Port Pirie Cohort Study: Childhood blood lead and neuropsychological development at age two years

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SUMMARY The Port Pirie Cohort Study is an ongoing prospective study of the relationship between exposure to environmental lead within a lead smelter community, and neuropsychological development in early childhood. Over 600 children, originally recruited during antenatal life, underwent serial blood lead estimations up to two years of age. Systematic interview information was collected on a range of variables, and formal developmental assessment (Bayley Scales of Infant Development) was carried out at 24 months of age.

Blood lead concentrations measured antenatally (maternal), at delivery (maternal and umbilical cord) and postnatally at 6, 15 and 24 months were negatively correlated ($p < 0.05$) with mental development at 24 months of age. Geometric mean blood lead concentrations ($\mu\text{g/dl}$) were 14.3, 20.8 and 21.2 at 6, 15 and 24 months of age respectively.

When multiple covariates, including maternal IQ, were controlled for in multiple regression analysis, a statistically significant ($p < 0.01$) inverse association was observed between blood lead concentration (PbB) measured at 6 months of age and mental development at 2 years of age. No such association was evident for psychomotor development. When the quality of the home environment (HOME Score) was added to the multiple regression model, the inverse association between blood lead concentration at 6 months of age and mental development at 2 years persisted, albeit less strongly ($p = 0.07$). From this analysis, it is estimated that a child with PbB of 30 $\mu\text{g/dl}$ at age 6 months will have a deficit of 3.3 points (approximately 3%) on the Bayley Mental Development Scale relative to a child with PbB of 10 $\mu\text{g/dl}$.

The neuropsychological sequelae of acute lead encephalopathy are well documented. Uncertainty persists about the nature of adverse effects of lesser levels of lead exposure upon the neuropsychological development of young children.^{1 2} A recent review has noted a progressive decline over the past 20 years in the lowest blood lead concentration (PbB) considered dangerous enough to warrant medical attention.³

In 1984, the UK Medical Research Council concluded from a literature review that "a moderate elevation of body lead burden as found in some British children has little or no effect on IQ".⁴ That review depended primarily on studies that were cross-sectional, relied on tooth-lead to estimate prior lead exposure, or were confined to children of school-age.^{1 4-6} More recently, a large cross-sectional study of children aged 6-9 years in Edinburgh reported an

inverse relationship between blood lead concentration and measures of cognitive ability and educational attainment.⁷

Few data exist about the effects of environmental lead exposure on the neuropsychological development of children under school age. Recently, results have been reported from two prospective studies. Among 249 children in Boston, USA, umbilical cord PbB was inversely related, after multiple confounder adjustment, to cognitive development measured at 6-monthly ages up to two years.⁸ However, no such relationship existed with postnatal PbB measures. A study in Cincinnati reported an inverse association between fetal and post-natal lead exposure and motor development in infancy.⁹

When the primary source of lead is exposure to lead-containing dirt/dust, childhood PbB peaks at

around two years of age.^{10 11} This suggests that maximum exposure to environmental lead occurs during the second year of life, thus overlapping with the period of rapid growth and development of the immature central nervous system. Hence studies of school-age children cannot examine the child's neuropsychological performance at an age when the developing nervous system may be most vulnerable to environmental influences.

During 1979–82, pregnant women were recruited for a prospective study of lead exposure in relation to pregnancy outcome and early childhood development. The women lived in the South Australian industrial city of Port Pirie (population 16 000) and the surrounding agricultural districts. Because of the longstanding operation of Australia's largest lead smelter on the immediate periphery, and upwind, of the city, the Port Pirie community has been exposed throughout this century to substantial accumulation of lead and other heavy metals in topsoil and dust.

The primary aim of this ongoing cohort study is to examine early childhood development, up to the age of 7 years, in relation to cumulative lead exposure, as assessed by lead concentrations in maternal blood, placenta, children's blood, and deciduous teeth. This paper describes the relationship between PbB, measured antenatally and postnatally, and child development as assessed at age two years.

Methods

The original cohort of 723 neonates represented approximately 90% of all children born in the city of Port Pirie or in the surrounding agricultural area, which includes four smaller towns, between September 1979 and October 1982.¹²

Venous blood samples were taken from the pregnant women on enrolment into the study (14–20 weeks gestation), early in the third trimester, and at delivery. Umbilical cord blood samples were collected at birth. At postnatal ages of 6, 15 and 24 months, and annually thereafter, capillary bloods samples were collected into heparin under standardised conditions¹³ by a trained nurse-interviewer who followed the capillary collection technique meticulously.

The validity of the capillary blood sampling was separately assessed on a sample of 47 metropolitan Adelaide children aged 2–4 years.¹⁴ A very close correlation ($r=0.97$) was observed between PbB values obtained by a capillary sampling technique (identical with that used in the Port Pirie study) and those obtained by simultaneous venous sampling. PbB was estimated by atomic absorption spectrometry with electrothermal atomisation after standard complexing and extraction of lead.¹⁵ PbB values were standardised to a packed cell volume of 35% for

pregnant women, 50% in cord blood, and 35% in infants.

At ages 6, 15 and 24 months, the numbers of children remaining in the cohort were 652, 619 and 601, respectively. Children were lost to follow-up primarily because of families leaving the Port Pirie district. For a smaller number of children, their families elected to discontinue their participation in the study. Three children were excluded from follow-up because of chronic neurological disorders not related to lead exposure.

At 24 months of age (± 2 weeks) the developmental status of each child was measured with the Bayley Scales of Infant Development.¹⁶ This instrument comprises a Mental Scale of 163 items and a Motor Scale of 81 items. The Mental Scale assesses sensory-perceptual acuities and discriminations, and ability to respond to these; it also assesses acquisition of "object constancy", memory, learning, problem-solving ability, early language and speech development, and ability to form generalisations and classifications. Results are expressed as a single standard score—the Mental Development Index (MDI). The Motor Scale measures gross and fine motor coordination. In assessing motor skills and coordination it is not concerned with functions that are primarily "mental" or "intelligent" in nature. Results are expressed as a single standard score—the Psychomotor Development Index (PDI).

From the original standardisation carried out in a large representative sample of children in the USA, aged 2–30 months, the expected mean score for each scale is 100 (standard deviation = 16). Both scales have good tester-observer reliability and test-retest reliability, and the MDI has good correlation ($r=0.57$) with the Stanford Binet Intelligence Scale over the age-range common to the two tests (24–30 months).¹⁶

A single research psychologist conducted all of the Bayley Scales testing. The psychologist was "blind" to the child's previous or current blood lead estimations. Developmental testing was conducted in a clinic setting on a different day from blood collection.

At the time of each blood collection, the nurse-interviewer obtained, by structured interview, information on a wide range of demographic, psychosocial, medical, behavioural and developmental variables. Data were collected on these variables because of their possible confounding (and interactive) effects upon any association between body lead burden and neuropsychological development.

When children were aged 3–4 years, maternal IQ was assessed with the Weschler Adult Intelligence Scale—Revised (WAIS—R).¹⁷ Maternal IQ scores were not obtained for 163 of the mothers, predominantly because of refusal to be tested; their

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children were assigned to a separate IQ category so that the remaining covariate information could still be incorporated in the multivariable analysis.

The HOME Inventory was also applied in all cases. This is an observation/interview technique that assesses the quality of stimulation available to the child in the home.¹⁸ It provides a more sensitive and direct measure than do structural and status indices such as parental occupation, education, family size, and type of dwelling. It measures processes that mediate the child's development, such as parent-child transactions, the types of play objects available, specific events and stimulating experiences that occur in the home environment, and the general quality of the physical home environment. The instrument comprises six sub-scales (emotional and verbal responsiveness of parent; parental acceptance of child; maternal involvement with child; organisation of home environment; provision of appropriate play materials; variety in daily stimulation), and those aspects of the home environment measured by this instrument have demonstrated a strong relationship with intellectual and language development in early childhood.^{18 19} It has been shown to have good reliability. Its use in such studies was recommended by the First International Lead Workshop (held in Cincinnati in 1981).²⁰ The instrument was administered during a visit to the child's home at age 3 years by a nurse trained in its use by a psychologist.

STATISTICAL ANALYSES

Since blood lead concentrations are log-normally distributed, geometric rather than arithmetic means are presented here. The standard error factor in the tables must therefore be interpreted as a multiplier. Log PbB was used in the calculations of correlations between PbB and Bayley scores. An "integrated PbB" has been calculated by trapezoidal integration of each individual's blood lead curve derived from serial PbB estimates from umbilical cord blood, and the 6, 15 and 24 month blood samples, and is presented as a summary estimate of total lead exposure in post-natal life.

Results

Variations in mean PbB by age are shown in table 1. The mean PbB rises sharply between the ages of 6 and 15 months. The maximum value occurred at 2 years of age (21.2 µg/dl), after which a slight but steady decline has occurred in this cohort at 3 and 4 years. There were no significant differences in PbB between females and males. The range of individual blood lead concentrations observed within this initial 2-year age span was 2–67 µg/dl.

Table 1 Geometric mean blood lead concentration by age

Age	No of children	Mean blood lead (µg/dl)	95% Confidence limits
Umbilical Cord	523	8.3	8.0–8.6
6 months	579	14.4	13.9–14.8
15 months	583	20.9	20.2–21.5
2 years	590	21.2	20.6–21.8
Integrated postnatal	497	18.1	16.5–19.6

The Bayley Scales of Infant Development were completed for 595 children at 24 months of age. The mean Bayley Mental Development Index (MDI) was 109.2 (SD = 15.3); and the mean Bayley Psychomotor Development Index (PDI) was 105.3 (SD = 14.8). There was no statistically significant difference in mean Index scores between the Port Pirie (n = 450) and non-Port Pirie (n = 145) children.

Table 2 Correlations between blood lead concentrations at serial ages and Bayley developmental indices at 24 months

Blood sample	Pearson correlation coefficient		
	Mental devt. index	Psychomotor devt. index	No of children
Maternal: 14–20 weeks gestation	–0.06	–0.05	509
After 20 weeks gestation	–0.08*	–0.02	560
Average prepartum	–0.11*	–0.06	586
At delivery	–0.03	–0.02	524
Child: Umbilical cord	–0.04	–0.04	520
6 months	–0.12*	–0.07	575
15 months	–0.12*	–0.02	579
24 months	–0.18†	–0.02	586
Integrated postnatal	–0.15†	–0.01	494

* <0.05 † <0.01

The Bayley Mental Development Index (MDI) was negatively correlated with PbB at all ages (table 2). The correlation attained statistical significance in both the antenatal and the postnatal periods, but not at time of birth (maternal and umbilical cord blood samples). Conversely, the correlations of the Bayley Psychomotor Index (PDI) with each PbB were weak, and none achieved statistical significance.

The relationship between PbB and Bayley MDI scores at 24 months was explored further by comparing groups of children who had had "raised" and "never-raised" PbB levels. Children were categorised as "raised" if their PbB had exceeded 30 µg/dl at least once at 6, 15 or 24 months of age. The children with raised PbB (n = 162) had a mean Bayley MDI of 105.5, compared with a mean MDI of 110.9 for children (n = 402) whose PbB was never raised.

A subsequent analysis, based on cumulative post-natal lead exposure, showed that when children were classified into three cumulative exposure groups, a strong inverse association between PbB history and MDI was evident (table 3).

Table 3 Association of Bayley MDI with blood lead history

Blood lead concentration	No of children	Integrated postnatal blood lead ($\mu\text{g/dl}$)	Mean MDI	SE
Persistently high*	51	29.9	102.2	1.6
Intermediate†	451	18.4	109.7	0.6
Persistently low‡	62	10.0	112.2	1.6

*PbB concentrations in highest quartile of PbB distribution on all three postnatal samplings (6, 15 and 24 months).

†All except high and low group

‡PbB concentrations in lowest quartile on all three occasions.

The relationship to Bayley MDI score of each of those variables considered to be potential determinants of childhood development was examined by univariate and multiple regression analyses. The relationships between 13 such variables

Table 4 Association of sociodemographic, neonatal and behavioural factors with Bayley MDI

Factor	No of children	Mean MDI	SE
Sociodemographic factors:			
Maternal age (years):			
<21	104	105.7	1.5
22–29	377	110.2	0.8
≥30	109	109.8	1.3
Father's secondary education (years):			
unknown	74	99.1	1.7
≤3	250	108.9	1.0
>3	271	112.5	0.9
Mother's secondary education (years):			
≤3	286	108.0	0.8
>3	289	111.0	0.9
Father's workplace:			
office	147	111.8	1.4
non-office	438	108.6	0.7
Mother's workplace:			
away from home	238	111.9	1.0
home	349	107.6	0.8
Parental relationship:			
living together	537	110.2	0.6
living apart	52	100.0	2.1
Mother's antenatal marital status:			
single, widowed, divorced	59	102.2	2.0
married or defacto	531	110.1	0.7
Child's birth rank:			
first born	274	109.9	1.0
second born	199	109.1	1.0
subsequent	122	108.3	1.3
Neonatal Factors:			
Neonatal oxygen use at birth:			
required	173	106.7	1.0
not required	411	110.5	0.8
Apgar score at 5 minutes:			
≤8	132	105.2	1.3
9 or 10	448	110.4	0.7
Neonatal jaundice:			
present	220	108.7	1.1
absent	366	109.7	0.8
Size for gestational age:			
small	33	101.2	2.9
appropriate	489	109.6	0.7
large	56	111.6	2.0
Behavioural factor:			
Mouthing activity at 15 months:			
frequent	243	107.9	0.9
intermediate	306	110.0	0.9
never	42	113.7	2.8

and MDI scores, as determined by stratified univariate analysis, are shown in table 4. Other variables which were examined but are not reported here were either highly correlated with variables reported, or provided no explanatory power in the analyses.

Parental education, parental workplace, and parental relationship were associated with Bayley MDI. The lowest mean Bayley MDI scores were for children of separated parents and for mothers with "single-parent" status in the antenatal period. (These two categories overlapped substantially with another category—"father's education unknown", a circumstance also associated with a low MDI score). Of the neonatal factors, oxygen requirement at birth, a neonatal Apgar rating of 8 or less at five minutes, and low birth weight for gestational age were each associated inversely with Bayley MDI score at 24 months.

At interview, parents were asked about their child's mouthing activity (placing objects in mouth, sucking fingers) whilst playing outside. An increased reported frequency of mouthing behaviour at 15 months of age was associated with a decrease in Bayley MDI score at 24 months (table 4).

Maternal intelligence is a well-established correlate of childhood development. A strong positive association is evident in table 5.

Table 5 Bayley MDI by maternal intelligence score (WAIS)

Maternal WAIS	No of subjects	Bayley MDI	SE
≤80	50	98.3	2.7
81–90	117	108.7	1.4
91–100	145	111.1	1.3
>100	94	114.0	1.6
Refused or unavailable	163	108.1	1.0
All mothers	592	109.3	0.6

A multiple regression analysis was undertaken with and without maternal IQ entered into the multivariable model. The linear model was not significantly improved by the addition of quadratic terms in continuous covariates. PbB was entered after the above-mentioned 13 other sociodemographic, neonatal and behavioural variables had been entered.

With maternal IQ absent from the model there was a statistically significant negative association ($p < 0.05$) between PbB, measured either at 6 months of age or as the integrated postnatal average, and Bayley MDI score at 24 months (table 6). When maternal IQ was introduced into the model the statistically significant association persisted for PbB at 6 months of age and for the integrated postnatal PbB.

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Table 6 Partial linear regression coefficients for each blood lead measure with and without maternal IQ and HOME score in the model*

Blood lead measure	Regression coefficients (change in MDI per unit change in blood lead [$\mu\text{g/dl}$])		
	Ignoring maternal IQ	Controlling for maternal IQ	Controlling for maternal IQ and HOME score
Average antenatal	-0.26	-0.21	-0.07
Delivery	+0.19	+0.27	+0.23
Cord	+0.05	+0.07	+0.10
6 months	-0.24 (p=0.01)†	-0.24 (p=0.01)	-0.16 (p=0.07)
15 months	-0.09	-0.06	-0.03
24 months	-0.16	-0.12	-0.05
Integrated postnatal	-0.26 (p=0.03)	-0.22 (p=0.05)	-0.12 (p=0.19)

*The model contains the 13 socioeconomic, demographic, neonatal and behavioural factors shown in table 4.

†One-tailed significance values

The relationships of PbB and a range of possible covariates to psychomotor development (Bayley PDI) were also examined. No statistically significant association was found.

In univariate analysis, there was a strong positive correlation between the HOME score and Bayley MDI. A very low HOME score also appeared to be associated with a low Bayley PDI, but there was otherwise no clear relationship between these two variables. Since the HOME score was negatively correlated with integrated postnatal PbB, thus making it a potential confounder, a multiple regression analysis was undertaken in which PbB measures were entered after both HOME scores and maternal IQ had been entered (table 6). Inclusion of the HOME score in the multivariable model resulted in attenuation of the residual effect of PbB on Bayley MDI. The relationship between PbB at 6 months and Bayley MDI remained almost statistically significant (p=0.07), whereas the existence of a real relationship between the integrated postnatal PbB and Bayley MDI became less probable (p=0.19).

The results of this multivariable analysis indicate that, other factors remaining constant, a child's MDI score at 2 years will decrease by 1.6 points (i.e. 1.5%) for every 10 $\mu\text{g/dl}$ rise in PbB at six months of age. Thus, it would be predicted that a child with a PbB of 30 $\mu\text{g/dl}$ at age six months would have a 3.2% deficit in mental developmental attainment at age two years relative to a child with a PbB of 10 $\mu\text{g/dl}$.

Discussion

The developing central nervous system of the young human becomes less sensitive to subtle environmental influences with increasing age.²⁰ It is therefore important to assess the neuropsychological effects of environmental lead exposure in very young children

when the impact of the exposure on the developing central nervous system is likely to be maximal.

The findings reported here indicate that elevations in PbB at six months of age have greater negative effect upon infant mental development than do elevations at other times in the antenatal period and the first two years of life. At six months of age few infants are independently mobile, and elevations in PbB may thus reflect sustained exposure to a lead-contaminated home environment. In contrast, children with elevated PbB at older ages could have episodic or transient exposure to environmental lead, dependent upon the level of contamination of various environmental loci in combination with the child's mobility and hand-to-mouth activity.

Bellinger and colleagues have recently reported, from their Boston cohort, a negative association between antenatal lead exposure (using umbilical cord blood lead concentration as the index) and MDI measures during the first two years of life.⁷ However, in this present study there was no clear association between cord PbB and infant development at two years. Such differences in the results of studies may reflect differences in the mean and range of PbB in the population of children being studied, and in the extent of environmental, social, and behavioural heterogeneity within the study population. Ease of detection of any relatively weak effects of lead would be enhanced by selecting an otherwise more homogeneous population of children. Another reason that no effect of umbilical PbB on Bayley MDI at 2 years has been observed in this cohort may be because of the likely greater impact of the much higher levels of PbB encountered postnatally.

The multiple regression strategy adopted in this study is potentially conservative in that those variables that are associated with a low Bayley MDI (for example, single parent family, father in non-office occupation, low maternal IQ, and low HOME score) may well exert some of their effect upon MDI through an associated increased exposure of the child to environmental lead. Therefore, by according priority in the multivariable model to these variables, with their associated but indeterminate lead-exposure content, the residual "unconfounded" effect of PbB on mental development may underestimate the true effect—and will also be more difficult to detect.

Consistent with earlier studies of the determinants of child development, parental education, the marital status of parents, and Apgar score each accounted for some of the variance in MDI scores within this study population. Inclusion of those variables, along with the HOME score and maternal IQ in the multiple regression model, attenuated the estimated independent effect of PbB on Bayley MDI. Nevertheless, and despite the conservative (potentially

over-controlled) multivariate data analysis, the inverse relationship between PbB at six months and Bayley MDI at two years retains borderline statistical significance. Further, the estimated partial regression coefficients for all PbB measures (excluding those measured at birth) remain negative (table 6, right-hand column).

These results indicate that, with other factors remaining constant, a child's MDI at 24 months will be 1.6 points (equivalent to 1.5%) lower for every 10 µg/dl rise in PbB at 6 months of age. Such a decrement may be of little clinical significance to the individual child. However, in population terms, a decrease of several percentage points in the mean score on a test of mental/intellectual ability for a group of children will be associated with an increased proportion of children with functionally significant deficit, compared with the general population of children.² Moreover, in view of the fit of a linear model in multiple regression analysis, these findings provide no evidence of a threshold effect.

Important in the interpretation of these results is the predictive value of tests of infant development for subsequent intellectual and academic performance throughout childhood. There is a high degree of correlation between Bayley MDI score and IQ score measured on the Stanford-Binet Intelligence Scale ($r=0.57$).¹⁶ Preliminary analysis of data obtained at age four years from children in this cohort shows a high correlation ($r=0.58$) between Bayley MDI and the General Cognitive Index of the McCarthy Scales of children's abilities.²² The negative relationship between postnatal PbB and children's mental ability persists at age four years within this cohort, and, from recently-completed analyses, appears to be stronger at this latter age. Those results will be the subject of a separate report.

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