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Dentine biomarkers of prenatal and early childhood exposure to manganese, zinc and lead and childhood behavior

Megan K. Horton[a], Leon Hsu[a], Birgit Claus Henn[b], Amy Margolis[c], Christine Austin[a], Katherine Svensson[a], Lourdes Schnaas[d], Chris Gennings[a], Howard Hu[e], Robert Wright[a], Martha María Téllez Rojo[f,*], Manish Arora[a]

[a] Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, One Gustave Levy Place, Box 1057, New York, NY 10029, United States of America
[b] Department of Environmental Health, Boston University School of Public Health, 715 Albany St., Boston, MA 02118, United States of America
[c] Division of Child and Adolescent Psychiatry, Columbia University Medical Center, 1051 Riverside Drive New York, New York 10032, United States of America
[d] Division of Research in Community Interventions, Instituto Nacional de Perinatología, Montes Urales 800, Lomas Virreyes, Mexico City CP 11000, Mexico
[e] Dalla Lana School of Public Health, University of Toronto, Health Sciences Building, 155 College Street, 6th floor, Toronto M5T 3M7, Canada
[f] Center for Nutrition and Health Research, National Institute of Public Health (Mexico), Universidad 655, Cuernavaca 62100, Mexico

A R T I C L E I N F O

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A B S T R A C T

Background: Metal exposure alters neurodevelopmental outcomes; little is known about critical windows of susceptibility when exposure exerts the strongest effect.
Objective: To examine associations between dentine biomarkers of manganese (Mn), zinc (Zn) and lead (Pb) and later childhood behaviors.
Methods: Subjects enrolled in a longitudinal birth cohort study in Mexico City provided naturally shed deciduous teeth. We estimated weekly prenatal and postnatal dentine Mn, Zn and Pb concentrations in teeth using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) and measured behavior at ages 8–11 years of age using the Behavior Assessment System for Children, 2nd edition (BASC-2). We used distributed lag models and lagged weighted quantile sum regression to identify the role of individual and combined dentine biomarkers of Mn, Zn and Pb on behavioral outcomes controlling for maternal education and gestational age.
Results: Among the 133 subjects included in this study, prenatal and early postnatal dentine Mn appeared protective against childhood behavioral problems, specifically hyperactivity and attention. Postnatal dentine Mn was associated with increased reporting of internalizing problems, specifically anxiety. At 6 months, a 1-unit increase (unit = 1 SD of log concentration) in Mn was associated with a 0.18-unit (unit = 1 SD of BASC-2 score) increase in internalizing symptoms score and a 0.25-unit increase in anxiety. Postnatal Pb was associated with increasing anxiety symptoms; at 12 months, a 1-unit increase in Pb was associated with a 0.4 unit increase in anxiety symptoms. When examined as a metal mixture, we observed two potential windows of susceptibility to increased anxiety symptoms: the first window (0–8 months) appeared driven by Mn, the second window (8–12 months) was driven by the metal mixture and dominated by Pb. A 1-unit increase in the mixture index was associated with a 0.7-unit increase in SD of anxiety symptoms.
Conclusions: Childhood behaviors may demonstrate postnatal windows of susceptibility to individual and mixed metal concentrations measured in deciduous teeth. Prenatal dentine Mn may be protective, while excessive early postnatal Mn may increase risk for adverse behaviors. In combination, higher concentrations of Mn, Zn and Pb may have an adverse impact on behavior.

Abbreviations: Ca, calcium; Mn, manganese; Pb, lead; BASC-2, Behavioral Assessment System for Children, 2nd edition; ELEMENT, Early Life Exposures in Mexico to Environmental Toxicants; rDLM, Reversed Distributed Lag Model; WQS, weighted quantile sum regression

* Corresponding author.
E-mail address: mmtellez@insp.mx (M.M.T. Rojo).

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1. Introduction

Up to one in five children worldwide experience mental health problems (Kieling et al., 2011), and the burden of childhood mental health problems may be increasing. Psychosocial problems identified by primary care practitioners in the Unites States increased from 7% in 1979 to 19% in 1996, with increases in both internalizing and externalizing problems (Kelleher et al., 2000). Internalizing disorders (i.e., negative behaviors that are focused inward, such as anxiety and depression), are now the most common psychiatric conditions afflicting children and adolescents (Anderson et al., 1987; Cohen et al., 1993a; Pine et al., 1998) representing the second and fifth, respectively, leading causes of disability in the United States (Murray et al., 2013). In Mexico, an estimated 40% of adolescents ages 12 to 17 have a mental health disorder, most commonly anxiety and depression (Benjet et al., 2009; Gallegos et al., 2012). Externalizing problems (i.e., negative behaviors directed outwards, such as hyperactivity and inattention) including attention-deficit/hyperactivity disorder (ADHD) and conduct disorders are also increasing (Cohen et al., 1993a; Loeber et al., 2000; Merikangas et al., 2009). Demonstration of internalizing and/or externalizing behaviors in childhood increases the risk for later-life mental health disorders (Campbell, 1995), substance abuse, and suicidal behaviors (Beesdo et al., 2009; Clark et al., 2007). While behavioral disorders can present as early as 4 to 5 years of age, a growing body of literature indicates that the susceptibility to develop mood disorders may be programmed by events occurring during fetal and early postnatal life (Angold et al., 1998; Beesdo et al., 2009; Kim et al., 2015; Pine et al., 1998). The root causes of the increasing prevalence of neurodevelopmental disorders, including internalizing problems, are only partly understood. Although genetic factors play a role, strong evidence exists that early life exposure to environmental chemicals is an important contributor to this increasing prevalence of neurodevelopmental disorders (Grandjean and Landrigan, 2006, 2014). While longstanding evidence suggests early-life metal exposures negatively impact cognitive outcomes such as IQ, more recent epidemiologic studies demonstrate associations between early life exposure to essential and nonessential metals and adverse behavioral outcomes such as internalizing and externalizing behaviors (Banks et al., 1997; Ericson et al., 2007; Gunier et al., 2015; Khan et al., 2012; Meyer-Baron et al., 2013; Mora et al., 2015; Needleman et al., 1990; Sanders et al., 2015; Yousef et al., 2011).

In this study, we focus on early-life exposure to three neuroactive metals; manganese (Mn), zinc (Zn) and lead (Pb), and their independent and combined associations with childhood internalizing and externalizing symptoms. Mn and Zn are both essential metals required by the body at low doses and neurotoxic at excessively high and/or low levels. Pb is a non-essential heavy metal, well-recognized as a neurotoxicant. We select these metals as 1) each is common in the environment due to anthropogenic activities such as mining, and smelting operations and industrial uses and they are often found together as a correlated mixture (Mehra and Thakur, 2016), 2) experimental and epidemiological evidence links early life exposure to each metal individually with adverse neurobehavioral outcomes, specifically with internalizing symptoms including anxiety and depression. Much of the experimental and epidemiologic studies demonstrating associations between occupational exposure to these metals and higher rates of anxiety and depression focus on adults (Betharia and Maher, 2012; Bouchard et al., 2009; Islam et al., 2013; Jung et al., 2017; Kim et al., 2015; Mlyniec et al., 2017; Shiue, 2015). Less is understood of the role of early life metal uptake in the development of childhood anxiety and depression. Affective behaviors are regulated in the brain within the prefrontal (e.g., medial prefrontal cortex; mPFC) and limbic (e.g., amygdala) regions (Duval et al., 2015; Kim et al., 2011). These brain regions develop throughout early gestation and childhood, making them vulnerable to early-life neurotoxic insults, which can override a normal growth trajectory toward a maladaptive phenotype (i.e., internalizing or externalizing disorder). Indeed, emerging studies link early-life environmental insults with the pathophysiology of abnormal neuronal circuitry in neuropsychiatric disorders (Money and Stanwood, 2013; Schlotz and Phillips, 2009). However, the critical time windows of developmental susceptibility to neurotoxic exposures are ill-defined (Adams et al., 2000; Bellinger, 2013; Selevan et al., 2000). While we know many metals, including Mn, Zn and Pb, readily cross the placental barrier, increasing exposure during early-life windows of developmental susceptibility (Chen et al., 2014; Goyer, 1990; Needham et al., 2011; Rudge et al., 2009; Yoon et al., 2009), limited data exist on the cumulative and life stage-specific effects of exposure on behavioral outcomes in childhood. Further, limited epidemiologic literature examine associations with co-exposure to correlated neurotoxicant metals. In one recent study examining metals in placenta, co-exposure to more than one toxicant metal increased the risk for adverse neurodevelopmental outcomes (Freire et al., 2018).

In this paper, we use our dentine biomarker to evaluate associations between early-life metal uptake of individual and mixed metals and internalizing and externalizing behaviors in children, identifying potential critical windows of developmental susceptibility to adverse outcomes. We hypothesized that variable early life biomarkers of Mn, Zn and Pb during critical developmental windows may be associated with higher reporting of internalizing and externalizing behaviors (i.e., anxiety and depression, hyperactivity and attention problems).

This study takes place among subjects enrolled in an ongoing longitudinal birth cohort study, Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT). As recently summarized by Claus Henn et al. (2018), this cohort is uniquely suited to a study of the effects of metal exposure because (1) air pollution, of which Mn and other metals are key components, is severe in Mexico City (Calderon-Garciduenas et al., 2013); (2) rich sources of Mn in the diet, such as beans, are commonly consumed in Mexican diets; (3) higher Pb and Mn exposure, measured in biological and environmental samples, has been reported in Mexico than in the U.S. and Canada (Claus Henn et al., 2018; Santos-Burgoa et al., 2001). We use deciduous "baby" teeth to reconstruct fine scale (1–2 weeks) exposure histories to Mn, Zn and Pb and identify the discrete developmental period(s) for each metal most associated with changes in children's behavior. We then use a novel statistical method, lagged weighted quantile sum (WQS) regression, to capture the time-varying association between the 3-metal mixture and children's behavioral outcomes.

2. Methods

2.1. Study population

Mother-child pairs in this study were drawn from four successively-enrolled longitudinal birth cohort studies in Mexico City that comprise the ELEMENT project. Detailed information on the study design and data collection procedures has been published previously detail elsewhere (Braun et al., 2012; Claus Henn et al., 2018; Ettinger et al., 2009; Hernandez-Avila et al., 2002). Between 1994 and 2001, ELEMENT enrolled healthy, low to moderate income mothers, between ages 18–39 from the National Institute of Perinatology (Instituto Nacional de Parinatologia) to investigate the long-term consequences of prenatal environmental factors on child development (Ettinger et al., 2009; Gonzalez-Cossio et al., 1997; Tellez-Rojo et al., 2004). Biomarkers, neurodevelopmental outcomes outcome, and covariate data from all cohorts were collected following standardized protocols by the same study staff, allowing us to pool data across cohorts. Exclusion criteria included an Apgar score of < or = 6 at 5 min, a condition requiring treatment in neonatal intensive care unit.

Of the 1079 children born into ELEMENT and followed until 5 years of age, 826 (77%) participated in an additional follow-up study at 6–16 years of age. At this follow-up, participants were asked to bring or mail in deciduous teeth as they were naturally shed for analysis of