Impact of ambient air pollution on birth outcomes: systematic review of the current evidences

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Summary
Background: *There is growing interest in the possible association between maternal exposure to air pollutants and reproductive outcomes, particularly birth weight and gestational duration. Four systematic reviews of data were published in 2004-2005, but the wide variability of methods and results among the different studies produced conflicting conclusions. This study was done to establish whether recent literature has provided more conclusive evidence regarding a link between air pollutants and birth outcomes.* **Methods:** *We reviewed 18 original epidemiological studies on maternal exposure to particulate matter (PM), NO_2, CO and O_3, and outcomes of preterm delivery or low birth weight published since 2004.* **Results:** *Large variability across studies in design, precision in maternal georeferentiation, methods in exposure assessment, and type of pollutant considered, limited the strength of the evidence of adverse affects of ambient air pollution on birth outcomes. Nevertheless, evidence suggests exposure to particulate matter, especially at its finest fraction ($PM_{2.5}$), may have the potential to adversely affect birth weight. We further found limited evidence of a possible association between maternal exposure to air pollutants during the first trimester and increased risk of preterm delivery.* **Discussion:** *The observed adverse effects were generally small. However, possible important factors such as maternal activity pattern, diet, smoking and occupation, that are usually not reported on the birth certificate, might have led to exposure misclassification and confounding and could have hidden moderately increased risks. In conclusion, additional studies since 2004 have not been able to conclusively show a definitive correlation between air pollution and adverse birth outcomes; although it appears that small size particulate matter could affect birth weight. Additional well-conducted studies that include detailed information on maternal risk factors and using validated models for estimating maternal exposure are needed to establish the extent of the association between air pollution and birth outcomes.*

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Riassunto

«Esposizione a inquinamento ambientale e esito al parto: revisione sistematica della letteratura». *Negli ultimi anni, è cresciuto l'interesse circa un possibile effetto avverso dell'esposizione a inquinamento durante la gravidanza e il benessere e l'accrescimento del feto. Quattro revisioni sistematiche sull'argomento sono state pubblicate nel biennio 2004-2005, ma la grande variabilità nei metodi e nei risultati fino ad allora disponibili ha portato a conclusioni non univoche. Scopo del presente lavoro è verificare se la letteratura più recente sia stata in grado di fornire maggiori evidenze circa una relazione tra inquinamento ambientale e esiti al parto. La nostra indagine ha individuato 18 studi originali che hanno valutato la relazione tra l'esposizione durante la gravidanza a particolato (PM), NO_2, CO e ozono, misurati mediante centrali di rilevamento ambientali e peso alla nascita e/o durata della gestazione. La grande variabilità riscontrata nei diversi studi circa il disegno dello studio, la metodologia di misura dell'esposizione, la precisione nella geo-referenziazione della donna e il tipo di inquinanti considerati, limita tuttora la forza dell'evidenza di un effetto avverso dell'inquinamento sulla gravidanza. Ciò nonostante, gli studi più recenti sembrano suggerire un effetto del particolato e in particolare delle polveri più fini ($PM_{2.5}$) sul peso alla nascita. Inoltre alcuni studi sembrano mostrare una relazione tra esposizione a inquinanti durante il primo trimestre e rischio di parto prematuro. Gli effetti evidenziati appaiano comunque di entità limitata. Il mancato controllo di variabili materne quali il fumo di sigaretta, la dieta e le possibili esposizioni occupazionali, variabili in genere non disponibili nei certificati compilati al momento del parto, potrebbero avere portato ad una misclassificazione della reale esposizione della donna con conseguenza distorsione e attenuazione degli effetti reali dell'inquinamento. Pertanto, gli studi pubblicati dal 2004 ad oggi non sono ancora in grado di fornire conclusioni definitive circa una relazione tra inquinamento e esiti al parto, ma suggeriscono l'esistenza di un effetto delle polveri più fini sul peso alla nascita. Ulteriori studi, che raccolgano dettagliatamente informazioni sui fattori di rischio materni e che verifichino i risultati valutando l'impatto di diversi modelli di esposizione e geo-referenziazione, sono necessari per stabilire le dimensioni dell'impatto dell'inquinamento sulla gravidanza.*

Introduction

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 (6, 27, 50). 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 (2, 3, 22).

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) (15, 29, 35, 53). 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 (7, 8, 10, 17, 34, 45, 47, 55, 57). 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 (29) 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. (30) 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 =

$$\frac{\ln(1.27)}{(64.57 - 45.94)/10} = 1.134 \text{ (see table 2)}$$

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 (1, 4, 13, 14, 18, 19, 26, 37, 39-41, 43, 51) and 7 papers that did not provide information about air pollution levels (25, 31, 38, 54, 58) or whose outcomes were not comparable (46, 52) with those considered by most other studies. The remaining 18 original studies were included in this review (5, 9, 12, 16, 20, 21, 23, 24, 28, 30, 32, 33, 36, 42, 44, 48, 49, 56). First authors, publication year, study location, period of investigation, exposure assessment methods and study design of these 18 studies are shown in table 1.

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 (56) to 50 Km (49) from maternal residence, while others used the mean value of all AQMSs within a given administrative unit, such as a county (5, 23, 48), citywide area (16, 20), city district (32), or ZIP code area (9, 44). 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 (16) while others considered the postcodes (24, 36, 49, 56). Two studies were able to perform a georeferentiation of maternal address (street level) (12, 42).

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, socioeconomic 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 (9, 24, 36, 49, 56). 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 (23) nested in a birth cohort (42) in which each preterm baby was matched with three controls with similar dates of conception to control for seasonal variation.

Table 1 - Main characteristics of the revised epidemiological studies

1st Author (pub yr) (ref. n°)	Study Location	Study Period	Study Design	Exposure assessment method
Bell (2007) (5)	MA, CT (USA)	1999 - 2002	Birth cohort	Mean of the AQMSs in each county
Brauer (2008) (9)	Vancouver (Canada)	1999 - 2002	Birth cohort	a) Based on closest postcode AQMS b) Distance weighted mean of the postcode nearest 3 AQMSs
Dugandzic (2006) (12)	Nova Scotia (Canada)	1988 - 2000	Birth cohort	Distance weighted mean of the AQMSs within 25 Km to the maternal address

(continued)

Table 1 - *continued*

1st Author (pub yr) (ref. n°)	Study Location	Study Period	Study Design	Exposure assessment method
Gouveia (2004) (16)	Sao Paulo (Brazil)	1997	Time series	Mean measures of all the city AQMSs
Hansen (2006; 2007) (20, 21)	Brisbane (Australia)	2000 - 2003	Time series	Mean measures of all the city AQMSs
Huynh (2006) (23)	California (USA)	1999 - 2000	Matched case-control study	Based on maternal residence closest AQMS (within 8.5 Km)
Jalaludin (2007) (24); Mannes (2005) (36)	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) (28)	Seoul (South Korea)	2001 - 2004	Birth cohort	Closest AQMS to the maternal address
Leem (2006) (30)	Incheon (South Korea)	2001 - 2002	Birth cohort	Ordinary block kriging based on AQMSs
Lin (2004) (31, 32)	Taiwan	1995 - 1997	Birth cohort	Based on city district closest AQMS (max 3 Km)
Liu (2007) (33)	Canada	1986 - 2000	Birth cohort	Mean of the AQMSs in each residential area
Parker (2005) (42)	California (USA)	2000	Birth cohort	Mean of AQMSs located within 8.5 Km to maternal address
Ritz (2007) (44)	California (USA	2007	Birth cohort	Each postcode area was associated to the closest AQMS
Sagiv (2005) (48)	Pennsylvania (USA)	1997 - 2001	Time series	Mean measures of all country AQMSs
Salam (2005) (49)	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)
Wilhelm (2005) (56)	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

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 μg/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, 30). 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 μg/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 μg/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 (20) and 1.072,(24) 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 μg/m^3. When trimester specific estimates were considered, significant increases in preterm delivery risk were reported for the first trimester in only one study (44). 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.

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 (12, 56) 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 esti-

Table 2 - Main characteristics of studies investigating preterm birth

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	OR	(CI 95%)
Kim (2007) (28)	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) (44)	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) (24)	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) (23)	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)
Hansen (2006) (20)	1st Trimester	PM_{10}	19.6 (9.4) μg/m^3	1.364	(1.138 - 1.642)
Brisbane (Australia), 28,200		NO_2	16.8 (7.8) μg/m^3	0.930	(0.779 - 1.121)
		O_3	53.4 (15.6) μg/m^3	1.177	(1.069 - 1.299)
	3rd Trimester	PM_{10}	19.6 (9.4) μg/m^3	1.071	(0.864 - 1.297)
		NO_2	16.8 (7.8) μg/m^3	1.035	(0.839 - 1.272)
		O_3	53.4 (15.6) μg/m^3	1.042	(0.920 - 1.179)

(continued)

Table 2 - *continued*

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	OR	(CI 95%)
Leem (2006) (30)	1st Trimester	PM_{10}	27.0 - 106.4 μg/m³	1.134	(1.021 - 1.264)
Incheon (South Korea), 52,113		CO	0.47 - 1.27 mg/m³	2.283	(1.231 - 2.844)
		NO_2	10.4 - 80.6 μg/m³	1.084	(1.033 - 1.138)
	3rd Trimester	PM_{10}	33.1 - 95.9 μg/m³	1.049	(0.949 - 1.157)
		CO	0.49 - 1.16 mg/m³	1.811	(1.041 - 3.224)
		NO_2	11.9 - 76.1 μg/m³	1.071	(1.025 - 1.120)
Wilhelm (2005) (56)	1st Trimester	PM_{10}	32.9 - 43.9 μg/m³	1.101	(0.923 - 1.314)
California (USA), 106,483		CO	1.13 - 2.17 mg/m³	1.178	(1.030 - 1.336)
		$PM_{2.5}$	18.0 - 25.4 μg/m³	0.974	(0.931 - 1.019)
	Last 6 Weeks	PM_{10}	31.8 - 44.1 μg/m³	1.097	(0.934 - 1.292)
		CO	1.0 - 2.11 mg/m³	1.009	(0.897 - 1.140)
Sagiv (2005) (48)	Last 6 Weeks	PM_{10}	25.3 (14.6) μg/m³	1.014	(0.996 - 1.034)
Pennsylvania (USA), 187,997					

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

mates (32, 49), 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 (5) showed a small but statistically significant adverse exposure-related effect (OR=1.024).

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/m³) and showed statistically significant increased risks with exposure in each trimester (1.153 in the first trimester to 1.128 in the second trimester).(33) 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 μg/m³). Hansen et al. looked at results associated with lower exposure levels (mean = 12.8 μg/m³) 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 (19, 33).

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 μg/m³ $PM_{2.5}$ 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 (36) showed a similar effect that was limited to the second trimester.

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

The effect of PM_{10} exposure during pregnancy

Table 3 - Main characteristics of studies investigating Low Birth Weight

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	OR	(CI 95%)
Brauer (2008) (9)	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) (28)	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) (5)	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) (12)	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)
Salam (2005) (49)	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) (56)	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) (31, 32)	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)

(continued)

Table 3 - *continued*

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	OR	(CI 95%)
Lin (2004) (31, 32)	3rd Trimester	PM_{10}	43.7 - 63.7 μg/m³	0.985	(0.900 - 1.082)
Taiwan, 92,288		CO	1.39 - 17.75 mg/m³	0.991	(0.979 - 1.002)
		NO_2	45.5 - 65.3 μg/m³	0.927	(0.842 - 1.015)
		O_3	37.8 - 91.4 μg/m³	1.009	(0.974 - 1.044)
	Entire Pregnancy	PM_{10}	46.4 - 63.1 μg/m³	0.893	(0.757 - 1.040)
		CO	1.50 - 17.6 mg/m³	0.984	(0.972 - 1.996)
		NO_2	49.9 - 62.8 μg/m³	1.046	(0.914 - 1.195)

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

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/m³. The six studies had different levels of exposure (17 to 60 μg/m³), 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,(16) California (49) and Connecticut (5). 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 (36) 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 μg/m³ 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 (5, 36, 42), 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.

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 lim-

Table 4 - Main characteristics of studies investigating Small for Gestational Age

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	OR	(CI 95%)
Kim (2007) (28)	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) (33)	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) (21)	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) (36)	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)
Parker (2005) (42)	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.

Table 5 - Main characteristics of studies investigating birth weight as a continuous variable

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	β (gr)	(CI 95%)
Hansen (2007) (21) Brisbane (Australia), 26,617	1st Trimester	PM_{10}	19.6 (9.4) μg/m^3	-4.0	(-14.9 - +6.9)
		NO_2	16.8 (7.8) μg/m^3	+15.8	(-4.0 - +35.5)
		O_3	53.4 (15.6) μg/m^3	+1.5	(-5.5 - +8.4)
	2nd Trimester	PM_{10}	19.6 (9.4) μg/m^3	+0.5	(-1.2 - +1.3)
		NO_2	16.8 (7.8) μg/m^3	+8.8	(-8.4 - +26.0)
		O_3	53.4 (15.6) μg/m^3	+2.30	(-6.0 - +10.6)
	3rd Trimester	PM_{10}	19.6 (9.4) μg/m^3	+4.5	(-8.6 - +17.5)
		NO_2	16.8 (7.8) μg/m^3	-9.1	(-27.0 - +8.8)
		O_3	53.4 (15.2) μg/m^3	+6.0	(-2.3 - +14.3)
Bell (2007) (5) MA, CT (USA), 358,504	1st Trimester	CO	0.76 (0.21) mg/m^3		(-32.1 - -28.2)
		$PM_{2.5}$	11.9 (1.6) μg/m^3		(-3.3 - -2.5)
	3rd Trimester	PM_{10}	22.3 (5.3) μg/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) μg/m^3		(-4.1 - -3.2)
	Entire Pregnancy	PM_{10}	22.3 (5.3) μg/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) μg/m^3	-9.7	(-11.8 - -7.6)
		$PM_{2.5}$	11.9 (1.6) μg/m^3	-6.7	(-7.8 - -5.6)
Kim (2007) (28) Seoul (South Korea), 1,514	1st Trimester	PM_{10}	89.7 (44.5) μg/m^3	+7.8	(+1.2 - +14.5)
	2nd Trimester	PM_{10}	89.4 (45.1) μg/m^3	-0.3	(-0.7 - +0.7)
	3rd Trimester	PM_{10}	88.8 (47.6) μg/m^3	-2.1	(-7.5 - +3.4)
Salam (2005) (49) California (USA), 3,901	1st Trimester	PM_{10}	46.6 (15.9) μg/m^3	-1.5	(-11.4 - +8.4)
		CO	2.09 (1.28) mg/m^3	-13.4	(-26.0 - -0.7)
		NO_2	69.9 (32.3) μg/m^3	-3.2	(-8.3 - +1.9)
		O_3	55 (28.2) μg/m^3	-3.1	(-8.4 - +2.3)
	2nd Trimester	PM_{10}	45.4 (14.8) μg/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) μg/m^3	+0.4	(-4.8 - +5.6)
		O_3	54 (25.6) μg/m^3	-10.0	(-15.8 - -4.2)
	3rd Trimester	PM_{10}	45.4 (15.5) μg/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) μg/m^3	-1.3	(-6.5 - +4.0)
		O_3	55 (26.6) μg/m^3	-10.4	(-16.1 - -4.6)
	Entire Pregnancy	PM_{10}	45.8 (12.9) μg/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) μg/m^3	-1.5	(-7.3 - +4.3)
		O_3	54.6 (17.4) μg/m^3	-19.7	(-27.9 - -11.4)
Mannes (2005) (36) Sidney (Australia), 138,056	1st Trimester	PM_{10}	16.8 (7.1) μg/m^3	-1.4	(-13.7 - +10.9)
		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)

(continued)

Table 5 - *continued*

1st Author (pub yr) (ref. n°) Study Location, Population	Time-window of Exposure	Pollutants considered	Exposure Level*	β (gr)	(CI 95%)
Mannes (2005) (36)	2nd Trimester	PM_{10}	16.8 (7.1) μg/m³	-20.5	(-33.6 - -7.4)
Sidney (Australia), 138,056		CO	0.93 (0.81) mg/m³	-9.2	(-19.9 - +1.4)
		NO_2	44.3 (14.1) μg/m³	-5.0	(-10.8 - +0.9)
		O_3	63.2 (29.2) μg/m³	-3.8	(-6.9 - -0.6)
		$PM_{2.5}$	9.4 (5.1) μg/m³	-4.1	(-6.8 - -1.4)
	3rd Trimester	PM_{10}	16.8 (7.1) μg/m³	-9.5	(-23.0 - +4.0)
		CO	0.93 (0.81) mg/m³	-5.7	(-16.0 - +4.6)
		NO_2	44.3 (14.1) μg/m³	-7.7	(-14.1 - -1.4)
		O_3	63.2 (29.2) μg/m³	-2.3	(-5.4 - +0.9)
		$PM_{2.5}$	9.4 (5.1) μg/m³	-1.0	(-3.7 - +1.8)
	Last Month	PM_{10}	16.8 (7.1) μg/m³	-12.1	(-23.1 - -1.1)
		CO	0.93 (0.81) mg/m³	-13.2	(-22.1 - -4.3)
		NO_2	44.31 (14.13) μg/m³	-4.0	(-9.0 - +1.0)
		O_3	63.2 (29.2) μg/m³	-0.6	(-2.8 - +1.7)
		$PM_{2.5}$	9.4 (5.1) μg/m³	-2.5	(-4.6 - -0.4)
Parker (2005) (42)	1st Trimester	CO	0.66 – 1.08 mg/m³	-17.5	(-71.1 - +35.9)
California (USA), 18,247		$PM_{2.5}$	11.9 - 18.4 μg/m³	-5.5	(-9.0 - -2.0)
	2nd Trimester	CO	0.66 – 1.08 mg/m³	+34.0	(-21.3 - +89.3)
		$PM_{2.5}$	11.9 - 18.4 μg/m³	-7.2	(-10.6 - -3.8)
	3rd Trimester	CO	0.66 – 1.08 mg/m³	-20.1	(-77.1 - +36.6)
		$PM_{2.5}$	11.9 - 18.4 μg/m³	-4.9	(-8.0 - -1.7)
	Entire Pregnancy	CO	0.66 – 1.08 mg/m³	+6.2	(-49.3 - +61.8)
		$PM_{2.5}$	11.9 - 18.4 μg/m³	-5.4	(-9.0 - -1.8)
Gouveia (2004) (16)	1st Trimester	PM_{10}	60.3 (25.2) μg/m³	-13.7	(-27.0 - -0.4)
Sao Paulo (Brazil), 179,460		CO	4.29 (1.86) mg/m³	-19.9	(-35.6 - -4.2)
		NO_2	117.9 (51.2) μg/m³	-7.0	(-14.3 - +0.3)
		O_3	63.0 (33.5) μg/m³	-1.6	(-12.8 - +9.5)
	2nd Trimester	PM_{10}	60.3 (25.2) μg/m³	-4.4	(-18.9 - +10.1)
		CO	4.29 (1.86) mg/m³	+2.8	(-15.7 - +21.1)
		NO_2	117.9 (51.2) μg/m³	+0.3	(-8.6 - +9.2)
		O_3	63.0 (33.5) μg/m³	-0.1	(-11.9 - +11.7)
	3rd Trimester	PM_{10}	60.3 (25.2) μg/m³	+14.6	(0 - +29.2)
		CO	4.29 (1.86) mg/m³	+1.6	(-15.7 - +19.0)
		NO_2	117.9 (51.2) μg/m³	+3.6	(-6.6 - 13.7)
		O_3	63.0 (33.5) μg/m³	-3.0	(-15.4 - +9.4)

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

ited 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 μg/m³ increase in $PM_{2.5}$ across different time windows.

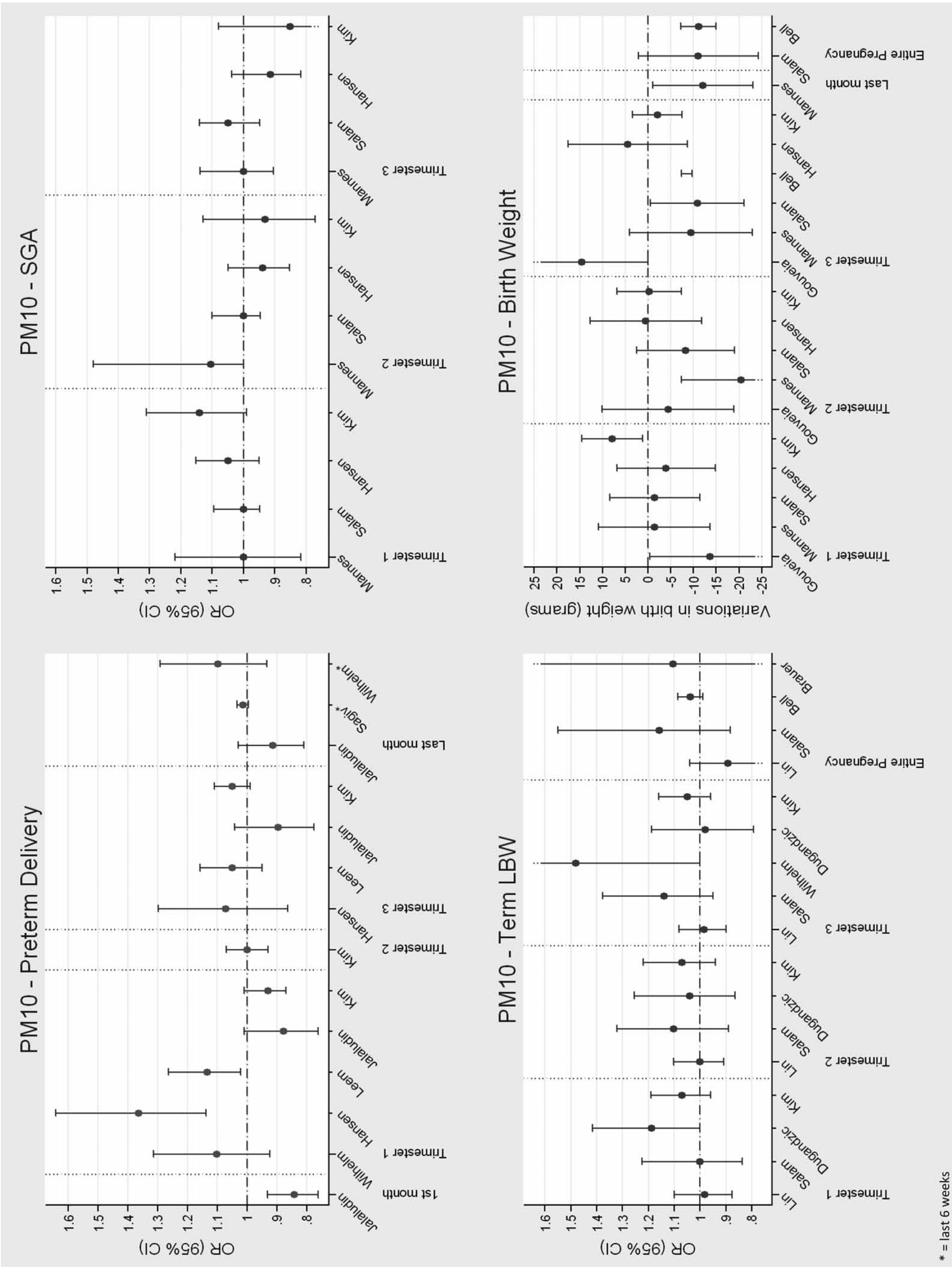

Figure 1 - PM_{10} and adverse pregnancy outcomes: results (ORs with relative 95% CIs) from the retrieved studies

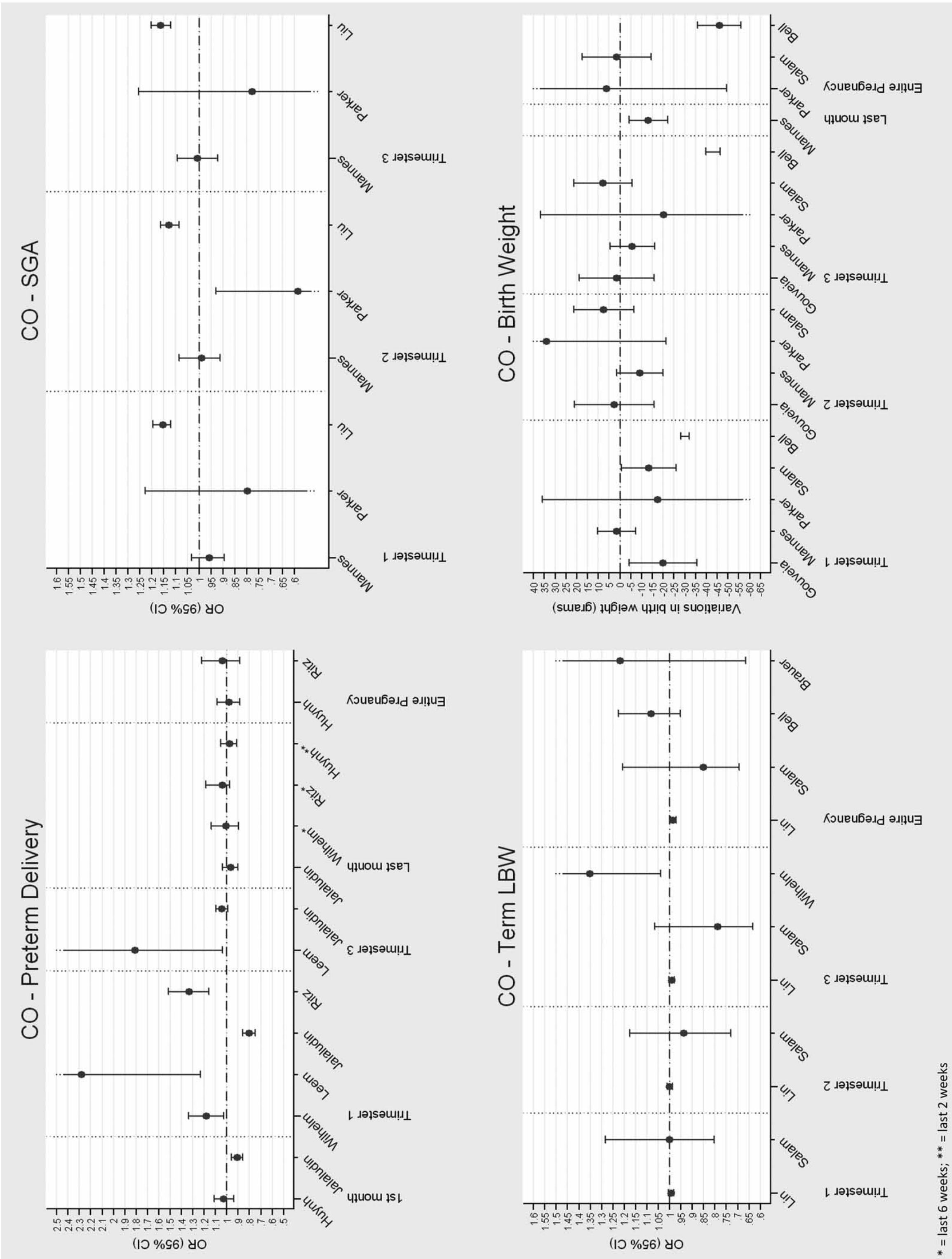

Figure 2 - CO and adverse pregnancy outcomes: results (ORs with relative 95% CIs) from the retrieved studies

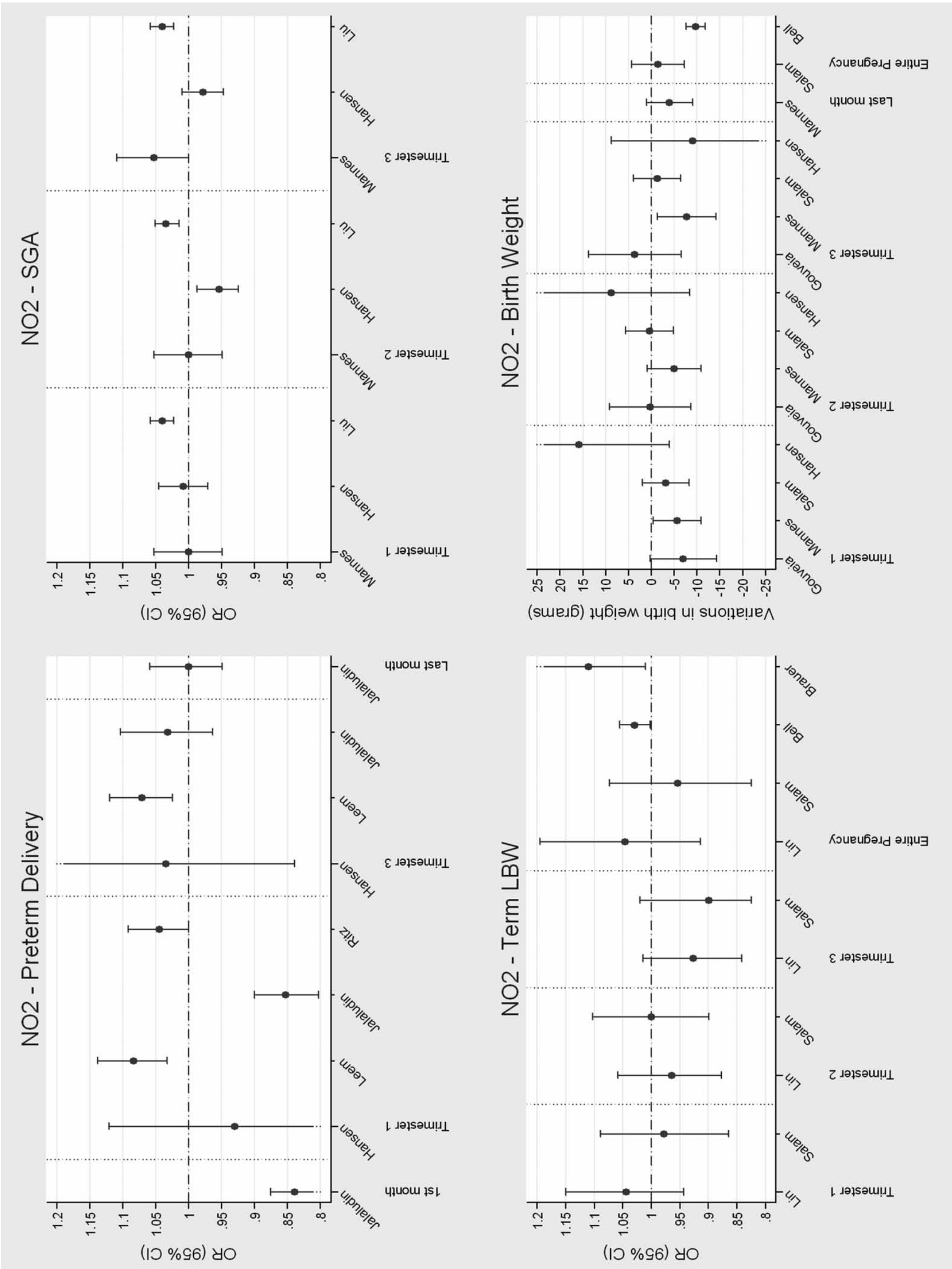

Figure 3 - NO_2 and adverse pregnancy outcomes: results (ORs with relative 95% CIs) from the retrieved studies

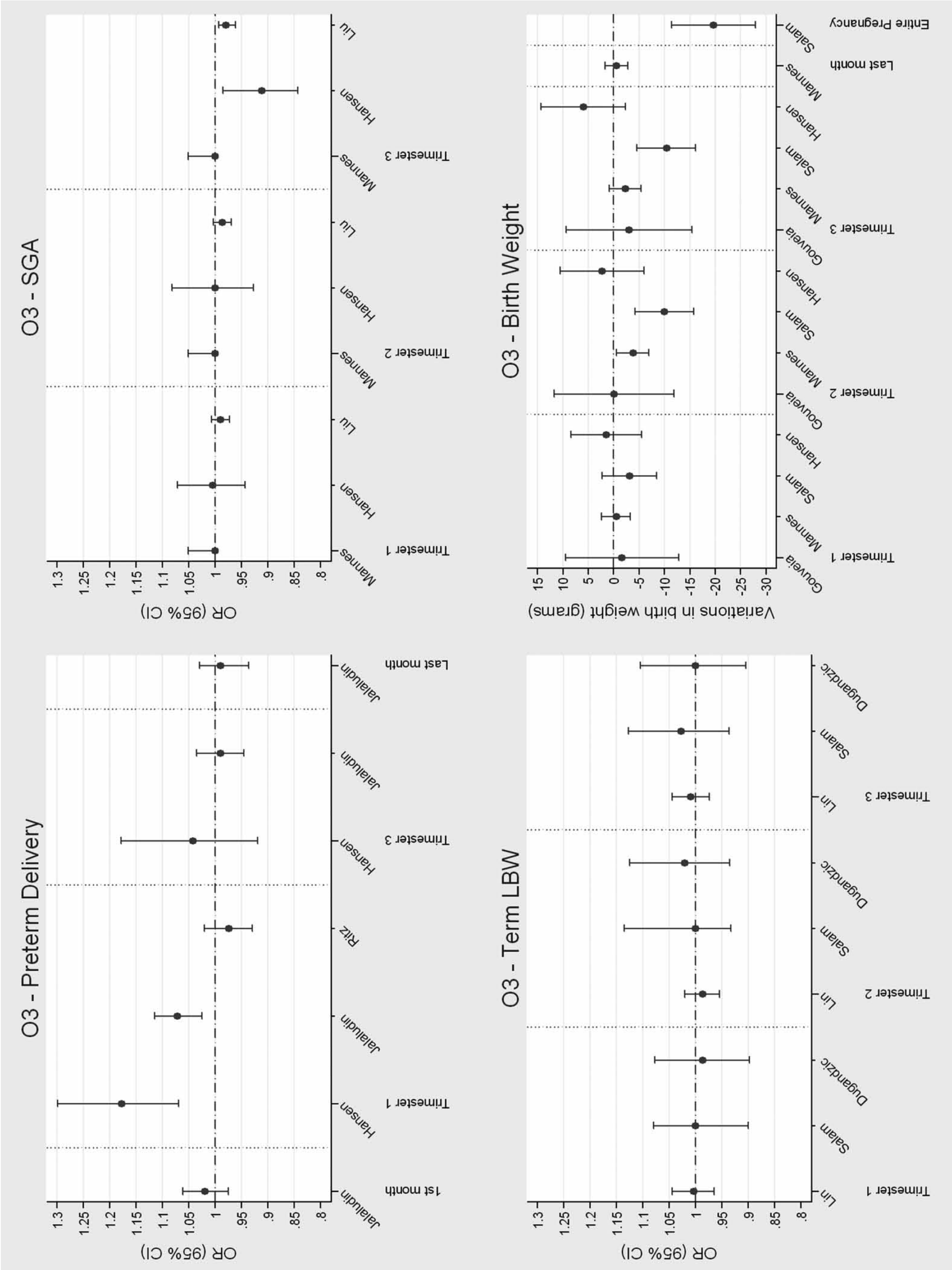

Figure 4 - O_3 and adverse pregnancy outcomes: results (ORs with relative 95% CIs) from the retrieved studies

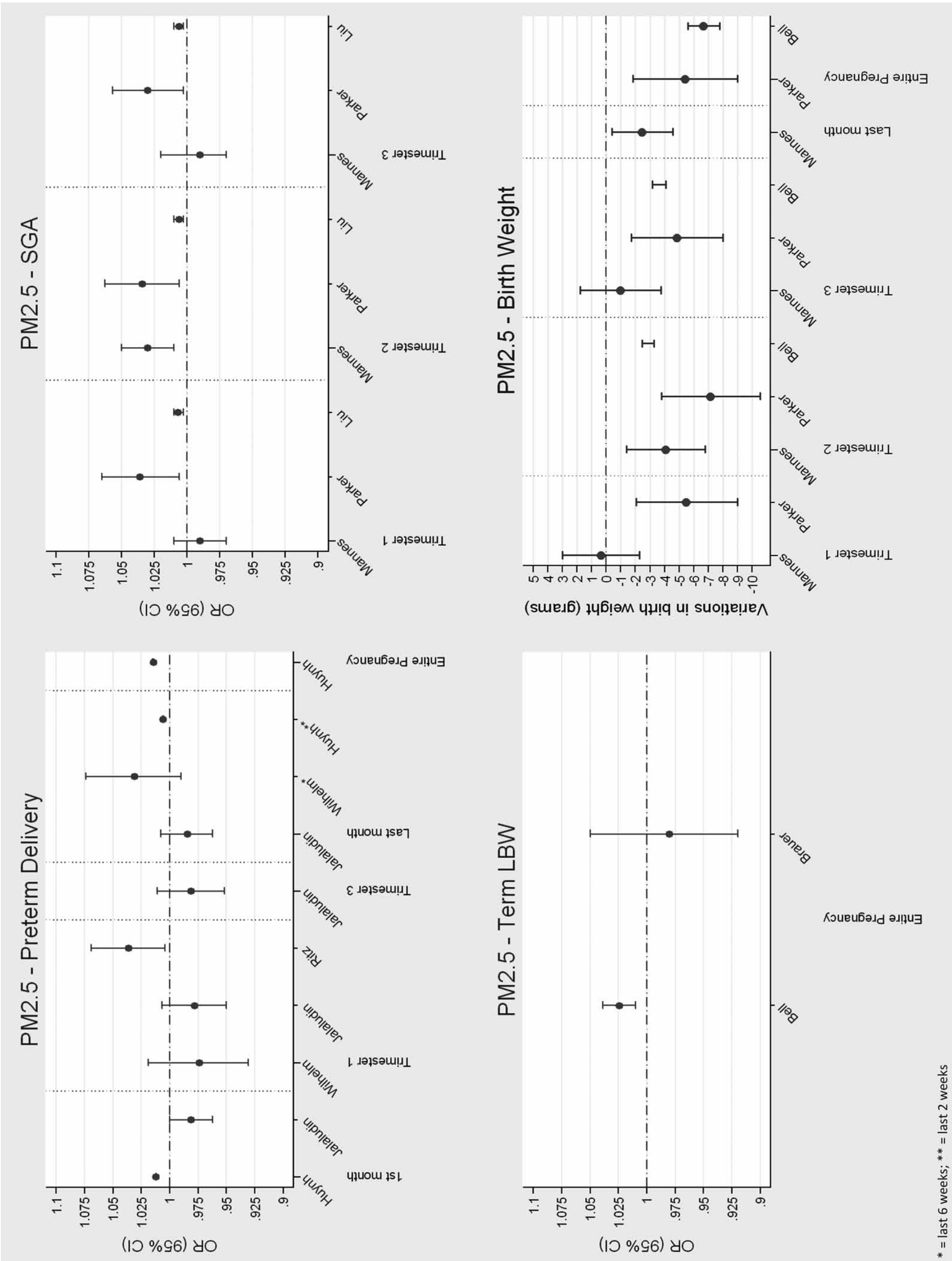

Figure 5 - $PM_{2.5}$ and adverse pregnancy outcomes: results (ORs with relative 95% CIs) from the retrieved studies

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 (43, 53). 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 (11).

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 (48) but does not take into account seasonal variations shown to be related to short-term changes in air pollution.(9) Slama et al. (51) 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 (23) 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 (24, 36). 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 (43). 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.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED

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