



Autism spectrum disorder and air pollution: A systematic review and meta-analysis

Frédéric Dutheil, Aurélie Comptour, Roxane Morlon, Martial Mermillod, Bruno Pereira, Julien S. Baker, Morteza Charkhabi, Maëlys Clinchamps, Nicolas Bourdel

► To cite this version:

Frédéric Dutheil, Aurélie Comptour, Roxane Morlon, Martial Mermillod, Bruno Pereira, et al.. Autism spectrum disorder and air pollution: A systematic review and meta-analysis. *Environmental Pollution*, 2021, 278, pp.116856. <10.1016/j.envpol.2021.116856>. <hal-03403803>

HAL Id: hal-03403803

<https://hal.science/hal-03403803v1>

Submitted on 15 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

Autism spectrum disorder and air pollution: a systematic review and meta-analysis

Frédéric Dutheil^{1*†}, Aurélie Comptour^{2†}, Roxane Morlon³, Martial Mermillod⁴, Bruno Pereira⁵, Julien S Baker⁶, Morteza Charkhabi⁷, Maëlys Clinchamps⁸, Nicolas Bourdel⁹

¹ Université Clermont Auvergne, CNRS, LaPSCo, Physiological and Psychosocial Stress, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Occupational and Environmental Medicine, WittyFit, Clermont-Ferrand, France

² INSERM, CIC 1405 CRECHE Unit, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Gynecological Surgery, Clermont-Ferrand, France

³ Université Clermont Auvergne, Faculty of Medicine, Occupational and Environmental Medicine, Clermont-Ferrand, France

⁴ Univ. Grenoble Alpes, LPNC, Grenoble, France & CNRS, LPNC, Grenoble, France

⁵ University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Biostatistics, Clermont-Ferrand, France

⁶ Hong Kong Baptist University, Physical Education and Health, Centre for Health and Exercise Science Research, Kowloon Tong, Hong Kong

⁷ National Research University Higher School of Economics, Moscow, Russia.

⁸ Université Clermont Auvergne, CNRS, LaPSCo, Physiological and Psychosocial Stress, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Occupational and Environmental Medicine, Clermont-Ferrand, France

⁹ Université Clermont Auvergne, UMR 6602, Pascal Institute, Endoscopy and Computer Vision Group, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Gynecological Surgery, Clermont-Ferrand, France

[†] Contributed equally to this work

***Corresponding author:** Frédéric Dutheil, Occupational and Environmental Medicine, CHU Clermont-Ferrand, France. 58, Rue Montalembert, 63003 Clermont Ferrand, Tel: +33 6 88 22 48 48, Fax: +33 4 73 27 46 49, fdutheil@chu-clermontferrand.fr

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Despite the widely-known effects of air pollution, pollutants exposure surrounding pregnancy and the risk for autism spectrum disorder (ASD) in newborns remains controversial. The purpose of our study was to carry out a systematic review and meta-analyses of the risk of ASD in newborns following air pollution exposure during the perinatal period (preconception to second year of life). The PubMed, Cochrane Library, Embase and ScienceDirect databases were searched for articles, published up to July 2020, with the keywords “air pollution” and “autism”. Three models were used for each meta-analysis: a global model based on all risks listed in included articles, a pessimistic model based on less favorable data only, and an optimistic model based on the most favorable data only. 28 studies corresponding to a total of 758 997 newborns were included (47190 ASD and 703980 controls). Maternal exposure to all pollutants was associated with an increased risk of ASD in newborns by 3.9 % using the global model and by 12.3% using the optimistic model, while the pessimistic model found no change. Each increase of $5\mu\text{g}/\text{m}^3$ in particulate matter $<2.5\mu\text{m}$ (PM_{2.5}) was associated with an increased risk of ASD in newborns, regardless of the model used (global +7%, pessimistic +5%, optimistic +15%). This risk increased during preconception (global +17%), during pregnancy (global +5%, and optimistic +16%), and during the postnatal period (global +11% and optimistic +16%). Evidence levels were poor for other pollutants (PM₁₀, NO_x, O₃, metals, solvents, styrene, PAHs, pesticides). PM_{2.5} was associated with a greater risk than PM₁₀ (coefficient 0.20, 95CI -0.02 to 0.42), NO_x (0.29, 0.08 to 0.50) or solvents (0.24, 0.04 to 0.44). All models revealed that exposure to pollutants, notably PM_{2.5} during pregnancy, was associated with an increased risk of ASD in newborns. Pregnancy and postnatal periods seem to be the most at-risk periods.

Keywords: Air pollution - Autism Spectrum Disorder – pregnancy

Capsule: air pollution surrounding pregnancy increases the risk of ASD in newborns.

Introduction

Air pollution is a major public health ¹ and economic ² issue. associated with increased risk of mortality ² and morbidity in multiple diseases, such as cancer ³, inflammatory ⁴, neurological ⁵ and respiratory and cardiometabolic diseases ⁶⁻⁸. Despite the considerable number of studies demonstrating the adverse health effects of air pollution, exposure to ambient air pollution surrounding pregnancy and the risk for Autism Spectrum disorder (ASD) in newborns remains controversial ⁹⁻¹². Genetic and environmental factors specifically during perinatal periods (preconception, pregnancy (first, second, third trimester), postnatal until 2nd year of life) have been found to increase risk of pathology and malformation in children ¹³⁻¹⁵. Air pollution is composed of a wide range of pollutants such as particulate matter (PM), nitrogen oxide (NOx), volatile organic compounds, pesticides, ozone (O₃) and metals ^{16,17}. Though few studies have focused on pregnancy and risk of ASD, air pollutants such as PM (PM₁₀, with an aerodynamic diameter $\leq 10 \mu\text{m}$), appear to have the highest levels of toxicity ^{18,19}. Among PM₁₀ ²⁰, PM_{2.5} which have an even smaller aerodynamic diameter $\leq 2.5 \mu\text{m}$ are particularly harmful, penetrating more rapidly, easily and deeply into the organism ^{18,19}. Despite a recent article ²¹, no meta-analysis to date has provided an overview or comparison of the effects of classes of air pollutants ²², or the effects of sociodemographic risk factors such as parental ages, gender of newborns, or smoking ²³⁻²⁵. In addition, there are no published guidelines as yet on how to manage different data relating to a same risk within an included article (e.g. crude odds ratio, or adjusted on different covariables) ²² and no meta-analysis presented both risks quantified either as continuous (per increment of air pollutants) or as categorical variables (high versus low exposure).

We hypothesized that there was an increased risk of developing ASD associated with air pollution during pregnancy. This meta-analysis focused on the association between children with ASD and exposure to air pollutants during the perinatal period (from preconception to the second year of life) and involved three models for each meta-analysis by air pollutant; a global model using all risks listed in included articles, a pessimistic model using less favorable data only, and an optimistic model using the most favorable data only. We also investigated related sociodemographic influences.

Methods

Literature search

We reviewed all studies reporting an association between air pollutants and ASD. The PubMed, Cochrane Library, ScienceDirect and Embase databases were searched for all original articles published up to July 2020, using the keywords “air pollution” and “autism” or synonyms (see Appendix 1 for detailed search strategy). Inclusion criteria included articles written in English or French, and that described our primary outcome variable i.e. the association between perinatal exposure to ambient air pollution and risk of ASD. The perinatal period included the preconception period to the second year of life. Studies were required to report risk estimates in the form of odds ratios (OR) with 95% confidence interval (95CI) or to provide data that allowed OR calculation. In order to identify studies not found through our database search strategy, a manually search of new articles was carried out using reference lists from all publications meeting inclusion criteria and systematic reviews. Our search strategy is presented in [Figure 1](#) and [Appendix 1](#). Two authors (AC and FD) separately conducted all literature searches, collated and, reviewed the abstracts based on selection criteria and decided on the suitability of articles for inclusion. When questions arose over

article suitability, a third author (NB) reviewed the articles. Having reached a consensus, all included articles were reviewed by the three authors.

Quality of assessment

The methodological quality of the studies was further evaluated using the Scottish Intercollegiate Guidelines Network (SIGN) model for case control and cohort studies ²⁶. The following 15 items were assessed: appropriate and clearly focused question, selection bias (2 items), performance bias (1 item), attrition bias (2 items), detection bias (6 items), confusion bias (1 item), presence of confidence intervals, and general level of evidence (Figure 2). Similar items were used to evaluate case control studies (Figure 2). We also used the Newcastle-Ottawa Quality Assessment Scale (NOS) model ²⁷ with the following 9 items: selection bias (4 items), comparability bias (2 items) and outcome bias (3 items) (Supplementary Figure 1). Each item was assigned a judgment of “Yes” (+), “No” (-), “Can’t say” (?), or “Not applicable” (NA), with the exception of item 2.1 (to minimize risk of bias or confounding) and the final item concerning evidence level of the SIGN checklist, which was assigned “0”, “+”, or “++”. Any disagreements over suitability were discussed with a third author (BP) and a consensus reached. Assessment of article quality was carried out for the two checklists by two authors (AC and FD).

Data analysis

The following data from articles were recorded: title, name of first author, journal and year of publication, main objective, time of exposure to air pollution (perinatal period, full pregnancy or during, first, second and/or third trimester of pregnancy and postnatal period), type and concentration of pollutants, crude and/or adjusted OR and lower and upper limits, and

population characteristics (number of participants per study, parental mean age at birth, gender of newborns, level of parental education, smoking).

Statistical considerations

Statistical analysis was conducted using Stata software (version 15, StataCorp, College Station, US)^{28–33}. Characteristics of pollutant exposure, of individuals or other variables were reported for each study as mean \pm standard-deviation (SD) and number (%) for continuous and categorical variables respectively (Table 1). When data could be pooled, we conducted random effects meta-analyses (DerSimonian and Laird approach)³⁴ on the risk (OR) of ASD in newborns following air pollutants exposure, centered at one. Particular attention was paid to the type of statistics retrieved from the included articles (OR or other risk measurements). Air pollutants exposure were quantified either as a continuous (per increment of air pollutants) or as categorical variables (high versus low exposure). For the highest level of proof, we first normalised all OR for a standardized increment in pollutant concentration (for example per 5 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}). We took into account the original increment of the pollutant and we assumed a linear exposure outcome relationship³⁵ using the following equation: $\text{OR}_{\text{standardized}} = e^{[\text{Ln}(\text{OR}_{\text{original}}) * 10 / (\text{Increment}_{\text{original}})]}$ ³⁶. When air pollutant levels were expressed in parts per billion (ppb), we transformed those levels in $\mu\text{g}/\text{m}^3$ (for example NO₂: 1 ppb = 1.88 $\mu\text{g}/\text{m}^3$; O₃: 1 ppb = 2 $\mu\text{g}/\text{m}^3$)³⁷. The effects expressed as interquartile (or quintile, or percentile differences) were converted into effects per concentration unit increase with the previous equation³⁶. Meta-analyses were computed by type of air pollutants (PM_{2.5}, PM₁₀, NO_x, O₃, metals, solvents, styrene, polycyclic aromatic hydrocarbons (PAHs), pesticides), periconceptional periods, and pregnancy trimester where sufficient data were available. For each meta-analysis, three models were used (a global model of all risks listed in the included articles, a pessimistic model using less favorable data

only, and an optimistic model using the most favorable data only). Finally, we computed the aforementioned meta-analyses categorical using OR based on categorical exposure (high versus low exposure). For air pollutants that were the most reported, we also computed sensitivity analyses depending on the methods to measure air pollutants. Heterogeneity between studies was evaluated through forest plots, and their confidence intervals (CI), and I-squared (I^2) – varying from 0 to 100%. Heterogeneity is considered low for $I^2 < 25\%$, modest for $25 < I^2 < 50\%$, and high for $I^2 > 50\%$. For example, a significant heterogeneity may be due to the variability between the characteristics of the studies, such as the exposure to air pollutants (type of air pollutants), periconceptional periods (preconception, pregnancy, postnatal), pregnancy trimester (first, second, third), characteristics of individuals (age of mothers and fathers, smoking, gender of newborns, etc). To ensure the robustness of our results, we conducted sensitivity analysis by searching for potential publication bias through funnel plots (metafunnels) of aforementioned meta-analyses. Then, we reperformed meta-analyses without the studies that were not evenly distributed around the funnel base ³⁸. When sample size allowed, meta-regressions were performed to investigate the relationship between risk of ASD in newborns following air pollutant exposure and putative variables such as type of air pollutant, periconceptional period, pregnancy trimester and population characteristics. Results were expressed as regression coefficients and 95% CI.

Results

An initial search identified 913 possible articles for inclusion (Figure 1). Following application of selection criteria and removal of duplicates 28 articles were selected ^{9–12,17,39–61} (Table 1), all of which were written in English.

Quality of articles

Use of the SIGN model, notably revealed selection and attrition bias in included studies. Most studies had a high level of evidence. Detailed characteristics of methodological quality assessment for each included study are provided in [Figure 2](#). Overall, for the SIGN model, most studies were shown to have a high level of evidence but performed, with lowest performance found response rate. The NOS model was also used to analyse the quality of included articles ([Supplementary Figure 1](#)).

Aims of included studies, study designs, and settings

All studies shared a similar *objective* i.e. the association of exposure to air pollution (PMs, NOx, O3, metals, PAHs, solvents, pesticides) during the perinatal period and the development of ASD. Six studies described a cohort *study design*^{11,12,40,41,56,58} using a historical birth/child cohort. The 22 remaining studies^{9,10,17,39,42–54,57,59–61} described case control studies. Most studies assessed exposure over several consecutive years with the exception of four studies which analyzed data from one year^{10,40,42,50,60}. *Countries of exposure* included North America for 20 studies (U.S.^{17,39–44,46,48–53,56,57,59–61}, Canada¹²), Europe for 5 studies (Denmark⁴⁷, Sweden^{9,10,58} and other European countries¹¹), and Asia for 3 studies (Iran⁵⁵, Israel⁴⁵, China⁵⁴).

Population

Sample size for children with ASD ranged from 124⁵⁴ to 15 387⁴⁵. Population size for controls (children without ASD) ranged from 156⁵² to 130 949¹². In total 751 170 individuals (47190 ASD and 703980 controls) were included in this meta-analysis.

Age of mothers at birth was expressed as a mean value in 11 articles^{9–12,45–50,56}, ranging from 29.5 ± 5.0⁴⁷ to 34.0 ± 4.0 years old⁴⁶ for mothers of ASD (mean age 31.6, 95CI 28.3 to 34.9), and 28.5 ± 6.0⁵⁰ to 33.7 ± 3.7⁴⁶ years for mothers of controls (mean age 31.7, 95CI

28.6 to 34.7). Twelve articles reported different classes of age^{17,39,42–44,51,54,55,57–60}, precluding further analyses. Five articles did not mention age of mothers (37,48,49,57,60).

Age of fathers at birth was not reported in most (19/28) articles^{9,11,12,17,40–44,48,51–54,56–59,61}.

Three articles expressed age of fathers at birth as classes^{39,55,60}, and six as mean values^{10,45–47,49,50}, ranging from 32.2 ± 6.1 ⁴⁷ to 36.8 ± 5.3 years⁴⁶ for fathers of ASD (mean age 33.9, 95CI 28.6 to 39.4), and 31.4 ± 6.6 ⁵⁰ to 33.7 ± 5.6 ⁴⁹ years for fathers of controls (mean age 33.9, 95CI 29.3 to 38.7).

Gender: All articles except two^{53,61} reported child with ASD gender, ranging from 29%⁵¹ to 87%⁵². Seven articles did not report child without ASD gender^{17,40–42,52,53,61}. 77% (95CI 73 to 81%) of children with ASD and 60% (95CI 55 to 65%) of children without ASD were boys.

Characteristics of air pollutant exposure

Types of pollutants analyzed in these articles included PM_{2.5} in 13 studies^{11,12,39,44,46,47,49,52,54,56,57,59,61}, PM₁₀ in 12 studies^{9–11,39,43,47,52,54–56,59,61}, NO_x in 12 studies^{9–12,39,45,47,52,56,58,59,61}, O₃ in 7 studies^{39,44,52,56,57,59,61}, metals in 7 studies^{17,40–42,48,50,60}, solvents in 5 studies^{17,42,50,55,60}, styrene in 3 studies^{17,42,50}, PAHs in 3 studies^{17,42,50}, and pesticides in 3 studies^{17,42,50}.

Type of exposure included a general outdoor exposure in 19 studies^{11,12,17,40–43,45–48,52,53,56,57,59,61}, in cities or regions of high human density in ten studies^{9,10,39,44,49,50,54,55,58,60}, with one study focusing on distance from homes to freeway and major roads⁵¹.

Perinatal periods of exposure: 6 studies analyzed exposure to air pollutants during preconception^{41–43,46,49,57}, 25 during pregnancy^{9–12,17,39–41,43–47,49–53,55–61}, 9 during the postnatal period^{9,10,43,46,48,49,54,56,57} and 5 during the two first years of life^{44,45,47,52,61}.

Quantification of exposure: Most studies^{9,11,12,17,39,40,43,45,47,48,50,54,55,57–59} assessed exposure to pollutants first by geocoding birth certificate residential addresses, followed by use of

different models (NATA for National-scale air toxics assessment^{17,40,48,50}; LUR model for Land Use Regression^{12,39,55}; CALINE4 line source air quality dispersion model^{53,61}) to estimate average pollutant concentration at participants' home address at time of birth..

Meta-analysis by air pollutants

PM 2.5: Each increase of $5\mu\text{g}/\text{m}^3$ in PM2.5 was associated with an increased risk of ASD in newborns, regardless of the model used (global +7%, pessimistic +5%, optimistic +15%). This risk increased during preconception (global +17%), during pregnancy (global +5%, and optimistic +16%), and during the postnatal period (global +11% and optimistic +16%) ([Figure 3](#)). The risk was increased during the first and third trimesters regardless of the model used (global +7% and +6%, pessimistic +7% and +7%, optimistic +7% and +7%, respectively) ([Figure 4](#)). Results by periconceptional periods (preconception, pregnancy, postnatal) ([Supplementary Figure 2](#)), and by pregnancy trimester (first, second, third) were similar using categorical data (high exposure versus low exposure): the risk of ASD in newborns increased regardless of the model used (global +11%, pessimistic +6%, optimistic +16%). Results were also similar ([Supplementary Figure 3](#)).

PM 10: Each increase of $5\mu\text{g}/\text{m}^3$ in PM10 was not associated with risk of ASD using the global model (-1%, non-significant), and was associated with a decreased risk of ASD using the pessimistic model (-3%), and with an increased risk using the optimistic model (+1%). Meta-analysis by periconception periods was associated with a decreased risk using the pessimistic model for the pregnancy period only (-4%) and with an increased risk using the optimistic model for the postnatal period only (+2%) ([Figure 3](#)). There was not enough data to perform meta-analysis by trimester using incremental risk (continuous data). Results were also similar by periconceptional periods (preconception, pregnancy, postnatal)

([Supplementary Figure 2](#)) using categorical data. Meta-analysis by trimester did not reveal any significant increase in risk, regardless of the model used ([Supplementary Figure 3](#)).

NO_x: Each increase of 10µg/m³ in NO_x was associated with an overall increased risk of ASD using the global (+2%) and optimistic models (+5%), as well as during pregnancy period. No significant results were found using the pessimistic model in all periods ([Figure 3](#)). Meta-analysis using categorical risks showed similar results ([Supplementary Figure 2](#)).

O₃: Using categorical risks, overall risk of ASD following O₃ exposure increased using the global (+3%) and optimistic models (+11%). Similarly, exposure during pregnancy led to an increase in risk, using the global (+3%) and optimistic (+10%) models only ([Supplementary Figure 2](#)).

Metals: Using categorical risks, exposure to metals did not lead to an increase in risk of ASD using the global model but decreased using the pessimistic model, and increased using the optimistic model ([Supplementary Figure 2](#)).

The meta-analysis on **solvent**, **styrene**, **PAH**, and **pesticide** exposure was based on a maximum of five studies. Solvent and styrene exposure was found to increase the risk of ASD using both the global and optimistic models, whereas the pessimistic model showed a decreased risk following solvent exposure. Pesticide exposure was associated with a decreased risk using the global and pessimistic model. PAH exposure did not modify the risk of ASD ([Supplementary Figure 2](#)).

All individual meta-analysis are compiled in [Supplementary Figure 4](#) for normalized OR (continuous data) and in [Supplementary Figure 5](#) for categorical data (high versus low exposure).

Overall meta-analysis

Taking into account all air pollutants levels as categorical levels (high versus low exposure), maternal exposure to air pollution was associated with an increased risk of ASD in newborns by 3.9 % using the global model (OR = 1.039, 95% CI 1.031 to 1.048, I²=70.9%), and by 12.3% using the optimistic model (1.123, 1.098 to 1.147, I²=83.0%), but not to increase when using the pessimistic model (0.975, 0.960 to 0.991, I²=70.4%). Meta-analysis by periconception periods demonstrated an increased risk during preconception with the optimistic model only, an increased risk during pregnancy with both the global and optimistic models, and an increased risk regardless of the model used during the postnatal period.

Metaregressions and sensitivity analyses

Using categorical levels of exposure, PM_{2.5} tended to lead to greater increased risk of having a child with ASD compared with exposure to PM₁₀ (coefficient 0.20, 95CI -0.02 to 0.42, p=0.073), NO_x (coefficient 0.29, 95CI 0.08 to 0.50, p=0.006), and solvents (coefficient 0.24, 95CI 0.04 to 0.44, p=0.017). No other differences between air pollutants exposure were noted, nor between periconceptional periods or trimesters. Neither parental age or gender of newborns were found to influence the risk of ASD (Figure 5). Due to insufficient data other sociodemographic variables were not analyzed. Results were similar using continuous levels of exposure. For PM_{2.5} and PM₁₀, meta-analysis depending on the methods to measure air pollutants showed similar results.

Discussion

The main findings revealed that air pollution particularly that of PM_{2.5} during the periconception period was associated with an increased risk of ASD in newborns, in all models used. The level of evidence is poor for other air pollutants. Exposure during

pregnancy (first and third trimesters) and postnatal periods may be the most at-risk periods. The increased risk of ASD following exposure to air pollutants surrounding pregnancy was not linked with sociodemographic factors.

Air pollution and risk of ASD in newborns

We demonstrated that global air pollution exposure in the perinatal period is a risk factor for ASD in newborns. Despite a previous meta-analysis²¹, there is the first to report a risk based on consideration of all air pollutants. As, exposures are in general multiple when quantifying risk, it is likely that overall risk is of most interest as reported by other authors^{51–53}. ASD was first described as a disorder in children with problems relating to others, highly sensitive to changes in their environment⁶². Prevalence of ASD appears to have increases over time^{63,64} possibly due to a modified definition of ASD, enhanced awareness and improved diagnosis^{65,66}, but also to a global increase in air pollutants in most megalopolis^{67,68}. The rigorous and sensitive statistical approach used in this meta-analysis allowed analysis of several included studies presenting different data for the same risk (e.g. several models adjusted on different covariables). There are presently no guidelines on how to manage this issue²². To avoid potential limitations, we created three models for each meta-analysis; a global model based on all risks reported in included articles, a pessimistic model using less favorable risks only (statistically speaking), and an optimistic model using the most favorable risks only. Unsurprisingly, use of optimistic models led to stronger results, but notably, we were unable to demonstrate an increased risk using the pessimistic model based on all air pollutants.

PM2.5: a public health issue

Risk of developing ASD in newborns increased using the global and optimistic models only for all air pollutants, with a strong high risk following exposure to PM2.5 whatever the model. Even use of the pessimistic model based on the least favorable data (those with the least

increased risk) revealed a minimum increased risk of 6% (up to 15% using the optimistic model). Nearly all individual studies showed that maternal exposure to PM_{2.5} was associated with increased risk of newborns with ASD^{39,44,46,47,49,53,54,56,57,59,61}. Thus indicating the high level of evidence concerning the deleterious effects of PM_{2.5} and related risk of ASD. PM_{2.5} particles appear to be the most dangerous pollutant due to their small size, and high volatility⁶⁹, able to be transported over longer distances⁶⁹. They also have a lower sedimentation velocity than other larger particles such as PM₁₀⁶⁹. PM are primarily composed of toxic particles such as PAHs, inorganic particles (sulfate, nitrate, ammonium), or organic carbon metals (copper, iron, nickel)^{70,71}. As road traffic is one of the primary sources of PM emission^{19,70,72} and predicted to double over the next twenty years⁷³, the impact of PM_{2.5} on health may become a major public health issue⁷⁴. As diesel is considered to emit more fine PM than gasoline^{72,75}, it may become a target for future preventive strategy. Levels of evidence are poor for the other air pollutants investigated.

Late pregnancy and early postnatal period: a key developmental periods

Late pregnancy and early postnatal periods were found to be the most at-risk periods for developing ASD following air pollution exposure. These periods are crucial in the development of the infant¹³, and can influence long-term health outcomes⁷⁶. Late pregnancy is important for placental function, fetal growth and brain developments and is also the period when maternal and fetal complications can occur, such as gestational diabetes, pre-eclampsia, hypoxia or brain injury⁷⁷⁻⁸⁰. Our result showing increased risk of ASD during late pregnancy is in accordance with previous meta-analyses²¹. Similarly, the early postnatal period can also impact health outcomes as has been shown with breastfeeding which may impact a wide range of parameters such as cognition, brain structure, structural development of the heart and lungs, bone health, or atopy^{81,82}. In comparison with the meta-analysis of Chun et al., we

highlighted the detrimental effects of air pollution leading to increased risk of ASD during the postnatal period, being previously analyzed in relation to the prenatal period. Our results show that the most at-risk periods for ASD were early and late pregnancy and the early postnatal period. These results are in accordance with other studies on air pollution that have showed these periods to also be the most at-risk for other birth outcomes such as hypertension, preeclampsia, pre-term birth, or low birthweight^{83–85}. Both late pregnancy and the early postnatal period appear key phases as regards vulnerability to air pollution⁴³

Influence of sociodemographic and other factors

Most often, etiologies of ASD remain unknown. Although, genetic susceptibility has been highlighted as a risk factor⁸⁶. No included studies in our meta-analysis indicated genetic susceptibility. Two further highlighted risk factors concern parental age and the newborn gender. Several studies have shown that maternal and/or paternal age^{87,88}, and male gender^{89,90} were associated with an increased risk of child neurodevelopmental outcomes such as ASD. In our meta-analysis, neither parental age or newborn genders were found to influence risk following exposure to air pollutants. However, our meta-regressions analyzed whether air pollution modifies this risk depending on parental age or newborn genders. Other investigated putative risk factors for ASD include maternal food intake⁹¹, low birthweight or preterm birth^{89,92}. As these factors were not assessed in the articles included in our meta-analysis, further analyses were precluded.

Limitations

Our study has some limitations. Despite the large number of studies, some air pollutants were only included in a few studies. Common air pollutants such as PM_{2.5}, PM₁₀, or NO_x, were however commonly assessed and as we included a large sample of 395 615 newborns, this

378 allowed the greater generalizability of our results. Our meta-analysis inherited the limitations
379 of the 28 included studies and was therefore subject to individual bias such as bias of
380 measures of exposure to air pollutants and bias of reporting of ASD. Despite the quality of
381 research reflected in the studies included in our meta-analyses, ASD covers a wide range of
382 severity that was not reported within included articles. Diagnostic method for ASD also
383 differed, limiting quality of data and precluding further analyses, although, most articles used
384 National ASD databases thus guaranteeing data accuracy. A further limitation concerns a
385 possible underestimation of our results. Diagnostic evidence of ASD can be underestimated
386 but is unlikely to be overestimated. Similarly, methods for detection or measurement of air
387 pollutant exposure differed between studies, thus precluding assessment of dose response
388 effects. In addition despite similarities, population characteristics between studies were not
389 identical. Data were collected in various countries, but excluded developing countries. The
390 majority of studies were conducted in the USA ^{17,39–44,46,48–53,56,57,59–61}, and to a lesser extent in
391 Europe ^{9–11,47,58}. The lack of data from Africa, Asia, and Oceania reduces potential
392 generalizability of our results, though. All ethnicities were included. Generalizability of our
393 results may also be lessened due to analysis of single-site studies, even if the majority of
394 included studies were multi-site. As studies differed in their study design, we performed
395 sensitivity analyses allowing demonstration of similar results whatever the design. In our
396 meta-analysis global model, some included studies appeared several times, with different data
397 for the same outcome depending on adjustment models. In the absence of clear consensus and
398 despite having more effect sizes within each meta-analyses when compared with studies
399 included in several highly-regarded published articles published ^{93,94}, the weight of studies
400 may have required ponderation ⁹⁵. This is one of the reasons for use of optimistic and
401 pessimistic models when only one data is available for each included article. A further
402 limitation of our meta-analysis concerns included studies using OR adjusted on different

factors between studies, even if adjusted OR may limit confusion bias. Finally, causality may also be a limitation in retrospective or case-control studies.

Conclusion

Exposure to air pollution, notably PM_{2.5} during pregnancy was associated with an increased risk of ASD in newborns regardless of the model used. The level of evidence concerning other air pollutants is however poor. Exposure during pregnancy and the postnatal period appear to be the most at-risk periods.

References

1. The Lancet,. UK air pollution and public health. *Lancet* 389, 1860 (2017).
2. Dockery, D. W. & Evans, J. S. Tallying the bills of mortality from air pollution. *Lancet* 389, 1862–1864 (2017).
3. Chen, G., Wan, X., Yang, G. & Zou, X. Traffic-related air pollution and lung cancer: A meta-analysis. *Thorac Cancer* 6, 307–318 (2015).
4. Møller, P. *et al.* Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles. *Mutat Res Rev Mutat Res* 762, 133–166 (2014).
5. Costa, L. G., Chang, Y.-C. & Cole, T. B. Developmental Neurotoxicity of Traffic-Related Air Pollution: Focus on Autism. *Curr Environ Health Rep* 4, 156–165 (2017).
6. Shah, A. S. V. *et al.* Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 382, 1039–1048 (2013).
7. Chiaverini, L. Asthma, particulates, and diesel exhaust. *Med Health R I* 85, 140–142 (2002).
8. Loxham, M., Davies, D. E. & Holgate, S. T. The health effects of fine particulate air pollution. *BMJ* 367, 16609 (2019).
9. Gong, T. *et al.* Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins. *Twin Res Hum Genet* 17, 553–562 (2014).
10. Gong, T. *et al.* Perinatal Exposure to Traffic-Related Air Pollution and Autism Spectrum Disorders. *Environ. Health Perspect.* 125, 119–126 (2017).
11. Guxens, M. *et al.* Air Pollution Exposure during Pregnancy and Childhood Autistic Traits in Four European Population-Based Cohort Studies: The ESCAPE Project. *Environ. Health Perspect.* 124, 133–140 (2016).

12. Pagalan, L. *et al.* Association of Prenatal Exposure to Air Pollution With Autism Spectrum Disorder. *JAMA Pediatr* 173, 86–92 (2019).
13. Georgieff, M. K., Tran, P. V. & Carlson, E. S. Atypical fetal development: Fetal alcohol syndrome, nutritional deprivation, teratogens and risk for neurodevelopmental disorders and psychopathology. *Dev Psychopathol* 30, 1063–1086 (2018).
14. Nypaver, C., Arbour, M. & Niederegger, E. Preconception Care: Improving the Health of Women and Families. *Journal of Midwifery & Women's Health* 61, 356–364 (2016).
15. Rodier, P. M., Ingram, J. L., Tisdale, B., Nelson, S. & Romano, J. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *J. Comp. Neurol.* 370, 247–261 (1996).
16. Lam, J. *et al.* A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder. *PLoS One* 11, e0161851 (2016).
17. Kalkbrenner, A. E. *et al.* Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study. *Environ. Health Perspect.* 126, 037004 (2018).
18. Oberdörster, G., Oberdörster, E. & Oberdörster, J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ. Health Perspect.* 113, 823–839 (2005).
19. de Kok, T. M. C. M., Drieste, H. A. L., Hogervorst, J. G. F. & Briedé, J. J. Toxicological assessment of ambient and traffic-related particulate matter: a review of recent studies. *Mutat. Res.* 613, 103–122 (2006).
20. Wilson, W. E. & Suh, H. H. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. *J Air Waste Manag Assoc* 47, 1238–1249 (1997).
21. Chun, H., Leung, C., Wen, S. W., McDonald, J. & Shin, H. H. Maternal exposure to air pollution and risk of autism in children: A systematic review and meta-analysis. *Environ. Pollut.* 256, 113307 (2020).
22. Dutheil, F. *et al.* Letter to the Editor: Comment on 'Maternal exposure to air pollution and risk of autism in children: A systematic review and meta-analysis'. *Environ. Pollut.* 264, 114724 (2020).
23. Kolevzon, A., Gross, R. & Reichenberg, A. Prenatal and Perinatal Risk Factors for Autism: A Review and Integration of Findings. *Arch Pediatr Adolesc Med* 161, 326–333 (2007).
24. Hao, X., Pan, J., Gao, X., Zhang, S. & Li, Y. Gut microbiota on gender bias in autism spectrum disorder. *Rev Neurosci* (2020) doi:10.1515/revneuro-2020-0042.
25. von Ehrenstein, O. S., Cui, X., Yan, Q., Aralis, H. & Ritz, B. Maternal Prenatal Smoking and Autism Spectrum Disorder in Offspring: a California Statewide Cohort and Sibling Study. *Am. J. Epidemiol.* (2020) doi:10.1093/aje/kwaa182.

26. Vandenberghe, J. P. *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 12, 1500–1524 (2014).
27. Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 25, 603–605 (2010).
28. Ollier, M., Chamoux, A., Naughton, G., Pereira, B. & Dutheil, F. Chest CT scan screening for lung cancer in asbestos occupational exposure: a systematic review and meta-analysis. *Chest* 145, 1339–1346 (2014).
29. Navel, V. *et al.* Efficacy of treatments for Demodex blepharitis: A systematic review and meta-analysis. *Ocul Surf* 17, 655–669 (2019).
30. Lanhers, C. *et al.* Creatine Supplementation and Upper Limb Strength Performance: A Systematic Review and Meta-Analysis. *Sports Med* 47, 163–173 (2017).
31. Benichou, T. *et al.* Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS ONE* 13, e0195166 (2018).
32. Benoist d'Azy, C., Pereira, B., Chiambaretta, F. & Dutheil, F. Oxidative and Anti-Oxidative Stress Markers in Chronic Glaucoma: A Systematic Review and Meta-Analysis. *PLoS ONE* 11, e0166915 (2016).
33. Courtin, R. *et al.* Prevalence of dry eye disease in visual display terminal workers: a systematic review and meta-analysis. *BMJ Open* 6, e009675 (2016).
34. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin Trials* 7, 177–188 (1986).
35. Shah, A. S. V. *et al.* Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 382, 1039–1048 (2013).
36. Orellano, P., Reynoso, J., Quaranta, N., Bardach, A. & Ciapponi, A. Short-term exposure to particulate matter (PM10 and PM2.5), nitrogen dioxide (NO2), and ozone (O3) and all-cause and cause-specific mortality: Systematic review and meta-analysis. *Environ Int* 142, 105876 (2020).
37. Jarvis, D. J., Adamkiewicz, G., Heroux, M.-E., Rapp, R. & Kelly, F. J. *Nitrogen dioxide. WHO Guidelines for Indoor Air Quality: Selected Pollutants* (World Health Organization, 2010).
38. Russo, M. W. How to Review a Meta-analysis. *Gastroenterol Hepatol (N Y)* 3, 637–642 (2007).
39. Becerra, T. A., Wilhelm, M., Olsen, J., Cockburn, M. & Ritz, B. Ambient air pollution and autism in Los Angeles county, California. *Environ. Health Perspect.* 121, 380–386 (2013).
40. Dickerson, A. S. *et al.* Autism spectrum disorder prevalence and associations with air concentrations of lead, mercury, and arsenic. *Environ Monit Assess* 188, 407 (2016).
41. Dickerson, A. S. *et al.* Autism spectrum disorder prevalence and proximity to industrial facilities releasing arsenic, lead or mercury. *Sci. Total Environ.* 536, 245–251 (2015).

42. Kalkbrenner, A. E. *et al.* Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. *Epidemiology* 21, 631–641 (2010).
43. Kalkbrenner, A. E. *et al.* Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. *Epidemiology* 26, 30–42 (2015).
44. Kaufman, J. A. *et al.* Ambient ozone and fine particulate matter exposures and autism spectrum disorder in metropolitan Cincinnati, Ohio. *Environ. Res.* 171, 218–227 (2019).
45. Raz, R. *et al.* Traffic-Related Air Pollution and Autism Spectrum Disorder: A Population-Based Nested Case-Control Study in Israel. *Am. J. Epidemiol.* 187, 717–725 (2018).
46. Raz, R. *et al.* Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis within the Nurses' Health Study II Cohort. *Environ. Health Perspect.* 123, 264–270 (2015).
47. Ritz, B. *et al.* Air pollution and Autism in Denmark. *Environ Epidemiol* 2, (2018).
48. Roberts, A. L. *et al.* Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. *Environ. Health Perspect.* 121, 978–984 (2013).
49. Talbott, E. O. *et al.* Fine particulate matter and the risk of autism spectrum disorder. *Environ. Res.* 140, 414–420 (2015).
50. Talbott, E. O. *et al.* Air toxics and the risk of autism spectrum disorder: the results of a population based case-control study in southwestern Pennsylvania. *Environ Health* 14, 80 (2015).
51. Volk, H. E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F. & McConnell, R. Residential proximity to freeways and autism in the CHARGE study. *Environ. Health Perspect.* 119, 873–877 (2011).
52. Volk, H. E. *et al.* Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. *Epidemiology* 25, 44–47 (2014).
53. Volk, H. E., Lurmann, F., Penfold, B., Hertz-Picciotto, I. & McConnell, R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry* 70, 71–77 (2013).
54. Chen, G. *et al.* Early life exposure to particulate matter air pollution (PM₁, PM_{2.5} and PM₁₀) and autism in Shanghai, China: A case-control study. *Environ Int* 121, 1121–1127 (2018).
55. Yousefian, F. *et al.* Long-term exposure to ambient air pollution and autism spectrum disorder in children: A case-control study in Tehran, Iran. *Sci. Total Environ.* 643, 1216–1222 (2018).
56. Jo, H. *et al.* Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. *Environ. Pollut.* 254, 113010 (2019).

57. McGuinn, L. A. *et al.* Early Life Exposure to Air Pollution and Autism Spectrum Disorder: Findings from a Multisite Case-Control Study. *Epidemiology* 31, 103–114 (2020).
58. Oudin, A. *et al.* Prenatal exposure to air pollution as a potential risk factor for autism and ADHD. *Environ Int* 133, 105149 (2019).
59. Goodrich, A. J. *et al.* Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. *Autism Res* 11, 69–80 (2018).
60. Windham, G. C. *et al.* Use of birth certificates to examine maternal occupational exposures and autism spectrum disorders in offspring. *Autism Res* 6, 57–63 (2013).
61. Kim, D. *et al.* The joint effect of air pollution exposure and copy number variation on risk for autism. *Autism Res* 10, 1470–1480 (2017).
62. Kanner, L. Autistic disturbances of affective contact. *Acta Paedopsychiatr* 35, 100–136 (1968).
63. Christensen, D. L. *et al.* Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Surveill Summ* 65, 1–23 (2016).
64. Zablotzky, B. & Black, L. I. Prevalence of Children Aged 3-17 Years With Developmental Disabilities, by Urbanicity: United States, 2015-2018. *Natl Health Stat Report* 1–7 (2020).
65. Zahorodny, W. *et al.* Increasing autism prevalence in metropolitan New Jersey. *Autism* 18, 117–126 (2014).
66. Dawson, G. & Bernier, R. A quarter century of progress on the early detection and treatment of autism spectrum disorder. *Development and Psychopathology* 25, 1455–1472 (2013).
67. Bouillon-Minois, J.-B., Lesage, F.-X., Schmidt, J. & Dutheil, F. Coronavirus and Exceptional Health Situations: The First Disaster With Benefits on Air Pollution. *Disaster Medicine and Public Health Preparedness* 1–3 (2020) doi:10.1017/dmp.2020.174.
68. Dutheil, F., Baker, J. S. & Navel, V. COVID-19 and cardiovascular risk: Flying toward a silent world? *Journal of Clinical Hypertension (Greenwich, Conn.)* (2020) doi:10.1111/jch.14019.
69. Yan, G. *et al.* Understanding PM2.5 concentration and removal efficiency variation in urban forest park-Observation at human breathing height. *PeerJ* 8, e8988 (2020).
70. Kim, K.-H., Kabir, E. & Kabir, S. A review on the human health impact of airborne particulate matter. *Environ Int* 74, 136–143 (2015).
71. Naimabadi, A. *et al.* Chemical composition of PM10 and its in vitro toxicological impacts on lung cells during the Middle Eastern Dust (MED) storms in Ahvaz, Iran. *Environ. Pollut.* 211, 316–324 (2016).

72. Cui, M. *et al.* Chemical composition of PM_{2.5} from two tunnels with different vehicular fleet characteristics. *Sci. Total Environ.* 550, 123–132 (2016).
73. IATA Forecasts Passenger Demand to Double Over 20 Years. <https://www.iata.org/en/pressroom/pr/2016-10-18-02/>.
74. Cohen, A. J. *et al.* Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 389, 1907–1918 (2017).
75. Assessment, U. E. N. C. for E. Health Assessment Document For Diesel Engine Exhaust (Final 2002). <https://cfpub.epa.gov/ncea/risk/recorddisplay.cfm?deid=29060>.
76. Esparza-Aguilar, M., Arroyo, P., Gómez-Verján, J. C. & Martín-Martín, V. Early life exposure and its association with diseases in adulthood: review of longitudinal studies. *Boletín Medico Del Hospital Infantil De Mexico* 77, 153–165 (2020).
77. Dugan, J. A. & Ma-Crawford, J. Managing gestational diabetes. *Journal of the American Academy of PAs* 32, 21–25 (2019).
78. Ellery, S. J. *et al.* Antenatal prevention of cerebral palsy and childhood disability: is the impossible possible? *J Physiol* 596, 5593–5609 (2018).
79. Schumacher, M., Liere, P. & Ghomari, A. Progesterone and fetal-neonatal neuroprotection. *Best Pract Res Clin Obstet Gynaecol* (2020) doi:10.1016/j.bpobgyn.2020.09.001.
80. Ridder, A., Giorgione, V., Khalil, A. & Thilaganathan, B. Preeclampsia: The Relationship between Uterine Artery Blood Flow and Trophoblast Function. *Int J Mol Sci* 20, (2019).
81. Santiago-Cruz, R. M. *et al.* [Breastfeeding and infant feeding in the first level of attention]. *Revista Medica Del Instituto Mexicano Del Seguro Social* 57, 387–394 (2019).
82. Lucas, A. Scientific Evidence for Breastfeeding. *Nestle Nutrition Institute Workshop Series* 90, 1–12 (2019).
83. Zhang, M. *et al.* Maternal Exposure to Ambient Particulate Matter ≤ 2.5 μm During Pregnancy and the Risk for High Blood Pressure in Childhood. *Hypertension* 72, 194–201 (2018).
84. Li, C. *et al.* Maternal exposure to air pollution and the risk of low birth weight: A meta-analysis of cohort studies. *Environ. Res.* 190, 109970 (2020).
85. Fang, J. *et al.* Prenatal PM_{2.5} Exposure and the Risk of Adverse Births Outcomes: Results from Project ELEFANT. *Environ. Res.* 110232 (2020) doi:10.1016/j.envres.2020.110232.
86. Lee, J. *et al.* Genetic Variation and Autism: A Field Synopsis and Systematic Meta-Analysis. *Brain Sci* 10, (2020).
87. Veldkamp, S. a. M. *et al.* Parental Age in Relation to Offspring's Neurodevelopment. *Journal of Clinical Child and Adolescent Psychology: The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53* 1–13 (2020) doi:10.1080/15374416.2020.1756298.

88. Gao, Y. *et al.* Association of Grandparental and Parental Age at Childbirth With Autism Spectrum Disorder in Children. *JAMA network open* 3, e202868 (2020).
89. Cogley, C., O'Reilly, H., Bramham, J. & Downes, M. A Systematic Review of the Risk Factors for Autism Spectrum Disorder in Children Born Preterm. *Child Psychiatry and Human Development* (2020) doi:10.1007/s10578-020-01071-9.
90. Ruigrok, A. N. V. & Lai, M.-C. Sex/gender differences in neurology and psychiatry: Autism. *Handb Clin Neurol* 175, 283–297 (2020).
91. Zhong, C., Tessing, J., Lee, B. K. & Lyall, K. Maternal Dietary Factors and the Risk of Autism Spectrum Disorders: A Systematic Review of Existing Evidence. *Autism Res* (2020) doi:10.1002/aur.2402.
92. Talmi, Z., Mankuta, D. & Raz, R. Birth weight and autism spectrum disorder: A population-based nested case-control study. *Autism Research: Official Journal of the International Society for Autism Research* 13, 655–665 (2020).
93. Aldridge, R. W. *et al.* Global patterns of mortality in international migrants: a systematic review and meta-analysis. *Lancet* 392, 2553–2566 (2018).
94. Fellmeth, G. *et al.* Health impacts of parental migration on left-behind children and adolescents: a systematic review and meta-analysis. *Lancet* 392, 2567–2582 (2018).
95. Cochrane Handbook for Systematic Reviews of Interventions. <https://handbook-5-1.cochrane.org/>.

Table 1. Characteristics of studies included in meta-analysis.

As: Arsenic; Ld: Lead; Hg: Mercury; * for median; #: see original articles (Gong 2014: see Figure 2; Kalkbrenner 2010: see Table 2 ; Kalkbrenner 2018: see Table 2)

Study	Country	Study design	Dates of inclusion	Perinatal periods	n ASD/ n total	Air pollutants		REF used for risk calculation	Concentration for REF of air pollutants	Type of risk	Adjustment of risk	Other variables
						Types	Mean levels (* for median)					
Becerra, 2013	USA	Case-control	1995-2006	Pregnancy	7594 / 83229	PM ₁₀ PM _{2.5} NO ₂ NO O ₃ , CO	-	IQR	PM ₁₀ : 8.3µg/m ³ PM _{2.5} : 4.7µg/m ³ NO ₂ : 10.5ppb NO: 29.7ppb O ₃ :11.5ppb	Odds ratio by IQR increase	Adjusted for maternal age, education, race/ethnicity, maternal place of birth, type of delivery, parity, insurance type, gestational weeks	Maternal place of birth, ethnicity, education, type of delivery, parity, insurance type
Chen, 2018	China	Case-control	2002-2011	Postnatal	124 / 1364	PM ₁ PM _{2.5} PM ₁₀	PM ₁₀ : 95.4µg/m ³ PM _{2.5} : 66.2µg/m ³ PM ₁ : 48.8µg/m ³	IQR	PM ₁₀ : 4.9µg/m ³ PM _{2.5} : 3.4µg/m ³ PM ₁ : 4.8µg/m ³	Odds ratio by IQR increase	Adjusted for birth weight; gestational weeks; disease, trauma, and mental health history; maternal age; familial history; parents' marital status, education, smoking, income; parental relationship; parenting	Gender
Dickerson, 2015	USA	Cohort	1992-2000	Pregnancy	2489 / 2489	Metals	-	>50 th centile of industrial facilities	>50 th centile: 46.9km from industry	Relative Risk by 10 th centile	Crude and adjusted for ethnicity and maternal education	Gender
Dickerson, 2016	USA	Cohort	2000-2008	Preconception Pregnancy	2489 / 2489	Metals	-	1 st quartile	As:<0.02ng/m ³ Ld:<1.49ng/m ³ Hg:<1.52ng/m ³	Relative Risk by quartile	Crude and adjusted for ethnicity, education, poverty	-
Gong, 2014	Sweden	Case-control	1992-2000	Pregnancy Postnatal	109 / 3051	PM ₁₀ NOx	PM ₁₀ : 3.3-4.2µg/m ³ NOx: 5.4-12.7µg/m ³	<5 th percentile	#	Relative Risk for >95 th percentile vs <5 th and by severity of ASD	Crude and adjusted for parity, gender, maternal age, smoking, marital status, education, income, neighborhood deprivation	Birth weight, ethnicity, gestational age, zygosity
Gong, 2017	Sweden	Case-control	1993-2007	Pregnancy Postnatal	5136 / 23373	PM ₁₀ NOx	PM ₁₀ : 4.2-4.4µg/m ³ NOx: 9.8-11.0µg/m ³	Arbitrary cut-off	PM ₁₀ : <10µg/m ³ NOx: <20µg/m ³	Odds ratio by 10µg/m ³ increase in PM ₁₀ and 20µg/m ³ in NOx	Crude and adjusted for sex; birth month; sibling order; parents' age, education, employment, income, birth countries; marital status; neighborhood deprivation	Birth weight, congenital malformation, intellectual disability
Goodrich, 2019	USA	Case-control	1997-2008	Pregnancy	346 / 606	PM ₁₀ PM _{2.5} NOx O ₃	-	< median	PM ₁₀ : <22.9 µg/cm ³ PM _{2.5} : <12.4µg/cm ³ NOx: <14.2ppb O ₃ : <33.4µg/cm ³	Odds ratio for > median vs < median	Adjusted for income, year of birth, vitamin A and zinc intake during pregnancy	Maternal age, education, birthplace; child ethnicity, sex; home ownership; preterm delivery; parity; gestational diabetes
Guxens, 2016	Europe (Italy, Spain, Netherlands, Sweden)	Cohort	1992-2008	Pregnancy	541 / 8079	PM ₁₀ PM _{2.5} NO ₂	*PM ₁₀ : 15-46µg/m ³ *PM _{2.5} : 8-22µg/m ³ *NO ₂ : 17-42µg/m ³ *NOx: 34-70µg/m ³	Arbitrary cut-off	*PM ₁₀ : <10µg/m ³ *PM _{2.5} : <5µg/m ³ *NO ₂ : <10µg/m ³ *NOx: <20µg/m ³	Odds ratio by 10µg/m ³ increase in PM ₁₀ and NO ₂ , and 5µg/m ³ in PM ₅ and 20µg/m ³ in	Adjusted for maternal education, country of birth, age, body mass index, height, smoking, parity, urbanicity; child's sex, season at birth, age at ASD diagnosis	-

										NOx		
Jo, 2019	USA	Cohort	1999-2009	Pregnancy Postnatal	2471 / 246420	PM ₁₀ PM _{2.5} NO ₂ O ₃	PM ₁₀ : 38.1µg/m ³ PM _{2.5} : 17.9µg/m ³ NO ₂ : 25.1ppb O ₃ : 41.6ppb	<5 th percentile	#	Hazard ratio for >95 th vs <5 th percentile	Adjusted for birth year, medical center, maternal age, ethnicity, parity, education, comorbidities; household income, child sex	-
Kalkbrenner, 2010	USA	Case-control	1992-1994 1994-1996	Perinatal	383 / 2829	Metals Solvents Styrene Pesticides PAHs	# (0.00001-2108 µg/m ³ depending on air pollutants)	<20 th percentile	#	Odds ratio for >80 th percentile vs <20 th	Adjusted for maternal age, education, ethnicity, smoking; marital status; household income; urbanicity	Gender, first born, married
Kalkbrenner, 2015	USA	Case-control	1994-1996-1998-2000	Preconception Pregnancy Postnatal	645 / 13079	PM ₁₀	PM ₁₀ by groups: 21.8-24.3µg/m ³	Arbitrary cut-off	PM ₁₀ : <10µg/m ³	Odds ratio by 10µg/m ³ increase in PM ₁₀	Adjusted for maternal age, ethnicity, education; household income, urbanization, week of birth	Gender, smoking, married
Kalkbrenner, 2018	USA	Case-control	1994-2007	Pregnancy	1540 / 2017	Metals PAHs Solvents Styrene Pesticides	# (155 pollutants)	<25 th percentile (or <5 th), and log-transformed	#	Odds ratio for >75 th vs <25 th (or >95 th vs <5 th)	Adjusted for air toxic levels in the family, birth year, education, income, population density	Gender, ethnicity, maternal age, number in siblings
Kaufman, 2019	USA	Case-control	2006-2010	Pregnancy Postnatal	428 / 6420	PM _{2.5} O ₃	PM _{2.5} : 66.2µg/m ³ O ₃ : 48.8µg/m ³	<5 th percentile and IQR	<5 th percentile: data not shown IQR: PM _{2.5} : 3.5µg/m ³ O ₃ : 16ppb	Odds ratio for >95 th vs <5 th percentile and by IQR increase	Adjusted for year of birth; maternal education, body mass index, birth spacing, month of conception, pollutants	Gender; maternal age, ethnicity, smoking, body mass index; gestational age, birth weight, previous births
Kim, 2017	USA	Case-control	1999-2008	Pregnancy Postnatal	158 / 147	PM ₁₀ PM _{2.5} NO ₂ O ₃	PM ₁₀ : 6.2µg/m ³ PM _{2.5} : 3.7µg/m ³ NO ₂ : 5.7ppb O ₃ : 6.2 ppb	<75 th percentile	data not shown	Odds ratio for >75 th vs <75 th percentile	Adjusted for education, ethnicity, child's sex	-
MCGuinn, 2020	USA	Case-control	2003-2006	Preconception Pregnancy Postnatal	674 / 1529	PM _{2.5} O ₃	PM _{2.5} : 12.7µg/m ³ O ₃ : 35.1ppb	Arbitrary cut-off	PM ₁₀ : <1.6µg/m ³ O ₃ : <6.6 ppb	Odds ratio by 1.6 µg/m ³ in PM _{2.5} and 6.6 ppb in O ₃	Adjusted for maternal age, education, ethnicity, smoking; study site; month and year of birth; exposure time	Gender, preterm
Oudin, 2019	Sweden	Cohort	1999-2009	Pregnancy	768 / 47865	NOx	NOx: 17.7µg/m ³	<1 st quartile and arbitrary cut-off	1 st quartile: <11.3 µg/m ³ Arbitrary cut-off: NOx: 10µg/m ³	Odds ratio by quartile and by 10µg/m ³ in NOx	Adjusted for gender of child; maternal age, parity, smoking, body mass index, education, income, country of birth	-
Pagalan, 2018	Canada	Cohort	2004-2009	Pregnancy	1307 / 132256	PM _{2.5} NO NO ₂	PM _{2.5} : 5.0-5.7µg/m ³ NO ₂ : 13.5-16.0µg/m ³ NO: 11.0-16.0µg/m ³	IQR	PM _{2.5} : 1.5µg/m ³ NO ₂ : 4.8ppb NO ₂ : 10.7ppb	Odds ratio by IQR increase	Crude and adjusted for gender, income, urbanicity, month and year of birth, maternal age, birthplace	Gestational age, multiple birth, parity
Raz, 2015	USA	Case-control	1993	Preconception Pregnancy Postnatal	245 / 1767	PM _{2.5}	PM _{2.5} : 14.6µg/m ³	IQR	PM _{2.5} : 4.42µg/m ³	Odds ratio by IQR increase	Crude and adjusted for child sex, year and month of birth, parents age, income	Birth weight, education, marital status, prematurity, smoking
Raz, 2017	Israel	Case-control	2005-2009	Pregnancy Postnatal	2098 / 56289	NO ₂	*NO ₂ : 16.7ppb	IQR	NO ₂ : 5.85ppb	Odds ratio by IQR increase	Adjusted for year and month of birth, ethnicity, paternal age, poverty	Birth weight, gestational age, income, population group, multiplicity of birth

Ritz, 2018	Denmark	Case control	1989-2013	Pregnancy Postnatal	15387 / 83526	PM ₁₀ PM _{2.5} NO ₂ SO ₂	-	IQR	PM ₁₀ : 3.80µg/m ³ PM _{2.5} : 3.61µg/m ³ NO ₂ : 11.41µg/m ³ SO ₂ : 2.80µg/m ³	Odds ratio by IQR increase	Crude and adjusted for parental age, birth place, neighborhood employment and housing, maternal smoking, pollutants exposure periods	Gender, birth weight, gestational age
Roberts, 2013	USA	Case-control	1987-2002	Postnatal	325 / 22426	Metals	-	1 st quintile	<1 st quintile: data not shown	Odds ratio by quintile	Adjusted for maternal age, year of birth, parents' education, income, and year	Gender, state of residence at birth, smoking
Talbott, 2015a	USA	Case-control	2005-2009	Preconception Pregnancy Postnatal	211 / 430	PM _{2.5}	PM _{2.5} : 15µg/m ³	IQR	PM _{2.5} : 2.84µg/m ³	Odds ratio by IQR increase	Crude and adjusted for maternal education, smoking, ethnicity, and age	Year and country of birth, multiple birth, birth weight, preterm birth
Talbott, 2015b	USA	Case-control	2005-2009	Pregnancy	216 / 4971	Metals Solvents PAHs Pesticides	# (30 pollutants)	1 st quartile	<1 st quintile: #	Odds ratio by quartile	Adjusted for maternal age, education, smoking, ethnicity, child's birth year and sex	Country of birth
Volk, 2011	USA	Case-control	1997-2006	Pregnancy	304 / 259	PM ₁₀ PM _{2.5} NOx O ₃	-	Last quartile of distance from freeway	Last quartile: >1.4km from freeway	Odds ratio by quartile	Adjusted for child sex, ethnicity; parents education; maternal age and smoking	Preterm delivery
Volk, 2013	USA	Case-control	1997-2008	Pregnancy Postnatal	279 / 524	PM ₁₀ PM _{2.5} NOx O ₃	-	1 st quartile	1 st quartile: <9.7ppb of global traffic air pollution levels	Odds ratio by quartile	Crude and adjusted for child's sex, ethnicity; parents education; maternal age and smoking	-
Volk, 2014	USA	Case-control	1997-2009	Pregnancy	251 / 156	PM ₁₀ PM _{2.5} NOx O ₃	-	<25 th percentile	PM ₁₀ : <29.2µg/m ³ PM _{2.5} : <16.0µg/m ³ NOx ₅ : <17.5ppb O ₃ : <41.8ppb	Odds ratio for >75 th vs <25 th percentile	Adjusted for child's sex, ethnicity; parents education; maternal age and smoking; home ownership	-
Yousefian, 2018	Iran	Case-control	2004-2012	Pregnancy	134 / 388	PM ₁₀ SO ₂ Solvents	PM ₁₀ : 105.1-107.9µg/m ³ SO ₂ : 22.8-26.4ppb Solvents: 60.7µg/m ³	per 1-unit increase in pollutants	per 1-unit increase in pollutants	Odds ratio per 1-unit increase in pollutants	Adjusted for maternal age, smoking; parents education; cousin marriage; birth order, gestational age, multiplicity, parents comorbidities	Gender, type of delivery
Windham, 2013	USA	Case-control	1994	Pregnancy	284 / 943	Solvents Pesticides Metals	-	Exposed workers vs non-exposed workers	Non-exposed workers: no concentrations given	Odds ratio exposed versus non-exposed workers	Crude and adjusted for child ethnicity, maternal age and education	Gender; paternal age, education; parity; birth weight; prematurity

Figure Legends

Figure 1. Search Strategy

Figure 2. Methodological quality of included articles using the SIGN checklist

Figure 3. Meta-analysis on risk of autism by air pollutant depending on perinatal periods (preconception, pregnancy and postnatal), using normalized Odds ratio (continuous data - incremental risk).

When available (more than one study), we computed three models for each meta-analysis (a global model using all risks listed in included articles, a pessimistic model using only the less favorable data, and an optimistic model using only the most favorable).

95%CI: 95% confidence intervals. Each meta-analysis is represented in the forest-plot by a dot on a horizontal line, with the corresponding number of articles (n studies (subgroups)) included within the meta-analysis. The white dots represent the odds ratio (OR), and the length of each line around the dots represent its 95% confidence interval (95CI). An overall summary pooled-estimate (result of the meta-analysis of meta-analyses) is represented by a blue lozenge at the end of the graph. The black solid vertical line represents the null estimate (with a value of 1 for OR). Horizontal lines that cross the null vertical line (OR=1) represent non-significant studies.

Figure 4. Meta-analysis on risk of autism for PM2.5 depending on trimester of pregnancy (first, second, third), using normalized Odds ratio (continuous data - incremental risk).

When available (more than one study), we computed three models for each meta-analysis (a global model using all risks listed in included articles, a pessimistic model using only the less favorable data, and an optimistic model using only the most favorable).

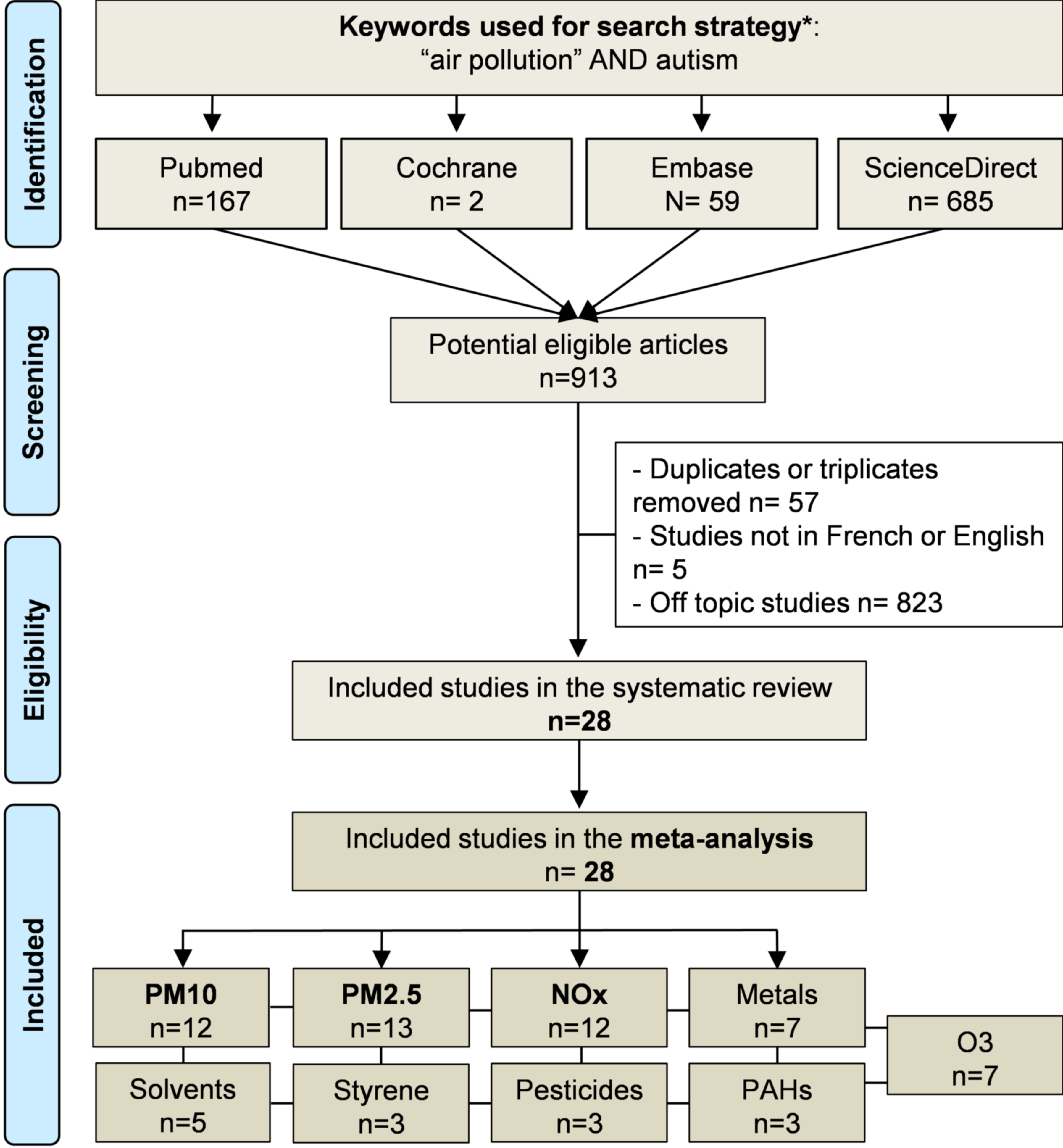
95%CI: 95% confidence intervals. Each meta-analysis is represented in the forest-plot by a dot on a horizontal line, with the corresponding number of articles (n studies (subgroups)) included within the meta-analysis. The white dots represent the odds ratio (OR), and the length of each line around the dots represent its 95% confidence interval (95CI). An overall summary pooled-estimate (result of the meta-analysis of meta-analyses) is represented by a blue lozenge at the end of the graph. The black solid vertical line represents the null estimate (with a value of 1 for OR). Horizontal lines that cross the null vertical line (OR=1) represent non-significant studies.

Figure 5. Meta-regressions

95%CI: 95% confidence intervals; t0: baseline; † Dropped because of collinearity.

The effect of each variable on the outcome is represented in the forest-plot by a dot on a horizontal line. The white dots represent the coefficient for each variable, and the length of each line around the dots represent their

95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 0). Horizontal lines that cross the null vertical line are non-significant variables.

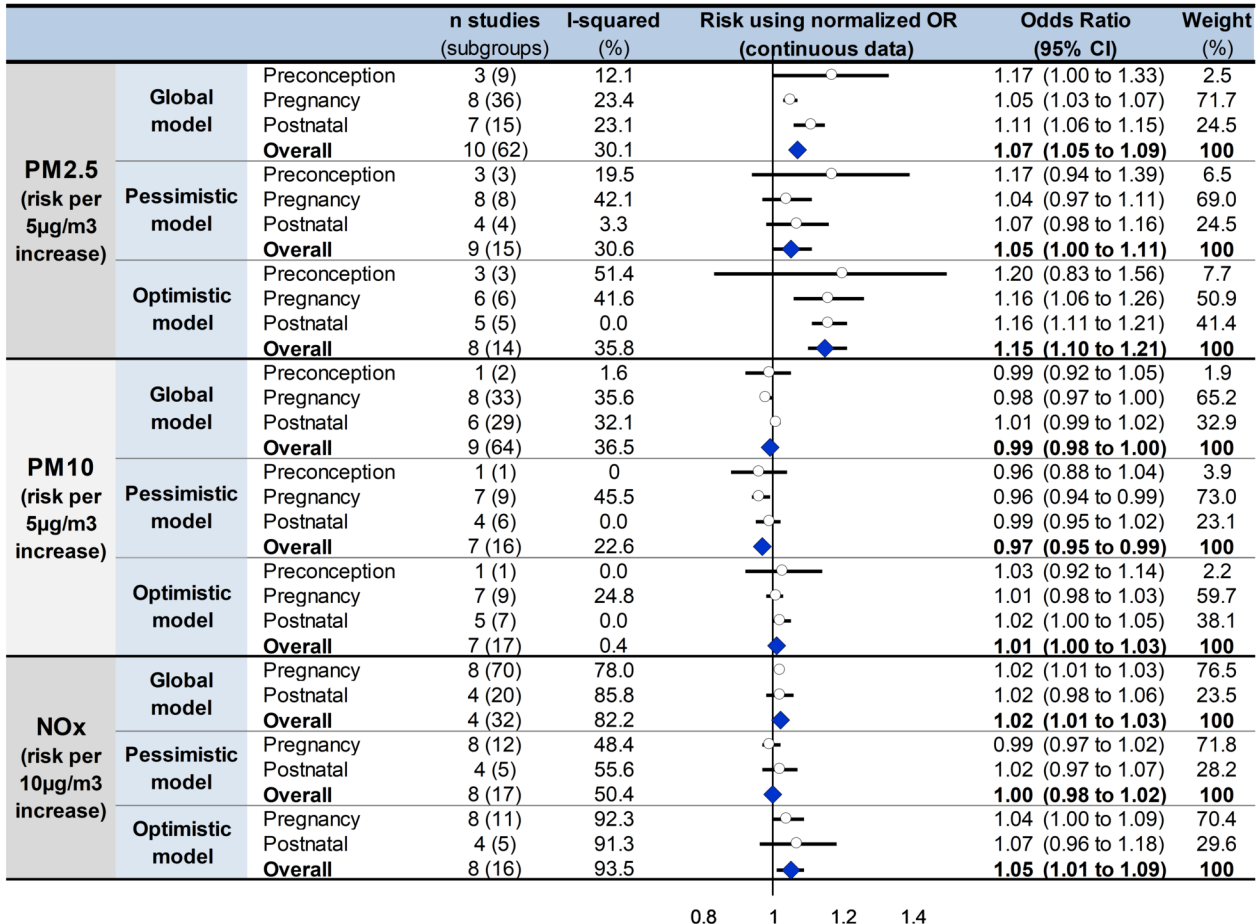


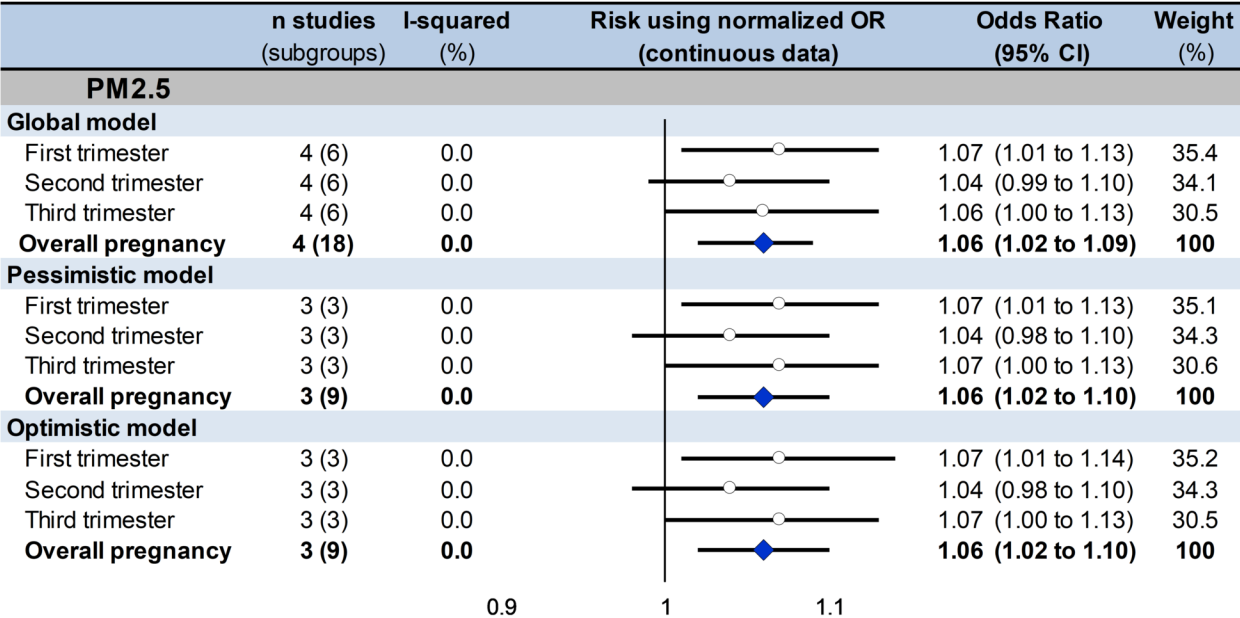
	Selection bias							Assessment bias	Con-founding bias	Sta-tistics	Overall assessment				
	Appropriate and clearly focused question	Selection bias (comparable groups)	Selection bias (same exclusion criteria in both groups)	Selection bias (participation rate of both groups)	Attrition bias (comparison included/non-included)	Adequate case definition	Controls are non-cases ?	Detection bias (blind assessments)	Detection bias (exposure status is well measured)	Potential confounders taken into account	Confidence intervals are provided	To minimise the risk of bias or confounders	Overall effect is due to the study intervention	Results applicable to the patient group targeted	General level of evidence
Becerra 2013	+	+	+	100	+	+	+	NA	+	+	+	++	+	+	++
Chen 2018	+	+	+	100	+	+	+	NA	+	+	+	++	+	+	++
Gong 2014	+	+	+	69	+	+	-	NA	+	?	+	+	+	+	+
Gong 2017	+	+	+	100	+	+	+	NA	+	+	+	+	+	+	++
Goodrich 2019	+	+	+	80	+	+	+	NA	+	+	+	+	+	+	+
Guxens 2016	+	+	+	62	+	+	+	NA	+	+	+	++	+	+	++
Kalkbrenner 2010	+	+	+	?	?	+	+	NA	+	+	+	0	+	+	+
Kalkbrenner 2015	+	+	+	93	-	+	+	NA	+	+	+	+	+	+	+
Kalkbrenner 2018	+	+	+	100	+	+	+	NA	+	+	+	++	+	+	++
Kaufman 2019	+	+	+	?	+	+	+	NA	+	+	+	+	+	+	++
Kim 2017	+	+	+	79	?	+	+	NA	+	+	+	++	+	+	+
MCGuinn 2020	+	+	+	?	?	+	+	NA	+	+	+	++	+	+	++
Raz 2015	+	+	+	88	-	+	+	NA	+	+	+	+	+	+	++
Raz 2017	+	+	+	99	+	+	+	NA	+	+	+	+	+	+	++
Ritz 2018	+	+	+	71	+	+	+	NA	+	+	+	+	+	+	+
Roberts 2013	+	+	+	84	-	+	+	NA	+	+	+	+	+	+	++
Talbott 2015a	+	+	+	98	+	+	+	NA	+	+	+	+	+	+	++
Talbott 2015b	+	+	+	81	?	+	+	NA	+	+	+	+	+	+	+
Volk 2011	+	+	+	100	+	+	+	NA	+	+	+	+	+	+	+
Volk 2013	+	+	+	100	+	+	+	NA	+	+	+	+	+	+	++
Volk 2014	+	+	+	63	-	+	+	NA	+	+	+	+	+	+	+
Yousefian 2018	+	+	+	96	?	+	+	NA	+	+	+	+	+	+	+
Windham 2012	+	+	+	?	?	+	+	NA	+	+	+	0	+	+	+

Case control studies

		Selection bias						Assessment bias					Con-founding bias	Sta-tistics	Overall assessment			
	Appropriate and clearly focused question	Selection bias (comparable groups)	Selection bias (participation rate)	Performance bias (use of sensitivity analyses)	Attrition bias (% of patients lost sight)	Attrition bias (comparison included/lost sight)	Outcomes clearly defined	Detection bias (blind assessments)	Detection bias (process measures are comparable)	Detection bias (measure of assessment is reliable)	Detection bias (outcome measures are defined)	Detection bias (exposure level is assessed)	Confusion bias (confounders taken into account)	Confidence intervals are provided	To minimise the risk of bias or confounders	Clear evidence of link between exposure & outcome	Results applicable to the patient group targeted	General level of evidence
Dickerson 2015					0													
Dickerson 2016					2.7													
Jo 2019																		
Oudin 2019																		
Pagalan 2018																		

Cohort studies





		Coefficient (95% CI)	p-value (%)
All			
Age of mothers		-0.05 (-0.13 to 0.02)	0.16
Age of fathers		0.03 (-0.19 to 0.25)	0.77
Sex of newborn, male as reference		0.00 (0.00 to 0.18)	0.21
Comparisons between pollutants			
PM2.5 vs PM10		0.20 (-0.02 to 0.42)	0.073
PM2.5 vs NOx		0.29 (0.08 to 0.50)	0.006
PM2.5 vs O3		0.15 (-0.07 to 0.39)	0.19
PM2.5 vs Metals		0.16 (-0.04 to 0.36)	0.13
PM2.5 vs Solvents		0.24 (0.04 to 0.44)	0.017
PM10 vs NOx		0.09 (-0.10 to 0.28)	0.37
PM10 vs O3		-0.05 (-0.26 to 0.17)	0.67
PM10 vs Metals		-0.05 (-0.23 to 0.14)	0.62
PM10 vs Solvents		0.04 (-0.14 to 0.22)	0.68
NOx vs O3		-0.13 (-0.34 to 0.07)	0.19
NOx vs Metals		-0.13 (-0.29 to 0.03)	0.12
NOx vs Solvents		-0.05 (-0.21 to 0.11)	0.56
O3 vs Metals		0.00 (-0.19 to 0.20)	0.99
O3 vs Solvents		0.09 (-0.11 to 0.28)	0.38
Metals vs Solvents		0.08 (-0.07 to 0.24)	0.29
Comparisons between periconceptual periods			
Preconception vs pregnancy		-0.01 (-0.28 to 0.26)	0.95
Preconception vs postnatal		0.02 (-0.27 to 0.32)	0.88
Pregnancy vs postnatal		0.03 (-0.11 to 0.17)	0.66
PM2.5			
Age of mothers		-0.04 (-0.31 to 0.23)	0.77
Age of fathers		0.05 (-0.27 to 0.37)	0.74
Sex of newborn, male as reference		0.03 (-0.01 to 0.07)	0.20
Comparisons between periconceptual periods			
Preconception vs pregnancy		0.18 (-0.49 to 0.85)	0.6
Preconception vs postnatal		0.02 (-0.72 to 0.76)	0.95
Pregnancy vs postnatal		-0.16 (-0.58 to 0.27)	0.47
Comparisons between stages of pregnancy			
First vs second trimester		-0.07 (-0.78 to 0.64)	0.84
First vs third trimester		0.09 (-0.56 to 0.73)	0.78
Second vs third trimester		0.16 (-0.62 to 0.94)	0.68
PM10			
Age of mothers		-0.11 (-0.48 to 0.26)	0.56
Age of fathers		-0.03 (-0.8 to 0.86)	0.94
Sex of newborn, male as reference		0.01 (-0.02 to 0.04)	0.45
Pregnancy vs postnatal		-0.03 (-0.31 to 0.26)	0.86
NOx			
Age of mothers		-0.10 (-0.43 to 0.23)	0.56
Age of fathers		-0.08 (-0.76 to 0.60)	0.81
Sex of newborn, male as reference		0.01 (-0.02 to 0.04)	0.53
Pregnancy vs postnatal		0.15 (-0.10 to 0.41)	0.24
O3			
Age of mothers		†	
Age of fathers		insufficient observations	
Sex of newborn, male as reference		0.03 (-0.05 to 0.12)	0.44
Comparisons between periconceptual periods			
Preconception vs pregnancy		0.06 (-1.14 to 1.26)	0.92
Preconception vs postnatal		0.00 (-1.24 to 1.24)	0.99
Pregnancy vs postnatal		-0.06 (-0.47 to 0.34)	0.75
Metals			
Age of mothers		0.02 (-0.08 to 0.13)	0.63
Age of fathers		0.28 (-1.41 to 1.97)	0.74
Sex of newborn, male as reference		0.01 (0.00 to 0.02)	0.21
Comparisons between periconceptual periods			
Preconception vs pregnancy		-0.11 (-0.45 to 0.23)	0.52
Preconception vs postnatal		-0.10 (-0.54 to 0.34)	0.66
Pregnancy vs postnatal		0.01 (-0.32 to 0.34)	0.94
Solvents			
Age of mothers		†	
Age of fathers		0.30 (-0.68 to 2.20)	0.3
Sex of newborn, male as reference		-0.02 (-6.75 to 1.42)	0.2

The risk of ASD following air pollutants exposure during pregnancy

