Environmental Pollution 212 (2016) 9–17

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

The use of a physiologically-based extraction test to assess relationships between bioaccessible metals in urban soil and neurodevelopmental conditions in children

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ARTICLE INFO

Article history:
Received 28 September 2015
Received in revised form
22 December 2015
Accepted 1 January 2016
Available online 1 February 2016

Keywords:
Physiologically based extraction test
Soil pollution
Intellectual disability
Cerebral palsy
Low birth weight

ABSTRACT

Intellectual disability (ID) and cerebral palsy (CP) are serious neurodevelopment conditions and low birth weight (LBW) is correlated with both ID and CP. The actual causes and mechanisms for each of these child outcomes are not well understood. In this study, the relationship between bioaccessible metal concentrations in urban soil and these child conditions were investigated. A physiologically based extraction test (PBET) mimicking gastric and intestinal processes was applied to measure the bioaccessibility of four metals (cadmium (Cd), chromium (Cr), nickel (Ni), and lead (Pb)) in urban soil, and a Bayesian Kriging method was used to estimate metal concentrations in geocoded maternal residential sites. The results showed that bioaccessible metal concentrations of Cd, Ni, and Pb in the intestinal phase were statistically significantly associated with the child outcomes. Lead and nickel were associated with ID, lead and cadmium was associated with LBW, and cadmium was associated with CP. The total concentrations and stomach concentrations were not correlated to significant effects in any of the analyses. For lead, an estimated threshold value was found that was statistically significant in predicting low birth weight. The change point test was statistically significant (p value = 0.045) at an intestine threshold level of 9.2 mg/kg (95% confidence interval 8.9–9.4, p value = 0.0016), which corresponds to 130.6 mg/kg of total Pb concentration in the soil. This is a narrow confidence interval for an important relationship.

1. Introduction

Intellectual disability (ID), and cerebral palsy (CP) are serious neurodevelopment conditions that develop *in utero* and become manifest during early childhood. Both conditions are developmental disabilities that have a substantial impact throughout life. ID is characterized by substantially reduced intellectual and adaptive functioning, manifest during childhood; the incidence rate is 10.37 per 1000 population (Maulik et al., 2011). Approximately 545,000 children receive treatment for ID each year (NICHCY, 2014) and 6.5 million people are living with ID in the USA. CP is a movement disorder that affects posture and balance, which affects more than two per 1000 live-born children (Himmelmann and Uvebrant, 2014). Genetic conditions, immunologic challenges during pregnancy, social deprivation, toxicological exposure and injury might cause or contribute to ID (Strømme and Hagberg, 2000). CP is associated with infection during pregnancy and prematurity (McIntyre et al., 2013). However, for a majority of cases, actual causes and mechanisms are poorly understood (McDermott et al., 2011; McMichael et al., 2015; Windham et al., 2006).

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http://dx.doi.org/10.1016/j.envpol.2016.01.001
0269-7491/Published by Elsevier Ltd.

Exposure to metals is through inhalation, dermal absorption mainly through feet and hands, and ingestion of contaminated foods, soils and dust (Imperato et al., 2003). The United States Environmental Protection Agency reports that the general population ingests soil and dust particles at the rate of 100 mg/day (children) and 50 mg/day (adults). This value could increase to 50,000 mg/day for people who engage in geophagy (USEPA, 2011). Some studies have investigated associations between heavy metals (lead, mercury, arsenic) in soil and child neurological outcomes and human health (Carroll et al., 2014; McDermott et al., 2014a, 2014b; Onicescu et al., 2014). However, these studies measured total concentration of metals in the soil, which may be insufficient to realistically estimate bio-uptake (Allen, 1993; Amiard et al., 2008).

Among the methods to measure bioaccessibility of metals, the physiologically based extraction test (PBET), which simulates gastrointestinal extraction, is the most widely used (Sialelli et al., 2010). Previous studies showed that PBET results are correlated with bioaccessibility determined by *in vivo* studies (Ruby et al., 1996). In addition, *in vitro* studies provide benefits and advantages because they are simpler, faster and lower in cost than *in vivo* studies (Miller et al., 1981). To date, several studies (Juhasz et al., 2013; Luo et al., 2012; Sialelli et al., 2010) used PBET method to estimate bioaccessibility of metals in urban soils. There are some other similar methods has been reported, such as Bioaccessibility Research Group of Europe (BARGE) method (UBM) (Farmer et al., 2011; Juhasz et al., 2013; Roussel et al., 2010) and Simplified Bioaccessibility Extraction Test (SBET) (De Miguel et al., 2012; Mingot et al., 2011). However, most of these studies focused on the bioaccessibility of metals in the soil or a comparison of the extraction efficiency among different methods. In no case was the data linked to epidemiology data.

The present study aims to investigate relationships between bioaccessible metals (Pb, Ni, Cr, Cd) in soils and child outcomes (ID, CP, low birth weight). The hypothesis for this study was that both higher total soil concentrations of Pb, Ni, Cr and Cd, and higher bioaccessible concentrations of Pb, Ni, Cr and Cd absorbed by the stomach or intestine were associated with the increased probability of having a child born with ID, CP or LBW. In this study, urban soils were collected from residential neighborhoods in South Carolina as described by Aelion and Davis (2007) and Davis et al. (2009). Actual addresses of pregnant women in the neighborhood were used to statistically estimate the metal concentration at each residence using the Kriging method (Aelion et al., 2009a). Analysis of the samples was conducted using the PBET process. The bioaccessibility metal data were combined with epidemiological data to develop statistical models, to investigate the relationship between bioaccessible metal concentrations in urban soil and child outcomes.

2. Methods

2.1. Study population

This is a retrospective cohort study of maternal child pairs, which used new laboratory and statistical analyses to explore relationships between exposure to metals during pregnancy and neurodevelopmental conditions of children. The study used data from individually linked mother–child pairs for children who were born in South Carolina from 1996 through 2002. Data for the mother–child pairs were acquired from Medicaid billing records, birth certificates, South Carolina Department of Education (DOE), and the South Carolina Department of Disabilities and Special Needs (DDSN). These individual data were linked through a unique personal identifier developed and maintained by the South Carolina Health and Demographics, Revenue and Fiscal Affairs Office (RFA). The children were followed in Medicaid and public school records for at least 8 years to identify the outcomes of intellectual disability (ID) and cerebral palsy (CP). This study was granted exempt status for human subjects research by the University of South Carolina Institutional Review Board based on procedures that assured confidentiality of the data.

2.2. Identification of birth weight, ID and CP

Birth weight: We identified each child's birth weight (BW) from the health department birth certificate file which contains the actual birth weight in grams. We then dichotomized each child's weight into two groups: (1) less than 2500 g (low birth weight or LBW) or (2) 2500 g or higher (normal birth weight or NBW).

Intellectual disability: The Ninth Revision of the International Classification of Disease (ICD–9) diagnosis codes was used to identify cases of ID and CP (CMS, 2005). The outcome of ID was determined by identifying all children with ICD9 code 317 (mild ID), 318 (other specified ID) or 319 (unspecified ID) or those who were placed into special education services for ID in public school. We excluded children diagnosed with known causes of ID, including trisomy 13, 16–18, other chromosomal aberrations, Prader–Willi syndrome, Rett's syndrome, phenylketonuria, fragile X syndrome, postnatal injury, prenatal rubella, meningitis, encephalitis, and fetal alcohol syndrome. We only included singleton births in our study.

Cerebral Palsy: Children with CP were identified using ICD9 code 343 (and all sub-codes).

Final dataset with mother–child variables and child outcomes: The final dataset included 3091 mother–child pairs among which 201 (6.50%) children had ID, 17 (0.55%) children had CP and 409 (13.34%) children had LBW.

2.3. Study areas and geocoding of maternal residences

The study area was a rectangular section of an urban metropolitan statistical area that contained residential neighborhoods. We obtained addresses from a Medicaid eligibility file for the 6th month of pregnancy and geocoded them by using ArcGIS version 9.3. Instead of the actual maternal residential addresses, we sampled the soil according to a grid throughout the residential area to maintain the confidentiality for the family. The intersection of the grid lines were sampling locations, referred to as grid nodes (Aelion et al., 2008, 2009a).

2.4. Soil sampling and metal analysis

Residential areas were identified based on birth rate and the occurrence of ID and CP in the area. The sampling area was approximately 105 km^2 in size, and a uniform grid was overlaid at locations 1.0–3.0 km apart. The data was mapped and the actual residential addresses were known, however to maintain confidentiality of the study group maps have not been displayed. The soil sampling grid did not coincide with the actual residential location of the pregnant women; instead a Global Positioning System (GPS) latitude and longitude were taken at each of the 120 sampling locations with a handheld GPS device (Garmin Etrex, Olathe, KS) and soil was collected at 5 cm depths (Aelion et al., 2008, 2009a, 2009b). After sampling, the 120 soil samples were dried, sieved and analyzed for total metal concentrations of Pb, Ni, Cr and Cd, by an independent analytical laboratory (Pace Analytical, Huntersville, NC), The samples were digested with nitric and hydrochloric acids (EPA method 3050B) and analyzed for (Cr, Cd, Pb, and Ni) (EPA method 6010B) using inductively coupled plasma-emission spectroscopy (ICP-OES). These data were used to calculate the percentage of physiologically-based extraction metals from the test (PBET).