Environmental Pollution 278 (2021) 116856

Contents lists available at ScienceDirect

Environmental Pollution

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

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

Frédéric Dutheil [a, *, 1], Aurélie Comptour [b, 1], Roxane Morlon [c], Martial Mermillod [d], Bruno Pereira [e], Julien S. Baker [f], Morteza Charkhabi [g], Maëlys Clinchamps [h], Nicolas Bourdel [i]

[a] Université Clermont Auvergne, CNRS, LaPSCo, Physiological and Psychosocial Stress, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Occupational and Environmental Medicine, WittyFit, Clermont-Ferrand, France
[b] INSERM, CIC 1405 CRECHE Unit, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Gynecological Surgery, Clermont-Ferrand, France
[c] Université Clermont Auvergne, Faculty of Medicine, Occupational and Environmental Medicine, Clermont-Ferrand, France
[d] Univ. Grenoble Alpes, LPNC, CNRS, LPNC, Grenoble, France
[e] University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Biostatistics, Clermont-Ferrand, France
[f] Hong Kong Baptist University, Physical Education and Health, Centre for Health and Exercise Science Research, Kowloon Tong, Hong Kong, China
[g] National Research University Higher School of Economics, Moscow, Russia
[h] Université Clermont Auvergne, CNRS, LaPSCo, Physiological and Psychosocial Stress, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Occupational and Environmental Medicine, Clermont-Ferrand, France
[i] Université Clermont Auvergne, UMR 6602, Pascal Institute, Endoscopy and Computer Vision Group, University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Gynecological Surgery, Clermont-Ferrand, France

ARTICLE INFO

Article history:
Received 16 October 2020
Received in revised form
22 February 2021
Accepted 23 February 2021
Available online 2 March 2021

Keywords:
Air pollution
Autism spectrum disorder
Pregnancy

ABSTRACT

Despite the widely-known effects of air pollution, pollutants exposure surrounding pregnancy and the risk for autism spectrum disorder (ASD) in newborns remains controversial. The purpose of our study was to carry out a systematic review and meta-analyses of the risk of ASD in newborns following air pollution exposure during the perinatal period (preconception to second year of life). The PubMed, Cochrane Library, Embase and ScienceDirect databases were searched for articles, published up to July 2020, with the keywords "air pollution" and "autism". Three models were used for each meta-analysis: a global model based on all risks listed in included articles, a pessimistic model based on less favorable data only, and an optimistic model based on the most favorable data only. 28 studies corresponding to a total of 758 997 newborns were included (47190 ASD and 703980 controls). Maternal exposure to all pollutants was associated with an increased risk of ASD in newborns by 3.9% using the global model and by 12.3% using the optimistic model, while the pessimistic model found no change. Each increase of 5 μg/m^3 in particulate matter <2.5 μm (PM2.5) was associated with an increased risk of ASD in newborns, regardless of the model used (global +7%, pessimistic +5%, optimistic +15%). This risk increased during preconception (global +17%), during pregnancy (global +5%, and optimistic +16%), and during the postnatal period (global +11% and optimistic +16%). Evidence levels were poor for other pollutants (PM10, NOx, O3, metals, solvents, styrene, PAHs, pesticides). PM2.5 was associated with a greater risk than PM10 (coefficient 0.20, 95CI −0.02 to 0.42), NOx (0.29, 0.08 to 0.50) or solvents (0.24, 0.04 to 0.44). All models revealed that exposure to pollutants, notably PM2.5 during pregnancy, was associated with an increased risk of ASD in newborns. Pregnancy and postnatal periods seem to be the most at-risk periods.

1. Introduction

Air pollution is a major public health (The Lancet, 2017) and economic (Dockery and Evans, 2017) issue. associated with increased risk of mortality (Dockery and Evans, 2017) and morbidity in multiple diseases, such as cancer (Chen et al., 2015),

* Corresponding author. Occupational and Environmental Medicine, CHU Clermont-Ferrand, 58, Rue Montalembert, 63003, Clermont Ferrand, France.
E-mail address: fdutheil@chu-clermontferrand.fr (F. Dutheil).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.envpol.2021.116856
0269-7491/

inflammatory (Møller et al., 2014), neurological (Costa et al., 2017) and respiratory and cardiometabolic diseases (Shah et al., 2013a; Chiaverini, 2002; Loxham et al., 2019). Despite the considerable number of studies demonstrating the adverse health effects of air pollution, exposure to ambient air pollution surrounding pregnancy and the risk for Autism Spectrum disorder (ASD) in newborns remains controversial[9,10,11, 12]. Genetic and environmental factors specifically during perinatal periods (preconception, pregnancy (first, second, third trimester), postnatal until 2nd year of life) have been found to increase risk of pathology and malformation in children (Georgieff et al., 2018; Nypaver et al., 2016; Rodier et al., 1996). Air pollution is composed of a wide range of pollutants such as particulate matter (PM), nitrogen oxide (NOx), volatile organic compounds, pesticides, ozone (O3) and metals (Lam et al., 2016; Kalkbrenner et al., 2018). Though few studies have focused on pregnancy and risk of ASD, air pollutants such as PM (PM10, with an aerodynamic diameter $\leq$ 10 μm), appear to have the highest levels of toxicity (Oberdörster et al., 2005; de Kok et al., 2006). Among PM10 (Wilson and Suh, 1997), PM2.5 which have an even smaller aerodynamic diameter $\leq$2.5 μm are particularly harmful, penetrating more rapidly, easily and deeply into the organism (Oberdörster et al., 2005; de Kok et al., 2006). Despite a recent article (Chun et al., 2020), no meta-analysis to date has provided an overview or comparison of the effects of classes of air pollutants (Dutheil et al., 2020a), or the effects of sociodemographic risk factors such as parental ages, gender of newborns, or smoking (Kolevzon et al., 2007; Hao et al., 2020; von Ehrenstein et al., 2020). In addition, there are no published guidelines as yet on how to manage different data relating to a same risk within an included article (e.g. crude odds ratio, or adjusted on different covariables) (Dutheil et al., 2020a) and no meta-analysis presented both risks quantified either as continuous (per increment of air pollutants) or as categorical variables (high versus low exposure).

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

2. Methods

2.1. Literature search

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

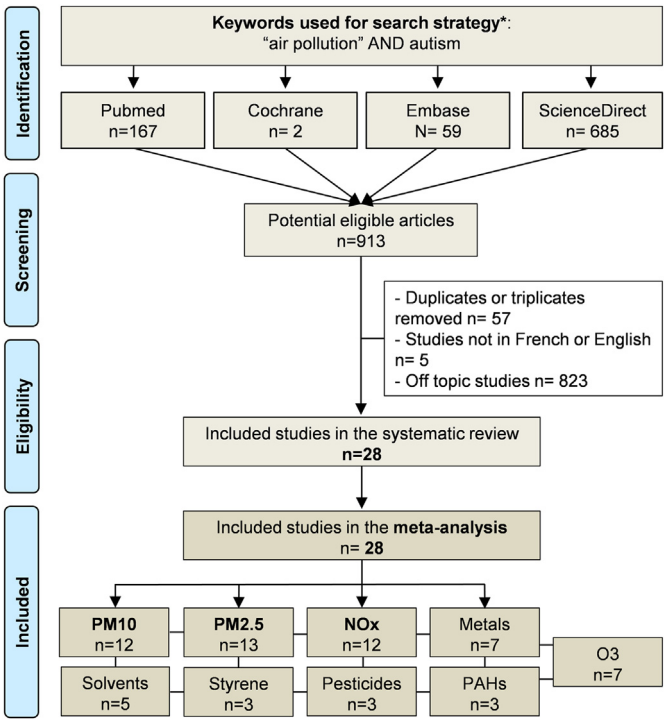

Fig. 1. Search strategy.

2.2. Quality of assessment

The methodological quality of the studies was further evaluated using the Scottish Intercollegiate Guidelines Network (SIGN) model for case control and cohort studies (Vandenbroucke et al., 2014). The following 15 items were assessed: appropriate and clearly focused question, selection bias (2 items), performance bias (1 item), attrition bias (2 items), detection bias (6 items), confusion bias (1 item), presence of confidence intervals, and general level of evidence (Fig. 2). Similar items were used to evaluate case control studies (Fig. 2). We also used the Newcastle-Ottawa Quality Assessment Scale (NOS) model (Stang, 2010) with the following 9 items: selection bias (4 items), comparability bias (2 items) and outcome bias (3 items) (Supplementary Figure 1). Each item was assigned a judgment of "Yes" (+), "No" (−), "Can't say" (?), or "Not applicable" (NA), with the exception of item 2.1 (to minimize risk of bias or confounding) and the final item concerning evidence level of the SIGN checklist, which was assigned "0", "+", or "++". Any disagreements over suitability were discussed with a third author (BP) and a consensus reached. Assessment of article quality was carried out for the two checklists by two authors (AC and FD).

2.3. Data analysis

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

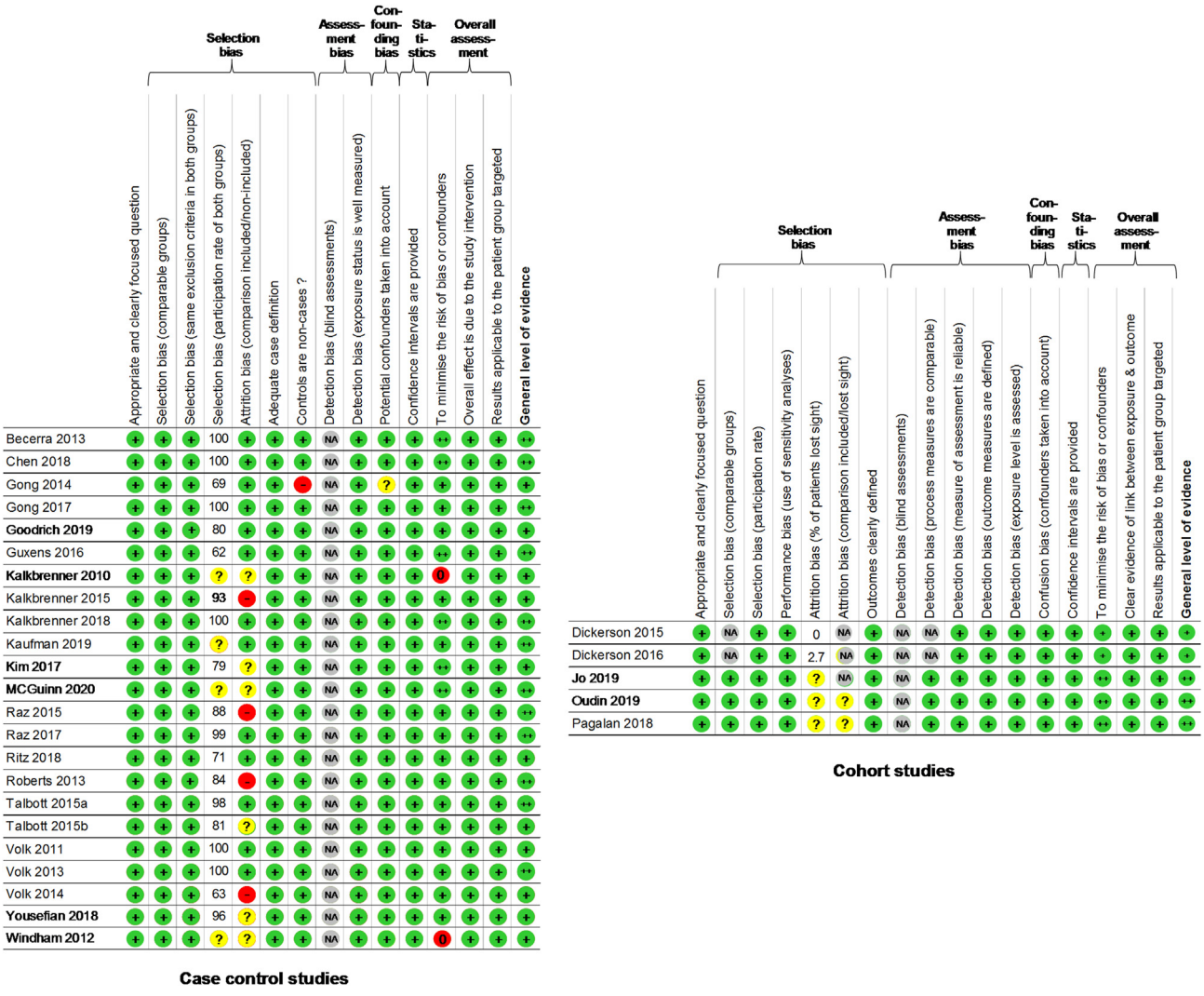

Fig. 2. Methodological quality of included articles using the SIGN checklist.

adjusted OR and lower and upper limits, and population characteristics (number of participants per study, parental mean age at birth, gender of newborns, level of parental education, smoking).

2.4. Statistical considerations

Statistical analysis was conducted using Stata software (version 15, StataCorp, College Station, US)(Ollier et al., 2014)[28], (Navel et al., 2019)[29],(Lanhers et al., 2017)[30], (Benichou et al., 2018)[31],(Benoist d'Azy et al., 2016)[32], (Courtin et al., 2016)[33]. Characteristics of pollutant exposure, of individuals or other variables were reported for each study as mean ± standard-deviation (SD) and number (%) for continuous and categorical variables respectively (Table 1). When data could be pooled, we conducted random effects meta-analyses (DerSimonian and Laird approach)(DerSimonian and Laird, 1986) on the risk (OR) of ASD in newborns following air pollutants exposure, centered at one. Particular attention was paid to the type of statistics retrieved from the included articles (OR or other risk measurements). Air pollutants exposure were quantified either as a continuous (per increment of air pollutants) or as categorical variables (high versus low exposure). For the highest level of proof, we first normalized all OR for a standardized increment in pollutant concentration (for example per 5 μg/m^3 increase in PM2.5). We took into account the original increment of the pollutant and we assumed a linear exposure outcome relationship (Shah et al., 2013b) using the following equation: OR standardized = e ^ [Ln(OR original) * 10/(Increment original)] (Orellano et al., 2020). When air pollutant levels were expressed in parts per billion (ppb), we transformed those levels in μg/m^3 (for example NO_2: 1 ppb = 1.88 μg/m^3; O_3: 1 ppb = 2 μg/m^3) (Jarvis et al., 2010) The effects expressed as interquartile (or quintile, or percentile differences) were converted into effects per concentration unit increase with the previous equation ((Orellano et al., 2020) Meta-analyses were computed by type of air pollutants (PM2.5, PM10, NOx, O_3, metals, solvents, styrene, polycyclic aromatic hydrocarbons (PAHs), pesticides), periconceptional periods, and pregnancy trimester where sufficient data were available. For each meta-analysis, three models were used (a global model of all risks listed in the included articles, a pessimistic model using less favorable data only, and an optimistic model using the most favorable data only). Finally, we computed the aforementioned meta-analyses categorical using OR based on categorical exposure (high versus low exposure). For air pollutants that were the most reported, we also computed sensitivity analyses depending on the methods to measure air pollutants. Heterogeneity between studies was evaluated through forest plots, and their confidence intervals

Table 1
Characteristics of studies included in meta-analysis. As: Arsenic; Ld: Lead; Hg: Mercury; * for median; #: see original articles (Gong et al., 2014: see Fig. 2; Kalkbrenner et al., 2010: see Table 2; Kalkbrenner et al., 2018: see Table 2).

Study	Country	Study design	Dates of inclusion	Perinatal periods	n ASD/ n total	Air pollutants Types	Air pollutants Mean levels (* for median)	REF used for risk calculation	Concentration for REF of air pollutants	Type of risk	Adjustment of risk	Other variables
Becerra, 2013	USA	Case-control	1995–2006	Pregnancy	7594/83229	PM_{10} $PM_{2.5}$ NO_2 NO O_3, CO	–	IQR	PM_{10}: 8.3 μg/m^3 $PM_{2.5}$: 4.7 μg/m^3 NO_2: 10.5 ppb NO: 29.7 ppb O_3:11.5 ppb	Odds ratio by IQR increase	Adjusted for maternal age, education, race/ethnicity, maternal place of birth, type of delivery, parity, insurance type, gestational weeks	Maternal place of birth, ethnicity, education, type of delivery, parity, insurance type
Chen et al., 2018	China	Case-control	2002–2011	Postnatal	124/1364	PM_1 $PM_{2.5}$ PM_{10}	PM_{10}: 95.4 μg/m^3 $PM_{2.5}$: 66.2 μg/m^3 PM_1: 48.8 μg/m^3	IQR	PM_{10}: 4.9 μg/m^3 $PM_{2.5}$: 3.4 μg/m^3 PM_1: 4.8 μg/m^3	Odds ratio by IQR increase	Adjusted for birth weight; gestational weeks; disease, trauma, and mental health history; maternal age; familial history; parents' marital status, education, smoking, income; parental relationship; parenting	Gender
Dickerson et al., 2015	USA	Cohort	1992–2000	Pregnancy	2489/2489	Metals	–	>50th centile of industrial facilities	>50th centile: 46.9 km from industry	Relative Risk by 10th centile	Crude and adjusted for ethnicity and maternal education	Gender
Dickerson et al., 2016	USA	Cohort	2000–2008	Preconception Pregnancy	2489/2489	Metals	–	1st quartile	As:<0.02 ng/m^3 Ld::<1.49 ng/m^3 Hg:<1.52 ng/m^3	Relative Risk by quartile	Crude and adjusted for ethnicity, education, poverty	–
Gong et al., 2014	Sweden	Case-control	1992–2000	Pregnancy Postnatal	109/3051	PM_{10} NOx	PM_{10}: 3.3–4.2 μg/m^3 NOx: 5.4–12.7 μg/m^3	<5th percentile	#	Relative Risk for >95th percentile vs < 5th and by severity of ASD	Crude and adjusted for parity, gender, maternal age, smoking, marital status, education, income, neighborhood deprivation	Birth weight, ethnicity, gestational age, zygosity
Gong et al., 2017	Sweden	Case-control	1993–2007	Pregnancy Postnatal	5136/23373	PM_{10} NOx	PM_{10}: 4.2–4.4 μg/m^3 NOx: 9.8–11.0 μg/m^3	Arbitrary cut-off	PM_{10}: <10 μg/m^3 NOx: <20 μg/m^3	Odds ratio by 10 μg/m^3 increase in PM_{10} and 20 μg/m^3 in NOx	Crude and adjusted for sex; birth month; sibling order; parents' age, education, employment, income, birth countries; marital status; neighborhood deprivation	Birth weight, congenital malformation, intellectual disability
Goodrich et al., 2018	USA	Case-control	1997–2008	Pregnancy	346/606	PM_{10} $PM_{2.5}$ NOx O_3	–	< median	PM_{10}: <22.9 μg/cm^3 $PM_{2.5}$: <12.4 μg/cm^3 NOx: <14.2 ppb O_3: <33.4 μg/cm^3	Odds ratio for > median vs < median	Adjusted for income, year of birth, vitamin A and zinc intake during pregnancy	Maternal age, education, birthplace; child ethnicity, sex; home ownership; preterm delivery; parity; gestational diabetes
Guxens et al., 2016	Europe (Italy, Spain, Netherlands, Sweden)	Cohort	1992–2008	Pregnancy	541/8079	PM_{10} $PM_{2.5}$ NO_2	*PM_{10}: 15–46 μg/m^3 *$PM_{2.5}$: 8–22 μg/m^3 *NO_2: 17–42 μg/m^3 *NO_x: 34–70 μg/m^3	Arbitrary cut-off	*PM_{10}: <10 μg/m^3 *$PM_{2.5}$: <5 μg/m^3 *NO_2: <10 μg/m^3 *NO_x: <20 μg/m^3	Odds ratio by 10 μg/m^3 increase in PM_{10} and NO2, and 5 μg/m^3 in PM_5 and 20 μg/m^3 in NOx	Adjusted for maternal education, country of birth, age, body mass index, height, smoking, parity, urbanicity; child's sex, season at birth, age at ASD diagnosis	
Jo et al., 2019	USA	Cohort	1999–2009	Pregnancy Postnatal	2471/246420	PM_{10} $PM_{2.5}$ NO_2 O_3	PM_{10}: 38.1 μg/m^3 $PM_{2.5}$: 17.9 μg/m^3 NO_2: 25.1 ppb O_3: 41.6 ppb	<5th percentile	#	Hazard ratio for >95th vs < 5th percentile	Adjusted for birth year, medical center, maternal age, ethnicity, parity, education, comorbidities; household income, child sex	
	USA			Perinatal					#			Gender, first born, married

Kalkbrenner et al., 2010		Case-control	1992–1994 1994–1996		383/2829	Metals Solvents Styrene Pesticides PAHs	# (0.00001–2108 μg/m^3 depending on air pollutants)	<20th percentile		Odds ratio for >80th percentile vs < 20th	Adjusted for maternal age, education, ethnicity, smoking; marital status; household income; urbanicity	
Kalkbrenner et al., 2015	USA	Case-control	1994-1996-1998-2000	Preconception Pregnancy Postnatal	645/13079	PM_{10}	PM_{10} by groups: 21.8–24.3 μg/m^3	Arbitrary cut-off	PM_{10}: <10 μg/m^3	Odds ratio by 10 μg/m^3 increase in PM_{10}	Adjusted for maternal age, ethnicity, education; household income, urbanization, week of birth	Gender, smoking, married
Kalkbrenner et al., 2018	USA	Case-control	1994–2007	Pregnancy	1540/2017	Metals PAHs Solvents Styrene Pesticides	# (155 pollutants)	<25th percentile (or (<5th), and log-transformed	#	Odds ratio for >75th vs <25th (or >95th vs < 5th)	Adjusted for air toxic levels in the family, birth year, education, income, population density	Gender, ethnicity, maternal age, number in siblings
Kaufman et al., 2019	USA	Case-control	2006–2010	Pregnancy Postnatal	428/6420	$PM_{2.5}$ O_3	$PM_{2.5}$: 66.2 μg/m^3 O_3: 48.8 μg/m^3	<5th percentile and IQR	<5th percentile: data not shown IQR: $PM_{2.5}$: 3.5 μg/m^3 O_3: 16 ppb	Odds ratio for >95th vs < 5th percentile and by IQR increase	Adjusted for year of birth; maternal education, body mass index, birth spacing, month of conception, pollutants	Gender; maternal age, ethnicity, smoking, body mass index; gestational age, birth weight, previous births
Kim et al., 2017	USA	Case-control	1999–2008	Pregnancy Postnatal	158/147	PM_{10} $PM_{2.5}$ NO_2 O_3	PM_{10}: 6.2 μg/m^3 $PM_{2.5}$: 3.7 μg/m^3 NO_2: 5.7 ppb O_3: 6.2 ppb	<75th percentile	data not shown	Odds ratio for >75th vs < 75th percentile	Adjusted for education, ethnicity, child's sex	–
McGuinn et al., 2020	USA	Case-control	2003–2006	Preconception Pregnancy Postnatal	674/1529	$PM_{2.5}$ O_3	$PM_{2.5}$: 12.7 μg/m^3 O_3: 35.1 ppb	Arbitrary cut-off	PM_{10}: <1.6 μg/m^3 O_3^- <6.6 ppb	Odds ratio by 1.6 μg/m^3 in $PM_{2.5}$ and 6.6 ppb in O_3	Adjusted for maternal age, education, ethnicity, smoking; study site; month and year of birth; exposure time	Gender, preterm
Oudin et al., 2019	Sweden	Cohort	1999–2009	Pregnancy	768/47865	NOx	NOx: 17.7 μg/m^3	<1st quartile and arbitrary cut-off	1st quartile: <11.3 μg/m^3 Arbitrary cut-off: NOx: 10 μg/m^3	Odds ratio by quartile and by 10 μg/m^3 in NOx	Adjusted for gender of child; maternal age, parity, smoking, body mass index, education, income, country of birth	
Pagalan et al., 2019	Canada	Cohort	2004–2009	Pregnancy	1307/132256	$PM_{2.5}$ NO NO_2	$PM_{2.5}$: 5.0–5.7 μg/m^3 NO_2: 13.5–16.0 μg/m^3 NO: 11.0–16.0 μg/m^3	IQR	$PM_{2.5}$: 1.5 μg/m^3 NO_2: 4.8 ppb NO_2: 10.7 ppb	Odds ratio by IQR increase	Crude and adjusted for gender, income, urbanicity, month and year of birth, maternal age, birthplace	Gestational age, multiple birth, parity
Raz et al., 2015	USA	Case-control	1993	Preconception Pregnancy Postnatal	245/767	$PM_{2.5}$	$PM_{2.5}$: 14.6 μg/m^3	IQR	$PM_{2.5}$: 4.42 μg/m^3	Odds ratio by IQR increase	Crude and adjusted for child sex, year and month of birth, parents age, income	Birth weight, education, marital status, prematurity, smoking
Raz et al., 2018	Israel	Case-control	2005–2009	Pregnancy Postnatal	2098/56289	NO_2	*NO_2: 16.7 ppb	IQR	NO_2: 5.85 ppb	Odds ratio by IQR increase	Adjusted for year and month of birth, ethnicity, paternal age, poverty	Birth weight, gestational age, income, population group, multiplicity of birth
Ritz et al., 2018	Denmark	Case control	1989–2013	Pregnancy Postnatal	15387/83526	PM_{10} $PM_{2.5}$ NO_2 SO_2	–	IQR	PM_{10}: 3.80 μg/m^3 $PM_{2.5}$: 3.61 μg/m^3 NO_2: 11.41 μg/m^3 SO_2: 2.80 μg/m^3	Odds ratio by IQR increase	Crude and adjusted for parental age, birth place, neighborhood employment and housing, maternal smoking, pollutants exposure periods	Gender, birth weight, gestational age
Roberts et al., 2013	USA	Case-control	1987–2002	Postnatal	325/22426	Metals	–	1st quintile	<1st quintile: data not shown	Odds ratio by quintile	Adjusted for maternal age, year of birth, parents' education, income, and year	Gender, state of residence at birth, smoking
	USA					$PM_{2.5}$		IQR				

(continued on next page)

Table 1 (*continued*)

Study	Country	Study design	Dates of inclusion	Perinatal periods	n ASD/ n total	Air pollutants Types	Mean levels (* for median)	REF used for risk calculation	Concentration for REF of air pollutants	Type of risk	Adjustment of risk	Other variables
Talbott et al., 2015a		Case-control	2005 −2009	Preconception Pregnancy Postnatal	211/ 430		$PM_{2.5}$: 15 μg/ m^3		$PM_{2.5}$: 2.84 μg/ m^3	Odds ratio by IQR increase	Crude and adjusted for maternal education, smoking, ethnicity, and age	Year and country of birth, multiple birth, birth weight, preterm birth
Talbott et al., 2015b	USA	Case-control	2005 −2009	Pregnancy	216/ 4971	Metals Solvents PAHs Pesticides	# (30 pollutants)	1st quartile	<1st quintile: #	Odds ratio by quartile	Adjusted for maternal age, education, smoking, ethnicity, child's birth year and sex	Country of birth
Volk et al., 2011	USA	Case-control	1997 −2006	Pregnancy	304/ 259	$PM_{10}PM_{2.5}$ $NOxO_3$	–	Last quartile of distance from freeway	Last quartile: >1.4 km from freeway	Odds ratio by quartile	Adjusted for child sex, ethnicity; parents education; maternal age and smoking	Preterm delivery
Volk et al., 2013	USA	Case-control	1997 −2008	Pregnancy Postnatal	279/ 524	PM_{10} $PM_{2.5}$ NOx O_3	–	1st quartile	1st quartile: <9.7 ppb of global traffic air pollution levels	Odds ratio by quartile	Crude and adjusted for child's sex, ethnicity; parents education; maternal age and smoking	–
Volk et al., 2014	USA	Case-control	1997 −2009	Pregnancy	251/ 156	PM_{10} $PM_{2.5}$ NOx O_3	–	<25th percentile	PM_{10}^{i}<29.2 μg/ m^3 $PM_{2.5}^{i}$<16.0 μg/m^3 NOx_5^{i}<17.5 ppb O_3:<41.8 ppb	Odds ratio for >75th vs < 25th percentile	Adjusted for child's sex, ethnicity; parents education; maternal age and smoking; home ownership	–
Yousefian et al., 2018	Iran	Case-control	2004 −2012	Pregnancy	134/ 388	PM_{10} SO_2 Solvents	PM_{10}: 105.1 −107.9 μg/m^3 SO_2: 22.8−26.4 ppb Solvents: 60.7 μg/m^3	per 1-unit increase in pollutants	per 1-unit increase in pollutants	Odds ratio per 1-unit increase in pollutants	Adjusted for maternal age, smoking; parents education; cousin marriage; birth order, gestational age, multiplicity, parents comorbidities	Gender, type of delivery
Windham et al., 2013	USA	Case-control	1994	Pregnancy	284/ 943	Solvents Pesticides Metals	–	Exposed workers vs non-exposed workers	Non-exposed workers: no concentrations given	Odds ratio exposed versus non-exposed workers	Crude and adjusted for child ethnicity, maternal age and education	Gender; paternal age, education; parity; birth weight; prematurity

(CI), and I-squared (I^2) – varying from 0 to 100%. Heterogeneity is considered low for I^2<25%, modest for 25<I^2<50%, and high for I^2>50%. For example, a significant heterogeneity may be due to the variability between the characteristics of the studies, such as the exposure to air pollutants (type of air pollutants), periconceptional periods (preconception, pregnancy, postnatal), pregnancy trimester (first, second, third), characteristics of individuals (age of mothers and fathers, smoking, gender of newborns, etc). To ensure the robustness of our results, we conducted sensitivity analysis by searching for potential publication bias through funnel plots (metafunnels) of aforementioned meta-analyses. Then, we reperformed meta-analyses without the studies that were not evenly distributed around the funnel base (Russo, 2007). When sample size allowed, meta-regressions were performed to investigate the relationship between risk of ASD in newborns following air pollutant exposure and putative variables such as type of air pollutant, periconceptional period, pregnancy trimester and population characteristics. Results were expressed as regression coefficients and 95% CI.

3. Results

An initial search identified 913 possible articles for inclusion (Fig. 1). Following application of selection criteria and removal of duplicates 28 articles were selected[9, 10, 11, 12,17,39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61] (Table 1), all of which were written in English.

3.1. Quality of articles

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

3.2. Aims of included studies, study designs, and settings

All studies shared a similar *objective* i.e. the association of exposure to air pollution (PMs, NOx, O3, metals, PAHs, solvents, pesticides) during the perinatal period and the development of ASD. Six studies described a cohort *study design* (Guxens et al., 2016; Pagalan et al., 2019; Dickerson et al., 2016; Dickerson et al., 2015; Jo et al., 2019; Oudin et al., 2019) using a historical birth/child cohort. The 22 remaining studies (Gong et al., 2014; Gong et al., 2017; Kalkbrenner et al., 2018; Becerra et al., 2013; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Kaufman et al., 2019; Raz et al., 2018; Raz et al., 2015; Ritz et al., 2018; Roberts et al., 2013; Talbott et al., 2015a; Talbott et al., 2015b; Volk et al., 2011; Volk et al., 2014; Volk et al., 2013; Chen et al., 2018; Yousefian et al., 2018; Jo et al., 2019; McGuinn et al., 2020; Oudin et al., 2019; Goodrich et al., 2018; Windham et al., 2013; Kim et al., 2017) described case control studies. Most studies assessed exposure over several consecutive years with the exception of four studies which analyzed data from one year (Gong et al., 2017; Dickerson et al., 2016; Kalkbrenner et al., 2010; Talbott et al., 2015b; Windham et al., 2013). *Countries of exposure* included North America for 20 studies (U.S (Kalkbrenner et al., 2018; Becerra et al., 2013; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Kaufman et al., 2019; Raz et al., 2018; Raz et al., 2015; Ritz et al., 2018; Roberts et al., 2013; Talbott et al., 2015a; Talbott et al., 2015b; Volk et al., 2011; Volk et al., 2014; Volk et al., 2013; Jo et al., 2019; McGuinn et al., 2020; Oudin et al., 2019; Goodrich et al., 2018; Windham et al., 2013; Kim et al., 2017), Canada (Pagalan et al., 2019)), Europe for 5 studies (Denmark (Ritz et al., 2018), Sweden (Gong et al., 2014; Gong et al., 2017; Oudin et al., 2019) and other European countries (Guxens et al., 2016)), and Asia for 3 studies (Iran (Yousefian et al., 2018), Israel (Raz et al., 2018), China (Chen et al., 2018)).

3.3. Population

Sample size for children with ASD ranged from 124 [54] to 15 387 [45]. Population size for controls (children without ASD) ranged from 156 [52] to 130 949 [12]. In total 751 170 individuals (47190 ASD and 703980 controls) were included in this meta-analysis.

Age of mothers at birth was expressed as a mean value in 11 articles [9, 10, 11, 12,45, 46, 47, 48, 49, 50,56], ranging from 29.5 ± 5.0 [47] to 34.0 ± 4.0 years old (Raz et al., 2015) for mothers of ASD (mean age 31.6, 95CI 28.3 to 34.9), and 28.5 ± 6.0 [50] to 33.7 ± 3.7 [46] years for mothers of controls (mean age 31.7, 95CI 28.6 to 34.7). Twelve articles reported different classes of age (Kalkbrenner et al., 2018; Becerra et al., 2013; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Kaufman et al., 2019; Volk et al., 2011; Chen et al., 2018; Yousefian et al., 2018; McGuinn et al., 2020; Oudin et al., 2019; Goodrich et al., 2018; Windham et al., 2013), precluding further analyses. Five articles did not mention age of mothers (37, 48, 49,57,60).

Age of fathers at birth was not reported in most (19/28) articles (Gong et al., 2014; Guxens et al., 2016; Pagalan et al., 2019; Kalkbrenner et al., 2018; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Kaufman et al., 2019; Roberts et al., 2013; Volk et al., 2011; Volk et al., 2014; Volk et al., 2013; Chen et al., 2018; Jo et al., 2019; McGuinn et al., 2020; Oudin et al., 2019; Goodrich et al., 2018; Kim et al., 2017). Three articles expressed age of fathers at birth as classes (Becerra et al., 2013; Yousefian et al., 2018; Windham et al., 2013), and six as mean values (Gong et al., 2017; Raz et al., 2018; Raz et al., 2015; Ritz et al., 2018; Talbott et al., 2015a; Talbott et al., 2015b), ranging from 32.2 ± 6.1 [47] to 36.8 ± 5.3 years (Raz et al., 2015) for fathers of ASD (mean age 33.9, 95CI 28.6 to 39.4), and 31.4 ± 6.6 [50] to 33.7 ± 5.6 [49] years for fathers of controls (mean age 33.9, 95CI 29.3 to 38.7).

Gender: All articles except two (Volk et al., 2013; Kim et al., 2017) reported child with ASD gender, ranging from 29% (Volk et al., 2011) to 87% (Volk et al., 2014). Seven articles did not report child without ASD gender (Kalkbrenner et al., 2018; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2010; Volk et al., 2014; Volk et al., 2013; Kim et al., 2017). 77% (95CI 73–81%) of children with ASD and 60% (95CI 55–65%) of children without ASD were boys.

3.4. Characteristics of air pollutant exposure

Types of pollutants analyzed in these articles included PM2.5 in 13 studies (Guxens et al., 2016; Pagalan et al., 2019; Becerra et al., 2013; Kaufman et al., 2019; Raz et al., 2015; Ritz et al., 2018; Talbott et al., 2015a; Volk et al., 2014; Chen et al., 2018; Jo et al., 2019; McGuinn et al., 2020; Goodrich et al., 2018; Kim et al., 2017), PM10 in 12 studies[9, 10, 11,39,43,47,52,54, 55, 56,59,61], NOx in 12 studies[9, 10, 11, 12,39,45,47,52,56,58,59,61], O3 in 7 studies (Becerra et al., 2013; Kaufman et al., 2019; Volk et al., 2014; Jo et al., 2019; McGuinn et al., 2020; Goodrich et al., 2018; Kim et al., 2017), metals in 7 studies (Kalkbrenner et al., 2018; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2010; Roberts et al., 2013; Talbott et al., 2015b; Windham et al., 2013), solvents in 5 studies (Kalkbrenner et al., 2018; Kalkbrenner et al., 2010; Talbott et al.,

2015b; Yousefian et al., 2018; Windham et al., 2013), styrene in 3 studies (Kalkbrenner et al., 2018; Kalkbrenner et al., 2010; Talbott et al., 2015b), PAHs in 3 studies (Kalkbrenner et al., 2018; Kalkbrenner et al., 2010; Talbott et al., 2015b), and pesticides in 3 studies (Kalkbrenner et al., 2018; Kalkbrenner et al., 2010; Talbott et al., 2015b).

Type of exposure included a general outdoor exposure in 19 studies (Guxens et al., 2016; Pagalan et al., 2019; Kalkbrenner et al., 2018; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Raz et al., 2018; Raz et al., 2015; Ritz et al., 2018; Roberts et al., 2013; Volk et al., 2014; Volk et al., 2013; Jo et al., 2019; McGuinn et al., 2020; Goodrich et al., 2018; Kim et al., 2017), in cities or regions of high human density in ten studies (Gong et al., 2014; Gong et al., 2017; Becerra et al., 2013; Kaufman et al., 2019; Talbott et al., 2015a; Talbott et al., 2015b; Chen et al., 2018; Yousefian et al., 2018; Oudin et al., 2019; Windham et al., 2013), with one study focusing on distance from homes to freeway and major roads (Volk et al., 2011).

3.4.1. Perinatal periods of exposure

6 studies analyzed exposure to air pollutants during preconception (Dickerson et al., 2015; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Raz et al., 2015; Talbott et al., 2015a; McGuinn et al., 2020), 25 during pregnancy (Gong et al., 2014; Gong et al., 2017; Guxens et al., 2016; Pagalan et al., 2019; Kalkbrenner et al., 2018; Becerra et al., 2013; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2015; Kaufman et al., 2019; Raz et al., 2018; Raz et al., 2015; Ritz et al., 2018; Talbott et al., 2015a; Talbott et al., 2015b; Volk et al., 2011; Volk et al., 2014; Volk et al., 2013; Yousefian et al., 2018; Jo et al., 2019; McGuinn et al., 2020; Oudin et al., 2019; Goodrich et al., 2018; Windham et al., 2013; Kim et al., 2017), 9 during the postnatal period (Gong et al., 2014; Gong et al., 2017; Kalkbrenner et al., 2015; Raz et al., 2015; Roberts et al., 2013; Talbott et al., 2015a; Chen et al., 2018; Jo et al., 2019; McGuinn et al., 2020) and 5 during the two first years of life [44,45,47,52,61].

3.4.2. Quantification of exposure

Most studies (Gong et al., 2014; Guxens et al., 2016; Pagalan et al., 2019; Kalkbrenner et al., 2018; Becerra et al., 2013; Dickerson et al., 2016; Kalkbrenner et al., 2015; Raz et al., 2018; Ritz et al., 2018; Roberts et al., 2013; Talbott et al., 2015b; Chen et al., 2018; Yousefian et al., 2018; McGuinn et al., 2020; Oudin et al., 2019; Goodrich et al., 2018) assessed exposure to pollutants first by geocoding birth certificate residential addresses, followed by use of different models (NATA for National-scale air toxics assessment (Kalkbrenner et al., 2018; Dickerson et al., 2016; Roberts et al., 2013; Talbott et al., 2015b); LUR model for Land Use Regression (Pagalan et al., 2019; Becerra et al., 2013; Yousefian et al., 2018); CALINE4 line source air quality dispersion model (Volk et al., 2013; Kim et al., 2017)) to estimate average pollutant concentration at participants' home address at time of birth.

3.5. Meta-analysis by air pollutants

3.5.1. PM 2.5

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

3.5.2. PM 10

Each increase of 5 $\mu g/m^3$ in PM10 was not associated with risk of ASD using the global model (−1%, non-significant), and was associated with a decreased risk of ASD using the pessimistic model (−3%), and with an increased risk using the optimistic model (+1%). Meta-analysis by periconception periods was associated with a decreased risk using the pessimistic model for the pregnancy period only (−4%) and with an increased risk using the optimistic model for the postnatal period only (+2%) (Fig. 3). There was not enough data to perform meta-analysis by trimester using incremental risk (continuous data). Results were also similar by periconceptional periods (preconception, pregnancy, postnatal) (Supplementary Figure 2) using categorical data. Meta-analysis by trimester did not reveal any significant increase in risk, regardless of the model used (Supplementary Figure 3).

3.5.3. Nox

Each increase of 10 $\mu g/m^3$ in NOx was associated with an overall increased risk of ASD using the global (+2%) and optimistic models (+5%), as well as during pregnancy period. No significant results were found using the pessimistic model in all periods (Fig. 3). Meta-analysis using categorical risks showed similar results (Supplementary Figure 2).

3.5.4. O3

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

3.5.5. Metals

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

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

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

3.6. Overall meta-analysis

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

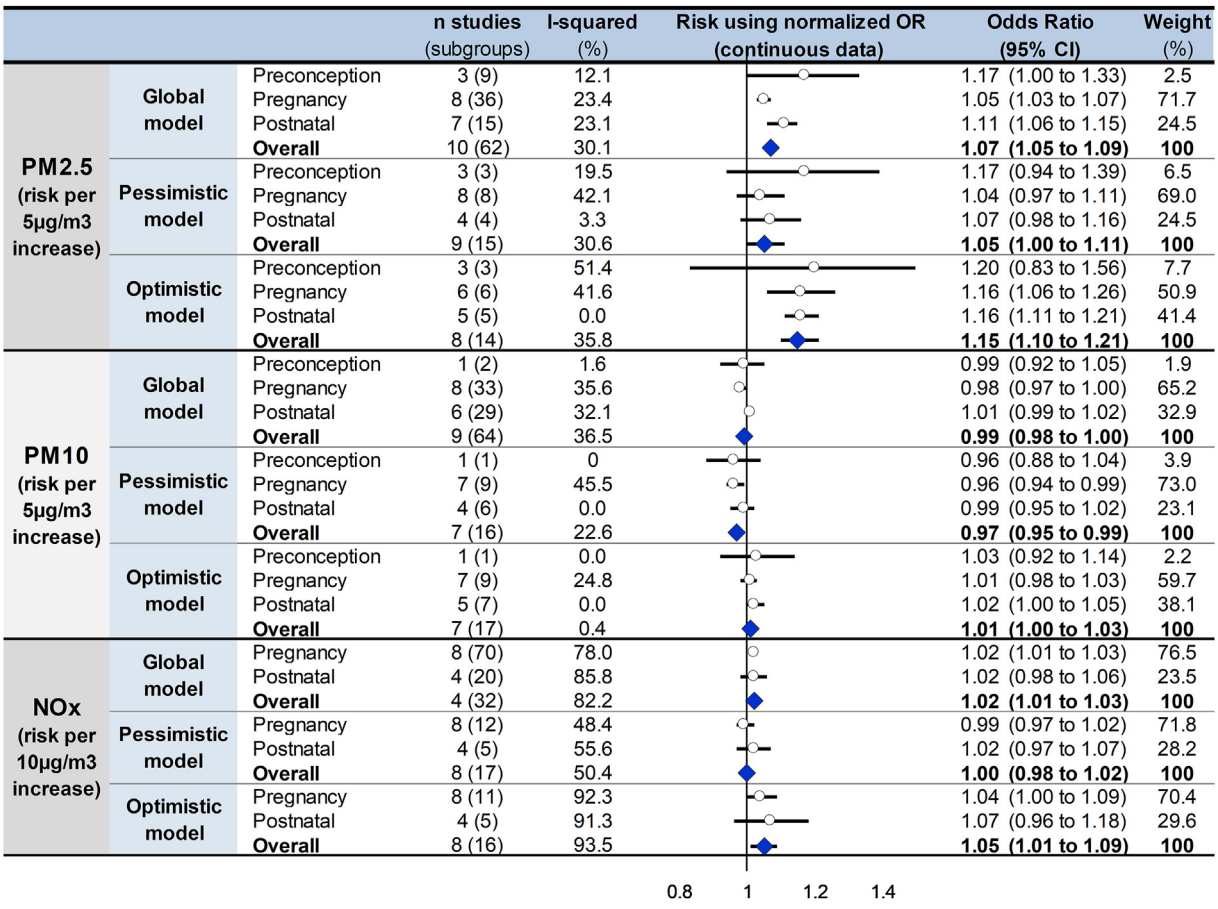

Fig. 3. Meta-analysis on risk of autism by air pollutant depending on perinatal periods (preconception, pregnancy and postnatal), using normalized Odds ratio (continuous data - incremental risk). When available (more than one study), we computed three models for each meta-analysis (a global model using all risks listed in included articles, a pessimistic model using only the less favorable data, and an optimistic model using only the most favorable). 95%CI: 95% confidence intervals. Each meta-analysis is represented in the forest-plot by a dot on a horizontal line, with the corresponding number of articles (n studies (subgroups)) included within the meta-analysis. The white dots represent the odds ratio (OR), and the length of each line around the dots represent its 95% confidence interval (95CI). An overall summary pooled-estimate (result of the meta-analysis of meta-analyses) is represented by a blue lozenge at the end of the graph. The black solid vertical line represents the null estimate (with a value of 1 for OR). Horizontal lines that cross the null vertical line (OR = 1) represent non-significant studies.

the optimistic model only, an increased risk during pregnancy with both the global and optimistic models, and an increased risk regardless of the model used during the postnatal period.

3.7. Metaregressions and sensitivity analyses

Using categorical levels of exposure, PM2.5 tended to lead to greater increased risk of having a child with ASD compared with exposure to PM10 (coefficient 0.20, 95CI −0.02 to 0.42, p = 0.073), NOx (coefficient 0.29, 95CI 0.08 to 0.50, p = 0.006), and solvents (coefficient 0.24, 95CI 0.04 to 0.44, p = 0.017). No other differences between air pollutants exposure were noted, nor between peri-conceptional periods or trimesters. Neither parental age or gender of newborns were found to influence the risk of ASD (Fig. 5). Due to insufficient data other sociodemographic variables were not analyzed. Results were similar using continuous levels of exposure. For PM2.5 and PM10, meta-analysis depending on the methods to measure air pollutants showed similar results.

4. Discussion

The main findings revealed that air pollution particularly that of PM2.5 during the periconception period was associated with an increased risk of ASD in newborns, in all models used. The level of evidence is poor for other air pollutants. Exposure during pregnancy (first and third trimesters) and postnatal periods may be the most at-risk periods. The increased risk of ASD following exposure to air pollutants surrounding pregnancy was not linked with socio-odemographic factors.

4.1. Air pollution and risk of ASD in newborns

We demonstrated that global air pollution exposure in the perinatal period is a risk factor for ASD in newborns Supplementary Figure 4. Despite a previous meta-analysis (Chun et al., 2020), there is the first to report a risk based on consideration of all air pollutants. As, exposures are in general multiple when quantifying risk, it is likely that overall risk is of most interest as reported by other authors (Volk et al., 2011; Volk et al., 2014; Volk et al., 2013). ASD was first described as a disorder in children with problems relating to others, highly sensitive to changes in their environment (Kanner, 1968). Prevalence of ASD appears to have increases over time (Christensen et al., 2016; Zablotsky and Black, 2020) possibly due to a modified definition of ASD, enhanced awareness and improved diagnosis (Zahorodny et al., 2014; Dawson and Bernier, 2013), but also to a global increase in air pollutants in most megalopolis (Bouillon-Minois et al., 2020; Dutheil et al., 2020b). The rigorous and sensitive statistical approach used in this meta-analysis

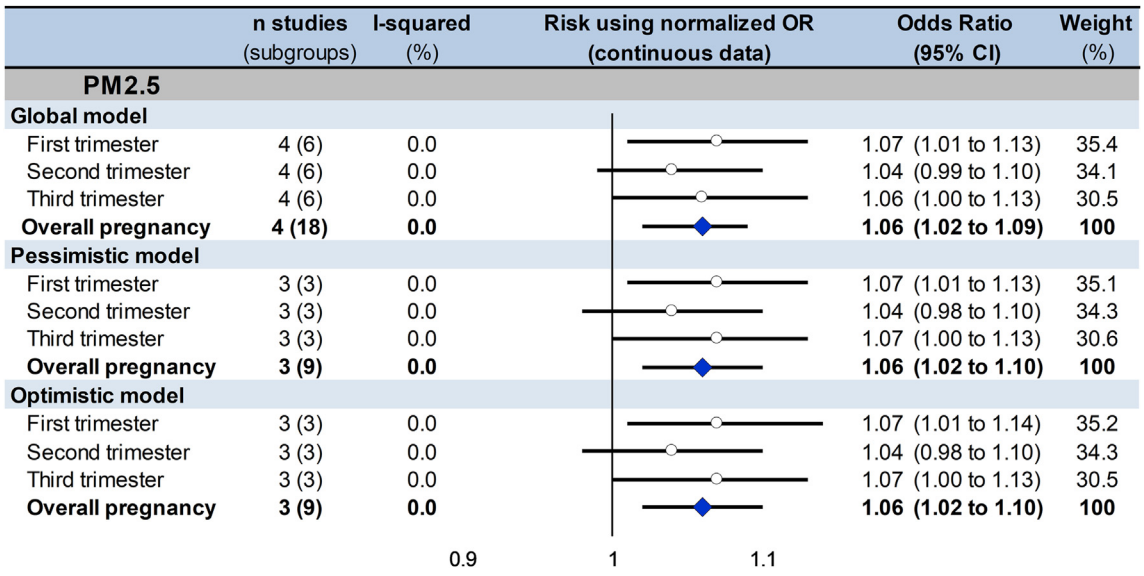

Fig. 4. Meta-analysis on risk of autism for PM2.5 depending on trimester of pregnancy (first, second, third), using normalized Odds ratio (continuous data - incremental risk). When available (more than one study), we computed three models for each meta-analysis (a global model using all risks listed in included articles, a pessimistic model using only the less favorable data, and an optimistic model using only the most favorable). 95%CI: 95% confidence intervals. Each meta-analysis is represented in the forest-plot by a dot on a horizontal line, with the corresponding number of articles (n studies (subgroups)) included within the meta-analysis. The white dots represent the odds ratio (OR), and the length of each line around the dots represent its 95% confidence interval (95CI). An overall summary pooled-estimate (result of the meta-analysis of meta-analyses) is represented by a blue lozenge at the end of the graph. The black solid vertical line represents the null estimate (with a value of 1 for OR). Horizontal lines that cross the null vertical line (OR = 1) represent non-significant studies.

allowed analysis of several included studies presenting different data for the same risk (e.g. several models adjusted on different covariables). There are presently no guidelines on how to manage this issue (Dutheil et al., 2020a). To avoid potential limitations, we created three models for each meta-analysis; a global model based on all risks reported in included articles, a pessimistic model using less favorable risks only (statistically speaking), and an optimistic model using the most favorable risks only. Unsurprisingly, use of optimistic models led to stronger results, but notably, we were unable to demonstrate an increased risk using the pessimistic model based on all air pollutants.

4.2. PM2.5: a public health issue

Risk of developing ASD in newborns increased using the global and optimistic models only for all air pollutants, with a strong high risk following exposure to PM2.5 whatever the model. Even use of the pessimistic model based on the least favorable data (those with the least increased risk) revealed a minimum increased risk of 6% (up to 15% using the optimistic model). Nearly all individual studies showed that maternal exposure to PM2.5 was associated with increased risk of newborns with ASD (Becerra et al., 2013; Kaufman et al., 2019; Raz et al., 2015; Ritz et al., 2018; Talbott et al., 2015a; Volk et al., 2013; Chen et al., 2018; Jo et al., 2019; McGuinn et al., 2020; Goodrich et al., 2018; Kim et al., 2017). Thus indicating the high level of evidence concerning the deleterious effects of PM2.5 and related risk of ASD. PM2.5 particles appear to be the most dangerous pollutant due to their small size, and high volatility (Yan et al., 2020), able to be transported over longer distances (Yan et al., 2020). They also have a lower sedimentation velocity than other larger particles such as PM10 [69]. PM are primarily composed of toxic particles such as PAHs, inorganic particles (sulfate, nitrate, ammonium), or organic carbon metals (copper, iron, nickel)(Kim et al., 2015; Naimabadi et al., 2016). As road traffic is one of the primary sources of PM emission (de Kok et al., 2006; Kim et al., 2015; Cui et al., 2016) and predicted to double over the next twenty years (Forecasts Passenger, 2016), the impact of PM2.5 on health may become a major public health issue (Cohen et al., 2017). As diesel is considered to emit more fine PM than gazoline (Cui et al., 2016; Assessmentf, 2002), it may become a target for future preventive strategy. Levels of evidence are poor for the other air pollutants investigated.

4.3. Late pregnancy and early postnatal period: a key developmental periods

Late pregnancy and early postnatal periods were found to be the most at-risk periods for developing ASD following air pollution exposure. These periods are crucial in the development of the infant (Georgieff et al., 2018), and can influence long-term health outcomes (Esparza-Aguilar et al., 2020). Late pregnancy is important for placental function, fetal growth and brain developments and is also the period when maternal and fetal complications can occur, such as gestational diabetes, pre-eclampsia, hypoxia or brain injury (Dugan and Ma-Crawford, 2019; Ellery et al., 2018; Schumacher et al., 2020; Ridder et al., 2019). Our result showing increased risk of ASD during late pregnancy is in accordance with previous meta-analyses (Chun et al., 2020). Similarly, the early postnatal period can also impact health outcomes as has been shown with breastfeeding which may impact a wide range of parameters such as cognition, brain structure, structural development of the heart and lungs, bone health, or atopy (Santiago-Cruz et al., 2019; Lucas, 2019). In comparison with the meta-analysis of Chun et al., we highlighted the detrimental effects of air pollution leading to increased risk of ASD during the postnatal period, being previously analyzed in relation to the prenatal period. Our results show that the most at-risk periods for ASD were early and late pregnancy and the early postnatal period. These results are in accordance with other studies on air pollution that have showed these periods to also be the most at-risk for other birth outcomes such as hypertension, preeclampsia, pre-term birth, or low birthweight (Zhang et al., 2018; Li et al., 2020; Fang et al., 2020). Both late pregnancy

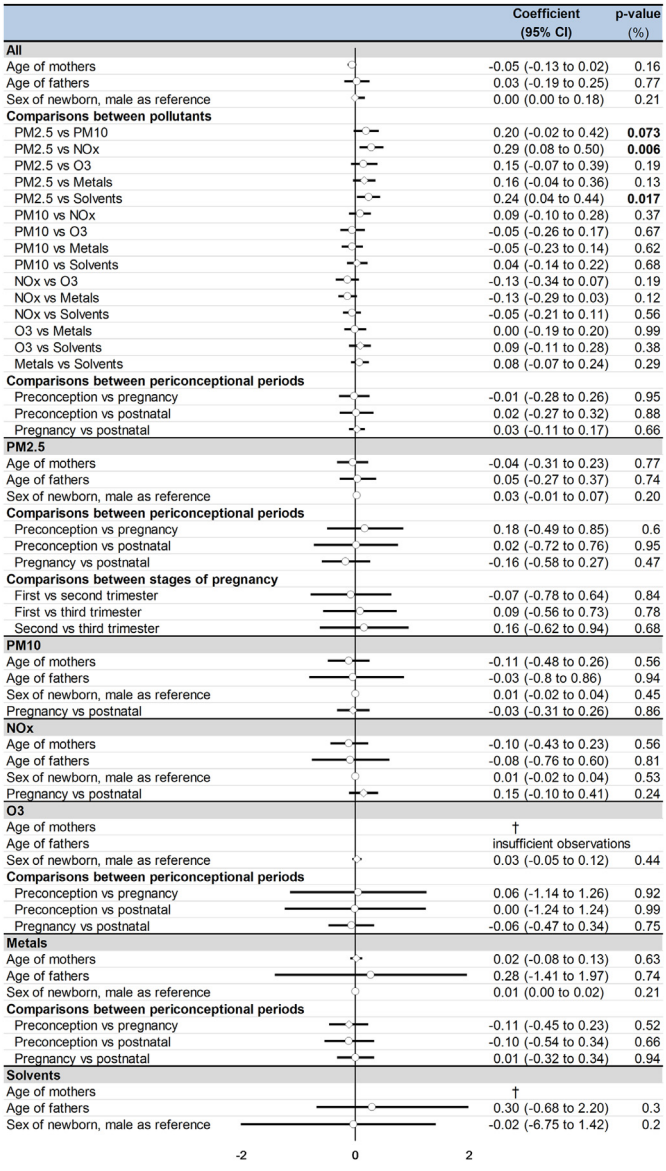

Fig. 5. Meta-regressions 95%CI: 95% confidence intervals; t0: baseline; † Dropped because of collinearity. The effect of each variable on the outcome is represented in the forest-plot by a dot on a horizontal line. The white dots represent the coefficient for each variable, and the length of each line around the dots represent their 95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 0). Horizontal lines that cross the null vertical line are non-significant variables.

and the early postnatal period appear key phases as regards vulnerability to air pollution (Kalkbrenner et al., 2015)

4.4. Influence of sociodemographic and other factors

Most often, etiologies of ASD remain unknown. Although, genetic susceptibility has been highlighted as a risk factor (Lee et al., 2020). No included studies in our meta-analysis indicated genetic susceptibility. Two further highlighted risk factors concern parental age and the newborn gender. Several studies have shown that maternal and/or paternal age (Veldkamp et al., 2020; Gao et al., 2020), and male gender (Cogley et al., 2020; Ruigrok and Lai, 2020) were associated with an increased risk of child neurodevelopmental outcomes such as ASD. In our meta-analysis, neither parental age or newborn genders were found to influence risk following exposure to air pollutants. However, our meta-regressions analyzed whether air pollution modifies this risk depending on parental age or newborn genders. Other investigated putative risk factors for ASD include maternal food intake (Zhong et al., 2020), low birthweight or preterm birth (Cogley et al., 2020; Talmi et al., 2020). As these factors were not assessed in the articles included in our meta-analysis, further analyses were precluded.

4.5. Limitations

Our study has some limitations. Despite the large number of studies, some air pollutants were only included in a few studies. Common air pollutants such as PM2.5, PM10, or NOx, were however commonly assessed and as we included a large sample of 395 615 newborns, this allowed the greater generalizability of our results. Our meta-analysis inherited the limitations of the 28 included studies and was therefore subject to individual bias such as bias of measures of exposure to air pollutants and bias of reporting of ASD. Despite the quality of research reflected in the studies included in our meta-analyses, ASD covers a wide range of severity that was not reported within included articles. Diagnostic method for ASD also differed, limiting quality of data and precluding further analyses, although, most articles used National ASD databases thus guaranteeing data accuracy. A further limitation concerns a possible underestimation of our results. Diagnostic evidence of ASD can be underestimated but is unlikely to be overestimated. Similarly, methods for detection or measurement of air pollutant exposure differed between studies, thus precluding assessment of dose response effects. In addition despite similarities, population characteristics between studies were not identical. Data were collected in various countries, but excluded developing countries. The majority of studies were conducted in the USA (Kalkbrenner et al., 2018; Becerra et al., 2013; Dickerson et al., 2016; Dickerson et al., 2015; Kalkbrenner et al., 2010; Kalkbrenner et al., 2015; Kaufman et al., 2019; Raz et al., 2015; Roberts et al., 2013; Talbott et al., 2015a; Talbott et al., 2015b; Volk et al., 2011; Volk et al., 2014; Volk et al., 2013; Jo et al., 2019; McGuinn et al., 2020; Goodrich et al., 2018; Windham et al., 2013; Kim et al., 2017), and to a lesser extent in Europe (Gong et al., 2014; Gong et al., 2017; Guxens et al., 2016; Ritz et al., 2018; Oudin et al., 2019). The lack of data from Africa, Asia, and Oceania reduces potential generalizability of our results, though. All ethnicities were included. Generalizability of our results may also be lessened due to analysis of single-site studies, even if the majority of included studies were multi-site. As studies differed in their study design, we performed sensitivity analyses allowing demonstration of similar results whatever the design. In our meta-analysis global model, some included studies appeared several times, with different data for the same outcome depending on adjustment models. In the absence of clear consensus and despite having more effect sizes within each meta-analyses when compared with studies included in several highly-regarded published articles published (Aldridge et al., 2018; Fellmeth et al., 2018), the weight of studies may have required ponderation (Cochrane Handbook for Sys). This is one of the reasons for use of optimistic and pessimistic models when only one data is available for each included article. A further limitation of our meta-analysis concerns included studies using OR adjusted on different factors between studies, even if adjusted OR may limit confusion bias. Finally, causality may also be a limitation in retrospective or case-control studies.

5. Conclusion

Exposure to air pollution, notably PM2.5 during pregnancy was associated with an increased risk of ASD in newborns regardless of the model used. The level of evidence concerning other air pollutants is however poor. Exposure during pregnancy and the postnatal period appear to be the most at-risk periods.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.116856.

References

Aldridge, R.W., et al., 2018. Global patterns of mortality in international migrants: a systematic review and meta-analysis. Lancet 392, 2553–2566.

Assessment, U. E. N. C. For E. Health Assessment Document for Diesel Engine Exhaust, 2002. Final. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=29060.

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, 380–386.

Benichou, T., et al., 2018. Heart rate variability in type 2 diabetes mellitus: a systematic review and meta-analysis. PloS One 13 e0195166.

Benoist d'Azy, C., Pereira, B., Chiambaretta, F., Dutheil, F., 2016. Oxidative and anti-oxidative stress markers in chronic glaucoma: a systematic review and meta-analysis. PloS One 11 e0166915.

Bouillon-Minois, J.-B., Lesage, F.-X., Schmidt, J., Dutheil, F. Coronavirus, Exceptional Health Situations, 2020. The first disaster with benefits on air pollution. Disaster Med. Public Health Prep. 1–3. https://doi.org/10.1017/dmp.2020.174.

Chen, G., Wan, X., Yang, G., Zou, X., 2015. Traffic-related air pollution and lung cancer: a meta-analysis. Thorac Canc. 6, 307–318.

Chen, G., et al., 2018. Early life exposure to particulate matter air pollution (PM1, PM2.5 and PM10) and autism in Shanghai, China: a case-control study. Environ. Int. 121, 1121–1127.

Chiaverini, L., 2002. Asthma, particulates, and diesel exhaust. Med. Health R. I. 85, 140–142.

Christensen, D.L., et al., 2016. Prevalence and characteristics of autism spectrum disorder among children aged 8 Years–Autism and developmental disabilities monitoring Network, 11 sites, United States, 2012. MMWR Surveill Summ. 65, 1–23.

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.

Cochrane Handbook for systematic reviews of interventions. https://handbook-5-1.cochrane.org/.

Cogley, C., O'Reilly, H., Bramham, J., Downes, M., 2020. A systematic review of the risk factors for autism spectrum disorder in children born preterm. Child Psychiatr. Hum. Dev. https://doi.org/10.1007/s10578-020-01071-9.

Cohen, A.J., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389, 1907–1918.

Costa, L.G., Chang, Y.-C., Cole, T.B., 2017. Developmental neurotoxicity of traffic-related air pollution: focus on autism. Curr. Environ. Health Rep. 4, 156–165.

Courtin, R., et al., 2016. Prevalence of dry eye disease in visual display terminal workers: a systematic review and meta-analysis. BMJ Open 6 e009675.

Cui, M., et al., 2016. Chemical composition of PM2.5 from two tunnels with different vehicular fleet characteristics. Sci. Total Environ. 550, 123–132.

Dawson, G., Bernier, R., 2013. A quarter century of progress on the early detection and treatment of autism spectrum disorder. Dev. Psychopathol. 25, 1455–1472.

de Kok, T.M.C.M., Driece, H.A.L., Hogervorst, J.G.F., Briedé, J.J., 2006. Toxicological assessment of ambient and traffic-related particulate matter: a review of recent studies. Mutat. Res. 613, 103–122.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Contr. Clin. Trials 7, 177–188.

Dickerson, A.S., et al., 2015. Autism spectrum disorder prevalence and proximity to industrial facilities releasing arsenic, lead or mercury. Sci. Total Environ. 536, 245–251.

Dickerson, A.S., et al., 2016. Autism spectrum disorder prevalence and associations with air concentrations of lead, mercury, and arsenic. Environ. Monit. Assess. 188, 407.

Dockery, D.W., Evans, J.S., 2017. Tallying the bills of mortality from air pollution. Lancet 389, 1862–1864.

Dugan, J.A., Ma-Crawford, 2019. J. Managing gestational diabetes. J. Am. Acad. PAs 32, 21–25.

Dutheil, F., et al., 2020a. Letter to the Editor: comment on 'Maternal exposure to air pollution and risk of autism in children: a systematic review and meta-analysis'. Environ. Pollut. 264, 114724.

Dutheil, F., Baker, J.S., Navel, V., 2020b. COVID-19 and cardiovascular risk: flying toward a silent world? J. Clinic. Hypertension (Greenwich, Conn. https://doi.org/10.1111/jch.14019.

Ellery, S.J., et al., 2018. Antenatal prevention of cerebral palsy and childhood disability: is the impossible possible? J. Physiol. 596, 5593–5609.

Esparza-Aguilar, M., Arroyo, P., Gómez-Verján, J.C., Martín-Martín, V., 2020. Early life exposure and its association with diseases in adulthood: review of longitudinal studies. Boletin Med. Del Hospital Infantil De Mexico 77, 153–165.

Fang, J., et al., 2020. Prenatal PM2.5 exposure and the risk of adverse births outcomes: results from project ELEFANT. Environ. Res. 110232 https://doi.org/10.1016/j.envres.2020.110232.

Fellmeth, G., et al., 2018. Health impacts of parental migration on left-behind children and adolescents: a systematic review and meta-analysis. Lancet 392, 2567–2582.

IATA forecasts passenger demand to double over 20 years. https://www.iata.org/en/pressroom/pr/2016-10-18-02/.

Gao, Y., et al., 2020. Association of grandparental and parental age at childbirth with autism spectrum disorder in children. JAMA Netw. Open 3 e202868.

Georgieff, M.K., Tran, P.V., Carlson, E.S., 2018. Atypical fetal development: fetal alcohol syndrome, nutritional deprivation, teratogens and risk for neurodevelopmental disorders and psychopathology. Dev. Psychopathol. 30, 1063–1086.

Gong, T., et al., 2014. Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins. Twin Res. Hum. Genet. 17, 553–562.

Gong, T., et al., 2017. Perinatal exposure to traffic-related air pollution and autism spectrum disorders. Environ. Health Perspect. 125, 119–126.

Goodrich, A.J., et al., 2018. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. Autism Res. 11, 69–80.

Guxens, M., et al., 2016. Air pollution exposure during pregnancy and childhood autistic traits in four European population-based cohort studies: the ESCAPE project. Environ. Health Perspect. 124, 133–140.

Hao, X., Pan, J., Gao, X., Zhang, S., Li, Y., 2020. Gut microbiota on gender bias in autism spectrum disorder. Rev. Neurosci. https://doi.org/10.1515/revneuro-2020-0042.

Jarvis, D.J., Adamkiewicz, G., Heroux, M.-E., Rapp, R., Kelly, F.J., 2010. Nitrogen Dioxide. WHO Guidelines for Indoor Air Quality: Selected Pollutants. World Health Organization.

Jo, H., et al., 2019. Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. Environ. Pollut. 254, 113010.

Kalkbrenner, A.E., et al., 2010. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology 21, 631–641.

Kalkbrenner, A.E., et al., 2015. Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. Epidemiology 26, 30–42.

Kalkbrenner, A.E., et al., 2018. Air toxics in relation to autism diagnosis, phenotype, and severity in a U.S. Family-based study. Environ. Health Perspect. 126, 037004.

Kanner, L., 1968. Autistic disturbances of affective contact. Acta Paedopsychiatr. 35, 100–136.

Kaufman, J.A., et al., 2019. Ambient ozone and fine particulate matter exposures and autism spectrum disorder in metropolitan Cincinnati, Ohio. Environ. Res. 171, 218–227.

Kim, K.-H., Kabir, E., Kabir, S., 2015. A review on the human health impact of airborne particulate matter. Environ. Int. 74, 136–143.

Kim, D., et al., 2017. The joint effect of air pollution exposure and copy number variation on risk for autism. Autism Res. 10, 1470–1480.

Kolevzon, A., Gross, R., Reichenberg, A., 2007. Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch. Pediatr. Adolesc. Med. 161, 326–333.

Lam, J., et al., 2016. A systematic review and meta-analysis of multiple airborne pollutants and autism spectrum disorder. PloS One 11 e0161851.

Lanhers, C., et al., 2017. Creatine supplementation and upper limb strength performance: a systematic review and meta-analysis. Sports Med. 47, 163–173.

Lee, J., et al., 2020. Genetic variation and autism: a field synopsis and systematic meta-analysis. Brain Sci. 10.

Li, C., et al., 2020. Maternal exposure to air pollution and the risk of low birth weight: a meta-analysis of cohort studies. Environ. Res. 190, 109970.

Loxham, M., Davies, D.E., Holgate, S.T., 2019. The health effects of fine particulate air pollution. BMJ 367, l6609.

Lucas, A., 2019. Scientific Evidence for Breastfeeding, vol. 90. Nestle Nutrition Institute Workshop Series, pp. 1–12.

McGuinn, L.A., et al., 2020. Early life exposure to air pollution and autism spectrum disorder: findings from a multisite case-control study. Epidemiology 31, 103–114.

Møller, P., et al., 2014. Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles. Mutat. Res. Rev. Mutat. Res. 762, 133–166.

Naimabadi, A., et al., 2016. Chemical composition of PM10 and its in vitro toxicological impacts on lung cells during the Middle Eastern Dust (MED) storms in Ahvaz, Iran. Environ. Pollut. 211, 316–324.
Navel, V., et al., 2019. Efficacy of treatments for Demodex blepharitis: a systematic review and meta-analysis. Ocul. Surf. 17, 655–669.
Nypaver, C., Arbour, M., Niederegger, E., 2016. Preconception care: improving the health of women and families. J. Midwifery Wom. Health 61, 356–364.
Oberdörster, G., Oberdörster, E., Oberdörster, J., 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health Perspect. 113, 823–839.
Ollier, M., Chamoux, A., Naughton, G., Pereira, B., Dutheil, F., 2014. Chest CT scan screening for lung cancer in asbestos occupational exposure: a systematic review and meta-analysis. Chest 145, 1339–1346.
Orellano, P., Reynoso, J., Quaranta, N., Bardach, A., Ciapponi, A., 2020. Short-term exposure to particulate matter (PM10 and PM2.5), nitrogen dioxide (NO2), and ozone (O3) and all-cause and cause-specific mortality: systematic review and meta-analysis. Environ. Int. 142, 105876.
Oudin, A., et al., 2019. Prenatal exposure to air pollution as a potential risk factor for autism and ADHD. Environ. Int. 133, 105149.
Pagalan, L., et al., 2019. Association of prenatal exposure to air pollution with autism spectrum disorder. JAMA Pediatr. 173, 86–92.
Raz, R., et al., 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, 264–270.
Raz, R., et al., 2018. Traffic-related air pollution and autism spectrum disorder: a population-based nested case-control study in Israel. Am. J. Epidemiol. 187, 717–725.
Ridder, A., Giorgione, V., Khalil, A., Thilaganathan, B., 2019. Preeclampsia: the relationship between uterine artery blood flow and trophoblast function. Int. J. Mol. Sci. 20.
Ritz, B., et al., 2018. Air pollution and autism in Denmark. Environ. Epidemiol. 2.
Roberts, A.L., et al., 2013. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. Environ. Health Perspect. 121, 978–984.
Rodier, P.M., Ingram, J.L., Tisdale, B., Nelson, S., Romano, J., 1996. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. J. Comp. Neurol. 370, 247–261.
Ruigrok, A.N.V., Lai, M.-C., 2020. Sex/gender differences in neurology and psychiatry: Autism. Handb. Clin. Neurol. 175, 283–297.
Russo, M.W., 2007. How to review a meta-analysis. Gastroenterol. Hepatol. 3, 637–642.
Santiago-Cruz, R.M., et al., 2019. [Breastfeeding and infant feeding in the first level of attention]. Rev. Med. Del Instit. Mexic. Del Seguro Soc. 57, 387–394.
Schumacher, M., Liere, P., Ghoumari, A., 2020. Progesterone and fetal-neonatal neuroprotection. Best Pract. Res. Clin. Obstet. Gynaecol. https://doi.org/10.1016/j.bpobgyn.2020.09.001.
Shah, A.S.V., et al., 2013a. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 382, 1039–1048.
Shah, A.S.V., et al., 2013b. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 382, 1039–1048.
Stang, A., 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur. J. Epidemiol. 25, 603–605.
Talbott, E.O., et al., 2015a. Fine particulate matter and the risk of autism spectrum disorder. Environ. Res. 140, 414–420.
Talbott, E.O., et al., 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.
Talmi, Z., Mankuta, D., Raz, R., 2020. Birth weight and autism spectrum disorder: a population-based nested case-control study. Autism Res.: Off. J. Int. Soc. Autism Res. 13, 655–665.
The Lancet, 2017. UK air pollution and public health. Lancet 389, 1860.
Vandenbroucke, J.P., et al., 2014. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Int. J. Surg. 12, 1500–1524.
Veldkamp, S.a.M., et al., 2020. Parental age in relation to offspring's neurodevelopment. Journal of clinical child and adolescent psychology: the official journal for the society of clinical child and adolescent psychology. Am. Psychol. Assoc. https://doi.org/10.1080/15374416.2020.1756298. Division 53 1–13.
Volk, H.E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F., McConnell, R., 2011. Residential proximity to freeways and autism in the CHARGE study. Environ. Health Perspect. 119, 873–877.
Volk, H.E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., McConnell, R., 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatr. 70, 71–77.
Volk, H.E., et al., 2014. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Epidemiology 25, 44–47.
von Ehrenstein, O.S., Cui, X., Yan, Q., Aralis, H., Ritz, B., 2020. Maternal prenatal smoking and autism spectrum disorder in offspring: a California statewide cohort and sibling study. Am. J. Epidemiol. https://doi.org/10.1093/aje/kwaa182.
Wilson, W.E., Suh, H.H., 1997. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manag. Assoc. 47, 1238–1249.
Windham, G.C., et al., 2013. Use of birth certificates to examine maternal occupational exposures and autism spectrum disorders in offspring. Autism Res. 6, 57–63.
Yan, G., et al., 2020. Understanding PM2.5 concentration and removal efficiency variation in urban forest park-Observation at human breathing height. PeerJ 8, e8988.
Yousefian, F., et al., 2018. Long-term exposure to ambient air pollution and autism spectrum disorder in children: a case-control study in Tehran, Iran. Sci. Total Environ. 643, 1216–1222.
Zablotsky, B., Black, L.I., 2020. Prevalence of children aged 3-17 Years with developmental disabilities, by urbanicity: United States, 2015-2018. Natl. Health Stat Rep. 1–7.
Zahorodny, W., et al., 2014. Increasing autism prevalence in metropolitan New Jersey. Autism 18, 117–126.
Zhang, M., et al., 2018. Maternal exposure to ambient particulate matter $\leq$2.5 μm during pregnancy and the risk for high blood pressure in childhood. Hypertension 72, 194–201.
Zhong, C., Tessing, J., Lee, B.K., Lyall, K., 2020. Maternal dietary factors and the risk of autism spectrum disorders: a systematic review of existing evidence. Autism Res. https://doi.org/10.1002/aur.2402.