HHS Public Access

Author manuscript

Sci Total Environ. Author manuscript; available in PMC 2016 January 21.

Published in final edited form as:

Sci Total Environ. 2015 December 1; 536: 245–251. doi:10.1016/j.scitotenv.2015.07.024.

Autism spectrum disorder prevalence and proximity to industrial facilities releasing arsenic, lead or mercury

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The findings and conclusions in this paper are those of the authors and do not necessarily represent the official views of the NCRR, NCATS, Research Data Center, National Center for Health Statistics, or the Centers for Disease Control and Prevention (CDC).

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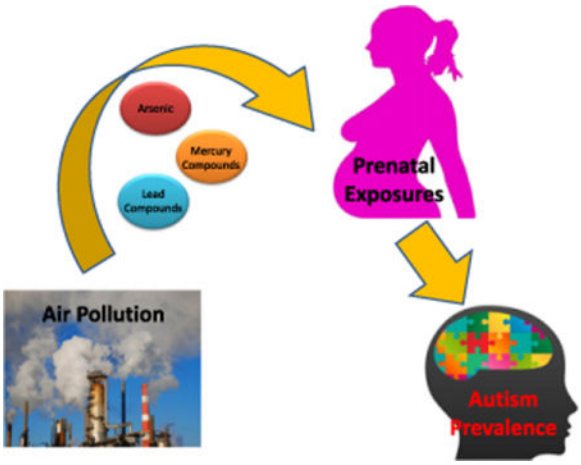
Abstract

Prenatal and perinatal exposures to air pollutants have been shown to adversely affect birth outcomes in offspring and may contribute to prevalence of autism spectrum disorder (ASD). For this ecologic study, we evaluated the association between ASD prevalence, at the census tract level, and proximity of tract centroids to the closest industrial facilities releasing arsenic, lead or mercury during the 1990s. We used 2000 to 2008 surveillance data from five sites of the Autism and Developmental Disabilities Monitoring (ADDM) network and 2000 census data to estimate prevalence. Multi-level negative binomial regression models were used to test associations between ASD prevalence and proximity to industrial facilities in existence from 1991 to 1999 according to the US Environmental Protection Agency Toxics Release Inventory (USEPA-TRI). Data for 2489 census tracts showed that after adjustment for demographic and socio-economic area-based characteristics, ASD prevalence was higher in census tracts located in the closest 10th percentile compared of distance to those in the furthest 50th percentile (adjusted RR = 1.27, 95% CI: (1.00, 1.61), $P = 0.049$). The findings observed in this study are suggestive of the association between urban residential proximity to industrial facilities emitting air pollutants and higher ASD prevalence.

Graphical abstract



Keywords

Metals; Autism spectrum disorder; Environment; Distance; Pollution

1. Introduction

1.1. Autism spectrum disorder

Autism spectrum disorder (ASD) is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* as a persistent impairment in social interaction and communication across multiple contexts that presents in early development and causes clinically significant social, educational, and occupational deficits (American Psychiatric Association, 2013). Recent surveillance studies estimate the prevalence of ASD in U.S. children to be about 1–2% (Autism and Developmental Disabilities Monitoring Network Surveillance Year, 2010 Principal Investigators, 2014; Blumberg et al., 2013). The etiology of ASD is poorly understood, but it has been hypothesized that exposure to environmental factors may trigger or enhance genetic risk (Volk et al., 2014).

1.2. Air pollutants and birth outcomes

Prenatal and perinatal exposures to air pollutants, such as carbon monoxide, nitrogen dioxide, and particulate matter, have been shown to adversely affect birth outcomes (Bell et al., 2010; Calderon-Garciduenas et al., 2011; Ezziane, 2013; Freire et al., 2010; Lakshmi et al., 2013; Munroe and Gauvain, 2012; Padula et al., 2013; Tang et al., 2014). Associated complications include developmental delay (Tang et al., 2014), congenital heart defects (Padula et al., 2013), low birth weight (Bell et al., 2010; Ezziane, 2013), cognitive deficits (Calderon-Garciduenas et al., 2011; Freire et al., 2010; Munroe and Gauvain, 2012), and mortality (Ezziane, 2013; Lakshmi et al., 2013). Prior research has shown residential proximity to point source pollution to be positively associated with congenital malformations, including chromosomal anomalies (Brender et al., 2008) and neural tube defects (Suarez et al., 2007), increased allergen-specific immunoglobulin-E in children (Patel et al., 2011), adverse birth outcomes (i.e. fetal death, preterm birth, and low birth weight) (Brender et al., 2011), and childhood brain cancer (Choi et al., 2006).

Both long-term and short-term exposures to ambient air pollutants have been shown to stimulate oxidative stress and inflammation in humans, which may also affect neurologic development (Block and Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2009). Studies have also shown that inflammation may contribute to the pathogenesis of ASD (Enstrom et al., 2009; Li et al., 2009). Thus, inflammation may serve as a link between ASD risk and ambient air pollutant exposure. In addition, lead (Jarup, 2003; Sanders et al., 2009; Zheng et al., 2003), mercury (Aschner and Aschner, 1990; Jarup, 2003; Zheng et al., 2003), and arsenic (Jarup, 2003) are well-established neurotoxicants known to cross the blood–brain barrier and effect neurodevelopment. Mercury has been shown to have harmful effects including intellectual and developmental disabilities (Counter et al., 2002) while studies have also indicated that higher arsenic levels are associated with decreased cognitive abilities including decreased attention, comprehension, and language skills (Calderon et al., 2001), reduced intelligence quotient (IQ) scores (Wang et al., 2007; Wasserman et al., 2004; Wright et al., 2006), and diminished verbal learning and memory (Wright et al., 2006). Furthermore, lead can have adverse effects on health of children, causing behavioral and neurological problems (Bellinger, 2008; Ha et al., 2009) and reduction in IQ scores (Canfield et al., 2003).

1.3. Air pollutants and ASD

Some recent studies have investigated the relationship between ASD and exposure to ambient air pollutants (Blanchard et al., 2011; Kalkbrenner et al., 2010, 2014; Ming et al., 2008; Palmer et al., 2009; Roberts et al., 2013; Volk et al., 2011, 2014; Windham et al., 2006). Several of these studies have demonstrated associations between ASD and prenatal or perinatal air concentrations of various air pollutants, including particulate matter (Becerra et al., 2013; Kalkbrenner et al., 2010, 2014; Roberts et al., 2013; Talbott et al., 2015; Windham et al., 2006). Additionally, proximity to sources of airborne pollutants, including industrial facilities (Palmer et al., 2009), agricultural pesticides (Shelton et al., 2014), and high-traffic roadways (Volk et al., 2011), have been associated with ASD diagnosis and school-reported administrative prevalence, respectively. Based on results from these studies, observed relationships should be further investigated on a larger scale using highly reliable data. For the current study, we used surveillance data from multiple states to evaluate the association between ASD prevalence of 8-year old children at the census tract level and proximity of tract centroids to point source industrial facilities with air releases of well-known and frequently released neurotoxic substances from waste facilities, arsenic, lead, and/or mercury, during 1991 to 1999.

2. Materials and methods

2.1. Data sources

We used data from the Autism and Developmental Disabilities Monitoring (ADDM) Network, a multi-state public health surveillance system for ASD and other developmental disabilities established by the CDC in 2000 to measure ASD prevalence among 8-year-old children in 2000, 2002, 2004, 2006, and 2008. Details of ASD case definition and ascertainment have been described previously (Rice et al., 2007; Van Naarden et al., 2007); a synopsis of the ADDM methodology follows. School and health sources are queried for children who have special education exceptionalities and/or diagnoses that trigger further evaluation for ASD. ASD case status of 8-year-old children is determined through a systematic review of records from healthcare and education sources such as primary care clinics, hospitals, schools, and diagnostic and treatment centers. These records are reviewed by expert clinician reviewers to determine if behaviors are described in the abstracted data which meet the number and pattern required for an ASD diagnosis based on the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (DSM-IV-TR) (American Psychiatric Association, 2000). Data for 8-year-old children identified with ASD during the ADDM surveillance years (even years) spanning from 2000 through 2008 were obtained through a data sharing agreement with the CDC for the following five participating sites: Arizona, Maryland, New Jersey, South Carolina, and Utah. These sites provided de-identified data aggregated by census tract, including total number of identified children with ASD along with race and sex distributions. It is important to note that for race distributions, virtually all Hispanics did not report race for this data source. Thus, Black and White categories exclude almost all Hispanic individuals.

2.2. Exposure assessment

Information for 201 industrial facilities with reported on-site air releases of arsenic, lead, and/or mercury was obtained from the U.S. Environmental Protection Agency Toxics Release Inventory (TRI). The TRI indexes the source and quantity of environmentally-released chemicals and waste from industrial facilities in the United States. It was established in 1986 under Section 313 of the Emergency Planning and Community Right-To-Know Act (EPCRA), industrial facilities that use >10,000 lb or manufacture/process >25,000 lb of established carcinogens and/or other toxins, including, but not limited to, heavy metals, benzene, and dioxin-like compounds, are required to report information annually on types and amounts of environmental toxins released into air, water, and land. These sites include, but are not limited to, mines, waste management facilities, textile mills, utility plants, and electronics manufacturers.

To coincide with the prenatal periods for children who would have been ascertained at 8 years of age during even numbered ADDM surveillance years, we used TRI data from sites with reported air releases of at least 100 lb of arsenic, lead, and/or mercury from 1991, 1993, 1995, 1997 and 1999. TRI sites were excluded if they did not release at least two of the three criteria toxicants (arsenic, lead, and/or mercury). Data were acquired for sites located in areas in and around ADDM surveillance sites, including those located in neighboring states, to identify industrial facility locations in closest proximity to the census tracts within the five ADDM geographic surveillance areas. Only facilities in existence during the entire study period (1991–1999) were included in the analysis, and 22% of total TRI sites examined were excluded solely for this reason. The distance between each facility and the center of census tracts within ADDM surveillance areas was determined by first entering the geographic address points (longitude and latitude) of the industrial facility and the XY geographical coordinates for the center (centroid) of each census tract, in accordance with Census 2000 boundaries, into Microsoft Excel software. Each census tract was linked to an industrial facility with closest proximity to its centroid. Subsequently each tract had a separate distance designation from industrial facilities (in kilometers). Radial distance was then coded into a discrete variable based on deciles (percentiles with increasing increments of 10%). Distance further than the 50th percentile served as a referent category during analysis.

2.3. Statistical analysis

The number of 8-year old children identified with ASD during ADDM surveillance years 2000 to 2008 was obtained for census tracts from five sites in the ADDM network, Arizona, Maryland, New Jersey, South Carolina, and Utah. The total population of children ages 0 to 9 years, according to the 2000 U.S. census, was obtained for each tract and rounded to the nearest 5 to prevent back coding of de-identified study site tracts obtained from the CDC. The median household income was also rounded to the nearest $5000 to maintain de-identification of participants.

Information was obtained for 644 tracts from Arizona, 631 from Maryland, 588 from New Jersey, 368 from South Carolina, and 327 tracts from Utah, totaling 2558 census tracts obtained. Total number of children with ASD in each tract was aggregated for five ADDM

surveillance years to ensure confidentiality of all ascertained ASD cases. Furthermore, to safeguard against back-coding of de-identified tract data, number of children ages 0 to 9 years of age were rounded to the nearest 5. Thus, 17 tracts (0.7%) were excluded due to a rounded total population of 0. Because the highest reported ASD prevalence to date is 1 in 50 children (Blumberg et al., 2013) and there were several tracts reporting small populations of children ages 0 to 9 years, possibly too small for identification of a single child, 52 (2.0%) tracts with a population size less than the 40 total children ages 0 to 9 were also removed from the dataset for analysis. From the remaining tracts, we analyzed 2489 tracts with 4486 ASD cases.

After examining the distribution of 8 year old ASD cases by census tract and determining that the data were not zero-inflated but were over-dispersed, we modeled ASD case counts using negative binomial regression, the model which best fit the data according to the Akaike Information Criterion (AIC). The number of cases for each census tract was entered into a negative binomial regression model as the outcome, with deciles for distance of tract centroids to emission sources as the predictor variable. Census tract residence for ASD cases was based on residence at the time of surveillance (at 8 years of age). This implies that we assume children did not move since birth from their residence. Furthermore, because the structure of the data is hierarchical, with census tracts (level 1) nested within counties (level 2), which were nested within states (level 3), we used multilevel modeling (Bryk and Raudenbush, 1992) by controlling for specified nested geographic levels (i.e. state, county, and tract) within the statistical coding. We calculated an estimated population from which 8-year-old children would have been ascertained in the biannual surveillance years. Because surveillance data were aggregated for five possible surveillance years (2000, 2002, 2004, 2006, and 2008) with no indication of which surveillance year in which each ASD case was ascertained, we assumed uniform age distribution of children ages 0 to 9 years old in each tract according to the 2000 U.S. census. For this reason, we divided the total population of children ages 0 to 9 years old by ten to account for each age group (i.e., 0 years, 1 year old, 2 years old…9 years old). We then multiplied the solution by the number of years the tract was included in surveillance to estimate the potential number of children who would have been ages 0, 2, 4, 6, and/or 8 years of age during the 2000 census, and thus 8 years of age during the aforementioned ADDM surveillance years as follows:[(total population 0–9 years / 10)] * (number of surveillance years). Because ASD prevalence is contingent on the total pool of available children for ascertainment and the number of ASD cases is the dependent count variable for our model, this estimated population total was log-transformed and used as an offset variable in models to account for different population sizes from which cases would have been drawn during surveillance.

We also examined potential confounders and effect modifiers including urban versus rural classification, race and ethnicity distributions, and neighborhood SES characteristics according to the 2000 census. Potential confounders, including percentage of tract residents who were black, white, and other races, percentage of Hispanic residents, percentage with a college education, and percent of residents below poverty, were determined by a *P*-value of ≤0.20 for the tested association of the potential confounder with both the proximity to industrial facilities as well as a *P*-value of ≤0.20 for the tested association of the potential

confounder with ASD prevalence (Szklo and Nieto, 2007). Because the proportional odds assumption for testing the associations between proximity to industrial facilities and potential confounders using ordinal logistic regression were violated, we collapsed proximity into a dichotomous variable with a cut-point at the 50th percentile and analyzed this using binary logistic regression. We examined associations of potential confounders with ASD prevalence using negative binomial regression. Additionally, because previous studies have indicated that ambient air pollutant levels are often higher in areas with lower SES (Evans and Kantrowitz, 2002), proportion of residents below the poverty line was included in the final multivariable model adjusting for potential confounders. Two-tailed tests with an alpha level of 0.05 were used to evaluate significance. All statistical analyses were done using SAS version 9.3 (SAS Institute Inc., 2011).

3. Results

The average proportion of male 8 year old ASD cases observed across all tracts was 81.6%. The average tract percentage of cases with a normal birth weight was 74.0% and the average tract percentage of cases with full-term birth (≥37 weeks) was 76.9%. A large majority of tracts (90.3%) were considered urban areas. Additionally, the mean proportion of White residents (57.5%) was higher in surveyed tracts than the proportion of Black residents (20.0%) and those of other races (4.8%). More information on demographic and descriptive tract level variables is shown in Table 1.

All tract population characteristics were significantly associated with ASD prevalence in unadjusted analysis. Specifically, reported ASD prevalence increased with proportion of White residents (Relative Risk [RR] = 1.09, 95% CI 1.08, 1.11), proportion of college-educated residents (RR = 1.07, 95% CI 1.04, 1.10), and median household income within the highest 25th percentile compared to income in the 0 to 75th percentile (RR = 1.39, 95% CI 1.28, 1.51). In contrast, prevalence of ASD was lower for proportion of Black residents (RR = 0.94, 95% CI 0.92, 0.96) and other races (RR = 0.81, 95% CI 0.78, 0.84), Hispanic ethnicity (RR = 0.86, 95% CI 0.84, 0.88), rural geography (RR = 0.50, 95% CI 0.40, 0.63), and proportion of residents below poverty line (RR = 0.79, 95% CI 0.75, 0.82). Details about these analyses are displayed in Table 2.

Median distance from tract centroids to industrial facilities was 39.12 km (24.3 miles) with an interquartile range of 67.31 km (41.82 miles). We also found several factors related to proximity to air pollutant releasing industrial facilities. For example, proximity to industrial facilities was significantly longer for tracts reporting a greater proportion of Black residents [RR = 1.04, 95% CI: (1.02, 1.06), $P < 0.001$]. In contrast, proximity was shorter for tracts with a greater proportion of White residents [RR = 0.96, 95% CI: (0.95, 0.98), $P < 0.001$] and Hispanic residents [RR = 0.96, 95% CI: (0.95, 0.97), $P < 0.001$]. As expected, rural geographic classification was inversely associated with proximity to industrial facilities [RR = 0.01, 95% CI: (<0.01, 0.24), $P < 0.001$]. More results are provided in Table 3.

Finally, we tested the unadjusted and adjusted associations between prevalence of ASD and proximity to air pollutant releasing industrial facilities. Table 4 shows details of univariable analyses examining incremental proximity categories (split into deciles) and as a binary

variable. After adjustment for tract population proportion with White race, Hispanic ethnicity, proportion of college-educated residents, rural geographic classification, and proportion below the poverty line, the association between the closest 10th percentile (closest distance) and ASD prevalence was still significant [RR = 1.27, 95% CI: (>1.00, 1.61), $P = 0.049$]. However, in adjusted analysis with binary proximity (highest 50th percentile versus lowest percentile), statistical significance was no longer apparent [RR = 1.04 (0.88, 1.22), $P = 0.65$]. However, for both the unadjusted and adjusted analyses, there was no evidence of a dose–response trend for closer proximity and ASD prevalence. More information is displayed in Table 4.

4. Discussion

4.1. Point source proximity and ASD

We observed a slightly increased prevalence of children with ASD for census tracts in the closest 10th percentile (closest distance) to air pollutant-releasing industrial facilities. Previous studies have demonstrated that concentrations of particulate matter and air pollutants are higher in areas closer to industrial facilities (Burstyn et al., 2007; Gildemeister et al., 2007). Therefore, our findings may support those of studies previously reporting associations between distance from point sources, duration and frequency of exposure to air pollutants, and subsequent higher body burden of toxicants for individuals living in those areas, including those reporting higher hair, urine, and blood levels of lead, mercury, and arsenic in those living closer to point sources such as agricultural land (Molina-Villalba et al., 2014), high-traffic roads (Ahamed et al., 2010; Gulson et al., 2006; Rahbar et al., 2002; Shen et al., 1997; Stroh et al., 2009), smelters (Do et al., 2011; Hegde et al., 2010; Hwang et al., 1997; Leroyer et al., 2000; Stroh et al., 2009), and mines (Basu et al., 2010; Wickre et al., 2004). Additionally, exposures to ambient air pollutants have been shown to stimulate oxidative stress and inflammation in humans, which may contribute to the pathogenesis of neurodevelopment and ASD. (Enstrom et al., 2009; Li et al., 2009). Furthermore, lead (Jarup, 2003; Sanders et al., 2009; Zheng et al., 2003), mercury (Aschner and Aschner, 1990; Jarup, 2003; Zheng et al., 2003), and arsenic (Jarup, 2003) are well-established, detrimental neurotoxicants. However, we acknowledge that our methods did not account for wind direction and other meteorological factors that could affect chemical composition and duration of air pollutant exposures in areas.

Our results of greater ASD prevalence with closer surveillance residence to TRI sites in existence during birth years are consistent with those of prior studies that have investigated the association between proximity to sources of pollution and ASD prevalence. For example, Volk et al. (2011) reported a positive association with ASD case-status and birth residence near freeways, which may also be a proxy for exposure to lead sources (Ahamed et al., 2010; Gulson et al., 2006; Rahbar et al., 2002; Stroh et al., 2009). Notably, Palmer et al. (2009) also reported an association with school system-based ASD prevalence, according to school records, and proximity of school districts to mercury emitting industrial facilities. Our results build on those from other studies by examining group-level prevalence and possible prenatal exposures to air pollutants, such as arsenic, lead, and mercury, while adjusting for area-based measures. However, it is important to note that Palmer et al. (2009)

modeled distance as a continuous variable for every 10 miles, assuming a linear association. In contrast Volk et al. (2011) modeled distance as a categorical variable; however, distance for the lowest 10th percentile for that study was < 309 m (0.2 miles) from the nearest freeway while the lowest 10th percentile (closest distance) for our study was equivalent to < 10,460 m (6.5 miles). Therefore, not only do our results support those showing associations between ASD and proximity to sources of pollution, but they suggest that exposure to pollutants released from industrial facilities, such as arsenic, lead, and mercury, may have an impact from a further distance.

4.2. Hazardous air pollutants and ASD

When evaluating ambient exposures to arsenic, investigators have reported no associations between ambient arsenic concentrations and of ASD (Kalkbrenner et al., 2010; Roberts et al., 2013; Windham et al., 2006). A recent study of 14 states from the Nurses' Health Study II reported significantly greater odds of ASD in children born in areas with the highest quintile of ambient lead exposure in comparison to those born in the lowest quintile of exposure (Roberts et al., 2013); however, some studies have reported no significant association between residential area air concentrations of lead at infancy and early childhood and ASD diagnoses (Kalkbrenner et al., 2010; Windham et al., 2006). Additionally, while several studies have suggested that risk of ASD is increased with greater ambient air levels of mercury (Blanchard et al., 2011; Palmer et al., 2009; Roberts et al., 2013; Windham et al., 2006), others have reported no significant association between ambient mercury compounds and ASD case status (Kalkbrenner et al., 2010). Although we cannot confirm that the associations seen in this study were contributed specifically to arsenic, lead, and mercury releases, these results support those of studies that have previously reported positive associations between ambient air exposures and ASD on an individual level.

4.3. SES and ASD prevalence

Although previous reports have shown that ASD diagnosis is commonly clustered in areas with more resources where air pollution is typically lower in high SES communities compared to lower income areas (Mazumdar et al., 2013), our evaluation for potential confounders yielded few associated SES factors. However, when we included measures of SES, such as percent with a college education and percent below poverty, results of multivariable analysis indicated that these variables had significant influence on the association between ASD prevalence and proximity to TRI sites. While all confounders influenced the effect measures, only proportion of Hispanic residents and rural geography contributed to loss of statistical significance when included in the model without other confounders. Notably, even after adjusting for SES characteristics, the association between the closest proximity to air pollutant releasing industrial facilities and ASD prevalence was still statistically significant.

4.4. Limitations

We acknowledge limitations to this analysis. To preserve the deidentification process for children with ASD in low-populated tracts, aggregated data for five surveillance years were provided. Because our analyses for total count of children with ASD within census tracts are not on an individual level, we are unable to determine the time point of exposure or measure

the exposure at the individual level for each child that was ascertained for the ADDM study. The use of an ecological study design also inhibits the ability to make inferences about exposures and outcomes on an individual level. Additionally, children ascertained through ADDM were only those who were previously identified by clinicians and/or schools, and may not include children who might have been undiagnosed due to milder symptomology or otherwise classified based on a co-existing condition. Aggregation of ADDM data also led to the use of only data from TRI sites in existence from 1991 to 1999, which excluded several sites that may have been closer to certain tracts when in existence and potentially influenced exposure classifications for certain tracts. Furthermore, population estimates for prevalence of combined surveillance years at the tract level were approximated using total number of children ages 0 to 9 years of age during the 2000 census. Because the total number of children in each tract was rounded to the nearest 5, we excluded 69 tracts with extremely low population sizes of fewer than 40 children ages 0 to 9 years old. However, it is important to mention that a sensitivity analysis evaluating the impact of removing these 69 tracts revealed no significant influence of these excluded tracts on the analysis. Although we measured proximity of each census tract to one TRI site each, we acknowledge that exposures to air pollutants from industrial facilities can occur from multiple point sources. For example, Ming et al. (2008) demonstrated a linear relationship between number of EPA superfund sites in a state and ASD rates. Additionally, although amounts of pollutant releases are checked for possible significant or excessive levels, reported amounts are not consistently monitored or confirmed, and may be inaccurate. Therefore, we did not account for the types and amounts of pollutants released from each facility in this analysis, cannot confirm that observed associations are attributed to air releases of arsenic, lead, and mercury only, and acknowledge that results may be confounded by other air pollution factors including presence of particulate matter. Exposure to air releases from various TRI sites may also be influenced by weather factors, such as wind direction. ASD prevalence has also increased overtime; however, as data for this analysis were provided in aggregate form, we could not evaluate associations between ASD prevalence and residence near TRI sites or total number of TRI sites over time. Reported residential tracts of children identified with ASD were based on the residence of the children at 8 years of age rather than residence at the time of birth. Additionally, only 72% of records could be matched to birth certificates. Thus, the aggregate data for variables obtained from birth records, such as maternal education, were only analyzed for these cases and analysis did not account for mobility from the original birth place. Although this may have resulted in some misclassification of the 72% of ASD cases for whom birth records were provided, model adjustment for residence in the same birth county had no significant effect on results. However, we acknowledge that results adjusted for maternal education and dependent on residential proximity at the time of assessment may be biased. Furthermore, because proximity measurements were determined from the centroid of census tracts, this analysis assumes that residences are clustered at the geographic center of each census tract, and does not account for dispersal of the population within each tract.

Despite the aforementioned limitations, our study also has several important strengths. We are using highly reliable surveillance data collected through a well-established ASD surveillance protocol that ascertains children with ASD from multiple sources, and

determines ASD case-status through records reviewed by expert clinician reviewers. This analysis was conducted with the intention of assessing associations between ASD prevalence and air pollutant exposures during prenatal periods. In this study we have examined area-based exposures in relation to ASD through proximity to air toxicant-releasing facilities using a large dataset of population-based surveillance data while also demonstrating associations between residential proximity to arsenic, lead, and/or mercury-emitting facilities and ASD prevalence.

5. Conclusions

Although the etiology of ASD is not well understood, especially with regards to environmental risk factors, our study adds to the literature on the relationship between proximity to point sources of ambient air pollutants and ASD prevalence. The results observed in this study are suggestive of the association between closer proximity to industrial facilities with reported air arsenic, lead and mercury emissions and increased prevalence of ASD. Future studies should test for associations with both group-level and individual-level exposures including exposure to outdoor and indoor toxicants and genetic variants that might influence ASD risk independently or through interaction. Future analysis using these data should also investigate proximity to TRI sites using closer distances. Additionally, analysis using geographic information systems (GIS) may provide more information on relationships between areas with clusters of children with ASD and proximity to multiple point sources. Longitudinal data on individual residence, industrial facilities, and types and amounts of toxicants released both during pregnancy and between birth and diagnosis should also be obtained to decipher which releases are more influential, and what the primary window of exposure may be. Considering the increased exposure to air pollutants experienced by children living near industrial facilities and the observed increased prevalence of ASD, more research is needed to assess the impact of these exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the schools and service providers in Arizona, Maryland, New Jersey, South Carolina, and Utah who provided records for surveillance of children with ASD to the participating ADDM sites. We also acknowledge the support and resources provided by the Biostatistics/Epidemiology/Research Design (BERD) component of the Center for Clinical and Translational Sciences (CCTS) for this project. CCTS is mainly funded by the NIH Centers for Translational Science Award (NIH CTSA) grant (UL1 RR024148), awarded to the University of Texas Health Science Center at Houston in 2006 by the National Center for Research Resources (NCRR) and its renewal (UL1 TR000371) by the National Center for Advancing Translational Sciences (NCATS).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2015.07.024.

References

Ahamed M, Verma S, Kumar A, Siddiqui MK. Blood lead levels in children of Lucknow, India. Environ Toxicol. 2010; 25:48–54. [PubMed: 19161238]

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR). American Psychiatric Publishing, Inc; Washington, DC: 2000.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). American Psychiatric Association; Arlington, VA: 2013.

Aschner M, Aschner JL. Mercury neurotoxicity: mechanisms of blood–brain barrier transport. Neurosci Biobehav Rev. 1990; 14:169–176. [PubMed: 2190116]

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators. Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2010. Centers for Disease Control and Prevention and Morbidity and Mortality Weekly Report; 2014. p. 63

Basu N, Abare M, Buchanan S, Cryderman D, Nam DH, Sirkin S, Schmitt S, Hu H. A combined ecological and epidemiologic investigation of metal exposures amongst Indigenous peoples near the Marlin Mine in Western Guatemala. Sci Total Environ. 2010; 409:70–77. [PubMed: 20952048]

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient air pollution and autism in Los Angeles county, California. Environ Health Perspect. 2013; 121:380–386. [PubMed: 23249813]

Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P, Leaderer BP. Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. Epidemiology. 2010; 21:884–891. [PubMed: 20811286]

Bellinger DC. Lead neurotoxicity and socioeconomic status: conceptual and analytical issues. Neurotoxicology. 2008; 29:828–832. [PubMed: 18501967]

Blanchard KS, Palmer RF, Stein Z. The value of ecologic studies: mercury concentration in ambient air and the risk of autism. Rev Environ Health. 2011; 26:111–118. [PubMed: 21905454]

Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 2009; 32:506–516. [PubMed: 19716187]

Blumberg, SJ.; Bramlett, MD.; Kogan, MD.; Schieve, LA.; Jones, JR.; Lu, MC. Changes in Prevalence of Parent-reported Autism Spectrum Disorder in School-aged U.S. Children: 2007 to 2011–2012. 65. 3-20-2013. Centers for Disease Control and Prevention (CDC); 2013. (Ref Type: Report)

Brender JD, Zhan FB, Langlois PH, Suarez L, Scheuerle A. Residential proximity to waste sites and industrial facilities and chromosomal anomalies in offspring. Int J Hyg Environ Health. 2008; 211:50–58. [PubMed: 17470415]

Brender JD, Maantay JA, Chakraborty J. Residential proximity to environmental hazards and adverse health outcomes. Am J Public Health. 2011; 101(Suppl. 1):S37–S52. [PubMed: 22028451]

Bryk, AS.; Raudenbush, SW. Hierarchical Linear Models: Applications and Data Analysis Methods. Sage Publication; Newbury Park, CA: 1992.

Burstyn I, Senthilselvan A, Kim HM, Cherry NM, Pietroniro E, Waldner C. Industrial sources influence air concentrations of hydrogen sulfide and sulfur dioxide in rural areas of western Canada. J Air Waste Manag Assoc. 2007; 57:1241–1250. [PubMed: 17972769]

Calderon J, Navarro ME, Jimenez-Capdeville ME, Santos-Diaz MA, Golden A, Rodriguez-Leyva I, Borja-Aburto V, Diaz-Barriga F. Exposure to arsenic and lead and neuropsychological development in Mexican children. Environ Res. 2001; 85:69–76. [PubMed: 11161656]

Calderon-Garciduenas L, Macias-Parra M, Hoffmann HJ, Valencia-Salazar G, Henriquez-Roldan C, Osnaya N, Monte OC, Barragan-Mejia G, Villarreal-Calderon R, Romero L, Granada-Macias M, Torres-Jardon R, Medina-Cortina H, Maronpot RR. Immunotoxicity and environment: immunodysregulation and systemic inflammation in children. Toxicol Pathol. 2009; 37:161–169. [PubMed: 19171930]

Calderon-Garciduenas L, Engle R, Mora-Tiscareno A, Styner M, Gomez-Garza G, Zhu H, Jewells V, Torres-Jardon R, Romero L, Monroy-Acosta ME, Bryant C, Gonzalez-Gonzalez LO, Medina-Cortina H, D'Angiulli A. Exposure to severe urban air pollution influences cognitive outcomes,

brain volume and systemic inflammation in clinically healthy children. Brain Cogn. 2011; 77:345–355. [PubMed: 22032805]

Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med. 2003; 348:1517–1526. [PubMed: 12700371]

Choi HS, Shim YK, Kaye WE, Ryan PB. Potential residential exposure to toxics release inventory chemicals during pregnancy and childhood brain cancer. Environ Health Perspect. 2006; 114:1113–1118. [PubMed: 16835067]

Counter SA, Buchanan LH, Ortega F, Laurell G. Elevated blood mercury and neuro-otological observations in children of the Ecuadorian gold mines. J Toxicol Environ Health A. 2002; 65:149–163. [PubMed: 11820503]

Do MT, Smith LF, Pinsent CL. Urinary inorganic arsenic in residents living in close proximity to a nickel and copper smelter in Ontario, Canada. Can J Public Health. 2011; 102:467–471. [PubMed: 22164561]

Enstrom A, Krakowiak P, Onore C, Pessah IN, Hertz-Picciotto I, Hansen RL, Van de Water JA, Ashwood P. Increased IgG4 levels in children with autism disorder. Brain Behav Immun. 2009; 23:389–395. [PubMed: 19136055]

Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002; 23:303–331. [PubMed: 11910065]

Ezziane Z. The impact of air pollution on low birth weight and infant mortality. Rev Environ Health. 2013; 28:107–115. [PubMed: 24192497]

Freire C, Ramos R, Puertas R, Lopez-Espinosa MJ, Julvez J, Aguilera I, Cruz F, Fernandez MF, Sunyer J, Olea N. Association of traffic-related air pollution with cognitive development in children. J Epidemiol Community Health. 2010; 64:223–228. [PubMed: 19679705]

Gildemeister AE, Hopke PK, Kim E. Sources of fine urban particulate matter in Detroit, MI. Chemosphere. 2007; 69:1064–1074. [PubMed: 17537480]

Gulson B, Mizon K, Taylor A, Korsch M, Stauber J, Davis JM, Louie H, Wu M, Swan H. Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline—preliminary results. Environ Res. 2006; 100:100–114. [PubMed: 16337847]

Ha M, Kwon HJ, Lim MH, Jee YK, Hong YC, Leem JH, Sakong J, Bae JM, Hong SJ, Roh YM, Jo SJ. Low blood levels of lead and mercury and symptoms of attention deficit hyperactivity in children: a report of the children's health and environment research (CHEER). Neurotoxicology. 2009; 30:31–36. [PubMed: 19100765]

Hegde S, Sridhar M, Bolar DR, Bhaskar SA, Sanghavi MB. Relating tooth- and blood-lead levels in children residing near a zinc-lead smelter in India. Int J Paediatr Dent. 2010; 20:186–192. [PubMed: 20409199]

Hwang YH, Bornschein RL, Grote J, Menrath W, Roda S. Environmental arsenic exposure of children around a former copper smelter site. Environ Res. 1997; 72:72–81. [PubMed: 9012374]

Jarup L. Hazards of heavy metal contamination. Br Med Bull. 2003; 68:167–182. [PubMed: 14757716]

Kalkbrenner AE, Daniels JL, Chen JC, Poole C, Emch M, Morrissey J. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology. 2010; 21:631–641. [PubMed: 20562626]

Kalkbrenner AE, Windham GC, Serre ML, Akita Y, Wang X, Hoffman K, Thayer BP, Daniels JL. Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. Epidemiology. 2014; 26(1):30–42. [PubMed: 25286049]

Lakshmi PV, Virdi NK, Sharma A, Tripathy JP, Smith KR, Bates MN, Kumar R. Household air pollution and stillbirths in India: analysis of the DLHS-II National Survey. Environ Res. 2013; 121:17–22. [PubMed: 23375552]

Leroyer A, Nisse C, Hemon D, Gruchociak A, Salomez JL, Haguenoer JM. Environmental lead exposure in a population of children in northern France: factors affecting lead burden. Am J Ind Med. 2000; 38:281–289. [PubMed: 10940965]

Li X, Chauhan A, Sheikh AM, Patil S, Chauhan V, Li XM, Ji L, Brown T, Malik M. Elevated immune response in the brain of autistic patients. J Neuroimmunol. 2009; 207:111–116. [PubMed: 19157572]

Mazumdar S, Winter A, Liu KY, Bearman P. Spatial clusters of autism births and diagnoses point to contextual drivers of increased prevalence. Soc Sci Med. 2013; 95:87–96. [PubMed: 23267775]

Ming X, Brimacombe M, Malek JH, Jani N, Wagner GC. Autism spectrum disorders and identified toxic land fills: co-occurrence across States. Environ Health Insights. 2008; 2:55–59. [PubMed: 21572830]

Molina-Villalba I, Lacasana M, Rodriguez-Barranco M, Hernandez AF, Gonzalez-Alzaga B, Aguilar-Garduno C, Gil F. Biomonitoring of arsenic, cadmium, lead, manganese and mercury in urine and hair of children living near mining and industrial areas. Chemosphere. 2014; 124:83–91. [PubMed: 25434277]

Munroe RL, Gauvain M. Exposure to open-fire cooking and cognitive performance in children. Int J Environ Health Res. 2012; 22:156–164. [PubMed: 22128885]

Padula AM, Tager IB, Carmichael SL, Hammond SK, Yang W, Lurmann FW, Shaw GM. Traffic-related air pollution and selected birth defects in the San Joaquin Valley of California. Birth Defects Res A Clin Mol Teratol. 2013; 97:730–735. [PubMed: 24108522]

Palmer RF, Blanchard S, Wood R. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. Health Place. 2009; 15:18–24. [PubMed: 18353703]

Patel MM, Quinn JW, Jung KH, Hoepner L, Diaz D, Perzanowski M, Rundle A, Kinney PL, Perera FP, Miller RL. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. Environ Res. 2011; 111:1222–1229. [PubMed: 21855059]

Rahbar MH, White F, Agboatwalla M, Hozhabri S, Luby S. Factors associated with elevated blood lead concentrations in children in Karachi, Pakistan. Bull World Health Organ. 2002; 80:769–775. [PubMed: 12471396]

Rice CE, Baio J, Van Naarden BK, Doernberg N, Meaney FJ, Kirby RS. A public health collaboration for the surveillance of autism spectrum disorders. Paediatr Perinat Epidemiol. 2007; 21:179–190. [PubMed: 17302648]

Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, Koenen KC, Ascherio A, Weisskopf MG. Perinatal air pollutant exposures and autism spectrum disorder in the children of nurses' health study II participants. Environ Health Perspect. 2013; 121:978–984. [PubMed: 23816781]

Sanders T, Liu Y, Buchner V, Tchounwou PB. Neurotoxic effects and biomarkers of lead exposure: a review. Rev Environ Health. 2009; 24:15–45. [PubMed: 19476290]

SAS Institute Inc. SAS® 9.3. SAS Institute Inc., NC; 2011.

Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Ritz B, Hansen RL, Hertz-Picciotto I. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. Environ Health Perspect. 2014; 122:1103–1109. [PubMed: 24954055]

Shen XM, Yan CH, Guo D, Wu SM, Li RQ, Huang H, Ao LM, Zhou JD, Hong ZY, Xu JD, Jin XM, Tang JM. Umbilical cord blood lead levels in Shanghai, China. Biomed Environ Sci. 1997; 10:38–46. [PubMed: 9099425]

Stroh E, Lundh T, Oudin A, Skerfving S, Stromberg U. Geographical patterns in blood lead in relation to industrial emissions and traffic in Swedish children, 1978–2007. BMC Public Health. 2009; 9:225. [PubMed: 19591669]

Suarez L, Brender JD, Langlois PH, Zhan FB, Moody K. Maternal exposures to hazardous waste sites and industrial facilities and risk of neural tube defects in offspring. Ann Epidemiol. 2007; 17:772–777. [PubMed: 17689262]

Szklo, M.; Nieto, J. Epidemiology: Beyond the Basics. Jones and Barlett; Mississauga, Ontario: 2007. p. 161-170.

Talbott EO, Arena VC, Rager JR, Clougherty JE, Michanowicz DR, Sharma RK, Stacy SL. Fine particulate matter and the risk of autism spectrum disorder. Environ Res. 2015; 140:414–420. [PubMed: 25957837]

Tang D, Li TY, Chow JC, Kulkarni SU, Watson JG, Ho SS, Quan ZY, Qu LR, Perera F. Air pollution effects on fetal and child development: a cohort comparison in China. Environ Pollut. 2014; 185:90–96. [PubMed: 24239591]

Van Naarden BK, Pettygrove S, Daniels J, Miller L, Nicholas J, Baio J, Schieve L, Kirby RS, Washington A, Brocksen S, Rahbar H, Rice C. Evaluation of a methodology for a collaborative multiple source surveillance network for autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2002. MMWR Surveill Summ. 2007; 56:29–40. [PubMed: 17287716]

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect. 2011; 119:873–877. [PubMed: 21156395]

Volk HE, Kerin T, Lurmann F, Hertz-Picciotto I, McConnell R, Campbell DB. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. Epidemiology. 2014; 25:44–47. [PubMed: 24240654]

Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, Han LL, Qiao XY, Wu ZM, Wang ZQ. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. Environ Health Perspect. 2007; 115:643–647. [PubMed: 17450237]

Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, van GA, Slavkovich V, LoIacono NJ, Cheng Z, Hussain I, Momotaj H, Graziano JH. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 2004; 112:1329–1333. [PubMed: 15345348]

Wickre JB, Folt CL, Sturup S, Karagas MR. Environmental exposure and fingernail analysis of arsenic and mercury in children and adults in a Nicaraguan gold mining community. Arch Environ Health. 2004; 59:400–409. [PubMed: 16268116]

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. Environ Health Perspect. 2006; 114:1438–1444. [PubMed: 16966102]

Wright RO, Amarasiriwardena C, Woolf AD, Jim R, Bellinger DC. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. Neurotoxicology. 2006; 27:210–216. [PubMed: 16310252]

Zheng W, Aschner M, Ghersi-Egea JF. Brain barrier systems: a new frontier in metal neurotoxicological research. Toxicol Appl Pharmacol. 2003; 192:1–11. [PubMed: 14554098]

HIGHLIGHTS

- We examined associations between autism prevalence and proximity to pollutant sources.
- We found that tracts in the closest 10th percentile had higher autism prevalence.
- We found that results were still significant after adjusting for socioeconomic status.

Table 1

Descriptive statistics for census tracts (n = 2489 tracts).

		Mean	SD
Case characteristics			
Number of children with ASD		1.8	2.2
% male		81.6	30.6
Race	% White	57.5	42.1
	% Black	20.0	35.4
	% other	4.8	16.6
	% missing	17.4	31.3
% Hispanic		14.6	29.8
% IQ ≤ 70[a]		41.0	40.3
Mother's education[b]	% high school graduate	77.5	35.0
	% with ≥Bachelor's degree	26.1	37.4
2000 census tract characteristics			
Total tract population of 0–9 years		669.8	383.2
Estimated study population[†]		230.4	176.3
% male		48.9	3.4
Race	% White	70.1	28.9
	% Black	20.9	29.5
	% other	11.5	12.6
% with Hispanic ethnicity		13.0	18.9
% college educated		24.8	16.9
% below poverty line		12.9	11.8
Median household income		$47,675	$21,643

ASD case characteristics were not reported for 802 tract reporting 0 cases.

SD = standard deviation.

[a] IQ data is missing for 1035 (23%) cases.

[b] Mother's education level is missing for 1981 (44%) cases.

[†] Study population estimate = [(Total population 0–9 years) / 10] * (Number of surveillance years).

Table 2

Association between prevalence of ASD and potentially confounding SES factors using multi-level negative binomial regression models.

n = 2489		RR	95% CI	*P*-value
Race	% White	1.09	(1.08, 1.11)	<0.001
	% Black	0.94	(0.92, 0.96)	<0.001
	% Other	0.81	(0.78 0.84)	<0.001
% Hispanic		0.86	(0.84, 0.88)	<0.001
% college education		1.07	(1.04, 1.10)	<0.001
Rural		0.50	(0.40, 0.63)	<0.001
% below poverty line		0.79	(0.75, 0.82)	<0.001
Median household income (highest 25th percentile)		1.39	(1.28, 1.51)	<0.001

Table 3

Association between proximity to air pollutant releasing industrial facilities and potential confounding factors using binary logistic regression models (n = 2489).

		≤50th percentile mean ± SD	>50th percentile mean ± SD	OR	95% CI	*P*-value
Race	% White	65.2 ± 33.0	77.2 ± 19.6	0.96	(0.95, 0.98)	0.001
	% Black	28.1 ± 33.6	10.5 ± 17.6	1.04	(1.02, 1.06)	<0.001
	% Other	9.1 ± 10.2	15.0 ± 14.6	1.01	(0.99, 1.03)	0.554
% Hispanic		8.2 ± 12.7	20.1 ± 23.6	0.96	(0.95, 0.98)	<0.001
% college education		25.2 ± 17.7	25.2 ± 15.6	0.99	(0.98, 1.01)	0.272
% below poverty line		12.7 ± 12.1	13.1 ± 12.0	1.00	(0.10, 1.03)	0.684
		N (%)	N (%)			
Rural		58 (24.0%)	184 (76.0%)	0.01	(<0.01, 0.24)	<0.001
Median household income (highest 25th percentile)		423 (63.0%)	249 (37.0%)	0.96	(0.57, 1.63)	0.888

Table 4

Relative risk of ASD for children by residential proximity to air pollutant releasing industrial facilities, based on negative binomial hierarchical models.

(n = 2489 tracts)	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Incremental proximity		
Closest <10th percentile (0.27 km to 10.46 km)	1.46 (1.13, 1.88)**	1.27 (1.00, 1.61)*
10th–20th percentile (10.47 km to 19.01 km)	1.30 (1.04, 1.63)*	1.08 (0.88, 1.34)
20th–30th percentile (19.03 km to 27.64 km)	1.43 (1.15, 1.76)**	1.08 (0.88, 1.32)
30th–40th percentile (27.67 km to 37.38 km)	1.32 (1.08 1.60)**	1.10 (0.91, 1.33)
40th–50th percentile (37.40 km to 46.91 km)	1.09 (0.89, 1.33)	0.94 (0.77, 1.13)
Furthest ≥50th percentile (46.92 km to 205.45 km)	Ref	Ref
Proximity divided at the median		
Closest <50th percentile (0.27 km to 46.91 km)	1.24 (1.04, 1.47)*	1.04 (0.88, 1.22)
Furthest ≥50th percentile (46.92 km to 205.45 km)	Ref	Ref

[a] Model adjusted for census tract % male, % White race, % Hispanic ethnicity, % college educated, rural geography, and % below poverty.

* Indicates *P*-value < 0.05.

** Indicates *P*-value < 0.01.