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ABSTRACT: Preterm birth (PTB) is a predictor of infant mortality and later-life morbidity. Despite recent declines, PTB rates remain high in the United States. Growing research suggests a relationship between a mother's exposure to air pollution and PTB of her baby. Many policy actions to reduce exposure to common air pollutants require benefit-cost analysis (BCA), and it's possible that PTB will need to be included in BCA in the future. However, an estimate of the willingness to pay (WTP) to avoid PTB risk is not available, and a comprehensive alternative valuation of the health benefits of reducing pollutant-related PTB currently does not exist. This paper demonstrates a potential approach to assess economic benefits of reducing PTB resulting from environmental exposures when an estimate of WTP to avoid PTB risk is unavailable. We utilized a recent meta-analysis and county-level air quality and PTB data to estimate the potential health and economic benefits of a reduction in air pollution-related PTB, with fine particulate matter ($PM_{2.5}$) as our case study pollutant. Using this method, a simulated 10% decrease from 2008 $PM_{2.5}$ levels resulted in a reduction of 5,016 PTBs and savings of at least $339 million, potentially reaching over one billion dollars when considering later-life effects of PTB.

KEYWORDS: air pollution, preterm birth, benefits, $PM_{2.5}$

JEL CODES: D61, I18, J13, Q51, Q53

Preterm Birth and Economic Benefits of Reduced Maternal Exposure to Fine Particulate Matter[*†]

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Introduction

Preterm birth (PTB), or birth before 37 weeks of gestation, is a leading predictor of infant mortality [1] and an important contributor to later-life disease and disability [2]. Prior analysis suggests that the relatively high rate of infant mortality [3] in the United States (U.S.) may largely be due to a high PTB rate, and decreasing the PTB rate could thereby significantly reduce infant mortality in the U.S. [4]. Research is also increasingly linking PTB to a broad array of childhood and later-life health outcomes, including neurodevelopmental, respiratory, digestive, immunological, and cardiovascular problems [2].

A growing body of evidence suggests a relationship between a mother's exposure to environmental contaminants during pregnancy and PTB of her baby [5-7]. The most extensive evidence of this relationship is for ambient air pollution. "Criteria air pollutants" are six pollutants —carbon monoxide, lead, nitrogen dioxide, ozone, particulate matter (PM), and sulfur dioxide—commonly found across the U.S. for which the Clean Air Act requires the U.S. Environmental Protection Agency (EPA) to set National Ambient Air Quality Standards (NAAQS).

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EPA currently considers existing evidence to be suggestive of a causal relationship between exposure to five of the six criteria pollutants and reproductive, developmental, and/or birth outcomes [8-12]. The potential relationship between criteria pollutants and PTB is especially concerning because a) by nature of the common presence of criteria pollutants, exposure is often unavoidable; and b) a disproportionate burden of exposure may be placed on individuals in disadvantaged communities, who are already subjected to multiple socioeconomic and health inequities [13-18].

Regulations promulgated under the Clean Air Act to limit or reduce exposure to criteria pollutants are subject to many requirements by statute, executive order (EO), and EPA policy. Though benefit-cost analysis (BCA) for setting primary NAAQS is not required by the Clean Air Act, it has been required for economically significant regulations—those with an annual effect on the economy of $100 million or more—by a series of executive orders dating back to 1981. As such, BCA has typically been conducted when setting primary NAAQS and for other economically significant rulemakings affecting emissions of criteria pollutants or their precursors.

Estimating human health benefits of reducing any exposure requires health risks to be quantified and then valued in monetary terms, but data limitations, as well as analytic choices in risk assessment, often preclude full quantification and valuation [19]. The lack of quantification for many health outcomes, including adverse birth outcomes such as PTB, poses a challenge for conducting complete BCAs of reducing harmful environmental exposures. Additionally, the preferred valuation measure for BCA is willingness to pay (WTP) for risk reduction, defined as the maximum amount of income one would give up to obtain reduction in

risk to one's health. In principle, WTP for reduced risk reflects the full set of health consequences associated with a given risk reduction, but many health effects, including PTB, lack an estimate of WTP in the economics literature [20]. An alternative, less comprehensive valuation approach is to focus on the costs avoided from expected reduced incidence in the population. This requires an estimate of the direct and indirect costs associated with PTB, such as incremental costs from birth hospitalization and medical care in infancy, special education, lost wages or productivity, and later-life health complications [21]. However, few studies exist on the economic costs of PTB, particularly those considering costs past the neonatal time period. These issues hinder identifying and adopting the most efficient or cost-effective policies and have been recognized by the Institute of Medicine (IOM), which, in its 2007 report on PTB, recommended investigation into the economic consequences of PTB in order to better evaluate policies for its prevention and treatment.

To date, EPA has not included PTB in any BCA. EPA practice for benefits analysis of criteria pollutant regulations is to consider for inclusion those effects with evidence judged to be "causal" or "likely causal." EPA's most recent Integrated Science Assessment (ISA) of PM, published in 2009, reported that the evidence for reproductive and developmental outcomes overall, including PTB, low birth weight, birth defects, and infant mortality, was suggestive of a causal relationship. However, the limited studies specifically examining fine particulate matter ($PM_{2.5}$) and PTB mostly reported statistically significant positive associations [8]. Newer studies of $PM_{2.5}$ and PTB published since 2008 will be considered in an updated ISA that is projected to be completed in 2019 [22]. With the developing evidence for environmental contaminants—especially air pollution—and PTB, it may be warranted to include PTB in a BCA in coming years.

How this would be done, however, is not immediately apparent, because of the aforementioned data limitations and complications regarding the many potential health outcomes also related to PTB.

This study outlines a framework and methodology to examine the potential economic benefits arising from reducing PTBs resulting from environmental exposures. To illustrate the process, environmental exposures of interest were first narrowed down to criteria pollutants because a) there is widespread human exposure to them, indicating high potential benefits of reducing PTB associated with criteria pollutant exposure; b) with rapid growth of the literature in recent years, there are now many studies of criteria pollutants and PTB, including meta-analyses; and c) well-established tools and methods for benefits analysis of these pollutants are available. We present a case study of maternal exposure to $PM_{2.5}$ to demonstrate a proposed approach to estimating the potential health and economic benefits of reducing pollutant-related PTB.

Methods

Overview. Quantification of $PM_{2.5}$-related PTB reduction and associated economic benefits entailed the following:

1) Calculation of the reduction in number of PTB cases attributable to a chosen air quality improvement via decreased ambient $PM_{2.5}$ levels; and
2) Valuation (monetization) of immediate and later-life consequences of the PTB cases derived above.

Primary Analysis: Calculation of Reduced Cases and Immediate Benefits in BenMAP

The Environmental Benefits Mapping and Analysis Program – Community Edition (BenMAP-CE or BenMAP) is an EPA computer program that quantifies and monetizes the health impacts of air pollution. BenMAP integrates exposure, population, and health data across a given space and enables translation of a health effect estimate into risk per increment of exposure [23]. Because BenMAP does not include data for Alaska or Hawaii, this analysis is for the contiguous U.S., and any mention of U.S. or national data or analyses in this paper hereafter refers to the contiguous U.S. This study utilized BenMAP to estimate the potential PTB benefits of a reduction of ambient concentrations of county-level $PM_{2.5}$ nationwide.

The impact of the air quality change on PTB was calculated within BenMAP by specifying the input factors seen in equation (1), the logistic health impact function used for this study, where y is the annual reduction in PTBs; y_0 is the annual baseline prevalence rate of PTB; β is the coefficient relating $PM_{2.5}$ and PTB; $\Delta PM_{2.5}$ is the simulated change in $PM_{2.5}$ concentration; $population$ is the number of women ages 15 to 44; and $fertility\ rate$ is the number of live births per year per woman ages 15 to 44.

$$\boldsymbol{y = y_0 \cdot \left[1 - \frac{1}{(1 - y_0) \cdot e^{\beta \cdot \Delta PM_{2.5}} + y_0}\right] \cdot population \cdot fertility\ rate} \qquad (1)$$

Health impact and valuation results were first calculated at the county level and then aggregated to provide state-level and national estimates.

Exposure. Daily 24-hour mean $PM_{2.5}$ measurements reported to the EPA Air Quality System from ambient air monitoring stations were used to estimate baseline county-level air quality.

BenMAP uses the Voronoi Neighborhood Averaging (VNA) method to interpolate multiple stationary monitor point values to a county-wide air quality estimate [24]. The VNA method calculates an inverse-distance weighted average of the monitors surrounding a county's center to represent the county's overall $PM_{2.5}$ level. (Predicted estimates tend to be less reliable in rural or remote areas due to fewer monitors being present [25, 26]. These data inherently represent smaller populations with few to no alternative measurements available, and measurement error was expected to be negligible for the purposes of this study). $PM_{2.5}$ measurements were taken from approximately 1,000 monitors in 2008, the most recent year for which EPA provided BenMAP-compatible air quality data at the time of this study. For this analysis, we simulated a 10% decrease in 2008 annual average county-level $PM_{2.5}$ concentrations across the country [27].

Population and fertility rate. The population of interest was women in the U.S. ages 15 to 44. Population data were programmed within BenMAP and originally derived from and predicted based on U.S. Census data [28]. The Centers for Disease Control and Prevention (CDC) defines fertility rate as the number of births per woman ages 15 to 44 in a given year [29]. Multiplying the population of women ages 15 to 44 by fertility rate yielded a unit of all births, or the denominator of the prevalence rate. All data were 1) at the county level and 2) from 2008 to match the most recent BenMAP-compatible air quality data.

Baseline prevalence rates. The numbers of PTBs and all births in each county were obtained from CDC WONDER for 2008. County-level baseline prevalence rates ($\boldsymbol{y_0}$) were calculated as all PTBs divided by all births in each county. The PTB and all birth values for any counties with a population of less than 100,000 in a given state were grouped together in CDC WONDER as

"Unidentified Counties" of the state. Any data representing a county with fewer than 10 births were suppressed in CDC WONDER. To represent rates for unidentified counties or counties with suppressed data, the statewide rates from the grouped Unidentified Counties were used.

Health impacts. The β coefficient of the health impact function relating $PM_{2.5}$ and PTB was derived from a 2015 meta-analysis by Sun et al. [7] of studies measuring the association between $PM_{2.5}$ and PTB. Sun et al. 2015 included 18 studies conducted mostly in North America, Europe and Australia, overall totaling over three million study participants. Effect estimates from each study were extracted and converted to regression coefficients per 10 $\mu g/m^3$ increase in $PM_{2.5}$ to obtain a pooled estimate. The authors reported results for PTB as pooled odds ratios (ORs) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ for varying exposure periods, exposure assessment methods, and study types. Thirteen of the aforementioned 18 studies included exposure data for the entire pregnancy. The pooled OR for maternal exposure to $PM_{2.5}$ during the entire pregnancy, derived from these 13 studies, was 1.13 (95% confidence interval (CI): 1.03, 1.24). We converted the central estimate of this pooled OR to a logistic regression β coefficient of 0.012 relating risk per 1 $\mu g/m^3$ increase in $PM_{2.5.}$ by using the general formula $\boldsymbol{ln(OR) = \beta \cdot \Delta PM_{2.5}}$ as illustrated in the BenMAP User Manual Appendices [30].

Economic valuation. The monetized benefits of the reduction in PTB resulting from the simulated air quality improvement were calculated within BenMAP, which applies a given valuation function to the cases of PTB calculated by the health impact function. Ideally, the analysis would employ a WTP value for reduced risk of PTB that would account not just for medical costs and lost productivity, but for all or most of the expected consequences associated with PTB, including long-term health consequences and any intangible effects on quality of life.

However, no such estimates exist in the economics literature. A second-best valuation strategy, which we adopt here, is to first estimate the immediate or early-life cost of illness (COI) associated with PTB and then to add the present value of costs associated with longer-term consequences.

For our primary analysis, we draw upon the IOM's report on PTB which included a COI estimate representing an average over all PTBs in 2005 dollars with costs after the first year of life discounted at a 3 percent rate. The report estimated costs for several consequences of PTB; for each of these consequences, the estimate represents the average cost of each PTB incremental to the average cost of a term birth. The COI included all incremental medical care costs from birth to age 5 years; incremental maternal delivery costs; early intervention costs, or costs of targeted services for children from birth to age 3 who have developmental delays or other delay-related health conditions; and medical care, special education, and individual lost productivity costs for the following four developmental disabilities (DDs), experienced by a subset of individuals born preterm and averaged over all PTBs, for ages 6 and older: cerebral palsy, intellectual disability (mental retardation), vision impairment, and hearing loss. These values are described in Table 1. The cost estimate for each category was converted to 2014 dollars within BenMAP.

Table 1. Summary of PTB costs as derived from IOM report.

Cost Categories	Average Incremental Costs per PTB (2005$)	Index used to update IOM estimate to 2014$
Medical Costs associated with: • Maternal Delivery • Birth to Age 5 Years • Cerebral palsy, intellectual disability, vision impairment, and hearing loss (4 DDs)	$37,022	Medical Costs
Early Intervention Special Education (4 DDs)	$3,353	All Goods
Lost Productivity (4 DDs)	$11,214	Wages
Total	$51,589	-

It is important to note that this PTB COI estimate does not account for several significant cost categories, such as costs after age 5 outside of those for the four aforementioned DDs or lost productivity costs for the parents of the person born preterm, thereby underestimating the value of reduced PTB [2]. For a more complete estimate of the value of reducing PTB, some additional PTB-related costs were estimated, as detailed in the next section. Furthermore, although the estimates from the IOM report have been widely used in the literature, the report also includes recommendations for refined analyses that would improve the accuracy of their estimates. These recommended improvements include undertaking multivariate modeling to better understand the large variance in economic burden across the population and performing analyses of the effects of race, ethnicity, and/or socioeconomic status on this burden.

Supplemental Analysis: Additional Benefits of Reduced PTB

Additional later-life outcomes of PTB were assessed for availability of adequate data on 1) evidence of their association with PTB, and 2) the WTP to reduce or avoid the later-life outcome or the COI of the outcome. Little or no information was found quantifying WTP or COI for most post-neonatal health outcomes, effects on familial dynamics, or earnings and education in the U.S. outside those already quantified by the IOM. However, the available data for intelligence quotient (IQ) deficits, asthma, and diabetes mellitus (types 1 and 2) included WTP or COI data as well as meta-analyses of their relationship with PTB, and thus were deemed adequate for the analysis. Benefits calculations were performed at the national level to provide a broad overview of these potential benefits. All values are present values discounted at 3 percent and are expressed in 2014 dollars.

Cognitive benefits: IQ. Kerr-Wilson et al. 2012 [31] conducted a meta-analysis of the relationship between PTB defined as both a binary variable (preterm vs. term) and a categorical variable (extremely, very, and moderately preterm, or <28, 28-31, and $\geq$32 weeks vs. term) and IQ deficits. The meta-analysis included 27 studies of 7,044 children total. The average gestational age of the preterm subjects in many of the studies was lower than that of PTBs in the U.S. overall. Because babies born preterm are on average moderately preterm—i.e. fewer babies are born at increasingly lower gestational ages—the moderately preterm category was used rather than the binary preterm category. Moderately preterm babies had a weighted mean IQ score 8.4 (95% CI: 6.6, 10.2) points lower than that of term babies.

EPA has routinely valued the benefits of avoided IQ decrements based on the effect of IQ on lifetime earnings, as was done to estimate the cognitive benefits of reduced exposure to

lead and methylmercury. In the most recent application [32] of this model, EPA derived average lifetime earnings values from U.S. Census data and used estimates from Salkever 1995 [33] to calculate an economic cost of $15,884 for each IQ point loss. EPA has also used Schwartz 1994 [34] estimates to derive $11,559 per IQ point; however, Salkever 1995 was re-examined in 2014 [35] and deemed to be better suited for use in the present analysis.

Asthma. Sonnenschein-van der Voort et al. 2014 [36] evaluated the relationship between PTB and school-age asthma defined as "asthma diagnosis reported between 5 and 10 years (no, yes)," preferably physician diagnosed, across 18 studies of European cohorts. The meta-analysis reported a pooled OR of 1.40 (95% CI: 1.18, 1.67). This OR and the prevalence of PTB and asthma [37] were used to estimate the number of asthma cases among PTBs.

Blomquist, Dickie, and O'Conor 2011 [38] used data from two surveys to estimate annual WTP for asthma control for selected ages of children and adults. To account for children between ages 4 and 17, the applicable survey elicited parents' values of controlling their children's asthma. The survey reported WTP estimates for ages 4, 5, 8, 11, 15, and 17, and a linear interpolation between these values was used to value intervening years. These values were used to approximate the present value at birth of WTP for diagnosis of asthma at "school-age" by discounting the stream of annual WTP estimates from ages 4-17 back to age zero using a discount rate of 3%. The estimated net present value was $38,541 per case.

Diabetes mellitus. Li et al. 2014 [39] conducted a meta-analysis of PTB and both type 1 and type 2 diabetes mellitus (T1D and T2D, respectively) separately. A total of 18 studies for T1D were from the U.S., Canada, Europe, and Australia. The total five T2D studies include four studies from Europe (UK, Sweden, Finland, Denmark) and one from China, with various

methods of outcome ascertainment ranging from self-report to physician diagnosis. Although for T2D there is uncertainty arising from the aforementioned traits of the study, this meta-analysis was still the most appropriate available at the time of the present study, and was deemed acceptable for use in the exploratory nature of this study. PTB was significantly associated with both T1D (OR = 1.18 (95% CI: 1.11, 1.25)) and T2D (OR = 1.51 (95% CI: 1.32, 1.72)). The respective ORs and prevalence of PTB, T1D, and T2D [40] were used to estimate the number of cases of each diabetes type.

The American Diabetes Association (ADA) [41] estimated annual costs per case of diabetes (type unspecified) of $8,298 in direct medical costs and $3,224 in reduced productivity costs. Reduced productivity costs were assumed to be additive to those calculated previously in this study, as those estimates were based on 1) the four DD's previously mentioned in the IOM report, and 2) IQ-related productivity. Costs of increased mortality from diabetes were only included in the form of productivity loss. Because approximately 95% of diabetes cases are T2D and approximately 5% are T1D, the cost estimates from the ADA were assumed to largely represent T2D costs and were therefore used to calculate benefits of reducing T2D cases. To derive an estimate of lifetime costs from the ADA's annual costs estimates, we assumed onset of T2D at age 50 and death at age 80—which were simplifying assumptions but generally consistent with conditional life expectancy at age 50 [42]—and discounted the resulting stream of costs back to birth at 3 percent. Lost workplace productivity costs were only included up to age 65. The estimated net present value was $48,508 per case.

Tao et al. 2010 [43] estimated expected lifetime medical costs and income loss from T1D in the U.S. by categories of age of onset from ages 3 to 45. To calculate present values, we

assumed costs were uniformly distributed within the specified age categories (e.g., from 3-9 years old) and then discounted these age-specific costs to age zero. Summing these values across all ages of onset resulted in a net present value of $199,313 of lifetime costs per case of T1D.

Results

Primary Analysis Results: Immediate Benefits

In 2008, there were 432,677 PTBs and 4,203,437 total births in the contiguous U.S., translating to a PTB rate of 0.103 (Table 2). The air quality data used for the baseline scenario, or before any simulated air quality change, indicated a nationwide range of county-level $PM_{2.5}$ of 4.60 to 18.62 $\mu g/m^3$, with a mean of 10.02 $\mu g/m^3$ and median of 10.45 $\mu g/m^3$ (Figure 1). The change in air quality from the simulated 10% decrease in county-level $PM_{2.5}$ ranged from 0.46 to 1.86 $\mu g/m^3$ across the states (Figure 2).

Table 2. Baseline scenario of preterm birth rates in the contiguous U.S. with no reduction in ambient $PM_{2.5}$ in 2008.

	All U.S.
Baseline PTBs (n)	432,677
Baseline All Births (n)	4,203,437
PTB Rate	0.103

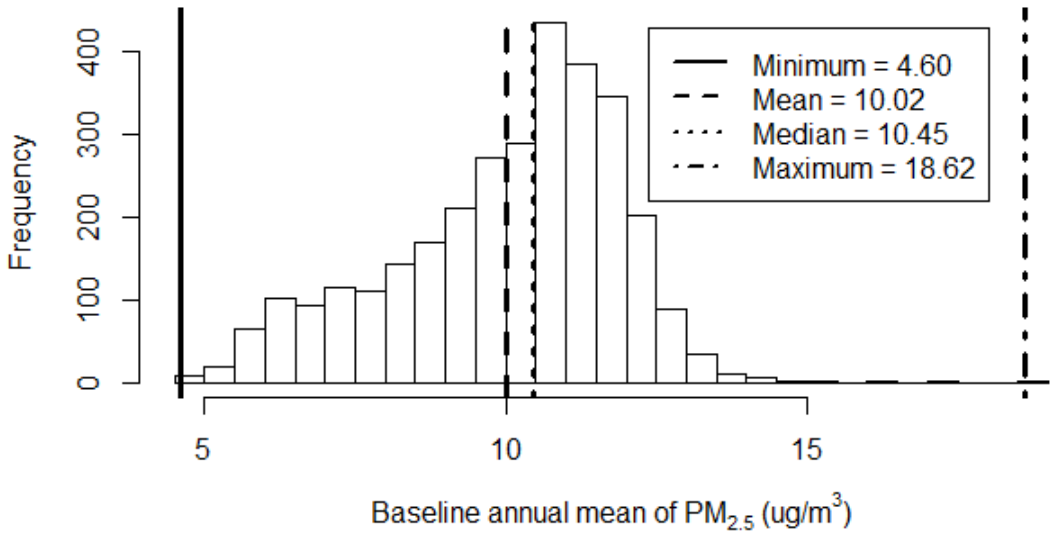

Figure 1. Distribution of baseline county-level $PM_{2.5}$ annual mean concentrations in the U.S. in 2008.

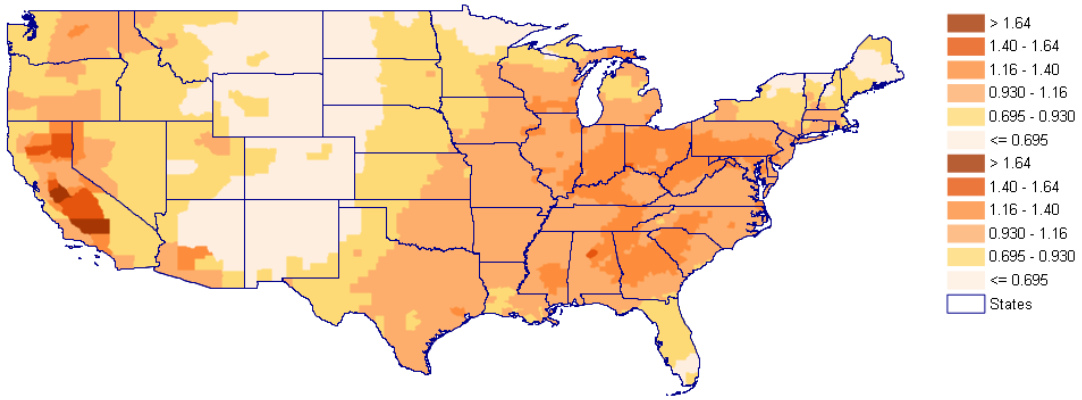

Figure 2. Changes in county-level $PM_{2.5}$ levels (µg/m^3) after a simulated 10% decrease from baseline 2008 levels.

A hypothetical 10% reduction from baseline 2008 county-level $PM_{2.5}$ levels was estimated to result in 5,016 fewer PTBs (1.16% of all PTBs) for a total of $339 million of benefits nationwide (Table 3). The majority of benefits were from reduced medical costs, which constituted about $251 million of the $339 million of benefits overall in the primary analysis. Numbers of reduced

cases and associated benefits varied by state, with the percentage of PTB cases reduced from the simulated $PM_{2.5}$ reduction ranging from 0.6 to 1.4% of the state's PTBs overall (Table 4).

Table 3. National changes in cases of preterm birth and associated economic benefits after a simulated 10% decrease in $PM_{2.5}$ from baseline 2008 levels (2014$).

Reduced PTB Cases (n)	5016
Benefits from Reduced PTB (2014$ millions)	$339.1
Medical Costs	$250.7
Special Education Costs	$ 20.4
Lost Productivity	$ 68.1

Table 4. State-level changes in cases of preterm birth and associated economic benefits after a simulated 10% decrease in $PM_{2.5}$ from baseline 2008 levels.

State	Baseline PTB Cases (n)	Reduced PTB Cases (n)	PTB Case Reduction (%)	Benefits from Reduced PTB (2014$ millions)
Alabama	8,263	102	1.2%	$6.9
Arizona	10,038	117	1.2%	$7.9
Arkansas	4,705	56	1.2%	$3.8
California	48,992	620	1.3%	$41.9
Colorado	6,679	51	0.8%	$3.5
Connecticut	4,056	47	1.2%	$3.2
Delaware	1,212	16	1.3%	$1.1
District of Columbia	1,090	14	1.2%	$0.9
Florida	25,623	211	0.8%	$14.2
Georgia	16,987	213	1.3%	$14.4
Idaho	2,342	20	0.8%	$1.3
Illinois	18,229	235	1.3%	$15.9
Indiana	9,369	125	1.3%	$8.4
Iowa	3,906	43	1.1%	$2.9
Kansas	3,845	40	1.0%	$2.7
Kentucky	6,832	88	1.3%	$5.9
Louisiana	8,163	85	1.0%	$5.8
Maine	1,176	10	0.9%	$0.7
Maryland	8,399	107	1.3%	$7.2
Massachusetts	6,694	72	1.1%	$4.9

Michigan	12,680	148	1.2%	$10.0
Minnesota	6,343	66	1.0%	$4.5
Mississippi	6,082	71	1.2%	$4.8
Missouri	8,283	98	1.2%	$6.6
Montana	1,240	10	0.8%	$0.7
Nebraska	2,574	24	0.9%	$1.6
Nevada	4,310	43	1.0%	$2.9
New Hampshire	1,142	11	1.0%	$0.7
New Jersey	11,779	142	1.2%	$9.6
New Mexico	2,933	19	0.6%	$1.3
New York	23,906	280	1.2%	$18.9
North Carolina	13,984	172	1.2%	$11.7
North Dakota	875	7	0.8%	$0.5
Ohio	15,871	217	1.4%	$14.6
Oklahoma	6,026	70	1.2%	$4.7
Oregon	3,847	37	1.0%	$2.5
Pennsylvania	15,126	202	1.3%	$13.6
Rhode Island	1,186	12	1.0%	$0.8
South Carolina	7,405	89	1.2%	$6.0
South Dakota	1,037	9	0.9%	$0.6
Tennessee	9,743	117	1.2%	$7.9
Texas	45,246	508	1.1%	$34.4
Utah	5,387	54	1.0%	$3.6
Vermont	529	5	0.9%	$0.3
Virginia	11,151	135	1.2%	$9.1
Washington	7,940	80	1.0%	$5.4
West Virginia	2,540	34	1.3%	$2.3
Wisconsin	6,091	79	1.3%	$5.3
Wyoming	821	6	0.7%	$0.4
U.S. Range	529 – 48,992	5 – 620	0.6 – 1.4%	$0.3 – 41.9

Supplemental Analysis Results: Additional Benefits

The previously estimate of 5,016 PTBs reduced was carried through to calculate the additional potential economic benefits from avoiding IQ decrements, asthma, T1D, and T2D cases. For this

simulation, the greatest category of benefits was by far from the avoided IQ point decrements, which yielded an estimated $669 million (Table 5).

Table 5. Additional benefits from avoided later-life health outcomes of preterm birth after a simulated 10% decrease in $PM_{2.5}$ from baseline 2008 levels.

	n (IQ points or Cases)	Benefits per n (2014$)	Total Benefits Estimation (2014$ millions)
IQ	42,134 IQ points	$15,884	$669.3
Asthma	160 cases	$35,272	$5.6
Type 1 Diabetes	4 cases	$199,313	$0.8
Type 2 Diabetes	190 cases	$48,508	$9.2

Discussion

PTB is an important health outcome for which epidemiological studies are increasingly finding associations with environmental contaminants. Estimates of the effects of a policy or risk management action on the incidence of PTB and the value of this change in incidence could be used to better inform decision-making. In this study, we explored an approach to quantifying the economic benefits of avoiding PTB and applied it to a simulated 10% reduction from 2008 $PM_{2.5}$ levels. Mean ambient $PM_{2.5}$ across the U.S. decreased by 21.7% from 2008 to 2015, suggesting that the hypothetical 10% decrease was not an unrealistic air quality improvement to simulate. We found that the potential annual PTB benefits from reducing $PM_{2.5}$ in our primary analysis may be in the order of hundreds of millions of dollars, possibly rising to over a billion dollars when also considering additional later-life health outcomes. For perspective, on a per-case-avoided basis, the value of PTB (including later-life health outcomes) is greater than for other non-fatal $PM_{2.5}$ health effects generally considered in EPA analyses except for chronic bronchitis [44].

EPA's most recent assessment of PM, published in 2009, determined that the evidence for $PM_{2.5}$ and reproductive and developmental outcomes, a category that included PTB, was suggestive of a causal association [8]. The epidemiologic literature on this topic is much more extensive now than when the previous assessment was completed, and it is conceivable that the new $PM_{2.5}$ assessment scheduled for completion in 2019 could determine that the weight of evidence is sufficient to conclude a likely causal or causal relationship between $PM_{2.5}$ and PTB. If so, PTB would become a strong candidate for inclusion in future analyses of the benefits of $PM_{2.5}$ reductions. However, even if the $PM_{2.5}$ evidence concerning PTB is not judged to rise to a likely causal or causal weight-of-evidence determination, the analysis presented in this paper of the benefits of reduced PTB will be applicable to any other environmental contaminants that may be found to have sufficient evidence. In either case, this type of benefits calculation would prove to be especially useful, as there is no existing WTP value for PTB, and the COI estimate in the IOM report, while useful, is dated and incomplete.

CDC WONDER reports data for continuous gestational age, and in theory, benefits could be estimated for changes in gestational age if 1) the $PM_{2.5}$ epidemiological literature provided adequate effect estimates for gestational age as a continuous variable, and 2) sufficient evidence of causality was found in the weight-of-evidence determination of the relationship between $PM_{2.5}$ and continuous gestational age. However, the binary variable was used in this study in accordance with the prevailing $PM_{2.5}$ epidemiological literature available.

We used a two-step procedure to estimate the secondary outcomes reported in this study (IQ, asthma, T1D, and T2D), in which the first step was to compute the number of cases of PTB avoided, and the second step was to apply quantitative relationships from the literature

regarding health consequences of PTB. The most recent PM ISA did not investigate the relationship between prenatal $PM_{2.5}$ exposure and the secondary outcomes reported in this study. If there were direct evidence of a possible relationship between prenatal $PM_{2.5}$ and IQ, asthma, T1D, or T2D, that evidence would be a primary consideration in a decision whether to include these secondary outcomes in a $PM_{2.5}$ benefits analysis. In the absence of such direct evidence, it is reasonable to assume that the health consequences of PTB indicated in the literature are outcomes that would be avoided with any reduction in PTBs that results from lowered exposure to $PM_{2.5}$.

We estimated that 5,016 PTBs would have been avoided in 2008 with a 10% reduction in $PM_{2.5}$, resulting in $339 million of immediate benefits and over $669 million of additional health benefits. We have fairly high confidence in the estimate of PTBs avoided, conditional on the assumption that increased $PM_{2.5}$ exposure increases the risk of PTB. The meta-analysis from which the PTB beta coefficient was derived, Sun et al. 2015 [7], was the most comprehensive meta-analysis available at the time of our current study, and integrates estimates from many studies conducted in geographically diverse populations with a majority of studies from the U.S. The OR was 1.13 with a 95% confidence interval of 1.03 to 1.24, indicating to us with relatively strong confidence that there is a moderate and significant effect of $PM_{2.5}$ on PTB. However, there remains uncertainty regarding the exact nature and magnitude of the $PM_{2.5}$-PTB relationship, such as effects potentially varying by phase of gestation. For example, Sun et al. 2015 indicated statistically significant heterogeneity among studies, which subgroup and sensitivity analyses revealed to be due in part, but not entirely, to exposure assessment, study design, and study settings. Additionally, the literature regarding trimester-specific effects or

predictive power remains mixed [45-49]. The pooled estimate used in this study was from 13 studies of whole-pregnancy exposure, for which there were the greatest number of studies available and therefore the most statistical power. The effect estimates from the first, second, and third trimesters separately were almost identical, but fewer studies examined trimester-specific data (ten, five, and nine studies respectively), and all trimester-specific estimates were statistically insignificant. Thus, Sun et al. 2015 did not allow us to draw any strong conclusions regarding possible trimester-specific differences.

Another source of uncertainty in our analysis comes from the limited availability of comprehensive health and costs data. In our primary analysis, we used the IOM's estimates of the costs of PTB, which included limited medical costs, early intervention and special education costs, and lost wages, and adjusted these costs to 2014 dollars to derive a valuation estimate. However, the IOM's estimates did not include many later-life health, earnings, or education costs. For the purposes of our supplemental analysis, health and cost data were insufficient or not available for most potential later-life outcomes. We searched the literature to identify later-life outcomes associated with PTB and found many outcomes that had been studied, but most, such as cardiovascular disease or autism spectrum disorder, were not included in our analysis for one or more of the following reasons: 1) Low birth weight (LBW) was used as a proxy outcome for PTB in many earlier epidemiological studies. Evidence increasingly suggests that LBW and PTB, while overlapping, also have distinct etiologies and effects [2]. Therefore, we did not consider it appropriate to include studies conflating the two outcomes; 2) For many potential health outcomes of interest, evidence was not considered sufficient for quantification—there were no meta-analyses available to use for estimating incidence, only a

few studies, mixed results, and/or results were statistically insignificant; 3) Some outcomes only had sufficient data for developing countries, which were assumed to differ greatly from the U.S., especially with regard to health care systems and economic outcomes; 4) The outcome definition differed between the health data and valuation data; and 5) Many outcomes simply lacked valuation estimates in the economics literature, even if they had epidemiologic evidence suitable for quantification. Among the outcomes we did include and value (IQ, asthma, T1D, and T2D), the body of literature regarding their relationship with PTB and their costs was not extremely comprehensive; additional research in these areas is expected to improve these estimates. The most robustly valued outcome was IQ, for which there could be uncertainty regarding the cost estimates used from Salkever, which have been debated in the literature [35, 50-53]. However, based on methodological choices—for example, other studies did not consider work participation rates, demographic changes, or more recent data—Salkever's IQ-earnings estimates were deemed most appropriate for this study. Cost estimates for IQ were based on earnings, which are likely to underestimate WTP. However, among the four outcomes that were valued, IQ was still the dominant driver of costs; costs for the other three outcomes (asthma, T1D, and T2D) were relatively small.

Finally, there is uncertainty regarding the estimate used for the quantitative relationship between PTB and IQ. The population of infants in the Kerr-Wilson et al. 2012 study [31] used to quantify this relationship was heavily skewed toward very or extremely preterm babies. As mentioned in the Methods section, because babies born preterm are on average moderately preterm (rather than very or extremely preterm), the moderately preterm category in Kerr-Wilson et al. 2012 was used over the binary preterm category to reduce possible

overestimation of benefits that could result from including the higher costs associated with very preterm babies. The moderately preterm estimate compares mean IQ for births at gestational ages of 34 to 36 weeks to mean IQ for births at gestational ages of 37 weeks and greater. Depending on how our estimated decrease in PTB affects the overall distribution of PTB, using the moderately preterm category could still be an overestimate. For the PTBs avoided from a reduction in $PM_{2.5}$, if we can assume that a child at any point of the preterm distribution can be re-assigned to any point of the term distribution, then a comparison of mean-to-mean costs for moderately preterm (which constitutes most preterm babies) and term babies is generally correct, and use of Kerr-Wilson et al. 2012's moderately preterm estimate should be accurate. However, if the simulated decrease in PTB results in a small but overall shift in the distribution of gestational ages, i.e. those right below the cutoff for term birth (very close to but not quite meeting 37 weeks) cross the somewhat arbitrary boundary for term birth (37 weeks and greater), then the average shift in gestational age may be much smaller than the shift underlying the Kerr-Wilson et al. 2012 estimate for moderately preterm births. This effect may occur because of differences by continuous gestational age within not only the moderately preterm category, but also the term category (e.g. outcomes may differ between babies born at 37 versus 40 weeks) [54]. Regardless, no alternate value with less uncertainty in these respects was available, and we found utilizing the moderately preterm category from Kerr-Wilson to be a reasonable estimate given the current state of knowledge.

Our study is, to the best of our knowledge, the first study to simulate a decrease in $PM_{2.5}$ and subsequent decrease in $PM_{2.5}$-related PTB, and to then quantify the PTB-related economic benefits arising from the simulated reduction in $PM_{2.5}$. Trasande et al. 2016 [55]

estimated the economic costs of all PTBs attributable to anthropogenic $PM_{2.5}$ exposure in 2010 [55]. $PM_{2.5}$ was assumed to be anthropogenic, rather than arising from natural sources such as wildfires, dust storms, or volcanoes, at levels above 8.8 $\mu g/m^3$, a reference level which was originally applied in the 2010 Global Burden of Disease estimates of $PM_{2.5}$-attributable disease [56]. The OR of 1.15 (1.14, 1.16) from Sapkota et al. 2012 [48], a meta-analysis which included 6 studies of the relationship between $PM_{2.5}$ and PTB, was utilized in the calculation of $PM_{2.5}$-attributable PTB cases; conversely, we used the Sun et al. 2015 meta-analysis, which was more recent, included many more studies, and reports a slightly lower OR. Medical costs from birth to age 5 and costs after age 5 for developmental disabilities were obtained from the 2007 IOM report also used in the present study, and lost economic productivity was measured through IQ loss. Kerr-Wilson et al. 2012 was also used in Trasande et al. 2016; however, Trasande et al. used the 11.9-point IQ decrement between term babies and all preterm babies on average in the study, whereas we used the 8.4-point IQ decrement between term babies and moderately preterm babies for the reasons stated above. Trasande et al. did not include other later-life outcomes, such as those that we evaluated in our study (asthma, T1D, and T2D). Additionally, rather than using the Salkever estimates as we did, Trasande et al. used the estimates of changes in earnings per IQ point from Grosse et al. 2002 [50], which are lower than the estimates proposed by Salkever 2014 [35]. They estimated 15,808 PTBs attributable to $PM_{2.5}$ in 2010, with nationwide costs of $5.09 billion (2010$) for medical care costs and lost economic productivity combined. Although the Trasande et al. study was different in that it quantified economic costs of all $PM_{2.5}$-attributable PTBs, while our study quantified costs for a fixed,

simulated decrease in $PM_{2.5}$ and PTB, the two are consistent in indicating a high economic burden of PTB in the U.S.

Our study is also the first to utilize BenMAP to assess effects of prenatal exposures. BenMAP is used by EPA to perform benefits analyses of reduction of criteria pollutant emissions and subsequent changes in incidence of health outcomes. Previously, its use was limited to health impacts on directly exposed populations; the capacity of BenMAP to evaluate health impacts of prenatal exposures provides potential for its use in a broader range of future benefits analyses.

A principal benefit of this analytical approach is that it provides a straightforward way to estimate benefits in the absence of an existing WTP estimate for reduced risk of PTB. Because this method does not rely on an overarching WTP estimate for reduced PTB, the growing scientific knowledge base and new literature on specific PTB-related health outcomes can quickly be incorporated into calculations, allowing for direct revisions of benefits calculations based on the prevailing science. These qualities allow researchers and policymakers to obtain a broad overview of the health benefits of adverse environmental exposure reductions in a timely manner.

The literature on environmental contaminants and birth outcomes is robust and growing [5, 57-64]. Stieb et al. 2012 [6], which analyzed multiple air pollution and birth outcomes in 62 studies by pollutant, outcome, and exposure period, already provides a foundation for potential future analyses for ozone, NO_2, or SO_2, which can be performed through BenMAP and for which BenMAP-compatible measurements can be obtained. In addition, specific health outcomes, such as high blood pressure [65], have suggested or

established relationships with PTB, and may therefore hold promise for future valuation estimates. This type of study could be undertaken to quantify economic effects of pollutant-related health outcomes currently unquantified in BCAs, which can contribute to more comprehensive analytical underpinnings of future decision-making.

Conclusions

Although PTB is an important health outcome with both short- and long-term consequences that may yield significant economic costs, there is not a robust body of economic literature to support an estimate of the WTP to reduce its risk. There is a need to develop methodologies and estimates that can provide information regarding the potential benefits of reducing such detrimental health outcomes. The analysis presented here of PTB and $PM_{2.5}$ indicate that previously unquantified benefits of reducing pollution-related cases of health outcomes may be substantial and are worthy of investment for future research.

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References

1. MacDorman, M.F., D.L. Hoyert, and T.J. Mathews, *Recent declines in infant mortality in the United States, 2005-2011.* NCHS Data Brief, 2013(120): p. 1-8.
2. Institute of Medicine, *Preterm Birth: Causes, Consequences, and Prevention*, ed. R.E. Behrman and A.S. Butler. 2007, Washington, DC: The National Academies Press.
3. OECD, *Infant mortality rates (indicator)*. 2016.
4. MacDorman, M.F. and T.J. Mathews, *Behind international rankings of infant mortality: how the United States compares with Europe.* NCHS Data Brief, 2009(23): p. 1-8.
5. Stillerman, K.P., et al., *Environmental exposures and adverse pregnancy outcomes: a review of the science.* Reproductive Sciences, 2008. **15**(7): p. 631-50.
6. Stieb, D.M., et al., *Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis.* Environ Res, 2012. **117**: p. 100-11.
7. Sun, X., et al., *The association between fine particulate matter exposure during pregnancy and preterm birth: a meta-analysis.* BMC Pregnancy Childbirth, 2015. **15**: p. 300.
8. U.S. Environmental Protection Agency, *Integrated Science Assessment for Particulate Matter (Final Report)*. 2009, U.S. EPA. EPA/600/R-08/139F: Washington, DC.
9. U.S. Environmental Protection Agency, *Integrated Science Assessment for Carbon Monoxide*. 2010: Research Triangle Park, NC.
10. U.S. Environmental Protection Agency, *Integrated Science Assessment for Lead*. 2013: Research Triangle Park, NC.
11. U.S. Environmental Protection Agency, *Integrated Science Assessment for Ozone and Related Photochemical Oxidants*. 2013: Research Triangle Park, NC.
12. U.S. Environmental Protection Agency, *Integrated Science Assessment for Oxides of Nitrogen – Health Criteria*. 2016: Research Triangle Park, NC.
13. Mikati, I., et al., *Disparities in Distribution of Particulate Matter Emission Sources by Race and Poverty Status.* American Journal of Public Health, 2018. **108**(4): p. 480-485.
14. Bell, M.L. and K. Ebisu, *Environmental Inequality in Exposures to Airborne Particulate Matter Components in the United States.* Environmental Health Perspectives, 2012. **120**(12): p. 1699-1704.
15. Miranda, M.L., et al., *Making the Environmental Justice Grade: The Relative Burden of Air Pollution Exposure in the United States.* International Journal of Environmental Research and Public Health, 2011. **8**(6): p. 1755-1771.
16. Federal Interagency Forum on Child and Family Statistics, *America's Children in Brief: Key National Indicators of Well-Being*. 2016: Washington, DC.
17. Hajat, A., C. Hsia, and M.S. O'Neill, *Socioeconomic Disparities and Air Pollution Exposure: A Global Review.* Current environmental health reports, 2015. **2**(4): p. 440-450.
18. Clark, L.P., D.B. Millet, and J.D. Marshall, *Changes in Transportation-Related Air Pollution Exposures by Race-Ethnicity and Socioeconomic Status: Outdoor Nitrogen Dioxide in the United States in 2000 and 2010.* Environ Health Perspect, 2017. **125**(9): p. 097012.
19. McGartland, A., et al., *Estimating the health benefits of environmental regulations.* Science, 2017. **357**(6350): p. 457-458.
20. *Guidelines for Preparing Economic Analyses*. 2010: Washington, DC.

21. Jo, C., *Cost-of-illness studies: concepts, scopes, and methods.* Clinical and Molecular Hepatology, 2014. **20**(4): p. 327-337.
22. *Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter*. 2016: Research Triangle Park, NC.
23. Sacks, J.D., et al., *The Environmental Benefits Mapping and Analysis Program – Community Edition (BenMAP–CE): A tool to estimate the health and economic benefits of reducing air pollution.* Environmental Modelling & Software, 2018. **104**: p. 118-129.
24. RTI International, *Environmental Benefits Mapping and Analysis Program - Community Edition User's Manual*. 2015, U.S. Environmental Protection Agency Office of Air Quality Planning and Standards: Research Triangle Park, NC.
25. Hubbell, B.J., et al., *Health-Related Benefits of Attaining the 8-Hr Ozone Standard.* Environmental Health Perspectives, 2005. **113**(1): p. 73-82.
26. Fann, N. and D. Risley, *The public health context for PM2.5 and ozone air quality trends.* Air Quality, Atmosphere & Health, 2013. **6**(1): p. 1-11.
27. U.S. Environmental Protection Agency. *Particulate Matter (PM2.5) Trends*. 2017; Available from: https://www.epa.gov/air-trends/particulate-matter-pm25-trends.
28. RTI International, *Environmental Benefits Mapping and Analysis Program - Community Edition User's Manual Appendices*. 2015, U.S. Environmental Protection Agency Office of Air Quality Planning and Standards: Research Triangle Park, NC.
29. *Natality Data Summary*. 2016, Centers for Disease Control and Prevention.
30. U.S. Environmental Protection Agency, *Environmental Benefits Mapping and Analysis Program: Community Edition (BenMAP-CE) User Manual and Appendices*. 2017: Research Triangle Park, NC, USA.
31. Kerr-Wilson, C.O., et al., *Meta-analysis of the association between preterm delivery and intelligence.* J Public Health (Oxf), 2012. **34**(2): p. 209-16.
32. U.S. Environmental Protection Agency, *Benefit and Cost Analysis for the Effluent Limitations Guidelines and Standards for the Steam Electric Power Generating Point Source Category*. 2015: Washington DC.
33. Salkever, D.S., *Updated estimates of earnings benefits from reduced exposure of children to environmental lead.* Environ Res, 1995. **70**(1): p. 1-6.
34. Schwartz, J., *Societal benefits of reducing lead exposure.* Environ Res, 1994. **66**(1): p. 105-24.
35. Salkever, D.S., *Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?* Environmental Research, 2014. **131**(Supplement C): p. 219-230.
36. Sonnenschein-van der Voort, A.M., et al., *Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children.* J Allergy Clin Immunol, 2014. **133**(5): p. 1317-29.
37. U.S. Environmental Protection Agency, *America's Children and the Environment, Third Edition*. 2013: Washington, DC.
38. Blomquist, G.C., M. Dickie, and R.M. O'Conor, *Willingness to pay for improving fatality risks and asthma symptoms: Values for children and adults of all ages.* Resource and Energy Economics, 2011. **33**(2): p. 410-425.

39. Li, S., et al., *Preterm birth and risk of type 1 and type 2 diabetes: systematic review and meta-analysis.* Obes Rev, 2014. **15**(10): p. 804-11.
40. Centers for Disease Control and Prevention, *National Diabetes Statistics Report, 2017*. 2017.
41. American Diabetes Association, *Economic Costs of Diabetes in the U.S. in 2012.* Diabetes Care, 2013. **36**(4): p. 1033-1046.
42. United States Social Security Administration, *Period Life Table, 2014*.
43. Tao, B., et al., *Estimating the cost of type 1 diabetes in the U.S.: a propensity score matching method.* PLoS One, 2010. **5**(7): p. e11501.
44. U.S. Environmental Protection Agency, *Environmental Benefits Mapping and Analysis Program: Community Edition (BenMAP-CE) User Manual and Appendices*. 2017: Research Triangle Park, NC, USA. p. 174.
45. Wilhelm, M. and B. Ritz, *Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA.* Environmental Health Perspectives, 2005. **113**(9): p. 1212-21.
46. Lee, P.C., et al., *First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA.* Matern Child Health J, 2013. **17**(3): p. 545-55.
47. Selevan, S.G., C.A. Kimmel, and P. Mendola, *Identifying critical windows of exposure for children's health.* Environ Health Perspect, 2000. **108 Suppl 3**: p. 451-5.
48. Sapkota, A., et al., *Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis.* Air Quality, Atmosphere & Health, 2012. **5**(4): p. 369-381.
49. Jalaludin, B., et al., *Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia.* Environ Health, 2007. **6**: p. 16.
50. Grosse, S.D., et al., *Economic gains resulting from the reduction in children's exposure to lead in the United States.* Environ Health Perspect, 2002. **110**(6): p. 563-9.
51. Robinson, L.A., *Benefits of Reduced Lead Exposure: A Review of Previous Studies*. 2007.
52. Robinson, L., *Lead: Regulations*, in *Encyclopedia of environmental management*, S.E. Jørgensen, Editor. 2013. p. 1636–1646.
53. Grosse, S.D., *How much does IQ raise earnings? Implications for regulatory impact analyses*. Vol. 27. 2007. 17-21.
54. Noble, K.G., et al., *Academic Achievement Varies With Gestational Age Among Children Born at Term.* Pediatrics, 2012. **130**(2): p. e257-e264.
55. Trasande, L., P. Malecha, and T.M. Attina, *Particulate Matter Exposure and Preterm Birth: Estimates of U.S. Attributable Burden and Economic Costs.* Environ Health Perspect, 2016. **124**(12): p. 1913-1918.
56. Lim, S.S., et al., *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, 2012. **380**(9859): p. 2224-60.
57. Bosetti, C., et al., *Ambient particulate matter and preterm birth or birth weight: a review of the literature.* Arch Toxicol, 2010. **84**(6): p. 447-60.

58. Grellier, J., et al., *Exposure to disinfection by-products, fetal growth, and prematurity: a systematic review and meta-analysis.* Epidemiology, 2010. **21**(3): p. 300-13.
59. Shah, P.S., T. Balkhair, and L.B.W.b. Knowledge Synthesis Group on Determinants of Preterm, *Air pollution and birth outcomes: a systematic review.* Environ Int, 2011. **37**(2): p. 498-516.
60. Ferguson, K.K. and H.B. Chin, *Environmental chemicals and preterm birth: Biological mechanisms and the state of the science.* Curr Epidemiol Rep, 2017. **4**(1): p. 56-71.
61. Nieuwenhuijsen, M.J., et al., *Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies.* Environ Health, 2013. **12**: p. 6.
62. Lamichhane, D.K., et al., *A meta-analysis of exposure to particulate matter and adverse birth outcomes.* Environmental Health and Toxicology, 2015. **30**: p. e2015011.
63. Li, X., et al., *Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis.* Environ Pollut, 2017. **227**: p. 596-605.
64. Perera, F.P., *Multiple Threats to Child Health from Fossil Fuel Combustion: Impacts of Air Pollution and Climate Change.* Environ Health Perspect, 2017. **125**(2): p. 141-148.
65. Parkinson, J.R., et al., *Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis.* Pediatrics, 2013. **131**(4): p. e1240-63.