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Environmental lead exposure is associated with neurocognitive dysfunction in children with chronic kidney disease

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Abstract

Background—Environmental lead exposure is associated with cognitive impairment in healthy children, with deficits seen in intelligence quotient (IQ), attention, and behavior. Neurocognitive dysfunction is also a well-described complication among children with chronic kidney disease (CKD). The objective was to evaluate the association between blood lead levels (BLL) and performance on neurocognitive assessments in a cohort of children with CKD.

Methods—Cross-sectional study of children with mild to moderate CKD from the Chronic Kidney Disease in Children (CKiD) multicenter prospective cohort study. The primary exposure was BLL. The primary outcome was performance on age-specific neurocognitive assessments evaluating IQ, executive functioning, attention, hyperactivity, and behavior. Multivariable linear regression was used to evaluate the association between BLL and neurocognitive performance, adjusted for key sociodemographic and clinical variables.

Results—A total of 412 subjects were included with median age 15.4 years, median estimated GFR 39 mL/min/1.73^2, median BLL1.2 mcg/dL, and median IQ score 99. In multivariable linear regression, higher BLL was associated with significantly lower IQ score (− 2.1 IQ points for every 1-mcg/dL increase in BLL, $p = 0.029$). Higher BLL was associated with worse scores on the Conners' Continuous Performance Test II Variability T-Score, a measure of inattention (+ 1.8 T-Score points for every 1-mcg/dL increase in BLL, $p = 0.033$).

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The CKiD protocol has been reviewed and approved by the institutional review boards of each participating center. All participants and/or guardians provided written informed consent.

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Conclusions—Low-level lead exposure is associated with significantly lower IQ and more inattention in children with CKD, a population already at high risk for neurocognitive dysfunction. Universal screening for elevated BLL should be considered for all children with CKD at age 12–24 months.

Keywords

Chronic kidney disease; Neurocognition; Lead; Heavy metals; Children

Introduction

Environmental lead exposure is a well-known cause of neurocognitive dysfunction in children [1–10]. Increasing evidence has demonstrated that even low-level lead exposure can have significant effects on cognition and behavior. In 1991, the Centers for Disease Control (CDC) lowered the blood lead level (BLL) of concern from 30 to 10 μg/dL in response to studies that showed that BLLs as low as 10 μg/dL were associated with adverse neurocognitive outcomes [11]. More recent studies have demonstrated neurocognitive abnormalities including impairments in academic achievement, verbal skills, impulsivity, attention, and behavior even among children with peak BLLs less than 10 μg/dL [2, 7, 12–18]. Therefore, the US Environmental Protection Agency considers no BLL safe for children [19]. Children with BLLs requiring intervention are now identified using the reference value corresponding to the 97.5th percentile of BLL distribution in US children age 1–5 years from the National Health and Nutrition Examination Survey (NHANES), which is currently 5 μg/dL [20].

Children with chronic kidney disease (CKD) are already at high risk for neurocognitive dysfunction. Impairments in intelligence quotient (IQ), verbal abilities, memory, attention, inhibitory control, and executive function have all been reported in this population [21–24]. Multiple factors have been associated with neurocognitive dysfunction in children with CKD including severity of kidney disease, hypertension, and psychosocial factors such as depression, stress, and school absences [21, 23–30].

Despite the known contributions of lead and kidney disease to cognition, to our knowledge, there are no prior studies evaluating the contribution of lead toxicity to neurocognitive dysfunction in children with CKD. Given that children with CKD are already vulnerable to neurocognitive deficits, we hypothesized that these children would be at even higher risk of lead-associated neurotoxicity. Using a large cohort of children with CKD, we sought to determine if lead is associated with neurocognitive dysfunction in this population.

Methods

Study population

The Chronic Kidney Disease in Children (CKiD) study is a prospective cohort study of CKD in children being conducted at 46 centers in North America. Eligibility criteria for enrollment include age 1 to 16 years and estimated glomerular filtration rate (eGFR) of 30 to 90 mL/min/1.73 m^2, calculated using the bedside CKiD equation [31]. Exclusion criteria

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include solid organ, bone marrow/stem cell transplant, cancer, or HIV. Full details of the CKiD protocol have been described previously [32].

Measures

BLLs were measured by high-resolution inductively coupled plasma mass spectrometry at the University of California, Santa Cruz, Environmental Toxicology Laboratory (Smith DR). Samples were analyzed on an Element XR inductively coupled plasma mass spectrometer (Thermo Scientific, West Palm Beach, FL, USA) using standardized protocols including confirmation that storage materials were not contaminated with background lead. No samples were below the analytical limit of detection (< 0.1 μg/dL). Accuracy was assessed using National Institute of Standards and Technology (NIST; Gaithersburg, MD, USA) standard reference materials (SRMs). Analyses using SRMs reflecting blood lead levels of 1.6 μg/dL and 25.3 μg/dL had percentage relative standard deviations (%RSDs) of 4.6 and 5.5, respectively. We assessed reproducibility by (a) analyzing replicate samples at intervals throughout the same analytic run, (b) analyzing samples in triplicate in the same run, and (c) analyzing replicate samples in separate runs. Percentage RSD for all reproducibility determinations was < 2.5%.

Participants had BLL measured at visit 2, visit 4, or visit 6, generally corresponding to 2, 4, or 6 years after study entry, respectively. For participants with more than one BLL measured, the BLL obtained most proximal to neurocognitive testing was used (defined as concurrent BLL). All BLLs were obtained prior to neurocognitive testing. A battery of age-specific neurocognitive assessments was administered at visit 3, 5, 7, or 9 after study entry. The last available neurocognitive results were used in order to evaluate long-term effects of lead toxicity on neurocognition.

Full-scale IQ was measured using age-appropriate assessments (Mullen Scales of Early Learning for subjects 12–29 months, Wechsler Preschool and Primary Scale of Intelligence-Third Edition for subjects 30 months to 5 years, and Wechsler Abbreviated Scale of Intelligence for subjects 6–18 years). Attention regulation was assessed with the Conners' Kiddies Continuous Performance Test (K-CPT) (subjects 4–5 years) or Conners' Continuous Performance Test-II (CPT-II) (subjects 6 years and older). The CPT-II is a computerized measure of attention that requires the individual to touch the mouse or space bar in conjunction with visual stimuli that are presented at the rate of about one per second over approximately 14 min. Scores include omission and commission errors, correct detection rate, response variability, and reaction time. Both the K-CPT and the CPT-II provide estimates of sustained attention and inhibitory control. Executive functioning was assessed with the Delis-Kaplan Executive Function System Tower Subset (subjects > 6 years) and the Behavior Rating Inventory of Executive Functions (BRIEF) (parent-reported for preschool version BRIEF-P for subjects 2–5 years and BRIEF for subjects 6–18 years, or self-reported adult version BRIEF-A for subjects 18 years and older). The BRIEF is a parent or self-completed scale that provides ratings on metacognition, behavior regulation, and overall executive functioning. Behavioral symptoms were assessed using the parental rating scales of the Behavior Assessment System for Children Second Edition (BASC-2). Components of the BASC-2 include externalizing and internalizing problem composite scores, adaptive

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skills, and scales of hyperactivity and attention. All of the tasks were administered/supervised by a licensed psychologist.

Data analysis

Demographic and clinical characteristics of the study population were assessed using means with standard deviations (SD) for normally distributed continuous variables, medians with interquartile ranges (IQR) for non-normally distributed continuous variables, or frequencies with percentages for categorical variables. To assess the association between lead and neurocognitive performance, multiple linear regression was performed for each neurocognitive measure, with test score as the dependent variable and BLL in μg/dL as a continuous variable as the main explanatory variable. Based on prior studies of neurocognitive dysfunction in children with CKD, we a priori defined a set of covariates to include in the analyses. Key sociodemographic variables included age, sex, race, poverty (defined based on income and family size using the 2009 Poverty Guidelines published by the United States Department of Health and Human Services) [33], and maternal education (categorized as high school education, some college, or college and more). Maternal education was included because this has previously been shown to be associated with cognition in children with CKD [23]. CKD-related variables included CKD stage, CKD duration, glomerular versus non-glomerular diagnosis, hypertension (defined as systolic or diastolic blood pressure ≥ 95th percentile for age/sex/height or self-reported hypertension with use of an anti-hypertensive medication), proteinuria (categorized as significant if urine protein:creatinine ratio was > 0.2 and < 2 mg protein/mg creatinine or nephrotic if urine protein/creatinine ratio was ≥ 2 mg protein/mg creatinine), and anemia (defined as hemoglobin < 5th percentile for age/sex/race). Given the high rate of prematurity and abnormal birth history in the CKiD cohort, a composite variable of abnormal birth history was used to include any subject with premature birth, low birth weight, or was small for gestational age. Time-varying covariate data such as age, eGFR, and laboratory studies were reported from date of neurocognitive testing. Time-fixed covariate data such as CKD diagnosis, race, ethnicity, income, and maternal education were reported from the study entry visit. Analyses were conducted using Stata, version 15.1 (Statacorp, College Station, Texas). A p value of < 0.05 was the threshold for statistical significance.

Results

Sample characteristics

The study sample included 412 participants from the CKiD cohort who had at least one BLL measurement. All subjects had BLL measured prior to neurocognitive testing. Mean time between BLL measurement and neurocognitive testing was2.3 years (SD 1.4). Median BLL was 1.2 μg/dL (range 0.1 to 5.1 μg/dL). Sociodemographic and clinical variables are summarized in Table 1. Median age was 15.4 years, 60% were male, 68% were Caucasian, 14% were Hispanic ethnicity, and 23% met criteria for poverty. Median estimated GFR was39.0 mL/min/1.73 m^2, median CKD duration was 13.6 years, 84% had non-glomerular CKD diagnosis, 31% had abnormal birth history, 42% had hypertension, 18% had nephrotic-range proteinuria, and 37% were anemic.

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Results of neurocognitive testing are summarized in Table 2. Mean IQ score was 98 (SD 16). Eighteen percent of subjects scored more than one SD below the normative mean value for IQ. A total of 27–39% of subjects scored more than one SD above the normative mean values for performance on the K-CPT or CPT-II (with higher scores reflective of worse ratings of performance on attention and inhibitory control). Thirty percent of subjects scored more than one SD above the normative mean on the BRIEF (with higher scores reflective of worse performance on assessments of executive functioning). A total of 24–32% of subjects scored more than one SD above the normative mean on the BASC-2 measures of overall behavior, hyperactivity, and attention (with higher scores reflective of more impaired performance), and 22% scored more than one SD below the normative mean on the adaptive composite (with higher scores reflective of more intact performance on assessments of adaptability).

Association between blood lead levels and neurocognitive results

Table 3 shows results of multivariable linear regression analysis evaluating the association of BLL and full-scale IQ score. Every 1-μg/dL increase in BLL was associated with a 2.1 lower IQ score (95% CI − 3.9 to − 0.2), after adjustment for both sociodemographic and CKD-related variables. Other variables that were significantly associated with lower IQ score included female sex, lower maternal education, abnormal birth history, and nephrotic-range proteinuria. Other markers of CKD severity including CKD stage, duration, glomerular diagnosis, hypertension, and anemia were not associated with IQ score.

Table 4 shows results of multivariable linear regression analysis evaluating the association of BLL and CPT variability score. Higher variability score is a marker of problems with sustained attention and attention regulation. Every 1-μg/dL increase in BLL was associated with a 1.8 increase (i.e., worse performance) in the CPT variability T-score (95% CI 0.2 to 3.5). Of other sociodemographic or clinical variables, only longer CKD duration was associated with variability score, with longer CKD duration associated with slightly better scores on attention.

In univariable analyses, higher BLL was associated with poorer performance on ratings of the global executive composite score from the BRIEF ($\beta = 1.7$, $p = 0.019$) and worse scores on parental ratings of total behavior problems ($\beta = 1.8$, $p = 0.004$), externalizing problems composite ($\beta = 2.1$, $p = 0.001$), adaptive skills composite ($\beta = -3.1$, $p = < 0.001$), hyperactivity scale ($\beta = 1.7$, $p = 0.012$), and attention scale ($\beta = 2.2$, $p = 0.001$) on the BASC-2. These associations did not remain statistically significant after adjusting for other sociodemographic and clinical variables.

Discussion

In this cohort of children with CKD, we found that higher BLL was associated with significantly lower IQ score and poorer performance on assessments of attention, adjusted for known sociodemographic and clinical contributors to neurocognitive dysfunction. Notably, the median BLL in this population was only 1.2 μg/dL, well below the current national reference value for BLL of 5 μg/dL. Although we do not have a control group in this study and the sample size is relatively small, the point estimate for the magnitude of the

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impact of lead on IQ in this population of children with CKD is of greater magnitude in comparison to historical data from healthy children. In this study, we have identified a potentially modifiable risk factor for neurocognitive dysfunction in this high-risk population.

The mechanism of lead exposure leading to neurocognitive dysfunction is likely multifactorial [34, 35]. Children who are exposed to environmental lead may be at higher risk of toxicity because a greater proportion of ingested lead is absorbed from the gastrointestinal tract, and the developing nervous system may be more susceptible to neurotoxins [34, 36]. Lead has a long half-life in the body due to sequestration in bone, so BLL can underestimate the true burden of lead exposure. This may explain why childhood lead exposure has long-term neurologic consequences [34] and may contribute to the neurologic vulnerability in children with CKD.

Neurocognitive dysfunction is a well-described complication among children and adults with CKD. Deficits have been demonstrated across a range of neurocognitive domains including IQ, memory, attention, inhibitory control, and executive functioning [21–24, 37]. In the CKiD study, 21–40% of children with mild to moderate CKD were identified as being at risk for some form of neurocognitive dysfunction [23, 38]. Neurocognitive deficits are also common in adults with CKD, especially among adults with advanced CKD and end-stage kidney disease [39–42]. Longer duration of disease, increased severity of disease, and younger age at CKD onset have been associated with a higher risk of neurocognitive dysfunction among children with CKD [23, 25, 43]. Hypertension, including ambulatory hypertension and increased blood pressure variability, has also been identified as a potential contributor to neurocognitive dysfunction in this population [24, 28, 44].

There have been several large cohort studies of healthy children evaluating the impact of environmental lead exposure on IQ. In a cohort of 148 children, Bellinger et al. found that higher BLL at 24 months was associated with lower full-scale IQ at age 10 years; for every 10-μg/dL increase in BLL, IQ declined by 5.8 points [7]. Canfield et al. reported a cohort of 172 children who had BLLs measured at multiple time points between ages 6 and 60 months. For every 10-μg/dL increase in lifetime average blood lead concentration, IQ declined by4.6 points. In a subgroup of 101 children whose maximum BLL was consistently below 10 μg/dL, every 1-μg/dL increase in lifetime average lead concentration was associated with a 1.4 decline in IQ, providing further evidence that even low-level lead exposure can have significant effects on neurocognition [13]. In 2005, Lanphear et al. published a study on low-level lead effects on IQ among 1333 children pooled from seven international population-based longitudinal cohort studies. As BLL increased from 2.4 to 30 μg/dL, there was a 6.9 point decline in IQ (95% CI 4.2–9.4). However, as lead increased from 2.4 to 10 μg/dL, IQ declined by 3.9 points (95% CI 2.4–5.3), indicating that the magnitude of lead-associated decline in IQ was greater at lower level lead exposure [14]. A study of over 1000 New Zealand children showed that for every 5-μg/dL increase in BLL as a child, there was a 1.61 point decline in IQ score as an adult (95% CI 0.7−2.5) [45]. Environmental lead exposure has also been associated with increased risk of attention deficit and hyper-activity disorder (ADHD) [46–50].

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In our study, we found that for every 1-μg/dL increase in BLL, IQ score decreased by 2.1 points, in comparison to a range of 0.3–1.4 reported in the cohorts of healthy children described above. Although we cannot make direct comparisons to these previously published cohorts, and we understand the statistical limitations inherent in studying a relatively smaller cohort of children selected for a different observational purpose, there is a suggestion that the magnitude of the effect of lead on IQ may be higher in this population of children with CKD. We hypothesize that children with "neurologic vulnerability" due to chronic diseases such as CKD may be more susceptible to the toxic effects of lead (and perhaps other toxins) compared to healthy children. We also found that female sex was associated with lower IQ. Although this has not been described in studies of healthy children, this association has been found in previous studies on neurocognition in the CKiD cohort [23, 28]. There is not an obvious biological explanation for this finding; it is possible that there is some residual confounding by diagnosis. We plan to further explore the effect of sex on neurocognition in future studies in children with CKD. We also found that longer duration of CKD was associated with slightly better CPT variability scores. However, the effect size was small and may not be clinically significant.

In addition to the CKD population, the impact of lead on cognition may extend to other groups of children with chronic disease in whom neurocognitive dysfunction is also common. Long-term neurocognitive deficits have been described in a variety of pediatric chronic diseases including cancer, sickle cell disease, congenital heart disease, and type 1 diabetes mellitus [51]. In the example of sickle cell disease, there have been prior reports of peripheral neuropathy occurring in the context of lead exposure. The authors postulated that children with sickle cell disease may have an increased risk of developing neuropathy after exposure to lead [52, 53]. Given the high risk of neurocognitive dysfunction in other children with chronic diseases, it is important to characterize the contribution of lead, as it would be a modifiable risk factor for adverse neurocognitive outcomes.

There are several limitations to this study. First, all patients in this study had CKD and there was no control group of healthy children. This was a cross-sectional study; therefore, causality cannot be determined. In addition, there was variability in the age at which BLL was measured, age at neurocognitive testing, and interval between the time of BLL measurement and neurocognitive testing. However, lead is known to have a very long half-life, and neurocognitive deficits persist for many years. We used concurrent BLL for patients with multiple lead measurements, as this is reflective of chronic lead exposure and has previously been highly correlated with IQ [14]. Finally, prenatal exposure to lead can impact neurocognitive outcomes, and data on maternal lead exposure was not available in this dataset.

Conclusion

Very low-level environmental lead exposure is associated with significantly lower IQ and problems with attention regulation in children with CKD. The impact of lead neurotoxicity may be greater in children with CKD compared to healthy children. The American Academy of Pediatrics (AAP) and the CDC currently recommend that asymptomatic children should be screened for elevated BLL according to federal, local, and state requirements. Targeted

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screening is recommended for children who live in communities with ≥ 25% of housing built before 1960 or ≥ 5% of children aged 12–24 months with BLL ≥ 5 μg/dL [54]. Based on the results of this study, we would suggest that clinicians consider universal lead screening for all children with CKD at age 12–24 months. In addition, children with CKD who are found to have elevated BLL should be followed closely for neurocognitive dysfunction. Interventions for treating lead exposure should follow the AAP Recommendations on Medical Management of Childhood Lead Exposure and Poisoning [55]. Future studies should focus on evaluating the association of lead and neurocognition in other populations of children with chronic diseases who may also be at higher risk of neurologic complications. Although the neurocognitive complications associated with CKD and other chronic childhood diseases may not be preventable, environmental lead exposure may be a modifiable risk factor that could lead to improvements in long-term neurocognitive outcomes.

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Table 1

Demographic and clinical characteristics

Variable	***N* = 412 subjects** ***N* (%) or median (IQR)**
Age, years	15.4 (11.9, 18.6)
Male sex	249 (60%)
Race	
Caucasian	282 (68%)
African American	68 (17%)
Other	21 (5%)
More than one excluding African American	23 (6%)
More than one including African American	18 (4%)
Hispanic	56 (14%)
Poverty[a]	
Yes	93 (23%)
No	310 (75%)
Missing	9 (2%)
Maternal education	
High school	161 (39%)
Some college	110 (27%)
College and more	129 (31%)
Missing	12 (3%)
Lead (mcg/dL)	1.2 (0.8, 1.8)
Estimated GFR, mL/min/1.73 m^2	39.0 (27.0, 54.3)
CKD Stage	
Stage 1	4 (1%)
Stage 2	64 (16%)
Stage 3	213 (52%)
Stage 4	126 (31%)
Stage 5	3 (1%)
Missing	2 (0.5%)
CKD duration, years	13.6 (9.9, 16.5)

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Variable	*N* = 412 subjects *N* (%) or median (IQR)
Etiology of CKD	
Non-glomerular	344 (84%)
Glomerular	68 (17%)
Abnormal birth history (premature, small for gestational age, or low-birth weight)	126 (31%)
Hypertension (SBP or DBP ≥ 95th percentile or self-reported hypertension plus antihypertensive use)	175 (42%)
Proteinuria	
None (UPC < 0.2)	113 (27%)
Significant (UPC 0.2 to < 2)	202 (49%)
Nephrotic (UPC ≥ 2)	76 (18%)
Missing	21 (5%)
Hemoglobin, g/dL	12.7(11.5, 13.8)
Anemia (hemoglobin < 5th percentile for age, sex, race)	
No	237 (58%)
Yes	152 (37%)
Missing	23 (6%)

[a]Based on 2009 poverty guidelines, http://aspe.hhs.gov/poverty/09poverty.shtml

GFR glomerular filtration rate, *CKD* chronic kidney disease, *UPC* urine protein to creatinine ratio, mg protein/mg creatinine

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Table 2

Neurocognitive testing results

Neurocognitive variable	*N*	Mean (SD)	*N* (%) at risk[a]
Full-Scale IQ	409	98 (16)	75 (18)
K-CPT or CPT-II			
Errors of omission	352	53 (16)	123 (35)
Errors of commission	355	52 (11)	140 (39)
Hit reaction	355	47 (12)	97 (27)
Correct detection	355	52 (11)	120 (34)
Variability scaled score	354	51 (12)	138 (39)
BRIEF Global Executive Composite	394	53 (12)	118 (30)
D-KEFS Tower Total Achievement Score	357	10 (3)	24 (7)
BASC-2 (parent report)			
Behavioral Symptoms Summary	369	49 (10)	89 (24)
Externalizing Problems Summary	367	49 (10)	87 (24)
Internalizing Problems Summary	368	49 (9)	92 (25)
Adaptive Behavior Summary	368	49 (11)	80 (22)
Hyperactivity Clinical Scale	372	50 (10)	101 (27)
Attention Clinical Scale	372	51 (10)	118 (32)

[a]Percent of subjects > 1 or < 1 standard deviation below normative mean. Please note that the directionality of the scores is different for each measure, with higher scores on several tests reflecting more intact performance and higher scores on other tests reflecting more impaired performance. Specifically, IQ scores are reported as standard scores with means of 100 and standard deviation of 15; higher scores reflect more intact performance. CPT and BRIEF scores are reported as T-score with a mean of 50 and SD of 10; higher scores reflect more impaired abilities. D-KEFS scores are reported as scaled scores, with a mean of 10 and SD of 3; higher scores reflect more intact performance. BASC-2 scores are reported as T-scores with a mean of 50 and SD 10. Higher scores reflect more impaired performance, except for the adaptive composite where higher scores reflect more intact performance

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Table 3

Multivariable linear regression model of full-scale IQ score ($N = 378$)

	Coefficient	*P* value	95% CI
Lead, mcg/dL	−2.1	0.029 *	−3.9, −0.2
Female sex	−4.2	0.008 *	−7.3, −1.1
Age	0.3	0.24	−0.2, 0.9
Non-white race	−2.3	0.18	−5.7, 1.0
Poverty	−3.8	0.05	−7.7, 0.04
Maternal education			
High school	Ref		
Some college	4.7	0.013 *	1.0, 8.4
College and more	11.6	< 0.001 *	7.9, 15.2
CKD stage	0.9	0.50	−1.7, 3.4
CKD duration	0.01	0.96	−0.5, 0.5
Glomerular CKD diagnosis	−1.0	0.70	−6.3, 4.2
Abnormal birth history	−6.6	< 0.001 *	−9.8, −3.4
Proteinuria			
None	Ref		
Significant	−1.0	0.60	−4.6, 2.7
Nephrotic	−5.1	0.042 *	−10.1, −0.2
Hypertension	0.1	0.97	−2.9, 3.1
Anemia	−2.2	0.21	−5.6, 1.2

* $p < 0.05$

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Table 4

Multivariable linear regression model of CPT variability score ($N = 329$)

	Coefficient	*P* value	95% CI
Lead, mcg/dL	1.8	0.033*	0.2, 3.5
Female sex	1.3	0.38	−1.5, 4.1
Age	0.2	0.51	−0.3, 0.7
Non-white race	0.4	0.82	−2.7, 3.5
Poverty	3.2	0.08	−0.3, 6.7
Maternal education			
High school	Ref		
Some college	0.2	0.90	−3.1, 3.5
College and more	−0.5	0.77	−3.8, 2.8
CKD Stage	−0.8	0.51	−3.1, 1.5
CKD duration	−0.5	0.024*	−1.0, −0.1
Glomerular CKD diagnosis	−2.5	0.29	−7.3, 2.2
Abnormal birth history	2.9	0.05	−0.01, 5.9
Hypertension	−1.0	0.46	−3.7, 1.7
Proteinuria			
None	Ref		
Significant	0.9	0.60	−2.4, 4.2
Nephrotic	2.6	0.26	−1.9, 7.1
Anemia	0.1	0.96	−3.0, 3.1

* $p < 0.05$