Maternal Exposures Associated with Autism Spectrum Disorder in Jamaican Children

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Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder with poorly understood etiology. Many maternal exposures during pregnancy and breastfeeding potentially interfere with neurodevelopment. Using data from two age- and sex-matched case-control studies in Jamaica (n = 298 pairs), results of conditional logistic regression analyses suggest that maternal exposures to fever or infection (matched odds ratio (MOR) = 3.12, 95% CI: 1.74 – 5.60), physical trauma (MOR = 2.02, 95% CI: 1.01 – 4.05), and oil-based paints (MOR = 1.99, 95% CI: 1.14 – 3.46) may be associated with ASD. Additionally, maternal exposure to oil-based paints may modify the relationship between maternal exposure to pesticides and ASD, which deepens our understanding of the association between pesticides and ASD.

Keywords

Fever; Physical Trauma; Volatile Organic Compounds; Pesticides; Autism Spectrum Disorder; Jamaica

Introduction

Autism Spectrum Disorder (ASD) is a pervasive developmental disorder characterized by deficits in social interaction, impaired communication, and stereotyped behaviors that persist throughout an individual's lifetime (Schreibman, 1988; American Psychiatric Association, 2013). Although the most recent prevalence estimate for ASD in the United States has increased to 1 in 68 (Developmental & Principal, 2014), the prevalence is currently unknown

in low and middle income countries (LMICs) such as Jamaica. The etiology of ASD is not well characterized, though many ASD cases likely result from a combination of environmental and genetic factors (Lyall et al., 2017a). There are many environmental factors that can interfere with neurodevelopment and are possibly involved in the manifestation of ASD, and since neurodevelopment spans from the first few weeks of pregnancy into adolescence (Budday, Steinmann, & Kuhl, 2015), exposures experienced by the mother during pregnancy or breastfeeding have the potential to interrupt fetal and infant neurodevelopmental mechanisms.

There is evidence in the literature that suggests that the immune system has a role in ASD etiology (McDougle et al., 2015). Viral and bacterial infections during pregnancy are thought to be associated with ASD in children (Lee et al., 2015; Atladottir et al., 2010), though some epidemiological studies have found no association (Dassa, Takei, Sham, & Murray, 1995). Additionally, there is evidence from epidemiologic studies that high maternal levels of immunoglobulin G (IgG), an antibody that protects against viral and bacterial infections, during pregnancy and breastfeeding has a protective effect on ASD in offspring (Grether et al., 2016).

Motor vehicle accidents (MVAs) and other types of blunt force trauma experienced by pregnant women are known to have resulted in adverse fetal outcomes (Chibber, Al-Harmi, Fouda, & El-Saleh, 2015), including negative effects on the fetal brain and nervous system (Baethmann, Kahn, Lenard, & Voit, 1996; Breysem et al., 2004). However, to the best of our knowledge, no studies have directly examined the association between this type of maternal injury during pregnancy and ASD in her child.

Volatile organic compounds (VOCs) are gaseous at room temperature and can be found in many common household products, including degreasers, paints, and paint thinners (Boyle et al., 2016). Common routes of exposure to VOCs include inhalation (Bari & Kindzierski, 2017) and ingestion or absorption through the skin via contaminated water (Brown, Bishop, & Rowan, 1984). They are ubiquitous in the environment and have previously been linked to a variety of human neurological problems, including congenital anomalies of the nervous system (Hjortebjerg, Andersen, Garne, Raaschou-Nielsen, & Sorensen, 2012), neurocognitive impairment (Till, Koren, & Rovet, 2001), impaired motor function (Laslo-Baker et al., 2004; Till et al., 2001), and behavior problems (Laslo-Baker et al., 2004). VOCs have also been linked to oxidative stress and interference with neurodevelopment (Kalkbrenner, Schmidt, & Penlesky, 2014), which are both mechanisms suspected to be involved in the manifestation of ASD.

Pesticides, which also contain VOCs, are also known to have neurotoxic effects, with evidence that exposure to pesticides may delay motor development (De Felice, Scattoni, Ricceri, & Calamandrei, 2015), alter neuroprotein levels (Lee, Eriksson, Fredriksson, Buratovic, & Viberg, 2015), and interfere with mechanisms related to oxidative stress (De Felice, Greco, Calamandrei, & Minghetti, 2016). Exposure to pesticides, including organophosphates (OP) (Shelton et al., 2014; D'Amelio et al., 2005), organochlorines (OC) (Roberts et al., 2007), and pyrethroids (Domingues et al., 2016), has also previously been linked to ASD.

Since a majority of the research on ASD etiology is done in developed countries, there are very limited data from LMICs (Khan et al., 2012). This is the case for data on the association between maternal exposures and ASD in Jamaica. The few studies that have been conducted reported positive associations between increased joint maternal and paternal age (Rahbar et al., 2012b), maternal stress levels (Siles & Samms Vaughan, 2001), and obstetric complications (Roberson, Onugha, Siles, & Samms Vaughan, 2001) and ASD in Jamaican children. However, to our knowledge no studies have been conducted to investigate the relationship between maternal exposures to fever and infection, physical trauma, products containing VOCs, or pesticides and ASD in Jamaica, though the Jamaican population may be at increased risk for such exposures.

Infectious diseases, particularly sexually transmitted infections (Snead et al., 2017; Lewis-Bell et al., 2013) and vector-borne diseases (Brown, Vickers, Salas, & Smikle, 2009; Wood et al., 2014), are of concern in the Jamaican population. For example, studies have reported 100% seroprevalence of dengue virus antibodies in the general population (Brown et al., 2009) and among pregnant women (Wood et al., 2014) in Jamaica. Compared to other Caribbean countries, pregnant women in Jamaica have higher seroprevalence of bacterial infections, including leptospirosis and spotted fever group rickettsioses (SGFR) (Wood et al., 2014). The relatively high prevalence of vector borne diseases coincides with poor knowledge and prevention practices in some areas in Jamaica (Alobuia, Missikpode, Aung, & Jolly, 2015). Additionally, analyses conducted in 2002 using data from the Jamaica Injury Surveillance System revealed that unintentional injuries and MVAs were the second and third most common types of injuries in Jamaica, comprising 33% and 15% of injuries, respectively, within a period of six months (Arscott-Mills, Gordon, McDonald, Holder, & Ward, 2002). To our knowledge, there is no literature to suggest that people in Jamaica have higher risk of exposure to VOCs. However, since VOCs are ubiquitous in the environment and found in many common household products (Boyle et al., 2016), we assume that exposures to VOCs are just as likely to occur in Jamaica compared to other countries. Furthermore, pesticides are regularly used in the Wider Caribbean Region (Fernandez, Singh, & Jaffe, 2007) and studies have reported that pregnant women in Jamaica have higher urine concentrations of pesticides compared to other Caribbean countries (Forde et al., 2015), the U.S., and Canada (Dewailly et al., 2014).

The objective of this study is to examine maternal exposures to fever or infection, physical trauma, products containing VOCs, and pesticides in relation to ASD in Jamaican children. Since the Jamaican population is at risk for these exposures, we hypothesize that they will be positively associated with ASD in Jamaican children.

Methods

Study Population

Since 2009, faculty at the University of the West Indies (UWI) have collaborated with faculty at the University of Texas Health Science Center at Houston (UTHealth) on two studies, "Epidemiological Research on Autism in Jamaica (ERAJ)" and "Epidemiological Research on Autism in Jamaica – Phase 2 (ERAJ-2)." These studies aimed to investigate the role of Jamaican children's exposure to heavy metals, polychlorinated biphenyls, and OC

pesticides, and the interaction of these exposures with the children's glutathione *S*-transferase (GST) genotypes in relation to ASD. The ERAJ and ERAJ-2 study populations and enrollment protocols have been described in detail previously (Rahbar et al., 2012b; Rahbar et al., 2013; Rahbar et al., 2012a). In summary, the study sample used for these analyses includes 298 pairs of children ages 2 – 8 years who were born in Jamaica. Each pair consists of one ASD case and one typically developing (TD) control, matched on sex and age (± 6 months). Eligible cases were recruited from all over Jamaica using the list of children diagnosed with ASD based on the Diagnostic Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2013) criteria and the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, DeVellis, & Daly, 1980) from the UWI Jamaica Autism Database. Each case was reassessed for ASD at the time of enrollment by administering the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999) or its second edition (ADOS-2) and the Autism Diagnostic Interview – Revised (ADI-R) (Rutter, LeCouteur, & Lord, 2003) to the children and their parents/guardians, respectively. Controls were recruited from local schools and well child clinics near Kingston, Jamaica. At the time of enrollment, the Lifetime form of the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) was administered to parents/guardians of controls to rule out ASD or other developmental disabilities. Controls were only included in this study if their SCQ score was at or below the cut-off value of 6, which is one standard deviation below the mean SCQ score for TD children (Mulligan, Richardson, Anney, & Gill, 2009). This cutoff was chosen to minimize the possibility of enrolling a child with any developmental disorders as a control, since an SCQ score of 15 indicates the possibility of pervasive developmental disorder. Parental consent was obtained for each participant at the time of enrollment. Written assent was obtained from participants 7–8 years of age,or those children who were able to sign their name, and verbal assent was obtained from participants under 7 years of age or those who were unable to sign their name.

Data Collection

The parent/guardian of each participant was asked to complete a socioeconomic status (SES) questionnaire at the time of enrollment. The SES questionnaire, which utilized questions that have been previously used in large Jamaican birth cohort studies (Samms-Vaughan & Planning Institute of Jamaica.Policy Development Unit, 2000; McCaw-Binns et al., 2011), obtained demographic data including car ownership of the parents, which serves as a measure of SES in this study since many families in Jamaica cannot afford to buy a car. For reference, there were only 188 motor vehicles per 1,000 people in Jamaica as of 2010 (World Bank, 2010). The questionnaire also included pregnancy data and several exposures spanning from 3 months before pregnancy to the end of breastfeeding, including exposure to fever over 101°F or infection requiring antibiotics, physical trauma such as a MVA, fall, or other injury, degreasers, oil-based paints, paint thinners, and pesticides. The ERAJ and ERAJ-2 studies focused on oil-based paints to distinguish from exposure to lead via lead paint, for which there have already been numerous studies.

Statistical Analysis

Demographic and other characteristics were categorized based on known cut-off values or the distribution of the data. For example, the World Health Organization (WHO) classifies

preterm birth into several categories based on gestational age, including moderate to late preterm (32 – 36 weeks), very preterm (28 – 31 weeks), and extremely preterm (< 28 weeks). (World Health Organization, 2017) In the present study, we collapsed the very preterm and extremely preterm categories together because of very small counts, so gestational age was categorized into full term (≥ 37 weeks), moderate to late preterm (32 – 36 weeks), and very to extremely preterm (< 32 weeks). In addition, the distribution of duration of breastfeeding was right-skewed so it was categorized based on 25th, 50th, and 75th percentiles, which corresponded to < 3 months, 3 –5.9 months, 6 – 15.9 months, and > 16 months of breastfeeding. All analyses were done using conditional logistic regression (CLR) models that account for within-pair correlation.

We used CLR to assess univariable associations of maternal exposures to fever over 101°F or infection requiring antibiotics, physical trauma (MVA/fall/other injury), degreasers, oil-based paints, paint solvents, and pesticides with ASD status of the child (case vs. control). We then applied multivariable CLR models to control for potential confounders obtained in the SES questionnaire. Potential confounders were included in the model if they were associated with both the maternal exposure and ASD, and if the magnitude of the adjusted matched odds ratio (MOR) differed from the crude MOR by ≥ 10%. Each maternal exposure was assessed for its own specific set of confounders, and the potential confounders included in the present study were age of the mother, age of the father, father's education, and parish. Unadjusted and adjusted MORs and the corresponding 95% confidence intervals (CIs) are reported. Interactions between maternal exposure variables in relation to ASD status of the child were also explored using multivariable CLR models. In the event that we found a departure from multiplicative interaction, the CONTRAST statement in SAS was used to calculate MORs and 95% CIs for different levels of the effect modifier.

All analyses were conducted using SAS 9.4 software (SAS Institute Inc., 2013) and results were interpreted at a significance level of $\alpha = 0.05$.

Results

At the time of enrollment in the ERAJ study, the mean (SD) age of ASD cases and TD controls was 61.3 (19.5) months and 61.8 (19.3) months, respectively. A majority of the study participants and their parents were Afro-Caribbean, including 96.0% of children, 96.8% of mothers, and 96.0% of fathers. A larger proportion of ASD cases were born prematurely compared to TD controls (11.2% vs. 7.4%), although this difference was not statistically significant. There was also no significant difference in duration of breastfeeding for ASD cases and TD controls, with 6 months being the median duration for both groups. In contrast, both the mothers and fathers of ASD cases were significantly older and had higher levels of education compared to mothers and fathers of TD controls (all p < 0.03). A larger proportion of parents of ASD cases had a relationship, defined as married, common law union, and visiting relationship, compared to parents of TD controls (61.9% vs. 57.8%, p < 0.01). Fewer ASD cases were from the urban Kingston parish compared to TD controls (27.9% vs. 63.1%, p < 0.01); however ASD cases were of a higher SES compared to controls, with 59.1% of case families owning a car compared to 39.9% of control families (p

< 0.01). Distributions of demographic and other characteristics of the study population are described in Table 1.

In univariable CLR models (Table 2), ASD in the children was significantly associated with several maternal exposures occurring from 3 months prior to pregnancy until the end of breastfeeding, including fever over 101°F or infection requiring treatment with antibiotics (MOR = 2.81, 95% CI: 1.59 – 4.98), physical trauma such as a MVA, fall, or other injury (MOR = 2.33, 95% CI: 1.19 – 4.59), degreasers (MOR = 2.63, 95% CI: 1.16 – 5.93), oil-based paints (MOR = 2.13, 95% CI: 1.30 – 3.50), and paint solvents (MOR = 1.94, 95% CI: 1.06 – 3.54). Exposure to oil-based paints and paint solvents most frequently occurred when the mother's home or workplace was being painted. Significant associations remained between ASD and maternal exposures to fever or infection after adjusting for age of the mother (adjusted MOR = 3.12, 95% CI: 1.74 – 5.60), physical trauma after adjusting for age of the father (adjusted MOR = 2.02, 95% CI: 1.01 – 4.05), and oil-based paints after adjusting for the child's parish (adjusted MOR = 1.99, 95% CI: 1.14 – 3.46). In contrast, the association between ASD and maternal exposure to degreasers became marginally significant after adjusting for age of the father, and the association between ASD and maternal exposure to paint solvents became nonsignificant after adjusting for age of the father and father's education level.

Maternal exposure to pesticides was also associated with ASD in the children in the crude model (MOR = 2.08, 95% CI: 1.14 – 3.08) and after adjusting for the child's parish (MOR = 1.67, 95% CI: 1.08 – 2.59) (Table 2). Among mothers who reported exposure to pesticides, the most commonly used brands were Baygon (28.8%) and Pyro (15.9%), which both contain pyrethroids (data not shown). However, further investigation revealed that maternal exposure to oil-based paints may be an effect modifier for the relationship between maternal exposure to pesticides and ASD in children, with overall interaction p-value = 0.02 and p-value = 0.04 in unadjusted and adjusted models, respectively, indicating a significant departure from multiplicative interaction (Table 3). Specifically, among those with maternal exposure to oil-based paints, those with maternal exposure to pesticides had 2.45 times greater odds of being an ASD case compared to those without maternal exposure to pesticides (MOR = 2.45, 95% CI: 1.41 – 4.26) in the unadjusted model. We found similar results after adjusting for the child's parish (MOR = 2.17, 95% CI: 1.21 – 3.92). This association was weaker among those with no maternal exposure to oil-based paints in both unadjusted (MOR = 1.74, 95% CI: 1.29 – 2.35) and adjusted models (MOR = 1.55, 95% CI: 1.12 – 2.14).

We observed similar interactive effects between maternal exposure to paint solvents and pesticides in relation to ASD (Table 4), where the association between ASD and maternal exposure to pesticides was much stronger among those with maternal exposure to paint solvents (MOR = 2.33, 95% CI: 1.19 – 4.56) compared to those with no maternal exposure to paint solvents (MOR = 1.78, 95% CI: 1.24 – 2.52) in the unadjusted model. However, the overall departure from multiplicative interaction was not statistically significant (p = 0.12). After adjusting for the child's parish, age of the father, and father's education level, the interaction remained non-significant (p = 0.26) and the difference in magnitude of the MORs decreased, i.e. the association between ASD and maternal exposure to pesticides was more

similar among those with (MOR = 1.84, 95% CI: 0.86 – 3.91) and without (MOR = 1.46, 95% CI: 0.98 – 2.18) maternal exposure to paint solvents.

No other combinations of maternal exposures to products containing VOCs resulted in statistically significant interactions in either unadjusted or adjusted models (Table 5).

Discussion

Findings from this study suggest that having a fever over 101°F or an infection requiring antibiotics any time from three months before conception until the end of breastfeeding may be associated with ASD in the children, even after adjusting for age of the mother. We also found a possible association of mothers experiencing physical trauma, such as a MVA, fall, or other injury from three months prior to pregnancy until the end of breastfeeding with ASD in the children, which remained marginally significant after adjusting for age of the father. Furthermore, we report possible associations between maternal exposures to common household products containing VOCs, including degreasers, oil-based paints, and paint thinners and ASD in the children. The association between ASD and maternal exposure to oil-based paint remained significant after adjusting for child's parish; however, associations between ASD and exposure to degreasers and paint solvents became nonsignificant in adjusted models. Additionally, maternal exposure to oil-based paints may be an effect modifier for the relationship between maternal exposure to pesticides and ASD in children, with a stronger association between maternal exposure to pesticides and ASD among those with maternal exposure to oil-based paints compared to those without maternal exposure to oil-based paints. Similar yet non-significant results were reported for the interaction between maternal exposures to paint solvents and pesticides. In the following sections, we discuss each of these findings separately.

Fever and Infection

Many studies have been conducted to investigate the relationship between maternal fever and ASD in her children. Some have reported increased risk of ASD when mothers experienced fever during pregnancy (Atladottir, Henriksen TB FAU - Schendel, Schendel DE FAU - Parner, & Parner, 2012), including the Childhood Autism Risks from Genetics and Environment (CHARGE) study, which found that fever at any point during pregnancy was associated with 2.12 times greater odds of ASD in the offspring, although this relationship was modified by antipyretic medication use. Specifically, mothers who did not take antipyretic medications to reduce fever had 2.55 times greater odds of ASD in their offspring while there was no association among mothers who took antipyretic medications (Zerbo et al., 2013). Data on antipyretic medication use were not collected as part of the ERAJ and ERAJ-2 studies, so it is possible that this interaction remains unaccounted for in the present study. In contrast, other studies have reported no association between maternal fever during pregnancy and ASD in the offspring (Juul-Dam, Townsend, & Courchesne, 2001).

Similarly, there are several reports in the literature of an association between maternal infection during pregnancy and ASD in the offspring. For example, Lee et al. found 1.37 times greater odds of ASD in children whose mothers had any infection requiring

hospitalization, an association that remained significant across all three trimesters (Lee et al., 2015). More specifically, several studies reported that viral infections in the first trimester (Lee et al., 2015; Atladottir et al., 2010), bacterial infections in the second trimester (Lee et al., 2015; Atladottir et al., 2010; Zerbo et al., 2015), and viral or bacterial infections during the third trimester (Lee et al., 2015) may be associated with increased risk of ASD in offspring. However, there is also evidence to contradict these associations. Several studies have reported no association between any infection (i.e. any type of bacterial or viral infection) at any point during pregnancy and having a child with ASD (Atladottir et al., 2010; Zerbo et al., 2015). There is also much conflicting evidence for the association between specific infections, including influenza (Atladottir et al., 2012; Dassa et al., 1995; Zerbo et al., 2013), respiratory infections(Atladottir et al., 2012; Lee et al., 2015; Zerbo et al., 2015), and genital infections (Atladottir et al., 2012; Langridge et al., 2013; Lee et al., 2015; Zerbo et al., 2015) during pregnancy and the risk of having a child with ASD, suggesting that maternal immune activation (MIA) in general may be more likely to be associated with ASD than any specific infection (Estes & McAllister, 2015).

As indicated by animal studies, there are many different ways in which MIA can have adverse effects on fetal or infant neurodevelopment including upregulation of proteins involved in brain development (Xu, Sajdel-Sulkowska, Iwasaki, & Koibuchi, 2013), dysregulation of the offspring's immune system (Hsiao, McBride, Chow, Mazmanian S.K., & Patterson, 2012), and increased presence of reactive oxygen species (Le Belle et al., 2014). Recent literature has provided evidence that MIA induces upregulation of the expression of proinflammatory cytokines, including IL-17a, which caused abnormal cortical development (Choi et al., 2016), and TNFα, which altered synaptic development in the cerebellum of exposed offspring (Pendyala et al., 2017). Upregulated expression of both IL-17a and TNFα also resulted in autism-like behaviors and deficits in social interaction in MIA-exposed offspring (Choi et al., 2016; Pendyala et al., 2017). Furthermore, upregulated expression of IL-17a and its receptor in the fetal brain may have led to the formation of cortical patches associated with MIA-induced behavioral abnormalities, though the exact mechanism is still unknown (Shin et al., 2017).

Physical Trauma

There is limited literature available on the relationship between maternal physical trauma during pregnancy or breastfeeding and ASD in the offspring. However, it is well known that blunt force trauma experienced by pregnant women is associated with severe fetal outcomes (Agran, Dunkle, Winn, & Kent, 1987; Chibber et al., 2015), including damage to the fetal central nervous system (Baethmann et al., 1996; Breysem et al., 2004). Studies have also shown that severe trauma can occur to the fetus regardless of whether the mother sustained minor or severe injuries (Agran et al., 1987; Breysem et al., 2004). Therefore, it is possible that blunt force trauma, such as MVAs or falls, during pregnancy could disrupt typical neurodevelopment, potentially leading to disorders such as ASD.

Furthermore, it is also known that injuries to body tissues result in the induction of an inflammatory response, including the recruitment of cytokines (Adair-Kirk et al., 2005). As discussed previously, components of the maternal immune system are suspected to be

involved in the association between MIA and ASD status of the offspring. Therefore, it is possible that the maternal immune system also plays a role in the potential association between maternal physical trauma and ASD status of the offspring. This relationship requires further investigation.

Volatile Organic Compounds

The literature on the association between VOCs and ASD is mostly limited to studies focused on VOCs measured in air pollution (Kalkbrenner et al., 2014), some of which report positive associations (Roberts et al., 2013) while others report no association (Windham, Zhang, Gunier, Croen, & Grether, 2006). Comparable to results from the present study, Kalkbrenner et al. (2010) reported that perinatal exposure to specific VOCs including styrene and xylene were individually associated with ASD in 8 year old children, however the associations became nonsignificant in adjusted models (Kalkbrenner et al., 2010). Many epidemiologic studies on the relationship between VOCs and ASD also reported wide confidence intervals, possibly due to instability from small proportions of exposed study participants (Kalkbrenner et al., 2014). We faced similar issues in the present study, with relatively small proportions of those exposed to degreasers possibly resulting in wider confidence intervals.

Toxic exposures to VOCs can occur through inhalation of products such as paints, paint thinners, and degreasers, inhalation through air pollution (Bari & Kindzierski, 2017), ingestion or absorption through the skin via contaminated water (Brown et al., 1984), among other pathways. VOCs are also linked to oxidative stress and interference with neurodevelopment (Kalkbrenner et al., 2014) which are both suspected to be involved in the manifestation of ASD. Furthermore, Martinez-Alfaro et al. have shown that prolonged exposure to paint thinner is associated with structural alterations to Purkinje cells in the cerebellum of rats, leading to altered balance and behavior. The authors speculated that the paint thinner interferes with intracellular calcium-buffering pathways (Martinez-Alfaro, Carabez-Trejo, Sandoval-Zapata, Morales-Tlalpan, & Palma-Tirado, 2014). Future studies that focus on the possible association between VOCs and autism are needed.

Pesticides

Pesticides have been implicated as a potential risk factor for ASD in several epidemiologic studies that used residential data and reported agricultural use of pesticides to estimate prenatal exposures. Some of these studies reported positive associations between residential proximity to pesticides during the first trimester (Roberts et al., 2007) or any point during pregnancy, especially the third trimester (Shelton et al., 2014). In contrast, studies using maternal biological markers to assess exposures have reported no association between pesticides and ASD (Lyall et al., 2017b) or autistic behaviors (Millenson et al., 2017). Another study using self-reported pesticide exposure data attempted to correct for exposure misclassification and found that the association varied when corrected for different degrees of exposure misclassification, leading the authors to suggest future validation studies to be conducted (Keil, Daniels, & Hertz-Picciotto, 2014). Since data in the present study is also self-reported, exposure classification bias may obscure our results.

Although many studies have been conducted to determine the effects of exposure to various VOCs and pesticides individually, few have explored the possibility of interaction between these chemicals despite the fact that exposures to VOCs and pesticides frequently occur in combination with each other and often share common biological pathways (Kalkbrenner et al., 2014; Shelton et al., 2014; Shelton, Hertz-Picciotto, & Pessah, 2012). By ignoring the potential interaction between exposure to VOCs and pesticides, their associations with ASD may be misinterpreted. Results from the present study show a significant departure from multiplicative interaction between maternal exposure to oil-based paints and pesticides, suggesting that the association between ASD and pesticide exposure is stronger among those also exposed to oil-based paints compared to those unexposed to oil-based paints. One other study has investigated an interaction between prenatal exposure to pesticides and another exposure, in this case low folic acid intake, in relation to ASD, reporting that mothers doubly exposed had the highest odds of having a child with ASD, followed by mothers with only one exposure, compared to doubly unexposed mothers. Although most of the ORs reported were greater than expected by additive and multiplicative models, none of the interactions were statistically significant (Schmidt et al., 2017).

Several animal studies have provided evidence that prenatal exposure to pesticides can interfere with motor development (De Felice et al., 2015) and neurodevelopment (Herzine et al., 2016), as well as induce oxidative stress (De Felice et al., 2016) and autism-like behavioral abnormalities (Mullen, Khialeeva, Hoffman, Ghiani, & Carpenter, 2012; Laugeray et al., 2014). Several biological mechanisms have been hypothesized to explain the association between exposure to pesticides and ASD (Shelton et al., 2012), however the actual mechanism of action likely varies between individuals depending on the presence of other environmental and genetic co-exposures. Additional studies are required to further understand the relationship between pesticides and ASD, and studies should emphasize the possibility of combinations of exposures and their interactions.

Limitations

This study had several limitations. Since we are the first to report these associations in Jamaica and recommend that future studies investigate them as well, we have not corrected our findings for multiple comparisons. However, even if we employ a very conservative method such as the Bonferroni correction, our results for fever and infection would remain statistically significant. Due to the retrospective nature of this study and the use of self-reported exposure data, there is potential for recall bias and exposure misclassification. The analyses presented in this paper were secondary analyses, and since maternal exposures were not part of the specific aims of the ERAJ and ERAJ-2 case-control studies, the SES questionnaire addressed limited details of maternal exposures. We do not have data on the timing of some maternal exposures including fever or infection and physical trauma, and while we do have such data for the remaining maternal exposures including degreasers, oil-based paints, paint solvents, and pesticides, these data were too sparse to conduct meaningful statistical analyses (80% - 98% missing data). The SES questionnaire did not distinguish between exposure to fever and infection, so it is possible that some mothers who were exposed to fever never sought medical attention and prescriptions to antibiotics or antipyretics, which could possibly be effect modifiers for this association with ASD. Future

studies should collect such data and investigate the interactions between fever and infections with these medications to further our understanding of this association. It is also possible that the child's sex modifies the associations described in this study, however we have not included these analyses due to limited proportions of exposed girls. Future studies with larger sample sizes should also consider the potential interaction between maternal exposures and the child's sex in relation to ASD. Additionally, since TD controls were more likely to be selected from the Kingston parish to match the ASD cases on age and sex, there is possible selection bias in which the control group is inherently different from the case group based on their parish (Kingston vs. Others). We acknowledge that because cases were more likely to live in non-urban parishes than controls, it is possible that mothers of cases had greater probability of exposures, particularly to pesticides. However, even after adjusting for parish, exposure to pesticides was significantly associated with ASD in all models. Finally, due to small proportions of participants who indicated exposure, there was possibly a lack of power to detect true associations, and some potential confounders frequently used in the literature were not included in some regression models to avoid reporting unstable estimates. For example, other epidemiologic studies on maternal infection adjusted for age of the father, maternal race/ethnicity, and family income in addition to maternal age. In the present study, however, these additional variables did not meet the definition of confounding described in this paper. We were able to include all variables that met this definition of confounding in each model.

Conclusions

Despite limitations in this study, our results suggest that, compared to TD controls, ASD cases had over three times greater odds of maternal exposure to fever over 101°F or infection requiring antibiotics (adjusted MOR = 3.12, 95% CI: 1.74 – 5.60), two times greater odds of maternal exposure to physical trauma such as MVA, fall, or other injury (adjusted MOR = 2.02, 95% CI: 1.01 – 4.05), and nearly two times greater odds of maternal exposure to oil-based paints (adjusted MOR = 1.99, 95% CI: 1.14 – 3.46) from 3 months prior to pregnancy until the end of breastfeeding. Additionally, maternal exposure to oil-based paints may be an effect modifier for the relationship between maternal exposure to pesticides and ASD in children, with a stronger association between maternal exposure to pesticides and ASD among those with maternal exposure to oil-based paints (adjusted MOR = 2.17, 95% CI: 1.21 – 3.92) compared to those without maternal exposure to oil-based paints (MOR = 1.55, 95% CI: 1.12 – 2.14). Similar yet non-significant results were reported for the interaction between maternal exposure to paint solvents and pesticides. These findings require replication in other populations.

Acknowledgments

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Table 1

Descriptive characteristics of the study population (298 case-control pairs)

Variables	Categories	ASD Cases N (%)	TD Controls N (%)	p-value [a]
Sex of child	Male	246 (82.6)	246 (82.6)	1.00
	Female	52 (17.4)	52 (17.4)	
Age of child at enrollment	< 48 months	84 (28.2)	76 (25.5)	0.07
	48 – 71.9 months	130 (43.6)	143 (48.0)	
	72 months	84 (28.2)	79 (26.5)	
Race of child	Afro-Caribbean	281 (94.3)	291 (97.6)	0.05
	Other [b]	17 (5.7)	7 (2.4)	
Gestational age	Full term (37 weeks)	263 (88.9)	276 (92.6)	0.15
	Moderate to late preterm (32 – 36 weeks)	24 (8.1)	19 (6.4)	
	Very to extremely preterm (< 32 weeks)	9 (3.0)	3 (1.0)	
Duration of breastfeeding[c]	< 3 months	48 (16.1)	52 (17.8)	0.14
	3 – 5.9 months	67 (22.6)	68 (23.3)	
	6 – 15.9 months	116 (39.1)	90 (30.8)	
	> 16 months	66 (22.2)	82 (28.1)	
Age of mother (at child's birth)	< 35 years	242 (81.2)	262 (87.9)	0.03
	35 years	56 (18.8)	36 (12.1)	
Age of father (at child's birth)	< 35 years	165 (55.4)	216 (72.5)	<0.01
	35 years	133 (44.6)	82 (27.5)	
Race of mother	Afro-Caribbean	285 (95.6)	292 (98.0)	0.12
	Other [b]	13 (4.4)	6 (2.0)	
Race of father[d]	Afro-Caribbean	281 (94.6)	287 (97.3)	0.10
	Other [b]	16 (5.4)	8 (2.7)	
Mother's education level[e] (at child's birth)	Up to high school [f]	149 (50.0)	190 (64.4)	<0.01
	Beyond high school [g]	149 (50.0)	105 (35.6)	
Father's education level[h] (at child's birth)	Up to high school [f]	168 (58.1)	228 (80.6)	<0.01

Variables	Categories	ASD Cases N (%)	TD Controls N (%)	*p*-value [a]
	Beyond high school [g]	121 (41.9)	55 (19.4)	
Relationship of parents[i]	Relationship [j]	206 (69.1)	170 (57.8)	<0.01
	No relationship [k]	92 (30.9)	124 (42.2)	
Parish of child's birth	Kingston	83 (27.8)	188 (63.1)	<0.01
	Other [l]	215 (72.2)	110 (36.9)	
High SES	Owns a car	176 (59.1)	119 (39.9)	<0.01
	Does not own a car	122 (40.9)	179 (60.1)	

[a] *p*-values based on Wald statistic from univariable conditional logistic regression;

[b] Includes Asian-Indian and Mixed;

[c] Data missing for 1 case and 6 controls;

[d] Data missing for 1 case and 3 controls;

[e] Data missing for 3 controls;

[f] Includes never attended school, attended primary/junior-secondary, and secondary/high/technical school;

[g] Includes attended HEART/vocational, tertiary college/university, and other tertiary school;

[h] Data missing for 9 cases and 15 controls;

[i] Data missing for 4 controls;

[j] Includes visiting relationship, common law union, and married;

[k] Includes divorced, separated, no relationship, and widowed;

[l] Includes Portland, Trelawny, Westmoreland, Clarendon, St. Andrew, St. Mary, St. James, St. Elizabeth, St. Catherine, St. Thomas, St. Ann, Hanover, and Manchester parishes

Table 2

Matched Odds Ratios for the association between various maternal exposures and Autism Spectrum Disorder using conditional logistic regression models (298 case-control pairs)

Maternal exposures	ASD Cases N (%)	TD Controls N (%)	Unadjusted			Adjusted		
			MOR (95% CI)[a]	p-value		MOR (95% CI)[a]	p-value	
Fever or infection[b]	51 (17.3)	22 (7.4)	2.81 (1.59 – 4.98)	0.0004		3.12 (1.74 – 5.60)[c]	0.0001	
Trauma[d]	29 (9.8)	13 (4.4)	2.33 (1.19 – 4.59)	0.0141		2.02 (1.01 – 4.05)[e]	0.0484	
Degreasers[f]	21 (7.1)	8 (2.7)	2.63 (1.16 – 5.93)	0.0202		2.29 (1.00 – 5.24)[e]	0.0502	
Oil-based paints[g]	55 (18.6)	29 (9.8)	2.13 (1.30 – 3.50)	0.0028		1.99 (1.14 – 3.46)[h]	0.0148	
Paint solvents[i]	34 (11.5)	19 (6.4)	1.94 (1.06 – 3.54)	0.0317		1.30 (0.68 – 2.50)[j]	0.4281	
Pesticides or herbicides[k]	104 (35.9)	66 (22.4)	2.08 (1.41 – 3.08)	0.0002		1.67 (1.08 – 2.59)[h]	0.0216	

[a] Matched Odds Ratio (MOR) and corresponding 95% Confidence Interval (95% CI);

[b] Data missing for 3 cases and 2 controls;

[c] Adjusted for age of the mother;

[d] Data missing for 2 cases and 2 controls;

[e] Adjusted for age of the father;

[f] Data missing for 4 cases and 1 control;

[g] Data missing for 2 cases and 1 control;

[h] Adjusted for parish;

[i] Data missing for 1 case and 3 controls;

[j] Adjusted for age of the father and father's education level;

[k] Data missing for 8 cases and 3 controls

Table 3

Matched Odds Ratios for the association between maternal exposures to pesticides/herbicides and Autism Spectrum Disorder stratified by maternal exposure to oil-based paints, based on interactive conditional logistic regression models

Maternal exposure to oil-based paints	Maternal exposure to pesticides/herbicides	ASD Cases[a] (n=288)	TD Controls[b] (n=295)	Unadjusted		Adjusted*	
				MOR (95% CI)[c]	p-value[d]	MOR (95% CI)[c]	p-value[e]
Exposed	Exposed	34	7	2.45 (1.41 – 4.26)	0.0015	2.17 (1.21 – 3.92)	0.0097
	Unexposed[f]	20	22				
Unexposed	Exposed	69	59	1.74 (1.29 – 2.35)	0.0003	1.55 (1.12 – 2.14)	0.0074
	Unexposed[f]	165	207				

*
Adjusted for parish;

[a]
Incomplete data for 10 cases;

[b]
Incomplete data for 3 controls;

[c]
Matched Odds Ratio (MOR) and corresponding 95% Confidence Interval (95% CI);

[d]
Overall interaction p = 0.0234;

[e]
Overall interaction p = 0.0369;

[f]
Referent category

Table 4

Matched Odds Ratios for the association between maternal exposures to pesticides/herbicides and Autism Spectrum Disorder stratified by maternal exposure to paint solvents, based on interactive conditional logistic regression models

Maternal exposure to paint solvents	Maternal exposure to pesticides/herbicides	ASD Cases[a] (n=289)	TD Controls[b] (n=294)	Unadjusted		Adjusted*	
				MOR (95% CI)[c]	p-value[d]	MOR (95% CI)[c]	p-value[e]
Exposed	Exposed	22	6	2.33 (1.19 – 4.56)	0.0132	1.84 (0.86– 3.91)	0.1150
	Unexposed[f]	12	13				
Unexposed	Exposed	81	59	1.78 (1.24 – 2.52)	0.0015	1.46 (0.98 – 2.18)	0.0628
	Unexposed[f]	174	216				

*
Adjusted for parish, age of the father and father's education level;

[a]
Incomplete data for 9 cases;

[b]
Incomplete data for 4 controls;

[c]
Matched Odds Ratio (MOR) and corresponding 95% Confidence Interval (95% CI);

[d]
Overall interaction p = 0.1198;

[e]
Overall interaction p = 0.2584;

[f]
Referent category

Table 5

Relationships between maternal exposures to products containing volatile organic compounds (VOCs) in relation to Autism Spectrum Disorder, based on interactive conditional logistic regression models

Potential Effect Modifier	Exposure of Interest	Unadjusted Interaction p-value	Adjusted Interaction p-value
Oil-based paints	Degreasers	0.5368	0.2752 [a]
	Paint Solvents	0.3141	0.2137 [b]
	Pesticides	0.0243[*]	0.0369 [*][c]
Paint Solvents	Degreasers	0.2136	0.2825 [d]
	Pesticides	0.1198	0.2584 [b]
Pesticides	Degreasers	0.8057	0.9538 [a]

[*] Statistically significant departure from expected multiplicative interaction effects at $\alpha = 0.05$;

[a] Adjusted for parish and age of the father;

[b] Adjusted for parish, age of the father, and father's education level;

[c] Adjusted for parish;

[d] Adjusted for age of the father and father's education level