Current Topics in Toxicology
Vol. 17, 2021

Mini-Review

The influence of environmental pollution on the incidence of autism spectrum disorders: Challenges and opportunities for research

Priyanka Kulkarni[1,*] and Annapurni Jayam-Trouth[2]

[1]Howard University College of Medicine, 520 W St, NW, Washington, DC 20059, USA;
[2]Department of Neurology, Howard University College of Medicine, 520 W St, NW, Washington, DC 20059, USA.

ABSTRACT

An increasing number of researchers have investigated the influence of various environmental pollutants on the incidence of autism spectrum disorders (ASD). It is important to understand the environmental causes of autism not only from a medical perspective but also from the government policy viewpoint. Based on the review of recent literature, we would postulate that research on the environmental epidemiology of ASD is subject to at least five challenges: (1) *Definitional challenges*, stemming from multiple etiologies for ASD; (2) *multiple biochemical pathways* underlying ASD, such as oxidative stress and cytokine storm, obscuring the cause-effect relationship; (3) *vast number of environmental pollutants*; (4) *confusion between the group level and individual level* findings; and (5) *cross-sectional as opposed to longitudinal* nature of much of research. We believe that addressing these challenges can substantially improve the validity of environmental epidemiology of ASD research and assist in the clarity of understanding of some significant issues in public health.

KEYWORDS: environmental epidemiology, autism, environmental pollution.

*Corresponding author
priyanka.kulkarni@bison.howard.edu

INTRODUCTION

The etiology of autism is uncertain. However, a significant amount of epidemiological research suggests that environmental pollution may impact the incidence of autism spectrum disorders (ASD) [1-6]. It is important to study the environmental epidemiology of ASD not only from a medical perspective but also from the government policy viewpoint.

The few studies cited below illustrate the increasing interest of researchers in examining the influence of environmental pollutants on the ASD incidence. Some authors have examined the relationship between traffic-related air pollution, air quality, and ASD [5]. Maternal exposure to nitrogen dioxide and particulate matter – PM_{10} and especially $PM_{2.5}$ during gestation and the first year of a child's life were also associated with autism. Some studies found a positive association between ASD incidence and the residence proximity to freeways (surrogate for air pollution) during pregnancy, adjusting for socio-demographic factors; and residence proximity to landfills [5, 6].

The research based on the differences in the blood and urine levels of heavy metals in autistic as opposed to normal children has produced mixed results [7, 8]. The Cd and Pb levels in urine were found to be significantly *lower* (unlike Cr levels that were *higher*) in children with autism compared to healthy subjects. The results suggest that

autism may be associated with significant decrease in excretion rate of Cd and Pb and a significant increase in the excretion rate of Cr in the urine. However, some studies found no significant differences in the serum levels of Pb among autistic and control populations [7, 8].

Despite extensive research on the impact of environmental pollution on autism incidence, we found that much of the research is fraught with several challenges.

METHOD

In order to find out about the limitations of existing research on the environmental pollution and ASD incidence, we conducted numerous database searches (the final search conducted during May-June 2020) using Pubmed, Google Scholar, and CINAHL for years 2017-2020. According to the search strategy, the terms 'autism' or 'ASD' had to be part of the title or subject. This was combined with terms, such as 'epidemiology,' 'pollution,' 'etiology,' 'heavy metals', 'mercury,' 'lead,' 'pesticides,' 'oxidative stress,' 'cytokines,' 'genetics,' 'longitudinal design,' and 'agent-based model' as keyword searches, where applicable. The references cited in identified publications were also searched to locate additional studies. Inclusion criteria were the relevance of the title and abstract to ASD. Studies that primarily covered animal models were discarded. Figure 1 lists the PRISMA flowchart.

Based on our review of the existing literature, we postulate that there are at least five challenges relevant to epidemiological research pertaining to the influence of environmental pollution on ASD incidence: (1) definitional challenges, (2) different biochemical pathways, (3) vast number of toxins, (4) group and individual level differences, and (5) cross sectional design. We believe that addressing these challenges can substantially improve the validity of environmental epidemiology in ASD research.

RESULTS

(1) Definitional challenges: Multiple etiologies

The broad spectrum of ASD symptoms suggests that there may be multiple etiologies instead of a single one [9-13]. ASD refers to a diverse range of

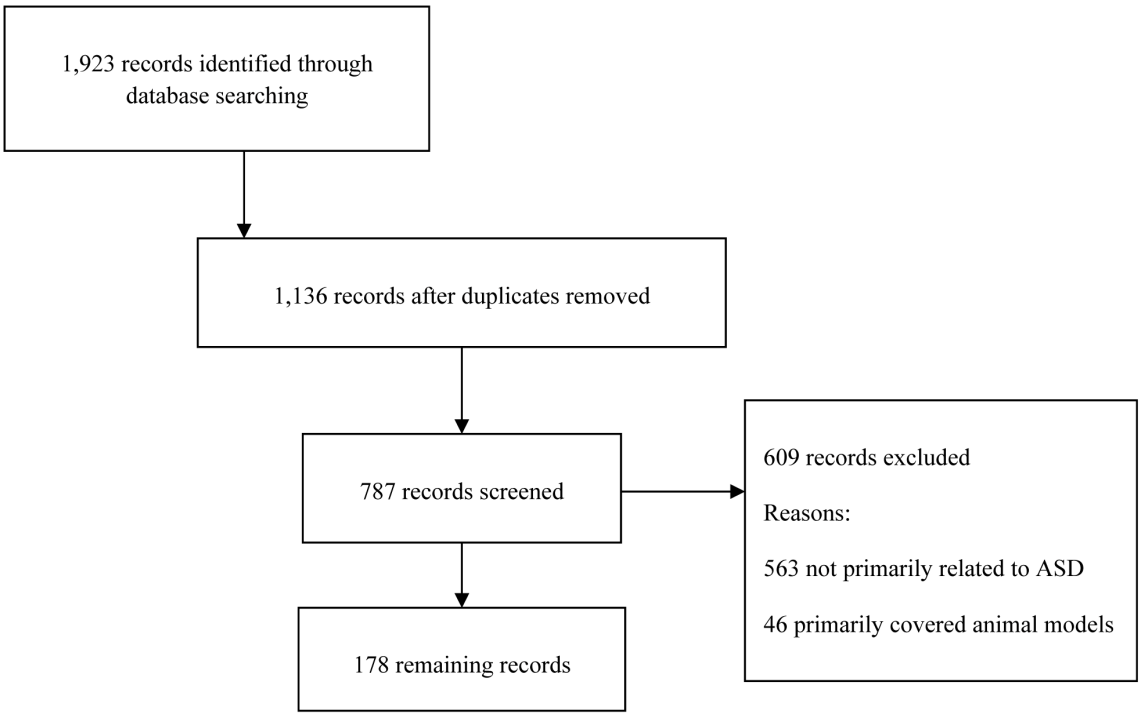

Figure 1. PRISMA flow chart.

disorders such as autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) that share common traits/deficits in mainly three areas – social interaction, communication, and repetitive or stereotypic behavior. Individuals with Asperger's disorder do not have significant language delays, and they exhibit average cognitive skills. Individuals with PDD-NOS show problems in the core social domain but the severity of symptoms in the other two domains is relatively limited.

There is some debate whether the distinction among the "sub-types" of ASD is warranted. Some researchers have argued that it may not be very useful to find distinct genes associated with the ASD sub-types; and Asperger's Syndrome and autistic disorder may not be qualitatively distinct [10-13]. Instead, there are quantitative differences in the severity of symptoms. On the other hand, some authors have suggested that the broad spectrum of symptoms may imply several etiologies instead of a single one [10-13]. There are numerous studies linking ASD phenotypes with genotypes. Indeed, ASD has strong genetic roots. It has a heritability of 80%, a monozygotic concordance rate of 70-90%, a dizygotic concordance rate of about 10%, and a 20-fold increase in risk for first-degree relatives [14, 15].

However, it is difficult to pinpoint the relationship between a specific genotype and phenotype due to the high level of genetic heterogeneity because ASD often involves multiple genes. For example, more than 100 genes and 380-820 loci have been identified in ASD [14-18]. According to one survey, there are about 103 ASD genes and 44 loci. This survey reveals that the most frequent abnormalities are 15q11–q13 duplications, and 2q37, 22q11.2 and 22q13.3 deletions. Some of the regions of interest identified in more than one genome screen are on chromosomes 1p, 2q, 5q, 7q, 15q, 16p, 17q, 19p, and Xq. One promising region appears to be the one located on chromosome 7q.

Furthermore, there may be different genetic systems (GS) underlying the differences in the ASD phenotypes [14-16]. They outline several possibilities or genetic scenarios at work that could affect communication skills and IQ of individuals with ASD: (1) GS 1 and GS 2 may independently influence communication and IQ; (2) GS 1 may influence both, communication and IQ; and (3) GS 1 may influence both, communication and IQ, and GS 2 may independently influence IQ.

Sometimes, ASDs can be attributed to mutations of single genes [15, 16]. The most common single gene mutation in ASDs is fragile X syndrome (FMR1), present in about 2% of cases. Other monogenic disorders in ASD include tuberous sclerosis (TSC1, TSC2), neurofibromatosis (NF1), Angelman syndrome (UBE3A), Rett syndrome (MECP2), to name a few. Monogenic Mendelian disorders show a tight genotype-phenotype correlation. But complex polygenic disorders may not follow a strict genotype-phenotype correlation because of the interaction between multiple gene variants, environmental influences, and broad phenotypic variability among individuals.

Early studies about the relationship between inherited genes and ASD phenotypes have largely failed to identify specific genetic systems. However, the studies about sporadic (non-familial) ASD have been somewhat more conclusive in identifying key *de novo* copy number variants (CNV) genes or regions such as SHANK1, CDH8, NRXN3, PTCHD1, and 16p11.2, among others [15, 16].

In summary, there is a lot of confusion about whether a separation of ASD phenotypes is warranted, based on the underlying genotypes. Furthermore, much of current epidemiological research aggregates different ASD sub-phenotypes. Therefore, the connection between environmental variables and the incidence of a particular type of autism is often masked.

(2) Vast number of environmental pollutants

Some researchers have begun to narrow down the list of chemicals so as to identify the potential neurotoxins in humans. For example, there are about 1000 experimental neurotoxins out of about 80,000 chemicals that are registered for commercial use with the U.S. Environmental Protection Agency [2, 19]. Many have further condensed this list to 202 known neurotoxins in humans. These include metals and inorganic compounds (e.g., arsenic compounds, lead compounds, methylmercury),

organic solvents (e.g., acetone, benzene, chloroform, toluene, ethanol, carbon disulphide, etc.), pesticides (e.g., DDT, chlorpyrifos, methyl parathion, etc.), and other organic substances (e.g., acrylonitrile, aniline, ethylene, hydrazine, phenol, etc.). Still, the list of potential neurotoxins is admittedly large.

Hundreds of chemicals have been implicated as potential mutagens and teratogens including lead, methylmercury, polychlorinated biphenyls, gasoline, and toluene, among others. However, some authors have argued that a toxin may be labelled as teratogenic only tentatively because a teratogenic exposure includes not only the agent but also a number of factors such as the dose and the time in pregnancy when the exposure occurs [2, 19, 20]. In fact, the dose is a crucial component in determining the teratogenic risk. Each teratogen has a threshold dose below which the risk of teratogenesis is insignificant irrespective of the stage of pregnancy. It is also easier to exclude an agent as a cause of birth defects than to conclude definitively that it is responsible for birth defects because of the existence of genocopies of some teratogenic syndromes [2, 19, 20].

It is indeed difficult to narrow the list of chemicals that may trigger ASD. However, some studies have shown that chemicals such as mercury, cadmium, nickel, trichloroethylene, and vinyl chloride significantly elevate the risk for mutagenesis [2, 19]. Although it may be a good idea to investigate the influence of a "working list" of a handful of chemicals on ASD epidemiology, there exists a significant potential for the influence of numerous other chemicals and their interactions. Coupled with the multiple biochemical pathways involved in autism, it is considerably difficult to identify the specific chemicals influencing ASD incidence.

(3) Multiple biochemical pathways

There are many possible biochemical pathways underlying ASD [21]. Therefore, the cause-effect relationship between a specific environmental toxin and ASD is not very clear. For example, there is an "oxidative stress hypothesis" particularly caused by defective sulfur metabolism in autistic children [22-26] and "cytokine storm" [27-30] to name only a couple.

Some authors have outlined a redox/methylation process as part of oxidative stress [22, 25], where environmental factors, coupled with genetic factors may result in impaired sulfur metabolism, which creates oxidative stress. Oxidative stress, in turn, can inhibit methionine synthetase activity. This results in: (a) interference with DNA methylation, which may trigger changes in gene expression and developmental delay; and (b) interference with dopamine-stimulated phospholipid methylation, an important trigger for neuronal synchronization, as well as attention and cognition.

Cytokines have also been implicated in ASD [27-30]. Cytokines are different types of proteins that usually originate in immune cells, and they control the immune response that may mediate the immune system and the nervous system. Cytokines are known to influence synaptic network formation and other aspects of neurodevelopment. In particular, the following cytokines have been associated with ASD because of their abnormal expression in the brain, peripheral blood and gastrointestinal tract of autistic children: They are interleukin (IL)-1β, IL-6, IL-4, interferon (IFN)-γ, and transforming growth factor beta (TGF-β).

Several environmental chemicals, such as heavy metals, pesticides, and aromatic halogenated hydrocarbons possibly have a potential to trigger ASD because they can cause *both* oxidative stress *and* cytokine imbalance, which illustrates the multiplicity of biochemical pathways underlying ASD:

Heavy metals: Heavy metals such as mercury, lead, nickel and cadmium are known to have a potential to cause oxidative stress [31, 32]. For example, they have an affinity for the thiol groups, and they can disrupt sulfur metabolism pathways [31-33]. Oxidized metabolites of xenobiotics contribute to oxidative stress and sulfur metabolism is important for the excretion of xenobiotics. Heavy metals combine with the thiolate anion. The inorganic divalent mercuric cation can simultaneously bind two thiolates, thereby significantly increasing mercury retention.

Elevated mercury levels are associated with ASD occurrence because of its oxidative stress potential, as indicated by the cerebellar levels of the oxidative stress marker 3-nitrotyrosine (3-NT) [26, 31, 33]. Mean 3-NT cerebellar levels were significantly elevated in autistic individuals as opposed to the control group.

Heavy metals also influence several cytokines. Mercury is known to affect cytokines such as IL-4, IFN-γ, and IL-6 [31, 33, 34]. Mercury interferes with cytokine-related signaling cascades including the protein complex NF-κB, a nuclear factor-kappa-light-chain-enhancer of activated B cells that controls DNA transcription, and p38-mitogen activated protein kinases. Autistic individuals exhibit significantly different levels of the cytokines IFN-γ and TGF-B from normal individuals [31, 33, 34].

Pesticides: Because many pesticides and preservatives function by disrupting redox events, they are expected to induce oxidative stress in humans [35-39]. Developmental exposure to several types of pesticides, such as organophosphates (OPs) and pyrethroids, is associated with neurological dysfunction and an increased risk for ASD.

Many pesticides *also* impact cytokine production, which may play a significant role in ASD [40-44]. For example, OPs induce a prolonged inflammatory state that may evolve into an adaptive response characterized by up-regulation of TH1 and TH2 cytokines. OPs increase the levels of inflammatory cytokines including IL-1B and IL-6 in multiple brain regions. Researchers have found abnormal levels of these cytokines in autistic brains. The inflammation brought on by OPs can be long-term.

Pyrethroids affect calcium signaling, interfere with voltage-sensitive sodium channels, and induce oxidative stress [35, 37, 39, 40]. They also suppress both IFN-γ and IL-4 expression in a time and concentration-dependent manner [35, 37, 40-43]. In a monocytic cell line, various synthetic pyrethroids and their metabolites reduced expression of immunoregulatory IL-10 and increased production of more inflammatory cytokines (IL-12 and TNF-α). The presence of environmentally relevant concentrations of various pyrethroids increased IL-1β expression. In primary human fetal astrocytes, the pyrethroid pesticide, cyfluthrin, was found to have an activating effect, and it increased the expression of genes involved in IFN-γ and IL-6 production and signaling.

(4) Confounding between group and individual levels

Several studies have shown that autism has about 70-90% monozygotic concordance among twins. This demonstrates the high level of autism heritability. For instance, a study of the whole-genome screens in multiplex families suggests interactions of at least 10 genes in the causation of autism [14-16]. It shows that a putative speech and language region at 7q31-q33 seems strongly linked to autism, with linkages to multiple other loci under investigation. Cytogenetic abnormalities at the 15q11-q13 locus are fairly frequent in people with autism, and a "chromosome 15 phenotype" was described in individuals with chromosome 15 duplications. Among other candidate genes are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22-q33 and the $GABA_A$ receptor subunit and UBE3A genes on chromosome 15q11-q13. Variant alleles of the serotonin transporter gene (5-HTT) on 17q11-q12 are more frequent in individuals with autism than in non-autistic populations. In addition, data from genome screens implicate the oxytocin receptor at 3p25-p26.

According to some authors [14-16], there are at least five genes that may potentially impact ASD: EN2 (Engrailed 2 gene), which is involved in cerebellum development; GABR (gamma amino butyric acid receptor genes), which regulate brain cell migration, differentiation, and synapse formation; OXTR (oxytocin receptor gene), which is involved in the response to stress and in social skills such as empathy; RELN (Reelin gene), which is involved in neuronal migration in the developing brain; and SLC6A4, a serotonin transporter gene that could account for phenotypic expression of happiness. Researchers have noted the differences between causal loci and susceptibility loci that increase the risk for ASD.

Some authors have implicated the SHANK3-NLGN4-NRXN1 genes among others [14-16]. Interestingly, these authors found strong evidence for the role of copy number variation (CNV) at 16p11.2 among autistic individuals.

It is possible that the autistic individuals may be immunologically prone to the influence of environmental toxins. For example, some genetic studies showed that high mercury levels were significantly associated with the expression of several immunologically relevant genes [31, 34, 35]. There may be a significant correlation between a heavy metal transport gene (SLC11A3)

and ASD (4). Genetic analyses also suggest that individuals with ASD may be less capable of excreting pesticides, due to expression of a less-active variant of the OP-metabolizing enzyme paraoxonase [39]. Children with ASD may also be uniquely susceptible to halogenated aromatic hydrocarbons. Postmortem analysis showed altered ryanodine receptor expression in the brain of autism subjects compared to controls, which could alter their sensitivity to Ryr-reactive compounds [38].

Despite the overwhelming genetic roots of ASD at the individual level, most of the epidemiological research that is currently available does not take the genetic differences at the individual level into consideration. Although one may assume that the genetic differences among a large number of individuals may be random, the group-level findings would be more validated if researchers better controlled for individual genetic differences as a variable.

(5) Cross-sectional research design

Much of ASD epidemiological research is cross-sectional in nature [45-48]. However, we need more studies that investigate whether an increase in environmental pollution levels *over time* is associated with an increase in the risk of producing progeny with ASD (perhaps through increased oxidative stress, cytokine imbalance, etc.).

Interestingly, there are relatively very few longitudinal studies that investigate ASD incidence [47, 48]. Drawing upon the data from the Baby Siblings Research Consortium, one study [48] included infants with an older biological sibling with ASD that were followed from early in life to 36 months, when they were classified as having or not having ASD. An ASD classification required surpassing the cutoff of the Autism Diagnostic Observation Schedule and receiving a clinical diagnosis from an expert clinician. A total of 18.7% of the infants developed ASD. Infant gender and the presence of more than one older affected sibling were significant predictors of ASD outcome, and there was an almost threefold increase in risk for male subjects and an additional twofold increase in risk if there was >1 older affected sibling. It would be interesting to find out if an increase in the environmental pollution levels significantly increases ASD recurrence rate among siblings.

Traditional epidemiologic study designs and statistical regression approaches are unable to examine many dynamic processes. These limitations have constrained the types of questions asked, the answers received, and the hypotheses and theoretical explanations that are developed. Agent-based models and other systems-dynamics models may help to address some of these challenges [49, 50]. Agent-based models are computer representations of systems consisting of heterogeneous micro-entities that can interact and change/adapt over time in response to other agents and features of the environment. Using these models, one can observe how macro-scale dynamics emerge from micro-scale interactions and adaptations. Several challenges and limitations exist for agent-based modeling. Nevertheless, use of these dynamic models may complement traditional epidemiologic analyses and yield additional insights into the processes involved and the interventions that may be most useful [50].

CONCLUSION

In summary, we have identified five areas that need to be addressed in the research on environmental epidemiology of ASD. These include resolution of definitional challenges, identification of biochemical pathways most likely to be involved, sifting through the vast numbers of environmental pollutants, resolving group and individual level differences, and changing study design from cross-sectional to *also* include longitudinal design. We hope that this analysis will help future researchers in overcoming these limitations, so as to improve the validity of their findings, to ultimately expose and contain factors that are contributing to the rapidly rising incidence of ASDs in the world.

FUNDING

None.

CONFLICT OF INTEREST STATEMENT

The authors do not have any conflict of interest. They have no affiliation with any organization or entity with any financial or non-financial interest

in the subject matter or materials discussed in this manuscript.

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