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Authors

Volk, Heather E
Perera, Frederica
Braun, Joseph M
et al.

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Prenatal air pollution exposure and neurodevelopment: A review and blueprint for a harmonized approach within ECHO

Heather E. Volk[a,*], **Frederica Perera**[b], **Joseph M. Braun**[c], **Samantha L. Kingsley**[c], **Kimberly Gray**[d], **Jessie Buckley**[e], **Jane E. Clougherty**[f], **Lisa A. Croen**[g], **Brenda Eskenazi**[h], **Megan Herting**[i], **Allan C. Just**[j], **Itai Kloog**[k], **Amy Margolis**[l], **Leslie A. McClure**[m], **Rachel Miller**[n], **Rosalind Wright**[o] **program collaborators for Environmental influences on Child Health Outcomes**[1]

[a]Department of Mental Health and Environmental Health and Engineering, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

[b]Columbia Center for Children's Environmental Health, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA

[c]Department of Epidemiology, Brown University, Providence, RI, USA

[d]National Institute of Environmental Health Sciences, Durham, NC, USA

[e]Department of Environmental Health and Engineering and Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

[f]Department of Environmental and Occupational Health, Dornsife School of Public Health, Drexel University, Philadelphia, PA, USA

[g]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

[h]Center for Environmental Research and Children's Health, School of Public Health, University of California Berkeley, Berkeley, CA, USA

[i]Department of Preventive Medicine, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA

[j]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[k]Department of Geography and Environmental Development, Faculty of Humanities and Social Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

[*]Corresponding author. Department of Mental Health and Environmental Health and Engineering Wendy Klag Center for Autism and Developmental Disabilities Bloomberg School of Public Health Johns Hopkins University, 624 N. Broadway, HH833, Baltimore, MD, 21210, USA. hvolk1@jhu.edu (H.E. Volk).

[1]See Appendix for full listing of collaborators.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110320.

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[l]Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[m]Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, PA, USA

[n]Department of Medicine, Department of Pediatrics, The College of Physicians and Surgeons, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA

[o]Department of Environmental Medicine and Public Health, And Pediatrics, Institute for Exposomics Research, Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Background: Air pollution exposure is ubiquitous with demonstrated effects on morbidity and mortality. A growing literature suggests that prenatal air pollution exposure impacts neurodevelopment. We posit that the Environmental influences on Child Health Outcomes (ECHO) program will provide unique opportunities to fill critical knowledge gaps given the wide spatial and temporal variability of ECHO participants.

Objectives: We briefly describe current methods for air pollution exposure assessment, summarize existing studies of air pollution and neurodevelopment, and synthesize this information as a basis for recommendations, or a blueprint, for evaluating air pollution effects on neurodevelopmental outcomes in ECHO.

Methods: We review peer-reviewed literature on prenatal air pollution exposure and neurodevelopmental outcomes, including autism spectrum disorder, attention deficit hyperactivity disorder, intelligence, general cognition, mood, and imaging measures. ECHO meta-data were compiled and evaluated to assess frequency of neurodevelopmental assessments and prenatal and infancy residential address locations. Cohort recruitment locations and enrollment years were summarized to examine potential spatial and temporal variation present in ECHO.

Discussion: While the literature provides compelling evidence that prenatal air pollution affects neurodevelopment, limitations in spatial and temporal exposure variation exist for current published studies. As >90% of the ECHO cohorts have collected a prenatal or infancy address, application of advanced geographic information systems-based models for common air pollutant exposures may be ideal to address limitations of published research.

Conclusions: In ECHO we have the opportunity to pioneer unifying exposure assessment and evaluate effects across multiple periods of development and neurodevelopmental outcomes, setting the standard for evaluation of prenatal air pollution exposures with the goal of improving children's health.

Keywords

Air pollution; Neurodevelopment; Prenatal exposure; Brain

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1. Introduction

While overall air quality has improved in the United States in recent years, reports still demonstrate that even low levels of ambient air pollution are associated with morbidity and mortality across the life span (Zigler et al., 2017). In aging populations, higher rates of cognitive decline are observed among individuals with greater exposure to air pollution (Power et al., 2016). Children exposed to high levels of air pollution show increased rates of asthma, decreased lung function growth, and increased risk of early markers of cardiovascular disease (Bourdrel et al., 2017; Gauderman et al., 2015; Hehua et al., 2017). The effects of early life air pollution exposure on neurodevelopment are an area of more recent and growing concern. Particulate matter (PM) and nitrogen dioxide (NO_2) exposures have been associated with increased risk of pre-term birth and low birth weight, both risk factors for neurodevelopmental problems (Li et al., 2017a, 2017b; Ng et al., 2017). The current literature now strongly suggests that prenatal air pollution exposure also has multiple effects on the developing brain, impacting cognition and behavior during childhood and early adolescence (Clifford et al., 2016).

The rationale for a focus on the early window of exposure is that the developing fetus and child are uniquely susceptible to the impacts of environmental exposures because of their rapid development, immature detoxification pathways, and increased exposure to some pollutants due to developmentally appropriate behavior, anatomy, and physiology (Braun 2017). Prenatal exposure to air pollution is especially detrimental to brain development and could produce lasting effects by altering developmental programming. While previous reports of this relationship have focused on specific disorders and neurocognitive domains, integration of findings across neurodevelopmental measures and outcomes to gain a broader perspective has not been conducted. Studies of this relationship face many methodological challenges, including adequate assessment of confounding, evaluation of outcome heterogeneity within and across neurodevelopmental domains and disorders, understanding of the strengths and limitations of diverse air pollution exposure methods, and the impacts of co-exposure to multiple airborne contaminants.

The present comprehensive review of the reported associations between prenatal exposure to air pollution and adverse neurodevelopmental outcomes highlights the unique opportunity provided by the National Institutes of Health (NIH)-funded Environmental influences on Child Health Outcomes (ECHO) program. ECHO pools 84 existing prospective cohorts in the United States, creating a “virtual cohort” with the features and sample size needed to determine how the early environment affects children’s neurodevelopment and health. Given the potential spatial and temporal variation that may be present across the ECHO participants and the large sample size of >50,000 subjects, collaborative projects from this initiative are well-suited to 1) address how air pollution exposure during the prenatal period affects early brain development, and 2) overcome methodologic limitations often present in studies of early life air pollution exposure and morbidity. Here we describe current methods for air pollution exposure assessment, summarize existing literature on the relationship between prenatal exposure to air pollution and neurodevelopment, and we present a blueprint for a new comprehensive analysis of the effect of prenatal air pollution exposure on neurodevelopment within ECHO.

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2. Materials and methods

2.1. Eligibility criteria for literature search

We identified peer-reviewed, original research in humans that examined the association between prenatal exposure to outdoor ambient air pollution and any neurodevelopment- or neurobehavior-related outcome from birth to 18 years of age. Neurodevelopment and neurobehavior outcomes included measures of cognition and intelligence, as well as specific clinical diagnoses, continuous phenotypes of clinical diagnoses, specific neurobehavioral components (e.g., working memory or processing speed), and measures of brain imaging. Clinical diagnoses included autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety, and depression.

We included studies examining air pollution exposure occurring from date of conception through the time of delivery, or assessed at birth (e.g., cord blood biomarkers or using birth certificate address to geocode and impute air pollution exposure). Outdoor air pollution included traffic-related or near-roadway air pollution/pollutants, criteria air pollutants (e.g., carbon monoxide, lead, ground-level ozone, NO_2, particulate matter, and sulfur), or hazardous air pollutants (also known as toxic air pollutants or air toxics; examples include benzene, perchlorethylene, methylene chloride, dioxins, asbestos, toluene, and metals such as cadmium, mercury, chromium, and lead). We excluded studies evaluating exposure to environmental tobacco smoke or pesticides, or that did not measure exposure during pregnancy. We also excluded studies that did not evaluate a neurodevelopmental or neurobehavioral outcome (described above) from birth through age 18. We excluded conference abstracts and non-research publications such as commentaries. Systematic reviews with included meta-analyses were examined.

2.2. Literature search strategy

We conducted our search using Medline (via PubMed) and the Institute for Scientific Information Web of Science on July 5, 2017. Publications were not limited by date but were limited to articles published in English. In PubMed, our search strategy used both Medical Subject Headings (MeSH) terms and their corresponding keywords in titles and abstracts (" [tiab]") to identify epidemiological studies of prenatal exposure to outdoor ambient air pollution and health outcomes related to neurodevelopment or neurobehavior. For more detailed information on the literature search strategy, see Supplemental Methods.

2.3. Collection and summary of ECHO meta data

The ECHO Data Analysis Center (DAC) developed several surveys to ascertain the prior collection of common data elements by each of the 84 ECHO cohorts participating in the initial two years of ECHO known as the UG3 phase. The DAC sent the surveys to the cohort personnel who could best address the questions, and this person specified whether data elements were ever collected for mothers, fathers, and children. If data elements were collected, cohorts then provided the life-stage(s) of data collection. The current paper relies on surveys ascertaining recruitment site locations and enrollment information (Module 2 release date: 01/31/2018), as well as street address and neurodevelopmental outcomes (Module 3 release date: March 07, 2018). The response rate for these surveys was 100%.

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SAS version 9.3 and R software were used for data analysis, and ArcGIS software version 10.5.1 was used to map recruitment site locations to the centroid of the zip code.

3. Results

3.1. Literature search

We found 886 publications in our literature search. After duplicates were removed, 677 publications were screened by title and abstract for eligibility. Altogether, 599 publications did not meet established inclusion criteria and were excluded leaving 78 articles of original research and review papers.

3.2. Summary, Strengths, and Limitations for Methods of Ambient Pollution Exposure Assessment

A number of exposure assessment methods have been used to examine the role of ambient air pollution in shaping neurocognitive and other early-life outcomes. These include geographic information systems (GIS) methods (used in many of the studies of neurodevelopment described below), personal and residential air monitoring methods, and biomarkers of exposure. To provide a rich context for the review of the literature on prenatal air pollution and neurodevelopment, we discuss existing methods for assigning ambient air pollution exposure in epidemiologic studies.

3.2.1. Geographic Information System (GIS)-Based Methods—GIS methods are particularly useful in assigning air pollution exposures to large epidemiologic cohorts. These methods all rely on mapping of address data. These methods most often reflect place of residence but can also be used to incorporate air pollution exposure at other common locations like schools or workplaces. As children and their parents spend differing amounts of time at these locations over the life-course, exposure assessments that allow for this flexibility will improve modeled exposure accuracy.

For criteria air pollutants, NO_2, ozone (O_3), particulate matter <0 μm in diameter (PM_{10}), and particulate matter <2.5 μm in diameter ($PM_{2.5}$), exposure assessment is done using the Environmental Protection Agency (EPA) Air Quality System (AQS) ambient monitor network. Most simply, geographic locations are mapped and air pollution exposures assigned based on the measure from the closest ambient monitor or the average of values for all ambient monitors within a specified buffer distance. While ambient monitors are located throughout the United States, a limited number of pollutants are assessed; and they are predominantly located in urban areas, thus offering limited spatial coverage. Many of the U.S. monitors do not operate continuously throughout the year, resulting in limited temporal information. For example, most $PM_{2.5}$ monitors record a 24-h measurement every three or six days. This limited temporal and spatial resolution makes investigating the health effects of cumulative exposures and rural environment exposures especially problematic. Nonetheless, many studies still assign exposures based on the monitor closest to the location of residence given the wide availability of the data. Simple interpolation methods (such as kriging) can produce more spatially resolved exposure estimates but fail to account for local emission sources, such as the presence of highways or stationary sources between two

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monitoring stations, rendering such interpolations inappropriate. Exposure metrics from such studies thus ignore intra-urban variation in exposure and may be missing data in rural areas.

Hazardous air pollutants (HAPs) are also often investigated through reliance on federal monitoring efforts via mapping of data from the National-scale Air Toxics Assessment (NATA), which is also administered by the EPA. While NATA includes measurements for a large number of air toxics, these data are only offered for specific years at the level of the census tract, limiting precision of assignment by both space and time.

Land use regression (LUR) is a commonly used GIS-based method that utilizes data from air pollution monitors and other geographic data to create statistical models to predict exposures. LUR models often include measures of traffic density, population density, climatological data, and other physical factors (e.g., green space) and have been used to predict a variety of airborne exposures (Briggs et al., 1997). Much variability exists in the application of LUR, including the factors included in the models, the approach to collecting monitoring data (e.g., temporally, spatially), and development and validation of models (Hoek et al., 2008). LUR models can more accurately capture long-term differences in exposure between locations. However, since the LUR terms are generally not time-varying, their temporal resolution tends to be limited and based on data from the sparse monitoring network. Due to this feature, a common method used to adjust GIS-based exposure estimates over time—given that these models focus on spatial variation in exposures—is to integrate these models with EPA AQS regulatory monitoring data or other repeated-measures data capturing longer-term temporal trends in air pollution. In doing so, researchers may better estimate exposures during key periods related to neurodevelopment, such as specific trimesters of pregnancy (Ross et al., 2013) or may estimate variation in exposures over a shorter period (i.e., months) as appropriate to a given outcome of interest. However, they can only assess long-term exposures, rather than acute ones with daily or weekly resolution. Moreover, lack of monitors in exurban and rural locations and small towns means participants from such locations are either excluded or are assigned estimates from the LUR that may have more error than those for urban participants. And because of the siting strategies for monitors and their modest number, certain exposure scenarios may be under- or over-represented in calibrating the land use regression (Sorek-Hamer et al., 2016).

Often, satellite-derived remote sensing data—indicators of spatially-distributed sources (e.g., impervious surface), sinks (e.g., green space), or concentration proxies (e.g., aerosol optical depth [AOD])—are integrated into LUR-based models. Satellite-derived data can be useful in filling in spatial and temporal gaps in monitoring data. In addition to incorporating remotely sensed data into LUR models, satellite-derived data have been used in hierarchical Bayesian models combining EPA monitoring data and community multi-scale air quality (CMAQ) estimates, using a variety of approaches to improve both spatial and temporal exposure prediction (Garcia 2006; McMillan et al., 2010). Some research has found strong correlations between satellite-derived measures of AOD and ground-level total aerosols in the atmosphere; however, correlations between AOD vary across model assumptions and meteorological conditions (Chu et al., 2003). Due to its large spatial coverage and reliable repeated measurements, satellite remote sensing provides another important tool for

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monitoring aerosols, particularly for areas and exposure scenarios where surface monitors are not available (Sorek-Hamer et al., 2016). Several groups over the past few years have shown how these hybrid models are able to robustly assess short-term and long-term human exposures to $PM_{2.5}$ (Kloog et al., 2014; Li et al., 2017a, 2017b), PM_{10} (Kloog et al., 2015; Stafoggia et al., 2017), NO_2 (Stafoggia et al., 2017), and O_3 (Di et al., 2017) in order to investigate both the acute and chronic effects of ambient particles and gases, respectively.

Several methods of assigning exposure based on traffic-related air pollution (TRAP) have been used in recent years (Pratt et al., 2014). Calculating the distance from an individual's residence to a road, most often a main road, carrying over a certain volume of vehicles is often used as a proxy for road traffic exposure. Another popular method is considering traffic flow along the street of residence or one in close proximity. The traffic count method is likely to be a more valid measure than distance to roads, but it relies on often limited data on counts or estimates of traffic. However, these data may increasingly become available from other data sources utilizing smartphone data.

3.2.2. Personal Monitoring, Residential Monitoring, and Biomarkers—In addition to GIS-based estimates of exposures to ambient pollution, techniques that include personal monitoring, residential monitoring, and measurement of biomarkers are able to capture individual measures of environmental exposures. These may be used as indicators of individual exposure alone or in combination with GIS-based estimates.

Personal monitoring, usually involving a sampler worn during usual activities, can capture changing exposure with more granularity than GIS-based estimates. Current technology may measure either fine particulates, gaseous (i.e., O_3, NO_2, volatile organic compounds (VOC), C0/carbon monoxide) pollutants, or classes of pollutants found in both modes (e.g., polycyclic aromatic hydrocarbons/PAH) (McKercher et al., 2017). Numerous personal monitors have been developed; many are commercially manufactured, including (but not limited to) Series 500 Portable Monitor, DC1100 Air Quality Monitor, microAethalometer AE51, microPEM, and other passive samplers/diffusion monitors. The sensing devices can be worn as shirts or other wearables, as bracelets, or within backpacks, and may capture an array of component pollutants (Lovinsky-Desir et al., 2016a, 2016b; McKercher et al., 2017; Panta et al., 2017; WIlliams et al., 2014).

The portability of such devices favors a more accurate exposure assessment for pollutants with high spatial and temporal variability and for people traveling to multiple locations beyond home over the course of a day. These devices can also measure exposures related to frequent changes in behaviors, levels of physical activity, and are associated with daily commutes to work, school, or other activities (WIlliams et al., 2014); (Barakat-Haddad et al., 2015; Brunst et al., 2015; Lei et al., 2016; S Lovinsky-Desir et al., 2016a, 2016b; Panta et al., 2017). The data also may be filtered into real-time computer navigation systems or smartphones and linked to GPS coordinates (McKercher et al., 2017). Moreover, personal measures may suffer from less misclassification following weather-related events, wind, and atmospheric conditions compared to levels measured by outdoor stationary monitors (Báumer and Vogel 2007; Cerveny and Balling 1998; McKercher et al., 2017; Schultz et al., 2007; WIlliams et al., 2014).

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The limitations of personal devices are that many tend to be expensive when deployed on a wide scale (McKercher et al., 2017; WIlliams et al., 2014) and procedures for evaluating accuracy and precision are labor-intensive (WIlliams et al., 2014). Individual devices vary in terms of the pollutants they capture, their durability (i.e., battery life), and needs for maintenance to ensure reproducibility (McKercher et al., 2017). Another concern may be that, despite their portability, they still may not accurately account for the individually inhaled dose, which can be influenced by the intensity of activity and by airway alveolar minute ventilation. They may also produce ambient noise. This field is developing rapidly, and technological advances in the monitors' hardware and software that address these concerns will be beneficial (McKercher et al., 2017).

Monitors also can be placed in homes or schools to capture personal exposures to indoor pollutants plus outdoor concentrations that penetrate indoor environments. In particular, they may capture indoor sources that may otherwise be missed using GIS, including emissions from heating units, incense or other in-home burning, gases emitted from ovens, combustion products emitted from wood stoves, fireplaces, and second-hand cigarette smoke. For some pollutants, indoor residential measures overwhelmingly represent high penetration of outdoor air and thus capture the spatial variability that drives concentrations exposing individuals (Breen et al., 2015; Costa et al., 2017; Kinney et al. 2002, 2005). Additional modeling of indoor exposure with regional air quality models that consider the influence of meteorological, infiltration factors, and information on time, activity, and locations indoors may provide more accurate estimates (Breen et al., 2015; Chithra and Naendra 2014; Han et al., 2015; Lane et al., 2015; MacNeill et al., 2014).

However, when deployed widely in population studies, residential devices can become expensive. Each device only captures emissions from that one site and may miss pollution emanating from other indoor environments. Outdoor sources that do not infiltrate inside well (Jung et al., 2010; Kinney et al., 2003) or whose levels of infiltration vary by season (Hänninen et al., 2011; Jung et al., 2010) may be underestimated. Non-airborne routes of exposure, including dermal and oral, are similarly not captured. Moreover, levels may vary by floor height, location of the monitor within the home, and whether the room faces a street, alley, or green area (Jung et al., 2011; S. Lovinsky-Desir et al., 2016a, 2016b). Time-activity adjustments may be needed.

Biomarkers related to air pollution exposure variously indicate internal dose, biologically effective dose, preclinical response or enhanced susceptibility (Perera and Weinstein 1982; Schulte et al., 1993). They can be measured in small amounts of biospecimens such as maternal blood or urine collected in pregnancy or at delivery, blood and placenta collected from the newborn at delivery, or child blood and urine. Their advantage is in their ability to integrate multiple routes of exposure and reflect an individual's absorption, distribution, metabolism, and excretion of that exposure. Biomarkers of air pollution exposure include measures of air pollution constituents (e.g., PAH metabolites or PAH-DNA adducts) (Perera and Weinstein 1982; Schulte et al., 1993).

Importantly, biomarkers vary in their ability to inform on whether the exposure is acute or chronic. For example, measures of sera or urinary metabolites of PAH are often used to

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complement measures of PAH-DNA adducts. In the former case, more acute (i.e., 1–2 day half-life) exposures may be captured (Jung et al., 2014); in the latter, more chronic exposure as well as information on early internal biological responses (i.e., metabolic activation, detoxification, host DNA repair capacity) may be reflected (Demetriou and Vineis 2015; Perera et al., 2004). Additional examples of established biomarkers of air pollution exposure include measurement of urinary leukotrienes (Rabinovitch 2012) and exhaled CO to capture short-term effects of TRAP (Lawin et al., 2017).

While biomarkers have been successfully used to sensitively, specifically, and quantitatively estimate exposure to an array of environmental pollutants (e.g., lead, mercury, PAH), air pollution is a heterogeneous mixture of multiple pollutants whose composition varies geographically, and there is no individual biomarker or panel of biomarkers that can fully capture this variation or characterize all air pollution exposures. Moreover, biomarkers vary in their ability to represent specific exposure sources or routes. Certain biomarkers in blood, serum, or urine may reflect exposure to the same pollutants found in ambient air via non-inhalation routes (ingestion, dermal) or sources such as smoking. Therefore, studies of the effects of air pollution must adjust for such potential co-exposures to avoid confounding. Finally, some biomarkers are expensive and can be logistically difficult to collect in large epidemiological studies. They also require extensive validation prior to deployment in epidemiological studies.

3.3. Personal versus proxy measures of ambient exposure

Personal exposure estimates via monitoring have utility in characterizing individual variation in exposure; however, personal monitors are often only practically deployed for small time periods or rely on integrated sensors (e.g., silicon wristbands as passive monitors). Measurements may also vary due to individual-level behaviors during the monitoring period and may not accurately reflect exposure levels over a longer time period. Biomarkers have the ability to characterize exposure, internal or target dose, and preclinical response; however, biomarkers may be subject to variation in pharmacokinetic parameters that are related to disease pathophysiology (Weisskopf and Webster 2017) and thus subject to confounding. They are also unlikely to be the regulated metric of exposure.

On the other hand, a commonly cited limitation of ambient exposure estimates is that measurement error from inaccurate models, modification by personal behaviors, and spatio-temporal misalignment in reconstructing exposures can all contribute to unsystematic measurement error, which generally bias effect estimates towards the null. However, the improvement in the accuracy of more recently developed air pollution models and the advancement of measurement error correction methods to account for spatio-temporal misalignment (e.g., spatial SIMEX) (Alexeeff et al., 2016) can help to address these limitations in the use of ambient air pollution models. Further, for a large consortium, adding personal assessment or biomarker measurements can be prohibitive in cost and cannot be used retrospectively if the necessary samples were not already collected. Instead, ambient modeling methods can be added to leverage richly phenotyped cohorts even across large regions, such as in the highly successful recent European ESCAPE (European Study of Cohorts for Air Pollution Effects) project consortium. Another advantage of modeled

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exposure is the ability to reconstruct exposures going back in time in ongoing studies. This can be done even if these studies did not include personal exposure monitoring. This is very relevant for ECHO, where there is no option of having prenatal exposure estimates for the majority of children. Such methods may also be expanded to include both school and residential locations as children age, more fully capturing exposures at relevant developmental stages. Finally, from an epidemiologic perspective, proxy exposures based on ambient models can avoid confounding and reverse causation issues known to impact personal exposure measurements (Weisskopf and Webster 2017).

Importance of Capturing the Relevant Time Period of Exposure.

Human brain development is a complex and synchronized process that begins *in utero* and continues into adolescence. During embryonic development, the neural tube is the substrate for the emerging central nervous system; and waves of cellular differentiation, proliferation, and migration produce neurons and glial cells (Larsen 2001). While much of brain architecture is formed *in utero*, synaptogenesis, dendritic growth, myelination, apoptosis, synaptic pruning, and neurotransmitter system maturation begins *in utero* and continues into childhood (de Graaf-Peters and Hadders-Algra 2006; Uylings, 2006; Luciana 2003; Thatcher, 1991, 1997; Rice and Barone 2000; Webb et al., 2001). Neurodevelopment continues during adolescence, with linear increases in white matter volume, non-linear changes in gray matter volume, maturation of the neurotransmitter systems, and enhancements of the connections between the prefrontal cortex and subcortical regions (Arain et al., 2013; Casey et al., 2008; Giedd et al., 1999).

The rapid and time-dependent nature of brain development makes it sensitive to environmental insults because subtle disruption of neurodevelopmental processes at any given time may produce a cascade of adverse effects that alter the course of normal development (Anderson et al., 2011; Rice and Barone 2000). The heightened sensitivity of the brain to environmental exposures at different developmental periods is illustrated by studies of neurotoxicants like methyl mercury and lead. In the case of methyl mercury, prenatal but not postnatal exposure is associated with reduced cognitive abilities and attention (Axelrad et al., 2007; Dalgard et al., 1994; Debes et al., 2006; Julvez et al., 2010). In contrast, early childhood lead exposure is more strongly associated with cognitive deficits and behavioral problems than prenatal exposures (Braun et al., 2012; Hornung et al., 2009; Lanphear et al., 2005; Pocock et al., 1994). The possibility of discrete periods of susceptibility necessitate epidemiological studies that measure exposures longitudinally because there may be specific periods of heightened sensitivity that could be missed when only a single measure is taken. Further, specific neurodevelopmental disorders (e.g., ADHD vs. ASD) may have different windows of susceptibility. In assessing the impact of prenatal exposure to air pollution, postnatal exposure must be taken into account and vice versa.

Examining windows of heightened susceptibility to air pollution requires appropriate statistical techniques to account for correlated exposures over time. Several studies of neurodevelopment have investigated susceptibility windows using period-averaged exposures during prespecified time windows such as trimesters or months (Becerra et al., 2013; Gong et al., 2014; Kalkbrenner et al., 2014; Raz et al., 2015; Talbott et al., 2015a;

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Volk et al., 2013). Emerging statistical approaches, such as extensions of distributed lag models (Bello et al., 2017; Gasparrini et al., 2017; Wilson et al., 2017) and multiple informant models (Sanchez et al., 2011), offer improved flexibility to identify susceptibility periods using finer temporally resolved exposure information. For example, Chiu et al. (2016) assessed associations of weekly average $PM_{2.5}$ during pregnancy with neurodevelopmental outcomes using distributed lag models and identified susceptibility periods that were not evident using trimester- or pregnancy-averaged exposure assignment.

Summary of Existing Studies on Prenatal Air Pollution and Neurodevelopment.

In the following sections we summarize current work on how prenatal ambient air pollution exposure affects the neurodevelopmental domains of general cognition, attention/ADHD, ASD, mood, and neuroimaging measures of brain structure and function. The literature, described in greater detail below, is summarized in Table 1. The literature strongly suggests that air pollution affects early brain development, with observed impacts ranging from intelligence to attention, autism, and mood.

3.4. Cognitive abilities

The majority of the literature examining the effects of prenatal exposure on neurodevelopment has focused on the assessment of cognitive abilities.

3.5. Hazardous air pollutants

Four studies from the United States and Spain have examined the association between prenatal hazardous air pollution exposures and cognitive abilities in early- and middle-childhood (Guxens et al., 2012; Lertxundi et al., 2015; Stingone et al. 2016, 2017). Sample sizes ranged from 438 to 201,559. Using LUR, the U.S. studies estimated residential air benzene, toluene, ethylbenzene, xylene, diesel particulate, and perchlorethylene exposure, while the Spanish studies used LUR to assess prenatal residential benzene exposure. In the U.S. study, cognitive outcomes included use of academic support services (e.g., speech therapy) and standardized math and language test scores in middle-childhood. Infant mental and psychomotor development was assessed with the Bayley Scales of Infant Development (BSID-II) in the Spanish studies.

To date, the number of studies and conclusions that can be made from them are limited. In the U.S. cohort, prenatal perchlorethylene and diesel particulate exposures were associated with reduced math scores and increased risk of failing to meet math standards; there were no associations with language scores (Stingone et al., 2016). Prenatal benzene was not associated with mental or psychomotor development in the Spanish cohorts (Guxens et al., 2012). However, fruit and vegetable intake during pregnancy modified the association between prenatal benzene and children’s mental development. Benzene was inversely associated with mental development among children born to women with low fruit and vegetable intake, but not among those children born to women with higher intakes.

3.5.1. Particulate matter (PM)—Seven studies from the United States, Spain, Germany, Italy, Greece, Taiwan, and Korea have examined the relations of prenatal residential PM_{10} or $PM_{2.5}$ with cognitive abilities in infancy, early-childhood, or middle-

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childhood (Fuertes et al., 2016; Guxens et al., 2014; Harris et al. 2015, 2016; Kim et al., 2014; Lin et al., 2014; Porta et al., 2016). Sample sizes ranged from 520 to 9482. Five of these studies assessed prenatal residential PM_{10} or $PM_{2.5}$ with LUR models and some incorporated aerosol optical density information into the $PM_{2.5}$ models (Fuertes et al., 2016; Guxens et al., 2014; Harris et al. 2015, 2016; Porta et al., 2016). The other two studies used inverse distance weighting or the nearest monitoring station to assess residential PM exposure (Kim et al., 2014; Lin et al., 2014). Six studies used valid and reliable psychometric instruments to assess infancy, early-childhood, and middle-childhood mental/psychomotor development, intelligence quotient (IQ), executive functions, motor skills, or memory, and one study used parent report of the learning disabilities dyscalculia and dyslexia.

The results of studies examining early life PM exposure and cognitive abilities are mixed. In a pooled analysis of approximately 9000 European children, both PM_{10} and $PM_{2.5}$ were inversely associated with infancy or early childhood psychomotor development, but not general cognition or language development; the associations were stronger for $PM_{2.5}$ (Guxens et al., 2014). In a Korean study, prenatal PM_{10} was associated with reduced mental and psychomotor development, but associations with repeated measures of the outcome weakened as children aged (Kim et al., 2014). In contrast to these findings, studies from the United States, Taiwan, and Italy did not find associations of prenatal PM exposure with several domains of children's cognitive abilities or parent-reported learning disabilities (Fuertes et al., 2016; Harris et al. 2015, 2016; Lin et al., 2014; Porta et al., 2016). In the U.S. study, the association between $PM_{2.5}$ and children's cognitive abilities was significant but was attenuated after adjustment for socioeconomic factors (Harris et al. 2015, 2016). Few studies have examined modifiers of the associations between PM exposure and children's cognitive abilities, although Harris and colleagues reported that child sex and maternal socioeconomic indicators did not modify these associations.

3.5.2. Traffic-related air pollutants (TRAP)—Eleven studies have assessed the relations between TRAP and cognitive outcomes in children from cohorts in the United States, Spain, Germany, Italy, Greece, Taiwan, and Korea (Cowell et al., 2015; Fuertes et al., 2016; Guxens et al. 2012, 2014; Harris et al. 2015, 2016; Kim et al., 2014; Lertxundi et al., 2015; Lin et al., 2014; Porta et al., 2016; Suglia et al., 2008). Sample sizes ranged from 202 to 9482. Most of these studies estimated residential TRAP using distance to roadway, traffic density, or LUR-based estimates of black carbon (BC) or NO_2, which are two markers of TRAP. These studies assessed mental/psychomotor development, IQ, executive functions, motor skills, or memory in infancy, early-childhood, or middle-childhood with valid and reliable psychometric tests. One study assessed the learning disabilities dyscalculia and dyslexia using parent report (Fuertes et al., 2016).

Most studies suggest that prenatal TRAP exposure is associated with decreased *early-childhood* mental and/or psychomotor development. In a European study of >9000 children, prenatal NO_2 exposure was associated with reduced early childhood psychomotor development, but not general cognition or language development (Guxens et al. 2012, 2014; Lertxundi et al., 2015). In a Korean study of 520 children, prenatal NO_2 exposure was inversely associated with mental and psychomotor development at age 6 months, but the

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magnitude of the associations attenuated as infants aged (Kim et al., 2014). There was no association of prenatal or infancy NO_2 exposure with infancy mental or psychomotor development in a study of Taiwanese children; however, air pollution exposure was estimated using only a single monitor in each of the 11 study cities (Lin et al., 2014).

The results of studies examining the association between TRAP and cognitive abilities in *middle-childhood* are mixed. In two studies from the United States and Italy, prenatal BC or NO_2 exposure were inversely associated with children's memory and full-scale or verbal IQ at ages 7–11, even after adjustment for sociodemographic factors (Porta et al., 2016; Suglia et al., 2008). In another U.S. cohort of >1000 children with an average age of 8 years, inverse associations between TRAP exposure and cognitive abilities were observed, but were attenuated after controlling for sociodemographic factors (Harris et al. 2015, 2016). Several other studies reported null associations of prenatal or childhood residential TRAP exposure with children's cognitive abilities or parent-reported dyscalculia or dyslexia (Cowell et al., 2015; Fuertes et al., 2016; Harris et al. 2015, 2016).

Several studies have examined modifiers of the association between TRAP exposure and children's cognitive abilities. Prenatal BC exposure was associated with lower attention scores among boys born to mothers with high prenatal stress (significant 3-way interaction) (Cowell et al., 2015). In another study, the inverse association between prenatal NO_2 exposure and early childhood mental development was stronger among children born to women who consumed fewer fruits and vegetables during pregnancy (Guxens et al., 2012). Breastfeeding duration, socioeconomic status, and child sex did not modify the associations between TRAP exposure and children's cognitive abilities in two cohorts in the United States and Europe (Guxens et al., 2012; Harris et al. 2015, 2016).

3.5.3. Polycyclic aromatic hydrocarbons (PAHs)—Fourteen studies from four cohorts in the United States, China, and Poland have examined the associations between prenatal PAH exposure and children's cognitive abilities (Edwards et al., 2010; Jedrychowski et al., 2015; Lee et al., 2017; Perera et al., 2008; Perera et al., 2012a, 2012b; Perera et al. 2015; Perera et al. 2006; Perera et al. 2007; Perera et al. 2009; Peterson et al., 2015; Tang et al., 2008; Tang et al., 2014; Vishnevetsky et al., 2015; Wang et al., 2010). One series of studies by Perera et al. followed children born between 1998 and 2006 to African-American and Dominican women in New York City. Another followed pregnant mothers and children in Krakow, Poland (Jedrychowski et al., 2015), and a third followed mothers and children in Chongqing, China (Perera et al., 2012a, 2012b). Sample sizes ranged from 40 in a pilot magnetic resonance imaging (MRI) study to 345 in the cohort studies. These studies assessed prenatal PAH exposure using personal 48-h air monitoring during the second or third trimester or cord or maternal blood PAH-DNA adducts as biomarkers. To reduce variation in PAH measures due to tobacco smoke exposure, these studies excluded active smokers, and controlled for secondhand tobacco smoke exposure. Cognitive abilities were assessed during infancy, early-childhood, and middle-childhood using valid and reliable measures of mental and psychomotor development and IQ.

Prenatal PAH exposure was associated with reduced cognitive abilities in early- and middle-childhood. Two studies reported that measures of PAH exposure were associated with

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decreased mental or psychomotor development in early-childhood. PAH exposure was inversely associated with mental development in the U.S. cohort (Perera et al., 2006); and exposure was inversely associated with both mental and psychomotor development in the China cohort (Tang et al., 2008). Three studies reported that airborne PAH concentrations or cord blood PAH-DNA adducts were associated with decreased IQ; and effect sizes were similar across the studies (Edwards et al., 2010; Perera et al., 2012a, 2012b; Perera et al., 2009; Vishnevetsky et al., 2015).

Two studies examined potential modifiers of the association between PAH concentrations and children's cognitive abilities. In the US cohort, socioeconomic hardship during pregnancy modified the association between PAH-DNA adduct concentrations and children's IQ scores, such that associations were stronger among women with more hardship compared to those without (Vishnevetsky et al., 2015). In a pooled analysis of the Polish and U.S. cohorts, the association between prenatal airborne PAH concentrations and children's cognitive abilities was not modified by genes involved in PAH metabolism (Wang et al., 2010).

3.5.4. Attention and attention deficit hyperactivity disorder (ADHD)—Air pollution has been linked to attentional problems in children in several population-based studies. There have been two birth cohort studies conducted in U.S. urban centers that have examined the relationship of air pollution and attentional problems. The exposures studied were PAH and $PM_{2.5}$. In the series of studies following African-American and Dominican women in New York City, prenatal PAH exposure was associated with increased attention problems based on maternal report on the Conners' Parent Rating Scale and/or the Child Behavior Checklist (CBCL) (at ages 4.8, 6–7, and 9 years) (Perera et al., 2014; Perera et al., 2011; Perera et al., 2012a, 2012b). Peterson et al. (2015) found that postnatal PAH (but not prenatal PAH) exposure was associated with reduced white matter in the left hemisphere, which in turn was correlated with ADHD symptoms based on maternal report on the CBCL (Peterson et al., 2015). However, prenatal PAH exposure was not correlated with ADHD symptoms in this small subsample.

In another birth cohort of 267 primarily Hispanic and African-American participants from Boston, Chiu et al. (2016) estimated $PM_{2.5}$ exposure based on maternal residence during pregnancy and used distributed lag models to identify a sensitive windows of gestation (Chiu et al., 2016). $PM_{2.5}$ levels averaged across pregnancy were not associated with performance on the Conners' Continuous Performance Test II when the children were 6.5 years old. However, when averaged across only the sensitive windows of gestation, higher $PM_{2.5}$ exposure was associated with increased omission errors (sensitive window 20–26 weeks gestation), slower hit reaction time (HRT) (32–36 weeks gestation), and higher HRT standard error (22–40 weeks gestation) among boys only. In girls, higher $PM_{2.5}$ exposure averaged across gestation was associated with lower performance on an attention/concentration memory task. In this same cohort, Cowell et al. (2015) did not observe a main effect of prenatal BC exposure on attention/concentration memory (Cowell et al., 2015). However, they found a three-way interaction between BC exposure, child sex, and prenatal stress. Among boys with high exposure to prenatal stress, prenatal BC exposure was

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associated with significantly worse performance on the attention/concentration subscale of a memory task at age 6.

Results from a meta-analysis of two German birth cohorts comprising 4745 children from two German birth cohorts did not find an association between levels of TRAP (i.e., NO_2, PM_{10}, $PM_{2.5}$) at participants' addresses at birth and hyperactivity/inattention scores based on maternal report on the Strengths and Difficulties Questionnaire at child age 10 or child self-report at age 15 years. However, there was a significant association between higher $PM_{2.5}$ levels at their current addresses and increased hyperactivity/inattention scores (Fuertes et al., 2016).

A number of large population-based studies in Asia and Europe report conflicting results on the relation between GIS-based measures of air pollutants and attentional problems in children. A stratified random sample of almost 9000 South Korean children born in 2002 found that higher cumulative PM_{10} and NO_2 exposure (extrapolated using GIS from residence from birth to diagnosis) was associated with a greater hazard of childhood ADHD diagnosis based on health insurance claims data (Min and Min 2017). A study (Yorifuji et al., 2017) using data from the Japanese nationwide population-based longitudinal survey of over 46, 000 births reported that higher suspended particulate matter (<7 μm in diameter) (SPM), NO_2, and sulfur dioxide concentrations in the municipality in the nine months before delivery were modestly associated with parents reporting that their children do not pay attention while crossing the street at age 8 (Yorifuji et al., 2017). Lastly, in a study of 3426 twin births in Stockholm from 1992 to 2000, there was no observed association of estimated PM_{10} and nitrogen oxide (NO_x) concentrations at the participants' home addresses during pregnancy and the first and ninth years of life (using dispersion modeling) with ADHD symptoms reported by parents on a phone interview when their child was age 9–12 years (Gong et al., 2014).

3.6. Autism spectrum disorder (ASD)

Several studies over the last decade strongly suggest that exposure to air pollution during the perinatal period may be a risk factor for ASD. Exposure to hazardous air pollutants around the time of pregnancy has been linked to ASD in four studies (Kalkbrenner et al., 2010; Roberts et al., 2013; von Ehrenstein et al., 2014; Windham et al., 2006), although the individual hazardous pollutants associated with increased risk (e.g., metals, methylene chloride, quinoline, styrene, vinyl chloride, diesel, 1,3-butadiene, meta/paraxylene, aromatic solvents, perchlorethylene, formaldehyde) varied across studies. Studies in the United States and Taiwan of residential proximity to roads (Volk et al., 2011) and exposure to ambient levels of NO_2 (Becerra et al., 2013; Jung et al., 2013; Volk et al., 2013), both markers of TRAP exposure, have been associated with ASD. In contrast, a European multi-site study combining population-based cohorts from Sweden, Italy, Spain, and the Netherlands reported no association between autistic traits and NO_2 exposure (Guxens et al., 2016). Nor did a Swedish study of twins observe an association between NO_x or traffic-specific PM_{10} and autistic traits (Gong et al., 2014). Two studies have reported associations between perinatal O_3 exposure and increased ASD risk (Becerra et al., 2013; Jung et al., 2013).

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A recent review and meta-analysis included human studies published between 2006 and 2015 from four different countries (Lam et al., 2016). While the studies collectively examined >100 different air pollutant chemicals, only 21 pollutants were examined in three or more studies, and only the studies involving PM_{10}, $PM_{2.5}$, O_3, and methylene chloride were considered to have a "probably low" risk of exposure assessment bias. Six studies measured PM_{10} and, of these, three measured $PM_{2.5}$ and were amenable to meta-analyses. Air pollution exposure was based on national or state air quality monitoring stations or emissions databases combined with dispersion models to estimate residential exposure. The studies were conducted in the United States and Sweden. The meta-analysis of the six studies (five case-control and one cohort) measuring PM_{10} (Becerra et al., 2013; Gong et al., 2017; Jung et al., 2013; Kalkbrenner et al., 2014; Raz et al., 2015; Volk et al., 2013) yielded an overall effect estimate of odds ratio (OR) = 1.07 (95% confidence interval [CI] 1.06–1.08) per 10-μg/m^3 increase in PM_{10}. The meta-analysis of the three studies measuring $PM_{2.5}$ (Becerra et al., 2013; Raz et al., 2015; Volk et al., 2013) yielded a pooled OR = 2.32 (95% CI 2.15–2.51) per 10-μg/m^3 increase in $PM_{2.5}$. For other air pollutants, such as metals, a general trend towards increased risk of ASD with increasing levels of exposure was observed; however, data were limited, point estimates were imprecise with 95% CIs overlapping the null value, and risk of biased exposure assessment was considered to be high for many of these air pollutants. Lam et al. concluded that there was limited evidence of an association between prenatal and early life exposure to air pollution and ASD. Since the review and meta-analysis by Lam et al. additional studies have been published. A population-based, case-control study conducted in Pennsylvania reported an association between ASD and $PM_{2.5}$ (Talbott et al., 2015a) and several air toxics, including styrene and chromium (Talbott et al., 2015b).

Another recent meta-analysis of eight studies addressing prenatal NO_2, O_3, $PM_{2.5}$, and PM_{10} exposures reported summary risk estimates of 1.34 (95% CI 0.83–2.17) for a 10 μg/m^3 increase in $PM_{2.5}$, 1.03 (95% CI 0.77–1.37) for a 10 μg/m^3 increase in PM_{10}, 1.05 (95% CI 0.99–1.11) for a 10 ppb increase in NO_2, and 1.05 (95% CI 1.01–1.10) for a 10 ppb increase in O_3 (Flores-Pajot et al., 2016). For $PM_{2.5}$, positive associations were seen for each trimester and were highest for third-trimester exposures, while associations with NO_2 did not vary by trimester.

3.7. Mood

A number of studies have examined the link between prenatal air pollution exposure with childhood mood, emotional regulation, and internalizing behaviors. These studies include cohorts from Japan, Poland, and the United States, and have largely utilized the CBCL. Pollutants that have been linked to these outcomes include PM, sulfur oxides (SO_x), and NO_x using air quality system-based estimates (Yorifuji et al. 2017, 2018) as well as PAH as indicated by personal air monitoring and maternal and/or cord blood levels of PAH-DNA adducts (Margolis et al., 2016; Perera et al., 2011; Perera et al., 2012a, 2012b) in the New York City cohort mentioned previously. In that study, higher prenatal PAH exposure was shown to be related to higher anxiety and depression symptoms at age 4.8 (Perera et al., 2011) and 6–7 years (Perera et al., 2011; Perera et al., 2012a, 2012b). Prenatal PAH exposure was associated with deficient emotional self-regulation (composite score based on

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anxiety/depression, attention, and aggression) at ages 7 and 9 years and, in turn, poorer social responsiveness at age 11 (Margolis et al., 2016). Similarly, prenatal PM and sulfur oxide exposure predicted the inability to express emotions at 2.5 years (Yorifuji et al., 2017) and increased aggression at 8 years old (Yorifuji et al., 2018). Evidence also suggests that maternal emotional distress may interact with prenatal exposure, resulting in increased risk of mood and emotional behavior outcomes in children. For example, high maternal demoralization and high prenatal PAH exposures have been found to interact to predict greater anxiety and depression symptoms at age 9 years (Perera et al., 2012a, 2012b). Together, these findings suggest that exposure to various air pollutants *in utero* may have distinct effects on mood and emotion regulation both in early and middle childhood and individuals exposed to both air pollutants and maternal distress may be at even greater risk for later mood-related problems in childhood.

3.8. Neuroimaging

Animal studies have shown the influence of prenatal exposure to air pollution on various neural outcomes, including increasing neuro-inflammation, structural changes in the neuron, neuronal apoptosis, alterations in neurotransmission, and oxidative damage (Calderon-Garciduenas et al., 2013; Cheng et al., 2016; Costa et al., 2014; Ejaz et al., 2014; Gerlofs-Nijland et al., 2010). Fewer studies to date have implemented MRI to study the impact of prenatal exposure on brain development in children. Peterson et al. (2015) examined cortical gray and white matter in a subset of 40 children (7–9 years) from the New York City cohort study examining prenatal PAH exposure and child behavior (Peterson et al., 2015). Higher prenatal PAH exposure was found to correlate with smaller white matter volumes of prefrontal, parietal, and temporal lobes of the left hemisphere. In turn, these smaller white matter volumes correlated with slower processing speed and greater externalizing problems, including ADHD symptoms. Finally, the association of prenatal exposure to air pollution and processing speed was mediated by white matter disturbance. More recently, in a cohort of >700 children, Guxens et al. have reported that exposure to fine particles during fetal life was associated with a thinner cortex in several regions of the brain when children were imaged at 6–10 years of age; these brain abnormalities were linked to difficulty with lower inhibitory control (Guxens et al., 2018).

4. Discussion

4.1. Advances that can Be made in ECHO

As summarized in the previous sections, the literature on prenatal air pollution exposure and neurodevelopment has evolved rapidly, but not without some limitations in sample size, timing and methods of evaluation of the outcomes, exposure assessment and multi-pollutant evaluation, evaluation of critical windows of exposure, and control for confounding factors. The collaborative framework created by the ECHO initiative provides a unique opportunity to create a “cohort of cohorts” that can be used to address many of these limitations. First, nearly 90% (n = 74) of the 84 ECHO cohorts participating in the UG3 phase have collected a maternal prenatal address or child infancy address (from birth to 12 months of age). Notably, only one cohort collected prenatal but not infancy addresses. The availability of

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these data allows for exploration of a unified, retrospective air pollution exposure assignment across ECHO.

Additionally, a broad distribution of recruitment years, complemented by large spatial variation will complement existing research on neurodevelopment that has largely focused on smaller populations in specific geographic regions. As seen in Fig. 1, ECHO cohort recruitment site locations span the continental United States, Hawaii, and Puerto Rico, and capture both urban and rural areas of the United States not previously examined in this context (Fig. 1). Notably, subjects in these cohorts were born over a period of nearly 40 years, with the majority collecting data since the mid-2000s (Fig. 2). This timespan presents the opportunity to evaluate trends in exposure over time and to evaluate dose-response effects of air pollution as regulated pollutant levels have significantly changed over time. As such, the ECHO cohorts will likely capture a range of exposure, including levels higher than current concentrations for some air pollutants (like PM_{10}). However, other pollutants, like ultra-fine particles (UFPs) are unregulated and may have increased over the time period of study. As reviewed above, publicly available regulatory data for criteria or hazardous air pollutant exposures provide a resource dating back to the mid-1990s. Although monitoring of criteria pollutants has become more routine since 2000, reliance on EPA network monitors provides limited spatial and temporal resolution. Thus, application of satellite-informed LUR or advanced spatio-temporal models may be preferable should existing and developing methods be expanded to relevant years of interest. We believe that such applications can leverage the temporal and spatial variability of ECHO to address important etiologic questions regarding air pollution and neurodevelopment.

In ECHO, efforts have been made to compile and harmonize the time periods and instruments used for neurodevelopmental assessment. Table 2 summarizes existing outcome data collected by the 74 ECHO cohorts that have a recorded prenatal or infancy street address. In addition to these existing data, the ECHO program has identified recommended instruments for assessment of neurodevelopmental constructs for subject re-contact in all ECHO cohorts. Of note, both categorical reports of diagnoses as well as quantitative measures have been collected by many cohorts, allowing for investigation of both types of outcomes with sufficient sample size for well-powered study of many phenotypes. It should be recognized that harmonization of neurodevelopmental measures, disorders, or traits is often complicated by the need for developmentally appropriate phenotype assessment. For example, symptoms of ADHD do not often manifest until school age, making assessment of ADHD in the very young difficult; and some symptoms of ADHD remit in adolescence and adulthood. As a result, reporting a lifetime diagnosis has appeal for harmonization but may limit subsequent research on age of diagnosis or onset of a trait. Here, the prospective data to be collected in a uniform manner across ECHO, when evaluated in the context of the valuable measures already collected on these cohorts, can enable researchers to evaluate such hypotheses with confidence.

Based on extant ECHO data among cohorts that collected either a maternal prenatal or child infancy address, 30 cohorts have information regarding a diagnosis of ASD over a child's lifetime, providing a broad indicator of disease that is easily harmonized (Table 2). However, considerable heterogeneity in the method of assessment of ASD was present across the

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ECHO cohorts. A total of 25 cohorts reported using the Social Responsiveness Scale (SRS), a quantitative measure of autism-related traits, in the child's lifetime. The SRS was completed over a range of developmental windows, allowing for comparison of severity of trait development and onset. These numbers are likely to increase as additional cohorts evaluate neurodevelopmental phenotypes. It should also be noted that the same careful consideration has been given to harmonization of relevant confounding factors, which may improve upon previous studies.

As noted earlier, while personal or in-home monitoring of air pollution exposure assessment may be ideal for capturing the full range of individual variation and sources of exposure, it is logistically infeasible for large studies or those where subject enrollment has occurred and data collection has been underway for many years, as for most contributing sites. For new recruitment efforts, such monitoring is often cost prohibitive. As new low-cost sensors are developed and validated, they may provide new avenues of exposure assessment for large-scale studies like ECHO. Many biomarkers of exposure, dose, and preclinical response have not yet matured to the point that they can be easily implemented in a project of this scale. We recognize that no single method of air pollution exposure assessment may be applicable for all cohorts and that use and integration of multiple exposure assessment methods may be necessary. Despite these difficulties, air pollution exposure provides a unique opportunity for uniform assignment of exposure regardless of the time period of enrollment. If residential history (address) data are available, application of GIS-based exposure methods can enable retrospective assignment for etiologically relevant periods. As new and additional models creating national surfaces of exposure for specific pollutants like $PM_{2.5}$ and NO_2 are developed, they can be applied systematically in ECHO to capture large spatial variation in exposure—information that is commonly lacking in studies to date.

The intersection of address data during developmentally relevant time periods and neurodevelopmental measures provides a unique opportunity to advance the state of knowledge on this topic. Identifying critical windows of susceptibility to environmental exposures is a strategic goal for the National Institute of Environmental Health Sciences (National Institutes of Health, 2012), highlighting the importance of air pollution research to elucidate biological mechanisms of neurotoxicity, improve effect estimation by reducing exposure misclassification, and provide data to inform the design of targeted exposure interventions. The increased power and exposure variability available through the ECHO consortium offers unique opportunities for methodological development and innovative etiologic research characterizing the timing of air pollution impacts on child neurodevelopment. When residential histories are available, the sample size available in ECHO should provide sufficient power for application of newer statistical methods to evaluate multiple time points in a single analytic model, exploiting the correlated nature of repeated air pollution exposures.

Given heterogeneity in phenotype assessment and inherent heterogeneity across the ECHO cohorts, based on the make-up of sociodemographic and recruitment factors, meta-analysis across the ECHO cohorts may be more appropriate than pooling in some instances. However, several contributing ECHO cohorts have successfully pooled data to examine the relationship between prenatal pesticide exposure and neurodevelopmental outcomes,

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establishing a precedent for feasibility of such work and collaboration (Engel et al., 2016). As in any epidemiologic research study, careful consideration of confounding is necessary. Given the heterogeneity in information collected, advanced statistical tools like propensity score matching may be appropriate and protect against unmeasured confounding. The potential sample size in ECHO may make it feasible to examine effect modification by some factors with poor power in previous studies, such as gender differences in exposure effects on ASD. Additionally, should GIS assignment be successful and implemented for many air pollutant methods (e.g., HAPs, criteria pollutant monitoring, spatio-temporal assignments), investigators will be able to assess the role of exposure mixtures and timing on neurodevelopmental outcomes. Such analyses might utilize adaptations of time series methods to identify widows of exposure or expand on clustering or Bayesian tools for assessment of mixture effects, both advancing statistical methodology.

In this review, we note that not all studies have consistent findings. Published reports vary in the method of air pollution assignment, racial/ethnic make-up of the population, tools and assessments used to measure a given neurodevelopmental construct, and measures of confounding included in the analysis. A key limitation across many of the current studies is the accuracy of the assessment of exposure to air pollution during developmentally relevant time periods. Many studies use surrogate measures of exposure, such as distance to freeway or area level measures from monitoring or modeling data to infer individual-level exposures. No studies examine maternal workplace exposure during pregnancy or the effect of commuting, and all rely primarily on exposure at the home. It is common for studies to rely on birth address as a proxy for prenatal residential location. However, this limits the ability of research to accurately identify susceptible prenatal windows of exposure. Despite these limitations, a significant body of work has been developed in a fairly short timeframe demonstrating the rapid advancement of the field and a need for additional research.

In ECHO we have the opportunity to collect, when not already in existence, residential histories for mothers and children allowing for application of GIS-based exposure methods. We can then apply cutting-edge air pollutant exposure assessment methods to exploit temporal and spatial variability in our large sample. Additionally, this method of exposure assignment could be complemented by employment of biomarker methods when appropriate samples are available and personal monitoring as sensors evolve in subgroups of the ECHO cohort to further enhance exposure accuracy. We may also have the opportunity, given uniform air pollution exposure assignment, to develop needed biologic signatures of exposure using epigenetic or other methods that have shown promise for other environmental contaminants (Joubert et al., 2016). Such work would allow for application of statistical methods developed for the assessment of health effects of mixtures of environmental exposures in a well-powered study, an area currently limited for environmental health researchers. Finally, the availability of multiple studies from different geographic areas and times will allow us to add in a meaningful way to our knowledge of the association between air pollution and neurodevelopment, while also exploring potential effect modifiers of this association.

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5. Conclusions

Given the widespread effects of prenatal air pollution exposure on various neurocognitive constructs, ranging from intelligence to attention, autism, and mood, future studies are warranted to thoroughly examine the influence of prenatal exposure on the developing brain during vulnerable windows of development. In ECHO we have the opportunity to carry out a new and meaningful evaluation of prenatal air pollution exposures with the goal of improving children's health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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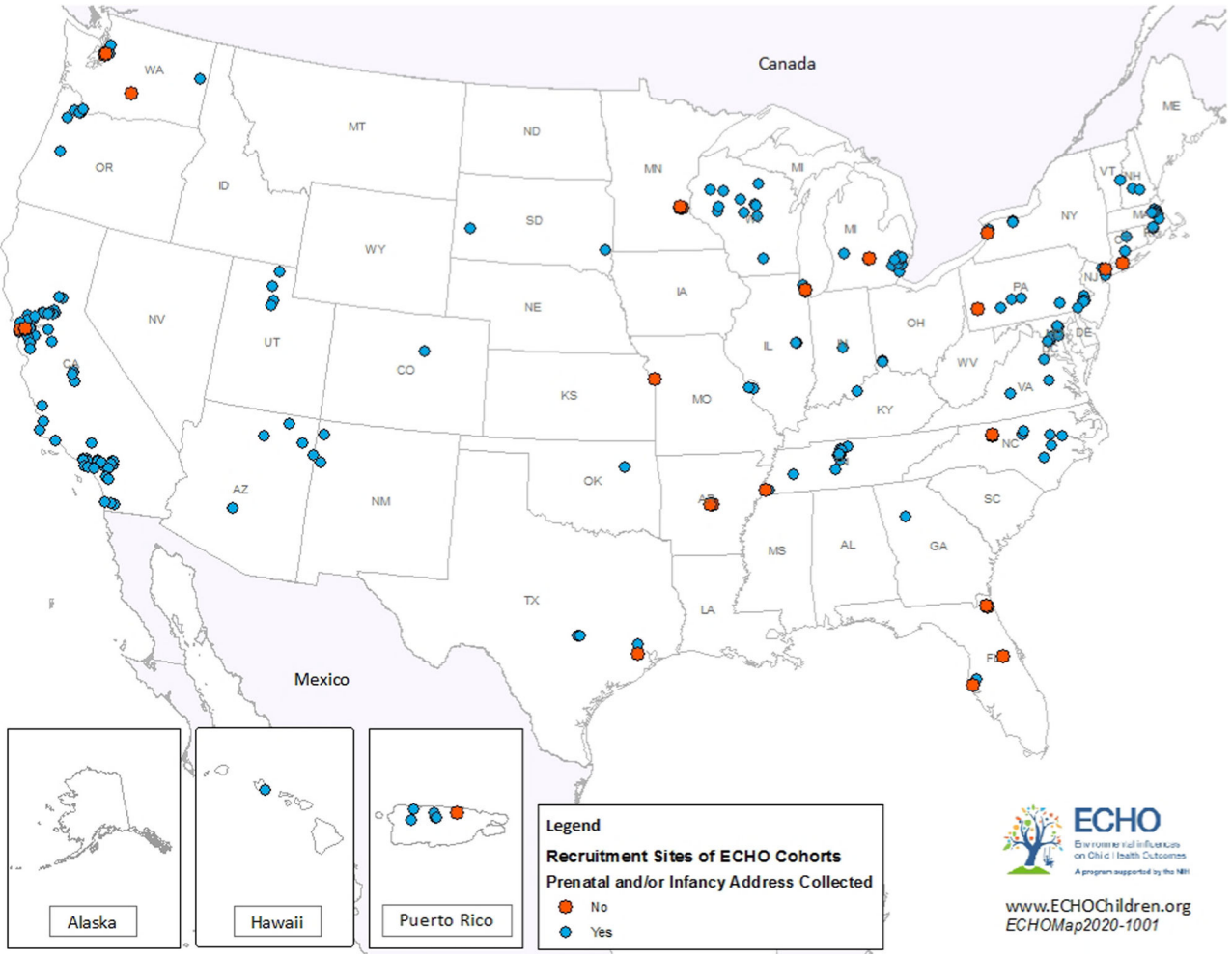

Fig. 1.
Recruitment locations for the ECHO Cohorts.

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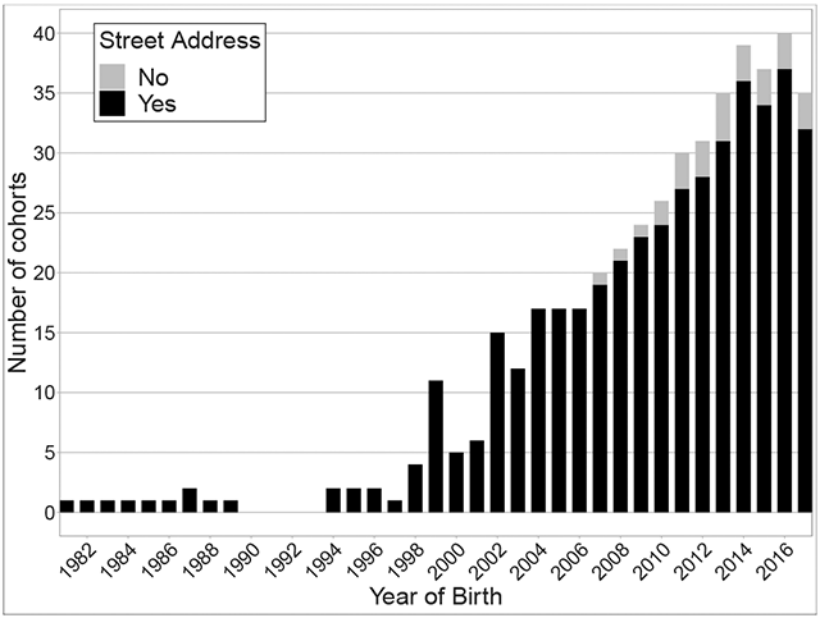

Fig. 2.
Birth year of ECHO cohort participants.

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Table 1

Summary of literature on prenatal air pollution exposure and neurodevelopment.

Author	Publication Year	Main Findings	Location	N Total or N Cases/N Controls	Neuro Outcome	Air Pollution Exposure(s)	Strengths	Limitations
Perera et al.	2006	Prenatal exposure to PAH was not associated with psychomotor development index or behavioral problems. However, high prenatal exposure to PAH (upper quartile) was associated with lower mental development index at age 3 [β = −5.69; 95% confidence interval (CI), −9.05 to −2.33; p < 0.01]. The odds of cognitive developmental delay were also significantly greater for children with high prenatal exposure (odds ratio = 2.89; 95% CI, 1.33 to 6.25; p = 0.01). General estimated equation analysis showed a significant age × PAH effect on mental development (p = 0.01), confirming the age-specific regression findings. Further adjustment for lead did not alter the relationships. There were no differences in effect sizes by ethnicity.	New York City, NY	183	Multiple Domains	PAH	Prospective design; adjusted for several important confounders; individual prenatal exposure data from personal monitoring, biomarker analyses, and extensive medical record and questionnaire data	Small sample size, findings may not be generalizable to other ethnic and socioeconomic backgrounds, uncontrolled confounding by socioeconomic status, lacked air monitoring data for all three trimesters, lacked postnatal personal air monitoring data for PAH and environmental lead exposure
Windham et al.	2006	The adjusted odds ratios (AORs) for autism were elevated by 50% in the top quartile of chlorinated solvents and heavy metals [95% confidence intervals (CIs), 1.1–2.1], but not for aromatic solvents. Adjusting for these three groups simultaneously led to decreased risks for the solvents and increased risk for metals (AORs for metals: fourth quartile = 1.7; 95% CI, 1.0–3.0; third quartile = 1.95; 95% CI, 1.2–3.1). The individual compounds that contributed most to these associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride. The results suggest a potential association between autism and estimated metal concentrations, and possibly solvents, in ambient air around the birth residence, requiring	San Francisco, CA	Cases = 284 and Controls = 657	Autism Spectrum Disorder	Hazardous Air Pollutants	Availability of valid sources for identifying a population-based sample of cases and confirmation of diagnosis by review of records, lack of recall bias on retrospective exposure data due to linkage to existing environmental exposure databases, and robust results across various reanalyzes of the data that included a less restrictive case definition or reassignment of census tract and exposure level	Covariate information available only from the birth certificate data causing uncontrolled confounding (e.g. no data on maternal conditions or habits), cases likely represent more severely affected children because of the nature of our case ascertainment sources, and underrepresentation of cases of lower SES who are more likely to be exposed

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		confirmation and more refined exposure assessment in future studies.						
Perera et al.	2007	No main effects of PAH-DNA adducts on MDI or PDI at age 3 years. ETS modified adduct-MDI association ($p < 0.05$). Each doubling in adducts was associated with 8 point lower MDI scores among ETS exposed children (95% CI: 17, 1).	New York, NY	98	Cognition	PAH	Biological-intermediate biomarker of PAH exposure, adjustment for several covariates, prospective follow-up. Participants were non-smokers.	Small sample size, unclear relevance of adducts to traffic-related pollution, residual confounding.
Perera et al.	2007	In multivariate analyses, there was a significant interaction between cord blood adducts and *in utero* exposure to ETS on mental development index score at 3 years of age ($p = 0.02$, $n = 98$) whereas neither adducts nor ETS alone was a significant predictor of (BSID-II) cognitive development. Removing two women who had preterm deliveries (≤258 days) did not affect the results (for continuous adducts × ETS, $\beta = -12.71$, $p = 0.02$). The interaction between adducts and prenatal ETS exposure on MDI remained significant after including postnatal exposure to ETS in the multiple linear regression model ($\beta = 11.96$, $p = 0.027$).	New York City, NY	98	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data) to measure individual exposure, explored mediation (birth weight), prepartum enrollment of exposed and unexposed women from a common clinical population, all women delivered at one of three lower Manhattan hospitals during the same time period, enrollment occurred before delivery and before the outcome of the pregnancy was known, subjects were geographically well dispersed during pregnancy with respect to the World Trade Center (WTC) site, and recruitment procedures improved generalizability of findings	Small sample size, effects of pollutant exposure during the third trimester could not be examined because such women would already have delivered before the beginning of this World Trade Center Disaster study, measured adduct values may underestimate the effect of the event on the biomarker and reduce our ability to link exposure to developmental outcomes, sample size limited the ability to examine whether outcomes differed depending on the week (or weeks) of exposure during pregnancy, other unmeasured pollutants released by the WTC fires could have influenced MDI, and they did not consider maternal distress during pregnancy which has been associated with decreased infant mental development
Perera et al.	2008	Extension of Tang et al. (2008). PAH-DNA adducts were associated with reductions in motor DQs among 2002 cohort (before coal power plant shutdown), but not in 2005 cohort after coal plant shutdown. Betas still inverse in later cohort. No PAHxcohort EMM.	Tongliang, China	227	Cognition	PAH	Prospective follow-up, Biological-intermediate biomarker of PAH exposure, use of two cohorts before and after reduction in exposure, adjustment for Pb. Participants were non-smokers.	Small sample size, exposure misclassification (non-PAH sources), residual confounding.

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Perera et al.	2008	Significant associations previously seen in the cohort enrolled before coal plant shutdown between elevated adducts and decreased motor area developmental quotient (DQ) (p = 0.043) and average DQ (p = 0.047) were not observed in the cohort enrolled after coal plant shutdown (p = 0.546 and p = 0.146). However, the direction of the relationship did not change. The findings indicate that neurobehavioral development in Tongliang children benefited by elimination of PAH exposure from the coal-burning plant, consistent with the significant reduction in PAH–DNA adducts in cord blood of children in the second cohort.	Tongliang, China	2002 cohort: n = 133 and 2005 cohort: n = 122	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data) to measure individual exposure, results are internally consistent and generalizable to other non-smoking Chinese women	Lacked data on postnatal levels of PAH-DNA or metals, small sample size of each cohort (limited ability to test for interactions)
Suglia et al.	2008	IQR increase in log BC was associated with decreases on the vocabulary scale (−2; 95% CI: 5.3, 1.3), matrices scale (−4.2; 95% CI: 7.7, −0.7), the composite subscale (−3.4; 95% CI: 6.6, −0.3) of the K-BIT, the visual learning scale (−5.2; −8.6, −1.7), and general index scale (−3.7; −7.2, −0.2) of the WRAML.	Boston, MA	202	Cognition	Traffic	Prospective design, adjustment for several confounders, validated LUR model.	Exposure misclassification (LUR model based on residential address only), residual confounding (income, noise), modest sample size.
Tang et al.	2008	Each log unit increase in PAH-DNA adducts was associated with reduced DQs in all domains, strongest for language > motor > adpative > social. Significant for full scale (−15; 95% CI: 29, −0.4). Increase in risk of motor or general DQ delay (<85th).	Tongliang, China	110	Cognition	PAH	Prospective follow-up, Biological-intermediate biomarker of PAH exposure, high exposure population. Participants were non-smokers.	Small sample size, exposure misclassification (non-PAH sources), residual confounding.
Tang et al.	2008	Decrements in one or more DQs were significantly associated with cord blood levels of PAH–DNA adducts and lead, but not mercury. Increased adduct levels were associated with decreased motor area DQ (p = 0.043), language area DQ (p = 0.059), and average DQ (p = 0.047) after adjusting for cord lead level, environmental tobacco smoke, sex, gestational age, and maternal education. In the same model, high cord blood lead level was significantly associated with	Tongliang, China	110	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data) to measure individual exposure	Small sample size, lacked data on postnatal blood PAH-DNA, lead, and mercury levels, and could not separate exposures by trimester

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		decreased social area DQ (p = 0.009) and average DQ (p = 0.038). The findings indicate that exposure to pollutants from the nearby coal fired power plant adversely affected the development of children living in Tongliang.						
Perera et al.	2009	After adjustment for maternal intelligence, quality of the home caretaking environment, environmental tobacco smoke exposure, and other potentially confounding factors, high PAH levels (above the median of 2.26 ng/m3) were inversely associated with full-scale IQ (P = 0.007) and verbal IQ (P = 0.003) scores. Children in the high-exposure group had full-scale and verbal IQ scores that were 4.31 and 4.67 points lower, respectively, than those of less-exposed children (≤2.26 ng/m3). The associations between logarithmically transformed, continuous, PAH levels and these IQ measures also were significant (full-scale IQ: β = −3.00; P = 0.009; verbal IQ: β = −3.53; P = 0.002). These results provide evidence that environmental PAH at levels encountered in New York City air can affect children's IQ adversely.	New York City, NY	249	Cognition	PAH	Prospective design, adjusted for several important confounders, explored interaction effects (PAH x ethnicity), individual prenatal exposure data from personal monitoring, biomarker data on lead and cotinine levels, extensive medical record and questionnaire data, and this is the first study to examine the effects prenatal PAH exposure on child IQ, and assessed intelligence at an age when IQ can be measured reliably	Lacked postnatal monitoring data (controlled indirectly for postnatal PAH exposure), findings may not be generalizable to women from other ethnic, cultural, or socioeconomic backgrounds
Edwards et al.	2010	Each log unit increase in PAH was associated with a −0.6 (95% CI: 1.0, −0.1) decrease in intelligence (RCPM) scores. Lower exposure range comparable to NYC cohort had larger decrease inintelligence per unit exposure (−1.2; 95% CI: 2.1, −0.4). Higher (above the median of 17.96 ng/m3) prenatal exposure to airborne PAH (range, 1.8–272.2 ng/m3) was associated with decreased RCPM scores at 5 years of age, after adjusting for potential confounding variables (n = 214). Further adjusting for maternal intelligence, lead, or dietary PAH did not alter this association. The reduction in	Poland	214	Cognition	PAH	Prospective cohort, personal monitoring of PAH, adjustment for several confounders, later childhood follow-up. Participants were non-smokers.	Substantial amount of missing maternal IQ data, loss to follow-up or missing outcome data, no adjustment for caregiving, and potential misclassification of monitored PAH (e.g., non-traffic sources).

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		RCPM score associated with high airborne PAH exposure corresponded to an estimated average decrease of 3.8 IQ points.						
Kalkbrenner et al.	2010	After adjustment for a priori demographic confounders, all estimates were attenuated, so that most adjusted estimates were near-null. For example, the OR for beryllium compounds and autism spectrum disorders was 1.5 (95% CI = 1.1–2.0) before adjustment and 1.0 (0.6–1.4) after adjustment. For xylenes, the unadjusted OR was 1.5 (1.2–2.0) and the adjusted was 1.0 (0.6–1.6). After adjusting for other air pollutants in semi-Bayes models, ORs were less precise and many remained near-null, but some were shifted upwards or downwards. Associations between many pollutants and autism spectrum disorders differed by both state and level of urbanicity when tested in single-pollutant adjusted models. This modification was less pronounced after adjusting for other pollutants in semi-Bayes models.	North Carolina and West Virginia	Cases = 383 and Controls = 2829	Autism Spectrum Disorder	Hazardous Air Pollutants	Examined many hazardous air pollutants and tested for interaction (by state and level of urbanity)	Age 8 address or access to developmental testing services could not be confirmed for children included from the birth certificate rosters, adjusted for a small number of relevant confounders, small sample size that limited the power to detect modification, lacked information on personal exposure to pollutants during early pregnancy (design assigned the average concentration for the mother's residential tract), exposure misclassification from temporal averaging, adjusting for multiple pollutants at the ecological level and assigning exposure using NATA
Wang et al.	2010	No consistent modidfying effect of individual SNPs across age or race. Some haplotypes had consistent modifying effects across ages or race, but not both.	New York, NY and Poland	Unclear	Cognition	PAH	Personal monitoring, prospective design, repeated neuro measures, examined modification by genes, multiple ethnicities.	Did not use repeated measure analyses, modest sample size for genetic EMM, misclassification of PAH exposure, residual confounding (pop start).
Wang et al.	2010	MDI at young ages can be modulated by common genetic variants in the key genes CYP1A1, CYP1A2, CYP1B1, GSTT2, and GSTM1. Interaction effects between single genetic markers (ht-SNPs) and PAH were observed in African American, Dominican, and Caucasian mothers and their newborns before Bonferroni correction for multiple comparisons, with more gene-PAH interaction effects observed in African Americans and Dominicans than in Caucasians. However, little consistency was observed across	New York City, NY & Krakow, Poland	African Americans n = 178, Dominicans n = 282, and Polish Caucasians n = 294	Cognition	PAH	Prospective design, adjusted for several important confounders, ability to explore gene-PAH interactions and haplotype-PAH interactions using ht-genetic-markers from genes known to be involved in metabolism and detoxification of PAH and are relevant to multiple effects of the same pollutants, MDI and environmental monitoring	Modest sample size that limited the power in detecting gene-environment interactions, the relationships observed for low-income minority women might be different for women of other ethnic and socioeconomic backgrounds, and uncontrolled socioeconomic factors

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		ethnic groups and across different MDI ages. No single marker-PAH interaction remained significant after Bonferroni correction.						
Perera et al.	2011	In the full Poisson model after adjusting for possible confounders, higher (vs. lower) cord PAH-DNA adducts were associated with the syndrome score of Anxious/ Depressed (β = 0.34, 95% CI, 0.04–0.64, p = 0.026) and Attention Problems (β = 0.38, 95% CI, 0.06–0.69, p = 0.018) at (mean) 4.8 years and with Attention Problems at (mean) 7 years (β = 0.22, 95% CI, 0.06 to 0.38, p = 0.009). After controlling for postnatal exposure to ETS at 24 months, the association between DNA adducts and the syndrome score of Attention Problems became more significant at 4.8 years with a higher beta (β = 0.45, p = 0.012, n = 85) and at age 7 years (β = 0.25, p = 0.006, n = 182) and remained significant for the syndrome score of Anxious/Depressed (β = 0.37, p = 0.031, n = 85) at 4.8 years of age. After controlling for PAH metabolites in child urine collected at 5 years of age, higher cord adducts were significantly associated with the syndrome score of Attention Problems at 7 years (β = 0.28, p = 0.028, n = 100). Using logistic regression on T-scores dichotomized at 65 for the syndrome scales, the results were significant for the syndromes of Attention Problems at 7 years [odds ratio (OR) = 3.30, 95% CI, 1.21–12.54] and Anxious/Depressed at 4.8 years (OR = 8.14, 95% CI, 1.21–54.94). Using DSM-oriented Anxiety Problems, the results show that higher cord adducts were associated with increased likelihood of borderline or clinical classification on the DSM-oriented Anxiety Problem Scale (OR = 8.30,	New York City, NY	215	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, had individual prenatal exposure data from personal monitoring, biomarker data, and extensive medical record and questionnaire data, and tested for interactions	Small sample size, attrition attributable to the exclusion of subjects who are missing complete covariate data or testing results, potential selection bias because there is a difference in the sex and ethnicity distribution of the included/excluded subjects, and reduced number of children with lead measurements that limited the interpretation of analyses controlling for lead exposure

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		95% CI, 1.13–60.71) at 4.8 years of age.						
Volk et al.	2011	Adjusting for sociodemographic factors and maternal smoking, maternal residence at the time of delivery was more likely be near a freeway (≤309 m) forautism cases than for controls [odds ratio (OR) = 1.86; 95% confidence interval (CI), 1.04–3.45]. Autism was also associated with residential proximity to a freeway during the third trimester (OR = 2.22; CI, 1.16–4.42). After adjustment for socioeconomic and sociodemographic characteristics, these associations were unchanged. Living near other major roads at birth was not associated with autism.	Sacramento, Los Angeles, San Francisco East, and North Bay, CA	Cases = 304 and Controls = 259	Autism Spectrum Disorder	Freeway (state or interstate highway)/major road	Assessed Autism through well-validated instruments and examined exposure prenatally and at birth	Limited by sample size, potential exposure misclassification (from participant residential addresses, birth certificate addresses, etc.), traffic metrics did not account for traffic volume or prevailing wind speed and direction, not able to examine specific pollutant concentrations
Guxens et al.	2012	Exposure to NO2 and benzene showed an inverse association with mental development, although not statistically significant, after adjusting for potential confounders [β (95% confidence interval) = −0.95 (−3.90, 1.89) and −1.57 (−3.69, 0.56), respectively, for a doubling of each compound]. Stronger inverse associations were estimated for both pollutants among infants whose mothers reported low intakes of fruits/vegetables during pregnancy [–4.13 (−7.06, −1.21) and −4.37 (−6.89, −1.86) for NO2 and benzene, respectively], with little evidence of associations in the high-intake group (interaction p-values of 0.073 and 0.047). Inverse associations were also stronger in non-breast-fed infants and infants with low maternal vitamin D, but effect estimates and interactions were not significant.	Spain	1889	Cognition	NO2 and benzene	Residential changes during pregnancy were accounted for in the exposure assessments, prospective design and expensive nutritional data, multiple imputation for missing values, and adjusted for several important confounders.	NO2 and benzene were measured instead of ultrafine PM, noise annoyance during pregnancy was collected by a self-report scale rather than by a direct measure of noise levels, residual confounding (parental intelligence), potential selection bias due to loss to follow-up, and used step-wise selection for confounder adjustment.
Perera et al.	2012	Both PAH adducts and second hand smoke (SHS) were associated with decrements in IQ (FSIQ beta for PAH: 2.4; 95% CI: 8.0, 3.1). Among those with no SHS, PAH beta was 0.7; and among 1-h SHS,	China	100	Cognition	PAH	Prospective follow-up, Biological-intermediate biomarker of PAH exposure, high exposure population, mid-childhood follow-up with	Exposure misclassification (non-traffic PAH sources), residual confounding, modest sample size, LTF and missing data.

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		PAH beta was −9.4. Results on PIQ and VIQ were similar, slightly weaker for PIQ.					validated IQ measure. Participants were non-smokers.	
Perera et al.	2012	After adjusting for potential confounders, neither DNA adducts nor exposure to environmental tobacco smoke have significant main effects on children's IQ. However, significant interactions between adducts and environmental tobacco smoke were observed on the full scale ($p = 0.025$) and verbal scale ($p = 0.029$) IQ scores, indicating that adverse effects at age 5 of prenatal PAH exposure became greater as exposure to environmental tobacco smoke increased. The interaction on performance IQ score was not significant ($p = 0.135$).	Tongliang, China	100	Cognition	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data) to measure individual exposure, and explored interaction effects (with prenatal ETS exposure and lead)	Lacking data on postnatal blood levels of PAH-DNA or ETS exposure, cotinine levels, other neurotoxicants in ETS (arsenic, carbon, monoxide), postnatal data on lead exposure, maternal intelligence, and quality of the home caretaking environment
Perera et al.	2012	In multivariate analyses, high prenatal PAH exposure, whether characterized by personal air monitoring (greater than the median of 2.27 ng/m3) or maternal and cord adducts (detectable or higher), was positively associated with symptoms of Anxious/Depressed and Attention Problems ($p \leq 0.05$).	New York City, NY	253	Multiple Domains	PAH	Prospective design, adjusted for several important confounders related to child neurobehavioral development, had individual prenatal exposure data from personal monitoring, biomarker data, and extensive medical record and questionnaire data	Small sample size, residual confounding from unmeasured factors such as other pollutants and stress, possible measurement error from share variance between PAH exposure and ETS, use of self-reported ETS exposure as a measure of smoking, and findings may not be generalizable to more at-risk populations (excluded active smokers, illicit drug users, and women with a pre-existing disease)
Becerra et al.	2013	Per interquartile range (IQR) increase, there was an estimated 12–15% relative increase in odds of autism for ozone [odds ratio (OR) = 1.12, 95% CI: 1.06, 1.19; per 11.54-ppb increase] and particulate matter ≤ 2.5 μm (OR = 1.15; 95% CI: 1.06, 1.24; per 4.68-μg/m3 increase) when mutually adjusting for both pollutants. Furthermore, we estimated 3–9% relative increases in odds per IQR increase for LUR-based nitric oxide and nitrogen dioxide exposure	Los Angeles, CA	Cases = 7594 and Controls = 75,635	Autism Spectrum Disorder	CO, NO2, NO, O3, PM10, and PM2.5	Large sample size, modeled novel LUR exposure measures for traffic-related pollution in addition to routine, government monitoring station data, selection bias due to participation is unlikely to have occurred	Potential unmeasured confounders (e.g. maternal physical and mental health history, maternal active or passive smoking, other SES-related factors), non-differential misclassification of exposure due to residential mobility during pregnancy, SES and distance from monitoring station, which could have biased estimates towards null, and

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		estimates. Land use regression (LUR)-based associations were strongest for children of mothers with less than a high school education. Measured and estimated exposures from ambient pollutant monitors and LUR model suggest associations between autism and prenatal air pollution exposure, mostly related to traffic sources.						gestational age may also be a mediator between air pollution and autism
Calderon-Garcideunas et al.	2013	Children highly exposed to air pollution exhibited significant increases in cerebrospinal-fluid (CSF) macrophage inhibitory factor (MIF) ($p = 0.002$), IL6 ($p = 0.006$), IL1Ra ($p = 0.014$), IL-2 ($p = 0.04$), and PrPC ($p = 0.039$) vs. controls. MIF serum concentrations were higher in exposed children ($p = 0.009$). The results suggest CSF as a MIF, IL6, IL1Ra, IL-2, and cellular prion protein (PrPC) compartment that can possibly differentiate air pollution exposures in children. MIF, a key neuro-immune mediator, is a potential biomarker bridge to identify children with CNS inflammation. Fine tuning of immune-to-brain communication is crucial to neural networks appropriate functioning, thus the short and long term effects of systemic inflammation and dysregulated neural immune responses are of deep concern for millions of exposed children.	Mexico City, Mexico	Total: n = 139, High pollution: n = 28 Low pollution: n = 111	Multiple Domains	O2, PM, SO2, NOx, CO, and Pb	Selection of multiplex platforms and knowledge of their ability to accurately and sensitively detect cytokines in CSF and blood (serum/plasma), use of standardized operating procedures for the recollection of CSF samples	CSF normal samples were taken from a population of children with a hematological workup for a neoplastic process while serum samples were from clinically healthy children, limited by small sample size and low statistical power
Jung et al.	2013	The risk of newly diagnostic ASD increased according to increasing O3, CO, NO2, and SO2 levels. The effect estimate indicating an approximately 59% risk increase per 10 ppb increase in O3 level (95% CI 1.42–1.79), 37% risk increase per 10 ppb in CO (95% CI 1.31–1.44), 343% risk increase per 10 ppb increase in NO2 level (95% CI 3.31–5.85), and 18% risk increase per 1 ppb in SO2 level (95% CI 1.09–1.27) was stable with different combinations of air pollutants in the multi-pollutant	Taiwan	49,073 (ASD = 342, non-ASD = 48,731)	Autism Spectrum Disorder	CO, NO2, SO2, PM10, and O3	Very representative national sample (covered 99% of entire population in Taiwan), large sample size and high statistical power, the longer follow-up period provided an opportunity to explore the risk of newly diagnostic ASD associated with postnatal exposure to long-term cumulative exposure, and this is the first study of the kind to be conducted	Unable to adjust for several important confounders (e.g. occupational exposure, genetic factors, parental education, parental age, and birthweight), possible non-differential misclassification of ASD, and potential misclassification of prenatal exposure

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		models. Our results provide evident that children exposure to O3, CO, NO2, and SO2 in the preceding 1 year to 4 years may have increased risk of ASD diagnosis.					in an Asian population (belonging to the Han ethnicity)	
Perera et al.	2013	Significant interactions between maternal demoralization and PAH exposure (high versus low) were identified for symptoms of anxious/depressed, withdrawn/depressed, social problems, aggressive behavior, internalizing problems, and externalizing problems. The effects of maternal demoralization on syndromes of anxious/depressed, withdrawn/depressed, rule-breaking, aggressive behavior, and the composite internalizing and externalizing scores were seen only in conjunction with high PAH exposure. Fewer significant effects with weaker effect sizes were observed in the low-PAH-exposure group.	Krakow, Poland	248	Multiple Domains	PAH	Prospective design, adjusted for several important confounders related to child neurobehavioral development, had individual prenatal exposure data from personal monitoring, biomarker data, and extensive medical record and questionnaire data	Small sample size, residual confounding from unmeasured factors such as other pollutants and stress, possible measurement error from share variance between PAH exposure and ETS, The Home Observation for Measurement of the Environment Inventory, a measure of the child's proximal caretaking environment, is not widely used in central Europe and was not administered in the Polish cohort.
Roberts et al.	2013	Perinatal exposures to the highest versus lowest quintile of diesel, lead, manganese, mercury, methylene chloride, and an overall measure of metals were significantly associated with ASD, with odds ratios ranging from 1.5 (for overall metals measure) to 2.0 (for diesel and mercury). In addition, linear trends were positive and statistically significant for these exposures ($p < 0.05$ for each). For most pollutants, associations were stronger for boys (279 cases) than for girls (46 cases) and significantly different according to sex. Perinatal exposure to air pollutants may increase risk for ASD.	US	Cases = 325 and Controls = 22,101	Autism Spectrum Disorder	Hazardous Air Pollutants	Very representative national sample of participants, mothers in this study (nurses) would have more homogenous health-seeking behaviours which may make ascertainment of cases more homogenous too, and adjusted for several important family and community socioeconomic indicators	US EPA air pollution prediction models provide only approximate measures of pollutant exposures (especially if primary source is indoor versus outdoor, residential location may be incorrect for nurses who moved residences around the time of pregnancy (may lead to exposure misclassification particularly for specific gestational ages), and did not measure income before birth that could be associated with unmeasured ASD risk factors or with ASD ascertainment
Volk et al.	2013	Autism cases were more likely to live at residences in the highest quartile traffic related pollution exposure during pregnancy (OR = 1.98, 95%CI 1.20–3.31) and the first year of life (OR = 3.10, 1.76–5.57) compared to controls.	Sacramento, Los Angeles, San Francisco East, and North Bay, CA	Cases = 279 and Controls = 245	Autism Spectrum Disorder	Traffic-related air pollution (TRP), PM2.5, PM10, O3, and NO2	Modeled pollutant exposures for developmentally relevant time points	Limited by sample size, there could be unmeasured confounding factors (e. g. lifestyle, nutritional, or other residential exposures), did not explore indoor sources of pollution,

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		Regional exposure measures of nitrogen dioxide (NO2) and particulate matter less than 2.5 and 10 μm in diameter (PM2.5 and PM10) were also associated with autism during gestation (NO2 OR = 1.81/2SD, 95%CI 1.37–3.09; PM2.5 OR = 2.08/2SD, 95%CI 1.93–2.25; PM10 OR = 2.17/2SD, 95%CI 1.49–3.16) and the first year of life (NO2 OR = 2.06, 95%CI 1.37–3.09; PM2.5 OR = 2.12, 95% CI 1.45–3.10; PM10 OR = 2.14, 95%CI 1.46–3.12).						confounding could have occurred if proximity to diagnosing physicians or treatment centers were also associated with exposure, and unable to disentangle trimester-specific effects or during the first week of life because of the high correlation across these time periods
Gong et al.	2014	No clear or consistent associations were found between air pollution exposure during any of the three time windows and any of the neurodevelopmental outcomes. For example, a 5–95% difference in exposure to NOx during pregnancy was associated with odds ratios (ORs) of 0.92 (95% confidence interval (CI): 0.44–1.96) and 0.90 (95% CI: 0.58–1.40) for ASD and ADHD respectively. A corresponding range in exposure to PM10 during pregnancy was related to ORs of 1.01 (95% CI: 0.52–1.96) and 1.00 (95% CI: 0.68–1.47) for ASD and ADHD.	Stockholm, Sweden	3426	Multiple Domains	NOx and PM10	Population-based, large sample of twins and data linkage to Swedish national registries, analyzed neurodevelopmental disorders categorically based on the DSM-IV criteria and additional cut-off values according to previous validation studies, and evaluated different trimesters during pregnancy, first year, and ninth year of life	Occurrence of neurodevelopmental outcomes may have differed in children participating in CATSS with completed A-TAC assessment versus the general population; compared to CATSS non-responders, children in the study had higher familial socio-economic status; power was limited for the analyses of sub-dimensional ASD/ADHD measures; and for the exposure time measured during the child's ninth year of life, the air pollution assessment may have occurred after the onset of disease
Guxens et al.	2014	NO2 exposure during pregnancy was associated with reduced psychomotor development (beta: 0.68 95% CI: 1.25, −0.11) per 10 μg/m3 increase in NO2. No associations between air pollution and cognitive development.	Europe (The Netherlands, Germany, France, Italy, Greece, and Spain)	9482	Multiple Domains	NO2, NOx, PM2.5, PM10, and PMcoarse	Large sample size, prospective design, adjusted for several important confounders, and performed many sensitivity analyses to assess validity of overall findings	Heterogeneity of instruments, evaluators, and ages of children at assessments across the 6 cohorts, air pollution levels were back-extrapolated to the pregnancy period using routine background monitoring network sites but monitoring data were not available for all pollutants in all study regions particularly for PM (causing non-differential misclassification), high

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								correlation between pollutants, and possible residual confounding (from road traffic noise).
Kim et al.	2014	Maternal exposure to PM10 resulted in reduced mental development index (MDI) (β = −2.83; p = 0.003) and psychomotor development index (PDI) (β = −3.00; p = 0.002) throughout the first 24 months of life. Maternal NO2 exposure was related with impairment of psychomotor development (β = −1.30; p = 0.05) but not with cognitive function (β = −0.84; p = 0.20). Tthere were significant effects of prenatal air pollution exposure on MDI (PM10: β = −4.60; p < 0.001, NO2: β = −3.12; p < 0.001) and PDI (PM10: β = −7.24; p < 0.001, NO2: β = −3.01; p < 0.001) at 6 months, but no significant association was found at 12 and 24 months of age.	South Korea	520	Cognition	PM10 and NO2	Prospective design, large sample size, repeated neuro measures in infancy and early childhood, used daily monitoring data over the entire pregnancy period, and adjusted for several important confounders.	Misclassification of PM/NO2 due to crude exposure assessment, did not examine postnatal exposure, limited assessment of maternal IQ, correlation between exposures during pregnancy and after birth, could not estimate particulates smaller than PM10, and may not have adjusted for some important socioeconomic and environmental confounding factors including maternal intelligence
Lin et al.	2014	At 18 months, poor subclinical neurodevelopment in early childhood is associated with the average SO2 exposure prenatally, during all trimesters of pregnancy, and at postnatal ages up to 12 months (first trimester β = −0.083, se = 0.030; second and third trimester β = −0.114, se = 0.045; from birth to 12 months of age β = −0.091, se = 0.034). Furthermore, below average scores for gross motor development at six months of age were associated with increased average non-methane hydrocarbon (NMHC) levels during the second and third trimesters (β = −8.742, se = 3.512). Low-level SO2 exposure prenatally and up to twelve months postnatally associated with adverse neurobehavioral effects at 18 months of age. Maternal NMHC exposure during the 2nd and 3rd trimesters of pregnancy was associated with poor gross motor	Taiwan	533	Cognition	Multiple (specify in notes)	Prospective design and adjusted for important confounders.	Exposure misclassification (pollutants measured from local monitors and not at residential address), exposures may vary with and more than one substance could have an effect over time, neurodevelopment may not be sufficiently sensitive to detect the effects of low-level exposure, TBCS scale is parent-reported, and residual confounding from income, noise, stress, etc.

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		development in children at 6 months of age.						
Perera et al.	2014	High prenatal exposure, measured by elevated maternal PAH-DNA adducts was significantly associated with all Conners Parent Rating Scale-Revised subscales when the raw scores were analyzed continuously (N = 233). After dichotomizing at the threshold for moderately to markedly atypical symptoms, high maternal adducts were significantly associated with the Conners Parent Rating Scale-Revised DSM-IV Inattentive (OR = 5.06, 95% CI [1.43, 17.93]) and DSM-IV Total (OR = 3.37, 95% CI [1.10, 10.34]) subscales.	New York City, NY	250	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, had individual pre- and postnatal exposure data from biomarker and questionnaire data, and use of two complementary age-appropriate instrument to measure ADHD-related behaviors	Small sample size, unmeasured factors such as other pollutants, stress, and noise that may have contributed to residual confounding, incomplete data on exposure to lead and mercury, unable to evaluate the effects of individual postnatal PAH metabolites that may have different toxicities, and reduced generalizability due to inclusion/exclusion criteria
Tang et al.	2014	Same analysis as Perera et al. (2008), but the two cohorts are combined into one. Average, motor, and adaptive DQ scores decreased per unit increase in cord PAH-DNA adducts.	Tongliang, China	217	Cognition	PAH	Prospective follow-up, Biological-intermediate biomarker of PAH exposure, adjustment for Pb. Participants were non-smokers.	Small sample size, exposure misclassification (non-PAH sources), residual confounding.
Tang et al.	2014	Lower levels of PAH-DNA adducts, higher concentrations of the mature BDNF protein (mBDNF) and higher DQ scores were seen in the 2005 cohort enrolled after closure of the coal burning power plant. In the two cohorts combined, PAH-DNA adducts were inversely associated with mBDNF as well as scores for motor ($p = 0.05$), adaptive ($p = 0.022$), and average ($p = 0.014$) DQ. BDNF levels were positively associated with motor ($p = 0.018$), social ($p = 0.001$), and average ($p = 0.017$) DQ scores. The findings indicate that the closure of a coal-burning plant resulted in the reduction of PAH-DNA adducts in newborns and increased mBDNF levels that in turn, were positively associated with neurocognitive development.	Tongliang, China	2002 cohort: n = 110 and 2005 cohort: n = 107	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data) to measure individual exposure, and explored mediation (whether BDNF was a mediator of the relationship between PAH-DNA adducts and DQ scores)	Small sample size and lack of data on postnatal ETS exposure
Volk et al.	2014	Subjects with both MET rs1858830 CC genotype and high air pollutant exposures were at increased risk of	Sacramento, Los Angeles, San Francisco	Cases = 252 and	Autism Spectrum Disorder	Traffic-related air pollution (TRP),	Examined gene-environment interactions,	Limited by small sample size and low statistical power, there could be

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		autism spectrum disorder compared with subjects who had both the CG/GG genotypes and lower pollutant exposures. A statistical test of multiplicative interaction identified a statistically significant effect between NO2 and MET CC genotype (p = 0.03).	East, and North Bay, CA	Controls = 156		PM2.5, PM10, O3, and NO2	adjusted for several important confounders	unmeasured confounding factors (e. g. lifestyle, nutritional, or other residential exposures), did not explore indoor sources of pollution, confounding could have occurred if proximity to diagnosing physicians or treatment centers were also associated with exposure, and unable to disentangle trimester-specific effects or during the first week of life because of the high correlation across these time periods
von Ehrenstein et al.	2014	Autism risks were increased per interquartile-range increase in average concentrations during pregnancy of several correlated toxics mostly loading on one factor, including 1,3-butadiene (OR = 1.59 [95% confidence interval = 1.18–2.15]), meta/para-xylene (1.51 [1.26–182]), other aromatic solvents, lead (1.49 [1.23–1.81]), perchlorethylene (1.40 [1.09–1.80]), and formaldehyde (1.34 [1.17–1.52]), adjusting for maternal age, race/ethnicity, nativity, education, insurance type, maternal birth place, parity, child sex, and birth year.	Los Angeles, CA	Cases = 768 and Controls = 147,954	Autism Spectrum Disorder	24 toxic air pollutants, including aromatic solvents, chlorinated solvents, volatime organics, total PAH, and several metals	Large sample of cases diagnosed with strict criteria, non-participation (selection) bias for those who were not in the Department of Developmental Services database, and adjusted for several important confounders	Potential non-differential exposure misclassification, not measuring neighborhood socioeconomic patterns, non-differential diagnostic biases, residual confounding due to unmeasured factors, co-pollutant confounding by measured or by unmeasured substances, and lack of information on maternal smoking
Cowell et al.	2015	Did not observe significant findings between BC and each WRAML2 index. In sex-stratified models, BC and Attention Concentration (AC) Index was significant for boys (−10.52; 95% CI: 18, −3), but not for girls. Similar findings for sex- and stress-stratfied analyses: higher BC assoc with decreased AC index for boys born to moms with high prenatal stress.	Boston, MA	258	Cognition	Traffic	Prospective design, adjustment for several confounders, validated LUR model.	Exposure misclassification (LUR model based on residential address only), residual confounding (income, noise), modest sample size.
Harris et al.	2015	Compared with children living ≥200 m from a major roadway at birth, those living <50 m away had lower nonverbal IQ [−7.5 points; 95% confidence interval (CI): 13.1,	Eastern MA	1109	Cognition	PM2.5 and BC	Prospective design, imputed missing covariates, large sample size, included multiple cognitive assessments,	Possible selection bias due to loss to follow-up, limitations in the spatial resolution (lack of data on the satellite aerosol optical

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		−1.9], and somewhat lower verbal IQ (−3.8 points; 95% CI: 8.2, 0.6) and visual motor abilities (−5.3 points; 95% CI: 11.0, 0.4). Prenatal and childhood exposure to traffic density and PM2.5 did not appear to be associated with poorer cognitive performance. Third-trimester and childhood BC exposures were associated with lower verbal IQ in minimally adjusted models; but after adjustment for socioeconomic covariates, associations were attenuated or reversed.					estimated traffic-related pollution during multiple periods of gestation and childhood, and adjusted for several important confounders.	depth), only 34 participants lived <50 m of a major roadway so findings should be interpreted carefully, estimated PM2.5 total mass instead of particular components of PM2.5, exposure misclassification (LUR and distance to roadway based on residential addresses only), and possible residual confounding (e.g. noise).
Jedrychowski et al.	2015	The prevalence of Verbal IQ Index (DepVIQ) was significantly higher in children with detectable PAH–DNA adducts compared to those with undetectable adducts (13.7 vs. 4.4%). Binary multivariable regression documented that the relative risk of DepVIQ increased threefold with a ln-unit increase in cord blood adducts (relative risk (RR) = 3.0, 95% confidence interval (CI) 1.3–6.8). Postnatal PAH exposure also increased the risk of DepVIQ (RR = 1.6, 95% CI 1.1–2.5).	Krakow, Poland	170	Cognition	PAH	Prospective design, adjusted for several important confounders (including factors known to affect intellectual development), and used PAH-DNA adducts to measure individual exposure	Relatively small sample size who have undergone cognitive evaluation and the 48-hr personal PAH monitoring
Kalkbrenner et al.	2015	Temporal patterns in PM10 were pronounced, leading to an inverse correlation between the first- and third-trimester concentrations (r = −0.7). For autism spectrum disorders, adjusted ORs were: for the first trimester, 0.86 (95% CI = 0.74–0.99), second trimester, 0.97 (0.83–1.15), and third trimester, 1.36 (1.13–1.63); and, after simultaneously including first- and third-trimester concentrations to account for the inverse correlation, the ORs were: first trimester, 1.01 (0.81–1.27) and third trimester, 1.38 (1.03–1.84).	North Carolina and San Francisco Bay Area in California	North Carolina Cases = 645 and Controls = 12,434 California Cases = 334 and Controls = 2232	Autism Spectrum Disorder	PM10	Large sample size (almost 1000 Autism cases), a standardized ascertainment of Autism, the inclusion of less-severe subtypes, and the ability to control for some sociodemographic factors (e.g. adjusted for the impact of season at birth	Lack of person-based monitoring (we assumed an ambient model of air pollutant concentrations represented individual exposure) that could bias estimates towards the null, exposure measurement error from residential mobility, residual confounding due to unmeasured nuances of socioeconomic position, and unable to address co-pollutant (e.g. PM2.5, NO2) confounding or the impact of mixtures
Lertxundi et al.	2015	Prenatal PM2.5 exposure was associated with a 1.14 (90% CI: 1.76, −0.53) point decrease in	Spain	438	Cognition	Multiple (specify in notes)	Prospective design and adjusted for important confounders.	Exposure misclassification (PM2.5 measured from local monitors and not at

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		motor scale. Prenatal NO2 exposure was associated with a 0.29 (90% CI: 0.47, −0.11) point decrease in mental scale. Benzene was not associated with mental and motor scores. Living near a facility listed on the Pollutant Release and Transfer Registry (PRTR) was associated with lower motor and mental scores.						residential address). Observed effects could be due to early childhood exposure (not measured) and prenatal exposure.
Perera et al.	2015	PAH-DNA adducts were associated with decreased MDI at 2 years (beta: 2.1; p-value = 0.04). Association with age 3 MDI was weaker (−1.4, p-value = 0.11). BaP associations were non-sig (no results).	New York, NY	345	Cognition	PAH	Prospective follow-up, Biological-intermediate biomarker of PAH exposure, examined biological intermediated (BDNF), imputed missing data. Participants were non-smokers.	Exposure misclassification (non-traffic PAH sources), residual confounding, and LTF.
Perera et al.	2015	PAH/aromatic-DNA adduct concentration measured by postlabeling was inversely associated with BDNF concentration (p = 0.02) and with MDI scores at 2 years (p = 0.04). BDNF level was positively associated with MDI scores (p = 0.003). Restricting to subjects having all three measures (PAH/aromatic-DNA adducts by postlabeling, MDI, and BDNF), results were significant but attenuated (p = 0.13, p = 0.05, p = 0.01, respectively). Associations between adducts and BDNF and adducts and MDI at age 2 years were not significant. At age 3 years, the positive association of BDNF with MDI was not observed. The results at age 2 suggest that prenatal exposure to a spectrum of PAH/aromatic pollutants may adversely affect early neurodevelopment, in part by reducing BDNF levels during the fetal period.	New York City, NY	505	Multiple Domains	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data), medical records, and questionnaires to measure individual exposure, and explored mediation	Lack of adequate data on lead levels to control for this known neurotoxic exposure, and lack of power to assess possible interactions with the genetic variant of BDNF (Val66met) that have been found to affect the gene's functioning
Peterson et al.	2015	There was a dose-response relationship between increased prenatal PAH exposure (measured in the 3rd trimester, but thought to index exposure for all of gestation) and reductions of the white matter	New York City, NY	40	Multiple Domains	PAH	Largest MRI study thus far of the brain effects of prenatal exposure to air pollutants and the first to report effects from prenatal exposure, and	Assessed the effects of PAH only at the cerebral and white matter surfaces, not deep within the brain's parenchyma; small sample size; prenatal PAH

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		surface in later childhood that were confined almost exclusively to the left hemisphere of the brain. Reduced left hemisphere white matter was associated with slower information processing speed during intelligence testing and more severe externalizing behavioral problems, including ADHD symptoms and conduct disorder problems.					tested for mediation effects	monitoring conducted only during third trimester; urinary metabolite concentrations measured at age 5 years represent different sources of PAH exposure besides air; cannot entirely exclude the possibility that the findings could have been caused by other co-occurring exposures (e. g. unmeasured air pollutants); and not necessarily generalizable to other populations (e.g. conducted on a minority, high-poverty sample)
Raz et al.	2015	PM2.5 exposure during pregnancy was associated with increased odds of ASD, with an adjusted odds ratio (OR) for ASD per interquartile range (IQR) higher PM2.5 (4.42 μg/m3) of 1.57 (95% CI: 1.22, 2.03) among women with the same address before and after pregnancy (160 cases, 986 controls). Associations with PM2.5 exposure 9 months before or after the pregnancy were weaker in independent models and null when all three time periods were included, whereas the association with the 9 months of pregnancy remained (OR = 1.63; 95% CI: 1.08, 2.47). The association between ASD and PM2.5 was stronger for exposure during the third trimester (OR = 1.42 per IQR increase in PM2.5; 95% CI: 1.09, 1.86) than during the first two trimesters (ORs = 1.06 and 1.00) when mutually adjusted. There was little association between PM10–2.5 and ASD.	All 50 states, US	Cases = 245 and Controls = 1522	Autism Spectrum Disorder	PM2.5 and PM10–2.5	Very representative sample of participants from a wide geographic distribution within a well-defined cohort that reduces the chances of selection bias, mothers in this study (nurses) would have more homogenous health-seeking behaviours which may make ascertainment of cases more homogenous too, and adjustment of several important confounders	Lack of exact dates for when mothers changed addresses (35% of nurses (cases and controls) changed their residential addresses from before pregnancy to after delivery) leading to exposure misclassification, no information on how much time the nurses spent at their residential or work addresses, unavailable information on indoor air pollution exposures and sources, residual confounding, did not examine other co-pollutants that co-varied with PM2.5, and did not have high temporal and spatial resolution data on other air pollution constituents or on specific PM2.5 constituents
Talbott et al.	2015	Comparing fourth to first quartile exposures for all births, for autirm spectrum disorder the adjusted OR for styrene was 2.04 (95% CI = 1.17–3.58, p = 0.013) for the interviewed case–control analysis	Southwestern Pennsylvania	Cases = 217, Frequency-matched Controls = 224, and	Autism Spectrum Disorder	Hazardous Air Pollutants	Was able to obtain full residential history information for the frequency-matched controls that decreased exposure	Random birth certificate controls did not have residential information during pregnancy other than the address reported at birth, unmeasured residual

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		and 1.61 (95% CI = 1.08–2.40, p = 0.018) for the analysis using birth certificate controls. In the birth certificate comparison, chromium also exhibited an elevated OR of 1.60 (95% CI = 1.08–2.38, p = 0.020), which was similarly elevated in the analysis using interviewed controls (OR = 1.52, 95% CI = 0.87–2.66). There were borderline significant ORs for the birth certificate comparison for methylene chloride (OR = 1.41, 95% CI = 0.96–2.07, p = 0.082) and PAH (OR = 1.44, 95% CI = 0.98–2.11, p = 0.064). Living in areas with higher levels of styrene and chromium during pregnancy was associated with increased risk of ASD, with borderline effects for PAH and methylene chloride.		Birth certificate (BC) Controls = 5007			misclassification bias, eliminated response bias in the random birth certificate controls, measured exposure at multiple sensitive time points during and after pregnancy, and adjusted for several important confounders	confounding, and lacked personal monitoring data
Vishnevetsky et al.	2015	PAH-DNA adducts were associated with IQ [beta: 3.5 (95% CI: 6.35, −0.55)]. Detectable PAH-DNA adducts were associated with lower FSIQ among children born to women (b: 5.8; 95% CI: 10, −1.3; n = 118) with prenatal hardship, but not among those children born to women without hardship (b: = 1.8; 95% CI: = 5.5, 1.9; n = 158). EMM p-value non-significant. Similar association with recurrent hardship. Associations stonger for working memory index and EMM p-value was significant.	New York, NY	276	Cognition	PAH	Prospective cohort, Biological-intermediate biomarker of PAH exposure, later childhood follow-up. Participants were non-smokers during pregnancy. Examination of important modifier. Accounted for loss to follow-up (LTF) with inverse probability weighting, results unchanged.	Exposure misclassification (non-traffic PAH sources), residual confounding, considerable number of children LTF.
Chiu et al.	2016	The authors found associations between higher PM2.5 levels at 31–38 weeks gestation with lower IQ, at 20–26 weeks with increased omission errors (OEs), at 32–36 weeks with slower hit reaction time (HRT), and at 22–40 weeks with increased HRT standard error (HRT-SE) among boys, while significant associations were found in memory domains in girls (higher PM2.5 exposure at 18–26 weeks with reduced visual memory (VIM), at 12–20 weeks with reduced general memory (GM)).	Boston, MA	267	Cognition	PM2.5	Prospective design, adjusted for several important confounders, estimated weekly address-specific particulate air pollution exposure, and first study to examine sex-specific effects of prenatal particulate air pollution on a range of neurodevelopment domains	Small sample size (potentially limited ability to see interaction effects), no data on dietary and other environmental factors that may co-vary with air pollution (e.g. noise), insufficient information on other sources of household secondhand smoking, not much data on parenting practices that may influence child neurobehavioral development (other than

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								breast feeding status), and reduced generalizability only to lower SES racial/ ethnic minority populations
Fuertes et al.	2016	IQR increases in PM2.5 mass and PM2.5 absorbance at 10 and at 15 year addresses were associated with hyperactivity/inattention. IQR increase in PM2.5 mass at 10 year address was associated with dyscalculia (OR = 1.29, 95% CI: 1.03, 1.61). No associaitons with dyslexia.	Germany	4745	Multiple Domains	NO2, PM10 mass, PM2.5 mass, and PM2.5 absorbance	Multiple exposure assessment time points, adjusted for many important covariates including parental psychopathology, and large sample size.	Unable to disentangle the effects of potential susceptibility windows, potential reporting bias as questionnaires were self-completed (except for hyperactivity/inattention), potential selection bias due to loss to follow-up, a substantial decrease in statistical power at 15 years of age and outcome misclassification, exposure misclassification (moved addresses between follow-up), results were not corrected for multiple testing and not generalizable to preterm and low birthweight babies.
Guxens et al.	2016	Prenatal air pollution exposure was not associated with autistic traits within the borderline/clinical range (odds ratio = 0.94; 95% CI: 0.81, 1.10 per each 10-μg/m3 increase in NO2 pregnancy levels). Similar results were observed in the different cohorts, for the other pollutants, and in assessments of children with autistic traits within the clinical range or children with autistic traits as a quantitative score. Prenatal exposure to NO2 and PM was not associated with autistic traits in children from 4 to 10 years of age in four European population-based birth/child cohort studies.	Europe (The Netherlands, Sweden, Italy, and Spain)	8079	Autism Spectrum Disorder	NO2, NOx, PM2.5, PM10, and PMcoarse	Large sample size in combination with the prospective and longitudinal study design, the use of a standardized and validated air pollution assessment in all countries, the assessment of exposure to a large number of air pollutants including NO2 and PM at the individual level, the assessment of autistic traits in childhood using standardized and validated neuropsychological tests, statistical analysis following a consensus protocol, and adjusted for many socioeconomic and lifestyle variables known to be associated with air pollution exposure and/or autistic traits in children	Four different tests were used in the different cohorts to assess autistic traits, of which only two were developed to specifically address autistic traits (SRS and CAST) and the other two (CBCL and A-TAC) have been most commonly used as screening tests for a broader range of behavioral profile and disorders including autistic traits - each instrument classifies children at risk for ASD in a slightly different way. There could also be non-differential misclassification of exposure since air pollution levels were back-extrapolated to the pregnancy period, there were differences in air pollution levels and sources, possible diagnostic bias related to

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								socioeconomic status-related difference in access to care, did not calculate trimester-specific associations, study population does not represent the phenotypic extreme, and residual confounding.
Harris et al.	2016	Higher BC exposure associations with higher teacher-rated BRIEF:BRI scores (indicating greater problems): at birth-age 6 (1; 95% CI:0, 2.1) and at year prior to assessment (1.7; 95% CI:0.6, 2.8). BC exposure in 4th, 5th, and 6th years of life was more strongly associated with teacher-rated BRIEF BRI scores than 1st, 2nd, and 3rd year of life, suggesting mid-childhood exposure has a greater effect and/or cumulative BC exposure is important. PM2.5 was not associated with outcomes in fully adjusted models. None of the parent-rated outcomes suggested adverse effects of air pollution.	Eastern MA	1212	Multiple Domains	PM2.5 and BC	Imputed missing covariates, large sample size, included multiple behavioral rating scales completed by parents and teachers, estimated multiple measures of traffic-related pollution during several time periods, adjusted for many important confounders.	Possible selection bias due to loss to follow-up, exposure misclassification (LUR and distance to roadway based on residential addresses only), did not have access to performance-based tests of neurobehavioral functions such as attention or inhibitory control, may not have captured potential effect of air pollution exposure on executive function that are better solidified later in development, lacked some measures of parental neurobehavior (e.g. executive function), limited generalizability as enrolled mothers all had health insurance coverage and access to early prenatal care and were on average highly educated and higher income, and residual confounding (noise).
Margolis et al.	2016	A significant interaction (at $p = 0.05$) of exposure with time was detected, in which the developmental trajectory of self-regulatory capacity was delayed in the exposed children. Multiple linear regression revealed a positive association between presence of detectable PAH-DNA adducts and problems with social competence ($p < 0.04$), level of dysregulation and problems with social competence ($p < 0.0001$), and evidence that self-regulation mediates the association	New York City, NY	Main analysis: n = 462 Mediation analysis: n = 262	Multiple Domains	PAH	Prospective, longitudinal dataset designed and implemented with gold standard epidemiologic methods, used PAH-DNA adducts (biomarker data) to measure individual exposure, collected independent measurements of self-regulatory capacity at 4 time points across childhood, adjusted for several important	Limited by small sample size and low statistical power, there could be unmeasured confounding factors (e. g. lifestyle, nutritional, or other residential exposures), there was missing data from loss to follow-up, there is survey but not direct measures of children's self-regulatory capacities across ages, and limited generalizability as study

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		of prenatal exposure to PAH with the Social Responsiveess Scale (SRS) ($p < 0.0007$).					confounders, and conducted mediation analyses	participants only included children born to minority women in large urban environments were studied
Porta et al.	2016	A 10 μg/m3 higher NO2 exposure during pregnancy was associated with lower verbal IQ (−1.4, 95% CI: 2.6, −0.2) and lower verbal comprehension IQ (−1.4, 95% CI: 2.7, −0.2). Similar associations were found for traffic intensity in a 100 m buffer around home. Stratified analyses showed a greater effect of NO2 among children born to mothers under 30 years old. PMcoarse, PM2.5 and PM2.5absorbance also showed negative associations but with larger confidence intervals that included zero.	Rome, Italy	719	Cognition	PM10, PMcoarse, PM2.5, PM2.5absorbance, and NO2	Prospective design, adjusted for several important confounders, employed a standardized method to estimate exposure, accounted for potential selection bias due to loss to follow-up with IPW, contacted cohort participants very often to collect information on residential changes, and findings of NO2 (a traffic pollutant) are reinforced by the findings of traffic intensity.	Residual confounding (e.g. maternal and paternal intelligence, an area-based socioeconomic index of the child), and did not adjust for multiple comparisons (even when examining four different measures of air pollution and three traffic indicators).
Stingone et al.	2016	Children in the highest quartile of exposure to both diesel PM and perchlorethylene had greatest decrements in math test scores (6% of a SD lower) and the greatest risk of failing to meet test-based curricula standards (RR 1.10 95% CI: 1.07, 1.12) compared to children in the lowest quartiles. No association between exposure and failing to meet ELA standards.	New York, NY	2,01,559	Cognition	Hazardous Air Pollutants	Large representative population-based study	Exposure misclassification (census tract-level only and at time of birth - no temporal variability), residual confounding (mom IQ, stress, noise),
Yorifuji et al.	2016	Air pollution exposure during gestation was positively associated with the risk of some developmental milestone delays at both ages. Specifically, air pollution was associated with verbal and fine motor development at age 2.5 years, and with behaviors related to inhibition and impulsivity at 5.5 years. In the fully-adjusted models, odds ratios following a one-interquartile-range increase in nitrogen dioxide and suspended particulate matter were 1.24 (95% confidence interval: 1.07, 1.43) for inability to compose a two-phrase sentence at ages 2.5 and 1.10 (1.05, 1.16) for inability to express	Japan	33,911	Multiple Domains	Suspended PM, NO2, SO2	Large, nationally representative sample, high response rates and high follow-up rates, and adjusted for several important confounders	Did not use several validated cognitive function tests, could not confirm whether the questions they used (at both ages) have been validated or selected from an established scale, possibility of non-differential misclassification of behavioral outcomes because of the subjective nature of the questions, reduced generalizability to other ethnic groups and populations or rural populations, did not estimate individual-level air

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		emotions at age 5.5 years, respectively.						pollution exposure, and possible residual confounding
Lee et al.	2017	PAH was associated with decreased LINE-1 methylation, but LINE-1 did not mediate association between PAH and cognitive measures.	China	227	Cognition	PAH	Prospective cohort, Biological-intermediate biomarker of PAH exposure, and examination of biological intermediate. Participants were non-smokers.	Modest sample size, exposure misclassification (non-traffic sources), residual confounding.
Lee et al.	2017	A significant inverse relationship was observed between PAH-DNA adducts and DNA methylation of long interspersed nuclear elements (LINE1) ($\beta = -0.010$, $p < 0.038$). A significant, positive association was present between LINE1 methylation and scores on the WISC full scale ($\beta = 85.31$, $p < 0.005$) and verbal scale ($\beta = 94.36$, $p < 0.003$) at age 5, but not on the GDS at age 2. LINE1 methylation in cord blood DNA was a positive predictor of IQ at age 5 and was decreased at higher levels of prenatal PAH exposure, measured by PAH-DNA adducts in cord blood. However, the adverse effects of prenatal exposure to PAH on IQ scores did not appear to be directly mediated by altered LINE1 methylation.	Tongliang, China	2002 cohort: n = 110 and 2005 cohort: n = 107	Cognition	PAH	Prospective design, adjusted for several important confounders, used PAH-DNA adducts (biomarker data) to measure individual exposure, and explored mediation (DNA methylation).	Small sample size and DNA hypomethylation in peripheral blood leukocytes (LINE1 methylation) is only a surrogate marker for PAH exposure or a predictor of neurodevelopmental outcomes.
Lubczyńska et al.	2017	Single element analysis resulted in negative association between estimated airborne iron and fine motor function (−1.25 points [95% CI −2.45 to −0.06] per 100 ng/m3 increase of iron). Association between the motorized traffic component, derived from principal component analysis, and fine motor function was not significant (−0.29 points [95% CI −0.64 to 0.06] per unit increase). None of the elements were associated with gross motor function or cognitive function, although the latter estimates were predominantly negative.	Europe (Netherlands, Germany, Italy and Spain)	7246	Cognitive and psychomotor function	Elemental composition of PM2.5 (copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc)	Large representative sample, standardized air pollution assessment which was based on validated measurements, use of advanced statistical methods including multiple imputation combined with inverse probability weighting to reduce possible attrition bias in the study, adjustment for various confounders (socioeconomic and lifestyle variables).	Non-differential exposure misclassification, the inability to estimate air pollution levels at the exact period of interest (i.e. at birth). Sampling campaigns were carried out between 3.5 and 9 years after the children were born and historical element data from routine monitoring stations in the study areas were not available to back extrapolate the levels to the period of interest.

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Sentís et al.	2017	Prenatal exposure to NO2 was associated with an impaired standard error of the hit reaction time (HRT(SE)) (increase of 1.12 ms [95% CI; 0.22 a 2.02] per 10 μg/m3 increase in prenatal NO2) and increased omission errors (6% [95% CI; 1.01 to 1.11] per 10 μg/m3 increase in prenatal NO2). Postnatal exposure to NO2 resulted in a similar but borderline significant increase of omission errors (5% [95% CI; = 0.99 to 1.11] per 10 μg/m3 increase in postnatal NO2). These associations did not vary markedly between regions, and were mainly observed in girls. Commission errors and lower detectability were associated with prenatal and postnatal exposure to NO2 only in some regions.	Spain	1298	Attentional dysfunction	NO2	Prospective design, strong exposure assessment during two periods— pregnancy and early life, adjusted for many socioeconomic and lifestyle variables that are known to confound the association between prenatal and postnatal air pollution exposure and attentional function in children.	Exposure misclassification (no data on air pollution exposure at the children's daycare centers and schools), residual confounding (noise exposure).
Stingone et al.	2017	HR comparing children in the 90th percentile of benzene exposure to those with lower exposure was 1.09 (95% CI: 1.05, 1.13). These findings were similar for the other exposure metrics.	New York, NY	2,01,559	Cognition	Hazardous Air Pollutants	Large representative population-based study	Exposure misclassification: BTEX exposures are an annual average for each census tract. Residual confounding (noise, other air pollutants)
Yorifuji et al.	2017	Air pollution exposure during gestation was positively associated with risk for behavioral problems related to attention and delinquent or aggressive behavior. In the fully adjusted models, odds ratios following a one-interquartile-range increase in suspended particulate matter were 1.06 (95% confidence interval: 1.01, 1.11) for interrupting others, 1.09 (1.03, 1.15) for failure to pay attention when crossing a street, 1.06 (1.01, 1.11) for lying, and 1.07 (1.02, 1.13) for causing public disturbance.	Japan	33,911	Multiple Domains	Suspended PM, NO2, SO2	Large, nationally representative sample, high response rates and high follow-up rates, and adjusted for several important confounders	Did not use several validated cognitive function tests, could not confirm whether the questions they used (at both ages) have been validated or selected from an established scale, possibility of non-differential misclassification of behavioral outcomes because of the subjective nature of the questions, reduced generalizability to other ethnic groups and populations or rural populations, did not estimate individual-level air pollution exposure, and possible residual confounding
Forns et al.	2018	Exposure to air pollution during pregnancy was not associated with	Europe (The Netherlands,	29,127	ADHD	PM2.5 and NO2	Large representative population-based study,	Exposure misclassification (residential address only),

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		a higher odds of ADHD symptoms within the borderline/clinical range (e.g., adjusted odds ratio [OR] for ADHD symptoms of 0.95, 95% confidence interval [CI] = 0.89, 1.01 per 10 μg/m increase in NO2 and 0.98, 95% CI = 0.80, 1.19 per 5 μg/m increase in PM2.5). Similar associations for ADHD were observed within the clinical range.	Germany, France, Italy, Sweden, Denmark and Spain)				adjusted for several important social confounders.	residual confounding (didn't control for some social factors), and ADHD potential assessment bias.
Guxens et al.	2018	Children exposed to higher particulate matter levels during fetal life had thinner cortex in several brain regions of both hemispheres (e.g., cerebral cortex of the precuneus region in the right hemisphere was 0.045 mm thinner (95% confidence interval, 0.028–0.062) for each 5-μg/m3 increase in fine particles). The reduced cerebral cortex in precuneus and rostral middle frontal regions partially mediated the association between exposure to fine particles and impaired inhibitory control. Air pollution exposure was not associated with global brain volumes.	Rotterdam, The Netherlands	783	Multiple Domains	PM10, PM2.5 and NO2	Prospective and longitudinal nature of the study, large number of study participants with imaging data, detailed information of air pollution estimations at the individual level during the entire fetal period, and control for socioeconomic and lifestyle factors known to be associated with both air pollution exposure and brain development.	Residual confounding (unavailability of other relevant potential confounding variables), selection bias, children with exposure and outcome data were more likely to have mothers from a higher socioeconomic position than were those children without these data, but who were recruited at the beginning of the cohort in early pregnancy.
Mortamais et al.	2019	An interquartile range increase in PM2.5 level (7 μg/m3) was significantly linked to a decrease in the body corpus collusum (CC) volume (mm3) (β = −53.7, 95%CI [−92.0, −15.5] corresponding to a 5% decrease of the mean body CC volume) independently of intracranial volume (ICV), age, sex, maternal education, socioeconomic vulnerability index at home, birthweight and mothers' smoking status during the third trimester of pregnancy. A 50 mm3 decrease in the body CC was associated with a significant higher hyperactivity subscore (Rate Ratio (RR) = 1.09, 95%CI [1.01, 1.17) independently of age, sex and ICV.	Barcelona, Spain	186	Multiple Domains	PM2.5	Strong sensitivity analyses running a linear mixed model with school as nested random effect to verify that the multilevel nature of the data did not influence the results. Regression linear models included exposures in all of the trimesters of pregnancy to determine which trimester may be the most predictive on the brain outcomes.	Small sample size, exposure misclassification (only used ambient modeled PM2.5 estimates and did not have personal monitoring or biomarkers), and did not observe any statistically significant associations between prenatal PM2.5 exposure and behavioral outcomes while such an association was found in previous work.
Pagalan et al.	2019	Adjusted odds ratios for ASD per interquartile range (IQR) were not significant for exposure to PM2.5	Metro Vancouver, British	1307	Autism Spectrum Disorder	PM2.5 and NO2	Largest population-based cohorts on ASD and air pollution, adjusted LUR	Did not test for multiple comparisons, direct exposure assessment was

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		during pregnancy (1.04 [95% CI, 0.98–1.10] per 1.5 μg/m3 increase [IQR] in PM2.5) or NO2 (1.06 [95% CI, 0.99–1.12] per 4.8 ppb [IQR] increase in NO2) but the odds ratio was significant for NO (1.07 [95% CI, 1.01–1.13] per 10.7 ppb [IQR] increase in NO).	Columbia, Canada,				models had high spatial and temporal resolutions, controlled for many potential confounders.	not possible particularly for exposures for the full 9-month duration of a pregnancy and the study design only tested associations for single pollutants. Very low exposure levels compared to other populations studied with respect to ASD.
Rivas et al.	2019	Inverse associations were identified between PM2.5 exposure during the fifth and sixth postnatal years and working memory, with boys showing much higher vulnerability. Regarding attention functions, exposure to higher PM2.5 levels during the prenatal period and from the fourth postnatal year were associated with a reduction in conflict network performance, though we found no association with attentiveness. The overall estimated cumulative effect of a 10 μg m−3 increase in PM2.5 resulted in a reduction in the working memory points and an increase in the conflict attentional network.	Barcelona, Spain	2897	Multiple Domains	PM2.5	Large sample size —this study is one of the largest conducted to date on the impact of air pollution on cognitive development in children.	Exposure misclassification (LUR model based on residential address only), residual confounding (maternal age at delivery, parental mental health status, or childrearing environment, mother's and child's diets).
Yolton et al.	2019	Exposure to ECAT was not significantly associated with parent-reported depression or anxiety. However, exposure to ECAT at birth was associated with increased child-reported depression and anxiety. Each 0.25 μg/m3 increase in ECAT was associated with a 3.5 point increase (95% CI 1.6–5.5) in CDI-2 scores and 2.3 point increase (95% CI 0.8–3.9) in Spence Children's Anxiety Scale (SCAS) total anxiety scores. Similar associations were observed between average childhood ECAT exposures but not for concurrent exposures at age 12.	Greater Cincinnati, Ohio region	344	Multiple Domains	Traffic-related air pollution (TRP), elemental carbon attributable to traffic (ECAT).	Adjusted for several important social confounders (parent depression, secondhand smoke exposure, race, household income).	Moderate sample size, exposure misclassification, self-report bias, parents reported children's depression and anxiety symptoms, residual confounding (unavailability of other relevant potential confounding variables).
Loftus et al.	2020	In fully adjusted models, 2 ppb higher prenatal NO2 was positively associated with an increase in externalizing behavior (6%; 95% CI: 1, 11%). Associations with	MidSouth, US	975	Childhood Behavioral Disorders	PM10 and NO2	Controlled for several SES variables at both the individual and neighborhood levels by using staged modeling.	Moderate sample size, residual confounding (noise associated with proximity to busy traffic), and exposure assessment

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		postnatal exposure were stronger (8% per 2 ppb NO2; 95%CI: 0, 16%). Prenatal NO2 exposure was also associated with an increased odds of clinically significant internalizing and externalizing behaviors. There was suggestive evidence that socioeconomic adversity and African American race increase susceptibility. PM10 and road proximity were not associated with outcomes.					Missingness of key covariates was very low and multiple imputation was used to additionally control for the HOME score, an observed measure of the home environment and important predictor of child neurodevelopment, with differential missingness in this sample.	provides limited information as to which components of air pollution drive associations with neurodevelopment.

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Table 2

Selected neurodevelopmental assessments among 64 ECHO cohorts with a recorded either prenatal or infancy street address by life stage, *n* of cohorts (%).

Neurodevelopmental Assessment	Collected (ever)[a]	Infancy (birth to <12 months)	Childhood (1 to <5 years)	Middle childhood (5 to <12 years)	Adolescence (≥12 years)
ASD-related phenotype					
Clinical diagnosis[b]	21 (32.8)	11 (17.2)	17 (26.6)	12 (18.8)	3 (4.7)
Social Responsiveness Scale (SRS)	15 (23.4)	7 (10.9)	12 (18.8)	9 (14.1)	2 (3.1)
Attention disorders-related phenotype					
Clinical diagnosis[b]	22 (34.4)	10 (15.6)	16 (25.0)	11 (17.2)	5 (7.8)
Conners Comprehensive Behavior Rating Scales (CBRS)	5 (7.8)	NA	NA	5 (7.8)	1 (1.6)
Brain imaging					
Brain magnetic resonance imaging (MRI)	15 (23.4)	11 (17.2)	11 (17.2)	8 (12.5)	2 (3.1)
Infant/Toddler Development					
Bayley Scales of Infant Development (BSID)	16 (25.0)	12 (18.8)	10 (15.6)	0	0
Other (non-BSID) developmental assessment	27 (42.2)	19 (29.7)	21 (32.8)	6 (9.4)	0
Intelligence Quotient (IQ)					
Wechsler Intelligence Scale for Children (WISC)/Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	13 (20.3)	NA	10 (15.6)	10 (15.6)	0
Language development					
MacArthur-Bates Communicative Development Inventories (CDI)	12 (18.8)	8 (12.5)	11 (17.2)	NA	NA
Externalizing/Internalizing Behavior Scoring					
Child Behavior Checklist (CBCL)	25 (39.1)	6 (9.4)	22 (34.4)	11 (17.2)	3 (4.7)
Behavior Assessment System for Children (BASC)	9 (14.1)	0	3 (4.7)	7 (10.9)	2 (3.1)
Depression scale					
Child Depression Inventory	8 (12.5)	NA	NA	6 (9.4)	5 (7.8)
Executive function test					
Behavior Rating Inventory of Executive Function (BRIEF)	18 (28.1)	NA	11 (17.2)	13 (20.3)	7 (10.9)
Gross motor development	32 (50.0)	24 (37.5)	22 (34.4)	12 (18.8)	1 (1.6)
Fine motor skills					
Pegboard	9 (14.1)	NA	8 (12.5)	7 (10.9)	5 (7.8)

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NA: Assessment is not applicable to this life stage and was not ascertained by the ECHO Data Analysis Center.

[a] Number (%) of 64 ECHO cohorts with the neurodevelopmental assessment at any life stage.

[b] Diagnosis based on clinician assessment or parent report of a clinical diagnosis.