EFFECT OF EARLY LEAD EXPOSURE ON CHILDREN'S POSTURAL BALANCE

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The literature relating to the neuromotor effects of long-term exposure to low levels of environmental lead (Pb) in children is not extensive. Except for recent publications from the Cincinnati Lead Project (Bhattacharya *et al.* 1993, Dietrich *et al.* 1993) and the Boston Lead Study (Stiles and Bellinger 1993), most of the research (Benetou-Marantidou *et al.* 1988) in this area has reported neuromotor effects at blood lead (PbB) levels considerably higher (>40µg/dL) than the current Centers for Disease Control (1991) action level of 10µg/dL. Dietrich *et al.* (1993) provided evidence of fine motor effects at lower Pb levels (mean lifetime PbB between 4.7 and 38.1µg/dL) with the use of the Bruininks–Oseretsky (B-O) Test of Motor Proficiency (Bruininks 1978) in 245 six-year-old enrolled in the Cincinnati Lead Study. However, they did not find any significant effects on gross postural balance (balance subscore from B-O test battery), perhaps because of the B-O test's insensitivity to postural balance changes occurring at lower Pb levels. Stiles and Bellinger (1993) investigated neuropsychological aspects of 148 middle- and upper-middle-class 10-year-old children to determine the relationship between postnatal PbB levels at six, 12, 24 and 57 months, and 10 years of age. The mean PbB level at all ages was below 8µg/dL. Their findings showed significant associations between the children's performance on the Wechsler Intelligence Scale for Children—Revised (WISC-R) and their PbB levels, but relatively few significant associations were observed between neuropsychological test scores and PbB levels. They concluded that the lack of significant findings on neuropsychological tests may be due to the insensitivity of the tests and/or individual differences in Pb-induced modification of the central nervous system.

We have refined and tested the use of a sensitive and objective measure of a child's ability to maintain upright balance as a biological marker of Pb-induced modifications of the neuromotor system. The measurement of upright balance characteristics also provides an opportunity to obtain indirect insight into the functional health status of the central as well as peripheral nervous systems, which are important for proper functioning of simple and complex neuromotor and neurocognitive activities.

The study of environmental Pb-induced effects on children's neuromotor function as characterized by their postural stability is relatively new. Earlier findings from our laboratory with a smaller subset of the Cincinnati Lead Project cohort have provided preliminary evidence that postnatal exposure to Pb is significantly

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associated with postural instability (Bhattacharya *et al.* 1990). The maintenance of upright balance is critical to almost all aspects of the daily activities of life: and for a growing child in particular, good balance is necessary for normal psychosocial interactions with peers, participation in games and sporting activities, and thus for self-esteem.

The purposes of this study were: (1) to present final findings from the cross-sectional study of postural balance and provide confirmation of the relationship (dose–effect) between PbB and postural balance in a larger group of Pb-exposed children, which permits better statistical control than was possible in earlier interim analyses; (2) to determine whether the PbB and postural balance correlation is evident for those children whose PbB never exceeded 20µg/dL (a level which the Centers for Disease Control of the USA consider safe enough not to need diagnostic evaluation or medical management); and (3) to identify the effect of Pb exposure on the various physiological pathway(s) relevant for postural balance.

Method

Subjects

A total of 202 children from the Cincinnati Lead Program Project were tested for postural balance.

The mothers of children in the Cincinnati Lead Program Project were recruited prenatally between 1979 and 1984. These mothers lived in older houses in poor condition and with chipping lead-based paint and lead-laden dust. The records of the City Health Department show that there is a history of childhood lead poisoning in this geographical area. 487 women were excluded because their pregnancies had been complicated by other factors such as diabetes, alcoholism, mental retardation and drug addiction; a further 23 women refused to participate. 76 neonates were excluded from postnatal recruitment because they fell into one or more of the following categories: less than 35 weeks gestation and/or 1500g birthweight, Apgar score of 5 or less at five minutes, medical conditions such as Down syndrome and significant congenital anomaly. In addition, 129 families refused to participate in the five-year postnatal follow-up. Other exclusion criteria have been detailed by Dietrich *et al.* (1987).

The postural balance study was initiated in 1987, after the postnatal recruitment of the Cincinnati cohort. All subjects from the Cincinnati study were included except for those who had been lost to follow-up after their fifth birthday. 202 children were eventually evaluated for postural balance.

Of the total sample, 40 children were excluded from data analyses for various reasons. 15 children fell during the postural balance test; another 15 were not willing to complete the test; seven children both fell and refused to co-operate; and there were corrupt data due to computer disk/hardware problems for three children, one of whom also fell during the postural balance test. The total number of subjects used for the analysis was 162.

All children in the study received standard periodic medical evaluations, quarterly PbB evaluations, and a series of age-appropriate neuromotor and neurocognitive tests. The test for postural balance was first administered at about the age of five years. On the day of the postural balance test, each subject's bodyweight, height and foot length/width were measured. The parents were administered a brief questionnaire about areas such as their child's health, amount of sleep the night before the balance test, time of last meal before the test, injuries sustained and participation in sporting activities. Middle-ear pressures were recorded using standard tympanometry to screen for possible subclinical otitis media.

Assessment of postural stability

Postural stability was measured with a microprocessor-based six-component strain gauge-type force platform system and custom-developed software, 'Body Balance' (all rights reserved by the University of Cincinnati 1991). The details of measurement accuracy and sensitivity of this instrument are given by Bhattacharya *et al.* (1987). The test–retest reliability of the postural sway technique has been evaluated by us in a smaller subset of the Cincinnati Lead

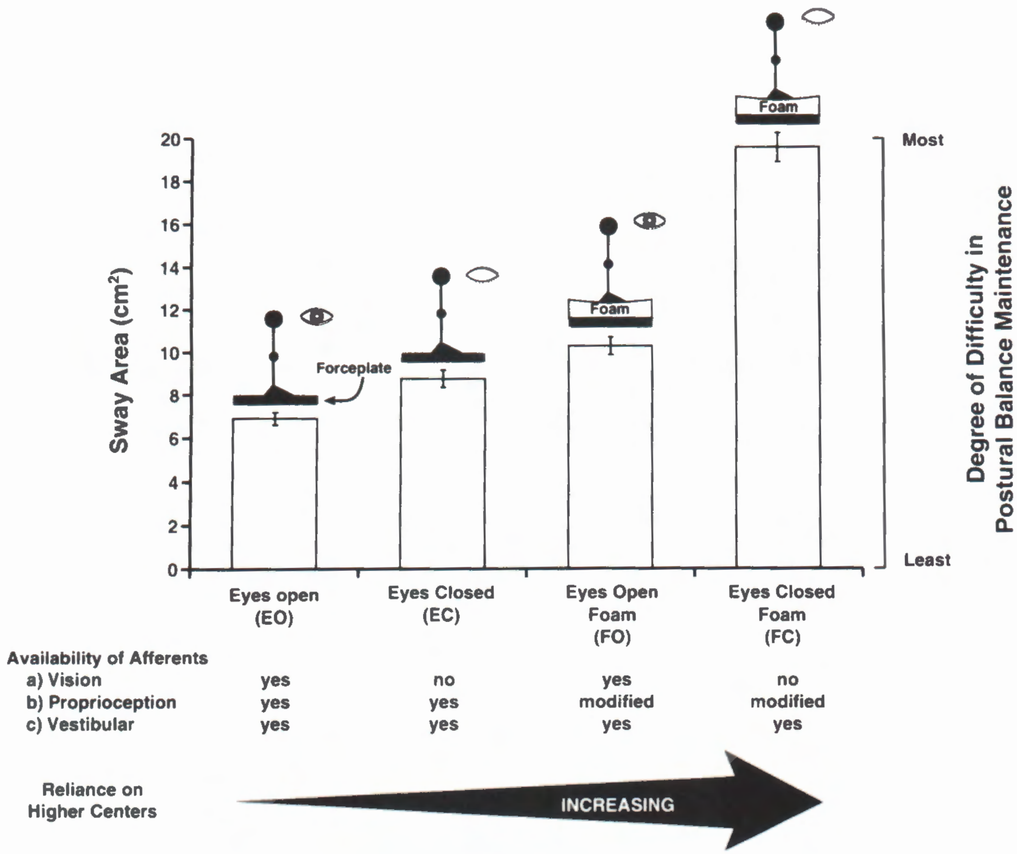

Fig. 1. Effect of postural balance tests on sway area and schematic representation of roles of various afferents associated with four test conditions.

Study cohort (Bhattacharya *et al.* 1988, 1990) as well as in studies involving adult subjects (Bhattacharya *et al.* 1987, Sack *et al.* 1993).

Each subject performed repeat trials of four 30-second tests while standing on the force platform. The average of the repeat trial data was used for analysis. The four test conditions were as follows: standing on the platform with eyes open (EO); standing on the platform with eyes closed (EC); standing on a three-inch high foam pad placed on the platform with eyes open (FO); and standing on a three-inch high foam pad placed on the platform with eyes closed (FC). These tests were designed to challenge indirectly, eliminate or minimize the contribution of afferents relevant for maintenance of upright balance (Sahlstrand 1978). The roles of various pathways for the control of postural balance during these four tests are schematically represented in Figure 1. The maintenance of postural balance in the EO test condition was carried out collectively by all three available physiological pathways (*i.e.* visual, proprioceptive and vestibular systems). For the EC test, the postural balance was maintained primarily by the proprioceptive and vestibular systems. For the FO test, however, while there was further reliance on the vestibular system, availability of vision tended to compensate for any postural modifications produced by the disturbed proprioception system (due to standing on the compliant surface). Finally, in the FC test, the postural balance was primarily maintained by the vestibular system as the proprioception system is modified and the vision is removed. The degree of difficulty presented to the postural balance

TABLE I
Study variables

Postural balance variables
Sway area (SA)
Sway length (SL)
Exposure variables
Prenatal maternal PbB
Maximum PbB level
In 1st yr (MaxPbB1)
2nd yr (MaxPbB2)
3rd yr (MaxPbB3)
4th yr (MaxPbB4)
5th yr (MaxPbB5)
Average PbB between birth and 5 years (PbB05)
Iron status variables
Mean haemoglobin for 1 to 5 years of life (Hgb)
Mean total iron-binding capacity for 1 to 5 years of life (TIBC)
Questionnaire variables
Time elapsed between last meal and sway test
Hours of sleep before sway test
Report of dizziness
Total number of sporting activities participated in
Number of reported injuries in lifetime
Anthropometric variables
Age
Sex
Current height
Current body mass
Current foot length/width
Birthweight and length
Acute/chronic ear infection incidence and related variables
Minimum middle-ear pressure
Combined number of occurrences of bilateral and unilateral otitis media over first 5 years of life
Number of known occurrences of bilateral otitis media over first 5 years of life
Socio-economic and related variables
Hollingshead Four Factor Index of social status (SES) (Hollingshead 1975)
Race
Home Observation for Measurement of Environment (HOME) (Caldwell 1979)
At 12 mths of age
24 mths of age
36 mths of age
Average of all three HOME assessments
Maternal variables
Maternal intelligence
Cigarette consumption during pregnancy

control system was therefore least for the EO test, and increased as various afferents were either removed or modified in the EC, FO and FC test conditions.

The data were collected with a microcomputer and stored on a computer diskette for off-line processing with the Body Balance software. This software calculates the *x–y* co-ordinates of the movement pattern of the body's center of pressure and provides two measures of postural balance: (1) sway area (SA), which is the area enclosed within the envelope of the outer perimeter of the *x–y* plot of the center of pressure, and (2) sway length (SL), which is the total distance traversed by the center of pressure during the 30-second test period. The *x–y* plot of the center of pressure is also known as a stabilogram.

In this study, data collected from the postural balance test and a series of other variables were used for analysis. These variables are listed in Table I.

TABLE II
Descriptive statistics: demographics (N=162)*

Variable	*Mean*	*SD*	*Minimum*	*Maximum*
Age (yrs)	6.0	1.03	4.9	10.1
Birthweight (g)	3144.6	454.7	1990.0	4400
Birth length (cm)	49.3	2.4	41.5	54
Current body mass (kg)	21.7	5.7	14.3	55
Current height (cm)	115.9	7.9	103.8	144.2
Middle-ear pressure (mmH_2O) (N=160)	–38.9	71.6	–300.0	72
Foot area (length × width; cm^2) (N=87)	151.1	25.6	81	223.7
Maternal IQ (N=161)	75.8	9.6	55	102
HOME score at 36 months (N=140)	33.0	6.5	16	48

*81 boys, 81 girls; 88.3 per cent African–American.

TABLE III
Descriptive statistics: blood lead levels (µg/dL) (N=162)

Period of blood sampling	*Geometric mean*	*Geometric SD*	*Minimum*	*Maximum*
Prenatal (N=138)	8.0	1.58	2	22
Maximum for 1st yr of life	14.9	1.7	5	56
Maximum for 2nd yr of life	20.5	1.6	6	83
Maximum for 3rd yr of life	19.7	1.5	7	69
Maximum for 4th yr of life	16.6	1.6	5	53
Maximum for 5th yr of life	13.9	1.7	4	53
Average PbB for 0–5 yrs of life	11.9	1.5	4	28
Average Hgb for 1–5 yrs of life (g%) (N=160)*	12.1	.76	9.8	14.3
TIBC for 1–5 yrs of life (mg/dL) (N=160)*	349.2	31.1	280.8	435.2

Bivariate correlation between average PbB for 0–5 yrs of life and maximum 2nd yr PbB: r=0.87 (p=0.0001); N= 162. (See Table I for abbreviations.)
*Mean and SD are arithmetic.

Data analysis

A list of potential candidate covariates and confounders was identified, based on our earlier publications (Bhattacharya *et al.* 1987, 1988, 1990, 1993). Pearson bivariate correlations were obtained between sway, PbB and other independent variables. These correlations were used to identify *bona fide* confounders/covariates. For this purpose, a non-zero correlation was presumed to exist if its p value was ≤0.1. A variable was considered to be a *bona fide* confounder if it exhibited a non-zero correlation with both the Pb exposure variable and the sway variable. If it correlated only with the sway variable and not with the Pb exposure variable, however, that variable was declared to be a covariate. If a variable was found to be a significant confounder for one sway test condition, then that variable was also used as a potential confounder for other sway test conditions for the purpose of multiple regression modelling. The final regression model was obtained by a backward stepwise elimination procedure (SAS 1989). Only those variables which showed a significance level of $p \leq 0.05$ were kept in the final model unless the variable was a *bona fide* confounder (*i.e.* correlated with both sway and PbB level). This process of statistical strategy of arriving at the final model was not strictly applied to those variables with substantial missing data; therefore, foot area (N=87) was not included in the multiple regression analysis. Both SA and SL variables (as well as PbB variables) were transformed to their natural logarithm for the analysis.

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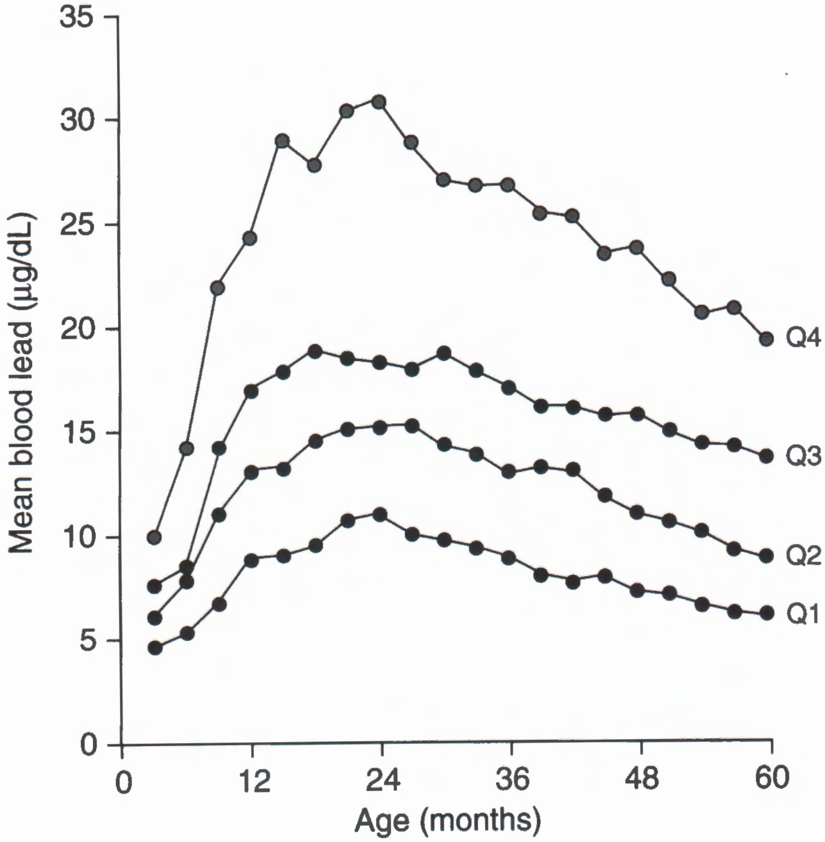

Fig. 2. *Age-dependent arithmetic average blood lead concentration profiles presented for children divided into four quartiles (Q1 to Q4) based on PbB05 concentration.*

Results

The demographic and Pb exposure data are presented in Tables II and III. The median age was 5.7 years. There were only three children between the ages of 9.0 and 10.1 years. The cohort was primarily African–American (88.3 per cent). There were equal numbers of males and females. Table III presents prenatal (maternal first trimester) and postnatal PBB data (average of about 20 consecutive quarterly determinations). In addition to the yearly average PbB data shown in Table III, Figure 2 presents the arithmetic mean PbB profiles of the study subjects when grouped into four quartiles based on PbB05 level (average lifetime exposure). There were 40 children with PbB05 <9.3µ/dL, 41 with PbB05 between 9.3 and <12µg/dL, 41 with PbB05 between 12 and ≤16µg/dL, and 40 with PbB05 >16µg/dL. Most children in each of the quartiles reached peak PbB concentrations between the ages of 18 and 24 months.

Statistical analysis (*t* test) showed that the children who fell during testing were somewhat different (*p*=0.04) from the remaining subjects for lifetime exposure. The PbB05 for children who fell was lower than that of the remaining subjects (mean for children who did not fall was 11.6 ± 1.5µg/dL and for those who fell was 9.4 ± 1.6µg/dL). However, the fallers did not differ significantly from the non-fallers for any of the yearly peak PbB concentration variables of MaxPbB1 to MaxPbB5. An analysis of variance of the postural SA showed that the SA was significantly greater (*p*=0.0001) for those who fell, as might be expected. However, the postural SL variable was not significantly different between the groups (*p*=0.13).

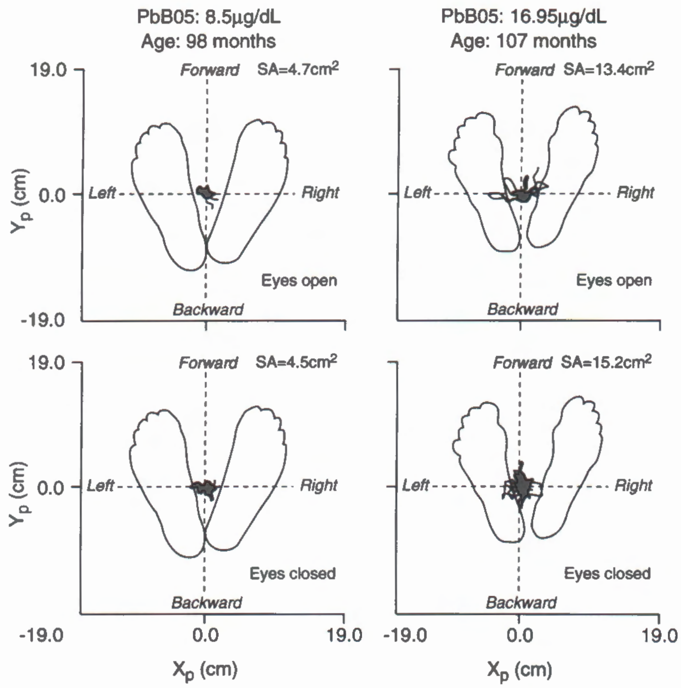

Fig. 3a. Stabilograms from two children representing lowest (Q_1 <9.3µg/dL) and highest (Q_4 >16µg/dL) exposure quartiles for EO and EC test conditions. Actual footprints of children shown provide measure of spread of stabilogram in relationship to their stability boundaries.

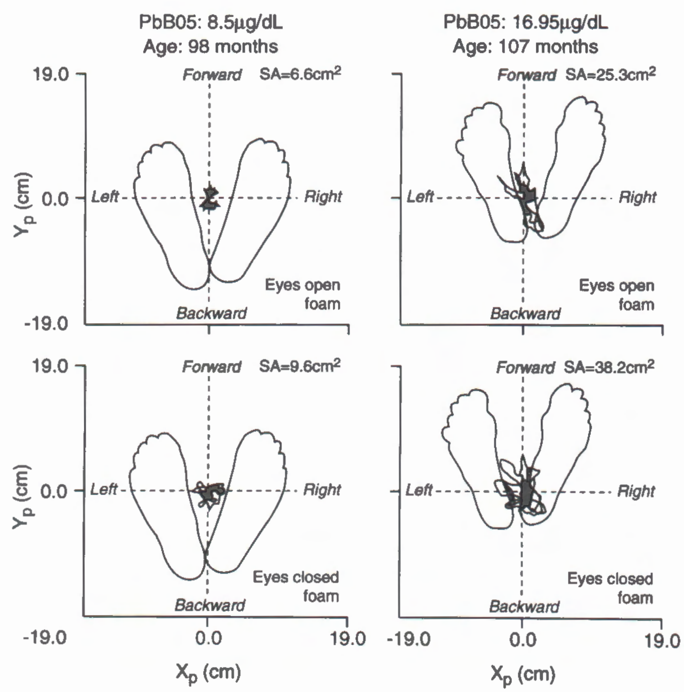

Fig. 3b. Stabilograms from two children representing lowest (Q_1 <9.3µg/dL) and highest (Q_4 >16µg/dL) exposure quartiles for FO and FC test conditions. Actual footprints of children shown provide measure of spread of stabilogram in relationship to their stability boundaries.

TABLE IV
Bivariate correlation with log sway area (cm^2) (N=162)

Test condition	*Prenatal (N=138)*		*MaxPbB1*		*MaxPbB2*		*MaxPbB3*		*MaxPbB4*		*MaxPbB5*		*PbB05*	
	r	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*
Eyes open	-0.01	(0.90)	0.08	(0.30)	0.10	(0.2)	0.11	(0.15)	0.13	(0.10)	0.14	(0.08)	0.13	(0.10)
Eyes closed	0.04	(0.60)	0.13	(0.10)	0.19	(0.02)	0.18	(0.02)	0.23	(0.003)	0.25	(0.001)	0.23	(0.003)
Eyes open, foam	-0.00	(1.00)	0.08	(0.32)	0.10	(0.17)	0.15	(0.06)	0.17	(0.03)	0.21	(0.009)	0.16	(0.04)
Eyes closed, foam	-0.06	(0.50)	0.10	(0.19)	0.08	(0.30)	0.12	(0.12)	0.17	(0.03)	0.16	(0.04)	0.16	(0.04)

$p \leq 0.10$ was considered statistically significant for inclusion in regression model. Positive correlation implies that children with higher PbB levels showed poorer postural balance (as evidenced by higher SA values). (See Table I for abbreviations.)

TABLE V
Bivariate correlation with log sway length (cm) (N=162)

Test condition	*Prenatal (N=138)*		*MaxPbB1*		*MaxPbB2*		*MaxPbB3*		*MaxPbB4*		*MaxPbB5*		*PbB05*	
	r	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*	*r*	*(p)*
Eyes open	0.16	(0.05)	0.27	(0.0006)	0.19	(0.02)	0.20	(0.009)	0.29	(0.0002)	0.32	(0.0001)	0.32	(0.0001)
Eyes closed	0.18	(0.04)	0.27	(0.0004)	0.19	(0.01)	0.21	(0.006)	0.30	(0.0001)	0.33	(0.0001)	0.33	(0.0001)
Eyes open, foam	0.17	(0.05)	0.26	(0.001)	0.18	(0.02)	0.20	(0.01)	0.28	(0.0002)	0.32	(0.0001)	0.31	(0.0001)
Eyes closed, foam	0.14	(0.1)	0.27	(0.0006)	0.18	(0.03)	0.20	(0.01)	0.28	(0.0003)	0.30	(0.0001)	0.31	(0.0001)

$p \leq 0.10$ was considered statistically significant for inclusion in regression model. Positive correlation implies that children with higher PbB levels showed poorer postural balance (as evidenced by higher SL values). (See Table I for abbreviations.)

TABLE VI
Bivariate correlations between log SA, log SL and cofactors (N=162)

Cofactors	*Sway variable*	*Eyes open*		*Eyes closed*		*Eyes open, foam*		*Eyes closed, foam*	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	SA	–0.34	0.0001	-0.28	0.0003	-0.22	0.006	-0.25	0.002
	SL	–0.39	0.0001	–0.38	0.0001	–0.41	0.0001	–0.44	0.0001
Height (cm)	SA	–0.23	0.003	–0.18	0.02	–0.16	0.04	–0.19	0.02
	SL	–0.42	0.0001	–0.41	0.0001	–0.44	0.0001	–0.48	0.0001
Body mass (kg)	SA	–0.10	0.2	–0.12	0.11	–0.1	0.2	–0.14	0.08
	SL	–0.34	0.0001	–0.35	0.0001	–0.37	0.0001	–0.43	0.0001
Birth length (cm) (N=161)	SA	–0.18	0.02	–0.07	0.3	–0.16	0.04	–0.16	0.04
	SL	–0.21	0.007	–0.21	0.006	–0.22	0.006	–0.25	0.002
Birthweight (g)	SA	–0.04	0.6	–0.04	0.6	–0.1	0.2	–0.08	0.30
	SL	–0.13	0.1	–0.15	0.06	–0.15	0.05	–0.16	0.04
Hgb (N=160)	SA	0.24	0.002	0.17	0.04	0.16	0.05	0.09	0.26
	SL	0.28	0.0003	0.27	0.0005	0.26	0.0008	0.24	0.002
TIBC (N=160)	SA	0.06	0.5	0.08	0.28	0.007	0.9	–0.01	0.90
	SL	0.18	0.02	0.18	0.02	0.17	0.04	0.14	0.08
Minimum middle-ear pressure (N=160)	SA	0.08	0.29	0.13	0.1	0.04	0.6	0.04	0.60
	SL	0.33	0.0001	0.3	0.0001	0.31	0.0001	0.25	0.002
Cigarette consumption in pregnancy	SA	0.05	0.5	0.02	0.7	0.07	0.4	0.01	0.90
	SL	0.19	0.01	0.18	0.02	0.2	0.009	0.16	0.04
HOME score at 36 months (N=140)	SA	0.01	0.9	–0.04	0.67	–0.15	0.07	–0.22	0.01
	SL	0.19	0.03	0.16	0.06	0.15	0.07	0.1	0.23
Foot area (cm^2) (N=87)	SA	–0.21	0.05	–0.23	0.03	–0.15	0.17	–0.19	0.08
	SL	–0.19	0.08	–0.18	0.1	–0.21	0.05	–0.26	0.01
Sports participation	SA	–0.09	0.26	–0.13	0.1	–0.07	0.36	–0.08	0.30
	SL	–0.35	0.0001	–0.33	0.0001	–0.35	0.0001	–0.32	0.0001

Cofactors associated with sway variables at $p<0.1$ were considered for inclusion in multiregression models. (See Table I for abbreviations.)

Figure 3 shows stabilograms (*x–y* plot of CP) from two children. One child belongs to the lowest quartile PbB (<9.3µg/dL) and the other belongs to the highest quartile (>16µg/dL). These figures also show the spread of stabilograms with respect to the subjects' actual foot size and stance. A qualitative comparison of stabilograms from both subjects illustrates that the subject with lower PbB (subject A) had a smaller spread of movement of his CP compared with that of subject B, who had a higher PbB value. As the test conditions became more challenging for the nervous system and relatively more reliance was placed on the higher centers for balance maintenance, the sway patterns became larger for the child with higher PbB than for the child with lower PbB. As the spread of the stabilogram increased, the locus of the center of pressure reached closer to the outer boundary of the child's base of support (defined by the outline of the feet), rendering him more unstable.

The data from sway tests showed an increase in SA and SL as the test conditions became progressively more challenging (to the postural control systems) from EO to EC to FO to FC. The mean (SE) SA response values were 6.96 (0.30), 8.77 (0.37), 10.3 (0.42) and 19.6cm^2 (0.70) for EO, EC, FO and FC test conditions, respectively. The mean (SE) SL values for EO, EC, FO and FC test conditions, were 181.2 (9.9), 189.7 (9.3), 194.1 (9.4) and 227.1cm (8.8), respectively. A larger response in a sway variable implies poorer postural balance. These response patterns are consistent with our earlier findings (Bhattacharya *et al.* 1988, 1993).

Pearson bivariate correlation analysis showed that, for the EC test condition only, there were significant correlations

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TABLE VII
Covariate adjusted regression model coefficient for log PbB05 and sway area SA and length SL relationships

Test condition	*Sway variable*	*Beta*	*Standard error*	*p*	*Model* R^2	*N*
Eyes open	SA	0.22	0.10	0.03	0.19	158
	SL	0.62	0.14	0.0001	0.41	137
Eyes closed	SA	0.33	0.10	0.001	0.14	158
	SL	0.57	0.13	0.0001	0.39	137
Eyes open, foam	SA	0.19	0.09	0.04	0.09	138
	SL	0.52	0.12	0.0001	0.42	137
Eyes closed, foam	SA	0.21	0.09	0.02	0.15	140
	SL	0.34	0.09	0.0001	0.42	156

Other variables in final models included those listed in Table VI, as well as race, HOME score at 36 months of age, and number of known occurrences of bilateral otitis media. Not all covariables were statistically significant ($p<0.05$) in all models.

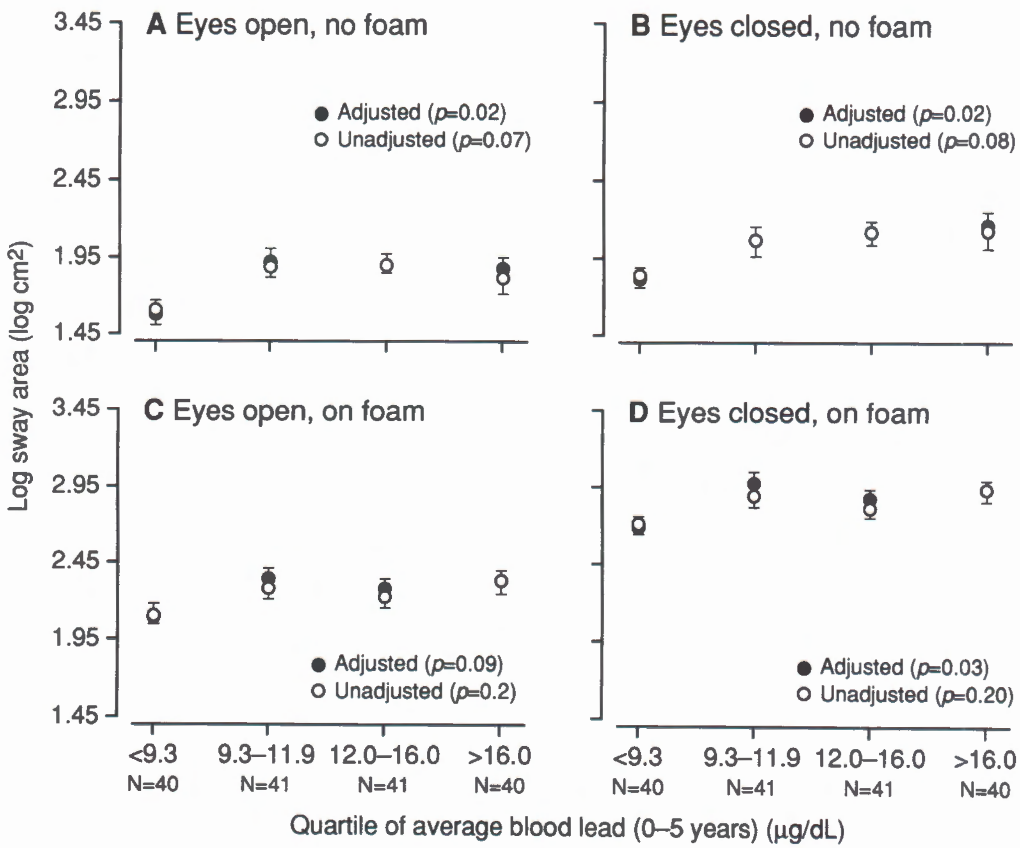

Fig. 4. (A, B) *Dose–effect relationship between PbB05 level quartile and sway area for eyes open and eyes closed test conditions. Both covariate-adjusted and unadjusted plots are shown. Two-way bars represent standard errors.* (C, D) *Dose–effect relationship between PbB05 level quartile and sway areas for eyes open (on foam) and eyes closed (on foam) conditons. Both covariate-adjusted and unadjusted plots are shown.Two-way bars represent standard errors*

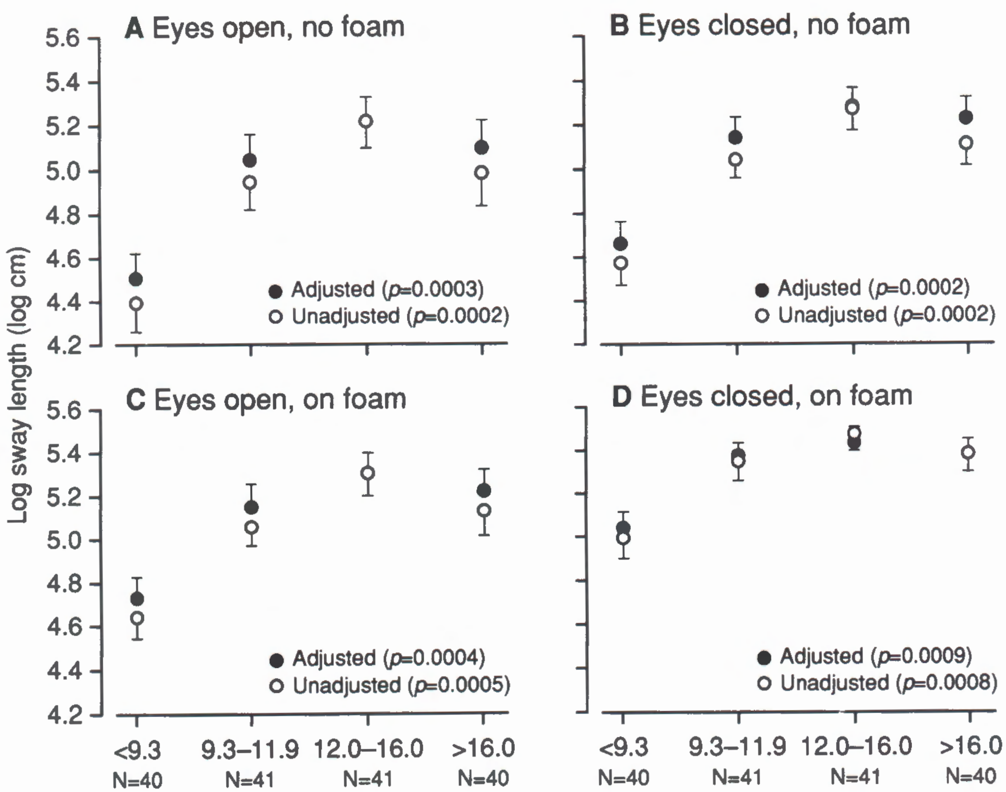

Fig. 5. *(*A, B*) Dose–effect relationship between PbB05 level quartile and sway length for eyes open and eyes closed test conditions. Both covariate adjusted and unadjusted plots are shown. Two-way bars represent standard errors. (*C, D*) Dose–effect relationship between PbB05 level quartile and sway length for eyes open (on foam) and eyes closed (on foam) test conditons. Both covariate-adjusted and unadjusted plots ae shown. Two-way bars represent standard errors.*

between SA and all PbB variables except prenatal PbB (Table IV). Table V shows bivariate correlation analysis results between SL and PbB variables. The correlations of SL with all the PbB variables were significant for all test conditions. The magnitude of the correlations was greatest for PbB05 and MaxPbB5. A positive correlation implies that the children with higher PBB levels showed poorer postural balance (as evidenced by higher SA or SL values).

Cofactors significantly associated with SA for all test conditions were age and height (Table VI). Other covariates which showed significant associations with SA in the expected direction for one or up to three test conditions included birth length, body mass, maternal intelligence, minimum middle-ear pressure, race, foot area (foot length × foot width), number of sporting activities participated in, and number of known occurrences of bilateral otitis media only over the first five years of life. However, significant associations between SA and Hgb and height were not in the expected direction. There were no significant correlations with TIBC, SES, cigarette consumption during pregnancy, birthweight, sex, combined number of occurrences of bilateral and unilateral otitis media over the first five years of life, hours of sleep before the sway test, and time elapsed between the last meal and the sway test.

Cofactors significantly associated with SL for one or more test conditions are also listed in Table VI. There was no significant correlation between hours of sleep before the sway test, time elapsed between the last meal and the sway test, race, sex, combined number of occurrences of bilateral and unilateral otitis media, number of known occurrences of bilateral otitis media only, the average of three HOME assessments, and SES for any

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of the test conditions.

A stepwise backward elimination multiple regression analysis was performed on the postural sway variables of SA and SL. The Pb exposure variable chosen for the primary analyses was PbB05, as this provides an overall lifetime postnatal exposure. The other variables included potential confounders and covariates listed in the Method section. Table VII presents the final regression models for SA and SL. The relationship between SA and PbB05 was most significant statistically for the EC test (p=0.001). On the other hand, the significance of the relationship between SL and PbB05, as well as the regression coefficient values (except for the FC test), were comparable for all four test conditions. 19 of 162 children underwent diagnostic and/or therapeutic chelation therapy for PB toxicity. The regression analysis was repeated without these children in the sample and the coefficients obtained were not significantly different than those obtained from the complete data set.

Figures 4 and 5 show the dose–effect association between SA, SL and PBB05. For both SA and SL variables, the sway responses for the second (≥9.3 to <12μg/dL), third (≥12 to ≤16μg/dL), and fourth quartiles (>16μg/dL) were significantly higher (p values between 0.03 and 0.0001) than that observed for the first quartile (<9.3μg/dL), based on the multiple group comparisons of the least-square means obtained following the analysis of variance (both with and without the covariates). This finding is consistent with our earlier results from a smaller subset of the Cincinnati Lead Study cohort (Bhattacharya *et al.* 1993). In general, the effect of covariate adjustment was minimal on the PbB05-sway relationship. For SA, the p values regarding the PbB–sway relationship were reduced after covariate adjustment (Fig. 4).

The dose–effect association was also evaluated with PbB05 categorized according to the guidelines of the Centers for Disease Control (1991) (<10μg/dL, >10 to 15μg/dL, >15 to 20μg/dL and >20μg/dL). Using the analysis of variance method, a multiple comparison of least-squares means for Log SA and SL was obtained between various PbB groups. As the PbB groupings according to the Centers for Disease Control guidelines were different than that of PbB quartile, the dose-effect relationship was not exactly the same as that shown in Figures 4 and 5. For the Centers for Disease Control grouping, only the SL relationship pattern was similar to that obtained for the PbB quartiles for the EO, EC and FO test conditions. In other words, for these three test conditions, the SL responses for the second (>10 to 15μg/dL), third (>15 to 20μg/dL), and fourth quartiles (> 20μg/dL) were significantly (p=0.07 to 0.003) higher than that observed for the first Centers for Disease Control PBB group (<10μg/dL). For the FC test, the SL responses for only second (p=0.01) and the fourth Centers for Disease Control (p=0.02) PbB groups were significantly higher than the first Centers for Disease Control group. Unlike the PbB quartile dose-effect relationship for SA, there were no significant differences in SA responses among various Centers for Disease Control-based PBB groups for EO, FO and FC. However, for the EC test, the SA response for the fourth Centers for Disease Control PbB group (>20μg/dL) was significantly (p=0.005) higher than that observed for the first Centers for Disease Control PbB group.

Discussion

The data from 162 children suggest that there is a significant association between postural sway response and lifetime postnatal exposure to Pb (Table VII, Figs. 4 and 5). This is shown by significant associations of sway with PbB05 for all test conditions for both the SA and SL variables (Table VII). In our earlier studies of a smaller subset of the Cincinnati Lead Project cohort, we have shown that this relationship was significant for the EC test condition only, implying potential functional impairment of the vestibular and/or proprioceptive systems (Bhattacharya *et al.* 1988, 1990). In the present analysis with a larger sample of children and a greater statistical power, the findings with EC were preserved and additional statistically significant relationships for the remaining three test conditions (EO, FO and FC) emerged.

The finding of significant sway *vs*

TABLE VIII
Covariate-adjusted regression model coefficient for log PbB05 and sway area: SA and length SL relationships for subjects with quarterly PbB never exceeding 20µg/dL

Test condition	*Sway variable*	*Beta*	*Standard error*	*p*	*Model* R^2	*N*
Eyes open	SA	0.73	0.22	0.002	0.31	64
	SL	1.80	0.36	0.0001	0.60	50
Eyes closed	SA	0.53	0.21	0.015	0.27	64
	SL	1.50	0.33	0.0001	0.54	50
Eyes open, foam	SA	0.57	0.20	0.005	0.26	52
	SL	1.40	0.30	0.0001	0.61	50
Eyes closed, foam	SA	0.68	0.23	0.005	0.28	52
	SL	10.70	3.70	0.007	0.65	50

Other variables in final models included those listed in Table VI, as well as race, HOME score at 36 months of age, number of reported injuries in lifetime, and number of known occurrences of bilateral otitis media. Not all covariables were statistically significant ($p<0.05$) in all models.

PbB05 relationship for the FO and FC conditions provides further evidence of potential Pb-associated modifications of the functional aspects of the proprioceptive and the vestibular systems. This can be explained by the fact that the degree of reliance on the vestibular system and the higher centers increases progressively as one is exposed to the EC, FO and FC test conditions (see Fig. 1) (Sahlstrand *et al.* 1978, Bhattacharya *et al.* 1987). In our earlier publications with a smaller data set (Bhattacharya *et al.* 1988, 1990: N=33 and 63, respectively), we observed a significant association of sway with PBB05 for the EC test only—implying potential Pb-induced modifications of the functional integration of the vestibular/proprioceptive systems. The roles of the vestibular/proprioceptive systems are further challenged in FO and FC tests. As the current larger data set (N=162) from these two tests also showed significant relationships of sway with PbB05, it further substantiates that the Pb-associated modification of the functional aspects of vestibular/proprioceptive systems significantly influenced the upright postural balance of the cohort. A factor analysis of a subset (N=100) of these data also suggests that the proprioceptive system was influenced by the Pb exposure (Shukla *et al.* 1991).

According to the multiple regression analysis, we were unable to detect any significant independent influence of SES, race, upbringing or other cofactors on the SA and SL *vs* PbB05 relationship.

Of all the cofactors, only age showed significant effects on SA for all four test conditions, implying that there was an age-related maturational influence on SA. The SA was also significantly influenced by Hgb and HOME scores for the EO and FC tests, respectively. The physiological significance of these findings is unclear. While SL was affected by HOME scores of the cohort for the EO, EC and FO test conditions, the direction of the effect was opposite to what was expected (range: β=0.02 to 0.03, p=0.002 to 0.0005). Therefore it appears that the statistical association of HOME score with SL was probably due to chance.

The other cofactors which showed significant associations with SL for all four test conditions were height of the children and number of sporting activities participated in by the subjects. The significant beneficial influence of sporting activities on postural balance was expected, as such activities can improve postural muscle strength, but this influence is likely to be bi-directional. Enhanced co-ordination brings more opportunities and motivation to participate in athletic activities. The significant association between SL and height implies that taller children show less movement of the body's center of pressure or have better balance. However, there is no physiological basis for the existence of such a relationship. One study of adults working with pesticides found a significant relationship between SL and the ratio of height and bodyweight (Sack 1993).

The other cofactors which showed significant associations with SL for one to three test conditions were minimum middle-ear pressure and Hgb. The physiological implications of these associations are also unclear.

An exploratory analysis was performed to discover how the relationship between sway variables and PbB05 would change if the analysis were performed on those children (64 of 162) whose quarterly PbB never exceeded 20μg/dL in their lifetime. Multiple regression analysis showed a statistically significant association (*p* values between 0.02 to 0.0001) between PbB05 and Log SA as well as Log SL for all test conditions (Table VIII). For the SA variable, covariate-adjusted regression coefficients for PbB05 ranged between 0.53 and 0.73 for all test conditions. For the SL variable, on the other hand, the covariate-adjusted regression coefficients of PbB05 ranged between 1.4 and 1.8 for the EO, EC, and FO test conditions. The coefficient for the FC condition was not interpretable as there were two variables (Hgb and minimum middle-ear pressure) interacting with PbB05. The interaction issue was further investigated. For lower levels of Hgb (10.7g per cent, fifth centile) or higher levels of minimum middle-ear pressure (23.1mmH_2O, 95th centile), the association between SL and PbB05 was much stronger than those obtained for the higher levels of Hgb (13.4g per cent, 95th centile) or lower levels of minimum middle-ear pressure (–246mmH_2O, fifth centile). The range of R^2 values for the overall regression models for all test conditions was 0.26 to 0.31 for the SA and 0.54 to 0.65 for the SL variable for all four test conditions. In this set of regression models, it was also found that the influence of rearing environment and other covariates was minimal for the SA variable compared with the SL variable. This exploratory analysis shows that, even after removing the children with high PbB levels (>20μg/dL) from the analysis, the associations between sway variables and PbB05 were still significant. For this subgroup of children (N=64), the dose–effect relationship between postural sway and the PbB05 was also evaluated to determine whether this relationship was different from that obtained for the complete data set (N=162). For this purpose, least-squares means comparisons among various quartiles were carried out for 64 children in two ways: (1) retaining original PbB groupings as per complete data set, and (2) using quartiles based on PbB data from a subgroup of 64 subjects. The children whose PbB never exceeded 20μg/dL essentially belonged to the first two PbB quartiles (<9.3μg/dL and ≥9.3 to <12.0μg/dL) based on the complete data set (N=162). For the 64 children, the statistical comparisons on the basis of the original PbB groupings show that both SL and SA means for PbB group 1 (<9.3μg/dL) were statistically different from that of the PbB group 2 (≥9.3μg/dL) for all test conditions (*p* values range between 0.001 and 0.02). This finding is similar to the one found for all the subjects (N=162). In order to study the dose–effect relationship for the subgroup of 64 subjects further, 'new' PbB quartiles were obtained: first quartile, <6.7μg/dL; second quartile, ≥6.7 to ≤8.6μg/dL; third quartile, >8.6 to ≤10 μg/dL; and fourth quartile, >10μg/dL. Since there were 'small' sample sizes in each quartile (N=16), the statistically non-significant differences between quartiles do not necessarily imply a lack of an association. A review of the statistically significant differences among PbB quartiles, however, indicated that SL exhibited similar dose–effect patterns as those obtained with the complete data set. In other words, the least-squares means for SL were increasing and then plateauing at higher PbB quartiles (>10μg/dL), which is comparable to the response pattern observed for the complete data set. In an attempt to comment on the presence or absence of a threshold for PbB effect, it suffices to say that the response means were generally increasing in magnitude with increasing PbB quartiles and thus suggested an absence of any definite threshold. Since there was a relatively small number of subjects per quartile, we cannot provide any more a definite answer to the presence or absence of a threshold for the effect.

In the present study, two correlated indices of sway (SA and SL) were obtained in four different test conditions. Thus the study examined possible associations between PB exposure and a total of eight correlated outcome measures. In order to reduce the likelihood of finding a false-positive association between PBB and Sway, we applied Bonferroni corrections to Tables VII and VIII. By applying Bonferroni corrections to Table VII, the conclusions of significant findings remain unchanged in five of eight test results. These were also the test conditions in which significant Pb–sway relationships were obtained in our earlier publications. Table VIII shows that Bonferroni corrections did not affect conclusions in seven of eight test results. Consequently, Pb–sway relationships with p values between 0.05 and 0.007 are to be interpreted as only suggestive of significant effects.

It has been observed that controlling for the influence of other variables usually tends to reduce the explanatory power of a particular independent variable. Occasionally the reverse may happen. On its own, PbB appears to have a significant association with sway variables. After controlling for covariables (such as age or height) the effect of PbB invariably increases. In the EC test condition, for instance, PbB by itself explained 5 per cent of the total variance in sway area, but its contribution increased to 8.2 per cent when age of child was included into the regression model. Similarly, for the sway length in the EC condition, PBB by itself contributed 9.8 per cent and the contribution increased to 12.1 per cent when height was included in the model. This phenomenon was generally observed for all the test conditions for both SA and SL. Such a characteristic is largely due to the intercorrelation among explanatory variables and their correlations with the outcome variable(s). For example, the age–sway area (and height–sway length) correlation is negative while the PbB–sway correlation is positive. Since the PbB–age correlation is positive, the PbB–sway relationship also includes the 'diluting' (or decreasing) effect of the age–sway relationship. When the effect of age on sway is separated from the effect of PbB on sway, the unique contribution of PbB on sway tends to increase.

Canonical correlation analysis was applied to determine which sway measurements (two sway parameters each for all four test conditions) were most closely related to PbB05. This method provides a linear combination of test results that is most highly correlated with PbB05, which is the first canonical correlation after adjusting for relevant covariates and confounders. In this case, because only one x variable (*i.e.* PbB05) is involved, the question is reduced to obtaining regression of PbB05 on all the test measurements after including the relevant covariates. This gives us the best linear combination of the test results most closely related to the lead exposure variable. It turned out that, indeed, all test measures can be summarized for SA (p=0.01 for the EC condition) and to a lesser degree for SL (p=0.06 for the EC condition). The covariates for this analysis were the number of occurrences of bilateral otitis media only and prenatal PbB. Note that the dependent variable for this analysis was PbB05.

The results of this analysis also confirm our earlier findings that the effect of lead exposure is most apparent in the EC test condition, which placed the greatest challenge on the proprioceptive and vestibular systems. This does raise the question as to whether the test for lead-associated balance modification should be evaluated with only the EC test. As the postural balance of these children did not appear to be fully mature, it is important to include at least two additional tests. The FO and FC tests will provide more insight into the effect of lead on the higher centers controlling upright balance.

As the data show that there is a significant increase in postural sway with higher PbB levels, it is worth mentioning the functional implications of larger sway. The major purpose of the postural control system is to reduce the deviations of the body's CP movement from its

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'upright' position. In general, the smaller and denser (*i.e.* less erratic) the sway pattern and the more centered it is within the foot boundary, the better the postural balance. The stability boundary is defined by the outer perimeter of the feet and a closer proximity of the center of gravity to the stability boundary which makes an individual more susceptible to postural imbalance that may result in a fall (Bagchee *et al.* 1933, Le Veau 1977, Bhattacharya *et al.* 1993). Impaired postural balance may discourage a young child from participating in sporting activities. On the other hand, as postural balance can be improved to a certain extent with appropriate conditioning of postural muscles, participation in sporting activities should help to improve the child's balance. However, in the present study, the association between SL and PbB05 was not affected by the total number of sporting activities participated in by the subjects.

Conclusions

The results from 162 children confirm the findings shown by our earlier data with a smaller number of subjects. One striking finding from the postural stability study was that the relationship between Pb exposure and postural sway response was not influenced by race, SES or the rearing environment of the cohort. With the number of subjects around 150, there was sufficient power (80 per cent) to detect 'small' effect sizes (proportion of variance explained for by a given cofactor around 5 per cent) at an alpha level of 0.05. Therefore, non-significant interactions presumably indicate almost zero effects (Cohen 1988). Because of the epidemiological nature of the study, our results provide evidence of an association rather than a cause. However, as these children were not exposed to any known neurotoxic agents other than lead (*e.g.* methylmercury or the organochlorines), we believe that the association found between lead exposure and postural balance is likely to reflect the influence of this metal on the development of the child's nervous system.

The exploratory analysis on children with quarterly PbB levels never reaching above 20μg/dL showed a significant association with sway variables. This finding implies that the postural balance measurement may be useful for assessing gross motor functions in children who are at or below the CDC Class III category (<20μg/dL). This simple, objective and quick technique may also be useful for monitoring the effectiveness of medical interventions aimed at reversing Pb-induced impairment of gross motor function which manifests as postural imbalance.

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SUMMARY
This study investigated the effect of chronic exposure to lead on children's ability to maintain upright postural balance as a biological marker of lead-induced modifications of the neuromotor system. For this study, 162 six-year-old children, with a five-year geometric mean lead concentration in blood of 11.9μg/dL (range 4.0–28.0μg/dL), were tested for postural balance with a microprocessor-based force platform system. An increase in blood lead was significantly associated with an increase in the variable postural sway—implying poorer postural balance. This association was not influenced by socio-economic, racial or environmental factors. This simple, objective and quick technique may be useful for assessing gross motor functions in children who are at or below

the United States Centers for Disease Control's class III category and/or for monitoring the effectiveness of medical interventions aimed at reversing lead-associated impairment of upright postural balance.

RÉSUMÉ

Effets de l'exposition précoce au plomb sur l'équilibre postural chez l'enfant

Cette étude a recherché les effects d'une exposition chronique au plomb sur la capacité des enfants à mainteniur un équilibre debout, comme marqueur biologique des moifications du système nerveux induites par le plomb. L'équilibre postural sur une plate-forme de force gérée par microprocesseur a été apprécié chez 1262 enfants de six ans chez qui la moyenne géométrique de la concentration de plomb dans le sang était de 19,9 microgrammes par lite (écarts de 4 à 28 micorgrammes). Un accroissement du plomb sanguin était significativement associé à un accroissement des oscillations posturales, révélant un équilibre postural moins bon. Cette association n'était pas relié aux facteurs socio-économmiques, raciaux ou d'environnement. Cette technique simple, objective, rapide peut être utile pour apprécier la fonction motrice globale pour les enfants qui sont au niveau ou au dessous de la classe III des Centres U.S. pour le contrôle des affections et/ou pour contrôler l'efficacité des interventions médicales destinées à corriger les troubles de l'équilibre debout liés au plomb.

ZUSAMMENFASSUNG

Auswirkungen einer frühen Bleiexposition auf die Haltungskontrolle bei Kindern

In dieser Studie wurde der Einfluß einer chronischen Bleiexposition auf eine stabile aufrechte Haltung bei Kindern im Sinne eines biolotgischen Markers für Blei-induzierte Modifikationen des neuromotorischen Systems untersucht. Bei 162 sechs-jährigen Kindern mit einer mittleren Blutbleikonzentration von 11,9µg/dl (Streubereich: 4,0–28,0µg/dl) über fünf Jahre wurde für diese Studie die Haltungskontrolle mit einer mit Mikroprozesor ausgerüsteten, Druck-registrierenden Plattform getestet. Eine Zunahme der Blutbleikonzentration ging einher mit einer gisnifikanten Zunahme der Haltungsunsicherheit, d.h. einter schlechteren Haltungskontrolle. Diese Korrelation war unabhängig von sozioökonomischen, völkischen oder Umweltfaktoren. Diese einfache, objektive und schnelle Methode könnte zur Beurteilung der grobmotorischen Funktionen bei Kindern hilfreich sein, die auf oder unter Stufe III der United States Centers for Disease Control sind und/oder zur Kontrolle der Wirksamkeit medizinischer Behandlungskonzepte für die Blei-induzierten Störungen der aufrechten Haltungskontrolle.

RESUMEN

Efecto de la exposición precoz al plomo sobre el equilibrio postural de los niños

Este estudio investigó el efecto del la exposición crónica al plomo sobre la capacidad de mantener el equilibrio postural erguido, como un marcador biológico de las modificaiones sobre el sistema neuromotor inducidas por el plomo. Para este estudio se examinó el equilibrio postural por medio de un sistema de lataforma basada en un microprocesador, en 162 niños de seis años de edad, con un promedio geométrico de concentracion de plomo en sangre de cinco años de 11'9 µg/dl (margen de 4'0–28'0µg/dl. Un aumento en el plomo de la sangre iba asociado significativamente a un aumento en la variable balance postural, indicando un equilibrio postural más pobre. Esta asociación no estaba influida por ningún factor sodioeconómico, racial o ambiental. Esta técnnica simple, objectiva préactica puede ser útil para evaluar las funciones motoras groseras—en niños que estan en o port debajo, en los Centros US para el control de la enfermedad, en la clase III y/o para monitorizar la eficacia de las intervenciones médicas encaminadas a revertir las alteraciones en el equilibrio postural asociadas al plomo.

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