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A comparison of blood and toenails as biomarkers of children's exposure to lead and their correlation with cognitive function.

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Abstract

This study sought to compare lead (Pb) concentrations in toenails and blood and to investigate the association of each biomarker with children's cognitive function. Toenails and whole blood samples were collected from 224 twelve-year-old children, and their full-scale intelligence quotient (FSIQ) was assessed using the Wechsler Intelligence Scale for Children–4th edition. Inductively coupled plasma-mass spectrometry was used to determine blood (BPb) and toenail (TPb) Pb concentrations. Log BPb and Log TPb were significantly correlated ($r^2 = 0.49$, $p < 0.001$). In unadjusted analyses, both log-transformed BPb and TPb were significantly associated with decreased FSIQ, but BPb accounted for approximately quadruple the FSIQ scores' variability than log-transformed TPb (model $R^2 = 0.12$ and $R^2 = 0.03$, respectively). After adjusting for neighborhood deprivation, caregiver intelligence (assessed with the Wechsler Abbreviated Scale of Intelligence–2nd edition), and child BMI, BPb remained significantly associated with decreased FSIQ, while TPb did not ($p = 0.16$). These results suggest that while concentrations of Pb in blood and toenails are correlated, TPb does not predict cognitive outcomes at these exposure levels. With

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Conflict of Interest.

The authors had no competing financial interests with relation to this work.

caution and in conjunction with BPb, TPb may be used as a population-based biomarker of Pb exposure.

Keywords

biomarker; lead; toenail; children's exposure

Introduction

Exposure to Pb, even at low-levels, is toxic to humans and has been consistently associated with worsened cognitive function in children (Baghurst et al., 1992; Bellinger et al., 1991; Bellinger et al., 1987; Bellinger et al., 1992; Dietrich et al., 1993; Dietrich et al., 1991; Reuben et al., 2017; Wasserman et al., 1997). In the early 1990s, both the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) set their levels of concern at a blood Pb (BPb) concentration of 10 µg/dL (CDC, 2012; WHO, 1995), but more recent evidence suggests that blood concentrations below this level are associated with cognitive deficits (Adler, 2005; Barbosa et al., 2005; Koller et al., 2004; Lanphear et al., 2005). This, along with the continuing decline in pediatric BPb levels, motivated both organizations to lower their definition of an elevated BPb level to 5 µg/dL (CDC, 2012; WHO, 2010). Indeed, in an international pooled analysis the largest fraction of IQ deficits were observed below 10 µg/dL (Adler, 2005) and suggested that there is no safe threshold for Pb exposure (Barbosa et al., 2005; Koller et al., 2004).

Recent widespread Pb exposure due to corrosion of the drinking water distribution system in Flint, MI, USA has highlighted the need for tools for surveillance of children's Pb exposure to aid in public health interventions (Hanna-Attisha et al., 2016). BPb is considered the gold-standard for assessing Pb exposure and is the most commonly used biomarker for population studies and as a clinical diagnostic test (Barbosa et al., 2005). In adults, the half-life of BPb is ~35 days (Rabinowitz et al., 1976; WHO, 1995), but it can persist in bone for decades (Lidsky and Schneider, 2003). Children undergo bone remodeling as they grow, resulting in the release of Pb into their blood (Gwiazda et al., 2005). Pb is repartitioned from bone to the blood more rapidly in children than adults. Additionally, it has been reported that the half-life of Pb in children's blood may be much longer than that in adults, at ~10 months (Manton et al., 2000). Thus, in children, BPb is a widely accepted biomarker for assessing total body burden of Pb.

Toenails have also been evaluated as a biological matrix to determine Pb exposure given that nails are formed in the nailbed, which has a blood supply. Pb concentrations in the nailbed blood supply are likely a major determinant of toenail Pb (TPb) concentrations and, therefore, may serve as a potential biomarker of Pb exposure (Rabinowitz et al., 1976). While there are relatively few studies of toenail growth rates, one small (n = 22) study found the average adult great toenail (whole nail) can reflect up to 10 months of exposure to some trace-elements (Yaemsiri et al., 2010). Another study indicates that collecting clippings from all 10 toenails represents an integrated period of exposure over 3–12 months (Longnecker et al., 1993). Toenails can be self-collected and are non-invasive compared to BPb, which

requires venipuncture (or in some situations capillary puncture) to be performed by a healthcare professional.

One previous study (Gulson, 1996), compared blood, urine, and toenail Pb in an adult man over a period of six months. The author concluded that toenails, compared to blood and urine, contained too much variation to serve as a reliable biomarker, and concluded that nails are unfit Pb biomarkers for non-exposed populations (Gulson, 1996). However, This study was limited in sample size (n=1) and its use of an adult. Due to the differing biological pathway of Pb in children (Gwiazda et al., 2005) and their susceptibility to worsened cognitive function as a result of Pb exposure (Baghurst et al., 1992; Bellinger et al., 1991; Bellinger et al., 1987; Bellinger et al., 1992; Dietrich et al., 1993; Dietrich et al., 1991; Wasserman et al., 1997), age is potentially a pertinent factor in evaluating toenails' effectiveness as a Pb biomarker. Although a comprehensive review (Sukumar, 2006) of nails as biomarkers found that age is not a significant factor in nail element levels, broadly, only one study (Hayashi et al., 1993) in the review investigated Pb specifically. This study found Pb levels varied considerably between individuals, sometimes due to age, sex, and season of collection (Hayashi et al., 1993). Despite concern over variability in nail Pb both within and across individuals, there are still relatively few studies concerning the efficacy of nails as a biomarker in children. Multiple studies have evaluated children's blood (Bellinger et al., 1991; Lanphear et al., 2005; Wasserman et al., 1997) and nail (Hussein Were et al., 2008; Oyoo-Okoth et al., 2010; Wilhelm et al., 1991) samples for Pb separately, but we are only aware of one previous study (Sanders et al., 2014) that has compared the Pb concentrations of blood and toenails in children. However, this study (Sanders et al., 2014) had a limited sample size (n=20), was conducted among exposed populations, and did not use cognitive function as a measure of actual impact. To our knowledge, our study is the only other one to compare blood and toenail Pb in children, and the only to correlate toenail Pb to cognitive function. Therefore, the objectives of this study were to compare TPb and BPb concentrations and examine the association of each biomarker with cognitive scores in a cohort of 12-year-old children.

Methods

Study design and subjects

Study participants were drawn from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a prospective cohort study of children and their caregivers residing in the Greater Cincinnati, Ohio metropolitan region (LeMasters et al., 2006; Ryan et al., 2005). Children enrolled in the CCAAPS cohort completed study visits at ages 1, 2, 3, 4, 7, and 12 years. The study was approved by the Institutional Review Boards of the University of Cincinnati, Cincinnati Children's Hospital Medical Center, and the New York State Department of Health. Participants and caregivers provided informed assent and consent, respectively, prior to participating in the age 12-year visit.

Cognitive testing and biospecimen collection and testing

All specimens and data included in the present analyses were collected at the age 12 study visit including direct assessment of child full-scale IQ using the Wechsler Intelligence Scale

for Children—4th edition (WISC-IV) and collection of whole blood and toenail samples. The Wechsler Intelligence Scale for Children-IV (WISC-IV) is a standardized, individually administered instrument for assessing the cognitive abilities of children ages 6–16 (Wechsler, 2003). Details regarding the test can be found in Wechsler (2003). Trained study staff administered the assessment in private rooms. A subset of CCAAPS participants completed a portion of the age 12 evaluation by mail and provided toenail samples.

Methods for blood lead analysis by ICP-MS have been described in detail previously (Palmer et al., 2006). Briefly, children's whole-blood samples were collected in 3 mL, pre-certified BPb collection tubes containing K₂EDTA, stored at 5° C, and shipped to the Wadsworth Center (New York State Department of Health, Albany, New York, USA) for analysis within six weeks of collection. Samples were analyzed for Pb using a Thermo Scientific XSeries 2 inductively coupled plasma-mass spectrometer (ICP-MS), with matrix-matched calibration (Palmer et al., 2006). Four levels of internal quality control (IQC) materials covering the range of human BPb levels expected were analyzed in each analytical run. All IQC samples were prepared in-house from whole blood obtained from Pb-dosed animals. Method accuracy was assessed throughout the study by analyzing National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 955c – Toxic Metals in Caprine Blood (NIST, Gaithersburg, MD). Method performance was monitored through successful participation in six external quality assessment schemes for trace elements that included BPb. The analysis was repeated for any BPb value >5 µg/dL to confirm the measurements. In addition, 2.5% of all blood specimens were randomly selected for re-analysis. The limit of detection (LOD), calculated according to IUPAC recommendations, reported for BPb was 0.072 µg/dL. The Wadsworth Center also provided a limit of quantitation (LOQ), which is calculated according to EPA guidelines (EPA, 1998), and is 0.240 µg/dL.

Children's toenails were collected with scissors and placed into envelopes. Nails were prepared and analyzed as we have previously described in detail (Unrine et al., 2019). Briefly, the nails were ultrasonicated for 10 minutes in a bath sonicator (Fisher Scientific, FS30) in polypropylene microcentrifuge tubes containing 1 mL trace-metal grade acetone, followed by 10 minutes in 1% (v/v) Citranox® acidic detergent, which is very low in metal content, followed by two repetitions with 18.2 MΩ cm⁻¹ deionized (DI) water. The nails were then placed in an oven at 60°C and dried to a constant mass. Nails that weighed more than 10 mg were digested in 15 mL metal-free polypropylene centrifuge tubes in a MARSXpress microwave digestion system (CEM, Matthews, NC, USA) by heating in 750 µL of ultra-pure HNO₃ (Aristar Ultra, BDH Chemicals) to 90°C and holding at that temperature for 10 minutes. This heating step was repeated with the addition of 250 µL of trace-metal grade H₂O₂ to each sample. Samples were then brought up to 15 mL with DI water and analyzed using ICP-MS (Agilent 7500cx, Santa Clara, CA, USA). Samples with masses below 10 mg were digested in 75 µL of nitric acid in fluoropolymer microcentrifuge tubes at 90 C for 2 days, then brought to 1.5 mL with DI water and transferred into a 15 mL metal-free centrifuge tubes for analysis. We used 10 µg/L Bi as an internal standard, and analyzed method blanks, duplicates, spike recovery samples, and standard reference materials (SRM; CRM #13, Human Hair, National Institute of Environmental Studies,

Tsukuba, Japan). Hair is the closest matrix match to nails currently available as an SRM, both being composed largely of keratin.

Statistical analysis

Both TPb and BPb were found to be log-normally distributed and transformed prior to additional analyses. We initially conducted descriptive analyses including calculating the Pearson correlation between TPb and BPb. Next, we examined the relationship between TPb and BPb using a linear regression model. Finally, we estimated the association between both measures of Pb exposure (TPb and BPb) and child full scale IQ in separate linear regression models, adjusting for *a priori* selected covariates including caregiver full-scale IQ assessed with the Wechsler Abbreviated Scale of Intelligence–2nd edition (WASI-2), body mass index (BMI) at age 12, and a measure of neighborhood-level deprivation based on census-tract level socioeconomic indicators (Brokamp et al., 2019) (https://github.com/cole-brokamp/dep_index). Descriptive statistics are expressed as mean and standard deviation. Data analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R (3.5.1; R Foundation for Statistical Computing).

Results

Baseline Characteristics

A total of 344 children and caregivers completed the age 12 study visit in-person and an additional 10 participants completed a portion of the age 12 visit by mail. Of these, 252 children provided toenail samples (247 in-person, 5 by mail) for analysis. An overview of the demographic, exposure, and other characteristics of the 252 participants with available toenail data is provided in Table 1. The majority of children who provided toenail samples were male (58.5%) and white (77.8%). Median (IQR) concentrations of Pb in toenails and blood were 0.66 (0.28) µg/g and toenails 0.46 (0.49) µg/dL, respectively.

Association Between TPb and BPb

Concentrations of Pb in toenails and blood were significantly and positively correlated ($r^2 = 0.49$, $p < 0.001$). Parameter estimates obtained from the linear regression model examining the association between log-transformed TPb and BPb also indicate that TPb is significantly associated with BPb ($\beta = 1.33$, 95% CI = 1.02 – 1.66) with approximately 24% of the variability in TPb explained by BPb concentrations (model $R^2 = 0.24$) (Figure 1).

Association between Pb Measured in Blood and Toenails and Childhood IQ

Both TPb and BPb were significantly associated with child FSIQ in unadjusted models ($p = 0.005$ and $p < 0.001$, respectively) (Table 2). After adjusting for caregiver IQ, community deprivation, and BMI, the association between BPb and FSIQ was attenuated but remained statistically significant ($p < 0.001$) gender was not statistically significant ($\beta = -13.15$, 95% CI = -20.42 – 5.88). After covariate adjustment the association between TPb and child IQ was no longer statistically significant ($p = 0.192$) (Table 2). Parameter estimates for the covariates used in the model are in Table 3.

Discussion

The results of our analyses demonstrate that, while Pb measured in toenails is correlated with BPb levels, the latter is more robust with respect to associated cognitive health effects. Few studies have evaluated using children's toenails as a biomarker for Pb exposure. A study in China with 317 children found a poor correlation between BPb and TPb with an r^2 value of 0.03, approximately ten times lower than in the present study (Wang et al., 2009). Interestingly, in the same study, the r^2 value for the relationship between BPb and spot urine Pb was 0.26, which is similar to our relationship between BPb and TPb. The BPb levels in that study were as high as about 4 $\mu\text{g}/\text{dL}$. A study in Vietnam (Sanders et al., 2014) of 20 children found a statistically significant correlation between TPb and BPb, with a Spearman's correlation coefficient of 0.65. Participants in that study included a population who lived near a site where used batteries were smelted to obtain Pb ingots. The children's BPb values ranged from 6.2 to 62.3 $\mu\text{g}/\text{dL}$, thus the study may not be relevant to typical exposures typically observed in the United States. Other studies have analyzed children's toenails for Pb, but did not compare it to other biomarkers for reference (Carneiro et al., 2011; Hussein Were et al., 2008; Oyoo-Okoth et al., 2010; Wickre et al., 2004), or did not compare it to blood, the standard biomarker for Pb (Priya and Geetha, 2011; Wilhelm et al., 1991; Wilhelm et al., 1994).

There is a need for tools to evaluate chemical exposures in large populations and help identify geographic areas with the greatest exposure for public health interventions (Hanna-Attisha et al., 2016). Toenails offer several potential advantages as a biomatrix including self-collection, shipped to labs by regular mail, and stored at room temperature. In contrast, collecting blood is more invasive, requires phlebotomy (or capillary puncture), and shipping must follow protocol that include biohazards. However, in our study TPb explained less than 25% of the variation in concentrations measured using the gold-standard biomarker, BPb. One possible explanation for this discordance is the variable time-frame of exposure integrated by the biomarkers. Toenails take approximately 10 months to grow in adults (Yaemsiri et al., 2010) and therefore clippings reflect the Pb body burden from up to a year prior to blood collection. In contrast, BPb levels reflects body burden at the time of collection. Although not conducted with Pb, one study found the reproducibility of toenail Se and As, for which toenails reflect exposure levels, have Spearman correlation coefficients of 0.48 and 0.54 for repeated specimens collected from the same subject, respectively. Other elements' within subject correlations varied from 0.26 (Cu) to 0.58 (Zn) (Garland et al., 1993). Although toenails may be a useful biomarker for some trace elements, random within-person variability may result in attenuation in measures of association in health studies. This is possibly reflected in the variance of the structure of the data as the coefficient of variation for BPb and TPb was 64% and 180%, respectively.

Interestingly, we did observe a significant decrease in IQ scores associated with BPb with the majority of the blood concentrations below 3.5 $\mu\text{g}/\text{dL}$, however the association with TPb levels failed to reach statistical significance. These findings add to the literature suggesting BPb levels < 3.5 $\mu\text{g}/\text{dL}$, which has been suggested as the new definition of an elevated BPb level for young children in the US, are associated with decreased cognitive function in children. For example, the least squares mean FSIQ score for the lowest exposure

concentrations of around 0.1 µg/dL was approximately 118, while the least squares mean FSIQ score for the 3.16 µg/dL was only approximately 90.

Conclusions, Limitations and Future Directions

There are some limitations to our study, including the cross-sectional nature of this analysis. To further evaluate the utility of TPb as a surveillance tool for research purposes, future studies should have a longitudinal design to account for differences in integrated exposure time between BPb and TPb. It is possible that TPb reflects exposure up to a year prior to sample collection. The growth rate of children's toenails has not been evaluated and would help to refine the exposure window for which TPb could be indicative. A larger sample size may also result in a statistically significant correlation between TPb and cognitive scores. In conclusion, our study suggests that Pb is deposited and measurable in toenails, though the uncertainty regarding within-person variability, toenail growth rates, and other factors requires additional research before TPb is considered a reliable biomarker for use in Pb exposure studies.

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Highlights

- Toenails may be useful for surveillance of children's lead exposure because they can be self-collected.
- Information on utility of toenails as a biomarker of children's lead exposure is limited.
- Blood and toenail lead were correlated in a cohort of 12 year old children from Cincinnati.
- Blood lead was correlated with cognitive scores but toenail lead was not.

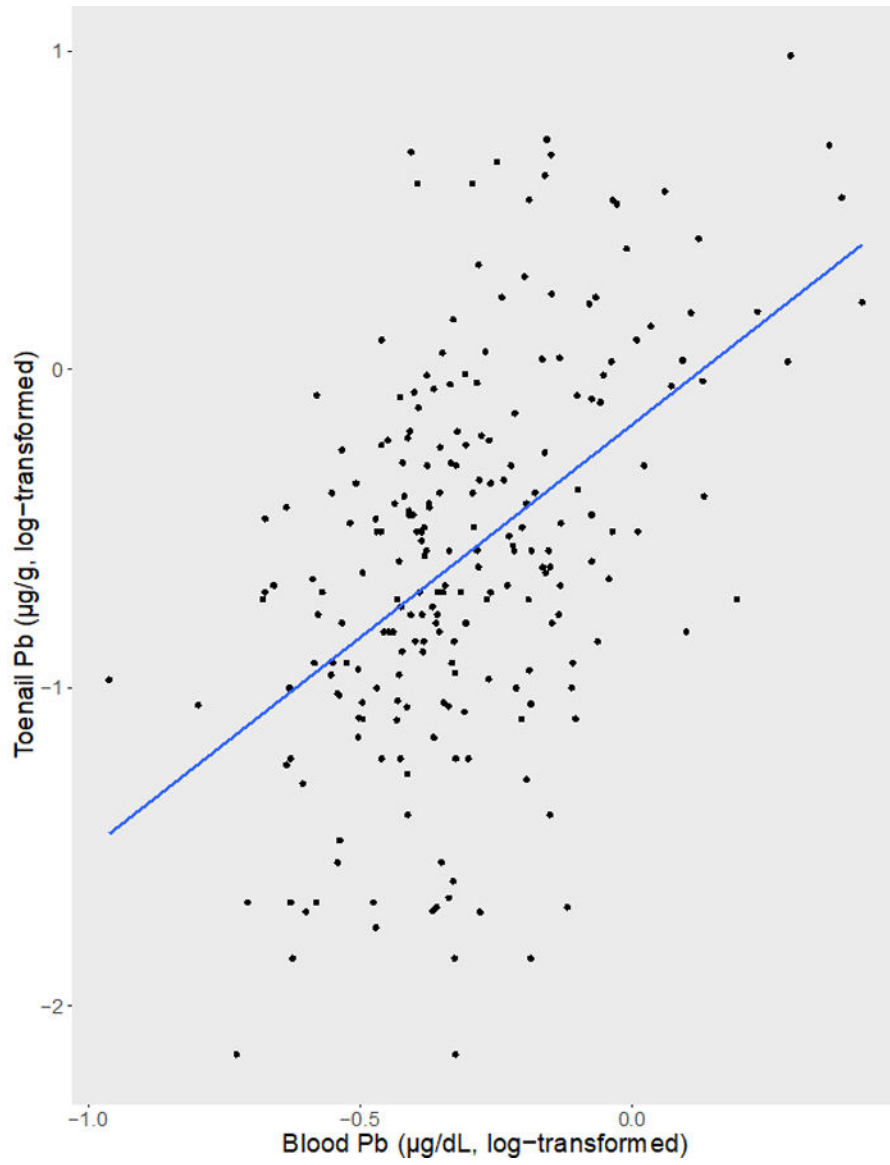


Figure 1. Linear Association Between log-transformed Blood Pb and Toenail Pb Concentrations.

Table 1.

Descriptive statistics broken down by gender and race. SD = standard deviation.

		Overall	Male	Female
	n^I	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	247	12.1 (0.80)	12.1 (0.80)	12.2 (0.80)
BPb (µg/dL)	224	0.57 (0.37)	0.64 (0.43)	0.47 (0.21)
TPb (µg/g)	252	0.66 (1.17)	0.71 (1.30)	0.57 (0.95)
Full-scale IQ (WISC-IV)	241	101.6	101.0 (15.5)	102.4 (14.2)
Caregiver IQ (WASI-2)	239	105.4 (13.4)	104.7 (14.1)	106.4 (12.3)
BMI	244	20.7 (5.2)	20.1 (5.2)	21.6 (5.2)
		Overall	White	Black / Mixed Race
	n^I	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	247	12.1 (0.80)	12.2 (0.82)	12.1 (0.73)
BPb (µg/dL)	224	0.57 (0.37)	0.51 (0.30)	0.76 (0.5)
TPb (µg/g)	252	0.66 (1.17)	0.55 (0.92)	1.00 (1.75)
Full-scale IQ (WISC-IV)	241	101.6	105.3 (13.4)	89.0 (13.0)
Caregiver IQ (WASI-2)	239	105.4 (13.4)	108.7 (11.5)	94.1 (13.6)
BMI	244	20.7 (5.2)	19.9 (4.8)	23.5 (5.7)

^I Number of participants with available information. Total does not sum to 252 due to incomplete data available for some participants. 224 individuals had both BPb and TPb measurements.

Table 2.

Unadjusted and adjusted associations between Pb measured in blood and toenails and child IQ.

Matrix	Unadjusted Association (β^2 , 95% CI)	Adjusted ¹ Association (β^2 , 95% CI)
Blood	-23.45 (-31.92 -14.98)	-13.15 (-20.42 - 5.88)
Toenail	-4.47 (-7.57 - 1.37)	-1.70 (-4.27 - 0.862)

¹Adjusted for caregiver IQ, community deprivation index, and BMI

²Parameter estimates for a log₁₀ change in exposure (i.e. a 10-fold increase in Pb concentrations).

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Table 3.

Parameter estimates for co-variates in the multiple regression model.

Matrix	Covariate	Parameter Estimate	P-value
Blood	Caregiver IQ	0.325	<0.001
	Deprivation Index	-17.7	0.001
	BMI	-0.849	<0.001
Toenail	Caregiver IQ	0.395	<0.001
	Deprivation Index	-17.6	0.001
	BMI	-0.745	<0.001

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