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Role of fruits, grains, and seafood consumption in blood cadmium concentrations of Jamaican children with and without Autism Spectrum Disorder

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Abstract

Human exposure to cadmium has adverse effects on the nervous system. Utilizing data from 110 age- and sex-matched case-control pairs (220 children) ages 2–8 years in Kingston, Jamaica, we compared the 75th percentile of blood cadmium concentrations in children with and without Autism Spectrum Disorder (ASD). In both univariable and multivariable Quantile Regression Models that controlled for potential confounding factors, we did not find any significant differences between ASD cases and typically developing (TD) controls with respect to the 75th percentile of blood cadmium concentrations, ($P > 0.22$). However, we found a significantly higher 75th percentile of blood cadmium concentrations in TD Jamaican children who consumed shellfish (lobsters, crabs) ($P < 0.05$), fried plantain ($P < 0.01$), and boiled dumpling ($P < 0.01$). We also observed that children living in Jamaica have an arithmetic mean blood cadmium concentration of 0.16μg/L which is similar to that of the children in developed countries and much lower than that of children in developing countries. Although our results do not support an association between blood cadmium concentrations and ASD, to our knowledge, this study is the first to report levels of blood cadmium in TD children as well as those with ASD in Jamaica.

Keywords

Cadmium; Autism Spectrum Disorder; Grains; Fruits; Seafood; Jamaica

1. Introduction

Cadmium (Cd) is a metallic contaminant found naturally in the earth's core, often as a deposit in copper, lead, and zinc ores (ATSDR, 2008). Cadmium has only one oxidative state (+2), but can form ionic complexes with both organic and inorganic complexes (ATSDR, 2008). Water-soluble forms of cadmium are highly mobile and can be ingested or absorbed by aquatic animals; however, mobility of cadmium deposited in soil is dependent on environmental conditions of the soil, such as moisture and pH, and can be inhaled when present in dust or transferred by wind (ATSDR, 2008). Cadmium has been classified as a human carcinogen (Jarup & Akesson, 2009; Nawrot et al., 2010; WHO & IARC, 1997) and has been associated with increased kidney damage (ATSDR, 2008; Jarup & Akesson, 2009; Nawrot et al., 2010), decreased lung function (ATSDR, 2008), and osteoporosis (Jarup & Akesson, 2009) in adults. Some studies have shown that it can also have adverse effects on neurodevelopment in exposed children including intellectual disabilities (Jiang, Han, & He, 1990; Marlowe, Errera, & Jacobs, 1983), decreased verbal IQ (Thatcher, Lester, McAlaster, & Horst, 1982), and learning disabilities (LD) (Capel, Pinnock, Dorrell, Williams, & Grant, 1981; Ciesielski et al., 2008). On the other hand, other studies have not reported significant associations between cadmium and neurodevelopment (Cao et al., 2009; Wright, Amarasiriwardena, Woolf, Jim, & Bellinger, 2006) or between cadmium and behavioral disorders (Szkup-Jablonska et al., 2012).

Common cadmium complexes and uses include, but are not limited to: 1) cadmium chloride, used as a pesticide, is the most toxic form of cadmium and can sometimes contaminate drinking water sources; 2) cadmium carbonate, which can be used as a pesticide and dissolves more easily in salt water; 3) cadmium oxide, used as a catalyst in electroplating and for batteries; 4) cadmium sulfate, also used in pesticides and as an intermediate for electroplating, is commonly inhaled through dust or water vapor; 5) cadmium sulfide, used as a yellow or red pigment, is the least toxic cadmium compound; and 6) cadmium stearate, which is used as a stabilizer for plastics (ATSDR, 2008; WHO & IARC, 1997; Cheng & Huang, 2006). Cadmium can be released into the air through natural processes such as volcanic eruptions, forest fires, and seawater vapor, or through human activity such as fossil fuel combustion, metal mining and refinery, waste incineration, and fertilizer/pesticide manufacture and application. As an air contaminant, cadmium can be transported and settle into surface water and soil (ATSDR, 2008). Others have identified plastic stabilizer, paint, and lacquers as sources of cadmium contaminants in farmland (Cheng & Huang, 2006). Compared with other heavy metals, cadmium in the soil can then be taken up easily by plants, introduced to humans in high concentrations, and accumulated through consumption of leafy vegetables (e.g., cabbage), root vegetables (e.g., sweet potato, yams and carrots), and grains (e.g., rice and wheat) (ATSDR, 2008; Jarup & Akesson, 2009; Cheng & Huang, 2007; Verma, George, Singh, & Singh, 2007). In addition to dietary exposure through crops, humans can also be exposed to accumulated cadmium through consumption of filter-feeding seafood, such as crabs and oysters, and beef and poultry, especially in the kidney and liver (ATSDR, 2008; Jarup & Akesson, 2009). Approximately 3–7% of ingested cadmium is absorbed through the intestines of healthy individuals, but 15–20% can be absorbed in individuals with iron deficiencies (WHO, 2011). However up to 50% of inhaled cadmium can be absorbed (WHO & IPCS, 1992). Children are primarily exposed to cadmium through contaminated food, contaminated air, tobacco smoke, and house dust (Schoeters et al., 2006). Bioaccumulation of cadmium in the liver and kidneys starts at a young age (WHO, 2011; Schoeters et al., 2006). A longitudinal study of urinary cadmium in rural Bangladesh showed that cadmium concentrations in infants' urine was correlated with concentrations in maternal breast milk, saliva, and urine (Kippler et al., 2010). More recently, Kippler *et al*., (2012) reported that maternal cadmium exposure during pregnancy was inversely associated with infants' physical growth (birth weight and head circumference) (Kippler et al., 2012).

Jamaica provides a unique opportunity to study the health effects of cadmium exposure, as it has an unusually high level of this naturally occurring metal (Lalor, 2008). Concentrations in soil are ubiquitous and exceptionally high in certain parishes, with some greater than 900mg/kg (Lalor, 2008; Wright, Rattray, Lalor, & Hanson, 2010). These levels drastically exceed the critical limits, values above which concentrations cause the soils to be considered inappropriate for any human use, which range from 0.3–2.0mg/kg (Lalor, 2008). The highest levels are seen in more fertile agricultural areas near central Jamaica, allowing cadmium in soil to accumulate in crops to concentrations of up to 15 mg/kg (Lalor, 2008). Concentrations in various crops including fruit, legumes, leafy vegetables, root vegetables, and especially yams are significantly higher than those seen in other countries (Howe, Fung, Lalor, Rattray, & Vutchkov, 2005; Lalor, 2008). Thus, increased exposure in those who consume locally grown foods is a concern (Howe et al., 2005). A study conducted in Jamaica by Wright *et al.* (2010) showed a positive association between cadmium soil levels and urinary cadmium levels, with a 3.25 times increased risk of urinary cadmium greater than 2.5μg/g for those in high/very high soil cadmium concentration areas compared to those in low/medium concentration areas, after adjusting for creatinine levels (Wright et al., 2010). Sediment in streams in Jamaica near soils with high cadmium levels can also have noticeable concentrations (Knight, Kaiser, Lalor, Robotham, & Witter, 1997). In addition, other studies have shown increased blood and urine levels of cadmium in people with a high dietary intake of crustaceans (e.g., lobster, crab, shrimp), mollusks (e.g., shellfish), and other sea creatures in Britain and France (Copes, Clark, Rideout, Palaty, & Teschke, 2008; Sirot, Samieri, Volatier, & Leblanc, 2008) indicating the possibility of similar results in Jamaica where seafood consumption is also high.

Autism Spectrum Disorder (ASD) is a complicated neurodevelopmental disorders that affect communication, language development and social interaction (Genuis, 2009; Volkmar & Chawarska, 2008). Many researchers believe that the etiology of ASD involves the combination of several factors including genetic and environmental factors (Gardener, Spiegelman, & Buka, 2011; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013; Hertz-Picciotto, 2013). While studies have shown that ASD are associated with polymorphic genetic variants (Kumar & Christian, 2009; Geschwind, 2013), many scientists believe that the disorder also has environmental components that act either in conjunction with genes (Hallmayer et al., 2011) or alone (Landrigan, 2010).

Several studies have investigated the association between exposure to cadmium and ASD (Windham, Zhang, Gunier, Croen, & Grether, 2006; Kern, Grannemann, Trivedi, & Adams, 2007; Yorbik, Kurt, Hasimi, & Ozturk, 2010; De Palma, Catalani, Franco, Brighenti, &

Apostoli, 2012; Albizzati, More, Di, Saccani, & Lenti, 2012; Adams et al., 2013) but the findings are conflicting. For example, a case-control study that involved 24 children with ASD (age 3–12 years) and 20 typically developing (TD) controls in Turkey reported that mean urine cadmium concentrations were significantly lower in ASD cases (0.45μg/g in ASD cases vs. 1.43μg/g in TD controls; $P<0.05$) (Yorbik et al., 2010). Another case-control study of 45 children with ASD (age 1–6 years) and 45 age-, sex-, and race-matched TD controls in Dallas, Texas, found lower mean cadmium levels in the hair of children with ASD (0.58μg/g in ASD cases vs. 0.82μg/g in TD controls; $P<0.05$) (Kern et al., 2007). A more recent study from Arizona that compared 55 children with ASD ages 5–16 years with 44 TD controls that had similar age and sex distributions also reported lower mean whole blood cadmium concentrations in children with ASD (0.64μg/L in ASD cases vs. 0.79μg/L in TD controls; $P = 0.003$) (Adams et al., 2013). On the other hand, a study from Italy that involved 17 children with ASD and 20 TD controls (age 6–16 years) reported no associations between cadmium levels and ASD based on hair and urine samples (Albizzati et al., 2012). However, none of these studies controlled for potential confounding factors, except for the factors that were controlled for as part of the study design (e.g., age and sex). In contrast, a study of 284 ASD cases and 657 sex- and age-matched controls in the San Francisco Bay area of California showed that the odds of having a child with an ASD was higher for those living in census tracts with cadmium distributions in the top quartile, after adjusting for maternal age, education, and race (AOR=1.54; 95% CI, 1.08–2.20) (Windham et al., 2006).

As mentioned previously, Jamaica has an excessive level of environmental cadmium, which is present in the agricultural soil and possibly the drinking water, consequently increasing its presence in vegetables, fruits, and feasibly seafood (Howe et al., 2005; Lalor, 2008). As our first objective, we investigated whether there is an association between blood cadmium concentrations and ASD in children living in or near Kingston, Jamaica. Secondly, we estimated blood cadmium concentrations in TD Jamaican children and identified factors associated with blood cadmium concentrations, with a particular focus on the food consumed by these children.

2. Materials and Methods

2.1. General description

The Jamaican Autism study is an age- and sex-matched case-control study. In December 2009, we began enrollment of children ages 2 to 8 years with the intention of investigating environmental exposures to certain heavy metals, including cadmium, and their potential association with ASD. The recruitment and assessment of ASD cases and TD controls has been previously described (Rahbar et al., 2012a; Rahbar et al., 2012b; Rahbar et al., 2013). In summary, children identified as potentially having an ASD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria (American Psychiatric Association, 2000) and the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, DeVellis, & Daly, 1980) in the University of the West Indies' (UWI) Jamaica Autism Database, were invited to be reassessed for ASD using the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview-

Revised (ADI-R) (Rutter, Le, & Lord, 2003). Inclusion criteria for study participants were that the child had to be born in Jamaica and be between 2–8 years of age at the time of enrollment. Children whose ASD diagnoses were confirmed by ADI-R and ADOS performed by trained clinicians were assigned an age- and sex-matched control. Potential controls were identified and recruited from schools and well child clinics, and their parents/ guardians were administered the Lifetime form of the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003). To ascertain that children in the control group did not have behavioral ratings suggestive of significant ASD symptomatology, we included children with SCQ scores between 0 and 6, as a SCQ score of 6 is one standard deviation above the mean SCQ score for TD children (Mulligan, Richardson, Anney, & Gill, 2009).

Pre-tested questionnaires were also administered to parents/guardians of cases and controls to gather demographic information, socioeconomic (SES) information such as ownership of certain household items (e.g., ownership of a car by the family), parental education levels, and potential exposure to cadmium through food by asking how often the child ate certain food items within a week, with a particular focus on the types and frequency of fruits, vegetables, grains (e.g., rice, wheat used for bread), and seafood. These food frequency data represent current typical consumption of food items by children (Rahbar et al., 2012a; Rahbar et al., 2013). Types of fruits and vegetables were categorized into the following groups based on their characteristics and species: 1) root vegetables [class 1A = (yam, sweet potato, or dasheen), class 1B = (carrot or pumpkin)]; 2) leafy vegetables [class 2A = (lettuce), class 2B = (callaloo, broccoli, or pakchoi), class 2C = (cabbage)]; 3) legumes (string beans); and 4) fruits (tomatoes, ackee, or avocado).

At the end of each interview, 2mL of venous whole blood were collected from each child for assessment of environmental exposures, including cadmium. Blood samples were shipped to the Michigan Department of Community Health (MDCH) Trace Elements Lab for analysis. Institutional Review Boards (IRBs) of the University of Texas Health Science Center at Houston and UWI approved this study. All participating parents/guardians provided written informed consent, in compliance with the IRBs. The data presented are from the analysis of 110 1:1 matched case-control pairs (220 children) from Jamaica (mainly the greater Kingston area) that were evaluated from December 2009 to March 2012.

2.2. Assessment of cadmium exposure

Cadmium has a long half-life ranging from 6 to 38 years in the kidneys and 4–19 years in the liver (ATSDR, 2008). There are several biomarkers which are used for assessment of cadmium exposure (De Silva & Donnan, 1981; Jung et al., 1993; ATSDR, 2008), but in this study, we assessed blood cadmium concentrations (Kawasaki et al., 2004). Whole venous blood samples were assayed for total cadmium by the Trace Metals Lab at MDCH, which is certified by the Centers for Disease Control and Prevention (CDC) for analysis of trace metals. All samples were diluted and analyzed on a PerkinElmer Elan DRC II inductively-coupled plasma mass spectrometer (PerkinElmer, Waltham, MA). This was accomplished at MDCH using a fully validated protocol for cadmium detection limits of 0.2μg/L. About 66% of our children had blood cadmium concentrations below the limit of detection. In data analyses, these study participants were assigned a blood cadmium concentration of 0.1μg/L (midpoint between 0.0–0.2μg/L).

2.3. Statistical analysis

We conducted descriptive analyses to compare demographic and socioeconomic (SES) characteristics of ASD cases and TD controls. Since 66% of children had blood cadmium concentrations below the limit of detection, we compared the 75th percentile of blood cadmium concentrations of ASD cases and TD controls using Quantile Regression Models with random effects (Bottai, Cai, & McKeown, 2010; Eilers, Roder, Savelkoul, & van Wijk, 2012). The random effects were designed to account for the age- and sex-matched case-control study design. In order to avoid potential effects of multicollinearity from the high correlation between maternal and paternal education, we generated a binary variable representative of education of both parents up to high school or at least one parent obtained education beyond high school.

As part of our effort to identify potential confounding variables when investigating an association between blood cadmium concentrations and ASD status, we first used Conditional Logistic Regression (CLR) models to assess associations between ASD case status and various exposure variables. Then, we performed univariable Quantile Regression analyses to identify exposure variables that were significantly associated with the 75th percentile of blood cadmium concentrations using a combined sample of ASD cases and TD controls. The identification of potential confounders was based on both *a priori* and empirical considerations. First, we considered important factors associated with ASD case status (e.g., parental education), as suggested from our previous work (Rahbar et al., 2012a) and from the literature (Cheng & Huang, 2007; Verma et al., 2007). Covariates determined to be potentially associated with ASD status, as evident by $P < 0.25$ in the univariable CLR models, and associated with the 75th percentile of the blood cadmium concentrations, as evident by $P < 0.25$ in the univariable Quantile Regression Models, were evaluated for their role as potential confounders. The covariates were considered to be potential confounders if they changed the regression coefficient by ≥20%, and were then included in the final multivariable analysis. Potential confounders considered included child's consumption of root vegetables (e.g., "yam, sweet potato, or dasheen"), leafy vegetables (e.g., cabbage), fruits (e.g., fried plantain), grains (e.g., white bread), and frequency of seafood consumption. We also kept parental education level in the model. For statistical analyses related to the estimation of blood cadmium concentrations in Jamaican children (i.e., second objective) we used data from the sample of TD children. We used univariable Quantile Regression Models to assess associations between blood cadmium concentrations and various exposure variables, such as consumption of root vegetables, leafy vegetables, grains, and seafood, along with demographic variables including maternal and paternal age, parental education level, and parish of child's birth (in "Kingston, St. Andrew, or St. Catherine parishes vs. other parishes). Finally, we fitted a multivariable Quantile Regression Model with random effects separately for the 75th percentile to identify independent factors associated with blood cadmium concentration among TD Jamaican children. All statistical analyses were conducted at 5% level of significance using SAS 9.3® statistical software (SAS Institute, 2011).

3. Results

Consistent with gender ratios observed in the ASD population, our sample consisted of 84.6% males. The mean age of our sample was approximately 67 months. As expected with the largely homogenous population in Jamaica, 92.7% of ASD cases and 99.1% of TD controls were Afro-Caribbean. Both maternal and paternal education were significantly higher in the ASD case group compared to the TD control group (48.2% of mothers and 44.9% of fathers in the case group had education beyond high school compared to 23.4% and 12.3% in the control group, respectively; $P < 0.01$). Additional information regarding demographic characteristics is presented in Table 1.

Univariable Quantile Regression analysis showed that the 75th percentile of blood cadmium concentrations were not significantly different between the ASD case group and the TD control group (for example for 75th percentiles = Q3; 0.25μg/L for cases vs. 0.27μg/L for controls; $P = 0.44$). As part of our investigation to identify potential confounding variables we found that parental education levels were significantly higher for ASD cases in comparison to TD controls [Matched Odds Ratio (MOR) = 3.36, 95% CI: (1.85, 6.10); $P < 0.01$]. Other comparisons showed that dietary intake differed significantly between ASD cases and TD controls, including the frequency of seafood, vegetables, and grains consumed. Parents of TD controls reported that their children had a significantly higher consumption of many fruits and vegetables than did ASD cases. In particular, parents of ASD cases were less likely to report that their children consumed fried plantain than parents of TD controls [MOR=0.20; 95% CI: (0.08, 0.52); $P< 0.01$]. Details regarding other associations between potential confounders and ASD case status are presented in Table 2.

We also investigated the associations of various exposures and levels of blood cadmium concentrations. The results from univariable Quantile Regression models, based on both ASD cases and TD controls, revealed that various factors were significantly associated with the 75th percentile of blood cadmium concentrations in these children including consumption of seafood (Q3= 0.27μg/L for those who ate seafood more than 6 meals per week vs. 0.16μg/L for those who did not; $P = 0.04$); eating “yam, sweet potato, or dasheen” (Q3= 0.27μg/L for those who ate these vegetables vs. 0.14μg/L for those who did not; $P = 0.02$); and eating cabbage (Q3= 0.27μg/L for those who ate cabbage vs. 0.15μg/L for those who did not; $P < 0.01$). Univariable Quantile Regression analyses related to the TD children also revealed that seafood, fruit, and grain consumption variables were significantly associated with blood cadmium concentrations in TD children such as consumption of fried plantain, (Q3= 0.24μg/L for those who ate fried plantain vs. 0.10μg/L for those who did not; $P < 0.01$) and eating boiled dumpling (Q3= 0.24μg/L for those who ate boiled dumpling vs. 0.10μg/L for those who did not; $P < 0.01$). In addition, the 75th percentiles of blood cadmium concentrations of TD children that consumed shellfish (lobster, crabs) were significantly higher than those who did not eat this food based on both univariable ($P < 0.05$) and multivariable analyses ($P = 0.03$). Associations between various exposures and the 75th percentiles of blood cadmium concentrations are presented in Table 3.

In our final model, we compared the 75th percentile of blood cadmium concentrations between ASD cases and TD controls, while controlling for several potential confounders.

For example, the final model for the 75th percentile of cadmium included parental education levels, parish of child's birth (in "Kingston, St. Andrew, or St. Catherine parishes vs. other parishes), consumption of seafood (more than 6 meals per week), "yam, sweet potato, or dasheen", cabbage, fried plantain, boiled dumpling, and white bread. According to the final model, there is no significant difference between ASD case and TD control groups with respect to adjusted 75th percentile of blood cadmium concentrations (0.22μg/L for ASD cases and 0.16μg/L for TD controls, $P = 0.22$).

4. Discussion

4.1. Blood cadmium concentrations and ASD

Our findings are not supportive of an association between postnatal blood cadmium concentrations in Jamaican children ages 2–8 years and ASD case status. Our results were consistent between the univariable and multivariable analyses. In our multivariable analysis for the 75th percentile of blood cadmium concentration, we adjusted for parental education levels, child's parish of birth ("Kingston, St. Andrew, or St. Catherine vs. other parishes"), seafood consumption (more than 6 meals per week), consumption of "yam, sweet potato, or dasheen", cabbage, fried plantain, boiled dumpling, and white bread. Our findings are in contrast with those of Windham *et al.* (2006) where higher adjusted odds of ASD for children with greater exposure to cadmium via contaminated air (AOR=1.54; 95% CI, 1.08–2.20) was found compared to controls in San Francisco, California (Windham et al., 2006). However, we recognize that that our method of assessing cadmium exposure (from whole blood) is very different from that of Windham *et al.* (2006) in which the observed levels of cadmium in the air for census tracts of birth residence of ASD cases and controls were used. In addition, our findings are in contrast with the findings of Adam *et al.* (2012) who reported lower mean whole blood cadmium concentrations in children with ASD compared to controls with similar age and sex distribution (0.64μg/L in ASD cases vs. 0.79μg/L in controls; $P = 0.003$) (Adams et al., 2013); however, we acknowledge that the methods used to analyze levels of exposure differed between our study and the study by Adam *et al.* (2012) (i.e. 75th percentiles vs. means). On the other hand, De Palma *et al.* (2012) reported a significantly higher median hair level of cadmium in male cases compared to male controls (0.01 μg/g in cases vs. 0.0003 μg/g in controls, $P = 0.006$), but no statistically significantly difference between median level of cadmium in ASD cases compared to controls for the entire sample (De Palma et al., 2012). Important to note is that none of the above studies adjusted for potential nutritional confounders. It is well established that children with ASD have a higher incidence of gastrointestinal problems (Horvath & Perman, 2002; Ibrahim, Voigt, Katusic, Weaver, & Barbaresi, 2009), and as a result their parents are very selective in choosing diets for their children with ASD. These observations together with findings in this study that consumption of some of the food items is significantly associated with blood cadmium concentrations, suggest that nutritional variables may be potential confounders. We believe the findings from the studies that did not control for potential confounders may be biased. Our results suggest that the lack of association seen between blood cadmium concentrations and ASD status stand firm when adjusted for potential nutritional confounding factors.

4.2. Blood cadmium concentrations in Jamaican children

When examining blood cadmium concentrations in TD Jamaican children, we observed that children living in Jamaica have mean blood cadmium concentrations similar to the children in developed countries (Wong & Lye, 2008). The arithmetic mean blood cadmium concentration of the TD control group for our Jamaica study was 0.16μg/L, which is similar to the 0.15μg/L (95% CI 0.12–0.18) reported by the 2007/2008 Canadian Health Measures Survey for adolescents ages 6–19 (Wong & Lye, 2008). On the other hand analysis of blood samples from children originally recruited to a multicenter, placebo-controlled, randomized clinical trial, with sites in Philadelphia, PA; Newark, NJ; Cincinnati, OH; and Baltimore, MD, for 767 lead-exposed children reported a geometric mean blood cadmium concentration of 0.20–0.21μg/L for their study sample (Cao et al., 2009). Although we cannot confidently compare the blood cadmium concentrations of children in Jamaica to children in the US, the arithmetic mean blood cadmium concentration of children in our Jamaican study do not seem to be significantly different from those of children in other developed countries such as Poland where a recent study of 78 families with children diagnosed with behavior disorders reported an arithmetic mean blood cadmium concentration of 0.215μg/L (Szkup-Jablonska et al., 2012). In addition, the arithmetic mean blood cadmium concentration of children in Jamaica is much lower than that of children in developing countries such as Bangladesh and China. A study of 73 children between ages 7–16 from Dhaka, Bangladesh, reported an arithmetic mean blood cadmium concentration of 0.74μg/L (Linderholm et al., 2011). Another study of 278 children 1–7 years of age in Chendian and Guiyu, China reported that arithmetic mean blood cadmium concentrations were 0.97μg/L for children in Chendian and 1.58μg/L in Guiya, a town where 60–80% of families are employed at e-waste recycling facilities (Zheng et al., 2008).

To our knowledge, there are no previously published reports regarding cadmium in blood, urine, or hair of Jamaican children; however, there are published reports suggesting high levels of cadmium in Jamaican soils, particularly in areas near central Jamaica (Howe et al., 2005; Lalor, 2008; Wright et al., 2010). The mean level of cadmium in Jamaican soils was found to be 14.3 times greater than the guidelines set for safe levels of cadmium in soil used for agriculture in Canada (Howe et al., 2005). Our analysis from combined samples of ASD and TD controls showed that children born in Manchester or surrounding parishes had a significantly higher arithmetic mean blood cadmium concentration than those who were not born in these areas (0.24μg/L vs. 0.16μg/L; $P = 0.01$). Since our study was conducted in the greater Kingston area, only a small proportion of children in our study (6.4%) was born in Manchester and surrounding parishes (13 ASD cases and 1 TD control). Our study suggests a baseline arithmetic mean blood cadmium concentration of 0.16μg/L for TD children (2–8 years) in Kingston, Jamaica. In the following we discuss factors associated with the 75th percentile of blood cadmium concentrations in TD Jamaican children.

4.3. Vegetable and fruit consumption and blood cadmium concentrations

Previous studies have reported a positive association between cadmium levels in soil and an increase in urinary cadmium concentrations in adults (Wright et al., 2010). Moreover, high levels of cadmium present in agricultural soil near central Jamaica allow accumulation in crops grown there (Lalor, 2008). Mean levels of cadmium in fruits, legumes, and leafy vegetables sampled from Jamaica were found to be approximately 7 times higher than levels found in samples from the US (Lalor, 2008; Howe et al., 2005). In the same study, the mean levels of cadmium found in root vegetables were greater than 28 times those of root vegetables sampled from the US and more than 36 times greater than those found in root vegetables from the UK (Howe et al., 2005; Lalor, 2008). Our results indicate that TD Jamaican children who consumed fried plantain had a significantly ($P < 0.01$) higher 75th percentile of blood cadmium concentrations than those who did not eat this fruit. Because previous studies have shown that consumption of fruits and vegetables positively affects cognitive development of children (Gale et al., 2009), and others show that cadmium exposure is associated with negative effects on cognitive development (Ciesielski et al., 2008; Jiang et al., 1990), we recommend additional research focused on risk assessment for vegetable consumption in Jamaican children.

4.4. Consumption of grains and blood cadmium concentrations

Just as cadmium can accumulate in crops, it can accumulate in grains, such as rice and wheat (ATSDR, 2008; Jarup & Akesson, 2009). Studies have shown rice to be a good indicator of cadmium intake in countries where rice is the main staple food, and concentrations of cadmium in the kidney cortex of adults living in countries such as Korea and Japan have been consistently higher than those seen in adults from other countries such as Germany and Sweden (Kawada & Suzuki, 1998). We attempted to test the association between rice consumption and blood cadmium concentrations in our sample of TD children; however, all of the TD children in our sample reported eating rice, which limited our ability to analyze this important exposure variable. Our results indicated that the 75th percentile of blood cadmium concentrations of TD children who ate boiled dumpling was significantly higher than that of children who did not eat this food (Q3= 0.24μg/L vs. 0.10μg/L; $P < 0.01$). Again, without any formal risk assessment studies focused on the overall potential health risk of various grains used in Jamaica, it would be difficult to make any evidence based recommendations regarding consumption of these essential food items in Jamaica.

4.5. Seafood consumption and blood cadmium concentrations

People residing on islands generally consume a higher amount of seafood than those who do not. Accumulation of cadmium can occur through dietary intake of filter-feeding seafood (ATSDR, 2008; Jarup & Akesson, 2009). Past studies have also shown an increase in cadmium concentrations in the blood and urine of people with a high seafood intake (Copes et al., 2008; Sirot et al., 2008). In this study, we found a significantly higher 75th percentile of cadmium concentrations for TD children who ate shellfish (lobster, crab) (Q3= 0.32μg/L vs. 0.24μg/L;$P < 0.05$). Considering the well-known benefits of seafood consumption, including the positive effects of omega-3 fatty acids, on cognitive function (Ginsberg & Toal, 2009; MacLean et al., 2005; Oken et al., 2005), it would be difficult to comment on the overall potential health risk of seafood consumption (De Gieter et al., 2002) without a well-designed risk-benefit study (Stern & Korn, 2011).

In summary, our findings from the final multivariable 75th Quantile Regression model, that controlled for potential confounding factors that included parental education levels, child's birth in "Kingston, St. Andrew, and St. Catherine" parishes, consumption of seafood (more

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than 6 meals per week), "yam, sweet potato, or dasheen", cabbage, fried plantain, boiled dumpling, and white bread, indicated that there was no significant association between ASD case status and blood cadmium concentrations. We also identified several risk factors for blood cadmium concentrations in TD Jamaican children. These include consumption of shellfish (lobster, crab), consumption of fried plantain, and boiled dumpling. These findings not only show that the null results seen for the association between blood cadmium concentrations and ASD status stand true when controlled for potential confounding factors, but they also highlight areas where there may be a need to conduct additional research focused on risk assessment for consumption of certain seafood, fruits, and grains by Jamaican children to reduce the potential burden due to blood cadmium concentrations.

5. Limitations

We are aware that there may be several limitations to this study. 1) Because our sample was selected from the Kingston area, it may not be representative of a random sample of children from all areas of Jamaica and thus the results may not be generalizable to populations other than that from which the sample was selected. 2) Although the cadmium level is highest in the soil in certain areas (e.g., Manchester and surrounding parishes), the availability of data for only a few children born in Manchester and surrounding parishes (13 ASD cases and 1 TD child) has limited our ability to include this variable in our multivariable analyses. 3) Although the frequency of seafood and vegetable consumption was measured using a culturally appropriate food questionnaire that had been used in the past in Jamaica, we recognize the potential for recall bias. 4) Even though we did not find differences in measured levels of cadmium exposure in ASD cases and TD controls, there is a possibility for individual susceptibility to cadmium through gene-environment interactions (Palmer, 2010). 5) Due to limited resources in this study, we assessed only total blood cadmium concentrations; however, we acknowledge that urine is recognized as a better indicator of total body cadmium burden due to impairment of renal tubular function (Jung et al., 1993). 6) The limit of detection for assessment of blood cadmium concentrations in our study was 0.2μg/L, and all participants whose blood cadmium concentrations were less than that, about 66% of our sample, were imputed with a value of 0.1μg/L (midpoint between 0.0–0.2μg/L). 7) We acknowledge that the blood cadmium concentrations in this study represent cadmium exposure only during the postnatal period, and we did not collect information regarding cadmium exposures during the perinatal and prenatal periods. Furthermore, the postnatal exposure to cadmium through diet may not necessarily represent cadmium exposure through diet during a time that may be causally related to ASD.

6. Conclusions

In this study, there was no significant association between ASD case status and blood cadmium concentration based on both univariable and multivariable analyses. The findings from the multivariable model indicate that the null findings observed for the association between cadmium and ASD status are not influenced by adjustment for potential confounding factors.

While our results did not support the association of cadmium and ASD, others have suggested that without analysis of gene-environment interaction, we cannot make a solid conclusion about our findings (Palmer, 2010). Therefore, future studies on the association between cadmium exposure and ASD should investigate potential gene-environment interaction. In addition, our study is the first, to our knowledge, to report blood cadmium concentrations of children living in Jamaica while showing that their levels are similar to those of children in more developed countries including Canada and the US. Additionally, we showed that eating certain seafood such as shellfish (lobster, crab), as well as eating fried plantain and boiled dumpling, were significantly associated with higher blood cadmium concentrations in TD Jamaican children. Although the blood cadmium concentrations in Jamaican children are considered much lower than in other developing countries, future studies should focus on conducting risk assessment for consumption of certain seafood, fruits, vegetables, and grains by Jamaican children in order to reduce the potential burden due to blood cadmium concentrations.

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Highlights (for review)

- We investigated the role of exposure to cadmium on autism in Jamaican children
- We did not find an association between autism and blood cadmium in Jamaican children
- We identified factors associated with blood cadmium levels in Jamaican children
- We found significantly higher blood cadmium levels in children eating shellfish
- We found higher blood cadmium levels in children eating fried plantain

Table 1

Demographic and socioeconomic characteristics of children and their parents by ASD case status

Variables	Categories	Case (n=110) N (%)	Control (n=110) N (%)	*P*-value
Sex of child	Male	93 (84.6)	93 (84.6)	1.00
Age of child (months)	Age < 48	21 (19.1)	18 (16.4)	0.29
	48 ≤ Age < 72	49 (44.5)	50 (45.5)	
	Age ≥ 72	40 (36.4)	42 (38.2)	
Maternal education [a] (at child's birth)	Up to high school *	57 (51.8)	82 (76.6)	<0.01
	Beyond high school **	53 (48.2)	25 (23.4)	
Paternal education [b] (at child's birth)	Up to high school *	59 (55.1)	93 (87.7)	<0.01
	Beyond high school **	48 (44.9)	13 (12.3)	
Number of children in the household (Age ≤ 18 years)	1 – 2	87 (79.1)	58 (52.7)	<0.01
	≥ 3	23 (20.9)	52 (47.3)	
Number of adults in the household (Age > 18 years) [c]	1 – 2	72 (65.5)	66 (61.1)	0.56
	≥ 3	38 (34.5)	42 (38.9)	
Assets owned	TV	54 (49.1)	83 (76.1)	0.10
	Refrigerator	108 (98.18)	103 (93.6)	<0.01
	Freezer	107 (97.3)	94 (85.5)	0.20
	Living room set	14 (12.7)	21 (19.1)	<0.01
	Washing machine	92 (83.6)	51 (46.4)	<0.01
	Cars or other vehicle	80 (72.7)	58 (52.7)	<0.01

* Up to high school education includes: attended primary, junior-secondary, and secondary/high/technical schools

** Beyond high school education includes: attended vocational, tertiary college, or university

[a] Maternal education was missing for 3 controls

[b] Paternal education was missing for 3 cases and 4 controls

[c] Number of adults was missing for 2 control families

Table 2

Association between potential confounders and case status using Conditional Logistic Regression (CLR) (110 Pairs)

Variables	Category		Case N (%)	Control N (%)	Matched OR (MOR)	95% CI for MOR[†]	*P*-value
Paternal age [a] (at child's birth)	More than 35 years		54 (50.9)	29 (28.7)	2.62	(1.38, 4.96)	<0.01
Maternal age [b] (at child's birth)	More than 35 years		28 (25.5)	11 (10.5)	3.13	(1.41, 6.93)	<0.01
Parental education levels [c] (at child's birth)	At least one of the parents had education beyond high school		71 (66.4)	32 (31.1)	3.36	(1.85, 6.10)	<0.01
Parish of child's birth	Kingston, St. Andrew, and St. Catherine parishes		83 (75.5)	107 (97.3)	0.04	(0.01, 0.30)	<0.01
Seafood consumption	High seafood consumption (More than 6 meals per week)		28 (25.5)	48 (43.6)	0.41	(0.22, 0.77)	<0.01
	Ate salt water fish		84 (76.4)	99 (90.0)	0.35	(0.17, 0.78)	<0.01
	Ate fresh water fish (Pond fish, tilapia)		48 (43.6)	60 (54.5)	0.61	(0.35, 1.09)	0.11
	Ate sardine, mackerel (Canned fish)		83 (75.5)	101 (91.8)	0.28	(0.12, 0.65)	<0.01
	Ate tuna (Canned fish)		35 (31.8)	48 (43.6)	0.57	(0.31, 1.03)	0.07
	Ate salt fish (Pickled mackerel)		77 (70.0)	100 (90.9)	0.21	(0.09, 0.50)	<0.01
	Ate shellfish (Lobsters, crabs)		7 (6.4)	14 (12.7)	0.42	(0.15, 1.18)	0.11
	Ate shrimp		22 (20.0)	30 (27.3)	0.65	(0.34, 1.25)	0.20
Fruits and vegetables consumption [d]	Root vegetables (class 1)	A. Yam, sweet potato, or dasheen	78 (70.9)	90 (82.6)	0.50	(0.26, 0.97)	0.04
		B. Carrot or pumpkin	95 (86.4)	107 (98.1)	0.14	(0.03, 0.63)	<0.01
	Leafy vegetables (class 2)	A. Lettuce	51 (46.4)	68 (62.4)	0.57	(0.35,0.94)	0.02
		B. Callaloo, broccoli, or pak choi	79 (71.8)	102 (93.5)	0.23	(0.10, 0.51)	<0.01
		C. Cabbage	73 (66.4)	102 (93.5)	0.19	(0.08, 0.42)	<0.01
	Legumes	String beans	36 (32.7)	46 (42.2)	0.69	(0.41, 1.15)	0.15
	Fruits	Tomatoes	67 (60.9)	91 (83.5)	0.29	(0.14, 0.58)	<0.01
		Ackee	64 (58.2)	101 (92.7)	0.05	(0.01, 0.21)	<0.01
		Avocado	30 (27.3)	74 (67.9)	0.17	(0.08, 0.34)	<0.01
		Green banana	74 (67.3)	99 (90.8)	0.29	(0.14, 0.56)	<0.01
		Fried plantain	78 (70.9)	97 (89.0)	0.20	(0.08, 0.52)	<0.01
Grains consumed	Rice [e]		107 (97.3)	109 (100)	NR[*]	NR[*]	NR[*]
	Fried dumpling		86 (78.2)	102 (92.7)	0.27	(0.11, 0.67)	<0.01

Variables	Category	Case N (%)	Control N (%)	Matched OR (MOR)	95% CI for MOR[†]	*P*-value
	Boiled dumpling	81 (73.6)	108 (98.2)	0.07	(0.02, 0.29)	<0.01
	White bread	54 (49.1)	85 (77.3)	0.30	(0.16, 0.55)	<0.01
	Whole wheat bread	82 (74.6)	67 (60.9)	2.30	(1.02, 3.14)	0.04
	Cakes/buns[f]	92 (83.6)	107 (98.2)	0.11	(0.03, 0.48)	<0.01
	Porridge (cornmeal, oatmeal)[g]	92 (83.6)	106 (97.2)	0.12	(0.03, 0.51)	<0.01
	Cold breakfast cereal[h]	81 (73.6)	101(92.7)	0.28	(0.13, 0.60)	<0.01
Organ meat consumed	Liver/kidney[i]	54 (49.1)	83 (76.1)	0.26	(0.13, 0.52)	<0.01
Smoking status	Mother is smoker[j]	6 (5.5)	16 (14.7)	0.38	(0.15, 0.96)	0.04
	Mother smoked while pregnant	4 (3.6)	6 (5.5)	0.67	(0.19, 2.36)	0.53
	Smoker lives in the home [k]	23 (20.9)	36 (33.0)	0.55	(0.30, 1.02)	0.06

[*]NR = Not Reported due to unstable estimates caused by a limited number of observation in at least one of the cells.

[†]If a 95% CI for the MOR does not include one, then we conclude a significant association at 5% level

[a]Paternal age was missing for 4 cases and 9 controls

[b]Maternal age was missing for 5 controls

[c]Parental education levels were missing for 3 cases and 7 controls

[d]Fruits and vegetables consumption was missing for 1 control

[e]Rice consumption was missing for 1 control

[f]Cakes/buns consumption was missing for 1 control

[g]Porridge consumption was missing for 1 control

[h]Cold breakfast cereal consumption was missing for 1 control

[i]Liver/kidney consumption was missing for 1 control

[j]Mother's smoking status was missing for 1 control

[k]Status of a smoker living in the home was missing for 1 case and 1 control

Table 3

Factors associated with 75th percentiles of blood cadmium concentrations for TD children (n=110) as well as combined samples of TD and ASD children (n=220) using Quantile Regression Model for all participants

Exposure variables	Category		Univariable and Multivariable Analysis for the TD Children (n=110) (75th percentile): Univariable Cd (μg/L) Yes [a]	Univariable Cd (μg/L) No [b]	Univariable *P*-value	Multivariable Cd (μg/L) Yes [a]	Multivariable Cd (μg/L) No [b]	Multivariable *P*-value	Univariable Quantile Regression for combined ASD & TD Controls (n=220) (75th percentile): Cd (μg/L) Yes	Cd (μg/L) No	*P*-value
Paternal age (at child's birth)	More than 35 years		0.26	0.24	0.55	-	-	-	0.27	0.26	0.69
Maternal age (at child's birth)	More than 35 years		0.22	0.24	0.79	-	-	-	0.26	0.27	0.89
Parental education levels (at child's birth)	At least one of the parents had education beyond high school		0.21	0.25	0.38	-	-	-	0.25	0.27	0.35
Parish of child's birth	Kingston, St. Andrew, and St. Catherine parishes		0.24	0.24	1.00	-	-	-	0.26	0.19	0.34
Seafood consumption	High seafood consumption (More than 6 meals per week)		0.26	0.23	0.50	-	-	-	0.27	0.16	0.04
	Ate salt water fish		0.24	0.24	1.00	-	-	-	0.27	0.15	0.04
	Ate fresh water fish (Pond fish, tilapia)		0.24	0.25	0.72	-	-	-	0.27	0.16	0.08
	Ate sardine, mackerel (Canned fish)		0.24	0.21	0.55	-	-	-	0.27	0.15	<0.01
	Ate tuna (Canned fish)		0.24	0.24	1.00	-	-	-	0.27	0.26	0.82
	Ate salt fish (Pickled mackerel)		0.24	0.21	0.59	-	-	-	0.27	0.16	<0.01
	Ate shellfish (Lobsters, crabs)		0.32	0.24	<0.05	0.25	0.17	0.03	0.29	0.26	0.51
	Ate shrimp		0.24	0.24	1.00	-	-	-	0.26	0.27	0.88
Fruits and vegetables consumption	Root vegetables (class 1)	A. Yam, sweet potato, or dasheen	0.24	0.27	0.70	-	-	-	0.27	0.14	0.02

Exposure variables	Category		Univariable and Multivariable Analysis for the TD Children (n=110) (75th percentile): Univariable Cd (μg/L) Yes [a]	Univariable Cd (μg/L) No [b]	Univariable P-value	Multivariable Cd (μg/L) Yes [a]	Multivariable Cd (μg/L) No [b]	Multivariable P-value	Univariable Quantile Regression for combined ASD & TD Controls (n=220) (75th percentile): Cd (μg/L) Yes	Cd (μg/L) No	P-value
		B. Carrot or pumpkin	0.24	0.24	1.00	-	-	-	0.27	0.15	<0.01
	Leafy vegetables (class 2)	A. Lettuce	0.24	0.25	0.74	-	-	-	0.26	0.27	0.87
		B. Callaloo, broccoli, or pakchoi	0.24	0.27	0.49	-	-	-	0.26	0.17	0.04
		C. Cabbage	0.24	0.26	0.71	-	-	-	0.27	0.15	<0.01
	Legumes	String beans	0.26	0.23	0.47	-	-	-	0.28	0.16	<0.01
	Fruits	Tomatoes	0.24	0.24	1.00	-	-	-	0.26	0.17	0.08
		Ackee	0.24	0.24	1.00	-	-	-	0.27	0.16	<0.01
		Avocado	0.24	0.25	0.77	-	-	-	0.27	0.16	0.04
		Green banana	0.24	0.27	0.52	-	-	-	0.27	0.15	<0.01
		Fried plantain	0.24	0.10	<0.01	0.28	0.14	0.05	0.27	0.14	<0.01
Grains consumption	Fried dumpling		0.24	0.10	0.59	-	-	-	0.27	0.16	0.12
	Boiled dumpling		0.24	0.10	<0.01	-	-	-	0.26	0.18	0.19
	White bread		0.24	0.24	1.00	-	-	-	0.26	0.17	0.10
	Whole wheat bread		0.25	0.24	0.76	-	-	-	0.27	0.26	0.88
	Cakes/buns		0.24	0.10	1.00	-	-	-	0.26	0.18	0.28
	Porridge (cornmeal, oatmeal)		0.24	0.33	0.66	-	-	-	0.27	0.14	0.05
	Cold breakfast cereal		0.24	0.33	0.61	-	-	-	0.26	0.28	0.82

Exposure variables	Category	Univariable and Multivariable Analysis for the TD Children (n=110) (75th percentile)						Univariable Quantile Regression for combined ASD & TD Controls (n=220) (75th percentile)		
		Univariable			Multivariable					
		Cd (μg/L)		P-value	Cd (μg/L)		P-value	Cd (μg/L)		P-value
		Yes [a]	No [b]		Yes [a]	No [b]		Yes	No	
Organ meat consumed	Liver/kidney	0.24	0.24	1.00	-	-	-	0.27	0.16	0.04
Smoking status	Mother is a smoker	0.24	0.24	1.00	-	-	-	0.25	0.27	0.58
	Mother smoked while pregnant	0.22	0.24	0.62	-	-	-	0.25	0.27	0.75
	Smoker lives in the home	0.23	0.24	0.77	-	-	-	0.26	0.27	0.94

[a]The “Yes” column includes subjects who met the category specified in front of each exposure variable.

[b]The “No” column includes subjects who did not meet the category specified in front of each exposure variable

Additional information is provided in the footnote of Table 2

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Table 4

Unadjusted and adjusted quantiles (the 75th percentiles) of blood cadmium concentrations for 110 ASD cases and their matched controls based on the Quantile Regression Models

	75th percentile of Cd (μg/L)		
	ASD Cases	**TD Controls**	***P*-value**
Unadjusted	0.25	0.27	0.44
Adjusted	0.22	0.16	0.22

[a] Factors adjusted for include: parental education levels, child’s birth in “Kingston, St. Andrew, and St. Catherine” parishes, consumption of seafood (more than 6 meals per week), “yam, sweet potato, or dasheen”, cabbage, fried plantain, boiled dumpling, and white bread