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Review article

Evidence of susceptibility to autism risks associated with early life ambient air pollution: A systematic review

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ABSTRACT

Background: Many studies have found associations between early life air pollution exposure and subsequent onset of autism spectrum disorder (ASD). However, characteristics that affect susceptibility remain unclear.
Objective: This systematic review examined epidemiologic studies on the modifying roles of social, child, genetic and maternal characteristics in associations between prenatal and early postnatal air pollution exposure and ASD.
Methods: A systematic literature search in PubMed and Embase was conducted. Studies that examined modifiers of the association between air pollution and ASD were included.
Results: A total of 19 publications examined modifiers of the associations between early life air pollution exposures and ASD. In general, estimates of effects on risk of ASD in boys were larger than in girls (based on 11 studies). Results from studies of effects of family education (2 studies) and neighborhood deprivation (2 studies) on air pollution-ASD associations were inconsistent. Limited data (1 study) suggest pregnant women with insufficient folic acid intake might be more susceptible to ambient particulate matter less than 2.5 μm ($PM_{2.5}$) and 10 μm (PM_{10}) in aerodynamic diameter, and to nitrogen dioxide (NO_2). Children of mothers with gestational diabetes had increased risk of ozone-associated ASD (1 study). Two genetic studies reported that copy number variations may amplify the effect of ozone, and MET rs1858830 CC genotype may augment effects of PM and near-roadway pollutants on ASD.
Conclusions: Child's sex, maternal nutrition or diabetes, socioeconomic factors, and child risk genotypes were reported to modify the effect of early-life air pollutants on ASD risk in the epidemiologic literature. However, the sparsity of studies on comparable modifying hypotheses precludes conclusive findings. Further research is needed to identify susceptible populations and potential targets for preventive intervention.

1. Introduction

Autism spectrum disorder (ASD) is a complex developmental disorder characterized by impairments in social interactions and communication and the presence of restricted, repetitive, and stereotyped patterns of behaviors (American Psychiatric Association, 2000). It is associated with lifetime social and emotional hardship for children (Kuhlthau et al., 2010) and their families (Rao and Beidel, 2009), as well as economic burdens on families and society (Buescher et al., 2014). The estimated prevalence of ASD in the United States increased from 0.66% in 2002 to 1.85% in 2016 (Centers for Disease Control and Prevention, 2007; Maenner et al., 2020), which is only partly explained by more

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widespread screening of children and an expanded definition of ASD since 2008 to include more mild cases (Blumberg et al., 2013; Hertz--Picciotto and Delwiche, 2009). ASD can be diagnosed starting around age 2, but subtle social and communication impairment may be present earlier (Bacon et al., 2018; Charman and Baird, 2002), suggesting determinants occur in utero or in early life. Although studies have shown a substantial heritability in ASD (Tchaconas and Adesman, 2013; Tick et al., 2016), environmental factors are likely to play an important role in causation.

In the last decade, many studies have examined associations between ASD and early-life exposure to ambient air pollutants [e.g. particulate matter <2.5 μm ($PM_{2.5}$) and <10 μm (PM_{10}) in aerodynamic diameter, nitrogen dioxide (NO_2), ozone (O_3), carbon monoxide (CO)], the near-roadway air pollution mixture, and, in the U.S., air toxics derived from the National-Scale Air Toxics Assessment. However, results were not uniformly consistent. For example, several studies in the United States showed that prenatal exposure to PM2.5 was associated with increased risk of ASD (Becerra et al., 2013; Jo et al., 2019b; Kalkbrenner et al., 2015; Kaufman et al., 2019; McGuinn et al., 2020; Raz et al., 2015; Talbott et al., 2015a; Volk et al., 2013). In contrast, studies conducted in Europe have reported no association (Gong et al., 2014, 2017; Guxens et al., 2016). Some studies of air toxics have found metals (mercury, cadmium, nickel, lead, and others), aromatic solvents, and chlorinated solvents to be associated with a higher risk of autism (Blanchard et al., 2011; Kalkbrenner et al., 2018; Lewandowski et al., 2009; Roberts et al., 2013; Talbott et al., 2015b; von Ehrenstein et al., 2014; Windham et al., 2006), but these findings also have not been consistent.

Three high-quality systematic reviews and meta-analyses described these inconsistencies and proposed some plausible explanations for differences between studies, including different levels of air pollutant exposures, diverse ASD ascertainment methods, and different ASD phenotypes (Chun et al., 2020; Flores-Pajot et al., 2016; Lam et al., 2016). However, none focused on possible differences in effects due to risk or protective factors that may have increased or decreased the susceptibility of some populations. ASD likely has a multifactorial etiology (Hertz-Picciotto et al., 2018), and in recent years a "second hit" hypothesis that exposures such as air pollution would require additional risk factor(s) to cause disease has been proposed (Bilbo et al., 2018; Estes and McAllister, 2016). Thus, susceptibility to air pollution might occur in children with other risk factors for ASD, such as male sex; maternal infections, diabetes mellitus, hypertension and other maternal inflammatory conditions, so-called "maternal immune activators" (K. Lyall, Schmidt and Hertz-Picciotto, 2014; Ornoy et al., 2015); in children of mothers with low nutritional intake of folic acid (Levine et al., 2018), medication for neuro- or neuropsychological disorders (Lisa A Croen et al., 2011); or in children from marginalized communities with low socioeconomic status (Mathiarasan and Hüls, 2021). Child's Genotypic variation increasing susceptibility to air pollution may help identify biological pathways (Huguet et al., 2013).

Synergistic associations of other risk factors could markedly increase the attributable burden of air pollution in concert with these other exposures. In addition, understanding patterns of susceptibility can help identify sensitive subpopulations that may benefit most from air pollution emission controls. The Clean Air Act in the United States requires that the regulatory standard protects everybody, including the most vulnerable, from adverse impacts of air pollution (O'Neill et al., 2003). Exposure reductions can also reduce environmental health disparities (Levy et al., 2002), as low socioeconomic status (SES) communities often experience greater air pollution exposure and larger effects for some outcomes (Evans and Kantrowitz, 2002; Fuller, Feeser, Sarnat and O'Neill, 2017; Hajat, Hsia and O'Neill, 2015).

The purpose of this review was to examine how ASD susceptibility to air pollution has varied among vulnerable subpopulations in studies to date. We identified knowledge gaps in our understanding of ASD susceptibility to air pollution and suggest possible approaches for future studies to address these gaps.

2. Methods

2.1. Eligibility criteria

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al., 2009). To be included in this review, a study met the following criteria: 1) It was published in a peer-reviewed journal; 2) The exposure was ambient criteria (regulated) air pollution or airborne toxics, thus, indoor airborne chemical and second-hand smoking exposures were not included; 3) The health outcome was ASD or related sub-phenotypes, 4) It was empirical, which excluded reviews, comments, replies, protocols, conceptual studies, and letters to the editor; 5) The study was in humans, thus, animal studies were not included; 6) The study was published in English; and 7) Effect modification was evaluated in stratified analyses or in interactions.

2.2. Search strategy and study selection

We identified articles published in peer-reviewed journals from PubMed and Embase database. The database search was conducted on May 1st, 2021. The search keywords were a combination of terms for exposures and health outcomes. For exposures, keywords were "air pollutants", "air pollution", "particulate matter", "PM", "nitrogen dioxide", "NO2", "nitrogen oxide", "NO", "ozone", "O3", "Sulfur/Sulfur dioxide", "SO2", "carbon monoxide", "CO", "vehicle emissions", and "traffic". For outcomes, key terms were "autism spectrum disorder", "ASD", "autistic", "pervasive developmental disorder", "PDD", "PDD-NOS", and "Asperger Syndrome". The search syntaxes for the two databases were shown in Supplementary Table S1 and Table S2. We also reviewed references cited in eligible studies to identify additional articles for inclusion; no additional eligible publications were added from the references.

The study selection was conducted in two steps. Step 1 involved screening titles and abstracts to identify human studies of ambient air pollution and ASD. Studies were identified sequentially according to the first six eligibility criteria (Section 2.1). If a study failed to meet an eligibility criterion, there was no further review of other inclusion criteria. For Step 2, full-text was reviewed to select articles reporting effect modification or interactions of air pollution with other factors in association with ASD. In this step, all 7 inclusion criteria were evaluated. Because there were few studies with comparable exposures and effect modifiers, we did not conduct a meta-analysis.

2.3. Data extraction

Two major categories of data were extracted from studies selected. The first included study characteristics including year, study design, study population, sample size, exposure measurement, outcome ascertainment, modifiers, and covariates. The second focused on effect sizes for effect modification. For stratified analyses, the estimated effect size and corresponding confidence interval from each modifying category were recorded. When interactions were tested, results of additive and multiplicative tests were also extracted.

2.4. Assessment of risk of bias

For each study, the assessment of risk of bias was based on the nine-point Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al., 2014). For case-control studies, the scale consists of three evaluation sections corresponding to (a) the possibility of bias in selection of cases and controls (4 points), (b) comparability of cases and controls and treatment of confounders on the basis of study design or data analysis (2 points), and (c) the quality and completeness of exposure assessment (3 points). For cohort studies, the three sections correspond to (a) the assessment of possible bias in the selection of both exposed and

nonexposed participants (4 points), (b) the comparability between exposed and nonexposed participants and treatment of confounders on the basis of study design or data analysis (2 points), and (c) the evaluation of potential bias in assessment of the outcome and in follow-up (3 points). A higher score represents a higher quality of study. A common cut-off score for an acceptable quality study is 7 (Chun et al., 2020; Flores-Pajot et al., 2016).

Additionally, we assessed the risk of bias for each study according to the qualitative guidelines developed by Lam et al. (2016). These guidelines are based on the GRADE principles (Guyatt et al., 2008). Five items from the guidelines were applicable for this study, including the source population representativeness, the misclassification of exposures and outcomes, the comprehensiveness of potential confounders, and the selective reporting of results. We added an evaluation of misclassification of effect modifiers (the sixth item), using similar rules to those for misclassification of pollution exposure. Each item was rated with 4 risk levels (low, probably low, probably high, and high) or not applicable (insufficient information to rate). Detailed criteria for the assessment of the six items are listed in Supplementary Table S3.

Database search, data extraction and assessment of risk of bias were conducted by two authors (XY and ZW) independently. Disagreements were resolved by a third author (MR).

2.5. Analytical approach

Effect modifiers evaluated based on the literature review included (1) child's sex, (2) markers for socioeconomic status (maternal education, race, and neighborhood deprivation and other characteristics from census data), (3) maternal factors (nutrition, maternal immune activators, such as diabetes), and (4) genetics. We summarized the results of effect modification from each study.

Additive or multiplicative interaction effects between the modifier and air pollution exposure were reported, if available. For studies that showed only results from stratified analyses by susceptibility factors, evaluation of effect modification was based on comparison of each subgroup's effect size, as described by Altman and Bland (2003). We calculated the original coefficients and standard errors from the reported odd ratios or hazard ratios and corresponding 95% confidence intervals reported in most studies. The difference between the original regression coefficients was assessed with the Wald test using the pooled standard error from the two strata. An example is presented in Supplementary Table S4.

3. Results

3.1. Study selection

Studies identified and then excluded at each step of selection are shown in the PRISMA flow chart (Fig. 1). A total of 1272 publications (N = 618 from PubMed and N = 654 from Embase) were identified through the database search, of which 296 were duplicates. The remaining 976 articles were screened by title and abstract and 937 publications that were not empirical human studies on the association between air pollution and ASD were excluded. A total of 39 articles studied the association between ambient air pollution and ASD were identified. In the full-text assessment, another 20 studies were excluded because they did not examine any effect modifiers (Supplementary Table S5). A total of 19 publications were included in this review.

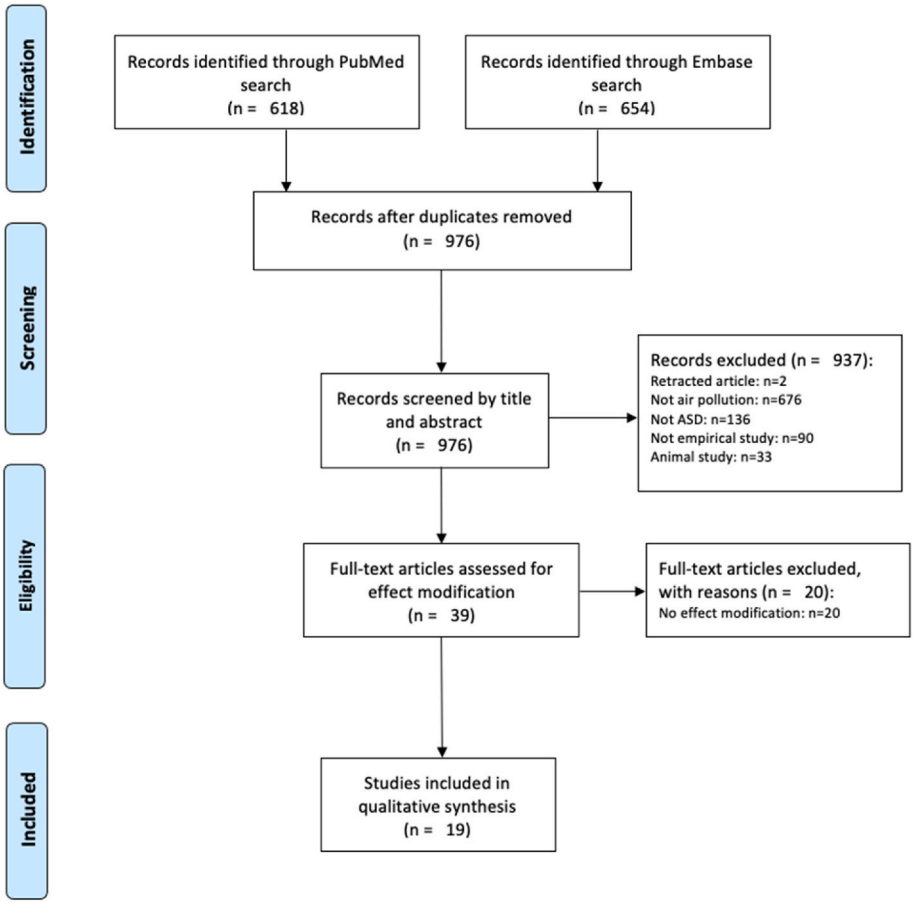

Fig. 1. Screening of studies for inclusion based on PRISMA criteria.

Table 1
Modification of regulated air pollutant ($PM_{2.5}$, PM_{10}, NO, NO_2, SO_2) associations with ASD by sex.[a].

Study and modifier	Exposure	Effect size by sex	P Interaction[b]	Effect size comparison[c]
Kalkbrenner et al. (2015) Boys (#case:828) Girls (#case: 151)	PM_{10} prepregnancy per 10 μ g/m^3	Boys: OR = 0.91 (0.78, 1.06) Girls: OR = 0.99 (0.71, 1.38)	0.96	OR(boys)/OR(girls): 0.92 (0.64, 1.33) (p = 0.65)
	PM_{10} 1st trimester per 10 μ g/m	Boys: OR = 0.89 (0.76, 1.04) Girls: OR = 0.74 (0.50, 1.08)	0.12	OR(boys)/OR(girls): 1.20 (0.79, 1.82) (p = 0.38)
	PM_{10} 2nd trimester per 10 μ g/m^3	Boys: OR = 1.00 (0.83, 1.19) Girls: OR = 0.95 (0.63, 1.45)	0.81	OR(boys)/OR(girls): 1.05 (0.67, 1.66) (p = 0.82)
	PM_{10} 3rd trimester per 10 μ g/m^3	Boys: OR = 1.33 (1.09, 1.63) Girls: OR = 1.46 (0.92, 2.32)	0.21	OR(boys)/OR(girls): 0.91 (0.55, 1.51) (p = 0.72)
	PM_{10} postpregnancy (0–3 months) per 10 μ g/m^3	Boys: OR = 1.01 (0.82, 1.26) Girls: OR = 1.52 (0.95, 2.44)	0.42	OR(boys)/OR(girls): 0.66 (0.40, 1.12) (p = 0.12)
	PM_{10} postpregnancy (3–6 months) per 10 μ g/m^3	Boys: OR = 0.75 (0.60, 0.93) Girls: OR = 0.63 (0.39, 1.03)	0.19	OR(boys)/OR(girls): 1.19 (0.70, 2.03) (p = 0.52)
	PM_{10} postpregnancy (6–9 months) per 10 μ g/m^3	Boys: OR = 0.87 (0.70, 1.08) Girls: OR = 0.85 (0.53, 1.38)	0.65	OR(boys)/OR(girls): 1.02 (0.61, 1.73) (p = 0.93)
	PM_{10} postpregnancy (9–12 months) per 10 μ g/m^3	Boys: OR = 1.14 (0.93, 1.41) Girls: OR = 1.52 (0.95, 2.45)	0.11	OR(boys)/OR(girls): 0.75 (0.45, 1.26) (p = 0.28)
Raz et al. (2015) Boys (#case:137) Girls (#case: 23)	$PM_{2.5}$ pregnancy per 4.4 μ g/m^3	Boys: OR = 1.73 (1.29, 2.31) Girls: OR = 1.12 (0.59, 2.12)	0.17	OR(boys)/OR(girls): 1.54 (0.76, 3.12) (p = 0.23)
Raz et al. (2018) Boys (#case:1435) Girls (#case: 286)	NO_2 prepregnancy (9 months) per 5.85 ppb	Boys: OR = 1.22 (0.88, 1.67) Girls: OR = 0.75 (0.37, 1.53)	Not reported	OR(boys)/OR(girls): 1.63 (0.75, 3.54) (p = 0.22)
	NO_2 pregnancy per 5.85 ppb	Boys: OR = 0.51 (0.35, 0.76) Girls: OR = 1.46 (0.61, 3.46)	Not reported	OR(boys)/OR(girls): 0.35 (0.14, 0.90) (p = 0.03)
	NO_2 postpregnancy (9 months) per 5.85 ppb	Boys: OR = 1.63 (1.17, 2.27) Girls: OR = 1.17 (0.57, 2.41)	Not reported	OR(boys)/OR(girls): 1.39 (0.63, 3.08) (p = 0.41)
Ritz et al. (2018) Boys (#case:11,853) Girls (#case: 3534)	NO_2 postpregnancy (9 months) per 11.41 μ g/m^3	Boys: OR = 1.06 (0.99, 1,14) Girls: OR = 1.12 (0.99, 1.26)	Not reported	OR(boys)/OR(girls): 0.95 (0.82, 1.09) (p = 0.44)
	SO_2 postpregnancy (9 months) per 2.80 μ g/m^3	Boys: OR = 1.25 (1.16, 1.35) Girls: OR = 1.11 (0.97, 1.27)	Not reported	OR(boys)/OR(girls): 1.13 (0.96, 1.31) (p = 0.13)
	PM_{10} postpregnancy (9 months) per 3.80 μ g/m^3	Boys: OR = 1.05 (1.00, 1.10) Girls: OR = 1.01 (0.93, 1.11)	Not reported	OR(boys)/OR(girls): 1.04 (0.94, 1.15) (p = 0.45)
	$PM_{2.5}$ postpregnancy (9 months) per 3.61 μ g/m^3	Boys: OR = 1.07 (1.01, 1.13) Girls: OR = 1.02 (0.92, 1.12)	Not reported	OR(boys)/OR(girls): 1.05 (0.94, 1.17) (p = 0.41)
Jo et al. (2019b) [d] Boys (#case:2030) Girls (#case: 441)	$PM_{2.5}$ pregnancy per 6.5 μ g/m^3	Boys: HR = 1.25 Girls: HR = 1.02	Not significant	HR(boys)/HR(girls): 1.23
	$PM_{2.5}$ 1st trimester per 6.5 μ g/m^3	Boys: HR = 1.18 (1.08, 1.27) Girls: HR = 0.90 (0.76, 1.07)	0.03	HR(boys)/HR(girls): 1.31 (1.09, 1.58) (p = 0.005)
	$PM_{2.5}$ 2nd trimester per 6.5 μ g/m^3	Boys: HR = 1.07 Girls: HR = 1.12	Not significant	HR(boys)/HR(girls): 0.96
	$PM_{2.5}$ 3rd trimester per 6.5 μ g/m^3	Boys: HR = 1.12 Girls: HR = 1.04	Not significant	HR(boys)/HR(girls): 1.08

(*continued on next page*)

Table 1 (*continued*)

Study and modifier	Exposure	Effect size by sex	P Interaction[b]	Effect size comparison[c]
	$PM_{2.5}$ postpregnancy (1 year) per 6.5 μ g/m^3	Boys: HR = 1.25 Girls: HR = 1.19	Not significant	HR(boys)/HR(girls): 1.05
Pagalan et al. (2019) [e] Boys (#case:1091) Girls (#case: 216)	$PM_{2.5}$ pregnancy per 1.5 μ g/m^3	Boys: OR = 1.04 (0.98, 1.10) Girls: OR = 1.03 (0.90, 1.18)	Not significant	OR(boys)/OR(girls): 1.01 (0.87, 1.17) p = 0.90)
	NO pregnancy per 10.7 ppb	Boys: OR = 1.09 (1.02, 1.15) Girls: OR = 0.98 (0.83, 1.13)	Not significant	OR(boys)/OR(girls): 1.11 (0.94, 1.31) (p = 0.21)
	NO_2 pregnancy per 4.8 ppb	Boys: OR = 1.07 (1.00, 1.13) Girls: OR = 1.00 (0.86, 1.16)	Not significant	OR(boys)/OR(girls): 1.07 (0.91, 1.26) (p = 0.41)
Al-Hamdan et al. (2018)	The percentages of days with unhealthy AQI (AQI>100) per 10%	Boys: OR = 1.10 (0.65, 1.87) Girls: OR = 1.06 (0.63, 1.78)	Not reported	OR(boys)/OR(girls): 1.04 (0.50, 2.18) (p = 0.92)

Abbreviations: HR, hazard ratio; OR, odds ratio.

[a] For additional details on study population, exposure measurement, outcome ascertainment, and covariates, see Table S6.

[b] P interaction column lists the qualitative or quantitative test results of interaction terms reported in each study. "Not reported" indicates the authors did not report the results either qualitatively or quantitatively. "Not significant" indicates the authors noted the results of interaction tests qualitatively or in figures, but the exact p-values were not reported.

[c] Based on method described by Altman and Bland (2003). An example of calculation is shown in Table S4.

[d] Confidence intervals for the effect size of average $PM_{2.5}$ during pregnancy and the 2nd and 3rd trimester were reflected in a figure.

[e] Confidence intervals for the effect size of $PM_{2.5}$, NO, and NO_2 for each trimester were reflected in a figure.

3.2. Study characteristics

A description of the 19 included studies is shown in Supplementary Table S6. All studies that evaluated effect modification were published since 2010. The majority (N = 15) were conducted in the United States, including 7 based on populations in California. There were four studies from other countries, one each from Sweden, Israel, Denmark, and Canada. Studies from other countries were not included because they did not examine effect modifiers. There were 13 case-control studies, 4 cohort studies and 2 ecological studies. The most widely examined air pollutant was particulate matter (PM); 11 publications studied the effect of $PM_{2.5}$ and 10 studied PM_{10}. Nitrogen oxides (NO_x, NO, and NO_2) were examined in 12 articles, ozone (O_3) in 6 studies, sulfur dioxide (SO_2) in 1 study, and carbon monoxide (CO) in 1 study. Nine studies examined more than one regulated air pollutant. In addition, three studies examined effects of the near-roadway air pollution mixture, and 5 examined effects of airborne toxicants. Except for two ecological studies, all studies examined exposure during pregnancy (N = 17) and 10 of these assessed trimester-specific effects. Five studies assessed pre-pregnancy effects, and 7 examined effects of postnatal exposure. Methods for ASD ascertainment were varied, including detailed clinical and neuropsychological evaluations, extraction from electronic medical records, and questionnaire surveys. Six studies further divided ASD into subphenotypes based on comorbidities.

3.3. Risk of bias

Both the NOS and the navigation guide from Lam et al. (2016) provided criteria for assessing bias in individual level observational studies. Therefore, two ecological studies (potentially subject to ecological fallacy) were excluded from the assessment of bias. NOS scores (the last column of Supplementary Table S6) for all the 17 observational studies with individual level data passed the cut-off score of 7 for acceptable quality.

The assessment of risk of bias corresponding to the guide from Lam is shown in Supplementary Table S7. Most studies were rated as "low" or "probably low" on all 6 criteria for bias, with some exceptions. For example, the source population representativeness had "probably high" bias in Kalkbrenner et al. (2018), because the study population was volunteers. Three studies of air toxics were rated as "probably high" risk of exposure misclassification bias because this dataset has high uncertainty in the exposure estimates (George et al., 2011; Xue and Jia, 2019). Among the effect modifiers, the measure of folic acid intake in Goodrich et al. (2018) had "probably high" bias, because the assessment of folic acid intake was based on retrospective recall in a telephone interview. The potential misclassification of urbanicity in Kalkbrenner et al. (2010) was classified as "probably high" because there was no description of how the "urbanicity" modifier was defined or obtained.

3.4. Effect measure modifiers

3.4.1. Social and demographic features

A total of 11 papers (7 of regulated pollutants and 4 of air toxics) examined effect modification by child's sex; 3 examined modification by maternal or family education level. Two studies assessed variation in air pollution effects by neighborhood deprivation and one by urbanicity. Effect modification by race and income were only evaluated in the two ecological studies.

- Child's sex:

Most studies reported that the effect estimates of early life exposures to both PM_{10} and $PM_{2.5}$ were stronger in boys than in girls (Table 1). Only Jo et al. (2019b)found that the hazard ratio in boys for the first trimester average $PM_{2.5}$ [HR = 1.18 (95% CI: 1.08, 1.27)] was statistically different from that in girls [HR = 0.90 (95% CI: 0.76, 1.07)]; p-interaction = 0.03. Larger but not significantly different $PM_{2.5}$ effects were observed in boys in the third trimester, for the entire pregnancy average exposure, and during the first year of life.

ASD-associated sex interactions with other regulated pollutants were not statistically significant (Table 1). One study found no association of NO_2 during pregnancy with ASD risk in girls [OR = 1.00 (95% CI: 0.86, 1.16)] and a positive effect in boys [OR 1.07(95% CI: 1.00, 1.13)], but interaction was not significant (Pagalan et al., 2019). NO exposure during pregnancy had a similar pattern of interactions with sex in the same study. Another study found average NO_2 exposure during pregnancy was associated with increased risk in girls [OR = 1.46 (95% CI: 0.61, 3.46)] but decreased risk in boys [OR = 0.51 (95% CI: 0.35, 0.76)]

Table 2
Modification of air pollutant ($PM_{2.5}$, PM_{10}, NO, NO_2, CO, O_3, traffic-related pollutants, airborne mercury) exposure associations with ASD by education level.[a].

Study and modifier	Exposure	Effect size by education level	P Interaction[b]	Effect size comparison[c]
Becerra et al. (2013) less than high school (#case: 1,725) high school (#case: 1,861) higher than high school (#case: 3,926)	Traffic NO pregnancy per 9.40 ppb	<high school: OR = 1.11 (1.05, 1.18) = high school: OR = 1.03 (0.97, 1.09) > high school: OR = 0.99 (0.95, 1.03)	not reported	OR(low)/OR(moderate): 1.08 (0.99, 1.17) (p = 0.08) OR(low)/OR(high): 1.12 (1.04, 1.20) (p = 0.0016)
	Traffic NO_2 pregnancy per 5.41 ppb	< high school: OR = 1.17 (1.10, 1.25) = high school: OR = 1.06 (1.00, 1.13) > high school: OR = 1.03 (0.99, 1.07)	not reported	OR(low)/OR(moderate): 1.10 (1.01, 1.21) (p = 0.03) OR(low)/OR(high): 1.14 (1.05, 1.22) (p = 0.0008)
	CO pregnancy per 0.55 ppm	< high school: OR = 0.90 (0.85, 0.96) = high school: OR = 1.03 (0.97, 1.09) > high school: OR = 1.09 (1.04, 1.14)	not reported	OR(low)/OR(moderate): 0.87 (0.80, 0.95) (p = 0.0017) OR(low)/OR(high): 0.83 (0.77, 0.89) (p < 0.0001)
	NO pregnancy per 29.67 ppb	< high school: OR = 0.96 (0.89,1.03) = high school: OR = 1.02 (0.95, 1.09) > high school: OR = 1.04 (0.99, 1.10)	not reported	OR(low)/OR(moderate): 0.94 (0.85, 1.04) (p = 0.24) OR(low)/OR(high): 0.92 (0.84, 1.01) (p = 0.08)
	NO_2 pregnancy per 10.47 ppb	< high school: OR = 0.97 (0.90, 1.04) = high school: OR = 1.08 (1.01, 1.16) > high school: OR = 1.07 (1.02, 1.12)	not reported	OR(low)/OR(moderate): 0.90 (0.81, 0.99) (p = 0.04) OR(low)/OR(high): 0.91 (0.83, 0.99) (p = 0.03)
	Ozone pregnancy per 11.54 ppb	< high school: OR = 1.09 (1.02, 1.16) = high school: OR = 1.07 (1.01, 1.14) > high school: OR = 1.04 (0.99, 1.09)	not reported	OR(low)/OR(moderate): 1.02 (0.93, 1.11) (p = 0.68) OR(low)/OR(high): 1.05 (0.97, 1.14) (p = 0.25)
	$PM_{2.5}$ pregnancy per 8.25 μ g/m^3	< high school: OR = 1.04 (0.96, 1.12) = high school: OR = 1.09 (1.01, 1.17) > high school: OR = 1.06 (1.00, 1.12)	not reported	OR(low)/OR(moderate): 0.95 (0.86, 1.06) (p = 0.39) OR(low)/OR(high): 0.98 (0.89, 1.08) (p = 0.70)
	PM_{10} pregnancy per 4.68 μ g/m^3	< high school: OR = 0.97 (0.91, 1.04) = high school: OR = 1.08 (1.01, 1.16) > high school: OR = 1.02 (0.97, 1.07)	not reported	OR(low)/OR(moderate): 0.90 (0.82, 0.99) (p = 0.03) OR(low)/OR(high): 0.95 (0.88, 1.03) (p = 0.23)
Gong et al. (2017) ≤ 12 years of education (#case: 2,564) >12 years of education (#case: 2,571)	Traffic NO_x pregnancy per 10 μ g/m^3	≤ 12 years: OR = 0.99 (0.88, 1.12) >12years: OR = 1.02 (0.94, 1.12)	0.65	OR(low)/OR(high): 0.97 (0.84, 1.13) (p = 0.69)
	Traffic NO_x postpregnancy (1st year of life) per 10 μ g/m^3	≤ 12 years: OR = 1.04 (0.91, 1.19) >12 years: OR = 1.04 (0.94, 1.15)	0.99	OR(low)/OR(high): 1.00 (0.85, 1.18) (p = 1.00)
	Traffic PM_{10} pregnancy per 20 μ g/m^3	≤ 12 years: OR = 0.89 (0.73, 1.08) >12 years: OR = 1.04 (0.88, 1.23)	0.13	OR(low)/OR(high): 0.84 (0.66, 1.11) (p = 0.24)
	Traffic PM_{10} postpregnancy (1st year of life) per 20 μ g/m^3	≤ 12 years: OR = 0.94 (0.76, 1.16) >12 years: OR = 1.07 (0.89, 1.28)	0.24	OR(low)/OR(high): 0.88 (0.66, 1.16) (p = 0.36)
Dickerson et al. (2016) Tracts below the average percent of college education (n = 1459) Tracts above the average percent of college education (n = 1030)	Mercury 4th quantile vs. 1st quantile	< average: RR = 1.37 (0.75, 2.49) >average: RR = 0.91 (0.50, 1.66)	0.02	OR(low)/OR(high): 1.51 (0.64, 3.52) (p = 0.34)

Abbreviations: HR, hazard ratio; OR, odds ratio.

[a] For additional details on study population, exposure measurement, outcome ascertainment, and covariates, see Table S6.

[b] P interaction column lists the qualitative or quantitative test results of interaction terms reported in each study. "Not reported" indicates the authors did not report interaction P-value either qualitatively or quantitatively.

[c] Based on method described by Altman and Bland (2003). An example of calculation is shown in Table S4.

and the difference in the effect estimates was significant (p = 0.03) (Raz et al., 2018). One ecological study reported no significant effect modification by sex in the association between exposure to unhealthy air (air quality index>100) and ASD prevalence (Al-Hamdan et al., 2018).

Four studies assessed the interaction of child's sex with air toxics exposure. More than 100 air toxics were studied. Therefore, we show only those for which there were significant interactions (Supplementary Table S8). With exceptions of ethylidene dichloride and polyaromatic hydrocarbons (von Ehrenstein et al., 2014), there was a consistent pattern of larger air toxics effects sizes for boys than girls. Two studies reported airborne lead to be a risk factor for ASD in boys but not in girls (Roberts et al., 2013; von Ehrenstein et al., 2014). Other metals (such as antimony, cadmium, and nickel) and volatile organic compounds were also reported as risk factors for ASD in boys not for girls (Kalkbrenner et al., 2018; Roberts et al., 2013).

- Education

Three studies (2 case-control and 1 ecological design) demonstrated no consistent pattern of effect modification of the air pollution-ASD association by education level (Table 2). Becerra et al. (2013) found that the effect of traffic-related NO_2 during pregnancy on ASD was statistically significantly higher in children whose mothers did not graduate from high school than in children whose mothers graduated high school. However, in the same study, stronger associations of CO and NO_2 exposure during pregnancy were observed in children with maternal education level greater than high school compared with those with less than high school, and these differences in point estimates were statistically significant. A Swedish study reported that associations of traffic-related NO_x and PM_{10} exposure during pregnancy and the first year of life were stronger in the more educated subgroup (with more than 12 years of education), but neither main effects nor interactions were statistically significant (Gong et al., 2017). An ecological study on air toxics found that the association of mercury with ASD risk was significantly higher in census tracts with below-average percentage of college educated households (Dickerson et al., 2016).

- Neighborhood characteristics

Two case-control studies examined the modifying effect of neighborhood deprivation, based on an index including income, education, unemployment and other socioeconomic characteristics in small socioeconomically homogeneous areas (Table 3). One U.S. study found that children living in the most deprived neighborhoods had stronger ASD associations with $PM_{2.5}$ (dichotomized at 12 $\mu g/m^3$) during the first year of life [OR = 2.17 (95%CI: 1.14, 4.15); interaction p-value 0.08] (McGuinn et al., 2019). When modeling $PM_{2.5}$ as a continuous variable, the interaction between neighborhood deprivation level also was not significant in the same study (Table 3). In contrast, a Swedish study found that traffic-related NOx and PM_{10} exposure during the first year of life were more strongly associated with ASD in less deprived neighborhoods (p-interaction = 0.09) (Gong et al., 2017). Kalkbrenner et al. (2010) reported that there were no modifying effects of census tract urbanicity (100% rural, mixed, and 100% urban) on the association of air toxics with ASD. Dickerson et al. (2016) found that children from census tracts with higher poverty rates had stronger associations of a combined metals index with ASD.

- Race

Racial differences in effects were examined in only one ecological study, in which there was an association of ASD with unhealthy air quality (AQI >100) only among Asians, which was not significant (OR = 3.59; 95%CI: 0.87, 14.8; p-value = 0.07) after adjustment for confounders (Al-Hamdan et al., 2018).

3.4.2. Maternal factors

Two studies reported effect modification by maternal factors (one for folic acid intake and one for maternal diabetes). In a case-control study, Goodrich et al. (2018) found that children of mothers with low folic acid intake during the first trimester (but not in other time periods) had stronger associations of ASD with NO_2 than mothers with sufficient folic acid intake [p-values for additive and multiplicative interaction<0.05] (Table 4). Jo et al. (2019a) reported increased ASD risk associated with first trimester O_3 exposure among mothers with gestational diabetes mellitus (GDM) diagnosed <24 weeks' gestation [adjusted HR 1.50 per 15.7 ppb O_3 (95% CI: 1.08, 2.09)], compared to mothers without diabetes. No O_3 associations with ASD were observed among children of mothers with later onset GDM or with pre-existing diabetes.

3.4.3. Genetic factors

Two studies of interactions with genetic factors were identified (Table 5). Kim et al. (2017) examined 15 interactions between 3 types of copy number variation (CNV) burden (duplication, deletion, and total) and 5 air pollutants (NO_2, O_3, $PM_{2.5}$ and PM_{10}, and near-roadway pollution). Only interactions of O_3 exposures during pregnancy (per 6.2 ppb) with CNV duplication burden per increase of 1,356,513 base pairs [OR = 1.55 (95% CI: 1.09, 2.21) and with total CNV burden OR = 1.36 (95% CI: 1.01, 1.81) were significant. In another study, ASD risk was increased in association with an interaction of exposure to high PM_{10}, NO_2, and dispersion-modeled near-roadway pollution (dichotomized at the 75th percentile of each distribution) with the MET receptor tyrosine kinase rs1858830 CC genotype (compared to MET CG or GG genotype) (Volk et al., 2014).

4. Discussion

Since Windham et al. (2006) published the first study of the association between prenatal air toxics and the risk of ASD in 2006, more than 30 papers have examined air pollution-ASD association in diverse populations and regions. In the last decade, studies have begun to examine susceptibility to air pollution. This approach has the potential to identify susceptible populations and potentially to explain some inconsistency in the main effects of air pollution. However, we found only limited evidence that male sex, low education, maternal folate deficiency and gestational diabetes, and child's copy number and MET receptor tyrosine kinase genotypic variation may increase risk of ASD associated with air pollution. There were few studies that examined each susceptibility characteristic, except sex of the child, and little consistency of findings across studies.

4.1. Susceptibility by sex

The most widely examined effect modifier was child's sex. In general, epidemiological studies found stronger effects of early life PM2.5 and air toxics exposure on the risk of ASD in boys than girls. These findings are consistent with toxicological studies showing that the activation of microglial cells induced by neuroinflammation may lead to synapse dysfunction involved in ASD (Bolton et al., 2017; Hammond et al., 2018). Males may be more sensitive to PM or other inflammatory insults because they have more microglia than females during gestational and early postnatal periods (Lenz and McCarthy, 2015). An alternative explanation is that higher prenatal testosterone levels during fetal brain development activate microglia, making males more vulnerable to air pollutants or other inflammatory insults (Auyeung et al., 2013; McCarthy, 2016). In human studies, the small sample of girls in many studies of air pollution and ASD limited ability to detect small differences between effects in boys and girls. For example, one study with 441 ASD cases in girls reported larger effect estimates in boys [boys (HR = 1.18; 95% CI, 1.08, 1.27) than in girls (HR = 0.90; 95% CI, 0.76, 1.07); p-interaction = 0.03)] (Jo et al., 2019b). In another study, a considerably larger PM2.5 effect in boys (OR = 1.73; 95% CI, 1.29, 2.31)

Table 3
Modification of air pollutant ($PM_{2.5}$, PM_{10}, NO, NO_2) exposure associations with ASD by neighborhood deprivation level.[a].

Study and modifier	Exposure	Effect size by neighborhood deprivation	P Interaction[b]	Effect size comparison[c]
Gong et al. (2017) high (#case: 2,030) moderate (#case: 1, 643) low (#case: 1,463)	Traffic NO_x pregnancy per 10 μ g/m^3	high: OR = 0.87 (0.72, 1.06) moderate: OR = 1.02 (0.93, 1.12) low: OR = 1.08 (0.96, 1.23)	0.16	OR(high)/OR(moderate): 0.85 (0.69, 1.06) (p = 0.15) OR(high)/OR(low): 0.81 (0.64, 1.01) (p = 0.07)
	Traffic NO_x postpregnancy (1st year of life) per 10 μ g/m^3	high: OR = 0.85 (0.67, 1.07) moderate: OR = 1.05 (0.94, 1.16) low: OR = 1.13 (0.97, 1.32)	0.09	OR(high)/OR(moderate): 0.81 (0.63, 1.05) (p = 0.11) OR(high)/OR(low): 0.75 (0.57, 1.00) (p = 0.05)
	Traffic PM_{10} pregnancy per 20 μ g/m^3	high: OR = 0.86 (0.66, 1.11) moderate: OR = 1.01 (0.84, 1.23) low: OR = 1.13 (0.91, 1.42)	0.24	OR(high)/OR(moderate): 0.85 (0.62, 1.18) (p = 0.33) OR(high)/OR(low): 0.76 (0.54, 1.07) (p = 0.12)
	Traffic PM_{10} postpregnancy (1st year of life) per 20 μ g/m^3	high: OR = 0.88 (0.67, 1.15) moderate: OR = 1.06 (0.86, 1.29) low: OR = 1.20 (0.93, 1.55)	0.20	OR(high)/OR(moderate): 0.83 (0.59, 1.16) (p = 0.28) OR(high)/OR(low): 0.73 (0.51, 1.06) (p = 0.10)
McGuinn et al. (2019)[d] high (#case: 187) moderate (#case: 235) low (#case: 252)	$PM_{2.5}$ pregnancy per 5 μ g/m^3	high: OR = 1.16 (0.63, 2.16) moderate: OR = 0.97 (0.55, 1.71) low: OR = 0.98 (0.58, 1.66)	0.79	OR(high)/OR(moderate): 1.20 (0.52, 2.76) (p = 0.68) OR(high)/OR(low): 1.18 (0.53, 2.66) (p = 0.68)
	$PM_{2.5}$ postpregnancy (1st year of life) per 5 μ g/m^3	high: OR = 2.45 (1.08, 5.56) moderate: OR = 1.88 (0.83, 4.25) low: OR = 1.83 (0.90, 3.70)	0.57	OR(high)/OR(moderate): 1.30 (0.41, 4.14) (p = 0.65) OR(high)/OR(low): 1.34 (0.45, 3.95) (p = 0.60)

Abbreviations: HR, hazard ratio; OR, odds ratio.
[a] For additional details on study population, exposure measurement, outcome ascertainment, and covariates, see Table S6.
[b] P interaction column lists the qualitative or quantitative test results of interaction terms reported in each study.
[c] Based on method described by Altman and Bland (2003). An example of calculation is shown in Table S4.
[d] Additive interactions were examined based on dichotomized pregnancy or postpregnancy PM2.5 concentrations (≤ 12.0 μ g/m^3 or > 12.0 μ g/m^3). No significant additive interactions were found at 0.05 alpha level.

than in girls (OR = 1.12; 95% CI, 0.59, 2.12)] was not significantly different (p-interaction = 0.17), but there were only 23 girls with ASD (Raz et al., 2015).

4.2. Susceptibility by socioeconomic characteristics

Sparse and inconsistent findings limit our ability to draw conclusions about how SES modifies air pollution effects. For example, Becerra et al. showed that the associations of NO_2 with ASD were stronger for children of mothers without high school degrees, but for CO stronger associations were observed among children of better educated women. Reasons for these findings are unclear. However, in general, larger effects among lower educated mothers might be expected if low-educated mothers were more likely to be at home (Cohn et al., 2014) and so residential exposure estimates during pregnancy were more accurate. More educated mothers may be more likely to work in indoor office jobs and in buildings that filter ambient pollution and therefore have little exposure. Highly educated mothers may be more likely to have diets supplemented with folate or rich in antioxidants that could diminish the effect of air pollution (Croft et al., 2018; Lim et al., 2019). One potential explanation for why smaller effects of ambient air pollution might be observed in children of less educated mothers comes from the cumulative risk model, based on a hypothesis that large effects of co-occurring other relatively high adverse exposures or social stressors may result in little additional risk from ambient air pollution (O'Neill et al., 2003).

One challenge in assessing effects of SES is that SES can have independent effects at both the individual level and the area level (O'Neill et al., 2003). Neighborhood SES markers such as average education, income, employment, rates of poverty or home values in the census tract have sometimes been found to more strongly modify effects of air pollution on cardiovascular outcomes than individual level education, occupation and income (Chi et al., 2016). According to the "double jeopardy" conceptual model (O'Neill et al., 2003), in addition to the generally greater concentrations of air pollution associated with neighborhood SES, deprived neighborhoods may be lacking in features such as healthy food availability and green space, contributing to a higher risk of chronic conditions, such as diabetes and obesity, which may increase susceptibility to ambient pollutants.

4.3. Susceptibility by maternal health conditions and nutrition intake

One study reported that increased ASD risk was associated with first trimester O_3 among mothers with gestational diabetes mellitus (GDM) diagnosed before 24 weeks' gestation (Jo et al., 2019a). Diabetes is one example of many conditions that cause maternal immune activation (MIA), including viral and bacterial infections (Jiang et al., 2016; Zerbo et al., 2013), asthma (L. A. Croen, Grether, Yoshida, Odouli and Van de Water, 2005), and preeclampsia (Dachew et al., 2018) that have been associated with higher risk of ASD. Common biological pathways of effects of MIA, O_3 and $PM_{2.5}$ include systemic inflammation and oxidative stress that are associated with increased reactive oxygen species in the placenta and fetus (Bonini and Sargis, 2018; Brown et al., 2001; Chen and Lippmann, 2009; Cuffe et al., 2017). Thus, it is biologically plausible to hypothesize that the presence of MIA during critical time windows may have synergistic effects with early-life air pollution on ASD, a "second hit" resulting in disease (Bilbo et al., 2018; Estes and McAllister, 2016). This hypothesis has the potential to identify new approaches to prevention based either on treatment, for example dietary approaches to reducing gestational diabetes, in addition to regulation of pollutant levels. Parenthetically, in the United States, regulated air pollutant exposure has been declining during the period of increasing rates of ASD (Sullivan et al., 2018). Therefore, it is not plausible that these air pollutant exposures alone are increasing the risk of ASD. However, increasing prevalence of maternal characteristics such as gestational diabetes that are known risk factors for ASD (Xiang et al., 2015) have the potential to increase the fraction of ASD attributable to

Table 4
Modification of air pollutant ($PM_{2.5}$,PM_{10}, NO_2, O_3, near-roadway pollution) exposure associations with ASD by maternal factors.[a].

Study and modifier	Exposure	Effect size	P Interaction[b]	Effect size comparison[c]
Goodrich et al. (2018) [d] Folic acid intake low: <800 μg (#case: 166) high: >800 μg (#case: 180)	NRP* 1st trimester Dichotomous: ≤15.58 ppb; >15.58 ppb Continuous: per 29.4 ppb	low: OR = 1.57 (0.92, 2.70) high: OR = 0.92 (0.59, 1.45)	0.09	OR(low)/OR(high): 1.71 (0.85, 3.44) (p = 0.14)
	NO_2 1st trimester Dichotomous: ≤14.18 ppb; >14.18 ppb Continuous: per 9.5 ppb	low: OR = 1.53 (0.91, 2.56) high: OR = 0.74 (0.46, 1.19)	0.01	OR(low)/OR(high): 2.07 (1.02, 4.17) (p = 0.04)
	PM_{10} 1st trimester Dichotomous: ≤22.88 μ g/m^3; >22.88 μ g/m^3 Continuous: per 13.32 μ g/m^3	low: OR = 1.33 (0.81, 2.19) high: OR = 0.94 (0.59, 1.49)	0.32	OR(low)/OR(high): 1.41 (0.72, 2.79) (p = 0.32)
	$PM_{2.5}$ 1st trimester Dichotomous: ≤12.40 μ g/m^3; >12.40 μ g/m^3 Continuous: per 10.02 μ g/m^3	low: OR = 1.13 (0.70, 1.83) high: OR = 0.97 (0.60, 1.59)	0.74	OR(low)/OR(high): 1.16 (0.59, 2.31) (p = 0.66)
	Ozone 1st trimester Dichotomous: ≤33.41 μ g/m^3; >33.41 μ g/m^3 Continuous: per 22.88 μ g/m^3	low: OR = 1.07 (0.66, 1.73) high: OR = 1.14 (0.71, 1.82)	0.92	OR(low)/OR(high): 0.94 (0.48, 1.84) (p = 0.85)
Jo et al. (2019a) none (#case: 2,167), GDM* diagnosed <24 weeks' gestation (#case: 73) GDM* diagnosed ≥ 24 weeks' gestation (#case: 160) pre-existing type 2 diabetes (#case: 71)	Ozone preconception (12 weeks) per 15.7 ppb	None: HR = 0.98 (0.92, 1.03) GDM<24 weeks: HR = 1.14 (0.76, 1.72) GDM ≥ 24 weeks: HR = 0.95 (0.77, 1.17) Pre-existing: HR = 1.09 (0.85, 1.38)	0.71	HR (GDM<24)/HR(None): 1.16 (0.77, 1.76) (p = 0.47) HR (GDM ≥ 24)/HR(None): 0.97 (0.78, 1.20) (p = 0.78) HR (pre-existing)/HR(None): 1.11 (0.87, 1.43) (p = 0.40)
	Ozone pregnancy per 15.7 ppb	None: HR = 1.10 (0.95, 1.27) GDM<24 weeks: HR = 1.96 (1.24, 3.11) GDM ≥ 24 weeks: HR = 0.83 (0.53, 1.29) Pre-existing: HR = 1.14 (0.53, 2.46)	0.07	HR (GDM<24)/HR(None): 1.78 (1.10, 2.89) (p = 0.02) HR (GDM ≥ 24)/HR(None): 0.75 (0.47, 1.20) (p = 0.24) HR (pre-existing)/HR(None): 1.04 (0.47, 2.26) (p = 0.93)
	Ozone 1st trimester per 15.7 ppb	None: HR = 0.95 (0.90, 1.01) GDM<24 weeks: HR = 1.50 (1.08, 2.09) GDM ≥ 24 weeks: HR = 0.90 (0.69, 1.18) Pre-existing: HR = 1.07 (0.69, 1.64)	0.05	HR (GDM<24)/HR(None): 1.58 (1.13, 2.21) (p = 0.01) HR (GDM ≥ 24)/HR(None): 0.95 (0.72, 1.25) (p = 0.70) HR (pre-existing)/HR(None): 1.13 (0.73, 1.74) (p = 0.59)
	Ozone 2nd trimester per 15.7 ppb	None: HR = 1.04 (0.98, 1.11) GDM<24 weeks: HR = 1.29 (0.95, 1.76) GDM ≥ 24 weeks: HR = 0.86 (0.72, 1.03) Pre-existing: HR = 1.05 (0.66, 1.65)	0.17	HR (GDM<24)/HR(None): 1.24 (0.91, 1.70) (p = 0.18) HR (GDM ≥ 24)/HR(None): 0.83 (0.68, 1.00) (p = 0.05) HR (pre-existing)/HR(None): 1.01 (0.64, 1.60) (p = 0.97)
	Ozone 3rd trimester per 15.7 ppb	None: HR = 1.06 (0.99, 1.12) GDM<24 weeks: HR = 0.97 (0.73, 1.30) GDM ≥ 24 weeks: HR = 1.03 (0.78, 1.35) Pre-existing: HR = 0.99 (0.73, 1.35)	0.85	HR (GDM<24)/HR(None): 0.92 (0.68, 1.23) (p = 0.56) HR (GDM ≥ 24)/HR(None):0.97 (0.73, 1.29) (p = 0.84) HR (pre-existing)/HR(None): 0.93 (0.68, 1.28) (p = 0.67)
	Ozone postpregnancy (1st year of life) per 15.7 ppb	None: HR = 0.93 (0.78, 1.10) GDM<24 weeks: HR = 2.01 (0.67, 6.07) GDM ≥ 24 weeks: HR = 0.72 (0.50, 1.02) Pre-existing: HR = 1.17 (0.63, 2.17)	0.01	HR (GDM<24)/HR(None): 2.16 (0.71, 6.59) (p = 0.18) HR (GDM ≥ 24)/HR(None):0.77 (0.52, 1.15) (p = 0.20) HR (pre-existing)/HR(None): 1.26 (0.66, 2.39) (p = 0.48)

* Abbreviations in alphabetical order: GDM, gestational diabetes mellitus; HR, hazard ratio; NRP, near-roadway pollution; OR, odds ratio.

[a] For additional details on study population, exposure measurement, outcome ascertainment, and covariates, see Table S6.

[b] P interaction column lists the quantitative test results of interaction terms reported in each study.

[c] Based on method described by Altman and Bland (2003). An example of calculation is shown in Table S4.

[d] Additive interactions were examined based on dichotomized air pollutant concentrations at the median values. The cut off points for NRP, NO_2, PM_{10}, $PM_{2.5}$, and ozone were 15.58 ppb, 14.18 ppb, 22.88 μ g/m^3, 12.40 μ g/m^3, and 33.41 μ g/m^3, respectively. A significant additive interaction was found only between NO_2 and folic acid.

air pollution even in the context of stable or decreasing regional pollutant levels.

We acknowledge that some MIA triggers, such as diabetes, may also be potential mediators in the association between air pollution and ASD. One recent study found little evidence of mediation effects of maternal immune biomarkers in the association between prenatal NO_2 exposure and ASD in children (Volk et al., 2020). However, the study did not examine interactions. Future research might examine both mediating and modifying roles of MIA in air pollution-associated ASD risk.

Because diet can be modified, dietary susceptibility to air pollution effects could have major public health significance (Adams et al., 2018). Sufficient folic acid and vitamin intake during pregnancy has been associated with reduced ASD risks in children (Levine et al., 2018; Schmidt, 2013; Schmidt et al., 2019). However, only one study examined the role of folic acid intake as a factor protecting against air pollution effects on autism (Goodrich et al., 2018). The timing of the largest protective effect of folic acid, during first trimester, suggests a window of vulnerability to pollution. Epigenetic dysregulation caused by air pollution is one pathway that may explain such effects (Lin et al., 2016; Marsit, 2015). Antioxidants in maternal diets can reduce the oxidative stress induced by air pollution (Block et al., 2012; Kannan et al., 2006). Other nutritional factors including vitamin D (Stubbs et al., 2016) and polyunsaturated fatty acids are also antioxidants and may improve autism symptoms in children with ASD (Kristen Lyall et al., 2013). These also merit investigation as potential modifiers of air pollution effects.

4.4. Genetic susceptibility to air pollution-associated ASD

There is substantial heritability in ASD (Tchaconas and Adesman, 2013; Tick et al., 2016). Hundreds of genes have been identified in biological pathways that may contribute to ASD (Chaste and Leboyer, 2012; Wisniowiecka-Kowalnik and Nowakowska, 2019). However, we identified only two studies that examined gene-environment interaction (air pollution with CNVs and with *MET* CC genotype) on the risk of ASD. CNV duplication and deletion burden increased the prenatal ozone exposure association with ASD risk in children (Kim et al., 2017). A few animal studies have provided evidence for ozone-induced oxidative stress and autism-like behavior (Bignami et al., 1994; Block et al., 2012; Sorace et al., 2001). In humans, oxidative stress is a key feature of the ASD phenotype (James et al., 2006; Yui et al., 2016). It is possible that CNVs contribute to genes altering reactive oxygen species (Kushima et al., 2018). Thus, CNVs and prenatal air pollution exposure can potentially share common biological pathways leading to ASD. Another study found interactions of a specific functional polymorphism, MET receptor tyrosine kinase rs1858830 CC genotype, with prenatal near-roadway air pollution and regional $PM_{2.5}$, PM_{10}, and NO_2. Genetic studies have shown that children with MET CC genotype had decreased expression of MET protein in brain, which is associated with ASD (Campbell et al., 2008; Campbell et al., 2006). Animal experiments have also shown that prenatal exposure to PAH (a component of traffic-related air pollution and PM) causes both decreased MET protein expression in the brain and autism-like behavior in mouse offspring (Sheng et al., 2010). Therefore, it is plausible that decreased MET protein expression is a biological pathway common to air pollution exposures and ASD, and MET genotype may play a role in the air pollution association with ASD. Future studies may investigate the interaction between air pollution and ASD polygenic risk.

One reason for the paucity of research on the interaction between genes and air pollution is that obtaining both genetic and environmental data for the same study population is expensive and time consuming (Kim et al., 2017). Opportunities exist for assigning early-life air

Table 5
Modification of regulated air pollutant ($PM_{2.5}$,PM_{10}, NO_2, O_3, traffic-related pollution) exposure effects of ASD by children's genotypes.[a].

Study	Air pollutants	Genotypes	Interaction Effect Size (95% CI)	P interaction[b]
Kim et al. (2017) [c]	TRP per 17.7 ppb	CNV burden[d]: Duplications	OR = 0.95 (0.73, 1.23)	Not reported
	NO_2 per 5.7 ppb	CNV burden: Duplications	OR = 0.94 (0.77, 1.15)	Not reported
	Ozone per 6.2 ppb	CNV burden: Duplications	OR = 1.55 (1.09, 2.21)	Not reported
	PM_{10} per 6.2 μ g/m^3	CNV burden: Duplications	OR = 0.93 (0.73, 1.19)	Not reported
	$PM_{2.5}$ per 3.7 μ g/m^3	CNV burden: Duplications	OR = 0.95 (0.72, 1.24)	Not reported
	TRP per 17.7 ppb	CNV burden: Deletions	OR = 0.81 (0.59, 1.11)	Not reported
	NO_2 per 5.7 ppb	CNV burden: Deletions	OR = 0.96 (0.73, 1.26)	Not reported
	Ozone per 6.2 ppb	CNV burden: Deletions	OR = 1.06 (0.83, 1.36)	Not reported
	PM_{10} per 6.2 μ g/m^3	CNV burden: Deletions	OR = 0.98 (0.73, 1.33)	Not reported
	$PM_{2.5}$ per 3.7 μ g/m^3	CNV burden: Deletions	OR = 0.83 (0.61, 1.13)	Not reported
	TRP per 17.7 ppb	CNV burden: Total	OR = 0.88 (0.68, 1.15)	Not reported
	NO_2 per 5.7 ppb	CNV burden: Total	OR = 0.92 (0.75, 1.14)	Not reported
	Ozone per 6.2 ppb	CNV burden: Total	OR = 1.36 (1.01, 1.81)	Not reported
	PM_{10} per 6.2 μ g/m^3	CNV burden: Total	OR = 0.87 (0.68, 1.11)	Not reported
	$PM_{2.5}$ per 3.7 μ g/m^3	CNV burden: Total	OR = 0.84 (0.65, 1.08)	Not reported
Volk et al. (2014) [e]	TRP$\geq$30.2 ppb	MET CC	OR = 2.9 (1.0, 10.6)	0.09
	TRP <30.2 ppb	MET CG/GG	OR = 1.0 (reference)	
	NO_2 $\geq$17.5 ppb	MET CC	OR = 3.6 (1.3, 12.7)	0.03
	NO_2 < 17.5 ppb	MET CG/GG	OR = 1.0 (reference)	
	Ozone$\geq$41.8 ppb	MET CC	OR = 0.95 (0.42, 2.2)	Not reported
	Ozone <41.8 ppb	MET CG/GG	OR = 1.0 (reference)	
	$PM_{10}\geq$29.2 μ g/m^3	MET CC	OR = 3.2 (1.3, 9.1)	Not reported
	PM_{10} < 29.2 μ g/m^3	MET CG/GG	OR = 1.0 (reference)	
	$PM_{2.5}\geq$16.0 μ g/m^3	MET CC	OR = 2.1 (0.92, 5.4)	Not reported
	$PM_{2.5}$<16.0 μ g/m^3	MET CG/GG	OR = 1.0 (reference)	

Abbreviations: CNV, copy number variation; OR, odds ratio.

[a] For additional details on study population, exposure measurement, outcome ascertainment, and covariates, see Table S6.

[b] P interaction column lists the qualitative or quantitative test results of interaction terms reported in each study. "Not reported" indicates the authors did not report the results either qualitatively or quantitatively.

[c] Each air pollutant was measured as an average from pregnancy to child's first 2 years of life in Kim et al. (2017).

[d] CNV burden was evaluated as a continuous variable. The OR for the interaction was per increase of 1,356,513 base pairs of CNV burden.

[e] Each air pollution was measured as pregnancy average in Volk et al. (2014).

pollution exposures to existing genetic studies that could advance our understanding of air pollution-gene interaction, including ASD polygenic risk, and biological pathways involved in ASD.

4.5. The quality of included studies

Overall, most studies included in this review were rated as "low" or "probably low" in risk of bias, especially for the relatively low bias in the measurements of air pollution and of effect modifiers, lending credibility to the effects observed. However, some limitations of these studies emerged during the review.

Large sample size is required to observe interaction effects for relatively uncommon diseases like ASD. Studies of air pollution-sex interaction generally did not identify statistically significant effects, potentially due to the small proportion of ASD cases in girls reducing the power to identify interactions. In the U.S., additional studies outside California could make the results more representative. Future reviews might also include studies of continuous measures of autistic traits, which may allow for detection of subtle effect modification in smaller sample sizes and reduce potential bias due to disparities in disease diagnosis by sociodemographic characteristics.

The role of effect modification was usually not the main research hypothesis for the studies reviewed; thus, the reported interactions may reflect selective reporting bias. The absence of a standard approach to reporting results of effect modification is another limitation. Some studies only reported the results of stratified analyses. Others reported the p-values of multiplicative interaction terms from statistical models. Only a few articles assessed interaction on both the additive and multiplicative scale. Reporting risk measures (relative risks, odds ratios, hazard ratios) for each stratum of exposure and the interaction on both additive and multiplicative scales is good practice (Knol and VanderWeele, 2012). The studies by Goodrich et al. (2018) and McGuinn et al. (2019) are examples of reporting additive and multiplicative interactions. Finally, most studies do not explicitly describe the theoretical or conceptual frameworks supporting the study hypothesis and design for assessing effect modification.

4.6. Strengths and limitations of this review

To our knowledge, this is the first systematic review summarizing the evidence on effect modifiers of the association between air pollution and the risk of ASD. The review followed the PRISMA checklist. The literature search was based on two most widely used databases, PubMed and Embase. The data extraction was thorough, including complementary results reported in supplementary materials. Rigorous assessment of risk of bias was conducted considering population representativeness, the potential for misclassification of exposure, ASD outcome, effect modifiers and the potential for selective reporting bias.

Because there were relatively few studies and results were not uniformly consistent, we did not attempt to conduct meta-analyses, and there were few definitive conclusions that could be drawn about how the association between air pollution and ASD was modified by the factors studied. We only included peer-reviewed studies published in English. It is possible that additional relevant information might be available in book chapters, non-English and grey literature.

5. Conclusions

This review synthesized studies of potential effect modifiers of the association between ambient air pollution and the risk of ASD. Maternal gestational diabetes, insufficient folic acid intake during pregnancy, low maternal education, child male sex and high CNV burden or MET rs1858830 CC genotype may increase susceptibility to the effect of prenatal air pollution exposure on ASD risk. However, the limited number of studies on each modifier precludes definitive conclusions. Additional investigation of these susceptibility characteristics would benefit from consistent definitions across studies with sample sizes sufficient to identify interactions and a priori hypotheses, for example that exposure to maternal immune activators would increase effects of air pollutants on ASD.

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Declaration of competing interest

The authors declare they have no actual or potential competing interests. Joel Schwartz declares that he has testified on behalf of the U.S. Department of Justice in a case involving a Clean Air Act violation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112590.

References

Adams, J.B., Audhya, T., Geis, E., Gehn, E., Fimbres, V., Pollard, E.L., Quig, D.W., 2018. Comprehensive nutritional and dietary intervention for autism spectrum disorder-A randomized, controlled 12-month trial. Nutrients 10 (3). https://doi.org/10.3390/nu10030369.

Al-Hamdan, A.Z., Preetha, P.P., Albashaireh, R.N., Al-Hamdan, M.Z., Crosson, W.L., 2018. Investigating the effects of environmental factors on autism spectrum disorder in the USA using remotely sensed data. Environ. Sci. Pollut. Res. Int. 25 (8), 7924–7936. https://doi.org/10.1007/s11356-017-1114-8.

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. BMJ 326 (7382), 219. https://doi.org/10.1136/bmj.326.7382.219.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders : DSM-IV-TR, fourth ed. American Psychiatric Association, Washington, DC.

Auyeung, B., Lombardo, M.V., Baron-Cohen, S., 2013. Prenatal and postnatal hormone effects on the human brain and cognition. Pflügers Archiv 465 (5), 557–571. https://doi.org/10.1007/s00424-013-1268-2.

Bacon, E.C., Courchesne, E., Barnes, C.C., Cha, D., Pence, S., Schreibman, L., Pierce, K., 2018. Rethinking the idea of late autism spectrum disorder onset. Dev. Psychopathol. 30 (2), 553–569. https://doi.org/10.1017/S0954579417001067.

Becerra, T.A., Wilhelm, M., Olsen, J., Cockburn, M., Ritz, B., 2013. Ambient air pollution and autism in Los Angeles county, California. Environ. Health Perspect. 121 (3), 380–386. https://doi.org/10.1289/ehp.1205827.

Bignami, G., Musi, B., Dell'Omo, G., Laviola, G., Alleva, E., 1994. Limited effects of ozone exposure during pregnancy on physical and neurobehavioral development of CD-1 mice. Toxicol. Appl. Pharmacol. 129 (2), 264–271. https://doi.org/10.1006/taap.1994.1251.

Bilbo, S.D., Block, C.L., Bolton, J.L., Hanamsagar, R., Tran, P.K., 2018. Beyond infection - maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. Exp. Neurol. 299 (Pt A), 241–251. https://doi.org/10.1016/j.expneurol.2017.07.002.

Blanchard, K.S., Palmer, R.F., Stein, Z., 2011. The value of ecologic studies: mercury concentration in ambient air and the risk of autism. Rev. Environ. Health 26 (2), 111–118. https://doi.org/10.1515/reveh.2011.015.

Block, M.L., Elder, A., Auten, R.L., Bilbo, S.D., Chen, H., Chen, J.C., Wright, R.J., 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33 (5), 972–984. https://doi.org/10.1016/j.neuro.2012.08.014.

Blumberg, S.J., Bramlett, M.D., Kogan, M.D., Schieve, L.A., Jones, J.R., Lu, M.C., 2013. Changes in Prevalence of Parent-Reported Autism Spectrum Disorder in School-Aged U.S. Children: 2007 to 2011-2012. Natl Health Stat Report(65), pp. 1–11, 11 pp. following 11. Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/24988818.

Bolton, J.L., Marinero, S., Hassanzadeh, T., Natesan, D., Le, D., Belliveau, C., Bilbo, S.D., 2017. Gestational exposure to air pollution alters cortical volume, microglial

morphology, and microglia-neuron interactions in a sex-specific manner. Front. Synaptic Neurosci. 9, 10. https://doi.org/10.3389/fnsyn.2017.00010.
Bonini, M.G., Sargis, R.M., 2018. Environmental toxicant exposures and type 2 diabetes mellitus: two interrelated public health problems on the rise. Curr Opin Toxicol 7, 52–59. https://doi.org/10.1016/j.cotox.2017.09.003.
Brown, D.M., Wilson, M.R., MacNee, W., Stone, V., Donaldson, K., 2001. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. Toxicol. Appl. Pharmacol. 175 (3), 191–199. https://doi.org/10.1006/taap.2001.9240.
Buescher, A.V., Cidav, Z., Knapp, M., Mandell, D.S., 2014. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA Pediatr. 168 (8), 721–728. https://doi.org/10.1001/jamapediatrics.2014.210.
Campbell, D.B., Li, C., Sutcliffe, J.S., Persico, A.M., Levitt, P., 2008. Genetic evidence implicating multiple genes in the MET receptor tyrosine kinase pathway in autism spectrum disorder. Autism Res. 1 (3), 159–168. https://doi.org/10.1002/aur.27.
Campbell, D.B., Sutcliffe, J.S., Ebert, P.J., Militerni, R., Bravaccio, C., Trillo, S., Levitt, P., 2006. A genetic variant that disrupts MET transcription is associated with autism. Proc. Natl. Acad. Sci. Unit. States Am. 103 (45), 16834–16839. https://doi.org/10.1073/pnas.0605296103.
Centers for Disease Control and Prevention, 2007. Prevalence of autism spectrum disorders–autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMWR Surveill Summ 56 (1), 12–28.
Charman, T., Baird, G., 2002. Practitioner review: diagnosis of autism spectrum disorder in 2- and 3-year-old children. JCPP (J. Child Psychol. Psychiatry) 43 (3), 289–305. https://doi.org/10.1111/1469-7610.00022.
Chaste, P., Leboyer, M., 2012. Autism risk factors: genes, environment, and gene-environment interactions. Dialogues Clin. Neurosci. 14 (3), 281–292. Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/23226953.
Chen, L.C., Lippmann, M., 2009. Effects of metals within ambient air particulate matter (PM) on human health. Inhal. Toxicol. 21 (1), 1–31. https://doi.org/10.1080/08958370802105405.
Chi, G.C., Hajat, A., Bird, C.E., Cullen, M.R., Griffin, B.A., Miller, K.A., Kaufman, J.D., 2016. Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. Environ. Health Perspect. 124 (12), 1840–1847. https://doi.org/10.1289/ehp199.
Chun, H., Leung, C., Wen, S.W., McDonald, J., Shin, H.H., 2020. Maternal exposure to air pollution and risk of autism in children: a systematic review and meta-analysis. Environ. Pollut. 256, 113307. https://doi.org/10.1016/j.envpol.2019.113307.
Cohn, D.V., Livingston, G., Wang, W., 2014. *After Decades of Decline, a Rise in Stay-At-Home Mothers*: Pew Research Center. Social & Demographic Trends Project.
Croen, L.A., Grether, J.K., Yoshida, C.K., Odouli, R., Hendrick, V., 2011. Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch. Gen. Psychiatr. 68 (11), 1104–1112.
Croen, L.A., Grether, J.K., Yoshida, C.K., Odouli, R., Van de Water, J., 2005. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch. Pediatr. Adolesc. Med. 159 (2), 151–157. https://doi.org/10.1001/archpedi.159.2.151.
Croft, D., Block, R., Cameron, S.J., Evans, K., Lowenstein, C.J., Ling, F., Rich, D.Q., 2018. Do elevated blood levels of omega-3 fatty acids modify effects of particulate air pollutants on fibrinogen? Air Qual. Atmos. Health 11 (7), 791–799. https://doi.org/10.1007/s11869-018-0586-0.
Cuffe, J.S., Xu, Z.C., Perkins, A.V., 2017. Biomarkers of oxidative stress in pregnancy complications. Biomarkers Med. 11 (3), 295–306. https://doi.org/10.2217/bmm-2016-0250.
Dachew, B.A., Mamun, A., Maravilla, J.C., Alati, R., 2018. Pre-eclampsia and the risk of autism-spectrum disorder in offspring: meta-analysis. Br. J. Psychiatry 212 (3), 142–147. https://doi.org/10.1192/bjp.2017.27.
Dickerson, A.S., Rahbar, M.H., Bakian, A.V., Bilder, D.A., Harrington, R.A., Pettygrove, S., Zahorodny, W.M., 2016. Autism spectrum disorder prevalence and associations with air concentrations of lead, mercury, and arsenic. Environ. Monit. Assess. 188 (7), 407. https://doi.org/10.1007/s10661-016-5405-1.
Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353 (6301), 772–777. https://doi.org/10.1126/science.aag3194.
Evans, G.W., Kantrowitz, E., 2002. Socioeconomic status and health: the potential role of environmental risk exposure. Annu. Rev. Publ. Health 23, 303–331. https://doi.org/10.1146/annurev.publhealth.23.112001.112349.
Flores-Pajot, M.C., Ofner, M., Do, M.T., Lavigne, E., Villeneuve, P.J., 2016. Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: a review and meta-analysis. Environ. Res. 151, 763–776. https://doi.org/10.1016/j.envres.2016.07.030.
Fuller, C.H., Feeser, K.R., Sarnat, J.A., O'Neill, M.S., 2017. Air pollution, cardiovascular endpoints and susceptibility by stress and material resources: a systematic review of the evidence. Environ. Health 16 (1), 58. https://doi.org/10.1186/s12940-017-0270-0.
George, B.J., Schultz, B.D., Palma, T., Vette, A.F., Whitaker, D.A., Williams, R.W., 2011. An evaluation of EPA's National-Scale Air Toxics Assessment (NATA): comparison with benzene measurements in Detroit, Michigan. Atmos. Environ. 45 (19), 3301–3308.
Gong, T., Almqvist, C., Bölte, S., Lichtenstein, P., Anckarsäter, H., Lind, T., Pershagen, G., 2014. Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins. Twin Res. Hum. Genet. 17 (6), 553–562. https://doi.org/10.1017/thg.2014.58.
Gong, T., Dalman, C., Wicks, S., Dal, H., Magnusson, C., Lundholm, C., Pershagen, G., 2017. Perinatal exposure to traffic-related air pollution and autism spectrum disorders. Environ. Health Perspect. 125 (1), 119–126. https://doi.org/10.1289/ehp118.
Goodrich, A.J., Volk, H.E., Tancredi, D.J., McConnell, R., Lurmann, F.W., Hansen, R.L., Schmidt, R.J., 2018. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. Autism Res. 11 (1), 69–80. https://doi.org/10.1002/aur.1885.
Guxens, M., Ghassabian, A., Gong, T., Garcia-Esteban, R., Porta, D., Giorgis-Allemand, L., Sunyer, J., 2016. Air pollution exposure during pregnancy and childhood autistic traits in four European population-based cohort studies: the ESCAPE project. Environ. Health Perspect. 124 (1), 133–140. https://doi.org/10.1289/ehp.1408483.
Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Group, G.W., 2008. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336 (7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD.
Hajat, A., Hsia, C., O'Neill, M.S., 2015. Socioeconomic disparities and air pollution exposure: a global review. Curr Environ Health Rep 2 (4), 440–450. https://doi.org/10.1007/s40572-015-0069-5.
Hammond, T.R., Robinton, D., Stevens, B., 2018. Microglia and the brain: complementary partners in development and disease. Annu. Rev. Cell Dev. Biol. 34, 523–544. https://doi.org/10.1146/annurev-cellbio-100616-060509.
Hertz-Picciotto, I., Delwiche, L., 2009. The rise in autism and the role of age at diagnosis. Epidemiology 20 (1), 84–90. https://doi.org/10.1097/EDE.0b013e3181902d15.
Hertz-Picciotto, I., Schmidt, R.J., Krakowiak, P., 2018. Understanding environmental contributions to autism: causal concepts and the state of science. Autism Res. 11 (4), 554–586. https://doi.org/10.1002/aur.1938.
Huguet, G., Ey, E., Bourgeron, T., 2013. The genetic landscapes of autism spectrum disorders. Annu. Rev. Genom. Hum. Genet. 14, 191–213. https://doi.org/10.1146/annurev-genom-091212-153431.
James, S.J., Melnyk, S., Jernigan, S., Cleves, M.A., Halsted, C.H., Wong, D.H., Gaylor, D. W., 2006. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am. J. Med. Genet. B Neuropsychiatr. Genet. 141B (8), 947–956. https://doi.org/10.1002/ajmg.b.30366.
Jiang, H.Y., Xu, L.L., Shao, L., Xia, R.M., Yu, Z.H., Ling, Z.X., Ruan, B., 2016. Maternal infection during pregnancy and risk of autism spectrum disorders: a systematic review and meta-analysis. Brain Behav. Immun. 58, 165–172. https://doi.org/10.1016/j.bbi.2016.06.005.
Jo, H., Eckel, S.P., Chen, J.C., Cockburn, M., Martinez, M.P., Chow, T., McConnell, R., 2019a. Gestational diabetes mellitus, prenatal air pollution exposure, and autism spectrum disorder. Environ. Int. 133 (Pt A), 105110. https://doi.org/10.1016/j.envint.2019.105110.
Jo, H., Eckel, S.P., Wang, X., Chen, J.C., Cockburn, M., Martinez, M.P., McConnell, R., 2019b. Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. Environ. Pollut. 254 (Pt A), 113010. https://doi.org/10.1016/j.envpol.2019.113010.
Kalkbrenner, A.E., Daniels, J.L., Chen, J.C., Poole, C., Emch, M., Morrissey, J., 2010. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology 21 (5), 631–641. https://doi.org/10.1097/EDE.0b013e3181e65d76.
Kalkbrenner, A.E., Windham, G.C., Serre, M.L., Akita, Y., Wang, X., Hoffman, K., Daniels, J.L., 2015. Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. Epidemiology 26 (1), 30–42. https://doi.org/10.1097/ede.0000000000000173.
Kalkbrenner, A.E., Windham, G.C., Zheng, C., McConnell, R., Lee, N.L., Schauer, J.J., Volk, H.E., 2018. Air toxics in relation to autism diagnosis, phenotype, and severity in a U.S. Family-based study. Environ. Health Perspect. 126 (3), 037004 https://doi.org/10.1289/ehp1867.
Kannan, S., Misra, D.P., Dvonch, J.T., Krishnakumar, A., 2006. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ. Health Perspect. 114 (11), 1636–1642. https://doi.org/10.1289/ehp.9081.
Kaufman, J.A., Wright, J.M., Rice, G., Connolly, N., Bowers, K., Anixt, J., 2019. Ambient ozone and fine particulate matter exposures and autism spectrum disorder in metropolitan Cincinnati, Ohio. Environ. Res. 171, 218–227. https://doi.org/10.1016/j.envres.2019.01.013.
Kim, D., Volk, H., Girirajan, S., Pendergrass, S., Hall, M.A., Verma, S.S., Selleck, S.B., 2017. The joint effect of air pollution exposure and copy number variation on risk for autism. Autism Res. 10 (9), 1470–1480. https://doi.org/10.1002/aur.1799.
Knol, M.J., VanderWeele, T.J., 2012. Recommendations for presenting analyses of effect modification and interaction. Int. J. Epidemiol. 41 (2), 514–520. https://doi.org/10.1093/ije/dyr218.
Kuhlthau, K., Orlich, F., Hall, T.A., Sikora, D., Kovacs, E.A., Delahaye, J., Clemons, T.E., 2010. Health-Related Quality of Life in children with autism spectrum disorders: results from the autism treatment network. J. Autism Dev. Disord. 40 (6), 721–729. https://doi.org/10.1007/s10803-009-0921-2.
Kushima, I., Aleksic, B., Nakatochi, M., Shimamura, T., Okada, T., Uno, Y., Ozaki, N., 2018. Comparative analyses of copy-number variation in autism spectrum disorder and schizophrenia reveal etiological overlap and biological insights. Cell Rep. 24 (11), 2838–2856. https://doi.org/10.1016/j.celrep.2018.08.022.
Lam, J., Sutton, P., Kalkbrenner, A., Windham, G., Halladay, A., Koustas, E., Woodruff, T., 2016. A systematic review and meta-analysis of multiple airborne pollutants and autism spectrum disorder. PLoS One 11 (9), e0161851. https://doi.org/10.1371/journal.pone.0161851.
Lenz, K.M., McCarthy, M.M., 2015. A starring role for microglia in brain sex differences. Neuroscientist 21 (3), 306–321.
Levine, S.Z., Kodesh, A., Viktorin, A., Smith, L., Uher, R., Reichenberg, A., Sandin, S., 2018. Association of maternal use of folic acid and multivitamin supplements in the

periods before and during pregnancy with the risk of autism spectrum disorder in offspring. JAMA Psychiatr. 75 (2), 176–184. https://doi.org/10.1001/jamapsychiatry.2017.4050.
Levy, J.I., Greco, S.L., Spengler, J.D., 2002. The importance of population susceptibility for air pollution risk assessment: a case study of power plants near Washington, DC. Environ. Health Perspect. 110 (12), 1253–1260. https://doi.org/10.1289/ehp.021101253.
Lewandowski, T.A., Bartell, S.M., Yager, J.W., Levin, L., 2009. An evaluation of surrogate chemical exposure measures and autism prevalence in Texas. J. Toxicol. Environ. Health 72 (24), 1592–1603. https://doi.org/10.1080/15287390903232483.
Lim, C.C., Hayes, R.B., Ahn, J., Shao, Y., Silverman, D.T., Jones, R.R., Thurston, G.D., 2019. Mediterranean diet and the association between air pollution and cardiovascular disease mortality risk. Circulation 139 (15), 1766–1775. https://doi.org/10.1161/circulationaha.118.035742.
Lin, V.W., Baccarelli, A.A., Burris, H.H., 2016. Epigenetics-a potential mediator between air pollution and preterm birth. Environ Epigenet 2 (1). https://doi.org/10.1093/eep/dvv008.
Lyall, K., Munger, K.L., O'Reilly, É.J., Santangelo, S.L., Ascherio, A., 2013. Maternal dietary fat intake in association with autism spectrum disorders. Am. J. Epidemiol. 178 (2), 209–220.
Lyall, K., Schmidt, R.J., Hertz-Picciotto, I., 2014. Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int. J. Epidemiol. 43 (2), 443–464. https://doi.org/10.1093/ije/dyt282.
Maenner, M.J., Shaw, K.A., Baio, J., Washington, A., Patrick, M., DiRienzo, M., Dietz, P. M., 2020. Prevalence of autism spectrum disorder among children aged 8 Years - autism and developmental disabilities monitoring network, 11 sites, United States, 2016. MMWR Surveill Summ 69 (4), 1–12. https://doi.org/10.15585/mmwr.ss6904a1.
Marsit, C.J., 2015. Influence of environmental exposure on human epigenetic regulation. J. Exp. Biol. 218 (Pt 1), 71–79. https://doi.org/10.1242/jeb.106971.
Mathiarasan, S., Hüls, A., 2021. Impact of environmental injustice on children's health—interaction between air pollution and socioeconomic status. Int. J. Environ. Res. Publ. Health 18 (2), 795.
McCarthy, M.M., 2016. Sex differences in the developing brain as a source of inherent risk. Dialogues Clin. Neurosci. 18 (4), 361–372. Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/28179808.
McGuinn, L.A., Windham, G.C., Kalkbrenner, A.E., Bradley, C., Di, Q., Croen, L.A., Daniels, J.L., 2020. Early life exposure to air pollution and autism spectrum disorder: findings from a multisite case-control study. Epidemiology 31 (1), 103–114. https://doi.org/10.1097/ede.0000000000001109.
McGuinn, L.A., Windham, G.C., Messer, L.C., Di, Q., Schwartz, J., Croen, L.A., Daniels, J. L., 2019. Air pollution, neighborhood deprivation, and autism spectrum disorder in the Study to Explore Early Development. Environ. Epidemiol. 3 (5) https://doi.org/10.1097/ee9.0000000000000067.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535. https://doi.org/10.1136/bmj.b2535.
O'Neill, M.S., Jerrett, M., Kawachi, I., Levy, J.I., Cohen, A.J., Gouveia, N., Socioeconomic, C., 2003. Health, wealth, and air pollution: advancing theory and methods. Environ. Health Perspect. 111 (16), 1861–1870. https://doi.org/10.1289/ehp.6334.
Ornoy, A., Weinstein-Fudim, L., Ergaz, Z., 2015. Prenatal factors associated with autism spectrum disorder (ASD). Reprod. Toxicol. 56, 155–169. https://doi.org/10.1016/j.reprotox.2015.05.007.
Pagalan, L., Bickford, C., Weikum, W., Lanphear, B., Brauer, M., Lanphear, N., Winters, M., 2019. Association of prenatal exposure to air pollution with autism spectrum disorder. JAMA Pediatr. 173 (1), 86–92. https://doi.org/10.1001/jamapediatrics.2018.3101.
Rao, P.A., Beidel, D.C., 2009. The impact of children with high-functioning autism on parental stress, sibling adjustment, and family functioning. Behav. Modif. 33 (4), 437–451. https://doi.org/10.1177/0145445509336427.
Raz, R., Levine, H., Pinto, O., Broday, D.M., Yuval, Weisskopf, M.G., 2018. Traffic-related air pollution and autism spectrum disorder: a population-based nested case-control study in Israel. Am. J. Epidemiol. 187 (4), 717–725. https://doi.org/10.1093/aje/kwx294.
Raz, R., Roberts, A.L., Lyall, K., Hart, J.E., Just, A.C., Laden, F., Weisskopf, M.G., 2015. 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 (3), 264–270. https://doi.org/10.1289/ehp.1408133.
Ritz, B., Liew, Z., Yan, Q., Cui, X., Virk, J., Ketzel, M., Raaschou-Nielsen, O., 2018. Air pollution and autism in Denmark. Environ. Epidemiol. (Philadelphia, Pa.) 2 (4), e028. https://doi.org/10.1097/ee9.0000000000000028.
Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Weisskopf, M.G., 2013. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. Environ. Health Perspect. 121 (8), 978–984. https://doi.org/10.1289/ehp.1206187.
Schmidt, R.J., 2013. Maternal folic acid supplements associated with reduced autism risk in the child. Evid. Base Med. 18 (6), e53. https://doi.org/10.1136/eb-2013-101311.
Schmidt, R.J., Iosif, A.M., Guerrero Angel, E., Ozonoff, S., 2019. Association of maternal prenatal vitamin use with risk for autism spectrum disorder recurrence in young siblings. JAMA Psychiatr. 76 (4), 391–398. https://doi.org/10.1001/jamapsychiatry.2018.3901.
Sheng, L., Ding, X., Ferguson, M., McCallister, M., Rhoades, R., Maguire, M., Hood, D.B., 2010. Prenatal polycyclic aromatic hydrocarbon exposure leads to behavioral deficits and downregulation of receptor tyrosine kinase, MET. Toxicol. Sci. 118 (2), 625–634. https://doi.org/10.1093/toxsci/kfq304.
Sorace, A., de Acetis, L., Alleva, E., Santucci, D., 2001. Prolonged exposure to low doses of ozone: short- and long-term changes in behavioral performance in mice. Environ. Res. 85 (2), 122–134. https://doi.org/10.1006/enrs.2000.4097.
Stubbs, G., Henley, K., Green, J., 2016. Autism: will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? Med. Hypotheses 88, 74–78.
Sullivan, T.J., Driscoll, C.T., Beier, C.M., Burtraw, D., Fernandez, I.J., Galloway, J.N., Watmough, S.A., 2018. Air pollution success stories in the United States: the value of long-term observations. Environ. Sci. Pol. 84, 69–73. https://doi.org/10.1016/j.envsci.2018.02.016.
Talbott, E.O., Arena, V.C., Rager, J.R., Clougherty, J.E., Michanowicz, D.R., Sharma, R. K., Stacy, S.L., 2015a. Fine particulate matter and the risk of autism spectrum disorder. Environ. Res. 140, 414–420. https://doi.org/10.1016/j.envres.2015.04.021.
Talbott, E.O., Marshall, L.P., Rager, J.R., Arena, V.C., Sharma, R.K., Stacy, S.L., 2015b. 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. https://doi.org/10.1186/s12940-015-0064-1.
Tchaconas, A., Adesman, A., 2013. Autism spectrum disorders: a pediatric overview and update. Curr. Opin. Pediatr. 25 (1), 130–144. https://doi.org/10.1097/MOP.0b013e32835c2b70.
Tick, B., Bolton, P., Happe, F., Rutter, M., Rijsdijk, F., 2016. Heritability of autism spectrum disorders: a meta-analysis of twin studies. JCPP (J. Child Psychol. Psychiatry) 57 (5), 585–595. https://doi.org/10.1111/jcpp.12499.
Volk, H.E., Kerin, T., Lurmann, F., Hertz-Picciotto, I., McConnell, R., Campbell, D.B., 2014. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Epidemiology 25 (1), 44–47. https://doi.org/10.1097/ede.0000000000000030.
Volk, H.E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., McConnell, R., 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatr. 70 (1), 71–77. https://doi.org/10.1001/jamapsychiatry.2013.266.
Volk, H.E., Park, B., Hollingue, C., Jones, K.L., Ashwood, P., Windham, G.C., Croen, L.A., 2020. Maternal immune response and air pollution exposure during pregnancy: insights from the Early Markers for Autism (EMA) study. J. Neurodev. Disord. 12 (1), 42. https://doi.org/10.1186/s11689-020-09343-0.
von Ehrenstein, O.S., Aralis, H., Cockburn, M., Ritz, B., 2014. In utero exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25 (6), 851–858. https://doi.org/10.1097/ede.0000000000000150.
Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2014. The Newcastle- Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Retrieved from. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
Windham, G.C., Zhang, L., Gunier, R., Croen, L.A., Grether, J.K., 2006. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. Environ. Health Perspect. 114 (9), 1438–1444. https://doi.org/10.1289/ehp.9120.
Wisniowiecka-Kowalnik, B., Nowakowska, B.A., 2019. Genetics and epigenetics of autism spectrum disorder-current evidence in the field. J. Appl. Genet. 60 (1), 37–47. https://doi.org/10.1007/s13353-018-00480-w.
Xiang, A.H., Wang, X., Martinez, M.P., Walthall, J.C., Curry, E.S., Page, K., Getahun, D., 2015. Association of maternal diabetes with autism in offspring. JAMA 313 (14), 1425–1434. https://doi.org/10.1001/jama.2015.2707.
Xue, Z., Jia, C., 2019. A model-to-monitor evaluation of 2011 national-scale Air toxics assessment (NATA). Toxics 7 (1). https://doi.org/10.3390/toxics7010013.
Yui, K., Kawasaki, Y., Yamada, H., Ogawa, S., 2016. Oxidative stress and nitric oxide in autism spectrum disorder and other neuropsychiatric disorders. CNS Neurol. Disord. - Drug Targets 15 (5), 587–596. https://doi.org/10.2174/1871527315666160413121751.
Zerbo, O., Qian, Y., Yoshida, C., Grether, J.K., Van de Water, J., Croen, L.A., 2013. Maternal infection during pregnancy and autism spectrum disorders. J. Autism Dev. Disord. 45 (12), 4015–4025. https://doi.org/10.1007/s10803-013-2016-3.