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## Environmental Chemical Exposures and Autism Spectrum Disorders: A Review of the Epidemiological Evidence

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### Abstract

In the past decade, the number of epidemiological publications addressing environmental chemical exposures and autism has grown tremendously. These studies are important because it is now understood that environmental factors play a larger role in causing autism than previously thought and because they address modifiable risk factors that may open up avenues for the primary prevention of the disability associated with autism. In this review, we covered studies of autism and estimates of exposure to 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. We included studies that had individual-level data on autism, exposure measures pertaining to pregnancy or the 1st year of life, valid comparison groups, control for confounders, and adequate sample sizes. Despite the inherent error in the measurement of many of these environmental exposures, which is likely to attenuate observed associations, 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. Whether any of these play a causal role requires further study. Given the limited scope of these publications, other environmental chemicals cannot be ruled out, but have not yet been adequately studied. Future research that addresses these and additional environmental chemicals, including their most common routes of exposures, with accurate exposure measurement pertaining to several developmental windows, is essential to guide efforts for the prevention of the neurodevelopmental damage that manifests in autism symptoms.

### Introduction and Scope of Review

Autism Spectrum Disorder, commonly called autism, is now known to occur in about 1 in 68 children in the U.S.,<sup>1</sup> increasing the likelihood that clinicians will care for children, adolescents, and adults with autism. All people with autism have difficulties in social communication and restricted interests and behaviors. The severity of the symptoms and the level of functional impairment vary widely. A review in this journal has covered the

important topics of screening/early warning signs, the role of the pediatrician within a multidisciplinary team, and the evidence base for treatments,<sup>2</sup> with another review covering pharmacological interventions, genetic testing, and treatment across the life course.<sup>3</sup>

Herein, we focus on processes occurring earlier in the life history of autism—exploring xenobiotic risk factors that tip the balance to cause the emergence of autism symptoms in a child. We have focused on environmental chemicals; agents that arise outside of the human body; and enter via the routes of ingestion, inhalation, dermal absorption, injection, and placental transport from mother to fetus. Other risk factors fit into the broader definition of environment and are likely important, such as nutrients, medications, obstetric complications, maternal medical conditions, and social/demographic influences, but were not included in this review.

The traditional environmental chemical exposures that we included are important in part because exposure to these factors can be reduced, opening up viable avenues for the primary prevention of autism. Increasingly, clinicians are called upon to play a role in identifying, researching, educating about, and advocating for change regarding these modifiable chemical exposures. For example, parents may desire guidance from clinicians regarding the potential risk to their fetus or infant from living with someone who smokes cigarettes or from the use of plastics or residential pesticides. Exercising behavioral or consumer choices, however, cannot entirely protect a patient from these widespread exposures, especially for chemicals that are ubiquitous, such as air pollution, or for contaminants that are unknown to the patient.

Environmental chemical exposures are increasingly understood to be important in causing autism, with current theories positing that autism is caused by the interplay of multiple genetic and environmental contributions that differ from individual to individual.<sup>4,5</sup> While initial studies suggested a strong genetic heritability of autism, recent studies with larger sample sizes have demonstrated a lesser influence, including a study of over 14,000 children with autism in Sweden that demonstrated a heritability of 50%, supporting an equally strong role for environmental risk factors.<sup>6</sup> Genetic and environmental factors may combine to disrupt the normal processes of nervous system development, interfering with neuron formation and migration, synapse formation, or neurological connectivity, ultimately causing autism. Environmental chemical exposures may act through pathophysiologies, including the direct disruption of cells and structures of the nervous system, endocrine hormone- or immune system-mediated impacts, epigenetic changes, and more (Table 1). The important role for environmental chemical exposures in these processes has received data support and increased attention.<sup>7–9</sup> These calls for research are bolstered by the dearth of understanding of the role of our complex, human-created chemical environment on development, with estimates that, out of a chemical universe topping 80,000 agents, over 1000 have laboratory evidence of neurotoxicity, but only a small fraction have been studied in humans during critical windows of development.<sup>10,11</sup> Human exposures to these chemicals are common: 250 xenobiotic chemicals were detected in biological samples from a 2013 representative sample of the U.S. in the National Health and Nutrition Examination Survey.<sup>12</sup> Furthermore, chemical mixtures predominate; in earlier data from this same study, 100% of pregnant women had detectable levels of five chemical classes that were examined.<sup>13</sup>

Although a mere decade ago publications addressing the environment and autism could almost not be found, now epidemiological publications have examined the association of autism with estimates of exposure to tobacco, air pollutants, volatile organic compounds, metals, pesticides, and organic pollutants, such as plasticizers and non-stick chemicals. The state of evidence regarding autism and exposures to some of these pollutants has been reviewed.<sup>14,15</sup> In this review, we provide contextual information about these chemicals, along with an assessment of the current state of epidemiological knowledge regarding exposures to these chemicals and autism, with special attention to assessing validity, integrating results, and evaluating evidence for causality. Our goal is to evaluate and summarize the current state of knowledge, while informing clinicians about the complexities surrounding study in this area together with current approaches. We seek to engage clinicians in the continued identification of, and ultimately, the reduction of, environmental factors that harm neurodevelopment, specifically autism (Box 1).

## Review Methodology: Evaluating the Epidemiological Evidence

In this review, we present study design details (in tables) and results (in figures) from valid research reports. Our inclusion criteria are listed in Box 2 and described in greater detail following.

### Population-Based Human Studies

This review focuses on evidence regarding environmental chemical exposures and autism from human, population-based literature, that is, epidemiological studies, published as primary research reports in English-language, peer-reviewed journals with publication dates prior to March 1, 2014. We also included articles under review when one of us was an author. Findings from controlled laboratory studies on other animals are important in elucidating mechanisms, screening many exposures, and creating highly controlled conditions that strengthen causal inference, but cannot directly address the full spectrum of autism or the real-world human living condition.

We separately included estimates for multiple chemicals within a publication that met our inclusion criteria, for example, reporting on inhaled diesel particles, metals, and volatile organic compounds from one publication.<sup>16</sup> We did not, however, include multiple measures for one chemical-autism question from a given publication, but instead included only the measure most illustrative of the findings, as follows: when results were presented for both the continuous autism phenotype and a dichotomous autism classification, we chose the association that had the most precision, or was of the same type of comparison as the other studies of the same chemical. When exposures were categorized into different levels or geographic distances, we chose either the results emphasized by the authors, or the comparisons that were the most extreme, such as presenting the 4th quartile comparison of an air pollutant rather than the 2nd quartile comparison, or the closest geographic distance to a pesticide application rather than a moderate distance.

### Individual-Level Data on Autism Diagnoses or Behaviors

We restricted our scope of review to studies that were able to include individual-level data on autism or the dimensional nature of autism-like symptoms in analyses, excluding those studies that only had access to aggregated data on autism occurrence (e.g., community-level or ecological outcome data). Although ecological studies are useful in generating hypotheses, we excluded such studies because of some inherent limitations in this design. In aggregate outcome data, it cannot be known that the individual experiencing the exposure is the same individual within the group that had an autism diagnosis. Furthermore, it is not possible to account for individual-level confounding influences in this type of design, biases that are critically important to remove before concluding that an observed statistical association represents a causal relationship.<sup>17,18</sup> In contrast, we did include studies that measured exposure at the community level (ecological *exposures*). Community-level exposures (e.g., an air toxic pollutant estimated for a census tract) often serve as reasonable proxies of individual-level exposure, although they include some degree of exposure measurement error. Importantly, when these studies include an individual measure of autism, proper confounding control is possible and they are not subject to the ecological fallacy.

The studies included in this review included data from multi-faceted research studies and from pre-existing records (Table 2). Different means of diagnosing autism or measuring autism symptoms and characteristics (the continuous autism phenotype) were included (Table 3). Measures of the continuous autism phenotype in a general population differ from clinical diagnoses because fewer study children will exhibit symptoms at the upper extreme that would lead to an autism diagnosis, and because the behavioral traits measured may differ from the constructs that led a clinician to diagnose autism. We have included these studies because the psychometric autism screening tests used have been validated, the continuous measures allow for robust statistical properties, all children are tested and so an outside comparison group is not needed, and these studies allow greater feasibility for prospective, and therefore more accurate, measurement of prenatal environmental exposures.

### Prenatal and Early Postnatal Exposures

We restricted this review to studies that addressed chemical exposures during, or pertaining to, conception, pregnancy, and the 1st postnatal year, to assure that the exposure could have been part of the multifactorial landscape that preceded and caused the emergence of autism symptoms. Although the precise critical periods of susceptibility to environmental factors for autism have not been fully elucidated, evidence from neuroanatomical, animal, and epidemiologic studies support the prenatal and early postnatal origins of autism.<sup>19–24</sup> A critical period in early pregnancy was suggested from a study of autism cases suspected to be caused by thalidomide exposure in early pregnancy.<sup>22</sup> Later pregnancy and early postnatal life are additionally implicated by accumulating molecular and pathological evidence pointing to altered neuronal connectivity and a resultant perturbation in signaling pathways, systems under intense development in these periods.<sup>25,26</sup> These developmental windows are a time of known neurodevelopmental susceptibility, and it is believed to be exposures during these times that can exert causal influences on developmental disorders.<sup>14,27,28</sup> By limiting to exposures pertaining to these periods, it is assured that the environmental chemical exposures occurred prior to the development of autism symptoms

and could not result from the sequelae of autism. For example, metals in hair during childhood may indicate altered metal metabolism and clearance, or altered diet or medication use, any of which could result from autism, instead of contributing to the development of autism. As illustration, we provided a partial list of publications excluded because of exposure timing criteria (Table 4), but this is not a comprehensive list, especially in the case of metal exposures, for which there is a large literature measuring metal exposure in childhood.

### Valid Comparisons

We included studies without major validity concerns of selection biases and confounding, because when these influences can be ruled out, epidemiological studies reporting associations can suggest a population-level causal association between the risk factor and autism. Across all studies, we evaluated whether the comparison group, typically children without autism, was a valid representation of the underlying population that generated the group of children with autism diagnoses. Selection bias is common in studies of autism because children receiving an autism diagnoses may differ from the set of all children who could, under ideal conditions, receive a diagnosis. For example, disadvantaged racial/ethnic or sociodemographic groups have been shown to have lower rates of diagnosis<sup>1,29</sup> and up to 20% of children are not diagnosed by 8 years of age,<sup>1</sup> perhaps because of limited health care access or parent knowledge of developmental milestones. We excluded a study when we assessed that the comparison population may be meaningfully different from the underlying population that generated the group of children with autism, when key confounding factors (which differed by chemical group) were not accounted for, or when publications did not provide the details to assess these considerations. We reported on the specific reasons for every publication excluded due to major validity problems that otherwise met inclusion criteria (Table 4).

### Adequate Sample Sizes and Statistical Precision

An alternate explanation of an elevated (or reduced) measure of association between an environmental chemical and autism is sampling error, often ruled out using standard statistical testing and *p* values. In this review, we emphasized the magnitude of the association together with the precision with which it was estimated, where the precision is reflected by the width of the confidence interval. We, and others, prefer this approach over dichotomizing results into those that do or do not pass a statistical significance threshold, because more information on the strength of the evidence is considered.<sup>30,31</sup> Study estimates that have greater precision (more narrow confidence intervals) contribute more strongly to the accumulated evidence, for example, they carry more weight when included in a meta-analysis.

We have excluded some estimates with poor precision, which we defined as estimates with a confidence interval ratio or difference (upper 95% CI divided by, for ORs, or with a subtraction of, for slopes, the lower 95% CI) >10. These estimates arose when fewer than five children with autism had the xenobiotic exposure, a commonly used criterion of insufficient sample size. Every publication excluded using precision criteria is listed in Table 4.

## Identifying and Reviewing Publications

We used a multi-method, iterative approach to locate all publications that met these inclusion criteria, as follows. We searched our personal libraries and performed online searches in PubMed and Google Scholar, including the PubMed feature “Related Citations.” These searches used the outcome keywords: autism, Pervasive Developmental Disorder, and social impairment, combined with keywords pertaining to the exposure (e.g., for air pollutants: air pollution, air toxic, and traffic). We then searched for additional publications by the authors and parent studies that were generated from the initial search (e.g., CHARGE). We reviewed all citations from each located primary publication, from two recent reviews of environmental factors and autism,<sup>14,32</sup> and from reviews of individual exposure groups, such as thimerosal-containing vaccines and autism,<sup>33,34</sup> and endocrine-disrupting compounds and autism.<sup>35</sup> When publications were located outside of the online literature searches, we then performed repeat online literature searches after adjusting our keywords and approach. We recognized that associations of tobacco and autism were often reported in descriptive tables of publications without being mentioned in the title or abstract, and so we widened our scope of consideration for tobacco publications. For each exposure group (e.g., pesticides) at least two of us performed independent, iterative searches.

Among primary, human population-based publications pertaining to our included chemical groups, we reviewed the abstract or complete publication for ecological outcome data and to determine the developmental timing of the exposure information. This resulted in a set of 58 publications that met inclusion criteria 1–5 (see Box 2). We thoroughly reviewed these 58 publications, excluding 26 due to validity and precision criteria 6–7 (Table 4), resulting in the final set of 32 publications included, several of which reported on multiple environmental chemicals.

## Evidence Regarding Environmental Chemical Pollutants

### Tobacco

Tobacco use, despite its known harmful health impacts, is still common: more than 13% of women smoked cigarettes during pregnancy in the U.S. in 1999–2006 and even more infants live with a parent who smokes.<sup>36</sup> Both direct smoke and secondhand smoke are complex mixtures including thousands of chemicals,<sup>37</sup> including nicotine, volatile organic compounds, and metals such as cadmium and lead,<sup>38,39</sup> and so tobacco smoke overlaps with chemical groups covered later in this review. Increasingly, it is understood that there are important differences in the chemical make-up of smoke inhaled by a smoker (direct) vs. smoke inhaled by a non-smoker (secondhand smoke), with each representing a different toxic load with suspected different impacts on neurodevelopment. These exposures are strongly suspected to disrupt the developing nervous system, with evidence supporting links with attention-deficit disorders and intellectual disabilities.<sup>40–42</sup> Mechanisms responsible for the harmful effects of tobacco include direct interaction of nicotine with the receptor of the neurotransmitter acetylcholine, impacts on the immune system, interference with folate homeostasis, general oxidative stress, epigenetic alterations, and placental blood flow impacts.<sup>43–49</sup>



Tobacco exposure is currently one of the more-studied chemical exposures in relation to autism, in part because it is reported on birth certificates and in medical registries, and so is often studied in concert with other obstetric factors (e.g., C-section and preterm birth). Because of the strong associations between tobacco use and lower income or education, which are related to many other health-detracting factors such as stress and poor nutrition, socioeconomic status is an especially important potential confounder of this question, and so we excluded studies that did not account for this (Table 4). We included seven studies (Table 5), taking place in the U.S., Canada, Sweden, Finland, Norway, and England/Wales. These studies included cohort and nested case-control samples and varying measures of autism, ranging from parent report of diagnosis to direct evaluation of children. Tobacco use in pregnancy was measured by parent recall, which is subject to some degree of under-reporting because of stigma, and by medical data (e.g., birth certificates) that was collected prospectively and considered reasonably valid for measuring *in utero* tobacco exposure,<sup>50</sup> but was still subject to under-reporting.<sup>36</sup>

Results of these studies were scattered above and below the null, with most confidence intervals crossing the null, consistent with no association between direct maternal smoking in pregnancy and Autism Spectrum Disorder diagnosis, overall (Fig. 1). Some studies also examined autism subtypes, including lower-functioning groups (e.g., autistic disorder and Autism Spectrum Disorder with co-occurring intellectual disability) and higher-functioning groups (e.g., Asperger's Disorder and Autism Spectrum Disorder without co-occurring intellectual disabilities). Associations between maternal smoking during pregnancy and higher-functioning autism were elevated compared to associations with lower-functioning autism for two studies, including a study for which one of us (A.K.) was an author (Fig. 1, green and purple).<sup>51,52</sup> Two studies examining the continuous autism phenotype also suggested that tobacco may impact higher-functioning autism (Fig. 1).<sup>53,54</sup> These associations between tobacco and higher-functioning autism and continuously measured autism behaviors could (1) indicate that direct maternal smoking causes elevation of some domains of autism, such as social functioning; (2) reflect random error; (3) be caused by confounding bias that acts differently for different autism subtypes; or (4) actually reflect associations with other neurodevelopmental disorders, for example, attention-deficit problems, which are suspected to be influenced by tobacco, and are highly comorbid with autism.<sup>55,56</sup>

The importance of social class confounding for studies of tobacco and autism was affirmed in the results: associations were altered after adjustment for factors such as maternal education or income. The direction of this confounding differed by country. In the U.S. and Canada, associations were higher after adjusting for sociodemographic variables,<sup>52,57</sup> whereas in European countries (Sweden, Finland, and Norway), associations were attenuated after adjustment.<sup>51,53,58,59</sup> These patterns may reflect different practices of autism screening and health services access between the U.S. vs. Scandinavian countries, and this hypothesis has direct data support.<sup>60</sup>

In summary, evidence does not support a strong causal link between direct maternal smoking during pregnancy and autism. A possible link with higher-functioning autism was suggested, but complicated by sociodemographic confounding and the phenotypic overlap with other

neurodevelopmental disabilities. The published literature on the role of tobacco is currently limited by the absence of any measures of secondhand smoke exposure to the mother during pregnancy. This is an important gap, given that (1) secondhand smoke is a different chemical mixture than primary smoke, (2) there is evidence that secondhand smoke exhibits neurodevelopmental toxicity,<sup>61,62</sup> and (3) it is a very common exposure. Given the complexity of tobacco mixtures and the biologic plausibility of impact, future studies should evaluate the role of secondhand exposure and consider biomarker measures of tobacco; these measures are objective, quantitative, and integrate all sources of exposure and, although not yet used in this literature due to the preponderance of retrospective designs, could be used when biologic materials have been stored or can be prospectively collected. Research on the neurotoxicity of tobacco should additionally resolve different components of the combustion mixture, which may open up more customized direction for preventive actions. Lastly, future studies should consider the possibility of confounding by genetics.<sup>59</sup> Women who continue to smoke when pregnant may be genetically predisposed toward addictive behavior, which in turn may pass along increased genetic loading for neuropathologies that are related to autism risk (e.g., through dopamine or serotonin pathways), complicating the study of tobacco and neurodevelopment.

### Regulated and Traffic-Related Air Pollutants

Outside air pollutants include hundreds of chemicals, present as particulates, droplets, or gases. These pollutants arise mostly from human activities, conventionally grouped into (1) point pollutants arising from spatially separated large plumes (factories, power plants, and waste incineration); (2) area pollutants associated with population density (gas stations, dry cleaners, and residential and commercial heating and cooling); and (3) mobile pollutants associated with vehicles, primarily from roadway traffic. After entering the atmosphere, pollutants move and undergo chemical reactions, creating new pollutants. In this section, we discuss air pollutants that arise from traffic or that are regulated in the U.S., such as particulate matter (PM), nitrogen dioxide (NO<sub>2</sub>), and ozone. In the next section, we cover volatile organic compounds (VOCs) in the outside air together with indoor sources of VOCs. Lastly, we cover airborne metals such as mercury, lead, and manganese in the section on metals. Although levels of some air pollutants have declined in the U.S. because of the Clean Air Act and vehicle emissions standards, these declines have not put an end to concerns about the health impacts of air pollutants, in part because the developmental impacts of current levels of ambient air pollutants have not been adequately studied. Furthermore, recent reductions may be offset by future population growth, climate change<sup>63</sup> and international transport of air pollutants.<sup>64</sup>

Air pollutants enter the human body via inhalation and by direct translocation from the nose to the brain via the olfactory bulb.<sup>65</sup> Particulate pollutants have mixed chemical properties and are defined by size, such as particulate matter <2.5 μm (PM<sub>2.5</sub>) and particulate matter <10 μm in diameter (PM<sub>10</sub>). Smaller particulate pollutants penetrate more deeply into the lungs than larger particulates and have greater surface area, increasing their biological activity. Chemical constituents of air pollution can enter blood circulation; the level of absorption and half-life in the body vary from chemical to chemical. Some air pollutants are known to induce oxidative stress and cause a systemic inflammatory reaction, a proposed



mechanism whereby air pollutant exposures may perturb neurodevelopment.<sup>66–68</sup> Fetuses can be exposed to the chemical constituents of the air pollutant itself (e.g., metals) and also to the elevated levels of inflammatory cytokines (or other resultant biologic factors) in the maternal circulation. Given the chemical and physical complexity of air pollutants, some likely cause additional pathophysiologies that have not yet been fully explored, such as epigenetic alterations.<sup>69</sup>

Air pollution exposures are widespread. While urban areas are hotspots for air pollutant mixtures—given that air pollutants arise from traffic and population density—rural areas can also have high levels of air pollutants when they are close to factories, waste incineration facilities, and the like. The spatial patterns of air pollutant exposures coincide with other drivers of autism occurrence and detection, necessitating the strong control of socioeconomic confounding for questions about air pollutants and autism. As an example, individuals with high pollutant exposures may be living near highways in neighborhoods that are impoverished, full of social stressors, and reduced access to healthy food or health care.

Seven publications of traffic-related and criteria air pollutants met our inclusion criteria for further consideration (Table 6). These studies all took place in the U.S. and included case–control studies with controls sampled from a population base and one prospective cohort study.<sup>70</sup> The studies had adequate sample sizes (ranging from 284 to 7594 children with autism) and controlled for appropriate confounders such as maternal age and parents' education level. Although confounding by such family social characteristics was expected, the degree of this confounding was not strong and acted in opposite directions across studies, attenuating ORs in some studies<sup>71,72</sup> and producing elevated ORs in other studies.<sup>73,74</sup> Season of birth is also an important potential confounder because the occurrence of autism varies by season of conception for unknown reasons, and because criteria air pollutant concentrations exhibit strong seasonal gradients, so that an observed association between an air pollutant and autism may actually reflect another seasonal risk factor (e.g., influenza infections and vitamin D levels). Season of birth was accounted for in one of the included studies.<sup>74</sup>

One potential confounding influence was not explored in any study: that of noise due to traffic. Noise can cause a stress response or interfere with sleep and has been associated with cognitive performance.<sup>75</sup> It is possible that associations observed between autism and air pollutants from traffic could be due wholly or in part to traffic noise, although one attempt to adjust for noise in studies of traffic pollution has not borne this out.<sup>76</sup>

Results for the included studies showed elevated associations between autism and measures of mixed air pollutant exposures and diesel particulate matter (Fig. 2) and for the individual air pollutants PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub>, with less consistently elevated associations for NO, ozone, and CO (Fig. 3). The size of the ORs was not consistent across studies, despite the standardized comparison of air pollutant concentrations that we calculated, for example, ORs were around 1.5 per 10 ppb increase in NO<sub>2</sub> for the California CHARGE study (Fig. 3, red),<sup>72</sup> but only 1.04 for the California Department of Developmental Services study (Fig. 3, green).<sup>73</sup> Reasons for this different size in impact could reflect air pollutant differences

between California regions, a greater degree of exposure measurement error in the DDS study, or that this study adjusted for a possible mediating factor, gestational age, which did result in the attenuation of ORs for some air pollutants.<sup>73</sup> For almost every pollutant and every study, associations were stronger for exposures in the 3rd trimester of pregnancy and the 1st year of life compared to in earlier pregnancy (Fig. 3).

All of these studies estimated exposure to outside levels of these air pollutants using historical data that could be related geographically to the home residence of the pregnant woman or infant. Direct person-based air sampling was not possible in these retrospective studies. The residence-based metrics included measurement error due to inaccuracies in geolocating residences, air modeling assumptions, and the inability to include time spent away from home, measurement error that would be expected to attenuate findings. Yet elevated associations were found for some air pollutants. As pointed out by the authors of these studies, the likelihood is low that exposure measurement error could have resulted in overestimated associations (possible if measurement error was related to autism status). It is therefore possible that these study results are conservative, that is, these air pollutants may have stronger associations with autism than suggested by the observed data.

In summary, the published literature shows associations between traffic-related and criteria air pollutants and the development of autism and possibly increased susceptibility when exposures occur in late pregnancy or early postnatal life. These findings are bolstered by strong study designs and consistent findings across different means of measuring pollutant concentration and identifying children with autism. Reasons for these findings include a true causal relationship, a consistent bias such as residual social class confounding, or the impacts of traffic noise. Questions about the size of the impact and the individual chemical pollutant most responsible for these findings remain, as most studies have not accounted for the correlations between multiple chemical pollutants or the differences in air pollutant mixtures between the West and East coasts of the U.S.

### **Volatile Organic Compounds/Solvents**

Volatile organic compounds (VOCs) include a large group of chemicals that become gaseous close to room temperature and are released/emitted from products or processes (sometimes called “off-gassing” or “out-gassing”), chemicals such as formaldehyde and benzene. VOCs overlap partly with other chemical groups: organic solvents (a group defined by their ability to dissolve other chemicals) and some air toxics (defined as chemicals detectable in outside air that are known to harm human health). VOCs are emitted from many human products and activities, including indoor residential and workplace paints, furnishings, and air fresheners; vehicle fuel combustion (benzene, toluene, ethyl benzene, and xylene, abbreviated BTEX); dry cleaning (tetrachloroethylene, also known as perchloroethylene or PERC); refrigeration; cigarette smoke (benzene, ethyl benzene, formaldehyde, and xylenes); hair and nail salons (toluene); and in other industries involving fuels, lubricants, paints, and more. Organic solvents have been reported as among the most prevalent occupational chemical exposures for women.<sup>77</sup> VOC concentrations are generally 2–5 times higher in indoor compared to outdoor air,<sup>78,79</sup> and have been hypothesized to cause Sick Building syndrome.<sup>80</sup> VOCs are ubiquitous and occur in combination with other VOCs and pollutants

covered elsewhere in this review: tobacco, traffic-related criteria air pollutants, and pesticides. Petroleum-based VOCs like benzene, toluene, ethyl benzene, and xylenes have been widely detected in biological samples from a U.S. representative sample in 2013.<sup>12</sup> These body burdens are especially notable given that the biological half-lives of VOCs range from minutes to days, indicating frequent exposure to these chemicals.

The primary route of exposure to VOCs is by inhalation, although VOCs can be ingested through contaminated drinking water and can be dermally absorbed.<sup>81</sup> Biologic mechanisms of harm include oxidative stress after metabolism by P450 enzymes and direct interference with cell membrane integrity for the many VOCs that are lipophilic.<sup>82</sup> VOCs interact with many organ systems, including the nervous system, as demonstrated by evidence in rats of neurodevelopmental toxicity.<sup>83</sup> Epidemiological studies of the impacts of early-life VOC exposures are few, but have demonstrated that women occupationally exposed to multiple VOCs have children with cognitive and visual-motor functioning deficits<sup>84,85</sup> and symptoms of attention-deficit disorder.<sup>86</sup>

The seven studies of VOCs included in our review (Table 7) measured exposures with the following methods: (1) self-report or birth certificate report of parental exposure in the workplace and occupation, which was coded into multiple chemical classes based on the work duties and products manufactured<sup>87,88</sup>; (2) parent report of exposure to “textiles” and “newly built homes”<sup>89</sup>; and (3) a vehicle and factory emissions-based air pollutant model of the U.S. Environmental Protection Agency that models census tract levels of air toxics for selected years, the National-scale Air Toxics Assessment (NATA), including a study for which one of us (A.K.) was an author.<sup>16,70,90</sup> The NATA model predicted concentrations of over 30 air toxics in 1996 and over 180 air toxics in 1999, 2002, and 2005. In summary, these exposure methods had the following strengths: (1) corresponding to the pertinent prenatal and early postnatal time periods; (2) independent expert verification/coding of occupational exposures<sup>87,88</sup>; and (3) prospective measurement, along with a reduced chance of a recall bias, in the studies of air toxics and the occupation study based on birth certificate-reported occupation.<sup>16,70,88,90</sup>

Results for VOC exposures and autism were scattered above and below the null, a pattern expected to result from sampling error when no causal relationship exists (Fig. 4). Upon closer inspection, a few groups of VOCs (paints and chlorinated solvents) showed elevated associations compared to other groups. Some individual VOCs had consistently elevated associations, although the VOC concentration comparisons differed somewhat across studies: methylene chloride, trichloroethylene, and styrene. Given this consistency, and that some of these associations had the statistical power to rule out no association, these VOCs deserve future study as candidate risk factors for autism.

Published results for this research question often had wide confidence intervals reflecting small numbers of exposed children with autism, especially for the occupational studies. This imprecision and uncertainty in estimates also resulted from the inherent measurement error of VOCs in these studies. Despite the strengths of the exposure methods, all of these methods provided only a rough approximation of the internal dose of VOCs to the developing nervous system. The emissions-based NATA model is especially problematic for

VOCs because it relies on proximity to sources emitting VOCs outdoors, such as traffic and large factories, ignoring the important unique indoor sources for several VOCs.<sup>79</sup>

In summary, studies of VOCs and autism, despite being underpowered with some degree of exposure measurement error, have shown patterns suggestive of causal associations that point to the need for more research on certain VOCs (e.g., methylene chloride, trichloroethylene, and styrene). Other VOCs are not cleared from culpability, but instead have simply not been adequately studied. Given that VOCs themselves occur in mixtures and also occur together with other pollutants, large studies with multiple detailed measured exposures would be required to disentangle a potential causal impact of an individual VOC, ubiquitous chemicals with high biologic plausibility of damaging the developing nervous system.

### **Metals From Air, Occupation, Dental Amalgams, and Diet**

Lead and mercury have strong and consistent evidence of harming the developing nervous system, resulting in impairments such as the loss of IQ points and behavioral problems.<sup>42</sup> Other metals, including arsenic, fluoride, and manganese, are increasingly recognized as also being human neurodevelopmental toxicants.<sup>11,91–93</sup> These health impacts are not restricted to high-exposure scenarios, but have been seen with typical exposure levels, leading to “silent toxicity.”<sup>94</sup> Metals cross the placenta and the blood–brain barrier, accumulate in developing brains, and interact directly at the cellular level through a variety of mechanisms, including interfering with key cellular receptors and causing reactive oxygen species.

Metals are widespread in the environment, each metal with different sources of exposure, via ingestion and inhalation, illustrated here using the examples of lead, arsenic, and mercury. Historically, leaded gasoline and lead-containing paint resulted in the contamination of homes and soils, and many families in the U.S. remain exposed to lead hazards, especially those living in poorly maintained older homes. Sociodemographic and neighborhood factors, therefore, are important potential confounders when studying lead (and other metal) exposures. Lead can still be measured in outside air, and air may constitute an important source of lead exposure for some families.<sup>95</sup> Arsenic is found in contaminated drinking water resulting from arsenical soil, including in some parts of the U.S., with secondary sources including arsenic-treated wood, arsenic-containing pesticides, and some dietary sources (e.g., rice). Mercury exposure, especially the most toxic form, methylmercury, occurs primarily from diet, because it bioaccumulates in the environment. Persistent environmental chemicals like mercury often have affinity for fatty tissues (they are lipophilic) and so are not readily broken down. After widespread use and distribution, such chemicals deposit in waterways and concentrate toward the top of the food chain in predatory fish and human milk. The same fish that contain methylmercury accumulate other persistent organic pollutants, such as those covered later in this review, and also contain beneficial nutrients (e.g., fatty acids), leading to problems of negative and positive confounding from the mixtures of chemicals present in some fish. Less important sources of mercury exposure include dental amalgams (during placement and from continual release of

trace amounts of mercury vapor for the life of the amalgam) and outside air near coal combustion and some industrial facilities.

Five epidemiological studies of metal exposure from air, occupation, dental amalgams, and diet were included (Table 8). The studies addressed multiple airborne metals among a panel of other air pollutant exposures measured using the emissions-based air toxics model, NATA,<sup>16,70,90</sup> metals from parental occupation in the California-based CHARGE Study,<sup>87</sup> mercury from dental amalgams present in mothers during pregnancy, and mercury in maternal hair studied in the Republic of Seychelles, a high fish-consuming island country in the Indian Ocean near Madagascar.<sup>96</sup>

Across all metals in these studies, results were predominantly above the null, a pattern consistent with either higher risk due to metal exposure or consistent residual confounding across designs, confounding not highly likely given that all of these studies adjusted for socioeconomic status and maternal age, but possible (Fig. 5). The pattern of elevated associations was especially striking given the measurement error inherent in the emissions-based air pollutant model used in three of these studies, which would be expected to attenuate observed ORs.<sup>16,70,90</sup>

For the metals chromium and nickel, the ORs were of consistent magnitude across studies, although the exposure concentration comparisons differed somewhat; if combined in a meta-analysis, the expectation would be that precision would improve, resolving elevated associations (Fig. 5). In one study, lead, and, to a lesser extent, manganese, appeared inversely related to autism risk, which could have been caused by a stronger association with the comparison group in this design: children with speech and language impairment (Fig. 5, purple).<sup>16</sup> Autism risk due to mercury exposure was supported by the studies of airborne mercury,<sup>70,90</sup> but not from the Seychelles longitudinal biomarker study reflecting all sources of mercury (Fig. 5, red).<sup>96</sup> One possible reason for the lack of observed elevated association in the Seychelles study is that mercury exposure was almost entirely from fish consumption in this population, so that the impacts of brain-enhancing nutrients contained in fish may have counteracted any toxic impact of mercury. Mercury from dental amalgams was also associated with increased autism severity (Fig. 5, dark green).<sup>97</sup> In this study, some typical confounders were not accounted for, but were unlikely to strongly bias results: maternal age, while a strong risk factor for autism diagnosis, may not be relevant for autism severity,<sup>98</sup> and sociodemographics were somewhat homogenous in this study population in which all study children had received an autism diagnosis and were attending a genetic clinic.

In summary, the existing studies of autism due to metals from air, occupation, dental amalgams, and diet are suggestive that metal exposure may cause autism but are, for the most part, limited in scope. The only biomarker study took place in a high fish-consuming population with limited generalizability to other populations. The other studies only pertained to less important routes of metal exposure (e.g., air), and so are unlikely to represent the full impact of these metals on autism risk. For example, although three studies measured arsenic in ambient air, no studies addressed the most common source of arsenic: drinking water, and no studies addressed lead exposure from ingestion of items contaminated with house dust and soil. Given the established neurotoxicity of many metals

and the suggested trends shown here, future research to address the common sources of metal exposure and autism is essential.

### **Metal (Ethylmercury) From Vaccinations**

Metal exposure, specifically ethylmercury from the vaccine preservative thimerosal, has been studied in relation to autism and we reviewed these publications. Thimerosal contains ethylmercury, considered a less toxic form of mercury compared to methylmercury.<sup>99</sup> Because of the biologic plausibility that thimerosal may pose neurotoxic harm, the U.S. Food and Drug Administration suggested removing, or reducing, thimerosal in childhood vaccines in 2001. Currently, the only vaccines containing more than trace amounts of thimerosal are some influenza vaccines, to which both infants and pregnant women may be exposed.<sup>100</sup> Of note, additional community and research attention regarding vaccines and autism has focused on measles, mumps, and rubella (MMR) vaccine, which never contained thimerosal and so is outside the scope of this review.

We included six epidemiological studies of thimerosal-containing vaccines and autism; these were conducted in the U.S., United Kingdom, and Denmark (Table 9). The included studies utilized pre-existing data from government health registries or linked medical records from health maintenance organizations participating in the Vaccine Safety Datalink or the U.S. National Health Interview Survey and were all cohort designs or case-control designs nested within these cohorts (Table 3). We included studies that adjusted for suspected confounders. Additionally, for this exposure (but not some others in this review), we also included studies that did not account for the potential confounding influences of maternal age or sociodemographics. This decision was based on our assessment that these factors did not act as strong confounders in the four studies that were able to adjust for these factors: ORs were identical after adjusting for maternal age (OR of 1.12 and 1.12),<sup>101</sup> similar when adjusting for education [OR of 3.0 vs. 2.8 (unadjusted)],<sup>102</sup> and similar in two studies that adjusted for both maternal age and education, among other factors [OR of 1.0 vs. 1.1 (unadjusted)]<sup>103</sup> and [OR of 1.12 vs. 1.13 (unadjusted)].<sup>104</sup>

For all but two of the associations between thimerosal and autism, results were most consistent with a pattern due to chance, demonstrated by ORs of small magnitude (most between 0.9 and 1.2), above and below the null, and with confidence intervals spanning the null, suggesting that thimerosal does not increase autism risk (Fig. 6). This assessment is consistent with previous reviews, including the Institute of Medicine review from 2004, which concluded that “the body of epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism,”<sup>105</sup> several other reviews,<sup>33,34,106–109</sup> and a meta-analysis published in 2014.<sup>110</sup> One exception to the pattern of no association was an estimate of thimerosal from multiple vaccines and Autism Spectrum Disorder with regression; this result was markedly protective/inverse but imprecise and inconsistent with biologic plausibility (Fig. 6, orange).<sup>104</sup> The second exception was from a study of thimerosal from hepatitis B vaccination in the 1st month of life, limited to males, that showed an elevated association (Fig. 6, purple).<sup>102</sup> This result has not been included in prior reviews. Alternate explanations of this elevated result include (1) the failure to adjust for temporal trends, (2) random error and a consequent bias away from the



null given that only 30 cases were included, or (3) that non-mercury constituents of the hepatitis B vaccine could increase autism risk.

Concluding that a factor like thimerosal is not causative using epidemiological studies is difficult, however, and requires ruling out biases that may artificially attenuate ORs. Although the studies we included met our validity criteria, some minor flaws may have created such an influence. For example, in a California study,<sup>103</sup> it was assumed that all children obtaining Rh immunoglobulin received thimerosal exposure even though only about 50% of market formulations contained thimerosal.<sup>15</sup> This situation could lead to attenuated observed ORs comparing between children who did and did not receive any RhIg vs. the ORs that would have been observed if thimerosal content was measured directly and was related to autism status. Another example of complications in this literature is that the healthiest babies may be given vaccines earlier, and may be independently less likely to develop autism, possibly leading to an artificial influence where earlier vaccines are associated with less autism.<sup>15</sup>

When patterns of autism risk were examined by the timing of the vaccine, more associations for prenatal vaccines were above null compared to the later postnatal vaccines, such as in the case-control study conducted using the Vaccine Safety Datalink (Fig. 6, orange).<sup>104</sup> Whether these data support that the earlier, prenatal, vaccines deserve more research for causing autism is tenuous, but warrants mention because the only vaccines currently containing more than trace levels of thimerosal (influenza vaccines given to pregnant women) can be given prenatally.

In summary, the published literature on thimerosal, although not consistently adjusted for some potential confounders and with other potential biases, does not suggest an association with autism. The public health importance of this controversial issue has diminished given the prophylactic removal of thimerosal from pediatric vaccines, although pregnant women may still receive thimerosal-containing influenza vaccines. Of note, these studies have not examined the potential influence of vaccine co-factors. Vaccines contain carriers and adjuvants (e.g., aluminum), each of which could possibly cause toxicity, and the active ingredient is an immune trigger that, itself, may be deleterious for the developing nervous system.

## Pesticides

Over 600 unique chemical pesticides and 20,000 commercial pesticide products, categorized by function as insecticide, herbicide, fungicide, rodenticide, fumigant, and repellent, are on the market, and over one billion pounds are used in the U.S. each year.<sup>111</sup> Though individual pesticides enter and leave the market quickly, pesticide classes remain the same, and of these, organophosphates (OP) and organochlorines (OC) have the most evidence of neurotoxicity. Pesticide exposure is widespread, for example, in a representative sample in the U.S., OC pesticides were detected in over 97% of bio-samples, while OP pesticide metabolites were detected in 70%.<sup>12</sup> Pesticides can pass through the placenta and the blood-brain barrier.<sup>113</sup>

Many pesticides act to control insects through direct impacts on the insect nervous system, with suspected analogous impacts on humans. Demonstrated biological mechanisms also suggest pesticides as candidate risk factors for autism.<sup>112</sup> OP pesticides inhibit acetylcholinesterase production in the brain,<sup>114</sup> restricting neurotransmission in the peripheral and central nervous systems, ultimately impacting synapse formation, axon transmission, cell maturation, and programmed cell death.<sup>115</sup> In contrast, OC pesticides act on the nervous system via gamma aminobutyric acid (GABA) receptor-mediated chloride ion channels<sup>116</sup> and may also derail neurodevelopment through their endocrine-disrupting properties.<sup>117</sup> Population-based human studies have shown some pesticides to cause neurodevelopmental decrements.<sup>118–121</sup>

OP and OC pesticides are currently used most often in agricultural applications,<sup>122</sup> and so the primary route of exposure to OP and OC pesticides is via diet.<sup>123,124</sup> Many different pesticides have been detected in fruits, vegetables, grains, and breast milk.<sup>125,126</sup> Secondary routes, especially for areas close to farms, include inhalation from pesticide drift after agricultural applications<sup>127</sup> and dermal absorption from direct contact with a pesticide, most common in occupational settings. OC pesticides are persistent pollutants and some are detectable in the environment and human tissues decades after they have been banned, such as the OC pesticide DDT.<sup>128</sup>

Pesticide exposures occur together with factors that may harm or benefit the developing nervous system, factors that can act as confounders in studies of pesticides and autism. Examples of pollutants that co-occur with pesticides in diet include metals from soil and chemicals in non-stick cookware (perfluorinated compounds or PFCs, discussed below).<sup>129</sup> Pesticide drift co-exposures include aerosols from high-pressure cleaning,<sup>130</sup> and ammonia from fertilizer and animal waste.<sup>131</sup> Beneficial co-exposures include vitamins and minerals from the fruits, vegetables, and grains that contain pesticide residues. Sociodemographics are also important to consider because dietary patterns, including the consumption of an organic diet, determine pesticide exposure and also the ability to obtain an autism diagnosis. Maternal age is another potential confounder because total body burden of pesticides increases with age<sup>132</sup> and advanced maternal age is a well-supported risk factor for autism.<sup>133,134</sup>

Seven epidemiological studies of pesticides and autism met our criteria for inclusion in this review (Table 10). All of these studies exhibited reliable information on autism diagnosis or characteristics, used suitable controls with limited selection bias, and accounted for important confounders such as social class and maternal age. OP and OC pesticides and their metabolites, as well as some other pesticides, were measured using maternal and child biological samples,<sup>135–137</sup> residential proximity to agricultural applications,<sup>138,139</sup> and retrospective parent questionnaires.<sup>87,140</sup> These studies generally supported an association with elevated risk of autism with pesticide exposure, with most point estimates above the null, many with large enough impacts and statistical precision to rule out sampling error (Fig. 7). Elevated associations were not limited to one pesticide class, but were found for OC, OP, and other types of pesticides, and were not limited to one exposure route, but seen across studies addressing agricultural drift, use of flea/tick pet treatments, and dietary sources as reflected by biomarkers (Fig. 7). The largest measured impacts were seen in a

study of agricultural drift for two developmental windows: a period in the 1st trimester of pregnancy corresponding to central nervous system development (pregnancy weeks: 1–7), and a period that emerged, *a posteriori*, from the data (pregnancy weeks: 4–12) (Fig. 7, orange).<sup>138</sup>

Limitations in these studies include that none adjusted for other agricultural exposures, and it is therefore possible that observed associations between pesticides and autism may, in actuality, be reflecting a causal influence of another chemical along for the ride. While possible, this co-pollutant confounding influence is not likely to be large: pesticides are chemicals with demonstrated neurotoxicity and these studies measured pesticides using different methods and across different settings. In one study among a largely Hispanic, agricultural community, the association between pesticides and autism may have been overestimated because of unusual performance of the psychometric test in this population and because the study used an OR, which is best suited for rare diseases, for a common outcome.<sup>15</sup>

The elevated associations observed across this literature may also be attenuated compared to the true relationship, given that pesticide exposure measurement methods included error. For example, residential proximity to agricultural applications may incur error from wind patterns, time spent away from home, or limitations in the pesticide application data sources.<sup>138,139</sup> Another example is that blood and urine pesticide/metabolite biomarkers used in some studies only reflected the past 48 h of exposure,<sup>135</sup> so that even repeated measures in pregnancy may not have accurately reflected the true dose to developing neurological structures. Another attenuating influence may be negative confounding by nutrients in the fruit and vegetables that contribute pesticides, which could counter-balance the toxic impact of the pesticide given some evidence that nutrients like folate are associated with reduced risk for autism.<sup>141,142</sup>

In summary, the results from these studies suggest that several types of pesticide exposures may, for some children, be part of what causes the emergence of autism. A period of susceptibility in early pregnancy was suggested by one study, but this trend did not hold in other studies and requires confirmation. Importantly, many pesticides have not been studied in relation to autism, though most give rise to neurotoxicity.<sup>143</sup> Continued study of varying pesticides, combinations, and developmental windows is necessary to substantiate the current evidence of the deleterious effects of pesticide exposure.

### **Polychlorinated Biphenyls, Flame Retardants, Non-Stick Chemicals, Phthalates, and Bisphenol A**

Persistent organic pollutants are synthetic, carbon-based chemicals that accumulate in the environment and in human tissues, including legacy chemicals that have since been banned along with chemicals currently used. Persistent organic pollutants that were banned by the Stockholm Convention in 2001 include PCBs (heat-stable lubricants used throughout industry) and some dioxins (such as 2,3,7,8-tetrachlorodibenzodioxin, TCDD, the dioxin present as a contaminant in the Vietnam-era defoliation compound, Agent Orange).<sup>144</sup> Currently used chemicals include polybrominated diphenyl ethers (PBDEs, used as flame-retardant additives to textiles and plastic casings of electronics) and perfluorinated

compounds (PFCs, used as non-stick coatings in cookware and outdoor gear). Some of the pesticides reviewed in the previous section are persistent organic pollutants (e.g., DDT).

Also covered in this section are two groups of non-persistent organic pollutants: bisphenol A (BPA) and phthalates. Although these chemicals are not persistent, that is, they are readily cleared from the human body in part because they are water soluble, exposure is ubiquitous and continuous, so is important to examine for chronic effects. BPA is used in plastics and resins, including linings of canned foods, receipts, toys, and medical equipment. High-molecular-weight phthalates are plasticizers, used in medical tubing, food packaging, and polyvinyl chloride (PVC) plastics and flooring. Low-molecular-weight phthalates are used in cosmetics, fragrances, and medication coatings.

These persistent and non-persistent chemical groups are all suspected to interfere with hormone systems and have thus been termed endocrine-disrupting chemicals. Some chemicals covered in other sections of this review, such as pesticides, also act to disrupt the endocrine system. Such chemicals have been shown to mimic, block, or alter hormone signaling of steroid hormones, oxytocin, or thyroid hormones.<sup>145</sup> For example, PBDEs are structurally similar to thyroid hormone, which is required during discrete periods of neurodevelopment.<sup>146</sup> Other pathophysiological mechanisms of these organic pollutants include neurotoxicity or immunotoxicity.<sup>147–149</sup> Epigenetic mechanisms are suggested by a mouse study that demonstrated transgenerational impacts on social recognition following BPA exposure,<sup>150</sup> and the involvement of mitochondrial impairment is supported by the demonstration that a flame retardant interfered with brain mitochondrial function in mice.<sup>151</sup> Human epidemiological studies have widely examined a role for these chemicals in various neurodevelopmental end points, with reviews concluding a plausible role in attention-deficit disorders<sup>121</sup> and autism.<sup>152</sup>

Diet is a predominant source of exposure for many persistent pollutants (PCBs, PBDEs, and PFCs), because they bioaccumulate in predatory fish and breast milk. In addition, these chemicals can be widely present in interior spaces because they are not chemically bound in the products in which they are used, and so are readily liberated into the environment, leading to further ingestion or inhalation. Examples here include PBDEs in indoor dust after release from computers or carpets and phthalates released from fragrances and scented products. All of these chemicals, whether banned or not, or persistent or not, are near-universally detected in representative human biological samples from the U.S.<sup>12</sup> Some chemicals are even increasing in body burden, for example, PBDE flame retardants<sup>153</sup> and some, but not all, types of phthalates.<sup>154</sup> Body burdens of PBDE flame retardants may correspond to regulatory standards: dust biomarker levels are especially high in California, where flammability standards had until recently been more strict than in the U.S. as a whole.<sup>155</sup> Additional drivers of exposure include lifestyle patterns, such as greater consumption of canned food or having older home upholstery or electronic equipment, and neighborhood, because of proximity to polluting sources, and so sociodemographic and neighborhood factors are plausible confounders for this question.<sup>156</sup> Calendar time and child-rearing practices are similarly important: maternal age, because older moms were living in times prior to chemical bans and incurred more years to accumulate body burdens,

and birth order and breast-feeding practices, in part because breast-feeding is one of the most effective methods of excreting lipophilic chemicals.<sup>157</sup>

Five studies, from different countries and using different valid measures of autism diagnosis or the continuous autism phenotype, met our inclusion criteria (Table 11). Two studies used parent questionnaire to measure exposures,<sup>58,89</sup> and three studies used prospective biomarkers pertaining to pregnancy, including a study for which one of us (A.K.) was an author.<sup>136,137,158</sup> Pregnancy biomarkers are especially valid for the persistent pollutants (PCBs, PBDEs, and PFCs) because they have long half-lives and reflect exposures over the entire relevant period. In contrast, biomarkers for phthalates and BPA may incur more measurement error because they only reflect exposure for a few days instead of the entire relevant period of development. Still, biomarkers of phthalates and BPA have strengths of being objective, quantitative measures, and in one study were collected more than one time in pregnancy.<sup>136</sup> All of these studies adjusted for important sociodemographic confounders, and all except for one adjusted for maternal age.<sup>58</sup>

Associations between PCBs (individual congeners and mixtures) and autism were scattered above and below the null and so were not consistent with a causal relationship. Associations between PCBs and autism from a pilot study in Finland were mostly elevated; however, the modest sample (75 children with autism) did not allow for precise, conclusive results, and the lack of adjustment for birth order may have slightly biased these findings (Fig. 8, purple).<sup>137</sup> Results for flame-retardant (PBDE) and non-stick (PFCs) chemicals, all from one publication, showed mixed findings, with suggestions that some congeners may be associated with more autistic behaviors (e.g., PBDE-28), whereas others may be associated with fewer autistic behaviors (e.g., PBDE-85 and PFOA) (Fig. 8, red).<sup>136</sup> Associations between autism and BPA from two studies were not consistent with a causal association.<sup>136,158</sup> Several phthalate congeners, in contrast, appeared associated with increased autism across three different studies, although results were not consistent across these studies and most lacked the statistical precision for conclusive results.<sup>58,136,158</sup>

In summary, the emerging literature on autism and persistent and non-persistent endocrine-disrupting compounds does not allow definitive conclusions regarding a role for PCBs, flame retardants, non-stick chemicals, or BPA, while results for phthalates are more suggestive that exposures to some phthalates may be risk factors for autism. Given the difficulty in measuring exposure, especially for phthalates and BPA, which have short half-lives, it is not possible to rule out any of these chemicals from causing neurodevelopmental harm. Their known endocrine-disrupting properties are also a reason not to dismiss concern regarding these chemicals. Two caveats deserve mention. Studies to date have focused on the important prenatal period, yet if transgenerational impacts are implicated via epigenetic mechanisms, these studies may completely miss the relevant exposures that occurred for parents or grandparents. Lastly, the studies to date have not addressed numerous other chemicals that disrupt hormone signaling and are ubiquitous in the environment, such as dioxin and the anti-bacterial compound, triclosan.

## Susceptibilities and Heterogeneity of Response to Xenobiotic Exposures

### Greater Susceptibility in Males or Females

Being a male is one of the strongest predictors of being diagnosed with autism, especially higher-functioning autism, and while reasons for this have been explored,<sup>159–162</sup> there is currently no definitive explanation. Given the link between autism and child's sex together with the endocrine activity of many environmental chemicals, there is good reason to explore sex-specific susceptibility to the impacts of xenobiotic exposures (i.e., sex modification or interaction). While greater susceptibility may be *a priori* expected in males as a driver of their higher autism prevalence, either sex may be more susceptible. Additionally, whether males or females are more susceptible may vary from one chemical to another.

Some studies reviewed here have addressed susceptibilities in males vs. females, without finding clear trends.<sup>70,136</sup> The very strength of the child sex-autism association presents a research challenge because the number of females with autism in any given study will be much smaller than the number of males, limiting the statistical power to assess sex × environment interactions. This is an important research area, and future studies may need to over-sample females with autism or pool data across studies to better answer questions about sex-specific susceptibilities.

### Genetic Susceptibilities

It is likely that the autism risk associated with a given xenobiotic exposure will differ based on the child's genes or the mother's genes. Genetic polymorphisms of possible relevance include those encoding proteins involved in the metabolism or biological activation of the xenobiotic, genes allowing improved resiliency to neurodevelopmental damages, or genes that confer some degree of autism risk that, when combined with xenobiotic damage, result in autism. Some examples of research in this area include a study demonstrating interaction between traffic-related air pollutants and a functional variant of the Met receptor tyrosine kinase (MET) gene with regard to autism risk,<sup>163</sup> and a study finding no interaction between OP pesticide exposure and polymorphisms in the gene encoding the detoxifying enzyme, paraoxonase 1 (PON1) with autism risk.<sup>164</sup>

In this report, we did not provide a comprehensive review of studies of gene–environment interaction in autism, but instead point to ways in which this area influences our knowledge about the main effects of a xenobiotic exposure. Failing to account for genetic susceptibilities may result in the missed identification of an environmental risk factor: If a genetically susceptible subgroup is combined with a non-susceptible group, the overall impact of the xenobiotic exposure on autism risk may be diluted or obscured. Future research is needed in this area, and will require expanded knowledge of biological pathways to select candidate polymorphisms and sufficiently large sample sizes required to detect gene × environment interactions.



## Different Responses Across the Spectrum of Neurodevelopmental Phenotypes

Epidemiological studies of environmental chemicals and autism are also complicated by the fact that children diagnosed under the autism umbrella exhibit a very wide range of symptoms, level of disability, and co-occurring conditions. Furthermore, autism, like other psychiatric disorders, is diagnosed based on observable symptom clustering, not causal pathways, and so diagnostic definitions may not be ideal for causal research, a phenomena termed “etiologic heterogeneity.”<sup>165–167</sup> The environmental chemical risk factors for a given phenotype, such as high-functioning autism, may be quite different from risk factors for children with severe autism and intellectual disability. When multiple autism subtypes are combined in a given study, true causal impacts may be diluted or masked. However, defining a discrete disorder that reflects a common causal pathway remains elusive. The defining variables are not known.

A corollary to etiologic heterogeneity is that autism is one manifestation of developmental neurological damage, part of the broader set of neurodevelopmental problems including cognitive impairments, attention-deficit disorders, sensory processing disorders, and more. Instead of studying autism in isolation, a more holistic approach would comprehensively define neurodevelopmental impairments along multiple cross-cutting dimensions of behavior and abilities, and this nuanced “phenome” approach may aid in the further discovery of modifiable, environmental chemical risk factors that may impact neurodevelopment.

## Conclusions

The environment is not one entity, and the question about whether environmental exposures/compounds, as a whole, cause autism, is not sufficient to guide the primary prevention of autism. Instead, important questions address individual environmental chemicals, during discrete critical periods of development for the fetus or infant, in relation to specific phenotypic domains of autism symptoms. Definitive causal conclusions cannot yet be drawn from this emerging body of literature. So far, evidence suggests that some criteria air pollutants, some metals, and several pesticides, with suggestions that some volatile organic compounds (e.g., methylene chloride, trichloroethylene, and styrene) and phthalates, may be linked to autism. These associations have emerged despite difficulties of study in this area, most notably the error in accurately measuring exposure concentrations and obtaining sufficient sample sizes.

Increasingly, studies that examine exposures by developmental time period suggest that all windows are not equal. Although evidence for a discrete developmental window of susceptibility for autism is in its early stages, results shown here suggest that early pregnancy may be a period of susceptibility to pesticides, whereas later pregnancy may be a period of susceptibility to criteria air pollutants. Different critical windows for different exposures is not unexpected given the various biological activities of environmental chemicals and the many, interwoven events of neurodevelopment, taking place during pregnancy and postnatal life, which, if disrupted, could manifest in autism symptoms.

The volume of questions that remain are staggering, constituting an important gap in pediatric health. The number of chemicals not yet studied is large—chemicals that are

widely detectable in humans and have animal or mechanistic evidence of the endocrine, immune, epigenetic, and other pathophysiologies that may be involved in causing autism. Even more daunting is the large number of permutations of relevant research questions when it is considered that each chemical exposure is best studied in combination with many critical windows of exposure, several autism phenotypic subdomains, each child's gender, and a myriad of genetic susceptibilities, many of which remain undiscovered. Lastly, the issue of potentiation due to chemical mixtures and autism, that is, whether the neurodevelopmental response to chemical X differs when combined with chemical Y (and Z, and so on), has only been addressed in a handful of reports.

In the meantime, clinicians have an important role to play in protecting the vulnerable brains of fetuses, infants, and children. Clinicians are on the front lines of autism diagnosis and can advocate for the equitable early diagnoses that are so important in assisting children toward appropriate therapy, diagnoses that ultimately support the validity of research studies in this area. The demonstrated racial/ethnic and social disparities in the timely receipt of an autism diagnosis remain pressing public health problems. Clinicians serve as the experts on autism symptomatology, raising observations that may provide the clues for future study, refining the understanding of autism phenotype, and participating as autism experts in epidemiological research. Clinicians advise pregnant women and parents toward avoiding harmful substances in their environment. Yet more powerful than these is the leadership role of the clinician in advocating for a healthy environment and the societal prevention activities that have the most impact. Clinicians increasingly must have a strong voice in advocating for policies that protect the public's health, including calls for research into environmental chemicals, potentially modifiable factors that may contribute to autism or other neurodevelopmental problems in childhood.

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**Box 1****Abbreviations**

CDC: United States Centers for Disease Control and Prevention

EPA: United States Environmental Protection Agency

FDA: United States Food and Drug Administration

DSM: Diagnostic and Statistical Manual of the American Psychiatric Association, various versions

ICD: International Classification of Diseases, morbidity and disease codes, various versions

ASD: autism spectrum disorder

AD: autistic disorder

Asp: Asperger's disorder

ASD w/ID: ASD with co-occurring intellectual disability

ASD w/o ID: ASD without co-occurring intellectual disability

ASD w/Reg.: ASD with developmental regression

ASD-NOS: ASD not otherwise specified

PDD: pervasive developmental disorder

PDD-NOS: PDD not otherwise specified

OR: odds ratio

95% CI: 95% confidence interval

NATA: National-scale Air Toxics Assessment model of the US EPA

CALINE4: California line source air emissions dispersion model

**Box 2****Review inclusion criteria**

Primary report of population-based human (epidemiological) research.

English-language peer-reviewed publication prior to March 1, 2014 or manuscript under review if one of us was included as an author.

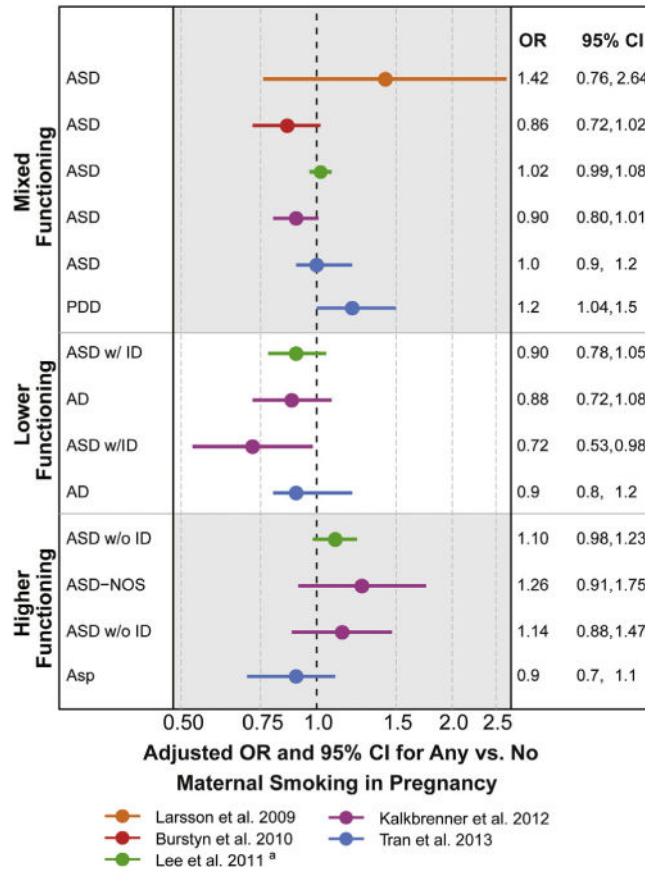
Odds ratio, slope, statistical test, or similar estimate describing the association between an environmental chemical exposure in regard to autism.

Individual-level data on autism diagnoses or a psychometric measurement of the continuous autism phenotype.

Environmental chemical measurements pertaining to exposures during conception, pregnancy, or the 1st postnatal year.

Valid comparison including appropriate sample selection and accounting for confounders.

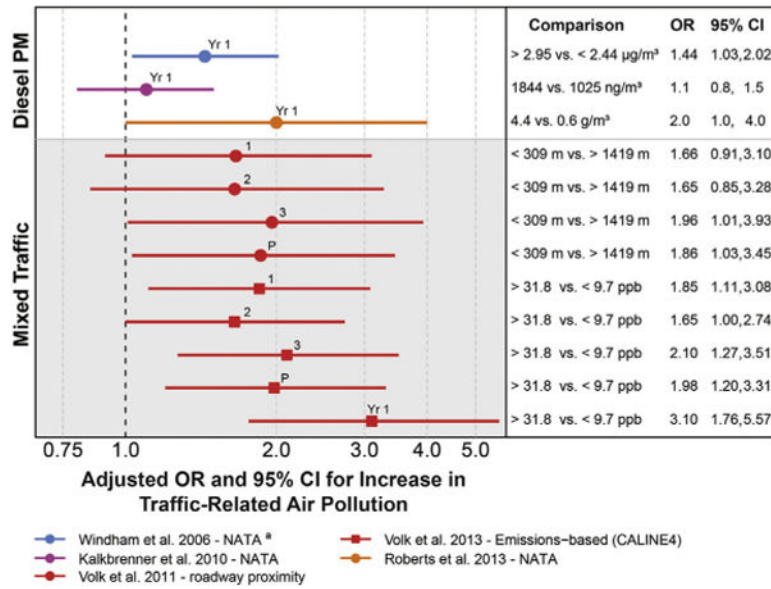
Adequate sample sizes to generate precise measures of association, defined as a confidence interval ratio or confidence interval difference <10.



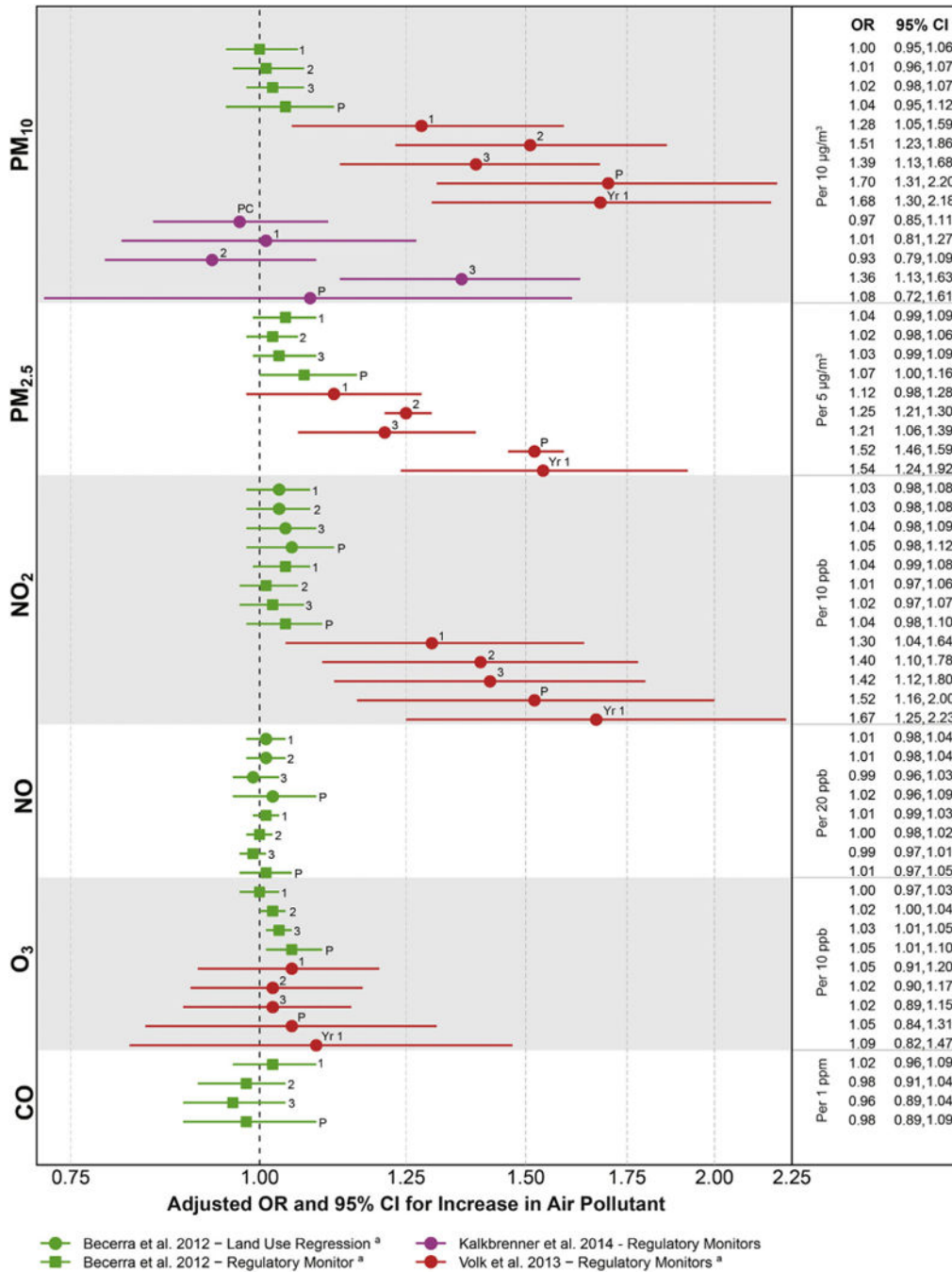
**Fig 1.**

Associations between autism and maternal smoking in pregnancy. Other results not reported as measures of association with confidence intervals included the following: Ronald et al.<sup>54</sup>—small positive adjusted correlations between smoking in pregnancy and autism symptoms reported by parents and teachers—and Indredavik et al.<sup>53</sup>—adjusted elevations of 1.4 points when mothers smoked during pregnancy compared to not smoking on the ASSQ, a scale with a maximum of 54 points. <sup>a</sup>Author provided information not included in the publication.





**Fig 2.** Associations between autism and estimates of exposure to mixed traffic and diesel air pollutants. Exposure measured during developmental windows: 1, trimester 1; 2, trimester 2; 3, trimester 3; P, pregnancy; Yr 1, 1st postnatal year. <sup>a</sup>Author provided information not included in the publication.



**Fig 3.** Associations between autism and estimates of exposure to individual traffic-related and criteria air pollutants. PM<sub>10</sub>, particulate matter <10 m in diameter; PM<sub>2.5</sub>, particulate matter <2.5 m in diameter; NO<sub>2</sub>, nitrogen dioxide; NO, nitrogen oxide; O<sub>3</sub>, ozone; CO, carbon monoxide. Exposure measured during developmental windows: PC, peri-conceptual; 1, trimester 1; 2, trimester 2; 3, trimester 3; P, pregnancy; Yr 1, 1st postnatal year. <sup>a</sup>We recalculated parameters to reflect a change in the exposure comparison to be consistent with

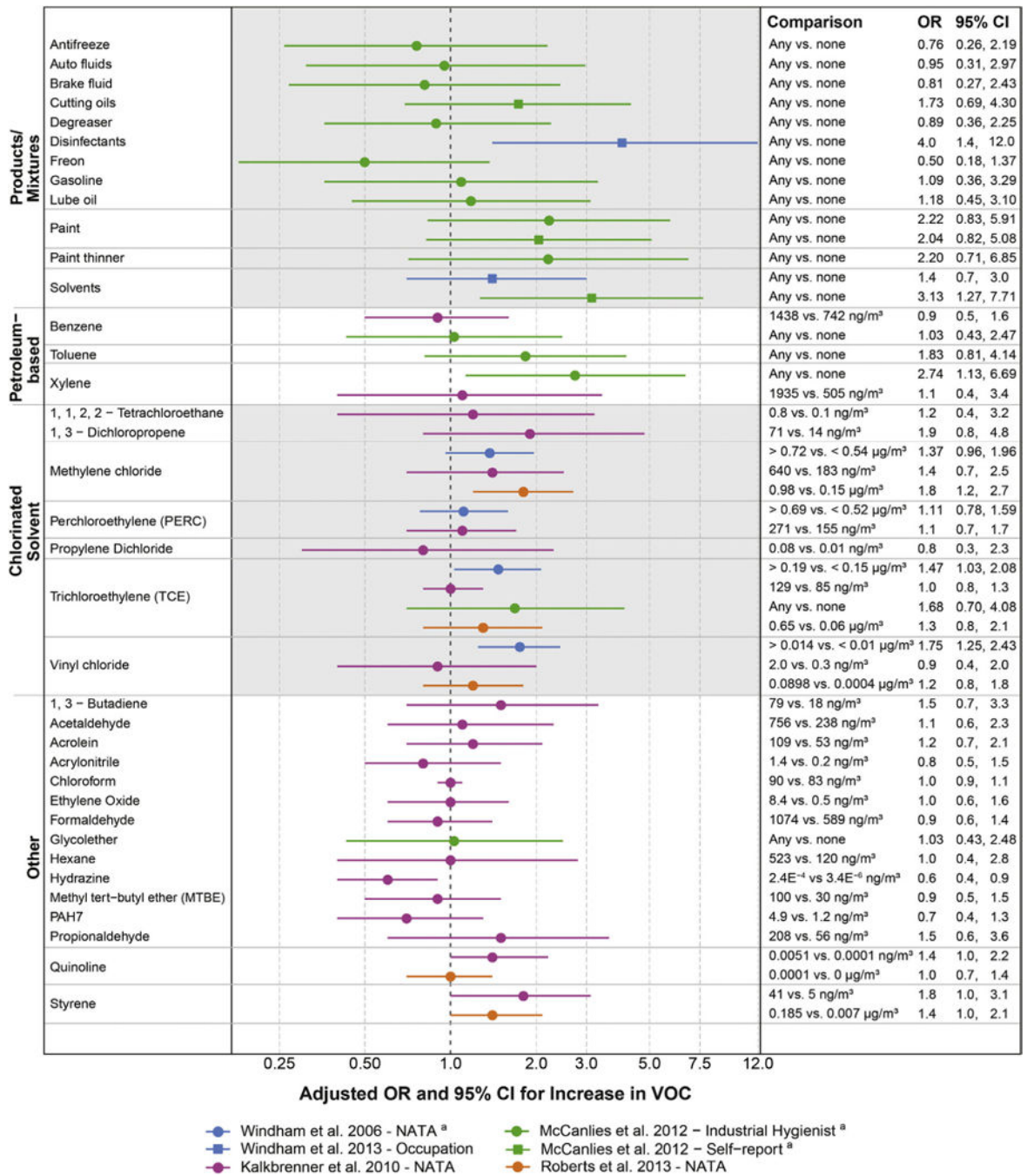
other comparisons in the figure, involving calculations assuming that parameters were normally distributed.

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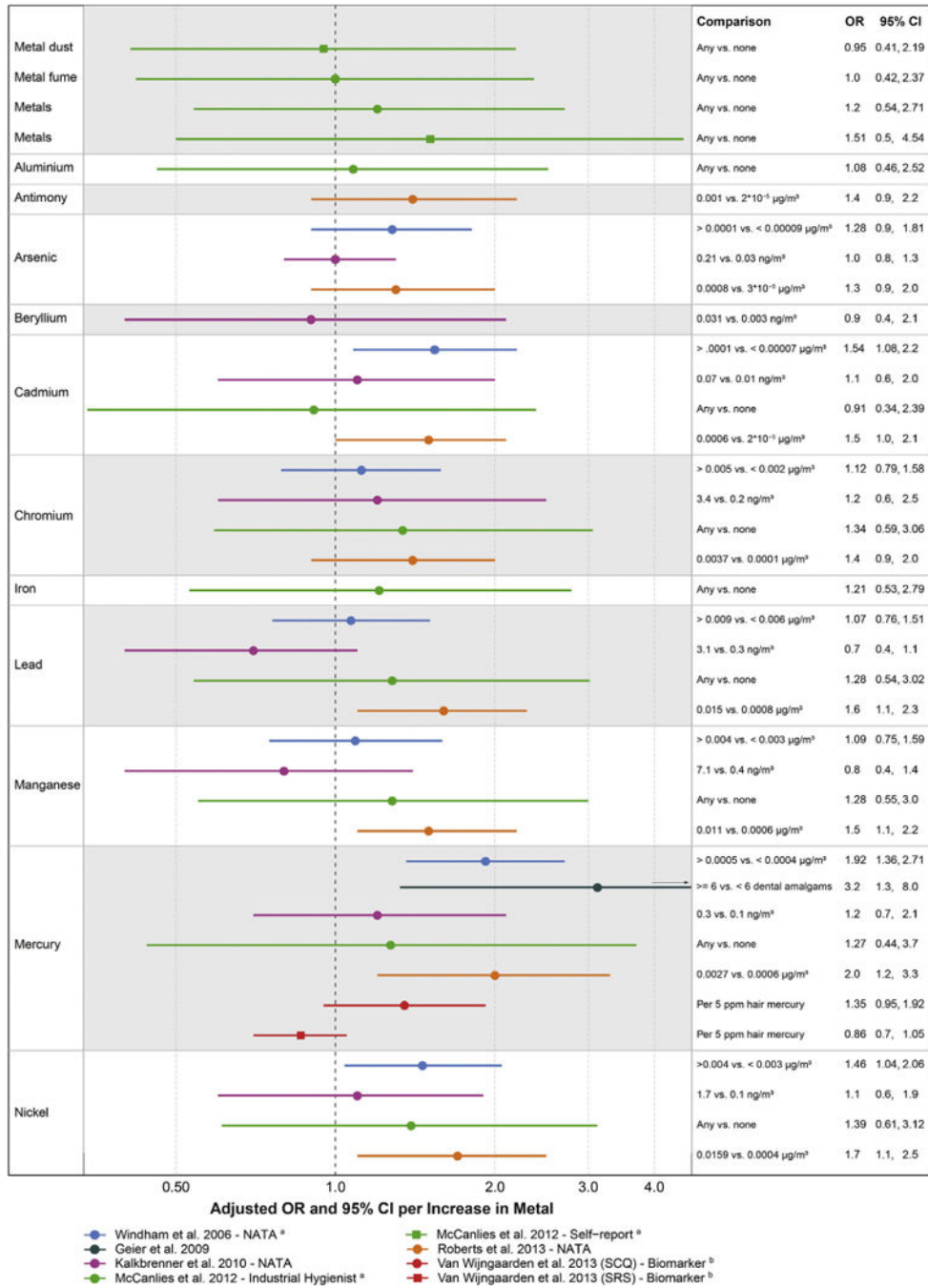
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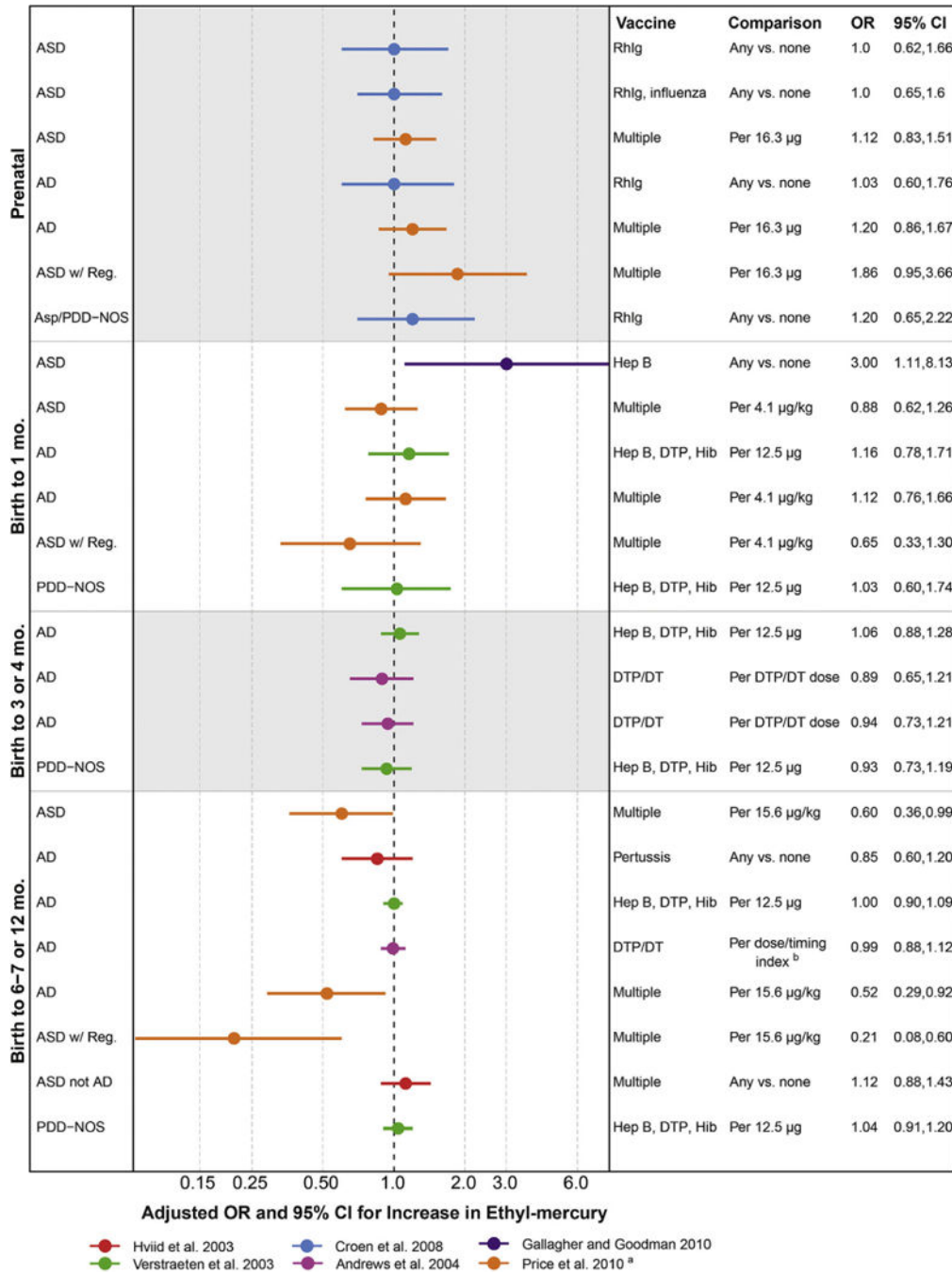
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**Fig 4.** Associations between autism and estimates of exposure to volatile organic compounds/ solvents. Other results not reported as measures of association with confidence intervals included Kim et al.<sup>89</sup>: higher retrospective reports of pregnancy exposures to “newly built homes” and “textiles” for children with autism compared to other children. VOC, volatile organic compounds; PAH7, mixed group of 7 polycyclic aromatic hydrocarbons. <sup>a</sup>Author provided information not included in the publication.

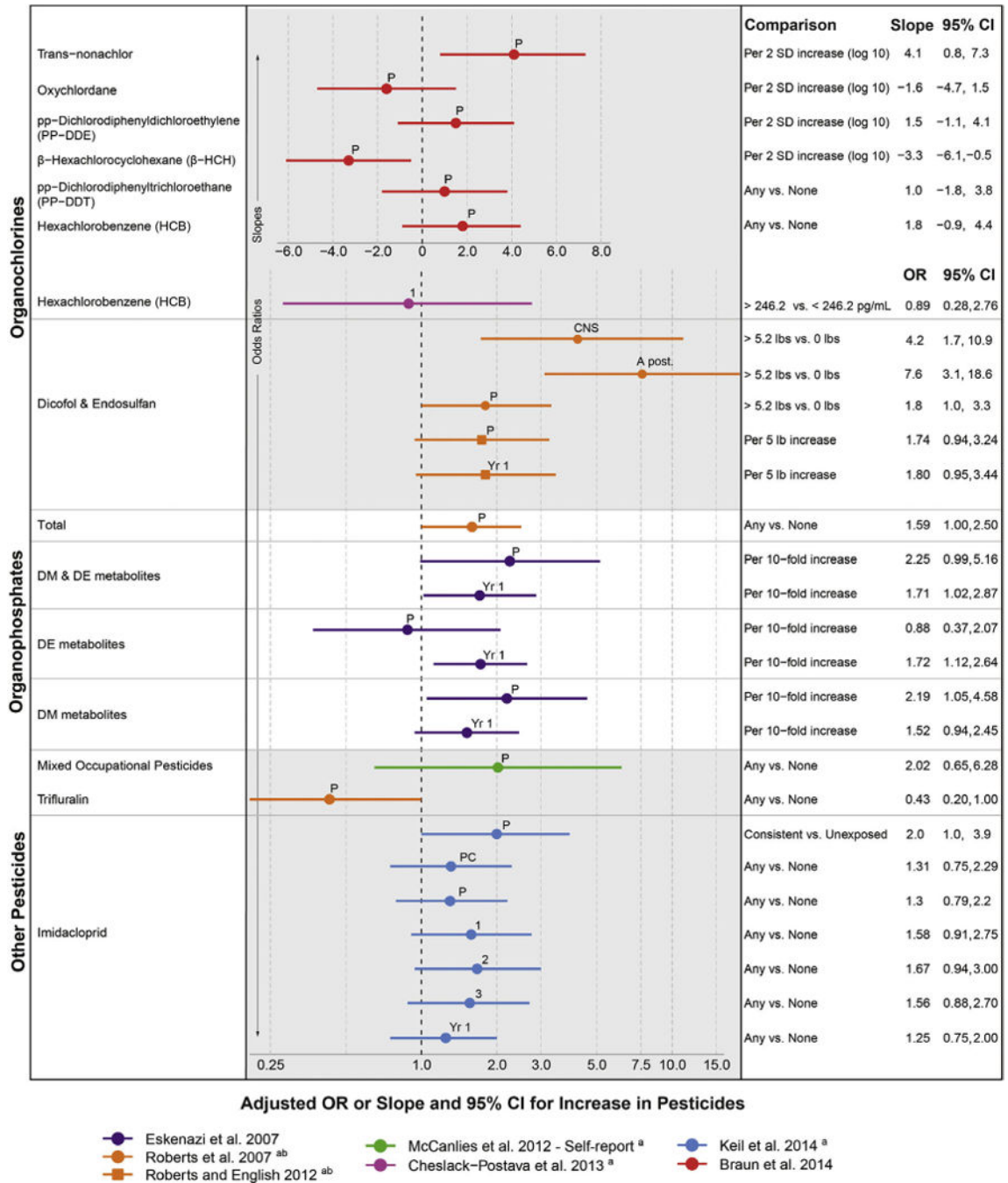


**Fig 5.** Associations between autism and estimates of exposure to metals from air, occupation, dental amalgams, and diet. <sup>a</sup>Author provided information not included in the publication. <sup>b</sup>We re-calculated parameters to reflect a change in the exposure comparison to be consistent with other comparisons in the figure, involving calculations assuming that parameters were normally distributed.



**Fig 6.** Associations between autism and estimates of exposure to mercury from thimerosal in vaccines. Rhlg, anti-D immune globulin injection; Hep B, hepatitis B vaccine; DTP, combined diphtheria, tetanus, and Pertussis vaccine; Hib, Haemophilus influenzae type B vaccine; DT, diphtheria–tetanus vaccine; <sup>a</sup>Vaccine exposure measured as µg of mercury per kg of child’s body weight. <sup>b</sup>Vaccine exposure measured as an index where higher numbers indicated more doses received earlier.





**Fig 7.** Associations between autism and estimates of exposure to pesticides. DE metabolites, diethyl phosphate metabolites of organophosphate pesticides; DM metabolites, dimethyl phosphate metabolites of organophosphate pesticides. Exposure measured during developmental windows: CNS, a priori period of central nervous system development (7 days pre-fertilization to 49 days postfertilization); A post., a posteriori period of development (26–81 days postfertilization); 1, trimester 1; 2, trimester 2; 3, trimester 3; P, pregnancy; Yr 1, 1st postnatal year. Other results not reported as measures of association

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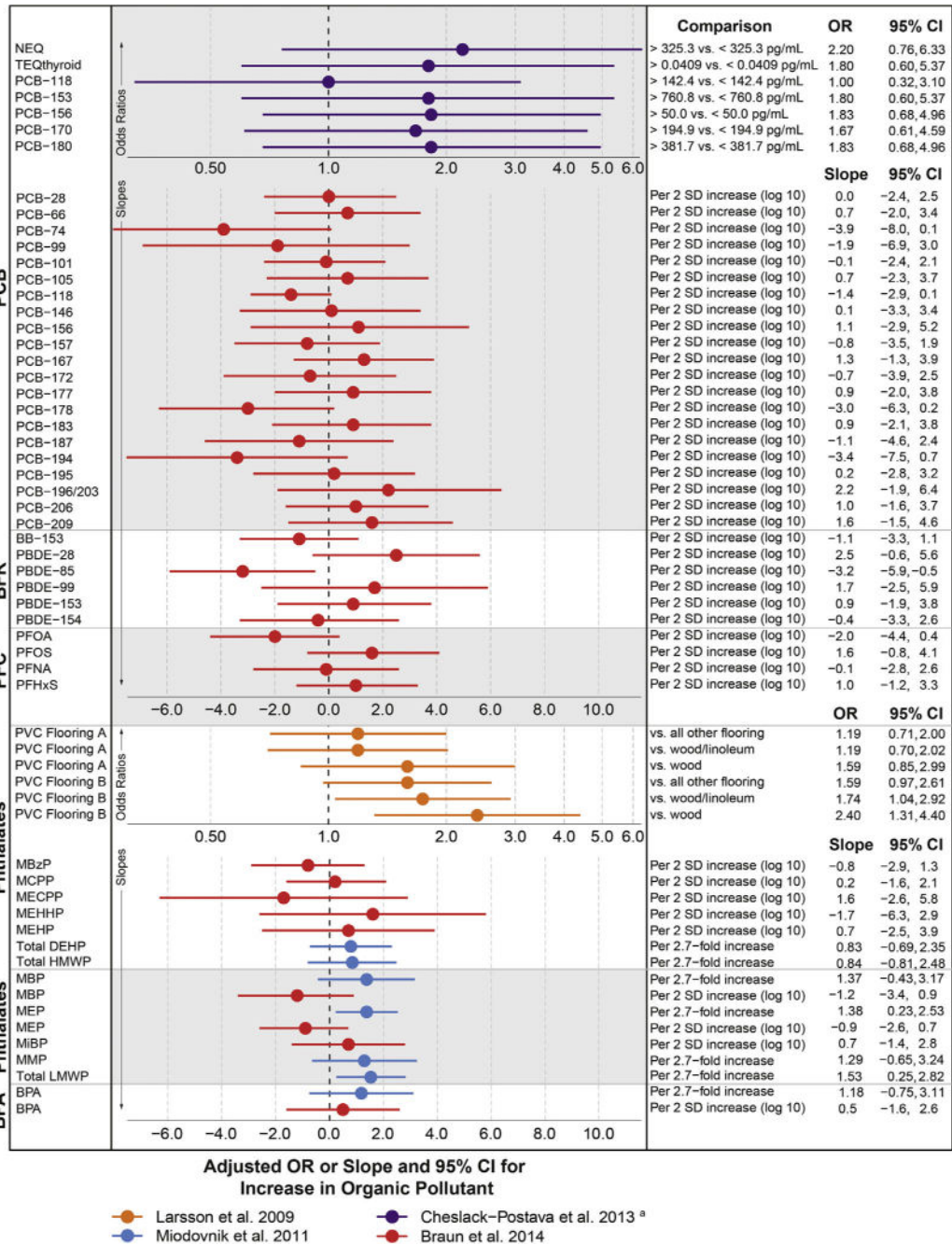
with confidence intervals included pesticides that were determined not to be associated with increased autism risk and were not included in subsequent analyses from Roberts et al.<sup>138</sup>: pesticide classes (cholinesterase inhibitors, copper-containing compounds, fumigants, avermectins, halogenated organics, N-methyl carbamates, pyrethroids, and thiocarbamates) and individual pesticide compounds (1,3-dichloropropene, chloropicrin, cypermethrin, fenarimol, methyl bromide, norflurazon, bromacil acid, chlorpyrifos, dazomet, glyphosate, molinate, oxadiazon, bifenthrin, diuron, metam-sodium, myclobutanil, and paraquat). <sup>a</sup>Author provided information not included in the publication. <sup>b</sup>We re-calculated parameters to reflect a change in the exposure comparison to be consistent with other comparisons in the figure, involving calculations assuming that parameters were normally distributed.

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**Fig 8.** Associations between autism and estimates of exposure to polychlorinated biphenyls, flame retardants, non-stick chemicals, phthalates, and bisphenol A. PCB, polychlorinated biphenyls; NEQ, neurotoxic equivalents, a weighted index of PCB congeners; TEQthyroid, thyroid hormone-based toxic-equivalent index of PCB congeners; BFR, brominated flame retardants, including: BB, brominated biphenyl; PBDE, polybrominated diphenyl ethers; PFC, polyfluorinated compounds (non-stick chemicals), including: PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfate; PFNA, perfluorononanoate; PFHxS, perfluorohexane sulfonate; HMW phthalates, high-molecular-weight phthalates, including:

from PVC, polyvinyl chloride; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; Total DEHP, di(2-ethylhexyl) phthalates = [MECPP, MEHHP, MEOHP, mono(2-ethyl-5-oxohexyl) phthalate and MEHP]; Total HMWP = MBzP and MCPP; LMW phthalates, low-molecular-weight phthalates, including: MBP, monobutyl phthalate; MEP, monoethyl phthalate; MiBP, mono-iso-butyl phthalate; MMP, monomethyl phthalate; Total LMW = MMP, MEP, MBP, MiBP. PVC Flooring A was in the child's bedroom, PVC Flooring B was in the parents' bedroom. Other results not reported as measures of association with confidence intervals included, for Kim et al.<sup>89</sup>: higher parent report of various non-specific exposures likely to include persistent and endocrine-disrupting compounds for children with autism. <sup>a</sup>Author provided information not included in the publication.

**TABLE 1**

Pathophysiological mechanisms hypothesized to mediate relationships between xenobiotic exposures and autism

<b>Mechanism</b>	<b>Rationale</b>
Immune	Close connection between immune cells and neurons during development, and evidence of immune alterations in children with autism, such as elevated cytokine levels. <sup>168-171</sup>
Endocrine	The male preponderance of autism, combined with requirements for thyroid and other endocrine hormones for optimal neurodevelopment. <sup>146,172</sup>
Epigenetic	Epigenetic alterations such as altered methylation act at the intersection between genetic and environmental factors and are implicated in the etiology of autism, including markers of reduced methylation capacity observed in children with autism and their mothers. <sup>173-178</sup>
Microbiome	Microbiome may regulate host immunity to pathogenic microbial or xenobiotic exposures and microbiota may differ in children with autism. <sup>179,180</sup>
Mitochondrial	Mitochondrial dysregulation has been shown in children with autism. <sup>181,182</sup>

**TABLE 2**

Research studies and data sources used in two or more studies of environment and autism

<b>Abbreviation</b>	<b>Full name</b>	<b>Description</b>	<b>Citation</b>
CHARGE	Childhood Autism Risks from Genetics and the Environment	Case-control study of environmental and genetic causes and risk factors for autism and developmental delay in central California.	183
ADDM	The Autism and Developmental Disabilities Monitoring Network	A group of programs funded by the CDC to estimate the number of children with autism spectrum disorders and other developmental disabilities living in different areas of the United States.	1,184
California DDS	Department of Developmental Services	The agency through which the state of California provides free diagnostic and therapeutic services to individuals with developmental disabilities.	185
VSD	Vaccine Safety Datalink	Established by the CDC to monitor immunization safety, includes linked electronic medical data from three Health Maintenance Organizations in Oregon and California.	186
FiPS-A	Finnish Prenatal Study of Autism and Autism Spectrum Disorders	A study examining prenatal serologic factors, mediating and moderating developmental antecedents, and autism, using government health data linkages and stored serum samples.	187

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TABLE 3

Psychometric tests to measure autism diagnoses and symptoms used in studies of environment and autism

Abbreviation	Full Name	Method of Administration	Description
ADI-R	Autism Diagnostic Interview-Revised <sup>188</sup>	Parent questionnaire	A 93-item scale assessing language and communications; reciprocal social interactions; and restricted, repetitive, and stereotyped behaviors and interests.
ADOS	Autism Diagnostic Observation Schedule <sup>189</sup>	Interactive observation by trained person	A semi-structured assessment using various activities allowing observation of social and communication behaviors related to the diagnosis of pervasive developmental disorders.
CAST	Childhood Asperger Syndrome Test <sup>190</sup>	Parent or teacher questionnaire	A 37-item questionnaire of yes/no question regarding a child's social behaviors and communication tendencies.
ASSQ	Autism Spectrum Screening Questionnaire <sup>191</sup>	Parent or teacher questionnaire	A 27-item checklist for completion by lay informants when assessing symptoms characteristic of Asperger's disorder and other high-functioning ASDs in children and adolescents with normal intelligence or mild mental retardation.
SRS	Social Responsiveness Scale <sup>192</sup>	Parent or teacher questionnaire	A 65-item rating scale that measures the severity of autism spectrum symptoms by assessing social impairments, social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits.
SCQ	Social Communication Questionnaire <sup>193</sup>	Parent questionnaire	A total of 40 yes-no questions to evaluate communication skills and social functioning in children who may have autism spectrum disorders.
CBCL	Child Behavior Checklist <sup>194</sup>	Parent questionnaire	Evaluates maladaptive behavioral and emotional problems across several domains, including internalizing and externalizing behaviors, including a DSM-oriented scale pertaining to PDD.

TABLE 4

Excluded publications<sup>a</sup>

Environmental exposure	Reason	Citations
Tobacco	No accounting for socioeconomic status, important in studies of tobacco and autism because of the strong associations between factors like income and education and tobacco use.	21,165,195–203
Regulated and traffic-related air pollutants VOCs/solvents	Measures of criteria pollutants pertained to postnatal periods after 1 year of age.	204 None
Metals—air, occupation, and diet	Biomarkers in childhood reflected, in part, exposures after the 1st year of life.	205–210
	Metals in acid-digested whole baby teeth included metal exposures up until the tooth was shed. <sup>211</sup>	212
	Limited information about maternal age or other sociodemographic characteristics of cases vs. controls and no adjustment for these factors.	213
	For placement of dental amalgams containing mercury in pregnancy: did not meet precision criteria—two children whose mothers had dental amalgams containing mercury. For seafood consumption as a source of metals, no description of measurement and no adjustment for confounders.	212
Metals—vaccines	Studies using the Vaccine Adverse Event Reporting System (VAERS) that did not account for temporal trends in vaccine formulations or autism prevalence or the voluntary nature of autism reporting, along with other limitations previously discussed. <sup>105</sup>	214–220
	A study reported as a letter to the editor without sufficient reporting on methods such as multivariable adjustment.	221,222
	No information on sociodemographic and maternal age characteristics of the cases and controls without adjustment for these factors.	223
	A study based on a convenience sample in a genetic clinic that did not account for temporal trends or maternal age.	224
	Did not meet precision criteria (1 child with autism)	225
Pesticides	Did not meet precision criteria.	226
PCBs, flame retardants, non-stick chemicals, phthalates, and bisphenol A	Measures of phthalates, PBDEs, or PCBs pertained to later childhood.	227–230
	Not meeting precision criteria (5 children with autism), external contamination of PCBs, and no adjustment for confounding.	231

<sup>a</sup>For the following publications, some odds ratios or slopes among several met precision criteria, whereas others did not and were excluded.<sup>87,88,136–138,226</sup>

TABLE 5

Included epidemiological publications of autism and maternal smoking in pregnancy<sup>a</sup>

Citation	Geographic location	Birth years	Sample size <sup>b</sup>	Study design	Autism data source <sup>c</sup>	Autism measurement <sup>d</sup>	Autism classification	Adjustment variables <sup>e</sup>	Exposure measurement	Exposure timing
Indredavik et al. <sup>53</sup>	Norway	1986–1988	77	Cohort	Part of a multicenter pregnancy cohort study	Autism Spectrum Screening Questionnaire (ASSQ)	Continuous autism phenotype	Gender, birth weight, socioeconomic status, single parent, mothers' use of alcohol, mothers' age, and mothers' mental health.	Daily smoking at the time of conception, reported by mothers during pregnancy.	Conception
Larsson et al. <sup>58</sup>	Sweden	1994–1999	72/4779	Cohort	Dampness in Buildings and Health Study	Parent report	ASD and Tourette's syndrome	Flooring material in parents' bedroom (PVC vs. wood), condensation on windows, child's sex and age, child's asthma status, and financial problems.	Retrospective maternal report of smoking in pregnancy, the child's 1st reporting (when child was 1–6 years old).	Pregnancy + early childhood combined
Ronald et al. <sup>54</sup>	England and Wales	1994–1996	13,690	Cohort	Twins Early Development Study	Childhood Asperger Syndrome Test (CAST) Parent rating using questionnaire based on DSM-IV Teacher rating using questionnaire based on DSM-IV	Continuous autism phenotype	Child cognitive ability and social class composite based on maternal education, paternal education, maternal occupation level, paternal occupation level, and maternal age at 1st child.	Retrospective parent questionnaire of number of cigarettes smoked by mom in pregnancy.	Pregnancy
Burstyn et al. <sup>57</sup>	Alberta, Canada	1998–2004	1122/215,217	Cohort	Record linkages in Alberta	ICD-9 codes 299.0 and 299.8 from records of Alberta Health and Wellness	ASD	Maternal age, maternal weight, pre-pregnancy diabetes, gestational diabetes, bleeding in pregnancy, poor weight gain, parity, socioeconomic status, breech presentation, induction of labor, C-section, Apgar score, child's gender, and birth year (low birth weight, prematurity, and pre-eclampsia).	Collection by hospital upon admission for delivery, recorded in Alberta Perinatal Health Program.	Pregnancy
Lee et al. <sup>51</sup>	Sweden	1984–2003	3958/38,983	Nested case-control	Stockholm Youth Cohort (Swedish registry based)	Screening followed by specialist diagnosis according to regional protocol	ASD ASD with comorbid ID ASD without comorbid ID	Birth year, gender, maternal age, paternal age, parity, education, occupational class, family income, and maternal origin of birth.	Medical Birth Register, self-reported to midwife at 1st prenatal visit.	First trimester
Kalkbrenner et al. <sup>52</sup>	Several sites in USA	n 1992, 1994, 1996, and 1998	3315/633,989	Nested case-control	ADDM surveillance	DSM-IV-R criteria applied to developmental evaluations	ASD ASD Higher-functioning ASD	Maternal education, race/ethnicity, marital status, and maternal age.	Birth certificate report.	Pregnancy
Tran et al. <sup>59</sup>	Finland	1990–2005	4020/16,185	Nested case-control	FIPS-A	ICD codes in the Finnish Hospital Discharge Register	ASD Autistic disorder Asperger's disorder PDD-NOS	Maternal age, maternal social class based on occupation or education, infant's weight for gestational age, and presence	Collection by maternity clinic nurses and reported to the Finnish Medical Birth Register.	First trimester Entire pregnancy

Citation	Geographic location	Birth years	Sample size <sup>b</sup>	Study design	Autism data source <sup>c</sup>	Autism measurement <sup>d</sup>	Autism classification	Adjustment variables <sup>e</sup>	Exposure measurement	Exposure timing
								of maternal psychiatric diagnoses!		

<sup>a</sup> Results in Figure 1.

<sup>b</sup> Sample size is presented by a single number when statistical models included a continuous measure of autism phenotype, or, otherwise, as the number of cases/controls.

<sup>c</sup> Autism data sources are described in Table 2.

<sup>d</sup> Autism diagnostic and psychometric tools are described in Table 3.

<sup>e</sup> Variables in parentheses were evaluated but not included in final models because they did not impact results.

TABLE 6

Included epidemiological publications of autism and traffic-related and regulated (criteria) air pollutants<sup>a</sup>

Citation	Geographic location	Birth years	Sample size	Study design	Autism data source <sup>b</sup>	Autism measurement <sup>c</sup>	Autism classification	Adjustment variables	Exposure measurement	Exposure timing
Windham et al. <sup>90</sup>	San Francisco Bay Area, California, USA	1994	284/687	Nested case-control	ADDM surveillance	DSM-IV-R criteria applied to developmental evaluations	ASD	Maternal age, education, and child race	National-Scale Air Toxics Assessment (NATA) (1996)	Annual average for year close to birth year
Kalkbrenner et al. <sup>16</sup>	West Virginia and Central North Carolina, USA	1992, 1994, and 1996	383/2829	Nested case-control	ADDM surveillance	DSM-IV-R criteria applied to developmental evaluations	ASD	State, year, race, maternal education, maternal age, smoking in pregnancy, census median income, census urbanity, and 33 other air toxics	National-Scale Air Toxics Assessment (NATA) (1996)	Annual average for year close to birth year
Kalkbrenner et al. <sup>74</sup>	San Francisco Bay Area, California and Central North Carolina, USA	1994, 1996, 1998, and 2000	979/14,666	Nested case-control	ADDM surveillance	DSM-IV-R criteria applied to developmental evaluations	ASD	State, birth year, race/ethnicity, maternal education, maternal age, census median income, census urbanity, and season of birth	Space-time interpolation between regulatory monitors	Pre-conception through 1st birthday
Volk et al. <sup>232</sup>	Central California, USA	1997-2006	305/259	Case-control	CHARGE	ADOS + ADI-R	Autistic disorder	Child's gender, child's ethnicity, education of parents, maternal age, and maternal smoking in pregnancy	Distance to roadway	Pregnancy trimesters and at birth
Volk et al. <sup>233</sup>	Central California, USA	1997-2006	279/245	Case-control	CHARGE	ADOS + ADI-R	Autistic disorder	Child's gender, child's ethnicity, education of parents, maternal age, and maternal smoking in pregnancy	CALINE4 traffic-based emissions model Interpolation between up to four regulatory monitors	Pregnancy trimesters and 1st year of life
Becerra et al. <sup>73</sup>	Los Angeles, California, USA	1995-2006	7594/635	Nested case-control	California DDS	DSM-IV-R determined by DDS staff	Autistic disorder	Birth year, sex, maternal age, race/ethnicity, maternal place of birth, type of birth, parity, insurance type, and gestational weeks at birth	Concentration from nearest regulatory monitor Land use regression model with seasonal adjustment	Pregnancy trimesters and entire pregnancy
Roberts et al. <sup>70</sup>	All 50 states, USA	1987-2002	325/22,101	Cohort	Children of Nurses' Health Study	Parent report of a diagnosis via questionnaire	ASD	Maternal age, year of birth, maternal parents' education, census tract median income, census tract percent college educated, and NATA model year	National-Scale Air Toxics Assessment (NATA) (1990, 1996, 1999, and 2002)	Annual average for a year within 2 years of birth year

<sup>a</sup>Results in Figure 2 (individual air pollutant chemicals) and Figure 3 (mixed traffic and diesel particulate matter).<sup>b</sup>Autism data sources are described in Table 2.<sup>c</sup>Autism diagnostic and psychometric tools are described in Table 3.

TABLE 7

Included epidemiological publications of autism and volatile organic compounds/solvents<sup>a</sup>

Citation	Geographic location	Birth years	Sample size	Study design	Autism data source <sup>b</sup>	Autism measurement <sup>c</sup>	Autism classification	Adjustment variables	Exposure measurement	Exposure timing
Windham et al. <sup>90</sup>	Described in Table 6.									
Windham et al. <sup>88</sup>	San Francisco Bay Area, California, USA	1994	284/659	Case-control	ADDM surveillance	DSM-IV-R criteria applied to developmental evaluations	ASD	Child's race, maternal age, and maternal education	Occupational medicine-certified physician-coded exposures from maternal usual occupation from California birth certificate into broad categories. Solvents = electronics, custodian, lab work, dry cleaning, cosmetology, painter, construction, mechanic. Disinfectants = hands-on medical occupations	Pregnancy
Kalkbrenner et al. <sup>16</sup>	Described in Table 6.									
Kim et al. <sup>89</sup>	Korea	In elementary school ~2010	106/324	Case-control	Newly recruited	Diagnosis by child psychiatrist, confirmed by government agency	ASD	No statistical adjustment, but no differences between cases and controls in maternal age, maternal education, socioeconomic status, breastfeeding, or alcohol consumption in pregnancy	Retrospective parent questionnaire of pregnancy exposure to "newly built houses" and "textiles"	Pregnancy
McCamlies et al. <sup>87</sup>	Central California, USA	1998-2003	93/81	Case-control	CHARGE	ADOS + ADI-R	ASD	Duration of breast-feeding, mother's age, mother's education, regional center, child's gender, child's age, and payment method	Retrospective phone questions of mothers' and fathers' occupations including list of specific substance exposures. Blinded industrial hygienist coding of parent report	3 Months prior to pregnancy until birth or weaning
Roberts et al. <sup>70</sup>	Described in Table 6.									

<sup>a</sup>Results in Figure 4.<sup>b</sup>Autism data sources are described in Table 2.<sup>c</sup>Autism diagnostic and psychometric tools are described in Table 3.



TABLE 8

Included epidemiological publications of autism and metals from air, occupation, dental amalgams, and diet<sup>a</sup>

Citation	Geographic location	Birth years	Sample size	Study design	Autism data source	Autism measurement <sup>b</sup>	Autism classification	Adjustment variables <sup>c</sup>	Exposure measurement	Exposure timing
Windham et al. <sup>90</sup>	Described in Table 6.									
Geier et al. <sup>97</sup>	USA	1990–1999	Autistic disorder: 40 ASD; 60	Cohort	Genetic Centers of America	Physician diagnosis of ICD-9R 299.00 (A.D.) or 299.80 (ASD) based on child observation and Autism Treatment Evaluation Checklist completed by parents	Severe (ICD-9R 299.00) or mild (299.80)	Child's age, gender, race, and region of the U.S. Study restricted to children without exposure to Rho (D) immune globulines or influenza vaccinations during pregnancy.	Medical history of number of dental amalgams present in moms during pregnancy.	Pregnancy
Kalkbrenner et al. <sup>16</sup>	Described in Table 6.									
McCamles et al. <sup>87</sup>	Described in Table 7.									
Roberts et al. <sup>70</sup>	Described in Table 6.									
Van Wijngaarden et al. <sup>96</sup>	Republic of Seychelles	1986–1990 and 2001	SCQ 149/1784 SRS 182/537	Cohort	Seychelles Child Development Study	SCQ 4.14 SRS 4.69 (males) SRS 4.64 (females)	Continuous autism phenotype	Child's sex, recruitment cohort (maternal and paternal age)	Laboratory analysis of methylmercury in maternal hair collected around birth	Pregnancy

<sup>a</sup>Results in Figure 5.<sup>b</sup>Autism diagnostic and psychometric tools are described in Table 3.<sup>c</sup>Variables in parentheses were evaluated but not included in final models because they did not impact results.

TABLE 9

Included epidemiological publications of autism and ethylmercury from thimerosal in vaccines.<sup>a</sup>

Citation	Geographic location	Birth years	Sample size	Study design	Autism data source <sup>b</sup>	Autism measurement <sup>c</sup>	Autism classification	Adjustment variables <sup>d</sup>	Exposure measurement	Exposure timing
Hviid et al. <sup>101</sup>	Denmark	1990–1996	467/450 (2,986,654 person-years) 440 Autistic Disorder 787 Other ASD	Cohort	Danish Psychiatric Central Register	ICD-8 or ICD-10 F84.0 or F84.1–F84.9	Autistic disorder Other ASD	Child's sex, child's place of birth, birth weight, 5-min Apgar, gestational age, mother's age, mother's country of birth, child's age, and calendar period.	Sum of mercury from pertussis vaccinations prior to thimerosal removal as reported to Danish National Board of Health, at about 1, 2, and 10 months of life	First year of life
Verstraeten et al. <sup>234</sup>	West Coast of USA	1991–1997	202 (Autistic Disorder), 108 (PDD-NOS)/110,883	Cohort	Vaccine Safety Datalink	ICD-9 299.0 or 299.8	Autistic disorder Asperger's disorder/PDD-NOS	Child's sex, birth month and year, usual clinic, and restriction to those with consistent health care seeking behavior.	Sum of mercury content from infant vaccines: HBV, DPT, and Hib, by month, from computerized databases of included HMOs.	<i>Postnatal:</i> Birth to 1 month Birth to 3 months Birth to 7 months
Andrews <sup>235</sup>	United Kingdom	1988–1997	106/107,152	Cohort	General Practitioner Research Database (GPRD)	ICD-8 or ICD-9 code 299.0	Autistic disorder	Child's sex and year of birth (month of birth).	Number of DTP/DT doses by age from the linked patient, medical, and prevention databases of the Office for National Statistics	<i>Postnatal:</i> Birth to 3 months Birth to 4 months All postnatal
Croen et al. <sup>103</sup>	Northern California, USA	1995–1999	400/410	Nested case-control	Membership in health plan; Kaiser Permanente	ICD-9-CM 299.0 or 299.8	Autistic disorder Asperger's disorder/PDD-NOS	Child's sex, birth year, hospital of birth, birth order, plurality, maternal age, maternal race/ethnicity, and maternal education.	Maternal Rh immunoglobulin or influenza vaccine abstracted from the prenatal medical record.	Pregnancy
Price et al. <sup>104</sup>	West Coast of USA	1994–1999	256 ASD/752 187 Autistic Disorder/724 49 ASD with regression/652	Nested case-control	Vaccine Safety Datalink	ICD-9 299.0 or 299.8 confirmed with ADOS and ADI-R	ASD Autistic disorder ASD with regression	Birth year, child's gender, managed care organization, birth weight, maternal age, and family income (maternal education, birth order, breastfeeding duration, adequacy of prenatal care, use of cholesterol screening, use of Pap test, maternal alcohol consumption, maternal folic acid use, maternal viral infection, child lead exposure, child	Sum of mercury from prenatal maternal and postnatal vaccinations, obtained from computerized medical records, medical charts, and maternal interviews, and linked with manufacturer information	Pregnancy <i>Postnatal:</i> Birth to 1 month Birth to 7 months

Citation	Geographic location	Birth years	Sample size	Study design	Autism data source <sup>b</sup>	Autism measurement <sup>c</sup>	Autism classification	Adjustment variables <sup>d</sup>	Exposure measurement	Exposure timing
Gallagher and Good-man <sup>102</sup>	USA	<1999 And in NHIS	30/7044	Cohort	National Health Interview Survey (NHIS)	Parent response to inquiry of whether health professional ever said that child had autism.	ASD	anemia, and child pica). <sup>e</sup> Race, two-parent household, and maternal education. Study restricted to males.	Interviewer transcription of dates and type of vaccination from vaccination record	Postnatal: Birth to 1 month

<sup>a</sup>Results in Figure 6.

<sup>b</sup>Autism data sources are described in Table 2.

<sup>c</sup>Autism diagnostic and psychometric tools are described in Table 3.

<sup>d</sup>Variables in parentheses were evaluated but not included in final models because they did not impact results.

<sup>e</sup>In Price et al., variables in parentheses were included in models of one, but not all, autism subgroups.

TABLE 10

Included epidemiological publications of autism and pesticides<sup>a</sup>

Citation	Geographic location	Birth years	Sample size <sup>b</sup>	Study design	Autism data source <sup>c</sup>	Autism measurement <sup>d</sup>	Autism classification	Adjustment variables <sup>e</sup>	Exposure measurement	Exposure timing
Eskenzazi et al. <sup>135</sup>	Salinas Valley, California, USA	2000–2001	51/304	Cohort	Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	>97% On PDD scale of CBCL	ASD	Child's sex and exact age at assessment, breastfeeding duration, HOME score, <sup>3</sup> household income above poverty threshold, parity, maternal PPVT, <sup>4</sup> maternal depression, and maternal age <sup>5</sup>	Maternal and child urine specimens, maternal prenatal blood sample	Pregnancy and birth to 24 months
Roberts et al. <sup>138</sup>	Central Valley, California, USA	1996–1998	465/6975	Nested case-control	California DDS	DSM-IV-R determined by DDS staff	Autistic disorder	Maternal education, race, and DDS regional center of diagnosis, and maternal age	Agricultural pesticide application data from the California Department of Pesticide Regulation linked to children using crop information and a geographic information system based on residential address.	Pregnancy: CNS development; gestational days 7–49. A posteriori gestational period: days 2–81. All of gestation: gestational days 14 to DOB
Roberts and English <sup>139</sup>	Central Valley, California, USA	1996–1998	465/6975	Nested case-control	California DDS	DSM-IV-R determined by DDS staff	Autistic disorder	Maternal race/ethnicity and educational attainment, and DDS regional center of diagnosis, and maternal age	Agricultural pesticide application data from the California Department of Pesticide Regulation linked to children using crop information and a geographic information system based on residential address.	Window in pregnancy: days 38–163 postfertilization, Postnatal window: days 346–529 postfertilization
McCamies et al. <sup>87</sup>					Described in Table 6.					
Cheslack-Postava et al. <sup>137</sup>	Finland	1991–2000	75/75	Case-control	FIPS-A	ICD code F84.0 from record linkages of the Finnish Medical Birth Registry and the Finnish Hospital and Outpatient Discharge Registry	Autistic disorder	Child's sex, birth year, maternal age, urban/Socioeconomic status was not associated with any persistent pollutant in this sample. ORs for DDE and HCB were also adjusted for co-pollutant: total PCBs.	Laboratory analysis of stored serum collected during pregnancy, usually in the 1st trimester.	Early pregnancy
Keil et al. <sup>140</sup>	Central California, USA	1997–2006	407/262	Case-control	CHARGE	ADOS + ADI-R	Autistic disorder	Child's sex, regional center of birth, and age, maternal education, race/ethnicity, and parity, and pet ownership during prenatal period	Retrospective Environmental Exposure Questionnaire via maternal phone interview	3 Months prior to pregnancy through termination of breast-feeding
Braun et al. <sup>136</sup>	Cincinnati, Ohio, USA	2003–2006	175	Cohort	Health Outcomes and	Social Responsiveness	Continuous autism phenotype	Maternal age at delivery, race, marital status, education,	Laboratory analysis of serum sample during	Pregnancy

Citation	Geographic location	Birth years	Sample size <sup>b</sup>	Study design	Autism data source <sup>c</sup>	Autism measurement <sup>d</sup>	Autism classification	Adjustment variables <sup>e</sup>	Exposure measurement	Exposure timing
					measures of the Environment (HOME) Study	Scale at ages 4 and 5 years		insurance status, IQ, serum cotinine, and employment, parity, household income, prenatal vitamin use, depressive symptoms in 2nd trimester, and HOME score	gestation, usually around 16 weeks, lipid normalized	

<sup>a</sup>Results in Figure 7.

<sup>b</sup>Sample size is presented by a single number when statistical models included a continuous measure of autism phenotype, or, otherwise, as the number of cases/controls.

<sup>c</sup>Autism data sources are described in Table 2.

<sup>d</sup>Autism diagnostic and psychometric tools are described in Table 3.

<sup>e</sup>Variables in parentheses were evaluated but not included in final models because they did not impact results.

Included epidemiological publications of autism and polychlorinated biphenyls, flame retardants, non-stick chemicals, phthalates, and bisphenol A<sup>a</sup>

TABLE 11

Citation	Geographic location	Birth years	Sample size <sup>b</sup>	Study design	Autism data source	Autism measurement <sup>c</sup>	Autism classification	Adjustment Variables <sup>d</sup>	Exposure Measurement	Exposure Timing
Larsson et al. <sup>58</sup>					Described in Table 5.			Condensation on windows, maternal smoking, child's sex and age, child's asthma status, and financial problems	Parent questionnaire at study baseline about type of flooring in the parent's and child's bedrooms.	Pregnancy + early childhood combined
Kim et al. <sup>89</sup>					Described in Table 7.				Retrospective parent questionnaire of exposure to "canned food," "plastics," "waste incinerators," "seafoods," "polyurethane foams," "fast food," "hot canned beverages," "old electronics," and "microwaveable food"	Pregnancy
Miodovnik et al. <sup>158</sup>	New York City, New York, USA	1998–2002	137	Cohort	Mt. Sinai Children's Environmental Health Study	SRS when child was 7–9 years	Continuous autism phenotype	Child race and sex, caregiver marital status, and urinary creatinine, a measure of urine dilution. (Maternal age, IQ, education, child IQ, and age at SRS)	Laboratory analyses of maternal spot urine samples from 25 to 40 weeks of pregnancy	Mid-late pregnancy
Cheslack-Postava et al. <sup>137</sup>							Described in Table 10.			
Braun et al. <sup>136</sup>					Described in Table 5.				PCBs, BFRs, and PFCs measured from laboratory analysis of serum (usually at 16 weeks of gestation) and lipid normalized. Phthalates and BPA measured in urine samples from pregnancy (around 16 and 26 weeks) and creatinine standardized.	Pregnancy

<sup>a</sup>Results in Figure 8.

<sup>b</sup>Sample size is presented by a single number when statistical models included a continuous measure of autism phenotype, or, otherwise, as the number of cases/controls.

<sup>c</sup>Autism diagnostic and psychometric tools are described in Table 3.

<sup>d</sup>Variables in parentheses were evaluated but not included in final models because they did not impact results.