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**Does the effect of air pollution on pregnancy outcomes
differ by gender? A systematic review**

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ABSTRACT

Gender is known to influence pregnancy outcomes. Recent studies have reported an association between air pollution exposure and adverse pregnancy outcomes, but gender differences have not been considered. In order to assess the current evidence of the interactive effects between gender and air pollution on pregnancy outcomes we undertook a systematic literature review. Using a comprehensive list of keywords, English language articles published between 1966 and 2005 were retrieved from major databases. Additional information on gender was obtained from the study authors. Studies were included if they contained well defined measurements of ambient air pollutants, investigated pregnancy outcomes and reported estimates by gender. In total 11 studies were included. The quality of the studies was assessed using the framework in Systematic Reviews in Health Care Meta-analysis in context and Bracken's Guidelines. Of the 11 studies, four evaluated low birth weight (LBW); one each evaluated very low birth weight and fetal growth and six examined preterm birth (PTB). Females were at higher risk of LBW: adjusted odds ratios (AOR) 1.07 to 1.62. Males were at higher risk for PTB: AORs 1.11 to 1.20. In addition, there was some evidence to suggest that the effect of air pollution on LBW is differential by gender; however the evidence was available only from four studies. This is the first systematic review to consider gender effect. Further high quality studies are needed to establish whether these findings prevail.

Keywords: gender; ambient air pollution; low birth weight; preterm birth; systematic review

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INTRODUCTION

For a number of adverse pregnancy outcomes, there is an observed difference according to the gender of the infant. A male excess has been reported in preterm birth (PTB) (MacGillivray et al., 1985; Cooperstock et al., 1996; Zeitlin et al., 2002; Zeitlin et al., 2004) congenital anomalies (Byron-Scott et al., 2005) and cerebral palsy (Jarvis et al., 2005). Male infants have consistently higher birth weight throughout gestation than females. Despite the weight advantage, newborn males experience higher perinatal mortality compared to females (Brothwood et al., 1986). Even in the extremely low birth weight and very low birth weight (VLBW) subgroups, male infants have poorer survival rates than females (Hoffman et al., 1990; Stevenson et al., 2000). Growth of the male fetus is also more susceptible to certain extraneous factors e.g. smoking (Zaren et al., 2000) and caffeine consumption (Vik et al., 2003) than the female fetus.

Research on air pollution and pregnancy outcomes has gained momentum in the last two decades. Ritz and colleagues (Ritz et al., 2000) have reported that a 50µg increase of PM₁₀ (particulate matter <10µm) exposure contributes to 20% increase in PTB. First trimester PM_{2.5} (particulate matter <2.5µm) exposure of >18.4µg/m³, increases the risk of small for gestational age (SGA) by 26% and a similar exposure during the second trimester increases the risk by 24% (Parker et al., 2004). Average three monthly carbon monoxide (CO) exposure of >5.5ppm was found to increase the risk of low birth weight by 22% (LBW) (Ritz et al., 1999). Using a continuous scale, Maisonet and colleagues reported a 31% increased risk of LBW associated with 1ppm increase in CO (Maisonet et al., 2001), and Salam and colleagues reported that birthweight reduced by 22g for an increase in 1.4ppm CO exposure (Salam et al., 2005). Similar findings were also reported from other studies. In Brazil, a 10µg/m³ increase in PM₁₀ and 1ppm increase in CO exposure in the first trimester reduced birth weight by 14g and 23g respectively (Gouveia et al., 2004). The risk of PTB was increased by 10% for each 100µg/m³ increase in total suspended particles (TSP) and by 26% for each unit increase of sulphur dioxide (SO₂) in the logarithmic scale (Xu et al., 1995). In Lithuania the high tertile exposure of nitrogen dioxide (NO₂) increases the risk of PTB by 68% and that of LBW by 54% (Marozine et al., 2002). Studies conducted in Vancouver (Liu et al., 2003), Taiwan (Lin et al.,

2004), UK (Bobak et al., 2001), the Czech Republic (Bobak et al., 1999; Bobak, 2000) and South Korea (Ha et al., 2001; Lee et al., 2003) have reported similar associations. However, several contemporary studies have found no association between exposure to CO, SO₂, nitrogen oxides, petrochemical pollutants and risk of LBW (Alderman et al., 1987; Landgren, 1996; Dolk et al., 2000; Oliveira et al., 2002), as well as between CO, SO₂, NO₂, particulate matter, Ozone (O₃), and SGA (Woodruff et al., 2003).

Overall the evidence suggests an association between exposure to air pollution and adverse pregnancy outcomes, albeit small (Glinianaia et al., 2004; Maisonet et al., 2004; Sram et al., 2005). As gender differences exist in a number of pregnancy outcomes, the aim of this review is to investigate whether the effects of air pollution on pregnancy outcomes are different for males and females.

MATERIALS AND METHODS

Literature search and inclusion/exclusion criteria

This review was based on published English language articles and conducted following the guidelines in the Cochrane Reviewers Handbook 2004 (Alderson et al., 2004) and "Systematic Reviews in Health Care Meta-analysis in context" (Egger et al., 2004).

Criteria for inclusion of studies into this systematic review were the following: 1) use of well-defined exposure measurements (including personal monitoring, approximation from ambient levels, modelled estimates and proximity to pollution sources); 2) specification of pollutants (TSP, PM₁₀, PM_{2.5}, Nitrogen Oxides (NO_x), CO, SO₂, O₃ etc.); 3) investigated air pollution exposure on pregnancy outcomes; and 4) reported estimates of effect based on infant gender. Studies were excluded if they included multiple births and occupational or accidental exposures. Multiple births were not considered as plurality is an important risk factor that determines fetal growth (Vorherr, 1982). This review is aimed at studying the effects of prolonged ambient exposure to air pollutants, so accidental and occupational exposures were excluded.

Medline (1966–2005), Embase (1980-2005), Science citation index (1981–2005), CINAHL (1982–2005), Cochrane library and other environmental databases (Environmental Science and Pollution Management (1981-2005), Pollution Abstracts (1981-2005), Toxicology Abstracts (1981-2005), Toxline (1993-2005), Health and Safety Sciences abstracts (1981-2005)) were searched. Reference lists of relevant articles were also scanned.

With the help of a comprehensive set of keywords (Box 1), we searched the databases listed above. Each of the keywords was first mapped to subject headings and then searched as keywords in the titles and abstracts. Articles that fulfilled the inclusion criteria were independently reviewed by at least two authors. Data from the individual studies were extracted using a data extraction tool from a previous review (Glinianaia et al., 2004).

Figure 1 shows the sequence of study selection. After reviewing the full text, 24 studies were excluded. Of these, 11 did not consider gender as a covariate in the regression model, and 13 adjusted for gender in the model but did not report a gender-specific estimate. In total, we found 11 articles that fulfilled the inclusion criteria.

Figure 1 about here

Additional information to investigate interaction was requested from the authors of the 11 articles. Authors were requested to provide contingency tables for which odds ratios (OR) were calculated for males and females for the highest (quartile, quintile etc.) versus lowest exposure category (quartile, quintile etc.) for each pollutant. We received additional information from four studies. Due to the heterogeneity in study design and the limited number of studies, we have summarised the results narratively.

Study quality

Study quality was assessed based on external validity (Greenhalgh, 1997) and internal validity (Alderson et al., 2004). A checklist was developed from the quality assessment framework in the Systematic Reviews in Health Care Meta-analysis in context (Juni et al., 2001) and Bracken’s guidelines (Bracken, 1989) for observational studies, to assess the methodological quality and to summarise the validity of the selected studies. The checklist

was incorporated in the data extraction tool. The study domains considered are summarised in Table 1. Studies were graded as fully met, satisfactorily met and failed to meet the quality assessment criteria.

Table 1 about here

Study quality is summarised in Table 1. All but one study (Chen et al., 2002) stated the design. In the case-control studies, control selection was clearly explained with a reasonable logic. Universal outcome definitions and measurements were used giving external validity to the studies. However, wide varieties of covariates were adjusted for in the models. Missing data constituted only a small proportion of the sample except in the VLBW study (Rogers et al., 2000). Three studies (Rogers et al., 2000; Wilhelm et al., 2003; Jedrychowski et al., 2004) adjusted for socio-economic status (SES) and three for maternal smoking (Rogers et al., 2000; Chen et al., 2002; Jedrychowski et al., 2004). We considered those studies which adjusted for SES and maternal smoking to fully meet the quality criteria. In the remaining studies residual confounding might have affected the results and therefore we considered the quality to be satisfactory.

Birth outcome definitions

In the studies LBW was defined as weight at birth less than 2500g, VLBW as birthweight less than 1500g and PTB as gestational age at birth less than 37 completed weeks.

RESULTS

Study Characteristics

Among the 11 studies (Table 2) included in the review, three were cohort studies (Wang et al., 1997; Chen et al., 2002; Jedrychowski et al., 2004) two case-control comparisons (Rogers et al., 2000; Wilhelm et al., 2003) and six semi-individual (SI) studies (Lin et al., 2001a; Lin et al., 2001b; Tsai et al., 2003; Yang et al., 2003a; Yang et al., 2003b; Yang et al., 2004). All of the studies used vital records to obtain the birth data. Additionally two studies (Rogers et al., 2000; Jedrychowski et al., 2004) collected some primary data.

Two studies assessed birth weight as a continuous as well as a dichotomous variable (Wang et al., 1997; Chen et al., 2002); two assessed LBW (Lin et al., 2001b; Wilhelm et al., 2003); one each assessed VLBW (Rogers et al., 2000); and fetal growth (Jedrychowski et al., 2004) and six examined PTB (Lin et al., 2001a; Tsai et al., 2003; Wilhelm et al., 2003; Yang et al., 2003a; Yang et al., 2003b; Yang et al., 2004).

Exposure measurements (Table 2) were estimated in four ways: 1) approximations from ambient monitoring; 2) statistical modelling using monitoring data; 3) personal monitoring and 4) comparison of pregnant women from polluted sites with those from relatively non-polluted sites.

Table 2 about here

Air pollution and adverse pregnancy outcomes

The risk of LBW reported across the studies ranged from OR 1.11 (CI, 0.71-1.71) to 1.77 (CI, 1.00-3.12) (Table 3). Jedrychowski and colleagues (Jedrychowski et al., 2004) reported 140.3g reduction in mean birth weight for an increase in PM_{2.5} exposure from 10 to 50µg/m³.

The excess risk of PTB ranged from OR 1.08 (CI, 1.01-1.15) to 1.41 (CI, 1.08-1.82) across the studies (Table 3). These results have been discussed in detail in earlier reviews (Glinianaia et al., 2004; Maisonet et al., 2004; Lacaana et al., 2005; Sram et al., 2005).

Table 3 about here

Gender and adverse pregnancy outcomes

Gender differences in pregnancy outcomes were reported in the 11 studies after adjusting for covariates including the pollutants (Table 3). Three studies reported excess risk in females for LBW compared to males, adjusted ORs are 1.49 (CI, 1.29-1.72) (Chen et al., 2002), 1.62 (CI, 1.03-2.74) (Lin et al., 2001b), and 1.44 (CI, 1.34-1.55) (Wilhelm et al., 2003). In contrast, Wang and colleagues (Wang et al., 1997) reported that males were at 7-8% higher risk of LBW than females. In another study female infants showed an increasing trend towards VLBW compared to males, OR 1.23 (CI, 0.75–1.43) (Rogers et al., 2000). The Polish study (Jedrychowski et al., 2004) reported a significantly lower mean birth weight (212.80g) and

smaller length and head circumference in females (lesser by 1.15cm and 0.78cm respectively).

Studies on PTB reported a reduced risk for females. A decrease in PTB in females compared to males was reported in six studies, and significant in four, ORs ranged from 0.83 (CI, 0.74-0.93) to 0.88 (CI, 0.82-0.96) (Table 3) (Lin et al., 2001a; Tsai et al., 2003; Wilhelm et al., 2003; Yang et al., 2004). Three other studies (Table 3) reported risks of comparable magnitude (Lin et al., 2001a; Tsai et al., 2003; Yang et al., 2004). Studies with different exposure such as traffic air pollution and cement air pollution also reported decreased risk for PTB in females OR 0.87 (CI, 0.84-0.91) (Wilhelm et al., 2003), 0.90 (CI, 0.71-1.14) (Yang et al., 2003a), and OR 0.89 (CI, 0.78-1.03) (Yang et al., 2003b). These estimates show that males are at higher risk for PTB.

Air pollution, gender and adverse pregnancy outcomes

Table 4 shows the interactive effects between air pollution and gender based on additional information obtained from the study authors. The OR for males in the VLBW study (Rogers et al., 2000) with TSP and SO₂ exposure was almost double that for females. The Chinese study (Wang et al., 1997) reported an adjusted OR for LBW in males which was 7-8% higher than for females for both SO₂ and TSP. In another study (Jedrychowski et al., 2004) there was no evidence of a significant difference in birth weight between the two genders for PM_{2.5} exposure. In the traffic air pollution study (Wilhelm et al., 2003) the OR was significant for NO₂ where males had 6% more risk of LBW than females and in the case of CO, the risk was higher by 4% in females. The differences in the risk of LBW for the two genders in the studies possibly suggests interaction between air pollution effects and gender (Wang et al., 1997; Rogers et al., 2000; Wilhelm et al., 2003).

Table 4 about here

DISCUSSION

Over the past decade a number of studies on air pollution and pregnancy outcomes have been published. Recent systematic reviews are suggestive of an association between air

pollution and pregnancy outcomes (Glinianaia et al., 2004; Maisonet et al., 2004; Sram et al., 2005). Existing studies have not adequately addressed whether fetal gender, a known factor influencing pregnancy outcomes, plays a role. In this systematic review, the first to investigate gender effects, we found that a possible differential effect of air pollution on pregnancy outcomes may exist.

The mean birth weight of female infants is generally lower than males. Consequently, a higher proportion of females tend to be LBW. Female gender and air pollution are two known risk factors for LBW (Table 3). In this review there is some evidence of interaction when the highest and lowest exposure groups were compared by gender. The risk of LBW was found to be higher in males in the presence of high levels of air pollution. Males infants are generally less mature than females at term, and also at earlier gestational ages (Torday et al., 1981; Leader et al., 1982; Catlin et al., 1990). The relatively less mature status may make them more vulnerable to extraneous factors such as air pollution than females. However, our results were based on four studies and with the limited data a proper test of interaction could not be undertaken.

Evidence of the differential nature of chemical insults on the growing fetus is available from recent studies. Tang and colleagues reported differential associations between cord blood polycyclic aromatic hydrocarbon (PAH)-DNA adduct levels and head circumference in males and females (Tang et al., 2006). Prenatal exposure to organochlorines was reported to have a differential effect on sex hormones in males and females (Kraemer et al., 2006). Animal studies also support differential effects of chemical exposure by gender (Bunn et al., 2001; Silva et al., 2005).

Some previous air pollution and pregnancy outcome studies have reported investigation of interaction but found them to be non-significant. It is well known that a study requires sufficient power to obtain statistically significant interaction. Tang and colleagues (Tang et al., 2006) did not find a significant interaction (n=150) but stratified analysis yielded differential results for males and females. Moreover, statistical interaction is sensitive to both the scale

and estimate used to measure interaction. An interaction that is not apparent when using a multiplicative scale with OR/RR measures, can become apparent when an additive scale with risk difference measure is used (Rothman, 2002) and vice-versa. Specialised estimates like relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (SI) have been suggested to measure interaction (Rothman, 1976; Skronidal, 2003) and with birth weight (outcome), interaction can be measured in additive (linear) and LBW in multiplicative scale (logistic model).

The interactive effects of air pollution, pregnancy outcomes and gender should be considered in light of known limitations such as exposure misclassification, bias and confounding.

Exposure misclassification

The potential for bias in air pollution studies arises when the surrogate measures misclassify true personal exposures. Short term personal monitoring may also not be representative of the entire pregnancy especially in the presence of seasonality. A study in this review (Jedrychowski et al., 2004) that used personal monitoring repeated the measurements on a small percentage of the sample in each trimester, and found exposure to be stable over the duration of pregnancy. On the other hand, approximations from ambient levels provide exposure information for longer periods. The six semi-individual studies included here measured exposure at the ecological level; thereby increasing the potential for misclassification. None of the studies in this review investigated indoor air pollution. Only the Chinese study (Wang et al., 1997) reported similar indoor and outdoor trends in particulate concentrations and concluded that lack of control for indoor air pollution would not alter the nature of the association but it might reduce the power to detect significance (Xu et al., 1995). Nonetheless, bias from exposure misclassification potentially exists in the reviewed studies.

Other sources of bias

Almost all of the studies were population based and control selection in the case-control studies was appropriate, hence selection bias is less of a concern. Performance and detection bias do not directly apply as the essence of blinding existed in all the studies.

Attrition bias is not relevant in the reviewed studies, as drop outs were at the analysis stage due to missing data. Moreover, missing data comprised a very small percentage of the total sample except in one study (Rogers et al., 2000) where one-fifth of the cases and one-tenth of the controls were lost.

Studies that reported a gender based estimate were those that reported a positive association between air pollution and adverse pregnancy outcomes. None of the studies that reported negative associations explored gender effects. Thus publication bias may be relevant here.

Confounding

Potential confounders associated with LBW (Kramer, 1987a) and PTB (Berkowitz et al., 1993; Berkowitz et al., 1998) are gestational age, maternal weight gain, SES, reproductive history, medical risks of the index pregnancy and behavioural (smoking) and environmental factors. Of these the most important is gestational age (Thomas et al., 2000). Three of the five birth weight studies (Rogers et al., 2000; Chen et al., 2002; Jedrychowski et al., 2004) adjusted for gestational age in the analysis while the other two (Lin et al., 2001b; Wilhelm et al., 2003) adjusted for it in the study design by restricting the sample to term and preterm LBW. The Chinese and Taiwanese studies were restricted to first parity pregnant women. Three studies (Rogers et al., 2000; Chen et al., 2002; Wilhelm et al., 2003) adjusted for SES and three for maternal smoking (Rogers et al., 2000; Chen et al., 2002; Jedrychowski et al., 2004). Given the importance of SES (Kramer, 1987b; Basso et al., 1997) and maternal smoking status (Kramer, 1987b; Zaren et al., 2000) in fetal growth and development, studies that did not control for these variables might have been affected by residual confounding.

Biological plausibility

CO is the only pollutant for which the biological mechanism on fetus is known. CO binds with haemoglobin and crosses the placenta by passive diffusion thereby reducing oxygen availability to the fetus (Longo, 1977). The higher affinity of fetal haemoglobin to CO compared to adults results in higher concentrations of stable carboxyhaemoglobin in the fetal blood than in the mother's (Gabrielli et al., 1995; Aubard et al., 2000). Male fetuses have been reported to have a higher growth rate and greater demands for blood circulation than female fetuses (Parker et al., 1984; Spinillo et al., 1994; Thomas et al., 2000). One possible explanation could be that owing to the higher rate of growth male fetuses require more oxygen, and carboxyhaemoglobin makes oxygen less available, which may be further aggravated by the relatively immature status of male compared to female fetuses at a given gestational age. Our suggestion of the possible differential effect of CO on male fetal growth can be supported by findings from recent research on maternal smoking. Maternal smoking is shown to have a differential negative effect on growth of male and female fetuses, being more pronounced for male fetuses (Wertelecki et al., 1987; Spinillo et al., 1994; Zaren et al., 2000) and CO is known to be a major constituent of tobacco smoke (Longo, 1977; Walsh, 1994).

The biological mechanisms of the effect of other pollutants, including particulates, on the fetus are poorly understood, so gender specific considerations can be at best speculative. The effect of any pollutants may be mediated through maternal conditions causing placental dysfunction and consequently affecting fetal growth; alternatively, the toxic components in the maternal circulation can cross the placenta and directly affect the fetus. The association between PM₁₀ and respiratory diseases have been reported in many studies (Pope III et al., 2006). Evidence of biological causality between PM₁₀ and respiratory conditions suggests that PM₁₀ may increase maternal susceptibility to infections during pregnancy, including intra-uterine infections. Male fetuses may be particularly vulnerable to intrauterine infections because their amniotic membranes are more prone to infection due to slower immunologic development compared to female fetuses (Hall et al., 1982; Perni et al., 2005). Moreover, exposure to PM₁₀ increases blood viscosity in adults (Zondervan et al., 1987; Knottnerus et al., 1990), which in turn may reduce placental perfusion. One can speculate that increased

blood viscosity may have a more pronounced effect on the placenta of the male fetus because placental dysfunction is more frequently observed in male than female births (Edwards et al., 2000; Ghidini et al., 2005). In addition, particulates may directly interfere sometimes forming adducts (PAH-DNA), affecting fetal growth (Perera et al., 1998; Dejmeek et al., 2000). There is no direct evidence of susceptibility of male fetuses to particulates leading to LBW. However, male fetuses are more prone to slower lung maturation than females (Torday et al., 1981; Catlin et al., 1990), while particulates are known to cause oxidative stress and increase permeability of the lung epithelium (Carter et al., 1997; Donaldson et al., 2001), which may result in a higher susceptibility for the male fetus.

In summary, the adjusted estimates from the air pollution and pregnancy outcome studies provided evidence consistent with existing knowledge that female infants are at an increased risk of LBW and males are at an increased risk of PTB. In addition, there was some evidence to suggest that air pollution effects on LBW may be differential by gender. Males were found to be at a higher risk of LBW in the presence of high levels of air pollution. However, the evidence was limited and inconclusive. Further investigation to ascertain interaction is required in high powered datasets across different populations.

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Table 1: Summary of the quality of studies by study domains

Study Domain	Number of studies		
	Birth weight studies (n=5)	Very low birth weight study (n=1)	Preterm birth studies (n=6)
<i>Design issues</i>			
Study design clearly stated	4	1	6
Study group selection specified	5	1	6
Control selection process specified	3 ^a	1	6
<i>Exposure measurements</i>			
Pollutants defined	5	1	1
Exposure duration clearly stated	5	1	6
Exposure measurement defined adequately	5	1	1
<i>Outcome measurements</i>			
Completeness of outcome measures	5	1	6
Missing data reported	5	1	6
<i>Analysis</i>			
Adequate adjustment for confounders ^b	3	1	1

^a remaining two were cohort studies

^b adjustment was considered inadequate if socio-economic status and other important confounders were not considered in the analysis

Table 2: Study characteristics

First Author (Year)	Location	Duration	Design	Pollutants	Exposure assessment	Pollutant values/study groups comparison
Chen (2002)	USA	1991 – 1999	Cohort	CO, PM ₁₀ , O ₃	24hr average of PM ₁₀ , 8hr average of CO and O ₃ approximated from ambient levels	^a PM ₁₀ – 31.53µg/m ³ (22.32) CO – 0.98ppm (0.55) O ₃ – 27.23ppb (10.62)
Lin (2001b)	Taiwan	1993 – 1996	Semi-individual	SO ₂ , PM ₁₀ , NO ₂	Approximation from ambient monitoring	^b SO ₂ – 6.04ppb (2.88) PM ₁₀ – 85.89µg/m ³ (1.71) NO ₂ – 12.09ppb (2.23)
Wang (1997)	China	1988 – 1991	Cohort	SO ₂ , TSP	Approximation from ambient monitoring	^c SO ₂ – 9 to 308µg/m ³ TSP – 211 to 618µg/m ³
Wilhelm (2003)	USA	1994 – 1996	Case control	CO, PM ₁₀ , NO ₂ , O ₃	Distance weighted traffic density measure and annual medians	^d CO – 1.73ppm PM ₁₀ – 41.11ppm NO ₂ – 4.35pphm O ₃ – 1.80pphm
Jedrychowski (2004)	Poland	Jan'01 – Mar'03	Prospective Cohort	PM _{2.5}	Direct personal monitoring	^a PM _{2.5} – 43µg/m ³ ^c PM _{2.5} – 10.3to147.3µg/m ³
Rogers (2000)	USA	Apr'86 – Mar'88	Case control	SO ₂ , TSP	Statistical modelling from ambient monitoring estimates	^d TSP – 5.93µg/m ³ SO ₂ – 3.80µg/m ³ TSPSO ₂ – 9.94µg/m ³
Lin (2001a)	Taiwan	1993 – 1996	Semi-individual	Petroleum refinery pollutants	Extreme point contrast	Births within petroleum municipalities were compared with those from the rest of Taiwan
Tsai (2003)	Taiwan	1994 – 1997	Semi-individual	Pollutants from industrial and petrochemical sites	Extreme point contrast	Polluted area defined by a circle of 2km around multiple sources, controls from the rest of Taiwan

Yang (2003a)	Taiwan	1992 – 1997	Semi-individual	Pollutants from vehicular traffic on a freeway	Extreme point contrast	Births within 500m from the freeway were compared with those within 500-1500m
Yang (2003b)	Taiwan	1992 – 1996	Semi-individual	Cement dust	Extreme point contrast	Births within 0-2km from the freeway were compared with those within 2-4km
Yang (2004)	Taiwan	1994 – 1997	Semi-individual	Oil refinery pollutants	Extreme point contrast	Births within circles of 3km radius from refineries with the rest of births in Taiwan

^a mean values (SD) of the pollutants
^b geometric mean values (geometric SD) of the pollutants of the exposed area
^c range of values of the pollutants
^d annual medians of the pollutants

Table 3: Summary of evidence on air pollution and pregnancy outcomes

First Author (Year)	Sample size		Pollutants	OR (CI) ^a	
	Study group	Controls		air pollution	gender (male as ref)
<i>Low birth weight</i>					
Chen (2002)	36,305	-	PM ₁₀ CO O ₃	1.11 (0.71–1.71) 0.91 (0.56–1.46) 0.78 (0.51–1.21)	1.49 (1.29–1.72)
Lin (2001b)	1677	868	-	1.77 (1.00–3.12)	1.62 (1.03–2.74)
Wang (1997)	74,671	-	SO ₂ TSP	1.39 (1.22–1.60) 1.24 (1.08–1.42)	1.09 (0.97–1.22) 1.07 (0.95–1.20)
Wilhelm (2003)	3771	26,351	-	1.14 (1.00–1.29)	1.44 (1.34–1.55)
<i>Birth weight (continuous)</i>					
Jedrychowski (2004) ^b	362		PM _{2.5}	-200.82 (-385.97– 15.67)	-212.80 (-293.91 – 131.69)
<i>Very low birth weight</i>					
Rogers (2000)	143	202	TSPSO ₂	2.88 (1.16–7.13)	1.23 (0.75–1.43)
<i>Preterm birth</i>					
Lin (2001a)	2027	49,673	-	1.41 (1.08–1.82)	0.83 (0.74–0.93)
Tsai (2003)	14,545	49,670	-	1.11 (1.02–1.21)	0.88 (0.82–0.95)
Yang (2003a)	3211	3040	-	1.30 (1.03–1.65)	0.90 (0.71–1.14)
Yang (2003b)	3067	14,049	-	1.30 (1.09–1.54)	0.89 (0.78–1.03)
Wilhelm (2003)	13,464	21,124	-	1.08 (1.01–1.15)	0.87 (0.84–0.91)
Yang (2004)	7095	50,388	-	1.14 (1.01–1.28)	0.88 (0.82–0.96)

^a adjusted for other covariates in the model

^b linear regression coefficients were reported for this study

Table 4: Odds ratios for air pollution and LBW/PTB by gender and pollutants ^a

Author	Pollutant	Male (CI)	Female (CI)
<i>Low birth weight</i>			
Rogers (2000)	TSPSO ₂	3.00 (0.95-9.67)	1.89 (0.48-7.47)
Wang (1997) ^b	SO ₂	1.16 (1.02-1.32)	1.09 (0.97-1.22)
Wang (1997) ^b	TSP	1.15 (1.01-1.32)	1.07 (0.95-1.20)
Jedrychowski (2004)	PM _{2.5}	p= 0.09 ^c	0.86 (0.13-5.48)
Wilhelm (2003)	PM ₁₀	1.01 (0.92-1.11)	0.95 (0.87-1.04)
Wilhelm (2003)	CO	1.05 (0.94-1.16)	1.09 (0.98-1.20)
Wilhelm (2003)	O ₃	0.94 (0.86-1.04)	0.93 (0.84-1.02)
Wilhelm (2003)	NO ₂	1.14 (1.04-1.25)	1.08 (0.99-1.19)
<i>Preterm birth</i>			
Wilhelm (2003)	PM ₁₀	1.04 (0.96-1.14)	1.03 (0.95-1.13)
Wilhelm (2003)	CO	1.11 (1.01-1.22)	1.06 (0.96-1.18)
Wilhelm (2003)	O ₃	0.86 (0.79-0.94)	0.90 (0.82-0.98)
Wilhelm (2003)	NO ₂	1.19 (1.09-1.29)	1.11 (1.02-1.21)

^a ORs were calculated from the additional data provided by the study authors

^b adjusted OR in this study and unadjusted OR in the rest

^c p value was reported from Fisher's exact test

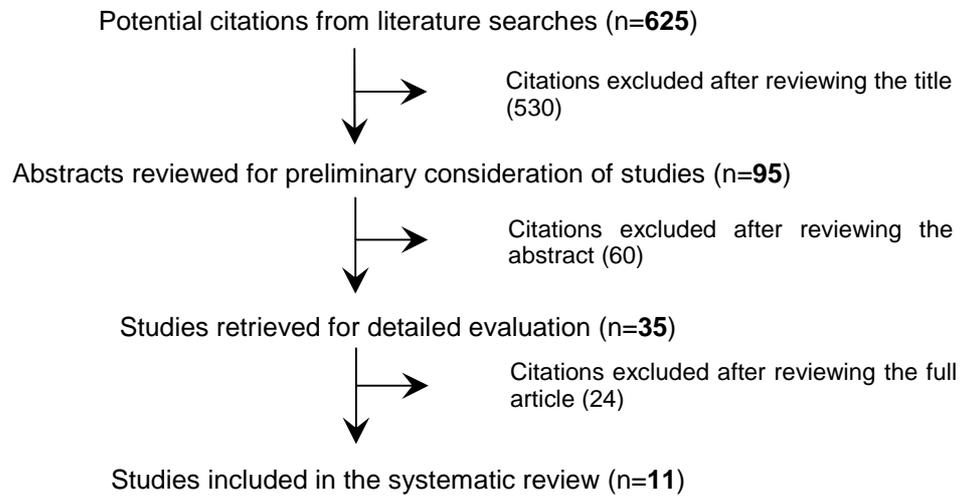


Figure 1. Sequence of the search and review of studies

ONLINE APPENDIX

BOX 1. List of keywords used in literature search[†]		
Pollution	Gender	Perinatal outcomes
air pollution* environmental pollutants air pollution, indoor indoor air pollution* ambient air pollution* total suspended particle* particulate matter particle size carbon monoxide nitrogen oxide nitrogen dioxide sulphur dioxide ozone PM10 PM2.5 CO NO NO2 SO2 O3	gender gender identity sex factors sex characteristics gender difference* sex sex differentiation sex distribution sex ratio sex difference* male female	birthweight infant low birthweight infant premature low birthweight infant newborn term low birthweight fetal weight fetal development fetal movement fetal organ maturity fetal viability gestational age fetal growth embryonic development fetal development intra uterine growth retardation* prematurity premature birth preterm birth infant, premature perinatal outcome* pregnancy outcome*

[†] keywords were combined using Boolean operators (OR/AND) and final results were restricted to human, English language and before 2005

* a wild-card was used in text-based searches to find words containing subsequent text