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Review

Effects of Air Pollution on the Risk of Congenital Anomalies: A Systematic Review and Meta-Analysis

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Abstract: Congenital anomalies are the main causes of preterm and neonatal mortality and morbidity. We investigated the association between congenital anomalies and mothers’ exposure to air pollution during pregnancy by combining risk estimates for a variety of air pollutants (SO2, NO2, PM10, PM2.5, CO and O3) and anomaly defect outcomes. Seventeen articles were included in the systematic review and thirteen studies were taken into account in the meta-analysis. Combined estimated were calculated separately according to whether the exposure metric was continuous or categorical. Only one significant combination was; NO2 concentrations were significantly associated with coarctation of the aorta (OR = 1.20 per 10 ppb, 95% CI, (1.02, 1.41)). This finding could stem from strong heterogeneity in study designs. Improved exposure assessment methods, in particular more accurate spatial measurements or modeling, standardized definition of cases and of better control of confounders are highly recommended for future congenital anomalies research in this area.

Keywords: meta-analysis; congenital anomalies; exposure; air pollution
1. Introduction

Today, air pollution is a major public health concern. Due to industrial emissions, urbanization and transport of goods and people by fuel-engine motor vehicles, air pollution affects everyone in developed and developing countries. Common pollutants such as nitrogen oxide (NO$_2$), sulfur dioxide (SO$_2$), particulate matter (PM) and carbon monoxide (CO) have been shown to be associated with several adverse health events such as asthma attacks and incidence [1,2], chronic obstructive pulmonary diseases [3], cardio and cerebrovascular conditions and lung cancer [4–6], and have been reported to reduce human fertility [7]. Environmental nuisances affect all age groups. However, fetus development, newborns and infants are recognized to be more particularly vulnerable to air pollution [8–10]. Exposure of pregnant women is linked with fetal growth retardation, low birth weight [11], preterm birth and neonatal mortality [12]. Maternal exposure to air pollution may be also related to congenital anomalies. However, the evidence is still weak due to the paucity of epidemiological studies.

Congenital anomalies are recognized to be a major risk factor of stillbirth and of neonatal and infant mortality. Worldwide, an estimated 10% deaths under five-years-old children are caused by congenital anomalies [13]. European Surveillance of Congenital Anomalies (EUROCAT), an organization of population-based registries for the surveillance of congenital anomalies in Europe, recorded the perinatal death rate 9.3 per 10,000 births of all congenital anomaly between 2008 and 2012. Among them, 23.7% was due to chromosomal anomalies, 22.6% to congenital heart defects, and 17.2% to nervous system anomalies [14]. About half of all major congenital malformations are of unclear etiology and are suggested to have multifactorial causes, including environmental exposures [15].

In the past decade, the number of studies investigating the association between congenital anomalies and air pollution has increased. The potential impact of environmental exposures to congenital anomalies has been recently reviewed [16,17]. The studies concluded that exposure to NO$_2$, SO$_2$ and PM$_{2.5}$ increased significantly the risk of congenital heart diseases. Since the last 2011 review, several new studies have been published [18–23]. In this setting, updating the literature synthesis may improve our understanding of the relationship between air pollution and congenital anomalies and also of the biological process through which air pollution could lead, directly or indirectly, to these outcomes. We, therefore, conducted a meta-analysis to assess the association between air pollution and the risk of congenital anomalies. We explored whether some subtype of anomalies could be particularly concerned by air pollution. Finally, we discussed hypotheses explaining the different routes by which air pollution might increase the risk of congenital anomalies.

2. Methods

The methodology adopted has been described in detail in the previous published review [16]. Meta-analyses were conducted for a minimum number of four individual studies. We separated the data set into two categories according to the metric used for exposure assessment (continuous or categorical). Combined odds ratios were computed in order to contrast the highest with the lowest quartiles of exposure when the individual studies reported categorical exposure metrics. When exposure was expressed as a continuous variable, if quantitative descriptors for air pollutants were available, we also converted effect estimates into ORs contrasting the highest versus the lowest exposure categories [24].
Otherwise, risk estimates which had been calculated from continuous exposure metrics were expressed as unit odds ratios, corresponding to an increase of 1 microgram per cubic meter (μg/m³) for sulfur dioxide (SO₂), 10 μg/m³ for particulate matter with diameter less than 10 μm (PM₁₀) and to an increase of 1 part per million (ppm) for carbon oxide (CO), and 5 part per billion (ppb) for ozone (O₃) and 10 ppb nitrogen dioxide (NO₂). Key features and definitions of exposure of each study are detailed in Table 1.

2.1. Search Methods

A literature search was conducted in the PUBMED database in order to select articles published between January 2011 and January 2014. The search strategy followed the PRISMA guidelines [25]. The keywords used for this review were (air pollution OR traffic pollution OR outdoor pollution) AND congenital anomalies. We also used the terms “traffic pollution” and “outdoor air pollution”. Searches were restricted to English-language articles. No restriction was put on the geographical location. Abstracts of all studies were then screened manually and excluded if they were not performed on human populations and did not present original data (review articles). Full manuscripts were checked thoroughly. Seven studies were published after 2011; one was not included because its main issue did not deal with the association between congenital anomalies and air pollutants [26]. We also included the eleven articles used in the previous literature synthesis published in 2011. Overall, seventeen articles were included.

2.2. Data Extraction

We selected measures from the adjusted models presented in each study. Odds ratios and similar metrics relating outcomes and pollutants were extracted. For cohort studies, we used risk ratios since the two ratios give equivalent results when the outcome is rare. In addition, the period of exposure during the pregnancy has been taken into account since the pregnancy weeks 3–8 constitute the critical window of exposure for embryogenesis; later exposures may not contribute to the etiology of major congenital anomalies [22].

2.3. Meta-Analysis

Heterogeneity was assessed for pollutant-congenital anomaly outcomes by using the Cochrane Q-test. Fixed effect models were used when the result of the Q-test gave a heterogeneity p-value higher than 0.1. In contrast, random effects models were used for p-values lower than 0.1. Following Higgins et al. [27], a low heterogeneity was determined for I² between 25%–50%, moderate between 50%–75%, and high for >75%, where I² is defined as the percentage of variation attributable to heterogeneity. Forest plots were generated to illustrate the combined risk estimates. Statistical analysis was performed using STATA 11 (TX, USA).
Table 1. Overview of studies included in the systematic review.

| Study                | Location          | Period            | Study Design                      | Congenital Categories                                                                 | Exposure Assessment                                                                 | Exposure Variable | Air Pollutants | Results                                      | Confounders                                                                 |
|----------------------|-------------------|-------------------|-----------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------|----------------|---------------------------------------------|----------------------------------------------------------------------------|
| Gianicolo et al. 2014 | Brindisi, Italy   | 2000–2010         | Case-control, individual matching | Congenital heart defects, atrial septal defects                                        | Daily average concentration of pollutants measured by 3 monitoring stations and performed for week 3–8 of gestation | Continuous and categorical | SO₂ and TSP      | Exposure to 90th percentile of SO₂ increased risk of CHD ($p = 0.01$) and VSD ($p < 0.05$) | No adjusted confounders; cases and controls were matching for gender, socio-economic deprivation and the year of pregnancy |
| Schembari et al. 2013 | Barcelona, Spain  | 1994–2006         | Case-control, no matching         | Congenital heart defects, neural tube defects, respiratory system defects, orofacial clefts, digestive system defects, abdominal wall | Daily spatio-temporal exposure estimates over week 3–8 of pregnancy | Continuous | NO₂, NOₓ, PM₁₀, PM₂.₅, PM₅₀ₑₑ                   | Statistically significant associations ($p = 0.05$) between NO₂ and coarctation of the aorta and digestive system defects, and between PM₅₀ₑₑ and abdominal wall defects | Maternal age, socio-economic status, year of birth, conception season |
| Padula et al., 2013   | California, USA   | 1997–2006         | Case-control, no matching         | Anotia/microtia, anorectal atresia/stenosis, craniostenosis, hypospadias degree, diaphragmatic hernia, transverse limb deficiency, intestinal atresia/stenosis, amniotic band syndrome, limb body wall complex, hydrocephaly, longitudinal limb deficiency, esophageal atresia | Residence-based assignments around stations, with daily average values during first two months of were collected; a maximum interpolation radius of 50 km was used | Categorical | NO₂, NO, CO, O₃, PM₁₀, PM₂.₅                  | No significant association had been revealed                               | Maternal ethnicity, education, and early prenatal vitamin use |
| Study | Location | Period | Study Design | Congenital Categories | Exposure Assessment | Exposure Variable | Air Pollutants | Results | Confounders |
|-------|-----------|--------|--------------|-----------------------|---------------------|-------------------|---------------|---------|-------------|
| Padula et al. 2013 [19] | California, USA | 1997–2006 | Case-control, no matching | Congenital heart diseases groups (27 subtypes) | Residence-based assignments around stations, with daily average values during first two months of were collected; a maximum interpolation radius of 50 km was used | Categorical | NO, NO₂, PM₁₀, PM₂·₅, CO, O₃ | No significant association had been revealed | Maternal ethnicity, education, and vitamin use |
| Agay-Shay K et al. 2013 [21] | Tel-Aviv, Israel | 2000–2006 | Case-control, no matching | Multiple congenital heart, atrial and atrial septal defects, isolated ventricular septal defects | Weekly means of exposures during pregnancy week 3–8 according to the distance from stations to each maternal address | Continuous | NO₂, SO₂, PM₁₀, PM₂·₅, CO, O₃ | No significant association had been revealed | Infant’s sex, plurality, religion, maternal age, marital status, maternal and paternal origin, paternal age, and the season of conception |
| Padula et al. 2013 [18] | California, USA | 1997–2006 | Case-control, no matching | Neural tube defects (spina bifida and anencephaly), orofacial clefts, gastrochisis | Residence-based assignments around stations, with daily average values during first two months of were collected; a maximum interpolation radius of 50 km was used | Categorical | NO₂, NO, PM₁₀, PM₂·₅, CO, O₃ | No significant association had been revealed | Maternal ethnicity, education, and vitamin use |
Table 1. Cont.

| Study          | Location      | Period       | Study Design                          | Congenital Categories                                                                 | Exposure Assessment                                      | Exposure Variable | Air Pollutants          | Results                                                                 | Confounders                                                                 |
|----------------|---------------|--------------|---------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------|-------------------|--------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Dadvand et al. 2011 [28] | Northeast of UK 1993–2003 | Case-control, frequency matching | Cardiac chambers and connection, cardiac septa, pulmonary and tricuspid valves, aortic and mitral valves, great arteries and veins, atrial septal defect, coarctation of aorta, pulmonary valve stenosis, tetralogy of Fallot, ventricular septal defect | Weekly average of pollutants at nearest monitors to maternal residential location | Continuous | SO₂, NO₂, CO, PM₁₀, O₃ | An association between NO₂ and congenital heart diseases, ventricular septal defect, cardiac septa malformations and tetralogy of Fallot; and CO exposure to ventricular septal defect, cardiac septa malformations and with congenital pulmonary valve stenosis | Socio-economic status, degree of urbanity, and season of conception; cases and controls were matching for the year of birth |
| Dadvand et al. 2011 [29] | Northeast of UK 1985–1996 | Case-control, frequency matching | Coarctation of aorta, tetralogy of Fallot, congenital pulmonary valve stenosis, atrial septal defect, ventricular septal defect, congenital cardiac chambers and connections, congenital carida septa, congenital pulmonary and tricuspid valves, congenital aortic and mitral valves, congenital great arteries and veins | Weekly exposure levels by two stage spatiotemporal modeling at each maternal place of residence | Categorical and continuous | SO₂, black smoke | An association between maternal exposure to black smoke and cardiac chambers and connections (only when using exposure as a continuous variable) | Birth year, socio-economic status, infant sex, season of conception, and degree of urbanity; cases and controls were matching for the year of birth |
| Study | Location | Period | Study Design | Congenital Categories | Exposure Assessment | Exposure Variable | Air Pollutants | Results | Confounders |
|-------|-----------|--------|--------------|-----------------------|---------------------|-------------------|---------------|---------|-------------|
| Marshall et al. 2010 [30] | New Jersey, US | 1998–2003 | Case-control, frequency matching | Cleft lip with cleft palate, cleft palate | Average concentration of exposures at nearest monitor stations (13–20 km) | Categorical | SO₂, NO₂, CO, PM₁₀, PM₂.₅, O₃ | No significant association had been revealed | Maternal age, ethnicity, smoking and alcohol, and season of conception; cases and controls were matching with maternal residence at birth |
| Dolk et al. 2010 [31] | Wessex, North West Thames, Oxford and Northern of UK | 1991–1999 | Cohort | Anomalies of cardiac chambers, transposition of great vessels, malformations of cardiac septa, atrioventricular septal defects, tetralogy of Fallot, malformations of valves, hypoplastic left heart syndrome, great arteries and veins, coarctation of aorta | Annual mean exposure at census level in 1996 | Continuous | SO₂, NO₂, PM₁₀ | A significant association between SO₂ and tetralogy of Fallot, and between PM₁₀ and omphalocele | Maternal age, socio-economic deprivation |
Table 1. Cont.

| Study | Location          | Period       | Study Design               | Congenital Categories                                                                 | Exposure Assessment                                      | Exposure Variable                                                                 | Air Pollutants          | Results                                                                 | Confounders                                                                                     |
|-------|-------------------|--------------|----------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Hansen et al. 2009 [32] | Brisbane, Australia | 1998–2004 | Case-control, individual matching | Aortic artery and valve defects, atrial septal defects, pulmonary artery and valve defects, ventricular septal defects, conotruncal defects, endocardial cushion and mitral valve defects, cleft lip, cleft palate, cleft lip with cleft palate | Daily average exposures at 18 monitors with the majority located within a 30 km radius of city | Continuous | SO₂, NO, CO, PM₁₀ and O₃ | No significant association had been revealed | Infant sex, birth order, season of birth, maternal age, education, alcohol, and body mass index; cases and controls were matching with mother’s age, marital status, number of previous pregnancies, month of LMP, area-level SES, and distance to pollution monitor |
| Rankin et al. 2009 [33] | Northern region, UK | 1985–1990 | Case-control, no matching | Nervous system, congenital heart defects, atrioventricular septal defects, tetralogy of fallot, hypoplastic left heart, coarctation of aorta, patent ductus arteriosus, ventricular septal defect, respiratory tract, cleft lip and palate, eye, ear, face and neck, digestive system, internal urogenital system, musculoskeletal, miscellaneous | Daily average exposures during the first trimester from monitors within 10 km of maternal residence | Continuous and categorical | SO₂, black smoke | A significant association between black smoke and nervous system anomalies. | Birth weight, infant sex, and maternal deprivation |
Table 1. Cont.

| Study          | Location | Period       | Study Design                  | Congenital Categories                                                                 | Exposure Assessment                                                                 | Exposure Variable | Air Pollutants | Results                                                                                                           | Confounders                  |
|----------------|----------|--------------|-------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------|----------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Strickland et al. 2009 [34] | Atlanta, USA | 1986–2003 | Cohort                        | Transposition of the great arteries, tetralogy of fallot, pulmonary stenosis and valvar, patent ductus arteriosus, hypoplastic left heart, coarctation of aorta, atrial septal defect, secundum, ventricular septal defect, muscular, ventricular septal defect, perimembranous, conotruncal defect, Left ventricular outflow tract defect, right ventricular outflow tract defect | Average of daily concentration from one central monitoring station                    | Continuous       | SO₂, NO₂, CO, PM₁₀, and O₃ | A significant association between PM₁₀ and patent ductus arteriosus                                              | No adjusted variables        |
| Hwang et al. 2008 [24]           | Taiwan   | 2001–2003    | Case-control, no matching     | Cleft lip                                                                               | Monthly average of exposures at 72 stations by using inverse distance weighting method during the first trimester | Continuous       | SO₂, NO₂, CO, PM₁₀ and O₃ | A significant association for first and second month O₃ exposure                                                   | Maternal age, infant sex, plurality, gestational age, population density, and season of conception |
Table 1. Cont.

| Study                  | Location         | Period     | Study Design                  | Congenital Categories                                                                 | Exposure Assessment                                                                 | Exposure Variable                      | Air Pollutants | Results                                                                                                                                                                                                 |
|------------------------|------------------|------------|-------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kim et al. 2007 [35]   | Seoul, Korea     | 2001–2004  | Birth cohort                  | Not specified                                                                           | Residence based average exposure levels at each trimester from nearest monitoring stations | Continuous and categorical              | PM$_{10}$       | Congenital anomalies were influenced by exposure to PM$_{10}$                                                                                                                                          |
| Giloba et al. 2005 [36]| Texas, USA       | 1997–2000  | Case-control, frequency matching | Aortic artery and valve defects, atrial septal defects, pulmonary artery and valve defects, ventricular septal defects, conotruncal defects, endo-cardial cushion and mitral valve defects, cleft lip with cleft palate, cleft palate | Average of daily measurements based on the first closest monitor (median distance 8.6–14.2 km) | Categorical                          | SO$_2$, NO$_2$, CO, PM$_{10}$ and O$_3$ | A significant association between exposure to SO$_2$ and VSD ($p < 0.0001$), CO and tetralogy of fallot ($p < 0.0017$), PM$_{10}$ and ASD ($p < 0.0001$), SO$_2$ with ASD (0.0017) | Maternal age, ethnicity, education, marital status, illness, tobacco use, season of conception, plurality, parity, infant sex, prenatal care, and gravidity; cases and control were matching with vital status, year, maternal county of residence at delivery |
| Study          | Location     | Period        | Study Design                  | Congenital Categories                                                                 | Exposure Assessment          | Exposure Variable        | Air Pollutants | Results                                                                 | Confounders                                                   |
|---------------|--------------|---------------|------------------------------|---------------------------------------------------------------------------------------|------------------------------|---------------------------|----------------|-------------------------------------------------------------------------|----------------------------------------------------------------|
| Ritz et al. 2002 [9] | California, USA | 1987–1993    | Case-control, no matching    | Aortic defects, Pulmonary valve, Conotruncal defects, Ventricular septal defects, Multiple cardiac or cleft defect, Syndrome with cardiac or cleft defect, Isolated cleft palate, Isolated cleft lip with/without palate | 24 h average measurements every 6 days over duration of pregnancy | Continuous and categorical | CO, O₃        | No significant association had been revealed                         | Maternal age, ethnicity, education, marital status, ill, tobacco use, season of conception, plurality §, parity, decade of infant’s birth, infant sex, access to prenatal care, time since last pregnancy and birth type |

Notes: SO₂, sodium dioxide; NO, nitrogen oxide; CO, carbon oxide; PM₁₀, particulate meter with diameter ≤ 10 μm; PM₂.₅, particulate meter with diameter ≤ 2.₅ μm; O₃, ozone; TSP, total suspended particulate; CHD, congenital heart defects; ASD, atrial septal defects. § Plurality stands for multiple births (including stillbirth) after one pregnancy.
3. Results

Seventeen articles met the inclusion criteria for the systematic review, and the characteristics of each study are shown in Table 1. Three articles published in 2013 were conducted by the same research group [18–20]. We considered them as three independent studies because each dealt with different outcomes. Another team also split results into two articles [28,29]. Seven studies were conducted in the United States [9,18–20,30,34,36], four in the United Kingdom [28,29,31,33] and only one in Australia [32], in Israel [21], in Italy [23], in South Korea [35], in Spain [22] and in Taiwan [24]. Overall, twelve studies were case-control studies and five were cohort studies. One did not specify congenital subgroups and diagnosed only birth defects (n = 14); it was not included in the meta analysis [35].

Most studies used a population-based case-control design, selecting cases from clinical or autopsy reports. Controls were randomly selected from birth registries. Cases included live birth, stillbirth or termination of pregnancy after a congenital anomaly diagnosis. One study collected only newborns with diagnosis of congenital anomalies [23]. Two studies focused specifically on orofacial defects [24,30] and therefore included only cases with a diagnosis of cleft lip with or without cleft palate. Definitions of cases with single or multiple congenital defects and criteria for splitting them into sub-groups varied across studies. Cases definition used in the studies published after 2010 were mainly coded according to the International Classification of Diseases, version 9 or 10 (ICD codes). Cardiovascular anomalies were the most frequently investigated defects, followed by neuron system.

Mother residence concentration estimates from air quality monitoring networks were frequently used for exposure assessment. Average concentrations of pollutants during the first or the first two months of pregnancy were calculated from the nearest monitors. The distance from monitors to maternal residence varied among studies, from 10 km to a maximum of 50 km. Classical air pollutants were measured, i.e., SO2, NO2, PM10, PM2.5, CO and O3 in most studies. Total suspended particulate (TSP), NO, NOx and black smoke were assessed in a small number of studies. Pollutant concentration distributions are shown in Table 2.

We conducted the meta-analysis for 21 combinations of air pollutants and congenital anomalies when at least four studies were available for the same combination. Heterogeneity tests (the Q-test) indicated four combinations with high values of I^2, for which random effects models were applied. Heterogeneity varied between 0% and 93.4%, which indicated that the measurement methods, sample property and characteristics varied among and within different congenital groups.
**Table 2.** Exposure distribution in studies included in the meta analysis.

| Studies            | Case          | Air Pollutants | Control       | Air Pollutants | Total                  |
|--------------------|---------------|----------------|---------------|----------------|------------------------|
|                     | Congenital    | CHD            | SO$_2$, mean 2.9 µg/m$^3$ | CHD            | SO$_2$, mean 2.8 µg/m$^3$ | -                      |
|                     | Defects       | VSD            | SO$_2$, mean 3.2 µg/m$^3$ | VSD            | SO$_2$, mean 2.8 µg/m$^3$ | -                      |
| Gianicolo et al.    | CHD           | VSD            | SO$_2$, mean 2.9 µg/m$^3$ | VSD            | SO$_2$, mean 2.8 µg/m$^3$ | -                      |
| 2014 [23]           |               |                |               |                |                        |                        |
| Schembari et al.    | -             | IQR: NO$_2$, 12.7 µg/m$^3$ | -             | NO$_2$, IQR 11.8 µg/m$^3$ | -                      |
| 2013 [22]           |                | PM$_{10}$, 2.8 µg/m$^3$ | -             | PM$_{10}$, IQR 3.0 µg/m$^3$ | -                      |
| Agay-Shay et al.    | -             |                | Minimum, median, maximum: |                |                        |
| 2013 [21]           |                |                | SO$_2$ 0.33 ppb, 2.1 ppb, 51.4 ppb; |                |                        |
|                     |                |                | CO, 0.15 ppm, 0.9 ppm, 13.5 ppm; |                |                        |
|                     |                |                | NO$_2$ 0.2 ppb, 23.1 ppb, 104.5 ppb; |                |                        |
|                     |                |                | O$_3$ 0.45 ppb, 26.5 ppb, 128 ppb; |                |                        |
|                     |                |                | PM$_{10}$, 3.8 µg/m$^3$, 43, 3183.4 µg/m$^3$ |                |                        |
| Padula et al.       | -             |                | Minimum, median, maximum: |                |                        |
| 2013 [18]           |                |                | CO, Q1 0.13–0.39 ppm, Q4 0.72–1.37 ppm; |                |                        |
|                     |                |                | NO$_2$, Q1 2.4–13.36 ppb, Q4 20.54–638.94 ppb; |                |                        |
|                     |                |                | O$_3$, Q1 10.49–29.05 ppb, Q4 62.65–91.92 ppb; |                |                        |
|                     |                |                | PM$_{10}$, Q1 7.9–25.24 µg/m$^3$, Q4 44.09–95.32 µg/m$^3$ |                |                        |
| Dadvand et al.      | -             |                | Percentile 25- percentile 75: CO, 0.39–0.64 mg/m$^3$; |                |                        |
| 2011 [29]           |                |                | NO$_2$, 29.2–38.4 µg/m$^3$; NO$_3$, 13.3–32.5 µg/m$^3$; |                |                        |
|                     |                |                | O$_3$, 33.2–42.4 µg/m$^3$; PM$_{10}$, 20.5–30.2 µg/m$^3$ |                |                        |
| Dadvand et al.      | -             |                | Percentile 25–percentile 75: SO$_2$, 17.6–31.2 µg/m$^3$ |                |                        |
| 2011 [28]           |                |                |                        |                |                        |
| Marshall et al.     | -             | Mean: PM$_{10}$, 28.7 µg/m$^3$; NO$_2$, 2.4E–2 ppm; SO$_2$, 5.3E–3 ppm; O$_3$, 2.5E–2 ppm; CO, 0.83 ppm | Mean: PM$_{10}$, 28.1 µg/m$^3$; NO$_2$, 2.4E–2 ppm; SO$_2$, 5.1E–3 ppm; O$_3$, 2.5E–2 ppm; CO, 0.85 ppm | - |
### Table 2. Cont.

| Studies       | Case Congenital Defects | Air Pollutants | Control Congenital Defects | Air Pollutants | Total |
|---------------|-------------------------|----------------|-----------------------------|----------------|-------|
| Dolk et al.   |                         |                |                             |                | Percentile 10, median, percentile 90: SO₂, 3.87 μg/m³, 7.86 μg/m³, 14.99 μg/m³
| 2010 * [31]   |                         |                |                             |                | NO₂, 21.48 μg/m³, 35.11 μg/m³, 47.78 μg/m³
|               |                         |                |                             |                | PM₁₀, 18.84 μg/m³, 21.97 μg/m³, 26.4 μg/m³ |
| Hansen et al. |                         |                |                             |                | Minumum, mean, maximum: SO₂, 0, 1.5 ppb, 7.1 ppb; CO, 0.02 ppm, 1.1 ppm, 7.0 ppm; NO₂, 1.4 ppb, 8.2 ppb, 22.7 ppb; O₃, 4.3 ppb, 25.8 ppb, 54.4 ppb; PM₁₀, 4.4 μg/m³, 18.0 μg/m³, 151.7 μg/m³ |
| 2009 [32]     |                         |                |                             |                |       |
| Rankin et al. |                         |                |                             |                | IQR: SO₂, 4.0 ppb; CO, 0.3 ppm; NO₂, 5.7 ppb; O₃, 29.9 μg/m³; PM₁₀, 14.2 μg/m³ |
| 2009 [33]     |                         |                |                             |                |       |
| Strickland et al. |                   |                |                             |                | Minumum, median, maximum: O₃, 16.7 ppb, 26.8 ppb, 45 ppb; CO, 25 pphm, 62 pphm, 277 pphm; NOₓ, 1.0 pph, 20.2 pphb, 44.2 pphb; PM₁₀, 20.8 μg/m³, 57.2 μg/m³, 78.1 μg/m³ |
| 2009 * [34]   |                         |                |                             |                |       |
| Hwang et al.  |                         |                |                             |                |       |
| 2008 [24]     |                         |                |                             |                |       |
| Gioboa et al. |                         |                |                             |                |       |
| 2005 [36]     |                         |                |                             |                |       |

Notes: CHD, congenital heart defects; VSD, ventricular heart defects; IQR, interquartile range.; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; * indicated cohort studies, others were designed as case-control studies; “-” no information.
Regarding cardiovascular anomalies, 16 combinations of pollutants-cardiac anomalies could be included in the meta-analysis (Figures 1–3). In all, exposure was expressed as continuous variables. We found a significantly increased meta-OR for exposure to NO$_2$ and the risk of coarctation of aorta (OR per 10 ppb = 1.20, 95% CI (1.02, 1.41)), which is in accord with the previous meta-analysis [16]. For all other combinations, the combined effects were close to one and not significant.

**Figure 1.** Forest plots for combinations of ventricular septal defects and pollutant (as a continuous variable). The size of each square represents the weight that contributes to the combined effect, respectively for: (A) SO$_2$; (B) PM$_{10}$; (C) NO$_2$; (D) CO; and (E) O$_3$.
Figure 2. Forest plots for combinations of atrial septal defects and pollutant (as a continuous variable). The size of each square represents the weight that contributes to the combined effect, respectively for: (A) SO$_2$; (B) PM$_{10}$; (C) NO$_2$; (D) CO and (E) O$_3$. 
Figure 3. Forest plots for combinations of two cardiac anomalies (coarctation of aorta and tetralogy of fallot) and pollutant. The size of each square represents the weight that contributes to the combined effect. (A), (C), (E) were combined effects of coarctation of aorta and SO\(_2\), PM\(_{10}\) and NO\(_2\). (B), (D) and (F) were combined effects of tetralogy of fallot and SO\(_2\), PM\(_{10}\) and NO\(_2\).

For oro-facial clefts, seven articles were included in the meta-analysis, with one study exhibiting a statistically significant association [24]: the OR comparing the 4th with the 1st quartiles of the exposure distribution was equal to 1.40 (95% CI (1.05, 1.91)). The meta-analysis found no significant association for the four other pollutants (Figure 4A–D). In most cases, the studies on cleft lips, for which exposure was expressed on a continuous scale, were less than four, except for those exploring the effect of exposure to NO\(_2\) whose result is presented in Figure 4E also showing no significant association.
Figure 4. Forest plots for a variety of pollutants and risk of orofacial defects. (A), (B), (C) and (D) showed combined effects of PM$_{10}$, NO$_2$, CO and O$_3$; (E) was the combined effect of NO$_2$ and cleft lip from continuous exposure risk estimates.

4. Discussion

Congenital anomalies are the leading cause of neonatal mortality. The prevalence in France reported by the national health surveillance institute is equal to 3.3% [37]. In this systematic review, we assessed the effects of air pollution on the risk of congenital anomalies based on the epidemiologic literature. We compared 21 combinations of air pollutants and congenital anomalies types and only one significant result was revealed. The input data of the 21 combinations were different; it is improbable that the number of statistical tests performed explains the result. But, as all significant results, we cannot exclude that it is a chance finding. The combined risk of coarctation of aorta was found significantly associated with NO$_2$ (OR per 10 ppb = 1.20, 95% CI (1.02, 1.41)). Our meta-analysis did
not reveal any other significant association for cardiac anomalies and oral-facial defects, which is in coherence with the previous meta-analysis published in 2010 by Vrijheid et al. [16].

However, these authors revealed a significantly increased risk between exposure to NO\textsubscript{2}, SO\textsubscript{2} and the tetralogy of fallot (OR per 10 ppb NO\textsubscript{2} = 1.25, 95% CI (1.02–1.51); and OR per 1 ppb SO\textsubscript{2} = 1.04, 95% CI (1.00–1.08), respectively) and coarctation of aorta (OR per 10 ppb NO\textsubscript{2} = 1.20, 95% CI (1.00–1.44); OR per 1 ppb SO\textsubscript{2} = 1.04; 95% CI (1.00–1.08)). We did not undertake the meta-analysis for these combinations because the number of studies was small. In the present work, we chose to realize two-separate meta-analyses according to the type (continuous or categorical) of the exposure variable, not to introduce too much heterogeneity in the meta-estimates, whereas Vrijheid et al. converted all continuous to categorical variables in order to increase their statistical power.

The present meta-analysis has several limitations. The first one deals with the sample size. Most of the combined effects were computed with about five studies; we did not try to compute combined effects for less than four studies. There was, however, a large total number of cases included in the meta-analysis (varying from 588 to 3874 according to the air pollutant-congenital anomaly combination), that provided enough statistical power to reveal significant associations. The numbers of cases and controls of each study are reported in Tables 3–7. We calculated the statistical power (a fixed alpha-risk = 5%) for the smallest sample size (Table 7) and the highest (Tables 5 and 6). With a statistical power equal to 90%, we will detect a statically significant health effect equal to 18% and 25% from the smallest and the highest sample size, respectively; note that, due to the small number of cases counted in the highest sample size (about 600 cases among a population of about 1.5 million because of the cohort studies include in the meta analysis), a smaller effect could be found significant from the smallest sample size. The statistical power will fall to 70% and 60% (respectively, in the smallest and highest samples sizes) to reveal a significant increase of the risk equal to 10%.

Secondly, we found differences in the methodologies adopted in the 17 individual studies included in the present review, which make difficult the comparisons and assessment of the combined effects. Certain studies relied on measurement of air quality at the birth residence [9,28–33,36], which is not necessarily the address during early pregnancy (the critical window time) and hence may lead to misclassification of exposure for several pregnant women. In addition, without distance-weighted calculation in the exposure assessments, the range of distance between maternal place and the nearest monitoring station may produce uncertain exposure estimates and thus lead also to exposure misclassification.
Table 3. Numbers of ventricular septal defects cases and number of controls in studies included in the meta analysis for 5 pollutants: SO$_2$, PM$_{10}$, NO$_2$, CO, O$_3$.

| Numbers of cases and controls exposed under various pollutants among different studies | Gianicolo et al. 2014 [23] | Schembari et al. 2013 [22] | Agay-Shay et al. 2013 [21] | Dadvand et al. 2011 [29] | Strickland et al. 2009 [34] | Hansen et al. 2009 [32] | Ritz et al. 2002 [9] | Total Number |
|---------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|--------------|
| SO$_2$                          | 40                   | 150                  | -                    | -                    | 493                  | 130,402              | 1154                 | 4616         | 1654        | 713,846     | 222                   | 1110                 | 235                   | 9049               | 3798                  | 859,173               |
| PM$_{10}$                       | -                    | -                    | 106                  | 903                  | 493                  | 130,402              | 1154                 | 4616         | 1654        | 713,846     | 222                   | 1110                 | 235                   | 9049               | 3864                  | 859,926               |
| NO$_2$                          | -                    | -                    | 351                  | 2869                 | 493                  | 130,402              | 1154                 | 4616         | 1654        | 713,846     | 222                   | 1110                 | -                     | -                   | 3874                  | 852,843               |
| CO                              | -                    | -                    | -                    | -                    | 493                  | 130,402              | 1154                 | 4616         | 1654        | 713,846     | 222                   | 1110                 | -                     | -                   | 3523                  | 849,974               |
| O$_3$                           | -                    | -                    | -                    | -                    | 493                  | 130,402              | 1154                 | 4616         | 1654        | 713,846     | 222                   | 1110                 | -                     | -                   | 3523                  | 849,974               |

Table 4. Numbers of atrial septal defects cases and number of controls in studies included in the meta analysis for 5 pollutants: SO$_2$, PM$_{10}$, NO$_2$, CO, O$_3$.

| Numbers of cases and controls exposed under various pollutants among different studies | Schembari et al. 2013 [22] | Agay-Shay et al. 2013 [21] | Dadvand et al. 2011 [29] | Strickland et al. 2009 [34] | Hansen et al. 2009 [32] | Ritz et al. 2002 [9] | Total Number |
|---------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|--------------|
| SO$_2$                          | -                    | -                    | 534                  | 130,402              | 274                  | 1096                 | 379         | 715,121     | 127        | 635          | -                   | -                   | 1314                  | 847,254               |
| PM$_{10}$                       | 106                  | 903                  | 534                  | 130,402              | 274                  | 1096                 | 379         | 715,121     | 127        | 635          | -                   | -                   | 1420                  | 848,157               |
| NO$_2$                          | 229                  | 2869                 | 534                  | 130,402              | 274                  | 1096                 | 379         | 715,121     | 127        | 635          | -                   | -                   | 1543                  | 850,123               |
| CO                              | -                    | -                    | 534                  | 130,402              | 274                  | 1096                 | 379         | 715,121     | 127        | 635          | 385                 | 300                 | 1699                  | 850,254               |
| O$_3$                           | -                    | -                    | 534                  | 130,402              | 274                  | 1096                 | 379         | 715,121     | 127        | 635          | 385                 | 300                 | 1699                  | 850,254               |
Table 5. Numbers of coarctation of aorta cases and number of controls in studies included in the meta analysis for 3 pollutants: SO$_2$, PM$_{10}$, NO$_2$.

| Pollutants | Schembari et al. 2013 [22] | Dadvand et al. 2011 [29] | Dadvand et al. 2011 [28] | Dolk et al. 2010 [31] | Strickland et al. 2009 [34] | Total Number |
|------------|-----------------------------|--------------------------|--------------------------|------------------------|-----------------------------|--------------|
| SO$_2$     | -                           | -                        | 125                      | 500                    | 127                         | 759,817      |
| PM$_{10}$  | 28                          | 890                      | 125                      | 500                    | 176                         | 715,225      |
| NO$_2$     | 69                          | 2869                     | 125                      | 500                    | 176                         | 711,050      |

Table 6. Numbers of tetralogy of fallot cases and number of controls in studies included in the meta analysis for the 3 pollutants: SO$_2$, PM$_{10}$, NO$_2$.

| Pollutants | Schembari et al. 2013 [22] | Dadvand et al. 2011 [29] | Dadvand et al. 2011 [28] | Dolk et al. 2010 [31] | Strickland et al. 2009 [34] | Total Number |
|------------|-----------------------------|--------------------------|--------------------------|------------------------|-----------------------------|--------------|
| SO$_2$     | -                           | -                        | 126                      | 504                    | 140                         | 715,201      |
| PM$_{10}$  | 17                          | 890                      | 126                      | 504                    | 146                         | 715,201      |
| NO$_2$     | 49                          | 2650                     | 126                      | 504                    | 146                         | 620,050      |

Table 7. Numbers of cleft lip cases and number of controls in studies included in the meta analysis for 4 pollutants: PM$_{10}$, NO$_2$, CO, O$_3$.

| Pollutants | Padula et al. 2013 [18] | Marshall et al. 2010 [30] | Hwang et al. 2008 [24] | Gilboa et al. 2005 [36] | Total Number |
|------------|--------------------------|---------------------------|------------------------|-------------------------|--------------|
| PM$_{10}$  | 75                       | 200                       | 92                     | 12,925                  | 653          | 3450         | 1110        | 23,105      |
| NO$_2$     | 59                       | 205                       | 92                     | 12,925                  | 653          | 3237         | 1089        | 22,897      |
| CO         | 45                       | 157                       | 92                     | 12,925                  | 653          | 3309         | 1083        | 22,921      |
| O$_3$      | 73                       | 201                       | 92                     | 12,925                  | 653          | 3594         | 1123        | 23,250      |
Different classifications of congenital anomalies also yield some heterogeneity. Specific definition of defects could ease detection of significant associations. Ventricular septal defects are the most common congenital subgroups that were studied and a variety of classifications were found. For example, ventricular septal defects were classified into three subgroups (ventricular septal defects-permembranous, muscular and conov) in the Padula et al. study [19], according to the classification proposed by Botto et al. [38], whereas in others they used two subgroups (ventricular septal defect, muscular and permembranous) [31] or only one global group [21,29,32,36]. Another example is the subcategory “conotruncal defect”: four studies used this outcome category to include other cardiovascular malformations, such as “tetralogy of fallot”, “transposition of the great arteries”, truncus arteriosus communis, “double outlet right ventricle” or “aorticopulmonary window” [9,31,32,36]; while, tetralogy of fallot and transposition of the great arteries were considered as an event in most other studies.

Confounding factors included in the individual studies are an additional problem. Few confounders, such as smoking [39], parental occupation [40], maternal age [41] and season conception [42] have been addressed in congenital anomalies research. Season and maternal age at conception were the most frequent confounders considered in the studies included in the present work. Seasonal variations of congenital anomalies incidence have been well described, with a higher risk in summer than in winter [42]. The association between maternal age and the risk of non-genetic congenital anomalies is still unclear. Previous studies analyzing the EUROCAT database found that teenage mothers were at higher risk but not older mothers (35–44 years). However, among European countries, the maternal age patterns are less clear. This suggests the influence of social factors, exposures or living habits, which might be associated with maternal age [41]. The prevalence of congenital anomalies is related to the social status, with higher values in deprived categories [43]. Now, few studies have addressed socioeconomic status/deprivation as confounders or effect modifiers [22,27,28,36]. One study matched cases and controls according to a neighborhood socioeconomic deprivation index but without considering other confounders in the statistical analysis [23]. One may consider that socioeconomic deprivation would constitute a good approximation of well-known risk factors of congenital abnormalities such as smoking habits or educational level. The wide range of confounders considered in the individual studies included in the present review might introduce heterogeneity when combining the data. Because of these limitations, this meta-analysis could detect only few significant associations between air pollution and birth defects; however it does not mean that the hypothesis should be definitively disregarded.

The different methods used in the studies, such as case and control definition, exposure assessment and confounding factors as all mentioned earlier, could damage the quality level of each study included in the meta-analysis and consequently the quality of the combined estimates. Assessing the quality of studies is important to understand properly each study to be used in meta analysis. It would be interesting to use the Newcastle-Ottawa Scale (NOS) [44] followed by quality score analysis as recommended by Detsky et al. [45] in order to assess the quality of each study. Then, including only studies with the highest quality score in the meta-analyses, we could measure more precisely the impact of the study quality on the point estimates. However, due to the limited number of studies in our meta-analyses, it was not possible to conduct this procedure.
Language selection may also bias the data basis. Non-English publications of relevant articles may have been ignored. Moreover, the risk of publication bias is inherent in systematic literature review. Unpublished results (probably, more likely to bear not significant results and the grey literature, which is not available on open sources) may distort the meta-analysis findings. So far, the two meta-analyses (the one published in 2010 and the present one) tend to suggest an adverse effect of air pollution on at least one type of birth defects, and this call for further studies in order to confirm the finding. We failed to assess publication bias by using funnel plots. According to the recommendations from Cochrane Handbook for Systematic Reviews of Interventions [46], there should be at least 10 studies in the meta-analysis to distinguish real asymmetry.

Air pollutants could directly exert adverse effects as pro-oxidants binding to lipid and proteins, therefore promoting oxidative stress and the production of free radicals, a process that may elicit a variety of diseases or defects [47]. This oxidative stress caused by air pollution during pregnancy has been pointed out in some studies [48,49]. In addition, there is recent evidence that air pollutants can contribute to epigenetic changes, including alteration of DNA methylation [50]. MicroRNA has been also studied with regard of the environmental changes and there is evidence that microRNA expression and regulation may be affected by environmental exposures, such as air pollution, smoking and heavy metal accumulation [51]. Such epigenetic modifications during pregnancy could impair normal embryo development and lead to birth defects.

5. Conclusions

Air pollution is a universal issue. Therefore, a small increase in risks may lead to serious public health problems. Congenital anomalies are the main causes of preterm and neonatal mortality and morbidity. Meta-analysis is an appropriate tool to enhance statistical power in the analysis of weak associations. It might shed new light on the association between air pollution and congenital anomalies insofar as new studies are conducted that overcome the limitations discussed in the present literature review. Improved exposure assessment methods, in particular more accurate spatial measurements or modeling, standardized definition of cases and accommodation of known or putative confounders are highly recommended for future congenital anomalies research on the effect of air pollution.

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Author Contributions

Esther Chen has conducted the statistical analysis and written the article under the supervision of Séverine Deguen. Séverine Deguen, coordinator of research projects dealing with environmental exposure related to social health inequalities including the congenital malformation, insured the good realization of the statistical analysis and their interpretation; she contributed also to the written of the article. Cindy Padilla and Denis Zmirou re-read the article and contributed to its improvement.
Conflicts of Interest

The authors declare no conflict of interest.

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