Environmental Research 151 (2016) ■■■–■■■

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis

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ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form
18 July 2016
Accepted 19 July 2016

Keywords:
Autism spectrum disorder
Air pollution
Fine particulate matter
Meta-analysis
Review

ABSTRACT

Background and objective: Genetic and environmental factors have been recognized to play an important role in autism. The possibility that exposure to outdoor air pollution increases the risk of autism spectrum disorder (ASD) has been an emerging area of research. Herein, we present a systematic review, and meta-analysis of published epidemiological studies that have investigated these associations.

Methods: We undertook a comprehensive search strategy to identify studies that investigated outdoor air pollution and autism in children. Overall, seven cohorts and five case-control studies met our inclusion criteria for the meta-analysis. We summarized the associations between exposure to air pollution and ASD based on the following critical exposure windows: (i) first, second and third trimester of pregnancy, (ii) entire pregnancy, and (iii) postnatal period. Random effects meta-analysis modeling was undertaken to derive pooled risk estimates for these exposures across the studies.

Results: The meta-estimates for the change in ASD associated with a 10 $\mu g/m^3$ increase in exposure in $PM_{2.5}$ and 10 ppb increase in NO_2 during pregnancy were 1.34 (95% CI:0.83, 2.17) and 1.05 (95% CI:0.99, 1.11), respectively. Stronger associations were observed for exposures received after birth, but these estimates were unstable as they were based on only two studies. O_3 exposure was weakly associated with ASD during the third trimester of pregnancy and during the entire pregnancy, however, these estimates were also based on only two studies.

Conclusion: Our meta-analysis support the hypothesis that exposure to ambient air pollution is associated with an increased risk of autism. Our findings should be interpreted cautiously due to relatively small number of studies, and several studies were unable to control for other key risk factors.

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http://dx.doi.org/10.1016/j.envres.2016.07.030
0013-9351/

1. Introduction

Autism spectrum disorder (ASD), or autism, are general terms for a complex series of developmental disability disorders characterized by impaired communication, lack of awareness, social interaction problems, and restricted behavior. ASD manifests in functional deficits, relations and work achievement that last a lifetime (APA, 2000). The global prevalence of ASD has been estimated to be one in 132 persons (Baxter et al., 2015), while in the US one in 68 eight year old children are thought to be affected (Baio, 2014). The prevalence rates of autism have been shown to vary by region (Ouellette-Kuntz et al., 2012), and although differences in diagnosis may contribute to these discrepancies, findings from epidemiological studies suggest that environmental factors may play a role (Rossignol et al., 2014).

Air pollution has been linked to a number of different health conditions. Previous studies point to a plausible biological pathway linked to autism, wherein components of air pollution cause a systematic inflammatory response that can contribute to neuronal injury and affect the development of the central nervous system (Hagberg and Mallard, 2005). A number of recently conducted epidemiological studies provide further support that traffic-related air pollution (TRAP) adversely affects neurodevelopmental effects (Becerra et al., 2013; Calderón-Garcidueñas et al., 2011; Jung et al., 2013; Volk et al., 2014; Volk et al., 2013). The investigation of environmental exposures during perinatal and postnatal stage, through a child's first year of life is essential since these are the periods of brain development during which an environmental chemical insult can perturb neurodevelopment (Rice and Barone Jr, 2000; Rodier et al., 1996). Exposure to air pollution represents an important exposure to consider in the etiology of autism, particularly given its ubiquitous nature and the potential at both a population, and individual-level to modify exposure.

Air pollution is a heterogeneous mixture of gases and particulate matter. Nitrogen dioxide (NO_2) has been associated with a variety of health endpoints, and given its strong correlation with roadways it is often used as a surrogate measure of TRAP. Among air pollution components, particulate matter (PM) has been seen as a major widespread threat and has been heavily implicated in disease (Møller et al., 2009; Nelin et al., 2012). While traffic is an important contributor to ambient PM concentrations, other sources include industrial emissions, secondary aerosols and even domestic heating (Viana et al., 2008). PM include components of various sizes: PM_{10}, which consists of particles with a median aerodynamic diameter of less than 10 μm in diameter, and fine particulate $PM_{2.5}$ whose particles have median aerodynamic diameters of less than 2.5 μm, and are included within the larger PM_{10} fraction.

Herein, we present the results of a meta-analysis that investigated the associations between ambient air pollution and the development of autism. To inform on possible pathways, we felt it necessary to examine associations based on periods of exposures. As such, our review focussed on studies that could inform on the temporal sequence between exposure and outcome. Therefore, we prioritized our identification of relevant studies to include longitudinal and case-control designs. While some cross-sectional studies have examined similar associations (Abid et al., 2014; Kicinski et al., 2015; van Kempen et al., 2012), these studies are limited in drawing causal inferences due to the inability to characterize associations temporally.

2. Materials and methods

2.1. Literature search

We undertook a search in the Cochrane Database of systematic reviews prior to the study to determine whether a previous systematic review had been done on this topic, and did not identify any such paper.

One team member (Flores-Pajot) proceeded to conduct the systematic review. Initially, we intended to study the impacts of the environment, urban greenness and air pollution on the development of childhood autism and based on this aim 396 articles were found. The search was then restricted to include only those studies that looked at associations between three air pollutants (NO_2, Ozone and PM) and ASD. This restriction was made because these represent three major air pollutants that have been most commonly studied in relation to human health outcomes. Studies were identified through PubMed, Web of Science, and Environmental Index databases using a specific search criteria, with boolean operators AND in combination with search terms including: Air pollution (Mesh), Traffic, “Particulate Matter”, “Nitrogen oxide”, “Nitrogen dioxide”, “ozone”, “Autis*”. For example, typical search terms included: 1) Traffic AND “Air pollution” AND autis*, 2) “Particulate matter” AND “Nitrogen oxide” AND autis*3) Traffic AND ozone AND autis*4) “Air pollution” AND “Particulate matter”, AND autis*, 5) Similar combinations using the terms above (Annexure). Citation lists from these initial articles were also examined. Papers had to be written in English, French or Spanish, before March 30th, 2016. The search yielded a total of 142 articles. Abstracts of articles were retrieved and examined if they were (i) relevant epidemiological studies and (ii) involving NO_2, O_3 or PM, which reduced the number to 26 articles. The search was then narrowed to only consider observational studies and then limited to only keep those epidemiological studies that were looking at NO_2, O_3 or PM and ASD for the systematic review, and that were either a case-control or cohort design for the meta-analysis. We excluded cross-sectional and ecological studies due to their limitations to inform on potential causal association. The combined search strategy outlined above produced 13 studies that were included in the systematic review, from those only one study did not provide the necessary quantitative data to be included in the meta-analysis, and from the 12 studies included in the meta-analysis one comprised six population-based cohorts (Guxens et al., 2015) (Fig. 1).

To assess the overall quality and potential for bias of the case-control and cohort studies, we used the Newcastle-Ottawa Scale (NOS). This scale was originally developed to evaluate quality of nonrandomized studies in order to support and strengthen the interpretation of meta-analytic results (Wells et al., 2000). The NOS is a nine-point scale that assigns points on the basis of the

Please cite this article as: Flores-Pajot, M.-C., et al., Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis. Environ. Res. (2016), http://dx.doi.org/10.1016/j.envres.2016.07.030

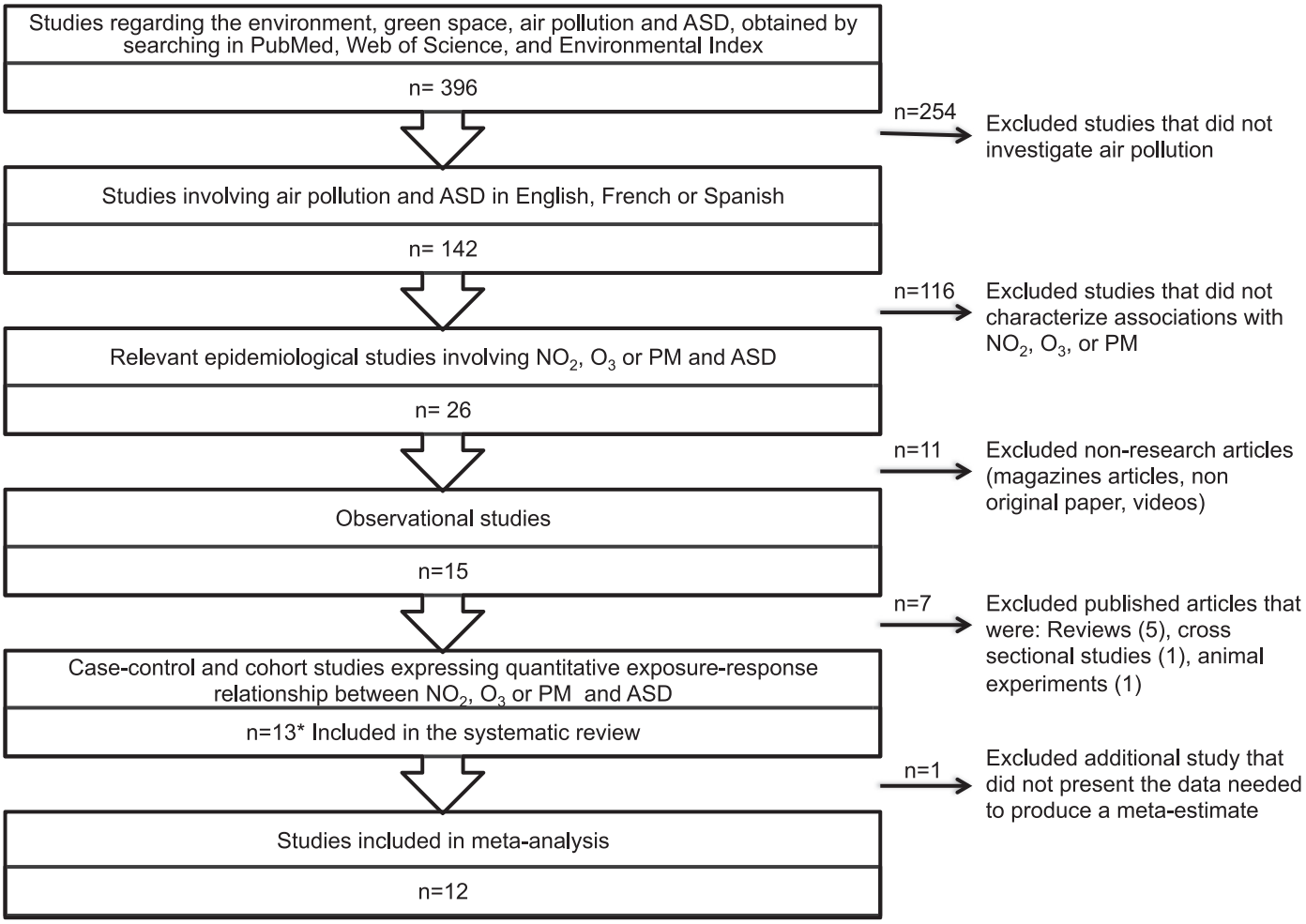

Fig. 1. Screening process to identify articles that formed basis of meta-analysis. *One identified study included six population-based cohorts.

process of selection of the cohorts or of the case and of the controls (0–4 points), of the comparability of the cohorts or of the case and of the controls (0–2 points), and of the identification of the exposure and of the outcomes of study participants (0–3 points). We restricted our meta-analysis to studies of low risk of bias with NOS $\geq$ 7. All the studies met the inclusion criteria and were identified as high-quality studies with overall NOS $\geq$ 7, (Tables 1,2).

2.2. Statistical analysis

Epidemiological studies that have investigated O_3 and NO_2, two gaseous pollutants, typically have measured exposure in parts per billion (ppb), parts per million (ppm) or $\mu g/m^3$, while particulate matter exposure is expressed in terms of $\mu g/m^3$. For comparability, the measures of association reported in the studies were converted to correspond to an increase in the incidence of autism according to a 10 ppb exposure in gaseous pollutants, using a conversion factors of 10 $\mu g/m^3 = 5.32$ ppb for NO_2 which is based on ambient pressure of 1 atm and a temperature of 25 °C (Vrijheid et al., 2011), and 10 $\mu g/m^3$ for particulate matter.

Since ASD is a relatively rare condition, within this paper we used the odds ratio extracted from several of these studies as an approximation of risk ratio disease. For the remainder of the papers, and in our tables, we describe the associations between air pollution and ASD using the risk ratio.

STATA software (v14.0) was used to conduct the meta-analysis of continuous data using inverse-variance weighting. Risk estimates that were adjusted for covariates from the previous studies were chosen for this review. A random effects model was used for the meta-analysis and include an I^2 value to estimate the percent of the total variance attributable to between studies inconsistency (DerSimonian and Laird, 1986). Forest and funnel plots were produced to provide a visual representation of the distribution of study specific effect estimates, to display the spread of risk estimates across studies, as well as to depict the pooled estimates of risk.

3. Results

3.1. Studies included

Three studies were identified that met the initial inclusion criteria through PubMed (Becerra et al., 2013; Kalkbrenner et al., 2015; Volk et al., 2013), one additional study through Web of Science (Gong et al., 2014), two through Environment Index (Raz et al., 2015; Talbott et al., 2015), one study through article references and discussion among co-authors (Jung et al., 2013), and one additional study was suggested through the initial peer-review process to be included due to it's relevance. This last one contains six population-based cohort within the same study and provides the data needed to produce meta-estimates using each individual cohort study (Guxens et al., 2015).

Table 1 summarizes the seven cohort studies that investigated NO_2, O_3 or PM and autism that were included in the meta-analysis, while Table 2 describes the characteristics of the six case-control

Table 1
Descriptions of cohort studies that have investigated associations between air pollution and autism spectrum disorders.

Study	Design	Location	Study period	Sample size	Time of exposure	Pollutant (s)	Effect estimates	Conclusion	Quality Assessment Score*
(Guxens et al., 2015)	Cohort	**CATSS:** Stockholm, Sweden	1992–2000	Total: 2437 ASD: 78 within borderline/clinical range, and 27 within clinical	Prenatal (whole pregnancy)	NO_2, NO_x, PM, traffic intensity, traffic load Source: TRAP and other sources such as space heating	Adjusted OR for children with autistic traits within the borderline/clinical range: 0.96 (95% CI: 0.80–1.16) per 10 μg/m^3 of NO_2; 1.01 (95% CI: 0.87–1.17) per 20 μg/m^3 of NO_x; 0.88 (95% CI: 0.60–1.27) per 10 μg/m^3 PM_{10} and 0.89 (95% CI: 0.58–1.35) per 5 μg/m^3 of $PM_{2.5}$	(/) Prenatal exposure to NO_2, NO_x and PM was not associated with autistic traits within the borderline/clinical range	S: 4 C: 2 O: 2 **T=8**
(Guxens et al., 2015)	Cohort	**Generation R**: Rotterdam, The Netherlands	2001–2005	Total: 3955 ASD: 336 within borderline/clinical range, and 143 within clinical	Prenatal (whole pregnancy)	NO_2, NO_x, PM, traffic intensity, traffic load	Adjusted OR for children with autistic traits within the borderline/clinical range: 1.03 (95% CI: 0.84–1.26) per 10 μg/m^3 of NO_2; 1.07 (95% CI: 0.89–1.28) per 20 μg/m^3 of NO_x; 1.07 (95% CI: 0.74–1.54) per 10 μg/m^3 PM_{10} and 0.38 (95% CI: 0.07–2.24) per 5 μg/m^3 of $PM_{2.5}$	(/) Prenatal exposure to NO_2, NO_x and PM was not associated with autistic traits within the borderline/clinical range	S: 4 C: 2 O: 2 **T=8**
(Guxens et al., 2015)	Cohort	**GASPII:** Rome, Italy	2003–2004	Total: 514 ASD: 63 within borderline/clinical range, and 15 within clinical	Prenatal (whole pregnancy)	NO_2, NO_x, PM, traffic intensity, traffic load	Adjusted OR for children with autistic traits within the borderline/clinical range: 0.98 (95% CI: 0.78–1.22) per 10 μg/m^3 of NO_2; 1.00 (95% CI: 0.85–1.17) per 20 μg/m^3 of NO_x; 0.72 (95% CI: 0.48–1.08) per 10 μg/m^3 PM_{10} and 0.35 (95% CI: 0.09–1.43) per 5 μg/m^3 of $PM_{2.5}$	(/) Prenatal exposure to NO_2, NO_x and PM was not associated with autistic traits within the borderline/clinical range	S: 4 C: 2 O: 2 **T=8**
(Guxens et al., 2015)	Cohort	**INMA:** Spain Gipuzkoa	2006–2008	Total: 357 ASD: 17 within borderline/clinical range, and 3 within clinical	Prenatal (whole pregnancy)	NO_2, NO_x	Adjusted OR for children with autistic traits within the borderline/clinical range: 0.94 (95% CI: 0.81–1.09) per 10 μg/m^3 of NO_2; 0.98 (95% CI: 0.88–1.09) per 20 μg/m^3 of NO_x	(/) Prenatal exposure to NO_2, NO_x and PM was not associated with autistic traits within the borderline/clinical range	S: 4 C: 2 O: 3 **T=9**
(Guxens et al., 2015)	Cohort	Sabadell	2004–2006	Total: 295 ASD: 10 within borderline/clinical range, and 2 within clinical	Prenatal (whole pregnancy)	NO_2, NO_x, PM, traffic load	Adjusted OR for children with autistic traits within the borderline/clinical range: 0.97 (95% CI: 0.81–1.16) per 10 μg/m^3 of NO_2; 1.00 (95% CI: 0.88–1.13) per 20 μg/m^3 of NO_x; 0.91 (95% CI: 0.66–1.25) per 10 μg/m^3 PM_{10} and 0.76 (95% CI: 0.38–1.52) per 5 μg/m^3 of $PM_{2.5}$	(/) Prenatal exposure to NO_2, NO_x and PM was not associated with autistic traits within the borderline/clinical range	S: 4 C: 2 O: 3 **T=9**
(Guxens et al., 2015)	Cohort	Valencia	2004–2005	Total: 521 ASD: 37 within borderline/clinical range, and 10 within clinical	Prenatal (whole pregnancy)	NO_2, NO_x, traffic load	Adjusted OR for children with autistic traits within the borderline/clinical range: 0.89 (95% CI: 0.76–1.05) per 10 μg/m^3 of NO_2; 0.96 (95% CI: 0.86–1.07) per 20 μg/m^3 of NO_x	(/) Prenatal exposure to NO_2, NO_x and PM was not associated with autistic traits within the borderline/clinical range	S: 4 C: 2 O: 3 **T=9**
(Jung et al., 2013)	Cohort	Taiwan	2000–2010	Total: 49,073 ASD: 342	Postnatal (up to 3years after birth)	O_3, CO, NO_2, SO_2, and PM_{10}. Source: air pollution, not specified	Based on air pollution concentration in the year before diagnosis: 59% risk increase of newly diagnostic ASD per 10 ppb increase in O_3 level (95% CI: 1.42–1.79), 37% risk increase per 10 ppb in CO (95% CI: 1.31–1.44), 340% risk increase per 10 ppb increase in NO_2 level (95% CI: 3.31–5.85), and 17% risk increase per 1 ppb in SO_2 level (95% CI: 1.09–1.27) was stable with different combinations of air pollutants in the multi-pollutant models.	(+) The risk of newly diagnostic ASD increased according to increasing O_3, CO, NO_2, and SO_2 levels in the year before diagnosis.	S: 4 C: 2 O: 3 **T=9**

95% CI, 95% Confidence Interval; OR, Odds Ratio; TRAP, Traffic-related air pollution; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, Ozone; PM_{10}, particle matter less than 10 μm; $PM_{2.5}$, particle matter less than 2.5 μm; CO, carbon monoxide; SO_2, sulphur dioxide.

* The Newcastle Ottawa quality assessment score (Wells et al., 2012) was used, S=Selection, C=Comparability, O=Outcome, T=total

studies. The tables report the main measure of association of individual exposures to $PM_{2.5}$, PM_{10}, NO_2 and O_3. The cohort study of Swedish twins by (Gong et al., 2014) met all the inclusion criteria but could not be included in our meta-analysis as it did not provide sufficient details on the concentration levels of the pollutants that were studied. The final dataset used in our meta-analysis included seven publications that represent 12 different studies that satisfied all inclusion criteria (Becerra et al., 2013; Guxens et al., 2015; Jung et al., 2013; Kalkbrenner et al., 2015; Raz et al., 2015; Talbott et al., 2015; Volk et al., 2013).

The studies that formed the basis of the meta-analysis employed different strategies to characterize exposure to air pollution. The most common techniques were land use regression (LUR) and dispersion modeling (DM). Volk et al. (2013) used two different exposure methods, line-source air quality dispersion and regional air quality data (fixed site monitors) within 50 km of residence. Exposure estimates from regional air quality data was used in the meta-analysis and forest plots because of the non-linear association with dispersion site monitors (Table 3).

When available, seasonalized estimates were used for this meta-analysis in order to take into account temporal variations in air pollution concentrations.

Each study considered the possible confounding influence for a number of risk factors. Most studies accounted for the following risk factors: age of child, sex, maternal age, maternal place of birth, maternal education, race/ethnicity, parental education, type of birth, parity, gestational weeks at birth, socio-economic status or income, and smoking in pregnancy. Table 3 summarizes the different methods used to characterize exposure among study participants, and provides a listing of the risk factors that were considered in each study.

3.2. Time of exposure

3.2.1. Prenatal period

3.2.1.1. Entire pregnancy. Eight different studies explored the associations between ASD and exposure to NO_2, O_3, $PM_{2.5}$ or PM_{10} during the prenatal period (Fig. 2). The summary risk meta-estimate of autism in relation to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.34 (95% CI: 0.83, 2.17). There was substantial heterogeneity in this risk estimate across the 8 studies ($p < 0.0001$). The summary risk estimates for a 10 $\mu g/m^3$ increase in PM_{10} and a 10 ppb increase in NO_2 were 1.03 (95% CI: 0.77, 1.37) and 1.05 (95% CI: 0.99, 1.11), respectively. There was a statistical significant association between exposure to ozone during pregnancy and autism with a 10 ppb increase producing a risk ratio of 1.05 (95% CI: 1.01, 1.10).

3.2.1.2. Trimester-specific. The forest plots generated from meta-analyses of the associations between autism and ambient pollution exposure in each of the three trimesters are found in Fig. 3A-C. Exposure to $PM_{2.5}$ was positively associated with autism in each of the three trimesters though the strength of the association was stronger in each successive trimester. Specifically, the risk ratios in relation to a 10 $\mu g/m^3$ increase across the three trimesters were 1.10, 1.21 and 1.33. In contrast, there was little difference in the strength of the association across the three trimesters for NO_2 as the risk ratios per 10 pbb increase ranged between 1.15 and 1.18.

3.2.2. Postnatal period

From the studies looking at exposure to NO_2, O_3, $PM_{2.5}$ or PM_{10} during the first year of postnatal period (Talbott et al., 2015; Volk et al., 2013), or 1–4 years before ASD diagnosis for Jung et al. (2013) paper (mean age of newly diagnostic ASD 6.26 ± 2.91), two pollutants were found to be strongly associated with higher risk of ASD. The pooled estimate of the relative risk in relation to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 2.43 (95%CI: 1.61, 3.68). The corresponding relative risk for a 10 ppb increase in NO_2 was 2.72 (95%CI: 1.04, 7.07) (Fig. 4). Exposures to PM_{10} (RR = 1.33; 95%CI: 0.86, 2.05) and O_3 (RR = 1.35; 95%CI: 0.94, 1.95) during the first year of birth did not show a significant association with ASD.

3.3. Quality assessment

Different funnel plots were created, looking at exposure to individual pollutants during a specific time, to explore the possibility of publication bias. In the absence of publication bias, it is presumed that the largest studies will be plotted in a funnel plot near the mean, and smaller studies will be spread evenly on both sides of the mean, creating a roughly funnel-shaped distribution (Egger et al., 1997). The funnel plots of studies looking at the exposure to $PM_{2.5}$ during the first trimester of pregnancy show a visually asymmetrical distribution, supporting the possibility that there has been publication bias (Fig. 5). These results are similar to the funnel plots of the eight studies looking at exposure to $PM_{2.5}$ during the entire pregnancy (Fig. 6), yet this later funnel plot has a relatively symmetric distribution at the top of the funnel, and only two smaller null studies at the bottom left, but we cannot rule out publication bias. The capacity to detect bias with funnel plots is limited due to the very small number of studies and the capacity to identify symmetry, therefore the results should be treated with caution.

4. Discussion

This paper provides a systematic review and meta-analysis that summarizes findings from epidemiological studies on the association between ambient air pollution and ASD. Overall, the associations were largely positive though many of the summary measures were not statistically significant which is largely influenced by the relatively small number of studies. The strength of the associations observed between exposure to $PM_{2.5}$ during the prenatal period and autism is similar to that found for health endpoints such as cardiovascular disease and diabetes, for which air pollution is a more established risk factor. Our meta-estimates of risk were even stronger for exposure to air pollution during the last trimester of pregnancy and after birth, though these findings are tenuous given the very small number of studies that investigated these exposures during this time window. Nonetheless, these findings are consistent with the observations that it is during this time interval that the human brain undergoes the most critical development and is most vulnerable to environmental factors during this period (Rice and Barone Jr, 2000).

We also observed positive associations between O_3 exposures during the prenatal period and ASD. Animal studies have suggested that specific O_3 exposure during gestation may subtly cause adverse neurobehavioral effects after birth (Petruzzi et al., 1995; Sorace et al., 2001). It is important to note that ozone is highly variable across the seasons particularly in regions with extreme weather changes (King and Vukovich, 1982). Hence, the characterization of the association between prenatal exposure to O_3 and autism in these regions should account for the month of birth. The studies by Becerra et al. (2013) and Volk et al. (2013) were both conducted in California which does experience higher ozone levels during the summer, however differences in concentration levels across seasons are not as large as in more northern cities.

Overall, there was little difference in the strength of the association between $PM_{2.5}$ and autism between exposures over the entire pregnancy (RR = 1.34), and those exposures during the third trimester (RR = 1.33). The risk was slightly attenuated for the early part of the pregnancy. We found a similar trend between autism risk and increasing gestational age with PM_{10}. There are two

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Table 2
Description of case-control studies that have investigated associations between air-pollution and autism spectrum disorders.

Study	Location	Study period	Sample size	Time of exposure	Pollutant	Effect estimates	Conclusion	Quality Assessment Score*
(Kalkbrenner et al., 2015)	Nested case-control in North Carolina and California US.	1994–2000	979 children with autism (645 in N. C, and 334 in S. F) and 14,666 controls	Prenatal (1st, 2nd, 3rd trimester) and postnatal (1st year after birth)	PM_{10} Source: Traffic, especially diesel traffic, as well as from wood smoke and power plants	Adjusted OR were, for the first trimester, 0.86 (95% CI: 0.74–0.99), second trimester, 0.97 (95%CI: 0.83–1.15), and third trimester, 1.36 (95%CI: 1.13–1.63); and, after simultaneously including first- and third-trimester concentrations to account for the inverse correlation, were: first trimester, 1.01 (95% CI: 0.81–1.27) and third trimester, 1.38 (95%CI: 1.03–1.84).	(+) Study shows a relation between TRAP and autism, and adds similar findings in an eastern US state, with results consistent with increased susceptibility in the third-trimester.	S: 3 C: 2 O: 2 **T=7**
(Raz et al., 2015)	US.	1990–2002	NHS II participants' children born 1990–2002 with ASD (n=245), and children without ASD (n=1522).	Prenatal (9 months before pregnancy, and entire pregnancy) and postnatal (9 months after birth).	PM_{10} and $PM_{2.5}$ Sources: N/A	Exposure during pregnancy was associated with increased odds of ASD, with an AOR of 1.57 (95% CI: 1.22–2.03) per IQR in PM2.5 (4.42 μg/m^3) among women with the same address before and after pregnancy. Association with the 9 months of pregnancy remained (OR=1.63; 95% CI: 1.08–2.47). The association between ASD and $PM_{2.5}$ was stronger for exposure during the third trimester (OR=1.42 per IQR increase in $PM_{2.5}$; 95% CI: 1.09–1.86) than during the first two trimesters (ORs=1.06 and 1.00) when mutually adjusted. There was little association between $PM_{10-2.5}$ and ASD.	(+) Higher maternal exposure to $PM_{2.5}$ during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.	S: 4 C: 2 E: 2 **T: 8**
(Talbott et al., 2015)	Six counties in Southwestern Pennsylvania.	2004–2011	217 cases and 226 controls.	Prenatal (3 months before pregnancy, 1st, 2nd, 3rd trimester) and postnatal (1st and 2nd year after birth) 3months before pregnancy, trimesters 1-3, years 1 and 2 of life.	$PM_{2.5}$ Source: Air pollution, not specified	Adjusted odds ratios (OR) were elevated for specific pregnancy and postnatal intervals (pre-pregnancy, pregnancy, and year one), and postnatal year two was significant, (OR = 1.45, 95% CI: 1.01–2.08). The effect of cumulative pregnancy periods; noting that starting with pre-pregnancy through pregnancy, the adjusted odds ratios are in the 1.46–1.51 range and significant for pre-pregnancy through year 2 (OR = 1.51, 95% CI: 1.01–2.26).	(+) Data indicate that both prenatal and postnatal exposures to $PM_{2.5}$ are associated with increased risk of ASD.	S: 4 C: 2 E: 3 **T=9**
(Gong et al., 2014)	Stockholm, Sweden	1992–2000	3426 twins 109 with ASD (109 ASD_{low}, 33 ASD_{high}, 47 ASD_{DSM-IV})	Prenatal (whole pregnancy) and postnatal (1st, 2nd, and 9th year after birth)	Residence concentrations of PM_{10}, and NOx from road traffic. Annual average levels. Source: road-traffic	5–95% difference in exposure to NOx during pregnancy was associated with ORs of 0.92 (95% CI: 0.44–1.96). Exposure to PM_{10} during pregnancy was related to ORs of 1.01 (95% CI: 0.52–1.96) for ASD.	(/) The data does not provide support for an association between pre- or postnatal exposure to air pollution from road traffic and neurodevelopmental disorders in children.	S: 3 C: 2 O: 4 **T=9**
(Becerra et al.,	Los Angeles,	1998–	7603 cases, 75,782	Prenatal (whole pregnancy)	Daily averages of gaseous	Per IQR, 12–15% relative increase	(+)	S: 4

2013)	California, US.	2009	controls		pollutants (CO, NO_2, NO, O_3) and 24 h measurements of PM_{10} and $PM_{2.5}$ Source: local TRAP	in odds of ASD for O_3 1.12 (95% CI: 1.06, 1.19) per 11.54-ppb increase, and $PM_{2.5}$ 1.15(95% CI: 1.06, 1.24) per 4.68-μg/m^3 increase.	Associations between ASD and prenatal air pollution exposure mostly related to traffic sources.	C: 2 E: 2 **T=8**
(Volk et al., 2013)	California, US.	1997–2008	279 cases, 245 controls	Prenatal and postnatal (1st, 2nd, 3rd trimester) and the first year of life.	Traffic related air pollution: O_3, NO_2, $PM_{2.5}$ and PM_{10}. Source: TRAP	Children with ASD were more likely to live at residences that had the highest quartile of exposure to TRAP, during gestation AOR 1.98 (95% CI: 1.20–3.31) and during the first year of life AOR 3.10 (95% CI: 1.76–5.57), compared with controls. Regional exposure measures of NO_2, $PM_{2.5}$ and PM_{10} were also associated with ASD during gestation: NO_2 AOR 1.81 (95% CI: 1.37–3.09); $PM_{2.5}$: AOR, 2.08 (95% CI: 1.93–2.25); exposure to PM_{10}: AOR, 2.17 (95% CI: 1.49–3.16) and during the first year of life exposure to NO_2 AOR, 2.06 (95% CI, 1.37–3.09); $PM_{2.5}$: AOR, 2.12 (95% CI: 1.45–3.10); PM_{10} AOR 2.14 (95% CI: 1.46–3.12).	(+) Exposure to TRAP, NO_2, $PM_{2.5}$, and PM_{10} during pregnancy and during the first year of life was associated with ASD.	S: 4 C: 2 E: 2 **T=8**

95% CI, 95% Confidence Interval; AOR, Adjusted Odds Ratio; OR, Odds Ratio; TRAP, Traffic-related air pollution; NO_2, nitrogen dioxide; NO, nitrogen oxide; O_3, Ozone; PM_{10}, particle matter less than 10 μm; $PM_{2.5}$, particle matter less than 2.5 μm; CO, carbon monoxide.

* The Newcastle Ottawa quality assessment score (Wells et al., 2012) was used, S=Selection, C=Comparability, E=Exposure, T=total.

Table 3
Description of the exposure assessment methods and of the risk factors accounted for each study.

Study	Inclusion criteria	Case definition	Range of pollutant levels	Exposure assessment method	Variants accounted for
(Guxens et al., 2015) **CATSS, Swedish cohort**	Children with air pollution, autistic traits, and potential confounders variables available.	Autistic Traits ASD module (A-TAC)	Median levels:NO_2: 17.9 μg/m^3 for the Swedish cohort and 42.2 μg/m^3 for the Italian cohort. $PM_{2.5}$: 8.4 μg/m^3 for the Swedish cohort and 22.4 μg/m^3 for the Italian cohort.	Land-use regression models	Maternal education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity. Child sex, season at birth, urbanicity at birth address, age at the autistic traits assessment, and evaluator of the autistic traits.
(Guxens et al., 2015) **Generation R, Dutch cohort**	Children with air pollution, autistic traits, and potential confounders variables available.	Autistic Traits PDP subscale CBCL½–5 Adapted 18-item version of SRS		Land-use regression models	Maternal education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity. Child sex, season at birth, urbanicity at birth address, age at the autistic traits assessment, and evaluator of the autistic traits.
(Guxens et al., 2015) **GASPII, Italian cohort**	Children with air pollution, autistic traits, and potential confounders variables available.	Autistic Traits PDP subscale CBCL½–5		Land-use regression models	Maternal education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity. Child sex, season at birth, urbanicity at birth address, age at the autistic traits assessment, and evaluator of the autistic traits.
(Guxens et al., 2015) **INMA, Spanish cohort**	Children with air pollution, autistic traits, and potential confounders variables available.	Autistic Traits CAST		Land-use regression models	Maternal education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity. Child sex, season at birth, urbanicity at birth address, age at the autistic traits assessment, and evaluator of the autistic traits.
(Kalkbrenner et al., 2015)	Random sample of singleton children without evidence of adoption or infant death, with maternal residence at birth in areas subsequently under autism surveillance in North Carolina and California born in 1994, 1996, 1998, 2000.	DSM-IV-R.	The average levels of PM_{10} ranged from 22.9 μg/m^3 (California 1996) to 25.0 μg/m^3 (North Carolina 1998)	Bayesian Maximum entropy geostatistical method.	Maternal education, age, race/ethnicity, neighborhood-level urbanization, median household income, year of birth, state, and nonparametric term for week of birth to account for seasonal trends.
(Raz et al., 2015)	Offspring born 1990 through 2002 of participants in the NHS II, a prospective cohort of 116,430 U. S. female nurses 25–43 years of age when recruited in 1989.	ADI-R, SRS and maternal report	The average ($\pm$SD) levels during pregnancy: $PM_{2.5}$: 14.6 $\pm$ 3.3 μg/m^3 PM_{10}: 9.9 $\pm$ 4.9 μg/m^3,	Spatiotemporal model for the continental United States and linked to residential addresses.	Mutually adjusted for other exposure periods (whole pregnancy, 9 months before conception, 9 months after birth), and adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, census income.
(Talbott et al., 2015)	Children who were not adopted, with English speaking parents, born between January 1st, 2005 and December 31st, 2009 in Allegheny, Armstrong, Beaver, Butler, Washington, or Westmoreland County and were currently residing in the six-county area.	SCQ, and ADOS	The average ($\pm$SD) levels during pregnancy: $PM_{2.5}$: 14.6 $\pm$ 1.5 μg/m^3	Merged-seasons Land-use regression model	Maternal age, education, race, and smoking status.
(Gong et al., 2014)	Twins aged 9–12 born in Stockholm with valid data on neurodevelopmental assessment and living address or air pollution data during pregnancy, 1st and 9th year of life.	Autism-Tics (based on the DSM-IV)	The yearly average levels of NOx from local traffic dropped from 12.7 μg/m^3 to 5.4 μg/m^3 during the observation period. The yearly average levels of PM_{10} were relatively constant: 3.3–4.2 μg/m^3.	Dispersion model	Maternal age at birth, smoking status, marital status, seasonal variation, parental education, gender, parity, gestational age, birth weight, SES.
(Becerra et al., 2013)	Children born in 1995–2006 to mothers who	DSMIVR	The average ($\pm$SD) levels of the pollutant	Land-use regression	Maternal and perinatal characteristics

	resided in Los Angeles County at the time of giving birth.		during pregnancy were: NO_2 30.8 ± 7.6 ppb NO 39.2 ± 20.5 ppb O_3 36.8 ± 8.9 ppb PM_{10} 36.3 ± 6.1 μg/m^3 $PM_{2.5}$ 19.6 ± 3.5 μg/m^3		including indicators of SES. Maternal age, place of birth, race/ethnicity, education; type of birth, parity; insurance type as an indicator of SES; and gestational age at birth.
(Jung et al., 2013)	Children age less than 3 at the baseline in Jan 1st, 2000 followed though December 31st, 2010, with no previous ASD diagnosis with address that has air pollution data.	Children with at least two-consensus diagnosis of autistic disorder, based on the ICD-9-CM code 299.0 criteria of that year.	The median levels: O_3: 106.43 ppb NO_2: 18.92 ppb PM_{10}: 57.96 mg/m^3 SO_2: 3.90 ppb	Inverse distance weighting method	Age, anxiety, gender, intellectual disabilities, obsessive-compulsive disorder, phobia, preterm, and SES.
(Volk et al., 2013)	Children from the CHARGE study. Controls were children from the general population who received a Social Communication Questionnaire score of less than 15 and who also showed no evidence of other types of delay.	Children with a diagnosis of full syndrome autism from both the ADOS and the ADI-R.	The average (± SD) levels during pregnancy: O_3 36 ± 8.1 ppb NO_2 17 ± 2 ppb $PM_{2.5}$ 14 ± 7.1 μg/m^3 PM_{10} 26 ± 7.7 μg/m^3	Two exposure methods were used: 1. Line-source air quality dispersion model 2. Regional air quality data (fixed site monitors) within 50km of residence	Sex, ethnicity, maximum education of parents, maternal age, and prenatal smoking.

ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; A-TAC, Autism-Tics, attention deficit and hyperactivity disorders, and other comorbidities inventory; CBCL, child behavior checklist; CAST, childhood autism spectrum test; DSM-IV-R, Diagnostic and Statistical Manual, Fourth Edition–Revised; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PDP, pervasive developmental problems; SCQ, Social Communication Questionnaire; SD, Standard Deviation; SRS, Social Responsiveness Scale

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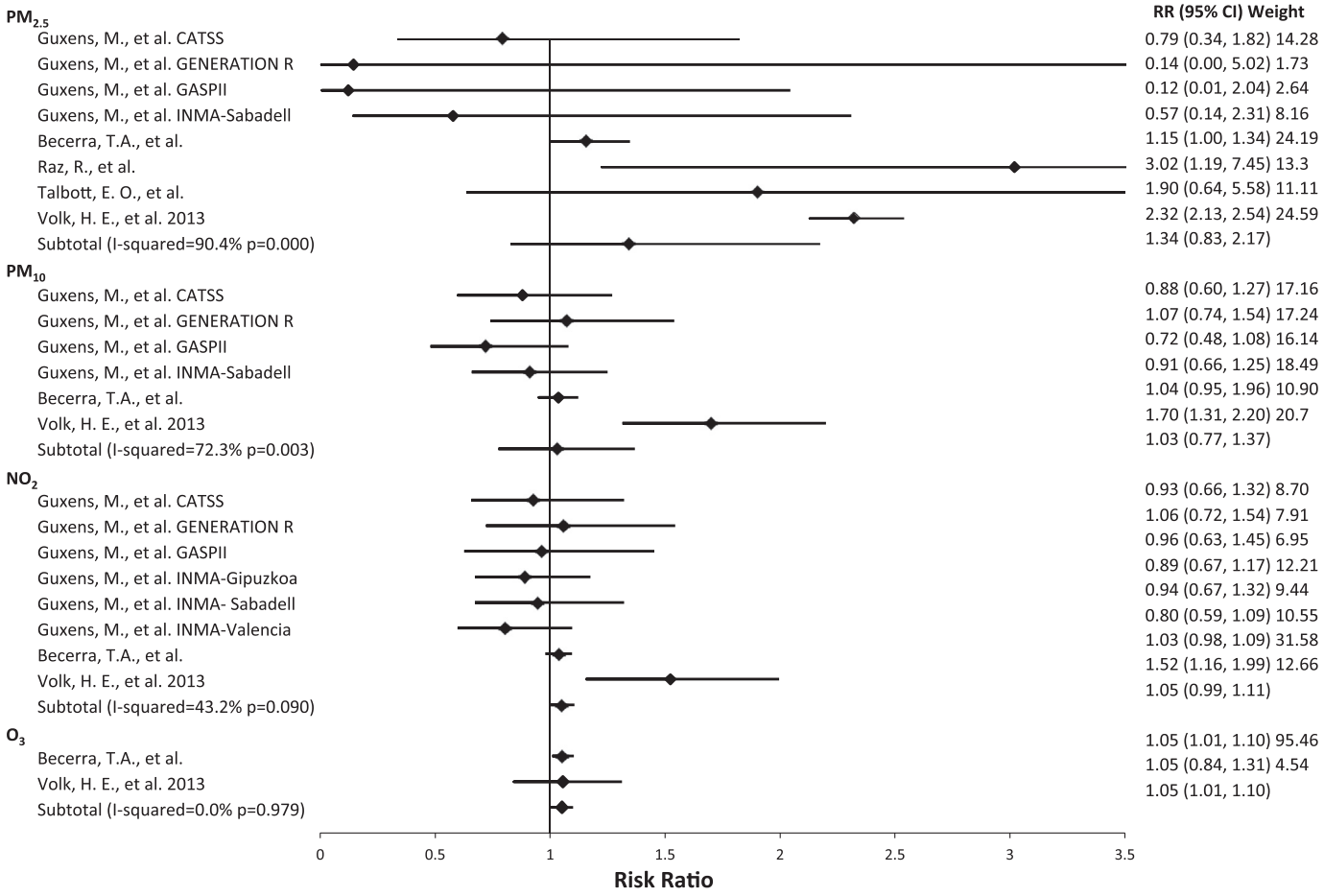

Fig. 2. Forest plot of study-specific estimates of risk ratio (RR) of autism associated with a 10 ppb increase in exposure during the entire pregnancy to NO_2 and O_3, and 10 μg/m^3 for $PM_{2.5}$ and PM_{10}. The meta-estimates and weights are estimated form random effects meta-analyses.

possible reasons that could explain stronger associations between air pollution and autism with exposure occurring in the last trimester. The first explanation relates to the theory that this is a more vulnerable period. As described by Rice and Barone Jr (2000) the later trimester of pregnancy represents a period where synapse formation, and neurotransmitter receptors formation are under development. This in turn may impact neuronal connectivity thereby perturbing signaling pathways which some have been implicated in the development of autism (Levitt and Campbell, 2009; Stamou et al., 2013). Alternatively, previous work suggests that healthy brain development is dependent on the functioning of the immune system. As it is well recognized that air pollution impacts a number of immune functions such as oxidative stress, this represents another pathway by which exposure to fine particulate matter late in pregnancy may increase the risk of autism. Previous epidemiological studies have suggested stronger association between $PM_{2.5}$ and some adverse birth outcomes including low birth weight with exposures occurring during the third trimester (Basu et al., 2014; Bell et al., 2010).

Apart from the third trimester representing a more biologically relevant period of exposure, stronger associations may be evident as a result of exposure misclassification. Many of the studies included in this meta-analysis that looked at differences in risk by trimester, relied on the place of residence at the time of birth (Becerra et al., 2013; Kalkbrenner et al., 2015). However, the study by Volk et al. (2013) has the desired feature of capturing changes in place of residence beginning three months before conception. As such, it was better positioned to evaluate differences in risk across trimesters. Volk et al. employed two distinct exposure strategies, one that relied on a dispersion model, the other on spatially interpolated fixed site monitoring. They found stronger associations between exposures in the third trimester and autism when compared to other periods of exposure when the former method was used, but not with the latter. Given the lack of consistency, and the few studies that have examined differences in risk across trimester, more studies that fully account for residential mobility are needed to better understand trimester-specific risks.

It is important to recognize that the approaches assigning air pollution exposure to study participants use area-level measures to infer individual-level exposure. Land-use regression methods and dispersion models, which are the most common measures of exposures used in the articles, have been proven successful for monitoring annual mean concentration of air pollutants over a specific study area, however small scale spatial variation still remains (Hoek et al., 2008). It is important to note that some pollutants, such as NO_2, exhibit greater spatial resolution within urban areas when compared to $PM_{2.5}$, which is influenced to a greater extent by long-range transportation of pollution. Approaches to exposure modeling that are able to partition local versus distal sources of pollution are ultimately needed to better understand how to mitigate air pollution concentrations so as to reduce human health risks for multiple conditions, including autism.

Interestingly, a recent commentary on whether the association between air pollution and autism is casual or explained by confounding, contends that examining ambient air pollution concentration as a proxy for personal exposure helps avoid exposure misclassification biases that could stem from differences in

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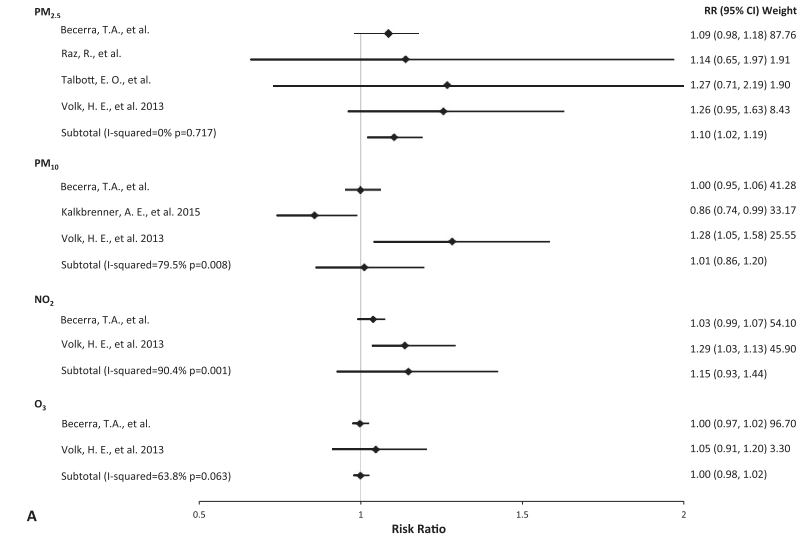

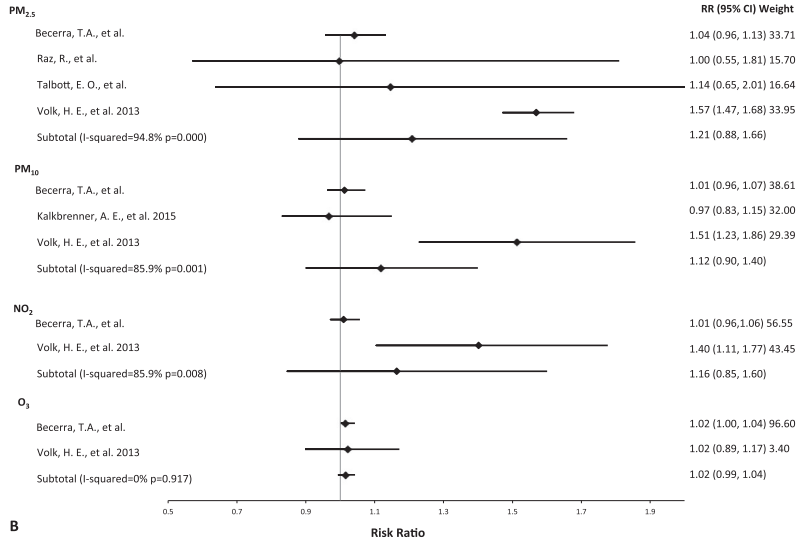

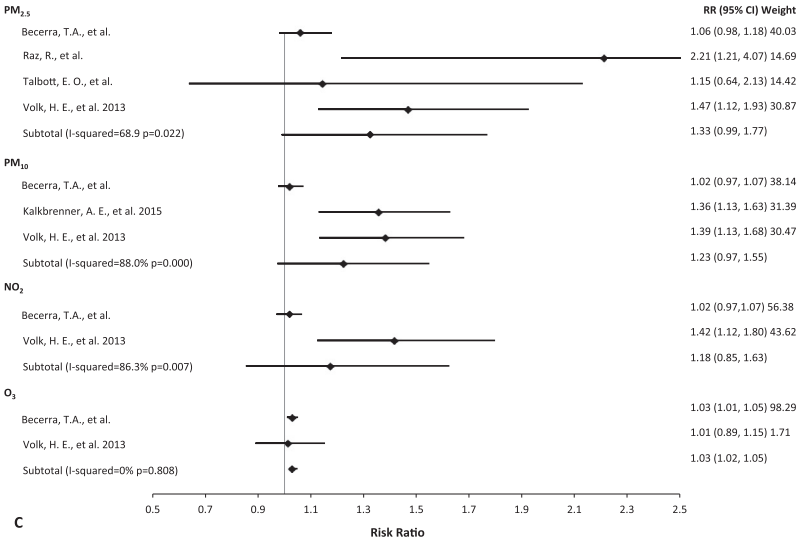

Fig. 3. A. Forest plot of study-specific estimates of risk ratio (RR) of autism associated with a 10 ppb increase in exposure during the first trimester of pregnancy to NO_2 and O_3, and 10 $\mu g/m^3$ for $PM_{2.5}$ and PM_{10}. The meta-estimates and weights are estimated form random effects meta-analyses. **B.** Forest plot of study-specific estimates of risk ratio (RR) of autism associated with a 10 ppb increase in exposure during the second trimester of pregnancy to NO_2 and O_3, and 10 $\mu g/m^3$ for $PM_{2.5}$ and PM_{10}. The meta-estimates and weights are estimated form random effects meta-analyses. **C.** Forest plot of study-specific estimates of risk ratio (RR) of autism associated with a 10 ppb increase in exposure during the third trimester of pregnancy to NO_2 and O_3, and 10 $\mu g/m^3$ for $PM_{2.5}$ and PM_{10}. The meta-estimates and weights are estimated form random effects meta-analyses.

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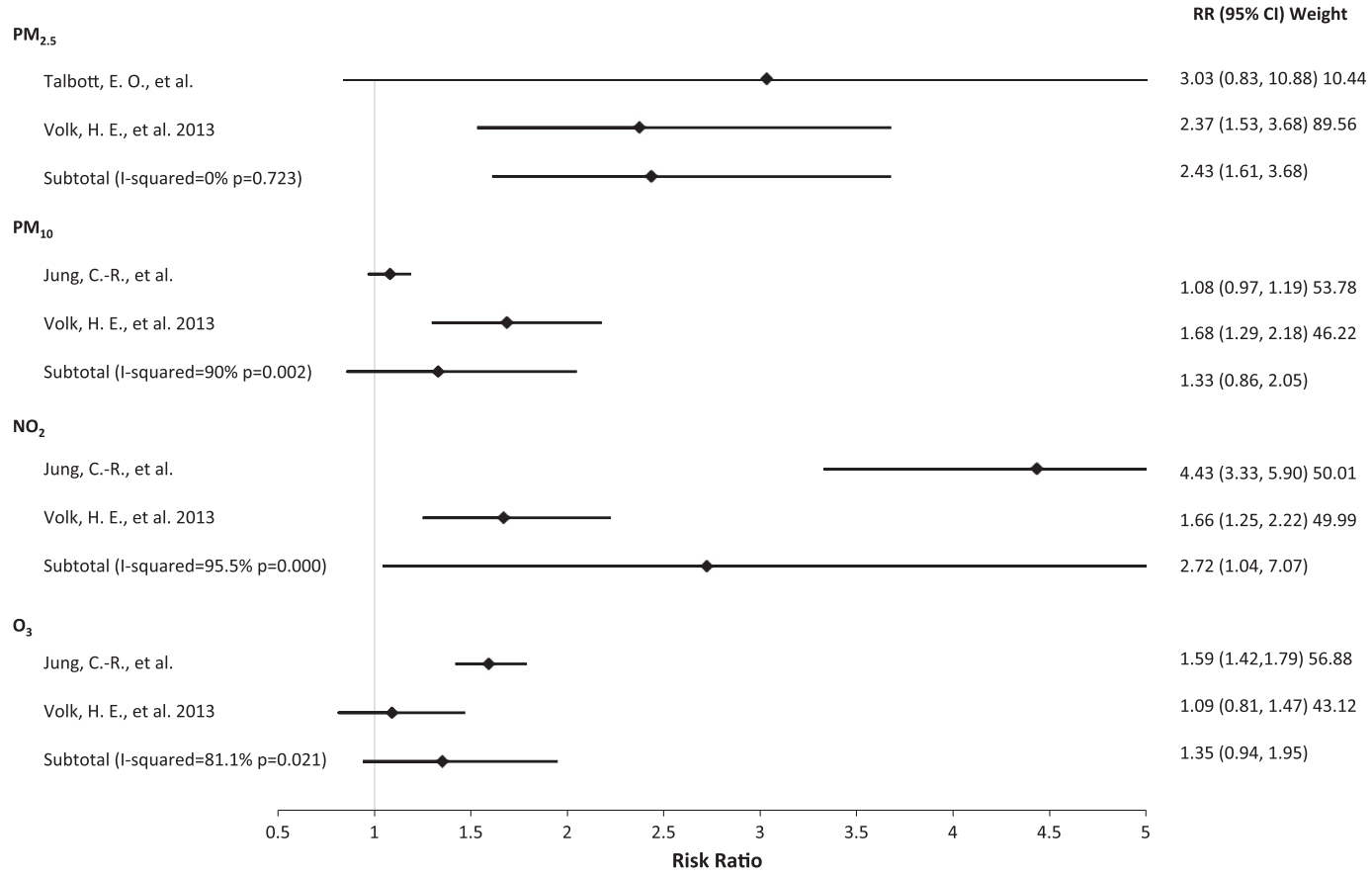

Fig. 4. Forest plot of study-specific estimates of risk ratio (RR) of autism associated with a 10 ppb increase in exposure after birth to NO_2 and O_3, and 10 μg/m^3 for $PM_{2.5}$ and PM_{10}. The meta-estimates and weights are estimated form random effects meta-analyses.

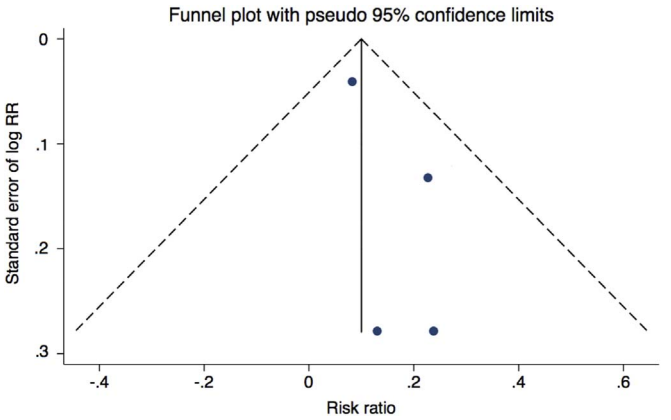

Fig. 5. Funnel plot of study-specific estimates of the risk ratio of ASD associated with a 10 μg/m^3 increase in exposure to $PM_{2.5}$ during the first trimester of pregnancy. The meta-estimate represented by the vertical solid line of the funnel plot is based on a random-effect meta analysis.

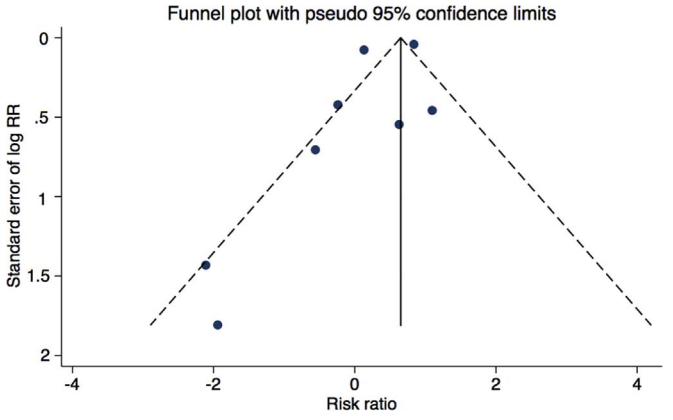

Fig. 6. Funnel plot of study-specific estimates of the risk ratio of ASD associated with a 10 μg/m^3 increase in exposure to $PM_{2.5}$ during the entire pregnancy. The meta-estimate represented by the vertical solid line of the funnel plot is based on a random-effect meta analysis.

personal behavior (Weisskopf et al., 2015). As highlighted by Weisskopf et al., confounding may be minimized because while changes in individual behaviors over the course of a pregnancy would impact personal exposures, there would be no such impact for ambient exposures that are based on larger areas. Nonetheless, it is important to recognize that some pollutants, such as NO_2, are more spatially variable within urban areas than others. Ultimately, if the association between air pollution and autism is causal, models that are able to differentiate between local and distal sources of air pollution are needed to develop strategies that can mitigate health risks. To date, few studies have employed different exposure measurement strategies that can shed light on this issue. One exception is the study by Volk et al. (2013) who found that regionally based measures of air pollution produced somewhat different measures of association when compared to those generated from the application of a dispersion model. Namely the strength of the association was stronger, and non-linear for the dispersion model when compared to the regional based measures of air pollution.

Our forest plots revealed substantial heterogeneity in the risk

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estimates. While this is undoubtedly due to differences in study design, characteristics of participants, and possible biases unique to each study, differences in the composition of the air pollution likely contributed to variation in risk. The studies included in the meta-analyses were undertaken in multiple countries with distinct meteorological features, and pollution mixtures. In terms of the specific sources of pollutions, three identified that the sources of the pollutants were specifically related to traffic (Becerra et al., 2013; Kalkbrenner et al., 2015; Volk et al., 2013). Some of the other studies highlighted contributions from space heating (Guxens et al., 2015), wood smoke and power plants (Kalkbrenner et al., 2015).

Unlike studies of air pollution and several other chronic diseases, ascertainment of ASD is more challenging, as the diagnosis of autisms is more complicated. The case definition on all studies was based on validated instruments, meeting diagnostic criteria and/or parental reports; yet two studies used screening tests for a boarder range of behavioral disorders (CBCL and A-TAC). All tests are valid tools for assessment of children's behavior in epidemiological studies (Constantino and Gruber, 2007; Larson et al., 2010; Lecavalier et al., 2009; Lord et al., 2012; Rutter et al., 2005; Sikora et al., 2008; Williams et al., 2005). Diagnostic issues could be problematic if bias is implied, for example if people in urban areas are more likely to use specialists that correctly diagnose autism compared to people who live in rural areas, this would contribute to a positive association between air pollution and ASD. However, some of the studies used different cut points for identifying autism (ex: clinical range of autism versus autistic traits in Guxens et al. (2015)) and the results did not substantially change. As highlighted by Weisskopf et al. (2015), differential ascertainment of autism by socio-demographic status may also introduce some bias, as those of lower socio-economic status (SES) may be more prone to live in areas of higher air pollution. Most studies in the meta-analysis included some adjustment for SES. Others performed a stratified analysis to evaluate whether SES modified associations between air pollution concentrations and autism. Of note was the finding by Becerra et al. (2013) who discovered that LUR-based associations were strongest for children of mothers with less than a high school education.

Concentration of many air pollutants, including diesel exhaust and PM, are increased near freeway and other major roads; these pollutants have been shown to affect the brain function and activity in toxicological studies (Hougaard et al., 2008; Ntziachristos et al., 2007; Perera et al., 2006). To our knowledge, a study of 304 autism cases and 259 typically developing controls based in California is the only one to date to investigate the association between childhood autism and proximity to a freeway. Volk et al. (2011) found living within 309 m from freeway during pregnancy to be positively associated with ASD. A British cross-sectional study of 2713 individuals compared the prevalence of mental illness, ASD, and behavioral disorder in people living in urban areas with those living in rural areas, and exposure to pollution and noise was one of the suggested hypotheses to explain a relationship between mental ill health and urbanization. This study found that ASD was more common in people living in rural areas. A proposed explanation for this is that there has been a development of higher numbers of specialist residential placements in the county to accommodate people with ASD (Kiani et al., 2013). The relationship between urbanization and mental health is an interesting topic worth exploring. More studies should use distance to roadways, volume of vehicles or urbanization as markers of exposure to traffic, in order to provide a better understanding of the association of ASD with traffic-related air pollutants.

The studies included in this systematic review and meta-analysis were conducted in diverse settings that capture varied exposure to air pollution. They also differ with respect to the methods used to characterize pollution levels, and the ability to account for the influence of other possible risk factors. Despite the relatively small number of studies conducted to date, the findings from these studies provide compelling support for the hypothesis that prenatal exposure to $PM_{2.5}$ and O_3 and postnatal exposure to $PM_{2.5}$ and NO_2 increases the risk of ASD.

Some recommendations for future studies to improve our understanding on the relationship between air pollution and ASD include: (i) increasing study size to increase power to detect smaller associations, (ii) tracking residential mobility during pregnancy to account for changes in exposure during this critical time-period, (iii) incorporating methods to characterize air pollution at both a local, and a regional level.

Funding

This work was supported by the Public Health Agency of Canada.

Annexure

Search criteria

(Traffic OR “Air Pollut*” OR “particulate matter” OR PM2.5 OR PM10 OR Nitrogen dioxide [OR NO2][Title/Abstract] OR NO [Title/Abstract] OR Nitrogen oxide [Title/Abstract] OR smog OR soot OR “Environmental Exposure”[Mesh].

AND ((“Child”[Mesh]) OR child*[Title/Abstract])).

AND ((((“Autistic Disorder”[Mesh]) OR autistic[Title/Abstract]) OR autism[Title/Abstract]) OR (((“Kanner Syndrome”[Title/Abstract]) OR “Kanner’s Syndrome”[Title/Abstract]) OR “Kanners Syndrome”[Title/Abstract]))) AND (“cohort studies”[mesh] OR “case-control studies”[mesh] OR “comparative study”[pt] OR “risk factors”[mesh] OR “cohort”[tw] OR “compared”[tw] OR “groups”[tw] OR “case control”[tw] OR “multivariate”[tw].

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Please cite this article as: Flores-Pajot, M.-C., et al., Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis. Environ. Res. (2016), http://dx.doi.org/10.1016/j.envres.2016.07.030