Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence

Nazeeba Siddika,1 Hamudat A Balogun,1 Adeladza K Amegah,1,2 Jouni J K Jaakkola1,3

ABSTRACT

Background Individual studies on the relations between ambient air pollution and the risk of stillbirth have provided contradictory results. We conducted a systematic review and meta-analysis to summarise the existing evidence.

Methods We conducted a systematic search of three databases: PubMed, Scopus and Web of Science, from their time of inception to mid-April, 2015. Original studies of any epidemiological design were included. Data from eligible studies were extracted by two investigators. To calculate the summary effect estimates (EE), the random effects model was used with their corresponding 95% CI.

Results 13 studies met the inclusion criteria. Although not reaching statistical significance, all the summary effect estimates for the risk of stillbirth were systematically elevated in relation to mean prenatal exposure to NO2 per 10 ppb (EE=1.066, 95% CI 0.965 to 1.178, n=3), CO per 0.4 ppm (EE=1.025, 95% CI 0.985 to 1.066, n=3), SO2 per 3 ppb (EE=1.022, 95% CI 0.984 to 1.062, n=3), PM10 0.4 μg/m3 (EE=1.080, 95% CI 1.002 to 1.161, n=2) and PM10 per 10 μg/m3 (EE=1.014, 95% CI 0.948 to 1.085, n=2).

Conclusions The body of evidence suggests that exposure to ambient air pollution increases the risk of stillbirth. Further studies are needed to strengthen the evidence.

INTRODUCTION

Ambient air pollution is a major environmental health problem in developed and developing countries, and is a major cause of several important diseases including lung cancer, acute lower respiratory infections, cardiovascular diseases, pregnancy outcomes, chronic obstructive pulmonary disease (COPD) and asthma. The WHO reports that in 2012 around 7 million people died—one in eight of total global deaths was as a result of air pollution exposure, 3.7 million of these were attributed to ambient air pollution due to exposure to particulate matter (PM10). This estimate is more than twofold of the previous estimates and suggests that air pollution is now the world’s largest single environmental health risk.

Fetal growth and pregnancy outcome are determined by several factors including maternal nutrition, environmental exposures and heredity. The prenatal stage of life is a very sensitive period such that exposure to harmful substances can have an adverse effect on the developing fetus. The effects of air pollution on fetal growth and pregnancy outcomes have been studied especially in developed countries and the results have been summarised in several reviews.9-12

The WHO reported that 2.6 million stillbirths occurred worldwide in 2009, according to the first comprehensive set of estimates published in a special series of *Lancet*, 2011. Every day, more than 7200 babies are stillborn.13 Previous studies have identified the important causes of stillbirth as umbilical cord accidents, congenital anomalies, placental abruption, maternal disease (diabetes, HIV, syphilis and hypertension), obesity, primiparity and smoking in pregnancy.14

Two previous reviews have suggested that ambient air pollutant exposure including nitrogen dioxide (NO2), sulfur dioxide (SO2), black carbon, carbon monoxide (CO), polycyclic aromatic hydrocarbons (PAHs) and particulate matter (PM), can also be an important cause of stillbirth, but both concluded that the evidence was weak at the time of conduct. There are also recent reviews indicating that air pollution from secondhand smoke13 and solid fuels16 increases the risk of stillbirth.

The two previous reviews of the effects of ambient air pollution evaluated three studies each, two of which were common to both reviews, with...
Glinaiana et al\textsuperscript{17} stating that the evidence available is insufficient to assess a possible association between PM and stillbirth. Lacasana et al\textsuperscript{18} reported a positive but not consistent association between ambient air pollution and stillbirth; this may be due to an insufficient number of studies available. A recent review by Zhu et al\textsuperscript{19} evaluated the effect of exposure to PM\textsubscript{2.5} on pregnancy outcomes but only included one study on stillbirth. A substantial number of studies have emerged since the conduct of these reviews, and this certainly calls for an evaluation of the evidence to provide insight into causality and identify gaps in knowledge. The objective of the present study was to assess the effect of prenatal ambient air pollution exposure on the risk of stillbirth through systematic review and meta-analysis.

METHODS

A systematic search of three databases—PubMed, Scopus and Web of Science—was carried out from their time of inception to mid-April, 2015, using Medical Subject Heading (MeSH) terms without any language restriction. The search terms used are listed in Table 1.

Two investigators (NS and HAB) independently searched for relevant studies from the databases by first screening the titles of the citations and subsequently reviewing the abstracts of relevant titles. Studies selected after the abstract review were retrieved in full and reviewed with articles selected for inclusion in the study satisfying the following criteria: (1) original articles of any epidemiological design; (2) conducted in a human population; (3) provided effect estimates for the relation between exposure to any outdoor air pollutant and the risk of stillbirth, or reported the occurrence of stillbirth among exposed and unexposed mothers. The reference lists of the included studies were also reviewed to identify additional eligible studies.

Data extraction and study quality appraisal

A data extraction form adapted from our previous review\textsuperscript{16} was used independently by two investigators (NS and HAB) to extract the relevant information from the studies meeting the inclusion criteria. The information extracted by the two investigators was compared with any differences resolved by repeatedly checking the original articles and through discussion with the third investigator (AKA) adjudicating in situations where there were disagreements. Methodological quality of the included studies was assessed by investigating evidence of selection, information and confounding bias, and evaluation of the case ascertainment protocols. The general quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS).\textsuperscript{20}

Statistical analysis

Owing to differences in study design, geographical settings and different study population, we anticipated the inconsistency in the studies and applied the random effect model in summary effect estimates with their corresponding 95% CI. Heterogeneity of the studies was assessed using the $I^2$ statistic, with a value >50% being deemed to indicate high heterogeneity, 25–50% indicating moderate and <25% indicating low heterogeneity. Individual studies included in the meta-analysis had their effect estimates with different magnitude of air pollutant exposure (except for NO\textsubscript{2} and PM\textsubscript{10}), therefore, before estimating the summary effects the individual effect estimates were converted with a common pollutant concentration such as per 3 ppb increase in SO\textsubscript{2}, per 0.4 ppm increase in CO, 4 µg/m\textsuperscript{3} in PM\textsubscript{2.5} and 10 ppb increase in O\textsubscript{3} exposure. With regard to the study providing only trimester specific effect estimates, we first combined the three (1st, 2nd and 3rd trimester) estimates using the fixed effects model to get the estimate for the entire pregnancy, and then applied the combined estimate in the overall meta-analysis. Forest plots corresponding to each summary effect estimate were visually assessed. Sensitivity analysis was not conducted due to the small number of studies included in the meta-analysis. Publication bias was assessed by visual inspection of the funnel plots and application of Begg’s and Egger’s tests. Statistical analyses were performed using Stata V13.0 (StataCorp LP, College Station, Texas, USA) software.

RESULTS

A total of 13 studies were included in the review. The study selection process is shown in Figure 1.

Characteristics of included studies

The characteristics of the included studies are presented in online supplementary table S1.

Of the 13 studies, two studies\textsuperscript{21,22} assessed the effects of short-term air pollution exposure with the remaining studies focusing on long-term air pollution exposure. Six studies\textsuperscript{23–28} assessed maternal exposure to air pollution on a trimester basis.

Of the 11 epidemiological studies with assessment of long-term air pollution exposure, six studies\textsuperscript{23,25–29} employed a cohort design, of which one\textsuperscript{29} was prospective. Two studies\textsuperscript{20,31} were semiecological, that is, the exposure was assessed at group level and the outcome at individual level, and another two studies were cross-sectional\textsuperscript{15,31} with one study\textsuperscript{24} applying a case control design. Of the two epidemiological studies with assessment of short-term air pollution exposure, one\textsuperscript{21} applied a case-crossover design with the hazard period defined as lag day 2 and reference periods selected by matching on the weekday within the same calendar month, and they also used two through 6 days before delivery as lag days. The other short-term air pollution exposure study\textsuperscript{22} was a time series analysis using Poisson regression and with lag effect of up to 5 days preceding delivery. Regarding the geographical location of the included studies, five studies were conducted in the USA, one in Latin America, three in East Asia, two in Europe, one in Russia and one in the UK. Seven of the included studies were published after the year 2005.

Eleven\textsuperscript{21–31} of the included studies relied on routine air monitoring data in their respective study areas in estimating maternal

### Table 1 Search terms

<table>
<thead>
<tr>
<th>Exposure MeSH Terms</th>
<th>Free text words</th>
<th>Outcome MeSH Terms</th>
<th>Free text words</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air pollution</td>
<td>Ambient air pollution</td>
<td>Stillbirth</td>
<td>Birth outcome</td>
</tr>
<tr>
<td>Environmental pollution</td>
<td>Outdoor air pollution</td>
<td>Perinatal mortality</td>
<td>Intrauterine mortality</td>
</tr>
<tr>
<td>Vehicular emission</td>
<td>Ambiant air quality</td>
<td>Fetal mortality</td>
<td>Fetal death</td>
</tr>
<tr>
<td>Particulate matter</td>
<td>Traffic exposure</td>
<td>Pregnancy</td>
<td>Outcome</td>
</tr>
<tr>
<td>PM</td>
<td>Nitrogen dioxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozone</td>
<td>NO\textsubscript{2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O\textsubscript{3}</td>
<td>Sulfur dioxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particulate matter</td>
<td>SO\textsubscript{2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
air pollution exposure. Landgren categorized each exposure in two ways, (1) above and below the mean exposure value (SO2: 8.0 µg/g, CH: 6.6 µg/g and NO: 14.7 µg/g) of all the included municipalities and (2) the municipality with the highest exposure level was compared with all other municipalities. Vassilev et al. used statewide combined modelled average concentrations for each census tract and categorized exposures into low (0.040 – 0.268 mg/m³), medium (0.269 – 0.610 mg/m³) and high exposure (0.611 – 2.830 mg/m³) level with low exposure serving as the reference in the analysis. The included studies measured 13 pollutants including SO2, NO2, CO, particles (PM2.5, PM10, SPM), O3, NO, POM, NOx, hydrocarbons (CH), black smoke, which was taken as equivalent to PM2.5 in the study that measured this pollutant,25 and suspended solids.

Of the 11 studies relying on air monitoring station data, seven studies21 23 24 27 28 32 and that by Vassilev et al.32 assigned exposures to mothers based on their residential addresses at the time of delivery. Regarding the studies conducted by Faiz et al.21 23 and DeFranco et al.,27 mothers had to live within a 10 km radius of the closest monitoring station; and Green et al.28 used a 20 km radius for PM2.5, O3, SO2 and a 5 km radius for CO and NO2 to be included in the studies. Whereas Hwang et al.24 applied a 25 km radius. The exposure assignments in the studies by Kim et al.,26 Pearce et al.24 and Vassilev et al.12 were not based on any fixed radius. The two ecological studies30 31 used annual mean concentrations of the pollutants studied to assign exposures. Dimitriev29 used monthly concentration of air pollutants in the study areas.

Six studies21 23 24 27 28 32 used a stillbirth cut-off point of >20 weeks of gestation, with three studies22 25 30 using a cut-off of >28 weeks of gestation. Landgren33 and Sakai31 did not provide a case definition in their reports. DeFranco et al.27 ascertained stillbirth by using both, last menstrual period (LMP) and ultrasound examination methods, whereas two other studies25 26 mostly used the LMP method but also used fetal ultrasound examination if there was either uncertainty about the LMP date or discordance between the two estimates. Two studies23 28 used the LMP method only, with Hwang et al.24 applying ultrasound examination. The type of stillbirth studied was not mentioned in any of the included studies except the study by Pereira et al.22 which identified the stillbirths as intrauterine mortality, which we assume to be antepartum stillbirth. The source of data on stillbirth was obtained from fetal death certificates in five studies,21 – 23 32 33 birth registry or vital statistics in three studies24 25 28 30 31 and hospital records in two studies.23 26 Dimitriev29 did not provide any information on how the stillbirths were ascertained.

Methodological quality of the included studies
Selection bias
Selection bias was very minimal in the included studies as most of the studies collected data from fetal death certificates or birth...
registries and are likely to have represented their source populations with high response rate also reported. The prospective cohort study, however, only included pregnant women who visited the hospital for prenatal care, excluding mothers with missing values for residential address and sociodemographic risk factors. Few studies excluded mothers without gestational age information and census tract coding (8%) from the analysis.

Information bias
There was evidence of potential information bias in all the included studies due to the reliance on proximity of maternal homes to the nearest air pollution monitoring stations and use of emission measurement and meteorological data in assessing exposure. Factors such as mother’s mobility, change of residence during pregnancy, occupation of mother and air exchange were not considered, and this may lead to a decrease in the accuracy of the exposure assessment and introduce a non-differential misclassification that might lead to an underestimation of the effects of air pollution. Also, the exposure source was not reported by the studies other than those by Hwang et al., Kim et al., and Vassilev et al. For the outcome measurement, the true dates of fetal death were unknown, hence an estimated time using date of delivery was recorded on the fetal death certificate and this may introduce bias. This was observed in the study by Faiz et al., Hwang et al., Kim et al., Green et al., Bobak and Leon, and Vassilev et al.

Control of confounding
Any determinant of the risk of stillbirth could be considered as a potential confounder in cohort, case-control and cross-sectional studies. The case-crossover study and time-series analyses eliminate any confounding related to individual characteristics and environmental exposures that are linked to the studied air pollutant. Most studies adjusted for the characteristics of the mother, such as age and family characteristics, at an individual level. Some of the studies applied control of confounding at group levels. When estimating the effect of an individual air pollutant, exposure to other air pollutants is a potential confounder. Only five studies fitted more than one air pollutant into the multivariate model, that is, applied multipollutant rather than single pollutant models.

Regarding the ecological studies, Bobak and Leon adjusted for several socioeconomic characteristics, which were obtained from the Czech Statistical Office, at the district level; whereas Sakai did not control for confounding. In the time series analysis, Pereira et al. adjusted for season and weather. Faiz et al. conducted a case-crossover study where they controlled for mean temperature of the corresponding lag days. Of the nine studies, three studies provided estimates for the relation of SO2 exposure (per 3 ppb, 1 ppb and 10 ppb increase in mean concentration) to stillbirth for the entire pregnancy period. The summary-effect estimate (EE) per 3 ppb increase in SO2 exposure in the random effects model was 1.022 (95% CI 0.984 to 1.062), with low heterogeneity between the studies observed (I²=19.6%). The case-crossover study reported increased risk of stillbirth with IQR (4.7 ppb) increase in mean SO2 exposure 2 days before delivery, and also found similar associations on all the lag days; whereas, another time series study, reported marginal association between daily counts of intrauterine mortality and SO2 concentration on the same day as delivery. One of the ecological studies also found significant positive correlation between spontaneous fetal death rate and SO2 concentration. However, Landgren and other ecological study (per 50 µg/m³ increase in annual mean concentration of SO2) however, did not find any association, even after adjustment with other pollutants SPM and NOx.

Findings of included studies and summary effect estimates
Summary effect estimates are presented in table 2 and the corresponding forest plot in figure 2.

Three studies provided estimates for the relation of SO2 exposure (per 3 ppb, 1 ppb and 10 ppb increase in mean concentration) to stillbirth for the entire pregnancy period, with the summary EE in the random effects model found to be 1.066 (95% CI 0.965 to 1.178) per 10 ppb increase in mean NO2 concentration and 1.025 (95% CI 0.985 to 1.066) per 0.4 ppm increase in mean CO concentration, respectively. Evidence of high heterogeneity was noted in the analysis (I²=79.6%). The case-crossover study reported increased risk of stillbirth with IQR increase of NO2 (16.4 ppb) and CO (0.54 ppm) in mean concentration, respectively, 2 days before delivery and also found similar associations on all the lag days. The time-series study reported strong significant dose–response relationship between daily counts of intrauterine mortality with NO2 concentration, and marginal association with CO concentration at 5 days and 3 days before delivery, respectively. The findings of CO exposure with stillbirth were, however, less consistent. Sakai also found a statistically significant positive correlation between NO2 concentration and spontaneous fetal death rate. Pereira et al. also developed an overall index of air pollution (combination of NO2, SO2, CO) and found a very robust significant association with dose–response relationship, whereas Faiz et al. used two pollutant models on lag day 2 but found estimates similar to those of the single pollutant models. Green et al. adjusted PM2.5 or ozone with NO2 and the associations were unaffected.

Two studies provided estimates for the relation of stillbirth per 10 µg/m³ increase in average PM10 concentration during the entire pregnancy duration to the summary EE in the random effects model found to be 1.014 (95% CI 0.948 to 1.085). Evidence of high heterogeneity was noted in the analysis (I²=85.0%). The time series study did not find any statistically significant associations.

Two studies provided estimates for the relation of stillbirth per 4 µg/m³ increase in average PM2.5 concentration during the entire pregnancy duration to the summary EE in the
random effects model found to be 1.021 (95% CI 0.996 to 1.046). No heterogeneity was noted in the analysis ($I^2=0\%$).

DeFranco et al. found non-significant 21% (OR: 1.21, 95% CI 0.96 to 1.53) increased risk in stillbirth with high PM$_{2.5}$ (15.67 μg/m$^3$) exposure during the entire pregnancy.

Two studies 24 28 provided estimates for the relation of stillbirth to per 10 ppb increase in average O$\_3$ concentration during the entire pregnancy duration to the summary EE in the random effects model found to be 1.002 (95% CI 0.971 to 1.034). Evidence of low heterogeneity was noted in the analysis ($I^2=19.6\%$). The time series study 22 evaluated the relation of stillbirth with high PM$_{2.5}$ (162.22 μg/m$^3$) increase in their time series analysis on all the lag days.

Whereas DeFranco et al. 27 found significant 42% (OR 1.42, 95% CI 1.06 to 1.91) increased risk in stillbirth with high PM$_{2.5}$ (162.22 μg/m$^3$) exposure only in the third trimester. Hwang et al. 24 evaluated increased risk of stillbirth in association with SO$_2$ per 1 ppb and PM$_{10}$ per 10 μg/m$^3$ increase during the first and second months of pregnancy, and was stable after adjustment for O$_3$ and either CO or NO$_2$ in multipollutant models. Green et al. 28 found robust association with third trimester O$_3$ exposure after addition of PM$_{2.5}$ and NO$_2$.

Dimitrijev 25 compared the occurrence of stillbirth in good and worse ecological areas assessed on the basis of monthly concentration of suspended solids, SO$_2$, CO, NO$_2$, and reported risk of stillbirth as 6.63 and 11.03 per 1000 births, respectively. The estimated risk ratio showed a 65% (RR 1.650, 95% CI 1.136 to 2.397) increased risk of stillbirth among mothers resident in polluted ecological areas.

Two studies 23 33 that investigated the relation of NO exposure to stillbirth also found no association. The association between stillbirth risk and per 10 μg/m$^3$ relating average weekly black smoke (equivalent to PM$_{4}$) exposure was evaluated by Pearce et al. 23 but did not find any significant association during pregnancy. Bobak and Leon 10 evaluated the effects of SPM and NO$_2$ (per 50 μg/m$^3$ increase in concentration), and found no significant association in the single pollutant model nor after

### Table 2

<table>
<thead>
<tr>
<th>Air pollutant</th>
<th>Studies contributing to the summary effect estimate</th>
<th>Fixed effects Summary effect estimates</th>
<th>Random effects Summary effect estimates</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Summary effect estimates</td>
<td>Summary effect estimates</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>SO$_2$ (3 ppb)</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.019 (0.989 to 1.049)</td>
<td>1.022 (0.984 to 1.062)</td>
<td>2.49</td>
</tr>
<tr>
<td>1st trimester</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>0.997 (0.975 to 1.020)</td>
<td>1.040 (0.962 to 1.125)</td>
<td>10.34</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.003 (0.977 to 1.030)</td>
<td>1.003 (0.977 to 1.030)</td>
<td>1.79</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>0.996 (0.967 to 1.026)</td>
<td>1.042 (0.951 to 1.142)</td>
<td>11.26</td>
</tr>
<tr>
<td>NO$_2$ (10 ppb)</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.049 (1.012 to 1.088)</td>
<td>1.066 (0.965 to 1.178)</td>
<td>9.78</td>
</tr>
<tr>
<td>1st trimester</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.025 (0.996 to 1.054)</td>
<td>1.035 (0.983 to 1.089)</td>
<td>4.43</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.005 (0.977 to 1.034)</td>
<td>1.007 (0.948 to 1.071)</td>
<td>5.83</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.015 (0.980 to 1.051)</td>
<td>1.015 (0.980 to 1.051)</td>
<td>1.88</td>
</tr>
<tr>
<td>CO (0.4 ppm)</td>
<td>Faiz 2012, Green 2015, Hwang 2011</td>
<td>1.022 (0.995 to 1.050)</td>
<td>1.025 (0.985 to 1.066)</td>
<td>2.52</td>
</tr>
<tr>
<td>PM$_{10}$ (10 μg/m$^3$)</td>
<td>Hwang 2011, Kim 2007</td>
<td>1.012 (0.986 to 1.039)</td>
<td>1.014 (0.948 to 1.085)</td>
<td>6.67</td>
</tr>
<tr>
<td>1st trimester</td>
<td>Hwang 2011, Kim 2007</td>
<td>1.015 (0.991 to 1.039)</td>
<td>0.998 (0.936 to 1.064)</td>
<td>2.18</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>Hwang 2011, Kim 2007</td>
<td>0.968 (0.944 to 0.993)</td>
<td>1.005 (0.905 to 1.116)</td>
<td>5.31</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>Hwang 2011, Kim 2007</td>
<td>0.995 (0.968 to 1.022)</td>
<td>1.021 (0.919 to 1.134)</td>
<td>10.96</td>
</tr>
<tr>
<td>PM$_{2.5}$ (4 μg/m$^3$)</td>
<td>Faiz 2012, Green 2015</td>
<td>1.021 (0.996 to 1.046)</td>
<td>1.021 (0.996 to 1.046)</td>
<td>0.18</td>
</tr>
<tr>
<td>1st trimester</td>
<td>Faiz 2012, Green 2015</td>
<td>1.002 (0.982 to 1.022)</td>
<td>1.042 (0.920 to 1.180)</td>
<td>2.35</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>Faiz 2012, Green 2015</td>
<td>1.011 (0.996 to 1.026)</td>
<td>1.040 (0.940 to 1.152)</td>
<td>1.92</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>Faiz 2012, Green 2015</td>
<td>1.000 (0.981 to 1.020)</td>
<td>1.000 (0.981 to 1.020)</td>
<td>0.23</td>
</tr>
<tr>
<td>O$_3$ (10 ppb)</td>
<td>Green 2015, Hwang 2011</td>
<td>1.005 (0.982 to 1.029)</td>
<td>1.002 (0.971 to 1.034)</td>
<td>1.24</td>
</tr>
<tr>
<td>1st trimester</td>
<td>Green 2015, Hwang 2011</td>
<td>1.001 (0.983 to 1.020)</td>
<td>1.001 (0.983 to 1.020)</td>
<td>0.13</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>Green 2015, Hwang 2011</td>
<td>1.004 (0.985 to 1.022)</td>
<td>0.991 (0.944 to 1.040)</td>
<td>3.18</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>Green 2015, Hwang 2011</td>
<td>1.025 (1.006 to 1.043)</td>
<td>1.012 (0.966 to 1.060)</td>
<td>2.72</td>
</tr>
</tbody>
</table>

adjustment with all pollutant (SPM, SO2, NOx) models. Vassilev et al.32 investigated POM exposure and, using low exposure as the reference category, found statistically significant increased risk of stillbirth with medium and high exposure (ORs of 1.21 (95% CI 1.04 to 1.40) and 1.19 (95% CI 1.02 to 1.39), respectively). The effect of CH was investigated by Landgren,33 but no association was found between stillbirth and levels of CH concentration in Swedish municipalities.

**Evaluation of publication bias**

Figure 3 presents the funnel plots for all the study specific effect estimates used to calculate the summary effect estimates. Online supplementary table S3 presents results from the Begg's and Egger's tests. There was no indication of publication bias present, although these results should be interpreted with caution because they were based on two or three study-specific effect estimates only.

**DISCUSSION**

Our systematic review and meta-analysis provided evidence that prenatal exposure to air pollution increases the risk of stillbirth. The summary effect estimates from the random effects models were systematically elevated, although they did not reach statistical significance. Per 10 ppb NO2, 0.4 ppm CO, 3 ppb SO2, 4 μg/m3 PM2.5 and 10 μg/m3 PM10, increase in mean exposure during the entire pregnancy duration, respectively, resulted in a 6.6% (EE=1.066, 95% CI 0.965 to 1.178), 2.5% (EE=1.025, 95% CI 0.985 to 1.066), 2.2% (EE=1.022, 95% CI 0.984 to 1.062), 2.1% (EE=1.021, 95% CI 0.996 to 1.046) and 1.4% (EE=1.014, 95% CI 0.948 to 1.083) increased risk of stillbirth.

The point estimates for the third trimester were slightly elevated for SO2, CO, PM10 and O3 consistently, with a hypothesis of a susceptible time window for the adverse effects, although the differences were not statistically significant. Two time series studies used lag day not more than 6 days preceding stillbirth and both found increased risk with certain pollutants.

**Validity of results**

We included all the studies identified in an extensive systematic search, so missing of important epidemiological studies is less likely to have happened. A significant number of studies have emerged since the last reviews; hence the critical assessment of the evidence is timely. Even though our review contains eight more studies and much more information than the previous reviews, we found a very limited number of estimates for each of the pollutants, and only five studies made attempts to adjust for other air pollutants when presenting effect estimates of each air pollutant. Therefore, we could not include all of the studies in the meta-analyses, and the reliability on the summary effect estimates is further compromised. However, the existing evidence is suggestive of causality for air pollution and stillbirth without precise identification of the timing of exposure. With the limited studies on the relevant topic, our review suggests strong priorities for future research. The visual inspection of the funnel plots and the statistical assessment did not indicate publication bias.

**Biological plausibility**

Fetuses are more affected by a variety of environmental toxicants because of differential exposure and physiological
Figure 3  Funnel plot with pseudo 95% confidence limits for the relation between ambient air pollutants and stillbirth.
immaturity. The biological mechanisms by which exposure to ambient air pollutants leads to fetal death is not very clear. Faiz et al suggested the direct crossing of air pollutants across the placenta, causing irreversible damage to the dividing cells of the growing fetus and triggering hypoxic damage or immunemediated injury during critical periods of development, as a possible mechanism.

Of all the pollutants, only the mechanism of the toxic effects of CO on the fetus is well established. CO reduces oxygen-carrying capacity of maternal haemoglobin that could seriously affect oxygen delivery to fetal circulation. Sangalli et al revealed that CO crosses the placental barrier and haemoglobin on fetal blood has greater affinity for binding CO than that in an adult; O2 delivery to fetal tissues is further compromised. Moreover, fetal elimination of carbon monoxide is slower than in the mother. There is also a significant dose-dependent relationship between CO and COHb, and a developing fetus can be deprived of adequate oxygenation due to high levels of COHb, which may even lead to fetal death.

Maternal exposures to particulate (PM) air pollutants during pregnancy can result in increased concentration of DNA adducts or may lower the efficiency of the transplacental function, resulting in decreased fetal health leading to stillbirth. The meta-analysis, we also found a 4.2% (EE 1.042, 95% CI 0.920 to 1.062) and CO 2.5% (EE 1.025, 95% CI 0.985 to 1.066) exposure for the entire pregnancy period in the meta-analysis. The short-term air pollution studies on these relationships and one of the ecological studies also reported an increased risk of stillbirth related to SO2 and CO exposure. The findings of CO exposure with stillbirth was, however, less consistent.

Lacasana et al stated that SO2 and CO also showed some, though less consistent, relationship with intrauterine mortality. In our review, we found that there is an increased risk of stillbirth associated with increased ambient concentrations of sulfur dioxide in early pregnancy, with pooled effect estimates of 4.0% (EE 1.040, 95% CI 0.962 to 1.125). Also, we found the highest pooled estimate of 5.2% (EE 1.052, 95% CI 0.973 to 1.138) for carbon monoxide in the last trimester.

For NO2, we observed a higher increase risk of stillbirth of 6.6% (EE 1.066, 95% CI 0.965 to 1.178) for the entire pregnancy. This finding is consistent with the study by Lacasana et al, which reported an increased risk of stillbirth with exposure to NO2.

Most of the pollutants in polluted ambient air, such as PM and CO, are also present in indoor air polluted by smoking and solid fuel combustion, although the concentrations are lower. Leonard-Bee et al conducted a meta-analysis of studies on the effects of secondhand smoking on the risk of stillbirth, presenting a 23% risk increase (EE 1.23, 95% CI 1.09 to 1.38). Amegah et al synthesised the effect of solid fuels showing an effect estimate of 29% for stillbirth. These findings are consistent with the present pollutant-specific summary effect estimates and thus strengthen the hypothesis that ambient air pollution increases the risk of stillbirth.

Conclusion, recommendations and implications for future research
Our results provide suggestive evidence that ambient air pollution is a risk factor for stillbirth. Pregnant women should be aware of the potential adverse effects of ambient air pollution, although the prevention against exposure to air pollutants generally requires more action by the government than by the individual. The healthcare sector can create awareness and engage other sectors contributing to ambient air pollution (such as the housing sector, transportation sector, industries and the energy sector), to develop and implement policies such as control of vehicular emissions, fuel quality improvement and control of industrial waste emission, to reduce the risk of air pollutants.

Most of the studies reviewed used data from monitoring stations to assess maternal exposure levels. Future studies should integrate the use of personal monitoring methods and also consider the activity of mothers, change in residence, air exchange, mother’s occupation and outdoor activities of the mothers. The pregnant women should also be monitored if possible from the first month of pregnancy in order to ascertain the exact period of the effect.

Acknowledgements The authors thank Svetlana Filatova, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Finland, for helping with the translation of the Russian study included in the review.

Contributors UKJK conceived the study and designed it with AKA, NS and HAB conducted the search and screened the articles, and contributed to the statistical analyses. AKA contributed to the evaluation of the manuscript, writing of the manuscript, statistical analyses and interpretation of the results. All the authors revised the manuscript for important intellectual content, and the final version has been approved by all the authors. UKJ takes responsibility for the integrity of the article.

Funding The University of Oulu strategic funds.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data needed for repeating the meta-analyses are presented in tables. Additional information on the methods or preliminary data can be requested from the corresponding author.

REFERENCES
et al.


‘Suggestive evidence’ for link between air pollution and heightened stillbirth risk

Tighter curbs on car exhaust and industrial waste and boost in fuel quality needed

There is ‘suggestive evidence’ for a link between air pollution and a heightened risk of stillbirth, indicates a summary of the available data, published online in *Occupational & Environmental Medicine*.

An estimated 2.6 million children worldwide were stillborn at 28 weeks or more in 2015, with the wide geographical variation in prevalence suggesting that most of these deaths were preventable, say the study authors.

To date, two reviews of the available evidence have pointed to a link between air pollution and stillbirth. But the strength of the association found was weak, and further evidence has since emerged, prompting the authors to carry out a systematic review of research published up to 2015.

Thirteen studies were eligible for inclusion in the summary, which found an association between exposure to air pollution—particularly during the third term of pregnancy—and a heightened risk of stillbirth.

Specifically, a 4 μg/m³ increase in exposure to small particulate matter of less than 2.5 in diameter (PM$_{2.5}$) was associated with a 2% increased risk of stillbirth, while exposure to nitrogen dioxide, carbon monoxide, PM$_{10}$ and ozone were also linked to a heightened risk.

The researchers say that differences in study design and the type of pollutant assessed, made it impossible to include all 13 studies in the final analysis, leaving three register based studies from the US and Asia.

And as a linked editorial by Dr Marie Pedersen, of the Centre for Epidemiology and Screening, University of Copenhagen, highlights, most of these previous studies were unable to take account of potentially influential factors, such as obesity, infections, alcohol, and occupation and stress, all of which have been associated with an increased risk of stillbirth.

Furthermore, most of the existing evidence relies on air monitoring data, which doesn’t adequately capture variations in levels within the same city.

Despite these caveats, the study authors conclude: “However, the existing evidence is suggestive of causality for air pollution and stillbirth without precise identification of the timing of exposure.”

But they add that further research is needed to strengthen the body of evidence available: “With the limited studies on the relevant topic, our review suggests strong priorities for future research,” they write.

“Stillbirth is one of the most neglected tragedies in global health today, and the existing evidence summarised by [the authors] deserves additional investigation,” writes Dr Pedersen.

“If the evidence of an association between ambient air population and stillbirth is confirmed in future studies, it would be of major public health importance,” she adds.
And she goes on to say that even though the size of the effect seems relatively small, the ubiquitous nature of ambient air pollution exposure suggests that exposure to it might have considerable impact on stillbirth risk at the population level.