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EXPOSURE TO AIR POLLUTANTS DURING PREGNANCY AND OUTCOME AT BIRTH. AN EPIDEMIOLOGICAL STUDY IN LOMBARDY 2004-2008.

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SECTION 1:

SYSTEMATIC REVIEW OF THE CURRENT EVIDENCES ABOUT THE IMPACT OF AMBIENT AIR POLLUTION ON BIRTH OUTCOMES.

BACKGROUND

Air pollution has been associated with several adverse effects on human health. Many large studies have demonstrated that increases in ambient air pollution result in increased morbidity and mortality in the general population.[1-3] In the last fifteen years, the possible link between exposure to air pollution and health effects has been intensively scrutinized, not only because of impacts to adults, but also because of a possible role in pregnancy outcomes. In fact, recent studies highlighted a possible relationship between high levels of air pollutants, such as particulate matter (PM), carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone (O_3) and pregnancy outcomes such as low birth weight, prematurity and intrauterine growth retardation. Low birth weight and preterm birth are quite common in the general population (5 – 10% of total live births) and are responsible for a large portion of perinatal morbidity and mortality in Western countries. Intrauterine growth retardation has been associated in several studies with an increased risk of developing chronic illnesses, such as diabetes, hypertension and cardiovascular diseases in adult life.[4-6]

Four systematic reviews examining air pollution exposure and pregnancy outcomes were published between 2004 and 2005. The outcomes of interest were preterm delivery (PD) (defined as birth < 37 weeks), and intrauterine growth retardation or low birth weight (LBW) (defined as weight at birth < 2500 g).[7-10] Reviewers evaluated a total of 31 original studies published between 1984 and 2004.

Most of the 31 studies were included in more than one review, and nine studies were included in all four of the reviews.[11-19] Conclusions of the four reviews were not consistent, and they failed to identify which adverse pregnancy outcome was more clearly associated with air pollution exposure, mainly because of the wide variability of the results among the different studies. Specifically, Sram and colleagues and Lacasaña and colleagues, while suggesting a strong association between air pollution and low birth weight, proclaimed the evidence of an effect of air pollution on preterm delivery was insufficient. In contrast, Maisonet and colleagues highlighted the possible association between air pollution and preterm delivery. Finally, Glinianaia and colleagues judged the available evidence as compatible with "*either a small adverse effect of particulate air pollution on fetal growth and duration of pregnancy or with no effect*".

All four reviews suggested the variability of results among studies could be attributed to the use of different study methods. First, the methods used to assign air pollution concentrations and exposure levels (selection of monitoring stations, distance from known source of pollution, etc.) differed greatly among studies, as did the periods of pregnancy considered and the outcomes studied. In addition, the control of many environmental and maternal factors that could be important confounders was insufficient. The heterogeneity of the published studies explains why only one of the four reviews [7] conducted a meta-analysis in a subgroup of papers considered sufficiently homogeneous - the studies investigating the possible effect of PM_{10}, SO_2 and CO exposure on low birth weight.

From 2004 on, researchers took better care to design studies that considered a number of methodological issues, including the need to distinguish between two main determinants of low birth weight: intrauterine growth retardation and shortening of the entire pregnancy (eventually resulting in a preterm delivery). It is essential to understand whether low birth rate refers to a term baby weighting less than 2500 g, or to a preterm baby having a weight appropriate for his or her gestational age. Researchers also took more care to identify the most dangerous among the various

air pollutants and highlight which period of pregnancy is more susceptible to the adverse effects of air pollution exposure.

In this paper, we review studies published from 2004 to 2008 that looked at how exposure to air pollutants may affect pregnancy outcomes. We discuss whether the recent literature was able to bridge the gap in knowledge that previous reviews concordantly identified, and offer suggestions for future research.

METHODS

Literature search strategy

We conducted a systematic search in the electronic database PubMed for the period January 2004 to December 2008. The following medical subject headings (MeSH terms) were used: "air pollution", "air pollutants", "pregnancy", "infant, premature", "obstetric labor, premature", "premature birth", "birth weight", "gestational age", "fetal growth retardation", "infant, small for gestational age". We limited our search to studies on humans and papers written in English and containing an abstract. Two authors independently screened the papers based on information in the abstracts and selected those papers considered relevant based on the screening criteria described below. Disparities were settled by consensus and full text paper copies of all relevant reports were obtained for further review.

Outcomes definition

The papers identified by the search were screened for at least one of the following outcomes at birth: preterm delivery, low birth weight, and/or Small for Gestational Age (SGA). Most authors defined preterm delivery as birth of a living baby at less than 37 weeks gestational age. Birth weight was investigated as a continuous variable (often using linear regression models) in studies considering baby weight at birth in grams. Term low birth weight was usually defined as a baby

born after 37 weeks gestation with a birth weight of less than 2500 g. Several studies included an evaluation of SGA newborns whose birth weight was below the 10^{th} percentile for their gestational age and gender. Normal distribution of birth weight for gestational age and gender are usually country- or region-based. Thus, the cutoff point by which a baby was considered SGA could slightly vary.

Data abstraction

For each original paper selected for our review we tabulated the first authors, year of publication, city (or region) and country in which pregnancies occurred, calendar year(s) in which pregnancies occurred (defined as study period), study design (dividing birth cohort, case-control and studies based only on temporal variability of exposure, i.e. time-series), exposure assessment method (describing how individual maternal exposure was estimated based on Air Quality Monitoring Stations (AQMSs) data), number of pregnancies investigated, and exposure concentration.

Both mean and standard deviation (SD) exposure concentrations were given in most studies. However, some studies only reported means (without SD) while others did not report the mean but provided minimum and maximum values. To compare different exposure levels among studies we expressed PM_{10}, $PM_{2.5}$, NO_2 and O_3 concentrations in $\mu g/m^3$ and CO concentrations in mg/m^3. When air concentrations of gaseous pollutants were reported as parts-per-million (ppm) or as parts-per-billion (ppb) we calculated the corresponding mass concentration using the following conversion factors (according to the European Commission data):

CO: 1 ppm = 1.16 mg/m^3; NO_2: 1 ppb = 1.91 $\mu g/m^3$; O_3: 1 ppb = 2.00 $\mu g/m^3$.

Studies were first grouped by outcome, and then by pollutant (PM_{10}, CO, NO_2, O_3 and $PM_{2.5}$) and finally by period of pregnancy (first, second, third trimester, entire pregnancy). For each "outcome-pollutant-pregnancy period" combination we reported relative measures of association with 95% confidence intervals. When birth weight was investigated as a continuous variable we reported

multiple linear regression coefficients (beta), while for preterm delivery, term low birth weight and SGA we reported the odds of an outcome, or the Odds Ratio (OR). When available, we reported results from the time series analysis. In addition, to minimize misclassification of maternal exposure, we used air pollution measurements from the smallest possible exposure area to more accurately reflect the local air pollution.

To increase comparability among studies, we calculated relative measures of effect for a standard increase in exposure, assuming a linear effect. Specifically, we reported beta/ORs for an increase of 10 $\mu g/m^3$ in PM_{10}, NO_2 and O_3 exposure, and 1 mg/m^3 for CO exposure and 1 $\mu g/m^3$ for $PM_{2.5}$ exposure. When original papers reported exposure quartiles with associated ORs we reported the last quartile-specific OR standardized by the difference between the upper level of the first quartile of exposure and the lower level of the fourth quartile. For example, Leem et al. [20] reported an OR of PD equal to 1.27 for PM_{10}, in the fourth quartile of exposure (first trimester); the first and last quartile exposure ranges were 26.99-45.94 $\mu g/m^3$ and 64.57-106.39 $\mu g/m^3$, respectively. We reported a unique standardized OR calculated as follow:

OR for a 10 $\mu g/m^3$ increase = $\frac{\ln(1.27)}{(64.57-45.94)/10} = 1.134$ (see Table 2).

RESULTS

Studies selected for review

Our search identified 38 relevant studies. Among these, we excluded 13 papers that presented no original data and focused on methodological issues only, [21-33] and 7 papers that did not provide information about air pollution levels [34-38] or whose outcomes were not comparable [39, 40] with those considered by most other studies. The remaining 18 original studies were included in this review.[20, 41-57] [49]First authors, publication year, study location, period of investigation, exposure assessment methods and study design of these 18 studies are shown in Table 1.

Table 1: main characteristics of the revised epidemiological studies.

1st Author (pub yr)	Study Location	Study Period	Study Design	Exposure assessment method
Bell (2007)	MA, CT (USA)	1999 - 2002	Birth cohort	Mean of the AQMSs in each county
Brauer (2008)	Vancouver (Canada)	1999 - 2002	Birth cohort	a) Based on closest postcode AQMS b) Distance weighted mean of the postcode nearest 3 AQMSs
Dugandzic (2006)	Nova Scotia (Canada)	1988 - 2000	Birth cohort	Distance weighted mean of the AQMSs within 25 Km to the maternal address
Gouveia (2004)	Sao Paulo (Brazil)	1997	Time series	Mean measures of all the city AQMSs
Hansen (2006; 2007)	Brisbane (Australia)	2000 - 2003	Time series	Mean measures of all the city AQMSs
Huynh (2006)	California (USA)	1999 - 2000	Matched case-control study	Based on maternal residence closest AQMS (within 8.5 Km)
Jalaludin (2007); Mannes (2005)	Sidney (Australia)	1998 - 2000	a) Time series b) Birth cohort	a) Mean measures of all the city AQMSs b) Mean of the AQMS data within 5 Km to maternal postcode of residence
Kim (2007)	Seoul (South Korea)	2001 - 2004	Birth cohort	Closest AQMS to the maternal address
Leem (2006)	Incheon (South Korea)	2001 - 2002	Birth cohort	Ordinary block kriging based on AQMSs
Lin (2004)	Taiwan	1995 - 1997	Birth cohort	Based on city district closest AQMS (max 3 Km)
Liu (2007)	Canada	1986 - 2000	Birth cohort	Mean of the AQMSs in each residential area
Parker (2005)	California (USA)	2000	Birth cohort	Mean of AQMSs located within 8.5 Km to maternal address
Ritz (2007)	California (USA	2007	Birth cohort	Each postcode area was associated to the closest AQMS
Sagiv (2005)	Pennsylvania (USA)	1997 - 2001	Time series	Mean measures of all country AQMSs
Salam (2005)	California (USA)	1975 - 1987	Birth cohort	a) Based on AQMS within 5 Km to the maternal postcode of residence b) Based on the maternal address closest AQMS (various distances)

1st Author (pub yr)	Study Location	Study Period	Study Design	Exposure assessment method
Wilhelm (2005)	California (USA)	1994 - 2000	Birth cohort	a) Based on closest AQMS within 3.5 Km to the maternal postcode of residence b) Distance weighted mean of the AQMS within 50 Km to the maternal postcode

Exposure assessment

In all 18 studies, exposure assessment was based on data from AQMSs the authors used to provide estimates of the concentrations of pollutants in a geographical region. Researchers mainly used two approaches to define an area related to one or more AQMS data: some authors used data from the closest AQMS within a given distance, ranging from 1.7 Km [57] to 50 Km [56] from maternal residence, while others used the mean value of all AQMSs within a given administrative unit, such as a county,[41, 47, 55] citywide area,[44, 45] city district,[50] or ZIP code area.[42, 54] Leem et al. used a third approach that utilized an ordinary kriging method based on AQMS data to construct spatial and temporal exposure models.

Maternal georeferentiation

All studies based maternal exposure estimates during pregnancy on residence at delivery. The precision of available residence data varied across studies, with some authors reporting only the city of residence [44] while others considered the postcodes.[48, 52, 56, 57] Two studies were able to perform a georeferentiation of maternal address (street level).[43, 53]

Study design

Thirteen of the 18 papers presented a birth cohort analysis that compared outcomes across locations with different levels of ambient air pollution. This approach takes advantage of both spatial and temporal exposure. To remove the influence of covariates across geographic locations (diet, socio-economic status, etc), six studies performed time-series analyses that compared temporal variation of pollutant levels in a given geographic area with the variations of time trends in adverse pregnancy outcomes.

Only five studies reported results that considered different models of exposure assessment.[42, 48, 52, 56, 57] Mannes et al. and Jalaludin et al. presented birth weight and gestational age results, respectively, by comparing a time series analysis of the mean pollutant level in Sydney (n = 14 AQMSs), with data from the closest AQMS to the maternal residence. Salam and collaborators conducted a sensitivity analysis comparing results from AQMSs within 5 Km of the maternal residence with distance-weighted means of the AQMSs within 50 km.

Wilhelm et al. compared analyses based on AQMSs within 3.4 Km (2 mi) to the maternal postcode of residence and results from the AQMSs at different distances (1, 2, 4 mi) from maternal address. Brauer et al. performed two different analyses based on AQMS data; one used data from the nearest station within 10 Km, and one used a distance-weighted mean of the three nearest AQMSs within 50 Km. Finally, we found only one case control study [47] nested in a birth cohort [53] in which each preterm baby was matched with three controls with similar dates of conception to control for seasonal variation.

Summary of evidence

The findings of the 18 studies are shown by pregnancy outcome in Tables 2 through 5, and by pollutant investigated in Figures 1 through 5 (online only material).

a) Preterm delivery (Table 2)

Eight studies evaluated the possible association between air pollution and preterm delivery. Six studies specifically examined the effect of PM_{10} exposure. We developed odds ratios for 14 pregnancy period-specific exposures standardized to an increase of 10 $\mu g/m^3$ PM_{10}. Eight out of the 14 cases showed a significant increase in preterm delivery risk with odds ratios ranging from 1.014 to 1.364. Two of the eight studies reported statistically significant increases in preterm delivery in the first trimester of pregnancy (13% and 36%, respectively).[20, 45] Exposure levels in these two studies were quite different and did not overlap.

The effect of carbon monoxide air pollution on preterm birth was investigated using data from five studies that allowed us to estimate 14 period-specific odds ratios standardized for an increase of 1 mg/m^3 in exposure. Most of the studies were associated with an increased risk of approximately 1.0, with the exception of data from Leem et al. (South Korea), which produced a two-fold increased risk in the first trimester and 78% increased risk in the third trimester. Data from Wilhelm et al. and Ritz et al. showed significant but smaller (ORs = 1.178 and 1.333, respectively) increases in preterm birth in the first trimester in women in California. Differences in exposure levels do not explain the different results among studies.

The effect of NO_2 exposure was investigated in four studies that gave 9 period-specific ORs. When adjusted for an increased exposure to 10 $\mu g/m^3$, the data from Leem and colleagues in South Korea and Ritz and colleagues in California showed mild, yet statistically significant increases in risk of

preterm delivery when exposures occurred in the first and third trimester, and in the first trimester, respectively.

Three studies evaluated only O_3 and the risk of preterm delivery. An increase of 10 $\mu g/m^3$ in exposure resulted in estimations of seven period-specific odds ratios that ranged from 0.974 to 1.177. Statistically significant increases for exposure during the first trimester were reported by authors of two Australian studies, where we estimated odds ratios of 1.177 [45] and 1.072,[48] respectively. No significant increases in preterm delivery risk were found associated with exposure in the second or third trimester of pregnancy.

We estimated 10 period-specific odds ratios (5 of them >1.00) based on four studies that investigated $PM_{2.5}$ exposure reported when concentrations were standardized to an increase of 1 $\mu g/m^3$. When trimester specific estimates were considered, significant increases in preterm delivery risk were reported for the first trimester in only one study.[54] The case-control study conducted by Huynh showed a significant increase of risk during the first month of pregnancy, and the last two weeks of pregnancy, as well as the entire pregnancy, but did not provide trimester-specific risk estimates. .

Table 2: main characteristics of studies investigating preterm birth

1st Author (pub yr) **Study Location, Population**	**Time-window of Exposure**	**Pollutants Considered**	**Exposure Level***	**OR**	**(CI 95%)**
Kim (2007)	1st Trimester	PM_{10}	89.7 (44.5) µg/m^3	0.930	(0.870 - 1.010)
Seoul (South Korea), 1,514	2nd Trimester	PM_{10}	89.4 (45.1) µg/m^3	1.000	(0.930 - 1.070)
	3rd Trimester	PM_{10}	88.8 (47.6) µg/m^3	1.050	(0.990 - 1.110)
Ritz (2007)	1st Trimester	CO	0.67 - 1.45 mg/m^3	1.333	(1.157 - 1.513)
California (USA), 66,795		NO_2	49.9 - 69.5 µg/m^3	1.045	(1.000 - 1.092)
		O_3	43.4 - 70.8 µg/m^3	0.974	(0.993 - 1.002)
		$PM_{2.5}$	18.6 - 21.4 µg/m^3	1.036	(1.004 - 1.069)
	Last 6 Weeks	CO	0.67 - 1.45 mg/m^3	1.039	(0.974 - 1.184)
	Entire Pregnancy	CO	0.67 - 1.45 mg/m^3	1.039	(0.886 - 1.224)
Jalaludin (2007)	First Month	PM_{10}	16.3 (6.38) µg/m^3	0.644	(0.761 - 0.932)
Sidney (Australia), 123,840		CO	1.04 (0.19) mg/m^3	0.910	(0.862 - 0.959)
		NO_2	44.7 (14.5) µg/m^3	0.839	(0.799 - 0.876)
		O_3	61.8 (28.4) µg/m^3	1.020	(0.975 - 1.061)
		$PM_{2.5}$	9.0 (3.94) µg/m^3	0.981	(0.962 - 1.000)
	1st Trimester	PM_{10}	16.3 (6.38) µg/m^3	0.877	(0.761 - 1.010)
		CO	1.04 (0.19) mg/m^3	0.802	(0.749 - 0.859)
		NO_2	44.7 (14.5) µg/m^3	0.853	(0.803 - 0.900)
		O_3	61.8 (28.4) µg/m^3	1.072	(1.025 - 1.115)
		$PM_{2.5}$	9.0 (3.94) µg/m^3	0.978	(0.950 - 1.007)
	3rd Trimester	PM_{10}	16.3 (6.38) µg/m^3	0.895	(0.776 - 1.041)
		CO	1.04 (0.19) mg/m^3	1.043	(0.991 - 1.094)
		NO_2	44.7 (14.5) µg/m^3	1.032	(0.964 - 1.104)
		O_3	61.8 (28.4) µg/m^3	0.990	(0.946 - 1.035)
		$PM_{2.5}$	9.0 (3.94) µg/m^3	0.981	(0.952 - 1.011)
	Last Month	PM_{10}	16.3 (6.38) µg/m^3	0.914	(0.809 - 1.030)
		CO	1.04 (0.19) mg/m^3	0.967	(0.904 - 1.036)
		NO_2	44.7 (14.5) µg/m^3	1.000	(0.949 - 1.059)
		O_3	61.8 (28.4) µg/m^3	0.990	(0.937 - 1.030)
		$PM_{2.5}$	9.0 (3.94) µg/m^3	0.984	(0.962 - 1.008)
Huynh (2006)	First Month	CO	0.99 (0.37) mg/m^3	1.026	(0.939 - 1.111)
California (USA), 42,692		$PM_{2.5}$	18.8 (7.0) µg/m^3	1.012	(1.012 - 1.012)
	Last 2 Weeks	CO	0.96 (0.45) mg/m^3	0.974	(0.913 - 1.052)
		$PM_{2.5}$	18.6 (10.3) µg/m^3	1.006	(1.005 - 1.006)
	Entire Pregnancy	CO	0.93 (0.27) mg/m^3	0.983	(0.887 - 1.086)
		$PM_{2.5}$	18.0 (5.2) µg/m^3	1.014	(1.014 - 1.015)

1st Author (pub yr) Study Location - Population	Time-window of Exposure	Pollutants Considered	Exposure Level*	OR	(CI 95%)
Hansen (2006)	1st Trimester	PM_{10}	19.6 (9.4) $\mu g/m^3$	1.364	(1.138 - 1.642)
Brisbane (Australia), 28,200		NO_2	16.8 (7.8) $\mu g/m^3$	0.930	(0.779 - 1.121)
		O_3	53.4 (15.6) $\mu g/m^3$	1.177	(1.069 - 1.299)
	3rd Trimester	PM_{10}	19.6 (9.4) $\mu g/m^3$	1.071	(0.864 - 1.297)
		NO_2	16.8 (7.8) $\mu g/m^3$	1.035	(0.839 - 1.272)
		O_3	53.4 (15.6) $\mu g/m^3$	1.042	(0.920 - 1.179)
Leem (2006)	1st Trimester	PM_{10}	27.0 - 106.4 $\mu g/m^3$	1.134	(1.021 - 1.264)
Incheon (South Korea), 52,113		CO	0.47 - 1.27 mg/m^3	2.283	(1.231 - 2.844)
		NO_2	10.4 - 80.6 $\mu g/m^3$	1.084	(1.033 - 1.138)
	3rd Trimester	PM_{10}	33.1 - 95.9 $\mu g/m^3$	1.049	(0.949 - 1.157)
		CO	0.49 - 1.16 mg/m^3	1.811	(1.041 - 3.224)
		NO_2	11.9 - 76.1 $\mu g/m^3$	1.071	(1.025 - 1.120)
Wilhelm (2005)	1st Trimester	PM_{10}	32.9 - 43.9 $\mu g/m^3$	1.101	(0.923 - 1.314)
California (USA), 106,483		CO	1.13 - 2.17 mg/m^3	1.178	(1.030 - 1.336)
		$PM_{2.5}$	18.0 - 25.4 $\mu g/m^3$	0.974	(0.931 - 1.019)
	Last 6 Weeks	PM_{10}	31.8 - 44.1 $\mu g/m^3$	1.097	(0.934 - 1.292)
		CO	1.0 - 2.11 mg/m^3	1.009	(0.897 - 1.140)
Sagiv (2005)	Last 6 Weeks	PM_{10}	25.3 (14.6) $\mu g/m^3$	1.014	(0.996 - 1.034)
Pennsylvania (USA), 187,997					

* = x (y) = mean (SD); x - y = min – max.

b) Term Low Birth Weight (Table 3)

The effect of PM_{10} concentration on the risk of delivering a term low birth weight baby was investigated in seven studies, with a total of 17 period specific odds ratios. Eleven studies showed increased risks ranging from 1.037 to 1.480, and two studies [43, 57] were borderline significant. Lin et al. reported no association consistently across each trimester.

Exposure to CO and low birth weight was considered in five birth cohort studies, resulting in 11 estimated odds ratios. None of the studies showed a clear association between exposure to CO and low birth weight, with the important exception of the study by Wilhelm and colleagues who

reported a 35% increase in risk for the third trimester. Unfortunately, the authors failed to present risk estimates for any other time period and for the entire pregnancy.

NO_2 exposure was analyzed in four of the same five cohort studies, resulting in 10 period specific ORs. Three out of the four studies showed a small adverse exposure-related effect (ranging from 1.029 to 1.110) when the entire pregnancy was considered. Two studies reported trimester specific estimates,[50, 56] but neither study showed increased risks.

We estimated trimester specific ORs for three studies that evaluated ozone exposure. None of the studies showed significantly increased odds of low birth weight.

Two studies investigated the effects of $PM_{2.5}$ exposure across the entire pregnancy, and only one [41] showed a small but statistically significant adverse exposure-related effect (OR=1.024).

Table 3: main characteristics of studies investigating Low Birth Weight

1st Author (pub yr) **Study Location, Population**	**Time-window of Exposure**	**Pollutants Considered**	**Exposure Level***	**OR**	**(CI 95%)**
Brauer (2008)	Entire Pregnancy	PM_{10}	12.5 µg/m^3	1.105	(0.599 - 2.159)
Vancouver (Canada), 70,249		CO	0.61 mg/m^3	1.219	(0.665 - 2.367)
		NO_2	32.5 µg/m^3	1.110	(1.010 - 1.230)
		$PM_{2.5}$	5.1 µg/m^3	0.980	(0.920 - 1.050)
Kim (2007)	1st Trimester	PM_{10}	89.7 (44.5) µg/m^3	1.070	(0.960 - 1.190)
Seoul (South Korea), 1,514	2nd Trimester	PM_{10}	89.4 (45.1) µg/m^3	1.070	(0.940 - 1.220)
	3rd Trimester	PM_{10}	88.8 (47.6) µg/m^3	1.050	(0.960 - 1.160)
Bell (2007)	Entire Pregnancy	PM_{10}	22.3 (5.3) µg/m^3	1.037	(0.988 - 1.087)
MA, CT (USA), 358,504		CO	0.76 (0.21) mg/m^3	1.082	(0.952 - 1.225)
		NO_2	33.2 (9.55) µg/m^3	1.029	(1.002 - 1.056)
		$PM_{2.5}$	11.9 (1.6) µg/m^3	1.024	(1.010 - 1.039)
Dugandzic (2006)	1st Trimester	PM_{10}	17 µg/m^3	1.188	(1.000 - 1.416)
Nova Scotia (Canada), 74,284		O_3	42.0 µg/m^3	0.986	(0.898 - 1.077)
	2nd Trimester	PM_{10}	17 µg/m3	1.040	(0.865 - 1.254)
		O_3	42.0 µg/m^3	1.021	(0.935 - 1.125)
	3rd Trimester	PM_{10}	17.0 µg/m3	0.980	(0.792 - 1.188)
		O_3	42.0 µg/m^3	1.000	(0.905 - 1.105)

1st Author (pub yr) Study Location, Population	Time-window of Exposure	Pollutants Considered	Exposure Level*	OR	(CI 95%)
Salam (2005)	1st Trimester	PM_{10}	46.6 (15.9) µg/m^3	1	(0.837 - 1.225)
California (USA), 3,901		CO	2.09 (1.28) mg/m^3	1.000	(0.803 - 1.284)
		NO_2	69.9 (32.3) µg/m^3	0.978	(0.865 - 1.089)
		O_3	55.0 (28.2) µg/m^3	1.000	(0.900 - 1.080)
	2nd Trimester	PM_{10}	45.4 (14.8) µg/m^3	1.101	(0.889 - 1.322)
		CO	2.09 (1.28) mg/m^3	0.937	(0.730 - 1.175)
		NO_2	69.1 (32.3) µg/m^3	1.000	(0.899 - 1.103)
		O_3	54.0 (25.6) µg/m^3	1.000	(0.933 - 1.135)
	3rd Trimester	PM_{10}	45.4 (15.5) µg/m^3	1.140	(0.949 - 1.378)
		CO	2.09 (1.28) mg/m^3	0.789	(0.632 - 1.065)
		NO_2	67.8 (31.7) µg/m^3	0.899	(0.825 - 1.020)
		O_3	55.0 (26.6) µg/m^3	1.028	(0.936 - 1.127)
	Entire Pregnancy	PM_{10}	45.8 (12.9) µg/m^3	1.157	(0.883 - 1.550)
		CO	2.09 (1.04) mg/m^3	0.852	(0.693 - 1.207)
		NO_2	68.95 (29.4) µg/m^3	0.954	(0.825 - 1.073)
Wilhelm (2005)	3rd Trimester	PM_{10}	32.8 - 43.4 µg/m^3	1.480	(1.000 - 2.190)
California (USA), 136,134		CO	1.06 - 2.11 mg/m^3	1.352	(1.039 - 1.740)
Lin (2004)	1st Trimester	PM_{10}	45.8 - 67.6 µg/m^3	0.982	(0.875 - 1.099)
Taiwan, 92,288		CO	1.28 - 16.47 mg/m^3	0.993	(0.981 - 1.006)
		NO_2	46.4 - 66.3 µg/m^3	1.044	(0.943 - 1.150)
		O_3	33.4 - 79.2 µg/m^3	1.004	(0.965 - 1.044)
	2nd Trimester	PM_{10}	44.6 - 64.2 µg/m^3	1	(0.909 - 1.102)
		CO	1.28 - 17.7 mg/m^3	1.000	(0.988 - 1.012)
		NO_2	45.8 - 65.7 µg/m^3	0.964	(0.877 - 1.059)
		O_3	34.8 - 88.6 µg/m^3	0.987	(0.955 - 1.021)
	3rd Trimester	PM_{10}	43.7 - 63.7 µg/m^3	0.985	(0.900 - 1.082)
		CO	1.39 - 17.75 mg/m^3	0.991	(0.979 - 1.002)
		NO_2	45.5 - 65.3 µg/m^3	0.927	(0.842 - 1.015)
		O_3	37.8 - 91.4 µg/m^3	1.009	(0.974 - 1.044)
	Entire Pregnancy	PM_{10}	46.4 - 63.1 µg/m^3	0.893	(0.757 - 1.040)
		CO	1.50 - 17.6 mg/m^3	0.984	(0.972 - 1.996)
		NO_2	49.9 - 62.8 µg/m^3	1.046	(0.914 - 1.195)

* = x (y) = mean (SD); x - y = min - max; x = mean, SD not given.

c) Small for Gestational Age (Table 4)

PM_{10} exposure and the risk of SGA were investigated in four studies, each resulting in three trimester specific ORs. The results of the four studies were not consistent. Sparse modest increased risks were seen, but they were not significant and occurred in different time windows.

CO exposure was investigated in three studies and produced nine ORs for SGA. The largest study (over 300,000 subjects) was characterized by the highest exposure levels (mean = 1.28 mg/m^3) and showed statistically significant increased risks with exposure in each trimester (1.153 in the first trimester to 1.128 in the second trimester).[51] The other two studies did not show increased risks with exposure to CO.

NO_2 exposure was also investigated in the same three cohort studies. Liu and collaborators reported significant adverse effects in each trimester, whereas Mannes et al. reported a 5% increase in risk of adverse effects only in the third trimester. The exposure levels were similar in both studies (around 45 $\mu g/m^3$). Hansen et al. looked at results associated with lower exposure levels (mean = 12.8 $\mu g/m^3$) and found no increased risks.

The same three cohort studies were also used to estimate risk estimates for ozone exposure. No adverse effect on birth outcomes was observed with exposures in any of the trimesters. Two studies showed a decreased risk of SGA when exposure occurred in the third trimester.[46, 51]

Three studies investigated $PM_{2.5}$ effects resulting in a total of nine trimester-specific ORs. The report by Liu and collaborators showed a very small, although significant, increase (<1% for a 1 $\mu g/m^3$ $PM_{2.5}$ increase) for exposure in each trimester of pregnancy. A 3% significant increase for each trimester was also found in the study by Parker et al., while a third study [52] showed a similar effect that was limited to the second trimester.

Table 4: main characteristics of studies investigating Small for Gestational Age

1st Author (pub yr) **Study Location, Population**	**Time-window of Exposure**	**Pollutants Considered**	**Exposure Level***	**OR**	**(CI 95%)**
Kim (2007)	1st Trimester	PM_{10}	89.7 (44.5) µg/m^3	1.140	(0.990 - 1.310)
Seoul (South Korea), 1,514	2nd Trimester	PM_{10}	89.4 (45.1) µg/m^3	0.930	(0.770 - 1.130)
	3rd Trimester	PM_{10}	88.8 (47.6) µg/m^3	0.850	(0.670 - 1.080)
Liu (2007)	1st Trimester	CO	1.28 mg/m^3	1.153	(1.12 - 1.195)
Canada, 386,202		NO_2	45.8 µg/m^3	1.040	(1.023 - 1.058)
		O_3	33 µg/m^3	0.990	(0.973 - 1.007)
		$PM_{2.5}$	12.2 µg/m^3	1.007	(1.003 - 1.010)
	2nd Trimester	CO	1.28 mg/m^3	1.128	(1.086 - 1.162)
		NO_2	45.8 µg/m^3	1.035	(1.015 - 1.051)
		O_3	33 µg/m^3	0.986	(0.969 - 1.003)
		$PM_{2.5}$	12.2 µg/m^3	1.006	(1.003 - 1.010)
	3rd Trimester	CO	1.28 mg/m^3	1.162	(1.12 - 1.204)
		NO_2	45.8 µg/m^3	1.040	(1.023 - 1.058)
		O_3	33 µg/m^3	0.980	(0.962 - 0.993)
		$PM_{2.5}$	12.2 µg/m^3	1.006	(1.003 - 1.010)
Hansen (2007)	1st Trimester	PM_{10}	19.6 (9.4) µg/m^3	1.050	(0.950 - 1.152)
Brisbane (Australia), 26,617		NO_2	16.8 (7.8) µg/m^3	1.008	(0.971 - 1.046)
		O_3	53.4 (15.6) µg/m^3	1.005	(0.943 - 1.072)
	2nd Trimester	PM_{10}	19.6 (9.4) µg/m^3	0.938	(0.852 - 1.050)
		NO_2	16.8 (7.8) µg/m^3	0.954	(0.925 - 0.987)
		O_3	53.4 (15.6) µg/m^3	1.000	(0.927 - 1.082)
	3rd Trimester	PM_{10}	19.6 (9.4) µg/m^3	0.913	(0.816 - 1.038)
		NO_2	16.8 (7.8) µg/m^3	0.978	(0.947 - 1.010)
		O_3	53.4 (15.6) µg/m^3	0.911	(0.843 - 0.985)
Mannes (2005)	1st Trimester	PM_{10}	16.8 (7.1) µg/m^3	1.000	(0.817 - 1.219)
Sidney (Australia), 138,056		CO	0.93 (0.81) mg/m^3	0.957	(0.896 - 1.034)
		NO_2	44.3 (14.1) µg/m^3	1.000	(0.949 - 1.053)
		O_3	63.2 (29.2) µg/m^3	1.000	(1.000 - 1.051)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	0.990	(0.970 - 1.010)
	2nd Trimester	PM_{10}	16.8 (7.1) µg/m^3	1.105	(1.000 - 1.480)
		CO	0.93 (0.81) mg/m^3	0.991	(0.913 - 1.086)
		NO_2	44.3 (14.1) µg/m^3	1.000	(0.949 - 1.053)
		O_3	63.2 (29.2) µg/m^3	1.000	(1.000 - 1.051)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	1.030	(1.010 - 1.050)
	3rd Trimester	PM_{10}	16.8 (7.1) µg/m^3	1.000	(0.904 - 1.138)
		CO	0.93 (0.812) mg/m^3	1.009	(0.922 - 1.094)
		NO_2	44.3 (14.1) µg/m^3	1.053	(1.000 - 1.109)
		O_3	63.2 (29.2) µg/m^3	1.000	(1.000 - 1.051)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	0.990	(0.970 - 1.020)

1st Author (pub yr) Study Location, Population	Time-window of Exposure	Pollutants Considered	Exposure Level*	OR	(CI 95%)
Parker (2005)	1st Trimester	CO	0.66 - 1.08 mg/m^3	0.798	(0.518 - 1.229)
California (USA), 18,247		$PM_{2.5}$	11.9 - 18.4 µg/m^3	1.036	(1.006 - 1.065)
	2nd Trimester	CO	0.66 - 1.08 mg/m^3	0.586	(0.37 - 0.93)
		$PM_{2.5}$	11.9 - 18.4 µg/m^3	1.034	(1.006 - 1.063)
	3rd Trimester	CO	0.66 - 1.08 mg/m^3	0.777	(0.502 - 1.256)
		$PM_{2.5}$	11.9 - 18.4 µg/m^3	1.030	(1.003 - 1.057)

* = x (y) = mean (SD); x - y = min - max; x = mean, SD not given.

d) Birth Weight as a continuous variable (Table 5)

The effect of PM_{10} exposure during pregnancy on birth weight was investigated in six original studies conducted in Brazil, Australia and the United States. Fourteen of 19 period specific risk estimates showed an association between exposure and lower birth weights (<25 g) when exposures were aligned to an increase of 10 µg/m^3. The six studies had different levels of exposure (17 to 60 µg/m^3), and all showed statistically significant decreases in birth weight. No consistency across studies was evident with regard to the period of pregnancy in which the effects were found.

CO exposure during pregnancy was analyzed in five studies (18 period specific estimates; 10 showing a decrease in birth weight). Significant adverse effects were observed in the first trimester in three of the studies, done in Brazil,[44] California [56] and Connecticut.[41] The Connecticut study also reported a decrease in birth weight in the third trimester and throughout the entire pregnancy. The three studies had very different mean exposure levels. A fourth study [52] showed a significant decrease in birth weight in the last month of pregnancy.

NO_2 exposure was included in five of the studies we reviewed, presenting a total of 15 period specific estimates, of which 10 suggested a decrease in birth weight. Data from Mannes et al. showed statistically significant decreases in birth weight in the first and third trimester. The report

by Bell et al. considered only the entire pregnancy, resulting in an estimated decrease in weight of 10 g for a 10 $\mu g/m^3$ NO_2 exposure increase.

Four studies investigated O_3 effects (14 period specific estimations). Three studies observed an inverse relationship between exposure and birth weight while an Australian cohort study showed an exposure related increase. Only one small study in California by Salam and colleagues produced statistically significant results.

Although $PM_{2.5}$ exposure was investigated only in three birth cohort studies [41, 52, 53], most of the estimates showed small but statistically significant decreases in birth weight for increasing levels of exposure in each trimester and also in the entire pregnancy.

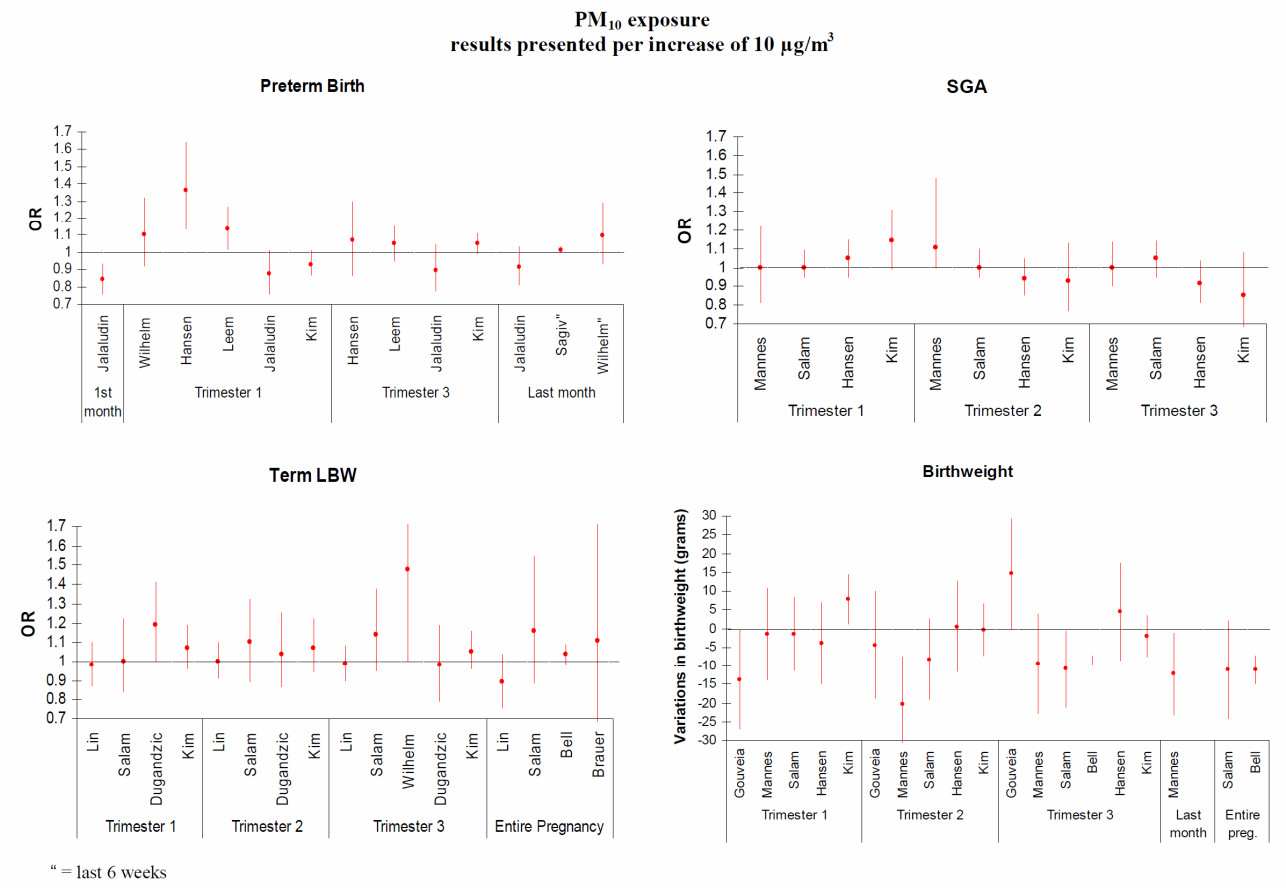
Table 5: main characteristics of studies investigating birth weight as a continuous variable

1st Author (pub yr) **Study Location, Population**	**Time-window of Exposure**	**Pollutants Considered**	**Exposure Level***	**β (gr)**	**(CI 95%)**
Hansen (2007)	1st Trimester	PM_{10}	19.6 (9.4) $\mu g/m^3$	-4.0	(-14.9 - +6.9)
Brisbane (Australia), 26,617		NO_2	16.8 (7.8) $\mu g/m^3$	+15.8	(-4.0 - +35.5)
		O_3	53.4 (15.6) $\mu g/m^3$	+1.5	(-5.5 - +8.4)
	2nd Trimester	PM_{10}	19.6 (9.4) $\mu g/m^3$	+0.5	(-1.2 - +1.3)
		NO_2	16.8 (7.8) $\mu g/m^3$	+8.8	(-8.4 - +26.0)
		O_3	53.4 (15.6) $\mu g/m^3$	+2.30	(-6.0 - +10.6)
	3rd Trimester	PM_{10}	19.6 (9.4) $\mu g/m^3$	+4.5	(-8.6 - +17.5)
		NO_2	16.8 (7.8) $\mu g/m^3$	-9.1	(-27.0 - +8.8)
		O_3	53.4 (15.2) $\mu g/m^3$	+6.0	(-2.3 - +14.3)
Bell (2007)	1st Trimester	CO	0.76 (0.21) mg/m^3		(-32.1 - -28.2)
MA, CT (USA), 358,504		$PM_{2.5}$	11.9 (1.6) $\mu g/m^3$		(-3.3 - -2.5)
	3rd Trimester	PM_{10}	22.3 (5.3) $\mu g/m^3$		(-9.7 - -7.3)
		CO	0.76 (0.21) mg/m^3		(-39.8 - -46.4)
		$PM_{2.5}$	11.9 (1.6) $\mu g/m^3$		(-4.1 - -3.2)
	Entire Pregnancy	PM_{10}	22.3 (5.3) $\mu g/m^3$	-11.1	(-7.2 - -15.0)
		CO	0.76 (0.21) mg/m^3	-46.1	(-56.0 - -35.8)
		NO_2	33.2 (9.55) $\mu g/m^3$	-9.7	(-11.8 - -7.6)
		$PM_{2.5}$	11.9 (1.6) $\mu g/m^3$	-6.7	(-7.8 - -5.6)
Kim (2007)	1st Trimester	PM_{10}	89.7 (44.5) $\mu g/m^3$	+7.8	(+1.2 - +14.5)
Seoul (South Korea), 1,514	2nd Trimester	PM_{10}	89.4 (45.1) $\mu g/m^3$	-0.3	(-0.7 - +0.7)
	3rd Trimester	PM_{10}	88.8 (47.6) $\mu g/m^3$	-2.1	(-7.5 - +3.4)
Salam (2005)	1st Trimester	PM_{10}	46.6 (15.9) $\mu g/m^3$	-1.5	(-11.4 - +8.4)
California (USA), 3,901		CO	2.09 (1.28) mg/m^3	-13.4	(-26.0 - -0.7)
		NO_2	69.9 (32.3) $\mu g/m^3$	-3.2	(-8.3 - +1.9)
		O_3	55 (28.2) $\mu g/m^3$	-3.1	(-8.4 - +2.3)
	2nd Trimester	PM_{10}	45.4 (14.8) $\mu g/m^3$	-8.3	(-1.9 - +0.2)
		CO	2.09 (1.28) mg/m^3	+7.5	(-6.4 - +21.4)
		NO_2	69.1 (32.3) $\mu g/m^3$	+0.4	(-4.8 - +5.6)
		O_3	54 (25.6) $\mu g/m^3$	-10.0	(-15.8 - -4.2)
	3rd Trimester	PM_{10}	45.4 (15.5) $\mu g/m^3$	-10.9	(-21.1 - -0.6)
		CO	2.09 (1.28) mg/m^3	+7.8	(-5.6 - +21.3)
		NO_2	67.8 (31.7) $\mu g/m^3$	-1.3	(-6.5 - +4.0)
		O_3	55 (26.6) $\mu g/m^3$	-10.4	(-16.1 - -4.6)
	Entire Pregnancy	PM_{10}	45.8 (12.9) $\mu g/m^3$	-11.1	(-24.2 - +2.1)
		CO	2.09 (1.04) mg/m^3	+1.6	(-14.4 - +17.5)
		NO_2	69 (29.4) $\mu g/m^3$	-1.5	(-7.3 - +4.3)
		O_3	54.6 (17.4) $\mu g/m^3$	-19.7	(-27.9 - -11.4)

1st Author (pub yr) Study Location, Population	Time-window of Exposure	Pollutants Considered	Exposure Level*	β (gr)	(CI 95%)
Mannes (2005)	1st Trimester	PM_{10}	16.8 (7.1) µg/m^3	-1.4	(-13.7 - +10.9)
Sidney (Australia), 138,056		CO	0.93 (0.81) mg/m^3	+1.6	(-7.2 - +10.4)
		NO_2	44.3 (14.1) µg/m^3	-5.6	(-10.8 - -0.4)
		O_3	63.2 (29.2) µg/m^3	-0.5	(-3.3 - +2.4)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	+0.4	(-2.3 - +3.0)
	2nd Trimester	PM_{10}	16.8 (7.1) µg/m^3	-20.5	(-33.6 - -7.4)
		CO	0.93 (0.81) mg/m^3	-9.2	(-19.9 - +1.4)
		NO_2	44.3 (14.1) µg/m^3	-5.0	(-10.8 - +0.9)
		O_3	63.2 (29.2) µg/m^3	-3.8	(-6.9 - -0.6)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	-4.1	(-6.8 - -1.4)
	3rd Trimester	PM_{10}	16.8 (7.1) µg/m^3	-9.5	(-23.0 - +4.0)
		CO	0.93 (0.81) mg/m^3	-5.7	(-16.0 - +4.6)
		NO_2	44.3 (14.1) µg/m^3	-7.7	(-14.1 - -1.4)
		O_3	63.2 (29.2) µg/m^3	-2.3	(-5.4 - +0.9)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	-1.0	(-3.7 - +1.8)
	Last Month	PM_{10}	16.8 (7.1) µg/m^3	-12.1	(-23.1 - -1.1)
		CO	0.93 (0.81) mg/m^3	-13.2	(-22.1 - -4.3)
		NO_2	44.31 (14.13) µg/m^3	-4.0	(-9.0 - +1.0)
		O_3	63.2 (29.2) µg/m^3	-0.6	(-2.8 - +1.7)
		$PM_{2.5}$	9.4 (5.1) µg/m^3	-2.5	(-4.6 - -0.4)
Parker (2005)	1st Trimester	CO	0.66 – 1.08 mg/m^3	-17.5	(-71.1 - +35.9)
California (USA), 18,247		$PM_{2.5}$	11.9 - 18.4 µg/m^3	-5.5	(-9.0 - -2.0)
	2nd Trimester	CO	0.66 – 1.08 mg/m^3	+34.0	(-21.3 - +89.3)
		$PM_{2.5}$	11.9 - 18.4 µg/m^3	-7.2	(-10.6 - -3.8)
	3rd Trimester	CO	0.66 – 1.08 mg/m^3	-20.1	(-77.1 - +36.6)
		$PM_{2.5}$	11.9 - 18.4 µg/m^3	-4.9	(-8.0 - -1.7)
	Entire Pregnancy	CO	0.66 – 1.08 mg/m^3	+6.2	(-49.3 - +61.8)
		$PM_{2.5}$	11.9 - 18.4 µg/m^3	-5.4	(-9.0 - -1.8)
Gouveia (2004)	1st Trimester	PM_{10}	60.3 (25.2) µg/m^3	-13.7	(-27.0 - -0.4)
Sao Paulo (Brazil), 179,460		CO	4.29 (1.86) mg/m^3	-19.9	(-35.6 - -4.2)
		NO_2	117.9 (51.2) µg/m^3	-7.0	(-14.3 - +0.3)
		O_3	63.0 (33.5) µg/m^3	-1.6	(-12.8 - +9.5)
	2nd Trimester	PM_{10}	60.3 (25.2) µg/m^3	-4.4	(-18.9 - +10.1)
		CO	4.29 (1.86) mg/m^3	+2.8	(-15.7 - +21.1)
		NO_2	117.9 (51.2) µg/m^3	+0.3	(-8.6 - +9.2)
		O_3	63.0 (33.5) µg/m^3	-0.1	(-11.9 - +11.7)
	3rd Trimester	PM_{10}	60.3 (25.2) µg/m^3	+14.6	(0 - +29.2)
		CO	4.29 (1.86) mg/m^3	+1.6	(-15.7 - +19.0)
		NO_2	117.9 (51.2) µg/m^3	+3.6	(-6.6 - 13.7)
		O_3	63.0 (33.5) µg/m^3	-3.0	(-15.4 - +9.4)

* = x (y) = mean (SD); x - y = min – max.

Figure 1



" = last 6 weeks

Figure 2

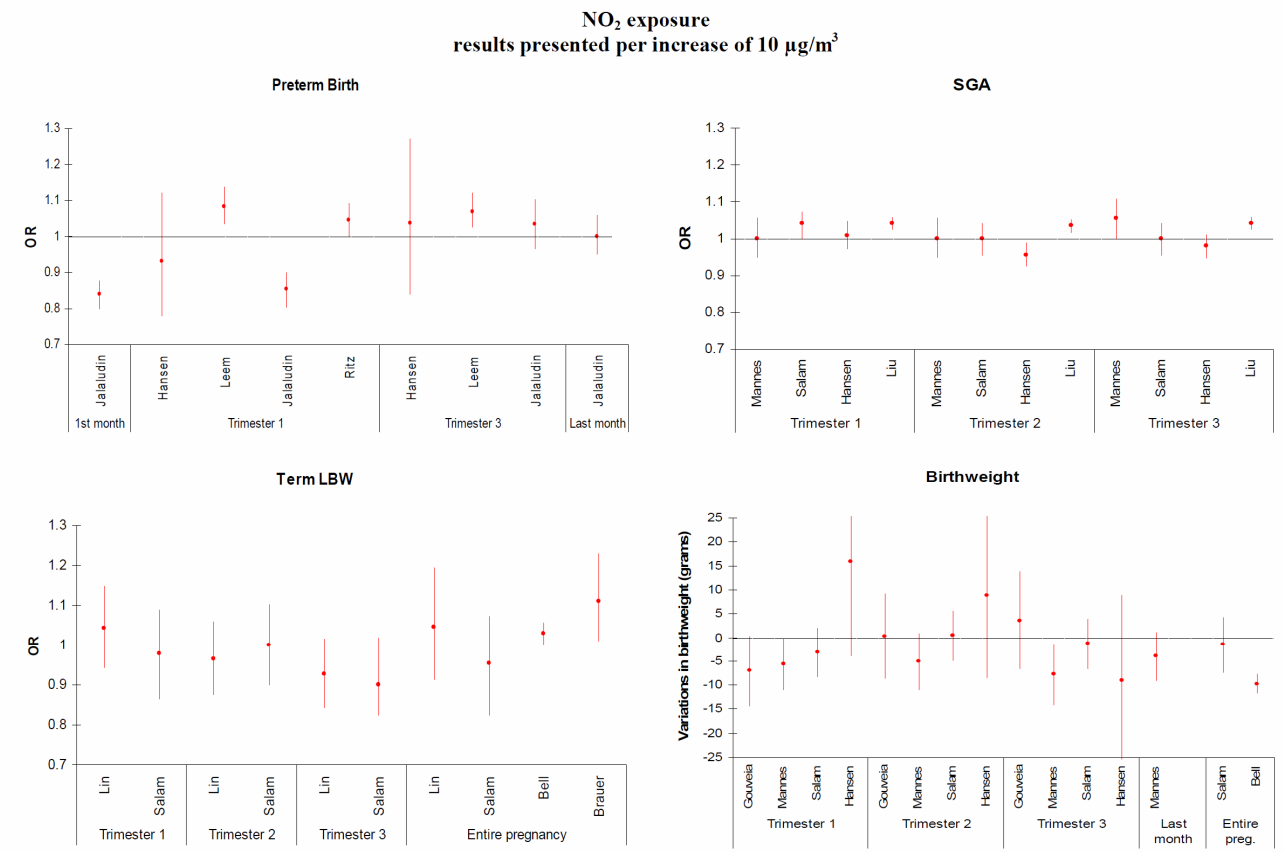

NO2 exposure
results presented per increase of 10 µg/m3
Preterm Birth
OR
1.3
1.2
1.1
1
0.9
0.8
0.7
Jalaludin
Hansen
Leem
Jalaludin
Ritz
Hansen
Leem
Jalaludin
Jalaludin
1st month
Trimester 1
Trimester 3
Last month
SGA
OR
Mannes
Salam
Hansen
Liu
Trimester 1
Trimester 2
Trimester 3
Term LBW
OR
Lin
Salam
Bell
Brauer
Trimester 1
Trimester 2
Trimester 3
Entire pregnancy
Birthweight
Variations in birthweight (grams)
25
20
15
10
5
0
-5
-10
-15
-20
-25
Gouveia
Mannes
Salam
Hansen
Trimester 1
Trimester 2
Trimester 3
Last month
Entire preg.
Bell

Figure 3

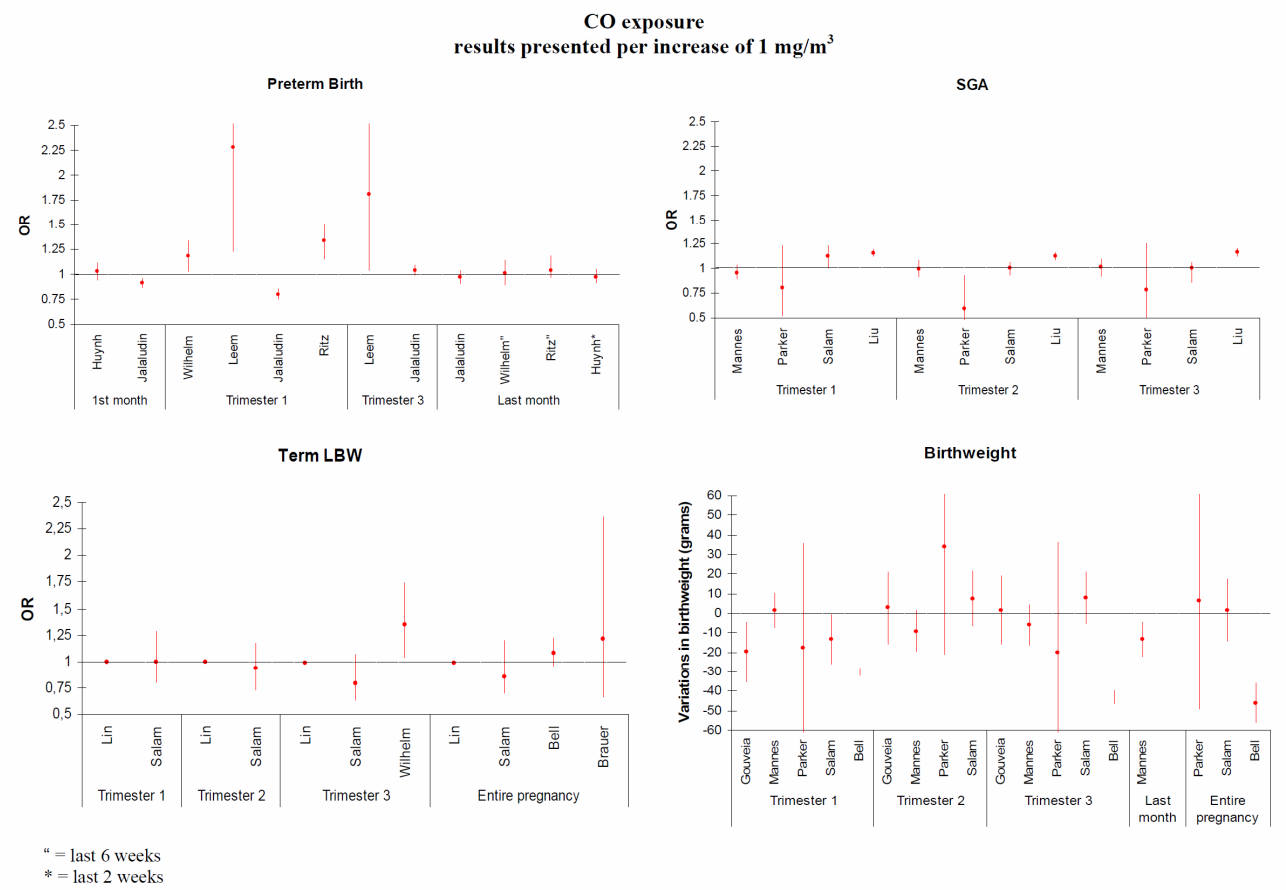

CO exposure
results presented per increase of 1 mg/m3
Preterm Birth
OR
Huynh
Jalaludin
Wilhelm
Leem
Jalaludin
Ritz
Leem
Jalaludin
Jalaludin
Wilhelm"
Ritz"
Huynh*
1st month
Trimester 1
Trimester 3
Last month
SGA
Mannes
Parker
Salam
Liu
Trimester 1
Trimester 2
Trimester 3
Term LBW
Lin
Salam
Wilhelm
Bell
Brauer
Entire pregnancy
Birthweight
Variations in birthweight (grams)
Gouveia
Bell
Last month
" = last 6 weeks
* = last 2 weeks

Figure 4

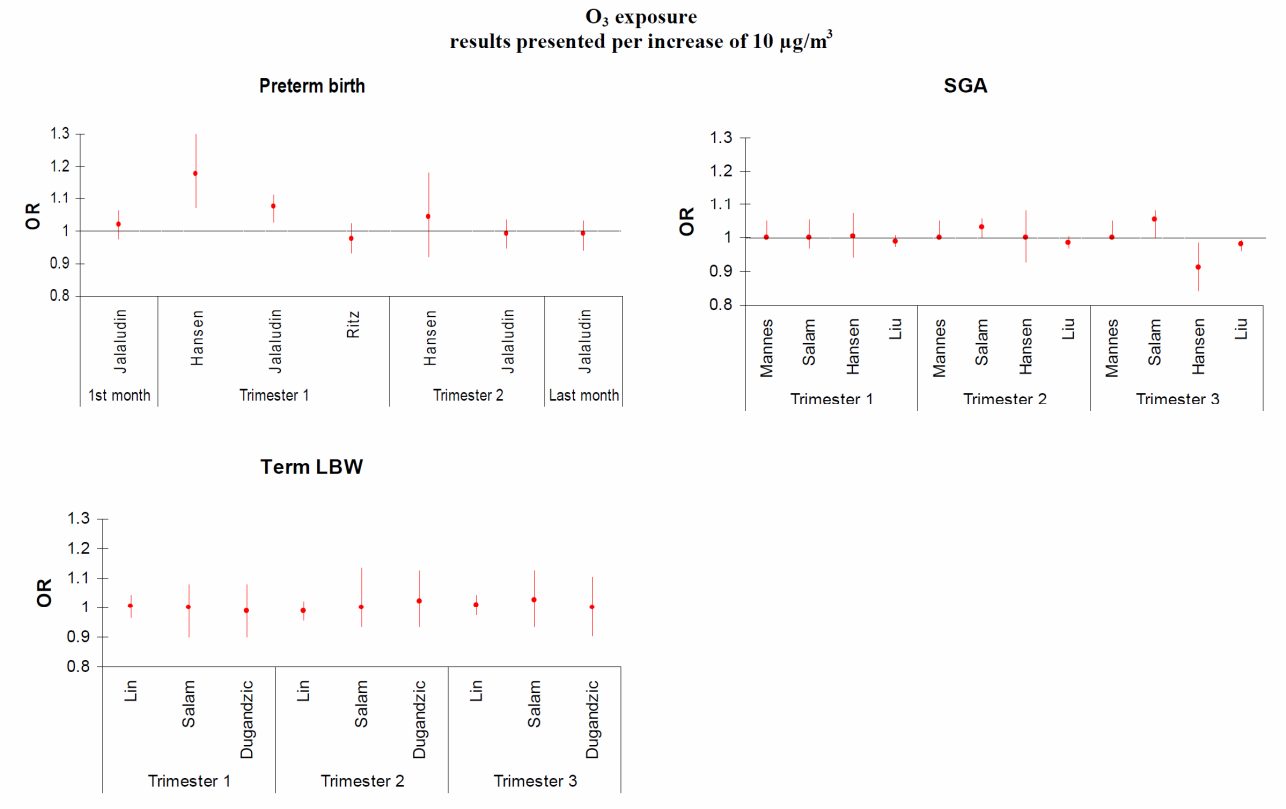
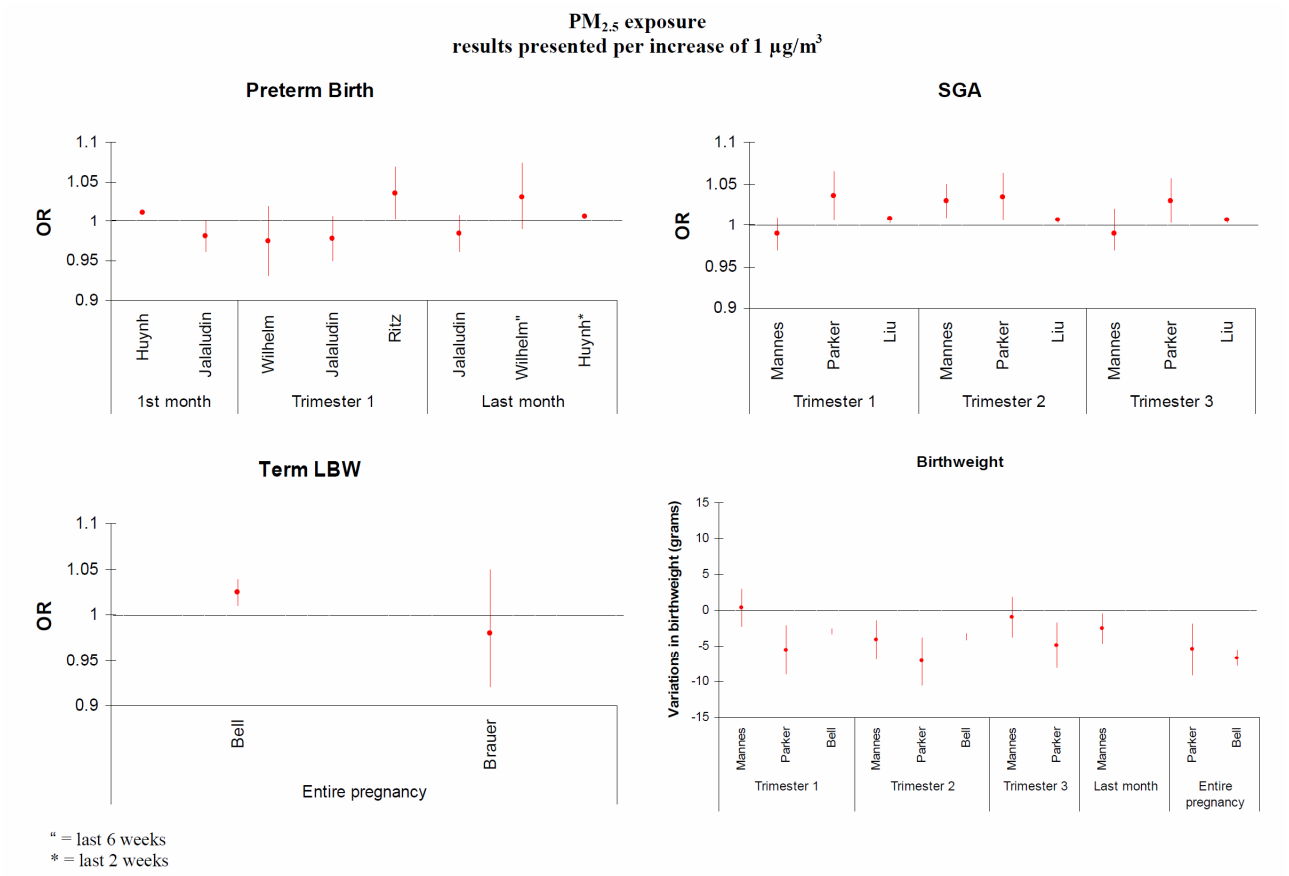

O3 exposure
results presented per increase of 10 µg/m3
Preterm birth
OR
1.3
1.2
1.1
1
0.9
0.8
Jalaludin
Hansen
Jalaludin
Ritz
Hansen
Jalaludin
Jalaludin
1st month
Trimester 1
Trimester 2
Last month
SGA
OR
Mannes
Salam
Hansen
Liu
Mannes
Salam
Hansen
Liu
Mannes
Salam
Hansen
Liu
Trimester 1
Trimester 2
Trimester 3
Term LBW
OR
Lin
Salam
Dugandzic
Lin
Salam
Dugandzic
Lin
Salam
Dugandzic
Trimester 1
Trimester 2
Trimester 3

Figure 5


PM2,5 exposure
results presented per increase of 1 µg/m3
Preterm Birth
OR
1.1
1.05
1
0.95
0.9
Huynh
Jalaludin
Wilhelm
Jalaludin
Ritz
Jalaludin
Wilhelm"
Huynh*
1st month
Trimester 1
Last month
SGA
Mannes
Parker
Liu
Trimester 1
Trimester 2
Trimester 3
Term LBW
Bell
Brauer
Entire pregnancy
Birthweight
Variations in birthweight (grams)
15
10
5
0
-5
-10
-15
Last month
Entire pregnancy
" = last 6 weeks
* = last 2 weeks

DISCUSSION

The aim of our review was to summarize the results of post-2004 studies that looked at a possible association between air pollution and adverse pregnancy outcomes. The goal was to update the state of our understanding since the latest reviews were published in 2005. To do this, we systematically evaluated all epidemiological original studies published between 2004-2008 that investigated the effect of maternal exposure to air pollution during pregnancy, estimated by AQMS data, on clinically relevant pregnancy outcomes such as preterm delivery and birth weight. A total of 18 original studies met the selection criteria. We then reported period specific odds ratios based on a unique exposure scale for each pollutant to facilitate comparability across studies and summarize results for each outcome.

Despite the growing number of studies, the epidemiological evidence of a clear effect of low levels of air pollution on pregnancy outcomes is still limited by the extreme inconsistency of the results. In particular, although a number of studies showed modest increased risks, the observed increases were not coherent across different time windows of exposure or different exposure levels in any of the outcomes or specific pollutants examined. Nevertheless, there is some evidence of an adverse effect of $PM_{2.5}$ on birth weight, with two of three studies of SGA showing elevated risk across each trimester (OR range: 1.006 to 1.036). Moreover, studies that evaluated birth weight as a continuous variable showed a coherent decrease of less than 10 g for a 1 $\mu g/m^3$ increase in $PM_{2.5}$ across different time windows.

Although the possible effects of particulate air pollution are unlikely to be large, it is important to establish if a causal association is present, since even a small change in the effect can have a substantial impact from a public health point of view. In interpreting the study results, we need to address potential biases and open questions that still limit conclusions about causality.

Biologic plausibility

The biological mechanisms of most air pollutants remain to be clarified and might involve different biological responses for each outcome.[8, 31] In the absence of an *a priori* clear hypothesis it's also difficult to establish critical time windows of exposure for each outcome. Most of the recent studies tried to overcome these limitations by presenting trimester-specific risk estimates. This effort, however, introduced another pitfall related to positive findings occurring by chance. Further, authors might report only positive period specific risk estimates, suggesting an in-study publication bias.[58]

Study design

The variability across studies could reflect important differences in study design. Birth cohort studies and time-series analyses were largely used. Birth cohorts based on spatial comparisons are subject to potential confounding because covariates (such as diet, maternal height, weight gain during pregnancy, alcohol and smoking consumption) not routinely collected on birth certificates may be differently distributed across different areas. Time series analysis removes inter-individual or inter-geographic variability [55] but does not take into account seasonal variations shown to be related to short-term changes in air pollution.[42] Slama et al. [21] suggested nesting case-control studies as an interesting option to collect more detailed information on possible confounders (i.e., smoking) and to enlarge the number of cases to increase study power. We only found one nested case-control study [47] to include in our review.

Exposure assessment

Exposure assessment method is a crucial issue. In general, two different approaches were used to assign air quality values to each woman. The values assigned were either measured by the closest

AQMS or were the mean values of AQMS data from within a given geographic area. Neither approach is based on personal exposure monitoring, but is instead an estimation of maternal exposure using ambient monitoring stations, resulting in possible non-differential exposure misclassification and leading to estimates biased toward the null. In addition, the comparison between studies is hindered by the fact that most authors did not clearly describe the chosen exposure assessment method and failed to perform a validation analysis of the applied strategy. Indeed, when more than one exposure method was used within the same study, results seemed to be affected by the chosen method. For example, the Australian studies found more adverse effects when levels from the closest AQMS were assigned compared with a city-wide time series analysis.[48, 52] These findings suggest the need of further methodological insights and sensitivity analyses to estimate the effect of different exposure assessment models.

Exposure misclassification can also occur when a women's time activity pattern is not considered. For example, using birth certificates to place subjects at their residence at delivery could misclassify women who moved during pregnancy.[31] Moreover, personal exposure estimates based on AQMS data do not address occupational exposures and indoor activity patterns that might be an important source of personal exposure.

Conclusions

Research exploring the effect of air pollution on fetal outcomes still needs further insights. Although the number of studies is growing, a consistent effect is not yet emerging, suggesting the need for further, more specific investigation. The most relevant exposure windows and types of pollutant have not been established, although recent studies suggest a need to focus on the finest particles ($PM_{2.5}$). There is a need for large collaborative studies to validate the results, through comparison of different exposure assessment methods. These studies need to take time activity-

patterns, maternal characteristics and behaviors, and spatial confounders into account. Studies of prospective cohorts, with the use of biomarkers of exposure might be particularly forthcoming. Meanwhile, because of the extreme susceptibility of the fetus and the impact of perinatal adverse events on adult health, it may be prudent to continue to try and reduce exposure of pregnant women to air pollution throughout the world.

SECTION 2:

RESULTS OF THE EPIDEMIOLOGICAL STUDY ON AIR POLLUTION EXPOSURE AND BIRTH OUTCOMES IN LOMBARDY 2004-2008

Materials and methods

Birth data

Birth records data were obtained from the regional registry of birth certificate (CErtificati Di Assistenza al Parto, CEDAP) for all registered birth in Lombardy Region from 1 January 2004 to 31 December 2008, covering a five years period (n=465,173). CEDAP is a regional based surveillance system routinely collected at birth by trained nursing personnel in each hospital of the region, covering all live birth and still births of at least 24 weeks of gestation.

Birth data included parental variable, information about gestation and delivery, and infant factors.

We excluded birth from mother who were not Italians (n=106,825, 22% of the total population), with residence outside the Lombardy region or in the Southern part of Pavia Province (n=11,924 equal to the 2.6% of the total), stillbirth delivery (n=807, 0.2%) and plural delivery (n=9818, 2.8%).

We then excluded further 3280 certificates (0.7 of the total) because reporting incongruent data on gestational length (less then 24 or more then 44 week of gestation at birth).

After the exclusion criteria, 332,519 births remained in the data set and represented our study population.

Air pollution exposure estimation

Air pollution exposure was estimated using a methodological approach previously described and validated in other epidemiological studies about air pollution effects in Lombardy Region [59, 60]. We obtained from the Regional Environmental Protection Agency (ARPA Lombardia) recordings of hourly air pollution data, measured from March 2003 to December 2008 by monitors located at 53 different sites throughout Lombardy Region (Fig.6). The 53 stations included in this study were selected by the Regional Environmental Protection Agency (ARPA Lombardia) from the approximately available 200 monitors of the Regional Air Monitoring Network on the basis of their reliability determined by standardized quality control procedures and by correlation with *in situ* measurements, of continuity of recording and of the ability to represent local background air pollution. We identified nine different study areas in the region (Fig.6) characterized by homogenous within-area air pollution concentrations and temporal variations. Within each study area, levels of air pollutants measured by different monitors were highly correlated. In addition, mobile monitoring in each of the study areas during the study period showed high concordance with measurements taken by the permanent monitors in the same area [ARPA Lombardia. *Rapporto sullo stato dell'ambiente in Lombardia*. Milan: Regione Lombardia, 2006.]. For each study area, mean hourly concentrations of PM_{10}, nitrogen dioxide (NO_2),) and ozone (O_3) were averaged using an algorithm that combined levels reported by multiple monitoring locations [61]. The Southern part of Pavia province (Fig.6) was excluded, because this area had no local monitoring stations and showed pollution patterns in repeated point mobile recordings that differed from those measured by stationary monitors located in neighbouring areas.

Outcome assessment

We used birth certificates to identify preterm births (gestational duration <37 complete weeks) and SGA births, defined as those with birth weights below the 10^{th} percentile of the cohort, stratified by sex, for each week of gestation.

In order to detect also small effect of pollutant on baby growth we analysed birthweight as a continuous variable using birthweight data (grams) from the birth certificates.

Statistical methods

We used date of delivery and last menstrual period (LMP), obtained from birth certificates, to estimate air pollution exposure in various time windows for each pregnancy.

Exposure to each pollutant during gestation was estimated by calculating the average of the atmospheric concentration of PM_{10}, NO_2, and ozone, in the first month (0-30 days), in the first trimester (0-90 days) and in the second trimester (91-180 days) after conception (calculated as 14 days after LMP) and in the last three months, in the last month and in the last 10 days before date of delivery.

We applied a logistic model to estimate the risk of preterm delivery and SGA births in our population and a liner regression model with birth weight as a continuous variable.

We presented, respectively for logistic and linear regression models, Odds Ratios (ORs) and linear regression coefficients (beta) for a 10 microg/m3 increase in PM10 and NO2 exposure and for a 1 microg/m^3 increase in ozone exposure, with 95% Confidence Intervals (CI).

Regression models included the following covariates:

1- Maternal age at delivery (in years as a continuous variable)
2- Baby gender
3- Maternal education (years of complete education, 4 categories: less then 8 years, 8-12 years, 13-15 years, more then 15 years)
4- Paternal occupation (6 categories: manager, self employed, white collar, blue collar, unemployed and babies with missing paternal data)
5- Mode of delivery (three categories, vaginal delivery, caesarean section, other)
6- Pregnancy complication (yes/no variable as reported on CEDAP)
7- Parity (dividing nulliparous and pluriparous mothers)
8- Number of ecographic examinations during pregnancy (4 categories: 0-1, 2-3, 4-6, more than 6 examinations)
9- Size of the Obstetrics and Gynaecology units (based on the total number of birth in the period 2004-08) dividing hospitals in three categories (less then 5000 total deliveries, 5000-8000 deliveries, and more then 8000 deliveries).

To account for confounding by seasonal determinants of birth weight and gestational duration, we adjusted also for season of birth.

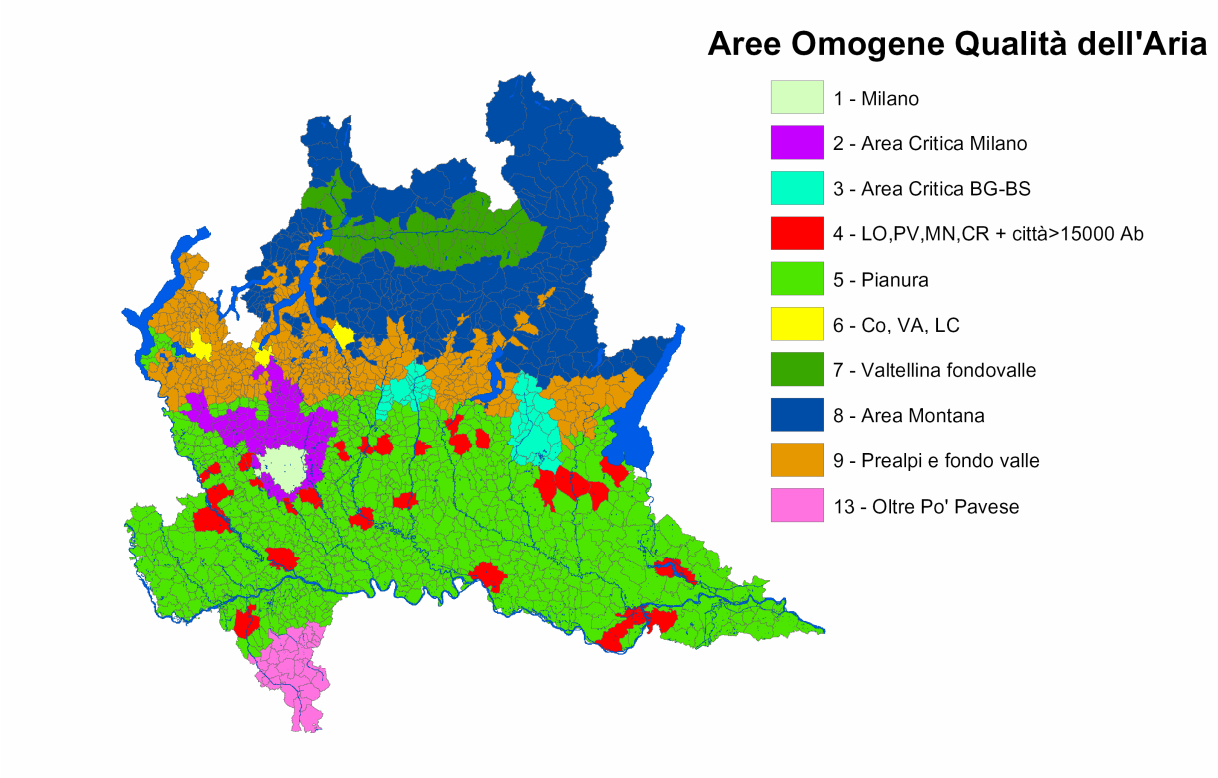
Covariates were chosen based on previous literature identifying potential risk factors for growth retardation or preterm delivery. We first applied linear and logistic models including all potential confounders listed above and excluding air pollution variable to explore whether expected association were observed [41]. Covariates showing a statistically significant relationship with birth outcomes were incorporated into models investigating air pollution exposure effects.

We performed our analyses within each of the nine regional areas characterised by homogenous levels of pollution. Within each area we investigated the association between birth outcomes and temporal variation of pollutant (time series approach). Time series analysis removes the influence of covariates that vary across individuals and geographic areas.

In order to obtain a whole region effect estimates we performed a random effects meta-analysis assuming heterogeneity of area-specific effects following the maximum likelihood method [62].

All statistical analyses were performed using STATA software version 11.0 (Stata Corp College Station, TX, USA).

Figure 6: subdivision of the Lombardy Region in nine geographic zones, homogeneous regarding air pollutant levels.



RESULTS

A total of 332519 birth records related to singleton birth from resident mothers were available from Lombardy between 2004 and 2008.

17601 babies (5.3%) were born after 37 complete week of gestation and were classified as preterm (see Table 6), while 33393 babies were classified as small for gestational age.

Mean maternal age at delivery was 32.8 years in the whole study population. When compared with normal babies (non-preterm and non-SGA), pretem babies were born from older women while SGA babies from slightly younger women.

In our population 51.5% of newborns were males; primiparous mother were 56% and the most frequent mode of delivery was vaginal (62%). Only 3.9% of women reported a pregnancy complication in the CEDAP.

The following covariates resulted independently and significantly associated with a higher risk of preterm delivery (Table 6): male gender of the newborn, lower maternal educational level, lower-income paternal occupational categories (blue collar or unemployed), pregnancy complications, caesarean section at delivery, primiparity, less than 2 ecographic scanner during pregnancy, delivery in a large hospital Gyn and Obs unit.

The same co-variates were also associated with the risk of SGA (with the only expected exception of baby gender).

We did not observed a clear seasonal variation in preterm delivery or SGA incidence.

Air pollution levels (Table 7) showed an important temporal and spatial variability across Regional zones. In all zones PM_{10} was significantly higher during the winter season (ranging from 65.7 μγ/m^3 in the Po valley (Zone 5) to 28.2 μγ/m^3 in alpine territory) than in the summer when air levels are almost halved (ranging from 30.1 μ/m3 in Milan urban area to 16.1μ/m3 in Alpine territory). The same trend was observed for NO_2 (range 39.2-11.9 μ/m^3 in winter and 25.7-5.0 μ/m^3 in summer). As expected, Ozone showed an opposite temporal variation with higher levels in summer time and very low levels in winter. Spatial distribution of Ozone across regional zones was more uniform with summer levels between 55.1 ppb (Po valley area) and 48.7 ppb (Milan urban area).

Table 8 presents association between air pollutants and birth weight measured as continuous variable analysed by one-pollutant multiple linear regression models.

We observed a very mild adverse effect of PM_{10} exposure on birthweight with a decrease of 5.2 grams for a 10 microg/m^3 increase considering the entire pregnancy period. Nevertheless the observed effect was statistically significant because of the large sample size. A negative association between PM_{10} levels and birth weight was observed considering each trimester with a larger effect (borderline significant) in the last three months of gestation.

Neither NO_2 nor Ozone exposure levels resulted clearly associated with birth weight .

Results of the analysis of the association between maternal exposure and the risk of delivery a SGA newborn are shown in Table 9. None of the measured pollutants resulted associated with a significant increase of SGA whichever of the pregnancy periods was considered as exposure windows. In particular, PM_{10} that had resulted to affect birth weight as continuous variable, was associated with only a 1.3% increased risk of SGA considering the entire pregnancy (non significant).

Results of multivariate logistic models analysing the association between maternal exposure and the risk of preterm delivery are presented in Table 10. For preterm delivery, we considered as exposure windows potentially related to adverse effect entire pregnancy, first month, first trimester, last trimester, last months and last ten days of gestation.

Maternal exposure to PM_{10} during the entire pregnancy was associated with a decrease risk of preterm delivery (OR for a 10 μ/m^3 increase=0.946, CI 95%: 0.897-0.997). The apparent "protective effect" was concentrated at the beginning of the gestation (first months and first trimester after conception) and was not confirmed when we analysed late gestation (last month and last ten days before delivery).

There was no evident association between risk of preterm delivery and maternal exposure to NO_2.

Ozone exposure during the entire pregnancy was associated with a non-significant increased risk of preterm delivery (OR=1.046, CI95%: 0.953 - 1.148) but the observed effect was not statistically significant. When different time windows of exposure were analysed, the most relevant effect (though non-significant) was observed in late gestation (last ten days).

Table 6 characteristic of all singleton births, Lombardy, 2004-2008

		All Pregnancies	Preterm	OR	p value	SGA	OR	p value
		N=332,519	N=17,601 (5.3%)			N=33,393 (10.1 %)		
Maternal Age (years)								
	Mean±SD	32.8±4.7	33.2±4.9	1.015	<0.0001	32.5±4.7	1.004	0.002
Sex of the newborn								
	Male	171,143 (51.5 %)	9,398 (53.4 %)	Ref		17,150 (51.4%)	Ref	
	Female	161,325 (48.5 %)	8,200 (46.6 %)	0.937	<0.0001	16,243 (46.6 %)	1.008	0.461
Maternal Education								
	>15 years	78,594 (23,6 %)	3,621 (20.6 %)	Ref		7,244 (21.7%)	Ref	
	13-15 years	158,416 (47.6 %)	8,237 (46.8 %)	1.146	<0.0001	15, 573 (46.6 %)	1.072	<0.0001
	8-12 years	91,022 (27.4 %)	5,440 (30.9 %)	1.302	<0.0001	10,015 (30 %)	1.227	<0.0001
	<8 years	2,489 (0.8 %)	198 (1.1 %)	1.606	<0.0001	340 (1 %)	1.672	<0.0001
	Missing data	1,998 (0,6 %)	495 (0.6 %)			221 (0.7 %)		
Paternal Occupation								
	Self employed	91,917 (27.6 %)	4,610 (26.2 %)	Ref		8,984 (26 %)	Ref	
	Manager	14,977 (4.5 %)	696 (3.9 %)	0.927	0.084	1,304 (3,9 %)	0.934	0.034
	White collar	97,598 (29.4 %)	4,878 (27.7 %)	0.995	0.843	9,171 (27.5 %)	0.98	0.23
	Blue collar	113.818 (34.2 %)	6,500 (39.9 %)	1.098	<0.0001	12,494 (37.4 %)	1.127	<0.0001
	Unemployed	7,192 (2.2 %)	422 (2.4 %)	1.303	<0.0001	806 (2.4 %)	1.196	<0.0001
	Missing data	7,017 (2.1 %)	495 (2.8 %)			934 (2.8 %)		
Mode of delivery								
	Vaginal	230,097 (62.2 %)	8,550 (48.6 %)	Ref		21,301 (63.8 %)	Ref	
	Cesarean section	90,248 (27.1 %)	8,635 (49 %)	2.459	<0.0001	10,814 (32.4 %)	1.219	<0.0001
	Other, specified	11,111 (3.3 %)	367 (2.1 %)	0.807	<0.0001	1,169 (3.5 %)	0.974	0.418
	Missing data	1,063 (0.3 %)	49 (80.3 %)			109 (0.3 %)		

		All Pregnancies N=332,519	Preterm N=17,601 (5.3%)	OR	p value	SGA N=33,393 (10.1 %)	OR	p value
Pregnancy complication								
	Phisological	316,884 (95.3 %)	13,669 (77.7 %)	Ref		30,307 (90.8 %)	Ref	
	Pathological	12,886 (3.9 %)	3,738 (21.2 %)	7.487	<0.0001	2,747 (8.2 %)	2.292	<0.0001
	Missing data	2,749 (0.8 %)	194 (1.1 %)			339 (1 %)		
Parity								
	Multiparous	146,214 (44 %)	6,747 (38.3 %)	Ref		10,640 (31.9 %)	Ref	
	Nulliparous	186,305 (56 %)	10,854 (61.7 %)	1.251	<0.0001	22,753 (68.1 %)	1.772	<0.0001
Ecographic examination during pregnancy (N)								
	2-3	102,654 (30.9 %)	5,087 (28.9 %)	Ref		8,993 (26.9 %)	Ref	
	0-1	8,500 (2.6 %)	658 (3.7 %)	1.389	<0.0001	1,013 (3.1 %)	1.269	<0.0001
	4-6	155,930 (46.9 %)	7,946 (45.1 %)	0.924	<0.0001	15,770 (47.2 %)	1.136	<0.0001
	>6	65,435 (19,7 %)	3,910 (22.2 %)	0.903	<0.0001	7,617 (22.8 %)	1.247	<0.0001
Hospital number of births 2004-08 (N)								
	<5000	87,912 (26.4 %)	3,485 (19,8 %)	Ref		8,528 (25.5 %)	Ref	
	5000-8000	94,358 (28,4 %)	5,095 (29 %)	1.372	<0.0001	9,364 (28.1 %)	1.021	0.196
	>8000	150,149 (45.2 %)	9,021 (51.2 %)	1.562	<0.0001	15,501 (46.4 %)	1.07	<0.0001
Season of conception								
	Jan-Mar	82,000 (24.7 %)	4,409 (25 %)	Ref		8,254 (24.7 %)	Ref	
	Apr-jun	82,567 (24.8 %)	4,331 (24,6 %)	0.98	0.381	8,411 (25.2 %)	1.018	0.261
	Jul-sep	82,507 (24.8 %)	4,287 (24.4 %)	0.971	0.202	8,109 (24.3 %)	0.994	0.72
	Oct-Dec	85,445 (25.7 %)	4,574 (26 %)	0.998	0.938	8,619 (25.8 %)	0.999	0.992

Table 7: Average levels of pollutants during the study period in the 9 different homogenous Regional zones, in each season

ARPA Zones	PM10 (μ/m3)				NO2 (μ/m3)				Ozone (ppb)			
	Jan-Mar	*Apr-Jun*	*Jul-Sep*	*Oct-Dec*	*Jan-Mar*	*Apr-Jun*	*Jul-Sep*	*Oct-Dec*	*Jan-Mar*	*Apr-Jun*	*Jul-Sep*	*Oct-Dec*
Zone 1 - Milan urban area	65.4	31.7	30.1	61.7	39.2	26.7	25.7	39.8	14.4	44.7	48.7	10.3
Zone 2 - Milan suburban area	62.0	29.1	26.4	55.4	31.4	17.8	15.7	29.1	17.0	47.0	52.8	11.6
Zone 3 - Bergamo and Brescia	59.7	32.1	29.4	48.6	27.2	16.4	13.8	25.1	18.4	48.7	52.8	13.6
Zone 4 - Po Valley (towns >15000)	56.0	32.1	31.9	54.5	30.6	18.8	15.8	26.6	18.8	53.4	55.1	12.0
Zone 5 - Po Valley (other territory)	65.7	37.2	33.9	55.1	25.6	15.3	13.7	23.4	19.2	51.6	53.6	13.2
Zone 6 - Varese, Como, and Lecco	44.1	25.3	23.5	34.7	31.8	23.6	20.9	28.9	19.1	45.8	48.8	13.4
Zone 7 - Valtellina Valley	49.0	24.5	19.3	41.5	19.6	9.5	8.9	17.6	27.6	51.5	50.8	19.6
Zone 8 - Alpine territory	28.2	16.8	16.1	23.9	11.9	4.8	5.0	11.2	39.1	55.4	49.5	29.2
Zone 9 - Pre-Alpine territory	60.8	32.0	28.5	48.7	32.6	24.9	19.8	28.6	14.5	40.9	51.5	13.0

Table 8 Association between air pollutants exposure and birth weight (as a continuous variable)

		Entire Pregnancy	First trimester*	Second Trimester*	Last 3 months+
PM10					
	B coef.(95 % CI) ‡	-5.231 (-9.777;0.685)	-1.266 (-2.879;0.346)	-0.976 (-2.879; 0.346)	-1.741 (-3.768; 0.286)
	p value	0.024	0.124	0.534	0.092
NO2					
	B coef (95 % CI) ‡	4.140 (-10.877;19.197)	0.435 (-9.528;10.397)	3.339 (-2.557;9.234)	-1.343 (-7.114;4.428)
	p value	0.478	0.911	0.145	0.549
Ozone					
	B coef (95 % CI) ‡	0.818 (-9.075;10.711)	-0.066 (-1.987;1.855)	0.303 (-3.526;4.132)	-0.385 (-4.099;3.330)
	p value	0.831	0.929	0.838	0.790

* calculated based on last menstrual period day
+ calculated based on date of birth
‡ β coefficient calculated for a pollutant specific model and adjusted for: gestational age at birth, maternal age, baby gender, maternal education (categorical), paternal occupation (categorical), mode of delivery, pregnancy complication (yes/no), parity, number of ecographical examination during pregnancy, hospital size (dividing tertiles), season of conception

Table 9 association between air pollutants exposure and risk of delivery a SGA baby.

		Entire Pregnancy	First trimester*	Second Trimester*	Last 3 months+
PM10					
	OR (95 % CI) ‡	1.013 (0.987 - 1.040)	1.006 (0.993- 1.019)	1.005 (0.983-1.028)	1.004 (0.988- 1.022)
	p value	0.313	0.379	0.565	0.527
NO2					
	OR (95% CI) ‡	0.996 (0.878-1.131)	0.997 (0.941-1.056)	0.994 (0.939-1.053)	1.009 (0.97-1.050)
	p value	0.939	0.894	0.792	0.558
Ozone					
	OR (95 % CI) ‡	1.008 (0.967-1.051)	1.002 (0.985-1.020)	1.001 (0.984-1.018)	0.998 (0.982-1.015)
	p value	0.623	0.76	0.888	0.793

* calculated based on last menstrual period day
+ calculated based on date of birth
‡ OR estimates expressed for a pollutant specific model and adjusted for: maternal age, maternal education (categorical), paternal occupation (categorical), mode of delivery, pregnancy complication (yes/no), parity, number of ecographical examination during pregnancy, hospital size (dividing tertiles), season of conception

Table 10 association between air pollutants exposure and risk of preterm delivery

		Entire Pregnancy	First month*	First trimester*	Last 3 months+	Last month+	Last 10 days+
PM10							
	OR (95% CI) ‡	0.946 (0.897-0.997)	0.986 (0.972-1.000)	0.979 (0.962-0.998)	0.985 (0.953-1.018)	0.990 (0.970-1.010)	1.000 (0.989-1.011)
	p value	0.037	0.051	0.026	0.375	0.242	0.966
NO2							
	OR (95% CI) ‡	0.960 (0.768-1.199)	1.007 (0.929-1.093)	0.998 (0.900-1.106)	0.970 (0.856-1.098)	0.971 (0.870-1.084)	0.995 (0.919-1.078)
	p value	0.632	0.813	0.957	0.525	0.495	0.876
Ozone							
	OR (95% CI) ‡	1.046 (0.953- 1.148)	1.008(0.984- 1.033)	1.004 (0.977-1.031)	1.016 (0.976-1.058)	1.015 (0.983-1.048)	1.021 (0.996-1.048)
	p value	0.343	0.521	0.773	0.442	0.442	0.352

* calculated based on last menstrual period day
+ calculated based on date of birth
‡ OR estimates expressed for a pollutant specific model and adjusted for: maternal age, baby gender, maternal education (categorical), paternal occupation (categorical), mode of delivery, pregnancy complication (yes/no), parity, number of ecographical examination during pregnancy, hospital size (dividing tertiles), season of conception

CRITICAL DISCUSSION OF THE RESULTS

In the present study we analyzed the relationship between maternal exposure during pregnancy to PM_{10}, NO_2, and Ozone and pregnancy outcomes, such as intra-uterine growth (measured as birthweight) and gestation duration (preterm delivery) in Lombardy during 2004-2008.
Maternal exposure was estimated based on the data of the Monitoring Stations located in the area of maternal residence, and pregnancy outcomes were retrieved from birth electronic records (CEDAP).

Lombardy Region is the most populated Region of Italy (more than 9 million of inhabitants) and is characterized by a large spatial and temporal variability in air pollutant levels due to geographical and meteorological local characteristics. The possibility to contemporary investigate zones with very high levels of pollutants (such as Milan urban area) and mountain/pre-mountain areas with very low exposure levels, lead to the advantage to evaluate a possible dose-effects gradient in air pollution effects.

We observed only a mild effect of PM_{10} measured during the entire pregnancy period on birthweight (-5 grams for a 10 $\mu g/m^3$ increase). The negative effect on bithweight was not concentrated in one specific trimester (although more pronounced during the last three months).
Figure 7 shows the details of the meta-analysis, with the effect estimates in each of the nine homogenous Regional zones, with relative 95% CI, for PM exposure during entire pregnancy and in the last trimester. Adverse effects were distributed quite homogenously, and we observed exposure related decreases in birthweight in most of the zones. We did not recognize a clear dose-effect trend across zones. The less populated (and less polluted) of them showed very imprecise effect estimates with wide confidence intervals. The clinical relevance of the observed effect is doubtful and is also

curbed by the fact that we did not observe any PM_{10} exposure- related increased risk in SGA incidence.

When we analyzed preterm delivery risk we observed a decreased risk among PM_{10} less exposed women, which is inconsistent with our hypothesis of a possible pro-inflammatory effect of air pollution that could lead to shortening gestation.

Also a previous study suggested a protective effect of PM_{10} and NO_2 exposure during pregnancy [45], but it is most likely that these results are artifacts given that, as shown in Figure 8, risk estimates are very heterogeneous across zones with the most polluted zones (Milan urban area and Milan suburban area) showing an increased risk of preterm delivery. The apparent "protective" effect was, in addition, concentrated in the first trimester, the period of gestation less relevant in determining the timing of delivery.

Our results were only partially coherent with those of previous epidemiological studies that investigated the effect of air pollution in pregnancy. Overall they failed to conclusively show a definite correlation between air pollution and adverse birth outcomes. They are hardly comparable, however, due to different exposure windows examined and exposure assessment method employed.

The results of the present study are fairly consistent with the evidence we found after systematically reviewing published studies of a small but significant effect of PM on bithweight. Previous study seem to suggest an important role of finer particles ($PM_{2.5}$) in determining adverse effect, but for the temporal period of the present study (2004-2008) only PM_{10} measurement were available and thus we were not able to estimate the effect of $PM_{2.5}$. ARPA Lombardy is currently developing a regional network of $PM_{2.5}$ monitoring stations and probably, in the near future, this gap will be bridged.

In our study we did not observed any clear adverse effect of ozone and NO_2. While for the former pollutant previous studies concordantly tend to rule out an independent and significant effect on pregnancy outcomes, several studies in different countries showed an adverse effect of NO_2 exposure, often concurrently with PM_{10} exposure effects. The lack of consistency of our finding may be due to the fact that commonly measured air pollutants may be surrogates of other unmeasured and more active toxicants present in the air pollution mix. If this is the, case, the different pollutants found to have a significant effect in different regions may simply be related to the local characteristics of that complex mixture of primary and secondary pollutants.

In the present study maternal exposure was estimated based on the average daily levels of pollutants measured by different area monitoring stations. Although monitoring stations within each of the nine different pollution areas showed spatially homogenous pollution patterns, a residual within-area measurement error could not be excluded. This would have biased the estimates toward the null and may have contributed to hide some of the air pollution effects.

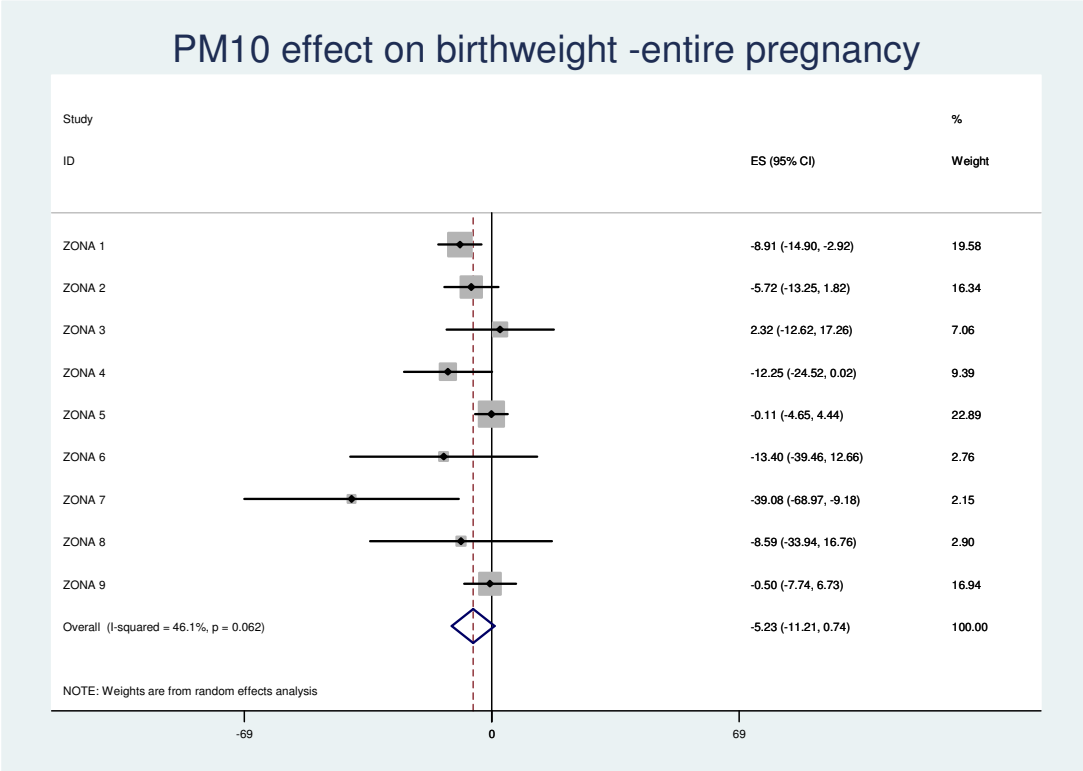
As with most studies of ambient air pollution and health, we assume that ambient concentration represent an individual actual exposure to pollutants, not accounting for time-activity patterns (indoor sources of exposure, commuting habits, place or type of work, time spent outdoor).
Measurement error was probably non-differential with respect to birth outcomes, which would most likely bias the point estimates toward the null.

Maternal factors such as pre-pregnancy weight, smoking consumption diet or stress can all influence pregnancy outcomes and were not available from CEDAP. Therefore, it could be argued that the results of the current study may be confounded. However, our study design (a meta-analysis of nine time-series studies) has based risk estimates on temporal variation within homogeneous

geographic zones, and it is unlikely that the results have been affected to the confounding effect of those variables. There is no evidence, in fact, suggesting that these factors are associated with temporal variations in air pollution.

The above mentioned limitation could all have contributed to a attenuation of our effect estimation.

Figure 7 Meta-analysis of the effect of PM10 exposure on birthweight (as continuos variable) across the nine regional zones. Random effect models



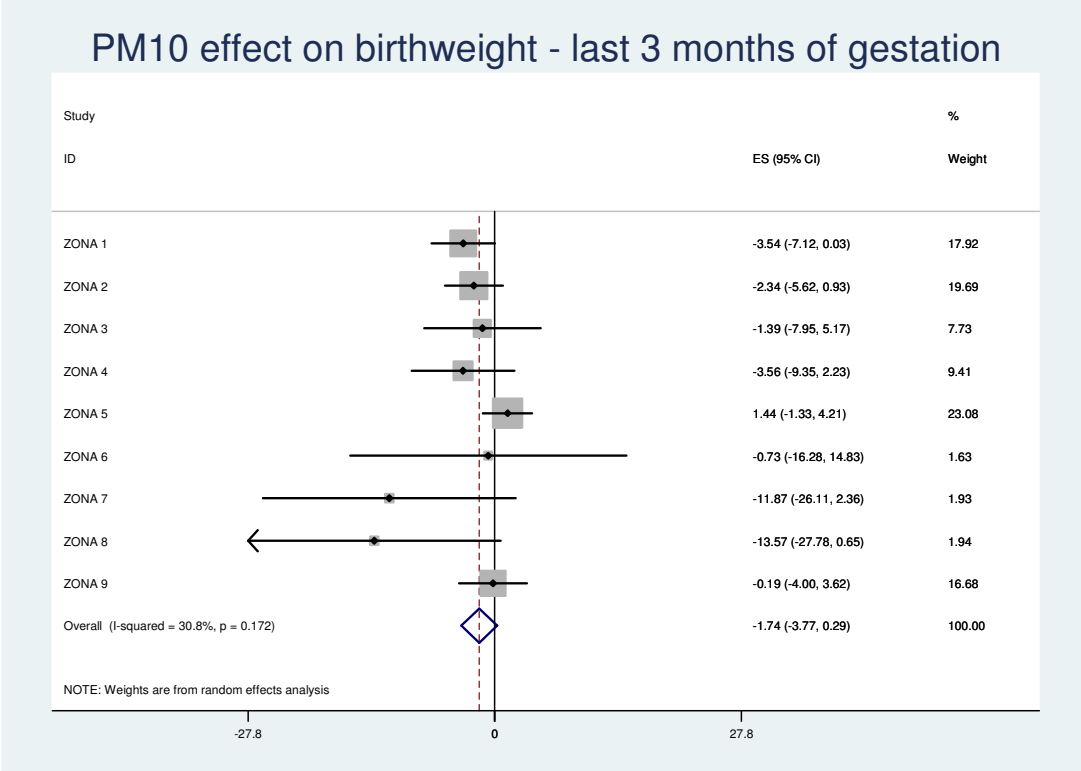
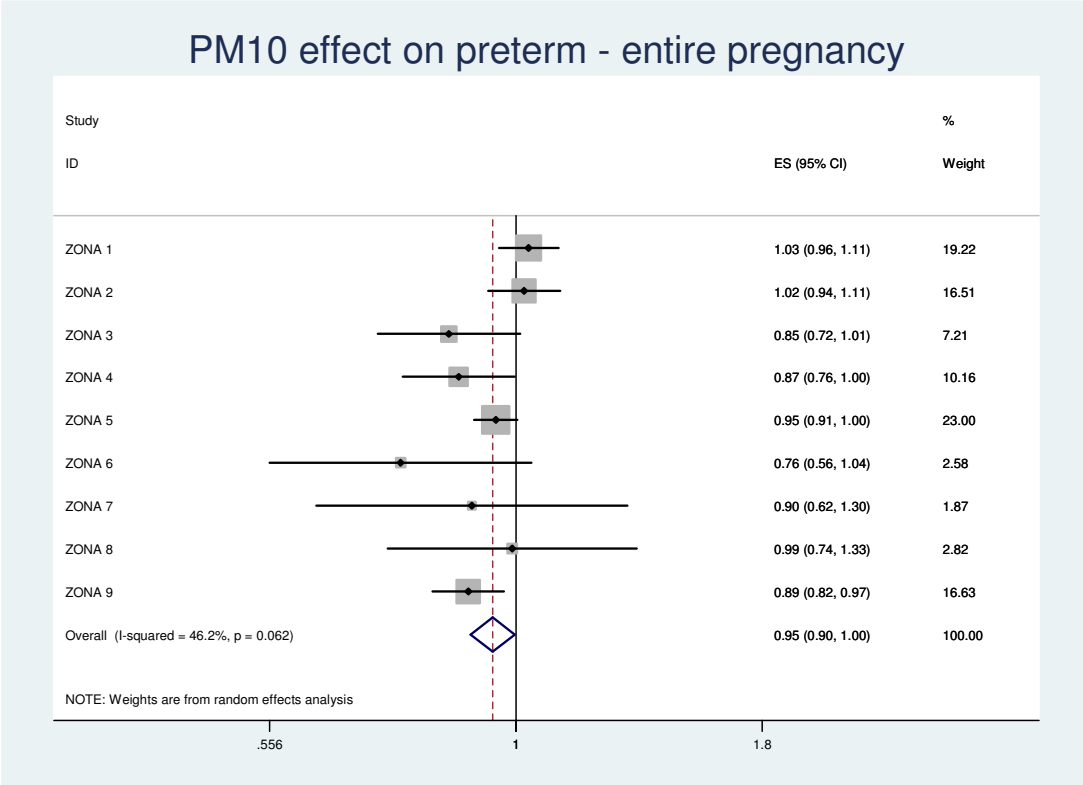
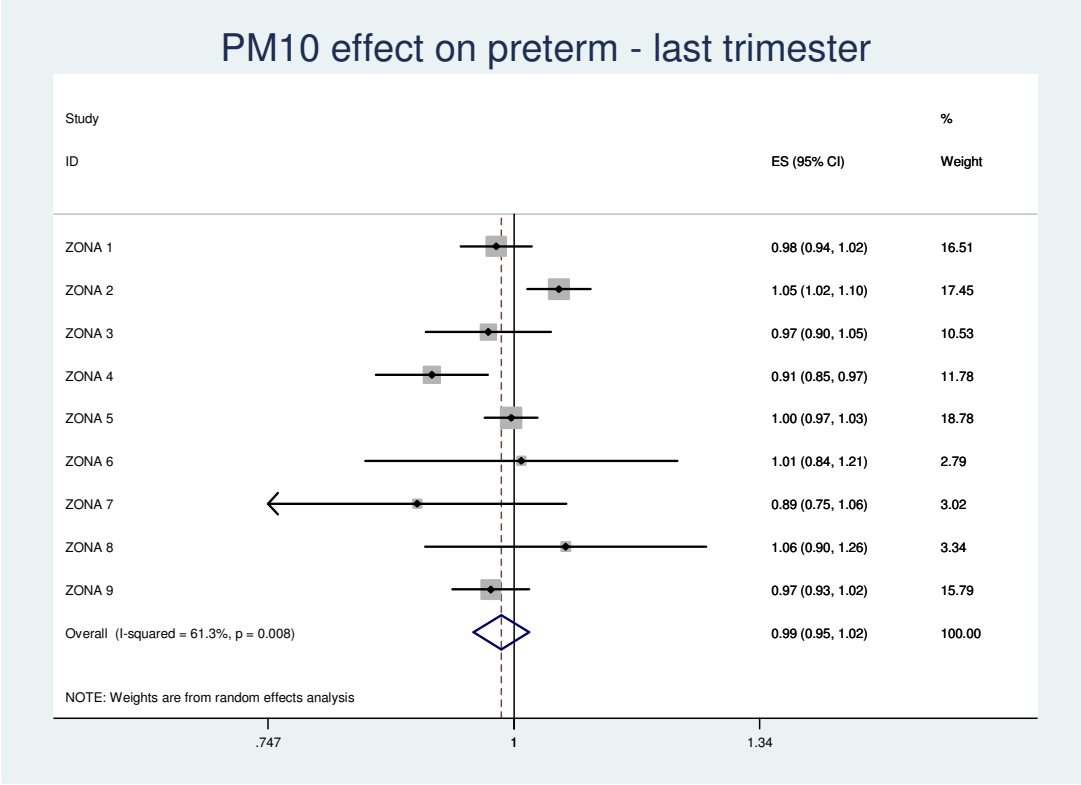


Figure 8 Meta-analysis of the effect of PM10 exposure on the risk of preterm delivery across the nine regional zones. Random effect models





CONCLUSIONS

Our study is the first epidemiological research that investigates the effect of ambient air pollution in Italy or in other Southern European countries.

We used existing air pollution and birth records data. This allowed us for a very large, population based study, not subject to selection bias, and conducted for a long period of time (5 years) in one of the most polluted European Region.

Our results, as the ones of the most of the recent published study all around the world, seems to rule out a more than moderate effect of air pollution on baby growth and gestational duration, but we confirm the evidence of a small adverse effect of PM on birthweight. .

As described in details in the systematic review, environmental studies based on monitoring station data and on routinely collected birth records although very efficient in collecting large birth cohorts, have shown important limits, and is not possible to dodge a residual misclassification of exposure and inadequate collection of maternal characteristics.

Therefore it is not easy to understand if the small size of the observed effect is a consequence of these important limitations which most likely led to an attenuated estimate of the true effect of air pollution.

However, given the number of exposed people, if these small effects are indeed causal, the public health impact could be considerable.

Additional studies in that field would thus be warranted, but there is a strong need of innovative approach that combine different exposure estimates methods (possibly using also personal monitoring), and that move forward in determining different components of air pollution and possible biomarkers of exposure to delineate the biological mechanism of such an effect.

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