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The association between ambient air pollution and selected adverse pregnancy outcomes in China: A systematic review

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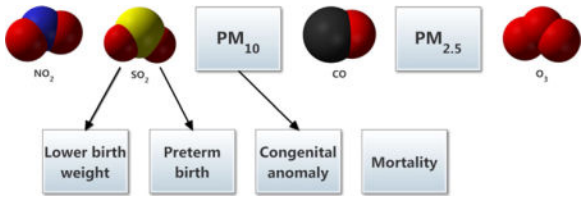
Abstract

The association between exposure to ambient air pollution and respiratory or cardiovascular endpoints is well-established. An increasing number of studies have shown that this exposure is also associated with adverse pregnancy outcomes. However, the majority of research has been undertaken in high-income western countries, with relatively lower levels of exposure. There is now a sufficient number of studies to warrant an assessment of effects in China, a relatively higher exposure setting. We conducted a systematic review of 25 studies examining the association between ambient air pollution exposure and adverse pregnancy outcomes (lower birth weight, preterm birth, mortality, and congenital anomaly) in China, published between 1980 and 2015. The results indicated that sulphur dioxide (SO_2) was more consistently associated with lower birth weight and preterm birth, and that coarse particulate matter (PM_{10}) was associated with congenital anomaly, notably cardiovascular defects.

Graphical abstract



Keywords

Pollution; Low birth weight; Preterm birth; Mortality; Congenital anomaly; Birth defects

1. Introduction

Exposure to air pollutants has been linked to a range of health problems including respiratory and cardiovascular morbidity (Cesaroni et al., 2013; Gurjar et al., 2010). There is

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also increasing evidence that exposure to air pollutants is associated with adverse pregnancy outcomes such as low birth weight (Bell et al., 2007; Pedersen et al., 2013), preterm birth (Bobak, 2000; Pereira et al., 2013), mortality (Pope et al., 2010; Woodruff et al., 1997) and congenital anomaly (Padula et al., 2013; Rankin et al., 2009). In addition, molecular epidemiological studies have shown that PAH-DNA adduct levels (biomarkers of exposure) are associated with adverse effects including intrauterine growth retardation (Šrám et al., 1999) and HPRT locus mutation frequency in infants (Perera et al., 2002). This suggests plausible biological mechanisms for the effects of air pollution on fetal growth and health (Šrám et al., 2005).

A recent systematic review (Stieb et al., 2012) examined the association between ambient air pollution and low birth weight, change in birth weight and preterm birth for pollutants including carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and particulate matter <10 and 2.5 μm in aerodynamic diameter (PM_{10} and $PM_{2.5}$). Of the 62 reviewed studies, nearly half (27) were conducted in North America, followed by Europe (18), Asia (10), Australia (4) and South America (3). Only one study was conducted in China.

A systematic review of 17 studies (Chen et al., 2014) examined the association between congenital anomaly and maternal exposure to ambient air pollutants during pregnancy. The most frequently-studied anomalies were cardiovascular, followed by nervous system defects. Seven of the studies in this review were conducted in the United States, four in the United Kingdom and the remainder in six different countries. None were conducted in China.

There have been relatively few systematic reviews on the association between ambient air pollution and mortality of infants and/or fetuses. The most recent one (Šrám et al., 2005) examined sudden infant death as well as intrauterine, perinatal, postneonatal and infant mortality. The authors observed a notable consistency in the results – the three largest studies produced very similar estimates of relative risk – and the evidence was sufficient to infer a causal relationship between particulate air pollution and respiratory deaths in the postneonatal period. For this review, studies were conducted in the Czech Republic, Britain, and the United States, Mexico and Brazil. None were conducted in China.

Compared with western countries, China has relatively high air pollution levels. According to the World Health Organization air pollution database (WHO, 2014), China had annual population weighted PM_{10} concentrations of 90 $\mu g/m^3$ compared to 21 $\mu g/m^3$ for the United States and the United Kingdom, 33 $\mu g/m^3$ for Italy and 23 $\mu g/m^3$ for Canada. Particulate matter is generally regarded as an important measure of air quality as studies have consistently demonstrated its toxicity (Hester and Harrison, 1998).

In addition to differences in the levels and physico-chemical composition of air pollutants between China and other countries studied, there exist relevant genetic and physiological differences in between cohort. For example, it has been shown that North-East Asians have significantly different lung dynamics than Caucasians (Quanjer et al., 2012). While this difference is less pronounced than for other groups (e.g. South-East Asians), it would potentially result in different dosage/deposition rates for the same exposure.

Previous reviews indicate accumulating evidence for an association between air pollution and adverse pregnancy outcomes but most evidence is derived from research conducted in western countries with relatively lower levels of exposure. A significant gap in the literature is the lack of review of effects for exposure in a country such as China, with among the highest levels of air pollution globally. To our knowledge, there has been no systematic review of the effects of ambient air pollution on pregnancy outcomes in China. Exposure-response associations from studies conducted in Western countries may not apply to populations in China due to the worse air quality, but also due to potential differences in the underlying population such as different baseline health status and health care systems (O'Neill et al., 2003).

We investigated the association between ambient air pollutant exposure (NO_2, SO_2, CO, PM_{10}, $PM_{2.5}$ and ozone (O_3)) and the following adverse pregnancy outcomes in China: decrease in birth weight, low birth weight, preterm birth, mortality and congenital anomaly. This review included both Chinese and English language articles.

2. Method

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.1. Study selection

A search of the following databases was undertaken: PubMed, Medline (Web of Science), Embase, CNKI (China National Knowledge Infrastructure) and Wanfang Data. The search was limited to English and Chinese papers published between 1980 and 2015 using the search terms in Fig. 1. The inclusion criteria were: 1) peer-reviewed articles in journals published from 1st January 1980 to 31st December 2015, 2) conducted in China, 3) ambient exposure to at least one of the following air pollutants: NO_2, SO_2, CO, PM_{10}, $PM_{2.5}$, O_3; and 4) health outcomes: low birth weight, preterm birth, stillbirth or death (in utero to age one year), or birth defects (congenital anomaly). Studies that measured occupational or accidental exposure, tobacco, exposure to other pollutants or a proxy for exposure were excluded. No case reports were included.

2.2. Quality assessment

We evaluated the quality of the selected studies using the following criteria (Berman and Parker, 2002): 1) source of the information (reputable, reliable, clearly identified); 2) study design clearly described and appropriate to the study questions; 3) exposures and outcomes well-defined, including methods of measurement; 4) adjustment for confounding variables; and 5) statistical methods appropriate.

2.3. Data extraction

The following items were extracted from each study: location, sample size (number of births), year/s of study, study design, adjustment variables, population, outcome ascertainment, exposure assessment, and quantitative findings.

3. Results

3.1. Included and excluded studies

Using the search terms in Fig. 1, a total of 1029 articles were identified, consisting of 193 papers written in English and 836 papers written in Chinese (Fig. 2). We included articles written in Chinese. The first screening, by title, eliminated duplicates and non-relevant titles, leaving a total of 83 possibly relevant articles. The second screening, an abstract review, resulted in 46 articles eligible for further review. A full-text review of these articles at the third screening identified 21 articles for inclusion. The reference lists of these articles were then examined and four additional papers were identified for inclusion. This resulted in the inclusion of 25 articles consisting of 14 papers written in Chinese and 11 papers written in English. Each study was assigned a number between one and 25 (Table 1), which was used to refer to the study in this review.

Of the 25 reviewed studies, the majority were conducted in large urban areas. Seven studies were based in the Guangdong province (including Guangzhou) and five were in Beijing. The most common study design was case-control (nine studies), followed by cross-sectional (eight studies). There were only two prospective cohort studies and both were conducted in Beijing.

3.2. Exposure ascertainment

The majority of the reviewed studies examined PM_{10}, NO_2 and SO_2 because these were the only pollutants routinely measured by the Chinese government monitoring network from 2000 to 2012 ($PM_{2.5}$, O_3 and CO were less well-studied). The most common method of exposure ascertainment was calculating the average concentration for each pollutant across all monitoring sites in the study area (17 out of 25 studies). Other methods involved using the nearest monitor (four studies) or inverse distance weighting (IDW, five studies), which is the weighted average of concentrations at monitoring sites whereby each site's concentration is assigned the reciprocal of the distance as the weight. One study used both the nearest monitor approach and inverse distance weighting (Study 5).

The majority of reviewed studies reported average pollutant concentrations over the study periods, which ranged from one to eight years (Tables 2–5). Mean concentrations of PM_{10}, NO_2 and SO_2 across all studies were 113 $\mu g/m^3$, 50 $\mu g/m^3$ and 61 $\mu g/m^3$, respectively, with maximum concentrations of 600, 468 and 630 $\mu g/m^3$, respectively. On average, studies in Taiyuan reported the highest concentrations of PM_{10} and SO_2 (165 $\mu g/m^3$ and 114 $\mu g/m^3$, respectively), while studies in Shanghai reported the highest concentrations of NO_2 (71 $\mu g/m^3$). The highest average pollutant levels overall were for studies in Beijing (population 19 million) and the lowest were for studies in Haikou (population 2 million).

3.3. Outcome assessment

3.3.1. Birth weight—Effects on birth weight were investigated as either the occurrence of low birth weight (<2500 g) or the change in birth weight (measured in grams). Study 11 further classified low birth weight as either low birth weight (<2500 g) or very low birth weight (<1500 g).

Of the nine studies that examined either birth weight or low birth weight, six studies restricted analyses to term births (≥37 weeks). The other three studies (Study 13, 18, 19) used the term 'Weichaner', which is defined in Chinese as ≥28 weeks gestational age. Of the five studies that investigated change in birth weight (continuous variable), only two (Study 6, 19) adjusted for gestational age.

3.3.2. Preterm birth—Preterm birth is defined as birth occurring before 37 weeks gestational age. However, in Study 5, preterm birth was classified as either moderate preterm (32–36 weeks) or very preterm (<32 weeks) and then further classified as either medically-indicated or spontaneous (with or without prelabour rupture of membranes). Medically-indicated preterm birth was defined as preterm birth without spontaneous onset of labour, and is often due to maternal or fetal complications including placental abruption, placenta previa, placental accreta, pregnancy hypertension and preeclampsia, intrauterine growth restriction, oligohydramnion, uterine rupture, and pre-gestational diabetes (Zhao et al., 2015).

Of the 11 studies that examined preterm birth, eight studies calculated gestational age as the number of completed weeks between the first day of the last menstrual period (LMP) and the date of birth. Study 1 did not specify how gestational age was calculated. In Study 3, gestational age was confirmed by sonographic examination prior to 20 weeks gestation. Study 8 used LMP and a clinical estimate of gestational age if LMP was missing. Compared to ultrasound scanning, LMP estimates overstate the duration of gestation by 2.8 days on average (Savitz et al., 2002).

3.3.3. Congenital anomaly—There were seven studies that examined congenital anomaly. Four studies examined a range of diagnosed birth defects (Study 10, 12, 14, 24). One study examined only congenital heart defects, divided into the following groups: pooled cases, congenital malformations of the great arteries, congenital malformations of cardiac septa, and isolated cases of patent ductus arteriosus (Study 23). Two studies did not specify the types of anomaly examined (Study 9, 11).

A clinical diagnosis of birth defects was generally made within 7 days after delivery. Within this period, all diagnosed birth defects were required to be reported. All studies undercounted birth defects considerably as not all birth defects are diagnosed shortly after birth. For example, a one year follow-up identified approximately 50% fewer births with birth defects compared to a six-year follow-up (King Edward Memorial Hospital, 2010).

3.3.4. Mortality—Five of the reviewed studies examined mortality. Types of mortality studied were (i) fetal loss <14 weeks gestation (Study 7); (ii) missed abortion ≤14 weeks where the embryo died but miscarriage had not yet occurred (Study 16); (iii) mortality between 28 weeks gestation to 7 days after birth, referred to as 'perineonate death' (Study 9, 11); and (iv) stillbirth, defined as death after 20 weeks (Study 25).

3.4. Adjustment variables

Of the 25 reviewed studies, 17 studies adjusted for maternal age (Table 6). Other variables commonly adjusted for were fetal/infant sex (11 studies), temperature (10 studies),

gestational age, humidity and other pollutants (8 studies). Eight studies accounted for socioeconomic status by adjusting for education, income and/or occupation variables. Time variables such as day of week/year, season and/or year were adjusted for in eight studies. Study 9 did not report any adjustment variables.

3.5. Quantitative results on association between pollution and pregnancy outcomes

Results were converted to effect estimates per 10 μg/m^3 increase in exposure over the relevant exposure period. All reported associations are with adverse health outcomes and are statistically significant ($p < 0.05$), unless stated otherwise.

3.5.1. Birth weight—Five of the reviewed studies examined change in birth weight (BW). All three studies that examined SO_2 reported significant associations with BW (e.g., 1.9 g decrease in BW for exposure over the entire pregnancy in Study 19) (Table 7). A prospective cohort study (Study 6) reported an association (0.7 g decrease in BW) for exposure in the third trimester.

The results were inconsistent for NO_2. Two out of three studies reported associations with BW (3.3 g decrease in BW for Study 19 for the first trimester and 14.8 g decrease for Study 3 for the third trimester). However, a *protective* association between NO_2 and BW was reported in the third trimester as well as the entire pregnancy (6.3 g *increase* in BW for the third trimester in Study 19).

Two studies (Studies 13 and 19) reported identical results for PM_{10}, namely an association with BW in the first two trimesters of pregnancy (2.7 g and 2.2 g decrease in BW in the first and second trimester, respectively) and a protective association in the third trimester (3.8 g increase in BW). However, another study did not report any significant associations between BW and PM_{10} (Study 3). Only one study examined the effects of CO and $PM_{2.5}$ on BW, and reported associations for both pollutants but only for the eighth month of pregnancy (0.5 g and 9.1 g decrease in BW for CO and $PM_{2.5}$, respectively, for Study 4).

The results indicate that there is more consistent evidence of a statistically significant association between exposure to SO_2 and lower birth weight.

3.5.2. Low birth weight—Five of the reviewed studies investigated low birth weight (LBW) (Table 8). Of the five studies that examined SO_2, three reported associations with LBW (adjusted odds ratio (AOR) = 1.04 in the first month for Study 14 and AOR = 1.08 in the first trimester for Study 22). A prospective cohort study (Study 6) reported an association (AOR = 1.01) for exposure in the third trimester.

Of the three studies that examined NO_2, one reported a weak protective association with LBW in the third trimester (AOR = 0.92 for Study 22). Two out of four studies that examined PM_{10} reported significant associations with LBW in late pregnancy. One study reported a weak protective association in the third trimester (AOR = 0.95 for Study 22), while another reported a weak protective association for the sub-outcome *very low birth weight* (<1500 g) in the 7th–9th months of pregnancy (AOR = 0.94 for Study 11).

The results indicate that there is more consistent evidence of a statistically significant association between exposure to SO_2 and low birth weight.

3.5.3. Preterm birth—Eleven of the reviewed studies examined preterm birth (PTB). Only one study examined O_3 and this study reported an association for exposure within the last two months before delivery (3.1% and 4.6% increase in the number of preterm births for the last four and eight weeks before delivery, respectively, for Study 8) (Table 9).

Three out of eight studies that examined NO_2 found a significant association with PTB. One study reported a 5.4% increase in the number of preterm births for exposure to NO_2 in the eight weeks before delivery (Study 8). Associations were also reported for the third trimester (AOR = 1.06 for Study 15) and for the entire pregnancy (AOR = 1.24 for Study 21). There was a weak *protective* association for the second trimester (AOR = 0.93 for Study 15).

Five out of 10 studies that examined PM_{10} reported significant associations. For PTB overall, associations were reported for different exposure periods, from three months before conception (AOR = 1.06 for Study 11) to two months before delivery (AOR = 1.04 for Study 14), as well as for the entire pregnancy (AOR = 1.03 for Study 21). One study reported a 4.4% increase in the number of preterm births for exposure to PM_{10} in the eight weeks before delivery (Study 8). For the sub-outcome *medically-indicated preterm birth* (defined in Section 3.3.1), respective adjusted odds ratios were 1.07 and 1.14 for the first trimester and the entire pregnancy (Study 5). For *very preterm birth* (<32 weeks), associations were observed in the last four, six and eight weeks before delivery (AOR = 1.07, AOR = 1.09 and AOR = 1.10, respectively for Study 5).

For SO_2, the majority (seven of nine) of studies reported significant associations for different exposure periods, ranging from the first month of pregnancy (AOR = 1.02 for Study 11) to one month before delivery (AOR = 1.06 for Study 14), as well as for the entire pregnancy (AOR = 1.06 for Study 21). Two studies reported identical results (RR = 1.01 for the entire pregnancy for Study 2 and 17). Moreover, a prospective cohort study (Study 1) also reported an association (AOR = 1.21 for each unit increase in $\ln(SO_2)$) over the entire pregnancy.

The results indicate that there is more consistent evidence of a statistically significant association between exposure to SO_2 and preterm birth.

3.5.4. Congenital anomaly—Seven studies examined congenital anomaly for NO_2, PM_{10} and/or SO_2. Of the four studies that examined NO_2, two reported associations with congenital anomaly (Table 10). Notably, strong associations were reported with congenital malformations of the great arteries (AOR = 2.03), isolated cases of patent ductus arteriosus (PDA) (AOR = 2.16) and pooled congenital heart defects (AOR = 2.11) for exposure over the entire pregnancy (Study 23).

Four out of five studies that examined PM_{10} reported associations for different exposure periods during pregnancy. Associations for all diagnosed birth defects were relatively weak (highest AOR = 1.13 in the third month of pregnancy for Study 24). However, higher effect estimates were reported for malformations of the cardiac septa (AOR = 1.44), great arteries (AOR = 1.36), and PDA (AOR = 1.31) as well as pooled heart defects (AOR = 1.35) over the

entire pregnancy (Study 23). There was a strong association with fetal cardiovascular deformity for exposure in the first three months of pregnancy (AOR = 2.22 for a one quartile increase in PM_{10} for Study 12).

Two out of five studies examining SO_2 reported significant associations. One study reported a weak protective association with all diagnosed birth defects for exposure in the third month of pregnancy (AOR = 0.97 for Study 11). However, another reported an association with malformations of the cardiac septa over the entire pregnancy (AOR = 2.35 for Study 23).

The results indicate that there is more consistent evidence of a statistically significant association between exposure to PM_{10} and congenital cardiovascular defects.

3.5.5. Mortality—Five of the reviewed studies examined mortality. Results for individual pollutants were not available for Study 9; however, the study reported that 'perineonate death' (defined in Section 3.3.4) was significantly higher in rural compared to city areas ($p < 0.001$). Of the two studies that examined NO_2, only one observed associations with mortality (Table 11). There was an association between fetal loss in early pregnancy (<14 weeks) and exposure to NO_2 one and two months before conception as well as one month after conception (all ORs = 1.05 for Study 7). Only one study examined O_3 and reported a weak protective association with stillbirth for full term births with exposure in the second trimester (AOR = 0.96 for Study 25).

For PM_{10}, two out of four studies reported significant associations with mortality. One study reported an association with perineonate death for exposure between the 7th and 9th months of pregnancy (AOR = 1.05 for Study 11). However, another reported weak protective associations with stillbirth for exposure in the second trimester (AOR = 0.96 for all births and AOR = 0.95 for full term births only for Study 25).

For SO_2, two out of three studies reported associations with mortality. There was an association between fetal loss in early pregnancy (<14 weeks) and exposure to SO_2 around the time of conception as well as one month after conception (both ORs = 1.03 for Study 7). There were also associations with stillbirth for preterm births for exposure in the first, second and third months of pregnancy as well as for the first trimester overall (including non-preterm births) (AOR = 1.15 for the first trimester for Study 25).

The results indicate that there is currently insufficient evidence for a statistically significant association between ambient air pollution exposure during pregnancy and mortality of the child.

4. Discussion

This is the first systematic review of the association between ambient air pollution and adverse pregnancy outcomes in China. We investigated the association between six different pollutants (SO_2, NO_2, PM_{10}, $PM_{2.5}$, CO and O_3) and five outcomes (decrease in birth weight, low birth weight, preterm birth, congenital anomaly and mortality) based on 25 reviewed studies. The results indicated that SO_2 was more consistently associated with lower

birth weight and preterm birth, and that PM_{10} was associated with congenital anomaly, notably cardiovascular defects. Significant associations were reported for different periods during pregnancy as well as for the entire pregnancy.

The results for other pollutants and outcomes were inconsistent. In some cases, weak protective associations were reported, particularly in the third trimester. Further studies are needed to clarify associations for other outcomes and pollutants, particularly CO, $PM_{2.5}$ and O_3, for which there were relatively few studies.

We note that effect sizes in the reviewed studies were higher than those reported in previous systematic reviews, conducted mainly in western countries. A meta-analysis (Chen et al., 2014) of 21 combinations of air pollutants and congenital anomalies reported only one statistically significant result: the pooled odds ratio for coarctation of the aorta was 1.09 (95% CI: 1.01, 1.18) per 10 $\mu g/m^3$ of NO_2. In contrast, the reviewed studies indicated a consistent, statistically significant association between exposure to PM_{10} and a range of congenital cardiovascular defects. The adjusted odds ratio for pooled heart defects was 1.35 (1.15, 1.60) and ranged from 1.31 (1.07, 1.60) for patent ductus arteriosus to 1.44 (1.04, 1.99) for defects of the cardiac septa per 10 $\mu g/m^3$ of PM_{10} over the entire pregnancy.

It is important to note that exposures for different time periods and concentrations of different air pollutants are correlated, making it difficult to determine the effects of individual pollutants (Šrám et al., 2005) or the most relevant window of exposure. Also, since many different types of pollutants are often emitted from the same sources, it is not possible to determine if the observed effects are due to the pollutants studied or if they are due to the effects of other unmeasured pollutants, or interactive effects of multiple mixed pollutants. Human chamber studies (Hackney et al., 1975) have been used to assess the effects of specific pollutants; however, this is not ethical when the subjects are pregnant women and infants/fetuses. In addition, pollution sources can vary by city, leading to potentially different chemical components and toxicity of PM_{10} or $PM_{2.5}$.

Although the mechanisms by which air pollution cause adverse pregnancy outcomes are not well-understood, inflammation is a biologically plausible mechanism. Air pollution might lead to preterm birth through early activation of cytokines favouring inflammation, which are otherwise part of the body’s normal preparation for parturition (Engel et al., 2005; Keelan et al., 2003). Placental inflammation in particular can affect transplacental nutrient exchange (Bobak, 2000), which can lead to fetal growth restriction, early delivery and their associated morbidities (Mestan et al., 2010). The role of inflammation in promoting adverse pregnancy outcomes is supported by observational evidence from the Boston Birth Cohort, for which intrauterine inflammation at birth was associated with fine particulate matter exposure (Nachman et al., 2016). Inflammatory effects are not restricted to particulate matter exposure. Animal studies have demonstrated lung inflammation after exposure to sulphur dioxide (Li et al., 2014) and controlled human exposure studies to sulphur dioxide have consistently observed increase in bronchoconstriction (Johns and Linn, 2011).

An important issue in epidemiological studies is adjustment for risk factors. The majority of studies reviewed adjusted for various factors such as meteorological variables, maternal age,

gestational age, gravidity, parity and fetal sex. Some studies also adjusted for socioeconomic variables such as education, occupation and family income. Only a few studies adjusted for smoking as a risk factor, but smoking rates among women living in Chinese cities are generally very low (Rich et al., 2015).

All of the reviewed studies used ambient air pollutant concentrations measured at routine monitoring sites with exposures estimated using average concentrations across monitoring sites or, if the subject's location was known, using the nearest monitor or an inverse-distance weighting approach. None of the reviewed studies undertook personal monitoring or satellite remote sensing. However, molecular epidemiological studies have shown that ambient air pollution levels translate to higher individual exposures (Šrám et al., 2005). The approaches used by these studies are consistent with those of similar studies conducted in other parts of the world due to the feasibility constraints of personal monitoring over long timeframes. Measurement error may differ by study due to differences in the monitoring network or spatial heterogeneity of pollutant by study area.

We attempted to mitigate publication bias by including articles written in Chinese. For low birth weight and preterm birth, there were a large number of articles in both English and Chinese. However, for congenital anomaly and mortality, the majority of articles were written in Chinese. An advantage of this study was that by including peer reviewed articles written in Chinese, we were able to include 14 additional studies on the topic that would not have been included had the review been limited to English language articles.

The study population in China differs in some aspects from the study populations in western countries. Notably, the rate of preterm birth differs for Chinese-born women living China versus those living in different countries, which may be due to factors such as smoking and sexual practices (Newnham et al., 2011). Although the preterm birth rate is lower in China (3%) than the United States (12%) (Martin et al., 2010), the number of preterm births in China per year is double that of the USA (about 500,000 compared to one million preterm births) (Blencowe et al., 2012). However, pregnancy outcomes at the population level are not comparable because China's Family Planning Policy from 1979 to 2015 restricted parity, and it is well-established that birth weights increase and preterm birth rates decrease with increasing parity, with the greatest decrease in risk observed from first to second birth. In contrast to many western countries such as Australia, the UK and the United States, the race/ethnicity of the population in China is relatively homogeneous, with the majority being Han Chinese. These population differences may result in different health effects for air pollution and pregnancy outcomes in China than in Western countries, due both to physiological differences highlighted earlier and different cultural or social practices.

5. Conclusion

China has a relatively higher level of air pollution, resulting in greater exposure to pollutant concentrations during pregnancy. Our results indicated that effect sizes for preterm birth, change in birth weight and congenital anomaly were demonstrably greater than those reported in western countries. Given the large number of births in China, at a population scale this has a considerable impact on fetal and infant health and consequent morbidities.

We conclude that, for pregnancies in China, there were consistent associations between (i) SO_2 exposure during pregnancy and preterm birth and lower birth weight; and (ii) PM_{10} exposure during pregnancy and congenital anomaly.

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HIGHLIGHTS

- Ambient air pollution was significantly associated with adverse pregnancy outcomes in China.
- Sulphur dioxide (SO_2) was consistently associated with lower birth weight and preterm birth.
- Particulate matter (PM_{10}) was consistently associated with congenital anomaly, especially cardiovascular defects.
- Results for nitrogen dioxide (NO_2) were inconsistent.
- Further studies are needed on the effects of fine particulate matter ($PM_{2.5}$), ozone (O_3) and carbon monoxide (CO).

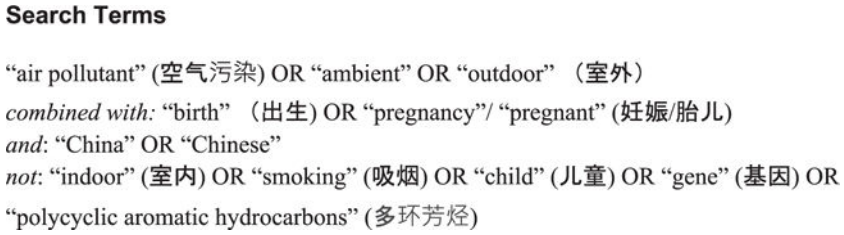

Fig. 1.
Search terms used to identify eligible studies.

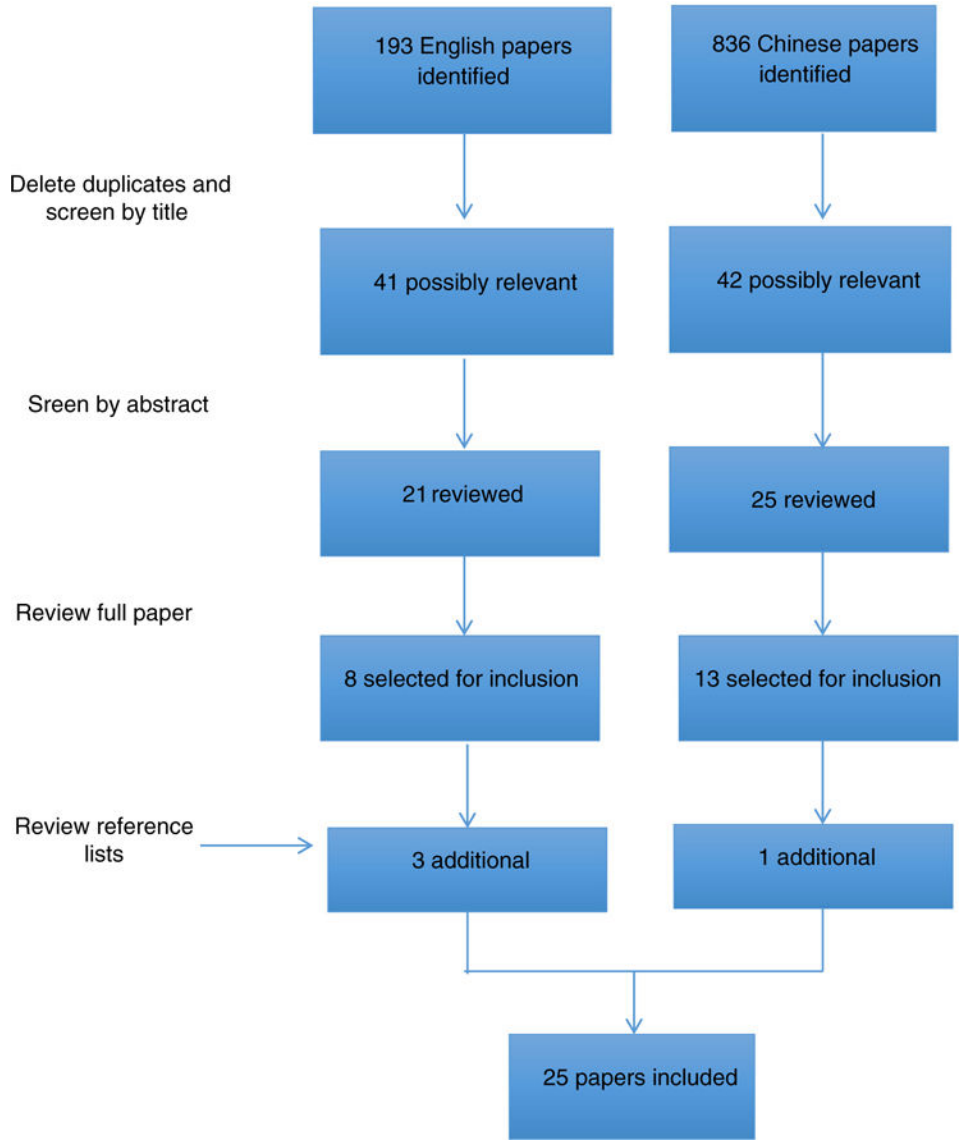

Fig. 2.
Flow diagram for the inclusion and exclusion of studies.

Table 1

Summary of studies included in this review, by outcome.

Outcome	Study	Reference	Study period	Area	Study type	Sample size	SO_2	NO_2	PM_{10}	$PM_{2.5}$	CO	O_3
BW	3	(Huang et al., 2015)	2006–2010	Beijing	Cross-sectional	50,874		+	−			
BW	4	(Rich et al., 2015)	2007–2010	Beijing	Cross-sectional	83,672	+	−		+	+	
BW	6	(Wang et al., 1997)	1988–1991	Beijing	Prospective cohort	74,671	+					
BW	13[a]	(Zhao and Li, 2008)	2003–2005	Guangzhou	Retrospective cohort	58,869			+			
BW	19[a]	(Zhao et al., 2008)	2003–2005	Guangzhou	Cross-sectional	58,837	+	+	+			
CA	9[a]	(Chen et al., 2012)	2002–2007	Tianjin	Cross-sectional	235,998						
CA	10[a]	(Zheng et al., 2013)	2001–2006	Tianjin	Case-control	1539 (459 cases, 1080 controls)	−	−				
CA	11[a]	(Zhang et al., 2007)	1997–2004	Taiyuan	Retrospective cohort	48,491	+		+			
CA	12[a]	(Shi et al., 2013)	2007–2012	Fuzhou	Case-control	534 (178 cases, 356 controls)			+			
CA	14[a]	(Aimaier et al., 2013)	2007–2009	Beijing	Retrospective cohort	23,187	−	+	−			
CA	23	(Jin et al., 2015)	2010–2012	Lanzhou	Retrospective cohort	8969	+	+	+			
CA	24	(Liang et al., 2014)	2009–2011	Haikou	Case-control	63,900 (509 cases, 63,391 controls)	−	−	+			
LBW	6	(Wang et al., 1997)	1988–1991	Beijing	Prospective cohort	74,671	+					
LBW	11[a]	(Zhang et al., 2007)	1997–2004	Taiyuan	Retrospective cohort	49,881	−		+			
LBW	14[a]	(Aimaier et al., 2013)	2007–2009	Beijing	Retrospective cohort	23,283	+	−	−			
LBW	18[a]	(Zhao et al., 2010b)	2007	Guangdong	Cross-sectional	7004	−	−	−			
LBW	22[a]	(Ruan et al., 2008)	2003–2005	Guangzhou	Case-control	2964 (1482 cases, 1482 controls)	+	+	+			
mortality	7	(Hou et al., 2014)	2001–2006	Tianjin	Case-control	1918(959 cases, 959 controls)	+	+	−			
mortality	9[a]	(Chen et al., 2012)	2002–2007	Tianjin	Cross-sectional	235,998						
mortality	11[a]	(Zhang et al., 2007)	1997–2004	Taiyuan	Retrospective cohort	49,910	−		+			
mortality	16[a]	(Hou et al., 2012)	2001–2006	Tianjin	Case-control	1918 (959 cases, 959 controls)			−			
mortality	25	(Hwang et al., 2011)	2001–2007	Taiwan	Case-control	102,575 (9325 cases, 93,250 controls)	+	−	+		−	+
PTB	1	(Xu et al., 1995)	1988	Beijing	Prospective cohort	25,370	+					
PTB	2	(Zhao et al., 2011)	2007	Guangzhou	Cross-sectional	7836	+	−	−			
PTB	3	(Huang et al., 2015)	2006–2010	Beijing	Cross-sectional	50,874		−	−			
PTB	5	(Zhao et al., 2015)	2010–2012	Lanzhou	Case-control	8969 (677 cases, 8292 controls)			+			

Outcome	Study	Reference	Study period	Area	Study type	Sample size	SO_2	NO_2	PM_{10}	$PM_{2.5}$	CO	O_3
PTB	8	(Jiang et al., 2007)	2004	Shanghai	Cross-sectional	3346	+	+	+			+
PTB	11[a]	(Zhang et al., 2007)	1997–2004	Taiyuan	Retrospective cohort	48,029	+		+			
PTB	14[a]	(Aimaier et al., 2013)	2007–2009	Beijing	Retrospective cohort	23,896	+	−	+			
PTB	15[a]	(Ruan et al., 2010)	2007–2012	Guangzhou	Case-control	9848 (4924 cases, 4924 controls)	−	+	−			
PTB	17[a]	(Zhao et al., 2010a)	2007	Guangdong	Cross-sectional	7836	+	−	−			
PTB	20[a]	(Xu et al., 2008)	2005–2007	Taiyuan	Retrospective cohort	31,145	−	−	−			
PTB	21[a]	(Zhang et al., 2008)	2005–2007	Taiyuan	Case-crossover	716	+	+	+			

+Statistically significant association ($p < 0.05$) – not statistically significant [blank] = not investigated, BW = birth weight, LBW = low birth weight, PTB = preterm birth, CA = congenital anomaly.

[a]Article written in Chinese.

Table 2

Nitrogen dioxide (NO_2) concentrations ($\mu g/m^3$) reported over the study periods for the reviewed studies.

Study	Location	Mean	SD	Min	25th	Median	75th	Max
4	Beijing	49	17	26	34	49	61	84
14	Beijing	54	23	10	38	50	66	152
3	Beijing	58	13	23				83
17	Guangdong	61	64	15	27	38	60	468
18	Guangdong	61	64	15	27	38	60	468
2	Guangzhou	61	64	15	27	38	60	468
15	Guangzhou	60						
19	Guangzhou	57	34		60	86		
22	Guangzhou	57	34		60	86		
24	Haikou	32	11					
23	Lanzhou	42						
8	Shanghai	71	1	17	52	67	84	169
25	Taiwan	44	16	7				81
20	Taiyuan	24	2					
21	Taiyuan	25	7	7	20	24	29	53
7	Tianjin					50		
10	Tianjin	51	18					

Table 3

Sulphur dioxide (SO_2) concentrations ($\mu g/m^3$) reported over the study periods for the reviewed studies.

Study	Location	Mean	SD	Min	20th	25th	40th	Median	60th	75th	80th	Max
1	Beijing	102										630
3	Beijing	38	32	8								142
4	Beijing	17	3	10		14		16		20		23
6	Beijing			9	18		55		146		239	308
14	Beijing	37	38	6		12		21		46		222
17	Guangdong	52	35	9		29		44		63		195
18	Guangdong	52	35	9		29		44		63		195
2	Guangzhou	52	35	9		29		44		63		195
15	Guangzhou	66										
19	Guangzhou	64	99			41		53				
22	Guangzhou	64	99			41		53				
24	Haikou	20	11									
23	Lanzhou	55										
8	Shanghai	56	1	11		36		52		71		163
25	Taiwan	16	8	6								45
11	Taiyuan	182	169									
20	Taiyuan	74	37									
21	Taiyuan	87	55	15		45		67		119		317
7	Tianjin							53				
10	Tianjin	70	59									

Table 4

Particulate matter <10 μm (PM_{10}) concentrations (μg/m^3) reported over the study periods for the reviewed studies.

Study	Location	Mean	SD	Min	25th	Median	75th	Max
3	Beijing	135	35	69				264
14	Beijing	126	81	12	70	111	150	600
12	Fuzhou			46	63	73	80	95
17	Guangdong	83	53	20	49	70	94	405
18	Guangdong	83	53	20	49	70	94	405
2	Guangzhou	83	53	20	49	70	94	405
13	Guangzhou	105	77		39	51	66	
15	Guangzhou	112						
19	Guangzhou	105	77		39	51		
22	Guangzhou	105	77		39	51		
24	Haikou	40	18					
5	Lanzhou	142	18					
23	Lanzhou	144						
8	Shanghai	101	3	22	59	83	130	333
25	Taiwan	73	23	34				126
11	Taiyuan	212	74					
20	Taiyuan	140	13					
21	Taiyuan	142	67	38	109	129	160	508
7	Tianjin					108		
16	Tianjin	114	45					

Table 5

Concentrations (μg/m^3) of carbon monoxide (CO), ozone (O_3) and particulate matter < 2.5 μm ($PM_{2.5}$) reported over the study periods for the reviewed studies.

Study	Location	Pollutant	Mean	SD	Min	25th	Median	75th	Max
25	Taiwan	CO	814	222	333				1490
3	Beijing	CO	1730	680	800				3900
4	Beijing	CO	987	247	740	740	863	1110	1600
8	Shanghai	O_3	65	2	5	38	56	87	251
25	Taiwan	O_3	76	20	30				130
4	Beijing	$PM_{2.5}$	61	11	44	52	60	71	85

Table 6

Variables adjusted for in the reviewed studies (by study number).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Maternal age	X				X	X	X			X	X	X	X	X	X	X			X	X		X	X	X	X
Maternal race																				X				X	
Gravidity							X					X	X		X	X			X			X			
Parity					X		X					X		X		X			X			X			
BMI																							X		
Maternal health																							X		
Drinking																				X					
Folic acid intake																				X			X		
Therapeutic drug use																							X		
Mother's education					X						X				X				X	X		X	X		
Father's education																						X			
Mother's occupation																			X	X		X			
Father's occupation																						X			
Household income					X															X			X		X
Smoking					X															X			X		
Residential area	X					X													X	X					
Mother's birth place													X									X			
Prenatal health care																				X					
Gestational age						X	X			X						X			X			X		X	X
Height of neonate																						X			
Fetal/infant sex	X					X					X		X	X	X				X	X		X		X	X
Day of week	X																X	X							
Day of year																	X	X							
Year						X																			X
Season	X				X	X														X			X		X
Temperature	X	X		X	X			X						X			X	X			X		X		
Humidity	X	X		X				X						X			X	X			X				
Wind speed														X											

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Other pollutants		X	X														X	X	X	X	X				X
Type of cooking fuel					X																		X		
Type of heating																				X					

Table 7

Results for change in birth weight for a 10 μg/m^3 increase in exposure.

Study		Pollutant	Result (95% CI)	Exposure period	Details
19	*	NO_2	3.3 g (1.1, 5.5)	Entire pregnancy	≥28 weeks
19	*	NO_2	−3.3 g (−4.9, −1.7)	Trimester 1	≥28 weeks
19		NO_2	1.6 g (0.0, 3.2)	Trimester 2	≥28 weeks
19	*	NO_2	6.3 g (4.7, 7.9)	Trimester 3	≥28 weeks
13		PM_{10}	−0.1 g (−1.9, 1.7)	Entire pregnancy	≥28 weeks
19		PM_{10}	−0.1 g (−1.9, 1.7)	Entire pregnancy	≥28 weeks
13	*	PM_{10}	−2.7 g (−3.7, −1.7)	Trimester 1	≥28 weeks
19	*	PM_{10}	−2.7 g (−3.7, −1.7)	Trimester 1	≥28 weeks
13	*	PM_{10}	−2.2 g (−3.4, −1.0)	Trimester 2	≥28 weeks
19	*	PM_{10}	−2.2 g (−3.4, −1.0)	Trimester 2	≥28 weeks
13	*	PM_{10}	3.8 g (2.8, 4.8)	Trimester 3	≥28 weeks
19	*	PM_{10}	3.8 g (2.8, 4.8)	Trimester 3	≥28 weeks
19	*	SO_2	−1.9 g (−3.5, −0.3)	Entire pregnancy	≥28 weeks
19	*	SO_2	−3.3 g (−4.5, −2.1)	Trimester 1	≥28 weeks
19		SO_2	−1.4 g (−2.8, 0.0)	Trimester 2	≥28 weeks
19		SO_2	1.4 g (0.0, 2.8)	Trimester 3	≥28 weeks
4		CO	−0.1 g (−0.5, 0.2)	1st month	Term births
4		CO	0.0 g (−0.4, 0.3)	2nd month	Term births
4		CO	0.0 g (−0.3, 0.4)	3rd month	Term births
4		CO	−0.2 g (−0.6, 0.1)	4th month	Term births
4		CO	−0.1 g (−0.4, 0.3)	5th month	Term births
4		CO	0.2 g (−0.2, 0.5)	6th month	Term births
4		CO	−0.2 g (−0.5, 0.2)	7th month	Term births
4	*	CO	−0.5 g (−0.8, −0.2)	8th month	Term births
4		NO_2	−6.9 g (−21.7, 8)	1st month	Term births
4		NO_2	0.0 g (−10.5, 10.1)	2nd month	Term births
4		NO_2	−4.3 g (−19.6, 10.5)	3rd month	Term births

Study		Pollutant	Result (95% CI)	Exposure period	Details
4		NO_2	−6.5 g (−21, 8.3)	4th month	Term births
4		NO_2	−2.5 g (−16.7, 11.2)	5th month	Term births
4		NO_2	8.0 g (−6.2, 21.7)	6th month	Term births
4		NO_2	−8.3 g (−21.7, 5.4)	7th month	Term births
4		NO_2	−12.3 g (−26.1, 1.1)	8th month	Term births
3		NO_2	−1.4 g (−17.2, 14.3)	Trimester 1	Term births
3		NO_2	−9.7 g (−28.9, 9.4)	Trimester 2	Term births
3	*	NO_2	−14.8 g (−29.1, −0.4)	Trimester 3	Term births
3		PM_{10}	−1.6 g (−5.7, 2.4)	Trimester 1	Term births
3		PM_{10}	2.5 g (−3.6, 8.7)	Trimester 2	Term births
3		PM_{10}	4.7 g (−2.8, 12.1)	Trimester 3	Term births
4		$PM_{2.5}$	−7.1 g (−15.2, 0.5)	1st month	Term births
4		$PM_{2.5}$	0.0 g (−8.1, 7.6)	2nd month	Term births
4		$PM_{2.5}$	−1.0 g (−9.1, 7.6)	3rd month	Term births
4		$PM_{2.5}$	−0.5 g (−8.6, 7.1)	4th month	Term births
4		$PM_{2.5}$	−0.5 g (−8.1, 7.1)	5th month	Term births
4		$PM_{2.5}$	−0.5 g (−7.6, 7.1)	6th month	Term births
4		$PM_{2.5}$	−4.0 g (−11.1, 3.5)	7th month	Term births
4	*	$PM_{2.5}$	−9.1 g (−16.2, −1.5)	8th month	Term births
4		SO_2	2.0 g (−27.6, 29.6)	1st month	Term births
4		SO_2	0.0 g (−27.6, 27.6)	2nd month	Term births
4		SO_2	−3.9 g (−33.5, 25.6)	3rd month	Term births
4		SO_2	−7.9 g (−35.5, 19.7)	4th month	Term births
4		SO_2	3.9 g (−21.7, 31.5)	5th month	Term births
4		SO_2	13.8 g (−11.8, 41.4)	6th month	Term births
4		SO_2	−13.8 g (−37.4, 13.8)	7th month	Term births
4	*	SO_2	−45.3 g (−70.9, −19.7)	8th month	Term births
6	*	SO_2	−0.7 g (−1.0, −0.4)	Trimester 3	Term births

*Statistically significant ($p < 0.05$).

Table 8

Quantitative results for low birth weight for a 10 μg/m^3 increase in exposure.

Study		Pollutant	Result (95% CI)	Exposure period	Details
18		NO_2	RR = 1.00 (1.00,1.01)	Entire pregnancy	≥28 weeks
18		PM_{10}	RR = 1.01 (1.00,1.01)	Entire pregnancy	≥28 weeks
18		SO_2	RR = 1.01 (1.00,1.02)	Entire pregnancy	≥28 weeks
14		NO_2	AOR = 1.01 (0.93,1.10)	1 month BD	Term births
14		NO_2	AOR = 0.95 (0.88,1.04)	1st month	Term births
14		NO_2	AOR = 0.97 (0.89,1.06)	2 months BD	Term births
14		NO_2	AOR = 0.93 (0.85,1.02)	2nd month	Term births
14		NO_2	AOR = 0.94 (0.86,1.03)	3rd month	Term births
14		NO_2	AOR = 0.98 (0.87,1.10)	Trimester 1	Term births
14		NO_2	AOR = 0.99 (0.89,1.09)	Trimester 3	Term births
22	*	NO_2	AOR = 0.92 (0.85,0.99)	Trimester 3	Term births
14		PM_{10}	AOR = 0.98 (0.95,1.01)	1 month BD	Term births
14		PM_{10}	AOR = 0.98 (0.95,1.01)	1st month	Term births
14		PM_{10}	AOR = 1.03 (0.99,1.06)	2 months BD	Term births
14		PM_{10}	AOR = 0.99 (0.95,1.03)	2nd month	Term births
14		PM_{10}	AOR = 1.00 (0.97,1.04)	3rd month	Term births
14		PM_{10}	AOR = 0.94 (0.89,1.00)	Trimester 1	Term births
14		PM_{10}	AOR = 1.00 (0.95,1.05)	Trimester 3	Term births
22	*	PM_{10}	AOR = 0.95 (0.90,0.99)	Trimester 3	Term births
14		SO_2	AOR = 1.02 (0.97,1.06)	1 month BD	Term births
14	*	SO_2	AOR = 1.04 (1.01,1.07)	1st month	Term births
14		SO_2	AOR = 0.98 (0.95,1.01)	2 months BD	Term births
14		SO_2	AOR = 1.02 (0.98,1.02)	2nd month	Term births
14		SO_2	AOR = 0.97 (0.93,1.01)	3rd month	Term births
22	*	SO_2	AOR = 1.08 (1.01,1.15)	Trimester 1	Term births
14		SO_2	AOR = 1.05 (1.00,1.10)	Trimester 1	Term births

Study		Pollutant	Result (95% CI)	Exposure period	Details
14		SO_2	AOR = 0.99 (0.95,1.04)	Trimester 3	Term births
6	*	SO_2	AOR = 1.01 (1.01,1.01)	Trimester 3	Term births
11		PM_{10}	AOR = 0.99 (0.94,1.04)	1st month	Very low birth weight
11		PM_{10}	AOR = 0.98 (0.93,1.04)	2nd month	Very low birth weight
11		PM_{10}	AOR = 1.02 (0.96,1.07)	3rd month	Very low birth weight
11		PM_{10}	AOR = 1.00 (0.92,1.04)	4–6th months	Very low birth weight
11	*	PM_{10}	AOR = 0.94 (0.89,0.99)	7–9th months	Very low birth weight
11		PM_{10}	AOR = 1.02 (0.97,1.06)	C-3	Very low birth weight
11		SO_2	AOR = 1.00 (0.95,1.06)	1st month	Very low birth weight
11		SO_2	AOR = 0.99 (0.95,1.02)	2nd month	Very low birth weight
11		SO_2	AOR = 0.96 (0.92,1.00)	3rd month	Very low birth weight
11		SO_2	AOR = 0.95 (0.91,1.00)	4–6th months	Very low birth weight
11		SO_2	AOR = 1.02 (0.98,1.06)	7–9th months	Very low birth weight
11		SO_2	AOR = 1.01 (0.98,1.05)	C-3	Very low birth weight
11		PM_{10}	AOR = 0.99 (0.98,1.00)	1st month	
11		PM_{10}	AOR = 0.99 (0.98,1.00)	2nd month	
11		PM_{10}	AOR = 1.00 (0.99,1.02)	3rd month	
11		PM_{10}	AOR = 1.01 (0.99,1.03)	4–6th months	
11		PM_{10}	AOR = 0.99 (0.98,1.00)	7–9th months	
11		PM_{10}	AOR = 1.00 (0.99,1.01)	C-3	
11		SO_2	AOR = 1.00 (1.00,1.01)	1st month	
11		SO_2	AOR = 1.00 (0.99,1.01)	2nd month	
11		SO_2	AOR = 0.99 (0.98,1.00)	3rd month	
11		SO_2	AOR = 0.99 (0.98,1.00)	4–6th months	
11		SO_2	AOR = 1.00 (0.99,1.01)	7–9th months	
11		SO_2	AOR = 1.00 (0.99,1.01)	C-3	

*Statistically significant ($p < 0.05$), C-3 = 3 months before conception, BD = before delivery, AOR = adjusted odds ratio

Table 9

Quantitative results for preterm birth for a 10 μg/m^3 increase in exposure.

Study		Pollutant	Result (95% CI)	Exposure period	Details
5	*	PM_{10}	AOR = 1.14 (1.02,1.28)	entire pregnancy	medically indicated
5		PM_{10}	AOR = 1.01 (0.94,1.08)	trimester 2	medically-indicated
5		PM_{10}	AOR = 1.04 (1.00,1.09)	last 4 weeks BD	medically-indicated
5		PM_{10}	AOR = 1.04 (1.00,1.09)	last 6 weeks BD	medically-indicated
5		PM_{10}	AOR = 1.03 (0.98,1.09)	last 8 weeks BD	medically-indicated
5	*	PM_{10}	AOR = 1.07 (1.01,1.14)	trimester 1	medically-indicated
5		PM_{10}	AOR = 1.05 (0.99,1.12)	trimester 3	medically-indicated
5		PM_{10}	AOR = 1.03 (0.96,1.10)	entire pregnancy	moderate preterm
5		PM_{10}	AOR = 1.01 (0.99,1.04)	last 4 weeks BD	moderate preterm
5		PM_{10}	AOR = 1.01 (0.98,1.03)	last 6 weeks BD	moderate preterm
5		PM_{10}	AOR = 1.00 (0.97,1.03)	last 8 weeks BD	moderate preterm
5		PM_{10}	AOR = 1.01 (0.97,1.05)	trimester 1	moderate preterm
5		PM_{10}	AOR = 1.01 (0.97,1.06)	trimester 2	moderate preterm
5		PM_{10}	AOR = 0.98 (0.95,1.02)	trimester 3	moderate preterm
5		PM_{10}	AOR = 1.02 (0.94,1.10)	entire pregnancy	spontaneous
5		PM_{10}	AOR = 1.01 (0.99,1.04)	last 4 weeks BD	spontaneous
5		PM_{10}	AOR = 1.01 (0.98,1.04)	last 6 weeks BD	spontaneous
5		PM_{10}	AOR = 1.00 (0.97,1.04)	last 8 weeks BD	spontaneous
5		PM_{10}	AOR = 0.97 (0.93,1.02)	trimester 1	spontaneous
5		PM_{10}	AOR = 1.02 (0.97,1.07)	trimester 2	spontaneous
5		PM_{10}	AOR = 0.97 (0.93,1.01)	trimester 3	spontaneous
5		PM_{10}	AOR = 0.96 (0.82,1.12)	entire pregnancy	very preterm
5	*	PM_{10}	AOR = 1.07 (1.02,1.13)	last 4 weeks BD	very preterm
5	*	PM_{10}	AOR = 1.09 (1.02,1.15)	last 6 weeks BD	very preterm
5	*	PM_{10}	AOR = 1.10 (1.03,1.17)	last 8 weeks BD	very preterm
5		PM_{10}	AOR = 0.97 (0.87,1.07)	trimester 1	very preterm

Study		Pollutant	Result (95% CI)	Exposure period	Details
5		PM_{10}	AOR = 1.02 (0.92,1.13)	trimester 2	very preterm
5		PM_{10}	AOR = 1.06 (0.97,1.16)	trimester 3	very preterm
14		NO_2	AOR = 0.97 (0.91,1.03)	1 month BD	
14		NO_2	AOR = 0.95 (0.89,1.01)	1st month	
14		NO_2	AOR = 0.91 (0.86,1.00)	2 months BD	
14		NO_2	AOR = 0.96 (0.90,1.03)	2nd month	
14		NO_2	AOR = 0.96 (0.90,1.03)	3rd month	
8		NO_2	−0.6% change in number of events (−3.6,2.4)	4 weeks BD	
8		NO_2	−2.0% change in number of events (−5.4,1.4)	6 weeks BD	
8	*	NO_2	5.4% change in number of events (1.8,9.1)	8 weeks BD	
21	*	NO_2	AOR = 1.24 (1.03,1.48)	entire pregnancy	
2		NO_2	RR = 1.00 (1.00,1.01)	entire pregnancy	
17		NO_2	RR = 1.00 (1.00,1.01)	entire pregnancy	
3		NO_2	AOR = 0.93 (0.70,1.25)	trimester 1	
14		NO_2	AOR = 0.99 (0.91,1.08)	trimester 1	
3		NO_2	AOR = 0.22 (0.68,1.08)	trimester 2	
15	*	NO_2	AOR = 0.93 (0.90,0.97)	trimester 2	
3		NO_2	AOR = 0.96 (0.72,1.29)	trimester 3	
14		NO_2	AOR = 0.94 (0.87,1.02)	trimester 3	
15	*	NO_2	AOR = 1.06 (1.03,1.09)	trimester 3	
8	*	O_3	3.1% change in number of events (0.2,6.0)	4 weeks BD	
8		O_3	3.0% change in number of events (−0.6,6.5)	6 weeks BD	
8	*	O_3	4.6% change in number of events (0.4,8.9)	8 weeks BD	
14		PM_{10}	AOR = 0.98 (0.95,1.00)	1 month BD	
11		PM_{10}	AOR = 1.00 (0.99,1.01)	1st month	
14		PM_{10}	AOR = 1.00 (0.98,1.03)	1st month	
14	*	PM_{10}	AOR = 1.04 (1.01,1.06)	2 months BD	
11	*	PM_{10}	AOR = 1.02 (1.01,1.02)	2nd month	
14		PM_{10}	AOR = 0.98 (0.95,1.00)	2nd month	

Study		Pollutant	Result (95% CI)	Exposure period	Details
11	*	PM_{10}	AOR = 1.05 (1.04,1.06)	3rd month	
14		PM_{10}	AOR = 0.98 (0.96,1.00)	3rd month	
8		PM_{10}	−0.2% change in number of events (−2.2,1.8)	4 weeks BD	
11	*	PM_{10}	AOR = 0.97 (0.96,0.99)	4–6th months	
8		PM_{10}	−0.9% change in number of events (−3.4,1.5)	6 weeks BD	
11	*	PM_{10}	AOR = 1.04 (1.03,1.05)	7–9th months	
8	*	PM_{10}	4.4% change in number of events (1.6,7.3)	8 weeks BD	
11	*	PM_{10}	AOR = 1.06 (1.05,1.07)	C-3	
5		PM_{10}	AOR = 1.02 (0.96,1.08)	entire pregnancy	
21	*	PM_{10}	AOR = 1.03 (1.01,1.05)	entire pregnancy	
2		PM_{10}	RR = 1.01 (1.00,1.01)	entire pregnancy	
17		PM_{10}	RR = 1.01 (1.00,1.01)	entire pregnancy	
5		PM_{10}	AOR = 1.02 (1.00,1.04)	last 4 weeks BD	
5		PM_{10}	AOR = 1.02 (0.99,1.04)	last 6 weeks BD	
5		PM_{10}	AOR = 1.01 (0.98,1.04)	last 8 weeks BD	
3		PM_{10}	AOR = 1.00 (0.92,1.08)	trimester 1	
5		PM_{10}	AOR = 1.00 (0.97,1.04)	trimester 1	
14		PM_{10}	AOR = 0.94 (0.90,1.00)	trimester 1	
3		PM_{10}	AOR = 0.97 (0.88,1.08)	trimester 2	
5		PM_{10}	AOR = 1.01 (0.97,1.05)	trimester 2	
3		PM_{10}	AOR = 1.01 (0.90,1.12)	trimester 3	
5		PM_{10}	AOR = 0.99 (0.96,1.03)	trimester 3	
14		PM_{10}	AOR = 1.01 (0.98,1.05)	trimester 3	
14	*	SO_2	AOR = 1.06 (1.03,1.09)	1 month BD	
14		SO_2	AOR = 1.01 (0.99,1.04)	1st month	
11	*	SO_2	AOR = 1.02 (1.02,1.03)	1st month	
14		SO_2	AOR = 1.00 (0.98,1.03)	2 months BD	
11		SO_2	AOR = 1.01 (1.00,1.01)	2nd month	
14		SO_2	AOR = 1.02 (1.00,1.05)	2nd month	

Study		Pollutant	Result (95% CI)	Exposure period	Details
14		SO_2	AOR = 1.00 (0.97,1.03)	3rd month	
11	*	SO_2	AOR = 0.98 (0.97,0.99)	3rd month	
8		SO_2	2.4% change in number of events (−1.0,5.9)	4 weeks BD	
11		SO_2	AOR = 1.00 (0.99,1.01)	4th–6th months	
8		SO_2	0.9% change in number of events (−3.3, 5.1)	6 weeks BD	
11		SO_2	AOR = 1.00 (1.00,1.01)	7th–9th months	
8	*	SO_2	11.9% change in number of events (6.7,17.1)	8 weeks BD	
11		SO_2	AOR = 1.00 (1.00,1.01)	C-3	
2	*	SO_2	RR = 1.01 (1.01,1.02)	entire pregnancy	
17	*	SO_2	RR = 1.01 (1.01,1.02)	entire pregnancy	
21	*	SO_2	AOR = 1.06 (1.02,1.10)	entire pregnancy	
14		SO_2	AOR = 1.04 (1.00,1.08)	trimester 1	
14		SO_2	AOR = 1.02 (0.99,1.06)	trimester 3	
15		SO_2	AOR = 1.03 (1.00,1.05)	trimester 3	

*Statistically significant ($p < 0.05$), C-3 = 3 months before conception, BD = before delivery, AOR = adjusted odds ratio

Table 10

Quantitative results for congenital anomaly for a 10 μg/m^3 increase in exposure.

Study		Pollutant	Result (95% CI)	Exposure period	Details
23		SO_2	AOR = 0.90 (0.71,1.13)	Trimester 1	Pooled heart defects
23	*	NO_2	AOR = 2.11 (1.24,3.63)	Entire pregnancy	Pooled heart defects
23		NO_2	AOR = 1.36 (0.93,1.99)	Trimester 1	Pooled heart defects
23	*	NO_2	AOR = 1.59 (1.13,2.23)	Trimester 2	Pooled heart defects
23		NO_2	AOR = 1.14 (0.84,1.56)	Weeks 3–8	Pooled heart defects
23	*	PM_{10}	AOR = 1.35 (1.15,1.60)	Entire pregnancy	Pooled heart defects
23	*	PM_{10}	AOR = 1.17 (1.04,1.33)	Trimester 1	Pooled heart defects
23	*	PM_{10}	AOR = 1.26 (1.13,1.42)	Trimester 2	Pooled heart defects
23		PM_{10}	AOR = 1.04 (0.96,1.14)	Weeks 3–8	Pooled heart defects
23		SO_2	AOR = 1.10 (0.70,1.73)	Entire pregnancy	Pooled heart defects
23		SO_2	AOR = 0.98 (0.75,1.28)	Trimester 2	Pooled heart defects
23		SO_2	AOR = 0.96 (0.80,1.14)	Weeks 3–8	Pooled heart defects
23	*	NO_2	AOR = 2.16 (1.13,4.14)	Entire pregnancy	Patent ductus arteriosus
23		NO_2	AOR = 1.50 (0.95,2.35)	Trimester 1	Patent ductus arteriosus
23	*	NO_2	AOR = 1.63 (1.08,2.46)	Trimester 2	Patent ductus arteriosus
23		NO_2	AOR = 1.18 (0.83,1.69)	Weeks 3–8	Patent ductus arteriosus
23	*	PM_{10}	AOR = 1.31 (1.07,1.60)	Entire pregnancy	Patent ductus arteriosus
23	*	PM_{10}	AOR = 1.21 (1.04,1.41)	Trimester 1	Patent ductus arteriosus
23	*	PM_{10}	AOR = 1.23 (1.08,1.41)	Trimester 2	Patent ductus arteriosus
23		PM_{10}	AOR = 1.07 (0.96,1.19)	Weeks 3–8	Patent ductus arteriosus
23		SO_2	AOR = 0.92 (0.52,1.62)	Entire pregnancy	Patent ductus arteriosus
23		SO_2	AOR = 0.88 (0.66,1.17)	Trimester 1	Patent ductus arteriosus
23		SO_2	AOR = 0.92 (0.67,1.28)	Trimester 2	Patent ductus arteriosus
23		SO_2	AOR = 0.94 (0.76,1.16)	Weeks 3–8	Patent ductus arteriosus
23	*	NO_2	AOR = 2.03 (1.11,3.71)	Entire pregnancy	Defect of great arteries
23		NO_2	AOR = 1.33 (0.87,2.05)	Trimester 1	Defect of great arteries

Study		Pollutant	Result (95% CI)	Exposure period	Details
23	*	NO_2	AOR = 1.67 (1.13,2.47)	Trimester 2	Defect of great arteries
23		NO_2	AOR = 1.12 (0.80,1.58)	Weeks 3–8	Defect of great arteries
23	*	PM_{10}	AOR = 1.36 (1.12,1.65)	Entire pregnancy	Defect of great arteries
23	*	PM_{10}	AOR = 1.22 (1.06,1.41)	Trimester 1	Defect of great arteries
23	*	PM_{10}	AOR = 1.25 (1.10,1.43)	Trimester 2	Defect of great arteries
23		PM_{10}	AOR = 1.08 (0.98,1.19)	Weeks 3–8	Defect of great arteries
23		SO_2	AOR = 1.13 (0.67,1.91)	Entire pregnancy	Defect of great arteries
23		SO_2	AOR = 0.94 (0.79,1.11)	Trimester 1	Defect of great arteries
23		SO_2	AOR = 0.98 (0.71,1.34)	Trimester 2	Defect of great arteries
23		SO_2	AOR = 0.98 (0.80,1.20)	Weeks 3–8	Defect of great arteries
23		NO_2	AOR = 1.48 (0.55,3.97)	Entire pregnancy	Defect of cardiac septa
23		NO_2	AOR = 0.96 (0.44,2.10)	Trimester 1	Defect of cardiac septa
23		NO_2	AOR = 1.41 (0.73,2.71)	Trimester 2	Defect of cardiac septa
23		NO_2	AOR = 0.96 (0.49,1.85)	Weeks 3–8	Defect of cardiac septa
23	*	PM_{10}	AOR = 1.44 (1.04,1.99)	Entire pregnancy	Defect of cardiac septa
23		PM_{10}	AOR = 1.13 (0.89,1.45)	Trimester 1	Defect of cardiac septa
23	*	PM_{10}	AOR = 1.32 (1.05,1.66)	Trimester 2	Defect of cardiac septa
23		PM_{10}	AOR = 1.04 (0.88,1.24)	Weeks 3–8	Defect of cardiac septa
23	*	SO_2	AOR = 2.35 (1.01,5.49)	Entire pregnancy	Defect of cardiac septa
23		SO_2	AOR = 0.97 (0.70,1.33)	Trimester 1	Defect of cardiac septa
23		SO_2	AOR = 1.16 (0.69,1.95)	Trimester 2	Defect of cardiac septa
23		SO_2	AOR = 1.07 (0.77,1.49)	Weeks 3–8	Defect of cardiac septa
10		NO_2	AOR = 1.00 (1.00,1.00)	1st month	Congenital heart disease, polydactyly, limb reduction defects and hypospadias
24		NO_2	AOR = 1.00 (0.86,1.16)	1st month	All diagnosed birth defects
24		NO_2	AOR = 0.99 (0.85,1.15)	2nd month	All diagnosed birth defects
24		NO_2	AOR = 0.98 (0.85,1.13)	3rd month	All diagnosed birth defects
24		PM_{10}	AOR = 1.08 (0.99,1.18)	1st month	All diagnosed birth defects
24		PM_{10}	AOR = 1.06 (0.97,1.16)	2nd month	All diagnosed birth defects
24	*	PM_{10}	AOR = 1.13 (1.03,1.23)	3rd month	All diagnosed birth defects

Study		Pollutant	Result (95% CI)	Exposure period	Details
24		SO_2	AOR = 1.10 (0.93,1.30)	1st month	All diagnosed birth defects
24		SO_2	AOR = 1.09 (0.92,1.29)	2nd month	All diagnosed birth defects
24		SO_2	AOR = 1.11 (0.94,1.32)	3rd month	All diagnosed birth defects
14	*	NO_2	AOR = 1.11 (1.01,1.22)	Weeks 3–8	24 types of birth defects
11		PM_{10}	AOR = 1.01 (0.98,1.03)	1st month	Birth deformities
11		PM_{10}	AOR = 1.03 (1.00,1.06)	2nd month	Birth deformities
11	*	PM_{10}	AOR = 1.05 (1.02,1.08)	3rd month	Birth deformities
11		PM_{10}	AOR = 1.03 (0.99,1.07)	4–6th months	Birth deformities
11	*	PM_{10}	AOR = 1.03 (1.01,1.05)	7–9th months	Birth deformities
11		PM_{10}	AOR = 1.02 (0.99,1.04)	C-3	Birth deformities
14		PM_{10}	AOR = 0.99 (0.95,1.03)	Weeks 3–8	24 types of birth defects
11		SO_2	AOR = 0.99 (0.97,1.01)	1st month	Birth deformities
11		SO_2	AOR = 0.98 (0.96,1.00)	2nd month	Birth deformities
11	*	SO_2	AOR = 0.97 (0.95,0.99)	3rd month	Birth deformities
11		SO_2	AOR = 0.99 (0.97,1.02)	4–6th months	Birth deformities
11		SO_2	AOR = 0.99 (0.97,1.01)	7–9th months	Birth deformities
11		SO_2	AOR = 1.00 (0.98,1.02)	C-3	Birth deformities
14		SO_2	AOR = 0.99 (0.94,1.03)	Weeks 3–8	24 types of birth defects

*Statistically significant ($p < 0.05$), C-3 = 3 months before conception, AOR = adjusted odds ratio

Table 11

Quantitative results for mortality for a 10 μg/m^3 increase in exposure.

Study		Pollutant	Result (95% CI)	Exposure period	Details
25		CO	AOR = 1.00 (1.00,1.00)	Entire pregnancy	Term births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 1	Term births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 2	Term births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 3	Term births
25		NO_2	AOR = 0.98 (0.94,1.02)	Entire pregnancy	Term births
25		NO_2	AOR = 0.99 (0.95,1.03)	Trimester 1	Term births
25		NO_2	AOR = 0.98 (0.94,1.01)	Trimester 2	Term births
25		NO_2	AOR = 0.99 (0.95,1.03)	Trimester 3	Term births
25		O_3	AOR = 0.97 (0.93,1.01)	Entire pregnancy	Term births
25		O_3	AOR = 1.00 (0.96,1.03)	Trimester 1	Term births
25	*	O_3	AOR = 0.96 (0.93,0.99)	Trimester 2	Term births
25		O_3	AOR = 1.00 (0.96,1.03)	Trimester 3	Term births
25		PM_{10}	AOR = 1.01 (0.97.,1.04)	1st month	Term births
25		PM_{10}	AOR = 1.01 (0.97,1.04)	2nd month	Term births
25		PM_{10}	AOR = 0.98 (0.95,1.02)	3rd month	Term births
25		PM_{10}	AOR = 0.96 (0.91,1.00)	Entire pregnancy	Term births
25		PM_{10}	AOR = 1.00 (0.96,1.04)	Trimester 1	Term births
25	*	PM_{10}	AOR = 0.95 (0.91,0.99)	Trimester 2	Term births
25		PM_{10}	AOR = 0.98 (0.94,1.01)	Trimester 3	Term births
25		SO_2	AOR = 1.00 (0.93,1.11)	1st month	Term births
25		SO_2	AOR = 1.00 (0.93,1.11)	2nd month	Term births
25		SO_2	AOR = 0.96 (0.90,1.07)	3rd month	Term births
25		SO_2	AOR = 0.96 (0.87,1.07)	Entire pregnancy	Term births
25		SO_2	AOR = 1.00 (0.90,1.07)	Trimester 1	Term births
25		SO_2	AOR = 0.96 (0.87,1.07)	Trimester 2	Term births
25		SO_2	AOR = 0.96 (0.90,1.07)	Trimester 3	Term births

Study		Pollutant	Result (95% CI)	Exposure period	Details
25		CO	AOR = 1.00 (1.00,1.00)	Entire pregnancy	Preterm births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 1	Preterm births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 2	Preterm births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 3	Preterm births
25		NO_2	AOR = 1.01 (0.97,1.05)	Entire pregnancy	Preterm births
25		NO_2	AOR = 1.02 (0.99,1.06)	Trimester 1	Preterm births
25		NO_2	AOR = 1.00 (0.96,1.03)	Trimester 2	Preterm births
25		NO_2	AOR = 0.99 (0.94,1.04)	Trimester 3	Preterm births
25		O_3	AOR = 1.00 (0.96,1.04)	Entire pregnancy	Preterm births
25		O_3	AOR = 1.01 (0.98,1.04)	Trimester 1	Preterm births
25		O_3	AOR = 1.00 (0.97,1.03)	Trimester 2	Preterm births
25		O_3	AOR = 0.99 (0.97,1.04)	Trimester 3	Preterm births
25		PM_{10}	AOR = 1.03 (1.00,1.06)	1st month	Preterm births
25		PM_{10}	AOR = 1.03 (1.00,1.06)	2nd month	Preterm births
25		PM_{10}	AOR = 1.02 (0.99,1.05)	3rd month	Preterm births
25		PM_{10}	AOR = 1.00 (0.96,1.05)	Entire pregnancy	Preterm births
25		PM_{10}	AOR = 1.03 (1.00,1.07)	Trimester 1	Preterm births
25		PM_{10}	AOR = 0.99 (0.95,1.02)	Trimester 2	Preterm births
25		PM_{10}	AOR = 0.97 (0.92,1.02)	Trimester 3	Preterm births
25	*	SO_2	AOR = 1.15 (1.07,1.23)	1st month	Preterm births
25	*	SO_2	AOR = 1.15 (1.04,1.23)	2nd month	Preterm births
25	*	SO_2	AOR = 1.11 (1.04,1.23)	3rd month	Preterm births
25		SO_2	AOR = 1.11 (1.00,1.23)	Entire pregnancy	Preterm births
25	*	SO_2	AOR = 1.15 (1.04,1.27)	Trimester 1	Preterm births
25		SO_2	AOR = 1.00 (0.80,1.27)	Trimester 2	Preterm births
25		SO_2	AOR = 1.04 (0.90,1.15)	Trimester 3	Preterm births
11		PM_{10}	AOR = 1.00 (0.96,1.04)	1st month	Perineonate death
11		PM_{10}	AOR = 0.99 (0.95,1.04)	2nd month	Perineonate death
11		PM_{10}	AOR = 1.02 (0.98,1.07)	3rd month	Perineonate death

Study		Pollutant	Result (95% CI)	Exposure period	Details
11		PM_{10}	AOR = 1.03 (0.97,1.09)	4th–6th months	Perineonate death
11	*	PM_{10}	AOR = 1.05 (1.02,1.08)	7th–9th months	Perineonate death
11		PM_{10}	AOR = 1.01 (0.97,1.04)	C-3	Perineonate death
11		SO_2	AOR = 1.00 (0.97,1.02)	1st month	Perineonate death
11		SO_2	AOR = 1.00 (0.98,1.03)	2nd month	Perineonate death
11		SO_2	AOR = 0.98 (0.95,1.01)	3rd month	Perineonate death
11		SO_2	AOR = 0.99 (0.96,1.02)	4th–6th months	Perineonate death
11		SO_2	AOR = 0.97 (0.95,1.00)	7–9th months	Perineonate death
11		SO_2	AOR = 0.99 (0.96,1.02)	C-3	Perineonate death
25		CO	AOR = 1.00 (1.00,1.00)	Entire pregnancy	All births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 1	All births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 2	All births
25		CO	AOR = 1.00 (1.00,1.00)	Trimester 3	All births
25		NO_2	AOR = 0.99 (0.96,1.02)	Entire pregnancy	All births
25		NO_2	AOR = 1.00 (0.98,1.03)	Trimester 1	All births
25		NO_2	AOR = 0.98 (0.96,1.01)	Trimester 2	All births
25		NO_2	AOR = 0.99 (0.96,1.02)	Trimester 3	All births
25		O_3	AOR = 0.99 (0.96,1.02)	Entire pregnancy	All births
25		O_3	AOR = 1.00 (0.98,1.03)	Trimester 1	All births
25		O_3	AOR = 0.98 (0.96,1.00)	Trimester 2	All births
25		O_3	AOR = 0.99 (0.97,1.02)	Trimester 3	All births
25		PM_{10}	AOR = 1.02 (1.00,1.05)	1st month	All births
25		PM_{10}	AOR = 1.02 (1.00,1.04)	2nd month	All births
25		PM_{10}	AOR = 1.00 (0.98,1.03)	3rd month	All births
25		PM_{10}	AOR = 0.98 (0.94,1.01)	Entire pregnancy	All births
25		PM_{10}	AOR = 1.02 (0.99,1.04)	Trimester 1	All births
25	*	PM_{10}	AOR = 0.96 (0.94,0.99)	Trimester 2	All births
25		PM_{10}	AOR = 0.97 (0.94,1.00)	Trimester 3	All births
25		SO_2	AOR = 1.07 (1.00,1.15)	1st month	All births

Study		Pollutant	Result (95% CI)	Exposure period	Details
25		SO_2	AOR = 1.07 (1.00,1.15)	2nd month	All births
25		SO_2	AOR = 1.04 (1.00,1.11)	3rd month	All births
25		SO_2	AOR = 1.04 (0.96,1.11)	Entire pregnancy	All births
25		SO_2	AOR = 1.07 (1.00,1.15)	Trimester 1	All births
25		SO_2	AOR = 1.00 (0.93,1.07)	Trimester 2	All births
25		SO_2	AOR = 1.00 (0.93,1.07)	Trimester 3	All births
7		NO_2	OR = 1.01 (0.98,1.05)	C + 0	≤14 weeks pregnancy
7	*	NO_2	OR = 1.05 (1.01,1.09)	C + 1	≤14 weeks pregnancy
7	*	NO_2	OR = 1.05 (1.01,1.08)	C−1	≤14 weeks pregnancy
7	*	NO_2	OR = 1.05 (1.01,1.10)	C−2	≤14 weeks pregnancy
7		NO_2	OR = 1.00 (0.97,1.05)	C−3	≤14 weeks pregnancy
7		PM_{10}	OR = 1.03 (1.00,1.06)	C + 0	≤14 weeks pregnancy
7		PM_{10}	OR = 1.01 (0.99,1.03)	C + 1	≤14 weeks pregnancy
7		PM_{10}	OR = 0.99 (0.961.01)	C−1	≤14 weeks pregnancy
7		PM_{10}	OR = 0.99 (0.971.01)	C−2	≤14 weeks pregnancy
7		PM_{10}	OR = 1.00 (0.991.02)	C−3	≤14 weeks pregnancy
7	*	SO_2	OR = 1.03 (1.011.04)	C + 0	≤14 weeks pregnancy
7	*	SO_2	OR = 1.03 (1.01,1.05)	C + 1	≤14 weeks pregnancy
7		SO_2	OR = 1.01 (1.00,1.03)	C−1	≤14 weeks pregnancy
7		SO_2	OR = 1.01 (0.99,1.02)	C−2	≤14 weeks pregnancy
7		SO_2	OR = 1.01 (0.99,1.02)	C−3	≤14 weeks pregnancy

* Statistically significant ($p < 0.05$) C ± X indicates X ± months post/prior to conception, AOR = adjusted odds ratio.