Is Autism Spectrum Disorder in Early Childhood Related to Antenatal Exposure to Air Pollution?

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SUMMARY

This case-control study was conducted to evaluate the association between prenatal exposures to airborne pollutants and autism spectrum disorder (ASD) in a large population-based cohort. Population comprised of all births in Metro Vancouver, British Columbia, Canada, from 2004 through 2009, with follow-up through 2014. Diagnosis of ASD was based on standardized assessment with the Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule. Mean exposures to particulate matter with a diameter less than 2.5 μm (PM 2.5), nitric oxide (NO), and nitrogen dioxide (NO_2) at the maternal residence during pregnancy were estimated monthly with temporally adjusted, high-resolution land use regression models. Sample size for the PM2.5-adjusted model was 129 439 children, and for NO and NO_2, it was 129 436 children; of these, 1276 (1.0%) were diagnosed with ASD. The association between prenatal air pollution exposures and the odds of developing ASD was evaluated using logistic regression adjusted for various parameters. Authors concluded that adjusted odds ratios for ASD per interquartile range (IQR) were significant for exposure of NO, and non-significant for PM2.5 and NO_2.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Autism, or more correctly Autism Spectrum Disorder (ASD) is a growing problem in developed as well as developing countries. Its etiology has not been clearly delineated although genetic factors and environmental exposures in early life have been implicated. Although there is supporting evidence for both streams of thought, conclusive proof is lacking.

Environmental pollution is suspected to be linked to development of ASD, and individual studies have resulted in systematic reviews on the issue. One such review examining exposure to environmental toxins during the pre-conception period, pregnancy and early postnatal life reported association of ASD with air pollutants, pesticides, phthalates, solvents and polychlorinated biphenyls, with less consistent effects with heavy metals [1]. The data were insufficient to confirm whether exposure during a specific trimester, compared to throughout pregnancy or the postnatal period, was more likely to be associated with ASD. Another review reported small but statistically significant higher odds of developing ASD with prenatal (but not postnatal) exposure to PM10 (particulate matter with mean diameter <10.0 μm) and an even more impressive odds with exposure to PM2.5 (particulate matter with mean diameter <2.5 μm) [2]. However, a recent review with data from multiple studies failed to show a statistically significant higher risk of developing ASD with increased exposure to PM2.5 and NO_2 during pregnancy [3]. Yet another systematic review reported an association between exposure to phthalate and development of ASD [4]. In contrast, one systematic review failed to find an association with exposure to neonicotinoids [5]. In summary, although exposure to various air pollutants during the period of brain development could be associated with later development of ASD, there is no robust proof. This is partly because of issues with study design, small sample sizes, variable definitions of ASD, difficulties in accurate estimation of exposure and/or timing of exposure, and multiplicity of confounding factors.

Against this backdrop of uncertainty, Pagalan, *et al*. [6] reported this case-control study attempting to iron out the deficiencies in previous studies exploring whether exposure of pregnant women to specific air pollutants is associated with ASD in their offspring. The investigators

examined the entire birth cohort in Metro Vancouver (British Columbia province of Canada) over a five-year period (2004-2009), following up the offspring till five years of age. Cases were those diagnosed with ASD, and controls were all the other children in the birth cohort. The specific exposures assessed were PM2.5, nitric oxide, and nitrogen dioxide. Outcomes were presented as adjusted odds ratio (aOR) for ASD (cases *versus* controls) for exposure to each of the three specific pollutants. The aOR for ASD with exposure during pregnancy were 1.07 (95% CI 1.01, 1.13) per 10.7 ppb IQR increase in NO; 1.04 (95% CI 0.98, 1.10) per 1.5 $\mu g/m^3$ IQR increase in PM2.5; and 1.06 (95% CI 0.99, 1.12) per 4.8 ppb IQR increase in NO_2. The investigators also identified that children with ASD were more often males, born to older age and multiparous mothers, and belonged to lower-income families. They concluded an association between NO exposure during pregnancy and subsequent development of ASD in the offspring, although their suggestion that reduced exposure to NO could reduce ASD occurrence is speculative, and not based on the data presented.

Critical appraisal: This was a carefully planned and well-executed study. Although a research question was not articulated, one can be derived as follows: Does high(er) exposure to PM2.5, nitric oxide, and nitrogen dioxide during pregnancy (*E=Exposure*), compared to low(er) exposure (*C=Comparison*) result in ASD (*O=Outcome*) among offspring born to these mothers (*P=Population*)? Although it can be argued that a comparative prospective cohort study is superior to address the question, financial and logistic considerations make a case-control design an attractive option.

The population base for this study was clearly defined in terms of geographic location as well as timeframe. Almost the entire birth cohort over a five-year period was eligible. Multiple databases were scoured to complete the list of eligible pregnancies delivered in institutions as well as at home. These databases enabled identification of gestational age, birth weight, postnatal morbidities, residence and socio-economic status.

Cases were identified using the diagnostic criteria for ASD prevalent in the region. These were based on two standardized instruments used by all clinicians in the region; thus, inter-observer practice variations were eliminated. However, the relationship of these to the current 'Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition' (DSM-5) criteria is unclear.

As the control group comprised of the entire birth cohort minus cases, issues such as selection bias, representativeness, matching, confounding and temporal variations in exposure were all neatly eliminated. The investigators chose covariates judiciously, including gender, birth month and year, maternal age, maternal country of origin, and socio-economic status.

Meticulous attention was paid to ascertainment of exposure to the three pollutants with quantification of exposure. This was done by using previously validated methods to obtain air quality data throughout the selected area within units as small as 10 square meters. Thus, the quantity of pollutants at the precise address of each pregnant woman could be determined with considerable accuracy. This facilitated calculation of exposure on a monthly basis, trimester basis and throughout pregnancy. However, the data were shown only for the model representing the entire duration of pregnancy.

Despite considerable effort to minimize bias in this study, some issues deserve attention. For example, it appears that outcome was not ascertained at the age of five years in all children. In fact, the median age for outcome measurement was 4.2 years. The reason(s) for this have not been clarified. It is also unclear whether the median age differed among cases and controls. Since the detection of ASD was through an apparently reactive mechanism (*i.e.* those with suggestive symptoms underwent detailed examination for a diagnosis), rather than a proactive system (*i.e.* universal screening of all children at an early age), it is possible that some cases could have been missed either because they were not brought to the notice of clinicians, or their symptoms were mild(er) enough to be missed at the age of outcome ascertainment.

One interesting finding (in this study) that has not been explored is the higher prevalence of ASD observed among children of mothers born in the Philippines and Vietnam, but lower prevalence when mothers were born in India or Hong Kong. The proportion of children with ASD was comparable to the general population among mothers born in China. These are intriguing observations because ASD prevalence is reported to be higher among immigrant families, although (to be fair) maternal birth place does not indicate the timing of immigration.

Can we conclude a causal relationship between air pollutants and development of ASD from this study? Although some of the Bradford-Hill criteria [7] are fulfilled *viz* Theoretical plausibility, Coherence (to some extent), Dose response relationship (partially), most of the criteria are not met. For example, the 'Strength of association' is weak at best, and that too for only one pollutant. The criterion of Temporality can be presumed to be fulfilled since exposure during pregnancy precedes the outcome

(ASD). However, exposure ascertainment was done in a retrospective manner. Further, the study did not consider the impact of ongoing postnatal exposure to air pollutants on the development of ASD. Overall, there is limited consistency in the available data for assigning a causal role to air pollution exposure in pregnancy and the development of ASD in the offspring. Some of the inconsistencies have been described already.

Perhaps the most serious threat to causality is with the criterion 'Specificity in the causes.' Like most complex disease conditions, ASD also probably results from a complex interplay of both genetic (nature) and environmental (nurture) factors, rather than either alone. Thus any potential 'cause' of ASD should be able to explain the well-known variations in incidence/ prevalence. For example, if air pollution during pregnancy is a 'cause' of ASD, there should be an explanation for the wide variation in prevalence between boys and girls, as well as higher incidence in some families.

Could air pollution have gender-specific effects? A recent systematic review exploring whether environmental toxins could have a gender-specific effect reported that exposure to thimerosal, some organochlorine pesticides, and even environmental pollution were associated with greater neurotoxicity among boys than girls with similar exposure [8]. Less consistent but significant effect on boys were observed with exposure to organophosphorus pesticides, and polychlorinated biphenyls. Another recent review suggested that the link between nature and nurture in development of ASD could be through epigenetic modifications [9]. Likewise, a systematic review examining potential genetic susceptibility to environmental toxins reported that 8 of 10 included studies identified several polymorphisms to be far more common in those with ASD than unaffected individuals [1].

It is well recognized that children belonging to immigrant families/communities have a higher risk of developing ASD than those born to native mothers [10]. This study [6] also showed some variations on the basis of maternal ethnicity. However, there was no consistency in terms of the country of origin of the mothers (as explained previously).

Conclusion: This well conducted case control study showed a weak association between maternal exposure to nitric oxide (air pollution) during pregnancy and the subsequent identification of ASD in their offspring. However, the study does not contribute to building a cause-and-effect hypothesis between pollution and ASD.

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Environmental Health Viewpoint

Effect of air pollution on human health is the most complex yet important aspect of public health, and the spectrum of diseases that list air pollution as one of the key risk factors is ever expanding. In case of congenital and acquired neurological and neuropsychiatric disorders, role of air pollution is being studied with interest. Strong evidence of association with preeclampsia, abortions, and preterm birth, low birth weight and intrauterine growth retardation exists in literature [1-6]. Similarly, studies point at air pollution

being a risk factor for Attention Deficit Hyperactivity Disorder (ADHD) [7].

This paper [8] examines the role of air pollution in Autism Spectrum Disorder (ASD). Of the three pollutants examined, nitric oxide (NO) showed a significant association. NO is a known molecule to effect the nervous system; hence, it's effect holds biological plausibility. $PM_{2.5}$ was not significantly associated with ASD, the reason being that the particulate matter is a mixture of several particles, and it is difficult to identify a particular molecule that could increase the risk. The strengths of the study are that it has a large sample size, and exposure parameters are based on good quality data covering the entire period of pregnancy. The regression model is adjusted for several known confounders and it incorporated land use regression model with high temporal resolution; it takes into account variations in pollutant concentration at short distances. But the study was conducted in areas where pollutant concentrations were low, almost within normal limits. This model cannot be applied to developing countries like India, where the concentration of $PM_{2.5}$ and other pollutants may be 4- to 15-fold higher and linear extrapolation may not work. Further, it must be seen in context of ASD incidence in Indian rural and urban population. Nonetheless it substantiates the need for controlling air pollution to reduce risk of ASD and other disorders.

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