Adverse Birth Outcomes Related to NO$_2$ and PM Exposure: European Systematic Review and Meta-Analysis

Valentin Simoncic 1,*, Christophe Enaux 1, Séverine Deguen 2,3 and Wahida Kihal-Talantikite 1

1 LIVE UMR 7362 CNRS (Laboratoire Image Ville Environnement), University of Strasbourg, 67000 Strasbourg, France; christophe.enaux@live-cnrs.unistra.fr (C.E.); wahida.kihal@live-cnrs.unistra.fr (W.K.-T.)
2 EHESP School of Public Health, 35043 Rennes, France; Severine.Deguen@ehesp.fr
3 Department of Social Epidemiology, Institut Pierre Louis d’Epidémiologie et de Santé Publique (UMRS 1136), Sorbonne Universités, UPMC Univ Paris 06, INSERM, 75646 Paris, France
* Correspondence: valentin.simoncic@live-cnrs.unistra.fr; Tel.: +33-626369642

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Abstract: There is a growing number of international studies on the association between ambient air pollution and adverse pregnancy outcomes, and this systematic review and meta-analysis has been conducted focusing on European countries, to assess the crucial public health issue of this suspected association on this geographical area. A systematic literature search (based on Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRISMA, guidelines) has been performed on all European epidemiological studies published up until 1 April 2020, on the association between maternal exposure during pregnancy to nitrogen dioxide (NO$_2$) or particular matter (PM) and the risk of adverse birth outcomes, including: low birth weight (LBW) and preterm birth (PTB). Fourteen articles were included in the systematic review and nine of them were included in the meta-analysis. Our meta-analysis was conducted for 2 combinations of NO$_2$ exposure related to birth weight and PTB. Our systematic review revealed that risk of LBW increases with the increase of air pollution exposure (including PM$_{10}$, PM$_{2.5}$ and NO$_2$) during the whole pregnancy. Our meta-analysis found that birth weight decreases with NO$_2$ increase (pooled beta = −13.63, 95% confidence interval (CI) (−28.03, 0.77)) and the risk of PTB increase for 10 µg/m$^3$ increase in NO$_2$ (pooled odds ratio (OR) = 1.07, 95% CI (0.90, 1.28)). However, the results were not statistically significant. Our finding support the main international results, suggesting that increased air pollution exposure during pregnancy might contribute to adverse birth outcomes, especially LBW. This body of evidence has limitations that impede the formulation of firm conclusions. Further studies, well-focused on European countries, are called to resolve the limitations which could affect the strength of association such as: the exposure assessment, the critical windows of exposure during pregnancy, and the definition of adverse birth outcomes. This analysis of limitations of the current body of research could be used as a baseline for further studies and may serve as basis for reflection for research agenda improvements.

Keywords: systematic review; meta-analysis; birth weight; low birth weight; preterm birth; exposure; air pollution; PM; NO$_2$

1. Introduction

Low birth weight (LBW) is defined by the World Health Organization (WHO) as birth weight less than 2500 g (referenced P07.0–P07.1 in the 10th revision of the international classification of diseases–ICD 10) [1]. In addition, preterm birth (PTB) is defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation (referenced P07.2–P07.3 in ICD 10). The WHO estimated...
that between 15% and 20% of births worldwide are LBW, representing 20 million births a year [1]. On the other hand, it is estimated that more than 15 million babies are born preterm every year, more than 1 in 10 babies around the world [2]. In developed countries, PTB rates have been reported to range from 5% to 7% of live births [3]. Moreover, these figures appear to be on the rise [4]. For European countries, according to the European Perinatal Health Report, low birthweight babies accounted for less than 4.5% of all births in Iceland, Sweden, Finland, etc. and around 10% in Spain, France, etc. [5]. The percentage of low birthweight babies was significantly higher in 2015 compared with 2010 in some countries. Comparisons in the preterm birth rate in 2010 and 2015 differed widely between countries significantly higher in 8 countries.

The consequences of LBW and PTB include fetal and neonatal mortality, and morbidity (60% to 80% of all neonatal deaths [6]), poor cognitive development and an increased risk of chronic diseases later in life [7–9]. Recent studies have demonstrated that LBW will increase the risk of diabetes and cardiovascular disease later in life (reduction in risk per kg increase in birthweight in both men: hazard ratio (HR) = 0.88, 95% confidence interval (CI): 0.84–0.91, and women: HR = 0.88, 95% CI: 0.82–0.95 [10]). PTB has long-term adverse consequences for health, too. It is well documented that children who are born prematurely are more likely to present cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared to children born at term [2,11–18]. Complications related to PTB are the leading cause of death for children under 5 years old, causing an estimated 1 million deaths worldwide in 2015 [6,19]. Therefore, with a range of both, short- and long-term consequences, LBW and PTB represent still today a major public health issue. Additionally, adverse consequences related to LBW and PTB contribute largely to the global health costs [1,19–22]. According to the European Union (EU) benchmarking report 2009/2010, the statistical data collected from 14 European countries demonstrate the significant and growing cost of prematurity in Europe. For instance, in Denmark each preterm birth cost near 55,460 euros for premature treatment and in France prematurity cost more than 1.5 Billion euro each year. [23].

Risk factors of PTB and LBW are still not completely understood, although the etiology is thought to be multifactorial [2]. It remains unclear whether these adverse outcomes could result from determinants which act independently or in combination. These factors include medical conditions of the mother or fetus, genetic influences, infertility treatments, behavioral and socioeconomic factors, iatrogenic prematurity, and environmental exposure [4,24,25]. Epidemiological studies indicate that currently the ambient air pollution could constitute an important environmental public health issue for individual and public health point of view [26]. In the last decade, a growing body of evidence has associated exposure to ambient air pollution, mainly particulate matter (PM) and nitrogen dioxide (NO₂), during pregnancy with adverse pregnancy outcomes, especially fetal growth and gestational duration [27–33]. Pregnancy may constitute a particular period of high susceptibility to pollutants contained in air pollution because of a high level of cell proliferation, organ development and the changing capabilities of fetal metabolism [34]. Molecular studies have provided reasonable biological mechanisms for the association between air pollution and fetal growth and development [35,36]. Ambient air pollution exposure is hypothesized to affect the fetus either directly through trans-placental exposure or indirectly by affecting physiological changes in the mother [37]. Although effects of ambient air pollution on general population, and on pregnancy specifically are relatively small, larger population attributable health risks may be expected due to the ubiquitous nature of ambient air pollution exposure and because all the population is in contact with ambient air and so all the population can be considered at risk [26]. Therefore, it is important that appropriate policies are adopted to diminish ambient air pollution emissions and to raise the awareness of pregnant women [38]. According to the WHO, the goal is to achieve a 30% reduction of the number of infants born with a weight lower than 2500 g by the year 2025 [39]. This would translate into a 3.9% relative reduction per year between 2012 and 2025 and a reduction from approximately 20 million to about 14 million infants with low weight at birth [1].

Based on this evidence, several environmental public health measures have been adopted and implemented at the individual and population level to improve the quality of ambient air, such as
promoting cleaner fuel sources and energy technologies, promoting smarter urban planning that aims to reduce urban density and traffic-related pollution, etc. [40]. So far, environmental policies designed to reduce air pollution issue have shown to be effective, with health benefits and helping to reach health policy objectives [41,42]. For instance: Japanese legislation has limited transportation-related emission since 2001. The average NO\textsubscript{2} concentration decreased from 30 to 21 ppb and PM\textsubscript{2.5} concentrations decreased from 38 to 26 mg/m\textsuperscript{3}. These reductions respectively led to 1.1% and 0.6% lower prevalence of pediatric asthma [43].

To date, Health Impact Assessments (HIA) are recognized to play a crucial role in evaluating different policy scenarios for reducing air-pollution levels; in assessing new air-quality directives; or in calculating the external monetary costs of air pollution or the benefits of preventive actions [44,45]. More precisely, an HIA in this field provides the number of health events attributable to air pollution in the target population [45] and, thereby, in our case, quantifies the air pollution burden of disease due to adverse birth outcomes as preterm birth and low birth weight complications in Europe [46]. Assessment of environmental burden of disease enable the identification of policy priorities. To implement a HIA, several data sources are needed, including the dose-response function; this function derives from epidemiological studies assessing statistical indicator as relative risk associated with the modelled and observed exposure [47]. In our case, this relative risk may come from Europe based meta-analysis providing pooled estimates. One substantial input of meta-analysis is to offer estimates within a specific vulnerable population as well as a closer match with the geographical context of exposure [48]. More often, the dose–response curve linking air pollution and health impacts is supposed to be linear which means that reductions in air-pollution levels, will have consequences for health effects independently to the starting point on the curve. Therefore, this linear relationship cannot capture the different level of an individual’s susceptibility to air pollution [49,50]. It is a reason why preventive action aimed at reducing air-pollution levels in general and not only focusing on air-pollution peaks. Focusing on the peaks of air pollution would only prevent a small number of health events [45].

Recently, there has been a growing number of studies investigating the relationship between adverse birth outcomes, as PTB and LBW, and air pollutant concentration. The possible effect of air pollution exposures on birth outcomes has been reviewed in several systematic reviews and meta-analyses [26,37,48,51–58]. To the best of our knowledge, no European systematic review was performed to consider more homogeneous level of exposure to air pollution. The European Union and WHO have drafted a legislative framework which establishes health-based standards and objectives for several air pollutants. For instance, the threshold for the particulate matter (PM\textsubscript{10}) concentrations is 40 μg/m\textsuperscript{3} on 1 year, for PM\textsubscript{2.5} 25 μg/m\textsuperscript{3} on 1 year, for NO\textsubscript{2} 40 μg/m\textsuperscript{3} on 1 year and for SO\textsubscript{2} it is 125 μg/m\textsuperscript{3} on 24 h, these regulations differ from one continent to another. In this way, the average concentration of various air pollutants differs from one country to another. For instance, the level of exposure to annual average concentration of NO\textsubscript{2} in the countries of the world, between 2000 and 2015 varied from 97 μg/m\textsuperscript{3} (NYC, USA) and 55 μg/m\textsuperscript{3} (Beijing, China) into 35 μg/m\textsuperscript{3} (Paris, France) and 26.1 μg/m\textsuperscript{3} (Valencia, Spain) [59–62].

In this setting, updating the literature synthesis of European studies may improve our understanding of the relationship between air pollution, and PTB (as well as LBW). Therefore, we conducted a meta-analysis to assess the association between air pollution and the risk of PTB and LBW, separately, in order to suggest future directions for European research and public health policies.

Our work investigated the following epidemiological question: among newborn in European countries, is air pollution exposure of women during pregnancy significantly related to a risk of adverse birth outcome including weight and term of birth in observational studies?

We focused our analysis only the European studies which investigated the relationship between PM and NO\textsubscript{2} and birth outcome—LBW and PTB—in order to produce an appropriate dose-response function within a specific European population as well as a closer match with the geographical context of exposure. Therefore, our European meta-analysis could go beyond the main limitation of HIAs performed today to quantify the environmental burden of disease.
2. Materials and Methods

2.1. Search Strategy

The systematic literature search was conducted with the PubMed platform in order to access to the Academic Search Complete databases and Medline, among articles published up until 1 April 2020. The search strategy followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [63] and was performed with the following keywords found in article titles and/or abstract:

“ambient air pollution” OR “outdoor air pollution” OR “atmospheric air pollution” AND “birth outcomes” OR “pregnancy outcomes” OR “low birth weight” OR “birth weight” OR “low-birth-weight” OR “birthweight” OR “birth-weight” OR “preterm birth” OR “gestational age” OR “LBW” OR “PTB” AND “Europe” OR “European” OR “Austria” OR “Belgium” OR “Bulgaria” OR “Croatia” OR “Cyprus” OR “Czech Republic” OR “Denmark” OR “Estonia” OR “Finland” OR “France” OR “Germany” OR “Greece” OR “Hungary” OR “Ireland” OR “Italy” OR “Latvia” OR “Lithuania” OR “Luxembourg” OR “Malta” OR “Netherlands” OR “Poland” OR “Portugal” OR “Romania” OR “Slovakia” OR “Slovenia” OR “Spain” OR “Sweden” OR “United Kingdom”

2.2. Studies Selection Strategy

Figure 1 summarizes the different steps of the selection process, in line with PRISMA recommendations.

At the first step, the inclusion criteria were human studies, peer-reviewed papers written in English and articles published after 1998.

We restricted our systematic review on geographical location with European study only—for the reason described above—on the pregnant women and pregnancy outcomes, and on ambient air pollution. Papers presenting non-original studies were ultimately excluded.

At the second step, the inclusion criteria were specific pregnancy outcomes definitions including birthweight, low birth weight, preterm birth or small for gestational age (SGA). Secondary criteria were studies investigated specific outdoor air pollutants measured including NO\textsubscript{2}, PM\textsubscript{10}, PM\textsubscript{2.5}.

Two authors (VS and WK) independently screened the papers based on information in the title, abstracts and full manuscripts to select those papers considered relevant based on the screening criteria described below.

At the last step, to perform meta-analysis, among articles included according to the inclusion criteria for the systematic literature review, the inclusion criteria were studies with measure of association between pollutant concentration and birth outcome.

In the last step, bibliographic reference lists of all included studies were searched manually to identify additional studies cited by the previous references.

Finally, meta-analysis was not performed when less than four studies were available for measures of association between a given outcome and a pollutant. Consequently, of the 14 articles included in this systematic literature review, 4 were excluded according to the inclusion criteria for the meta-analysis. Finally, 10 articles were included in the meta-analysis.
Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 Flow Diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6: e1000097. doi:10.1371/journal.pmed1000097 [63].

2.3. Data Extraction

For each study, we extracted and reported in several tables the following information:

- General information: first author’s name, country of origin and date of study;
- Main study characteristics: study design, period, location, statistical methods, population size, main findings (related to PTB, LBW, BW, SGA outcomes and NO$_2$, PM$_{10}$, and PM$_{2.5}$ only);
- Participants’ characteristics: information on confounders, exposure measure;
- Outcome measures (definition, outcomes classification and source).

Assessments of association including odds ratios (ORs), hazard ratios (HRs), relative risks (RRs) and other metrics measuring the strength of association between outcomes and exposure to different pollutants including NO$_2$, PM$_{10}$, PM$_{2.5}$ were extracted. When several measures of association were available, we reported those one from the fully adjusted models.

The two authors (VS and WK) independently extracted all data from selected studies.
2.4. Meta-Analysis

When at least four studies were available, the pooled estimate between pregnancy outcomes and exposure to air pollutant was computed. Studies’ risk and beta estimates were expressed as unit corresponding to an increase of 10 \( \mu g/m^3 \). A fixed or random model based on the Cochran Q-test, the I-square statistic, and the associated p-value, was used to obtain the combined effect. The level of heterogeneity between studies is quantified with the I-square indicator \( (I^2) \). When the Cochran Q-test do not reveal significant heterogeneity between studies, a fixed model was applied; inversely, a random model was implemented when the Cochran Q-test was significant. Q-test value between 25% and 50% correspond to a low level of heterogeneity, between 50% and 75% a medium level of heterogeneity and >75% corresponds to a high level of heterogeneity. Forest plots were used to visualize the combined risk estimates. Statistical analysis was performed using the STATA 11 software.

3. Results

3.1. Studies Selected for Review

In accordance with criteria summarized in Figure 1, in all 134 published selected, a total of 84 studies were excluded based on titles. At the second step, titles of the 134 were screened by two authors (VS and WK) independently. A total of 84 studies were excluded based on the criteria described above. At the third step, the abstracts of the remaining 50 articles (of the 134 articles initially selected) were thoroughly read independently by two experts (VS and WK, authors of this article); 16 were then excluded following criteria described above.

Full manuscripts of the remaining 30 articles (of the 134 articles initially selected) were thoroughly read and 16 articles were excluded. Finally, a total of 14 articles were included according to the inclusion criteria for the systematic literature review. Finally, bibliographic reference lists of all included studies were searched manually to identify additional studies cited by the previous references. No additional article was found. Selected studies are defined in Table 1.

In order to perform a meta-analysis, studies were excluded where there was with a measure of exposure not expressed as a pollutant concentration (for instance: exposed/not exposed) or without measure of association, or when the outcome or the exposure (NOx in summer season) was not pertinent for the meta-analysis.

At last, meta-analysis was performed when at least four studies were available for measures of association between a given outcome and a pollutant. Consequently, of the 14 articles included in this systematic literature review, 4 were excluded according to the inclusion criteria for the meta-analysis. Finally, 10 articles were included in the meta-analysis.
Table 1. Main characteristics of the selected studies, order by year of publication.

| Authors                        | Study Design, Period Location | Population Size | Outcomes           | Pollutants | Statistical Methods | Confounders/Stratification                                                                 | Main Findings                                                                                     |
|--------------------------------|-------------------------------|-----------------|--------------------|------------|---------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Maroziene and Grazuleviciene, 2002, [64] | Population based study, Kaunas (Lithuania), 1998 | 3988 newborns | LBW (<2500 g), PTB (<37 w) | NO₂ | Multivariate logistic regression | - Maternal characteristic: parity, age, marital status, education, maternal and paternal smoking, birth characteristics: gestational age, others season of birth | Results suggest significant association between NO₂ exposure during first trimester and PTB risk. |
| Lee et al., 2008, [65]          | Time-series analysis London (United Kingdom), 1988–2000 | 482,765 newborns | PTB (<37 w) | PM₁₀      | Regression model      | - Other: temperature, rainfall, sunshine, relative humidity, barometric pressure, largest drop in barometric pressure | No significant association had been revealed.                                                    |
| Slama et al., 2007, [66]        | cohort, Munich (Germany) Jan 1998–Jan 1999 | 1016 newborns | Birth weight (<3000 g) | PM₂.₅ NO₂ | Poisson regression, | - Maternal characteristic: gestational duration, sex, smoking, height, weight, and education | Significant association between increase only in exposure to PM₂.₅ and decrease in term birth weight mainly during the third trimester. |
| Aguilera et al., 2009 [67]     | Cohort study, Sabadel (Spain), between June 2004 and July 2006 | 570 newborns | Birth weight | NO₂ | Linear regression models | - Maternal characteristic: tobacco smoking during pregnancy, Passive smoking during pregnancy, parity, education, race/ethnicity, age, gestational age, height, pre-pregnancy weight, birth characteristics: child’s sex, others: season of conception, Paternal height, paternal weight. | Significant association between birth weight exposure to NO₂. |
| Authors               | Study Design, Period Location                     | Population Size | Outcomes                          | Pollutants | Statistical Methods                          | Confounders/Stratification                                                                 | Main Findings                                                                 |
|----------------------|--------------------------------------------------|-----------------|-----------------------------------|------------|---------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Ballester et al., 2010, [68] | Prospective birth cohort, valencia (Spain), April, June and Nov 2004 and Feb 2005. | 785 newborns 51 PTB | Birth weight, length, head circumference, SGA | NO$_2$     | Generalized additive models                | - Maternal characteristic: lifestyle variables twice during their pregnancy, maternal age, pre-pregnancy weight, height, gestational weight gain, parity, education, smoking during pregnancy, country of origin, season of last menstrual period <br>- birth characteristics: sex, neighborhood characteristics: socio-demographic characteristics, others: environmental exposure, paternal height | Significant association between NO$_2$ exposure during the first trimester with birth weight. Significant association between NO$_2$ exposure during first and second trimester and SGA. |
| Llop et al., 2010, [69]     | Cohort study, Valencia (Spain), February 2004 June 2005. | 785 newborns 47 PTB | PTB (<37 w)                        | NO$_2$     | Multivariate logistic regression model and multivariate segmented logistic regression model | - Maternal characteristic: age, pre-pregnancy weight, parity, educational level, socioeconomic status, country of origin, working status, cohabitation with the baby's father, smoking, and the consumption of coffee and alcohol during pregnancy <br>- birth characteristics: sex, neighborhood characteristics: place of residence, others season of last menstruation | Significant association between PTB and NO$_2$ exposure during second, third trimester and entire pregnancy only when women were exposed to NO$_2$ levels higher than 46.2 µg/m$^3$. |
Table 1. Cont.

| Authors                        | Study Design, Period Location | Population Size | Outcomes          | Pollutants | Statistical Methods | Confounders/Stratification                                                                 | Main Findings                                                                 |
|--------------------------------|-----------------------------|----------------|------------------|------------|-------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Madsen et al., 2010 [70]       | Medical Birth Registry based study, Oslo (Norway), 1999–2002 | 25,229 newborns 303 LBW 2422 SGA | Birth weight, LBW (term, <2500 g), SGA | NO₂, PM₁₀, PM₂.⁵ | Logistic regression models, and general linear regression models | - Maternal characteristic: gestational length in weeks, education, smoking status, ethnicity, age, parity. birth characteristics: sex | No significant association had been revealed. |
| Estarlich et al., 2011, [71]   | Multicenter cohort, Spain, November 2003-February 2008 | 2337 newborns | Birth weight | NO₂ | Linear regression models | - Maternal characteristic: age, height, pre-pregnancy weight, pre-pregnancy body mass index (BMI), weight gain, education, working status, socioeconomic status, country of origin, cohabitation with the father of the baby, smoking, and environmental tobacco exposure], paternal height birth characteristics: infant sex - neighborhood characteristics: type of zone (urban vs. rural), - others: season of last menstrual period. | Invers but non-significant association between Increase in NO₂ during the second trimester and reduction of birth weight. |
| Rahmalia et al., 2012, [72]    | Cohort study, Potters, Nancy (France), February 2003-January 2006 | 1154 newborns | Birth weight, NO₂ | NO₂, PM₁₀ | Linear regression models | - Maternal characteristic: height, pre-pregnancy weight, parity, age at end of education, second trimester smoking, active smoking; birth characteristics: gestational duration, infant sex, - others: season of last menstrual period, center of recruitment | No significant associated had been revealed. |
### Table 1. Cont.

| Authors                  | Study Design, Period Location | Population Size | Outcomes | Pollutants | Statistical Methods | Confounders/Stratification | Main Findings                                                                 |
|--------------------------|-------------------------------|-----------------|----------|------------|--------------------|-----------------------------|------------------------------------------------------------------------------|
| Pedersen et al., 2013 [73]| Multicenter cohort study, 11 European country, February 1994–June 2011 | 74,178 newborns 1257 LBW | Term LBW (>37 w And <2500 g) Birth weight | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Logistic regression models linear regression models | - Maternal characteristic: parity, active smoking, and education birth characteristics: sex | Significant association between increased risk of low birthweight at term and PM$_{2.5}$ exposure. |
| Schifano et al., 2013 [74]| Time series analysis, Rome (Italia), 2001–2010 | 132,691 newborns 847 PTB (22–32 w) 6412 PTB (33–36 w) | PTB (>22 <36 w) | PM$_{10}$ NO$_2$ | Poisson generalized additive model | - Maternal characteristic: Socio-demographic, long-term trend others: seasonality and for days of holiday. - Stratification: cold season/warm season | A significant association between PTB and PM$_{10}$ exposure at a lag-period of 12–22 days during the warm season. |
| Dadvand et al., 2014, [75]| Cohort study, Barcelona (Spain), 2001–2005 | 6438 newborns 190 term LBW. 803 SGA | Term LBW, SGA | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Logistic regression models | - Maternal characteristic: ethnicity, education level, marital status, age, smoking during pregnancy, alcohol consumption during pregnancy, body mass index at the time of admission, diabetes status), infection, parity, birth characteristics: sex of baby, - neighborhood characteristics: neighborhood socio-economic status - others season of conception and year of conception | Significant association between increase in term LBW risk and increase third-trimester exposure to PM$_{2.5}$ and PM$_{10}$. |
| Authors                  | Study Design, Period Location | Population Size | Outcomes | Pollutants | Statistical Methods | Confounders/Stratification | Main Findings                                                                 |
|--------------------------|-------------------------------|-----------------|----------|------------|--------------------|----------------------------|------------------------------------------------------------------------------|
| Sellier et al., 2014 [76]| Cohort study, Nancy and Poitiers (France), 2002–2005 | 1026 pregnant women (PM$_{10}$ study area) 776 pregnant women (NO$_2$ study area) | Birth weight (g) | NO$_2$, PM$_{10}$ | Linear regressions adjusted | - Maternal characteristic: gestational age, height, pre-pregnancy weight, age at the end of education, active and passive smoking during the relevant time-window under study - birth characteristics: sex, birth order - neighborhood characteristics: city - others: month of conception | The association with birth weight tended to be negative with exposure during the 1st trimester of pregnancy, positive with the 2nd trimester of pregnancy and null with the 3rd trimester of pregnancy. |
| Arroyo et al., 2016 [77] | Time-series analysis, Madrid, 2001–2009 | 298,705 newborns 24,620 PTB 20,442 VPTB 4176 EPTB | PTB (<37 w) VPTB ([30–37 w]) EPTB (<30 w) | PM$_{2.5}$, PM$_{10}$, NO$_2$ | Over-dispersed Poisson regression models | - No cofounders/stratification | Significant association between short term exposure to PM$_{2.5}$ and PTB. |
| Bertin et al., 2015, [78] | Prospective birth cohort, Bretagne (France) 2002–2006 | 2509 newborns 83 PTB | PTB (<37 W) | NO$_2$ | Logistic regression models | - Maternal characteristic: high blood pressure before/during pregnancy, gestational diabetes, maternal level of education, fish intake, BMI | Significant increased risk of PTB was associated to exposure to NO$_2$ concentrations >16.4 µg m$^{-3}$ only in urban areas. |
| Dibben et al., Clemens, 2015 [79] | Longitudinal study Scotland, 1994–2008 | 23,086 newborns 21,843 newborns (at term) 457 LBW | LBW (<2500), Birthweight for term births PTB (33–37, <33 W) | NO$_2$, PM$_{10}$ | Multilevel logistic, linear and multinomial regression model | - Maternal characteristic: age, parity, educational level, social class, ethnicity, lone parenthood, tobacco neighborhood characteristics: area crime rate - others: season of birth | Increase risk of LBW with the increase of NO$_2$ and of PM$_{10}$. Non-significant association of PTB with NO$_2$, as well as with PM$_{10}$. Significant association between birthweight for term birth and mean annual levels of NO$_2$ and PM$_{10}$. |
| Authors                  | Study Design, Period Location | Population Size | Outcomes               | Pollutants       | Statistical Methods                  | Confounders/Stratification                                                                 | Main Findings                                                                 |
|-------------------------|-------------------------------|-----------------|------------------------|------------------|--------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Schembari et al., 2015 [80] | Cohort study Bradford (England), 2007–2010 | 9067 newborns   | Birthweight (g)        | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Multivariate linear regression models   | Maternal characteristic: ethnicity (for adjust and stratified), age, height, pregnancy weight at first gynecological visit, parity, active smoking during pregnancy, education, and housing tenure - birth characteristics: sex, gestational age, 2-h post load plasma glucose test - others: season of conception | No significant association had been revealed. |
| Arroyo et al., 2016 [81]   | Time-series study, Madrid, 1 January 2001 to 31 December 2009 | 298,705 newborns | LBW (<2500 g), prematurity (<37 w) | PM$_{2.5}$ NO$_2$ | Poisson regression models            | Others: pollinic pollution                                                                  | A significant association between LBW and exposure to NO$_2$ during second trimester. A significant association between LBW and exposure to PM$_{10}$ during second trimester. |
| Bijnens et al., 2016 [82] | Prospective birth cohort, East Flanders, Belgium, 2002–2013 | 4760 twins, 2380 PTB | Birth weight, SGA      | PM$_{10}$ NO$_2$ | Multilevel regression analysis and generalized linear model | Maternal characteristic: parity, gestational age (linear and quadratic), age, zygosity and chronicity, maternal age - birth characteristics: sex, birth order, neighborhood characteristics: neighborhood household income - others: season of birth, birth year | Significant association between higher PM$_{10}$ and NO$_2$ exposure during the third trimester and lower birth weight and higher risk of small for gestational age. |
| Authors                  | Study Design, Period Location | Population Size | Outcomes | Pollutants | Statistical Methods | Confounders/Stratification                                    | Main Findings                                                                                                                                 |
|-------------------------|-------------------------------|-----------------|----------|------------|---------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Clemente et al.; 2016, [83] | Prospective birth cohort, Spain, (2004–2008), Belgium (2010–2013) | 376 newborns (Spain) 550 newborns (Belgium) | Birthweight | NO\textsubscript{2} | Land use regression (LUR), and kriging interpolation Method, land cover data satellite images | - Maternal characteristic: age, ethnicity, parity, smoking status, education, pre-pregnancy maternal BMI, birth characteristics: gestational age, sex, others: season of birth | Significant association between increase NO\textsubscript{2} exposure and decrease in birth weight. |
| Diaz et al., 2016 [84]  | Time-series analysis, Madrid (Spain), 2001–2009 | 298,705 newborns 3290 LBW 1492 term LBW 236 ELBW | LBW (VLBW: 1500 g to 2500 g and ELBW: <1500 g) | PM\textsubscript{2.5}, PM\textsubscript{10}, NO\textsubscript{2} | Over dispersed Poisson regression models | - Others: controlled for trend and seasonality | Significant association between increase risk of LBW and VLBW and exposure to PM\textsubscript{2.5} during third months. Significant association between increase risk of ELBW and exposure to PM\textsubscript{2.5} during eight months. No significant association with the two other pollutants. |
| Estarlich et al., 2016, [85] | Birth cohort study, November 2003–February 2008, Asturias, Gipuzkoa, Sabadell and Valencia (Spain) | 2409 pregnant women 115 PTB | PTB (<37 w) | NO\textsubscript{2} | Logistic regression models | - Maternal characteristic: socio-economic status, active smoking during pregnancy, maternal age birth characteristics: infant’s sex, neighborhood characteristics: socio-demographic characteristics, environmental exposures, zone of residence others: parental season of delivery | No statistically significant associations between exposure to NO\textsubscript{2} and PTB. Significant association between NO\textsubscript{2} exposure during the second trimester and whole pregnancy and PTB only a woman spending more time at home. |
| Authors                          | Study Design, Period Location                                                                 | Population Size       | Outcomes          | Pollutants | Statistical Methods                      | Confounders/Stratification                                                                 | Main Findings                                                                 |
|---------------------------------|----------------------------------------------------------------------------------------------|-----------------------|-------------------|------------|-----------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Giorgis-Allemand et al., 2017, [86] | Cohort study, 1994–2001 (ESCAPE, European Study of Cohorts for Air Pollution Effects from 11 European countries) | 71,493 newborns 3533 PTB | PTB (<37 w) | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Logistic regression models with a random effect Survival model a discrete-time Cox model | - Maternal characteristic: age, education, mother alone, parity, smoking, height and weight, pregnancy hypertension - birth characteristics: sex, cesarean delivery neighborhood characteristics: country - others: meteorological factors, season of conception, outdoor temperature, humidity, and atmospheric pressure | No significant association.                                                  |
| Schifano et al., 2016, [87]     | Population-based pregnancy cohorts, Rome (Italia) 2001–2010, Barcelona (Spain), 2007–2012 | 78,633 newborns (Rome), 27,255 newborns (Barcelona) 4325 PTB: in Rome 1227 PTB: in Barcelona | PTB (<36 weeks), birth (>22 or >24 w) | PM$_{10}$ NO$_2$ | Cox regression models                      | - Maternal characteristic: long time trend, age, education level, age, nationality, eclampsia and chronic pathologies, obstetric diseases in the current pregnancy and chronic diseases in both the current pregnancy and in the past two years neighborhood characteristics: citizenship - others: seasonality, year | Significant association between PM$_{10}$ and increased risk of PTB in Barcelona and with a decreased risk in Rome. Significant association between decreased risk and exposure to NO$_2$. |
| Clemens et al., 2017, [88]      | Cohort study, North-East Scotland, 2002–2011                                                | 13,775 newborns, 12,467 mothers | Birthweight | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Mixed effects regression models | - Maternal characteristic: age at delivery, parental social class, parity, height and weight in early pregnancy, smoking birth characteristics: sex - others: year of scan | Significant association between exposure to PM$_{10}$ only and reduction of birthweight. |
| Authors                          | Study Design, Period Location | Population Size | Outcomes                             | Pollutants | Statistical Methods | Confounders/Stratification                                                                 | Main Findings                                                                                                                                                  |
|---------------------------------|------------------------------|-----------------|--------------------------------------|------------|---------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Giovannini et al., 2017, [89]   | Prospective study, Lombardia (Italia), January 2004–December 2006 | 3614 women      | Birth weight (g), placental weight, umbilical artery PH | PM$_{10}$  | Linear regression model | - Maternal characteristic: age, educational level, parity, disease in pregnancy (diabetes and hypertension), normal or pathological course of pregnancy, use of medication, pre-pregnancy BMI, weight gain during pregnancy, gestational age, birth characteristics: gender and bimester of delivery, others: number of ultrasounds | Significant negative association between exposure to PM$_{10}$ during the first trimester and Birth weight. |
| Deguen et al., 2018, [90]       | Ecological study, Paris (France), January 2008–December 2011 | 105,346 newborns 4871 PTB | PTB ($\leq$36 W) | NO$_2$     | Spatial scan statistic, spatial clustering approach | - Neighborhood characteristics: socioeconomic deprivation index interaction between socioeconomic deprivation index and NO$_2$ | Spatial excess risk of PTB was explained by spatial variation of NO$_2$ concentrations and socio-economic deprivation. |
| Mariet et al., 2018, [91]       | Retrospective study, Besançon, Dijon (France), 2005–2009 | 249 multiple pregnancies 506 newborns 94 SGA | fetal growth restriction (FGR), SGA | NO$_2$     | Multivariable logistic regression and model multilevel model | - Maternal characteristic: age older than 35 years at delivery, smoking during pregnancy, malnutrition, nulliparity, gestational hypertension and diabetes neighborhood characteristics: low neighborhood socioeconomic level, others: the adjustment for major infant congenital abnormalities in addition to the 7 previous factors led to the same results | No significant association had been revealed for SGA. |
| Authors                  | Study Design, Period Location | Population Size | Outcomes | Pollutants | Statistical Methods | Confounders/Stratification                                                                 | Main Findings                                                                 |
|-------------------------|--------------------------------|-----------------|----------|------------|--------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Arroyo et al., 2019     | Time-series analysis, Spain, 2001–2009 | 1,468,622 newborns 127,722 PTB | PTB (<37 w) | PM$_{10}$, NO$_2$ | Generalized linear models with link Poisson | - Others: trend, seasonality, temperature in periods of heat and/or cold waves | Significant increase risk of PTB for 10µg/m$^3$ increase in NO$_2$ and PM$_{10}$. |
| Siddika et al., 2019,   | Population-based cohort study, Espoo (Finland), 1984–1990 | 2568 newborns 195 PTB | PTB (<37 w) | PM$_{2.5}$, NO$_2$ | Poisson regression analysis | - Maternal characteristic: age, smoking during pregnancy, exposure to environmental tobacco smoke during pregnancy, single parenthood birth characteristics: sex neighborhood characteristics: exposure to other air pollutants, family’s socioeconomic status | No significant association between PTB and exposure to PM$_{2.5}$, PM$_{10}$ or NO$_2$. |

PM: particulate matter; PM$_{2.5}$: particulate matter with an aerodynamic diameter up to 2.5 µm; PM$_{10}$: particulate matter with an aerodynamic diameter up to 10 µm; NO$_2$: nitrogen, LBW: low birth weight, VLBW: very low birth weight, PTB: preterm birth, VPTB: very preterm birth, EPTB: extremely preterm birth, SGA: small for gestational age, w: week(s).
3.2. General Description

There were 30 studies published since 1998, including more than 47,805 low birth weight newborns (and subtypes), 311,432 preterm birth (and subtypes) and 3319 newborns small for gestational age, in order to estimate the association between adverse pregnancy outcomes and exposure to three ambient pollutants, NO$_2$, PM$_{10}$ and PM$_{2.5}$. About 10 were eligible for the meta-analyses with the exclusion of 4 studies [75,81,89,91]. Of these, LBW, VLBW, ELBW, PTB, VPTB, EPTB, SGA, gestational age and birth weight were investigated (Table 1). About 4046 cases of preterm birth were included in the meta-analyses and 12,502 births were used to study the birth weight.

3.3. Study Design and Location

Most of the studies (10 studies) were conducted in Spain [67–69,71,75,77,81,84,85,92]. There were also 5 studies conducted in France [72,76,78,90,91], 2 studies in: Scotland [79,88], Italy [74,89], England [65,80] and only one study in Germany [66], Norway [70], Lithuania [64], Finland [93], Belgium [82]. In addition, two studies included several (more than 10) European countries [73,86], one study included Spain and Belgium [83] and one study included Spain and Italy [87]. Our systematic review group different study designs: the majority of the studies are cohort studies [66–69,71–73,75,76,78,80,82,83,85,86,88,93]; others are ecological time-series studies [64,65,70,77,81,84,87,90,92], spatial approach study [90] and longitudinal study [79]. Prospective study [89], retrospective study [91].

3.4. Cases Definition and Data Sources

Several studies investigated the birth weight [66–68,70,72,76,80,82,88,89] or gestational age [67], but most investigated specific pathological outcomes. First, several studies investigated LBW and subtypes [64,66,70,73,75,81,84]. Several studies investigated PTB and subtypes [64,65,69,74,77–79,81,85,87,90,92,93]. Finally, some studies investigated SGA: birth weight or length below the 10th percentile according to standard percentile charts for sex and gestational age in the population [68,70,75,82,91] (Table 2).

Databases were drawn mainly from birth certificate information and health database from hospital information systems while other form institutes of national health statistics and cohort databases were also used.
| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|----------------------|------------------------|------------------|-----------------------------------|----------------|---------------|
| Birth weight         | All singleton newborns | Exclusion criteria Women < 16 years of age, who not visited the public health center of Sabadell in the 12th week of pregnancy and not planning to deliver at the Hospital of Sabadell (followed an assisted reproduction program) | 570 newborns | Cohort of women’s attendance at prenatal care in the public health center of Sabadell | Aguilera et al., 2009, [67] |
| Birth weight         | All live singleton newborns | | 785 newborns | INMA (INfancia y Medio Ambiente) cohort in Valencia, pregnant women attending the prenatal population-based screening program at the reference hospital | Ballester et al., 2010, [68] |
| Birth weight         | All live twins without congenital malformation excluded twins with missing data (birthweight, gestational age, zygosity, maternal age, parity) | | 4760 newborns | East Flanders Prospective Twin Survey (EFPTS) a population-based register of multiple births in the province of East Flanders (Belgium) | Bijnens et al., 2016, [82] |
| Birth weight         | Singleton births       | | 13,775 newborns, 12,467 mothers | Aberdeen Maternity and Neonatal Databank (AMND) which has archived routinely acquired data from clinical activity at Aberdeen Maternity Hospital (AMH) since 1950 | Clemens et al., 2017, [88] |
| Birth weight         | All newborn from January 2004 through December 2006 (from woman born in Italia and living in Lombardy) | | 3614 newborns | Clinica Mangiagalli, the largest maternity clinic in Milan | Giovannini et al., 2018, [89] |
| Birth weight         | Singleton term live births with at least 37 weeks with weight >300 g registered between 1 January 1999 and 31 December 2002 | Exclusion criteria: maternal address outside Oslo during the pregnancy, plural deliveries, term births with weight <1000 g, or births with missing information on offspring’s gender or weight. Pregnancies with missing exposure on ambient air pollution from the dispersion model were also Excluded. | 25,229 newborns | Medical Birth Registry of Norway (MBRN) | Madsen et al., 2010, [70] |
Table 2. Cont.

| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|----------------------|------------------------|------------------|-----------------------------------|----------------|---------------|
|                      |                        |                  | EDEN (Etudes des Déterminants pré et postnataux précurseurs du développement et de la santé de l’ENfant) mother–child cohort maternity records | Rahmalia et al., 2012, [72] |
|                      |                        |                  | Medical records of Bradford Royal Infirmary Born in Bradford (BiB) | Schembari et al., 2015, [80] |
|                      |                        |                  | EDEN mother–child cohort maternity records | Sellier et al., 2014, [76] |
|                      |                        |                  | Munich LISA (Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Children) birth cohort. | Slama et al., 2007, [66] |
|                      |                        |                  | Madrid Regional Directorate-General of Economic Statistics and Technological Innovation | Arroyo et al., 2016, [81] |
|                      |                        |                  | Cohort based on the data collected from Hospital Clinic de Barcelona | Dadvand et al., 2014, [75] |
|                      |                        |                  | Perinatal health databases of public hospitals in Madrid | Diaz et al., 2016, [84] |

- All singleton live births between February 2003 and January 2006
  Exclusion criteria: all multiple fetuses, diabetes or planning to deliver outside the university hospital or to move out from the study region within 3 years of recruitment
  Sample Size: 1154 newborns

- All singleton live births between March 2007 and November 2010
  Exclusion criteria: stillbirths, multiple pregnancies, infants whose maternal ethnic origin was not white British or Pakistani origin.
  Sample Size: 9067 newborns

- Mothers enrolled between 26 gestational weeks at maternity wards of Nancy and Poitiers university hospitals, from 2002 to 2005
  Exclusion criteria: women diabetes, multiple pregnancy, or intention to deliver outside the university hospital or to move out of the study area within 3 years.
  Sample Size: 1026 newborns

- All singleton live births between January 1998 and January 1999.
  Exclusion criteria: women diabetes, long-term use of medication, birth weight < 2500 g, gestational duration < 37 completed weeks, congenital malformation, symptomatic neonatal infection, antibiotic medication, and hospitalization or intensive medical care during neonatal period, twin births and women who changed home during pregnancy.
  Sample Size: 1016 newborns

- All live singleton births from 1 January 2001 to 31 December 2009 (woman living in Madrid)
  Sample Size: 298,705 newborns
  LBW: 39,583

- Singleton term births (i.e., gestational age at delivery ≥37 weeks) occurring at the obstetrics department of the Hospital Clinic de Barcelona between January 2001 and June 2005 to mothers residing in the city of Barcelona.
  Sample Size: 6438 newborns
  Term LBW: 190

- All live singleton full term birth in the period 1 January 2001 to 31 December 2009 to whose mothers resided in the Madrid city area
  Sample Size: 298,705 newborns
  LBW: 3290
  Term LBW: 1492
# Table 2. Cont.

| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|-----------------------|------------------------|------------------|-----------------------------------|----------------|--------------|
| Singleton term live births with at least 37 weeks with weight > 300 g registered between 1 January 1999 and 31 December 2002. Exclusion criteria: maternal address outside Oslo during the pregnancy, plural deliveries, term births with weight < 1000 g, or births with missing information on offspring’s gender or weight. Pregnancies with missing exposure on ambient air pollution from the dispersion model were also excluded. | Singleton term live births with at least 37 weeks with weight > 300 g registered between 1 January 1999 and 31 December 2002. Exclusion criteria: maternal address outside Oslo during the pregnancy, plural deliveries, term births with weight < 1000 g, or births with missing information on offspring’s gender or weight. Pregnancies with missing exposure on ambient air pollution from the dispersion model were also excluded. | 25,229 newborns LBW: 303 | Medical Birth Registry of Norway (MBRN) | Madsen et al., 2010, [70] |
| All singleton births from 1 January 1998 through 31 December 1998. | All singleton births from 1 January 1998 through 31 December 1998. | 3988 newborns LBW: 140 | Lithuanian National Birth Register | Maroziene and Grazuleviciene, 2002, [64] |
| Singleton births between 11 February 1994, and 2 June 2011 and for whom information about home addresses during pregnancy, infant birthweight, gestational age, and sex was available (pooled data from 14 European mother–child cohort studies in which birthweight was not part of inclusion criteria) | Singleton births between 11 February 1994, and 2 June 2011 and for whom information about home addresses during pregnancy, infant birthweight, gestational age, and sex was available (pooled data from 14 European mother–child cohort studies in which birthweight was not part of inclusion criteria) | 74,178 newborns LBW: 1257 | European Study of Cohorts for Air Pollution Effects (ESCAPE): data from 14 European mother–child cohort studies, MoBa (Norway); BAMSE (four centers; Sweden); DNBC (Denmark); KANC (Lithuania); BB (England); ABCD, GENERATION R, and PIAMA (three centers; Netherlands); DIUSBURG (Germany); EDEN (two centers; France), APREG (Hungary); GASPII (Italy); INMA (five centers; Spain), and RHEA (Greece) | Pedersen et al., 2013, [73] |
| All non-premature singleton live births between January 1998 and January 1999. Exclusion criteria: women diabetes), long-term use of medication, birth weight < 2500 g, gestational duration < 37 completed weeks, congenital malformation, symptomatic neonatal infection, antibiotic medication, and hospitalization or intensive medical care during neonatal period, twin births and women who changed home during pregnancy. | All non-premature singleton live births between January 1998 and January 1999. Exclusion criteria: women diabetes), long-term use of medication, birth weight < 2500 g, gestational duration < 37 completed weeks, congenital malformation, symptomatic neonatal infection, antibiotic medication, and hospitalization or intensive medical care during neonatal period, twin births and women who changed home during pregnancy. | 1016 newborns LBW: 142 | Munich LISA (Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Children) birth cohort. | Slama et al., 2007, [66] |
| All live singleton full term birth in the period 1 January 2001 to 31 December 2009 to whose mothers resided in the Madrid city area | All live singleton full term birth in the period 1 January 2001 to 31 December 2009 to whose mothers resided in the Madrid city area | 298,705 newborns VLBW: 1176 | Perinatal health databases of public hospitals in Madrid | Diaz et al., 2016, [84] |
| All live singleton full term birth in the period 1 January 2001 to 31 December 2009 to whose mothers resided in the Madrid city area | All live singleton full term birth in the period 1 January 2001 to 31 December 2009 to whose mothers resided in the Madrid city area | 298,705 newborns ELBW: 236 | Perinatal health databases of public hospitals in Madrid | Diaz et al., 2016, [84] |
| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|----------------------|------------------------|------------------|-----------------------------------|----------------|--------------|
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | All live singleton births from 1 January 2001 to 31 December 2009 | 298,705 newborns PTB: 24,586 births | Madrid Regional Directorate-General of Economic Statistics and Technological Innovation | Arroyo et al., 2016, [81] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | All birth registered in the period of nine years from 2001 through 2009. | 1468,622 newborns PTB: 127,722 | National Statistics Institute (INE, 2018) | Arroyo et al., 2019, [92] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | Singleton live born infants without any major congenital malformation from 2002 to 2006 | 2509 newborns PTB: 83 | PELAGIE cohort | Bertin et al., 2015, [78] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | Live births registered over the period 2008–2011 | 105,346 newborns PTB: 4871 | First birth certificate information registered by Maternal and Child Care department of Paris | Deguen et al., 2018, [90] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | Singleton live birth recruited between November 2003 and February 2008 | 2409 newborns PTB: 115 | main public hospital or reference health center in four study areas: Asturias, Gipuzkoa, Sabadell, and Valencia | Estarlich et al., 2016, [85] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | Live singleton births more than 24 weeks from 1988 to 2000. Exclusion criteria: babies weighing 200 g or less were either associated with a gestational age of less than 24 weeks or considered an error, congenital anomalies | 482,765 newborns PTB: 29,716 | St. Mary’s Maternity Information System (SMMIS) | Lee et al., 2007, [65] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | Live singleton births between February 2004 and June 2005. Women attending the prenatal population-based screening program at their referring hospital who met the inclusion criteria (In their first trimester, subjects had to reside in the study area, be at least 16 years old, have a singleton pregnancy, have their first prenatal visit in the main public hospital or health center of the area, not have followed any program of assisted reproduction, intend to deliver in the reference hospital, and have no communication problems) | 785 newborns PTB: 47 | INMA cohort in Valencia | Llop et al., 2010, [69] |
| PTB PTB < 37         | ICD-10: P07.2–P07.3   | All singleton births from 1 January 1998 through 31 December 1998 | 3988 newborns PTB: 203 | Lithuanian National Birth Register | Maroziene and Grazuleviciene, 2002, [64] |
| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|----------------------|------------------------|------------------|----------------------------------|----------------|---------------|
| PTB 33–37            | Singleton live term births years 1994 to 2008 inclusive and birth weights ranging from 500 to 6000 g | All newborn between 1 January 1984 and 31 March 1990, included all the children of the city of Espoo, Finland, born Random sample of children living in Espoo in 1991 from the roster of Statistics Finland | 21,843 newborns PTB: 1049 | Scottish Longitudinal Study | Dibben et Clemens, 2015, [79] |
| PTB 22–36            | All singleton live births (>22 w) by natural delivery or cesarean sections with spontaneous onset of labor between 1 January 2001 and 31 December 2010 Exclusion criteria: multiple births, all cesarean sections where spontaneous onset of labor was not reported, labor inductions, births referred with congenital malformations, and stillbirths. Mothers younger than 11 years or older than 55 years. | All live singleton births (>22 w) between 1 April 2001 and the 31 October 2010. Barcelona- All live singleton births (>24 w) between 1 April 2007 and 31 October 2012. Exclusion criteria: multiple births, all cesarean sections where spontaneous onset of labor was not reported, labor inductions, births referred with congenital malformations, and stillbirths. Mothers younger than 11 years or older than 55 years. | 132,691 newborns PTB 22–32 w: 847 PTB 33–36 w: 6412 | Certificate of Delivery Care Registry Lazio regional hospital information system | Schifano et al., 2013, [74] |
| PTB 30–37            | All live singleton births between 1 January of 2001 and 31 December 2009 | All live singleton births (>22 w) between 1 April 2001 and the 31 October 2010. Barcelona- All live singleton births (>24 w) between 1 April 2007 and 31 October 2012. Exclusion criteria: multiple births, all cesarean sections where spontaneous onset of labor was not reported, labor inductions, births referred with congenital malformations, and stillbirths. Mothers younger than 11 years or older than 55 years. | 298,705 newborns PTB: 24,620 VPB: 20,442 EPTB: 4178 | Madrid Regional Directorate-General of Economic Statistics and Technological Innovation | Arroyo et al., 2015, [77] |
| VPTB < 33            | Singleton live term births years 1994 to 2008 inclusive and birth weights ranging from 500 to 6000 g | All live singleton births between 1 January of 2001 and 31 December 2009 | 21,843 newborns VPTB: 193 | Scottish Longitudinal Study | Dibben et Clemens, 2015, [79] |
| VPTB < 30            | All live singleton births between 1 January of 2001 and 31 December 2009 | All live singleton births (>22 w) between 1 April 2001 and the 31 October 2010. Barcelona- All live singleton births (>24 w) between 1 April 2007 and 31 October 2012. Exclusion criteria: multiple births, all cesarean sections where spontaneous onset of labor was not reported, labor inductions, births referred with congenital malformations, and stillbirths. Mothers younger than 11 years or older than 55 years. | 298,705 newborns PTB: 24,620 VPB: 20,442 EPTB: 4178 | Madrid Regional Directorate-General of Economic Statistics and Technological Innovation | Arroyo et al., 2015, [77] |
| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|-----------------------|-----------------------|------------------|-----------------------------------|----------------|--------------|
| EPTB < 22             | Rome-All live singleton births (>22 w) between 1 April 2001 and 31 October 2010. Barcelona-All live singleton births (>24 w) between 1 April 2007 and 31 October 2012. Exclusion criteria: multiple births, all cesarean sections where spontaneous onset of labor was not reported, labor inductions, births referred with congenital malformations, and stillbirths. Mothers younger than 11 years or older than 55 years. | 78,633 newborns (Rome) 27,255 newborns (Barcelona) PTB in Rome: 4325 PTB in Barcelona: 1227 | Cohort based on certificate of Delivery Care Registry for Rome and the Birth Registry of the Catalan Institute of Statistics in Barcelona | Schifano et al., 2016, [87] |
| EPTB < 24             | All live singleton newborns | 785 newborns PTB: 51 | INMA cohort in Valencia | Ballester et al., 2010, [68] |
| SGA                   | Birth weight or length below the 10th percentile according to standard percentile charts for sex and gestational age in the population | All live twins without congenital malformation | 4760 newborns | East Flanders Prospective Twin Survey (EFPTS) a population-based register of multiple births in the province of East Flanders (Belgium) | Bijnens et al., 2016, [82] |
|                       | singleton term births (i.e., gestational age at delivery ≥37 w) occurring at the obstetrics department of the Hospital Clinic de Barcelona between January 2001 and June 2005 to mothers residing in the city of Barcelona. | 6438 newborns Term LBW: 190 SGA: 803 | Cohort based on the data collected from Hospital Clinic de Barcelona | Dadvand et al., 2014, [75] |
|                       | Singleton term live births with at least 37 weeks with weight > 300 g registered between 1 January 1999 and 31 December 2002 Exclusion criteria: maternal address outside Oslo during the pregnancy, plural deliveries, term births with weight < 1000 g, or births with missing information on offspring’s gender or weight. Pregnancies with missing exposure on ambient air pollution from the dispersion model were also Excluded. | 25,229 newborns LBW: 303 SGA: 2422 | Medical Birth Registry of Norway (MBRN) | Madsen et al., 2010, [70] |
| Type(s) or Subtype(s) | Outcome Classification | Population Study | Sample Size (Studies Population) | Database Study | Authors, Date |
|----------------------|------------------------|------------------|----------------------------------|----------------|---------------|
|                      | Stillborn and live newborns, whose births occurred after 22 completed weeks of gestation and/or with birth weight > 500 g between 1 January 2005 and 31 December 2009 | 506 newborns | Besançon computerized medical records and the Burgundy perinatal network records and paper medical records for Dijon | Mariet et al., 2018, [91] |
| Gestational age      | All singleton newborn, exclusion criteria: women <16 years of age, who not visited the public health center of Sabadell in the 12th week of pregnancy and not planning to deliver at the Hospital of Sabadell (followed an assisted reproduction program) | 570 newborns | Cohort of women’s attendance at prenatal care in the public health center of Sabadell | Aguilera et al., 2009, [67] |

w: week(s), PTB: Preterm birth, VPTB: very preterm birth, EPTB: Extremely preterm birth, LBW: Low birth weight, VLBW: Very Low birth weight.
3.5. Pollutants Investigated

Most frequently, the studies investigate exposure to air pollutants separately $\text{NO}_2$, $\text{PM}_{10}$ and $\text{PM}_{2.5}$ [70,73,75,77,80,86,88] or exposure to $\text{PM}_{2.5}$ and $\text{NO}_2$ [66,81,84,93] or exposure to $\text{PM}_{10}$ and $\text{NO}_2$ [72,74,76,79,82,87,92] or exposure to $\text{NO}_2$ [64,67–69,71,78,83,85,90,91] or exposure to $\text{PM}_{10}$ [65,89]. Some papers have used a monitoring station-based approach with average from all monitoring stations [89,92] or average from existing monitoring stations [64,65,74,77,81,84,87] but most used a modeling-based approach with, on the one hand, land-use regression, LUR [66–69,71,73,75,76,78,80,83,85,86], and on the other hand dispersion models [70,72,76,79,88,90,91]. Few studies use other models as spatial temporal interpolation method (Kriging method) [82] and system for integrated modeling of atmospheric composition (SILAM model) [93].

Table 3 describes the approaches used to assess the residential exposure measures and level of exposure assigned to the population of all studies included in the systematic review (n = 30).

3.6. Window of Exposure

The different definitions of critical windows of exposure considered in the 30 studies included in the systematic review is described in Table 4. Short- and long-term exposure to air pollutants were used to investigate the relationship between LBW, PTB, SGA and residential exposure (at home address). Long-term exposures were the most explored cumulative exposure windows [64,66–73,75,76,80–89,91–93]. Moreover, few studies chose not to focus on a particular window of exposure, instead measuring annual average pollutant concentrations at residence [78,79,90].

3.7. Overview of Current Evidence Concerning Possible Effects on Birth Outcomes of Exposure to Air Pollution

In this section, the results of studies are presented in Figures 2–4, structured by window of exposure of different pollutants ($\text{NO}_2$, $\text{PM}_{10}$, $\text{PM}_{2.5}$). Overall, results show the risk of adverse birth outcomes increases for a 10 $\mu$g/m$^3$ increase $\text{NO}_2$ exposure. Therefore, 19 results tend to show an association between the increase of risk of adverse pregnancy outcomes and $\text{NO}_2$ exposure while 10 results which tend to show a decrease of these risks. Our review reveals that for 10 $\mu$g/m$^3$ increase in $\text{NO}_2$ exposure (Figure 2) newborn have increased risk of:

- Preterm birth (OR = CI 95%) OR = 1.67 (1.28–2.18) [64] for the first trimester, OR = 1.06 (0.86–1.32), 1.13 (0.90–1.40) [64,85] for the second trimester, OR = 1.19 (0.96–1.47) [64] for the third trimester.
- Small for gestational age (OR = CI 95%) OR = 1.18 (0.89–1.56), OR = 1.37 (1.01–1.85), OR = 1.19 (0.91–1.56), respectively for the windows of exposure of 1st, 2nd and 3rd trimester [68],
- Low birth weight (OR = CI 95%) OR = 1.03 (0.97–1.09), OR = 1.02 (0.95–1.09), OR = 1.34 (0.94–1.92) respectively for the windows of exposure of 1st, 2nd and 3rd trimester [64,73,75].
Table 3. Summary of approaches used to assess the residential exposure measures.

| Approach                      | Database/Model Used                                                                 | Pollutants | Indicators         | Data Sources of Air Pollution                                                                 | Level EXPOSURE Assigned to the Population | Authors, Date                  |
|-------------------------------|-------------------------------------------------------------------------------------|------------|--------------------|------------------------------------------------------------------------------------------------|------------------------------------------|-------------------------------|
| Monitoring station-based      | Monitoring stations of each province capital during the period 2001–2009           | PM$_{10}$, NO$_2$ | Weekly average     | Ministry of Agriculture and Environment (MAGRAMA, n.d.)                                       | Province capital level                   | Arroyo et al., 2019 [92]     |
| Average from all monitoring   | fixed monitoring stations at 53 different sites throughout the region.             | PM$_{10}$  | Daily average      | The Department of the Regional Environmental Protection Agency                                | Geographical area level                  | Giovannini et al., 2017 [89] |
| station                        | 27 urban background stations                                                      | PM$_{2.5}$, NO$_2$, | Daily mean         | Madrid Municipal Air Quality Monitoring Grid                                                 | City level                               | Arroyo et al., 2016 [81]     |
| Average from                   | 27 urban background stations                                                      | PM$_{2.5}$, PM$_{10}$, NO$_2$, | Daily mean         | Madrid Municipal Air Quality Monitoring Grid                                                 | City level                               | Arroyo et al., 2016 [77]     |
| Monitoring stations            | 27 urban background stations, gravimetric method                                   | PM$_{2.5}$, NO$_2$, | Daily average      | Madrid Municipal Air Quality Monitoring Grid                                                 | City level                               | Diaz et al., 2016 [84]       |
| existing                      | One monitoring station located in Bloomsbury                                        | PM$_{10}$  | Daily average      | UK National Air Quality Archive                                                              | City level                               | Lee et al., 2007 [65]        |
|                               | 12 municipal monitoring sites, one in each residential district                    | NO$_2$     | Daily average      | Kaunas’ municipal ecological monitoring data                                                 | Residential district                     | Marozâi and Grazulevičiene, 2002 [64] |
|                               | three fixed stations in the urban area                                             | PM$_{10}$, NO$_2$, | Daily mean         | Lazio Environmental Protection Agency                                                        | City level                               | Schifano et al., 2016 [74]  |
|                               | Rome, three fixed stations, one of background and two within the urban area        | PM$_{10}$, NO$_2$, | Daily mean         | Rome, Lazio Environmental Protection Agency                                                   | City level                               | Schifano et al., 2016 [87]  |
|                               | Barcelona, data was obtained from a single urban background station                | PM$_{10}$, NO$_2$, | Daily mean         | Barcelona, network of the Catalan Government                                                  | City level                               |                               |
| Modeling based approach       | LUR model, passive samplers and fixed monitoring station                            | NO$_2$     | Daily mean         | Individual level                                                                             |                                          | Aguiñera et al., 2009 [67]  |
Table 3. Cont.

| Approach | Database/Model Used | Pollutants | Indicators | Data Sources of Air Pollution | Level EXPOSURE Assigned to the Population | Authors, Date |
|----------|---------------------|------------|------------|-------------------------------|------------------------------------------|---------------|
| LUR model, passive samplers and fix monitoring station and kriging interpolation model | NO₂ | Daily average | Radiello®, Fondazione Salvatore Maugeri, Padua/Italy and monitoring network within 5 km or less of the study area | Individual level | Ballester et al., 2010, [68] |
| LUR model, satellite and ground-based measurements and 12 monitoring stations | NO₂ | Annual mean | The nationwide French NO₂ concentrations | Individual level | Bertin et al., 2015, [78] |
| spatial temporal interpolation method (Kriging) and monitoring stations | PM₁₀, NO₂ | Daily mean | Corine land cover data set, Belgian telemetric air quality networks | Individual level | Bijnens et al., 2016, [82] |
| Dispersion kernels model-Pollution Climate Mapping approach. | PM₂.₅, PM₁₀, NO₂ | Annual mean | United Kingdom Department for the Environment, Food and Rural Affairs (DEFRA), National Atmospheric Emissions Inventory (NAEI) | Postcode level | Clemens et al., 2017, [88] |
| LUR model and kriging interpolation method, passive samplers | NO₂ | Annual average | INMA: Radiello, Fundazione Salvatore Maugeri, Padua, Italy ENVIRONAGE: Belgian telemetric air quality network, point sources and line sources land cover data satellite images, | Individual level | Clemente et al., 2016, [83] |
| LUR | PM₂.₅, PM₁₀, NO₂ | Weekly exposure | European Study of Cohorts for Air Pollution Effects (ESCAPE) | Individual level | Dadvand et al., 2014, [75] |
| Approach | Database/Model Used | Pollutants | Indicators | Data Sources of Air Pollution | Level EXPOSURE Assigned to the Population | Authors, Date |
|----------|---------------------|------------|------------|------------------------------|------------------------------------------|---------------|
| Dispersion model-deterministic model. STREET dispersion model | NO$_2$ | Annual average | local air quality monitoring networks Airparif, The ESMERALDA inter-regional platform for air quality mapping and forecasting Emissions for traffic roads: COPERT III European database for the 2002–2006 period, and COPERT IV for the 2007–2012 period. meteorological data, Division of the NCAR Earth System Laboratory | Census block level | Deguen et al., 2018, [90] |
| Dispersion kernel modelling: pollution climate mapping model approach | NO$_2$, PM$_{10}$ | Annual average | United Kingdom Atomic Energy Authority (AEA) (now Ricardo-AEA), air quality by the UK government. National Atmospheric Emissions Inventory | Postcode level | Dibben et Clemens, 2015, [79] |
| LUR and monitoring station, passive samplers | NO$_2$ | Daily mean | Radiellos, Fondazione Salvatore Maugeri, Padua, Italy | Individual level | Estarlich et al., 2016, [85] |
| LUR, passive samplers and monitoring station | NO$_2$ | Daily mean | Radiellos, Fondazione Salvatore Maugeri, Padua, Italy | Individual level | Estarlich et al., 2011, [71] |
| LUR and monitoring station | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Annual mean | | Individual level | Giorgis-Allemand et al., 2016, [86] |
| kriging and LUR and monitoring station | NO$_2$ | Annual average (and daily variation) | Radiellos-type Valencia monitoring network | Individual level | Llop et al., 2010, [69] |
| EPISODE, a dispersion model and monitoring station | NO$_2$, PM$_{10}$ PM$_{2.5}$ | Daily mean | Norwegian Institute for Air Research | Individual level (home and work address) | Madsen et al., 2010, [70] |
| dispersion model | NO$_2$ | Monthly mean | traffic data using CIRCU’AIR software, French Air Quality Monitoring Agencies COPERT IV European standard methodology | Individual level | Mariet et al., 2018, [91] |
| LUR and monitoring station | PM$_{2.5}$ PM$_{10}$ NO$_2$ | Annual mean | | Individual level | Pedersen et al., 2013, [73] |
Table 3. Cont.

| Approach                                      | Database/Model Used                              | Pollutants | Indicators | Data Sources of Air Pollution                                      | Level EXPOSURE Assigned to the Population | Authors, Date       |
|-----------------------------------------------|-------------------------------------------------|------------|------------|--------------------------------------------------------------------|------------------------------------------|---------------------|
| Dispersion model implemented in ADMS-Urban software. | NO2, PM2.5                                         | Hourly mean |            | Individual level                                                   |                                          | Rahmalia et al., 2012, [72] |
| LUR models and monitoring station            | PM2.5, PM10, NO2                                   | Daily average |            | European Study of Cohorts for Air Pollution Effects                 | Individual level                         | Schembari et al., 2015, [80] |
| Nearest AQMS model                           | NO2, PM10                                         | Annual average |            | European Commission, Corine land cover 2006 (EEA 2005)              | Individual level                         | Sellier et al., 2014, [76]    |
| Temporally adjusted geostatistical model     | PM2.5                                             | Daily mean   |            | Finnish Meteorological Institute                                   | Individual level                         | Siddika et al., 2019, [93]    |
| LUR model                                    | PM2.5, NO2                                        | Annual average |            | City of Munich                                                     | Individual level                         | Slama et al., 2007, [66]     |
| LUR and monitoring station                   | PM2.5, NO2                                        | Annual average |            | City of Munich                                                     | Individual level                         | Slama et al., 2007, [66]     |
| TRAPCA II model                               | PM2.5, NO2                                        | Annual average |            | City of Munich                                                     | Individual level                         | Slama et al., 2007, [66]     |

NO2: nitrogen dioxide; PM: Particulate Matter; PM2.5: particulate matter with an aerodynamic diameter up to 2.5 μm; PM10: particulate matter with an aerodynamic diameter up to 10 μm.

Table 4. Definition and assessment of window of exposure.

| Windows of Exposure | Pollutants | Indicators | Authors       |
|---------------------|------------|------------|---------------|
| **Daily exposure**  |            |            |               |
| Lag 0               | PM10       | Daily average | Lee et al., 2007, [65] |
| Lag 1               | PM10, NO2  | Daily mean  | Schifano et al., 2013, [74] |
| lags: 0 to lags 7 lagged days. | PM2.5, PM10, NO2 | Daily mean  | Schifano et al., 2013, [74] |
| lags: 0 to lags 30 lagged days | PM10 NO2  | Daily mean  | Schifano et al., 2013, [74] |
| Windows of Exposure                          | Pollutants | Indicators | Authors                      |
|----------------------------------------------|------------|------------|------------------------------|
| Cumulative Exposure                          |            |            |                              |
| Over 1 days before birth (Lag 0–1)           | PM$_{10}$  | Daily average | Lee et al., 2007, [65] |
| Over 2 days before birth (Lag 0–2)          | PM$_{10}$  | Daily average | Lee et al., 2007, [65] |
| Over 3 days before birth (Lag 0–3)          | PM$_{10}$, NO$_2$ | Daily average | Schifano et al., 2016, [87] |
| Over 4 days before the birth (Lag 0–4)      | PM$_{10}$  | Daily average | Lee et al., 2007, [65] |
| Over 5 days before birth (Lag 0–5)          | PM$_{10}$  | Daily average | Lee et al., 2007, [65] |
| Over 6 days before the birth (Lag 0–6)      | PM$_{10}$  | Daily average | Lee et al., 2007, [65] |
| Last week of pregnancy                      | PM$_{10}$, NO$_2$ | Daily mean  | Bijnens et al., 2016, [82] |
| Long-term exposure                          |            |            |                              |
| Weekly exposure                              |            |            |                              |
| 7 week before                                | PM$_{2.5}$, NO$_2$, PM$_{10}$, NO$_2$ | Daily mean  | Arroyo et al., 2016, [81] |
|                                               | PM$_{2.5}$, PM$_{10}$, NO$_2$ | Annual mean | Clemens et al., 2017, [88] |
|                                               | PM$_{2.5}$, NO$_2$, PM$_{10}$, NO$_2$ | Daily average | Diaz et al., 2016, [84] |
|                                               | PM$_{10}$, NO$_2$ | Daily mean  | Schifano et al., 2016, [87] |
| Last month of pregnancy                      | PM$_{2.5}$, NO$_2$, PM$_{10}$, NO$_2$ | Daily mean  | Bijnens et al., 2016, [82] |
| 2 months before delivery                     | NO$_2$    | Monthly mean | Mariet et al., 2018, [91] |
| The first 2 trimester (t1-t2)                | PM$_{2.5}$, PM$_{10}$, NO$_2$ | Annual mean | Giorgis-Allemand et al., 2016, [86] |
| By trimester of pregnancy                    | NO$_2$    | Daily mean Annual average | Aguilera et al., 2009, [67] |
|                                               | NO$_2$    | daily average | Ballester et al., 2010, [68] |
|                                               | PM$_{10}$, NO$_2$ | Daily mean  | Bijnens et al., 2016, [82] |
|                                               | NO$_2$    | Annual average | Clemente et al., 2016, [83] |
|                                               | PM$_{2.5}$, PM$_{10}$, NO$_2$ | Weekly exposure | Dadvand et al., 2014, [75] |
|                                               | NO$_2$    | Daily mean  | Estarlich et al., 2016, [85] |
|                                               | NO$_2$    | Daily mean  | Estarlich et al., 2011, [71] |
|                                               | PM$_{10}$  | Daily average | Giovannini et al., 2017, [89] |
| Windows of Exposure | Pollutants | Indicators | Authors |
|---------------------|------------|------------|---------|
| NO₂                 | Annual average (and daily variation) | Llop et al., 2010, [69] |
| NO₂, PM₁₀ PM₂.₅    | Hourly mean, Daily mean | Madsen et al., 2010, [70] |
| NO₂                 | Monthly mean | Mariet et al., 2018, [91] |
| NO₂                 | Daily average, | Maroziene and Grazuleviciene, 2002, [64] |
| PM₂.₅, PM₁₀, NO₂    | Annual mean (daily) | Pedersen et al., 2013, [73] |
| NO₂, PM₁₀           | Hourly mean | Rahmalia et al., 2012, [72] |
| PM₂.₅, PM₁₀, NO₂    | Daily average estimate | Schembari et al., 2015, [80] |
| NO₂ PM₁₀            | Annual average | Sellier et al., 2014, [76] |
| PM₂.₅ NO₂           | Annual average | Slama et al., 2007, [66] |
| NO₂                 | Daily mean, Annual average | Aguilera et al., 2009, [67] |
| NO₂                 | daily average | Ballester et al., 2010, [68] |
| NO₂                 | Annual average | Clemente et al.; 2016, [83] |
| PM₂.₅, PM₁₀, NO₂    | Weekly exposure | Dadvand et al., 2014, [75] |
| NO₂                 | Daily mean | Estarlich et al., 2016, [85] |
| NO₂                 | Daily mean | Estarlich et al., 2011, [71] |
| PM₂.₅, PM₁₀, NO₂    | Annual mean | Giorgis-Allemand et al., 2016, [86] |
| NO₂                 | Annual average (and daily variation) | Llop et al., 2010, [69] |
| NO₂, PM₁₀ PM₂.₅    | Hourly mean, daily mean | Madsen et al., 2010, [70] |
| NO₂                 | Monthly mean | Mariet et al., 2018, [91] |
| NO₂                 | Daily average | Maroziene and Grazuleviciene, 2002, [64] |
| PM₂.₅, PM₁₀, NO₂    | Annual mean (daily) | Pedersen et al., 2013, [73] |
| NO₂, PM₁₀           | Hourly mean | Rahmalia et al., 2012, [72] |
| PM₂.₅, PM₁₀, NO₂    | Daily average estimate | Schembari et al., 2015, [80] |
| PM₁₀, NO₂           | Daily mean | Schifano et al., 2016, [87] |
| NO₂ PM₁₀            | Annual average | Sellier et al., 2014, [76] |
| PM₂.₅               | Daily mean | Siddika et al., 2019, [93] |

During the 9 months of pregnancy

**Table 4. Cont.**
### Table 4. Cont.

| Windows of Exposure | Pollutants   | Indicators   | Authors                      |
|---------------------|--------------|--------------|------------------------------|
| PM$_{2.5}$, NO$_2$  | Annual average | Slama et al., 2007, [66] |
| No specific windows | NO$_2$       | Annual mean  | Bertin et al., 2015, [78]   |
|                     | NO$_2$       | Annual average | Deguen et al., 2018, [90]   |
|                     | NO$_2$, PM$_{10}$ | Annual average | Dibben et Clemens, 2015, [79] |

PM: Particulate Matter; PM$_{10}$: particulate matter with an aerodynamic diameter up to 10 µm; PM$_{2.5}$: particulate matter with an aerodynamic diameter up to 2.5 µm; NO$_2$: nitrogen.
Figure 2. Risk of birth outcome for NO$_2$ exposure during different windows of exposure during pregnancy.
Figure 3. Risk of birth outcome for PM$_{10}$ exposure during different windows of exposure during pregnancy.
Figure 4. Risk of birth outcome for PM$_{2.5}$ exposure during different windows of exposure during pregnancy.
Furthermore, as shown in Figures 2–4 (Appendix A), the LBW risk increases for outdoor air pollutant exposure during the windows of exposure of whole pregnancy.

- A 10 µg/m$^3$ increase NO$_2$ exposure: OR = 1.03 (0.96–1.10), OR = 1.28 (0.97–1.68), OR = 1.09 (1.00–1.19) [64,73,75].
- A 10 µg/m$^3$ increase PM$_{10}$ exposure OR = 1.46 (0.95–2.24) and 1.16 (1.00–1.35) [73,75]
- A 10 µg/m$^3$ increase PM$_{2.5}$ exposures OR = 1.98 (0.92–4.19) and 1.39 (1.12–1.77) [73,75]

However, several results were not significant, except studies [64,68,75].

Among studies focusing on critical windows, during each window of exposure the number of results which tend to show an association between PTB or SGA and air pollutant are the same and do not increase or decrease with the trimester of pregnancy, for any windows of exposure only three results tend to show an association [64,68,85].

Whereas the risk of LBW seems to increase as the pregnancy progresses. In this way, our review reveals that two results tend to show this association during the second trimester of pregnancy (Appendix B) and four results tend to show this association during the third trimester (Appendix D).

In addition, when studies consider the exposure of the entire pregnancy, seven results found an association between air pollutant exposure and the increase of the risk of LBW against only 3 results for PTB and SGA in the same windows (Appendix A).

Among studies focusing on the 1st trimester of exposure the risk of adverse birth outcomes ranges from 0.78 to 1.67 with confidence interval range from 0.53 to 2.18. For the 2nd trimester of exposure results (OR) range from 0.83 to 1.67 with a confidence interval range from 0.58 to 2.98. For the 3rd trimester of exposure results (OR) range from 0.88 to 2.00 with a confidence interval range from 0.62 to 3.62. These inconsistent results illustrate the lack of uniformity in the methods employed, difference between cross section, variability of variable’s definition, and the lack of studies, particularly in Europe.

For studies focusing on the whole pregnancy for the relationship between pregnancy adverse outcomes risk and air pollutant exposition: NO$_2$ [64,68,73,75,85,86,91,93], PM$_{10}$ [73,75,86,93], PM$_{2.5}$ [73,75,86,93], only two studies had significant results. Maroziene and Grazulviciene, 2002 [64] suggest that the risk of PTB increases with NO$_2$ exposure (OR = 1.25; 1.07–1.46), while Pedersen et al., 2013 [73] found increased LBW risk with PM$_{2.5}$ exposures (OR = 1.39; 1.12–1.77).

The Pedersen’s study also had nearly significant results for NO$_2$ exposure associated with LBW (OR = 1.09; 1.00–1.19) and for PM$_{10}$ exposure associated with LBW (OR = 1.16; 1.00–1.35). Overall, the results reveal that the risk of adverse outcomes including: PTB [64,85,86,93], LBW [64,73,75], SGA [68,91] was not found to be significantly associated with any of the pollutants. As for the other windows of exposure (each pregnancy trimester), results are very heterogeneous and there appears to be no clear trend regardless of the model used. For NO$_2$ exposure results (OR) range from 0.81 to 1.28 with a confidence interval range from 0.91 to 1.74. For PM$_{10}$ exposure results (OR) range from 0.97 to 1.46 with a confidence interval range from 0.74 to 2.24. And for PM$_{2.5}$ exposures, results (OR) range from 0.92 to 1.98 with a confidence interval range from 0.72 to 4.19.

4. Meta-Analysis

4.1. Main Characteristics

The meta-analysis presented in this study was conducted for 2 combinations between one air pollutant and two birth outcomes during different windows of exposure, when at least four studies were available for the same combination. More precisely, the 2 combinations were NO$_2$ exposure and related with birth weight and PTB. Table 5 describes the measures of the association of the studies included in the meta-analysis.
Table 5. Definitions of measures of association for meta-analysis.

| Type(s) or Subtype(s) Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|---------------------------------|------------------|-------|------------------------|----------------|--------------|
| Birth weight NO\textsubscript{2} | Trimester 1       | LUR   | Beta = 3.3 (~33.2, 39.7) | First Trimester 32.66 µg/m\textsuperscript{3} | Aguilera et al., 2009, [67] |
|                                 |                   |       | Beta = −12.762 (~34.5, 8.9) | 37.9 µg/m\textsuperscript{3} | Ballester et al., 2010, [68] |
|                                 |                   | Dispersion model implemented in ADMS-Urban software. | Beta = −3 (~42, 35) | 24.9 µg/m\textsuperscript{3} in Nancy 16.1 µg/m\textsuperscript{3} in Poitiers | Rahmalia et al., 2012, [72] |
|                                 |                   | LUR and monitoring station | Odds ratio (OR) = 0.96 (0.73, 1.20) | 35.8 µg/m\textsuperscript{3} | Slama et al., 2007, [66] |
|                                 | Trimester 2       | LUR   | Beta = −44.1 (~77.4, −10.8) | INMA: 26.1 µg/m\textsuperscript{3} ENVIRONAGE: 20.7 µg/m\textsuperscript{3} | Clemente et al.; 2016, [83] |
|                                 |                   |       | Beta = −9.961 (~32.5, 12.6) | 35.9 µg/m\textsuperscript{3} | Ballester et al., 2010, [68] |
|                                 |                   | Dispersion model implemented in ADMS-Urban software. | Beta = 11 (~28, 50) | 24.9 µg/m\textsuperscript{3} in Nancy 16.1 µg/m\textsuperscript{3} in Poitiers | Rahmalia et al., 2012, [72] |
|                                 |                   | LUR and monitoring station | OR = 1.18 (0.95, 1.44) | 35.8 µg/m\textsuperscript{3} | Slama et al., 2007, [66] |
|                                 |                   | LUR and kriging interpolation Method, land cover data satellite images | Beta = −36.2 (~70.9, −1.6) | INMA: 25.6 µg/m\textsuperscript{3} ENVIRONAGE: 20.8 µg/m\textsuperscript{3} | Clemente et al.; 2016, [83] |
|                                 | Trimester 3       | LUR   | Beta = 16.8 (~18.8, 52.4) | 32.67 µg/m\textsuperscript{3} | Aguilera et al., 2009, [67] |
|                                 |                   |       | Beta = −4.294 (~25.9, 17.3) | 37 µg/m\textsuperscript{3} | Ballester et al., 2010, [68] |
|                                 |                   | Dispersion model implemented in ADMS-Urban software. | Beta = −3 (~43, 37) | 24.9 µg/m\textsuperscript{3} in Nancy 16.1 µg/m\textsuperscript{3} in Poitiers | Rahmalia et al., 2012, [72] |
Table 5. Cont.

| Type(s) or Subtype(s) Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|----------------------------------|------------------|-------|------------------------|----------------|--------------|
| LUR models and monitoring station | Beta = 4 (−13, 22) | 21.4 µg/m³ | Schembari et al., 2015, [80] |
|                                   | OR = 1.13 (0.91, 1.35) | 35.8 µg/m³ | Slama et al., 2007, [66] |
| LUR and kriging interpolation method, land cover data satellite images | Beta = −37.5 (−71.4, −3.6) | INMA: 25.7 µg/m³ ENVIRONAGE: 21.4 µg/m³ | Clemente et al., 2016, [83] |
| LUR | Beta = 8.8 (−23.8 to 41.5) | 9 months 32.17 µg/m³ | Aguilera et al., 2009, [67] |
| LUR and kriging interpolation model and monitoring station | Beta = −9.729 (−33.218; 13.760) | 36.9 µg/m³ | Ballester et al., 2010, [68] |
|                                   | Beta = −47.5 (−86.6, −8.5) | INMA: 25.5 µg/m³ ENVIRONAGE: 21.1 µg/m³ | Clemente et al., 2016, [83] |
| Dispersion model implemented in ADMS-Urban software. | Beta = 4 (−38 to 46) | 24.9 µg/m³ in Nancy 16.1 µg/m³ in Poitiers | Rahmalia et al., 2012, [72] |
|                                   | Beta = −9 (−15, 34) | 21.4 µg/m³ | Schembari et al., 2015, [80] |
|                                   | OR = 1.21 (0.86, 1.68) | 35.8 µg/m³ | Slama et al., 2007, [66] |
|                                   | Beta = −1 (−6, 4) | 26.2 µg/m³ | Pedersen et al., 2013, [73] |
| Trimester 1 | LUR and kriging interpolation model and monitoring station | Beta = −40.349 (−96.267; 15.568) | 36.9 µg/m³ | Ballester et al., 2010, [68] |
| Trimester 2 | LUR and kriging interpolation model and monitoring station | Beta = −37.546 (−96.231; 21.140) | 36.9 µg/m³ | Ballester et al., 2010, [68] |
| Trimester 3 | LUR and kriging interpolation model and monitoring station | Beta = 26.656 (−28.239; 81.551) | 36.9 µg/m³ | Ballester et al., 2010, [68] |
| Whole pregnancy | LUR and kriging interpolation model and monitoring station | Beta = −33.292 (−84.874; 18.290) | 36.9 µg/m³ | Ballester et al., 2010, [68] |
| NO₂ >40µg/m³ | | | | | |
Table 5. Cont.

| Type(s) or Subtype(s) | Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|-----------------------|------------|------------------|-------|------------------------|----------------|---------------|
|                       |            | Trimester 1      | Network of fixed monitoring stations at 53 different sites throughout the Lombardy region, Northern Italy and representatively distributed in eight geographical areas | Beta = −22.2 (−35.7, −8.7) | 51.0 µg/m³ | Giovannini et al., 2017, [89] |
|                       |            |                  | Dispersion model implemented in ADMS-Urban software. | Beta = −8 (−104–88) | 23.3 µg/m³ in Nancy 16.2 µg/m³ in Poitiers | Rahmalia et al., 2012, [72] |
|                       | PM₁₀       | Trimester 2      | Network of fixed monitoring stations at 53 different sites throughout the Lombardy region, Northern Italy and representatively distributed in eight geographical areas | Beta = −10.1 (−24.2, 4.0) | 51.0 µg/m³ | Giovannini et al., 2017, [89] |
|                       |            |                  | Dispersion model implemented in ADMS-Urban software. | Beta = −4 (−105, 97) | 23.3 µg/m³ in Nancy 16.2 µg/m³ in Poitiers | Rahmalia et al., 2012, [72] |
|                       | PM₁₀       | Trimester 3      | Network of fixed monitoring stations at 53 different sites throughout the Lombardy region, Northern Italy and representatively distributed in eight geographical areas | Beta = −5.1 (−18.4, 8.2) | 51.0 µg/m³ | Giovannini et al., 2017, [89] |
|                       |            |                  | Dispersion model implemented in ADMS-Urban software. | Beta = −18 (−116 to 80) | 23.3 µg/m³ in Nancy 16.2 µg/m³ in Poitiers | Rahmalia et al., 2012, [72] |
|                       |            |                  | LUR models and monitoring station | Beta = −13 (−42, 16) | 21.4 µg/m³ | Schembari et al., 2015, [80] |
|                       | PM₁₀       | Whole pregnancy  | Dispersion model implemented in ADMS-Urban software. | Beta = −6 (−124 to 111) | 23.3 µg/m³ in Nancy 16.2 µg/m³ in Poitiers | Rahmalia et al., 2012, [72] |
|                       |            |                  | LUR models and monitoring station | Beta = −9 (−41, 23) | 21.4 µg/m³ | Schembari et al., 2015, [80] |
|                       |            |                  |                  | Beta = −8 (−19, 3) | 25.4 µg/m³ | Pedersen et al., 2013, [73] |
| Type(s) or Subtype(s) | Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|----------------------|------------|------------------|-------|------------------------|----------------|--------------|
| **PM$_{2.5}$**       |            | Trimester 3      | LUR models and monitoring station | Beta = −12 (−33, 8) | 12.7 µg/m$^3$ | Schembari et al., 2015, [80] |
|                      |            | Whole pregnancy  | LUR models and monitoring station | Beta = −7 (−17, 2) | 16.5 µg/m$^3$ | Pedersen et al., 2013, [73], Schembari et al., 2015, [80] |
|                      |            |                  | LUR models and monitoring station | Beta = −11 (−33, 1) | 12.7 µg/m$^3$ | Pedersen et al., 2013, [73], Schembari et al., 2015, [80] |
|                      |            | Trimester 1      | LUR and monitoring station       | OR = 1.02 (0.61–1.71) | 28.8 µg/m$^3$ | Estarlich et al., 2016, [85] |
|                      |            |                  |                                  | OR = 0.97 (0.92, 1.02) | Missing information | Giorgis-Allemand et al., 2016, [86] |
|                      | **NO$_2$** | Trimester 2      | LUR and monitoring station       | OR = 1.06 (0.86–1.32) | 28.8 µg/m$^3$ | Estarlich et al., 2016, [85] |
|                      |            |                  |                                  | OR = 0.96 (0.92, 1.01) | Missing information | Giorgis-Allemand et al., 2016, [86] |
|                      |            |                  | 12 municipal monitoring sites, one in each residential district | OR = 1.67 (1.28, 2.18) | 11.69 µg/m$^3$ | Maroziene and Grazuleviciene, 2002, [64] |
|                      |            | Trimester 3      | LUR and monitoring station       | OR = 1.02 (0.81–1.27) | 28.8 µg/m$^3$ | Estarlich et al., 2016, [85] |
|                      |            |                  | 12 municipal monitoring sites, one in each residential district | OR = 1.19 (0.96, 1.47) | 11.69 µg/m$^3$ | Maroziene and Grazuleviciene, 2002, [64] |
|                      |            | Whole pregnancy  | LUR and monitoring station       | OR = 1.11 (0.86–1.45) | 28.8 µg/m$^3$ | Estarlich et al., 2016, [85] |
|                      |            |                  | 12 municipal monitoring sites, one in each residential district | OR = 0.96 (0.91, 1.01) | Missing information | Giorgis-Allemand et al., 2016, [86] |
|                      |            | Whole pregnancy  | integrated modelling of atmospheric composition (SILAM) | OR = 0.83 (0.25, 2.74) | (ppb) 4.31 | Siddika et al., 2019, [93] |
|                      |            | Last Week        | LUR and monitoring station       | OR = 0.98 (0.94, 1.01) | Missing information | Giorgis-Allemand et al., 2016, [86] |
|                      |            | Last Month       | LUR and monitoring station       | OR = 0.96 (0.92, 1.00) | Missing information | Giorgis-Allemand et al., 2016, [86] |
Table 5. Cont.

| Type(s) or Subtype(s) | Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|-----------------------|------------|------------------|-------|------------------------|----------------|---------------|
| PM₁₀                  |            |                  |       |                        |                |               |
| Trimester 1           | LUR and monitoring station | OR = 0.98 (0.90, 1.07) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Trimester 2           | LUR and monitoring station | OR = 0.98 (0.90, 1.06) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Whole pregnancy       | LUR and monitoring station | OR = 0.97 (0.87, 1.07) | Missing information | Giorgis-Allemand et al., 2016, [86] |
|                       | Integrated modelling of atmospheric composition (SILAM) | OR = 0.98 (0.74, 1.31) | 21.35 µg/m³ | Siddika et al., 2019, [93] |
| Last week             | LUR and monitoring station | OR = 0.99 (0.95, 1.04) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Last month            | LUR and monitoring station | OR = 0.97 (0.91, 1.03) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Lag 0                 | One monitoring station located in Bloomsbury | OR = 1.00 (1.00, –1.00) | 27 µg/m³ (red on study’s figure) | Lee et al., 2007, [65] |
| Trimester 1           | LUR and monitoring station | OR = 0.98 (0.91, 1.05) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Trimester 2           | LUR and monitoring station | OR = 0.96 (0.90, 1.03) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Whole pregnancy       | LUR and monitoring station | OR = 0.96 (0.87, 1.04) | Missing information | Giorgis-Allemand et al., 2016, [86] |
|                       | Integrated modelling of atmospheric composition (SILAM) | OR = 1.00 (0.72, 1.38) | 19.62 µg/m³ | Siddika et al., 2019, [93] |
| Last week             | LUR and monitoring station | OR = 1.00 (0.96, 1.03) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Last month            | LUR and monitoring station | OR = 0.97 (0.91, 1.02) | Missing information | Giorgis-Allemand et al., 2016, [86] |
| Lag 20                | Network of 27 urban background stations | OR = 1.026 (1.018, 1.034) | 17.1 µg/m³ | Arroyo et al., 2016, [81] |
| Lag 1                 | Network of 27 urban background stations | OR = 1.038 (1.002, 1.074) | 17.1 µg/m³ | Arroyo et al., 2015, [77] |
| Type(s) or Subtype(s) | Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|----------------------|------------|------------------|-------|------------------------|----------------|--------------|
| **LBW**              |            |                  |       |                        |                |              |
|                      |            | Trimester 1      | LUR   | OR = 1.06 (0.94, 1.20) | Median pregnancy: 55.5 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        | 12 municipal monitoring sites, one in each residential district | Maroziene and Grazulevicenie, 2002, [64] |
|                      |            | Trimester 2      | LUR   | OR = 1.04 (0.91, 1.18) | Median pregnancy: 55.5 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        | 12 municipal monitoring sites, one in each residential district | Maroziene and Grazulevicenie, 2002, [64] |
|                      | NO₂        | Trimester 3      | LUR   | OR = 1.03 (0.90, 1.18) | Median pregnancy: 55.5 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        | 12 municipal monitoring sites, one in each residential district | Maroziene and Grazulevicenie, 2002, [64] |
|                      |            | Whole pregnancy  | LUR   | OR = 1.05 (0.94, 1.17) | Median pregnancy: 55.5 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        | 12 municipal monitoring sites, one in each residential district | Maroziene and Grazulevicenie, 2002, [64] |
|                      |            | Lag 14           | LUR   | OR = 1.09 (1.00, 1.19) | 26.2 µg/m³ | Pedersen et al., 2013, [73] |
|                      |            |                  |       |                        | Network of 27 urban background stations | Arroyo et al., 2016, [81] |
|                      |            | Lag 20           | LUR   | OR = 1.014 (1.011, 1.017) | 59.4 µg/m³ | Arroyo et al., 2016, [81] |
|                      | PM₁₀       | Trimester 1      | LUR   | OR = 1.00 (0.82, 1.22) | Median pregnancy: 39.2 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        |                      |              |
|                      |            | Trimester 2      | LUR   | OR = 1.20 (0.96, 1.48) | Median pregnancy: 39.2 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        |                      |              |
|                      |            | Trimester 3      | LUR   | OR = 1.26 (1.06, 1.51) | Median pregnancy: 39.2 µg/m³ | Dadvand et al., 2014, [75] |
|                      |            |                  |       |                        |                      |              |
|                      |            | Whole pregnancy  | LUR   | OR = 1.16 (0.98, 1.37) | Median pregnancy: 39.2 µg/m³ | Dadvand et al., 2014, [75] |
Table 5. Cont.

| Type(s) or Subtype(s) | Pollutants | Critical Windows | Model | Measure of Association | Mean Study Area | Authors, Date |
|----------------------|------------|------------------|-------|------------------------|-----------------|---------------|
|                      |            |                  |       |                        |                 |               |
|                      | PM$_{2.5}$ | Trimester 1      | LUR   | OR = 1.16 (1.00, 1.35) | 25.4 µg/m$^3$  | Pedersen et al., 2013, [73] |
|                      |            | Trimester 2      | LUR   | OR = 1.07 (0.88, 1.29) | Median pregnancy 16.9 µg/m$^3$ | Dadvand et al., 2014, [75] |
|                      |            | Trimester 3      | LUR   | OR = 1.19 (0.97, 1.45) | Median pregnancy 16.9 µg/m$^3$ | Dadvand et al., 2014, [75] |
|                      |            | Whole pregnancy  | LUR   | OR = 1.24 (1.03, 1.49) | Median pregnancy 16.9 µg/m$^3$ | Dadvand et al., 2014, [75] |
|                      | SGA        | Trimester 1      | LUR and kriging interpolation model and monitoring station | OR = 1.182 (0.894; 1.563) | 37.9 µg/m$^3$ | Ballester et al., 2010, [68] |
|                      | NO$_2$     | Trimester 2      | dispersion model | OR = 0.78 (0.55, 1.12) | 23.1 µg/m$^3$ | Mariet et al., 2018, [91] |
|                      |            | Trimester 3      | LUR and kriging interpolation model and monitoring station | OR = 1.369 (1.013; 1.849) | 35.9 µg/m$^3$ | Ballester et al., 2010, [68] |
|                      |            | dispersion model | OR = 0.83 (0.58, 1.19) | 23.1 µg/m$^3$ | Mariet et al., 2018, [91] |
|                      |            | Whole pregnancy  | LUR and kriging interpolation model and monitoring station | OR = 1.186 (0.906; 1.532) | 37 µg/m$^3$ | Ballester et al., 2010, [68] |
|                      |            | dispersion model | OR = 0.88 (0.62, 1.25) | 23.1 µg/m$^3$ | Mariet et al., 2018, [91] |
|                      |            | Las two month    | Dispersion model | OR = 0.88 (0.62, 1.25) | 23.1 µg/m$^3$ | Mariet et al., 2018, [91] |

LUR: land-use regression, LBW: low birth weight, PTB: preterm birth, w: week(s), NO$_2$: nitrogen dioxide, PM: particulate matter; PM$_{10}$: particulate matter with an aerodynamic diameter up to 10 µm; PM$_{2.5}$: particulate matter with an aerodynamic diameter up to 2.5 µm, ADMS: Atmospheric Dispersion Modelling System.
In order to differentiate the health effect related to each trimester and entire pregnancy, stratified analyses have been performed, only when this is possible. For the combination between NO$_2$ and preterm birth, it was conducted for the entire pregnancy only. Following these conditions, we produced, finally, 5 meta-analyses. Of these, heterogeneity (Q-test) tests indicated one meta-analyses with high $I^2$ (I-square indicator) values (above or close to 50%) for which random effects models were applied (for the other four combinations, fixed models were used). Heterogeneity varied from 25.2% to 72.3%, indicating that measurement methods, sample properties, and characteristics varied both among and within different studies.

4.2. Birth Weight

As shown in Figure 5, the exposure of NO$_2$ during any windows of exposure on birth weight was not statistically significant. The overall analysis did not reveal a significant decrease of birth weight in pooled beta for any windows of exposure: for second trimester the pooled beta is: $-8.35$, 95% CI ($-23.04, 6.34$) (Figure 6), for the third trimester: pooled beta $= -7.04$, 95% CI ($-19.90, 5.81$) (Figure 7). It is interesting to note here that the exposure of NO$_2$ during the first trimester tends to show a nearly significant decrease of birth weight in pooled beta $= -13.63$, 95% CI ($-28.03, 0.77$). Finally, regarding whole pregnancy, as shown in the Figure 8, the exposure of NO$_2$ during the entire pregnancy on birth weight was not statistically significant. The overall analysis did not reveal a significant decrease of birth weight in pooled beta (fixed models: pooled beta $= -1.40$, 95% CI ($-6.08, 3.29$)).

4.3. Preterm Birth

As shown in Figure 9, the exposure of NO$_2$ during the entire pregnancy on birth weight was not statistically significant, and did not reveal a significant increase of the risk of preterm birth in pooled OR (pooled OR $= 1.07$, 95% CI (0.90, 1.28)).

4.4. Sensitivity Analysis

To estimate the stability of our results, sensitivity analysis was performed by recalculating the pooled effects estimates after omitting one study each time as long as there remained at least 4 studies (Appendix B). We found that the effect estimates of each 10 $\mu$g/m$^3$ increase in NO$_2$ exposure during the entire pregnancy on birth weight showed no significant change by removing one single study, suggesting that the combined results were relatively stable and reliable. This is except for the sensitivity analysis of the association between birth weight and NO$_2$ exposure during the third trimester of pregnancy, where the omission of the study of Clemente et al. (2016) [83] induced a reverse of the association that was hitherto negative (Table A1); however, the result was still not statistically significant (beta $= 2.5$, 95% CI $= (-9.18, 14.30$)). Small variations were visible, and while point combined estimates were rather similar, the precision level of the confidence interval decreased.
Figure 5. Association between birth weight and NO$_2$ exposure during the first trimester of pregnancy.
Figure 6. Association between birth weight and NO$_2$ exposure during the second trimester of pregnancy.
Figure 7. Association between birth weight and NO$_2$ exposure during the third trimester of pregnancy.
Figure 8. Association between birth weight and NO₂ exposure during the entire pregnancy.
Figure 9. Association between preterm birth and NO₂ exposure during the entire pregnancy.
5. Discussion

5.1. Main Finding

Our systematic review does not show significant results, but despite this a trend is apparent in that NO\textsubscript{2} exposure during the whole pregnancy seems to increase the prevalence of LBW. In addition, the result of published European studies included in our systematic review tend to show an increased risk of LBW with a 10 µg/m\textsuperscript{3} increase in PM\textsubscript{2.5} and PM\textsubscript{10}, specifically for long-term exposure including exposure during last trimester and whole pregnancy. By contrast, no significant excess risk of adverse birth outcomes has been found regardless of pollutant or short-term window of exposure (each trimester).

Our meta-analysis does not reveal a significant result, and the exposure of NO\textsubscript{2} during the first, second or third trimester on birth weight was not statistically significant. The overall analysis did not reveal a significant decrease of birth weight in pooled beta. For the PTB outcome and the exposure of NO\textsubscript{2} during the entire pregnancy, the overall analysis did not reveal a significant increase of the risk of preterm birth in pooled-OR.

The characteristics of the different studies (design, adjustment, definition of the outcomes ....) (see Appendix F, Tables A3 and A4) did not change the meta-risks estimated with the classical meta-analysis approach (data not shown).

These results for long-term exposure converge with international meta-analysis (see results in Appendix G) which show positive correlation between PM\textsubscript{2.5}, PM\textsubscript{10}, NO\textsubscript{2}, exposures during the entire pregnancy and LBW. Conversely, international studies tend to show significant association between LBW and ambient air pollutant also during short-term exposure.

These results could be partially explained by methodological limitations inherent in the heterogeneity of the method of exposure assessment, definition of adverse birth outcome, definition of confounders and critical windows of exposure, thus limiting the number of studies usable in the meta-analysis which can reduce the statistical significance of possible risk.

The main hypotheses for the biological mechanism are that ambient air pollution could cause inflammation, oxidative stress, affect placental growth, decrease placental exchange, lead to endocrine disruption, etc. More specifically, oxidative stress induces DNA damage and mitochondrial DNA damage, and fosters inflammation, which appear to be important mechanisms of fetal growth. Another specific mechanism affects the placenta; the maternal and fetal circulation are separated by the placental barrier; this barrier contains placental transporters that can regulate or facilitate external compounds. Transient receptor potential channels are highly expressed in the placenta, and they can be affected by air pollution exposure. Non-human animal studies reveal that these receptors play important roles in placental development and regulating the fetal–maternal interface in mice models.

5.2. Outcome Data: Case Selection

We identified many pathways whose outcome information can lead to a bias in the assessments of association. Firstly, outcome definition itself could constitute a source of uncertainty and lead to qualification bias. Many studies investigated birth weight or gestational age, but most investigated specific pathological outcomes; first, several studies investigated LBW and subtypes (VLBW, ELBW): birth weight <2500 g International Classification of Diseases 10th Revision; ICD-10: P07.0–P07.1 [64,70,73,75,81,84], birth weight <3000 g [65], VLBW between 1500 g and 2500 g [83] and ELBW <1500 g [83]. Several studies investigated PTB and subtypes: birth occurring before the 37th week of pregnancy; ICD-10: P07.2–P07.3 [64,65,69,78,81,85,87,90,92,93] birth occurring between the 33th and the 37th week of pregnancy [79], birth occurring between the 22th and the 36th week of pregnancy [74], birth occurring between the 30th and the 37th week of pregnancy [77], birth occurring before the 33th week of pregnancy [79], birth occurring before the 30th week of pregnancy [77], birth occurring before the 24th week of pregnancy [87]. Last but not least, some studies...
investigated SGA: birth weight or length below the 10th percentile according to standard percentile charts for sex and gestational age in the population; ICD10 codes in medical records, O36.5, P05.0, P05.1 [68,70,75,82,91]. Databases were drawn mainly from birth certificate information and health database from hospital information systems while other from institutes of national health statistics and cohort database. In addition, the databases used to collect health data including maternal and newborn characteristics are another source of limitation. PTB and LBW were the most frequently investigated outcomes in included studies. This is an expected finding because, according to the WHO, these outcomes are technically simple parameters to monitor prenatal health in a population and have short- and long-term public health implications. Assessment of gestational duration was most often based on the date of last menstrual period, which could introduce misclassification with recall bias depending on postconceptional bleeding, but also, menstrual irregularities, or late access to prenatal care [70].

5.3. Confounding Factors

Our findings need to be interpreted with prudence due to weaknesses that could affect the significance of the associations and then the redaction of accurate conclusions. The different adjustment factors used in each study and the different sample size may lead to difficulties between studies comparisons.

Indeed, most studies were adjusted for mothers’ characteristics (smoking during pregnancy, passive smoking during pregnancy, parity, education, race/ethnicity, age, gestational age, height, pre-pregnancy weight, etc.) [64,66–76,78–80,82,83,85–90,93] Some studies used birth characteristics (sex, birth order, fetal size) [67–73,75,76,78,80,82,83,85,86,88,89,91,93]. Other used neighborhood characteristic (city, exposure to other air pollutants, socioeconomic status, type and length of roads, population density, land coverage around the home address, temporal variations in pollution during pregnancy . . . ) [66,68–71,75,76,78,79,82,85–87,90,91,93]. Some of them used other characteristics like meteorological characteristic (e.g., temperature, humidity, season of conception or birth) [64,65,67–72,74–76,78–89,91–93]. Only one study did not use any covariates [77].

5.4. Exposure Assessment

Our systematic review revealed that several approaches for exposure assessment during pregnancy were implemented, and this could induce misclassification of exposure. Some papers have used average from monitoring existing stations [64,65,74,77,81,84,87] or a monitoring station-based approach with an average from all monitoring stations [89,92]. The size of the study area and the number of monitoring stations vary between studies and this may increase the level of heterogeneity of air pollution measurement. The number of monitoring stations varied between a minimum of 1 [65,87] and a maximum of 53 [89]. Consequently, there is a risk of bias when a small number of monitoring stations cover a wide area. The weak spatial representativeness of exposure influences the assessment of the residential exposure of pregnant women. Moreover, collection of these data is often based on national air quality guidelines and legislation and thus may not be optimal in the assessment of exposure and use with health data.

Most of the studies used modeling-based approaches with, on the one hand, LUR [66–69,71,73,75,76,78,80,83,85,86], and on the other hand dispersion models [70,72,76,79–91]. Few studies use other models as spatial temporal interpolation method (Kriging method) [81] and SILAM model [93]. These models allow to quantify individual levels of exposure and investigate the health consequences of exposure.

Even if modelling is the gold standard for environmental and health impact assessment, some bias may exist. Overall modelling approaches did not consider residential and daily mobility of pregnant women across the study area and thus exposure misclassification may occur. Finally, environmental modelling can hardly be applied for outdoor and indoor pollution concurrently; notably because of a
lack of information on the correlation of indoor and outdoor air pollution depends on geographical and meteorological conditions, building types and systems, and air exchange rates [103].

5.5. Critical Windows of Exposure

The definition of window of exposure could induce exposure misclassifications. In our systematic review, two main approaches define the window of exposure in order to investigate the relationship between birth outcomes and residential exposure: long-term exposure, and short-term exposure.

To investigate pollutant exposure, studies used diverse windows of exposure, some of them used short-term daily exposure [65,74,77] or short-term cumulative exposure [65,82,87]. For example, different indicators for daily exposure were identified: the day of the birth (Lag0) [65,74], the day before birth (Lag1) [74] or longer lags such as from lag 1 to lag7 [74,77], or from lag 1 to lag 30 [74] (see Table 4). The studies that investigated short-term cumulative exposure examined also different windows of exposure including over 1 days before birth (lag0–1) [65], over 2 days (Lag0–2) [65,87], 3 days (Lag0–3) [65], 4 days (Lag0–4) [65], 5 days (Lag 0–5) [65], over 6 days before death (Lag 0–6) [65] or for the last week of pregnancy (lag 0–7) [82]. Several studies used long-term exposure, based on cumulative exposure during a given period of pregnancy, with diverse windows [82,84,86,91], but most used weekly exposure [81,84,87,88,92], trimester of pregnancy exposure [64,67–73,75,76,80,82,83,85,89,91,92] and 9 months of pregnancy exposure [64,66–73,75,76,80,83,85–87,91,93]. Finally, some studies investigated with no specific windows and used annual exposure [78,79,90] (see Table 4). Previously, certain meta-analysis and systematic reviews have reported that 1st trimester, 3rd trimester and last gestational month may be a possible critical window of exposure for preterm birth [25].

5.6. Assessment Approach and Mean Level of Exposure

The results found in the studies selected may vary according to mean level of exposure in each country, and particularly in each area of study. Our systematic review reveals that the risk of adverse birth outcome tends to be higher among study areas with low air pollutant average concentration. However, we highlight that these studies used mainly monitoring station. Some studies tried to estimate the discrepancy between results in the association between air pollution and birth outcome with different methods for estimating exposure [104,105]. They found that the level of NO2 during pregnancy estimated by the nearest air quality monitoring station (AQMS) and by the temporally adjusted geostatistical model (TAG), tend to show the same associations [104,105]. For PM, the use of the nearest AQMS or dispersion models indicated consistent results both in terms of exposure estimates and association with birth weight [105]. Studies tend to show that AQMS and kriging rather predict the average level of pollutant in the urban area, whereas local patterns of variation and LUR might be the most robust methods to predict long-term exposure in complex areas [106]. In this way, pertinence of the method used for the exposure assessment mainly depends on the time-window length and endpoints considered, the spatio-temporal variability of the pollutants and the population’s mobility [76].

5.7. Limitations and Risk Estimate of Birth Outcome

The features of the studies described above—such as study population, study design, sample size, the classification and definition of infant death, exposure assessment, difference between interquartile (IQR) used to assess the increase of exposure (Appendix H) and confounding factors—could all, independently or in combination, affect the quality of each study itself and, also, their comparison in our systematic review. Some factors may overestimate while other one may underestimate the risk of birth outcome.

The loss of precision inherent to such a general classification scheme (the definition of outcome and included all live birth) may reduce the likelihood of detecting an association between low birth weight and the study exposures. For instance, broad groupings of low birth weight into all LBW
including term and preterm birth have also hampered the ability to examine associations for specific LBW by diluting relevant cases.

One source of such limitation lies in the databases. Using linked birth-hospital databases may reduce the likelihood of missing information, because it includes all birth information collected throughout birth, rather than only from institutes of national health statistics and cohort databases. Missing data, if not included, may yield the same effect, so that risk estimates of birth outcome, in particular, may be inaccurate.

In addition, the various confounding factors included in the individual studies make difficult the comparisons between studies. An absence of systematic adjustment for commonly known factors may affect the measure of association and thus the comparisons of all the risk estimates—for instance, folic acid supplementation, or information on dietary factors which are known to decrease the risk of birth outcome. These risk factors tend to vary across the unit of analysis and if they are coincident with the exposure measures, then these spatial confounders will bias the results of the study.

Exposure misclassification may occur where the birth certificate address does not reflect the mother’s true residence during the relevant window of fetal development. To assign exposure, many studies used maternal address at delivery rather than address around conception and during each trimester. This can have a particular impact on studies exploring the risk of birth outcome. Misclassification of exposure may occur following changes in residence during the pregnancy. Some studies revealed that residential mobility among pregnant women between conception and delivery ranged from about 12% in the former to 32% according country. In addition, this residential mobility may vary according to certain individual and contextual characteristics such as age, race, socioeconomic status and other factors including socioeconomic characteristics. This means that the exposure misclassification error due to using delivery address might be greater among younger mothers than among older ones, a phenomenon that might result in confounding—because age is also associated with the risk of poor pregnancy outcome. Therefore, where authors have restricted their analysis to women who resided at the address noted on the medical record before delivery, a slight increase of risk estimate may be observed.

Finally, misclassification of exposure may result from the use of postcode, census block or city level to define the location of maternal residence. These spatial units might not be valid measures of exposure level because they vary considerably in size and are irregular in shape. Therefore, the larger the spatial unit, the more likely it is that bias will be introduced due to heterogeneity within these units, and ecological fallacy may result.

5.8. European Versus International Systematic Review: Comparison with Previous International Systematic Reviews

The limited systematic review of European studies may explain the result obtained. Appendix D summarizes the main characteristics and results of previous systematic review and meta-analysis studies selected to compare our results. Most of the earlier reviews were based on cohort design studies like our systematic review. However, all previous systematic review was based on mostly US studies. Similar methodological issues were identified by previous systematic review including outcome and difference in the characterization of exposure and outcome and control of confounding factors.

However, the European average concentration of air pollutants seems to be lower than international average concentrations, moreover the results found in the studies selected may vary according to mean level of exposure in each country, and particularly in each area study. Our results reveal that, in Europe-based studies, the risk of adverse birth outcome tends to be higher among study area with low air pollutant average concentration.

Our findings for long-term exposure converge with international meta-analysis (see results in Appendix D) which show a positive correlation between PM$_{2.5}$, PM$_{10}$, NO$_2$, exposures during the entire pregnancy and LBW [94]. Conversely, international studies tend to show significant association between LBW and ambient air pollutant also during short-term exposure.
5.9. Limitations

To complement the limitations described earlier, both our systematic review and our meta-analysis, present their own strengths and limitations. First, our search could suffer from study selection biases. Non-English publications of relevant articles may have been ignored. Furthermore, we cannot exclude the possibility that our systematic review could be impacted by publication bias. Indeed, unpublished results (including grey literature and results not statistically significant, which are not available) may influence our meta-analysis findings towards the statistical significance of the risk estimates.

6. Public Health Implication

To date the main inherent limitation of environmental health risk assessments is related to uncertainties of the assumptions made about the dose–response function. More particularly, the potential limitations of geographic extrapolation of the shape of the risk function may be less well-defined in some geographic areas with the lowest concentrations. In some studies, the authors used the exposure–response function from only one cohort US study [107] while the other one used meta-analysis as a source to estimate the burden [108]. To our knowledge no European meta-analysis permits us to provide a more appropriate source of risk function in order to perform HIAs in European countries with the lowest concentration levels. Thus, the burden could derive from a non-coherent shape risk function that carries larger uncertainties. Our meta-analysis results provide pooled-risk for 5 combinations of air pollutant and birth weight and PTB, which may provide a coherent exposure–response function for environmental health risk assessments in European countries.

7. Conclusions

In spite of the limited number of epidemiological studies selected in the present literature review, our finding suggests that an increase air pollution exposure during pregnancy might contribute to adverse birth outcomes, especially LBW. This body of evidence has limitations that impede the formulation of firm conclusions and so new well-focused European studies are called for.

Our findings need to be interpreted with prudence due to weaknesses that could affect the significance of the associations and hence the drawing of accurate conclusions. Further studies, well-focused on European countries, are called for to resolve these limitations; in particular, the definition of the exposure assessment, the critical windows of exposure and the different adverse birth outcomes, which could affect the strength of association. Future studies could be based on this analysis of limitations of the current body of research, which may provide inspiration for research agenda improvements.

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Figure A1. Risk of birth outcome for air pollutant exposure during overall pregnancy.
Figure A2. Risk of birth outcome for air pollutant exposure during first trimester.
Appendix C

Figure A3. Risk of birth outcome for air pollutant exposure during second trimester.
Appendix D

Figure A4. Risk of birth outcome for air pollutant exposure during third trimester.
Appendix E

Table A1. Sensitivity analysis: birth weight and NO\textsubscript{2} exposure during the third trimester of pregnancy.

| Study Omitted       | Beta       | [95% Confidence Intervals] |
|---------------------|------------|---------------------------|
| Aguilera et al., 2009 [67] | -4.29      | -16.48                    | 7.60         |
| Ballester et al., 2010 [68] | -0.82      | -13.74                    | 12.10        |
| Rahmalia et al., 2012 [72] | -1.63      | -13.18                    | 9.92         |
| Schembari et al., 2015 [80] | -5.59      | -19.93                    | 8.76         |
| Clemente et al., 2016 [83] | 2.55       | -9.18                     | 14.30        |
| Pooled estimate     | -1.95      | -14.50                    | 10.54        |

Table A2. Sensitivity analysis: birth weight and NO\textsubscript{2} exposure during the whole pregnancy.

| Study Omitted       | Beta       | [95% Confidence Intervals] |
|---------------------|------------|---------------------------|
| Aguilera et al., 2009 [67] | -1.60      | -6.33                     | 3.13         |
| Ballester et al., 2010 [68] | -1.05      | -5.83                     | 3.73         |
| Clemente et al.; 2016 [83] | -0.72      | -5.44                     | 3.99         |
| Rahmalia et al., 2012 [72] | -1.47      | -6.18                     | 3.25         |
| Schembari et al., 2015 [80] | -1.79      | -6.57                     | 2.98         |
| Pedersen et al., 2013 [73] | -4.26      | -17.69                    | 9.16         |
| Pooled estimate     | -1.81      | -8.01                     | 4.37         |

Appendix F

Text. Quality effect model methods

Individual quality assessment methodology was adapted from Croteau et al. in 2009 and doi and Thalib in 2008. The checklist was defined by researcher consensus. It assigned a maximum of 1.00 point for the different methodological criteria and a quality score (\( Q_i = \left( \frac{\sum_{j=1}^{10} \text{score criteria}_j}{10} \right) \)) is calculated for each study included in the meta-analysis.

Ten criteria are defined as follows:

1- Sample size (1): completely satisfactory/justified by power analysis; (0.5): somewhat satisfactory; (0): not sufficient/not justified.

2- Design (1): cohort; (0.75): case-crossover; case-control; (0.5): ecological; time series

3- Country where the study was carried out (1): With good working and living conditions/high socio-economic standard; (0.5): Difficult conditions/lower socio-economic standard; (0.25): Very difficult conditions/very low socio-economic standard; (0): Not reported. (1: USA, UK, Sweden, Latin America; 0.5: China)

4- Timeframe (1): Reported; (0): Not reported.

5- Geocodage rate (1): ≥80%/considerable part of the population; (0.75): Not reported.

6- Definition of infant death (1): infant death excluding death due to accident and external causes or specific cause death; (0.75): death among singleton birth or among term birth; (0.5): overall death.

7- Assessment of infant death (1): valid database; (0.5): self-report; (0): not specified.

8- Assessment of the exposure (1): individual measure; (0.75): fine spatial level (zip code, municipality, ward level) (0.5): country level

9- Adjustments for covariates (cov) (1): At least 1 (cov) in each of the three covariates (baby’s characteristic, mother’s characteristics, or meteorological condition), (0.75): At least 1 (cov) baby’s characteristic and at least 1 (cov) mother’s characteristic (or meteorological condition); (0.5): At least 1 (cov) in meteorological condition; (0): no covariates

10- Effect size calculation for meta-analysis based on odds ratios (1): no transformations and no data imputation; (0.75): mild transformation and no data imputation; (0.5): several transformations and no data imputation; (0.25): considerable transformations and data imputation
Table A3. Qualitative analysis (part 1).

| Auteurs                      | Population size | Study design, period location, Country | Timeframe | Monitoring station or model | Assessment of birthweight | Adjustments for personal covariates |
|------------------------------|-----------------|----------------------------------------|-----------|-----------------------------|---------------------------|-------------------------------------|
| Aguilera et al., 2009 [67]   | 570 (1)         | Sabadel, Spain (1)                     | 2004–2006 (1) | LUR model, passive samplers and fix monitoring station (1) | recorded by specially trained midwives at delivery (1) | - Maternal characteristic: tobacco smoking during pregnancy, Passive smoking during pregnancy, Parity, Education, Race/ethnicity, Age, Gestational age, Height, Pre-pregnancy weight |
| Ballester et al., 2010, [68] | 785 (1)         | Valencia, Spain (1)                    | 2004–2005 (1) | Land-use regression model, kriging interpolation model and monitoring station (1) | recorded by specially trained midwives at delivery (1) | - Maternal characteristic: lifestyle variables twice during their pregnancy, Maternal age, Pre-pregnancy weight, Height, Gestational weight gain, Parity, Education, Smoking during pregnancy, Country of origin, Season of last menstrual period, Birth characteristics: Sex, Neighborhood characteristics: Socio-demographic characteristics, Others: Environmental exposure, Paternal weight (1) |
| Clemente et al., 2016. [83]  | 376 (1)         | Spain, Belgium (1)                     | 2004–2008, 2010–2013 (1) | LUR and monitoring station (1) | recorded by specially trained midwives at delivery (1) | - Maternal characteristic: age, Maternal smoking status, Education, Pre-pregnancy maternal BMI, Birth characteristics: Gestational age, Sex, Others: Season of birth (1) |
| Pedersen et al., 2013 [73]   | 74,178 (1)      | European country (1)                   | 1994–2011 (1) | LUR and monitoring station (1) | recorded by specially trained midwives at delivery and self-report (0.5) | - Maternal characteristic: parity, Active smoking, and education. Birth characteristics: Sex, (0.75) |
| Rahmalia et al., 2012, [72]  | 1154 (1)        | Poitiers, Nancy, France (1)            | 2003–2006 (1) | Dispersion model implemented in ADMS-Urban software (1) | recorded by specially trained midwives at delivery (1) | - Maternal characteristic: height, Pre-pregnancy weight, Parity, Age at end of education, Second trimester smoking, Active smoking, Birth characteristics: Gestational duration, Infant sex, Others: Season of last menstrual period, Center of recruitment (1) |
| Schembari et al., 2015 [80]  | 9067 (1)        | England (1)                            | 2007–2010 (1) | LUR models and monitoring station (1) | recorded by specially trained midwives at delivery (1) | - Maternal characteristic: ethnicity (for adjusted and stratified), Age, Height, Pregnancy weight at first gynecological visit, Parity, Active smoking during pregnancy, Education, and Housing tenure Birth characteristics: Sex, Gestational age, 2-hr post load plasma glucose test, Others: Season of conception, (1) |

| Exposure level               | Individual level (1) | Individual level (1) | Individual level (1) | Individual level (1) | Individual level (1) | Individual level (1) |
|------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Geocodage rate               | Not reported (0.75)  | Not reported (0.75)  | Not reported (0.75)  | Not reported (0.75)  | Not reported (0.75)  | Not reported (0.75)  |
| Quality index (Qi)           | 0.972                | 0.972                | 0.972                | 0.972                | 0.806                | 0.972                |
Table A4. Qualitative analysis (part 2).

| Auteurs          | Population size | Study design, period location, | Country                  | Timeframe        | Monitoring station or model | Assessment of birthweight | Adjustments for personal covariates | Exposure level | Geocodage rate | Quality index (Qi) |
|------------------|-----------------|-------------------------------|--------------------------|------------------|-----------------------------|----------------------------|-------------------------------------|----------------|----------------|--------------------|
|                   | 2409 (1)        | cohort (1)                    | Asturias, Gipuzkoa, Sabadell and Valencia, Spain (1) | 2003–2008 (1)   | LUR and monitoring station (1) | Medical data and Self-report (0.5) | - Maternal characteristic: socio-economic status, Active smoking during pregnancy, maternal age | Individual level (1) | Not reported (0.75) | 0.917 |
|                   | 71,493 (1)      | cohort (1)                    | 11 European countries (1) | 1994–2001 (1)   | LUR and monitoring station (1) | Medical data and Self-report (0.5) | - Maternal characteristic: age, education, mother alone, parity, smoking, height and weight, pregnancy hypertension birth characteristics: sex, cesarean delivery neighborhood characteristics: country-others: meteorological factors, season of conception, Outdoor temperature, humidity, and atmospheric pressure, (1) | Individual level (1) | Not reported (0.75) | 0.917 |
|                   | 3988 (1)        | cohort (1)                    | Kaunas, Lithuania (1)    | 1998 (1)        | valid database (1)            | Medical data and Self-report (0.5) | Maternal characteristic: parity, age, marital status, education, maternal and paternal smoking, birth characteristics: gestational age others season of birth (1) | Residential district (0.75) | Not reported (0.75) | 0.889 |
| Siddika et al., 2019, [93] | 2568 (1)        | cohort (1)                    | Espoo, Finland (1)       | 1984–1990 (1)   | valid database (1)            | valid database (1)           | Maternal characteristic: age, smoking during pregnancy, exposure to environmental tobacco smoke during pregnancy, single parenthood birth characteristics: sex neighborhood characteristics: exposure to other air pollutants, family’s socioeconomic status, (1) | Individual level (1) | Not reported (0.75) | 0.972 |
## Appendix G

### Table A5. Meta-analysis comparison.

| First Author          | Number of Study Included | Main Location | Main Design | Main Exposure Assessment | Pollutant | Outcomes |
|-----------------------|-------------------------|---------------|-------------|--------------------------|-----------|----------|
|                       |                         |               |             |                           | PM<sub>10</sub> |          |
| Li et al., 2017 [56]  | 23                      | USA           | cohort design | ground-based monitoring data | NO<sub>2</sub> | NA       |
|                       |                         |               |             |                           | PM<sub>2.5</sub> |          |
|                       |                         |               |             |                           | NO<sub>2</sub> |          |
| Stieb et al., 2012 [32] | 61                     | North America | central site monitoring data | NA | NA |
|                       |                         |               |             |                           | PM<sub>10</sub> |          |
|                       |                         |               |             |                           | PM<sub>2.5</sub> |          |
|                       |                         |               |             |                           | NO<sub>2</sub> |          |
| Klepac et al., 2018 [26] | 48                     | North America | cohort design | routine monitoring data | NA | NA |

| Pollutant | PTB OR (95%CI) | BW Beta (95%CI) | LBW OR (95%CI) |
|-----------|----------------|-----------------|----------------|
| PM<sub>10</sub> | 1T 1.03 (1.00, 1.06) | 2T 1.01 (0.93, 1.10) | 3T 1.02 (0.99, 1.04) |
|           | EP 1.02 (0.93, 1.12) | EP (IQR) 1.03 (1.01, 1.05) |          |
| NO<sub>2</sub> | 1T 0.97 (0.87, 1.07) | 2T 0.95 (0.91, 0.99) | 3T 1.06 (1.03, 1.11) |
|           | EP 1.35 (0.97, 1.90) |                   |          |
| PM<sub>2.5</sub> | 1T 0.85 (0.60, 1.20) | 3T 1.05 (0.98, 1.13) | EP 1.16 (1.07, 1.26) |
|           |                   |                   |          |
| NO<sub>2</sub> | 1T 0.87 (0.64, 1.17) | 3T 1.06 (0.96, 1.18) | EP 1.16 (0.83, 1.63) |
|           |                   |                   |          |
| PM<sub>10</sub> | 1T 1.04 (1.01, 1.08) | 2T 1.04 (0.98, 1.09) | 3T 1.00 (0.99, 1.00) |
|           | 1M 1.05 (0.90, 1.24) | 1M 1.01 (0.99, 1.03) |                   |
|           |                   |                   |          |
| PM<sub>2.5</sub> | 1T 1.09 (1.03, 1.16) | 2T 1.03 (0.95, 1.11) | 3T 1.05 (1.02, 1.09) |
|           | 1M 1.04 (0.91, 1.19) | 1M 1.04 (0.98, 1.10) |                   |
|           |                   |                   |          |
| First Author | Number of Study Included | Main Location | Main Design | Main Exposure Assessment | Pollutant | Outcomes |
|--------------|--------------------------|---------------|-------------|--------------------------|-----------|----------|
|              |                          |               |             |                          | NO2       | PTB OR (95%CI) | BW Beta (95%CI) | LBW OR (95%CI) |
|              |                          |               |             |                          |           | 1T 0.99 (1.95, 1.03) | NA | NA |
|              |                          |               |             |                          |           | 2T 1.02 (0.97, 1.08) | NA | NA |
|              |                          |               |             |                          |           | 3T 1.02 (0.96, 1.08) | NA | NA |
|              |                          |               |             |                          |           | 1M 0.91 (0.80, 1.04) | NA | NA |
|              |                          |               |             |                          |           | LM 1.03 (1.00, 1.05) | NA | NA |
|              |                          |               |             |                          |           | EP 1.05 (0.99, 1.11) | NA | NA |

PM$_{10}$ and PM$_{2.5}$: per 10 mg/m$^3$ increment and 20 mg/m$^3$ increment (depending on study) NO$_2$: per 10 ppb increment, OR: odds ratio, PTB: preterm birth, BW: birthweight, LBW: low birth weight, PM: particulate matter; PM$_{10}$: particulate matter with an aerodynamic diameter up to 10 µm; PM$_{2.5}$: particulate matter with an aerodynamic diameter up to 2.5 µm; NO$_2$: nitrogen, 1T: first trimester, 2T: second trimester, 3T: third trimester, 1M: first month, LM: last month, EP: entire pregnancy.
Appendix H

Table A6. Interquartile range (IQR) table for NO$_2$ exposure ($\mu$g/m$^3$).

| Studies                     | First Trimester IQR | Second Trimester IQR | Third Trimester IQR | Whole Pregnancy IQR |
|-----------------------------|--------------------|----------------------|---------------------|---------------------|
| Aguilera et al., 2009 [67] | 12.27              | 12                   | 12.47               | 9.51                |
| Ballester et al., 2010 [68] | 10                 | 10                   | 10                  | 10                  |
| Rahmalia et al., 2012 [72] | 10                 | 10                   | 10                  | 10                  |
| Schembari et al., 2015 [80]| NA                 | NA                   | 10                  | 10                  |
| Clemente et al., 2016 [85] | 10                 | 10                   | 10                  | 10                  |
| Estarlich et al., 2016, [85]| 10                 | 10                   | 10                  | 10                  |
| Maroziene and Grazuleviciene, 2002 [64] | 10 | 10 | 10 | 10 |
| Giorgis-Allemand et al., 2016 [86]| 10 | 10 | NA | 10 |
| Siddika et al., 2019 [93] | NA                 | NA                   | NA                  | 18.8                |
| Dadvand et al., 2014 [75] | 20.5               | 19.9                 | 18.7                | 16.8                |
| Pedersen et al., 2013 [73] | NA                 | NA                   | NA                  | 10                  |
| Mariet et al., 2018 [91]  | 10                 | 10                   | 10                  | 10                  |

Table A7. IQR table for PM$_{10}$ exposure ($\mu$g/m$^3$).

| Studies                     | First Trimester IQR | Second Trimester IQR | Third Trimester IQR | Whole Pregnancy IQR |
|-----------------------------|--------------------|----------------------|---------------------|---------------------|
| Rahmalia et al., 2012 [72] | 10                 | 10                   | 10                  | 10                  |
| Schembari et al., 2015 [80]| NA                 | NA                   | 10                  | 10                  |
| Giorgis-Allemand et al., 2016 [86]| 10 | 10 | NA | 10 |
| Siddika et al., 2019 [93] | NA                 | NA                   | NA                  | 10                  |
| Dadvand et al., 2014 [75] | 5.7                | 5.6                  | 5.2                 | 3.9                 |
| Pedersen et al., 2013 [73] | NA                 | NA                   | NA                  | 10                  |
| Giovannini et al., 2017, [89]| 10 | 10 | 10 | NA |

Table A8. IQR table for PM$_{2.5}$ exposure ($\mu$g/m$^3$).

| Studies                     | First Trimester IQR | Second Trimester IQR | Third Trimester IQR | Whole Pregnancy IQR |
|-----------------------------|--------------------|----------------------|---------------------|---------------------|
| Schembari et al., 2015 [80]| NA                 | NA                   | 5                   | 5                   |
| Giorgis-Allemand et al., 2016 [86]| 5 | 5 | NA | 5 |
| Siddika et al., 2019 [93] | NA                 | NA                   | NA                  | 10                  |
| Dadvand et al., 2014 [75] | 3.4                | 3.4                  | 3.1                 | 2.3                 |
| Pedersen et al., 2013 [73] | NA                 | NA                   | NA                  | 5                   |

References

1. WHO. WHA Global Nutrition Targets 2025: Low Birth Weight Policy Brief. Available online: https://www.who.int/nutrition/topics/globaltargets_lowbirthweight_policybrief.pdf (accessed on 24 April 2020).
2. Beck, S.; Wojdyla, D.; Say, L.; Bertran, A.P.; Merialdi, M.; Requejo, J.H.; Rubens, C.; Menon, R.; Van Look, P.F.A. The worldwide incidence of preterm birth: A systematic review of maternal mortality and morbidity. Bull. World Health Organ. 2010, 88, 31–38. [CrossRef] [PubMed]
3. Lawn, J.E.; Cousens, S.N.; Darmstadt, G.L.; Bhutta, Z.A.; Martines, J.; Paul, V.; Knippenberg, R.; Fogstad, H. 1 year after The Lancet Neonatal Survival Series—Was the call for action heard? Lancet 2006, 367, 1541–1547. [CrossRef]
4. Goldenberg, R.L.; Culhane, J.F.; Iams, J.D.; Romero, R. Epidemiology and causes of preterm birth. Lancet 2008, 371, 75–84. [CrossRef]
5. Euro-Peristat Project. European Perinatal Health Report. Core Indicators of the Health and Care of Pregnant Women and Babies in Europe in 2015. November 2018. Available online: www.europeristat.com (accessed on 15 April 2020).
6. WHO. Preterm Birth. Available online: https://www.who.int/news-room/fact-sheets/detail/preterm-birth (accessed on 23 April 2020).
7. World Health Organization. International Classification of Diseases and Related Health Problems, 10th ed.; World Health Organization: Geneva, Switzerland, 1992.
8. Huddy, C.L.J. Educational and behavioural problems in babies of 32–35 weeks gestation. *Arch. Dis. Child.-Fetal Neonatal Ed.* 2001, 85, F23–F28. [CrossRef]

9. Wang, M.L.; Dorer, D.J.; Fleming, M.P.; Catlin, E.A. Clinical Outcomes of Near-Term Infants. *Pediatrics* 2004, 114, 372–376. [CrossRef] [PubMed]

10. Risnes, K.R.; Vatten, L.J.; Baker, J.L.; Jameson, K.; Sovio, U.; Kajantie, E.; Osler, M.; Morley, R.; Jokela, M.; Painter, R.C.; et al. Birthweight and mortality in adulthood: A systematic review and meta-analysis. *Int. J. Epidemiol.* 2011, 40, 647–661. [CrossRef]

11. Barker, D. The Developmental Origins of Adult Disease. *J. Am. Coll. Nutr.* 2004, 23, 5885–5955. [CrossRef]

12. Gopinath, B.; Baur, L.A.; Wang, J.J.; Teber, E.; Liew, G.; Cheung, N.; Wong, T.Y.; Mitchell, P. Smaller Birth Size is Associated with Narrower Retinal Arterioles in Early Adolescence. *Microcirculation* 2010, 17, 660–668. [CrossRef]

13. Howson, C.P.; the Born Too Soon Preterm Birth Action Group; Kinney, M.V.; McDougall, L.; Lawn, J.E. Born Too Soon: Preterm birth matters. *Reprod. Health* 2013, 10, S1. [CrossRef]

14. Mathewson, K.J.; Chow, C.H.T.; Dobson, K.G.; Pope, E.I.; Schmidt, L.A.; Van Lieshout, R.J. Mental health of extremely low birth weight survivors: A systematic review and meta-analysis. *Psychol. Bull.* 2017, 143, 347–383. [CrossRef]

15. Osmond, C.; Barker, D.J. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ. Healthy Perspect.* 2000, 108, 545–553. [CrossRef]

16. Wilcox, A. On the importance—And the unimportance—Of birthweight. *Int. J. Epidemiol.* 2001, 30, 1233–1241. [CrossRef]

17. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. *Preterm Birth: Causes, Consequences, and Prevention*; Behrman, R.E., Butler, A.S., Eds.; National Academies Press: Washington, DC, USA, 2007; p. 1162. ISBN 978-0-309-10159-2.

18. Van Lieshout, R.J.; Boyle, M.H.; Saigal, S.; Morrison, K.; Schmidt, L.A.; Van Lieshout, R.J. Mental health and effects of pre-pregnancy body mass index and gestational weight gain on neonatal birth weight* #. *J. Zhejiang Univ. Sci. B* 2017, 40, 263–271. [CrossRef] [PubMed]

19. Klepac, P.; Locatelli, I.; Korošec, S.; Künzli, N.; Kukec, A. Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. *Environ. Res.* 2018, 167, 144–159. [CrossRef] [PubMed]

20. Bonzini, M.; Carugno, M.; Grillo, P.; Mensi, C.; Bertazzi, P.A.; Pesatori, A.C. Impact of ambient air pollution on birth outcomes: Systematic review of the current evidences. *La Med. Lav.* 2010, 101, 341–363.

21. Dadvand, P.; Parker, J.; Bell, M.L.; Bonzini, M.; Brauer, M.; Darrow, L.A.; Gehring, U.; Glinianaia, S.V.; Gouveia, N.; Ha, E.-H.; et al. Maternal Exposure to Particulate Air Pollution and Term Birth Weight: A Multi-Country Evaluation of Effect and Heterogeneity. *Environ. Healthy Perspect.* 2013, 121, 267–273. [CrossRef]

22. Polichetti, G.; Capone, D.; Grigoropoulos, K.; Tarantino, G.; Nunziata, A.; Gentile, A. Effects of Ambient Air Pollution on Birth Outcomes: An Overview. *Crit. Rev. Environ. Sci. Technol.* 2013, 43, 752–774. [CrossRef]
30. Lu, C.; Zhang, W.; Zheng, X.; Sun, J.; Chen, L.; Deng, Q. Combined effects of ambient air pollution and home environmental factors on low birth weight. *Chemosphere* 2020, 4, 124836. [CrossRef]

31. Sapkota, A.; Chelikowsky, A.P.; Nachman, K.E.; Cohen, A.J.; Ritz, B. Exposure to particulate matter and adverse birth outcomes: A comprehensive review and meta-analysis. *Air Qual. Atmosphere Healthy* 2010, 5, 369–381. [CrossRef]

32. Stieb, D.M.; Chen, L.; Eshoul, M.; Judek, S. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. *Environ. Res.* 2012, 117, 100–111. [CrossRef]

33. Zhu, X.; Liu, Y.; Chen, Y.; Yao, C.; Che, Z.; Cao, J. Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: A meta-analysis. *Environ. Sci. Pollut. Res.* 2014, 22, 3383–3396. [CrossRef]

34. Selevan, S.G.; Kimmel, C.A.; Mendola, P. Identifying critical windows of exposure for children’s health. *Environ. Healthy Perspect.* 2000, 108, 451–455. [CrossRef]

35. Sram, R.J.; Binková, B.; Rössner, P.; Rubeš, J.; Topinka, J.; Dejmek, J. Adverse reproductive outcomes from exposure to environmental mutagens. *Mutat. Res. Mol. Mech. Mutagen.* 1999, 428, 203–215. [CrossRef]

36. Šrám, R.J.; Binková, B.; Dejmek, J.; Bobak, M. Ambient Air Pollution and Pregnancy Outcomes: A Review of the Literature. *Environ. Healthy Perspect.* 2005, 113, 375–382. [CrossRef]

37. Glinianaia, S.V.; Rankin, J.; Bell, R.; Pless-Mulloli, T.; Howel, D. Particulate Air Pollution and Fetal Health. *Environ. Res.* 2014, 135, 36–45. [CrossRef]

38. Joss, M.K.; Eeftens, M.; Gintowt, E.; Kappeler, R.; Künzli, N. Time to harmonize national ambient air quality standards. *Int. J. Public Health* 2017, 62, 453–462. [CrossRef]

39. Resolution WHA65.6. Comprehensive Implementation Plan on Maternal, Infant and Young Child Nutrition. In Sixty-fifth World Health Assembly Geneva, 21–26 May 2012. *Resolutions and Decisions, Annexes*; World Health Organization: Geneva, Switzerland, 2012; pp. 12–13. Available online: http://www.who.int/nutrition/topics/WHA65.6_resolution_en.pdf?ua=1 (accessed on 18 April 2020).

40. Hooper, L.G.; Kaufman, J.D. Ambient Air Pollution and Clinical Implications for Susceptible Populations. *Ann. Am. Thorac. Soc.* 2018, 15, S64–S68. [CrossRef] [PubMed]

41. Schraufnagel, D.E.; Balmes, J.R.; DeMatteis, S.; Hoffman, B.; Kim, W.J.; Perez-Padilla, R.; Rice, M.; Sood, A.; Vanker, A.; Wuebbles, D.J. Health Benefits of Air Pollution Reduction. *Ann. Am. Thorac. Soc.* 2019, 16, 1478–1487. [CrossRef] [PubMed]

42. Environmental Protection Agency. *The Benefits and Costs of the Clean Air Act from 1990 to 2020: Summary Report*; Environmental Protection Agency: Washington, DC, USA, 1990; p. 35.

43. Hasunuma, H.; Ishimaru, Y.; Yoda, Y.; Shima, M. Decline of ambient air pollution levels due to measures to control automobile emissions and effects on the prevalence of respiratory and allergic disorders among children in Japan. *Environ. Res.* 2014, 131, 111–118. [CrossRef]

44. WHO. *Quantification of the Health Effects of Exposure to Air Pollution—Report of a WHO Working Group.* European Centre or Environment and Health; WHO: Bilthoven, The Netherlands, 2000; p. 34.

45. SPF Air Pollution and Health: A European Information System (APHEIS) Health Impact Assessment of Air Pollution in 26 European Cities Second-Year Report. 2000–2001. Available online: http://www.who.int/health-topics/air-pollution-and-health—a-european-information-system-aphesis-health-impact-assessment-of-air-pollution-in-26-european-cities-second-year-report (accessed on 22 August 2020).

46. Health Impact Assessment. Available online: https://www.who.int/westernpacific/health-topics/health-impact-assessment (accessed on 22 August 2020).

47. Ostro, B. *Outdoor Air Pollution: Assessing the Environmental Burden of Disease at National and Local Levels*; World Health Organization: Geneva, Switzerland, 2004; ISBN 978-92-4-159146-1. [CrossRef]

48. Kihal-Talantikite, W.; Marchetta, G.P.; Deguen, S. Infant Mortality Related to NO2 and PM Exposure: Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Healthy* 2020, 17, 2623. [CrossRef] [PubMed]

49. Schwartz, J. Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. *Environ. Healthy Perspect.* 2000, 108, 563–568. [CrossRef]

50. Daniels, M.J.; Dominici, F.; Samet, J.M.; Zeger, S.L. Estimating particulate matter-mortality dose-response curves and threshold levels: An analysis of daily time-series for the 20 largest US cities. *Am. J. Epidemiol.* 2000, 152, 397–406. [CrossRef]
51. Guo, T.; Wang, Y.; Zhang, H.; Zhang, Y.; Zhao, J.; Wang, Q.; Shen, H.; Wang, Y.; Xie, X.; Wang, L.; et al. The association between ambient PM2.5 exposure and the risk of preterm birth in China: A retrospective cohort study. *Sci. Total. Environ.* 2018, 633, 1453–1459. [CrossRef]

52. Pedersen, M.; Stayner, L.; Slama, R.; Sørensen, M.; Guxens, M.; Foradada, C.M.; Sunyer, J.; Heinrich, J.; the LISA Study Group. Traffic-Related Atmospheric Pollutants Levels during Pregnancy and Offspring's Term Birth Weight: A Study Relying on a Land-Use Regression Exposure Model. *Environ. Health Perspect.* 2007, 115, 1283–1292. [CrossRef] [PubMed]

53. Aguilera, I.; Guxens, M.; García-Esteban, R.; Corbella, T.; Nieuwenhuijsen, M.J.; Foradada, C.M.; Sunyer, J. Association between GIS-Based Exposure to Urban Air Pollution during Pregnancy and Birth Weight in the INMA Sabadell Cohort. *Environ. Health Perspect.* 2009, 117, 1322–1327. [CrossRef] [PubMed]

54. Shah, P.S.; Balkhair, T. Air pollution and birth outcomes: A systematic review. *Environ. Int.* 2011, 37, 498–516. [CrossRef]

55. Jacobs, M.; Zhang, G.; Chen, S.; Mullins, B.; Bell, M.; Jin, L.; Guo, Y.; Huxley, R.; Pereira, G. The association between ambient air pollution and selected adverse pregnancy outcomes in China: A systematic review. *Sci. Total. Environ.* 2017, 579, 1179–1192. [CrossRef]

56. Li, X.; Huang, S.; Jiao, A.; Yang, X.; Yun, J.; Wang, Y.; Xue, X.; Chu, Y.; Liu, F.; Liu, Y.; et al. Association between fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. *Environ. Pollut.* 2017, 227, 596–605. [CrossRef]

57. Yuan, L.; Zhang, Y.; Gao, Y.; Tian, Y. Maternal fine particulate matter (PM2.5) exposure and adverse birth outcomes: An updated systematic review based on cohort studies. *Environ. Sci. Pollut. Res.* 2019, 26, 13963–13983. [CrossRef] [PubMed]

58. Liu, C.; Sun, J.; Liu, Y.; Liang, H.; Wang, M.; Wang, C.; Shi, T. Different exposure levels of fine particulate matter and preterm birth: A meta-analysis based on cohort studies. *Environ. Sci. Pollut. Res.* 2017, 24, 17976–17984. [CrossRef]

59. Kheirbek, I.; Haney, J.; Douglas, S.; Ito, K.; Matte, T. The contribution of motor vehicle emissions to ambient fine particulate matter public health impacts in New York City: A health burden assessment. *Environ. Healthy* 2016, 15, 1–14. [CrossRef]

60. AirParif. *Surveillance et information sur la qualit de l’air à Paris en; AirParif: Paris, France, 2016.

61. Li, W.; Cao, Y.; Li, R.; Ma, X.; Chen, J.; Wu, Z.; Xu, Q. The spatial variation in the effects of air pollution on cardiovascular mortality in Beijing, China. *J. Expo. Sci. Environ. Epidemiol.* 2018, 28, 297–304. [CrossRef]

62. Maroziene, L.; Grazuleviciene, R. Maternal exposure to low-level air pollution and pregnancy outcomes: A population-based study. *Environ. Healthy* 2002, 1, 6. [CrossRef]

63. Lee, S.J.; Hajat, S.; Steer, P.J.; Filippi, V. A time-series analysis of any short-term effects of meteorological and air pollution factors on preterm births in London, UK. *Environ. Res.* 2008, 106, 185–194. [CrossRef]

64. Slama, R.; Morgenstern, V.; Cyrys, J.; Zutavern, A.; Herbarth, O.; Wichmann, H.-E.; Heinrich, J.; the LISA Study Group. Ambient Air Pollution and Pregnancy-Induced Hypertensive Disorders. *Hypertension* 2014, 64, 494–500. [CrossRef]

65. Libéral, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009, 339, b2700. [CrossRef]

66. Libéral, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009, 339, b2700. [CrossRef]

67. Gómez, Ó.; Esteban, R.; Corbella, T.; Nieuwenhuijsen, M.J.; Foradada, C.M.; Sunyer, J. Association between GIS-Based Exposure to Urban Air Pollution during Pregnancy and Birth Weight in the INMA Sabadell Cohort. *Environ. Health Perspect.* 2009, 117, 1322–1327. [CrossRef] [PubMed]

68. Esplugues, A.; Ballester, F.; Estarlich, M.; Íñiguez, C.; Llop, S.; Ramón, R.; Esplugues, A.; Lacasaña, M.; Rebagliato, M. Air pollution exposure during pregnancy and reduced birth size: A prospective birth cohort study in Valencia, Spain. *Environ. Health* 2010, 9, 6. [CrossRef]

69. Llop, S.; Ballester, F.; Estarlich, M.; Esplugues, A.; Rebagliato, M.; Íñiguez, C. Preterm birth and exposure to air pollutants during pregnancy. *Environ. Res.* 2010, 110, 778–785. [CrossRef]
70. Madsen, C.; Gehring, U.; Walker, S.E.; Brunekreef, B.; Stigum, H.; Næs, Ø.; Nafstad, P. Ambient air pollution exposure, residential mobility and term birth weight in Oslo, Norway. *Environ. Res.* **2020**, *110*, 363–371. [CrossRef]

71. Estarlich, M.; Ballester, F.; Aguilera, I.; García-Castro, L.; Lertxundi, A.; Llop, S.; Freire, C.; Tardón, A.; Basterrrechea, M.; Sunyer, J.; et al. Residential Exposure to Outdoor Air Pollution during Pregnancy and Anthropometric Measures at Birth in a Multicenter Cohort in Spain. *Environ. Healthy Perspect.* **2011**, *119*, 1333–1338. [CrossRef]

72. Rahmalia, A.; Giorgis-Allemand, L.; Lepeule, J.; Phillippat, C.; Galineau, J.; Hulin, A.; Charles, M.-A.; Slama, R. Pregnancy exposure to atmospheric pollutants and placental weight: An approach relying on a dispersion model. *Environ. Int.* **2012**, *48*, 47–55. [CrossRef] [PubMed]

73. Pedersen, M.; Giorgis-Allemand, L.; Bernard, C.; Aguilera, I.; Andersen, A.-M.N.; Ballester, F.; Beelen, R.M.J.; Chatzi, L.; Cirach, M.; Danileviciute, A.; et al. Ambient air pollution and low birthweight: A European cohort study (ESCAPE). *Lancet Respir. Med.* **2013**, *1*, 695–704. [CrossRef]

74. Schifano, P.; Lallo, A.; Asta, F.; De Sario, M.; Davoli, M.; Michelozzi, P. Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001–2010. *Environ. Int.* **2013**, *61*, 77–87. [CrossRef]

75. Dadvand, P.; Ostro, B.; Figueras, F.; Foraster, M.; Basagaña, X.; Valentin, A.; Martínez, D.; Beelen, R.; Cirach, M.; Hoek, G.; et al. Residential Proximity to Major Roads and Term Low Birth Weight. *Epidemiology* **2014**, *25*, 518–525. [CrossRef]

76. Sellier, Y.; Galineau, J.; Hulin, A.; Caimi, F.; Marquis, N.; Navel, V.; Bottagisi, S.; Giorgis-Allemand, L.; Jacquier, C.; Slama, R.; et al. Health effects of ambient air pollution: Do different methods for estimating exposure lead to different results? *Environ. Int.* **2014**, *66*, 165–173. [CrossRef]

77. Arroyo, V.; Díaz, J.; Ortiz, C.; Carmona, R.; Sáez, M.; Linares, C. Short term effect of air pollution, noise and heat waves on preterm births in Madrid (Spain). *Environ. Res.* **2016**, *145*, 162–168. [CrossRef]

78. Bertin, M.; Chevrier, C.; Serrano, T.; Monfort, C.; Rouget, F.; Cordier, S.; Viel, J.-F. Association between prenatal exposure to traffic-related air pollution and preterm birth in the PELAGIE mother–child cohort, Brittany, France. Does the urban–rural context matter? *Environ. Res.* **2015**, *142*, 17–24. [CrossRef] [PubMed]

79. Díben, C.; Clemens, T. Place of work and residential exposure to ambient air pollution and birth outcomes in Scotland, using geographically fine pollution climate mapping estimates. *Environ. Res.* **2015**, *140*, 535–541. [CrossRef]

80. Schembari, A.; De Hoogh, K.; Pedersen, M.; Dadvand, P.; Martinez, D.; Hoek, G.; Petherick, E.S.; Wright, J.; Nieuwenhuijsen, M.J. Ambient Air Pollution and Newborn Size and Adiposity at Birth: Differences by Maternal Ethnicity (the Born in Bradford Study Cohort). *Environ. Healthy Perspect.* **2015**, *123*, 1208–1215. [CrossRef]

81. Arroyo, V.; Díaz, J.; Carmona, R.; Ortiz, C.; Linares, C. Impact of air pollution and temperature on adverse birth outcomes: Madrid, 2001–2009. *Environ. Pollut.* **2016**, *218*, 1154–1161. [CrossRef] [PubMed]

82. Bijnen, E.M.; Derom, C.; Gielen, M.; Winckelmans, E.; Fierens, E.; Vlietinck, R.; Zeegers, M.P.; Nawrot, T.S. Small for gestational age and exposure to particulate air pollution in the early-life environment of twins. *Environ. Res.* **2016**, *148*, 39–45. [CrossRef]

83. Clemente, D.B.; Casas, M.; Vilahur, N.; Begiristain, H.; Bustamante, M.; Carsin, A.-E.; Fernández, M.F.; Fierens, F.; Gyseelaers, W.; Iniguez, C.; et al. Prenatal Ambient Air Pollution, Placental Mitochondrial DNA Content, and Birth Weight in the INMA (Spain) and ENVIR ON AGE (Belgium) Birth Cohorts. *Environ. Healthy Perspect.* **2016**, *124*, 659–665. [CrossRef]

84. Díaz, J.; Arroyo, V.; Ortiz, C.; Carmona, R.; Linares, C. Effect of Environmental Factors on Low Weight in Non-Premature Births: A Time Series Analysis. *PloS ONE* **2016**, *11*, e0164741. [CrossRef]

85. Estarlich, M.; Ballester, F.; Davdand, P.; Llop, S.; Esplugues, A.; Fernández-Somoano, A.; Lertxundi, A.; Guexn, M.; Basterrrechea, M.; Tardón, A.; et al. Exposure to ambient air pollution during pregnancy and preterm birth: A Spanish multicenter birth cohort study. *Environ. Res.* **2016**, *147*, 50–58. [CrossRef]

86. Giorgis-Allemand, L.; Pedersen, M.; Bernard, C.; Aguilera, I.; Beelen, R.M.J.; Chatzi, L.; Cirach, M.; Danileviciute, A.; Dedele, A.; Van Eijden, M.; et al. The Influence of Meteorological Factors and Atmospheric Pollutants on the Risk of Preterm Birth. *Am. J. Epidemiol.* **2017**, *185*, 247–258. [CrossRef] [PubMed]

87. Schifano, P.; Asta, F.; Dadvand, P.; Davoli, M.; Basagaña, X.; Michelozzi, P. Heat and air pollution exposure as triggers of delivery: A survival analysis of population-based pregnancy cohorts in Rome and Barcelona. *Environ. Int.* **2016**, *88*, 153–159. [CrossRef]
88. Clemens, T.; Turner, S.; Dibben, C. Maternal exposure to air pollution and fetal growth in North-East Scotland: A population-based study using routine ultrasound scans. *Environ. Int.* **2017**, *107*, 216–226. [CrossRef]

89. Giovannini, N.; Schwartz, L.; Cipriani, S.; Parazzini, F.; Baini, I.; Signorelli, V.; Cetin, I. Particulate matter (PM10) exposure, birth and fetal-placental weight and umbilical arterial pH: Results from a prospective study. *J. Matern. Neonatal Med.* **2017**, *31*, 651–655. [CrossRef]

90. Deguen, S.; Ahlers, N.; Gilles, M.; Danzon, A.; Carayol, M.; Zmirou-Navier, D.; Kihal-Talantikite, W. Using a Clustering Approach to Investigate Socio-Environmental Inequality in Preterm Birth—A Study Conducted at Fine Spatial Scale in Paris (France). *Int. J. Environ. Res. Public Health* **2018**, *15*, 1895. [CrossRef]

91. Mariet, A.-S.; Mauny, F.; Thiriez, G.; Sagot, P.; Riethmuller, D.; Boilleaut, M.; Defrance, J.; Houot, H.; Parmentier, A.-L.; et al. Multiple pregnancies and air pollution in moderately polluted cities: Is there an association between air pollution and fetal growth? *Environ. Int.* **2018**, *121*, 890–897. [CrossRef]

92. Arroyo, V.; Linares, C.; Diaz, J. Premature births in Spain: Measuring the impact of air pollution using time series analyses. *Sci. Total. Environ.* **2019**, *660*, 105–114. [CrossRef]

93. Siddika, N.; Rantala, A.K.; Antikainen, H.; Balogun, H.; Amegah, A.K.; Ryti, N.R.; Kukkonen, J.; Sofiev, M.; Jaakkola, M.S.; Jaakkola, J.J. Synergistic effects of prenatal exposure to fine particulate matter (PM2.5) and ozone (O3) on the risk of preterm birth: A population-based cohort study. *Environ. Res.* **2019**, *176*, 108549. [CrossRef]

94. Li, C.; Yang, M.; Zhu, Z.; Sun, S.; Zhang, Q.; Cao, J.-Y.; Ding, R. Maternal exposure to air pollution and the risk of low birth weight: A meta-analysis of cohort studies. *Environ. Res. Public Health* **2020**, *190*, 109970. [CrossRef]

95. Kannan, S.; Misra, D.P.; Dvorch, J.T.; Krishnakumar, A. Exposures to Airborne Particulate Matter and Adverse Perinatal Outcomes: A Biologically Plausible Mechanistic Framework for Exploring Potential Effect Modification by Nutrition. *Environ. Healthy Perspect.* **2006**, *114*, 1636–1642. [CrossRef]

96. Bose, S.; Hansel, N.N.; Tonorezos, E.S.; Williams, D.L.; Bildersbaek, A.; Breyssse, P.N.; Diette, G.B.; McCormack, M.C. Indoor Particulate Matter Associated with Systemic Inflammation in COPD. *J. Environ. Prot.* **2015**, *6*, 566–572. [CrossRef]

97. Møller, P.; Danielsen, P.H.; Karottki, D.G.; Jantzen, K.; Roursgaard, M.; Jensen, D.M.; Vest Christoffersen, D.; Hemmingsen, J.G.; Cao, Y.; et al. Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles. *Mutat. Res. Mutat. Res.* **2014**, *762*, 133–166. [CrossRef]

98. Byun, H.-M.; Baccarelli, A.A. Environmental exposure and mitochondrial epigenetics: Study design and analytical challenges. *Qual. Life Res.* **2014**, *133*, 247–257. [CrossRef]

99. Hou, L.; Zhu, Z.-Z.; Zhang, X.; Nordio, F.; Bonzini, M.; Schwartz, J.D.; Hoxha, M.; Dionis, L.; Marinelli, B.; Pegoraro, V.; et al. Airborne particulate matter and mitochondrial damage: A cross-sectional study. *Environ. Health* **2010**, *9*, 48. [CrossRef] [PubMed]

100. Wick, P.; Malek, A.; Manser, P.; Meili, D.; Maeder-Althaus, X.; Diener, P.-A.; Diener, L.; Von Mandach, U. Barrier Capacity of Human Placenta for Nanosized Materials. *Environ. Healthy Perspect.* **2010**, *118*, 432–436. [CrossRef]

101. Myllynen, P.; Pasanen, M.; Pelkonen, O. Human placenta: A human organ for developmental toxicology research and biomonitoring. *Placenta* **2005**, *26*, 361–371. [CrossRef]

102. Weldy, C.S.; Turner, S.; Liggitt, H.D.; Chin, M.T. In Utero Exposure to Diesel Exhaust Air Pollution Promotes Adverse Intrauterine Conditions, Resulting in Weight Gain, Altered Blood Pressure, and Increased Susceptibility to Heart Failure in Adult Mice. *PLoS ONE* **2014**, *9*, e88582. [CrossRef] [PubMed]

103. Li, Y.; Wang, H.; Wei, S.; Zhang, L.; Zhao, Q. The Correlation between Indoor and Outdoor Particulate Matter of Different Building Types in Daqing, China. *Procedia Eng.* **2017**, *205*, 360–367. [CrossRef]

104. Lepeule, J.; Caini, F.; Bottagisi, S.; Galineau, J.; Hulin, A.; Marquis, N.; Bohe, A.; Siroux, V.; Kaminiski, M.; Charles, M.-A.; et al. Maternal Exposure to Nitrogen Dioxide during Pregnancy and Offspring Birth Weight: Comparison of Two Exposure Models. *Environ. Healthy Perspect.* **2010**, *118*, 1483–1489. [CrossRef]

105. Debret, E.; Briggs, D.; Van Reeuwijk, H.; Fischer, P.; Smallbone, K.; Harssema, H.; Kriz, B.; Gorynski, P.; Elliott, P. Small area variations in ambient NO2 concentrations in four European areas. *Atmos. Environ.* **2020**, *34*, 177–185. [CrossRef]

106. Gulliver, J.; De Hoogh, K.; Fecht, D.; Vienneau, D.; Briggs, D. Comparative assessment of GIS-based methods and metrics for estimating long-term exposures to air pollution. *Atmos. Environ.* **2001**, *45*, 7072–7080. [CrossRef]
107. Kaiser, R.; Romieu, I.; Medina, S.; Schwartz, J.; Krzyzanowski, M.; Künzli, N. Air pollution attributable postneonatal infant mortality in U.S. metropolitan areas: A risk assessment study. *Environ. Health* **2004**, *3*, 4. [CrossRef]

108. Kihal-Talantikite, W.; Legendre, P.; Le Nouveau, P.; Deguen, S. Premature Adult Death and Equity Impact of a Reduction of NO2, PM10, and PM2.5 Levels in Paris—A Health Impact Assessment Study Conducted at the Census Block Level. *Int. J. Environ. Res. Public Health* **2018**, *16*, 38. [CrossRef] [PubMed]

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