention*. Washington (DC):National Academies Press.

Johnson S, Bobb JF, Ito K, Savitz DA, Elston B, Shmool JL, et al. 2016. Ambient Fine Particulate Matter, Nitrogen Dioxide, and Preterm Birth in New York City. *Environ Health Perspect*.

Kerr-Wilson CO, Mackay DF, Smith GCS, Pell JP. 2012. Meta-analysis of the association between preterm delivery and intelligence. *Journal of Public Health* 34:209-216.

Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. 2012. Using new satellite based exposure methods to study the association between pregnancy PM(2).(5) exposure, premature birth and birth weight in Massachusetts. *Environmental health : a global access science source* 11:40.

Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. 2016. A Statewide Nested Case-Control Study of Preterm Birth and Air Pollution by Source and Composition: California, 2001-2008. *Environ Health Perspect*.

Levin M. 1953. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* 9:531-541

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2224-2260.

Max W. 2013. Present Value of Lifetime Earnings, 2009. Unpublished tables, Institute for Health and Aging, University of California, San Francisco.

McCabe ER, Carrino GE, Russell RB, Howse JL. 2014. Fighting for the next generation: US Prematurity in 2030. *Pediatrics* 134:1193-1199.

Norman M. 2013. Preterm birth and the shape of the heart. *Circulation* 127:160-161.

Perrin JM, Bloom SR, Gortmaker SL. 2007. The increase of childhood chronic conditions in the United States. *JAMA* 297:2755-2759.

Qin C, Dietz PM, England LJ, Martin JA, Callaghan WM. 2007. Effects of different data-editing methods on trends in race-specific preterm delivery rates, United States, 1990-2002. *Paediatr Perinat Epidemiol* 21 Suppl 2:41-49.

Rappazzo KM, Daniels JL, Messer LC, Poole C, Lobdell DT. 2014. Exposure to fine particulate matter during pregnancy and risk of preterm birth among women in New Jersey, Ohio, and Pennsylvania, 2000-2005. *Environ Health Perspect* 122:992-997.

Saigal S, Doyle LW. 2008. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 371:261-269.

Sapkota A, Chelikowsky A, Nachman K, Cohen A, Ritz B. 2012. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Qual Atmos Health* 5:369-381.

Stieb DM, Chen L, Eshoul M, Judek S. 2012. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. *Environmental Research* 117:100-111.

Trasande L, Thurston GD. 2005. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol* 115:689-699.

Trasande L, Liu Y. 2011. Reducing The Staggering Costs Of Environmental Disease In Children, Estimated At \$76.6 Billion In 2008. *Health Affairs* 30:863-870.

Trasande L, Massey RI, DiGangi J, Geiser K, Olanipekun AI, Gallagher L. 2011. How developing nations can protect children from hazardous chemical exposures while sustaining economic growth. *Health Aff (Millwood)* 30:2400-2409.

Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, et al. 2015. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab* 100:1245-1255.

US Department of Labor Bureau of Labor Statistics. 2014. Consumer Price Index, Medical Care. Available: <http://data.bls.gov/cgi-bin/surveymost?cu> [accessed 8 May 2014].

USEPA. 2011. Our Nation's Air - Status and Trends through 2010. Available at <http://www.epa.gov/airtrends/2011/> (accessed 13 August 2015).

USEPA. 2013. Integrated Science Assessment of Ozone and Related Photochemical Oxidants
(Final Report). Available at

<http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492#Downloaddeid=247492#Download>

(Accessed 12 March 2014).

USEPA. 2014. Fused Air Surfaces Using Downscaling. Available at

http://www.epa.gov/esd/land-sci/lcb/lcb_faqs.html (Accessed 13 January 2015).

Woodruff TJ, Parker JD, Darrow LA, Slama R, Bell ML, Choi H, et al. 2009. Methodological issues in studies of air pollution and reproductive health. *Environmental Research* 109:311-320.

Zhang J, Yu KF. 1998. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 280:1690-1691.

Table 1. Live Births and Preterm Births in the 48 US States examined

Parameter	Value
Total Births, 48 contiguous US states, 2010	3,963,694
Preterm Births, 48 contiguous US states, 2010 (%)	475,368 (12.0%)
Reference Level, Base Case (Sensitivity Analysis)	8.8 mcg/m ³ (5.8) ^a
Odds Ratio per 10 mcg/m ³ above Reference Level (Sensitivity Analysis)	1.15 (1.07-1.16)

^a For sensitivity analysis, a scenario with a 5.8 µg/m³ threshold was also used, above which all PM_{2.5} was considered of anthropogenic origin and an environmentally attributable fraction of 100% was applied.

Table 2. Estimated Economic Costs of PM_{2.5}-attributable Preterm Births

Parameter	Base Scenario ^a	Low Scenario ^a	High Scenario ^a
Range of Relative Risks	1.000-1.352	1.000-1.159	1.000-1.429
Median Relative Risk (IQR) ^b	1.003 (1.000-1.045)	1.002 (1.000-1.021)	1.043 (1.011-1.089)
Percentage with RR above 1 (RR=1 indicates risk unchanged)	63.4%	63.4%	91.7%
Attributable Fraction	3.32%	1.58%	6.30%
Attributable Preterm Births	15,808	7,532	29,968
Lost Economic Productivity, PM _{2.5} -Attributable Preterm Births ^c	\$4.33 billion	\$2.06 billion	\$8.22 billion
Additional Medical Care, PM _{2.5} -Attributable Preterm Births ^d	\$760 million	\$362 million	\$1.44 billion
Total Costs, PM_{2.5}-Attributable Preterm Births	\$5.09 billion	\$2.43 billion	\$9.66 billion

^a Base scenario estimates are based on OR of 1.15; low and high scenario estimates are based on OR 1.07 and 1.16, respectively. For calculations, please see methods section.

^b Median RR estimated using the MEDIAN function in excel.

^c Lost economic productivity due to reduced cognitive potential was measured as an indirect cost of PM_{2.5}-attributable PTB. PTB-associated IQ loss was calculated, using data from a systematic review that estimates a 11.9 point IQ decrement on average in PTB children (95% CI: 10.5–13.4). See methods section.

^d Two types of direct costs of PTB were estimated: costs for treatment of PTB-associated medical conditions in the first five years of life, and costs after the first five years of life due to PTB-associated developmental disability. See methods section.

Table 3. Results by State for a 10- $\mu\text{g}/\text{m}^3$ increment in $\text{PM}_{2.5}$ Above the Reference Level of 8.8 $\mu\text{g}/\text{m}^3$ (Base Case Estimates).

State	Estimated Attributable Fraction	Estimated Attributable Preterm Births	Estimated Attributable Lost Lifetime Economic Productivity	Estimated Attributable Medical Care Costs
Alabama	4.31%	404	\$110 million	\$19.4 million
Arizona	0.58%	61	\$16.8 million	\$2.95 million
Arkansas	3.18%	156	\$42.8 million	\$7.50 million
California	4.27%	2149	\$589 million	\$103 million
Colorado	0.43%	31	\$8.50 million	\$1.49 million
Connecticut	2.87%	112	\$30.6 million	\$5.36 million
Delaware	4.70%	68	\$18.8 million	\$3.29 million
Florida	0.87%	249	\$68.4 million	\$12.0 million
Georgia	5.17%	950	\$260 million	\$45.7 million
Idaho	0.90%	22	\$5.92 million	\$1.04 million
Illinois	4.87%	976	\$268 million	\$46.9 million
Indiana	5.40%	532	\$146 million	\$25.6 million
Iowa	2.94%	132	\$36.1 million	\$6.32 million
Kansas	2.63%	113	\$31.1 million	\$5.44 million
Kentucky	4.62%	354	\$97.1 million	\$17.0 million
Louisiana	2.32%	218	\$59.8 million	\$10.5 million
Maine	0.85%	11	\$2.94 million	\$515,000
Maryland	4.67%	438	\$120 million	\$21.1 million
Massachusetts	2.44%	190	\$52.2 million	\$9.15 million
Michigan	3.81%	533	\$146 million	\$25.6 million
Minnesota	2.46%	172	\$47.1 million	\$8.26 million
Mississippi	2.65%	187	\$51.2 million	\$8.97 million
Missouri	3.48%	323	\$88.5 million	\$15.5 million
Montana	0.33%	5	\$1.31 million	\$229,000
Nebraska	1.64%	48	\$13.3 million	\$2.33 million
Nevada	0.57%	28	\$7.76 million	\$1.36 million

New Hampshire	1.61%	19	\$5.31 million	\$931,000
New Jersey	3.95%	490	\$134 million	\$23.6 million
New Mexico	0.12%	4	\$1.05 million	\$185,000
New York	3.67%	1032	\$283 million	\$49.6 million
North Carolina	4.23%	658	\$181 million	\$31.6 million
North Dakota	0.44%	4	\$1.21 million	\$211,000
Ohio	5.44%	924	\$253 million	\$44.4 million
Oklahoma	2.47%	182	\$50.0 million	\$8.77 million
Oregon	1.63%	74	\$20.2 million	\$3.55 million
Pennsylvania	5.04%	819	\$224 million	\$39.4 million
Rhode Island	1.99%	24	\$6.59 million	\$1.16 million
South Carolina	3.88%	321	\$87.9 million	\$15.4 million
South Dakota	0.87%	12	\$3.21 million	\$563,000
Tennessee	4.17%	425	\$116 million	\$20.4 million
Texas	2.47%	1251	\$342 million	\$60.1 million
Utah	1.70%	97	\$26.5 million	\$4.65 million
Vermont	1.12%	6	\$1.61 million	\$282,000
Virginia	3.71%	444	\$122 million	\$21.4 million
Washington	1.12%	98	\$26.9 million	\$4.71 million
West Virginia	4.62%	114	\$31.4 million	\$5.50 million
Wisconsin	3.85%	286	\$78.4 million	\$13.7 million
Wyoming	0.12%	1	\$264,000	\$46,400
District of Columbia	4.73%	59	\$16.2 million	\$2.84 million

Base case scenario refers to OR of 1.15 per 10 $\mu\text{g}/\text{m}^3$ increment in $\text{PM}_{2.5}$ and the reference level of 8.8 $\mu\text{g}/\text{m}^3$.

Estimated Attributable Fraction: the fraction of PTBs attributable to outdoor air pollution

Estimated Attributable Preterm Births: estimated number of PTBs attributable to outdoor pollution

Estimated Attributable Lost Lifetime Economic Productivity: PTB-associated IQ loss resulting in lost economic productivity

Estimated Attributable Medical Care Costs: costs for treatment of PTB-associated medical conditions in the first five years of life and costs after the first five years of life due to PTB-associated developmental disability

Figure Legend

Figure 1. Fraction of Preterm Birth Attributable to Air Pollution, county level data.

Notes: Births in each county were obtained from the CDC WONDER database, as were county-level PTB rates, and multiplied together to calculate the number of preterm births in a county in 2010. For counties with population <100,000, the overall rate (0.15) for those counties was applied. The number of preterm births in each county was multiplied by the AF for each county to estimate the number of PM_{2.5}-attributable premature births in 2010. Source for PM_{2.5} data: US Environmental Protection Agency.

Figure 1.

