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EFFETTI DELL'INQUINAMENTO ATMOSFERICO NEI PRIMI 1000 GIORNI DI VITA SULLO SVILUPPO NEUROPSICOLOGICO DEL BAMBINO. UNA REVISIONE DELLA LETTERATURA

A cura del gruppo di lavoro **"I primi 1000 giorni"**

Questo documento nasce nell'ambito del progetto Coorti di nuovi nati, esposizioni ambientali e promozione della salute nei primi 1000 giorni di vita: integrazione dei dati di esposizione con dati molecolari ed epigenetici (CUP: C92F17003030001)
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Effetti dell'inquinamento atmosferico nei primi 1000 giorni di vita sullo sviluppo neuropsicologico del bambino

Tabella 1. Strategia di ricerca utilizzata in PubMed

Database: Pubmed Data ricerca: 01/03/2019		N° record
Exposure terms	"air pollution"[tiab] OR "air pollutant"[tiab] OR "air pollutants"[tiab] OR "sulphur dioxide"[tiab] OR "SO2"[tiab] OR "nitrogen oxide"[tiab] OR "nitrogen oxides"[tiab] OR "NOx"[tiab] OR "NO2"[tiab] OR ozone[tiab] OR "O3"[tiab] OR "particulate matter"[tiab] OR (PM*[tiab] NOT ("prospective memory" [tiab] OR postmenopaus*[tiab] OR "phosphamide mustard" [tiab]) OR "pregnancy morbidity"[tiab]) OR ("PAH"[tiab] NOT ("pulmonary arterial hypertension"[tiab] OR "Phenylalanine hydroxylase"[tiab])) OR "Volatile Organic Compounds"[tiab] OR ("VOC"[tiab] NOT "vaso-occlusive crisis"[tiab]) OR "black carbon"[tiab] OR "elemental carbon"[tiab] OR "organic carbon"[tiab]	182289
Outcome	"Neurodevelopmental Disorders"[Mesh] OR autism*[tiab] OR autistic*[tiab] OR Asperger*[tiab] OR "pervasive development"[tiab] OR cognition*[tiab] OR "learning disability"[tiab] OR "Attention-Deficit Hyperactivity Disorder"[tiab] OR "ADHD"[tiab]	260338
Population	Infant[tiab] OR newborn[tiab] OR toddler[tiab] OR child*[tiab] OR "Child"[Mesh] OR "Infant"[Mesh] OR preschool*[tiab] OR prenatal[tiab] OR pregnancy[tiab] OR birth[tiab] OR perinatal[tiab] OR gestation[tiab] OR fetal[tiab] OR "Adolescent"[Mesh] OR adolescent*[tiab] OR teen*[tiab]	4288925
	("Animals"[Mesh] OR "Plants"[Mesh] OR "Bacteria"[Mesh]) NOT "Humans"[Mesh]	5485531
	1 AND 2 AND 3	311
	5 NOT 4	298

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Tabella 2. Tavola sinottica con descrizione delle 12 revisioni sistematiche identificate sull'associazione tra esposizione ad inquinanti atmosferici e sviluppo neuropsciologico del bambino

Author, year, journal	Subjects	Years, studies	Exposure	Outcomes	Results
Perera F (2018) Environ Res	Children	January 1, 2000 - April 30, 2018. 61 studies included (case-control and cohort studies and meta-analyses).	Fossil fuel combustion by-products, including particulate matter (PM2.5), polycyclic aromatic hydrocarbons (PAH), nitrogen dioxide (NO2) and carbon dioxide (CO2)	Preterm birth (PTB), low birthweight (LBW), autism, attention deficit hyperactivity disorder, IQ reduction, and asthma.	Although study results on adverse cognitive and behavioral outcomes have been inconsistent, there is evidence of an association of PM2.5 with certain adverse cognitive outcomes, with suggestive evidence for ADHD supported by MRI findings. Significant associations between an ASD diagnosis and prenatal exposure to PM2.5. A clustered meta-analysis of three US studies found a significant pooled effect estimate (OR = 2.32 (95% CI: 2.15, 2.51)) per 10 µg/m3 increase in PM2.5 (Lam et al., 2016). Another meta-analysis of seven cohort and five case-control studies, including the European multi-site study, estimated the change in ASD diagnoses associated with a 10 µg/m3 increase in exposure in PM2.5 to be 1.34 (95% CI:0.83, 2.17)

Morales-Suarez-Varela M (2017) Environ Res	children	PubMed November 2015 - January 2016. Cohort and case-control studies. 13 studies	Particulate matter (PM)	Health outcomes related to ASD.	Four of the studies found no association between PM exposure and ASD. The other 8 studies show positive associations restricted to specific exposure windows, which however do not reach statistical significance at times. There is an association between PM exposure and ASD whose strength varies according to the particle size studied with the association with PM2.5 and diesel PM being stronger.
Lam J (2016) Plos One OMS	children	23 studies (17 case-control, 4 ecological, 2 cohort).	airborne pollutants, including particulate matter air pollutants and others (e.g. pesticides and metals).	Autism Spectrum Disorder (ASD).	Statistically significant summary odds ratios (ORs) of 1.07 (95% CI: 1.06, 1.08) per 10-mug/m3 increase in PM10 exposure (n = 6 studies) and 2.32 (95% CI: 2.15, 2.51) per 10-mug/m3 increase in PM2.5 exposure (n = 3 studies).
Ng M (2017) Health Promot Chronic Dis Prev Can	children	MEDLINE, PsycINFO and ERIC 1 January, 2003 - 12 July, 2013. 315 studies (234 studies, 2 metanalysis 19 systematic reviews); 44 about chemical	Physical and social environments: chemical, physiological, nutritional and social factors	Autism spectrum disorder (ASD)	Several risk factors emerged consistently: chemical factors such as traffic-related air pollutants; physiological factors including advanced parental age, preterm birth, low birth weight, hyperbilirubinemia and clustering of pregnancy complications; and maternal immigrant status. No association with vaccines.

Clifford A (2016) Environ Res OMS	Children and adults	Web of Knowledge, Pubmed, SciVerse Scopus, CINAHL, PsychInfo and Science Direct up to October 2015. 31 studies 2006 - 2015, from the Americas (n=15), Asia (n=5) and Europe (n=11)	Pollution exposure in utero (nitrogen dioxide, black carbon, ozone, particulate matter)	Cognitive functioning and impairment across the life course and cognitive parameters (cognition, cognitive function, cognitive impairment, neurodevelopment, dementia, Alzheimer) memory, attention, executive functions).	Many studies showed weak but quantified relationships between various air pollutants and cognitive function. Pollution exposure in utero has been associated with increased risk of neuro-developmental delay. Exposure in childhood has been inversely associated with neuro-developmental outcomes in younger children and with academic achievement and neurocognitive performance in older children.

Vrijheid M (2016) Int J Hyg Environ Health *Revisione narrativa di review sistematic he OMS	Children	PubMed 2010-2015. systematic review articles and international meta-analyses.	Prenatal/maternal intra-uterine exposures or post-natal childhood exposures (0–18 years). Environmental pollutants (air pollutants, heavy metals, organochlorine compounds, perfluoroalkyl substances, polybrominated diphenyl ethers, pesticides, phthalates and bisphenol)	Foetal growth and prematurity, neurodevelopment, respiratory and immune health, and childhood growth and obesity.	Findings of recent prospective studies and meta-analyses have corroborated previous good evidence, often at lower exposure levels, for effects on foetal growth of air pollution and polychlorinated biphenyls (PCBs), for neurotoxic effects of lead, methylmercury, PCBs and organophosphate pesticides, and for respiratory health effects of air pollution. Moderate evidence has emerged for a potential role of environmental pollutants in attention deficit hyperactivity disorder and autism (lead, PCBs, air pollution). Moderate evidence that certain chemicals of relatively recent concern may be associated with adverse child health outcomes, specifically perfluorooctanoate and foetal growth, and polybrominated diphenyl ethers and neurodevelopment. For other chemicals of recent concern, such as phthalates and bisphenol A, the literature is characterised by large inconsistencies preventing strong conclusions.

Appleton AA (2016) Curr Environ Health Rep	Children	PubMed and Web of Science to march 2016. 41 studies. 15, 14, 12 studies focused on asthma, cognition/ behavior, and perinatal outcomes, respectively.	Early-life social and environmental exposures and social factors	Asthma, cognition/ behavior, and perinatal outcomes	Across all studies reviewed, 72 % observed significant synergistic associations between social and environmental exposures. Air pollution was the most frequently studied environmental exposure, and socioeconomic status was the most commonly studied social factor.
Flores-Pajot MC (2016) Environ Res OMS	Children	Cochrane Database of systematic reviews, PubMed, Web of Science, Environmental Index databases. 7 cohorts and 5 case-control studies met the inclusion criteria for the meta-analysis. 26 (cohort and case-control) studies	Air pollution. Critical exposure windows: (i) first, second and third trimester of pregnancy, (ii) entire pregnancy, and (iii) postnatal period.	Autism spectrum disorder (ASD)	The meta-estimates for the change in ASD associated with a 10 mug/m3 increase in exposure in PM2.5 and 10 ppb increase in NO2 during pregnancy were 1.34 (95% CI:0.83, 2.17) and 1.05 (95% CI:0.99, 1.11), respectively. Stronger associations were observed for exposures received after birth, but these estimates were unstable as they were based on only two studies. O3 exposure was weakly associated with ASD during the third trimester of pregnancy and during the entire pregnancy, however, these estimates were also based on only two studies.

Suades-Gonzalez E (2015) Endocrinology OMS	children.	MEDLINE, Web of Science, and Science direct. January 1, 2012 - June 12, 2015. 31 studies	Air pollution	Neuropsychological developmental (brain, cognition and behavior)	Evidence sufficient for: pre- or postnatal PAHs exposure and decreased global IQ; fine particulate matter (PM2.5) and autism spectrum disorder. Limited evidence was encountered between nitrogen oxides and autism spectrum disorder. For other outcome reviewed (ADHD, behavioural problems, executive functions, memory, ecc) the evidence was inadequate or insufficient due to the reduced number of studies, deficient quality or low consistency of the results between studies.

Rossignol DA (2014) Transl Psychiatry	Children	Pubmed, Scopus, EMBASE, Google Scholar, CINAHL, ERIC, AMED, PsychInfo and Web of Science through November 2013. 37 (a) + 40 (b) + 10 (c) studies	(a) toxicant exposures in the environment (pesticides, phthalates, polychlorinated biphenyls (PCBs), solvents, toxic waste sites, air pollutants and heavy metals) during the preconceptional, gestational and early childhood periods; (b) biomarkers of toxicants; and (c) potential genetic susceptibilities to toxicants.	Autism spectrum disorders (ASD)	In the first category (a) examining ASD risk and estimated toxicant exposures in the environment, the majority of studies (34/37; 92%) reported an association. The strongest evidence found for air pollutants and pesticides. Gestational exposure to methylmercury (through fish exposure, 1 study) and childhood exposure to pollutants in water supplies (2 studies) were not found to be associated with ASD risk.

Kalkbrenner AE (2014) Curr Probl Pediatr Adolesc Health Care	children.	PubMed and Google Scholar to 2014. 32 studies (7 about traffic related air pollutants)	tobacco, air pollutants, volatile organic compounds and solvents, metals (from air, occupation, diet, dental amalgams, and thimerosal-containing vaccines), pesticides, and organic endocrine-disrupting compounds such as flame retardants, non-stick chemicals, phthalates, and bisphenol A. Exposure in pregnancy or the 1st year of life	Autism	Some environmental exposures showed associations with autism, especially traffic-related air pollutants, some metals, and several pesticides, with suggestive trends for some volatile organic compounds (e.g., methylene chloride, trichloroethylene, and styrene) and phthalates.
Fu P (2019) Science of the Total Environment	Children and adults	PubMed and CNKI databases; articles published until June 2018. 80 studies. 6 on ASD.	PM2.5	Stroke, dementia, Alzheimer's disease, **autism spectrum disorder (ASD)**, Parkinson's disease, and mild cognitive impairment (MCI).	Short- and long-term PM2.5 exposure was associated with increased risks of ASD (1.68, 95% CI 1.20–2.34)

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Tabella 3. Tavola sinottica con descrizione degli articoli originali contentuti nelle 12 revisioni sistematiche, selezionati sulla base della finestra di esposizione definita (gravidanza e primi anni di vita).

1 Author, year	Design	Subjects	Exposure	Outcomes	Results
Abid (2014)	Cross-sectional	6 –15 y; n = 1257; United States	PAH Postnatal	Learning disability, special education. Test: Parental report	PAH 1-pyrene: < ADHD and learning disability among females 1-napthol: — 2-napthol: — 2-fluorene and > Special education, 3-fluorene: particularly in males 1-phenanthrene: — 2-phenanthrene: — 3-phenanthrene: —
Becerra (2013)	Nested case-control	Children 3-5 y, born in 1995–2006 to mothers who resided in Los Angeles County at the time of giving birth. Los Angeles, California, US. 1998– 2009 7603 cases, 75,782 controls	Prenatal (whole pregnancy). Daily averages of gaseous pollutants (CO, NO2, NO, O3) and 24 h measure- ments of PM10 and PM2.5 Source: local TRAP	Autistic disorder (DSM-IV-R determined by DDS staff). Adjustment for Maternal and perinatal characteristics	Mean [PM]=19.6 µg/m3 PM2.5 per 4.68 µg/m3 increase Adj OR 1,07 (95%CI 1 to 1,15); Mean [PM]=36.3 µg/m3 PM10 per 8.25 µg/m3 increase Adj OR 1,03 (95%CI 0,96 to 1,1)
Bellinger (1988)	prospective	n = 204, 24 months	lead, prenatal	cognitive development	Synergistic association with socio-economic exposures: Higher levels of lead exposure were associated with worse cognitive development among lower socioeconomic strata

Bellinger (1990)	prospective	n = 170, 5 years	lead, prenatal	cognitive development	Synergistic association with socio-economic exposures: Deleterious effect of higher levels of lead exposure persisted rhrough 5 years among children with lower SES, less enriched home environments
Calderón-Garcidueñas (2008)	Cross-sectional	n=73 Mean age 9.5 years 52% female (Mexico)	Urban or rural area of residence (Mexico City or Polotitlán)	Intelligence WISC-R. Confounded measured - Age.	Polotitlán children performed within normative level of cognitive development on all measures. Mexico City children performed significantly behind chronological age on several subscales: Information (t=2.35, p=0.019); Similarities (t= 2.60, p=0.009); Vocabulary (t=2.95, p=0.003); Comprehension (t= 2.50, p=0.013); Digit span (t= 4.61, po0.001); Object assembly (t=2.42, p=0.016); Coding (t= 3.80, po0.001); Verbal IQ (t=3.13, p=0.002); Full Scale IQ (t= 2.25, p=0.002) ; Arithmetic (t=0.86, ns); Picture completion (t=1.17, ns); Picture arrangement (t=0.72, ns); Block design (t=0.15, ns); Mazes (t=0.82); Performance IQ (t=1.38, ns).
Calderón-Garcidueñas (2012)	Prospective cohort	7 y; n = 20; Mexico	CO, NO, O3, PM, SO2, lead: Postnatal (livelong residency in Mexico City)	Global IQ. Test: WISC-R	CO, NO, O3, PM, SO2, lead: >Cognitive performance on measures related to temporal/parietal/frontal neurocognitive networks

Calderón-Garcidueñas (2015)	Cross-sectional	13.4 (4.8) y; n = 50; Mexico	O3, PM: Lifelong residency in Mexico City (including pregnancy)	APOE status on global IQ. Test: WISC-R	O3, PM: < Short and working memory, reasoning and knowledge and a negative difference for verbal and global IQ
Chiu (2013)	prospective; Birth cohort	n=174 Age 7–14 years 53% female (USA)	Lifetime home exposure to black carbon exposure estimated using land-use regression model. Interquartile range 0.53– 69g/m3(median 0.63 µg/ 0.3 µ m)	Cognitive functioning CPT. Confounded measured - Maternal race and educational status, child's IQ, sex, age at CPT assessment, exposure to preand post-natal ETS, blood lead, community violence exposure	2nd quartile of black carbon associated with increased: Omission error (β=2.66,6.34 to 11.66) Commission error (β=6.15, 2.03 to 10.27) Slower RT (β =6.51, 0.43–12.59) 3rd quartile of black carbon associated with increased: Omission error (β=4.89,4.71 to 14.49) Commission error (β=4.75, 0.36–9.14) Slower RT (β =6.14,0.35 to 12.63) 4th quartile of black carbon associated with increased: Omission error (β=0.62,8.57 to 9.81) Commission error (β=3.32, 0.87 to 7.51) Slower RT (β =1.75,4.44 to 7.94)
Chiu (2016)	Cohort	267 children U.S. 2002–2007	PM2.5 - Varying 'sensitive' windows of pregnancy/ Per 10 μg/ m3 increase	IQ, attention and memory at age 6.5	Significant for IQ & attention in boys. Significant for memory in girls

Clark (2012)	Cross-sectional	9 –10 y; n = 960; United Kingdom	NO2: Postnatal	Reading comprehension Episodic memory Working memory Health. Test: Suffolk reading scale Child memory scale “The search and the memory task” SDQ Self-rated health	NO2: —
Cowell (2015)	prospective	n = 258, prenatal - 6 years	black carbon	memory and learning	Synergistic association with socio-economic exposures: Among boys, high levels of prenatal black carbon and maternal stress were associated with worse attention concentration scores compared to boys with low levels of exposures
Edwards (2010)	prospective	214 children Poland 2001–2006	polycyclic aromatic hydrocarbons (PAH) - High vs. Low exposure (cut at median of 18.0 ng/m3) or Per Ln(PAH) increase. Personal 48hr monitoring of PAH during second or third trimester of pregnancy	IQ RCPM (at age 5). Confounded measured - Prenatal ETS in the home, sex of the child, maternal education, maternal intelligence, postnatal urinary metabolites, change of neighbourhood	Above median PAH exposure associated with reduced IQ (1.3, 2.48 to 0.23). Increased levels of PAH exposure (log continuous) associated with reduced IQ (–0.56, 1.00 to 0.11).

Fuertes (2016)	2 cohorts	Total N = 4,745 Germany 1995-1999	PM2.5, NO2, PM10 - Meta-analyses: Per IQR increase	Hyperactivity/ Inattention by age 10-15	PM2.5 - Exposure at birth address –OR: 1.06 (95% CI:0.96, 1.17) Exposure at 10 yr. address – OR: 1.12 (95% CI:1.01, 1.23) Exposure at 15 yr. address –OR: 1.11 (95% CI: 1.01, 1.22) Average exposure at birth, 10 and 15 yr. addresses: 1:13 (95% CI: 1.03, 1.24) PM10 - Exposure at birth address –OR: 1.07 (95% CI: 0.96, 1.18) Exposure at 10 yr. address –OR: 1.05 (95% CI: 0.95, 1.17) Exposure at 15 yr. address –OR: 1.04 (95% CI: 0.94, 1.15) NO2 - Birth exposure –OR: 1.03 (95% CI: 0.94, 1.12) 10-yr exposure –OR: 1.04 (95% CI: 0.93, 1.17) 15-yr exposure –OR: 1.02 (95% CI: 0.93, 1.11)

Gong (2014)	case-control	Twins aged 9–12 born in Stockholm with valid data on neurodevelopmental assessment and living address or air pollution data during preg- nancy, 1st and 9th year of life. Stockholm, Sweden 1992-2000. 3426 twins 109 with ASD (109 ASD low, 33 ASD high, 47 ASDDSM-IV)	Prenatal (whole pregnancy) and postnatal (1st, 2nd, and 9th year after birth). Residence concentra- tions of PM10, and NOx from road traffic. Annual average levels. Source: road-traffic	Autism-Tics (based on the DSM-IV) Adjustment for Maternal age at birth, smoking status, marital status, seasonal variation, par-ental education, gender, parity, gesta-tional age, birth weight, SES. Adjustment for Maternal age at birth, smoking status, marital status, seasonal variation, par-ental education, gender, parity, gesta-tional age, birth weight, SES.	5–95% difference in exposure to NOx during pregnancy was associated with ORs of 0.92 (95% CI: 0.44–1.96). Exposure to PM10 during pregnancy was related to ORs of 1.01 (95% CI: 0.52–1.96) for ASD. The data does not provide support for an association between pre- or post- natal exposure to air pollution from road traffic and neurodevelopmental disorders in children.
Gong (2017)	Nested case-control	5136 cases, 18,237 controls Sweden 1993–2007	PM10 - Entire pregnancy	ASD	Per 10 µg/m3 increase OR: 1.00 (95% CI: 0.86, 1.15)
Guxens (2012)	Cohort	1889 children Spain 2003–2008	NO2 - Entire pregnancy/Doubling of NO2 levels (Mean: 15.4 ppb)	Mental development at 14 mths	Performance abilities, memory and early language skills –β: –0.95 (95% CI: –3.90,1.89)

Guxens (2014)	Birth cohort. Combination of prospective studies (European Study of Cohorts for Air Pollution Effects)	9,482 children (age 1-6) Netherlands, Germany, Italy, France, Greece, Spain 1997–2008	In utero PM2.5, PM10 and NO2 estimated from land use regression models. Median NO2 range 11.5– 43.9 µg/ m3between studies. Median PM2.5range 13.4– 3 22.3 µg/ mbetween studies.	Psychomotor, cognitive development from ages 1 to 6. General cognition, language development and psychomotor development MCDI, MIDI, BSID-I, II and III, Ages and Stages Questionnaire, DDST-II, MSCA. Confounded measured - Maternal age at delivery, maternal education, maternal country of birth, maternal smoking in pregnancy, parity, maternal height and weight, pre-pregnancy BMI, child gender, date of birth, age, evaluator, urbanicity, changes of residence	Increase in NO2 by10 µg/m3 associated with global cognition:0.23 (0.96 to 0.50), language development: 0.15 (0.39 to 0.70), psychomotor development: 0.68 (1.25 to0.11). Increase in PM10 by 10 µg/m3 associated with global cognition: 0.75 (1.72 to 3.21), language development: 0.08 (0.99 to 0.82), psychomotor development: 0.87 (1.91 to 0.18). Increase in PM2.5 by 5 µg/m3 associated with global cognition: 0.09 (2.95 to 3.12), language development: 0.64 (1.64 to 0.36), psychomotor development: 1.64 (3.47 to 0.18).

Guxens (2015)	Prospective. Birth cohorst and child cohort	Children. CATSS: Stockholm, Sweden 1992– 2000 Total: 2437 ASD: 78 within borderline/clinical range, and 27 within clinical ASD	Prenatal (whole pregnancy). NO2, NOx, PM, traffic intensity, traffic load	Autistic Traits ASD module (A-TAC) Adjustment for Maternal education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity. Child sex, season at birth, urbanicity at birth address, age at the autistic traits assessment, and evaluator of the autistic traits. Adjustment for Maternal education, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, and parity. Child sex, season at birth, urbanicity at birth address, age at the autistic traits assessment, and evaluator of the autistic traits.	Adjusted OR for children with autistic traits within the borderline/clinicalrange: 0.96 (95% CI:0.80–1.16) per10 mg/m3 of NO2; 1.01(95%CI:0.87–1.17)per 20 mg/m3 of NOx; 0.88 (95%CI:0.60–1.27) per10 mg/m3 PM10 and 0.89 (95%CI:0.58–1.35) per5 mg/ m3 of PM2.5 Prenatal exposure to NO2, NOx and PM was not associated with autistic traits within the border- line/clinical range

		Children. 18-item version of SRS Generation R: Rotterdam, The Netherlands 2001–2005 Total: 3955 ASD: 336 within bor- derline/ clinical range, and 143 within clinical ASD	Id	Id	1.03 (95% CI: 0.84–1.26) per 10 mg/m3 of NO2; 1.07 (95% CI: 0.89–1.28) per 20 mg/m3 of NOx; 1.07 (95% CI: 0.74–1.54) per 10 mg/m PM10 and 0.38 (95% CI: 0.07–2.24) per 5 mg/ m3 of PM2.5 Prenatal exposure to NO2, NOx and PM was not associated with autistic traits within the border- line/clinical range
		Children. GASPII: Rome, Italy 2003– 2004 Total: 514 ASD: 63 within bor- derline/ clinical range, and 15 within clinical ASD	Id	Id	0.98 (95% CI: 0.78–1.22) per 10 mg/m3 of NO2; 1.00 (95% CI: 0.85–1.17) per 20 mg/m3 of NOx; 0.72 (95% CI: 0.48–1.08) per 10 mg/m PM10 and 0.35 (95% CI: 0.09–1.43) per 5 mg/ m3 of PM2.5 Prenatal exposure to NO2, NOx and PM was not associated with autistic traits within the border- line/clinical range

		Children with air pollution, autistic traits, and INMA: Spain Gipuzkoa 2006– 2008 Total: 357 ASD: 17 within bor- derline/ clinical range, and 3 within clinical ASD	Id	Id	0.94 (95% CI: 0.81–1.09) per 10 mg/m3 of NO2; 0.98 (95% CI: 0.88–1.09) per 20 mg/m3 of Nox Prenatal exposure to NO2, NOx and PM was not associated with autistic traits within the border- line/clinical range
		Sabadell 2004– 2006 Total: 295 ASD: 10 within bor- derline/ clinical range, and 2 within clinical ASD	id	Id	0.97 (95% CI: 0.81–1.16) per 10 mg/m3 of NO2; 1.00 (95% CI: 0.88–1.13) per 20 mg/m3 of NOx; 0.91 (95% CI: 0.66–1.25) per 10 mg/m PM10 and 0.76 (95% CI: 0.38–1.52) per 5 mg/ m3 of PM2.5 Prenatal exposure to NO2, NOx and PM was not associated with autistic traits within the border- line/clinical range
		Valencia 2004– 2005 Total: 521 ASD: 37 within bor- derline/ clinical range, and 10 within clinical ASD	id	Id	0.89 (95% CI: 0.76–1.05) per 10 mg/m3 of NO2; 0.96 (95% CI: 0.86–1.07) per 20 mg/m3 of Nox Prenatal exposure to NO2, NOx and PM was not associated with autistic traits within the border- line/clinical range

Guxens (2016)	Cohort	8079 children Netherlands, Sweden, Italy, Spain 1992–2008	PM10 - Entire pregnancy/Per 10 µg/m3 increase	ASD	Autistic traits Borderline/clinical range –OR: 0.90 (95% CI: 0.68, 1.19) Clinical range only –OR: 0.92 (95% CI: 0.55, 1.54)

Harris (2015)	Birth cohort	1109 Age 8 years (range 6.6–10.9) 50% female (Project Viva, USA)	Proximity of residence to nearest major roadway/near residence traffic density. BC and PM2.5. PM2.5 - 3rd tri/ Per 3.8 μg/m3 increase Birth to age 6/Per 3.8 μg/m3 increase. BC: Prenatal (3rd trimester of pregnancy) and postnatal (the year before each cognitive assessment, the first 6 y of life)	Neuro-development/ IQ in mid- childhood (mean age 8 yrs). Verbal and non-verbal IQ, visual motor, design and picture memory WRAML2, KBIT-2, WRAVMA. Confounded measured - Household income, Home Observation for Measurement of the Environment–Short Form, maternal IQ, lead in utero, sex, age, breastfeeding duration, maternal age, marital status, education, race, ethnicity, smoking, exposure to ETS in utero, blood lead in early childhood, alcohol consumption during pregnancy, father education, gas stove, neighbourhood, seasonal trends	Near-residence traffic density at birth (log transformed) associated with: Verbal IQ: 0.2 (–0.3, 0.8); Nonverbal IQ: 0.8 (0.1, 1.6); Visual motor 0.7: (–0.1, 1.5); Design memory: 0.1 (0.0, 0.2); Picture memory: 0.1 (0.0, 0.2). BC in utero associated with: Verbal IQ: 0.2 (–0.9, 1.3); Nonverbal IQ: 1.3 (–0.2, 2.7); Visual motor: 0.9 (–0.6, 2.4); Design memory: –0.1 (–0.3, 0.2); Picture memory: –0.1 (–0.3, 0.2). PM2.5 in utero associated with: Verbal IQ: –0.2 (–1.4, 1.1); Nonverbal IQ: –0.2 (–1.8, 1.4); Visual motor: 0.9 (–0.8, 2.5); Design memory: –0.1 (–0.3, 0.2); Picture memory: 0.1 (–0.2, 0.4).

Harris (2016)	Cohort	1,212 children U.S. 1999–2002a	PM2.5 - 3rd tri/Per 3.8 μg/m3 increase Birth to age 6/Per 2.1 μg/m3 increase	Behavioral problems (teacher-rated) in mid-childhood (mean age 8 years)	3rd tri exposure –GEC β: -0.1 (95% CI: -1.2, 0.9) BRI β: 0.2 (95% CI: -0.8, 1.3) MI β: -0.3 (95% CI: -1.4, 0.8) SDQ β: -0.3 (95% CI: -0.7, 0.1) Birth to age 6 exposure –GEC β: 0.5 (95% CI: -0.5, 1.4) BRI β: 0.7 (95% CI: -0.2, 1.6) MI β: 0.3 (95% CI: -0.7, 1.3) SDQ β: 0.1 (95% CI: -0.4, 0.6)
Horton (2012)	prospective	n = 335, prenatal - 7 years	chlorpyrifos (organophosphorus insecticide)	working memory	No significant interaction: Main effects but no significant interactions were observed between CFP exposure and home environment or parental nurturance in relation to child memory outcomes
Jedrychowski (2015)	Birth cohort	170 children Poland 2000–2003. n=170 Age 7 years 53% female	PAH: Prenatal (from 8th to 13th wk of pregnancy)	Neuro-development/ IQ at age 7. WISC-R. Confounded measured - Birth season, birth season cord blood adducts, maternal education, gender, parity, breastfeeding duration	Verbal IQ (depressed): RR: 3.0 (95% CI: 1.32, 6.79). 1-unit increase in PAH (log transformed) associated with increased risk of depressed verbal IQ: RR=1.6 (1.1–2.5; p=0.027)

Jung (2013)	Cohort	Children age less than 3 at the baseline in Jan 1st, 2000 followed though December 31st, 2010, with no previous ASD diagnosis with address that has air pollution data. Taiwan 2000– 2010 Total: 49,073 ASD: 342	Postnatal (up to 3years after birth). O3, CO, NO2, SO2, and PM10. Source: air pollution, not specified.CO: Postnatal (preceding 1– 4 y newly diagnostic ASD). PM. 1–4 years preceding diagnosis - Average concentration from nearest three monitoring stations	ASD (ICM-9-CM). Adjustment for Age, anxiety, gender, intellectual dis-abilities, obsessive-compulsive dis- order, phobia, preterm, and SES. Adjustment for Age, anxiety, gender, intellectual dis-abilities, obsessive-compulsive dis- order, phobia, preterm, and SES.	The risk of newly diagnostic ASD increased according to increasing O3, CO, NO2, and SO2 levels in the year before diagnosis. Based on air pollution concentration in the year before diagnosis: 59% risk increase of newly diagnostic ASD per 10 ppb increase in O3 level (95% CI: 1.42–1.79), 37% risk increase per 10 ppb in CO (95% CI: 1.31–1.44), 340% risk increase per 10 ppb increase in NO2 level (95% CI: 3.31–5.85), and 17% risk increase per 1 ppb in SO2 level (95% CI: 1.09–1.27). PM10 per 10 µg/m3 increase: Preceeding 1 year Adj OR 1,08 (95%CI 0,97 to 1,19); Preceeding 2 years Adj OR 1,02 (95%CI 0,91 to 1,13); Preceeding 3 years Adj OR 0,94 (95%CI 0,84 to 1,05); Preceeding 4 years Adj OR 0,92 (95%CI 0,81 to 1,04)

Kalkbrenner (2010)	Case-control study	children aged 8 years in North Carolina (born in 1994 and 1996) and West Virginia (born in 1992 and 1994). Study group included 383 children with ASD and 2,829 children with speech and language impairment as controls. - comparator: All children in the surveillance system in North Carolina and West Virginia with school designation of speech and language impairment without documentation of other serious developmental problems (i.e., autism spectrum disorder, intellectual disabilities, etc.).	Census tract of birth residence linked to concentration estimates from the 1996 US EPA NATA database for 35 HAPs.	ASD cases and controls with speech and language impairment identified from records-based surveillance of children conducted by ADDM in North Carolina and West Virginia.	Authors estimated many near-null ORs, including those for metals, established human neurodevelopmental toxicants, and several pollutants that were elevated in a similar study in California. Hazardous air pollutants with more precise and elevated OR estimates included methylene chloride, 1.4 (95% CI = 0.7-2.5), quinoline, 1.4 (1.0-2.2), and styrene, 1.8 (1.0-3.1).

Kalkbrenner (2015)	Nested case-control	Children born in North Carolina in 1994 (8 counties), 1996 (8 counties), 1998 (9 counties), and 2000 (10 counties) and born in 6 San Francisco Bay area counties in 1996. Study group was 645 children with autism and 12,434 controls for North Carolina and 334 children with autism and 2,232 controls for California. - comparator: Controls randomly selected from study counties and birth years, removing multiple births, infant deaths, and known autism cases.	Prenatal (1st, 2nd, 3rd trimester) and postnatal (1st year after birth). PM10 Source: Traffic, especially diesel traffic, as well as from wood smoke and power plants	ASD (DSM-IV-R). Adjustment for Maternal education, age, race/ethni-city, neighborhood-level urbanization, median household income, year of birth, state, and nonparametric term for week of birth to account for sea-sonal trends. Adjustment for Maternal education, age, race/ethni-city, neighborhood-level urbanization, median household income, year of birth, state, and nonparametric term for week of birth to account for sea-sonal trends.	Adjusted OR: first trimester, 0.86 (95% CI: 0.74–0.99), second trimester, 0.97 (95%CI: 0.83–1.15), and third trimester, 1.36 (95%CI: 1.13–1.63); after simultaneously including first- and third-trimester concentrations to account for the inverse correlation, were: first trimester, 1.01 (95% CI: 0.81–1.27) and third trimester, 1.38 (95%CI: 1.03–1.84). Post natal quarter 1 1,09 (95%CI 0,9 to 1,32); Post natal quarter 2 0,76 (95%CI 0,63 to 0,93); Post natal quarter 3 0,85 (95%CI 0,7 to 1,04); Post natal quarter 4 1,19 (95%CI 0,98 to 1,43)

Kicinski (2015)	Cross-sectional	n=606 Age 13–17 years (mean14.9) (Belgium)	Traffic exposure: Postnatal. Distance weighted traffic density. Trans,trans-muconic acid in urine. Mean residential traffic density 245; mean school traffic density 232.	Sustained attention, short term memory, motor speed CPT, DMST, finger tapping. Confounded measured - Gender, age, exposure to ETS, maternal education, family so-cio-economic status, time of day, day of week, smoking status	Increase in traffic density by 1sd associated with reduced: Sustained attention: 0.26 sd (0.51,0.02) Short term memory: 0.17 sd, (0.38, 0.04) Motor speed: 0.10 sd (0.27, 0.07).
Kim (2014)	Birth cohort	6, 12, and 24 mo; n = 520; South Korea	NO2; PM10: Prenatal (entire pregnancy)	Cognitive development Psychomotor development. Test: K-BSID-II	NO2: < Psychomotor development. PM10: < Cognitive and psychomotor development
Kim (2014a)	Cohort	455 children South Korea 2006–2008	NO2 - Entire pregnancy/Per 10 ppb increase; PM10 - Entire pregnancy/Per 10 μg/m3 increase	Psychomotor and mental development at 6 mths	NO2: Psychomotor Development Index –β: –3.01 (95% CI: –4.78, –1.24) Mental Development Index –β: –3.12 (95%CI: –4.55, –1.68) PM10: Psychomotor Development Index –β: –7.24 (95% CI: –9.79, –4.69) Mental Development Index –β: –4.60 (95% CI: –6.71, –2.49)

Lertxundi (2015)	prospective	438 children 2006–2008. Age 15 months (range 13–18) 55% female (INMA Environment and Childhood study, Spain)	PM2.5, NO2 and benzene. Distance from residential address to major traffic and industrial activity. PM2.5 - Entire pregnancy/Per 1 *μ*g/m3 increase. NO2 - Entire pregnancy/Per 0.53 ppb increase	Mental development at 13–18 mths. Confounded measured - Child age, sex, gestational age, parity, social class, breastfeed-ing duration, maternal fruit and vegetable intake during pregnancy, neuropsychologist, distance from road	PM2.5: Mental Scale Score –β: -0.39 (90% CI: -0.94,-0.17) Motor Scale Score –β: -1.14 (90% CI: -1.76,-0.53) NO2.: Mental Scale Score –β: –0.29 (90% CI:–0.47, –0.11) Motor Scale Score –β: –0.12 (90% CI: –0.32, 0.08) 1 µg/m3increase in PM2.5 associated with decrease in mental score (0.39;0.90,0.17). 1 µg/m3increase in NO2 associated with decrease in mental score (0.29;0.47,0.11). 1 µg/m3increase in benzene associated with decrease in mental score (2.35;8.46, 3.75; ns). Increase in mental score with increased distance from road (r100 m mean score 99.7; 100–300 m mean score 100.3; 4300 m mean score 103.4; ns).

Lin (2014)	Birth cohort	533 children Taiwan 2003–2004. Age 6 and 18 months 44% female	NO2 - Entire pregnancy through 6 mths of life/ Per 1 ppb increase PM10 - Entire pregnancy through 6 mths of life/Per 1 g/m3 increase CO, O3, PM10, SO2, NO2, THC and NMHC measured from air quality monitoring stations CO: Prenatal and postnatal (beginning of gestational period to 18 mo of age)	Neuro-behavioral development at 6 mths. Gross motor, fine motor, language, social ability. Confounded measured - Maternal education, maternal nationality, ETS exposure, infant gestational age, breastfeeding duration, parental nursery type	NO2 - 1st tri β: 0.023 (SE: 0.070) 2nd & 3rd tri β: –0.110 (SE: 0.093) Birth to 6 mths β: 0.002 (SE: 0.062) PM10 - 1st tri β: 0.033 (SE: 0.044) 2nd & 3rd tri β: –0.022 (SE: 0.050) Birth to 6 mths β: 0.006 (SE: 0.022) Increased NMHC levels during 2nd and 3rd trimester associated with reduced gross motor skills at 6 months (β= 8.842, SE=3.512). Increased SO2 associated with reduced fine motor skills at 18 months (exposure in 1st trimester: β= 0.083, SE=0.030; exposure in 2nd and 3rd trimester: β= 0.114, SE=0.045; exposure from birth to 12 months: β = 0.091, SE=0.034). No other significant associations. CO: — Hydrocarbons: (<nd and 3rd trimesters): < Gross motor scores at 6 mo of age NO2: — O3: — PM10: — SO2: (all pregnancy to >< months of age): < Fine motor development at >8 mo of age

Lovasi (2014)	Birth cohort	227 children. 5 y. U.S. 1998–2006	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/High vs. Low exposure (cut at median of 2.26 ng/ m3) Accounting for neighborhood social context	IQ at age 5. WPPSI-R	Full-scale IQ – β: –3.45 (95% CI: –6.63, –0.27) Verbal IQ –β: – 3.90 (95% CI: –6.98, –0.81) Performance IQ – β: –1.67 (95% CI: –4.89, 1.55)
Margolis (2016)	Cohort	187 children U.S. 1998–2006	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/Cord PAH-DNA adducts	Neuro-psychiatric outcomes at age 9	Anxiety/depression –β: 1.4 (p = 0.02) Aggressive –β: 1.7 (p = 0.01) Attention problems –β: 1.5 (p = 0.03) Deficient emotional self-regulation –β: 4.6 (p = 0.0004)
Min and Min (2017)	Cohort	8936 infants Korea 2002	NO2 - Cumulative exposure from birth to diagnosis (or end of study)/ 0.53 ppb) increase PM10 - Cumulative exposure from birth to diagnosis (or end of study)/ Per 1 µg/m3 increase	Childhood ADHD	NO2 - HR: 1.03 (95% CI: 1.02, 1.04) PM10 - HR: 1.18 (95% CI: 1.15, 1.21)

Mortamais (2017)	Cohort	242 children Spain 2012	polycyclic aromatic hydrocarbons (PAH) - Age 8–12 yrs (concentration acquired at schools; average of two one-wk measures)/Per 1 pg/m3 increase (mean (SD): 1458 (704) pg/m3)	Hyper-activity/ inattention problems or ADHD at age 8-12	ADHD –RR: 1.02 (95% CI: 0.81, 1.29) Inattention –RR: 1.03 (95% CI: 0.82, 1.30) Hyperactivity –RR: 1.03 (95% CI: 0.79, 1.35)
Newman (2013)	Birth cohort	7 y; n = 576; United States	ECAT: Postnatal (1st year of life)	Behavior. Test: BASC-2	ECAT: > hyperactivity scores (stronger association in children whose mothers had higher education)

Perera (2006)	prospective	N=183 Age 12, 24 and 36 months 54% female (USA) 1998–2006	Personal monitoring of PM2.5 during third trimester of pregnancy Range 0.65–36.47 ng/m3 (average 3.49 ng/m3) polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/4th Q: 4.16 ng/m3 vs. all other Q	Mental development at 36 mths. Confounded measured - Ethnicity, sex, gestational age, home environment, prenatal environmental tobacco smoke exposure, prenatal pesticide chlorpyrifos, maternal IQ, maternal education, exact age at test administration, birth weight, birth head circumference, cord lead	PM2.5 - High levels of PM2.5 (>44.16 µg/m3) associated with reduced mental development index at age: 12 months (β=0.48, ns); 24 months (β = 1.73, ns); 36 months (β= 5.69, 9.05 to 2.33). High levels of PM2.5 (44.16 µg/m3) associated with increased risk of moderate mental developmental delay at age: 12 months (OR=0.82, ns); 24 months (OR=0.86, ns); 36 months (OR=2.89, 1.33–6.25). PAH - OR: 2.89 (95% CI: 1.33, 6.25)

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Perera (2009)	Prospective	249 children U.S. 1998–2003 Age 5 years 54% female	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/High vs. Low exposure (cut at median of 2.26 ng/m3) Personal monitoring of PM2.5 during third trimester of pregnancy–ng/m3 Range 0.4934.483 (median 2.26 ng/m)	IQ at age 5. WPPSI-R. Confounded measured - ETS exposure during pregnancy and after delivery, cord blood lead, cord blood cotinine, cord blood chlorpyrifos, gender, maternal education, ethnicity, HOME score, TONI-3 score	PAH - Full-scale IQ –β: –4.31 (p = 0.007) PM2.5 - Above median PM2.5 levels associated with reduced: Full-scale IQ (β =4.31,7.41 to1.21); Verbal IQ (β=4.67,7.73 to1.61); Performance IQ (β =2.37,5.75 to 1.01). Increased levels of PM2.5 (log continuous) associated with reduced: Full-scale IQ (β = 3.00, 5.24 to0.77); Verbal IQ (β=3.53,5.73 to 1.33); Performance IQ (β =1.47,3.91 to 0.96). Verbal IQ –β: –4.67 (p = 0.003) Performance IQ –β: –2.37 (p = 0.170)
Perera (2012)	Birth cohort	253 children U.S. 1998–2003. 5 y; n = 100; China	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/High vs. Low exposure (cut at median of 2.27 ng/m3) or Cord PAH-DNA adducts (detectable vs. non-detectable at < 0.25 adducts/108 nucleotides)	Neuro-psychiatric outcomes at age 6–7. Global IQ. Test: WPPSI	High vs. Low exposure – Attention problems OR: 3.79 (95% CI: 1.14, 12.66) Anxious/depressed OR: 8.89 (95% CI: 1.70, 46.51) Cord PAH-DNA adducts – Attention problems OR: 4.06 (95% CI: 0.99, 16.63) Anxious/depressed OR: 2.56 (95% CI: 0.69, 9.43) PAH: — Interaction with environmental tobacco smoke: < global and verbal scores

Perera (2013)	Prospective	248 children - 9 years - Poland 2000–2003	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/High vs. Low exposure (cut at median of 22.11 ng/m3)	Neuro- psychiatric outcomes at age 9	PAH x maternal psychological distress (interaction)-CBCL –Anxious/depressed β: 0.35 (p = 0.023) Withdrawn/ depressed β: 0.81 (p = 0.003) Aggressive behavior β: 0.50 (p = 0.0004) Internalizing problems β: 0.45 (p = 0.0002) Externalizing problems β: 0.48 (p < 0.0001)
Perera (2014)	Birth cohort	9 y; n = 250; United States 1998–2006	PAH: 1st y and 9th y) Prenatal (cord and maternal blood)	ADHD at age 9. Test: CBCL CPRS	DSM-IV Total – OR: 3.37 (95% CI: 1.10, 10.34) DSM-IV Hyperactive/ Impulsive – OR: 1.58 (95% CI: 0.55, 4.52) DSM-IV Inattentive –OR: 5.06 (95% CI: 1.43,17.93)
Peterson (2015a) (2015b)	Cohort	40 children U.S. 1998–2006	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/Per 1 ng/m3 increase	MRI at age 7–9 Association PAH and anatomical brain changes Correlation of anatomical changes with behavioral measures	Reductions of the white matter surface almost exclusively in left hemisphere of the brain –Correlation coefficients (95% CI): from –0.50 (–0.71, –0.22) to 0–0.57 (–0.75,–0.30) White matter surface changes in left hemisphere correlated inversely and significantly with externalizing problems and ADHD sympt

Porta (2016)	Cohort	474 children Italy 2003–2004	PM2.5 - Entire pregnancy/Per 10 μg/m3 increase NO2 - Entire pregnancy/Per 5.3 ppb increase	Cognitive development/IQ at age 7	PM2.5 - Full-scale IQ –β: -1.9 (95% CI: -7.9, 4.1) Verbal IQ –β: 0.4 (95% CI: -5.5, 6.4) Performance IQ –β: -4.1 (95% CI: -3.4, 1.2) NO2 - Full-scale IQ –β: –1.10 (95% CI: –2.30, 0.10) Verbal IQ –β: –1.40 (95% CI: –2.60, –0.20) Performance IQ –β: –0.58 (95% CI: –1.90, 0.73)

Raz (2015)	Nested case-control	Offspring born 1990 through 2002 of participants in the NHS II, a prospective cohort of 116,430 U. S. female nurses 25–43 years of age when recruited in 1989. 1990– 2002 NHS II participants' children born 1990– 2002 with ASD (n=245), and children without ASD (n=1522).	Prenatal (9 months before pregnancy, and entire preg- nancy) and postnatal (9 months after birth).. PM10 and PM2.5 Sources: N/A	ADI-R, SRS and maternal report Adjustment for Mutually adjusted for other exposure periods (whole pregnancy, 9 months before conception, 9 months after birth), and adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, census income. Adjustment for Mutually adjusted for other exposure periods (whole pregnancy, 9 months before conception, 9 months after birth), and adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, census income.	Exposure during pregnancy was associated with increased odds of ASD, with an AOR of 1.57 (95% CI: 1.22–2.03) per IQR in PM2.5 (4.42 µg/m3) among women with the same address before and after pregnancy. Association with the 9 months of pregnancy remained (OR=1.63; 95% CI: 1.08–2.47). The association be- tween ASD and PM2.5 was stronger for exposure during the third trimester (OR=1.42 per IQR increase in PM2.5; 95% CI: 1.09–1.86) than during the first two trimesters (ORs=1.06 and 1.00) when mutually adjusted. There was little association between PM10–2.5 and ASD. Higher maternal exposure to PM2.5 during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD. Mean [PM]=14.6 µg/m3 PM2.5 per 4.42 µg/m3 increase ; Adj OR 1,57 (95%CI 1,22 to 2,03); 1st trimester Adj OR 1,23 (95%CI 1,01 to 1,49); 2nd trimester Adj OR 1,27 (95%CI 1,05 to 1,54); 3rd trimester Adj OR 1,49 (95%CI 1,2 to 1,85); Mean [PM]=9.9 µg/m3 PM10–2.5 per 5.15 µg/m3 increase;

Roberts (2013)	Birth cohort	Not provided; n = 22 426; United States 1987–2002	PM. Annual average for a year within two years of birth year - National-Scale Air Toxics Assessment (NATA) 1990, 1996, 1999 and 2002	ASD (Parent report of a diagnosis via questionnaire)	Diesel PM; 2nd quintile 1.06 g/m3 OR 1,1 (95%CI 0,6 to 2,2); 3rd quintile 1.48 g/m3 OR 1,3 (95%CI 0,7 to 2,5); 4th quintile 2.00 g/m3 OR 1,2 (95%CI 0,6 to 2,5); 5th quintile 4.40 g/m3 OR 2 (95%CI 1 to 4)

Sunyer (2015)	Prospective cohort	n=2715 Age 7–10 years (mean 8.5 years) 50% female (Spain)	Postnatal (throughout 1 y of follow-up) PM2.5, black carbon and ultrafine particles at school. Black carbon mean 0.44 mg/m3 (indoor); 0.58 mg/m3 (outdoor). PM2.5 mean 11.5 mg/m3 (indoor); 25.9 mg/m3 (outdoor). Ultrafine particles mean 8034 cm3 (indoor); 11,939 cm3(outdoor).	Working memory, inattentiveness, attentional network test. Test: ANT N-back task. Confounded measured - Age, sex, maternal education, socioeconomic status, air pollution exposure at home, family origin, gestational age and weight, breastfeeding duration, parental education, occupation, marital status, smoking during pregnancy, ETS exposure at home, commuting mode, use of computer games, height, weight, classroom noise	Children exposed to higher level of traffic pollution fell further behind those exposed to low levels of traffic pollution over 12 months on: working memory (2-back): change from5.3 (1.6, 5.1) points to9.9 (16,3.5) points. Working memory (3-back): change from1.4 (10, 7.1) points to5.8 (11,0.74) points. Inattentiveness: change from 5.2 (6.2, 17) points to 5.2 (0.68, 9.7) points (higher score=poorer performance).

Surkan (2008)	prospective	n = 379, perinatal - 36 months	lead, perinatal - 36 months	neurodevelopment (mental and psychomotor indices)	Synergistic association with socio-economic exposures: The negative effects of exposure to lead on child neurodevelopment were larger in children of mothers with low levels of self-esteem

Talbott (2015)	Case-control	Children 3–7 y; 217 cases, 219 controls; US, born between January 1st, 2005 and December 31st, 2009 in six counties in Southwestern Pennsylvania.	Prenatal (3 months before pregnancy, 1st, 2nd, 3rd trimester) and postnatal (1st and 2nd year after birth) 3months before pregnancy, trimesters 1-3, years 1 and 2 of life.. PM2.5 Source: Air pollution, not specified. Polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/4th vs. 1st Q comparison Interviewed-Cases: 4th Q: > 15.87 ng/m3, 1st Q: < 8.85 ng/m3 controls: 4th Q: > 14.60 ng/m3, 1st Q: < 8.65 ng/m3 Birth certificate-cases: 4th Q: > 15.72 ng/m3, 1st Q: < 8.85 ng/m3 controls: 4th Q: > 15.70 ng/m3, 1st Q: < 8.34 ng/m3	ASD. Test: ADOS SCQ. Adjustment for Maternal age, education, race, and smoking status.	PM2.5 - Mean [PM]=14.5 µg/m3 PM2.5 per 2.84 µg/m3 increase. Adj OR: Pre pregnancy 1,13 (95%CI 0,94 to 1,35); 1st trimester 1,07 (95%CI 0,91 to 1,25); 2nd trimester 1,04 (95%CI 0,88 to 1,22); 3rd trimester 1,04 (95%CI 0,88 to 1,24); Pregnancy 1,2 (95%CI 0,88 to 1,63); Year 1 1,37 (95%CI 0,95 to 1,97); Year 2 1,45 (95%CI 1,01 to 2,08); Year 1 Adj OR (95%CI to); Pre pregnancy through 1st trimester 1,2 (95%CI 0,95 to 1,52); Pre pregnancy through 2nd trimester 1,29 (95%CI 0,94 to 1,76); Pre pregnancy through pregnancy 1,46 (95%CI 0,98 to 2,19); Pre pregnancy through year 1 1,47 (95%CI 0,98 to 2,21); Pre pregnancy through year 2 1,51 (95%CI 1,01 to 2,26) PAH - Interviewed –OR: 1.33 (95% CI: 0.76, 2.32) Birth certificate –OR: 1.44 (95% CI: 0.98, 2.11)
Tang (2008a)	Cohort	110 children China 2002	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy	Motor development at age 2	OR: 1.91 (95% CI: 1.22, 2.97) per 0.1 adduct/108 nucleotide increase

Tang Lee (2014)e	Birth cohort	2 y; n = 308; China	PAH: Prenatal (cord and maternal blood)	Global IQ. Test: GDS	PAH: < Global, motor and adaptive scores
Tong (2000)	prospectiv e	n = 375, birth to 11-13 years	lead, birth to 11-13 years	cognitive development	Synergistic association with socio-economic exposures: the deleterious effect of higher lifetime lead exposure on child IQ was larger among children from low SES backgrounds. Effect modification was not observed for psychosocial factors
Vishnevets ky (2015)	Cohort	276 children US 1998–2006	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/Cord PAH-DNA adducts (detectable vs. non-detectable at < 0.25 adducts/108 nucleotides) in high hardship group	Neuro-development/ IQ at age 7	Full-scale IQ –β: –5.81 (95% CI: –10.35, –1.26) Verbal comprehension –β: –3.36 (95% CI: –7.61, 0.90) Processing speed –β: –4.17 (95% CI: –9.75, 1.41) Perceptual reasoning –β: –5.44 (95% CI: –10.27, –0.61) Working memory –β: –6.67 (95% CI: –11.38, –1.95) NS for low hardship group

Volk (2011)	Case-control	n = 305 cases 259 controls California, USA 1997–2006	PM. Pregnancy trimesters and birth - Distance to freeway	Autistic disorder (ADOS + ADI-R)	< 309 m OR 1,86 (95%CI 1,03 to 3,45); < 309 m (decile) OR 2,48 (95%CI 1,17 to 5,39); < 309 m (residential histoy data) OR 2,22 (95%CI 1,16 to 4,42); 309–647 m OR 0,96 (95%CI 0,58 to 1,56); 647–1419 m OR 1,11 (95%CI 0,73 to 1,67); > 1419 m = Reference = 1
Volk (2013)	Case-control	Children from the CHARGE study. 24 – 60 mo; n = 279 cases 245 controls; California, US. 1997– 2008	Prenatal and postnatal (1st, 2nd, 3rd trimester) and the first year of life.. Traffic related air pollu- tion: O3, NO2, PM2.5 and PM10. Source: TRAP	ASD. Test: ADI-R ADOS Mullen scales of early learning. Vineland adaptive behaviour scale. Adjustment for Sex, ethnicity, maximum education of parents, maternal age, and prenatal smoking. Adjustment for Sex, ethnicity, maximum education of parents, maternal age, and prenatal smoking.	Adjusted OR: PM2.5 per 8.7 µg/m3 increase; 1st trimester 1,22 (95%CI 0,96 to 1,53); 2nd trimester 1,48 (95%CI 1,4 to 1,57); 3rd trimester 1,4 (95%CI 1,11 to 1,77); Pregnancy 2,08 (95%CI 1,93 to 2,25); Year 1 2,12 (95%CI 1,45 to 3,1); PM10 per 14.6 µg/m3 increase ; 1st trimester 1,44 (95%CI 1,07 to 1,96); 2nd trimester 1,83 (95%CI 1,35 to 2,47); 3rd trimester 1,61 (95%CI 1,2 to 2,14); Pregnancy 2,17 (95%CI 1,49 to 3,16); Year 1 2,14 (95%CI 1,46 to 3,12)

Volk (2014)	case-control	2–5 y; n = 251 cases 156 controls; United States	PM2.5: Prenatal (entire pregnancy)	Relationship of air pollution exposure and genotype (MET rs1858830 CC) with ASD. Test: ADI-R ADOS	PM2.5: > ASD PM10: > ASD O3: — NO2: > ASD MET rs>858830 CC genotype and high air pollutant exposure: > ASD
von Ehrenstein (2014)	Case-control	557 ASD cases and 108,505 controls 3.5 km buffer: 268 ASD cases and 49,993 controls U.S. 1995–2006	polycyclic aromatic hydrocarbons (PAH) - Entire pregnancy/Per 0.79 ppb increase	ASD. Test: DSM-IV-R	ASD at age 6 –5 km OR: 1.03 (95% CI: 0.84, 1.26) 3.5 km OR: 1.05 (95% CI: 0.79, 1.39) ASD at age 5 –Impaired expressive language OR: 0.02 (95% CI: 0.75, 1.37) Less impaired expressive language OR: 1.48 (95% CI: 0.95, 2.31)
Von Ehrenstein (2014)	Birth cohort	31–71 mo; n = 768; United States	24 toxics, including aromatic solvents, chlorinated solvents, volatile organics, total PAHs, and metals Prenatal (entire pregnancy)	ASD. Test: DSM-IV-R	24 toxics, including aromatic solvents, chlorinated solvents, volatile organics, total PAHs, and metals > ASD; particularly, exposure during >st trimester
Vreugdenhil (2002)	prospective	n = 418, prenatal - 6.5 years	prenatal PCBs, dioxins	cognitive and motor abilities	Synergistic association with socio-economic exposures: worse cognitive and motor abilities were observed among children with high levels of PCBs and low-SES, parental IQ, and lower-quality home environment

Windham (2006)	Nested case-control	284 cases 687 controls; San Francisco Bay area, CA, USA 1994	PM. Annual average for year close to birth year - National-Scale Air Toxics Assessment (NATA) 1996	ASD (DSM-IV-R criteria applied to developmental evaluations)	Diesel PM; 3.37 µg/m3 average OR 1,44 (95%CI 1,03 to 2,02)
Xu (2015)	prospective	n = 192, prenatal to 7-15 years	lead, prenatal to 7-15 years	ADHD behaviour	Synergistic association with socio-economic exposures: Higher maternal self-esteem was associated with lower child inattention, with the association stronger among those exposed to low levels of lead
Yorifuji (2016)	Cohort	33,890 children Japan 2001	NO2 - Entire pregnancy/Per 10.9 ppb increase	Behavioral development at age 2.5 and 5.5	At 2.5 yrs, unable to: Compose two-phrase sentence –OR: 1.24 (95% CI: 1.07, 1.43) Say his/her own name –OR: 1.14 (95% CI: 1.04, 1.25) At 5.5 yrs, unable to: Focus on one task –OR: 1.10 (95% CI: 1.01, 1.21) Express emotions –OR: 1.17 (95% CI: 1.09, 1.26)
Yorifuji (2017)	Cohort	33,890 children Japan 2001	NO2 - Entire pregnancy/Per 10.8 ppb increase	Behavioral development at age 8	Attention problem: Failure to pay attention when crossing a street –OR: 1.10 (95% CI: 1.02, 1.19)

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Tabella 4. Tavola sinottica con descrizione degli studi primari posteriori alla data delle revisioni sistematiche

Author, year	Subjects	Type of study	Exposure	Outcome	Results
Liu XY (2019)	348 toddlers	Birth cohort study.	Polycyclic aromatic hydrocarbons (PAH) during pregnancy. Measurement of PAH-DNA adduct in umbilical cord blood	Autism spectrum disorder (ASD)-related behaviors. Child Behavior Checklist (CBCL) and Autism Behavior Checklist (ABC) were used to evaluate behavior problems at the age of 36 months.	The detection rate of PAH-DNA adduct in umbilical cord blood was 52.3%, and the median concentration was 0.68 ng/mL. The median total scores of CBCL and ABC scales were 23 and 8 respectively. In children aged 36 months, the concentration of PAH-DNA adduct was positively correlated with the score of social withdrawal in the CBCL scale (rs=0.205, P<0.05), the total score of the ABC scale (rs=0.412, P<0.05), and the self-care score of the ABC scale (rs=0.355, P<0.05). The concentration of PAH-DNA adduct was closely associated with the total score of the ABC scale in children aged 36 months (beta=0.122, P<0.05).

Geng R (2019)	296 3-6 years old Chinese children (99 confirmed autism cases and 198 their age-gender matched control subjects)	Case-control study	Estimated PM2.5 during the first three years of life.	Autism spectrum disorder (ASD).	The mean levels of PM2.5 exposures in ASD and typical developmental children during the first three years of life were 89.8 [standard deviations (SD): 6.1] mug/m(3) and 87.3(6.6) mug/m3, respectively (p = 0.002). A statistically significant positive correlation was found between the serum levels of PM2.5 and the Childhood Autism Rating Scale (CARS) score indicating severity of autism (r = 0.259; p = 0.010). Based on the receiver operating characteristic (ROC) curve, the optimal cutoff value of PM2.5 levels as an indicator for auxiliary diagnosis of ASD was projected to be 89.5ug/m(3), which yielded a sensitivity of 65.4% and a specificity of 63.2%, with the area under the curve at 0.61 (95% confidence intervals [CIs], 0.54-0.68; P < 0.001). Multivariate analysis models were used to assess ASD risk according to PM2.5 quartiles (the lowest quartile [Q1] as the reference), with the adjusted odds ratios (ORs) (95% CIs) were recorded. The 3rd and 4th quartile of PM2.5 were compared against the Q1, and the risks were increased by 103% (OR = 2.03; 95%CI: 1.13-5.54; p = 0.015) and 311% (4.15; 2.04-9.45; p = 0.002), respectively.

Jo H (2019)	246,420 singleton children born in Kaiser Permanente Southern California (KPSC) hospitals between 1999 and 2009. The cohort was followed from birth through age five to identify 2471 ASD cases from the electronic medical record.	Retrospective cohort study	Prenatal and first year of life exposures to PM2.5. Ambient PM2.5 and other regional air pollution measurements (PM less than 10mum, ozone, nitrogen dioxide) from regulatory air monitoring stations were interpolated to estimate exposure during each trimester and first year of life at each geocoded birth address.	Autism spectrum disorder (ASD)	Adjusted HRs per 6.5mug/m(3) PM2.5 were elevated during entire pregnancy [1.17 (95% confidence interval (CI), 1.04-1.33)]; first trimester [1.10 (95% CI, 1.02-1.19)]; third trimester [1.08 (1.00-1.18)]; and first year of life [1.21 (95% CI, 1.05-1.40)]. Only the first trimester association remained robust to adjustment for other exposure windows, and was specific to boys only (HR=1.18; 95% CI, 1.08-1.27); there was no association in girls (HR=0.90; 95% CI, 0.76-1.07; interaction p-value 0.03). There were no statistically significant associations with other pollutants. PM2.5-associated ASD risk was stronger in boys.

Kaufman (2019)	ASD cases (n=428) diagnosed at Cincinnati Children's Hospital Medical Center were frequency matched (15:1) to 6420 controls from Ohio birth records.	case-control study	Ambient fine particulate matter (PM2.5) and ozone concentrations during the prenatal period through the second year of life. Daily PM2.5 and ozone estimates for 2005-2012 from US EPA's Fused Air Quality Surface adjusting for maternal- and birth-related confounders, both air pollutants, and multiple temporal exposure windows.	Autism spectrum disorder (ASD),	Elevated aORs for PM2.5 during the 2nd trimester, 1st year of life, and a cumulative period from pregnancy through the 2nd year (aOR ranges across categories: 1.41-1.44, 1.54-1.84, and 1.41-1.52 respectively), and for ozone in the 2nd year of life (aOR range across categories: 1.29-1.42). Per each change in IQR, we observed elevated aORs for ozone in the 3rd trimester, 1st and 2nd years of life, and the cumulative period (aOR range: 1.19-1.27) and for PM2.5 in the 2nd trimester, 1st year of life, and the cumulative period (aOR range: 1.11-1.17). CONCL. Limited evidence of linear exposure-response relationships for ASD with increasing air pollution, but the elevated aORs detected for PM2.5 in upper exposure categories and per IQR unit increases were similar in magnitude to those reported in previous studies, especially for postnatal exposures.

Chen (2018)	Children. 124 ASD cases and 1240 healthy controls	Case-control study with a multi-stage random sampling design.	Ambient particulate matter (PM) pollution. PM1, PM2.5 and PM10 during the first three years after birth estimated with satellite remote sensing data. The median levels of PM1, PM2.5 and PM10 exposures during the first three years of life were 48.8mug/m(3), 66.2mug/m(3) and 95.4mug/m(3), respectively, and the interquartile range (IQR) for these three pollutants were 4.8mug/m(3), 3.4mug/m(3) and 4.9mug/m(3), respectively.	Autism spectrum disorder (ASD)	The adjusted odds ratios (and 95% confidence intervals) of ASD associated with an IQR increase for PM1, PM2.5 and PM10 were 1.86 (1.09, 3.17), 1.78 (1.14, 2.76) and 1.68 (1.09, 2.59), respectively. Higher ORs of ASD associated with PM pollution were observed in the second and the third year after birth. CONCLUSIONS: Exposures to PM1, PM2.5 and PM10 during the first three years of life were associated with the increased risk of ASD and there appeared to be stronger effects of ambient PM pollution on ASD in the second and the third years after birth.

Forns (2018)	Eight European birth/child cohorts, including 29,127 mother-child pairs.	Population-based birth/child cohorts,	Air pollution concentrations (nitrogen dioxide [NO2] and particulate matter [PM]) were estimated at the birth address by land-use regression models based on monitoring campaigns performed between 2008 and 2011. Authors extrapolated concentrations back in time to exact pregnancy periods.	Attention-deficit/ hyperactivity disorder (ADHD) symptoms.Teachers or parents assessed ADHD symptoms at 3-10 years of age (classified as having ADHD symptoms within the borderline/ clinical range and within the clinical range using validated cutoffs)	2,801 children had ADHD symptoms within the borderline/clinical range, and 1,590 within the clinical range. Exposure to air pollution during pregnancy was not associated with a higher odds of ADHD symptoms within the borderline/clinical range (e.g., adjusted odds ratio [OR] for ADHD symptoms of 0.95, 95% confidence interval [CI] = 0.89, 1.01 per 10 microg/m increase in NO2 and 0.98, 95% CI = 0.80, 1.19 per 5 microg/m increase in PM2.5). We observed similar associations for ADHD within the clinical range. CONCLUSIONS: There was no evidence for an increase in risk of ADHD symptoms with increasing prenatal air pollution levels in children aged 3-10 years.

Goodrich (2018)	346 ASD cases and 260 typically developing controls from the CHARGE case-control study.	Case-control study.	Periconceptional folic acid (FA) and exposure to air pollution. Self-reported FA intake for each month of pregnancy was quantified. Estimates of exposure to near roadway air pollution (NRP) and criteria air pollutant measures were assigned based on maternal residential history.	Autism spectrum disorder (ASD)	Among mothers with high FA intake (>800 mug) in the first pregnancy month, exposure to increasing levels of all air pollutants, except ozone, during the first trimester was associated with decreased ASD risk, while increased ASD risk was observed for the same pollutant among mothers with low FA intake (</=800 mug). This difference was statistically significant for NO2 (e.g., NO2 and low FA intake: OR = 1.53 (0.91, 2.56) vs NO2 and high FA intake: OR = 0.74 (0.46, 1.19), P-interaction = 0.04). Mothers exposed to higher levels (>/= median) of any air pollutant during the first trimester of pregnancy and who reported low FA intake were at a higher ASD risk compared to mothers exposed to lower levels of that air pollutant and who reported high first month FA intake. Joint effects showed significant (alpha < 0.10) departures from expected interaction for NRP and NO2 .

Guxens (2018)	Birth cohort in Rotterdam, The Netherlands (2002-2006) (n = 783).	Data from a population-based birth cohort s	Air pollution exposure during fetal life. Entire fetal period were calculated using land-use regression models.	Brain morphology and association between air pollution exposure during fetal life and cognitive function in school-age children. Structural neuroimaging and cognitive function were performed at 6 to 10 years of age. Models were adjusted for several socioeconomic and lifestyle characteristics.	Mean fine particle levels were 20.2 mug/m(3) (range, 16.8-28.1 mug/m(3)). Children exposed to higher particulate matter levels during fetal life had thinner cortex in several brain regions of both hemispheres (e.g., cerebral cortex of the precuneus region in the right hemisphere was 0.045 mm thinner (95% confidence interval, 0.028-0.062) for each 5-mug/m(3) increase in fine particles). The reduced cerebral cortex in precuneus and rostral middle frontal regions partially mediated the association between exposure to fine particles and impaired inhibitory control. Air pollution exposure was not associated with global brain volumes.

Kalkbrenner (2018)	Participants of a U.S. family-based study [the Autism Genetic Resource Exchange (AGRE)] who were born between 1994 and 2007. ASD diagnosis (1,540 cases and 477 controls)	Prospective study and case-control	Perinatal exposure to air toxics, including some metals and volatile organic compounds. Average annual concentrations at birth for each of 155 air toxics from the U.S. EPA emissions-based National-scale Air Toxics Assessment	Autism spectrum disorder (ASD); a continuous measure of autism-related traits, the Social Responsiveness Scale (SRS, among 1,272 cases and controls); and a measure of autism severity, the Calibrated Severity Score	ASD diagnosis was positively associated with propionaldehyde, methyl tert-butyl ether (MTBE), bromoform, 1,4-dioxane, dibenzofurans, and glycol ethers and was inversely associated with 1,4-dichlorobenzene, 4,4'-methylene diphenyl diisocyanate (MDI), benzidine, and ethyl carbamate (urethane). These associations were robust to adjustment in two-pollutant models. Autism severity was associated positively with carbon disulfide and chlorobenzene, and negatively with 1,4-dichlorobenzene. There were no associations with the SRS.
Kerin (2018)	327 children with ASD	case only study	Prenatal exposure to air pollution. Nitrogen dioxide (NO2), particulate matter (PM2.5 and PM10), ozone, and near-roadway air pollution for each trimester of pregnancy and first year of life.	Autism spectrum disorder (ASD) severity or functioning. Cognitive ability, adaptive functioning, and ASD severity were assessed.	Increasing prenatal and first year NO2 exposures were associated with decreased MSEL and VABS scores. Increasing PM10 exposure in the third trimester was paradoxically associated with improved performance on the VABS. ASD severity was not associated with air pollution exposure.

Markevych (2018)	Children residing in Saxony. 66,823 children, all beneficiaries of the statutory health insurance company AOK PLUS and born between 2000 and 2004, followed until 2014.	Prospective study	Air pollution and greenspace. Children's home addresses were known up to their four-digit postal code area. Population-weighted mean values of particulate matter with diameter of <10mum (PM10), nitrogen dioxide (NO2), and MODIS Normalized Difference Vegetation Index (NDVI) were calculated for 186 postal code areas.	Attention deficit hyperactivity disorder (ADHD)	2044 children (3.06%) were diagnosed with ADHD within the observation period. An increase of PM10 and NO2 by 10mug/m(3) raised the relative risk of ADHD by a factor of 1.97 [95% CI: 1.35-2.86] and 1.32 [1.10-1.58], respectively. A 0.1-unit increase in NDVI decreased the relative risk of ADHD by a factor of 0.82 [0.68-0.98]. Better access to child/adolescent psychiatrists was the most important confounder that increased ADHD risk across all models.

Pagalan (2018)	All births in Metro Vancouver, British Columbia, Canada, from 2004 through 2009, with follow-up through 2014. 132256 births	Population-based cohort study.	Prenatal exposures to airborne pollutants. Monthly mean exposures to particulate matter with a diameter less than 2.5 microm (PM2.5), nitric oxide (NO), and nitrogen dioxide (NO2) at the maternal residence during pregnancy were estimated with temporally adjusted, high-resolution land use regression models. Adjustment for child sex, birth month, birth year, maternal age, maternal birthplace, and neighborhood-level urbanicity and income band.	Autism spectrum disorder (ASD). Children were diagnosed with ASD using a standardized assessment with the Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule.	1307 children (1.0%) were diagnosed with ASD by the age of 5 years. The final sample size for the PM2.5-adjusted model was 129439 children, and for NO and NO2, it was 129436 children; of these, 1276 (1.0%) were diagnosed with ASD. Adjusted odds ratios for ASD per interquartile range (IQR) were not significant for exposure to PM2.5 during pregnancy (1.04 [95% CI, 0.98-1.10] per 1.5 mug/m3 increase [IQR] in PM2.5) or NO2 (1.06 [95% CI, 0.99-1.12] per 4.8 ppb [IQR] increase in NO2) but the odds ratio was significant for NO (1.07 [95% CI, 1.01-1.13] per 10.7 ppb [IQR] increase in NO). Odds ratios for male children were 1.04 (95% CI, 0.98-1.10) for PM2.5; 1.09 (95% CI, 1.02-1.15) for NO; and 1.07 (95% CI, 1.00-1.13) for NO2. For female children, they were for 1.03 (95% CI, 0.90-1.18) for PM2.5; 0.98 (95% CI, 0.83-1.13) for NO; and 1.00 (95% CI, 0.86-1.16) for NO2.

Perera (2018)	Nonsmoking African-American and Dominican pregnant women in New York City between 1998 and 2006; their children followed through 9 years of age.	Prospective cohort study	Polycyclic aromatic hydrocarbons (PAH). As a biomarker of prenatal PAH exposure, PAH-DNA adducts were measured in maternal blood at delivery and were dichotomized at the limit of detection (to indicate high vs. low exposure). Maternal material hardship (lack of adequate food, housing, utilities, and clothing) was self-reported prenatally and at multiple time points through child age 9.	Attention Deficit Hyperactivity Disorder (ADHD) behavior problems at age 9, assessed using the Conners Parent Rating Scale- Revised.	Among 351 children in our sample, across all hardship groups, children with high prenatal PAH exposure (high adducts) generally had more symptoms of ADHD (higher scores) compared to those with low PAH exposure. The greatest difference was seen among the children with hardship persisting from pregnancy through childhood. Although the interactions between high PAH exposure and hardship experienced at either period ("persistent" hardship or "any" hardship) were not significant, we observed significant differences in the number of ADHD symptoms between children with high prenatal PAH exposure and either persistent hardship or any hardship compared to the others. These differences were most significant for combined high PAH and persistent hardship: ADHD Index ($p < 0.008$), DSM-IV Inattentive ($p = 0.006$), DSM-IV Hyperactive Impulsive problems ($p = 0.033$), and DSM-IV Index Total ($p = 0.009$).

Raz (2018)	Children born during 2005-2009 in the central coastal area of Israel. Cases were identified through the National Insurance Institute of Israel (n = 2,098). Controls were a 20% random sample of the remaining children (n = 54,191).	Nested case-control study	Perinatal air pollutant exposures. Exposure was based on an optimized dispersion model.	Autism spectrum disorder (ASD)	In models mutually adjusted for the 2 periods, the odds ratio per 5.85-parts per billion (ppb) increment of nitrogen dioxide exposure during pregnancy (median, 16.8 ppb; range, 7.5-31.2 ppb) was 0.77 (95% confidence interval: 0.59, 1.00), and the odds ratio for exposure during the 9 months after birth was 1.40 (95% confidence interval: 1.09, 1.80). A distributed-lag model revealed reduced risk around week 13 of pregnancy and elevated risk around week 26 after birth. These findings suggest that postnatal exposure to nitrogen dioxide in Israel is associated with increased odds of ASD, and prenatal exposure with lower odds. The latter may relate to selection effects.

Saez (2018)	Cases and controls (children free of the disease) by sex and year of birth (n=5193, 78.9% boys). The cases were children born between 1998 and 2012 and diagnosed with ADHD (n=116).	Population-based case-control study	Environmental variables: distance to agricultural areas, distance to roads (stratified into three categories according to traffic density and intensity), distance to petrol stations, distance to industrial estates, and land use.	Attention deficit hyperactivity disorder (ADHD)	North-south pattern containing two clusters (one in the centre of the study region and another in the south) in relation to the risk of developing ADHD. The results from the multivariate model suggest that these clusters could be related to some of the environmental variables. Specifically, living within 100m from an agricultural area or a residential street and/or living fewer than 300m from a motorway, dual carriageway or one of the industrial estates analysed was associated (statistically significant) with an increased risk of ADHD.

Yousefian (2018)	134 children born between 2004 and 2012 diagnosed with ASD whose mothers were resident in Tehran during their pregnancy, and controls were 388 children without ASD randomly selected from public schools and kindergartens.	Case-control study	Exposure to ambient particulate matter with aerodynamic diameter </=10mum (PM10), sulfur dioxide (SO2), benzene, toluene, ethylbenzene, p-xylene, o-xylene, m-xylene (BTEX), and total BTEX.	Autism spectrum disorder (ASD) among 2 to 10-year-old children.	The odds ratios per 1 unit increase in pollutants in the adjusted models were 1.00 (95% CI: 0.99, 1.01) for PM10, 0.99 (95% CI: 0.99, 1.00) for SO2, 0.96 (0.83, 1.11) for benzene, 1.00 (0.96, 1.04) for toluene, 0.95 (0.79, 1.16) for ethylbenzene, 1.00 (0.78, 1.27) for p-xylene, 1.09 (0.94, 1.27) for o-xylene, 1.01 (0.92, 1.12) for m-xylene, and 0.99 (0.97, 1.01) for total BTEX. We did not find the evidence of association between estimated annual mean exposure to abovementioned ambient air pollutants and increased odds of ASD in children.

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