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Dietary contributions to increased background lead, mercury, and cadmium in 9–11 Year old children: Accounting for racial differences

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ABSTRACT

Background: Initial interest in the adverse consequences of exposure to lead (Pb), mercury (Hg), and cadmium (Cd) focused on relatively high exposures through environmental or occupational sources; however, recent evidence suggests even low-level background exposure to non-essential metals might be detrimental, particularly for children's health and development. One potentially important source of increased background levels of non-essential toxic metals is diet.
Objectives: We considered whether differences in diet are associated with levels of non-essential metals in blood and whether racial differences in metals are mediated by dietary differences.
Methods: We assessed blood levels of Pb, Hg, and Cd in a sample of 9–11 year-old children ($N = 295$) comprised of 42% European Americans (EAs), 58% African American (AAs), and 47% female. Diet was assessed using 24-h dietary recalls during phone interviews administered to parents on two consecutive days (Friday and Saturday). The Healthy Eating Index-2105 (HEI-2015) was calculated to assess diet quality.
Results: The current study identified significant dietary sources of non-essential metal exposure – namely total fruit for Pb, total protein for Hg, and greens and beans for Cd. Moreover, AAs were found to have significantly higher blood levels of Pb and Hg than EAs and these racial differences were significantly mediated by these dietary differences.
Discussion: This study is one of very few to consider total diet in children and exposure to the non-essential metals Pb, Hg, and Cd, and the first to demonstrate that racial differences in increased background blood levels of non-essential toxic metals can be accounted for by racial differences in diet. Given regional differences in food consumption patterns and specific farm and store sources for the foods, the generalizability of the current findings has yet to be determined; however, commonly consumed foods appear to be a significant source of low-level non-essential metals.

A great deal of research has demonstrated the psychological and physical health impacts of relatively high levels of exposure to non-essential metals such as lead (Pb; Bellinger et al., 2003; Kim et al., 2013; Ris et al., 2004), mercury (Hg; Palumbo et al., 2000; Strain et al., 2015), and cadmium (Cd; Barregard et al., 2016; Carroll, 1966; Tellez-Plaza et al., 2008). Aside from occupational exposure, typical exposure vectors for these relatively high levels of non-essential metals have been traced to air, water, and soil pollution as well as lead-based paint for exposure to Pb (Campbell et al., 2016; Han et al., 2018; O'Connor et al., 2018; Shen et al., 2018), fish consumption and metal filings for exposure to Hg (Al-Saleh and Al-Sedairi, 2011; Valera et al., 2013; van Wijngaarden et al., 2006), and air pollution and smoking for exposure to Cd (Mezynska and Brzoska, 2018; Ozden et al., 2007). Although it remains important to continue research to fully understand the consequences of these relatively isolated acute exposures, recent evidence suggests that even increased "background levels" (i.e., levels below 5 μg/dL for blood Pb, the current CDC definition of

Abbreviations: AA, African American; Cd, cadmium; CDC, Centers for Disease Control and Prevention; CVD, cardiovascular diseases; EA, European American; EECHO, Environmental Exposures and Child Health Outcomes; Hg, mercury; MDL, method detection limits; Pb, lead; SES, socioeconomic status; TDS, Total Diet Survey

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elevated but still well above pre-industrial levels, Patterson et al., 1991) have significant impact on psychological and physiological functioning (Bellinger et al., 1992; Gump et al. 2011, 2017bib_Gump_et_al_2011 bib_Gump_et_al_2017). In fact, the CDC now acknowledges that there is "no safe blood lead level in children" (CDC, 2019). As such, there is a need for a better understanding of the sources for these low level "everyday" chronic exposures that are prevalent and may have long-term consequences. This distinct line of research is analogous to work on the "wear-and-tear" associated with chronic stress (Seeman et al., 2001) in contrast to the health consequences of acute stressors such as missile attacks (Meisel et al., 1991) and automobile accidents (Mcfarlane et al., 1997). One potentially important source of exposure to increased background levels of non-essential metals is diet (Awata et al., 2017; Davis et al., 2014; Dewailly et al., 2001; Fontaine et al., 2008; Spungen, 2019). The present study considered associations between diet and increased background levels of Pb, Hg, and Cd (defined as levels below the 95%tile for NHANES data for 6–11 year old children in 2009–2010) for a cohort of 9–11 year old children.

With respect to a brief review of associations between diet and increased background levels of non-essential metals, we have attempted to review literature on dietary contributions in the US, avoiding some of the regionally-specific dietary sources; for example, significant association between Pb and waterfowl consumption in Inuit adults (Dewailly et al., 2001). The most comprehensive assessment of US food sources of heavy metal exposure comes from the FDA's "Total Diet Study" (Gunderson, 1995; Murray et al., 2008). This study involved buying samples of food at retail outlets throughout the U.S., preparing the foods as they would be consumed, and then analyzing the foods for levels of selected toxicants, including non-essential metals. Based on those samples, the most highly contaminated foods were 1) Pb: shrimp, sweet cucumber, canned peaches, beef liver, and canned fruit cocktail, 2) Hg: canned tuna, haddock, shrimp, tuna noodle casserole, fish sticks, as well as lower but detectable levels in spinach and oatmeal, and 3) Cd: spinach, infant food creamed spinach, beef liver, iceberg lettuce, and potato chips (Capar and Cunningham, 2000). Taking into account actual consumption patterns, a recent study of Pb and Cd exposures in US children using this TDS and associated NHANES data identified grains, fruit, dairy, and mixtures (e.g. hamburgers, pizza, lasagna, soups) as the major contributors to Pb exposure as well as grains, mixtures, and vegetables as major contributors to Cd exposure (Anastacio et al., 2018; Spungen, 2019). Additional evidence of fruit as a source of significant Pb exposure in children is supported by numerous studies of fruit juice in the US (Wilson et al., 2012) as well as across the globe (Anastacio et al., 2018; Fathabad et al., 2018).

These studies of metals in food and dietary consumption patterns represent indirect methods for estimating exposures and do not directly assess whether dietary differences are actually reflected in levels of non-essential metals in the body. This is a potentially critical omission as body burden would be a function of both the quantity of toxicants in the specific food items (with large potential geographic variation) as well as the quantity consumed. In an attempt to address both these variables, one study used NHANES data to combine 24-hr dietary data with corresponding estimates of toxicant levels for specified food groups (using data from the Total Diet Survey (TDS; Murray et al., 2008) to estimate diet-based exposures (Awata et al., 2017). This study confirmed that estimates of toxicant exposure based on these calculations were significantly associated with blood levels, but only in Asian-Americans and only for Hg and arsenic. In addition to indirect exposure estimates, there are many studies of targeted consumption of specific foods (e.g., fish) and corresponding blood levels of certain metals (Xu et al., 2016). In fact, as far as we are aware, the present study represents the first to administer a comprehensive dietary intake assessment in children and determine if particular food consumption patterns are significantly associated with blood levels of Pb, Hg, and Cd. Based on prior research reviewed above, we predicted that blood Pb levels would be significantly associated with fruit and fruit juices, blood Hg levels would be significantly associated with seafood, and blood Cd levels would be significantly associated with greens/leafy vegetables.

It is also important to note that consumption of certain foods and corresponding intake of important nutrients are presumed to reduce the body burden of non-essential metals. For example, based on existing research to date, the CDC published a set of guidelines in 2002 for nutritional management of those with elevated Pb (Centers for Disease Control and Prevention, 2002). These guidelines encourage parents and caregivers to provide children with an adequate intake of foods containing iron, vitamin C, and calcium. Specifically, for iron-rich foods the CDC recommends pureed meats as soon as the child is developmentally ready and lean red meat per day to older children. For vitamin C-rich foods, the recommendation is for fruit daily and fruit juices in moderation. To ensure adequate intake of calcium, dairy products or other calcium-rich foods are recommended. However, a recent commentary on these recommendations raises two important concerns (Kordas, 2017). First, given that diet can be both a source of non-essential metals as well as a source of nutrients that might reduce metal absorption, it is important to consider the net benefits from any dietary recommendations. Second, most evidence of potential benefits from nutrients has focused on populations with relative high exposure to non-essential metals. The consequence of dietary-driven nutritional changes on children with low-level non-essential metal exposure is unknown. The present study considers association between dietary nutritional components and increased background non-essential metals in 9–11 year old children. We did not make any hypotheses with respect nutrients, as it is possible that some nutritional components reduce non-essential metals as suggested in those with elevated blood Pb levels or, alternatively, perhaps foods that contain these "beneficial" nutrients are the same foods that contain non-essential metals and thereby raise children's levels of blood metals.

1. Method

1.1. Participants

The participants were drawn from the Environmental Exposures and Child Health Outcomes (EECHO) study, a research project investigating the relationships among exposures to environmental toxicants and cardiovascular risk indices in 9–11 year-old children living in low-to middle-income neighborhoods in a midsize city in upstate New York. The EECHO sample contains an approximately equal number of African American (AA) and European American (EA), male and female children. Given EECHO's focus on AA vs. EA differences and the corresponding need to have an adequately powered study, we excluded any children who are not self-identified as either AA or EA. In addition, we excluded those that are not 9–11 years-old, do not meet zip code residence selection criteria (designed to target low SES neighborhoods and roughly equal numbers of AA and EA children), those with serious medical or developmental disabilities, and those who were on medication that might affect their cardiovascular system. Eligible siblings were allowed to participate to circumvent parents opting out altogether in order to avoid excluding a child when more than one child was eligible (something that occurred when we initially attempted this exclusion). Syracuse University's Institutional Review Board (IRB) approved this research and all participants provided assent and corresponding parents provided consent. Although we recruited 297 children for participation in EECHO, 2 participants did not produce enough blood for measurement of non-essential metals. For the analysis of demographic differences, we used this full sample of 295. However, for analysis of dietary data, we did not have diet data due to participant availability or non-response ($N = 31$) for the interview and two participants were excluded from analysis because of low kilocalorie values (less than 500 per day). Therefore, we only analyzed 264 participants. A comparison of included and excluded participants is reported below, in the Results section. With respect to joint participation from the same family, 155 children participated alone, 44 children participated with 1 sibling, and 7 children participated with 2 siblings. With respect to participation by multiple siblings from the same family, we report the analytic approach for addressing this nested data as well as the corresponding results (largely unchanged) in the Supplemental file. Results varied slightly using this analytic approach (see Supplemental file), perhaps reflecting the fact that participation by multiple siblings was more common with lower SES families (see Supplemental Table 1). The parent/caregiver informant was usually the mother (86%); in some cases the informant was a father (9%), grandmother (2%), or other custodian (e.g., aunt; 3%).

1.2. Procedure

Participants arrived at our laboratory and blood draw center located on the Syracuse University campus and signed an assent form while a parent signed a separate consent form approved by the Institutional Review Board of Syracuse University. As part of a more extensive blood draw protocol, a certified phlebotomist drew 5-mL venous blood into a plastic lavender-top (EDTA), certified by the analyzing laboratory for measurement of blood levels of Cd, Pb, and total Hg concentrations. Blood specimens were immediately placed on ice and within 2 h of the blood draw the samples were transferred into 5-mL cryovials (certified by the analyzing laboratory) and frozen at −80 °C pending shipment to the trace elements section of the Laboratory for Inorganic and Nuclear Chemistry at the New York State Department of Health's Wadsworth Center, Albany, NY. During the initial laboratory visit and a subsequent visit 1.5 weeks later, questionnaires were administered using iPads and Qualtrics Survey software (Quatrics, Provo, UT).

1.3. Measures

Exposure to Nonessential Metals: Child's Blood Cd, Pb and Hg Levels. Whole blood was analyzed for Cd, Pb, and total Hg using a well-established biomonitoring method optimized for a Thermo XSeries2 Inductively Coupled Plasma-Mass Spectrometer (ICP-MS), which was used throughout this study (Thermo Fischer Scientific, MA). A complete description of the biomonitoring method has been described elsewhere (Palmer et al., 2006). The ICP-MS instrument was calibrated for each of the metals using a matrix-matched (blood) protocol, with calibration standards traceable to the National Institute of Standards and Technology (NIST, Gaithersburg, MD). Method detection limits were calculated during the study using the IUPAC recommendations for each metal in a blood matrix: 0.03 μg/L for Cd; 0.10 μg/dL for Pb; and 0.12 μg/L for Hg. Internal quality control (IQC) materials (four levels) covering the range of exposures expected in the US population were analyzed at the beginning, end and throughout each analytical run. All IQC samples were prepared in-house from whole blood obtained from Pb-dosed animals, and supplemented with inorganic salts of Cd and Hg, and methylmercury chloride. Typical repeatability, or between-run imprecision, was 2.0% for Cd; 2.6% for Pb; and 4.0% for Hg. Method accuracy was assessed throughout the study by analyzing NIST Standard Reference Material (SRM) 955c – Toxic Metals in Caprine Blood. Method performance was monitored through successful participation in six external quality assessment schemes for trace elements that included these three metals in whole blood. The analysis was repeated for any elevated value: > 4 μg/L for Cd, > 5 μg/dL for Pb, and > 10 μg/L for Hg. In addition, 2.5% of all blood specimens were randomly selected for re-analysis.

Dietary Assessment. Diet in the children was measured using two days of dietary intake data (one weekday and one weekend day) collected from the parent for each child with the assistance from a trained nutrition researcher. Dietary intake data for 24-h recalls were collected and analyzed using the Automated Self-Administered 24-h (ASA24) Dietary Assessment Tool, versions 2011 and 2016, developed by the National Cancer Institute, Bethesda, MD (Subar et al., 2012). The ASA24 provides comprehensive data for kilocalories, macronutrients and micronutrients. Using the dietary data, the Healthy Eating Index-2015 (HEI-2015) was calculated to examine diet quality of the children. A switch was made in April of 2017 to the version of the ASA24 used in data collection since the ASA24-2011 was discontinued during the data collection period. ASA24 versions prior to 2016 used different food pattern equivalents. Therefore, HEI-2015 scores were calculated separately for each ASA24 version based on SAS code provided by the National Cancer Institute (2018) to generate results from the two versions that correctly calculated HEI-2015 scores. The HEI-2015 is scored out of 100 points and aligns with the 2015–2020 Dietary Guidelines for Americans (National Cancer Institute, 2018). Scores are based on adequacy of nine food components (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids) and the amount of four less desirable nutrients and foods (refined grains, sodium, added sugar, saturated fats). Top food contributors to HEI categories that were associated with non-essential metals were determined and percent contribution of foods within the food categories were calculated. Notable but not surprising (given this urban population), there was no game fowl consumption reported that might have represented a significant exposure route for Pb via ingestion of gun shot (cf. Dewailly et al., 2001).

Additional predictors. Participant sex and race were self-reported. Date of birth was reported by participants and confirmed by the parent or guardian. Participants' parents reported their annual household income and the occupation and education level of both parents (when known or available). Parental education level was based on a 1–7 scale and parental occupation was based on a 1–9 scale, as described in Hollingshead, (1975). Parental income was based on a 1–10 scale and adjusted by dividing income by the square root of the number of people living in the household (Rognerud and Zahl, 2006). Occupation, income, and education data from each of these three indices was averaged across parents if data from both parents was available. The income, education, and occupation data were each converted into a z-score and averaged (Gump et al., 2014).

1.4. Statistical analyses

All statistical analyses were conducted using SAS 9.4. Analyses of diet as a function of age, gender, race, and SES were conducted using general linear models (PROC GLM). In these initial models, age was represented as three groups (9, 10, or 11; linear contrast used to test associations) and SES dichotomized into low and high using a median split. These results were largely confirmed when analyzed using multiple regression models with age and SES as continuous variables and race and gender as dummy variables (0 = male, 1 = female; 0 = AA, 1 = EA); any differences as a function of analytic approach are outlined in the results section below. Analyses of dietary associations with non-essential metals were conducted using multiple linear regression models (PROC REG) with dietary variables regressed on metals, after controlling for age, gender, race, and SES. Mediational models were tested using the SAS PROCESS macro (v. 2.13; model 4) developed by Hayes (Hayes accessed on Jan 20, 2016). These models were set to 1000 bootstrap samples in order to minimize sampling error and for the estimation of bias corrected bootstrap confidence intervals for indirect effects.

2. Results

2.1. Sample characteristics

The sample consisted of 295 children with an average age of 10.49 (SD = 0.93), 58.0% were AA, 42.0% were EA, and 46.8% were female (see Table 1). The sample was diverse in terms of household income and parental education; however, the median was low-middle SES as expected based on targeted zip codes: 33.7% of the participants' families made less than $15,000 per year, 32.7% made between $15,000 and $35,000, 34.0% made above $35,000, and 12% were missing income

Table 1
Characteristics (Mean and SD, or %) of participants ($N = 295$).

Measure	Mean (SD) or %	Range
Child age (yrs)	10.49 (0.93)	8.99–12.16
Gender	46.8% Female	
Race (EA/AA)	58.0% AA	
Socioeconomic Status[a]		
Education (average of 2 parents)[b]	4.84 (1.46)	1.00–8.00
Occupation (score)	3.35 (2.88)	0.00–9.00
Income [c]	6.03 (2.93)	1.00–10.00
SES Score (combined)	0.06 (0.82)	−1.56–2.07
Blood Pb (μg/dL)	1.02 (1.03)	0.19–14.73
Blood Hg (μg/L)	0.36 (0.78)	< 0.12–11.65
Blood Cd (μg/dL)	0.11 (0.04)	0.03–0.39

[a] As indicated in the methods section, the three measures of socioeconomic status (education, occupation, and income) were converted to z-scores and combined to yield a single measure of SES.

[b] On this education scale, a score of five corresponds to "some college". As outlined in the methods section, education was averaged across parents.

[c] On this income scale, a score of six corresponds to "$20,000–25,000". As outlined in the methods section, this income was subsequently adjusted for the number of persons living in the household.

data. For participants' highest level of parental education, 12.2% did not earn a high school degree, 22.8% earned a high school degree, 29.4% completed some college, 16.4% earned a college degree, 3.4% completed some graduate school, and 16.8% earned a graduate degree. Given our selection criteria, our sample predictably had "background" low-level exposure to Cd ($M = 0.11$ μg/L, $SD = 0.04$), Hg ($M = 0.36$ μg/L, $SD = 0.78$)), and Pb ($M = 1.02$ μg/dL, $SD = 1.03$) in their blood. Specifically, 99.2% of participants had levels below 0.24, the 95%tile for Cd established in NHANES, 98.1% of participants had levels below 1.88, the 95%tile for Hg established in NHANES, and 92.4% of participants had levels below 2.01, the 95%tile for Pb established in NHANES.

An analysis of the differences in sample characteristics between those with dietary data (included in analyses below) and those excluded due to missing dietary data revealed only one significant difference between excluded and included participants – excluded participants had significantly lower SES scores and higher Cd levels, as shown in Supplemental Table 2. For all other baseline characteristics, there was no significant difference between included and excluded participants (p values > 0.05; see Supplemental Table 2).

Non-essential metals and diet as a function of children's age, race, gender, and SES.

As shown in Table 2, blood Pb significantly declined as a function of age ($\beta = -0.18$, $p = 0.002$), was higher in AAs relative to EAs ($\beta = -0.13$, $p = 0.033$), and was lower in children with higher SES ($\beta = 0.16$, $p = 0.008$). Blood Hg was significantly higher in AAs relative to EAs ($\beta = -0.15$, $p = 0.017$). With respect to diet, AA children ate significantly more total protein ($\beta = -0.20$, $p = 0.003$) and fatty acids ($\beta = -0.23$, $p = 0.001$); higher ratio of unsaturated to saturated fats), and significantly less refined grains ($\beta = -0.19$, $p = 0.005$) and saturated fats (βs $= -0.20$, $p = 0.003$) than EA children. In sum, AA children had significantly higher total HEI scores than EA children signifying a healthier diet based on this measure ($\beta = -0.20$, $p = 0.003$). With respect to gender, girls ate more vegetables than boys ($\beta = 0.13$, $p = 0.038$). For SES, increasing SES was associated with significantly more whole fruit ($\beta = 0.22$, $p < 0.001$) but not as strongly with total fruit when analyzed as a continuous variable ($\beta = 0.09$, $p = 0.170$). With increasing age, there was decreasing sodium ($\beta = -0.16$, $p = 0.009$) and total fruit ($\beta = -0.12$, $p = 0.054$).

With respect to nutrient levels, a number of significant effects were found with a multiple regression approach and confirmed with multilevel models. With increasing age, there was increasing fiber ($\beta = 0.14$, $p = 0.024$), magnesium ($\beta = 0.13$, $p = 0.039$), phosphate ($\beta = 0.16$, $p = 0.012$), and sodium ($\beta = 0.24$; $p < 0.001$), as well as decreasing intake of sugar ($\beta = -0.12$, $p = 0.048$), zinc ($\beta = -0.13$, $p = 0.039$), copper ($\beta = -0.16$, $p = 0.013$), selenium ($\beta = -0.16$, $p = 0.012$), niacin ($\beta = -0.16$, $p = 0.008$), vitamin B6 ($\beta = -0.14$, $p = 0.025$), and vitamin B12 ($\beta = -0.14$, $p = 0.027$). With respect to race, AA children had a significantly higher intake of vitamin C ($\beta = -0.18$, $p = 0.007$) relative to EA children. With respect to gender, boys had a significantly higher intake of total kilocalories ($\beta = -0.15$, $p = 0.016$), protein ($\beta = -0.18$, $p = 0.004$), and carbohydrates ($\beta = -0.12$, $p = 0.044$) relative to girls. With increasing SES, there was decreasing selenium ($\beta = -0.13$, $p = 0.046$) and vitamin B6 ($\beta = -0.13$, $p = 0.042$). Unlike our finding when age and SES were treated as categorical variables for findings in Table 2, a multiple regression model with SES as a continuous variable did not confirm a number of those prior findings, with many only marginally significant in these new models. All of the aforementioned findings were confirmed using multilevel models to account for the nested nature of the data.

2.2. Dietary predictors of blood metal levels

As shown in Table 3, a number of dietary components were associated with blood levels of non-essential metals in multiple regression models. Specifically, we found that: 1) total fruit consumption was associated with significantly higher levels of blood Pb ($p = 0.003$); 2) total protein was associated was associated with significantly lower levels of blood Pb ($p = 0.037$); 3) perhaps as a partial reflection of the positive association with total fruit, the total HEI score was associated with significantly higher blood Pb levels ($p = 0.031$); 4) total protein was associated with significantly higher levels of blood Hg ($p < 0.001$); 5) higher sodium intake was associated with significantly higher levels of blood Hg ($p = 0.026$); and 6) greater consumption of greens and beans is associated with significantly higher levels of blood Cd ($p = 0.004$).

A review of specific foods comprising these HEI categories revealed that total fruit was largely a function of consumption of fruit juice, apples, and bananas (comprising 33%, 22%, and 7% of servings consumed in this category, respectively), total protein was largely a function of consumption of chicken, milk, and pizza (comprising 13%, 10%, and 9% of grams consumed in this category, respectively), and greens and beans were largely a function of consumption of mixed salad greens and lettuce, broccoli, and chili with beans (comprising 19%, 14%, and 7% of kilocalories consumed in this category, respectively).

2.3. Micro- and macronutrient associations with blood metal levels

The ASA24 provides quantification of a number of micro- and macronutrient. These analyses (associations, controlling for gender, race, age, and SES) revealed a number of significant associations (see Table 4). Specifically, we found that higher levels of blood Pb were associated with greater intake of carbohydrates ($p = 0.025$), fiber ($p = 0.009$), potassium ($p = 0.007$), and vitamin C ($p < 0.001$). These associations remained significant in multi-level models. Higher levels of blood Hg were associated with less intake of carbohydrates ($p = 0.006$), sugar ($p = 0.038$), zinc ($p = 0.011$), copper ($p = 0.024$), selenium ($p = 0.015$), niacin ($p = 0.036$), vitamin B6 ($p = 0.012$), vitamin C ($p = 0.040$), and vitamin B12 ($p = 0.030$).

2.4. Mediational analyses

Based on the results shown in Tables 2 and 3, we tested the following potential mediational pathways: Race → total fruit → Pb and Race → total protein → Hg. Mediational analyses with bootstrapping and PROCESS models (Hayes accessed on Jan 20, 2016) revealed a significant indirect effect for both models (see Fig. 1), estimate = −0.05, 95% CI: 0.10, −0.01) and estimate = −0.01, 95% CI: 0.03, −0.00), respectively. Vitamin C rich foods may serve as a marker for a particular item(s) that carries Pb; therefore, we also tested vitamin

Table 2
Mean blood metal levels and healthy eating indicators as a function of age, race, gender, and SES (all entered in single model; N = 295 for analysis of metals, N = 264 for analysis of dietary variables). For age, a linear contrast across increasing age was used to test for significance.

	Age			Race		Gender		SES	
	9	10	11	AA	EA	Female	Male	Low	High
Metals									
Pb (μg/dL)	0.91	0.85	0.74 *	0.91	0.76 *	0.79	0.89	0.93	0.76 *
Hg (μg/L)	0.20	0.20	0.19	**0.23**	**0.16** *	0.20	0.19	0.19	0.20
Cd (μg/dL)	0.10	0.10	0.11 #	0.10	0.10	0.10	0.10	0.10	0.10
Health Eating Index (HEI)									
Vegetables	2.00	2.14	2.05	2.12	2.01	2.23	1.90 *	2.18	1.95
Greens and Beans	1.02	0.93	0.90	1.08	0.83	1.06	0.84	1.11	0.80
Total Fruit	**3.03**	**2.89**	**2.49** *	3.02	2.58 #	2.98	2.63	**2.53**	**3.07** *
Whole Fruit	2.54	2.49	2.45	2.57	2.42	2.47	2.52	**2.05**	**2.93** *
Whole Grains	2.23	2.51	1.94	2.22	2.23	2.21	2.24	2.12	2.34
Dairy	6.84	6.52	6.67	6.35	7.01 #	6.57	6.79	6.72	6.64
Total Protein	3.94	4.08	3.84	**4.18**	**3.73** *	3.95	3.97	4.05	3.86
Seafood and Plant Protein	2.05	2.18	2.20	2.02	2.27	2.19	2.10	2.05	2.24
Fatty Acids	3.80	3.86	3.75	**4.44**	**3.16** *	3.50	4.10	3.84	3.76
Sodium[a]	**4.11**	**3.90**	**3.24** *	3.54	3.89	3.61	3.82	3.49	3.94
Refined Grains[a]	4.05	4.28	4.29	**4.92**	**3.49** *	4.51	3.93	4.08	4.34
Saturated Fats[a]	5.62	5.24	5.60	**5.97**	**5.00** *	5.31	5.66	5.58	5.39
Added Sugar[a]	5.98	6.23	5.29 #	5.64	6.03	5.85	5.81	6.10	5.57
Total Score	47.11	47.27	44.71	**48.06**	**44.66** *	46.43	46.29	45.90	46.82
Micro- and Macronutrients									
Total calories	1922.74	2012.80	2004.21	2001.26	1958.58	1899.17	2060.67 *	1983.95	1975.89
Protein (g)	72.70	74.15	71.58	74.27	71.35	**68.06**	**77.56** *	74.01	71.61
Total Fat (g)	70.93	76.56	74.67	74.37	73.73	71.48	76.62	74.09	74.02
Carbohydrates (g)	253.25	261.92	267.35	263.46	258.22	251.55	270.14 #	260.26	261.42
Sugar (g)	423.28	277.72	299.42	277.08	389.94	319.16	347.86	**431.37**	**235.65** *
Fiber (g)	**10.22**	**12.68**	**12.23** *	11.89	11.53	11.75	11.67	10.90	12.52 #
Calcium (mg)	725.86	876.93	858.37 #	812.33	828.45	802.00	838.77	764.92	875.86 #
Iron (mg)	21.25	17.13	22.24	18.01	22.31	20.33	20.09	**23.17**	**17.25** *
Magnesium (mg)	196.85	227.11	218.56 #	216.79	211.55	211.82	216.53	**204.19**	**224.16** *
Phosphorus (mg)	**927.35**	**1114.57**	**1099.40** *	1066.78	1027.43	1022.93	1071.28#	**972.15**	**1122.06** *
Potassium (mg)	1824.60	2053.34	1952.42	2039.26	1847.65 #	1887.25	1999.66	1874.86	2012.05
Sodium (g)	**2484.34**	**3032.56**	**3250.38** **	**3132.96**	**2711.86** *	2854.44	2990.41	**2720.15**	**3124.70** *
Zinc (mg)	56.70	35.23	38.85	34.48	52.71	39.10	48.09	**59.65**	**27.54** *
Copper (μg)	**265.50**	**129.41**	**127.58** *	133.36	214.96	138.38	209.94	**255.07**	**93.26** *
Selenium (μg)	**515.23**	**307.80**	**304.54** *	289.36	462.36 #	326.89	424.83	**522.43**	**229.28** *
Niacin (mg)	**655.42**	**375.95**	**292.43** *	340.74	541.80	360.38	522.15	**651.41**	**231.12** *
Vitamin B6 (mg)	3.55	2.82	2.61 #	2.83	3.15	2.66	3.32	**3.66**	**2.33** *
Thiamin (mg)	1.68	1.64	1.74	1.66	1.71	1.72	1.65	1.79	1.59
Vitamin C (mg)	81.89	85.77	82.66	**97.21**	**69.66** ***	88.95	77.92	80.84	86.03
Vitamin B12 (μg)	78.18	53.72	41.33 #	47.70	67.78	50.12	65.36	**84.07**	**31.42** *

[#]p < 0.10; *p < 0.05; **p < 0.01.
[a]These are scored such that higher numbers reflect less of these dietary components.

C in a mediational model to account for the association between race and Pb. This mediational model (Race → vitamin C → Pb) was also significant, estimate = −0.03, 95% CI: 0.07, −0.01.

3. Discussion

A number of important findings emerged from these analyses of race, diet, and blood levels of non-essential metals in 9–11 year old children. First, AA children in this population had significantly higher levels of Pb and Hg relative to EA children. Second, there were a number of racial differences in diet – AA children ate significantly more total protein and fatty acids and significantly less refined grains and saturated fats than EA children. In general (i.e., using the total score for the HEI), AA children had a significantly healthier diet relative to EA children. Thompson and colleagues (Thomson et al., 2018) found similar results when evaluating diet quality in children from the HEI-2015 using NHANES data. Non-Hispanic EA children below the poverty level had the lowest diet quality scores compared to children from other racial and ethnic groups below the poverty level. Of note, the overall diets of children in the study were of poor quality, with children meeting 47% of the maximum score for overall diet quality. When using a grading approach, theses overall HEI scores would earn an F (Krebs-Smith et al., 2018). Yet, the overall diet quality scores are similar to (though slightly lower) than diet quality scores from national data (Krebs-Smith et al., 2018). With respect to specific nutrients, AA children had a significantly higher intake of vitamin C and lower intake of calcium than EA children. Third, increased background levels of Pb were significantly associated with dietary consumption of total fruit, increased background levels of Hg were significantly associated with dietary consumption of total protein, and increased background levels of Cd were significantly associated with dietary consumption of greens and beans. Given the pattern of these findings, we also confirmed via mediational analyses that race differences in Pb and Hg were significantly mediated by dietary differences in total fruit and total protein, respectively; however, a direct pathway remained significant for Pb suggesting other exposure routes also contributed to racial differences.

The food sources for “total fruit” are typically from fruit juice and common whole fruits such as apples, bananas, watermelon, grapes, and oranges (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). Consistent with this pattern, the top three foods that were categorized as total fruit in the current sample were fruit juice, apples, and bananas. The food sources for “total protein” are typically from beef (especially ground), chicken, pork, processed meats, and eggs (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). However, the top three foods that were categorized as total protein in the current sample were

Table 3
Dietary predictors of blood metal levels (standardized βs), in models controlling for age, gender, race, and SES (significant associations found in both multiple regression and multi-level models are in bold).

Health Eating Index (HEI)	Metal		
	Pb	Hg	Cd
Vegetables	0.01	0.01	0.09
Greens and Beans	−0.03	−0.03	**0.17** **
Total Fruit	**0.18** **	−0.08	−0.03
Whole Fruit	0.09	0.00	−0.02
Whole Grains	0.01	0.01	0.03
Dairy	0.04	−0.05	0.07
Total Protein	−0.12*[b]	**0.21** **	−0.07
Seafood and Plant Protein	−0.09	0.03	0.08
Fatty Acids	0.05	−0.01	0.00
Sodium[a]	−0.08	0.14*[b]	0.01
Refined Grains[a]	−0.03	−0.03	0.02
Saturated Fats[a]	−0.11 #	0.09	−0.06
Added Sugar[a]	−0.10	−0.08	−0.01
Total Score	0.13 *[b]	−0.03	0.07

#p < 0.10; *p < 0.05; **p < 0.01.
[a] For purposes of calculating the total HEI score, these are scored such that higher numbers reflect less of these dietary components. However, for ease of interpreting the associations in this table, the signs were reversed so that positive correlations reflect when an increase in the dietary component is associated with an increase in the non-essential metal.
[b] Although significant in multiple regression models, these associations were only marginally significant when analyzed using the more conservative multi-level models that accounted for multiple participants in the same family, i.e., nesting of children within family (see Supplemental File).

Table 4
Macro- and Micronutrient from the ASA24 as predictors of blood metal levels (standardized βs), in models controlling for age, gender, race, and SES (significant associations found in both multiple regression and multi-level models are in bold).

Nutrients	Metal		
	Pb	Hg	Cd
Total calories	0.08	−0.07	−0.05
Protein (g)	0.04	0.08	−0.05
Total Fat (g)	0.00	0.01	−0.09
Carbohydrates (g)	**0.13** *	**−0.17** **	0.00
Sugar (g)	−0.02	−0.13 *[a]	−0.03
Fiber (g)	**0.16** **	0.01	0.07
Calcium (mg)	0.09	0.01	0.04
Iron (mg)	0.06	−0.02	0.06
Magnesium (mg)	0.11 #	0.00	0.02
Phosphorous (mg)	0.08	0.09	0.03
Potassium (mg)	**0.16** **	−0.02	−0.01
Sodium (µg)	0.06	0.10	0.03
Zinc (mg)	−0.03	**−0.16** *	−0.03
Copper (µg)	−0.04	**−0.14** *	−0.04
Selenium (µg)	−0.03	**−0.15** *	−0.03
Niacin (mg)	−0.06	**−0.13** *	−0.04
Vitamin B6 (mg)	−0.01	**−0.16** *	−0.05
Thiamin (mg)	0.07	0.01	0.00
Vitamin C (mg)	**0.23** ***	−0.13 *[a]	−0.06
Vitamin B12 (µg)	−0.02	**−0.14** *	−0.02

#p < 0.10; *p < 0.05; **p < 0.01; ***p < 0.001.
[a] Although significant in multiple regression models, these associations were only marginally significant when analyzed using the more conservative multi-level models that accounted for multiple participants in the same family, i.e., nesting of children within family.

chicken (breast, thighs, nuggets), milk, and pizza. Finally, “greens and beans” are typically from lettuce (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015) and in the current sample the top three food items were mixed salad greens/lettuce, broccoli, and chili with beans.

Although there is limited prior research on total diet and children with presumed “normal” non-essential metals, these findings are consistent with some prior work. Fruits and fruit juices are known to contain detectable levels of Pb (Capar and Cunningham, 2000; Tvermoes et al., 2014) and may thereby provide an important exposure route for children in the normal-to-high normal range of Pb blood levels. The role of “total protein” in Hg exposure is more difficult to interpret. Although seafood is clearly a significant source of Hg, many children in the current sample had little to no consumption of seafood and this perhaps explains the lack of an association between seafood consumption and blood Hg in the current sample. One interesting pathway may be through bioaccumulation in commercially farmed animals being fed fish meal (Dorea, 2006, 2009). Further research is needed to identify if this is the significant source of increased background Hg exposure in children. With respect to Cd exposure, the finding that “beans and greens” are a significant source in children is consistent with a great deal of research identifying greens such as lettuce as a significant source of Cd (Davis, 1984; Gunderson, 1995; Wolnik et al., 1983).

It is important to compare our findings with one recent study (Gavelek et al., 2020) that has similarly attempted to evaluate which food sources account for significant toxicant exposure in this age group – adopting the important principle that “key sources of lead exposure are not necessarily the foods/food groups with the highest lead concentrations but in most cases are the foods with the highest consumption” (p. 107). For 7–17 year olds, Gavelek et al. combined data from the NHANES What We Eat in America (WWEA) with corresponding estimates of toxicant levels for specified food groups from the TDS (Murray et al., 2008). The food groups contributing most to Pb exposure in those children were grains (31.1%), mixtures (26.4%), dairy (14.5%), and fruit (11.4%). A direct comparison of our results is difficult as the WWEA uses different food categories – for example, the TDS uses a broad category for grains (including desserts) whereas the HEI provides estimates of components of grains, namely refined grains, whole grains, and added sugars. Similarly, the HEI does not assess “mixtures” but rather the components of those mixtures. The one common category across methods – fruit – was identified as a significant source of dietary Pb in both this study and our data. It should be noted, however, using Gavelek et al.‘s approach to estimate dietary consumption in Asian American adults did not reveal a significant association between these estimates of exposure and corresponding biomarkers of Pb and Cd, but did confirm an association between these biomarkers and dietary estimates for As and Hg (Awata et al., 2017).

In addition to our analysis of potential food sources, we considered associations between non-essential metals and specific nutrients in foods. Specifically, we considered whether iron, vitamin C, and calcium were associated with lower Pb levels. These are the nutrients recommended by the CDC as a means to reduce Pb in those with elevated levels. In the current study, iron and calcium were unrelated to blood Pb (as well as Hg and Cd) and vitamin C showed a significant positive association with blood Pb, suggesting that perhaps the food source for vitamin C (e.g., fruit) was also a source of Pb exposure. These findings are consistent with other research suggesting that nutrient intake may be ineffective in mitigating exposure to non-essential metals (Kordas, 2017); however, our sample was not testing the effects of nutrients in children with high exposures nor were we able to directly test moderation (e.g., Pb exposure x vitamin C) because the source of Pb exposure in the current sample (total fruit) was also the source of vitamin C.

Are these associations between diet and increased background non-essential metals clinically or functionally important? A number of studies have demonstrated that background exposure to non-essential metals have significant impact on the cardiovascular system (Gump et al. 2005, 2011), immune system (Eggers et al., 2018), neuroendocrine system (Gump et al., 2008), and on cognitive functioning (Bellinger et al., 1992). In fact, for the cohort analyzed above we have already documented an association between increased background levels of Pb and Hg and psychological and behavioral problems (Gump et al., 2017).

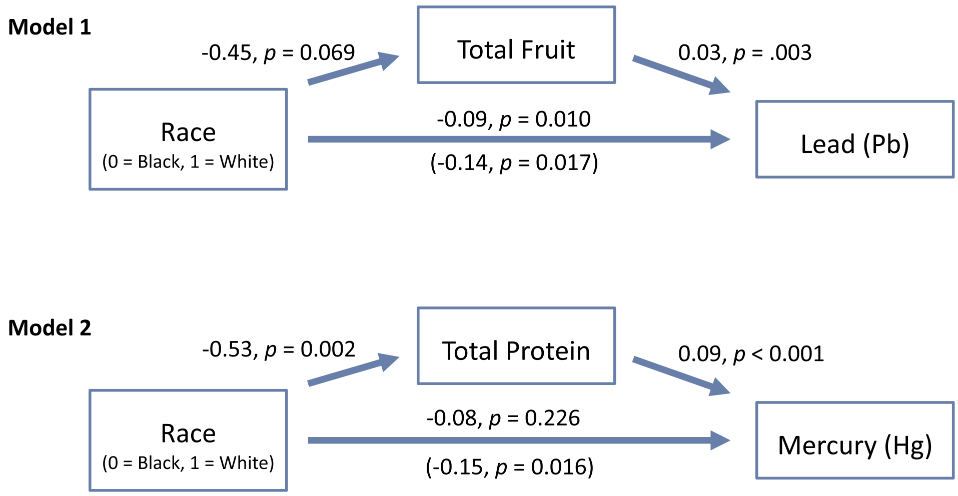

Fig. 1. Mediational models demonstrating that race differences in increased background levels of blood Pb and Hg are a function of (i.e., mediated by) specific dietary differences. Direct pathways from race to metals are reported before (with parentheses) and after (no parentheses) the indirect pathway is added.

There are notable limitations with the present study. First, the cross-sectional study design makes it difficult to establish causality and the direction for any associations. For example, it is possible that foods and nutrients affect the absorption of non-essential metals from non-dietary sources. However, with the possible exception of iron, calcium, and vitamin C, we are unaware of any literature demonstrating dietary effect of non-essential metal absorption into the body. Moreover, vitamin C was positively related to blood Pb in the current sample. In addition to the possibility of this reverse causality, there also exists the possibility that other variables covary with both dietary intake and non-essential metal exposures from non-dietary sources. To reduce this likelihood, we controlled for the most logical potential confounds, namely gender, age, race, and SES. Second, we are inferring dietary contributions to blood levels of non-essential metals. Without a duplicate diet method approach (i.e., producing a second identical plate of food to what is consumed by the child for measuring non-essential metals in the actual food being consumed), we are making indirect assumptions regarding dietary sources based on food recall. Additionally, the study is limited by parent-reported dietary intake that can result in misreporting. Also, the study is limited by our inability to determine the exact source of food (i.e., the farm where it was grown/raised or the store where it was purchased). Finally, given regional and age differences in food consumption patterns, the generalizability of the current findings has yet to be determined. For example, consumption patterns of fish vary considerably by geographic location and may represent a significant source of Hg for some children, such as found for inhabitants of Menorca Island in the Mediterranean in which a large proportion of the food that is consumed is generated locally (Junque et al., 2017). Similarly, infant sources of toxicants have focused on formula and cereals due to their high consumption rates at that age (Jean et al., 2018).

4. Conclusions

The present study demonstrated that children's relatively high consumption of certain foods (e.g., fruit juice) at 9–11 years of age may produce important exposures despite these foods being "safe" based on FDA levels. The current study also identifies the specific dietary sources of this exposure – namely total fruit for Pb, total protein for Hg, and greens and beans for Cd. Moreover, racial differences in blood Pb and Hg were significantly mediated by these dietary differences in foods consumed. A reasonable question follows from these findings: is it important to identify food sources for low-level dietary exposures? The historic focus on high-level exposures is akin to a "high-risk" approach to primary prevention (Emberson et al., 2004) – on the other hand, the recognition that even low-level exposures have adverse consequences (reviewed above) suggests a need to shift our focus to a "population" approach to primary prevention through identifying and addressing the low level exposures from everyday sources (such as frequently consumed foods).

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CRediT authorship contribution statement

Brooks B. Gump: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing - original draft. **Bryce Hruska:** Methodology, Project administration, Supervision, Writing - review & editing. **Patrick J. Parsons:** Formal analysis, Methodology, Validation, Writing - review & editing. **Christopher D. Palmer:** Formal analysis, Methodology, Validation, Writing - review & editing. **James A. MacKenzie:** Funding acquisition, Formal analysis, Project administration, Writing - review & editing. **Kestutis Bendinskas:** Funding acquisition, Formal analysis, Project administration, Writing - review & editing. **Lynn Brann:** Methodology, Project administration, Validation, Writing - original draft.

Declaration of competing interest

The other authors have indicated they have no potential conflicts of interest to disclose.

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Appendix A. Supplementary data

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