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Detectable Blood Lead Level and Body Size in Early Childhood

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Abstract

Rates of childhood obesity have risen at the same time rates of high blood lead levels (BLL) have fallen. Recent studies suggest higher BLL is inversely associated with body size in older children (ages 3–19 years). No contemporaneous studies have examined if having a detectable BLL is associated with body size in very early childhood. We examined if detectable BLL is associated with body size in early childhood. A total of 299 birth cohort participants completed a study visit at ages 2–3 years with weight and height measurements; prior to this clinic visit a BLL was drawn as part of routine clinical care. Body mass index (BMI) percentile and Z-score were calculated; BMI ≥85th percentile was considered overweight/obese at age 2 years. Detectable BLL was defined as BLL ≥1 μg/dL. A total of 131 (43.8%) children had a detectable BLL measured at mean age 15.4±5.5 months. Mean age at body size assessment was 2.2±0.3 years (53.2% male, 68.6% African-American). After adjusting for race, sex and birth weight, children with a detectable BLL had a 43% lower risk of BMI ≥85th percentile (P=0.041) and a 0.35 unit lower BMI Z-score (P=0.008) compared to children without a detectable BLL. Neither race nor sex modified this association (all interactions P>0.21). Consistent with recent studies in older children, having a detectable BLL was associated with smaller body size at ages 2–3 years. Additional research on the mechanism of this association is needed, but may include mechanisms of appetite suppression via lead.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Keywords

Lead; Childhood disease; Obesity; Population health; Pediatrics

Introduction

There are no known safe blood lead levels (BLL) in children [1]. Children with exposure to lead even below the US Centers for Disease Control and Prevention current reference range (<5 μg/dl) have potential negative long-lasting health consequences [1]. Despite successful interventions to reduce lead exposure in children (e.g. elimination of lead in gasoline), based on 2007–2010 National Health and Nutrition Examination Survey (NHANES) data, ~2.6% of US children ages 1–5 years have a BLL≥5 μg/dl [2]. The greatest burden of elevated BLL in children is found in racial-ethnic minorities (i.e. 5.6% of Black children have BLL≥5 μg/dl) and those living in higher poverty areas [2].

Although children with higher BLL tend to live in poorer areas where childhood obesity rates are higher [3], lead itself does not appear to be obesogenic. While earlier NHANES data (1988–1994) did not find associations between BLL and weight or body mass index (BMI) in children ages 1–7 years [4], more recent data from NHANES suggests that higher lead level is associated with lower BMI Z-score in both adults and in children and adolescents [5, 6]. In NHANES 1999–2002 data, higher lead concentration in urine was inversely associated with both BMI and waist circumference in children (6–18 years of age) [5]. In data from NHANES 1999–2006, higher BLL was inversely associated with BMI Z-score and risk of obese and overweight in children/adolescents ages 3–19 years [6].

To our knowledge, despite changing prevalence over time in both childhood obesity and elevated BLL, no recent studies have examined whether BLL is associated with body size in very early childhood (ages 2–3 years). We hypothesized that having a detectable BLL would be inversely associated with body size at ages 2–3 years, measured as BMI Z-score and BMI category, in children participating in the racially and socioeconomically diverse Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort (Detroit, Michigan) [7–9]. We also examined whether associations between BLL and body size varied by sex or race.

Methods

Study Population

WHEALS recruited pregnant women with due dates from September 2003 through December 2007, and who were seeing a Henry Ford Health System (HFHS) obstetrics practitioner at one of five clinics to establish an unselected birth cohort [7–9]. All women were in their second trimester or later, were aged 21–49 years, and were living in a predefined geographic area in western Wayne County, Michigan that included the western portion of the city of Detroit as well as the suburban areas west of the city. Home visits were conducted at 1, 6 and 12 months of age. Children and their parent/guardian were invited to return for a clinic visit at child age 2 years for a health assessment. All participants provided

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written, informed consent and study protocols were approved by the Institutional Review Board at HFHS. There were a total of 1,258 births to WHEALS mothers.

A total of 696 children (56.1%) completed a 2-year follow-up clinic visit. We excluded 10 children who were part of twin pairs. Thirty-seven children missing height and weight information at the 2-year visit were excluded. As part of routine well-child care, children being seen at HFHS pediatrics clinics typically undergo blood lead screening at least once between ages 1 and 2 years. 350 children with a 2-year visit did not have blood lead testing before the 2-year clinic visit, either because the blood lead testing occurred after the 2-year visit (n= 42), they were not seen by a HFHS pediatric provider after age 6 months (n=133) or they were seen by a HFHS pediatric provider but did not have blood lead testing (n=175). Our final analytic sample size consisted of 299 children with blood lead testing results before the 2-year clinic visit with height and weight measured at the 2-year clinic visit.

Blood Lead Assessment

As part of clinical care, lead is measured in whole blood using graphite furnace atomic absorption spectrophotometry in the HFHS Department of Pathology, Chemistry Division Laboratory (lower limit of detection is 1 μg/dL) [10–12]. Briefly, venous blood samples are obtained in EDTA Vacutainer tubes and are prepared in a 1:11 dilution. Calibration standards (8, 16, 32, 48, and 64 ug/dL) are prepared from a working lead standard (80 μg/dL) (Sigma Aldrich, St. Louis MO) and 2 controls (blanks) are prepared simultaneously consisting of 200 μL of high purity double deionized-H20. Each run also contains 3 lyphochek human based whole blood controls (Bio-Rad, Hercules CA).

Medical record abstraction of the WHEALS child charts was completed to obtain all available blood lead testing results. For the purposes of this study, we defined a detectable BLL as ≥1 μg/dL. A small number of children (n=32; 10.7%) had more than 1 blood lead test available; for children with more than 1 blood lead test available, the maximum result was used in analysis. We compared the classification (detectable vs. undetectable BLL) of the 32 children with more than 1 BLL test; most (n=25; 78.1%) were classified identically across all tests.

Body Size Measurement

At the 2-year clinic visit, trained field staff measured child height in stocking feet with a wall stadiometer; child weight was measured with the child in light clothing using a balance beam physician scale. BMI was calculated as weight (in kg) divided by the square of height (m^2). Height-for-age Z-scores, weight-for-age Z-scores and BMI Z-scores and percentiles were calculated according to the 2000 Centers for Disease Control and Prevention age- and gender-specific growth charts. Overweight was defined as BMI between the 85th and 95th percentile and obesity was defined as BMI≥95th percentile [13].

Covariate Measurement

Maternal race was self-reported. Delivery records for WHEALS women were abstracted to obtain delivery type, birth weight and gestational age at delivery. Maternal prenatal care records were abstracted to obtain BMI at first prenatal care visit; maternal obesity was

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defined as BMI≥30 kg/m^2. Gender- and gestational-age adjusted birth weight Z-scores were calculated using the US population as a reference [14].

At the 1 and 6 month home visits, trained interviewers evaluted home cleanliness using a housekeeping index, which is a Likert scale assessing overall home cleanliness [15]. We utilized the 6 month measure of home cleanliness (1 month visit information was used for 38 children missing the 6 month visit information); data were collapsed into categories of below average, average, and above average home cleaniness.

Statistical Analysis

For descriptive purposes, maternal, newborn and child characteristics were compared by having a detectable BLL using a chi-square test for discrete characteristics and a t-test for continuous characteristics. Linear regression was utilized to examine the association of detectable BLL on the continuous BMI Z-score. A previous study suggested that BLL was inversely associated with both overweight and obesity in children/adolescents [6]; given that we had small numbers of children with overweight or obesity, we combined children who were overweight or obese into a single category. Log-binomial regression was utilized to model the association between having a detectable BLL with the combined overweight/obesity category (compared to combined underweight/normal weight category) and relative risk (RR) was calculated [16]. Log-binomial regression was used instead of logistic regression as the prevalence of overweight/obesity was not rare (i.e. >10%) [17]. Models were fit (1) unadjusted and (2) adjusted for race, sex and birth weight Z-score. Other covariates were evaluated as potential confounding factors by examining if their addition to the model resulted in a ≥10% change in the parameter estimate for the association of detectable BLL on body size measure [18]. Potential covariates included maternal age at delivery, maternal education, marital status, maternal smoking in pregnancy, total household income, maternal body size during pregnancy, gestational age at delivery, firstborn status, ever breastfed and child's current age; no factors met the criteria for inclusion as a confounder. To examine if the associations between having a detectable BLL and BMI variables at age 2–3 years varied by sex or race, models were fit including either a detectable BLL-by-sex or a detectable BLL-by-race interaction term.

We conducted several sensitivity analyses. We dichotomized our blood lead data into a categorical variable (detectable vs. not detectable) as most children (59%) were under the lower limit of detection. However, this approach does not take advantage of the continuous nature of BLL data. We conducted a sensitivity analysis using Tobit regression, which is a useful statistical method when a large number of data is censored below the detection threshold [19]. In our primary analyses, we utilized the maximum BLL value available to define detectable vs. undetectable BLL; we repeated our analysis using first available BLL data. Finally, in order to determine if detectable BLL was associated with stature alone or weight alone, linear regression models were fit examining height-for-age Z-score and weight-for-age Z-score as the outcome variable.

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Results

We compared the 299 children in the analytic sample (blood lead testing and a 2-year visit) to the 350 children not in the analytic sample (no blood lead testing but had a 2-year clinic visit). Compared to children who were not in the analytic sample, children in the analytic sample were more likely to have a mother who was not married (37.1% vs. 29.1%), to be African-American (68.6% vs. 47.7%), and to be first born (43.5% vs. 31.7%) (all $P<0.05$). There was no difference in BMI Z-score ($P=0.36$) or BMI category ($P=0.23$) between these two groups.

Out of the 299 children screened, 12 (4.0%) had BLL ≥5 μg/dL (of these, 3 had BLL ≥10 μg/dL). A total of 131 (43.8%) children had a detectable BLL. Participant characteristics are presented by BLL in Table 1. Compared to those with an undetectable BLL, those with a detectable BLL were statistically significantly more likely to be African-American ($P=0.007$), to have below average house cleanliness ($P=0.032$) and to be female ($P=0.024$). There was also a small difference in maternal age at delivery (30.8±5.3 years in those with detectable BLL compared to 29.7±5.5 years in those with undetectable BLL; $P=0.081$). Children with detectable BLL were less likely to have a mother with maternal obesity at the first prenatal care visit ($P=0.067$) and were less likely to be first born ($P=0.061$). Of the 12 children with BLL ≥5 μg/dL, nearly all (n=10; 83.3%) were normal weight (BMI≥5th and <85th percentile) and the remaining two were overweight (BMI≥85th and <95th percentile).

Children with a detectable BLL had statistically significantly lower mean BMI ($P=0.009$), BMI Z-score ($P=0.012$) and BMI percentile ($P=0.009$) compared to children with undetectable BLL (Table 1). More children with detectable BLL had BMI<85th percentile compared to children with undetectable BLL (Table 1). There was no difference in age at BLL test ($P=0.41$) or time between BLL test and 2-year clinic visit ($P=0.51$) between those with and without a detectable BLL.

Table 2 presents the association of having a detectable BLL with BMI≥85th percentile and BMI Z-score. After adjusting for race, sex and birth weight Z-score, having a detectable BLL was associated with a relative risk for BMI≥85th percentile of 0.57 (95% CI: 0.33, 0.98; $P=0.041$). Compared to those with an undetectable BLL, having a detectable BLL was associated with a 0.35 [95% CI 0.10, 0.60] unit lower BMI Z-score ($P=0.008$), after adjusting for race, sex and birth weight Z-score.

There was no evidence that race or sex modified the association between detectable BLL and body size at age 2–3 years (all interactions $P>0.21$). Using the Tobit approach, inferences were similar suggesting an inverse association between BMI category ($P=0.055$) and BMI Z-score ($P=0.011$) with BLL after adjusting for race, sex and birth weight. A small number of children (n=32) had more than one BLL available; repeating the analysis with first available BLL, inferences were similar. Finally, after adjusting for race, sex and birth weight, detectable BLL was not associated with weight-for-age Z-score ($P=0.20$) or height-for-age Z-score ($P=0.29$).

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Discussion

Our study provides evidence suggesting that having a detectable BLL (i.e., BLL ≥1 μg/dL) is associated with smaller body size in children as young as 2–3 years. Our results are consistent with findings from two other studies in older children [5, 6]. From an ecological standpoint, the rise in obesity rates has mirrored the decline in BLL over the past three decades [5]. However, we caution that this does not imply that lead should be considered potentially "protective" against obesity, rather, given the overwhelming negative sequelae of lead on child health, understanding how lead may influence body size and/or what other exposures are related to lead exposure (or lead non-exposure) may provide utility in better understanding childhood obesity.

Data from animal models suggests that lead may impact body size (e.g. weight) via various mechanisms. Rats exposed to lead have decreased body weight, potentially due to a reduced appetite mediated by both a systemic mechanism and a gut mechanism [20–22]. Minnema and Hammond (1994) suggest that lead affects food-satiety signals in rats, leading to premature termination of food intake during a meal [20]. Studies specifically investigating the impact of lead on appetite and satiety signaling in children are needed and could inform potential interventions for childhood obesity.

The association between BLL and body size may vary by the underlying burden of lead exposure in the population under study. In a study of children conducted in India with high lead exposures (76% with BLL between 5 and 20 μg/ml; mean BLL at ages 12–35 months 11.8±6 μg/dl), higher BLL was associated with greater weight-for-height percentile at age <3 years [23]. In NHANES III, 31% of children ages 1–5 years had BLL ≥5 μg/dl, with a geometric mean BLL of 3.6 μg/dl (3.2–3.9 μg/dl) in phase 1 [24]; in NHANES III, there was no association between BLL and BMI [4]. Significant inverse associations between childhood lead exposure and body size have been detected in more recent studies (NHANES years 1999–2006) [5, 6], where the prevalence of BLL ≥5 μg/dl was much lower (e.g., 8.6% in NHANES 1999–2002 and 4.1% in 2003–2006; geometric mean BLL in NHANES 1999–2004 was 1.9 μg/dl) [2, 24].

We did not find evidence that detectable childhood BLL was associated with either weight or height Z-scores at ages 2– 3 years. This is in contrast to two recent studies examining prenatal lead exposure. Afeiche et al (2011) demonstrated that prenatal lead exposure, measured as maternal bone lead, was associated with decreased weight at age 5 years, but only among female children [25]. Prenatal lead exposure, measured in maternal blood, was associated with reduced weight and length Z-scores in offspring at age 2 years participating in the Mothers and Children's Environmental Health Study [26]. Our findings were restricted to those based on BMI, which may suggest that early life exposure to lead is associated with a weight disproportionate to height, rather than to weight or height alone. Alternatively, the impact of prenatal lead exposure, as opposed to early childhood exposure, may differ with respect to height and weight alone.

Intensive home cleaning efforts have been found to reduce BLL [27, 28]. In our study, higher interviewer-rated home cleanliness was associated with reduced detectable BLL,

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although adjusting for home cleanliness did not attenuate the association between detectable BLL and body size at age 2 years. In addition to reducing the exposure to lead, home cleaning practices may alter the environmental (home) microbiome [29, 30]. The human gut microbiome is associated with the home microbiome [31]; cleaning practices that impact the environmental microbiome may also impact an individual's microbiome, with greater cleanliness potentially reducing exposures to beneficial microbes. Differences in gut microbiome structure and function are associated with obesity/body size [32–35]. It is possible that children living in the cleaner environment – who are less likely exposed to lead - may also be exposed to a less diverse home microbiome and thus have increased body size due to differences in the gut microbiome. However, this speculation requires specific investigation.

While previous studies have suggested reverse causality, that is, weight loss leading to release of lead from body stores and subsequently higher BLL [5, 36], it is less likely that weight loss would explain the results we found in the current study, for several reasons. First, the measurement of BLL preceded body size measurement. Second, unless at high risk for overweight/obesity and under the direction of a healthcare provider, weight loss would not be normal in children in this age range (i.e. <age 3 years).

There are several limitations to the current study. Only a subset of WHEALS participants had blood lead screening data, thus, our results may be subject to selection bias. However, there were no differences in BMI variables between children with and without screening, and, among the 299 children screened, 12 (4.0%) had BLL≥5 μg/dL, which is consistent with rates in the US between 2003–2006 and 2007–2010 of 4.1% and 2.6%, respectively [2]. Our measurement of lead exposure was the BLL, which reflects lead level at a single point in time [37]. However, a previous study in older individuals (≥age 6 years) suggested minimal within-person variability in BLL [38], and in our small sample of children with multiple BLL tests separated by an average of 6 months, nearly 80% were identically classified. Bone lead levels, a measure of past/cumulative exposure [37], were not available. While bone lead measures may provide greater accuracy with respect to exposure assessment; the radiation exposure to young children in order to obtain such data are not justified. Blood lead levels earlier in life (e.g. at birth) were unavailable; future studies examining blood lead level trajectory over early life are needed. We did not obtain information on the quantity of food consumed by participating children. It is possible that undernourished children may have more pica and thus increase their lead exposure. Data from NHANES suggests that diet only explains ~2.9% of the variation in BLL in children, with consumption of both whole milk and apple juice positively correlated with higher BLL in children [39]. It is possible that specific dietary components influence BLL and body size in opposite directions, however, this requires additional study.

There are also several strengths in this study. Our sample was diverse, allowing us to examine if there were racial differences in the association of BLL and body size. Blood lead screening preceded measurement of body size by an average of ~11 months. We were able to account for home cleanliness, which is a potential modifiable factor associated with BLL exposure. All BLL were based on venipuncture, not finger or heel stick, which is considered a more reliable blood lead screening method [10].

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In summary, children with detectable BLL had a smaller BMI Z-score and were less likely to be overweight/obese at age 2 years than children without a detectable BLL. Further study on how lead impacts appetite and satiety signaling in young children is needed.

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Table 1

Maternal, birth and child characteristics by whether or not blood lead level (BLL) was detectable among 299 WHEALS participants with a two-year visit.

		Detectable BLL N=131 (43.8%)	Undetectable BLL N=168 (56.2%)	*P*
Maternal Characteristics				
Age at Delivery (years)		30.8±5.3	29.7±5.5	0.081
>High school education		107 (81.7%)	138 (82.1%)	0.92
Married		79 (60.3%)	109 (64.9%)	0.42
Smoking during pregnancy		11 (8.4%)	21 (12.5%)	0.25
Total household income <$40,000[a]		44 (39.6%)	50 (34.7%)	0.42
Race				0.007
	African-American	102 (77.9%)	103 (61.3%)	
	White	15 (11.4%)	40 (23.8%)	
	Other	14 (10.7%)	25 (14.9%)	
BMI at 1st prenatal care visit (kg/m^2)[b]		29.6±8.2	30.8±7.7	0.19
Maternal obesity[b]		47 (36.4%)	79 (47.0%)	0.067
House cleanliness[c]				0.032
	Below average	34 (26.9%)	24 (14.8%)	
	Average	59 (45.4%)	81 (50.0%)	
	Above average	34 (26.8%)	57 (35.2%)	
Newborn Characteristics				
Male		60 (45.8%)	99 (58.9%)	0.024
Gestational age at birth (weeks)[d]		38.9±1.5	38.8±1.8	0.51
Birth weight (kg)[e]		3310±544	3404±601	0.17
Birth weight Z-score[f]		−0.14±0.92	0.04±1.04	0.12
First Born		49 (37.4%)	81 (48.2%)	0.061
Child Characteristics at age 2 clinic visit				
Age at clinic visit (years)		2.2±0.2	2.2±0.3	0.86
Ever Breastfed		110 (85.3%)	126 (77.8%)	0.10
Weight Z-score		0.53±1.17	0.32±1.07	0.11
Height Z-score		0.57±1.06	0.61±1.02	0.77
BMI (kg/m^2)		16.4±1.5	16.9±1.7	0.009
BMI Z-score		−0.04 ± 1.09	0.28 ± 1.10	0.012
BMI percentile		49.0 ± 29.2	57.9 ± 28.7	0.009
BMI category				0.14
	Underweight (BMI<5th percentile)	10 (7.6%)	8 (4.8%)	
	Normal Weight (BMI=5th and <85th percentile)	103 (78.6%)	120 (71.4%)	
	Overweight (BMI=85th and <95th percentile)	7 (5.4%)	18 (10.7%)	
	Obese (BMI=95th percentile)	11 (8.4%)	22 (13.1%)	
Blood Lead Test Characteristics				

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	Detectable BLL N=131 (43.8%)	Undetectable BLL N=168 (56.2%)	*P*
Age at test (months)	15.1 ± 5.4	15.7 ± 5.7	0.41
Time between blood lead test and 2-year clinic visit (months)	11.6 ± 5.7	11.1 ± 6.4	0.51
BLL (μg/dL)	2.45 ± 2.53	N/A	---

Data are mean±standard deviation or N (%). P-value comparing those with and without detectable BLL.

BMI, body mass index

[a]n=44 with missing or refused income information;

[b]n=2 with missing data;

[c]n=10 missing data;

[d]n=3 with missing data;

[e]n=8 with missing data;

[f]n=10 with missing data

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Table 2

Association of having a detectable blood lead level (BLL) with body mass index (BMI) measures at age 2 years in WHEALS.

Delivery Mode	BMI=85th percentile RR (95% CI)	*P*	BMI Z-score β (95% CI)	*P*
Model 1				
Detectable BLL	0.58 (0.35, 0.96)	0.034	−0.32 (−0.57, −0.07)	0.012
Model 2				
Detectable BLL	0.57 (0.33, 0.98)	0.041	−0.35 (−0.60, −0.10)	0.008

Model 1 is unadjusted. Model 2 is adjusted for race, sex and birth weight Z-score.

RR, relative risk; CI, confidence interval; β, parameter estimate; se, standard error