



Review

Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis

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ABSTRACT

Low birth weight and preterm birth have a substantial public health impact. Studies examining their association with outdoor air pollution were identified using searches of bibliographic databases and reference lists of relevant papers. Pooled estimates of effect were calculated, heterogeneity was quantified, meta-regression was conducted and publication bias was examined. Sixty-two studies met the inclusion criteria. The majority of studies reported reduced birth weight and increased odds of low birth weight in relation to exposure to carbon monoxide (CO), nitrogen dioxide (NO₂) and particulate matter less than 10 and 2.5 microns (PM₁₀ and PM_{2.5}). Effect estimates based on entire pregnancy exposure were generally largest. Pooled estimates of decrease in birth weight ranged from 11.4 g (95% confidence interval −6.9–29.7) per 1 ppm CO to 28.1 g (11.5–44.8) per 20 ppb NO₂, and pooled odds ratios for low birth weight ranged from 1.05 (0.99–1.12) per 10 µg/m³ PM_{2.5} to 1.10 (1.05–1.15) per 20 µg/m³ PM₁₀ based on entire pregnancy exposure. Fewer effect estimates were available for preterm birth and results were mixed. Pooled odds ratios based on 3rd trimester exposures were generally most precise, ranging from 1.04 (1.02–1.06) per 1 ppm CO to 1.06 (1.03–1.11) per 20 µg/m³ PM₁₀. Results were less consistent for ozone and sulfur dioxide for all outcomes. Heterogeneity between studies varied widely between pollutants and outcomes, and meta-regression suggested that heterogeneity could be partially explained by methodological differences between studies. While there is a large evidence base which is indicative of associations between CO, NO₂, PM and pregnancy outcome, variation in effects by exposure period and sources of heterogeneity between studies should be further explored.

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1. Introduction¹

Preterm birth and low birth weight are well-known to be associated with increased neonatal morbidity and mortality as well as possible increased morbidity in adulthood (Behrman and Butler, 2007). In 2005, the prevalence of low birth weight in the US was 8.2% and that of preterm birth was 12.6%; 67% of low birth weight infants were born preterm, while 43.3% of preterm infants were low birth weight (Martin et al., 2007). Complications of preterm birth include both early effects on the respiratory, gastrointestinal, immunologic and central nervous systems as well as late effects on motor, cognitive, visual, hearing, behavioral, and social-emotional function, and diverse effects on health and growth (Behrman and Butler, 2007). The annual economic burden associated with preterm birth in the United States in 2005 was estimated to be at least \$26.2 billion (\$51,600 per infant), approximately 65% of which (\$16.9 billion or \$33,200 per infant) was attributed to medical care (Behrman and Butler, 2007).

Numerous studies have been conducted of the association between ambient air pollutants and pregnancy outcome, including preterm birth and birth weight. Several reviews have been published (Bonzini et al., 2010; Bosetti et al., 2010; Ghosh et al., 2007; Glinianaia et al., 2004; Maisonet et al., 2004; Shah and Balkhair, 2010; Sram et al., 2005; Stillerman et al., 2008), but they have generally been based on a small number of studies, and only one has provided pooled estimates of effect size for particulate pollutants only (Sapkota et al., 2010). Examination in primary studies of varied combinations of pollutants and exposure periods (month, trimester and other periods), and treatment of exposure as both a continuous and categorical variable, have made it difficult to generalize about the true nature of these associations. This is reflected in the conclusions of previous reviews, which have generally characterized effects as heterogeneous and at best small in magnitude. We present a systematic review and meta-analysis of over 60 studies examining associations between ambient air pollution and birth weight and preterm birth. We provide summary estimates of effect by gestational period, quantify heterogeneity, evaluate publication bias, and conduct meta-regression and numerous sensitivity analyses.

2. Materials and methods

2.1. Study identification and data extraction

Studies were identified using electronic searches of bibliographic databases with assistance from a science librarian, and review of reference lists of all relevant papers. The following databases were searched: EMBASE, MEDLINE, Scopus, Current Contents, Global Health, Cochrane, TOXLINE and the Canadian Research Index. Search terms were based on the following inclusion criteria: non-occupational non-accidental exposure to outdoor nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃), carbon monoxide (CO), and particulate matter of median diameter < 10, 2.5 µm (PM₁₀, PM_{2.5}); human live birth; gestational age > 20 weeks at birth; outcome of preterm birth (< 37 weeks gestation)/gestational age, birth weight/low birth weight (LBW) (< 2500 g)/small for gestational age (SGA)/intrauterine growth restriction (IUGR) (< 10th percentile for gestational age); and publication in English on/after January 1, 1980. Daily time series studies, case reports, case series and studies available only in abstract form were excluded. Searches were last updated in January 2011. Relevance of citations for inclusion was evaluated independently by two investigators (LC and ME or ME and DS), differences between whom were resolved by consensus.

¹ BW, birth weight; CI, confidence interval; CO, carbon monoxide; GA, gestational age; IUGR, intrauterine growth restriction; LBW, low birth weight; NO₂, nitrogen dioxide; O₃, ozone; OR, odds ratio; PM_{2.5}, particulate matter of median diameter < 2.5 µm; PM₁₀, particulate matter of median diameter < 10 µm; PM_{10-2.5}, particulate matter of median diameter between 2.5, 10 µm; ppb, parts per billion; ppm, parts per million; PT, preterm birth; SES, socioeconomic status; SGA, small for gestational age; SO₂, sulfur dioxide; TSP, total suspended particulate; VLBW, very low birth weight; VSGA, very small for gestational age.

Data extraction from relevant studies was also conducted independently by two investigators (LC and ME or ME and DS), including study design, location, dates of data collection, data sources, sample size, descriptive information on study subject characteristics, outcome frequency, distribution of exposure, method of exposure characterization, statistical analysis methods, effect size estimates, covariates examined jointly with air pollution, and conduct of subgroup or sensitivity analyses. Study quality was assessed based on design, exposure characterization and adjustment for covariates, and sensitivity analyses were conducted where feasible based on these factors. We requested additional results from study authors when they indicated that analyses were undertaken but were not reported (see Supplementary materials). References were managed in Ref-Works (ProQuest, Bethesda, Maryland) and data were analyzed using Excel 2007 (Microsoft, Redmond, Washington) and Stata 10.1 (StataCorp LP, College Station, Texas).

There were five instances where results were reported for the same outcome, pollutant and population in more than one paper. We selected the result that was based on the larger number of observations (Dejmek et al., 2000 for PM₁₀ vs. Dejmek et al. 1999; and Lee et al., 2003 vs. Ha et al., 2001) or which reported the primary results (Bell et al., 2007) where another paper reported sensitivity analyses (Bell et al., 2008). Jedrychowski et al. (2004, 2009) reported results for PM_{2.5} and birth weight for different gestational periods so both were included, while two other papers only reported results based on categorical exposures (Jedrychowski et al., 2007, 2010). Results for CO and PM_{2.5} from Morello-Frosch et al. (2010) were also selected over those from Parker et al. (2005) and Basu et al. (2004) because the former covered a longer period which wholly overlapped the latter.

2.2. Statistical analysis

For each pollutant and outcome, effect estimates were grouped by gestational period (week, month, trimester, entire pregnancy, etc.), and pollutant averaging time (e.g., daily one or eight hour maximum, 24 h average for gases only) in order to identify the combination of gestational period and averaging time with the greatest number of effect estimates. Estimates based on other averaging times and similar gestational periods were then added (e.g., last month or six weeks to trimester three). Conversion of a regression coefficient (linear or logistic) for averaging time *a* to averaging time *b* was made by multiplying it by the ratio of the average of concentration *a* over the average of concentration *b* based on an analysis of 24 Canadian cities between 1981 and 2006. Pooled estimates of effect were calculated where appropriate using random effects models (DerSimonian and Laird, 1986), quantifying heterogeneity among estimates from primary studies using the *I*² statistic (25%, 50% and 75% were used as rules of thumb for low, moderate and high heterogeneity) (Higgins et al., 2003). In order to facilitate comparisons of effect sizes among pollutants, effect size estimates and pooled estimates were expressed in terms of pollutant increments equal to typical mean concentrations of pollutants in Canadian cities (1 part per million (ppm) CO; 20 parts per billion (ppb) NO₂; 20 ppb O₃; 20 µg/m³ PM₁₀; 10 µg/m³ PM_{2.5}; 5 ppb SO₂). Most effect estimates relating to dichotomous outcomes (low birth weight, preterm birth) were expressed as adjusted odds ratios derived from logistic regression analysis. In a few instances, relative risks were reported. In the interest of comparability with the majority of other estimates, we converted these to odds ratios based on the approximation described by Zhang and Yu (1998).

In a number of studies, effects were reported relative to categorical exposures (e.g., by quartile), limiting our ability to compare results between different studies employing differing exposure categories. We explored the utility of estimating effect estimates based on continuous exposures using methods described by Berlin et al. (1993) and operationalized in Stata using the generalized least squares (gls) and weighted least squares (wls) procedures (Orsini et al., 2006). Publication bias was examined using Funnel plots and Begg's and Egger's tests (Sterne and Harbord, 2004; Harbord and Higgins, 2008).

3. Results

3.1. Descriptive summary of studies

After review of the title and abstract of 2026 unique records identified in the literature search, 301 were selected by either reviewer for review of the full paper to determine eligibility for inclusion. 61 studies met the inclusion criteria and one additional study was identified through review of the reference lists of relevant papers (Fig. 1). Characteristics of individual studies are summarized in Table 1. Most employed a retrospective cohort design using administrative birth record data, while five were case-control studies and two were classified as ecologic because annual average air pollution concentrations were used to represent exposures, rather than accounting for gestational periods in

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