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## Environment and Autism: Current State of the Science

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### Abstract

Research into environmental risk factors for autism has grown dramatically over the past 10 years, providing evidence that non-genetic factors acting during the prenatal period may influence the underlying neurodevelopmental processes. This paper reviews the evidence on modifiable preconception and/or prenatal factors that have been associated with autism spectrum disorder (ASD), including only human studies with at least 50 cases of ASD, having a valid comparison group, conducted within the past decade, and focusing on maternal lifestyle or environmental chemicals. Consistent results have been reported for an association of higher maternal intake of certain nutrients and supplements with reduction in ASD risk, with the strongest evidence for folic acid supplements. A number of studies have demonstrated significant increases in ASD risk with estimated exposure to air pollution during the prenatal period, particularly for heavy metals and particulate matter. A few studies suggest a link with organophosphate pesticides. More rigorous ascertainment of exposure is needed for studies of substance use; most investigations adjusting for potential confounders, but relying on self-reported use, have shown no links between maternal smoking or alcohol consumption and ASD. Little research has assessed other persistent and non-persistent organic chemical pollutants, such as are found in common household or personal care products, in association with ASD specifically. More work is needed to examine fats, vitamins, and other maternal nutrients, as well as endocrine-disrupting chemicals and pesticides, in association with ASD, given sound biological plausibility and evidence regarding other neurodevelopmental outcomes. In addition, the field could be advanced by the use of large-scale epidemiologic studies, attention to critical etiologic windows and how these vary by exposure, interactions with genetic susceptibility, and a focus on underlying mechanisms.

### Introduction

In the past decade there has been an exponential growth in the number of environmental factors studied in association with autism spectrum disorder (ASD). Although genetic factors are clearly involved in ASD risk, evidence supports a substantial environmental contribution. Furthermore, both genetic and environmental research points to the complexity of the disorder, with multiple causes likely to be acting in one individual. Although postnatal influences may also contribute to risk, this review covers exposures occurring during the preconception and prenatal periods. We focus on maternal lifestyle factors and environmental chemical exposures that can potentially be modified at the individual or societal level; only human studies with adequate sample sizes (at least 50 cases) that examined an ASD diagnosis or a scale score for ASD symptoms are reviewed.

Environmental exposures may influence brain development at different stages, acting directly on signaling or receptors in neuronal tissue, or through immune dysregulation, hormonal aberrations, oxidative stress, nutrient deficiencies, epigenetic alterations, and/or by inducing de novo DNA changes. Some environmental factors may be markers rather than causes of higher risk, but are

useful in providing etiologic clues; examples include season of birth or conception (1-3) and short inter-pregnancy interval (PI) (4-6). The former may be related to factors that vary by season, such as viral infections, vitamin D levels or pesticide use, while the latter could result in maternal nutrient deficiencies.

## 1. Maternal lifestyle factors

Table 1: Summary of Maternal Lifestyle Factors Associated with Autism

Environmental Factor and Study Reference, Location, and Name	Study Design	Exposure Assessment	Results	State of Evidence
<b>Prenatal Vitamins</b>				
Schmidt et al., 2011 California, USA (CHARGE)	Case-control (429 ASD, 278 controls)	Parental report via telephone-administered questionnaire	Associated with decreased risk for ASD if taken before or near conception especially in combination with certain one-carbon metabolism genotypes	Additional studies examining multivitamins or prenatal vitamins are needed. Interaction with certain one-carbon metabolism genotypes needs to be replicated.
<b>Folic Acid</b>				
Schmidt et al., 2012 California, USA (CHARGE)	Case-control (429 ASD, 278 controls)	Total mean folic acid quantified from frequency of intake of supplement and cereal brands parentally reported via telephone-administered questionnaire	Folic acid intake near conception associated with reduced risk for ASD, especially if mother or child has <i>MTHFR</i> 677 T-allele. Dose-response trend observed	Association between supplemental folic acid intake near conception and reduced risk for autism/ASD replicated. Dose-response trend and effect modification by maternal and child <i>MTHFR</i> 677 T-allele and other gene variants needs replication. Dietary folate needs consideration.
Surén et al., 2013 Norway (MoBa)	Birth cohort (85,176 children, 114 with autism, 56 with Asperger syndrome, 100 with PDD-NOS)	Folic acid supplement intake before conception and in early pregnancy obtained through questionnaire report at week 18 of gestation	Folic acid intake near conception (4 weeks before – 8 weeks after LMP) associated with reduced risk for autism, not Asperger syndrome or PDD-NOS	
<b>Fish &amp; Fish Oil</b>				
Kim et al., 2010 South Korea	Case-control (106 ASD, 324 control)	Maternal report of seafood consumption starting third trimester of pregnancy	No difference in seafood exposure	Evidence suggests no association for maternal fish or fish oil in two large cohort studies with prospective exposure collection and adjustment for appropriate confounders. Both studies relied on self-report. Additional studies examining fish and fish oil intake during pregnancy are needed to replicate the findings and investigate dose effects.
Lyall et al., 2013 United States (Nurses' Health Study II)	Nested case-control (317 mothers of children with ASD, 17,728 control mothers)	Fish intake collected using validated food frequency questionnaire	No association found for maternal fish intake	
Surén et al., 2013 Norway (MoBa)	Birth cohort (85,176 children, 114 with autism, 56 with Asperger syndrome, 100 with PDD-NOS)	Fish oil supplement intake before conception and in early pregnancy reported on questionnaire at week 18 of gestation	No association found for maternal fish oil taken near conception (4 weeks before – 8 weeks after LMP)	
<b>Fatty Acids</b>				
Lyall et al., 2013 United States (Nurses' Health Study II)	Nested case-control (317 mothers of children with ASD, 17,728 control mothers)	Self-administered food frequency questionnaire for diet during the year the child was born	Decreased ASD risk with increased maternal polyunsaturated fat intake, especially omega-6 fatty acids. Very low omega-3 intake was associated with increased ASD risk	Preliminary evidence for decreased ASD risk with increased omega-6 fatty acids and very low omega-3 intake associated with increased risk. Results need to be replicated, use objective measurements, and examine timing.
<b>Vitamin D</b>				
Whitehouse et al., 2012 Australia (Raine Study)	Cohort (n=929, including 3 with ASD)	Serum 25(OH)-vitamin D concentrations measured at 18 weeks' pregnancy using an enzyme immunoassay kit (a subset also had LCMS measurements)	Maternal gestational serum levels were not associated with offspring autism phenotypes (using autism-spectrum quotient); a weak association was found with the attention switching subscale.	Maternal gestational vitamin D does not appear to be associated with offspring autism phenotypes in a general population study; studies examining maternal vitamin D in relation to ASD diagnosis in the child are needed.

Environmental Factor and Study Reference, Location, and Name	Study Design	Exposure Assessment	Results	State of Evidence
<b>Smoking</b>				
Hultman et al., 2002 Sweden	Population-based nested case-control study; 408 autism cases, 2,040 controls	Self-report to midwives at registration for antenatal care	Significant association between daily smoking and increased risk for infantile autism	Evidence is inconsistent, though a number of studies with appropriate adjustment for SES do not support maternal cigarette smoking as a strong risk factor for ASD. Some indication for an association with high-functioning ASD. All studies relied on self-reported smoking, often from birth records, which can be inaccurate. Early studies often did not adjust for SES, which was a strong confounder. Few studies considered environmental cigarette smoke exposure, and those that did had other limitations. Further studies investigating high-functioning ASD and potential gene x environment interactions, and utilizing objective markers of cigarette smoking (i.e. serum cotinine levels) are needed to rule out an effect.
Williams et al., 2003 Kentucky	Case-control (102 autism, 106 developmentally disabled controls without autism)	Prospectively collected maternal report	No significant difference in proportion of mothers reporting prenatal smoking, without adjustment for confounders	
Larsson et al, 2005 Denmark	Population-based nested case-control study; 238 cases, 5,810 controls with smoking data	Self-report at first antenatal visit	No association with infantile or atypical autism without adjustment for confounders	
Maimburg et al., 2006 Denmark	Population-based case-control study; 473 cases, 4,730 controls matched 10:1 on sex, year and birth county	Prospective self-report to midwives at the first antenatal visit generally at 12 weeks	No association with autism	
Indredavik et al., 2007 Norway	Population-based prospective study of 84 adolescents (age 14 years)	Maternally reported at enrollment, before the 20 <sup>th</sup> week of pregnancy	Mothers, fathers, and teachers reported higher social problems score on ASEBA for the smoking exposed adolescents; ASSQ sum score for social sensitivity (as a screen for high functioning ASD) was strongly associated with smoking exposure during pregnancy	
Bilder et al., 2009 United States (ADDM)	Population-based nested case-control; 132 ASD cases, 13,200 controls	Birth record data	No significant association; trend towards decreased risk	
Larsson et al., 2009 Sweden (Dampness in Buildings and Health Study)	Population-based cohort study; 4,779 children, including 72 ASD cases	Parent-report collected for pregnancy when child was age 1-6 years	Significant association with 2-fold higher risk for ASD and maternal smoking; Association with paternal smoking non-significant	
Burstyn et al., 2010 Alberta, Canada	Population-based cohort study; 218,890 children including 1,138 with ASD (215,220 total, 1122 ASD with smoking data)	Birth record self-reported data	No significant association between any maternal smoking and ASD (trend in protective direction)	
Zhang et al., 2010 Tianjin, China	Case-control (95 autism, 95 typically developing controls)	Retrospective parental report on self-administered questionnaire	Increased maternal exposure to second-hand smoke during pregnancy reported by mothers of children with autism	
Ronald et al., 2010 England and Wales	Population-based cohort of 13,690 twins (subset with teacher data); 154 potential ASD cases	Retrospective parental-report of exposure during pregnancy collected when the child was around 1.5 years old	Significant positive correlation between number of cigarettes smoked and autistic-like features at 7 and 8 years of age	

Environmental Factor and Study Reference, Location, and Name	Study Design	Exposure Assessment	Results	State of Evidence
Hvidtjorn et al, 2011 Denmark	Population-based case-control study; 3602 ASD cases, 582,694 controls	Birth record data	Significantly higher proportion of mothers of children with ASD reported smoking	
Lee et al., 2012 Sweden	Registry-based nested case-control study of 3,958 ASD cases and 38,983 controls	Self-reported information on smoking prospectively recorded by midwives at the first prenatal visit approximately 8–12 weeks after conception	No association between maternal smoking during pregnancy and ASD, after adjustment for confounders	
Kalkbrenner et al. 2012 United States	Population-based case-cohort study; 633,989 children, including 3,315 with ASD (1,310 autistic disorder, 375 ASD-NOS)	Birth certificate report	No association with ASD or autistic disorder; modest association with ASD-NOS, after adjustment for confounders	
Tran et al., 2013 Finland	Population-based nested case-control study; 4048 ASD cases, 16,582 controls without ASD or severe intellectual disability (4019 ASD, 16,582 controls with smoking data)	Prospectively collected medical record data; self-report	Maternal smoking during entire pregnancy associated with PDD; no association with first trimester smoking. No association with AU or Asperger's.	
Visser et al., 2013 Netherlands (DIANE)	Nested case-control (196 ASD [121 AU, 75 PDD-NOS], 311 typical controls)	Retrospective parent-questionnaire administered prior to diagnostic assessments	Trend towards higher prenatal tobacco use for ASD vs. controls; significantly higher use in PDD-NOS vs. AU	
<b>Alcohol</b>				
Williams et al., 2003 Kentucky, USA	Case-control (102 autism, 106 developmentally disabled controls without autism)	Prospectively collected maternal report	Significantly lower proportion reporting prenatal alcohol exposure in mothers of children with autism compared to mothers of developmentally disabled children	No increased risk from light to moderate maternal alcohol consumption. Needs replication in a study with adjustment for potential confounders. Accurate exposure assessment difficult to achieve.
Eliassen et al., 2010 Denmark	Population-based prospective cohort study (n=80,552, including 157 with autism)	Self-reported alcohol consumption collected through telephone interview during pregnancy	No increased risk from light to moderate maternal alcohol consumption	
Kim et al., 2010 South Korea	Case-control (106 ASD, 324 control)	Maternal report of alcohol consumption before and during pregnancy	No difference in proportion of mothers reporting alcohol consumption before or during pregnancy	
Visser et al., 2013 Netherlands (DIANE)	Nested Case-control (196 ASD, 311 typical controls)	Retrospective parent-questionnaire administered prior to diagnostic assessments	ASD case parents reported significantly lower alcohol use than control parents (same for AD and PDD)	

Abbreviations: ASEBA=Achenbach System of Empirically Based Assessment, ASSQ= Autism Spectrum Screening Questionnaire

## Maternal Nutrition

Few autism studies have explored maternal nutrition, which is essential to fetal brain development. Maternal nutrient deprivation has been associated with increased risk of other adverse neurodevelopmental outcomes (7-12). Nutritional insufficiencies are common during pregnancy because of the greater metabolic demands of the growing placenta, fetus, and maternal tissues (13,14), and have been shown to influence brain structure and function.

### *Prenatal Vitamins and Folate*

Two population-based studies found that taking supplements high in folic acid near conception, but not other time points, was associated with a 40% lower risk of autism (15,16). In further work, Schmidt and colleagues (17) reported that ASD risk decreased as mean daily folic acid intake from vitamins, supplements, and breakfast cereals increased (Ptrend = 0.001). Significant gene-environment interactions suggested even stronger protection from folic acid supplements or higher folic acid when the children or their mothers carried gene variants leading to less efficient folate metabolism (15,18).

These findings present a possibility of reducing risk for autism by increasing maternal folic acid intake. As folate provides an abundant source of methyl groups, mechanisms involving methylation changes and resultant alterations in expression or activity of genes, proteins, and neurotransmitters may link folic acid to ASD (17,19,20).

### *Fish and Fish Oil Supplements*

Maternal fish intake may confer either protective effects as a source of fatty acids and vitamin D, or increased risks of harm from accumulated mercury and other contaminants. Higher fish intake has also been associated with improved neurodevelopmental scores (21). Studies to date on maternal fish and fish oil intake have found no association with ASD (16,22), possibly the net result of two opposing effects.

### *Fatty Acids*

Developing fetuses require maternal stores of omega-3 fatty acids for optimal brain development (23,24). Higher intake of polyunsaturated fatty acids (PUFAs) before and during pregnancy, measured using validated food frequency questionnaires, was associated with reduced risk of ASD in a large U.S. prospective cohort study. Very low intakes (the lowest 5% of the distribution) of omega-3 fatty acid were linked to a significantly increased risk of ASD. Replication and identification of optimal or threshold levels are needed.

### *Vitamin D*

Although low maternal (and thus fetal) vitamin D levels have been hypothesized as risk factors for ASD (25), few studies have examined prenatal exposure. In one of these studies, maternal serum 25-hydroxyvitamin D concentrations measured around the 18th week of pregnancy did not predict the child's Autism-Spectrum Quotient (AQ) scores in early adulthood (26) but the sample size was too small to examine ASD diagnoses. Other reports provide indirect support for an association, e.g. increased rates of ASD among children of dark-skinned immigrant mothers who moved to high latitudes (27) and among children born or conceived in certain seasons (3,28). Biologic plausibility for a role of vitamin D comes through its influence on neuronal differentiation, metabolism of neurotrophic factors and neurotoxins, protection from brain inflammation, endocrine functions, and fetal brain growth.

## Substance use

### *Cigarette Smoking*

Numerous investigations have assessed maternal smoking in association with ASD, each with limitations, and overall produced inconsistent findings (29-41). Earlier work lacked adjustment for socioeconomic factors that were likely to have confounded associations (29-32), or adjusted for potentially mediating variables (i.e. birthweight) (35,36), which could have masked an elevated risk.

Studies that did adjust for sociodemographic factors generally do not support a large association with ASD (35,37,38,41). Two studies found an association of maternal smoking with high-functioning autism or pervasive developmental disorder but not with lower functioning cases (37,38,41). Nevertheless, data on smoking may be subject to under-reporting in medical records, self-report or birth certificates (40), which could lead to bias towards the null.

Though evidence to date of an association with ASD is weak, maternal smoking could influence neurodevelopment and risk for ASD through mechanisms such as placental insufficiency, reduced blood flow and oxygen deprivation in the brain (42), changes in fetal brain gene expression (43), altered nicotinic receptors (44), persistent changes in neurotransmitter activity and turnover (45,46), and/or increased intrauterine testosterone (47). Prenatal smoking in some mothers may also be an indicator of underlying psychological problems that themselves could influence risk in the offspring (48). Effects of second-hand tobacco smoke exposure and interactions with genetic susceptibility should be further explored.

### *Alcohol*

Maternal alcohol consumption can be teratogenic; high prenatal alcohol exposure impairs neurodevelopment in humans (49-51) and in animal studies produces social avoidance (52). Surprisingly few rigorous studies have examined maternal alcohol use and ASD risk. Those conducted to date do not support an association with low to modest maternal alcohol intake but studies suggest a potential association with levels high enough to induce fetal alcohol syndrome (39,49,53).

## **2. Environmental Chemicals**

Despite historical evidence of reproductive and neurodevelopmental aberrations with exposure to chemicals like lead or pesticides, federal requirements to test substances for long-term behavioral consequences have been slow to evolve, and thousands of compounds remain unregulated (58).

### *Air Pollution*

A growing literature has emerged on air pollution, or proxies for it, in relation to ASD (55-61). Many of these studies linked household addresses to U.S. Environmental Protection Agency (EPA) models to derive exposure information. Most have reported modest increases in the risk of ASD, with an odds ratio (OR) around 1.5 to 2, for those individuals with higher estimated exposure to air pollution. Two large studies, one with data across the United States, found elevated risk for ASD with higher levels of chlorinated solvents, heavy metals, diesel particles, and other specific compounds (62,66).

Residential proximity (<309 m) to a major freeway, a major source and strong predictor of high pollutant levels, has also been linked to a near doubling of odds of having a child with ASD, as compared to further distances, in a large population-based case control study (59). Elevated risks were also found with gestational and first year of life exposures for overall traffic-related air pollution, nitrogen dioxide, and particulate matter less than 2.5 and less than 10  $\mu\text{m}$  in diameter (PM<sub>2.5</sub> and PM<sub>10</sub>). Gene-environment interaction was identified: children homozygous for the MET C allele were especially vulnerable to the effects of air pollution: ORs for top quartile CC genotype vs. bottom three quartiles CT or TT genotype were 3-fold or higher for PM<sub>10</sub> and nitrogen dioxide (67).

A large investigation from Los Angeles (55) also reported an elevated risk of ASD for higher estimated ozone and NO<sub>2</sub> exposure during the entire pregnancy, in models adjusted for numerous sociodemographic confounders. Stronger associations were found for those in the lowest educational stratum.

Thus, a growing literature suggests air pollutant exposure during pregnancy may increase ASD risk. Because air pollution is a complex and variable mixture of compounds that are highly correlated, impact of any specific chemical is unclear. Additionally, although most analyses adjusted for socio-demographic factors, residual confounding factors could be present, particularly socio-economic

factors, that influence the likelihood of a diagnosis. Confounding by other predictors of child outcomes, e.g. noise pollution through sleep disturbances, should also be considered. Further work is needed to elucidate potential biological pathways.

### *Persistent Organic Pollutants*

Persistent organic pollutants (POPs) are widely distributed throughout the environment and are toxic to both wildlife and human health. These include certain pesticides, industrial chemicals, and by-products of industrial processes. Several POPs, including dioxins, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) are endocrine-disrupting chemicals (EDCs). A pilot investigation (64) found a non-significant elevation of the odds for ASD associated with higher measured concentrations of PCBs in maternal samples taken at delivery. Another recent study found that higher scores on a scale of autism traits were associated with greater concentrations of 2,3,7,8-tetrachlorodibenzodioxin (the most toxic dioxin) in the mothers' breast milk (69).

EDCs may influence neurodevelopment through disruption of maternal thyroid hormones (66), essential for neuronal growth, cell migration and differentiation during early gestation (67). A human study on ASD and thyroid hormones found an association with very low levels at birth (68). The strong male: female ratio in autism of over four may indicate a role for steroid hormones or their targets (69) in early sexual differentiation of the brain. A number of EDCs alter production or activity of sex steroids; both testosterone and estradiol influence fetal brain development.

### *Pesticides*

Some pesticides are POPs (<http://chm.pops.int/Convention/ThePOPs/tabid/673/Default.aspx>) and/or EDCs (70) and are designed to damage the nervous systems of the targeted species, often acting on neurotransmission.

Organochlorine pesticides, originally used to control malaria but still applied agriculturally, were linked, when exposures were in the first trimester, with elevated ASD risk in children from nearby residences (75).

Organophosphate insecticides degrade rapidly; they have been widely applied both agriculturally and residentially, though use in residential products was banned by the U.S. EPA in 2001. Agricultural organophosphate applications near the home at any point in pregnancy were associated with elevated ASD risk (71) in two independent California studies, both with adjustment for confounders and one of which had confirmed cases. Symptoms for pervasive developmental disorder (PDD) were associated, in two different cohorts of mother-child pairs, with higher levels of metabolites in urine samples (72) or of chlorpyrifos, a common organophosphate, in umbilical cord blood plasma (73). Other investigations support behavioral and cognitive deficits (74,75), as well as differences in brain volume (81), associated with organophosphates.

Other pesticides that have become increasingly common and are ubiquitously used (77) warrant scrutiny, including synthetic pyrethroids or their naturally-derived counterparts, pyrethrins (78), and imidacloprid and fipronil. The latter are used in insecticides and other products to eliminate pests, and frequent use during pregnancy was reported more often by mothers of ASD children than by those of typically developing controls. These products might influence neurodevelopment through a variety of mechanisms (79), including interference with serotonergic systems, altered GABA function, mitochondrial dysfunction, endocrine disruption (66) and alterations in calcium signaling (80,81).

## **Non-persistent Organic Pollutants**

Several short-lived compounds in common household or personal care products may act as neurodevelopmental toxicants. Two of these compounds, bisphenol A (BPA), and phthalates, have also been linked to thyroid dysfunction, which could lead to neurodevelopmental consequences. Phthalates have anti-androgenic properties and are found in cosmetics, lotions, fragrances and building materials (82). In children, prospective research found associations of some phthalate



metabolites with body size (83), conduct disorder or attention problems (84) and social deficits (85). Phthalate metabolites in third trimester maternal urine were associated with poorer scores on several subscales of the Social Responsiveness Scale (SRS) (85). A doubling of ASD risk was reported in one study in children whose homes had vinyl (PVC) flooring (34), which is a significant source of airborne phthalates (86). No studies to date (87) have been conducted on prenatal BPA exposure and ASD diagnosis, though two studies found no evidence for an association ASD symptoms as assessed by the SRS .

Several short-lived compounds in common household or personal care products may act as neurodevelopmental toxicants. Two of these compounds, bisphenol A (BPA), and phthalates, have also been linked to thyroid dysfunction, which could lead to neurodevelopmental consequences. Phthalates have anti-androgenic properties and are found in cosmetics, lotions, fragrances and building materials (82). In children, prospective research found associations of some phthalate metabolites with body size (83), conduct disorder or attention problems (84) and social deficits (85). Phthalate metabolites in third trimester maternal urine were associated with poorer scores on several subscales of the Social Responsiveness Scale (SRS) (85). A doubling of ASD risk was reported in one study in children whose homes had vinyl (PVC) flooring (34), which is a significant source of airborne phthalates (86). No studies to date (87) have been conducted on prenatal BPA exposure and ASD diagnosis, though two studies found no evidence for an association ASD symptoms as assessed by the SRS.

Table 2: Summary of Environmental Chemicals Potentially Associated with Autism















Environmental Factor and Study Reference, Location, and Name	Study Design	Exposure Assessment	Results	State of the Evidence
<b>Air Pollution: Metals, Solvents, PAHs</b>				
Windham et al., 2006 San Francisco, USA	Retrospective nested case-control, (284 ASD cases; 657 population controls with no known developmental disability)	U.S. EPA-modeled estimates (in 2 <sup>nd</sup> year of life) assigned to Census tract of home	Census tract residence in top quartile of metal exposures (collectively and individually for cadmium, mercury and nickel), chlorinated (but not aromatic) solvents, at higher risk for ASD.	Use of objective measures of exposures and adjustment for numerous sociodemographic factors in most of these studies are strengths. Consistently elevated risk observed for metals and some solvents (methylene chloride) in two of three studies. One study observed high OR for methylene chloride in urban areas. Associations not consistent across studies for lead and vinyl chloride. Available studies used same exposure database, which represents only select years of modeling. A problematic discrepancy is with tobacco smoke, which contains many of the same constituents (e.g., metals, PAHs, as well as particles (below)), but has not been consistently associated with ASD. Further work with additional control for other exposures, investigation into defining windows of susceptibility, attention to mechanistic investigations, and resolution of the apparent discordance with the literature on tobacco smoke would move the field forward.
Kalkbrenner et al 2010 North Carolina & West Virginia, USA	Case-control (374 ASD cases; 3177 controls with speech or language impairment)	U.S. EPA-modeled estimates for 1996 (births were in years 1992, 1994, and 1996)	Quinoline and styrene associated with elevated risk. Methylene chloride also elevated, particularly in urban areas, though not with precision.	
Roberts et al 2013 United States (Nurses' Health Study II)	Retrospective cohort (325 ASD cases; 22,101 population controls without ASD)	U.S. EPA-modeled estimates for year nearest birth year assigned to Census tract of birth home	Census tract residence in top quintile of metal exposures (collectively and individually for mercury, lead, manganese & nickel) at higher risk for ASD. Dose-response observed.	
<b>Air Pollution: Particles, Ozone, Nitric Oxide, Nitrogen Dioxide</b>				
Windham et al., 2006 San Francisco, USA	Retrospective nested case-control, (284 ASD cases; 657 population controls with no known developmental disability)	U.S. EPA-modeled estimates (in 2 <sup>nd</sup> year of life) assigned to Census tract of home	Census tract residence in top quartile of diesel particles at higher risk for ASD	Use of objective measures of exposures and adjustment for numerous sociodemographic factors are strengths of this literature. Results for diesel particles are not consistent, although different control groups may explain the differences. Two distinct studies implicate criteria pollutants including NO <sub>2</sub> and PM <sub>2.5</sub> . A single study examined ozone and found consistent associations across various models adjusted for a second pollutant. Although all studies adjusted for multiple socioeconomic & demographic factors, possible residual confounding cannot be precluded. Additionally, the lack of consistent evidence for an association with tobacco smoke, which contains NO <sub>2</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> , as well as volatile and semi-volatile compounds, raises concerns about coherence of findings. As above, control for other exposures, defining susceptible exposure windows and mechanisms, and clarification of the relationships with tobacco smoke are needed.
Kalkbrenner et al 2010 North Carolina & West Virginia, USA	Case-control (374 ASD cases; 3177 controls with speech or language impairment)	U.S. EPA-modeled estimates for 1996 (births were in years 1992, 1994, and 1996)	No association with diesel particles	
Volk et al., 2011 California, USA (CHARGE)	Case-control (304 ASD cases; 259 typically developing population controls)	Proximity of home to nearest freeway	Higher risk for those residing <309 m from nearest freeway. No association with living near other major roads	
Volk et al., 2012 California, USA (CHARGE)	Case-control (279 ASD cases; 245 typically developing population controls)	Estimated levels of NO <sub>2</sub> , PM <sub>2.5</sub> , and PM <sub>10</sub> at geocoded home address by time period (gestation and first year of life) from LINE-1 dispersion model and regional air monitoring programs	NO <sub>2</sub> , PM <sub>2.5</sub> , and PM <sub>10</sub> each associated with approximate doubling of risk from gestational exposures; somewhat greater risk from 1 <sup>st</sup> year of life exposures. Both traffic-related and regional pollutant estimates were robust when one was adjusted for a different pollutant in other group.	
Becerra et al., 2013 Los Angeles County, USA	Nested case-control (7603 cases, 76,782 population controls with no known ASD dx)	Estimated daily NO <sub>2</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> levels at geocoded home address based on monitoring data and land use regression	Ozone from monitoring and NO <sub>2</sub> estimated from land-use regression were associated with elevated risk in single and two-pollutant models. Similarly for ozone and PM <sub>2.5</sub> , both estimated from air monitoring	

Environmental Factor and Study Reference, Location, and Name	Study Design	Exposure Assessment	Results	State of the Evidence
<b>Endocrine Disrupting Chemicals (EDCs)</b>				
<b>Phthalates</b>				
Larsson et al., 2009 Sweden (Dampness in Buildings and Health Study )	Cohort (n=4779, including 72 cases)	Maternal report of household flooring material via questionnaire when children were 1-6 years of age	Association of ASD with vinyl flooring in bedrooms, a major indoor contributor to phthalates	Suggestive risk for ASD from two very different studies with different sources of exposures, and different measures of outcome. Further work needed with more attention to timing of exposure information. Need to consider the possibility that different phthalates may have different effects.
Miodovnik et al., 2011 New York, USA	Cohort (n=404)	Maternal 3 <sup>rd</sup> trimester urine samples	Low molecular weight phthalate metabolite concentrations associated with poorer Social Responsiveness Scale scores (Social Cognition, Communication, Awareness domains)	
<b>PCBs</b>				
Cheslack-Postava et al., 2013 Finland (FIPS-A)	Pilot nested case-control (75 each)	Archived maternal pregnancy serum samples	No significant associations, though elevated OR (1.91) for sum of PCBs above 90 <sup>th</sup> percentile of control levels	Insufficient to draw conclusions on risk for ASD
<b>Pesticides</b>				
<b>Organophosphates (OP)</b>				
Rauh et al., 2006 New York, USA	Prospective cohort (n=228; <5% PDD cases)	Measures of chlorpyrifos in plasma (cord or maternal)	Highest chlorpyrifos exposure group had greater risk for PDD as defined by scores on Child Behavior Checklist (CBCL)	Four studies using different methods consistently show elevated risk. Exposure measurements or other information all pertain to the prenatal period. Outcomes not based on clinical assessment in majority of studies. Studies suggest potential association between an organophosphate pesticide and ASD or related symptoms. However, use of one or two isolated measurements may not provide valid surrogates for overall prenatal or infant exposures. Further research with confirmation of diagnoses using gold standard protocols and better measures of individual-level exposures over time is needed.
Eskenazi et al., 2007 California, USA (CHAMACOS)	Prospective cohort (n=355; 51 PDD cases)	Prenatal & child OP (organophosphate) urinary metabolite levels	Prenatal and postnatal dialkylphosphate (DAP) metabolites associated with more than two-fold higher risk for PDD as defined by scores on Child Behavior Checklist	
Roberts E., et al., 2007 California, USA	Case-control (n=465 cases and 6,975 matched controls)	Proximity to agricultural applications of organophosphates	ASD community diagnosis modestly associated with organophosphate applications within 250m, during gestation	
Shelton J.F., et al., 2014 California, USA (CHARGE)	Case-control (486 ASD cases; 316 typically developing population controls)	Proximity to agricultural applications of organophosphates	Clinically confirmed ASD diagnosis associated with organophosphate applications within 1.5 km during pregnancy, particularly chlorpyrifos during 2 <sup>nd</sup> trimester	
<b>Other Pesticides</b>				
Roberts E., et al., 2007 California, USA	Case-control (n=465 cases and 6,975 matched controls)	Proximity to agricultural applications of organochlorine insecticides, or pyrethroid insecticides	ASD community diagnosis strongly associated with residential proximity to organochlorine applications during 1 <sup>st</sup> trimester, and moderately for the pyrethroid, bifenthrin, during the overall gestation	Analyses from one report suggesting a strong association of ASD with organochlorines and a moderate one with a pyrethroid require confirmation in independent samples, preferably with gold standard diagnoses. Results on imidacloprid potentially related to differences in reporting accuracy between cases and controls.
Keil et al., 2014 California, USA (CHARGE)	Population-based case-control (n=407 ASD, and 262 typically developing controls)	Maternal report of common flea or tick treatment for pets (imidacloprid)	Using Bayesian methods, no overall association. Higher risk in those with frequent use. Sensitivity analyses to address misclassification yielded inconclusive results	

## Summary and Future Directions

A number of the factors reviewed here have associations with a broader class of neurodevelopmental or psychiatric conditions and therefore may not be unique risk factors for ASD. Furthermore, genetic factors or critical time periods may influence whether these exposures result in ASD as opposed to other deficits. Considerable progress has been made recently in uncovering clues about environmental contributions to autism. Evidence regarding a protective association of maternal nutrition with ASD, particularly folic acid, is strong. The literature on air pollution shows remarkable consistency, though possible residual confounding factors need to be addressed. A few studies support associations with organophosphate pesticides and with phthalate exposures. For most other modifiable environmental factors in the periconception and prenatal periods, the literature is inconsistent and/or of insufficient quality and quantity. Infections, medications and pregnancy complications, not discussed here, have also been associated with ASD and may operate as co-factors. In addition, numerous endocrine-disrupting compounds deserve careful scrutiny. Additional research gaps include large gene-environment interaction studies, determination of critical etiologic windows for environmental exposures (see Figure 1), and disentangling the roles of maternal and paternal influences. Although the preconception and prenatal periods are likely to have the strongest impact, continued plasticity of the central nervous system implies that exposures in the first year or two of life may also contribute to risk of ASD. It is clear that there is no single or universal cause of autism; rather, many environmental and genetic factors are likely to be involved and the specific subset of factors will vary across different individuals.

Figure 1: Critical periods of Susceptibility indicated from Studies of Autism Spectrum Disorder

Trimester	First									Second			Third		
Gestational Weeks	1	2	3	4	5	6	7	8	9	16	20	22	28	38	
<b>Brain Pathology</b>															
Neurogenesis <sup>1-3</sup>	Weeks 1-20														
Neuronal Migration <sup>1,4</sup>	Weeks 1-16														
Neuronal Maturation <sup>1,5</sup>	Weeks 1-24														
Cortical Layer Formation, Organization, and Neuronal Differentiation <sup>6</sup>	Weeks 1-30														
<b>Exposure</b>															
Freeway Proximity <sup>7</sup>													3 <sup>rd</sup> Trimester		
Traffic-related Air Pollution <sup>8</sup>	1 <sup>st</sup> , 2 <sup>nd</sup> , and 3 <sup>rd</sup> Trimester														
Pesticides <sup>9-11</sup>				Days 26-81											
Prenatal Vitamins <sup>12</sup>	1 <sup>st</sup> Month and 3 Months Before														
Folic Acid <sup>13,14</sup>	1 <sup>st</sup> Month <sup>a</sup>														
Rubella Infection <sup>15,16</sup>	Weeks 1-8														
Fever <sup>17,18</sup>	1 <sup>st</sup> and 2 <sup>nd</sup> Trimester														
Thalidomide <sup>19</sup>			Days 20-24												
Valproic Acid <sup>20,21</sup>			Days 22-28												
SSRI <sup>22, 23</sup>	1 <sup>st</sup> Trimester <sup>b</sup>														
Prenatal Stressors <sup>24</sup>													Weeks 25-28		

Neuropathology (autopsy and imaging) studies of brains of individuals with autism spectrum disorder found evidence of dysregulated neurogenesis, neuronal migration, and neuronal maturation compared to brains of typically developed individuals, processes that generally occur in the first half of pregnancy. Figure 1 shows windows of critical periods indicated by evidence from epidemiological studies of environmental factors demonstrating an association with autism spectrum disorder. Not all exposures shown in the figure are covered in this review, but they are included as exemplary of critical time windows. Time periods of higher risk within pregnancy have variable results, but tend to congregate in the first half of pregnancy. Days=Fetal days after conception. For exposures with more than one study, dark blue indicates overlapping period and light blue indicates timing suggested by one but not all studies. Images adapted from those in *The Developing Human: Clinically Oriented Embryology*, 6th Edition (1998). This material is reproduced with permission of John Wiley and Sons, Inc.

a The study by Suren et al.<sup>14</sup> indicated that up to 6 weeks prior to (and 6 weeks after) conception (4 weeks before LMP to 8 weeks after) was important.

b The study by Rai et al.<sup>23</sup> collected information on use since becoming pregnant at the first antenatal visit which usually takes place before the end of the first trimester (median 10 weeks gestation).

**Please note: These references refer only to fig.1.**

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## GP Comment.

### What have I learned from this paper?

1. Although much of the emphasis on determining risk factors for autism has rightly been on genetic research, this paper provides surprisingly strong evidence for environmental factors in pregnancy either protecting against or increasing the risk of autism in the offspring.
2. As with many other conditions, the interaction between genetic and environmental factors may be of major importance.
3. Folic acid supplements during pregnancy seem to protect against ASD, while very poor intake of omega-3 fatty acid appears to increase the risk.
4. It is surprising that the research on smoking and alcohol consumption during pregnancy has not given us clear answers, although it seems likely that these would be risk factors.
5. It was particularly interesting to see that there seems to be quite strong evidence for maternal exposure to air pollution increasing the risk of ASD.

Perhaps we should all move to the country, away from air pollution, and have a healthy diet with plenty of fresh food to provide the folate and enough oily fish to provide the necessary omega-3. We might feel healthier ourselves and also reduce the risk of ASD in our children.

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