Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience

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Abstract

Objectives—An epidemiological study of young adults was conducted to determine whether environmental exposure to lead during childhood was associated with current adverse neurobehavioural effects.

Methods—The exposed group consisted of 281 young adults who had been exposed environmentally to lead as children and the unexposed referent group consisted of 287 age and sex frequency matched subjects. Information on demographics, past and current health, and past exposures to neurotoxicants, and responses to the Swedish Q16 questionnaire were collected by interview. Standard neurobehavioural and neurophysiological tests were administered by computer or trained technicians. K x ray fluorescence was used to estimate tibial bone lead concentrations among the exposed and unexposed groups. Associations were examined between the exposed group and referents and tibial bone lead concentration and the neurobehavioural and neurophysiological outcomes of interest.

Results—Among the measures of peripheral nerve function, after controlling for confounders, sural sensory nerve evoked response amplitude, peroneal motor nerve compound motor action potential amplitude, vibrotactile thresholds of fingers and toes, and standing steadiness were significantly associated with exposure group. Among the neurobehavioural tests, hand-eye coordination, simple reaction time latency, trails B latency, symbol digit latency, serial digit, and learning error score were also significantly associated with exposure group after controlling for confounders. Exposed subjects had significantly more neuropsychiatric symptoms than the referents. Associations between tibial bone lead concentration and scores for vocabulary, vibrotactile thresholds of the fingers, and vibrotactile thresholds of the toes approached significance.

Conclusions—Significant adverse central and peripheral neurological effects were found in a group of young adults 20 years after childhood environmental exposure to lead when compared with non-exposed controls. The absence of a significant association between neurological outcomes and tibial bone lead concentration, and the presence of significant associa-

tions between neurological outcomes and exposure group may be due to either the magnitude of measurement uncertainty in K x ray films relative to the actual tibial bone lead concentration in these young non-occupationally exposed subjects, or uncontrolled confounding of the exposure group.

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The effects of inorganic lead on occupationally exposed adult populations have been well studied.¹⁻³ Less well studied and more controversial are the effects on adults of exposure to lead sustained during childhood. Some investigators have associated moderate exposure to lead in infancy and childhood with impairments of both the central nervous system (CNS) and peripheral nervous systems (PNS) in adults.⁴⁻¹¹ However, other investigations have not consistently shown such effects.¹²⁻¹⁴ Previous studies of community exposures to lead have relied on surrogate measures of the total body burden of lead or cumulative lifetime dose. For example, blood lead concentrations obtained once or integrated over time have been used to estimate lifetime exposure to lead.¹⁵⁻¹⁶

K x ray fluorescence (KXRF) measurements of tibia lead content have been shown to be a measure of cumulative exposure to lead¹⁵⁻²⁰ and the technique has been applied in studies of both occupational and environmental exposure to lead.¹⁵⁻²¹⁻²² The technique is a direct measure of a person's lead burden and may therefore clarify exposure-effect relations which have previously been studied and assessed by other methods. Although potentially powerful, this method of exposure assessment has not been widely applied in the study of long term neurobehavioural and neurological effects among adults possibly resulting from childhood environmental exposure to lead.

KXRF was applied in the current epidemiological study of a sample of a larger cohort of young adults who were exposed to lead during childhood while living near a lead smelter in the Silver Valley, Idaho, USA. The objectives of the study were to determine whether childhood exposure to lead was associated with neurobehavioural, reproductive, and kidney function among adults. This report focuses on neurobehavioural and neurophysiological test results and on neurological symptoms.

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Methods

SUBJECTS

The cohort consisted of 917 young adults 19–29 years of age who were from 9 months to 9 years of age during the period 1 January 1974 to 31 December 1975 and resided in one of five towns surrounding the lead smelter in the Silver Valley. The 1974–5 period was chosen because the smelter was known to have been operating without appropriate emission reducing devices during this period. Monthly lead emissions from the smelter averaged 8.3 metric tonnes in the years 1955–64, 11.7 metric tonnes from 1965 to September 1973, and 35.3 metric tonnes from October 1973 to September 1974.⁸ Also, data from past blood lead surveillance of this population showed that mean blood lead concentrations among children 9 months to 9 years of age were 50.0 µg/dl in 1974 and 39.6 µg/dl in 1975. Cohort members 9 months to 4 years of age were located from birth records and those 5–9 years of age from school records.

Birth and school records identified 2145 children who met these criteria. Of these, 43 were determined to be ineligible because the subject either had died or had not lived in one of the five towns; therefore, the final cohort comprised 2102 subjects. During initial locating efforts, 636 cohort members could not be located. From locating efforts that included Equifax credit bureau searches of cohort members or their parents, a review of current telephone directories from the Silver Valley, and a review of 1974 and 1975 telephone directories, 1466 subjects were successfully traced to their current address or telephone number. In July 1994, 325 cohort members could not be located, 92 could not be reached during the study period, 39 were identified as ineligible when contacted, and 93 refused to participate. The overall response rate was 91% (917 of 1010).

To identify control subjects, records were used from the Washington Department of Licensing Records. The names of 42 232 male and female licensed drivers between the ages of 19 and 29 who resided in Spokane, Washington, were received on computer disk in June 1994. A random sample of 6993 records of licensed drivers was obtained, from which current telephone numbers and addresses were located for 2489 subjects. Of the 2489 subjects for whom addresses and telephone numbers were available, 1267 were ineligible because they no longer lived at the address, were unavailable for interview, or had previously lived in the Silver Valley; 468 refused to participate, and 754 completed telephone interviews. The overall response rate from control subjects was 62% (754/1222).

To obtain a subsample of the larger cohort for invitation to participate in medical testing, a random sample was drawn from exposed and referent subjects who completed telephone interviews. A total of 563 of the 917 interviewed exposed subjects were asked to participate in medical, neurobehavioural, and laboratory testing, and of these, 281 (50%) agreed to participate. A total of 463 of 754 interviewed

referent subjects were asked to participate in the study and 287 (62%) agreed to participate. The results presented here were obtained during the medical testing phase of the study.

DATA COLLECTION

Telephone interviews were conducted with the 917 cohort members between 10 July and 7 August 1994. Information was collected about medical, reproductive, occupational, and residential histories. Socioeconomic and demographic characteristics were included in the telephone interview. Also, a 16 item standardised questionnaire designed to assess chronic neuropsychiatric disturbances was administered.²³

Participation in medical testing consisted of completion of a battery of neurophysiological and neurobehavioural tests (see later) that was used to determine the functional status of both the CNS and PNS. Also, KXR of tibial bone lead concentration (see exposure assessment) was performed on each subject. Both exposed and referent subjects were tested between 8 August and 15 September 1994, at Sacred Heart Medical Center in Spokane, Washington. All subjects who participated in the clinical portion of the study provided informed consent.

EXCLUSIONS

One cohort member was excluded from the analysis because his mental disability required proxy responses from a family member. People with chronic conditions were removed from the analysis depending on which neurological test was assessed. For example, in analyses of vibration sensitivity measurements, subjects with current nerve damage as a result of trauma or other injury to the hand, arm, shoulder, or spine were removed ($n=29$), as were subjects reporting diabetes ($n=7$) and carpal tunnel syndrome ($n=18$). In analyses from the neurobehavioural evaluation system, subjects were removed from the analyses for conditions or medications that may affect either the PNS or CNS; table 1 shows these conditions and medications.

NEUROBEHAVIOURAL AND NEUROPHYSIOLOGICAL TESTS

Study participants underwent manual and computerised neurobehavioural testing, as well as electrophysiological testing.^{24–36} All tests were performed in private rooms by technicians blinded to the subjects' exposure status. The testing protocol had seven components (table 2): electrophysiological; sensory; standing steadiness; motor; cognitive; mood; and Swedish Q16.

Twenty neurobehavioural outcome variables were initially selected to be sensitive indicators of a wide range of CNS and PNS functions. A portion of the questionnaire included the Swedish Q16 that asked about neurological symptoms and was administered one month before neurobehavioural testing.³⁷

Table 1 Subject exclusion criteria for analyses of peripheral and central nervous system outcomes

Reason	PNS	CNS	Exposed		Unexposed	
			n	%	n	%
Medications:						
Antidepressant		x	4	1.4	2	0.7
Antipsychotic		x	0	0.0	1	0.4
Anxiolytic		x	1	0.4	0	0.0
Hypoglycaemic	x	x	2	0.7	1	0.4
Opiate		x	1	0.4	1	0.4
Antiseizure		x	0	0.0	1	0.4
History of:						
Cancer	x		1	0.4	3	1.1
Diabetes	x		2	0.7	1	0.4
Seizures		x	7	2.5	3	1.1
Renal dialysis (current)	x	x	1	0.4	0	0.0
Mental retardation		x	1	0.4	0	0.0
Hereditary polyneuropathy	x		1	0.4	0	0.0
Multiple sclerosis	x	x	1	0.4	0	0.0
Self reported heavy drinking	x	x	7	2.5	3	1.1
Subjects excluded (total n)						
PNS outcomes			13	4.6	7	2.4
CNS outcomes			24	8.5	11	3.8
Subjects not excluded (total n)						
PNS outcomes			268	95.4	280	97.6
CNS outcomes			257	91.5	276	96.2

EXPOSURE ASSESSMENT

KXRF was used to measure tibia lead concentration, expressed as $\mu\text{g Pb/g}$ bone mineral, as an index of long term exposure.¹⁸ About 3 cm of the left tibia midshaft was measured. Before measurement the skin surface was cleaned with isopropyl alcohol to reduce contamination. Each measurement took 30 minutes and required an effective dose of 35 nSv.²⁰ System

performance, defined as twice the median individual uncertainty on in vivo results, was 9 $\mu\text{g Pb/g}$ bone mineral. Two similar systems were used, one from the University of Maryland,¹⁷ the other from McMaster University.¹⁹ To ensure compatibility of data, the same set of calibration and quality assurance standards were used for both systems and both systems used the same analytical software to derive lead concentrations. When true bone lead concentrations are near zero and measurement uncertainty is large, the distribution of bone lead concentration includes negative values. These conditions are often present when KXRF measures of bone lead concentration are performed on non-occupationally exposed subjects, and consequently, negative values for bone lead concentrations are commonly found when this technique is used in such populations.

STATISTICAL METHODS

All statistical analyses were performed with the SAS statistical software package.³⁸ Exposure was defined as ever or never having lived in one of the five towns surrounding the smelter during the period 1974–5. Also, tibial bone lead measurements were used as a cumulative exposure to lead index. After excluding from data analysis those subjects meeting earlier exclusion criteria—for example, diabetes or mental retardation—differences in mean test

Table 2 Tests of neurophysiological and neurobehavioural function administered to referents and young adults exposed to lead as children

Test	Function/domain	Direction of performance†	Score
Electrophysiological ³³ :	Sensory/motor		
Sural sensory NCV		+	Velocity (m/s)
Sural sensory amplitude		+	μV
Peroneal motor NCV		+	Velocity (m/s)
Peroneal motor amplitude		+	mV
Peroneal F wave (latency)		+	ms
Heart rate variability ³⁴	Autonomic	–	CV of R-R intervals
Sensory:			
Contrast sensitivity ³⁵	Vision/sensory	+	Correct (n)
Peripheral vibration sensitivity ^{29–31}	Sensory		
Dominant hand		–	Log_{10} μm displacement
Non-dominant hand		–	Log_{10} μm displacement
Dominant toe		–	Log_{10} μm displacement
Non-dominant toe		–	Log_{10} μm displacement
Standing steadiness ³² :	Balance/vestibular	–	Sway speed (cm/s)
Motor:			
Dynamometer ²⁸	Strength/motor	+	Grip strength (kg)
Grooved peg board ²⁵	Coordination/fine motor		
Dominant hand		–	Seconds to completion
Non-dominant hand		–	Seconds to completion
Santa Ana ²⁴			
Dominant hand	Coordination/motor	+	Pegs/30 s (n)
Hand-eye*	Coordination/motor	–	Root mean square error
Finger tapping*	Coordination/motor	+	Taps/30 s (n)
Cognitive:			
Simple reaction time*	Attention	–	Mean latency (ms)
Trail making test ²⁷			
Form A	Cognitive tracking	–	Time to completion (s)
Form B	Concept shifting	–	Time to completion (s)
Symbol digit substitution*	Coding	–	Errors (n)
Serial digit learning*	Learning/attention	–	Errors (n)
Raven's progressive matrices ²⁶	Non-verbal intelligence	–	Errors (n)
Vocabulary*	Verbal intelligence	+	Correct (n)
Mood:*			
Tension	Tension/mood	–	Symptom rated (1–5)
Depression	Depression/mood	–	Symptom rated (1–5)
Anger	Anger/mood	–	Symptom rated (1–5)
Fatigue	Fatigue/mood	–	Symptom rated (1–5)
Confusion	Confusion/mood	–	Symptom rated (1–5)
Swedish Q16	Symptoms	–	Yes responses (n)

*Computer administered neurobehavioural evaluation system (NES2).³⁶

†+ = higher score indicates better performance; – = higher score indicates poorer performance.

Table 3 Demographic and other characteristics for exposed and referent populations

Characteristic	Exposed			Referent		
	n	Mean	SD	n	Mean	SD
Age (y)	257	24.3	3.18	276	24.2	3.02
Sex (%):						
Male	122	47.7		137	49.6	
Female	135	52.3		139	50.4	
Age distribution (%):						
19–21	64	24.9		62	22.5	
22–24	62	24.1		85	30.8	
25–27	78	30.4		71	25.7	
28–30	53	20.6		58	21.0	
Race/ethnicity (%):						
White	252	98.0		260	94.2	
Aleut Eskimo or Native American	3	1.2		4	1.4	
Asian or Pacific Islander	0	0.0		2	0.7	
African American	0	0.0		3	1.1	
Other	2	0.8		7	2.5	
Income (per annum) (%):						
<\$10 000	33	12.8		22	8.0	
\$10 000–19 999	77	30.0		59	21.4	
\$20 000–29 999	55	21.4		57	20.7	
\$30 000–39 999	32	12.5		48	17.4	
\$40 000–49 999	24	9.3		29	10.5	
>\$50 000	19	7.4		38	13.8	
Refused to declare	17	6.6		23	8.3	
Years of education (%)	257	12.6	1.67	276	13.8	1.64
<12	33	12.8		9	3.3	
12	112	43.6		66	23.9	
13–16	108	42.0		190	68.8	
>16	4	1.6		11	4.0	
Missing	1	0.4		0	0.0	
Height (cm):						
Male	121	178.1	6.21	137	179.1	5.76
Female	135	164.1	7.40	139	165.7	6.14
Weight (kg):						
Male	121	83.8	18.84	137	83.8	16.66
Female	135	72.4	20.54	139	71.5	19.64
BMI (kg/m ²):						
Male	121	28.3	5.34	137	26.0	4.28
Female	135	26.8	7.32	139	26.0	6.92
Current blood lead (mean µg/dl)	257	2.9	3.25	273	1.6	1.36
Blood lead 1974–5 (mean µg/dl)	43	49.3	22.38	—	—	—
Bone lead (µg/g) (%):						
<1	76	31.5		130	50.4	
1–5	58	24.4		66	25.6	
5–10	53	22.3		50	19.4	
>10	52	21.8		12	4.7	
Cigarette smoking:						
Current smokers (%)	72	28.0	8.15	54	19.6	7.19
Cigarettes/day	72	12.5		54	13.1	
Alcohol consumption:						
Current drinkers (%)	177	68.9	3.93	196	71.0	
Drinks/week	174	2.6		195	3.0	4.65

scores between exposed and unexposed groups were compared with simple *t* tests. Crude analyses with the mean (SD) were conducted on all examiner administered manual, computer administered neuropsychological and electrophysiological tests.

Subsequently, backward elimination stepwise multiple linear regression models were fitted separately to each of the 20 neurobehavioural test score variables to control for potentially confounding effects of important covariates of the neurological and neurobehavioural outcomes in this population. The initial set of covariates for the PNS outcomes included age, sex, height, body mass index (BMI), and skin temperature. The set of potential covariates of CNS function were age, sex, education (highest year completed), visual acuity, and an index of self reported effort in performing the tests (coded 1 to 4). Vocabulary score was used as an outcome rather than as a covariate because exposure to lead had occurred during the period of cognitive (including vocabulary) development, and controlling for a variable also affected by exposure to lead would have artifactually attenuated the esti-

mates of associations between childhood exposure to lead and performance on the other neuropsychological tests. Average annual income was considered as a potential covariate, but was not included in the set because reduced current income might result from the effects of childhood exposure to lead on neurobehavioural function; also, controlling for current income would result in overcontrolling and biased estimates of the effect of exposure to lead on the outcomes. Although reduced years of education might be an effect of childhood exposure to lead,³⁹ education was included as a potential covariate, even though doing so risked overcontrolling. Exposure group was forced into all the backward elimination stepwise regression models. The potential covariates were eliminated until only variables related (at the *p*<0.10 level) to the outcome variable remained in the model. In general, any covariate that accounted for at least 1% of the total variance was retained in the models.

Results of these analyses are presented in terms of the standardised regression coefficients of the variables remaining in the models. Additional backward elimination stepwise regression models were fitted with the bone lead concentrations found (first as a continuous variable, then as a four level stratified variable) instead of the dichotomised exposure group variable in the models.

Frequencies of positive reporting of neuropsychiatric symptoms of the Swedish Q16 questionnaire in each of the two exposure groups and their corresponding crude odds ratios (ORs) were calculated for the 16 individual items and a dichotomised composite score (>4 symptoms *v* ≤4 symptoms). Backward elimination stepwise logistic regression models were also fitted to these variables with age, sex, and education included as potential covariates.

Results

Table 1 shows the number of participants in each exposure group excluded from data analyses of PNS and CNS outcomes due to their meeting initial exclusion criteria. Significantly more participants were excluded from the exposed group (8.5%) than from the referent group (3.8%), mainly due to self reported history of seizures and excessive current alcohol intake.

Table 3 shows the sociodemographic characteristics of the exposed and referent groups. The groups were comparable in terms of the age, sex, and race distributions. Compared with the referent group, the exposed population was less well educated, had lower annual incomes, consumed slightly more tobacco, consumed slightly less alcohol (after exclusion of subjects from both groups who reported drinking >5 drinks a day), and were slightly shorter (about 1 cm). Weight and BMI were similar for the two groups. The mean current blood lead concentration was slightly higher for the exposed group (2.9 µg/dl) than for the referent group (1.6 µg/dl), but both were quite low. Historical blood lead concentrations

Table 4 Mean (SD) of concentrations of lead in bone* in exposed and referent groups by age

Age group	Exposed			Referent			<i>t</i> Test <i>p</i> Value
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	
19–21	58	1.47	8.35	61	1.27	6.60	0.88
22–24	60	4.48	7.45	81	−0.61	6.19	<0.001
25–27	69	4.82	8.92	64	0.60	8.60	0.006
28–30	51	6.64	9.53	52	1.74	6.42	0.002

*Bone lead concentrations are in µg Pb/g bone mineral.

available for 43 of the exposed subjects examined were high, averaging 49.3 µg/dl. This information was available from data collected by the Idaho Department of Health and Welfare.

Mean tibia lead concentrations were 4.6 µg Pb/g bone mineral (range −28.9 to 37.0) in the exposed group and 0.6 µg Pb/g bone mineral (range −46.4 to 17.4) in the referent group. In the exposed group, 31% of subjects had concentrations <1 µg Pb/g bone mineral and 22% had concentrations >10 µg Pb/g bone mineral. By contrast, 50% of the referent group had concentrations <1 µg Pb/g bone mineral and 5% had concentrations >10 µg Pb/g bone mineral. Bone lead correlated significantly with age in the exposed group, but not in the referent group. When the subjects were divided into age subgroups (table 4) bone lead was significantly higher in all exposed subgroups except for those aged 19–21 years. For all subjects taken together, there was a weak correlation between current bone lead concentration and current blood lead concentration ($r=0.24$).

For those exposed subjects for whom blood lead data were available from 1974–5 ($n=46$), there was a modest correlation between current bone lead concentration and past blood lead concentration ($r=0.39$).

Table 5 shows the crude mean scores for the neurological and neurobehavioural outcomes. All the observed crude differences in exposure group were in the direction of poorer performance by the exposed group than the referent group.

Among the electrophysiological measures, the crude mean sural sensory amplitude and peroneal motor amplitudes were found to be slightly smaller among the exposed group than among the referents. The corresponding nerve conduction velocities were similar between the two groups. Among the behavioural tests of peripheral nerve function, the crude mean vibrotactile thresholds of the fingers and standing steadiness both with eyes open and eyes closed showed differences that were significant between the exposed and referent groups. The crude mean coefficient of variation of the electrocardiographic R-R interval, visual contrast sensitivity, and vibrotactile thresholds of the toes seemed to be similar between the referent and the exposed groups. Crude mean differences for 11 of 12 motor and cognitive function tests were significant. The largest crude effects of exposure group were found for the hand-eye coordination, trails B, symbol digit, serial digit learning, Raven progressive matrices, and vocabulary tests. Only for mean grip strength

Table 5 Mean (SD) of neurological tests in exposed and referent groups

Neurological test	Exposed		Referent		<i>t</i> Test <i>p</i> Value
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Electrophysiological:					
Sural sensory NCV	263	47.8 (5.31)	271	47.7 (5.87)	0.83
Sural sensory amplitude	263	16.8 (8.56)	271	18.3 (10.0)	0.07
Peroneal motor NCV	265	49.9 (4.19)	273	49.9 (3.81)	0.98
Peroneal motor amplitude	266	5.8 (2.54)	276	6.2 (2.53)	0.03
CV of R-R (rest)	267	5.9 (3.03)	277	6.0 (3.21)	0.07
Sensory:					
Contrast sensitivity	267	5.5 (1.36)	278	5.6 (1.25)	0.39
Vibration sensitivity:					
Dominant hand	267	1.4 (0.64)	278	1.3 (0.42)	0.007
Non-dominant hand	268	1.3 (0.41)	278	1.2 (0.38)	0.003
Dominant foot	267	2.9 (1.14)	277	2.7 (0.96)	0.18
Non-dominant foot	266	2.9 (1.33)	278	2.7 (1.02)	0.07
Standing steadiness:					
Eyes open	255	1.3 (0.28)	276	1.2 (0.24)	0.003
Eyes closed	255	1.9 (0.59)	276	1.8 (0.51)	0.03
Motor:					
Dynamometer	267	36.7 (12.8)	278	38.0 (12.49)	0.22
Grooved peg board					
Dominant hand	267	61.9 (9.96)	278	59.7 (7.97)	0.003
Non-dominant hand	268	67.2 (11.7)	277	64.5 (11.22)	0.005
Santa Ana (dominant hand)	267	46.2 (5.58)	278	47.6 (5.56)	0.004
Hand-eye coordination	266	1.8 (0.38)	280	1.6 (0.35)	<0.0001
Finger tapping	267	149.2 (20.3)	280	153.2 (21.2)	0.02
Cognitive:					
Simple reaction time	256	258.6 (37.1)	276	250.42 (29.3)	0.004
Trailmaking A	257	25.6 (7.97)	274	24.0 (7.10)	0.01
Trailmaking B	256	62.0 (22.6)	274	51.4 (15.7)	<0.0001
Symbol digit	256	1.8 (0.32)	276	1.7 (0.31)	<0.0001
Serial digit learning	256	3.4 (3.45)	276	2.3 (2.34)	<0.0001
Raven progressive matrices	257	10.6 (4.68)	274	8.5 (4.40)	<0.0001
Vocabulary	255	13.3 (6.76)	276	17.0 (6.26)	<0.0001
Mood:					
Tension	252	2.8 (0.78)	275	2.5 (0.77)	<0.0001
Depression	252	2.0 (0.78)	275	1.8 (0.65)	<0.001
Anger	252	2.2 (0.84)	275	1.9 (0.68)	<0.0001
Fatigue	252	3.0 (0.83)	275	2.7 (0.81)	<0.001
Confusion	252	2.4 (0.79)	275	2.0 (0.67)	<0.0001
Swedish questionnaire 16	252	4.7	275	2.3	0.0001

dynamometry were crude group differences not significant. Large crude mean differences were also found for all five of the mood scores and the neuropsychiatric symptom summary score from the Swedish Q16.

To control for potential confounding, backward elimination stepwise multiple linear regression models were fitted to all outcome variables. Table 6 shows the standardised regression coefficients from these models. In the final backward elimination stepwise linear regression models, sural sensory amplitude and peroneal motor amplitude were significantly related to exposure group. Height, BMI, and skin temperature remained in the model as significant covariates for sural sensory amplitude; and age, BMI, and skin temperature remained in the model as significant covariates for peroneal motor amplitude. Vibration threshold of the fingers and toes was significantly related to exposure. No covariates were retained in the model for the finger measure, whereas sex and height were retained in the model for the toe measure. Standing steadiness with eyes open as well as with eyes closed was significantly associated with exposure group after controlling for height and BMI. Regardless of significance, the estimated effect of being in the exposed group was negative for 11 of the 12 PNS outcomes analysed. The total variance accounted for by the multiple regression models of PNS outcomes varied widely ($R^2=0.03-0.53$).

For the motor and cognitive outcomes, and after controlling for the effects of relevant covariates, exposure group was significantly associated with poorer performance on the hand-eye coordination, simple reaction time, trails B, symbol digit, serial digit learning, Raven progressive matrices, and vocabulary tests (table 6). Regardless of significance, the

estimated effect of being in the exposed group was negative for all 12 of the motor and cognitive outcomes analysed. Education was a significant covariate for all cognitive outcomes, regardless of the significance of the effect of exposure group. Age, sex, and self report of effort in performing the tests, as well as interviewer (not shown), were significantly related to some of the motor and cognitive outcomes. Also, the score from the Swedish Q16 was significantly associated with exposure group after controlling for the effects of relevant covariates. The total variance accounted for by the multiple regression models of motor and cognitive outcomes ranged from 0.06 to 0.69.

To investigate relations between tibial bone lead and neurological and neurobehavioural variables, additional backward elimination stepwise multiple regression models were fitted that were identical to those just described except that tibial bone lead concentration was forced into the models rather than exposure group. Tibial bone lead concentration was not significantly related to any of the outcomes analysed. However, a trend for three measures approached significance: finger vibrotactile threshold ($p=0.09$), toe vibrotactile threshold ($p=0.08$), and vocabulary score ($p=0.06$). Similar results were found when an exposure variable representing stratified (four strata) tibial bone lead concentration was used in the models rather than tibial bone lead concentration as a continuous measure.

In crude analyses, 15 of the 16 neuropsychiatric symptoms from the Swedish Q16 were found significantly more often among exposed than referent subjects. Relative frequencies of positive responses for the 15 items ranged from a low of 15.2% for perspire for no reason for

Table 6 Standardised regression coefficients from stepwise regression models for neurological and neurobehavioral outcomes

Dependent variable	Exposure group†	Age	Sex	Height	BMI	Skin temperature	Education	Try hard	Model R^2
Electrophysiological:									
Sural sensory NCV	0.002	—	—	-0.249	0.168	—	—	—	0.092
Sural sensory amplitude	-0.102**	—	—	-0.255	-0.125	-0.256	—	—	0.179
Peroneal motor NCV	-0.026	—	—	-0.404	—	0.284	—	—	0.207
Peroneal motor amplitude	-0.100*	-0.089	—	—	0.131	-0.184	—	—	0.054
Peroneal F wave latency‡	-0.009	-0.057	—	-0.734	—	0.077	—	—	0.534
CV of R-R intervals	-0.022	-0.112	—	-0.119	—	—	—	—	0.027
Sensory:									
Visual contrast sensitivity (D)	-0.011	—	—	0.103	—	—	—	—	0.011
Vibration threshold, fingers‡	-0.163****	—	—	—	—	—	—	—	0.027
Vibration threshold, toes‡	-0.098**	—	-0.23	-0.427	—	—	—	—	0.096
Standing steadiness:									
Eyes open‡	-0.120**	—	—	-0.150	-0.120	—	—	—	0.050
Eyes closed‡	-0.100**	—	—	-0.272	-0.174	—	—	—	0.111
Motor:									
Dynamometer	-0.32	0.076	-0.614	—	—	—	0.160	—	0.689
Grooved pegboard‡	-0.071	—	0.283	—	—	—	0.215	—	0.113
Santa Ana pegboard	-0.026	0.076	-0.093	—	—	—	0.131	—	0.073
Hand-eye coordination‡	-0.193****	—	-0.332	—	—	—	0.140	0.085	0.197
Finger tapping	-0.046	—	-0.327	—	—	—	0.100	—	0.131
Cognitive:									
Simple reaction time‡	-0.090*	—	-0.223	—	—	—	0.216	—	0.076
Trails A latency‡	-0.036	—	0.172	—	—	—	0.297	—	0.079
Trails B latency‡	-0.169****	—	0.183	—	—	—	0.373	0.090	0.183
Symbol digit latency‡	-0.117**	-0.199	0.288	—	—	—	—	0.088	0.277
Serial digit learning error‡	-0.155***	—	—	—	—	—	0.154	—	0.063
Raven errors‡	-0.115**	—	—	—	—	—	0.282	0.118	0.133
Vocabulary score	-0.167****	0.109	—	—	—	—	0.337	0.077	0.214
Swedish Q16:									
Score‡	-0.238****	—	-0.106	—	—	—	0.327	—	0.230

* $p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$.

†Exposure group was coded as 0 = unexposed, 1 = exposed.

‡Scores inverted so that higher score indicates better performance.

the exposed group *v* 3.3% for the referent group to a high of 48.1% *v* 31.6% for have headache at least once a week. Crude ORs ranged from 1.79 for less interested in sex than normal to 5.33 for perspiring for no reason. Only the symptom difficulty buttoning or unbuttoning clothes, which is a negative control item in the Swedish Q16, did not show a significant difference between exposed (2.0%) and referent (1.1%) groups (crude OR=1.81, 95% CI 0.43 to 7.66). Backward elimination logistic regression analyses containing variables for age, sex, and education as potential covariates yielded similar results. All of the items except two had parameter estimates that were significantly different from zero. Those two items were have headache at least once a week and the control item difficulty buttoning or unbuttoning clothes. Additional backward elimination stepwise logistic regression analyses did not show significant relations between tibial bone lead concentration and any of the neuropsychiatric symptoms.

Discussion

Results of central and peripheral neurological measures among a group of adults aged 19–29 years who were exposed environmentally to lead between ages 9 months and 9 years were compared with a similar group which was not known to be exposed to lead. Participants were classified as exposed and unexposed by location of residence, and tibial bone lead was measured by KXRF fluorescence to provide a biological assessment of current bone lead concentrations.

Among the tests of peripheral neurological function, while adjusting for potential confounders, evoked response amplitudes of the sural sensory and peroneal motor nerves, as well as vibrotactile threshold and postural stability measures, were significantly associated with exposure group. Among the CNS outcomes, after adjusting for potential confounders, significant associations were found between exposure group and hand-eye coordination, simple reaction time, trails B, symbol digit, serial digit learning, Raven progressive matrices, and vocabulary tests, as well as the Swedish Q16 score. For all CNS outcomes and nearly all of the PNS outcomes, the estimated effect of exposure group was in the direction of poorer performance among the exposed than the referent group, even for those differences that did not achieve significance.

SOURCES OF BIAS

Several potential biases should be considered when interpreting the results of the present study. These include confounding bias, information bias in the form of error in estimation of exposure (reporting bias and measurement error), and error in identification of health outcome (observer and reporting bias, measurement error) and selection bias (poor response rates).

Firstly, it is possible that the associations found when exposure was dichotomised were, in fact, due to uncontrolled confounding by variables associated with group status. Efforts

were made to measure the most important covariates of the outcomes used—for example, age and height for PNS outcomes, and sex and education for CNS outcomes—and to account for them with multivariate linear statistical models. It is possible that other variables, unmeasured in the current study, were not controlled and produced confounding bias that was unrecognised. For example, the referent group was identified from another community and may have differed for variables that have the potential to influence the outcomes used—for example, parental IQ and quality of public education systems. However, these potential confounders were not measured, and historical data for them were not available.

Controlling the effects of neurological and neurobehavioural covariates that are likely themselves to be affected by exposure to lead—such as education—was particularly difficult. On a population basis, many of the neurobehavioural outcomes included in this study are, in part, a function of education. In turn, educational attainment has been shown to be dependent, in part, upon exposure to lead.³⁹ Inclusion of educational attainment as an independent variable in models in which a measure of exposure to lead is also an independent variable would result in overcontrolling the association between lead and the outcome, and therefore attenuate the observed association. Despite this potential null bias, education was included in the statistical models of neurobehavioural outcome.

Because participants were not blinded to their exposure group, reporting bias may have occurred for some measures, especially those requiring subjective responses (such as the Swedish Q16) and those requiring a high level of effort and motivation by the participant, such as the neurobehavioural tests. However, several of the outcomes that were significantly associated with exposure group—for example, peroneal and sural nerve evoked response amplitudes—were completely objective and were, therefore, not subject to such reporting bias. These findings suggest that reporting bias is, at least, not fully responsible for the observed associations of neurological and neurobehavioural outcomes with exposure group.

It is unlikely that the neurophysiological and neurobehavioural test outcomes were influenced by observer bias. The technicians administering these tests were unaware of either each participant's exposure group or the results of tibial bone lead concentrations. Many of the tests were computerised and, therefore, consistent in their administration, making observer bias even less likely.

Several important biases in the null effect direction were likely to have occurred in the present study. In particular, heterogeneity of actual exposure within each of the exposure group categories, and errors in measurement of both tibial bone lead concentration and neurological or neurobehavioural outcomes were likely to have attenuated the observed associations between exposure and outcome. Specifically, exposure-effect relations between exposure group and neurological outcome

would have been attenuated if relatively unexposed people were included in the exposed group and relatively exposed people were included in the referent group. Review of occupational and vocational histories did not show any known sources of exposure to lead among participants in either group other than the one actually used to define the exposure group (residence in the communities near the smelter). Also, current blood lead concentrations were low in both groups, suggesting no substantial current exposure to lead. However, the considerable overlap of the distributions of tibial bone lead concentrations among the two exposure groups suggests that, to some extent, exposure may have been misclassified despite the occupational histories and current blood lead concentrations.

Error in KXRF measures was substantial in this study, although not dissimilar to error found in other studies of similar, non-occupationally exposed groups. In the current study, the mean uncertainty of the KXRF measures (a standardised estimate of measurement precision) was 4.8 µg/g across all participants (mean tibial bone lead=2.7 µg/g). By comparison, Kim *et al*⁴⁰ obtained a mean uncertainty of 5.0 µg/g in a population with a mean tibial bone lead of 1.3 µg/g and Hoppin *et al*⁴¹ obtained a mean uncertainty of 3.9 µg/g in a population with a tibial bone lead of 4 µg/g. The relatively modest precision of this exposure estimate likely resulted in attenuation of observed associations between exposure and the neurological and neurobehavioural outcomes.

Error in measurement of neurobehavioural outcomes can be substantial, which limits the practical sensitivity of these measures in detecting the effects of exposures in epidemiological studies. However, this type of error can be overcome to some extent by increasing sample size. The sample size in the present study was large for this type of study. The precision in measurement of neurobehavioural outcomes in the present study was sufficient to find expected relations to known covariates that accounted for as little as 1% of the total variance. Also, the magnitude of the residual error in the regression analyses, which varied substantially among outcome measures, was similar to that found in other studies of neurobehavioural function.⁴²

It is possible that the sample of subjects who actually participated in the current study were not representative of the actual exposed population. The overall response rate for the first phase of the study (telephone interviews) was 91% for exposed and 62% for referents and for the second phase (KXRF and neurological and neurobehavioural testing) was 50% among the exposed group and 62% among the referents. It is possible that associations found in the current study were biased by differences between those who chose to participate in the study and those who did not. Also, selection bias may have been introduced because the referent population was drawn from driver's licence records and included only those people without neurological effects that might prevent

them from obtaining a driver's licence. Reconstructing the referent population from birth and school records and subsequent tracing would not have been possible.

COMPARISON WITH OTHER STUDIES OF TIBIAL BONE LEAD MEASURED BY KXRF

The average tibia lead content of the exposed subjects in this study, 4.6 µg Pb/g bone mineral, is much lower than concentrations found in studies of occupationally exposed subjects.^{15 43 44} Tibia lead contents have been reported for several community based studies for several age groups. Average tibial concentrations have ranged from three to 21 µg Pb/g bone mineral and some dependence with age has been found.⁴⁵⁻⁵⁰ The concentrations determined here for young adults are comparable with other studies of environmental exposure within this age group.

COMPARISON WITH OTHER STUDIES OF NEUROBEHAVIOURAL AND NEUROLOGICAL EFFECTS OF LEAD

The results of the present study are supported by previous studies of adults exposed to lead during childhood.^{39 51 52} White *et al* followed up adults 50 years after childhood lead poisoning (hospital records showed symptoms consistent with blood lead concentrations of 60–100, 90–120 and >120 µg/dl); results showed poorer performance on cognitive and motor function tests.⁵¹ The neurological tests investigated in the present study did not allow direct comparison with the study of White *et al* because the mean age of that study population was 55 years and the exposure to lead was presumably acute lead poisoning, whereas the mean age of the present study population was 24 years and the exposure was to environmental lead from a lead smelter.

Needleman *et al*³⁹ investigated a cohort 11 years after childhood exposure to lead (exposure to lead was determined from dentine concentrations of teeth shed at ages 6 and 7 years). Results showed deficits in cognitive and motor function tests. Furthermore, subjects were seven times more likely not to have graduated from high school if their previous dentine lead concentrations were >20 ppm. It is noteworthy that in the present study, more exposed subjects than referents reported having less than a 12th grade education, 14.2% *v* 3.1%, respectively.

A smaller subset of the cohort of Needleman *et al* was investigated by Bellinger *et al*⁵² who recruited 79 subjects, aged 19 and 20 years, with dentine concentrations >24 µg/g or <8.7 µg/g. Exposure to lead was also determined by KXRF of the tibia and showed an average concentration of 1.6 µg/g (range -9 to 19). Results showed that dentine lead concentrations were inversely related to scores on two of four attention performance tests. Tibial bone lead was inversely related to scores for both digit symbol and cancellation tests. The investigators concluded that tibial bone lead was not associated with neuropsychological test scores, although significant differences were observed on two tests.

Numerous past investigations have examined the relation between occupational exposure to lead and nerve conduction velocity. Only a few studies have reported results of evoked response amplitude associated with exposure to lead. In past studies of occupationally exposed subjects, the nerve conduction results found have not been entirely consistent. However, associations have been found between exposure to lead and both conduction velocity and evoked response amplitude.⁵³⁻⁵⁵ We are aware of no studies of young adults in which either conduction velocities or evoked response amplitudes were reported. In the present study, nerve conduction velocity was not associated with any measure of exposure, but evoked response amplitudes of the peroneal motor nerve and sural sensory nerve were associated with exposure group.

ASSOCIATIONS BETWEEN DICHOTOMISED EXPOSURE GROUP AND KXRF

Nearly all health outcome measures associated more strongly with dichotomised exposure classification (exposed *v* referent) than with the continuously distributed tibia lead concentration. Possible explanations for this finding include: (a) poor analytical methods; (b) high relative measurement variation at low bone lead concentrations; (c) an inherently weak relation between current bone lead and the toxicologically meaningful dose at the time of exposure; and (d) possible uncontrolled confounding of exposure group status.

It is unlikely that measures of tibial bone lead concentration were performed poorly. State of the art equipment was used and values obtained were similar to those obtained by other investigators. Mean values for members of the exposed group were higher than those for members of the unexposed group, as expected. Other factors are more likely to explain the lack of association between tibial bone lead concentration and neurological and neurobehavioural outcomes, factors such as the variability in KXRF measurements. Recently published studies have shown that, among non-occupationally exposed groups, substantial variability is found in KXRF tibial bone lead measurements. Bellinger *et al*⁶² found substantially stronger associations with dentine lead than with tibial or patellar bone lead concentrations and concluded that the KXRF measures of bone lead were not sufficiently precise to serve as markers of childhood lead absorption. Hoppin *et al*⁶⁰ also found substantial variability and had similar concerns about KXRF precision among non-occupationally exposed people. In the light of these observations, it is likely that the uncertainty of the KXRF measurements resulted in considerable attenuation of the associations found between tibial bone lead concentration and the neurological and neurobehavioural outcomes tested.

Finally, regardless of the precision of measurement, tibial bone lead concentration in young adulthood may not be a strong indicator of the toxicologically important dose of lead actually delivered to the critical target neurological tissues in childhood. Bone is a

dynamic tissue; remodelling and turnover of mineral content associated with growth may result in bone lead concentrations that are not strongly associated with the actual historical dose.⁵⁶

Conclusions

The current study is the only large epidemiological study to date to examine associations between tibial bone lead concentration and neurological and neurobehavioural outcomes. It was hypothesised that tibial bone lead concentration might be a useful surrogate for biologically meaningful community exposure to lead in young adults who were exposed 20 years earlier. In the current study, significant associations were found between dichotomised exposure group and neurobehavioural outcomes, but not between tibial bone lead concentration and neurobehavioural outcomes. Although tibial bone lead measurements from occupationally exposed groups have been useful in determining lead body burden, they may not currently have the precision necessary to measure community based exposure to lead in young adults. An alternative explanation may be that the associations found between neurobehavioural outcomes and exposure, classified as never or ever, may have resulted from uncontrolled confounding of exposure group.

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