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Effect of early lead exposure on the maturation of children's postural balance: A longitudinal study

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Abstract

This prospective study investigated the impact of early exposure to lead on the maturation of children's postural balance. The effect of lead exposure on age-associated maturation of postural balance was investigated on 91 children from the Cincinnati Lead Study (CLS) with a 5-year geometric mean lead concentration in blood of 11.66 μg/dL (range 3.89–28.33 μg/dL) by re-assessing their postural balance approximately every 20 months starting at mean age of 6.6 years through mean age of 12.1 years. The results presented in this paper provide evidence that low to moderate lead exposure in early childhood has a measurable and statistically significant impact on the maturation of postural balance. In comparison to less exposed children, of those in the higher lead group showed an impaired postural balance response. The results from this study suggest that children with early childhood lead exposure may need additional time to approach (or "catch up" with) their maturational postural balance status. As these subjects are now adults in their early to mid-twenties, poor postural balance may impact their daily living tasks and pose a higher risk of potential injuries at home and work.

Keywords: Lead effects; Postural balance; Quantitative posturography; Children; Neurotoxicology

1. Introduction

The purpose of this study was to determine whether subjects with higher early childhood blood lead (PbB) levels would experience a different time-dependent maturation of their postural balance than those with lower early childhood PbB. The main hypothesis for this study was that, in comparison to early childhood lower level lead (Pb) exposure, children with higher PbB levels will experience a permanent deficit in and/or a delayed maturation of postural balance as assessed by the microprocessor-based quantitative posturography technique [8].

Several studies have reported that low level Pb exposure during early childhood is associated with neuromotor dysfunction such as unsteadiness, clumsiness and fine motor deficits [3,8,9,17,42]. Most of these studies have shown that neuromotor impairment is identified at PbB levels lower than 15 μg/dL. The long-term persistence of such Pb-associated effects on neuromotor function has been reported in even fewer studies. Since Pb has a long half-life (decades) in the skeleton [28,34,43], it is reasonable to assume that it will continue to be resorbed into the blood and tissue compartments and its detrimental effects will persist [1]. Neurocognitive effects have been shown to be persistent at later stages in life [18,20,36]. White et al. [44] followed up 34 Pb-poisoned children after 50 years who were originally treated at age 4 years. The authors

Abbreviations: Pb, lead; PbB, blood lead; EO, eyes open on force platform; EC, eyes closed on force platform; FO, eyes open on 4-in.-thick foam pad placed on the force platform; FC, eyes closed on 4-in.-thick foam pad placed on the force platform; AVHEM5, mean hemoglobin for 1 to 5 years; AVTIBC, mean total iron binding capacity for 1 to 5 years of life; ACTVSCOR, total number of sporting activities participated in; BMI, body mass index; MEPSL and MEPSR, minimum middle ear pressure for left ear and right ear; SES, Hollingshead Four Factor Index of Social Status; HOME, Home Observation for Measurement of Environment at age 36 months; SA, sway area; SL, sway length; Max PbB1, maximum PbB in first year; Max PbB2, maximum PbB in second year; Max PbB3, maximum PbB in third year; Max PbB4, maximum PbB in fourth year; Max PbB5, maximum PbB in fifth year; PbB05, average PbB between birth and 5 years; PbB5–6, average PbB between fifth and sixth years; CLS cohort, Cincinnati Lead Study cohort; L-4 cohort, subjects with four common visits; L-5 cohort, subjects with five common visits; Q1, PbB quartile 1; Q2PbB quartile 2; Q3, PbB quartile 3; Q4, PbB quartile 4.

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concluded that acute Pb poisoning in childhood caused chronic subclinical cognitive decrement evident in adulthood. In an 11-year follow-up study by Needleman et al. [30], adolescents with elevated dentin Pb levels first measured in first and second grade showed poorer performance in both cognitive and neuromotor tests at follow-up. In a prospective study, Bellinger et al. [4] showed that Pb-associated cognitive decrements first observed at age 2 years were still present at age 10 years, even though blood Pb was less than 3 μg/dL.

Dietrich et al. [17] in the Cincinnati Lead Study found that fine motor function impairments at 72 months were still persistent at 16 [36]. We have evaluated gross motor function as measured by postural balance in the same cohort at 5–6 years. In our study of postural balance, we showed that early childhood Pb exposure was associated with impairment in postural balance measured with a microprocessor-based force platform system [8].

Postural balance is a common body function which humans must perform to carry out their daily living tasks including those performed at the workplace [2,6,11,13,14]. Postural balance in healthy children usually matures or reaches its adult-like state sometime between the ages of 10 and 12 years [41]. Therefore, by quantifying the developmental pattern of postural balance in a longitudinal study such as the Cincinnati Lead Study, we can determine the long-term effect of early childhood Pb exposure on the maturation of postural stability. Impaired postural balance carried into adulthood may pose a risk of potential occupational and non-occupational injuries in the future [24].

2. Methods

2.1. Subjects

In order to investigate the effect of Pb exposure on age-associated maturation of postural balance, the postural balance of 246 children from the Cincinnati Lead Study (CLS) was re-assessed approximately every 20 months (average 20.2 months) starting at about 5 years of age. Out of 246 subjects, 57 were excluded who did not meet the inclusion criteria. This gave us a sample of 189 subjects at the first visit or evaluation. The exclusion criteria were the same as those used in our previous publications [8,19]. Briefly, exclusion criteria were: subjects who could not complete the postural balance test because they fell during the test and/or were not cooperative; corrupt data due to computer disk/hardware problems; children with medical conditions such as Down syndrome, fetal alcohol syndrome and significant congenital anomalies, subjects undergoing Pb chelation therapy; children born at less than 35 weeks of gestation and/or <1500 g birth weight; and Apgar score of 5 or less at 5 min. In addition, during prenatal recruitment, women with the following disorders were also excluded: addiction to drugs, alcoholism or diabetes, known neurologic disorders, psychosis or mental retardation. A test of cofactors and average blood Pb levels between the excluded group and the eligibles showed no statistically significant differences. The data from children with four common visits (longitudinal cohort, L-4; $N=91$) were analyzed to determine the age-dependent longitudinal effect of early childhood Pb exposure on the maturation of their postural balance. A comparison of demographics (birth weight, birth length, maternal IQ, Home Observation for Measurement of Environment at 36 months, Hollingshead Four Factor Index of Social Status, mean hemoglobin for 1 to 5 years and mean total iron binding capacity for 1 to 5 years of life) at birth and blood Pb profiles (prenatal PbB, PbB from years 1 to 5, average PbB 0 to 5 years, average PbB between 5 and 6 years of age) between the L-4 cohort and the remaining subjects revealed no statistically significant differences between the groups. However, at their first visit for postural balance evaluation, the children in the L-4 cohort were younger, lighter in body weight, shorter and had smaller foot area compared to the remaining subjects. In the final analysis of the Pb–sway relationship of the L-4 cohort, we statistically controlled for body weight, height and foot area. This was done because the final model included all significant ($p<0.05$) cofactors so that an independent effect of PbB on sway could be assessed.

2.2. Postural balance assessment

The subject's postural balance was quantitated with a microprocessor based strain-gauge type force platform system. The details of the force platform system and the test protocol are explained in our earlier publications [7,8]. Briefly, the force platform is designed to capture three orthogonal forces and three moments produced by the human body while undergoing the postural balance test on the force platform. These forces and moments are processed by our custom software ("Posture60" Copyright All Rights Reserved, University of Cincinnati, 1987–2004), which allows calculation of x–y coordinates of the center of pressure (CP) movement of the subject during the test period [7]. All subjects underwent a 30-s trial in each for four test conditions. All subjects were administered the following tests: EO: eyes open on the force platform, EC: eyes closed on force platform, FO: eyes open on a 4-in.-thick foam pad placed on the force platform and FC: eyes closed on a 4-in.-thick foam pad placed on the force platform. These tests were repeated in the reverse order. The mean of two trials was used for statistical analysis. The test protocol was designed to indirectly and non-invasively challenge or eliminate the contributions of the afferents (i.e. visual, vestibular and proprioceptive systems) relevant for postural balance [7,8,39]. Table 1 shows a list of postural balance and other study variables, which were used for data analysis.

2.3. Data analysis

All statistical analyses proceeded from the univariate to the bivariate to the multivariate level.

The key sway measures, namely sway length (SL) and sway area (SA), were transformed to their natural logarithms to meet the normal distribution requirement for regression analyses. With regards to the key exposure measure (PbB), subjects from the L-4 cohort were categorized into four quartiles based on their mean PbB between birth and 5 years of age. The cut-off points for the quartile means PbB(0–5) are reported in Table 3.

Table 1
Study variables and abbreviations

Postural balance variables
Sway area (SA)
Sway length (SL)

Exposure variables
Prenatal maternal PbB
Maximum PbB level
In 1st year (max PbB1)
2nd year (max PbB2)
3rd year (max PbB3)
4th year (max PbB4)
5th year (max PbB5)
Average PbB between birth and 5 years (PbB05)
Average PbB between 5th and 6th years (PbB5–6)

Iron status variables
Mean hemoglobin for 1 to 5 years (AVHEM5)
Mean total iron binding capacity for 1 to 5 years of life (AVTIBC)

Questionnaire variables
Total number of sporting activities participated in (ACTVSCOR)

Anthropometric variables
Age
Sex
Current height
Current body mass
Foot area (length × width)
Birth weight, length and body mass index (BMI)

Acute ear infection-related variable
Minimum middle ear pressure for left ear (MEPSL) and right ear (MEPSR)

Socio-economic and related variables
Hollingshead Four Factor Index of Social Status (SES)
Race
Home Observation for Measurement of Environment (HOME) at age 36 months

Maternal variable
Maternal intelligence (IQ)

Association between any two continuous variables, including those between Pb exposure and sway, were obtained by Pearson's bivariate correlation coefficients. For each of the test conditions (EO, EC, FO and FC), separate models were tested for the dependent variables of log SL and log SA, and the exposure variables of PbB05, PbB quartiles and evaluation visit number for all subjects (L-4 cohort, $N=91$) who underwent postural balance evaluations during four visits. Based on our previous publication [8], covariates included were body mass index, mean hemoglobin for 1 to 5 years, minimum middle ear pressures for left and right ears, Home Observation for Measurement of Environment at 36 months and total number of sporting activities in which the subject participated. Least square means (LS means) of sway variables SA and SL corresponding to each sway test visit for each of the four PbB quartiles were calculated by the SAS MIXED Procedure with repeated measures on each subject. These LS means were compared to ascertain postural sway changes for groups with different PbB levels in order to assess their maturation or lack thereof. Since our hypothesis was to determine the differences in the postural sway maturation between the lower and the higher PbB quartiles (using L-4 cohort), a particular approach was applied to compare the results of age-associated changes in postural sway from quartile 1 to that of quartile 4. An analysis to account for repeated observations as well as significant ($p<0.05$) covariates was employed. The program uses the methodology of Generalized Estimating Equations (GEE) and is written in SAS macro. The GEE approach was used because of its robustness to mis-specification of the underlying correlation structure among repeated observations. The dependent variables were log SA and log SL. In order to assess the impact of lead exposure on age-related maturation of postural balance, a regression model was developed which included PbB quartiles (represented by three dummy variables), age at assessment and three variables indicating age by PbB interactions. This model allowed us to assess if the higher quartiles had somewhat different age-related postural balance maturation compared to low exposure quartiles. Results from lowest and highest quartile are summarized in this paper.

3. Results

Tables 2 and 3 provide demographic and Pb exposure statistics for the longitudinal cohorts. The quartile mean PbB levels are given in Table 3. Table 3 also provides mean age and SD values of all subjects by quartile and by visits. The mean age for subjects was comparable for each visit among all quartiles. Fig. 1 provides blood Pb (PbB05) profiles during the first 5 years of life for the L-4 cohort.

Fig. 2 shows examples of changes in stabilograms for the eyes closed, firm surface test for two children representing the lowest average PbB quartile and the highest average PbB quartile as they approach age 12 years when, in unexposed children, an adult-like postural balance is expected. Both children's postural balance variables decreased at the fourth visit in comparison to their values at the first visit implying that postural balance is undergoing a maturational process. While both children with age show maturation of their postural balance with respect to their initial postural sway status, their absolute postural balance status as documented by SA and SL values were remarkably different from each other at the fourth

Table 2
Descriptive statistics of subjects with four consecutive evaluation or visits ($N=91$)[a]

Variables	Mean	S.D.	Minimum	Maximum
Age (years)	5.8	0.98	4.5	8.8
Birth weight (g)	3136.7	466.9	1990	4400
Birth length (cm)	49.1	2.4	43.0	54
Current body mass (kg)	22.5	7.2	14.4	55.0
Current height (cm)	115.4	8.0	101	137.5
Foot area (cm^2), $n=49$	150.1	26.4	81.0	218.4
Maternal IQ	75.0	9.8	55	102
HOME score at 36 months, $n=80$	32.9	6.3	16.0	45.0
SES	17.3	5.1	11.0	37.0
AVHEME5, $n=89$	12.1	0.63	9.8	13.43
AVTIBC5, $n=89$	348.4	29.9	280.8	435.2

[a] 88% African–American, 43 boys and 48 girls.

Table 3
Demographics by visit and average childhood PbB (based on PbB05 values) quartiles for L-4 cohort (N=91)

PbB05 quartile (μg/dL)	Variable [a]	N	Visits			
			1	2	3	4
Q-1 ≤ 8.52	Age (months)	23	70.03 (2.8)	91.74 (3.5)	113.30 (3.15)	132.13 (2.75)
	Height (cm)	23	116.61 (1.71)	127.4 (2.13)	138.63 (2.08)	148.2 (2.08)
	Body mass (kg)	23	22.07 (1.37)	28.6 (1.78)	35.43 (2.26)	42.81 (2.71)
	Foot area (cm^2)	23	143.81 (6.12)	170.13 (5.84)	186.15 (6.44)	208.14 (6)
Q-2 > 8.52–11.7	Age (months)	23	72.00 (2.27)	87.28 (3.9)	108.14 (4.8)	128.32 (4.33)
	Height (cm)	23	116.21 (1.54)	124.8 (2.46)	135.51 (2.87)	145.25 (2.55)
	Body mass (kg)	23	22.18 (1.08)	27.10 (1.62)	35.45 (3.01)	44.62 (4.01)
	Foot area (cm^2)	23	148.56 (4.43)	166.25 (5.73)	185.04 (6.57)	202.81 (4.81)
Q-3 > 11.7–15.5	Age (months)	23	68.00 (2.21)	92.47 (4.7)	113.05 (4.12)	132.29 (3.14)
	Height (cm)	23	115.06 (1.66)	127.6 (2.67)	138.64 (2.66)	148.16 (2.66)
	Body mass (kg)	23	23.98 (2.09)	31.92 (2.99)	42.13 (4.49)	52.56 (5.23)
	Foot area (cm^2)	23	159.77 (12.15)	181.51 (5.74)	198.91 (6.45)	210.73 (7.13)
Q-4 > 15.5	Age (months)	22	72.11 (2.32)	89.35 (4.31)	109.90 (4.17)	131.45 (2.99)
	Height (cm)	22	114.4 (1.73)	123.10 (2.95)	133.17 (2.85)	144.06 (2.4)
	Body mass (kg)	22	21.89 (1.35)	27.61 (2.37)	34.06 (2.74)	43.19 (3.03)
	Foot area (cm^2)	22	167.72 (13.72)	180.31 (9.57)	190.16 (7.10)	205.79 (6.71)

[a] Mean (S.E.M.).

visit. A comparison of postural sway responses at each visit between the lower Pb child and higher Pb child reveals that the higher Pb child had significantly greater postural sway values and increased scatter in the stabilograms, which are indicative of slower maturation of postural balance. This type of response pattern was also found in the remaining subjects of the study cohort.

3.1. Bivariate correlations

For the SL correlations with PbB values, only Max PbB for the first year showed significant associations for the first three visits for all four test conditions. The SL correlations with Max PbB years 2 to 5, PbB05 and PbB5–6 were significant only for the first two visits for all four test conditions. There were only sporadic correlations between SL and prenatal PbB concentration implying these findings may be due to chance. In general, with subsequent visits to the lab for postural sway evaluations, the SL correlation coefficients (r) values either stayed the same (as the first visit) or decreased. For the SA correlations with PbB values, there were only few sporadic significant correlations with prenatal PbB and Max PbB5–6.

Bivariate correlations between cofactors and Sway variables for L-4 cohort were also investigated. For both SA and SL, the consistent significant negative correlations with age support the fact that as these children aged their postural sway decreased implying maturation of postural balance. A significant negative association between SL, SA and height suggests that human postural sway decreases with increasing height, a phenomenon indicative of increased postural control. A significant negative correlation between SA, SL and body mass is expected and implies that an increase in body mass lowers the center of gravity of the subject causing the postural sway to decrease. There were significant negative correlations between SA, SL

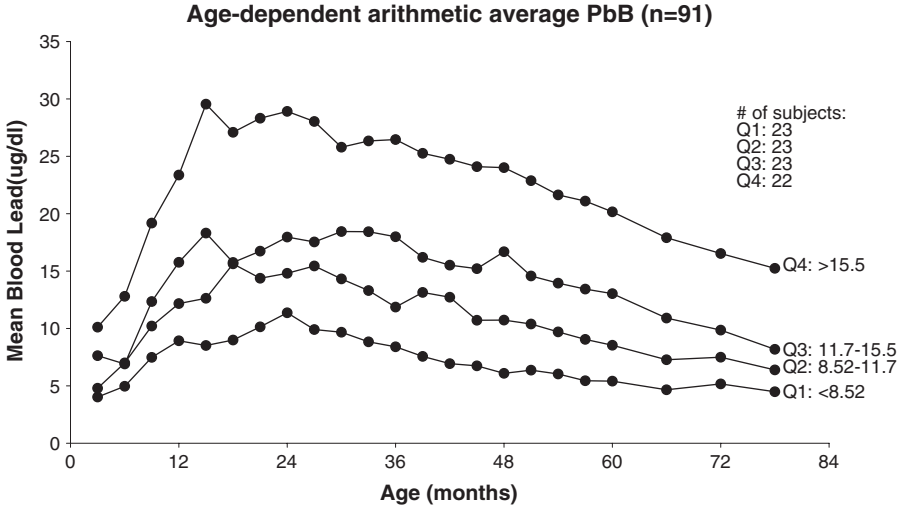


Fig. 1. Age-dependent arithmetic average blood lead concentration profiles presented for children in four quartiles (Q1 to Q4) based on PbB05 for the cohort with four visits (n=91).

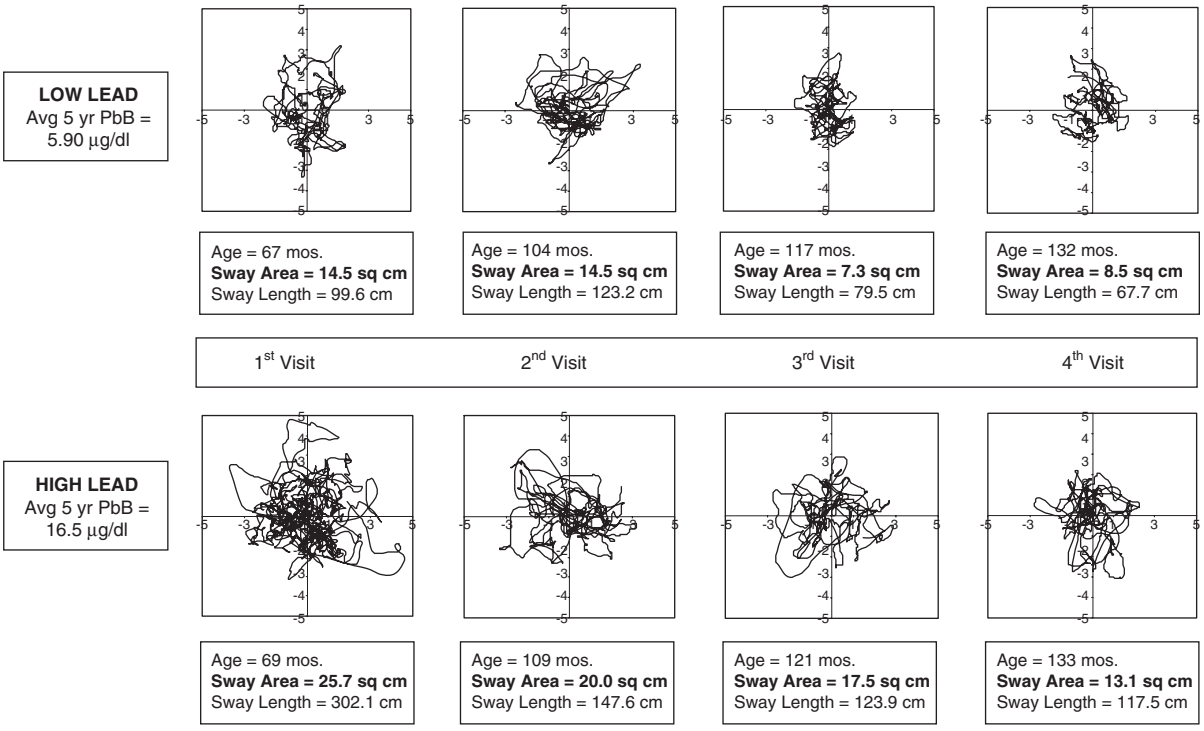


Fig. 2. Comparison of postural sway stabilogram patterns from two children representing lowest (Q1) and highest (Q4) exposure quartiles for eyes closed, compliant surface condition (FC).

and foot area, which suggest that with increasing foot size the subjects' base of support increased thereby reducing postural sway, an indication of maturation. The correlations between SA and SL and HOME and SES were rare and not necessarily always in the expected direction, i.e., they are not always consistent. First of all, SA did not correlate with HOME for any of the four test conditions and four visits. For the SL vs. HOME, out of 16 correlations, only 2 were significant which could be chance occurrences. In addition, for both SA and SL, the correlations with SES, out of 32 bivariate correlations for both sway variables (SA or SL), only 4 were significant which could be chance occurrences. The variables of maternal IQ and hours of sleep before the postural sway test were not significant for both SA and SL for all test conditions for all visits. All the remaining covariates showed sporadic significant correlations for some of the visits and test conditions implying that these correlations were probably occurring by chance.

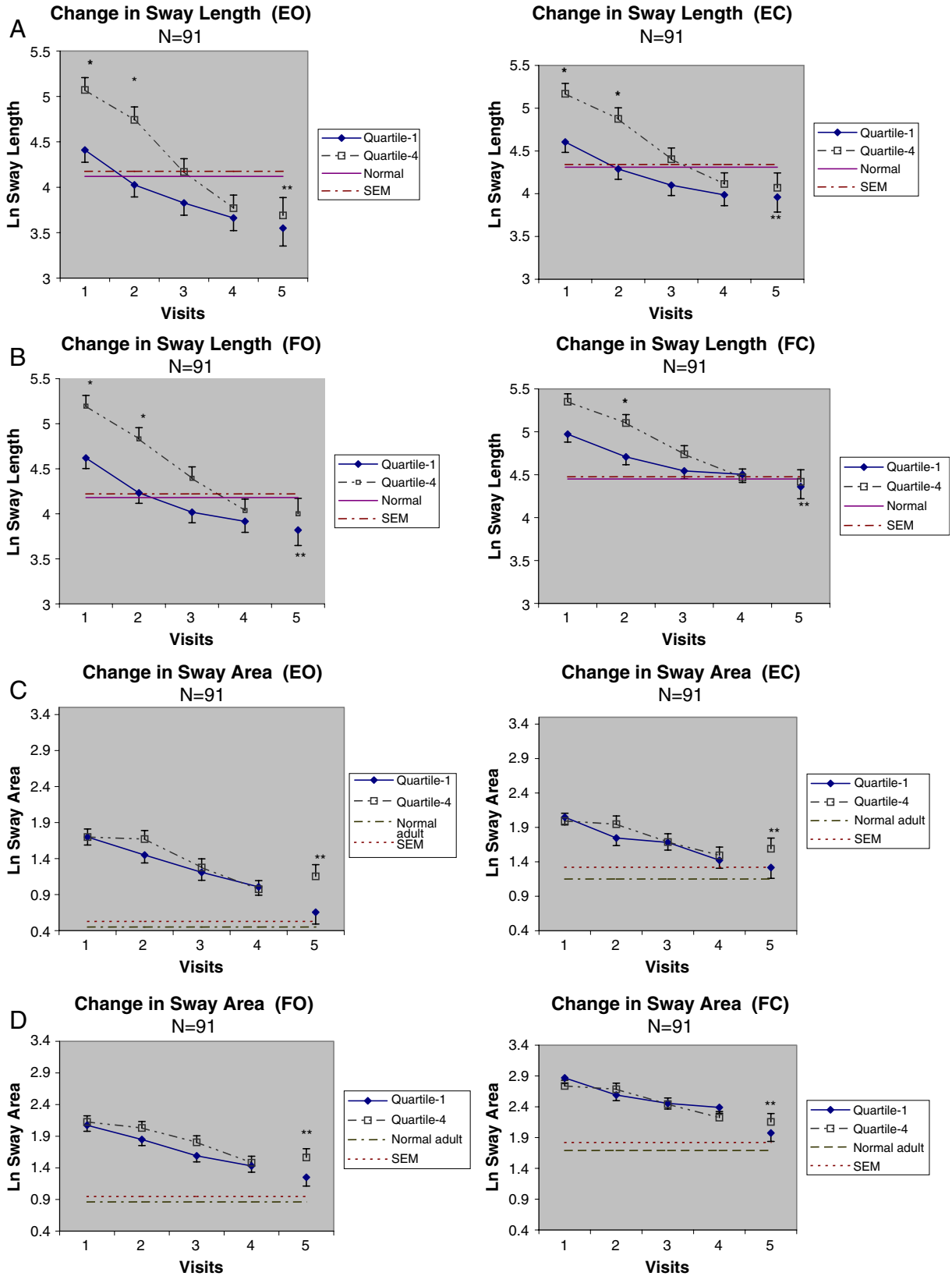
3.2. Lead-associated postural sway maturation patterns

There were statistically significant differences in SL responses between different PbB quartiles for different visits (Fig. 3A and B). The SL response was significantly higher among the subjects in PbB quartile 4 compared to those in PbB quartile 1 for the test conditions of EO, EC and FO for visits 1and 2 only. For the FC test, the SL response was significantly higher for subjects in PbB quartile 4 compared to those in PbB quartile 1 for visit 2 only. Also, the SL response was significantly higher among the subjects in PbB quartile 3 compared to those in PbB quartile 1 for the test condition of FO in visit 1 only. In comparison to SL, the SA responses did not show statistically significant differences among different quartiles (Fig. 3C and D).

Within each quartile, there were, however, several statistically significant differences in both SL and SA responses

Fig. 3. (A) Least squares mean response (adjusted for co-variates) of SL by visits for lowest PbB quartile (Q1) and the highest PbB quartile (Q4) from L-4 cohort (those completing first four visits; $N=91$) for EO and EC test conditions. Also shown as reference are SL responses from an unexposed normal adult group (mean age 34.3 years, S.D. 2.8 years, $n=14$). The dotted lines represent standard errors for the unexposed normal adults. Bars represent standard errors. *Significantly different between Q1 and Q4 ($p<0.05$). **Mean SL response from those subjects ($N=44$) who completed the fifth visit. (B) Least squares mean response (adjusted for co-variates) of SL by visits for lowest PbB quartile (Q1) and the highest PbB quartile (Q4) from L-4 cohort (those completing first four visits; $N=91$) for FO and FC test conditions. Also shown as reference are SL responses from an unexposed normal adult group (mean age 34.3 years, S.D. 2.8 years, $n=14$). The dotted lines represent standard errors for the unexposed normal adults. Bars represent standard errors. *Significantly different between Q1 and Q4 ($p<0.05$). **Mean SL response from those subjects ($N=44$) who completed the fifth visit. (C) Least squares mean response (adjusted for co-variates) of SA by visits for lowest PbB quartile (Q1) and the highest PbB quartile (Q4) from L-4 cohort (those completing first four visits; $N=91$) for EO and EC test conditions. Also shown as reference are SA responses from an unexposed normal adult group (mean age 34.3 years, S.D. 2.8 years, $n=14$). The dotted lines represent standard errors for the unexposed normal adults. Bars represent standard errors. **Mean SA response from those subjects ($N=44$) who completed the fifth visit. (D) Least squares mean response (adjusted for co-variates) of SA by visits for lowest PbB quartile (Q1) and the highest PbB quartile (Q4) from L-4 cohort (those completed first four visits; $N=91$) for FO and FC test conditions. Also shown as reference are SA responses from an unexposed normal adult group (mean age 34.3 years, S.D. 2.8 years, $n=14$). The dotted lines represent standard errors for the unexposed normal adults. Bars represent standard errors. **Mean SA response from those subjects ($N=44$) who completed the 5th visit.

among various visits. In general, both SL and SA responses showed a statistically significant decreasing trend from visit 1 to visit 4, implying age-associated maturational changes in postural balance. (Fig. 3A to D). In addition to the statistical results presented above, SL and SA responses by quartile and by visit are provided in the following to demonstrate the differences in the age-associated trend in maturation of children's postural balance between lower (quartile 1) and



higher (quartile 4) PbB quartiles. While the above results are based on statistical analysis performed on the L-4 cohort only (through four visits of evaluations), we wanted to qualitatively observe how the SA and SL responses appeared when the response from subjects with a fifth visit (out of 91 subjects in L-4 cohort 44 completed the fifth visit) were plotted in Fig. 3A to D. In comparison to age-associated decreases in mean SL (range of % decrease from visit 1 to visit 5 for all quartiles for four test conditions: 12.3–28.7%), the decrease in mean SA (range of % decrease from visit 1 to visit 5 for all quartiles for four test conditions: 20.2–61%) were somewhat higher. Fig. 3A to D also include as a reference SA and SL mean response values from a non-exposed adult group (mean age: 34.3±2.8 years, $N=14$) from our laboratory database. These SA and SL values from the adult non-exposed group provide a reference as to how much "catching up" needs to be done by the Pb exposed L-4 cohort to accomplish their postural balance maturation.

We examined the impact of PbB exposure (quartile 1 vs. quartile 4) on age-related maturation of balance (using measures log SL and log SA) by including the PbB exposure interaction with age in the regression models. The interaction term was statistically significant ($p<0.05$) only for log SL and not significant for log SA. Therefore, age-related decreases in SA were similar in the low PbB quartile as well as in the high PbB quartile. As indicated by the significant interaction for log SL, age-related maturation was steeper for quartile 4 subjects than for quartile 1 subjects with the two lines intersecting at around 11 years of age (data not shown). For the SL response (LS means), comparison between quartiles 1 and 4 over the entire age range and all four test conditions showed a statistically significant larger SL for quartile 4 (p range: <0.0001 to 0.0004). For the predicted SA response (LS means), comparison between quartiles 1 and 4 over the whole age range for all test conditions showed a larger SA for quartile 4; however, only the FO test condition was statistically significant ($p=0.04$).

4. Discussion

The results presented in this paper provide evidence that low to moderate Pb exposure in early childhood has a measurable and statistically significant impact on the maturation of postural balance. Based on the results from the longitudinal cohort, L-4, both SA and SL did decrease significantly with age implying postural balance maturation. Similar age-associated changes have been reported by Shumway-Cook and Woollacott [41] in non-exposed children.

The level of age-associated maturational decrease in SL was different between the lowest quartile and the highest quartile subjects (L-4). As shown in Fig. 3A to B, SL responses at the first postural balance evaluation for all test conditions, as expected, were higher for those in the highest quartile than those in the lowest quartile. This implies that postural muscles of children with higher PbB burden had to work harder than those with the lowest PbB burden even though the children in the quartile 4 were older than those in the quartile 1 and had the advantage of an age-associated maturational process. In other words, the age-associated maturational process (which in a normally developing nervous system decreases postural sway) was not sufficient to offset the detrimental effect of Pb in the highest quartile children. As these children aged over the next 60 months, the rate of decrease in SL in the highest PbB quartile appeared to be much steeper than that observed in the lowest quartile children (Fig. 3A and B) at least through the fourth postural balance evaluation visit (mean age for quartile 1: 132.13 months and mean age for quartile 4: 131.45 months) implying some level of catch-up. However, for those subjects in the highest quartile, who completed the fifth visit, mean SL responses appeared to show a plateauing trend for all test conditions.

In contrast to the mean SL response, the mean SA levels were comparable between the lowest and the highest quartile groups at their first visits. Age-associated decreasing patterns in SA were somewhat different than those for SL. Age-associated decreases in SA responses between the two extreme quartile subjects were comparable throughout their maturational age period. However, subjects in the highest quartile who completed the fifth visit appeared to plateau for FO and FC tests and actually showed an increasing trend for EO and EC tests but the increase was not statistically significant. This implies that, in spite of increased postural muscle contractions (as implied by higher SL response) by the subjects in the highest quartile (quartile 4), their mean SA response was still higher than those in the lowest quartile. A qualitative comparison of SL responses of high and low PbB quartile groups with those of non-exposed adults shows a shorter SL implying potentially better balance (Fig. 3A to B). However, the children's SA response is still several fold higher than that of non-exposed adults (Fig. 3C and D). In other words the mean SL response (implying postural muscular contractions) achieved by the both cohorts was not sufficient to exhibit mean SA responses comparable to those in the normal adults. This potential deficit may be overcome once all the subjects reach the age of 12 years or older.

The above finding shows that mean SL and mean SA responses present different patterns, which may shed some light into the potential physiological pathways affected by early Pb exposure. Yasuda et al. [45] have shown that control of the body's sway area (SA) is maintained by the labyrinth and the velocity of sway (which is highly correlated with SL) is maintained by the proprioception systems. Their study with patients with vestibular (bilateral canal paresis) and proprioception disorders (severe decreased sensory vibration sensitivity) showed different SA and SL response patterns. Patients with a vestibular disorder tended to have a much higher SA than SL, while those with a proprioception disorder showed a much higher SL response than SA. Irrespective of membership in the lowest or highest PbB quartile, as children in our study underwent age-associated changes in postural sway, their SA responses were much higher than the normal adult subjects, even though SL response was markedly lower than that of the normal adult subjects. Based on Yasuda's study, it appears that Pb exposed children, even near their maturation age of approximately 12 years, showed potential impairment in their vestibular systems' functionality (more of the otolithic system than the semicircular canals or more so than their proprioception

system) related to postural balance. This implication of vestibular system dysfunction was more prominent in the highest quartile 4 subjects than those in the lowest quartile 1 (Fig. 3C to D). This finding of potential vestibular involvement was also speculated for this cohort at age 5–6 years in our previous report [8] and the prospective follow-up data on this cohort suggests that there is continued decrement in the functionality of the vestibular system. The persistence of decreased functionality of the vestibular system for postural balance under Pb exposure was also suggested in a clinical case. The results from a clinical case study [10] of a Pb-poisoned teenager provided some evidence that postural balance under the FC test requiring relatively higher reliance on the vestibular system was not improved after succimer therapy, while postural balance was much improved under the EO, EC and the FO tests implying that Pb exposure has a long lasting impact on the vestibular system.

Vestibular involvement has been also reported by Mameli et al. [28] with Pb exposure in a rodent study where the results suggested Pb-associated modification of the depolarization properties of the membranes of the vestibular receptors. Other animal studies have shown that Pb affects the depolarization mechanism of vestibular receptors [22,29]. Furthermore, there is some evidence in the literature with animal models showing detrimental effects of Pb on cerebellar Purkinje neurons [31,32,35]. Patrick and Anderson feline model for chronic early Pb exposure revealed Pb-associated increased dendritic spines and altered patterns of dendritic growth and pruning [31,32]. The researchers suggested that such a hyperspiny condition and modified dendritic growth might affect afferent input to the cerebellar Purkinje cells, which are critical for postural balance control. Other studies have also implicated Pb as having a detrimental impact on the cerebellum [5,33].

A detrimental impact of Pb on vestibulo-cerebellar and spino-cerebellar afferent pathways has been reported in Pb workers [46]. Yokoyama et al. [46], using a fast Fourier transform method for frequency analysis of postural sway data of Pb workers, implied a potential detrimental impact on their vestibulo-cerebellum and spinocerebellar afferent pathways at PbB levels between 7 and 36 μg/dL. In summary, the observed decrement in vestibular functionality as suggested by postural sway response patterns in this cohort may be-associated with a variety of Pb exposure-related factors such as slowed vestibular nerve conduction velocity [27], myelin destruction [16] and disruption of ion channels for calcium which are present on the gelatinous plate of the vestibular hair cells.

The Mamelli [34] study implied that Pb affects brain stem and cerebellum and thereby influences the vestibule-ocular reflex (VOR), which appears to be important for postural control as reported during posturography evaluations[15,21]. Rocchi et al.'s results suggest that the basal ganglia to brain stem centers are involved in postural control so the impact of Pb at the brain stem level could have detrimentally affected the postural balance of the subjects in the present study [37]. In other words, Pb exposure may have influenced the basal ganglia to brain stem level centers' ability to properly integrate the proprioceptive afferents needed for postural control.

While the half-life of Pb in blood is fairly short (several weeks), its toxic impact on the brain is much longer [26]. In our clinical case study [10], a teenage child with Pb poisoning undergoing succimer therapy showed improved postural balance for all test conditions except for the FC test which requires relatively more reliance on the vestibular system for postural control. In other words succimer therapy was not sufficiently effective in providing beneficial effects on the vestibular system's ability to maintain upright balance. This preliminary finding from a clinical case study and the fact that the mean SA response of the L-4 cohort at visit 4 (and a subset of subjects who completed visit 5) were higher than that of a non-exposed adult cohort suggest that these children may need additional time to approach their expected maturation level of postural balance. The current data from our cohort along with animal models of the role of Pb-associated vestibular receptor malfunction provides further support to the concept that there is a potential long-term detrimental impact of Pb on the vestibular system's ability to maintain postural balance, which is not completely overcome by the age-associated maturation of the postural balance.

As these children are now adults, poor postural balance may impact their tasks of daily living, which may pose a higher risk of potential injuries at home and work. There is preliminary evidence that early childhood Pb exposure may be associated with the prevalence of injuries at home and the workplace [24]. Another study showed an association between exposure to neurotoxicants and increased risk of slips/trips and falls among painters [23]. In addition, early childhood Pb exposure may also have detrimental delayed health consequences such as development of Parkinsonism. Seidler et al. [40] and others [25,38] have reported an association between long-term exposure to a combination of specific metals such as Pb, mercury and manganese and risk of development of Parkinsonism. Kuhn et al. [25] studied the effect of occupational chronic low-level exposure to lead sulfate batteries and found an association with the development of Parkinsonism. The patients in Kuhn's study also showed axonal neuropathy, which provides further support for a potential association between exposure to Pb and/or sulfate compounds and Parkinsonian symptoms. Rybicki et al. [38] reported a gene–environment interaction in his cohort exposed to occupational Pb and copper indicating a higher risk of Parkinsonism development among individuals with a family history of Parkinson's disease (PD). A preliminary study [12] from our group with the Cincinnati Lead Study cohort has provided some evidence of gene-environment interaction in modifying the Pb-associated changes in postural balance. This study suggests that the polymorphisms at the DRD3 and VDR genes may moderate the effects of Pb exposure on neuromotor functions (in particular postural balance) in children. Future studies are needed to further explore the impact of gene–environment interactions in modifying neuromotor outcomes in subjects with exposure to Pb.

In summary, the longitudinal data presented from the L-4 cohort provides measurable evidence that early Pb exposure is associated with a detrimental impact on the maturation of children's postural balance. The results also suggest a

detrimental influence of early Pb exposure on the vestibular system, which is one of the afferents necessary for maintaining postural balance. The findings are correlational and therefore care should be exercised in the interpretation of the findings. The results at this stage do not necessarily provide direct evidence of how long it may take for subjects to achieve adult-like postural balance but it appears that the children's postural balance maturation is "catching up". In addition, the cohort (predominantly African American) used in this study may not be representative of the US population. However, Pb effects on neuromotor development (not necessarily postural balance) have been reported in other populations [3,42]. As maintenance of proper upright balance is critical in the conduct of tasks of daily living at home and work, any detrimental postural balance impact caused by early Pb exposure may pose a risk for potential injuries. Future studies are needed to address this issue further.

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