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The Changing Epidemiology of Autism Spectrum Disorders

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition with lifelong impacts. Genetic and environmental factors contribute to ASD etiology, which remains incompletely understood. Significant advances in ASD epidemiology have been seen in the past decade. Current prevalence is estimated to be at least 1.5% in developed countries, with recent increases primarily among those without comorbid intellectual disability. Genetic studies have identified a number of rare de novo mutations, and gained footing in the areas of polygenic risk, epigenetics, polygenic risk, and gene x environment (GxE) interaction. Epidemiologic investigations focused on non-genetic factors have established advanced parental age and preterm birth as ASD risk factors, indicated that prenatal exposure to air pollution and short inter-pregnancy interval are potential risk factors, and suggest that further exploration of certain prenatal

nutrients, metabolic conditions, and exposure to endocrine-disrupting chemicals is warranted. Future challenges and goals for ASD epidemiology are discussed.

Keywords

Autism; epidemiology; genetics; air pollution; environmental exposures

INTRODUCTION

Autism spectrum disorder (ASD) is a brain-based neurodevelopmental condition characterized and diagnosed by impairments in social communication and social interaction in the presence of restricted, repetitive behaviors or interests (1). Current population prevalence is estimated at ~1.5% in developed countries around the world (2, 3). Though the full range of etiologies underlying ASD remains largely unexplained, progress has been made in the past decade in identifying some neurobiological and genetic underpinnings of, and risk factors for, this complex condition. ASD is highly heritable, but environmental factors are also implicated in ASD (4, 5). Multiple lines of evidence suggest the etiology of ASD has prenatal origins (6).

This review covers the changing landscape of the epidemiology of ASD, highlighting the most relevant research over the decade since our last review was published (7) through June 2016, including both descriptive epidemiology and genetic and environmental risk factor investigations.

PHENOTYPE AND DIAGNOSIS

Onset of ASD symptoms typically occurs by age 3, although symptoms may not fully manifest until school age or later, and some research suggests symptoms can emerge between 6 and 18 months (8). More severely affected children are more likely to be identified and reliably diagnosed at younger ages than milder cases(9). The hallmark of ASD is impaired social interaction and communication ability, coupled with restricted and repetitive patterns of behaviors or interests. Approximately 4 males are affected with ASD for every female, though the sex ratio appears to decrease with increasing severity (10). Though this pronounced sex disparity is found in all populations studied and has been historically consistent, differences in symptom presentation in females and potential attendant diagnostic biases (11), though unlikely to fully explain observed differences, are worthy of additional investigation.

Common ASD-associated impairments include intellectual disability (currently estimated to occur in ~30% of cases (3); historically estimated at ~70%) and attention deficits (occurring in ~30–40% of cases, though estimates outside this range are common), as well as sensory sensitivities, gastrointestinal problems, immune deficits, anxiety and depression, sleep disturbances, and a range of comorbid medical conditions (12,13). Up to 15% of cases can be linked to a known genetic cause via monogenic syndromes (such as Fragile X syndrome, Tuberous Sclerosis, and Timothy Syndrome) (14).

A clinical diagnosis of ASD relies on expert judgment to detect significant impairment in the core behavioral domains. In 2013, the fifth revision of the Diagnostic and Statistical Manual (DSM-5)(1) changed ASD diagnostic criteria (15), eliminating diagnostic subtypes (which had included Autistic Disorder, Asperger's syndrome, and Pervasive Developmental Disabilities Not Otherwise Specified), and creating a single category formally designated as ASD. Previously distinct social and communication deficit criteria were combined into one domain and a severity rating was incorporated. A new diagnosis, Social Communication Disorder (SCD), was also added outside of ASD (1).

Standardized research assessment tools, most notably the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R), have been designed following DSM-IV criteria; however, these tools will likely still prove useful in the research context under DSM-V given the changes largely represent a reorganization of the same core constructs (16). More streamlined research case-confirmation approaches are also under development (17).

Though still a DSM-5 diagnosis, conceptualizing ASD as a discrete phenotype is being increasingly questioned. The NIMH Research Domain Criteria (RDoC) initiative encourages researchers to deconstruct diagnostic categories and focus on core behavioral and neurobiologic features that cross diagnostic categories in the hopes of improving our understanding of typical versus pathological (18). Tools designed to measure the range of behavioral dimensions fundamental to ASD have been developed and are being more widely used in research (for example, the Social Reciprocity Scale and the Childhood Autism Spectrum Test). Twin studies that estimate ASD heritability using such measures have suggested similar conclusions regardless if autistic traits were assessed discretely or continuously (19, 20). Approaches for creating continuous scores measuring severity among those diagnosed with ASD have also been developed (21). The concept of dimensionality of the ASD-related phenotype also has implications beyond epidemiology. A growing neurodiversity advocacy movement that rejects ASD as a disorder (22) is raising important and challenging questions about the broad societal response to ASD.

PUBLIC HEALTH IMPACT

ASD is one of the most serious neurodevelopmental conditions in the U.S., with significant caregiver, family, and financial burdens. The annual total costs associated with ASD in the U.S. have been estimated to approach $250 billion with lifetime individual ASD-associated costs in the $1.5 to $2.5 million range (estimates in 2012 U.S. dollars) (23). These costs are likely underestimated due to historical under-diagnosis of ASD in older cohorts – largely because of this, one forecast suggests that total ASD-attributable costs will rise to over $450 billion by 2025 (24). Though thought of as a childhood condition, ASD impairments are generally life-long. In addition to core deficits and associated psychiatric comorbidity (25), ASD has been associated with increased risk of non-behavioral health outcomes, including injury (26) and elevated mortality risk (27, 28). The amount of research on ASD in adulthood has increased markedly in the past decade, and lifelong decrements in quality of life related outcomes for individuals with ASD have now been empirically documented (29).

This has led to calls for greater focus on research that can be more directly translated into improved lifecourse outcomes (30).

PATHOPHYSIOLOGY

The neural mechanisms underlying impairment observed in ASD remain unknown, though recent work from genetic (summarized in the Genetic Epidemiology section below), imaging, molecular biology, and gross anatomy investigations has provided insights. Evidence of early brain overgrowth in ASD has been fairly consistently supported, including in a recent meta-analysis (31). Imaging studies have also indicated changes in functional connectivity, and hypoconnectivity across brain structures is common in individuals with ASD (32). Anatomic differences in brain sub-structures, often within the cerebral cortex and cerebellum, continue to be found, though the direction and magnitude of differences reported is variable (33, 34). Recently launched longitudinal imaging studies, as well as work examining white matter integrity in specific brain structures, may help to clarify neuroanatomic features influencing behaviors in ASD (35).

Metabolism, gut and immune function abnormalities have also frequently been described in ASD. Among children with ASD, gastrointestinal symptoms have also been associated with more frequent challenging behaviors (36). However, there is not a clear consensus on the prevalence and potential causes of reported gut pathologies among children with ASD (37). Defects in mitochondrial function, redox sensitive metabolism, and carbon metabolism have also been reported in smaller subsets of ASD cases (38), though how these multi-system comorbidities may aid understanding of pathophysiology or potential etiologic subgroups remains to be determined.

DESCRIPTIVE EPIDEMIOLOGY

In the U.S., the Centers for Disease Control and Prevention (CDC) estimated approximately 1.5% of children aged 8 years in 2012 had an ASD, based on active surveillance and expert review of health and education records (3). The 2012 estimate was similar to that in 2010, marking the first time CDC surveillance prevalence did not exceed a previous estimate since first reported in 2002 as 0.66% (39). However, a slightly higher U.S. national prevalence estimate (2.2%) for children 3–17 years of age in 2011–2014 was estimated according to a large telephone survey relying on parent report of ASD diagnosis in their child (40). Much of the increase in CDC estimates over the last decade has been in milder cases of ASD, with less dramatic changes observed in the prevalence of ASD with co-occurring intellectual disability(41). Efforts to use administrative data to parse change in ASD prevalence due to change in true risk from that due to other factors (42–44) are challenged by the inherent complexity of accounting for simultaneous changes in diagnostic practice, coding tendency, and community awareness. Further, prevalence estimates under DSM-5 are not yet widely available, and the prospective impact of the change in diagnostic criteria, including the potential influence of the new SCD diagnosis, on prevalence remains to be seen. Multiple studies have assessed the proportion of individuals with DSM-IV^{TR} ASD meeting criteria under DSM-5 - with resulting estimates ranging widely (38% to 93%) (45).

The World Health Organization estimated 0.76% of the world's children had ASD in 2010 (2), though this estimate was based on studies in countries representing only 16% of the global child population (46). Other systematic reviews of prevalence studies internationally have produced similar summary estimates, of approximately 0.7%(2, 47), though lower estimates were reported from a review in China(48). Yet, summary estimates mask considerable variability across geography, methodological approach, and time. The highest recent international prevalence estimate was 2.64%, for 7–12 year old children in South Korea in 2005–2009. This estimate was based on a two-stage screening-confirmation approach (49). National registries in Scandinavian countries provide a unique resource for estimating temporal trends. In 2011, ASD prevalence based on registry estimates exceeded 1% in Finland and Sweden and 1.5 % in Denmark. These 2011 estimates reflect steady increases in age-specific ASD prevalence across birth year cohorts from 1990 to 2007 (50), mirroring reports in the U.S. (3). In Sweden, much of the increase was attributed to improved documentation and, as seen in the CDC data, identification of milder ASD (e.g., without accompanying intellectual disability) (51). However, this and other attempts (52, 53) to dissect causes of secular trends in international ASD prevalence face similar challenges as efforts in the U.S. Lastly, reliable prevalence data from developing countries is still sparse, and, despite growing interest over the past decade, formal study of the influence of global cultural variations on ASD awareness and diagnosis remains limited (47, 54).

Within the U.S., non-white race, Hispanic ethnicity, and low socioeconomic status (SES) have been associated with lower ASD prevalence and delayed diagnosis (3, 43). Disparities in prevalence have narrowed over time in some U.S. regions and are less prominent when ASD is accompanied by intellectual disability (55). In contrast, ASD diagnosis tends to correlate with factors related to lower SES in Scandinavian countries (56).

Also worth noting is that virtually all ASD descriptive epidemiology has focused on children. To date there has been only one rigorous study of ASD prevalence in adults, conducted in England in 2007 (57). This investigation actively sampled adults from the community and used an active two-stage screening-confirmation approach to generate an estimate of 1%. ASD case-finding in population samples of adults is particularly challenging as efficient sampling frames are far more difficult to develop, non-risk related birth cohort effects are magnified, and lifecourse influences increase phenotypic variability.

GENETIC EPIDEMIOLOGY

The genetic contribution to ASD etiology is strongly supported historically by twin and family studies, with recent heritability estimates in the U.S. and Europe ranging from 50% to 95%(58–60). Additionally, estimates of recurrence risk among siblings of autistic children range from 3% to 18% (60–62). Over the past decade, genetic studies have been quite successful at identifying rare genetic variation, including inherited and *de novo* mutations and copy number variations (CNVs), related to autism or autistic features(63). However, observations of specific rare *de novo* and inherited CNVs have been limited to a small portion (about 10%) of children with non-syndromic autism (64). Several strong candidate genes have been identified including post-synaptic scaffolding genes, e.g., *SHANK3*, contactin genes, eg *CNTN4*, neurexin family genes, e.g. *CNTNAP2*, and chromatin

remodeling genes, *e.g. CHD2* (https://sfari.org/resources/sfari-gene). As described in more detail below (within the Genomics and neurobiology section), evidence is mounting to suggest genetic risk variants identified among individuals with ASD converge on common genetic pathways. The cumulative effect of multiple common genetic variants, i.e. polygenic risk, is now being recognized as an important indicator of risk for other psychiatric disorders and for ASD(64, 65). Common variants contributing to polygenic risk in ASD are also thought, at least in part, to be shared with other neurodevelopmental and psychiatric disorders (66). Large-scale genome-wide ASD and cross-disorder association studies with enough statistical power to estimate small effects from common genetic variants are only now emerging and require combining data sets from multiple, large population samples.

I. Gene-environment interaction (GxE)

While there is a clear genetic contribution to ASD, the considerable phenotypic and genetic heterogeneity support a multifactorial etiology. There is conflicting evidence about the contribution of environmental factors in the etiology of ASD, with some samples showing liability predominately driven by additive genetic influences, and others reporting a nearly equal contribution from heritable and non-heritable shared environmental factors(67). In addition, failure to accommodate heterogeneity by environmental exposure could lead to attenuation of genetic main effect signals in traditional GWAS (genome-wide association studies).

Despite growing interest in evaluating GxE in ASD, only a few such studies have been published to date (68–70). This is primarily due to lack of availability of both genotype and high quality exposure information within the same data set, combined with the need for large sample sizes in GxE analyses to avoid imprecision and false positive findings. To overcome these challenges and to increase the research in this area, several investigations have begun to collect suitable datasets. Additionally, work to develop novel tools that would enable meta-GxE analyses across studies and application of recently established well-powered GxE methods (e.g., (71, 72)) is underway. These approaches have had successes in other complex chronic conditions, and may generalize well to ASD research.

While published results have been few, and replication is needed, analysis of both biologically driven and genomic burden-based metrics have shown promise in identifying GxE in ASD. All three of the GxE studies published to date were based on either candidate gene or global CNV burden, as opposed to full genome-wide GxE analyses that would require millions of tests. These reports suggested interactions between the *MET* gene risk variant and prenatal exposure to air pollutants (70), variants in the one carbon metabolism pathway and maternal use of prenatal vitamins (69), and a set of ASD-associated CNVs and maternal prenatal infection (68); however, replication of these findings is necessary.

II. Epigenetics

Epigenetics is a term used to describe a wide-range of molecular information that “sits on top of” the DNA sequence and regulates a diverse set of cellular processes including imprinting, gene expression, and organismal development. In recent years, there has been increasing interest in examining epigenetic marks in ASD due to their potential mechanistic

involvement in etiology, particularly to explain the effects of environmental exposure or gene-environment interaction associations with ASD, or to serve as a biomarker of previous exposure or of disease (73). Studies have shown that DNA methylation (DNAm), a type of epigenetic change, can be controlled by genetic variation(74) and that it can change with exposure to environmental factors (75–77). Interestingly, Rett Syndrome, Fragile X, and Angelman Syndrome are all caused by epigenetic dysregulation (78–80) and each shares phenotypic overlap with ASD. Epigenetic changes have been found in the brains of individuals with ASD, including hypo- and hyper-methylation (81) and spreading of histone 3 lysine 4 trimethylation marks (82), as well as in DNA derived from a range of more accessible tissues, highlighting the future potential for epigenetics to serve as a biomarker of disease. Interestingly, rare genetic variants for ASD implicate chromatin remodeling, another aspect of epigenetic regulation. Chromatin structure has not been extensively examined in ASD, given the need for immediate processing of large amounts of biospecimen tissue.

III. Genomics and neurobiology

There has been considerable recent focus on leveraging genomics to define common biological processes implicated across genetic discoveries in ASD. Analysis of rare variants linked to ASD has revealed three common biological pathways - chromatin remodeling, synaptic cell adhesion and scaffolding, and neuronal signaling and development (63, 83). Transcriptomics studies considering ASD-associated co-expression patterns in postmortem brain have identified networks of brain development genes(84) implicated in ASD and specified mid-fetal development as a critical period for initiation of ASD neuropathology (85). In addition, these studies have also found networks of genes related to immune response (84, 86) and activation of M2 microglia (86) to be differentially co-activated in ASD brains, although questions remain as to whether this has etiologic implications or is a downstream consequence of other events.

ENVIRONMENTAL RISK FACTORS

I. Prenatal and perinatal factors

Systematic reviews and meta-analyses (87–90) suggest more than 20 individual, familial, pre-, peri- and neonatal factors with some level of converging evidence for ASD risk (e.g., significant positive associations across 2 or more individual studies). The candidate risk factors most commonly investigated over the past decade are discussed further below.

Parental age—ASD risk in association with parental age, particularly maternal age, has been examined in many studies, and increased parental age is one of the most consistently identified perinatal risk factors for ASD (90–92). Both older mother's age and older father's age appear to independently influence ASD risk; there is also evidence for variation in risk across parental age combinations (93), recently demonstrated in a large, multinational study (94). A range of potential mechanisms may underlie these associations, including epigenetic modification, confounding by genetic liability or social determinants of reproductive age, and mediation by age-associated pregnancy risks (95).

Interpregnancy interval—Increases in risk of ASD with a short (<12 months) interpregnancy interval (IPI) have been consistently reported (96–102), and although evidence is more limited, three studies reported increased risk from long IPI (>60->84 months) (97, 100, 102). The potential mechanisms underlying such associations are unknown, but are hypothesized to relate to maternal nutrient deprivation, inflammation, stress, infertility, or other reproductive characteristics.

Immune factors—Maternal hospitalization with infection during pregnancy has been associated with increased risk of ASD in a few recent studies (103, 104). Evidence is mixed with regard to the importance of the type (e.g. bacterial vs. viral) and timing of infection, though the largest study of over 2,000,000 individuals supported increases in risk of both maternal bacterial and viral infections(103). These epidemiological results are consistent with animal models that demonstrate maternal immune activation can result in autism-like phenotypes in offspring (105), and, as noted above, modification of the effect of prenatal exposure by ASD-associated CNVs has been reported (68).

Familial history of autoimmune disease has also been associated with increased risk of ASD (106–108), findings perhaps suggesting some shared genetic liability. Maternal immune-mediated conditions (104, 109) and autoimmune reactions could, however, also influence risk of ASD through transfer of antibodies and impact of immune markers on the developing nervous system. Several small-sample studies have all found maternal antifetal brain antibodies in subsets of ASD cases with no evidence of these antibodies in controls, as recently reviewed (110). Animal studies have demonstrated altered neurobehavioral activity in pups of dams injected prenatally with human IgG from women with ASD-affected children (111, 112).

Recent studies assessing biomarker-based evidence of differential immune function during etiologically relevant (i.e., prenatal or neonatal) windows have suggested increased ASD risk associated with altered levels of c-reactive protein (CRP)(113, 114) and other immune markers, including IFN-γ, IL-4 and IL-5 (115), in maternal sera, with more conflicting results for levels of immune markers measured in newborn blood spots (116–118). Methodological limitations in these studies, including small sample size and high correlation among immune markers, suggest further work is needed to determine the importance of individual immune markers.

Medication use—Beyond historical examples of increased ASD risk following exposure to certain medications with teratogenic properties (7), more recent associations between ASD and prenatal medications include antidepressants, anti-asthmatics (especially $\beta-2$ adrenergic receptor agonists or B2ARs), and antiepileptics. Although considerably different in pharmacological activity, these drugs have the ability to cross the placenta and blood-brain barrier, and can also be transferred to the child through breast milk, and have supporting animal model evidence for neurological effects in offspring prenatally exposed (119–121). Antidepressants, particularly selective serotonin-reuptake inhibitors (SSRIs), have been the most investigated; evidence is conflicting, with six studies reporting increased risk and five finding no association(122). Recent studies of antiepileptics (123–125) and

B2ARs (126, 127) have consistently identified increased risk of ASD or autistic traits with exposure during pregnancy(124,125).

Other prenatal and perinatal factors—Both lower gestational age/preterm birth (128–132), as well as small- or large-size-for-gestation appear to independently increase risk of ASD (129, 130), though these factors may also be markers or mediators of other pregnancy risks. Study results also provide general support for increased ASD risk from maternal metabolic conditions (including gestational weight gain, diabetes, and hypertension) and potentially their interplay; these conditions influence mechanisms relevant to ASD (e.g., chronic inflammation, fetal hypoxia, oxidative stress, insulin resistance) (133–136).

Other factors recently examined in multiple studies, with less consistency for increased ASD risk, include caesarian delivery and assisted conception. A meta-analysis including 21 studies(137) indicated a small increased risk with caesarian delivery, though subsequent studies reported no risk and possible familial confounding(138,139). The weight of evidence suggests little or no increased ASD risk with assisted conception overall (140,141), with sociodemographic and suspected mediating perinatal factors playing a large role in observed modest associations (142). It is possible that risk may be elevated with some specific treatments (143–145), but adequately powered studies are needed to examine rarer therapies and separate the influence of indicating infertility condition from treatment (142).

Etiologic implications of pre- and perinatal associations—Recent studies of composite scores combining pregnancy-related conditions(99, 146) are consistent with historical reports that increasing numbers of suboptimal conditions in pregnancy generally pose increasing risk of ASD and adverse developmental outcomes (147–149). A number of key considerations for future research can be drawn from this finding. First, etiologic insights may be gained by investigating the underlying pathogenic mechanisms shared by multiple pre- and perinatal factors (such as immune dysregulation)(150). Further, given the lack of outcome specificity to ASD of many of these factors (151, 152), future inclusion of broader autism phenotype and comorbidity patterns may advance understanding of brain development processes that impact a range of adverse neurodevelopmental outcomes. Finally, detailed dissection of directionality and mechanisms of causation across pregnancy risks and obstetric sub-optimality, including consideration of the roles of confounding by indication (particularly for medications/treatments), and of genetic liability, deserves analytical attention, may prove etiologically informative (148, 149).

II. Maternal dietary and lifestyle factors

Maternal prenatal diet is known to influence fetal neurodevelopment, with established associations between folic acid and neural tube defects, as well as with other adverse neurodevelopmental outcomes (153). Only recently have maternal dietary factors during pregnancy been considered in association with risk of ASD.

Folic acid and related nutrients—Two studies (one in the U.S. and the other in Norway) (69, 154) have suggested an approximately 40% reduction in risk for ASD with periconceptional folic acid supplement use. As mentioned above, the U.S. study reported

significant gene-environment interaction, with greater reductions in risk of ASD from prenatal vitamins when the children or their mothers carried gene variants leading to less efficient folate metabolism, and also found a significant trend of decreasing ASD risk with increasing mean daily folic acid intake(155). However, a third study (conducted in Denmark), reported no association between preconceptional and prenatal folic acid and multivitamin use and ASD (156). Only one study to date has *measured* folate blood concentrations during pregnancy (at 11–21 weeks gestation), and found no association with ASD traits as measured by SRS scores. Differences across countries in fortification practices (157) and folate levels, as well as in genetic background, particularly of variants along the one carbon pathway previously shown to modify associations between prenatal vitamins and ASD (69), and timing of exposure assessment, could be involved in discrepant findings. Other nutrients involved in one-carbon metabolism and methylation, including vitamin B12, choline, and homocysteine, have not been specifically studied in association with ASD, but would further inform the role of the folate metabolism pathway and its cofactors. Further review of folate and ASD, including discussion of mechanisms, is provided elsewhere (158).

Other prenatal nutrients—Other nutrients have been associated with ASD, but to date their examination during the prenatal period has been extremely limited. One study reported a reduction in risk of ASD for retrospectively-measured prenatal maternal iron intake (159); another suggested attention deficits but not ASD with lower levels of prenatal maternal vitamin D levels (160); and another found a significant decrease in risk of ASD with higher prospectively-reported prenatal polyunsaturated fatty acid (PUFA) intake (161). Maternal fish intake (161) or fish oil supplements (154, 161) (a source of PUFAs, but the former also of mercury, a known neurotoxicant) have not been associated with ASD in 1 and 2 studies respectively, though power was quite limited in one study. Additional epidemiologic research is needed on these and other maternal dietary factors, including more rigorously designed prospective studies incorporating biomarkers.

III. Alcohol and smoking

While smoking and alcohol during pregnancy are known to cause adverse neonatal outcomes, and though the extant literature has a number of methodological limitations, the available evidence points to an overall lack of an effect of maternal prenatal use of these substances on ASD risk. A recent meta-analysis of 15 studies from multiple countries found no evidence that maternal smoking during pregnancy was associated with risk of ASD overall (162). Fewer studies have been conducted regarding maternal prenatal alcohol consumption, though the largest study to date found no association (163).

IV. Environmental chemicals

Certain environmental chemicals cross the placenta and the blood–brain barrier, accumulate in developing brains, and interfere with normal neurodevelopment. Others disrupt hormone pathways or act on inflammatory pathways that may have downstream effects on brain development. Epidemiologic investigation of environmental chemicals as potential ASD risk factors has increased over the last decade, with most work being done in the areas of air pollution and potential endocrine disrupting chemicals, thus our focus here.

Air pollution—Over the past decade, prenatal exposure to air pollution has emerged as a candidate risk factor for ASD, with eleven U.S. studies published to date (164–174). These studies have generally focused on air toxics (also referred to as Hazardous Air Pollutants (HAPs)), criteria air pollutants (including nitrogen dioxide (NO_2), ozone, and particulate matter less than 2.5 or 10 microns in diameter ($PM_{2.5}$ or PM_{10})), and traffic exposure.

The first study of HAPs and ASD, conducted in Northern California, found moderately increased risks of autism with several metals and chlorinated solvents (174). Four subsequent studies have been conducted in several regions, with additional toxics implicated and some replication of results for metals (cadmium, lead, mercury, etc.), solvents, methylene chloride and styrene, and diesel particulate matter (165, 168, 170, 173). All these studies based exposure assessment on U.S. National Air Toxics Assessment data, which includes 187 HAPs and uses emissions and source data from a single year. This data source is somewhat limited in its spatial and temporal interpretability creating potential exposure misclassification.

For criteria air pollutants, two studies from California have suggested associations with NO_2, $PM_{2.5}$ and PM_{10} (164, 172). Studies over larger spatial areas in the U.S. report increased ASD risk with increasing PM_{10} exposure (in North Carolina and Northern California)(166), as well as with $PM_{2.5}$ exposure (across regions of the U.S.) (167, 169). Exposure assignment for these studies has been based on linkages to the AirNow network, which monitors near- roadway air pollution through dispersion models, traffic density, and distance to roadways. Two of these studies specifically indicated the third trimester as the most important exposure window (166, 167). As mentioned above, one study also found susceptibility to NO_2 exposure to be increased by the presence of a genetic variant near the *MET* gene locus (70).

The few studies conducted outside the U.S. have disparate findings. A recent publication from a joint analysis of four European birth cohorts found no association of NO_2 exposure with ASD traits (175) and examination of the air pollution-autistic traits relationship in a Swedish twin sample yielded null results (176). In contrast, analysis of a large cohort from Taiwan suggested increased ASD risk with higher exposures to four pollutants, including ozone and NO_2 (177). The greater variability in findings outside the U.S. could be related to a number of factors. The international studies assessed ASD or related traits using different methods and at different ages than most U.S. studies. Methods used to assess air pollution exposure were also variable across these studies, though not dissimilar to some work in the U.S. The U.S. studies could be more vulnerable to residual confounding due to social factors that correlate with both air pollution and ASD status (especially for the U.S. studies relying on community-acquired ASD diagnoses). However, while similar criteria pollutants were examined across these studies, the levels and mix vary across countries and regions, suggesting that the exposures may not be directly comparable.

This rapidly growing evidence base suggests that further investigation of associations between air pollution and ASD risk is warranted (178). A contemporaneous body of epidemiologic research has also supported associations between prenatal air pollution exposure and more broadly defined early life cognitive and behavioral impairment (179). *In*

vivo and *in vitro* studies have begun testing potential underlying mechanisms, considering both indirect (i.e. systemic responses like immune activation or oxidative stress) and direct (i.e., small particle deposition in the developing nervous system) effects. Moving forward, epidemiologic research will need to: address the outcome, exposure and confounding measurement issues identified; more carefully consider the effects of mixtures of highly correlated air pollutants; examine windows of vulnerability (challenged by high correlation in exposure across prenatal time periods); and incorporate exposure to pollutants that are unregulated and less commonly measured, such as PM <0.1.

Endocrine disrupting chemicals (EDCs)—Endocrine disrupting chemicals (EDCs) include environmentally-persistent organic pollutants as well as certain non-persistent chemicals. Exposure to EDCs is ubiquitous in developed countries, and they are commonly detected in U.S. biosamples (180). EDCs are of concern because they interfere with the activity of hormones critical in neurodevelopment (181), may interfere with immune system activity (182), and have been associated with a range of neurodevelopmental endpoints (183).

Several recent studies have investigated prenatal pesticide exposures, some reporting associations with ASD. Statistically elevated associations were seen for maternal urinary concentrations of dialkyl phosphate (DAP) metabolites, a marker of organophosphate (OP) pesticide exposure, and maternally reported symptoms consistent with pervasive developmental disorder (PDD) in 2-year-olds (184); higher maternal serum concentration during pregnancy of trans-nonochlor, an organochlorine (OC) pesticide, and more autistic behaviors as measured by maternal report on the SRS (185); residential proximity to OC pesticide applications during early gestation and ASD (186); and residential proximity to fields applied with OP pesticides in mid to late pregnancy and ASD (187). However, in each of these studies, additional pesticides and/or metabolites studied were not statistically associated with ASD risk, demonstrating inconsistency in results for this class of chemicals.

Two studies examining risk of ASD in relation to prenatal levels of poly-chlorinated biphenyls (PCBs) produced conflicting findings. One reported a suggestive association with total PCBs measured and ASD (188), while the other found an inverse association with PCB-178 and no significant associations with other PCB congeners for autistic behaviors measured by the SRS (189). Only one study has reported on prenatal exposure to PBDEs, and found inconsistent patterns of association with autistic behaviors for different congeners measured in maternal serum (189).

Prenatal exposure to BPA has been examined in two studies, and neither found an association with autistic behaviors as measured by the SRS (189, 190). In the work, levels of prenatal phthalate metabolites were associated with greater autistic symptoms in one study(190), but significant associations overall were not found in the other (189). In studies with surrogate phthalate assessments, a positive association was reported between ASD and PVC flooring in the home (191), but phthalates in house dust, which may not have represented prenatal exposure, were not associated with ASD in another study (192). Only two studies have examined exposure to perflourinated compounds in association with ASD phenotype; one found that increasing prenatal maternal PFOA levels were associated with

fewer autistic behaviors (189), in contrast to a large study from Denmark which found no associations between prenatal levels of PFCs and autism (193).

At this point, epidemiologic evidence with respect to early life exposure to EDCs and ASD risk remains sparse, and future studies should address limitations of previous work by expanding sample size, incorporating data on exposure during different potential etiologic windows, and considering exposure mixtures. In addition, investigations incorporating genomic and epigenomic data might reveal susceptible subgroups and thoughtful consideration of ASD's sexual dimorphism in the context of these hormonally acting exposures is warranted.

Other environmental chemicals—Heavy metals such as lead and mercury are established neurotoxicants with documented impacts on cognitive and developmental outcomes, while some metals may also act as EDCs (194). Epidemiologic evidence to date has consistently shown no increased risk of ASD with vaccines (195, 196). ASD risk following prenatal exposure to mercury through fish or other sources has received little study, but has not been associated with ASD in available evidence (161). Low-level exposure to lead in association with ASD has not been studied in depth, though work examining prenatal levels of these and other chemicals from shed deciduous teeth is emerging, and may prove informative. The potential impacts of range of environmental chemicals, including metals, on risk of ASD is the subject of another review (197).

FUTURE DIRECTIONS AND CONCLUSIONS

In the United States, and the rest of developed world, ASD is now accepted as one of the most common serious developmental conditions, and the staggering economic burden of ASD throughout the lifespan is now being quantified. With recent prevalence increases in ASD driven by those without cognitive impairment (41), the population impact of the condition's dimensionality, and the need to enable and support individuals with ASD having a range of abilities and disabilities, are more fully recognized. Challenges in ASD descriptive epidemiology for the next decade include: characterization of the impact of the shift to DSM 5; deeper exploration of the interplay of race, ethnicity and SES on ASD distribution and addressing diagnostic disparities related to these factors as well as to sex; more robust comparisons of ASD characteristics across sexes; and enhanced effort to describe the epidemiology of ASD over the life course and in developing nations around the world. Perhaps also, the coming decade will see increased population-level surveillance of key continuous traits underlying the ASD phenotype in addition to the condition itself.

Recent developments continue to reveal complexity in the genetic epidemiology of ASD. Identification of etiologically significant rare variants has proliferated, and the field also seems poised to move into a period of common variant discovery. Although any one variant's associated attributable risk is small, the combined knowledge of biologic systems affected downstream contributes to an improved mechanistic understanding of ASD. In addition, given the *de novo* nature of many of these rare variants, modifiable determinants upstream may also be discovered. Initial empirical evidence supporting gene-environment interaction has emerged over the last decade (68–70), though replication of individual

findings is needed, and combining genomic and environmental exposure information in large datasets needs to be a major research goal.

Epidemiologic investigation of potentially modifiable risk factors has grown markedly over the past decade. Multi-study bodies of evidence have established parental age and preterm birth as true ASD risk factors requiring further mechanistic dissection, and have newly identified short IPI as a risk factor for ASD. Prenatal air pollution exposure has also emerged as a potentially modifiable risk factor of great interest (178), but one necessitating further investigation to address gaps described above.

In addition to focused follow-up on modifiable risk factors, and continued efforts to identify new risk factors, advances in the coming decade might also be catalyzed via innovation around biomarkers of exposure and exposure response prompted by increased broad interest in the field of exposomics (198). The development or synthesizing of large epidemiologic cohorts of children containing informative outcome data, relevant biosamples for exposomics, and available genomic data is now being put into practice; however, the extent to which ASD-related outcomes are incorporated into such cohorts, and the utility of exposomics technology, including its ability to reach back into the critical windows for ASD etiology, remains to be seen. Notably, because many environmental factors, such as nutritional factors and chemicals, represent opportunities to reduce risk of ASD through actionable policy implications and public health interventions, these create exciting future research opportunities. Equally or even more important is determining whether and how real-world mixtures of exposures may compound risk and/or identifying individual “bad actors” or groups of exposures that may be intervened upon for widespread public health impact.

Considerable progress in understanding the epidemiology of ASD has been made over the past decade. Continued evaluation of genetic factors, environmental toxicants, nutritional and lifestyle factors, and prenatal complications, individually and in combination with one another, employing novel methodologies, over the coming years is critically needed to take this progress even further in our understanding of, and ability to have a positive impact on, ASD.

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