



Maternal exposure to air pollution and risk of autism in children: A systematic review and meta-analysis^{*}

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ABSTRACT

Background: The number of children diagnosed with autism spectrum disorder (ASD) has been increasing. Previous studies suggested potential association between pregnancy air pollution exposure and ASD. This systematic review and meta-analysis is intended to summarize the association between maternal exposure to outdoor air pollution and ASD in children by trimester based on recent studies.

Methods: A systematic literature search in 3 databases (Medline, Embase, and Web of Science) was performed using subject headings related to ASD and air pollution since 2007. Eligible studies were screened and evaluated based on predetermined criteria. For meta-analyses, the studies were grouped by air pollutant and exposure time (prenatal period and trimesters). Within-group studies were standardized by log odds ratio (OR) and then combined by three meta-analysis methods: frequentist fixed and random effects models, and Bayesian random effects model.

Results: Initial search identified 1564 papers, of which 25 studies remained for final analysis after duplicates and ineligible studies were removed. Of the 25 studies, 13, 14, 12, and 7 studies investigated ASD in children associated with PM_{2.5}, PM₁₀, NO₂, and ozone, respectively. The frequentist and Bayesian random effects models resulted in different statistical significance. For prenatal period, frequentist meta-analysis returned significant pooled ORs with 95% confidence intervals, 1.06(1.01,1.11) for PM_{2.5} and 1.02(1.01,1.04) for NO₂, whereas Bayesian meta-analysis showed similar ORs with wider 95% posterior intervals, 1.06(1.00,1.13) for PM_{2.5} and 1.02(1.00,1.05) for NO₂. Third trimester appeared to have higher pooled ORs for PM_{2.5}, PM₁₀, and ozone, but patterns in the time-varying associations over the trimester were inconsistent.

Conclusions: For positive association between maternal exposure to ambient air pollution and ASD in children, there is some evidence for PM_{2.5}, weak evidence for NO₂ and little evidence for PM₁₀ and ozone. However, patterns in associations over trimesters were inconsistent among studies and among air pollutants.

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1. Introduction

Autism spectrum disorder (ASD) is a complex group of developmental disorders characterized by difficulties in communication and social interaction and the presence of repetitive body movements or behaviors that can persist throughout life (APA, 2013). According to the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA) of the US, recently

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more children are being diagnosed with ASD. The overall prevalence of ASD increased from 1.1% in 2012 to 1.7% in 2014, based on an analysis of medical and school records of 8-year-olds from 11 monitoring sites across the US (Baio et al., 2018; Dawson and Bernier, 2013; US EPA, 2013). Some of the increase in the prevalence of ASD may be related to increased monitoring and a broadening of diagnostic criteria (Rice et al., 2012; Dawson and Bernier, 2013).

It is unclear whether and to what extent environmental factors have contributed to the recent increase in ASD. Previous studies suggested that both genetic and environmental factors might play a role in ASD (Flores-Pajot et al., 2016). One environmental risk factor of interest in the etiology of ASD is exposure to ambient air pollution. There are six common air pollutants, called criteria pollutants, identified by the US Clean Air Act of 1970: ground-level ozone (ozone), lead, particulate matter (PM), carbon monoxide (CO), nitrogen dioxide (NO₂), and sulfur dioxide (SO₂), which are the only air pollutants under national air quality standards.

PM is a complex mixture classified by size into PM_{2.5} ($\leq 2.5 \mu\text{m}$ in diameter) and PM₁₀ ($\leq 10 \mu\text{m}$) that vary by place and time depending on local industries and infrastructure. Main emission sources of the others have been known chemical reactions, transportation, and other combustion products (Roberts et al., 2013; Volk et al., 2011, 2013; Talbott et al., 2015a,b; US EPA, 2018).

While a few studies in Europe have reported no association (Gong et al., 2014; Guxens et al., 2016; Gong et al., 2017), a number of studies in the US and other countries have reported associations between maternal exposure to ambient air pollution and ASD in children (Volk et al., 2011, 2013; Becerra et al., 2013; Roberts et al., 2013; Kalkbrenner et al., 2010, 2015; Raz et al., 2015; Talbott et al., 2015a). The different findings may be related to several factors: ASD ascertainment method, air pollutant and study population. The European studies took into account autistic traits and also examined NO_x and PM₁₀ instead of NO₂ and PM_{2.5}, or multi-countries which would be more heterogeneous than a single country. The differences between US and Europe could be explained by differences on air pollution levels and sources.

Even though epidemiologic studies found maternal exposure to air pollutants associated with the ASD, the mechanism underlying this association was not clearly understood. Recent animal experiments with mice found that exposure to unhealthy levels of particulate matter during pregnancy could cause subtle changes in the structure of the cerebral cortex (the outer layer of neural tissue of the cerebrum of the brain), as seen in the brains of autistic patients (Chang et al., 2019). A possible mechanism is related to increased neuroinflammation, which leads to decreased expression of the protein reelin—which activates a signaling pathway required for proper positioning of neurons in the brain—both events common with autism (Chang et al., 2019).

Some studies on human pregnancy have found that prenatal exposure to air pollution during the developmental stage of the central nervous system may be linked to a systemic inflammatory response, which could result in neuronal injury (Sunyer, 2008; Kalkbrenner et al., 2015; Kerin et al., 2018). Other studies have also reported that prenatal exposure to environmental toxicants may be associated with ASD (Rossignol et al., 2014; Wong et al., 2015; Ye et al., 2017). However, the relationship between exposure time and fetal development remains unclear.

There have been some differences in findings and approaches by previous systematic reviews and meta-analyses (Lam et al., 2016; Flores-Pajot et al., 2016; Yang et al., 2017). Lam et al. concluded that there was limited evidence for associations between overall air pollution exposure in early life and ASD, but they found sufficient evidence, most notably, between prenatal exposures to PM_{2.5} or PM₁₀ and ASD. Flores-Pajot et al. investigated varied exposure times

and found evidence that prenatal exposure to PM_{2.5} and ozone and postnatal exposure to PM_{2.5} and NO₂ were associated with ASD. Yang et al. pointed out that a semi-Bayesian logistic model might improve the plausibility and stability of estimates. They discussed the need for some well-designed studies with a large sample, less misclassification or measurement of individual-level exposures, and consideration of multiple confounders.

For meta-analysis there are four areas for further investigations regarding associations between air pollutants and ASD development in children: which pollutant (among the criteria pollutants), to what extent (significance), what method (fixed vs random effects model), and when (exposure time). Adverse health effect of maternal exposures to ambient air pollution on children may vary according to the exposure time. A natural question is: if there is a critical time window of exposure that is more associated with ASD development in children.

In this systematic review, we conducted a systematic search of literature on maternal exposure to ambient air pollution and ASD since 2007, which resulted in an ultimate focus on PM_{2.5}, PM₁₀, NO₂, and ozone. This focus was mainly due to eligible studies' availability, not our preference for the four pollutants. We also examined the exposure time by trimester, considering fetal development during pregnancy.

2. Materials and methods

2.1. Search strategy

The protocol of this study was registered in PROSPERO (Chun et al., 2018; No. CRD42018104041). A systematic literature search in Medline, Embase, and Web of Science was performed using the combination of Medical Subject Headings (MeSH) related to ASD and maternal exposure (3 trimesters and prenatal period) to air pollution since 2007. We included criteria air contaminants, hazardous air pollutants (HAP) and related pollutants (e.g., SO₂, NO_x, VOCs), persistent organic pollutants (e.g., dioxins and furans), heavy metals (e.g., mercury), and toxicants (e.g., benzene). We used several keywords for HAP with the help of a librarian at the Ottawa Hospital. Searches were limited to studies with an abstract published in the English language with a publication date between January 1, 2007, and April 30, 2019, to focus on recent research.

2.2. Study eligibility criteria

We used Covidence (version 2018) to screen studies based on title and abstract. Covidence is a Cochrane technology platform that enables the whole review team to collaborate remotely by keeping full records of who voted to include a study and capturing reasons for exclusion so reviewers can resolve any disagreements. We identified eligible articles for this study using the following inclusion criteria: (1) study design was observational, including ecological, case-control, and cohort studies; (2) study participants included children and/or mothers; (3) ASD diagnosis was made based on clinical assessments, self-report questionnaires or structured interviews; (4) measure of air pollution exposure or during conception and pregnancy (prenatal exposure) or at the time of birth (perinatal exposure) or during childhood (postnatal exposure) and (5) information on the sample size and air pollution. The exclusion criteria were: (1) studies that used animal models; (2) full article not in English; and (3) abstracts, case reports, comments, reviews, conference proceedings, or book chapters.

2.3. Data extraction

After reviewing abstracts, we short-listed full-text articles for

the eligibility assessment, uploading all the original studies to Covidence and extracting data. Extracted information included: authors, year of publication, title, journal, study location (country), study design, study population, case and control (if applicable), exposure time and measurement method, ASD ascertainment method, outcome, analysis model, covariates, and main findings from each full-text article.

2.4. Assessment of risk of bias

Risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2014) and Lam et al.'s navigation guide (2016). The NOS consists of eight items to evaluate sources of bias, such as definition and selection of case and controls, adequate sample size, comparability of cases and controls on the basis of the design or analysis, and non-response rate. Studies were given a maximum of 1 point for each of the seven items and 2 points for comparability only, making the maximum score 9 points. Higher scores suggested a lower risk of bias. According to Lam et al.'s navigation guide, we also rated each study as "high quality", "moderate quality" and "low quality" in terms of exposure assessment, selective outcome reporting, and confidence in effect estimates. We set up a cut-off score of 7 with the NOS and "moderate quality" with the navigation guide for this review study to maintain low risk of bias.

2.5. Meta-analysis

First, we categorized eligible studies by air pollutant ($PM_{2.5}$, PM_{10} , NO_2 , and ozone), exposure time (all the prenatal period and each trimester separately), study design (cohort, case-control, ecological), and modelling (population, covariates, and regression). The 4 exposure time periods were included to assess time-varying associations. Second, we derived meta-estimates for ASD associated with the 4 air pollutants. We applied both frequentist and Bayesian approaches for fixed effect model and random effects model for each air pollutant and each exposure time to calculate the pooled odds ratios (ORs) per 10 units of that pollutant: $PM_{2.5}$ and PM_{10} in $\mu\text{g}/\text{m}^3$, and NO_2 and ozone in parts per billion (ppb).

Since we were concerned with the small number of studies included for each air pollutant, we employed a Bayesian random effects model in addition to frequentist fixed and random effects models. The Bayesian pooling method can reflect more uncertainty of pooled OR than frequentist pooling (Shin et al., 2014). For a given air pollutant, we assumed that the observed study-specific ORs (log scale) were normally distributed with unknown true study-specific mean and variance, and that the true study-specific means were normally distributed with unknown air pollutant-specific mean (μ_i) and variance (σ_i^2), which indicated the heterogeneity among the studies.

Since information on both mean (μ_i) and variance (σ_i^2) was limited, non-informative priors, diffused over a large range for each mean and standard deviation, were applied. In this study the median of the posterior distribution of the mean μ_i will be reported as the meta-analysis pooled log (OR) along with 95% posterior interval (more details in Appendix B).

Various tests for heterogeneity using I^2 and Q-statistic with degrees of freedom as well as the p-value of the test were done. In addition, we included Egger test and Funnel plots to show the publication bias since publication of positive findings has been an important concern in meta-analytic reviews of the literature. The degree of symmetry found in funnel plots indicates absence of publication bias (Egger et al., 1997).

Sensitivity analyses over study design and exposure time were also undertaken to assess the robustness of the results. All

statistical analyses for this study were conducted using statistical software R Stan and Metafor (version 3.4.4).

3. Results

3.1. Search results

Our study selection process following the PRISMA flow chart is shown in Fig. 1 (Moher et al., 2009). A total of 1564 publications were identified through the search strategy, of which 994 publications were included once duplicates were removed. After excluding studies that were non-human or non-air pollutant, 62 articles were short-listed for the full-text assessment, which resulted in further exclusion of 37 articles for various reasons. Finally, 25 eligible articles were included in our review.

3.2. Study characteristics

Table 1 shows the characteristics of the included studies sorted by publication year. The 25 eligible studies were conducted in 11 countries: USA (16), Sweden (3), Netherlands (1), Italy (1), Spain (1), Taiwan (1), China (1), Canada (1), Denmark (1), Iran (1), and Israel (1). While 24 studies were done for a single country, a study by Guxens et al. was conducted in the 4 countries in Europe simultaneously. As for study design, there were 21 case-control studies, 3 cohort studies, and 1 ecological study. While the case-control and cohort designs were based on individual level data, the ecological design used either exposure or ASD occurrence at group level. Studies published between 2007 and 2019 were initially searched to minimize discrepancy in their ASD definition and diagnosis methods, considering recent year studies more comparable. Of those, studies for 2010–2019 were considered for systematic review based on the four selected air pollutants, and studies for 2013–2019 were included for meta-analysis based on the exposure time (trimesters and prenatal period), given the sudden increase in the prevalence of ASD that might be related to broadening diagnostic criteria (Rice et al., 2012; Dawson and Bernier, 2013). This is desirable for meta-analysis because it reduced between-study differences related to diagnosis methods.

Among the 25 eligible studies, 23 (with the exception of two on the postnatal period), specifically assessed prenatal air pollution, and of those, 11 included trimester-specific analyses. The most commonly assessed air pollutant was PM_{10} , which was included in 14 studies, followed by $PM_{2.5}$ (13 studies), NO_2 (12 studies), ozone (7 studies), traffic-related air pollution (5 studies), and SO_2 (3 studies). Nineteen studies identified ASD cases using records from existing autism databases, such as the US Autism and Developmental Disabilities Monitoring (ADDM) Network, the California Department of Developmental Services (DDS) and the British Columbia Autism Assessment Network. Other studies utilized ASD screening tools, such as the Autism-Tics, ADHD, and other Comorbidities (A-TAC) inventory, to ascertain cases to be included in the studies. The other 2 studies used maternal reports and validated by Autism Diagnostic Interview (Raz et al., 2015; Roberts et al., 2013). See more details on model covariates, air pollutant concentration measurement methods, and ASD ascertainment methods in Table A1 in Appendix. We looked at the studies by study period since the prevalence of ASD has risen dramatically in recent years and there is a need to see how air pollution might be contributing to the increased prevalence. However, recent studies with recent birth cohort show that there is no association between maternal air pollution exposure and ASD indicating that little was known about the potential association between exposure and ASD.

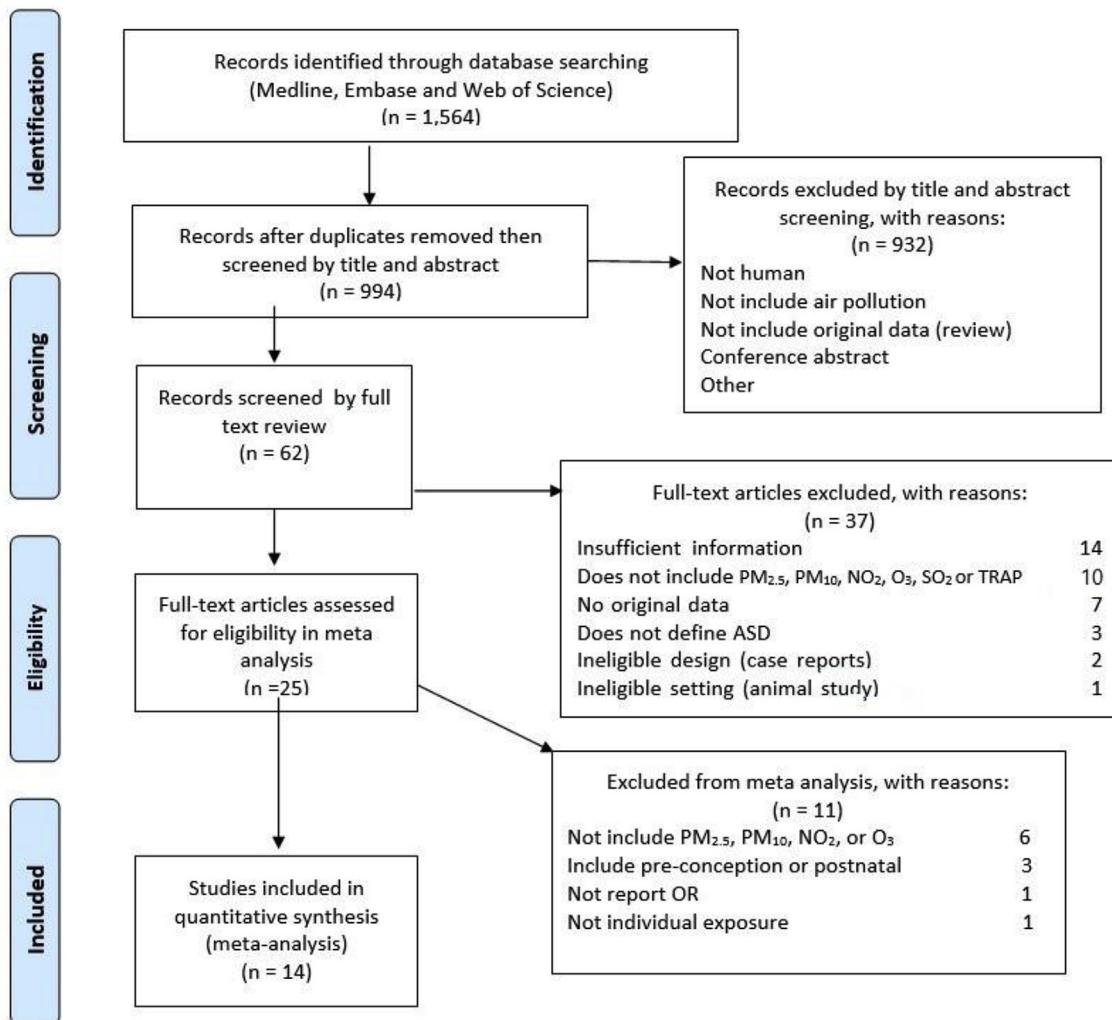


Fig. 1. PRISMA diagram of systematic review.

3.3. Inclusion and exclusion of studies for meta-analysis

We applied both the NOS (quality assessment scale) and Lam et al.'s navigation guide to the 25 eligible studies based on their characteristics in Table 1 and Table A1 (Appendix A). By inclusion/exclusion criteria we found that four air pollutants (PM_{2.5}, PM₁₀, NO₂, and ozone) had at least 3 comparable studies with comparable exposure time (prenatal period), which were required for meta-analysis. We excluded 11 studies since they reported other air pollutants (6 studies), examined pre-conception or post-natal period (3 studies), or other reasons (2 studies) as summarized in Fig. 1, from which 14 studies remained for our meta-analysis. Both screening tools resulted in the same quality of the 14 selected studies for the meta-analysis. The 14 studies had a median score of 8 (out of 9) from the NOS, and high or moderate quality from the navigation guide, indicating low bias.

3.4. Study findings from systematic review: association between air pollutants and ASD

PM_{2.5}: Of the 13 studies that assessed PM_{2.5} exposure, 5 found significant associations with ASD. In 2013, Becerra et al. and Volk et al. both used California DDS records for ASD cases and reported significant ORs: 1.07 (1.00, 1.15) per 4.68 µg/m³ and 2.08 (1.93, 2.25)

per 8.87 µg/m³, respectively. In 2018, however, 2 other studies, Goodrich et al. and Kerin et al., found no association, even though their study populations also consisted of Californian children. In 2015, Raz et al. found an increased OR of 1.42 (1.09, 1.86) per 4.40 µg/m³ especially for trimester 3 based on the Nurses' Health Study II. Furthermore, in 2017 Kim et al. found PM_{2.5} and total copy number variations (CNV), a type of genomic changes that contribute to autism susceptibility, together were associated with a higher risk of ASD than PM_{2.5} alone. There is also evidence to suggest an association between postnatal PM_{2.5} exposure and ASD. In 2018, Chen et al. found that PM_{2.5} exposure in the 2nd and 3rd year of life resulted in an OR of 1.50 (1.01, 2.22) and 1.78 (1.05, 3.02), respectively, per 3.4 µg/m³. As well, in 2018 Ritz et al. reported that at 9 months of age, there is an OR of 1.04 (1.00, 1.08) per 3.61 µg/m³. Excluding 4 studies (Al-Hamdan et al., 2018; Kerin et al., 2018; Kim et al., 2017; Chen et al., 2018) due to ecological study designs, different methods of ascertaining cases and controls, or longer exposure time (e.g., prenatal and postnatal period combined), we included the remaining 9 studies for our meta-analysis. Meta-analyses with 11 studies with postnatal studies (Kim et al., 2017; Chen et al., 2018) were done in the sensitivity analysis later.

PM₁₀: Of the 14 studies that assessed the association between PM₁₀ exposure and ASD, 3 studies found significant associations. In 2013, Volk et al. found an increased OR of 2.17 (1.49, 3.16) per

Table 1
Characteristics of included studies.

Authors & year	Study design	Study population birth year	Study population	Cases/ Controls	Exposure (Air pollutant)	Exposure Time	Main Findings
Roberts et al. (2013)	Case-Control	1987–2002	Children of the subjects of the Nurses' Health Study II (US)	325/22101	14 hazardous air pollutants (HAPs, e.g., diesel PM, Pregnancy lead, mercury, styrene) assessed by the US EPA National Air Toxics Assessment in 1990, 1996, 1999, and 2002		Diesel particulate matter exposure associated with increased OR for ASD
Ritz et al. (2018)	Case-control	1989–2013	Children born between 1989 and 2013 in Denmark.	15387/68139	NO ₂ , SO ₂ , PM _{2.5} and PM ₁₀	Pregnancy and postnatal	NO ₂ exposure during all trimesters, SO ₂ exposure during 1st trimester, and NO ₂ /SO ₂ /PM _{2.5} exposure at 9 months of age are all associated with increased OR of ASD
Raz et al. (2015)	Case-Control	1990–2002	Children of the subjects of the Nurses' Health Study II (US)	245/1522	PM _{2.5} , PM ₁₀	Pre-conception, trimester 1, 2, 3, pregnancy, 9 month after birth	PM _{2.5} exposure during third trimester associated with increased OR for ASD
Kalkbrenner et al. (2010)	Case-Control	1992/1994 1994/1996	Children registered to the ADDM Network born in West Virginia or North Carolina (US)	383/2829	35 hazardous air pollutants (HAPs, e.g., diesel PM, Perinatal metals, solvents) assessed by the US EPA National Air Toxics Assessment in 1996.		No association between exposures and ASD
Al-Hamdan et al. (2018)	Ecological	1992–2004	8-year-old children identified from 15 US ADDM Network sites from 2000 to 2012 (US)	22153	Unhealthy Air Quality Index (AQI) level (which accounts for PM, ozone, CO, and SO ₂), PM _{2.5} , sunlight, heat index	Pregnancy	No association between exposures and ASD
Gong et al. (2014)	Case-Control	1992–2000	Twins from the Child and Adolescent Twin Study (Sweden)	109/3051	NO _x , PM ₁₀	Pregnancy, year 1, year 9	No association between exposures and ASD
Guxens et al. (2016)	Cohort	1992–2005	Children within 4 European cohorts (Netherlands, Italy, Spain, and Sweden)	541/7538	NO ₂ , PM _{2.5} , PM ₁₀	Pregnancy	No association between exposures and ASD
Windham et al. (2013)	Case-Control	1994	Children born in the San Francisco Bay Area (US)	284/659	8 chemical groups, including exhaust or combustion products (e.g. PM)	Pregnancy	Exhaust exposure associated with increased OR for ASD
Kalkbrenner et al. (2015)	Case-Control	1994, 1996, 1998, 2000	Children registered to the ADDM Network born in North Carolina or San Francisco (US)	979/14666	PM ₁₀	Pre-conception, trimester 1, 2, 3, postnatal	PM₁₀ exposure during third trimester associated with increased OR for ASD
Becerra et al. (2013)	Case-Control	1994–2006	Children born in Los Angeles County (US)	7594/75635	CO, ozone, NO, NO ₂ , PM _{2.5} , PM ₁₀	Trimester 1, 2, 3, entire pregnancy	O₃, PM_{2.5} exposure associated with increased OR for ASD
Kalkbrenner et al. (2018)	Case-Control	1994–2007	Participants in the Autism Genetic Resource Exchange (AGRE) study (US)	1540/477	155 air toxics (e.g. diesel PM) assessed by the U.S. EPA National Air Toxics Assessment in 1996, 1999, 2002, and 2005	Pregnancy	Diesel particulate matter exposure associated with increased OR for ASD
Gong et al. (2017)	Case-Control	1997–2003	Children in the Stockholm Youth Cohort, 1997 to 2003 (Sweden)	5136/18237	NO _x from 1990, 1995, 2000, 2002–2004; PM ₁₀ from 2004	Pregnancy, year 1	No association between exposures and ASD
Jung et al. (2013)	Cohort	1997–2000	Children aged less than 3 years in 2000 (Taiwan)	342/48731	Ozone, CO, NO ₂ , PM ₁₀ , SO ₂	Postnatal	O ₃ , CO, NO ₂ , SO ₂ exposure associated with increased OR for ASD
Goodrich et al. (2018)	Case-Control	1997–2008	Children in the CHARGE study (US)	346/260	Near roadway air pollution (NRP) based on CALINE4 line-source air quality dispersion model, PM _{2.5} , PM ₁₀ , ozone, NO ₂ ; vs. folic acid supplementation	Pregnancy, Trimester 1, 2, 3	NO₂ exposure with low folic acid consumption associated with increased OR for ASD
Kim et al. (2017)	Case-Control	1998–2007	Children in the CHARGE study who were 24–60 months of age during 2003–2009 (US)	158/142	Traffic-related air pollution (based on the CALINE4 line-source air quality dispersion model), NO ₂ , ozone, PM _{2.5} , PM ₁₀ vs. copy number variation	Pregnancy through first 2 years of life	PM _{2.5} and PM ₁₀ exposure when CNV burden is low associated with increased OR for ASD
Volk et al. (2011)	Case-Control	1998–2007	Children in the CHARGE study who were 24–60 months of age during 2003–2009 (US)	304/259	Traffic-related air pollution (e.g. PM) based on distance from nearest freeway.	Pregnancy, trimester 1, 2, 3	Closest 10th percentile of residences to freeways associated with increased OR for ASD
Volk et al. (2013)	Case-Control	1998–2007	Children in the CHARGE study who were 24–60 months of age during 2003–2009 (US)	279/245	PM _{2.5} , PM ₁₀ , NO ₂ , Ozone, traffic-related air pollution	Pregnancy, trimester 1, 2, 3, year 1	PM_{2.5}, PM₁₀, NO₂ and TRAP exposure for all trimesters associated with increased OR for ASD
Kerin et al. (2018)	Case-Control	1999–2007	Children in the CHARGE study (US)	325/227	Near-roadway air pollution (based on the CALINE4 line-source air quality dispersion model), NO ₂ , ozone, PM _{2.5} , PM ₁₀	Pregnancy, trimester 1, 2, 3, year 1	Increasing prenatal NO ₂ exposure associated with decreased MSEL and VABS scores.

(continued on next page)

Table 1 (continued)

Authors & year	Study design	Study population birth year	Study population	Cases/Controls	Exposure (Air pollutant)	Exposure Time	Main Findings
Chen et al. (2018)	Case-control	2002 –2011	3–12 year old children from 96 kindergartens, 55 primary schools and 28 special education schools that were randomly selected in June 2014 in Shanghai China	124/ 1240	PM _{2.5} , PM ₁₀	Postnatal	PM2.5 exposure during second and third year of life is associated with increased OR for ASD
Pagalan et al. (2019)	Cohort	2004–2009	Children born in Metro Vancouver between 2004 to 2009. Children born between 2004 to 2012 in Tehran, Iran.	1276/ 129436	PM _{2.5} , NO ₂	Trimester 1, 2, 3	No association between exposures and ASD
Yousefian et al. (2018)	Case-control	2004–2012	Children born in the central coastal area of Israel between 2005 and 2009 (US)	134/388 541/91	PM ₁₀ , SO ₂ NO ₂	Pregnancy	No association between exposures and ASD
Raz et al. (2018)	Case-Control	2005–2009	Children born in six counties in Southwestern Pennsylvania (US)	2088/ 54191	NO ₂	Pre-conception, pregnancy, 9 months after birth	No association between exposures and ASD
Talbot et al. (2015a)	Case-Control	2005–2009	Children born in six counties in Southwestern Pennsylvania (US)	211/219 6420	PM _{2.5} , PM ₁₀	Pre-conception, pregnancy, trimester 1, 2, 3, year1, year2	No association between exposures and ASD
Talbot et al. (2015b)	Case-Control	2005–2009	Children born in six counties in Southwestern Pennsylvania (US)	217/ 4971	30 air toxics (e.g. diesel PM, metal components, aromatic solvents, chlorinated solvents, other HAPs) assessed by the US EPA National Air Toxics Assessment in 2005.	Pregnancy	No association between exposures and ASD
Kaufman et al. (2019)	Case-control	2006–2010	Children born between 2006–2010 in Cincinnati, Ohio.	428/ 6420	PM _{2.5} , Ozone	Pregnancy to first 2 years of life	Pregnancy to first 2 No association between exposures and ASD

Notes: Bold indicates those studies included for meta-analysis for respective air pollutants (PM_{2.5}, PM₁₀, NO₂, and Ozone).

14.6 µg/m³ during prenatal period. Two years later in 2015, Kalkbrenner et al. found trimester 3 only associated with an increased OR of 1.40 (1.13, 1.72) per 10 µg/m³. In 2017, Kim et al. found the effects of PM₁₀ combined with the CNV led to a higher OR than PM₁₀ alone. With regards to postnatal exposures, in 2018, Chen et al. reported an OR of 1.73 (1.11, 2.68) per 4.9 µg/m³ for PM₁₀ exposure in the second year of life. In contrast, the other 10 studies (Becerra et al., 2013; Jung et al., 2013; Gong et al., 2014; Raz et al., 2015; Guxens et al., 2016; Gong et al., 2017; Goodrich et al., 2018; Kerin et al., 2018; Ritz et al., 2018; Yousefian et al., 2018) found no association. For meta-analysis (T4) we combined 9 studies after excluding 5 studies (Jung et al., 2013; Kalkbrenner et al., 2015; Kim et al., 2017; Kerin et al., 2018; Chen et al., 2018) due to a different measurement (no reported OR) or postnatal period.

NO₂: Of the 12 studies that assessed maternal exposure to NO₂ in relation to ASD, 6 studies found significant associations. In 2013, Volk et al. found significant OR of 1.82 (1.23, 2.65) per 14.1 ppb for prenatal period, but Jung et al. found a significant association at different time periods depending on ASD diagnosis: during the one year that preceded a diagnosis at relative risk of 4.43 (3.33, 5.90) per 10 ppb. In 2018, Ritz et al. found NO₂ exposure in all trimesters to be associated with an increased OR of ASD, reporting an OR of 1.10 (1.06, 1.13) per 11.41 µg/m³ increase in NO₂ during the entire pregnancy period. Also in 2018, Kerin et al. assessed the association with various air pollutants more broadly, including ASD severity, cognitive abilities, and adaptive functions. In the same year, Goodrich et al. assessed NO₂ along with diet for mothers with high NO₂ and found a statistically significant difference between low and high prenatal folic acid intake. On the other hand, the other 7 studies (Becerra et al., 2013; Gong et al., 2014; Guxens et al., 2016; Gong et al., 2017; Kim et al., 2017; Raz et al., 2018; Pagalan et al., 2019) reported no associations. We combined 7 studies for meta-analysis after excluding 5 studies (Jung et al., 2013; Gong et al., 2014; Gong et al., 2017; Kim et al., 2017; Kerin et al., 2018) with longer exposure time than prenatal period or NO_x.

Ozone: Out of 7 studies that assessed a link between maternal exposure to ozone and ASD, 2 found significant associations. In 2013, Becerra et al. found that in a two-pollutant model with ozone and PM_{2.5}, the prenatal exposure to ozone resulted in an increased OR of 1.12 (1.06, 1.19) per 11.54 ppb. Jung et al. also found an increased hazard ratio of ASD for ozone exposure during the one year prior to an ASD diagnosis. However, 5 studies (Goodrich et al., 2018; Kerin et al., 2018; Kim et al., 2017; Volk et al., 2013; Kaufman et al., 2019) found no associations. Among the 7 studies, we included 4 studies for meta-analysis, excluding 3 studies (Jung et al., 2013; Kim et al., 2017; Kerin et al., 2018) with longer exposure time.

3.5. Meta-analysis

3.5.1. Air-pollutant-specific association with ASD

3.5.1.1. Association between PM_{2.5} and ASD. Nine studies were included in the meta-estimate of the association between maternal exposure to PM_{2.5} and ASD. While 8 studies estimated the OR for each trimester and prenatal period, 1 study (Guxens et al.) did for the prenatal period (T4) only. **Table C1** (Appendix C) summarizes the study-specific ORs and 95% confidence intervals by exposure time. As displayed in **Fig. 2**, the between-study differences were more visible than the differences between-exposure time for each trimester. The heterogeneity test ($Q(df = 8) = 174.94$, $p\text{-val} < .0001$, $I^2 = 91.22\%$) suggests significant between-study differences (Viechtbauer, 2010). The meta-estimates and 95% posterior intervals on the right in **Fig. 2** are for T4 only, indicating inconsistent results between frequentist and Bayesian models. While the frequentist fixed and random models resulted in statistically

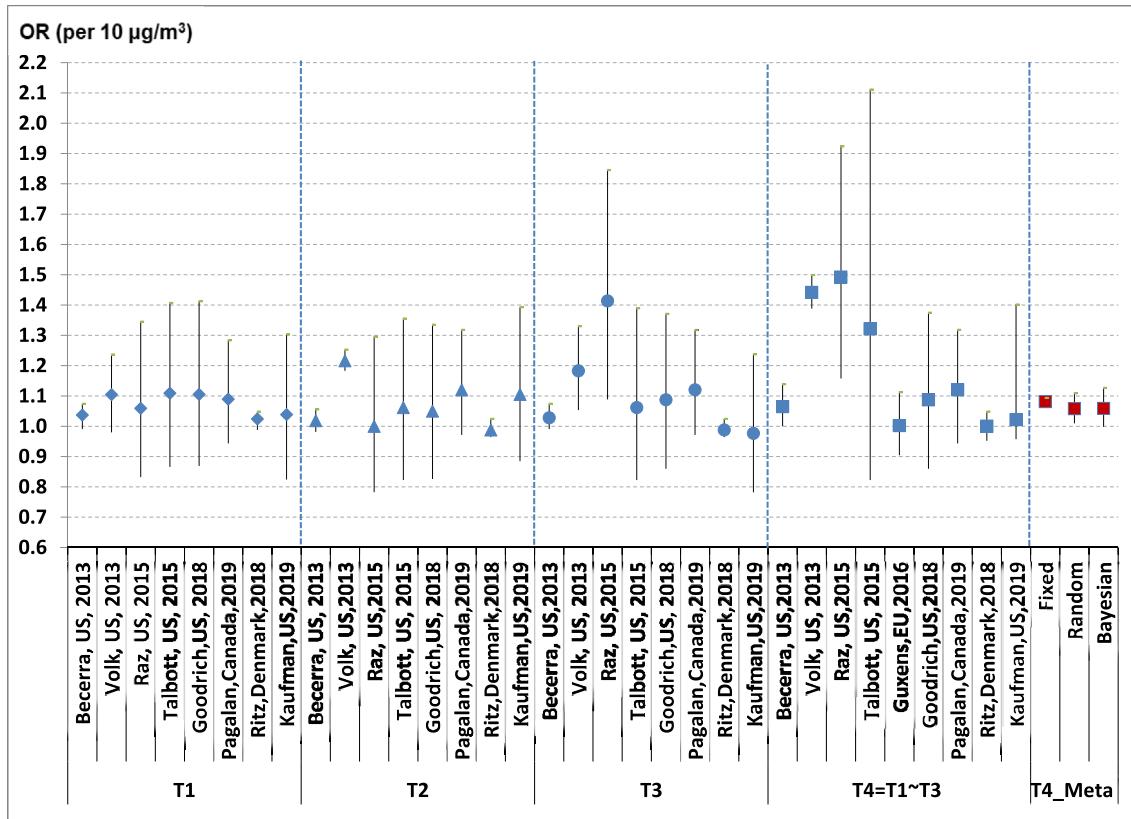


Fig. 2. Comparisons of odds ratios on PM_{2.5}-ASD over exposure time by trimester. T1: trimester 1 (in diamond); T2: trimester 2 (in triangle); T3: trimester 3 (in circle); T4: whole pregnancy period combining three trimesters (in square); and T4_Meta: meta-analysis pooled estimates for prenatal period (T4) only (in red square). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

significant ORs, the Bayesian random effects model resulted in a marginally significant OR per 10 µg/m³: 1.08 (1.07, 1.09), 1.06 (1.01, 1.11), and 1.06 (1.00, 1.13) from fixed, random and Bayesian models, respectively (See Fig. F1 for log-scale in Appendix F.).

3.5.1.2. Association between PM10 and ASD. Nine studies were considered for the meta-estimate and Table C2 summarizes the study-specific ORs. While 4 studies estimated the OR for each trimester and the prenatal period, 1 study (Kalkbrenner et al., 2015) did for T1, T2 and T3 separately only, and 2 studies (Gong et al., 2017; Guxens et al., 2016) did for T4 only. The heterogeneity test ($Q(df=8)=20.33$, $p\text{-val}=.0092$, $I^2=74.96\%$) suggests considerable heterogeneity among the studies. The meta-estimates from 3 methods (Fig. 3) indicate no significant ORs (See Fig. F2 for log-scale in Appendix F.).

3.5.1.3. Association between NO2 and ASD. Seven studies were considered for the meta-estimate and Table C3 summarizes the study-specific ORs. The heterogeneity test ($Q(df=6)=17.58$, $p\text{-val}=.0074$, $I^2=58.31\%$) suggests considerable heterogeneity among the studies. The meta-estimates show no significant ORs (Fig. 4). The frequentist fixed and random models returned same and significant ORs, but the Bayesian random effects model did not: 1.02 (1.01, 1.03), 1.02 (1.01, 1.04), and 1.02 (1.00, 1.05) per 10 ppb from fixed, random and Bayesian models, respectively (See Fig. F3 for log-scale in Appendix F.).

3.5.1.4. Association between ozone and ASD. Four studies were considered for the meta-estimate and Table C4 summarizes the study-specific ORs. The heterogeneity test ($Q(df=3)=5.64$, $p\text{-val}=.12$,

$\text{val}=.13$, $I^2=55.4\%$) suggests no heterogeneity. The meta-estimates of ozone returned inconsistent results between frequentist and Bayesian models (Fig. 5) (See Fig. F4 for log-scale in Appendix F.).

3.5.2. Time-specific associations with ASD

3.5.2.1. During pregnancy (T4). Guxens et al. reported the ORs for the prenatal period only (T4) for EU and 4 individual countries. We considered this particular study as one (EU in total) for meta-analysis. We checked publication bias through funnel plots for prenatal period (T4) only (not shown). None displayed considerable publication bias, as all plots showed symmetric distributions. In addition, Egger's test (i.e. $z=0.54$, $p=.59$) was not statistically significant, so there's no evidence of publication bias according to this test (Egger et al., 1997). Among the 4 air pollutants, PM_{2.5} and ozone returned the highest and lowest OR, respectively (Table 2). The two frequentist fixed and random effects models returned significant pooled OR for PM_{2.5} and ozone, but not for PM₁₀ and NO₂ (Appendix D. Fig. D1a and b in log scale). No Bayesian model returned significant pooled OR.

3.5.2.2. First trimester (T1). Table C5 summarizes the meta-estimates for trimester 1. PM_{2.5} and ozone returned the highest and lowest OR, respectively. Both frequentist models (denoted by Fixed and Random) returned significant OR for PM_{2.5} and NO₂, whereas Bayesian random effects models did not for PM₁₀, NO₂ and ozone (Fig. D2a and b in log scale).

3.5.2.3. Second trimester (T2). Table C6 summarizes meta-estimates for trimester 2. Again PM_{2.5} and ozone returned the highest and lowest OR, respectively. Both frequentist models

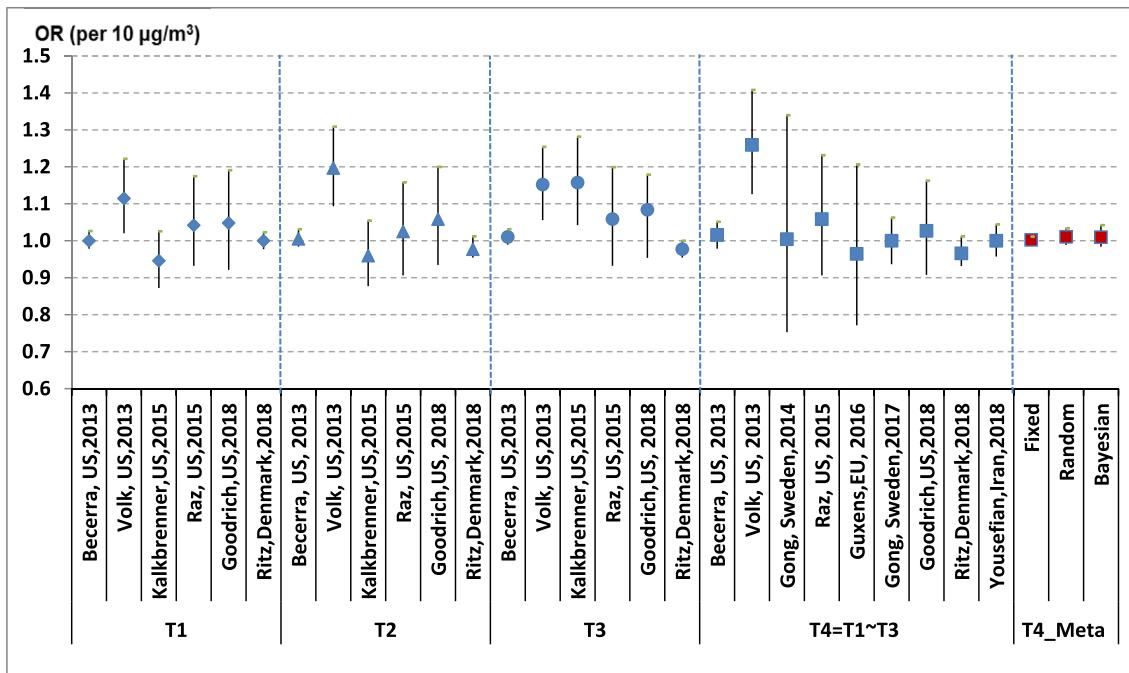


Fig. 3. Comparisons of odds ratios on PM₁₀-ASD over exposure time by trimester. T1: trimester 1(in diamond); T2: trimester 2 (in triangle); T3: trimester 3 (in circle); T4: whole pregnancy period combining three trimesters (in square); and T4_Meta: meta-analysis pooled estimates for prenatal period (T4) only (in red square). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

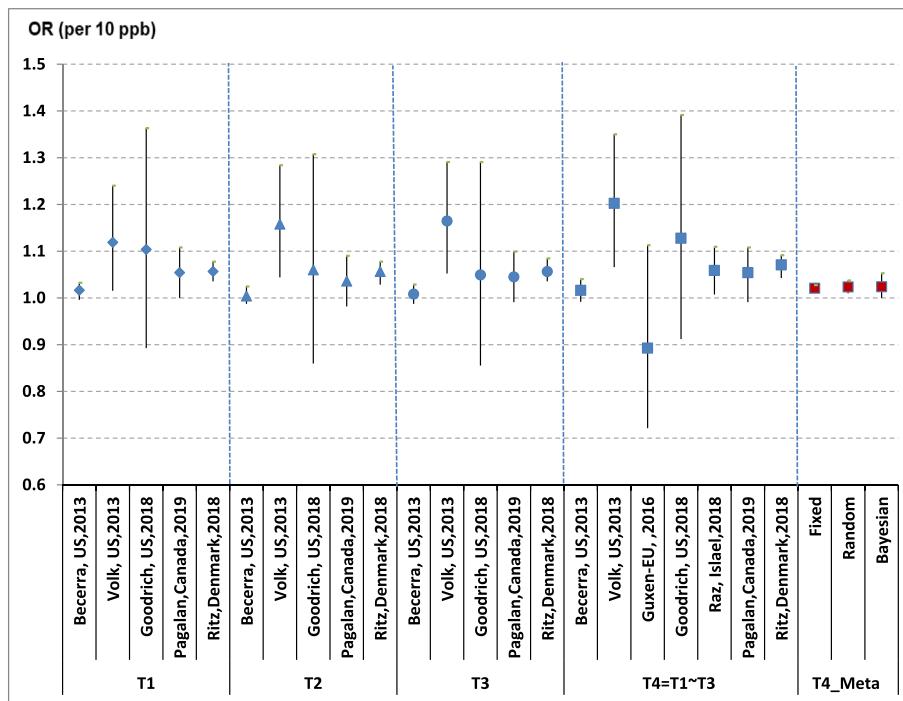


Fig. 4. Comparisons of odds ratios on NO₂-ASD over exposure time by trimester. T1: trimester 1(in diamond); T2: trimester 2 (in triangle); T3: trimester 3 (in circle); T4: whole pregnancy period combining three trimesters (in square); and T4_Meta: meta-analysis pooled estimates for prenatal period (T4) only (in red square). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

returned significant OR for PM_{2.5} and NO₂, whereas the Bayesian random effects models did not for all air pollutants (Fig. D3a and b in log scale).

3.5.2.4. Third trimester (T3). Table C7 summarizes meta-estimates

for trimester 3, which was different from the two earlier trimesters. Both frequentist models returned significant ORs for PM_{2.5}, NO₂ and ozone. However the Bayesian random effects model did not show significant ORs for all air pollutants (Fig. D4a and b in log scale).

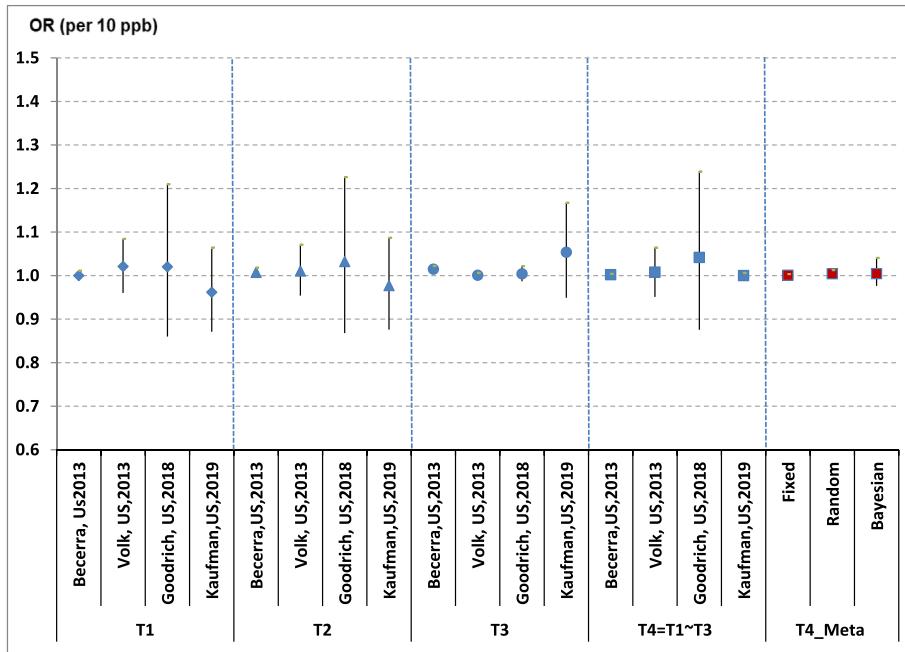


Fig. 5. Comparisons of odds ratios on Ozone-ASD over exposure time by trimester. T1: trimester 1(in diamond); T2: trimester 2 (in triangle); T3: trimester 3 (in circle); T4: whole pregnancy period combining three trimesters (in square); and T4_Meta: meta-analysis pooled estimates for prenatal period (T4) only (in red square). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Association between ASD and air pollutant during prenatal period (T4).

Exposure	Number of studies	Method ^a	OR	OR.low	OR.up
PM _{2.5} _2013-19	9	Fixed	1.08	1.07	1.09
		Random	1.06	1.01	1.11
		Bayesian	1.06	1.00	1.13
PM ₁₀ _2013-18	9	Fixed	1.00	0.99	1.01
		Random	1.01	0.99	1.03
		Bayesian	1.01	0.98	1.04
NO ₂ _2013-19	7	Fixed	1.02	1.01	1.03
		Random	1.02	1.01	1.04
		Bayesian	1.02	1.00	1.05
Ozone_2013-19	4	Fixed	1.00	1.00	1.00
		Random	1.00	1.00	1.01
		Bayesian	1.00	0.98	1.04

^a Fixed: frequentist fixed effect model; Random: frequentist random effects model; and Bayesian: Bayesian random effects model. Bold indicates statistical significance; Round off the ORs to two decimal digits.

3.5.2.5. Temporal changes in associations over trimesters. Fig. 6 displays eight studies with inconsistent temporal patterns and a meta-estimate for PM_{2.5} only. Overall, they showed most and least consistency for T1 and T3, respectively. Combining the 8 studies, the Bayesian meta-estimates returned a slightly increasing trend but not statistically significant changes in the ORs: 1.02, 1.04, and 1.04, for trimesters 1 to 3, respectively.

For PM_{2.5}, PM₁₀, NO₂, and ozone, Table C8 summarizes meta-estimates. Overall, except for NO₂, an increasing trend over the trimester was in common among the 4 air pollutants.

3.5.3. Sensitivity analysis (study design and exposure time)

The Funnel plots in Fig. E1 (Appendix E) overall shows little bias of publication. Fig. E2 demonstrates each study's relative contribution to the meta-estimates for each air pollutant. We found 1 to 3 studies contributed at least 20% of each pollutant: two out of 9 studies (Volk et al., and Ritz et al.) for PM_{2.5}; three out of 9 studies

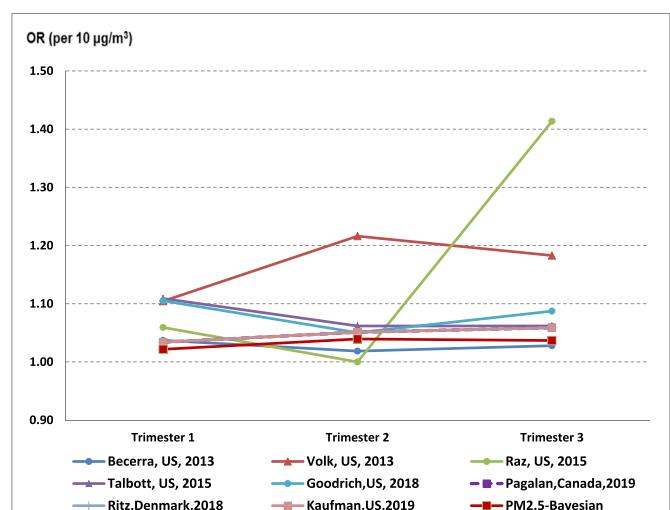


Fig. 6. Temporal changes in PM_{2.5} – ASD association over trimester.

(Becerra et al., Ritz et al. and Yousefian et al.) for PM₁₀; two out of 7 studies (Ritz et al. and Becerra et al.) for NO₂; and one out of 4 studies (Kaufman et al.) for ozone. This implies the meta-estimates are overall sensitive to a few specific studies.

While all studies contained case-control designs except 2 studies: Pagalan et al. (2019) and Guxens et al. (2016). Guxens et al. used a cohort study for the prenatal period only (T4) for PM_{2.5}, PM₁₀, and NO₂, reporting the ORs for EU and 4 individual countries. We approached this study for our meta-analysis in two ways: (a) excluding it to include case-control studies only and (b) including it as four individual studies, meaning a total of 12 studies for PM_{2.5}, 12 studies for PM₁₀, and 10 studies for NO₂. Overall the meta-estimates were comparable with little difference in significance regardless of the Guxens study (Table C9).

To focus on maternal exposure, our meta-analysis excluded two studies in Table 1 because they reported the ORs for a postnatal period only (Jung et al., 2013) or a combined period with prenatal period (Kim et al., 2017) but included 5 studies that reported pre-conception or post-natal periods along with prenatal period (Kalkbrenner et al., 2015; Raz et al., 2015, 2018; Talbott et al., 2015a; Volk et al., 2013). We combined these studies in 3 ways as shown in Table C10 to extend exposure time periods:

- T4, preconception period only or T4+preconception combined;
- T4, postnatal period only or T4+ postnatal period combined; and
- T4, preconception period, postnatal period or combined period.

If one study included before (preconception) and after (postnatal) the prenatal period (T4), respectively, we included the study as 3 individual studies with each exposure time. Thus the number of studies is bigger than reported in Table C9. The meta-estimates of ORs within each air pollutant are consistently higher for the period of prenatal or post-natal combined but lower for the period of prenatal or pre-conception combined. Overall meta-estimates of the prenatal combined with postnatal period appeared to be higher than the prenatal period only.

4. Discussion

This systematic review summarized 25 studies that examined the association between maternal exposure to ambient air pollutants and ASD in children. The study findings were inconsistent and meta-analyses were applied to pool the study results. We grouped the study-specific ORs by air pollutant ($PM_{2.5}$, PM_{10} , NO_2 , and ozone) and exposure time (trimesters), and found limited evidence for positive associations. Among the four air pollutants, $PM_{2.5}$ resulted in the highest OR for the prenatal period: 1.06(1.01,1.11) and 1.06(1.00,1.13) from frequentist and Bayesian random effects model, respectively. The odds of ASD in children were 6% higher through maternal exposure to $PM_{2.5}$. However, $PM_{2.5}$ is a mixture of various fine particles, and thus further investigations to examine specific PM components linked to ASD are necessary to analyze this difference between $PM_{2.5}$ and the other three pollutants.

Exposure time differences in 4 pre-determined periods (trimester 1 to 3 and prenatal) and 2 more extended periods to pre-conception and postnatal period were examined under sensitivity analysis. All meta-estimates were comparable, implying little difference regarding exposure time related to pregnancy. However, there was an uncertain indication that postnatal exposures might be more linked to the ASD than pre-conception, which was consistent among the 4 pollutants. The trend in the trimester-specific ORs was investigated. Trimester 3 was found to be more associated with the ASD than the others. The myelin sheath is a plasma membrane extension that is laid down in regularly spaced segments along axons of the nervous system. This process involves extensive changes in oligodendrocyte cell shape and membrane architecture. Myelination starts around 24–25 weeks of gestation and reaches its peak by 1 year of age (Purves et al., 2012). Imaging and biopsy of the brains of autistic children have shown a deficit in myelination as compared to normal children (Aoki et al., 2013; Zikopoulos and Barbas, 2010). Such a diminution would weaken the operation of the axon-target synapse, thereby accounting for the malfunction of areas of the brain involved in behavior. This would include the prefrontal and temporal areas of the brain. As the myelination process starts late second trimester, it could have more impact on the third trimester. This might explain a finding of this study that the associations between air pollution and the ASD are likely higher for the third trimester compared to the others A

temporal trend in associations during pregnancy cannot be concluded due to the discrepancies between studies and the disagreements in significance between meta-analysis methods (significance by frequentist vs insignificance by Bayesian).

It is widely recognized that the etiology of ASD is complex and related to many factors, including genetic background, environmental risk factors, and gene-environment interactions (Landrigan et al., 2012; Dawson and Bernier, 2013). Earlier research on the cause of ASD focused largely on genetic changes or mutations (Autism Genome Project Consortium et al., 2007; Landrigan et al., 2012; Von Ehrenstein et al., 2014). However, it is now understood that the perinatal period is critical for brain development. Thus exposure to environmental chemicals during this time could disturb normal neurodevelopment (Eskenazi et al., 2007; Landrigan et al., 2012; Ye et al., 2017), therefore providing a plausible link between environmental risk factors and ASD. Our systematic review, which is updated by including more recent studies, provides similar findings to the previous studies (Becerra et al., 2013; Raz et al., 2015). While there was some evidence indicating maternal exposure to $PM_{2.5}$ may increase the risk of ASD, evidence for the effect of ozone, PM_{10} , and NO_2 on ASD is weak or limited. An increase in the number of studies for a future meta-analysis would improve statistical power to identify associations between air pollutants and ASD.

4.1. Difference by exposure time

The five studies in Fig. 6 show difference between trimesters. In practice, the difference can be detected when the maternal exposure concentrations vary over time or when some effect modifiers including behaviors (physical and mental) changes over time. For example, the former can be explained if the mothers avoided going outside during a specific trimester, and the latter can result if they were on medications or dietary supplements for a specific trimester.

While two air pollution studies (Kalkbrenner et al., 2015; Raz et al., 2015) concluded ASD associations to be specific to the third trimester, the mechanism remains largely unknown. Weisskopf et al. (2015) speculated that women working outside the home may be more focused on prescribed rest or maternal leave in the third trimester. This work-pattern change may open more time for outside activities which in turn could affect the amount of PM exposure. However, other potentially relevant studies on physical and mental behavior changes suggest varied results, often in different trimesters with involvement of certain biological events or personal behavior (Weisskopf et al., 2015; Ng et al., 2017).

Attempts were made to quantify changes in leisure-time physical activity (LTPA) during the first half of pregnancy compared with the year prior to pregnancy (Amezcuia-Prieto et al., 2013). After studying 1175 healthy pregnant women, it was concluded that pregnancy involved a decrease in LTPA, not only in frequency, but also duration and intensity. Physical activity can be further reduced due to musculoskeletal pain in the back, hand-wrist and hip, factors which complicate pregnancy and mobility especially in the third trimester (Kesikburun et al., 2018). As pregnancy progresses, a period of emotional and behavioral changes (Lagadec et al., 2018) ensues. This can include: different nutritional choices, efforts to quit smoking and gestational weight gain (Levine et al., 2015). An increase in stress can follow causing a depletion of metabolic resources. Seebacher et al. (2013) concluded that in late-stage pregnancy, the metabolic cost of activity or behavior could render reproduction sensitive to environmental changes.

It should be noted that the maternal exposures by trimester are correlated, which would reduce statistical power to detect differences in ASD development of children by trimester. Studies

focusing on time-varying associations will be necessary before a conclusion can be reached regarding a critical time window of exposure associated with an increased risk of ASD development. Identifying the critical exposure time may become an important step in guiding and counseling pregnant women.

4.2. Strengths of this review

Our approach for systematic review in this study is not much different from other systematic studies on the ASD. For example, search strategy and meta-analysis are comparable. However, we focused on five areas including study publication time, environmental cause of the ASD, target population, meta-analysis method and time-varying associations. (1) We examined more recent studies published by April 2019 and thus could update study findings. (2) The environmental causes of the ASD are still unknown and we focused on specific ambient air pollution. (3) As the diagnosis methods ASD have changed, we focused, in particular, on children to reduce the discrepancy in diagnosis ASD. (4) As mentioned in Discussion, we compared three meta-analysis methods: frequentist fixed and random effects models, and Bayesian random effect model. (5) We demonstrated inconsistent time-varying associations over trimesters between air pollutants and between studies. We believe that this study added updated findings in these five areas.

Applying a Bayesian random effects model and its associated rigors is the primary strength. While the fixed effects model considers sampling variation within individual studies only, the random effects model also consider between-study variations, thus producing larger standard error of estimates (wider interval estimates). There are 2 approaches for the random effects model, the frequentist and Bayesian methods. Typically, the frequentist random effects model has been applied to most meta-analysis: for example, recently by [Lam et al. \(2016\)](#) and [Flores-Pajot et al. \(2016\)](#). A small sampling of studies often results in considerable discrepancies between these methods. When discrepancies appear, as shown in [Figs. 2–5](#), the Bayesian estimates are more reliable in integrating multiple studies on the same or comparable research questions, even though they return weaker evidence than the frequentist estimates. In addition, there is another reason to consider the Bayesian model: when there are unusually higher or lower study estimates than the others. For example, [Volk et al. \(2013\)](#) returned higher ORs with relatively smaller intervals compared to the other studies. The influence of this specific study on the meta-estimate is reduced by the Bayesian model. This is also a preferred feature for integrating multi-study results by reducing bias in meta-analysis.

Secondly, the differences in exposure-time during pregnancy for each pollutant was evaluated. The time variation pattern can differ among pollutants. While one could be more critical to the earliest stage of pregnancy, others could affect later stages of pregnancy. Previous studies centered mainly on the entire pregnancy period and assumed the association constant with pregnancy. While [Flores-Pajot et al. \(2016\)](#) captured critical exposure windows during pregnancy (i.e., first, second, and third trimester), the conclusion was that there is a need to track residential mobility during pregnancy to account for changes in exposure. Similarly, [Lam et al. \(2016\)](#) highlighted the inaccuracy of exposure assessment methods in their study limitations. Flores-Pajot et al. and Lam et al. considered misclassifications of exposures during pregnancy. To understand observed differences between trimesters, this study considered maternal changes in physical, behavioral and emotional aspects.

4.3. Limitations of this review

[Lyall et al. \(2014\)](#) confirm that several studies have shown significant increases in ASD risk associated with particulate matter and heavy metals. However, diesel exhaust, chemicals from traffic-related pollutants and heavy metals could not be examined since many studies (at least 3) reported the 4 air pollutants only. Studies with long-term exposure time (i.e., pregnancy to postnatal) were excluded since many mainly reported the prenatal period. We reviewed articles in English only and thus our meta-analysis excluded other study results reported in non-English languages. This could bring in unexpected and unmeasurable bias in our meta-estimates, which is also a limitation of this review.

In a scoping review for environmental factors associated with ASD, [Ng et al. \(2017\)](#) summarized the risk factors as: traffic-related air pollutants; advanced parental age; preterm birth; low birth weight; hyperbilirubinemia and clustering of pregnancy complications; and maternal immigrant status. These factors for the meta-analysis could not be considered due to limited studies. Due to these limitations, this study focused on the 4 air pollutants for prenatal period only.

This study reports meta-estimates of the OR based on several case-control studies, which is the ratio of odds of exposure among the cases to that of the controls. The OR approximates the relative risk, which estimates the magnitude of the association between exposure to the specified ambient air pollutants and the ASD. While the OR provides relative difference between exposed and unexposed groups, another measure—attributable risk—indicates absolute difference in the incidence of the ASD between the two groups. It quantifies the incidence of the ASD in the exposed group that could be reduced if not exposed. However, this study cannot provide the attributable risk, since the incidence could not be determined from the case-control studies examined in this study. With the small, barely significant ORs (such as 1.06 and 1.02), we expect the contribution of the specified pollutants to the overall prevalence of ASD is quite small.

5. Conclusion

Our meta-analysis on the association between maternal exposure to ambient air pollution during the prenatal period and ASD in children has produced some evidence for PM_{2.5}, weak evidence for NO₂, little evidence for PM₁₀, and inconclusive evidence for ozone (due to small number of studies). The time-varying effects of maternal exposure over the 3 trimesters were inconsistent, and our meta-analysis returned insignificant changes over trimester. However the noticeable difference in the trimesters among studies merits further investigation.

Declaration of competing interest

The authors declare they have no actual or potential competing financial interests.

Acknowledgments

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Appendix A. Study characteristics (in the same order as in Table 1)

Table A1

Characteristics of included studies.

Authors	Model Covariates (Model)	Air pollutant measurement method ^{a)-c)a}	ASD ascertainment method ^{d)-f)a}
Roberts et al. (2013)	Year of birth, calendar month of birth, population group, paternal age, and census poverty index (logistic)	Dispersion models using HAP, NATA from US EPA linked to residence at birth (b)	Maternal reporting, with subset of 50 cases validated by Autism Diagnostic Interview-Revised (ADI-R) (e)
Ritz et al. (2018)	Maternal age, paternal age, location of birth, neighborhood SES-employment, neighborhood SES-housing, and maternal smoking during pregnancy (conditional logistic)	Danish Air Quality Monitoring Program which utilizes the geographic information system (GIS)-based air pollution and human exposure modelling system (Air GIS) (b)	Identification through the Danish National Patient Register and the Danish Psychiatric Central Register (e)
Raz et al. (2015)	Maximum education level of parents, child's sex and child's ethnicity (based on ancestry informative markers in the genome) (multivariable logistic)	Spatiotemporal models using data from US EPA (b)	Autism, Asperger's, or "other autism spectrum" by maternal reporting, with subset of 50 cases validated by Autism Diagnostic Interview-Revised (ADI-R) (e)
Kalkbrenner et al. (2010)	Age, anxiety, gender, intellectual disabilities, obsessive compulsive disorder, phobia, preterm, and SES (logistic)	Gaussian air quality dispersion model, National-scale Air Toxics Assessment (NATA) from US EPA (b)	Diagnosis of ASD based on DSM-IV-TR criteria, Identification through ADDM Network (e)
Al-Hamdan et al. (2018)	Gender, race, smoking, socioeconomic status (multivariable logistic regression)	US Environmental Protection Agency's (EPA) Air Quality Index (AQI), PM _{2.5} sunlight and max heat index over the period 1992–2011. Regression models from satellite-derived and ground-level measurements (b)	Biennial ASD prevalence data for 15 sites within USA for the years 2000–2012, Identification through Autism and Developmental Disabilities Monitoring (ADDM) Network. (e)
Gong et al. (2014)	Census tract % male, % White race, % Hispanic ethnicity, % college educated, rural geography, and % below poverty (multivariate regression)	Dispersion model using data from historical emission databases, with data from suburban monitoring stations for sensitivity analysis (b)	Diagnosis of ASD using Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC) telephone interviews (e)
Guxens et al. (2016)	Self-reported financial hardship between 3 months before pregnancy to time of interview (yes/no), child's year of birth, vitamin A and zinc intake during the first month of pregnancy (logistic)	Land use regression models using data from air monitoring campaigns in the study areas (b)	Parent reported questionnaires (A-TAC), the Pervasive Developmental Problems (PDP) subscale of the Child Behavior Checklist for Toddlers (CBCL1½–5) or Social Responsiveness Scale (SRS) or psychologist-administered Childhood Autism Spectrum Test (CAST) (e)
Windham et al. (2013)	Child sex, child race/ethnicity, maximum education of parents, maternal age (>35 years vs. ≤ 35 years), occupational medicine-certified physician (c) and maternal smoking during pregnancy (logistic)	Self-reported occupations were coded by an occupational medicine-certified physician (c)	Diagnosis of ASD from (1) a qualified medical professional; (2) qualification for special education under an autism exceptionality; or (3) autistic behaviors that meet Diagnostic and Statistical Manual of Mental Disorders (4th edition). (e)
Kalkbrenner et al. (2015)	Race, maternal age/education, smoking during pregnancy, marital status, census tract median household income, urbanicity (logistic)	Bayesian Maximum entropy geostatistical method using data from US EPA monitoring stations linked to birth certificate address (b)	Diagnosis of ASD based on DSM-IV-TR criteria, Identification through ADDM Network (e)
Becerra et al. (2013)	Maternal age, education, race/ethnicity, maternal place of birth; type of birth, parity, insurance type, gestational weeks at birth (continuous) (conditional logistic)	Land use regression models using data from ground-monitoring stations (b)	Diagnosis of autistic disorder based on Diagnostic and Statistical Manual (DSM-IV-R) criteria, Identification through California Department of Developmental Services (DDS) records (e)
Kalkbrenner et al. (2018)	State, birth year, race, maternal age/education, census group median household income, census group urbanization, calendar week of child's birth (logistic)	National-scale Air Toxics Assessment (NATA) from US EPA linked to residence address at pregnancy (b)	Diagnosis of ASD based on ADI-R, with assessment of autism severity based on the Calibrated Severity Score, Identifications through Autism Genetic Resource Exchange (AGRE), a volunteer research repository of families from across the United States in which typically two or more siblings have a diagnosis of ASD (e)
Gong et al. (2017)	Parity, gender, (2015)maternal age during pregnancy, maternal smoking during pregnancy, maternal marital status at birth year, parental education, family income, and neighborhood deprivation at birth year (conditional logistic)	Gaussian air quality dispersion model using data from historical emission databases, with data from suburban monitoring stations for sensitivity analysis (b)	Diagnosis of ASD based on International Classification of Diseases (ICD-9/10) or DSM-IV criteria, Identification through the National Patient Register (NPR), the Clinical Database for Child and Adolescent Psychiatry in Stockholm (PASTILL), the Habilitation Register (HAB), and the Stockholm Regional Health Care Data warehouse (VAL) (e)
Jung et al. (2013)	Maternal characteristics (education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity), child's sex, season at child's birth, urbanicity at child's birth address, and child's age at autistic traits assessment, and evaluator of the autistic traits (co-proportional hazard)	Inverse distance weighting method using data from Taiwan EPA monitoring stations (b)	Diagnosis of ASD based on ICD-9-CM criteria, Identification through National Health Insurance claims. (e)
Goodrich et al. (2018)	Sex, birth month, sibling order, maternal age, paternal age, mother's marital status, parents' birth countries, mother's education/employment, father's education/employment, disposable income within household, and neighborhood deprivation (unconditional logistic)	Near roadway air pollution (NRP) based on CALINE4 line-source air quality dispersion model. PM _{2.5} , PM ₁₀ , NO ₂ , ozone from US EPA data (b)	Diagnosis of ASD based on ADOS and ADI-R, Identification through California DDS records (e)
Kim et al. (2017)	Sex, max education in the home, referral center, race, mother's age, prenatal smoking, season of conception and home ownership (logistic)	Near roadway air pollution (NRP) based on CALINE4 line-source air quality dispersion model. US EPA data (b) Distance to nearest major roadway (b)	Diagnosis of ASD based on ADOS and ADI-R, Identification through California DDS records (e)

Table A1 (continued)

Authors	Model Covariates (Model)	Air pollutant measurement method ^{a)-c)a}	ASD ascertainment method ^{d)-f)a}
Volk et al. (2011)	Mother's age, education, race, smoking, child's birth year (continuous), and child's sex (logistic)	Near roadway air pollution (NRP) based on CALINE4 line-source air quality dispersion model. US EPA data. (b)	Diagnosis of ASD based on ADOS and ADI-R, Identification through California DDS records. (e)
Volk et al. (2013)	Child sex, child race/ethnicity, maximum education of parents, maternal age (> 35 years vs. ≤ 35 years), and maternal smoking during pregnancy (logistic)	Near roadway air pollution (NRP) based on CALINE4 line-source air quality dispersion model. US EPA data. (b)	Diagnosis of ASD based on ADOS and ADI-R, Identification through California DDS records (e)
Kerin et al. (2018)	Year of birth, race/ethnicity, number of siblings in the family, maternal age and census block group population density/education level/median rent(linear)	Near roadway air pollution (NRP) based on CALINE4 line-source air quality dispersion model. US EPA data (b)	Diagnosis of ASD based on ADOS and ADI-R, using both DSM-IV-TR and DSM-V criteria, Identification through California DDS records (e)
Chen et al. (2018)	Birth weight, gestational weeks, disease history, trauma history, maternal age, familial mental health history, parents' marital status, parental relationship, parenting, income, parents' educational level and smoking status (logistic)	Random forests model using ground measured PM _{2.5} and PM ₁₀ data were obtained from 1497 stations of the China National Environmental Monitoring Center (CNEMC) (b)	Social Communication Questionnaire (SCQ) was first completed by parents and teachers to screen for ASD cases. Positive screens were then diagnosed by experienced pediatricians using DSM-V criteria (d)
Pagalan et al. (2019)	Sex, birth month, birth year, maternal age, maternal birthplace, and neighborhood-level urbanicity and income band (logistic)	Land use regression models at 10m ² spatial resolution ³⁰ with continuous monitoring data (2003–2014) from Metro Vancouver's Air Quality Monitoring Network	Diagnosis of ASD based on ADOS and ADI-R, Identification through British Columbia Autism Assessment Network (e)
Yousefian et al. (2018)	Maternal age at birth, maternal education, paternal education, cousin marriage, maternal smoking during pregnancy, birth order, gestational age (weeks), multiple births, maternal disease, paternal disease (multivariable logistic)	Land use regression models based on 23 monitoring sides around Tehran (b)	Identification through 1) Center for Autism Diagnosis and Treatment, 2) ASD support groups, and 3) School-based special education services (d)
Raz et al. (2018)	Sex, year of birth, month of birth, maternal age at birth, paternal age at birth, and census income (logistic)	Dispersion models using data from the air pollution monitoring database of the Technion Center of Excellence in Exposure Science and Environmental Health (b)	Identification from National Insurance Institute of Israel (NII) claims (d)
Talbott et al. (2015a)	College education, smoking, race, and mom's age (logistic)	NATA from US EPA linked to census tract of residence at birth (b)	Score ≥ 15 on the Social Communication Questionnaire and written documentation from a child psychiatrist/psychologist of ASD diagnosis(d)
Talbott et al. (2015b)	Maternal age at birth, year of birth, maternal parents' education, Census tract median income, Census tract % college educated, and HAP model year (logistic)	Land use regression models using data from air monitoring campaigns in the study areas (b)	Score ≥ 15 on the Social Communication Questionnaire and written documentation from a child psychiatrist/psychologist of ASD diagnosis(d)
Kaufman et al. (2019)	Year of birth, mother's education, birth spacing, maternal pre-pregnancy BMI, and month of conception (multivariable logistic)	United States EPA's Fused Air Quality Surface Using Downscaling (FAQSD) model was used to calculate averages of daily maximum eight-hour average ozone estimates and 24-h-average PM _{2.5} estimates (b)	Diagnosis of ASD based on ADOS. Identification through Cincinnati Children's Hospital Medical Center EMR (e)

^a) monitored only; b) model-derived (land use regression, distance, satellite); c) other models; d) independent validation; e) record linkage or based on self-reports; and f) self-report only or no description. Bold indicates those studies included for meta-analysis.

Appendix B. Bayesian meta-analysis

For a given air pollutant, i , and study, j , we assumed that the observed study-specific ORs (log scale β_{ij}) were normally distributed with unknown study-specific mean (β_{ij}) and variance ($\widehat{\nu}_{ij}$), and that the unknown study-specific means (β_{ij}) were normally distributed with unknown mean (μ_i) and variance (σ_i^2), which indicated the heterogeneity among the studies. In equation we write:

$$\widehat{\beta}_{ij} | \beta_{ij} \sim N(\beta_{ij}, \widehat{\nu}_{ij}), \text{ and} \quad (1)$$

$$\beta_{ij} \sim N(\mu_i, \sigma_i^2) \quad (2)$$

Since information on both mean (μ_i) and variance (σ_i^2) was limited, non-informative priors diffused over a large range for each mean and standard deviation (SD) were applied as follows:

$$\mu_i \sim N(0, 1000) \text{ and } \sigma_i \sim U(0, 10) \quad (3)$$

When we considered time-varying associations, we needed to add one more variable in equations (1)–(3) for the exposure time window, t . For example, β_{ij} and μ_i are to be changed to β_{ijt} and μ_{it} .

We then compared μ_{it} for $t = T1, T2$, and $T3$ (three trimesters) to detect any variations associated with the time of exposure.

β_{ij} , β_{ij} and $\widehat{\nu}_{ij}$ in equation (1) represent the reported (known) estimate for study-specific log (OR), the unknown true study-specific log (OR), and the estimated study-specific sampling variance given β_{ij} , $\text{var}(\widehat{\beta}_{ij} | \beta_{ij})$, respectively, for a chosen air pollutant i , and study j . Equation (1) assumes that the within-study variation (ν_{ij}) is not fixed, varying over the study depending on its sample size. However, equation (2) assumes a fixed between-study variation (σ_i^2) for a selected air pollutant, which indicates that all studies were equally likely far from their mean μ_i regardless of the study's scale.

In (2), we consider that the four pollutants can have different mean values of log (OR), but all studies for a specific pollutant are from a normal distribution sharing the mean and dispersion, i.e., μ_i and σ_i . Here the pollution-specific mean (μ_i) is the main parameter to be estimated, called pooled or meta-estimate. In (3), a random sampling of 300,000, in addition to 30,000 burn-in, through three chains provides the posterior distribution for the pollution-specific mean, and this study reports the 95% highest posterior density posterior interval (collection of most likely values of the pollution-specific mean).

Appendix C. Association Estimates

Table C1
Association between ASD and PM_{2.5} (per 10 unit).

Exposure Time ^a	Author-Country-Year	OR	OR.low ^b	OR.up ^c
T1	Becerra,US,2013	1.04	0.99	1.07
	Volk,US,2013	1.10	0.98	1.24
	Raz,US,2015	1.06	0.83	1.34
	Talbott,US,2015	1.11	0.87	1.41
	Goodrich,US,2018	1.11	0.87	1.41
	Palagan,Canada,2019	1.09	0.94	1.28
	Ritz,Denmark,2018	1.02	0.99	1.05
	Kaufman,US,2019	1.04	0.82	1.30
T2	Becerra,US,2013	1.02	0.98	1.06
	Volk,US,2013	1.22	1.18	1.25
	Raz,US,2015	1.00	0.78	1.30
	Talbott,US,2015	1.06	0.82	1.36
	Goodrich,US,2018	1.05	0.83	1.33
	Palagan,Canada,2019	1.12	0.97	1.32
	Ritz,Denmark,2018	0.99	0.96	1.02
	Kaufman,US,2019	1.11	0.88	1.39
T3	Becerra,US,2013	1.03	0.99	1.07
	Volk,US,2013	1.18	1.05	1.33
	Raz,US,2015	1.41	1.09	1.85
	Talbott,US,2015	1.06	0.82	1.39
	Goodrich,US,2018	1.09	0.86	1.37
	Palagan,Canada,2019	1.12	0.97	1.32
	Ritz,Denmark,2018	0.99	0.96	1.02
	Kaufman,US,2019	0.98	0.78	1.24
T4 = T1-T3	Becerra,US,2013	1.06	1.00	1.14
	Volk,US,2013	1.44	1.39	1.50
	Raz,US,2015	1.49	1.16	1.92
	Talbott,US,2015	1.32	0.82	2.11
	Guxens,EU,2016	1.00	0.90	1.11
	Goodrich,US,2018	1.09	0.86	1.37
	Palagan,Canada,2019	1.12	0.94	1.32
	Ritz,Denmark,2018	1.00	0.95	1.05
T4_Meta ^d	Fixed	1.08	1.07	1.09
	Random	1.06	1.01	1.11
	Bayesian	1.06	1.00	1.13

^a T1-T3:trimesters and T4:whole pregnancy period.

^b Lower bound of 95% confidence interval.

^c Upper bound of 95% confidence interval.

^d Meta-analysis pooled estimates for prenatal period only; Fixed:Frequentist fixed effect model; Random:Frequentist random effects model; and Bayesian:Bayesian random effects model. Bold indicates statistical significance.

Table C2 (continued)

Exposure Time ^a	Author-Country-Year	OR	OR.low ^b	OR.up ^c
T3	Becerra,US,2013	1.01	0.99	1.03
	Volk,US,2013	1.15	1.06	1.25
	Kalkbrenner,US,2015	1.16	1.04	1.28
	Raz,US,2015	1.06	0.93	1.20
	Goodrich,US, 2018	1.08	0.95	1.18
	Ritz,Denmark,2018	0.98	0.95	1.00
	Gong,Sweden,2014	1.00	0.75	1.34
	Raz,US,2015	1.06	0.91	1.23
T4 = T1-T3	Becerra,US,2013	1.02	0.98	1.05
	Volk,US,2013	1.26	1.13	1.41
	Gong,Sweden,2014	1.00	0.75	1.34
	Raz,US,2015	1.06	0.91	1.23
	Guxens,EU, 2016	0.96	0.77	1.21
	Gong,Sweden,2017	1.00	0.94	1.06
	Goodrich,US,2018	1.03	0.91	1.16
	Ritz,Denmark,2018	0.97	0.93	1.01
T4_Meta ^d	Yousefian,Iran,2018	1.00	0.96	1.04
	Fixed	1.00	0.99	1.01
	Random	1.01	0.99	1.03
	Bayesian	1.01	0.98	1.04

^a T1-T3:trimesters and T4:whole pregnancy period.

^b Lower bound of 95% confidence interval.

^c Upper bound of 95% confidence interval.

^d Meta-analysis pooled estimates for prenatal period only: Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model.

Table C3
Association between ASD and NO₂ (per 10 unit).

Exposure Time ^a	Author-Country-Year	OR	OR.low ^b	OR.up ^c
T1	Becerra, US,2013	1.02	1.00	1.03
	Volk, US,2013	1.12	1.02	1.24
	Goodrich, US,2018	1.10	0.89	1.36
	Palagan, Canada,2019	1.05	1.00	1.11
	Ritz, Denmark,2018	1.06	1.04	1.08
	Becerra, US,2013	1.00	0.99	1.02
	Volk, US,2013	1.16	1.04	1.28
	Goodrich, US,2018	1.06	0.86	1.31
T2	Palagan, Canada,2019	1.04	0.98	1.09
	Ritz, Denmark,2018	1.06	1.03	1.08
	Becerra, US,2013	1.01	0.99	1.03
	Volk, US,2013	1.16	1.04	1.28
	Goodrich, US,2018	1.06	0.86	1.31
	Palagan, Canada,2019	1.04	0.98	1.09
	Ritz, Denmark,2018	1.06	1.03	1.08
	Becerra, US,2013	1.01	0.99	1.03
T3	Volk, US,2013	1.16	1.05	1.29
	Goodrich, US,2018	1.05	0.86	1.29
	Palagan, Canada,2019	1.05	0.99	1.10
	Ritz, Denmark,2018	1.06	1.04	1.08
	Becerra, US,2013	1.01	0.99	1.03
	Volk, US,2013	1.16	1.05	1.29
	Goodrich, US,2018	1.05	0.86	1.29
	Palagan, Canada,2019	1.05	0.99	1.10
T4 = T1-T3	Ritz, Denmark,2018	1.06	1.04	1.08
	Becerra, US,2013	1.02	0.99	1.04
	Volk, US,2013	1.20	1.07	1.35
	Guxen-EU,2016	0.89	0.72	1.11
	Goodrich, US,2018	1.13	0.91	1.39
	Raz, Israel,2018	1.06	1.01	1.11
	Palagan, Canada,2019	1.05	0.99	1.11
	Ritz, Denmark,2018	1.07	1.04	1.09
T4_Meta ^d	Fixed	1.02	1.01	1.03
	Random	1.02	1.01	1.04
	Bayesian	1.02	1.00	1.05

^a T1-T3:trimesters and T4:whole pregnancy period.

^b Lower bound of 95% confidence interval.

^c Upper bound of 95% confidence interval.

^d Meta-analysis pooled estimates for prenatal period only: Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model.

Table C4

Association between ASD and ozone (per 10 unit).

Exposure Time ^a	Author-Country-Year	OR	OR.low ^b	OR.up ^c
T1	Becerra, US,2013	1.00	0.99	1.01
	Volk, US,2013	1.02	0.96	1.08
	Goodrich, US,2018	1.02	0.86	1.21
	Kaufman, US,2019	0.96	0.87	1.06
T2	Becerra, US,2013	1.01	1.00	1.02
	Volk, US,2013	1.01	0.95	1.07
	Goodrich, US,2018	1.03	0.87	1.23
	Kaufman, US,2019	0.98	0.88	1.09
T3	Becerra, US,2013	1.01	1.00	1.02
	Volk, US,2013	1.00	0.99	1.01
	Goodrich, US,2018	1.00	0.99	1.02
	Kaufman, US,2019	1.05	0.95	1.17
T4 = T1-T3	Becerra, US,2013	1.00	1.00	1.00
	Volk, US,2013	1.01	0.95	1.06
	Goodrich, US,2018	1.04	0.88	1.24
	Kaufman, US,2019	1.00	0.99	1.01
T4_Meta ^d	Fixed	1.00	1.00	1.00
	Random	1.00	1.00	1.01
	Bayesian	1.00	0.98	1.04

^a T1-T3: trimesters and T4: whole pregnancy period.^b Lower bound of 95% confidence interval.^c Upper bound of 95% confidence interval.^d Meta-analysis pooled estimates for prenatal period only: Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model.**Table C5**

Association between ASD and air pollutant during Trimester 1 (per 10 unit).

Exposure	Number of studies	Method ^a	OR	OR.low	OR.up
PM _{2.5} _2013-19	8	Fixed	1.02	1.01	1.03
		Random	1.02	1.01	1.03
		Bayesian	1.02	1.00	1.06
PM ₁₀ _2013-18	6	Fixed	1.00	0.99	1.01
		Random	1.00	0.99	1.01
		Bayesian	1.00	0.98	1.03
NO ₂ _2013-19	5	Fixed	1.02	1.01	1.02
		Random	1.02	1.01	1.03
		Bayesian	1.02	1.00	1.06
ozone_2013-19	4	Fixed	1.00	1.00	1.00
		Random	1.00	1.00	1.00
		Bayesian	1.00	0.97	1.04

^a Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model. Bold indicates statistically significance.**Table C6**

Association between ASD and air pollutant during Trimester 2 (per 10 unit).

Exposure	Number of studies	Method ^a	OR	OR.low	OR.up
PM _{2.5} _2013-19	8	Fixed	1.04	1.03	1.04
		Random	1.04	1.01	1.07
		Bayesian	1.04	1.00	1.09
PM ₁₀ _2013-18	6	Fixed	1.00	0.99	1.01
		Random	1.01	0.98	1.04
		Bayesian	1.01	0.97	1.06
NO ₂ _2013-19	5	Fixed	1.01	1.01	1.02
		Random	1.02	1.00	1.04
		Bayesian	1.02	0.99	1.06
ozone_2013-19	4	Fixed	1.00	1.00	1.01
		Random	1.00	1.00	1.01
		Bayesian	1.00	0.97	1.04

^a Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model. Bold indicates statistically significance.**Table C7**

Association between ASD and air pollutant during Trimester 3 (per 10 unit).

Exposure	Number of studies	Method ^a	OR	OR.low	OR.up
PM _{2.5} _2013-19	8	Fixed	1.01	1.00	1.02
		Random	1.04	1.00	1.08
		Bayesian	1.04	0.99	1.10
PM ₁₀ _2013-18	6	Fixed	1.00	1.00	1.01
		Random	1.03	1.00	1.05
		Bayesian	1.02	0.99	1.07
NO ₂ _2013-19	5	Fixed	1.01	1.01	1.02
		Random	1.02	1.00	1.04
		Bayesian	1.02	0.99	1.06
ozone_2013-19	4	Fixed	1.01	1.00	1.01
		Random	1.01	1.00	1.01
		Bayesian	1.01	0.98	1.05

^a Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model. Bold indicates statistically significance.**Table C8**

Association between ASD and air pollutant for each trimester (per 10 unit).

Air pollutant & Trimester	Meta-Analysis ^a		
	Fixed	Random	Bayesian
PM _{2.5} -T1	1.02	1.02	1.02
PM _{2.5} -T2	1.04	1.04	1.04
PM _{2.5} -T3	1.01	1.04	1.04
PM ₁₀ -T1	1.00	1.00	1.00
PM ₁₀ -T2	1.00	1.01	1.01
PM ₁₀ -T3	1.00	1.03	1.02
NO ₂ -T1	1.02	1.02	1.02
NO ₂ -T2	1.01	1.02	1.02
NO ₂ -T3	1.01	1.02	1.02
ozone-T1	1.00	1.00	1.00
ozone-T2	1.00	1.00	1.00
ozone-T3	1.01	1.01	1.01

^a Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model. Bold indicates statistically significance.**Table C9**

Sensitivity Analysis with/without Guxens et al. (T4 only).

Exposure	Guxens et al.	Number of studies	Meta-analysis Method ^a	OR	OR.low	OR.up
PM _{2.5} 2013-19	No Guxens et al.	8	Fixed	1.09	1.07	1.10
			Random	1.07	1.01	1.12
			Bayesian	1.07	1.00	1.15
Guxens-EU ^b	Guxens-EU ^b	9	Fixed	1.08	1.07	1.09
			Random	1.06	1.01	1.11
			Bayesian	1.06	1.00	1.13
Guxens-4 countries	Guxens-4 countries	12	Fixed	1.08	1.07	1.10
			Random	1.05	1.00	1.10
			Bayesian	1.05	0.97	1.11
PM ₁₀ 2013-18	No Guxens et al.	8	Fixed	1.00	0.99	1.01
			Random	1.01	0.99	1.04
			Bayesian	1.01	0.98	1.05
Guxens-EU ^b	Guxens-EU ^b	9	Fixed	1.00	0.99	1.01
			Random	1.01	0.99	1.03
			Bayesian	1.01	0.98	1.04
Guxens-4 countries	Guxens-4 countries	12	Fixed	1.00	0.99	1.01
			Random	1.01	0.99	1.03
			Bayesian	1.01	0.98	1.04
NO ₂ 2013-19	No Guxens et al.	6	Fixed	1.02	1.01	1.03
			Random	1.02	1.01	1.04

(continued on next page)

Table C9 (continued)

Exposure	Guxens et al.	Number of studies	Meta-analysis Method ^a	OR	OR.low	OR.up
			Bayesian	1.03	1.00	1.06
Guxens-EU ^b	7	Fixed	1.02	1.01	1.03	
		Random	1.02	1.01	1.04	
		Bayesian	1.02	1.00	1.05	
Guxens-4 countries	10	Fixed	1.02	1.01	1.03	
		Random	1.02	1.01	1.04	
		Bayesian	1.02	0.99	1.04	

^a Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model. Bold indicates statistically significance.

^b Used for the main meta-analysis (Table 2).

Appendix D. Comparisons of meta-estimates of OR by fixed and random effects models

Table C10

Sensitivity Analysis with pre-conception or post-natal periods (Guxens-4 counties^a).

Exposure	Exposure time	Number of studies	Meta-analysis Method ^b	OR	OR.low	OR.up
PM _{2.5} 2013–19	T4, pre-conception, or both combined	14	Fixed	1.09	1.07	1.10
			Random	1.06	1.01	1.11
			Bayesian	1.06	1.00	1.11
	T4, post-natal, or both combined	23	Fixed	1.08	1.07	1.09
			Random	1.08	1.04	1.13
			Bayesian	1.08	1.04	1.14
	T4, pre- or post-natal, or all combined	25	Fixed	1.08	1.07	1.09
			Random	1.09	1.05	1.13
			Bayesian	1.09	1.04	1.13
PM ₁₀ 2013–18	T4, pre-conception, or both combined	13	Fixed	1.00	0.99	1.01
			Random	1.01	0.99	1.02
			Bayesian	1.01	0.98	1.03
	T4, post-natal, or both combined	22	Fixed	1.01	1.00	1.02
			Random	1.02	1.00	1.04
			Bayesian	1.02	1.00	1.05
	T4, pre- or post-natal, or all combined	23	Fixed	1.01	1.00	1.01
			Random	1.02	1.00	1.04
			Bayesian	1.02	1.00	1.04
NO ₂ 2013–19	T4, pre-conception, or both combined	11	Fixed	1.02	1.01	1.03
			Random	1.02	1.01	1.03
			Bayesian	1.02	1.00	1.04
	T4, post-natal, or both combined	15	Fixed	1.03	1.02	1.03
			Random	1.05	1.01	1.09
			Bayesian	1.05	1.00	1.10
	T4, pre- or post-natal, or all combined	16	Fixed	1.03	1.02	1.03
			Random	1.05	1.01	1.09
			Bayesian	1.05	1.00	1.09
ozone 2013–19	T4, pre- or post-natal, or all combined	9	Fixed	1.00	1.00	1.00
			Random	1.03	1.00	1.05
			Bayesian	1.03	1.00	1.06

Bold indicates statistically significance, comparable to Table C9.

^a Four individual countries, not EU, reported by Guxens et al. (2016) were used.

^b Fixed: Frequentist fixed effect model; Random: Frequentist random effects model; and Bayesian: Bayesian random effects model.

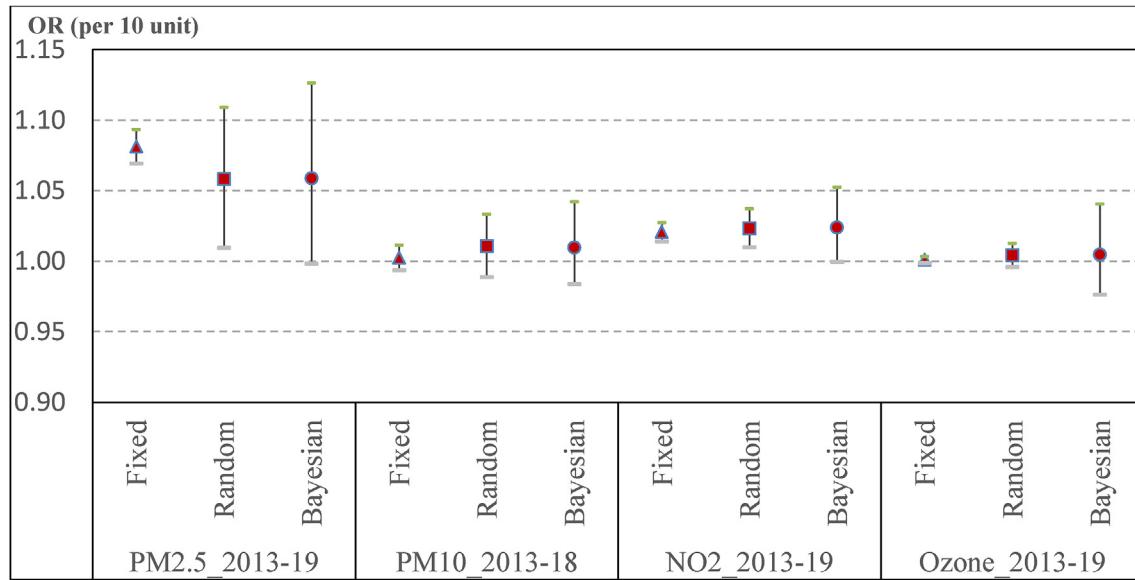


Fig. D1. a. Prenatal pregnancy (T4): comparisons of pooled OR per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

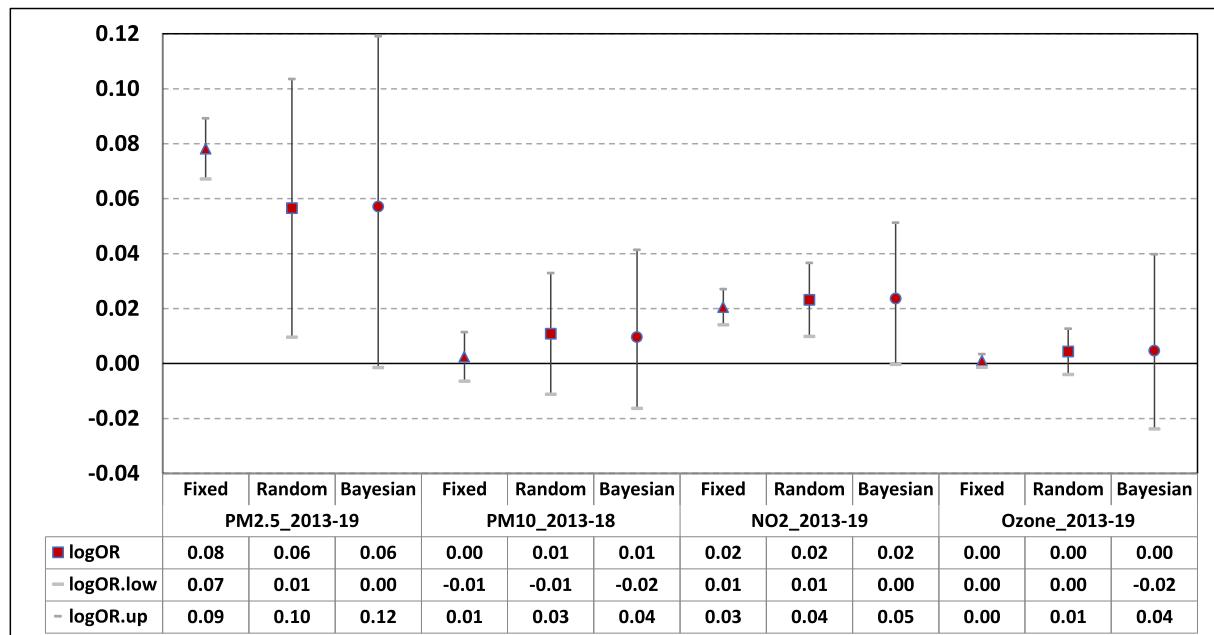


Fig. D1. b. Prenatal pregnancy (T4) in log scale: comparisons of pooled log(OR) per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

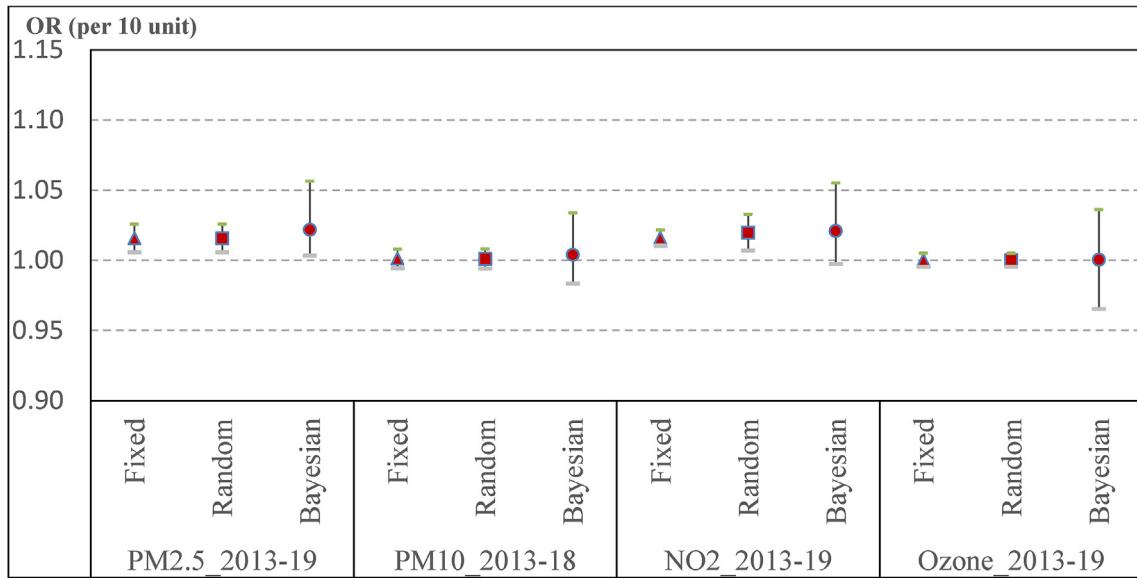


Fig. D2. a. Trimester 1 (T1): comparisons of pooled OR per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

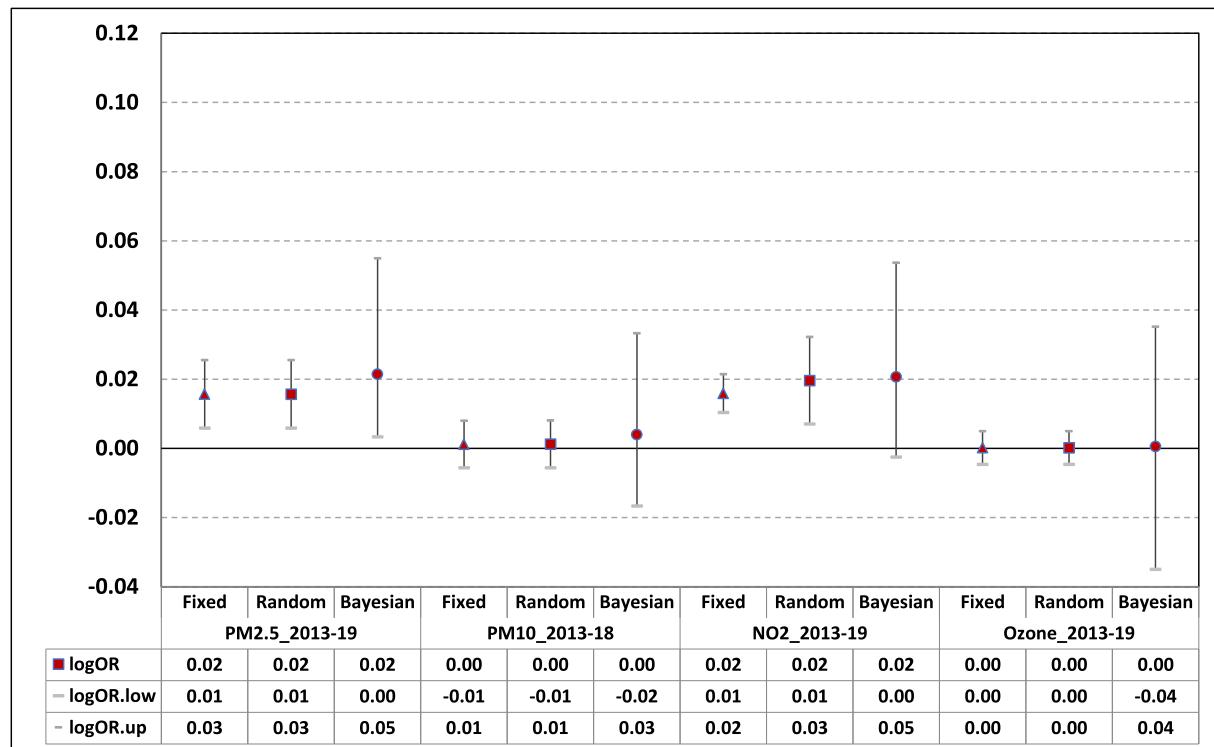


Fig. D2. b. Trimester 1 (T1) in log scale: comparisons of pooled log(OR) per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

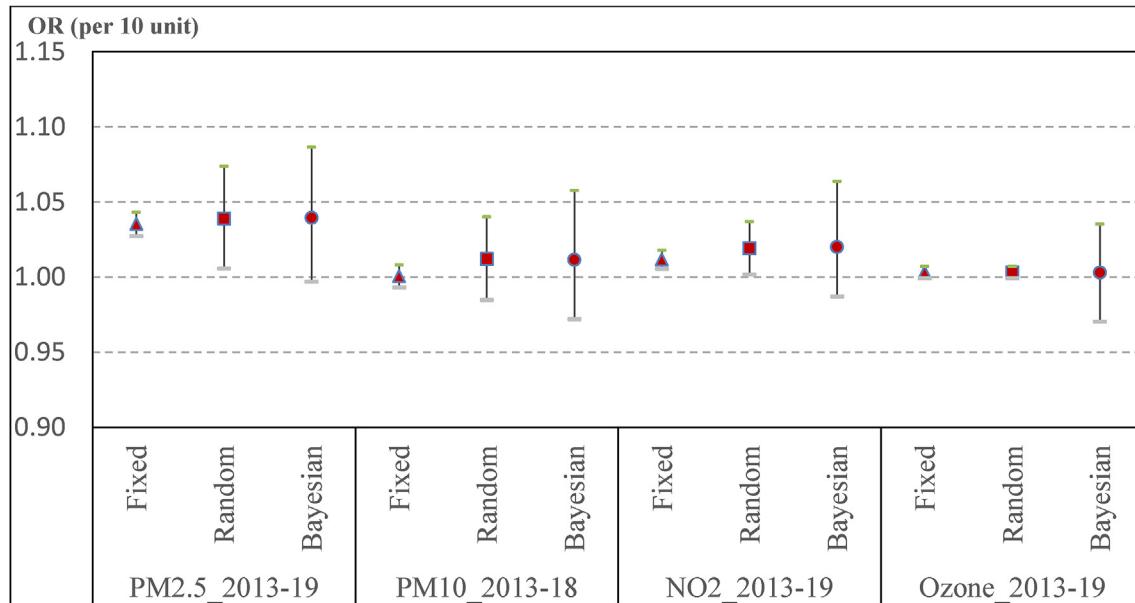


Fig. D3. a. Trimester 2 (T2): comparisons of pooled OR per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

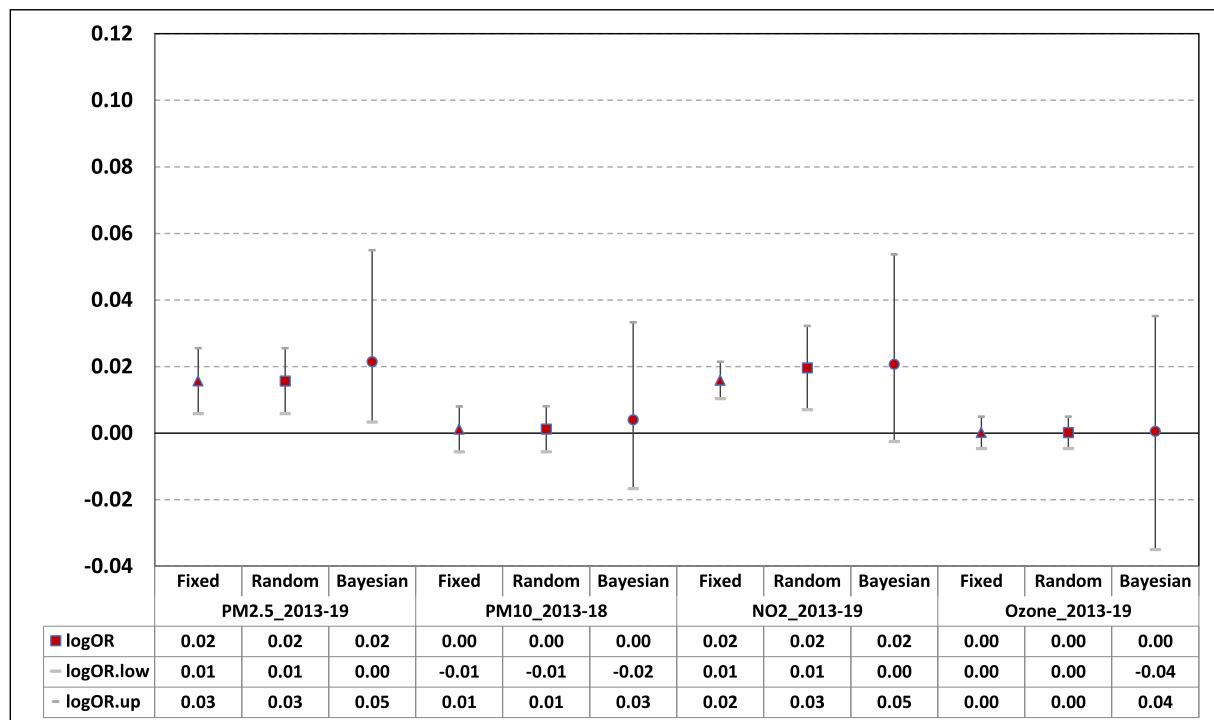


Fig. D3. b. Trimester 2 (T2) in log scale: comparisons of pooled log(OR) per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

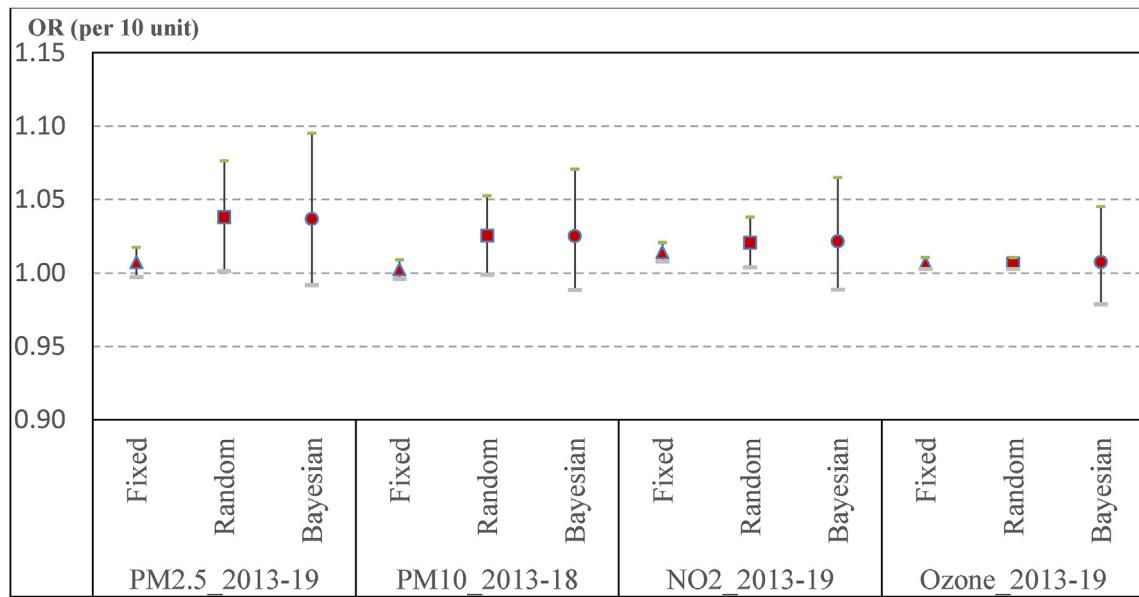


Fig. D4. a. Trimester 3 (T3): comparisons of pooled OR per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.

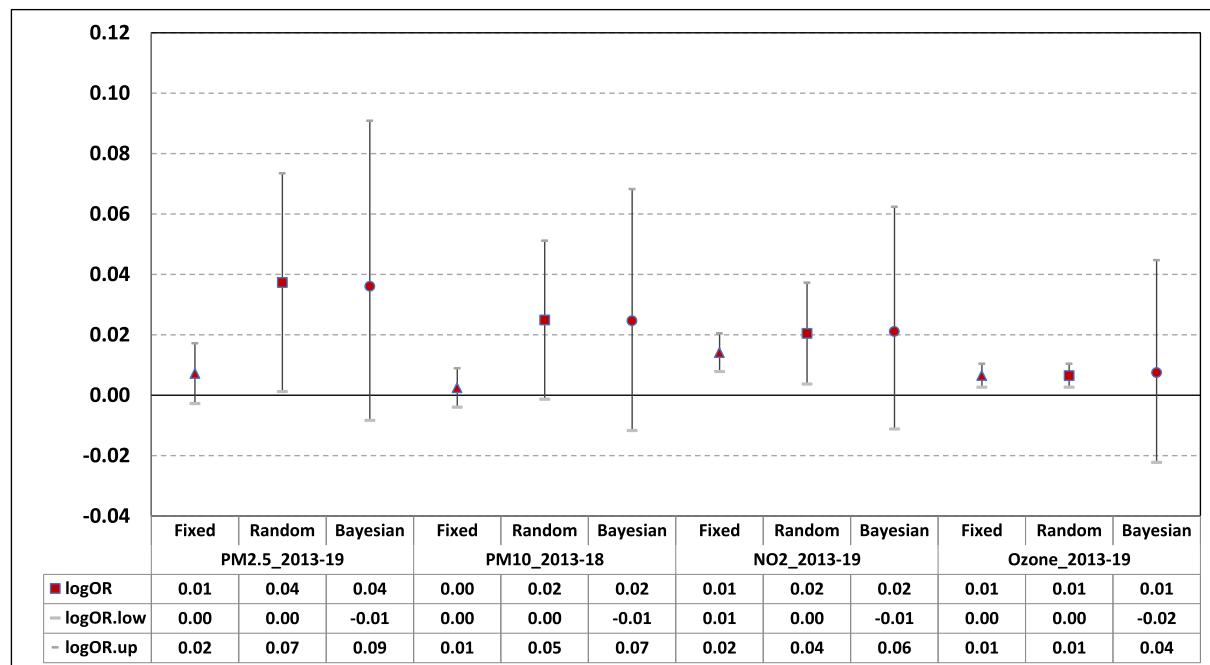


Fig. D4. b. Trimester 3 (T3) in log scale: comparisons of pooled log(OR) per 10 units by 3 meta-analysis methods, frequentist fixed and random effects models and Bayesian random model.9

Appendix E. Funnel plots and study contribution

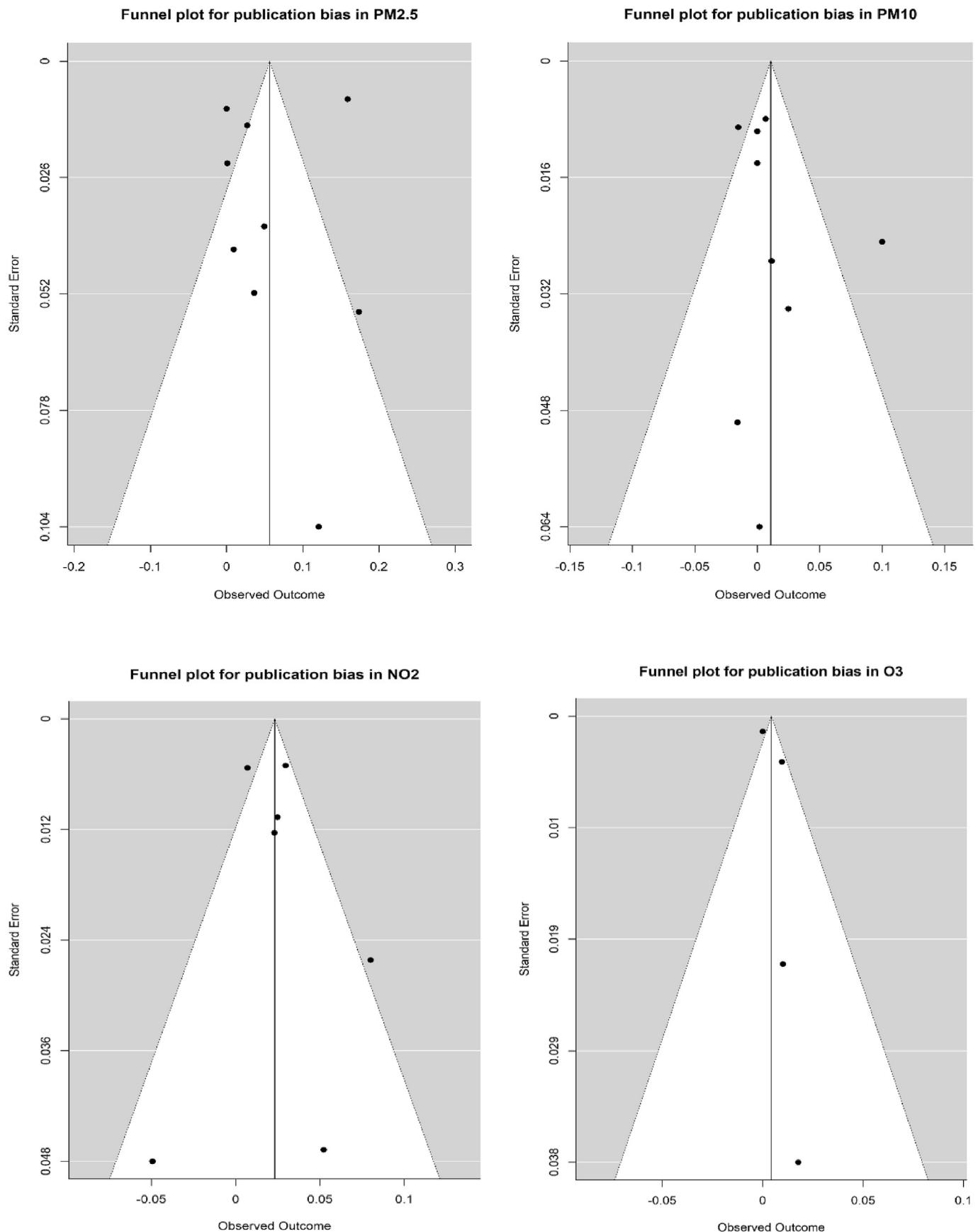


Fig. E1. Funnel Plots (top left) PM_{2.5}; (top right) PM₁₀; (bottom left) NO₂; and (bottom right) Ozone.

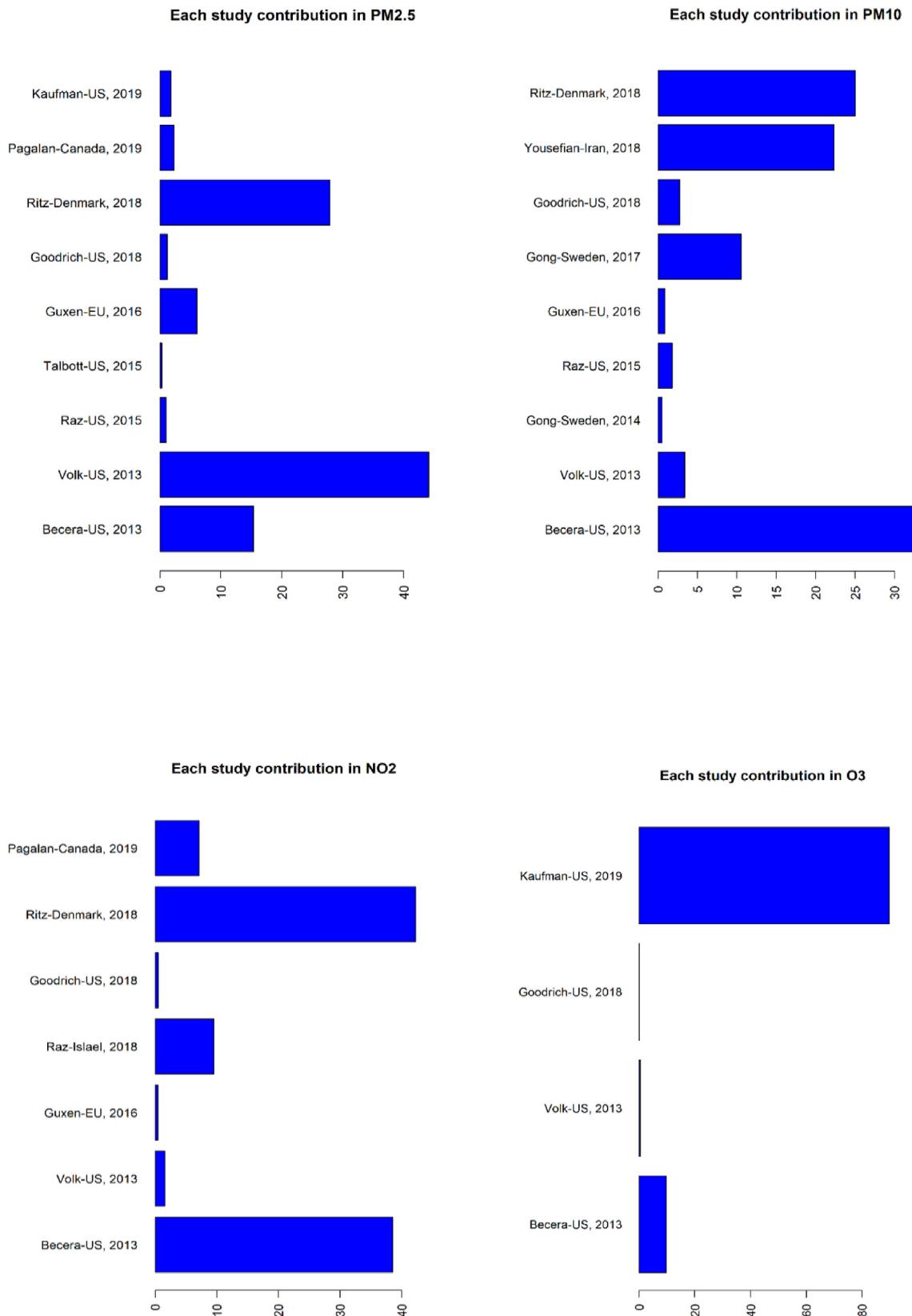


Fig. E2. Each study's contribution to meta-estimates for four air pollutants: (top left) PM_{2.5}; (top right) PM₁₀; (bottom left) NO₂; and (bottom right) Ozone.

Appendix F. Odd Ratios in log scale

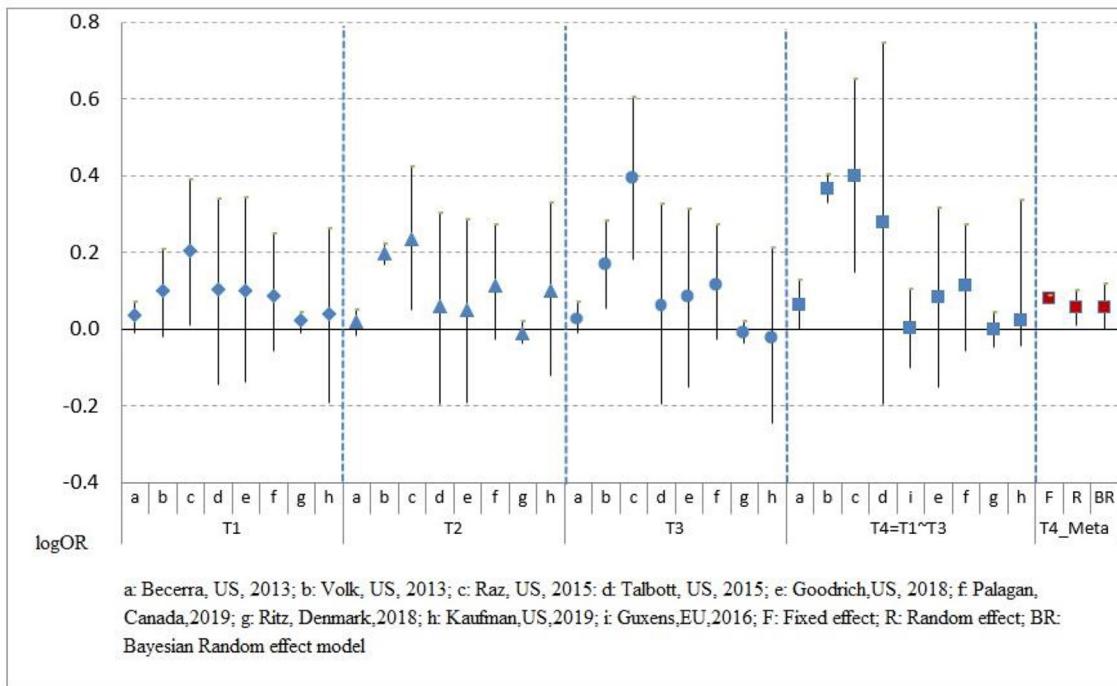


Fig. F1. (corresponding to Fig. 2). Comparisons of odds ratios on PM2.5-ASD over exposure time by trimester in log scale. T1: trimester 1 (in diamond); T2: trimester 2 (in triangle); T3: trimester 3 (in circle); T4: whole pregnancy period combining three trimesters (in square); and T4_Meta: meta-analysis pooled estimates for prenatal period (T4) only (in red square).

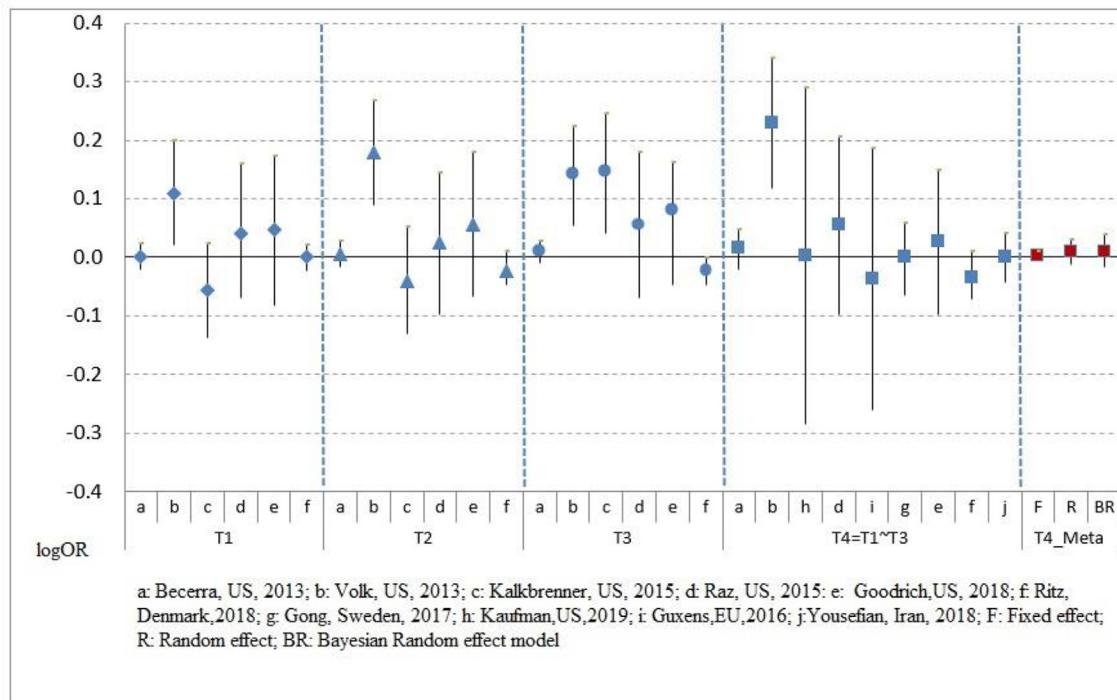
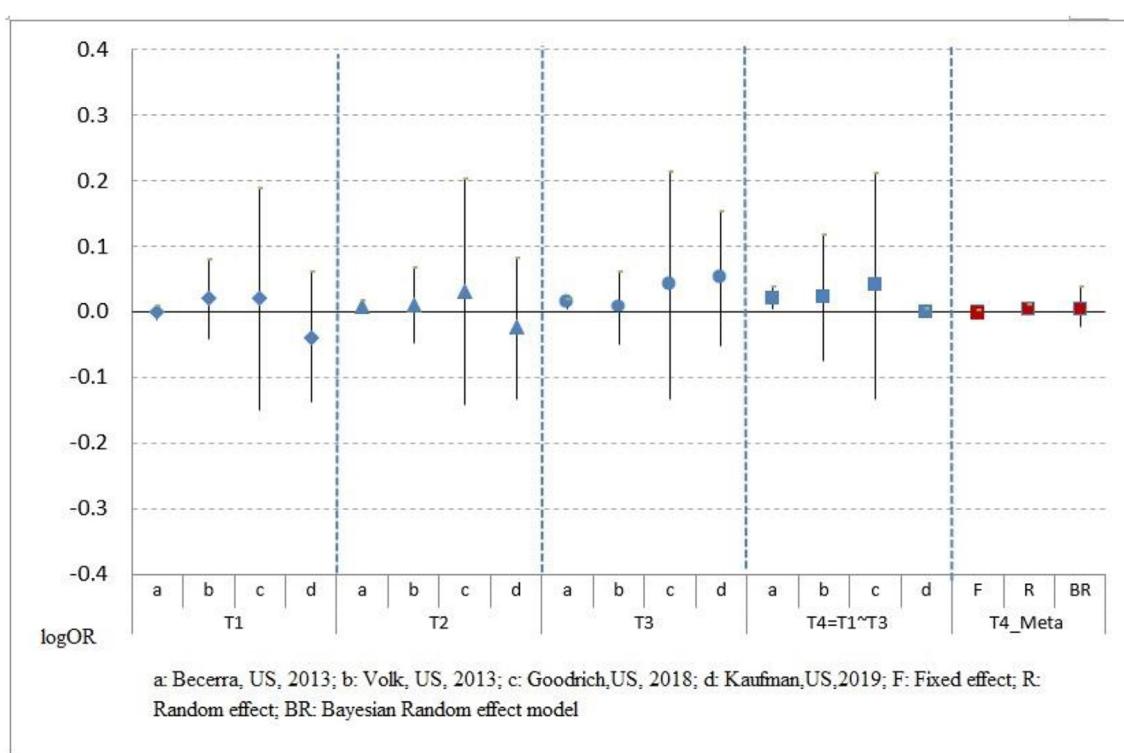
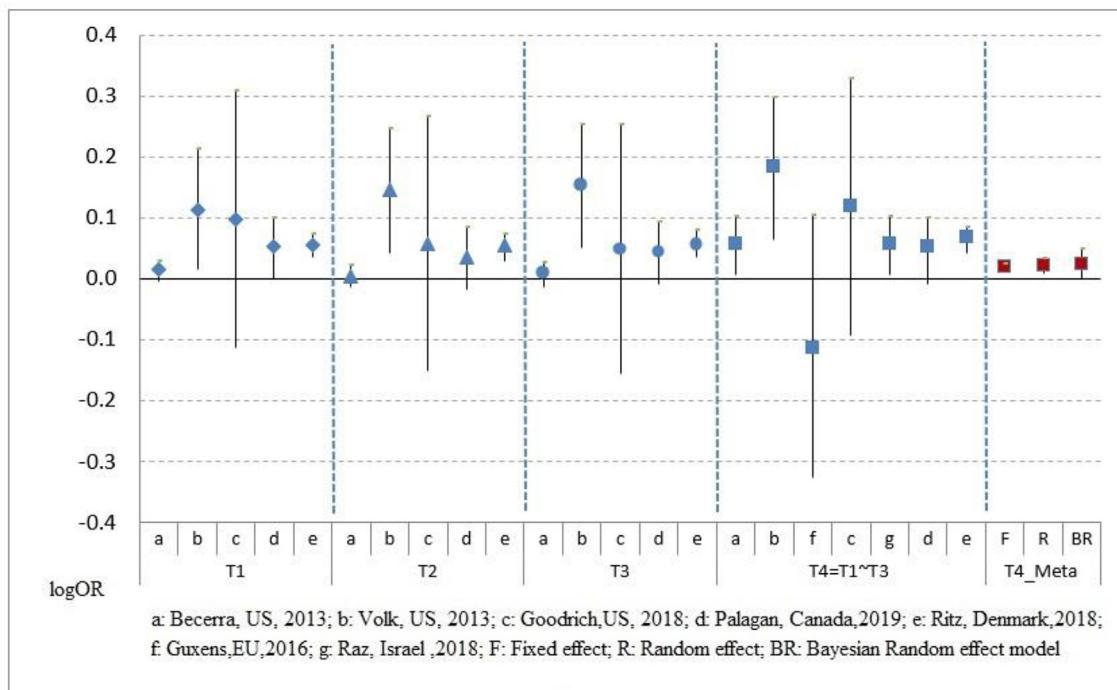


Fig. F2. (corresponding to Fig. 3). Comparisons of odds ratios on PM10-ASD over exposure time by trimester in log scale. T1: trimester 1 (in diamond); T2: trimester 2 (in triangle); T3: trimester 3 (in circle); T4: whole pregnancy period combining three trimesters (in square); and T4_Meta: meta-analysis pooled estimates for prenatal period (T4) only (in red square).



Appendix G. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2019.113307>.

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