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Brief Communication

Autistic Regression and Exposure to Industrial Chemicals: Preliminary Observations

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ABSTRACT: Exposure to industrial pollutants is a potential risk factor not fully explored in ASD with regression (ASD+R). We studied geographical collocation patterns of industrial air chemical emissions and the location of homes of children with ASD+R at different exposure times, compared with ASD cases without regression (ASD−R). Fifteen of 111 emitted chemicals collocated with ASD+R, and 65 with ASD−R. ASD+R collocated more strongly with different neurotoxicants/immunotoxicants a year before diagnosis, whereas ASD−R were moderately collocated with chemicals across all exposure periods. This preliminary exploratory analysis of differences in exposure patterns raises a question regarding potential pathophysiological differences between the conditions.

RÉSUMÉ : Régression dans le cadre de l'autisme et exposition à des produits chimiques industriels : des observations préliminaires. L'exposition aux polluants industriels est un facteur potentiel de risque qui n'a pas été entièrement étudié dans le cas des troubles du spectre de l'autisme avec régression (TSAR). Nous avons ainsi étudié la configuration géographique des émissions chimiques industrielles dans l'air et l'emplacement du domicile des enfants atteints d'un TSAR, et ce, à différents moments d'exposition et en comparaison avec des cas de TSA sans régression. Au total, 15 substances chimiques émises sur 111 ont été associées à la localisation de cas de TSAR alors que 65 d'entre elles ont été ont été associées à la localisation de cas de TSA sans régression. Du coup, les cas de TSAR ont été plus fortement associés à différentes substances neurotoxiques et immunotoxiques un an avant l'établissement d'un diagnostic tandis que les cas de TSA sans régression ont été modérément associés à des produits chimiques pendant toutes les périodes d'exposition. Cette analyse exploratoire préliminaire des différences en matière de configuration géographique de l'exposition soulève donc une question en ce qui concerne les différences physiopathologiques potentielles entre ces problèmes de santé.

Keywords: Autism regression; children; air pollution; industrial chemicals; toxicants; Alberta

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Autism spectrum disorders (ASDs) cover a broad range of neurodevelopmental conditions that affect lifelong social functioning and self-sufficiency. Most patients present with developmental concerns beginning in infancy. However, historically, it has been conceptualized that some demonstrate developmental regression, mainly in the second year of age. This latter variant is known as autism spectrum disorder with regression (ASD+R). Neonatal insults, prematurity or seizures have been associated with ASD+R. Immune dysregulation has also been hypothesized.[1] Nevertheless, this variant is poorly understood, and the mechanisms involved may differ from that of nonregressive ASD (ASD−R), despite increasing numbers. The recent increased prevalence of ASD has been linked to potential environmental influences. The interaction between known ASD susceptibility genes and environmental toxicants suggests that autism genetic polymorphisms influence sensitivity to chemicals due to their role in brain–barrier function.[2] Recent evidence indicates that air pollution increases the risk for ASD.[3] Data suggest particulate matter (PM), a chemically complex air pollutant, can reach the brain through various pathways.[4] Currently, there is not enough evidence to fully understand their role. There is also no literature exploring environmental pollutants comparing ASD+R and ASD−R. We focused on patterns of collocation of industrial air pollutants in the vicinity of homes of children with ASD+R and ASD−R across different exposure periods.

This research was approved by the Ethics Research Board [Pro00087885]. We conducted a retrospective review of electronic medical records of children who were seen at the Glenrose Rehabilitation Hospital (GRH), Edmonton, Alberta, Canada, between 2014 and 2018, who were born after 2003 and diagnosed with ASD before or in 2017 (based on Diagnostic Statistical Manual (DSM 5) criteria). Regression was defined according to the Autism Diagnostic Interview-Revised (ADI−R) criteria[5] and identified based on clinical assessment and history documented by the referring health care professional, parental reports, and a

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Table 1: Description of the study population in Alberta Health Zone 4 by autism spectrum disorder (ASD) diagnosis; −R indicates nonregressive variant and +R indicates regressive variant

Category	All cases		ASD−R		ASD+R	
Sex	Male	Female	Male	Female	Male	Female
No. (%) $N = 901$	706 (78)	203 (22)	592 (66)	167 (18)	106 (12)	36 (4)
Age at diagnosis, mean months (SD)	46 (13)	46 (11)	46 (12)	46 (11)	43 (13)	44 (9)
Total surrounding 0–9-year-olds, mean count (SD)	107 (62)	111 (66)	107 (62)	112 (63)	109 (62)	104 (77)
Proportion of 0–9-year-olds diagnosed, mean (SD)	0.013 (0.01)	0.013 (0.009)	0.013 (0.011)	0.013 (0.009)	0.013 (0.009)	0.014 (0.011)
Situational vulnerability, mean index (SD)	−0.261 (0.514)	−0.27 (0.529)	−0.274 (0.496)	−0.298 (0.515)	−0.218 (0.556)	−0.138 (0.581)

developmental pediatrician. Those with known/suspected genetic/congenital conditions, seizure, and movement disorders or a history of any perinatal or postnatal acquired brain injury or prematurity (<37 weeks gestation) were excluded. We extracted the children's full address at the time of diagnosis and delivery, age at diagnosis, year and month of birth, and sex.

We focused on industrial chemicals emitted into the air, as reported in the National Pollutant Release Inventory (NPRI).[6] The chemicals were classified as immunotoxicants (I) or neurotoxicants (N) in humans, according to the Agency for Toxic Substances and Disease Registry, Integrated Risk Information System, PubChem, and the Toxics Release Inventory, available in a single downloadable dataset.[7] To assign exposure at the residential level, we used kernel density (KD) to reflect tonnes emitted within a 10-km radius of point sources. Single-year (year prior to birth, birth year, year prior to diagnosis, and diagnosis year) and multi-year (average of all years and cumulative sum of all years) exposure periods were examined.

We adjusted for road density around homes (traffic pollution) and socioeconomic status (2016 Canadian Index of Multiple Deprivation assigned to each location).[8] To adjust for the total child population, we linked residential location to the total number of 0–9-year-olds living within 250 m (the smallest standard geographic area used by the Canada Census 2016) and the mean age distribution of this population. We used generalized linear regression to explore the collocation of ASD with each chemical and modeled ASD−R and ASD+R separately for the six periods. ArcGIS Pro 2.5 Release 2.5 (2019) was used for spatial analysis, geocoding, and mapping.

We identified 901 ASD children between the ages of 19 and 140 months in age at diagnosis (Table 1). Of these, 142 had ASD+R, and 759 had ASD−R. The male-to-female ratios were 3.5:1 (all ASD), 3.0:1 (ASD+R), and 3.6:1 (ASD−R). Two hundred and forty facilities emitted 111 different chemicals. Sixty-six chemicals were positively associated with any ASD variant. Fifteen chemicals collocated with only ASD+R and 65 only with ASD−R. Fourteen chemical collocations were common for both. For ASD-R, 59 collocations were noted for average exposure across years and 53 for cumulative exposure. For ASD+R, eight collocations occurred during the diagnosis year and seven during the pre-birth year. Mercury, total polycyclic aromatic hydrocarbons, formaldehyde, and methanol collocated during two periods for ASD+R/−R (Figure 1).

Among the chemicals that collocated with ASD+R and/or ASD−R, there were 5 immunotoxicants, 19 neurotoxicants, 3 with both toxicities, and 39 substances of no known toxicity. Across all six exposure periods, chemicals with both types of toxicity demonstrated the fewest collocations with increased numbers for immunotoxicants, followed by neurotoxicants. Neurotoxicants dominated all six exposure periods for ASD−R and all exposure periods but the diagnosis year for ASD+R.

Links have been observed between ASD and environmental toxicants; however, to our knowledge, the differential pattern of collocations for ASD+R and ASD−R variants has not been previously reported. Our work suggests that chemical type and exposure period differ between both groups. Several chemicals were common to both variants, but notably, the period of exposure and type of toxicants differed (Figure 1).

These results showed that neurotoxicants often had stronger associations. Immunotoxicants, some with dual immunological/neurological toxicity, collocated with both variants, possibly supporting a co-existing relationship between brain development and the immune system.[9] Although many of the identified chemicals are immunotoxic and/or neurotoxic, a large proportion has not yet been toxicologically characterized for humans.

We raise the question of whether the differences in type and period of exposure between children diagnosed with ASD+R and ASD−R may reflect the pathophysiological effects of toxicants at different stages of brain development. The neuroanatomical phases of nervous system development coincide with acquiring different developmental skills.[10] A hypothesis may be that shorter exposures during later stages of childhood affect the development of more advanced stages of cellular structure and function and potentially manifest as developmental autistic regression. In the context of ASD and neuroinflammation, apoptosis and demyelination were reported in animal models due to exposure to neurotoxicants and may represent potential pathways for regression if occurring at later stages of brain development.

This preliminary work explored spatial associations between patterns of industrial chemicals, periods of exposure, and ASD variants. Future work will need to focus on more robust analyses of these associations. Our findings are from a single major metropolitan area. However, they concur with a similar study on industrial emissions, suggesting that residential proximity to industrial facilities is associated with higher ASD prevalence[11] and more robust evidence from the case–control CHARGE study linking ASD with proximity to agricultural pesticide application.[12]

In summary, these findings suggest that there might be a differential association between exposure to industrial chemical emissions and ASD variants. Several chemicals were associated with both, but others were specific to only one variant. The period of exposure also varied. More work needs to be done to explore these relationships.

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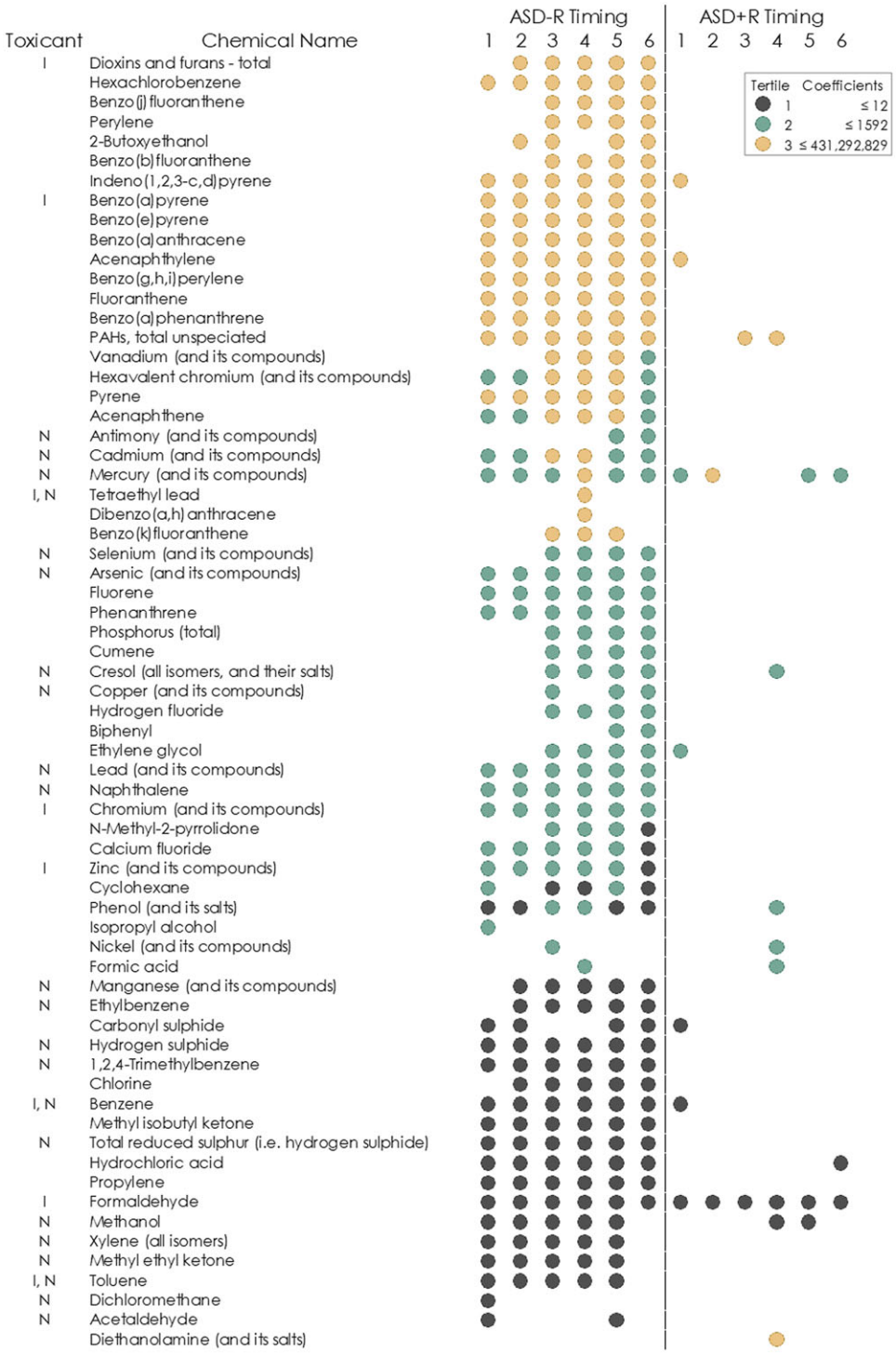

Figure 1: Regression coefficients represent collocation coefficients – adjusted for sex, age at diagnosis, situational vulnerability, and road density – are shown as different colors, where yellow indicates strong collocation, green is moderate, and black is low. The period of exposure assignment is displayed along the *x*-axis, according to the diagnosis of ASD−R (nonregressive) and ASD+R (regressive): 1 = year prior to birth; 2 = birth year; 3 = year prior to diagnosis; 4 = diagnosis year; 5 = average of all years; and 6 = accumulative sum of all years. The 66 statistically significant ($p < 0.05$) collocations are listed by chemical name along the *x*-axis and sorted in descending magnitude of the coefficients; toxicant classifications of suspected immunotoxicants (I) and/or neurotoxicants (N) precede each chemical name.

Data availability statement. The data used in the study are confidential and not publicly available.

Statement of authorship. Study concept and design: HG, AOV, and CN; acquisition, analysis, and interpretation of data: all authors; statistical analysis: CN and AOV; drafting of the manuscript: HG, AOV, CN, and SY; critical revision of the manuscript: all authors.

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Competing interests. The authors declare no conflicts of interest.

Informed consent statement. In the retrospective chart review, only anonymized data were used with no personal identifiers; ethics panel approval to conduct the chart review did not require consent.

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