Environmental lead and children's intelligence: a systematic review of the epidemiological evidence

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Abstract

***Objective*—To quantify the magnitude of the relation between full scale IQ in children aged 5 or more and their body burden of lead.**

***Design*—A systematic review of 26 epidemiological studies since 1979: prospective studies of birth cohorts, cross sectional studies of blood lead, and cross sectional studies of tooth lead.**

***Setting*—General populations of children ≥5 years.**

***Main outcome measures*—For each study, the regression coefficient of IQ on lead, after adjustment for confounders when possible, was used to derive the estimated change in IQ for a specific doubling of either blood or tooth lead.**

***Results*—The five prospective studies with over 1100 children showed no association of cord blood lead or antenatal maternal blood lead with subsequent IQ. Blood lead at around age 2 had a small and significant inverse association with IQ, somewhat greater than that for mean blood lead over the preschool years. The 14 cross sectional studies of blood lead with 3499 children showed a significant inverse association overall, but showed more variation in their results and their ability to allow for confounders. The seven cross sectional studies of tooth lead with 2095 children were more consistent in finding an inverse association, although the estimated magnitude was somewhat smaller. Overall synthesis of this evidence, including a meta-analysis, indicates that a typical doubling of body lead burden (from 10 to 20 μg/dl (0·48 to 0·97 μmol/l) blood lead or from 5 to 10 μg/g tooth lead) is associated with a mean deficit in full scale IQ of around 1-2 IQ points.**

***Conclusion*—While low level lead exposure may cause a small IQ deficit, other explanations need considering: are the published studies representative; is there inadequate allowance for confounders; are there selection biases in recruiting and following children; and do children of lower IQ adopt behaviour which makes them more prone to lead uptake (reverse causality)? Even if moderate increases in body lead burden adversely affect IQ, a threshold below which there is negligible influence cannot currently be determined. Because of these uncertainties, the degree of public health priority that should be devoted to detecting and reducing moderate increases in children's blood lead, compared with other important social detriments that impede children's development, needs careful consideration.**

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Introduction

In the past 15 years public health interest in the potential impact of environmental exposure to lead on children's intelligence has led to an abundance of observational studies. This article presents a systematic review of 26 epidemiological studies,[1-21] so as to quantify the overall magnitude of the relation between full scale IQ in children aged 5 years or more and their body burden of lead. The relatively small size of each study, combined with limitations in the representativeness of the study sample and problems in allowing for parental and social confounders, means that generalisable conclusions cannot be reached from any one study. Several narrative reviews[22-27] have attempted to assimilate evidence across studies into an overall assessment. However, it is well recognised that such rather unstructured reviews lack any formalised objective combination of evidence, and interpretations tend to depend on subjective opinion.

Here our systematic review of the overall evidence attempts to achieve standards of objectivity and critical appraisal which have often been lacking in previous reviews. Specific characteristics of our approach include:

(1) Formal criteria on which studies are eligible for inclusion, thus avoiding selection bias regarding inclusion or exclusion of studies;

(2) Recognition of the extent to which each study has allowed for parental and social confounders, which is an important consideration given that children who are more disadvantaged tend to have higher lead exposure;

(3) Use of a consistent statistical method, based on regression coefficients, to express all statistical associations between lead and child IQ on the same scale;

(4) Expression of the statistical uncertainties inherent in each study by appropriate use of confidence intervals;

(5) Seeking from authors specific information not otherwise available in published articles;

(6) Recognition that studies have adopted quite different design strategies—in particular, recent studies of prospective birth cohorts are first considered separately from cross sectional studies of blood lead and tooth lead at ages 5 and over;

(7) In allowing for the heterogeneity of study designs, we have resisted the temptation to emphasise a single crude "meta-analysis" result, on the basis that this would be an unjustified simplicity from such a variety of studies. Previous meta-analyses have paid less attention to these design considerations[28,29];

(8) Interpretation of results takes account of the limitations of observational epidemiology in inferring causality and in determining thresholds of undesirable exposure.

This systematic review is timely in that it incorporates new evidence on lead and child IQ from all the prospective studies of birth cohorts. We are thus able to consider objectively how this more detailed longitudinal evidence complements the larger, and mostly earlier, body of evidence from cross sectional studies.

Methods

CRITERIA FOR INCLUSION OF STUDIES

The original aim was to identify all observational studies that used a generally accepted measure of IQ on children aged 5 or more and related it to some current or earlier measures of body burden of lead. Within this broad goal, it became evident that the scientific quality of the overall evidence would be enhanced by imposing certain restrictions.

(1) Studies published before 1979 are excluded, in recognition of the generally poorer standards of study design and reporting before 1979.

(2) Studies with fewer than 100 children (amounting in total to around 6% of all children studied) are excluded for similar reasons, plus the concerns that publication bias is more of a problem in small studies, that it becomes more difficult to allow adequately for confounders, and that the required regression coefficients are mostly not available.

(3) Studies using hair lead (recognised as an unreliable measure of body burden) are excluded. With tooth lead, the reliability and comparability of the various measurement techniques are open to debate. Our decision has been to include studies using whole tooth or dentine lead but to exclude studies using circumpulpal lead. All blood lead studies otherwise eligible have been included.

(4) It was decided not to impose any further restrictions on study selection. For instance, studies vary considerably in the extent of control for confounding factors, but this is taken into account in interpretation of the evidence rather than exclusion of studies. Also, the quality and style of statistical reporting in the original papers is variable, but this has largely been resolved by the consistency of our more systematic statistical approach.

IDENTIFICATION OF STUDIES

In the light of previous reviews we and other researchers have undertaken, the great majority of studies were identified by personal knowledge and use of reference lists,[22-27] in the United States Environmental Protection Agency and United Kingdom Medical Research Council reviews, for example. We were members of the World Health Organisation's International Program of Chemical Safety's Task Force on Inorganic Lead and are grateful to the programme for access to its extensive database during 1993. Searches of the Medline and Toxline databases were also carried out, but no further studies were identified.

Most studies have included extensive test batteries assessing, as well as intelligence, a number of outcomes such as educational attainment or other specific skills. Other than for intelligence, there has been little comparability in the skills or outcomes assessed and the tests used. In addition the prospective studies have assessed developmental status in the early years of life by means of the Bayley scales of infant development. The predictive significance, and correlation of these scores with later IQ measures, is low.[30] For these reasons it was decided to confine this review to measures of full scale intelligence.

TYPES OF STUDY

The studies in this systematic review can be classified into three main types.

(1) Prospective studies of birth cohorts, in which children have been followed from before birth to age 5 or more, with repeated measures of blood lead being taken during this time. These studies were planned collaboratively, so that although there is still variation in their design and methodology, there is also some consistency in the allowance for confounders.

(2) Cross sectional blood lead studies, in which children aged 5 or more have had their IQ and blood lead measured at around the same age.

(3) Cross sectional tooth lead studies, in which children have been asked to donate one or more shed deciduous teeth for analysis of lead content, which is then related to a measure of child IQ made at around the same age. Studies using circumpulpal dentine have been excluded as the lead levels reported are much higher (about five times as high, on average, as whole tooth lead measures) and bear little relation to whole tooth lead levels.[31]

The conceptual advantage of the prospective studies is that they enable investigation into how lead exposure from before birth through early childhood might relate to subsequent neuropsychological development. The cross sectional studies of blood lead can measure only recent exposure, with the consequent risk of falsely representing the true impact of past lead exposure. Tooth lead has been used as a measure of integrated lead exposure over time. It is appropriate first to present results separately for these three types of study design, before pulling them together in a cohesive overall picture.

STATISTICAL METHODS

Our objective is to present statistical results of all studies in the same format. This is based on each study's multiple regression of full scale IQ on lead (blood lead or tooth lead) and several parental and social confounders, from which we have obtained the regression coefficient for lead and its standard error. This coefficient has then been used to derive for each study an estimated change in IQ for either a specific doubling of blood lead from 10 μg/dl to 20 μg/dl (0·48 to 0·97 μmol/l) or a specific doubling of tooth lead from 5 μg/g to 10 μg/g.

These are of course arbitrary choices of interval, chosen because they tend to be in the mid-range of blood lead or tooth lead for most of the studies. Nevertheless they provide a convenient summary of the observed magnitude of association between lead and IQ in each study. The 95% confidence interval is presented around each estimated change as a valuable indicator of the extent of statistical uncertainty, attributable primarily to the limited number of children in any one study.

Several practical and technical issues arise in doing this. Firstly, some studies have used the log transform for blood lead or tooth lead, while others have not. This discrepancy has been overcome by the conversion of each coefficient to the estimated change for a specific doubling of blood lead or tooth lead. Experience from a number of studies has indicated that the estimates, and their significance, are little affected by whether the log transform is used or not.

Secondly, studies have varied considerably in the use of parental and social covariates in the regression models. Our policy has been to identify the authors' main covariate-adjusted model and also to identify which covariates have been included. When it is available we have compared this lead coefficient with that obtained from a univariate regression without covariate adjustment. Some studies performed only univariate regression: they have still been included, though with appropriate recognition of this limitation.

Thirdly, some study publications did not explicitly state the regression coefficients and standard errors in the form we required, and we are grateful to the authors for providing this information on our request. Three studies reported only correlation coefficients, but with knowledge of the standard deviation of blood lead and IQ we have been able to calculate the regression coefficient and its standard error.

Results

PROSPECTIVE STUDIES

Table I summarises the design and reporting features of the five prospective studies (in Cleveland, Boston, and Cincinnati in the United States and Port Pirie and Sydney in Australia).[1-5] The three American studies have recruited from contrasting populations: the Cincinnati and Cleveland cohorts are disadvantaged, inner city children while the Boston cohort has a predominantly middle class group, and this is reflected in the differences in mean IQ and blood lead concentrations. The cohort from the smelter town Port Pirie is much the largest (n=494) and also has the highest mean blood lead. For IQ assessment, all except Cleveland used the Wechsler intelligence scale for children—revised; the Wechsler preschool and primary scale of intelligence was more appropriate for the younger age of testing in Cleveland. The Boston cohort were older by the time of IQ assessment (mean age 10 years).

Each prospective study made repeated measures of blood lead in each child from birth to the age of IQ assessment; all except the Boston study made antenatal measures in the mother. The Cincinnati cohort had the most frequent measures (every three months up to age 5), while the Cleveland cohort had just three measures after birth, for each of which there is a substantial proportion of missing values. In relating blood lead to full scale IQ, studies have used a variety of summary measures of blood lead, the number of reported analyses ranging from five to 12 per study. Each prospective study has adjusted for a substantial number of parental and social covariates, including the HOME score[32] and maternal IQ. Three out of the five have used log transforms for blood lead. To extract some cohesion out of this mix of analysis strategies, we focused on three specific summary measures of blood lead: around birth, around age 2 years, and the postnatal mean. Each covariate adjusted regression coefficient (and its standard error) was converted into the estimated change in full scale IQ (and its 95% confidence interval) for an increase in blood lead from 10 μg/dl to 20 μg/dl (see fig 1).

Blood lead around birth

One of the main original motivations of the prospective studies was to relate very early measures of body lead burden to subsequent neuropsychological development, on the basis that neurotoxic effects might occur in the fetus or shortly after birth. The most complete early data relate to around birth (blood lead in the umbilical cord in four studies and at 10 days after birth in the Cincinnati cohort) (fig 1a). None of these data show any association with full scale IQ. Four studies also analysed maternal antenatal blood, and this also showed no association with IQ.

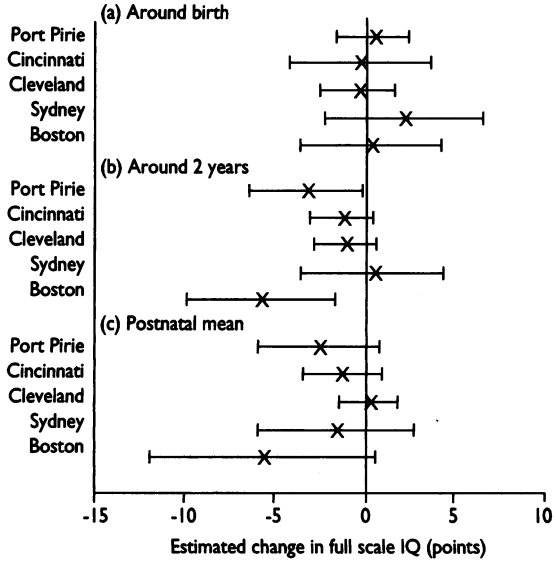

FIG 1—*Prospective studies: estimated change in full scale IQ (and 95% confidence interval) for increase in blood lead from 10 to 20 μg/dl, using three measures of blood lead in each study*

Blood lead around age 2 years

It has been repeatedly shown that blood lead tends to reach its peak concentration around 2 years of age, and this seems a logical age to focus on for the early years of exposure. However, only the Cleveland and Boston studies presented results specifically for blood lead at 2 years. As the nearest substitutes, we used for Port Pirie the mean blood lead for years 0 to 3, for Cincinnati the mean blood lead in year 3, and for Sydney the mean blood lead in years 1 and 2. (For Port Pirie and Cincinnati alternatives were means of years 0 to 2 and mean in year 2 respectively, both of which result in estimates slightly closer to zero.)

Figure 1b shows fairly strong evidence of an inverse association between blood lead and IQ. The Boston study is the most positive; the Port Pirie study also showed a significant association (its confidence interval did not include zero), but the other three studies did not.

Mean postnatal blood lead

In an attempt to summarise the cumulative lead exposure since birth it is sensible to adopt some overall mean blood lead over time in each study. Use of such a

TABLE I—*Main features of five prospective studies relating lead concentrations and IQ*

			IQ measurement			Blood lead measurement				Statistical analysis	
						Mean concentration at 2 years					
Location	Nature of sample	No of children	Age	Measure	Mean full scale score	μg/dl	μmol/l	No of measures	Ages	Log transform	Covariates
Port Pirie[1] (Australia)	Smelter town and rural surroundings	494	7	WISC-R	105	21·2*	1·02	10	Antenatal† 0, ½, 1¼, 2, 3, 4, 5, 6, 7 years	Yes	HOME, mother's IQ, 11 others
Cincinnati[2] (USA)	Inner city, black, disadvantaged	231	6·5	WISC-R	87	17·5	0·85	25	Antenatal 10 days, ¼, ½, 5, 5½, 6, 6½ years	No	HOME, mother's IQ, 4 others
Cleveland[3] (USA)	Inner city, disadvantaged; 50% mothers alcoholic	212	5	WPPSI	88	16·7	0·81	5	Antenatal, 0, ½, 2, 3 years	Yes	HOME, mother's IQ, 11 others
Sydney[4] (Australia)	Mixed urban	175	7	WISC-R	?	14·2*	0·69*	12	Antenatal, 0, ½, 1, 3½, 4, 5, 7 years	Yes	HOME, mother's IQ, 4 others
Boston[5] (USA)	Middle class, advantaged	148	10	WISC-R	119	6·8	0·33	7	0, ½, 1, 1½, 2, 5, 10 years	No	HOME, mother's IQ, 8 others

WISC-R=Wechsler intelligence scale for children—revised; WPPSI=Wechsler preschool and primary scale of intelligence; HOME=score of caregiving environment assessed by home observation for the measurement of the environment inventory.
*Geometric mean. †Antenatal blood lead in the mother.

TABLE II—*Main features of the cross sectional blood lead studies*

Location	Nature of sample	No of children	IQ measurement: Age (mean age) (years)	IQ measurement: Measure	IQ measurement: Mean full scale score	Mean blood lead: µg/dl	Mean blood lead: µmol/l	Statistical analysis: Covariates*	Statistical analysis: Log transform
Lavrion* (Greece)	Historic smelter town	509	6-12	WISC-R	87	23·7	1·14	Up to 24, including mother's IQ	No
Edinburgh[7] (UK)	Mixed urban (previously high water lead)	501	6-9	BAS	112	11·5*	0·56*	33, including mother's IQ	Yes
European study:				WISC short form				Gender, age, social class, mother's education	
Bucharest[8a]	General population	301	(9·2)			18·9*	0·91*		Yes
Budapest[8b]	General population	254	(8·5)			18·2*	0·88*	(Not maternal education)	Yes
Moden	Industrial city; lead industry	216	(7·8)			11·0*	0·53*		Yes
Sofia	General population	142	(7·3)			18·2*	0·88*		Yes
Dusseldorf I[8c]	Industrial city, near smelter	109	(6·5)			8·3*	0·40*		Yes
Dusseldorf[8d]	Industrial city, near smelter	109	(8·3)			7·4*	0·36*		Yes
Dunedin[9] (New Zealand)	Mixed rural/urban cohort	579	11	WISC-R	109	11·1	0·54	None	Yes
London[10] (UK)	Middle class, suburban	194	(9)	WISC-R	103	12·9	0·62	Age, social class	Yes
Birmingham[11] (UK)	Mixed, inner city	177	5·5	WPPSI	106	12·3	0·60	None	No
Shanghai[12] (China)	Near battery plant; rural control	157	6-14	WISC-R	89	21·1	1·02	Mother's education, 4 others	No
Greenwich[13] (UK)	Near lead works	129	6-12	WISC-R	98	13·5	0·65	Age, sex, social class	Yes
Nordenham[14] (Germany)	Smelter town; rural surroundings	122	7	WISC-R	120	8·2	0·40	Age, sex, hereditary background	Yes

WISC=Wechsler intelligence scale for children (R=revised); BAS=British ability scale; WPPSI=Wechsler preschool and primary scale of intelligence.
*Geometric mean.

mean will also help to reduce any random error due to within subject variability in blood lead concentrations. Studies have used differing numbers of measurements, covered different age spans, and adopted different summarising techniques as follows: Port Pirie, ages 0 to 7 using a trapezoidal method; Cincinnati, mean of first 20 quarterly measures and ages 5½ and 6; Cleveland, mean of ages 6 months, 2 years and 3 years; Sydney, mean of eight measures at six month intervals and ages 5 and 7; Boston, mean of four measures at six month intervals and ages 4¾ and 10 (this last is an unpublished analysis). Despite this heterogeneity of summarising technique, it is plausible that studies are achieving reasonable internal consistency in ranking children's cumulative lead exposure before IQ testing.

Figure 1c shows rather less convincing evidence of an association of IQ with mean postnatal blood lead. The results for Port Pirie and Boston are no longer significant, and the findings in Cincinnati and Cleveland are closer to no association than are the results for blood lead around 2 years.

CROSS SECTIONAL STUDIES OF BLOOD LEAD

Fourteen published cross sectional studies relating children's blood lead to their full scale IQ have satisfied our eligibility criteria[6-14]; their main design and reporting characteristics are presented in table II. The studies are listed in an order that reflects two key issues: the extent of allowance for potential confounding factors and the number of children. Only two of these studies, in Lavrion and Edinburgh, have incorporated an extensive consideration of such confounders, including maternal IQ, and both include around 500 children. Six centres from the European multicentre study made some allowance for confounders (sex, age, paternal occupation, and maternal education) but not for maternal IQ or any assessment of the home environment. Although Lavrion was one of the European study's centres, it has also been reported separately with greater allowance for confounders, and this is the version we used. The other seven studies listed in table II also made little or no allowance for confounders. The largest, in Dunedin, reported only an unadjusted correlation coefficient between blood lead and full scale IQ ($r=-0·05$) and did not proceed with further analysis because of the lack of significance. This illustrates how confining attention only to studies that allowed fully for potential confounders would have introduced biased selection into this review.

The samples of children in these studies are all from the general population, though some (Lavrion, Shanghai) are from areas with industrial lead exposure and consequently had higher mean blood lead. IQ assessment was based on the Wechsler intelligence scale for children—revised and its translations for all studies except Edinburgh (British ability scale) and Birmingham (the Wechsler preschool and primary scale of intelligence). The European study and Nordenham used only a shortened form of the Wechsler intelligence scale for children. The ages of children varied considerably, from 5½ years in Birmingham to 11 in Dunedin, and some studies had a wide age range—for example, 6 to 14 in Shanghai. Mean full scale IQ also varied substantially between studies, ranging from 87 in Lavrion to 120 in Nordenham. Most studies used a log transform for blood lead in regression analysis.

The regression coefficients for blood lead for the analysis in each study that takes the most considered account of confounders (no account in some instances) were used to derive the estimated change in full scale IQ for an increase in blood lead from 10 to 20 µg/dl, as shown in figure 2. The extent of statistical uncertainty in each estimate is indicated by 95% confidence limits.

The most convincing evidence of an inverse association between blood lead and IQ is shown for Lavrion and Edinburgh. Both studies estimate a highly significant reduction in IQ of around 2·7 IQ points, and their

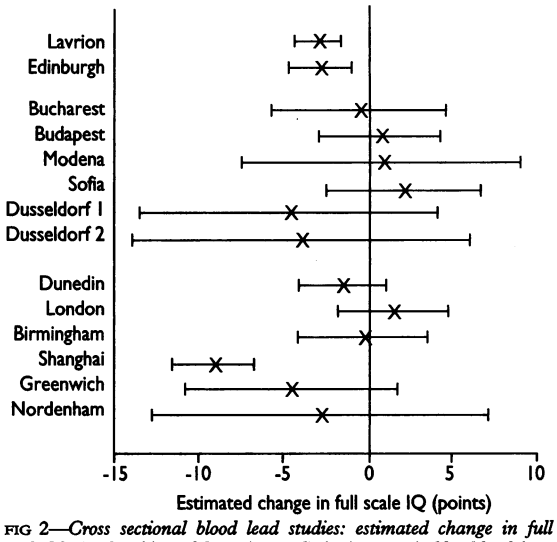

FIG 2—*Cross sectional blood lead studies: estimated change in full scale IQ (and 95% confidence interval) for increase in blood lead from 10 to 20 µg/dl*

confidence intervals are relatively narrow due to the large sample sizes (each over 500 children). However, the Dunedin study (even larger) showed a much smaller association, though without any adjustment for confounders. The Shanghai study seems something of an outlier, with a very strong inverse association, while the 11 other studies individually showed no firm evidence of association.

CROSS SECTIONAL STUDIES OF TOOTH LEAD

We identified seven studies relating full scale IQ to the lead concentration in shed incisor teeth (as measured by whole tooth or dentine lead).[15-21] Study characteristics are presented in table III, in order of study size. The largest study, in Christchurch, had IQ assessment at both ages 8 and 9; we chose age 8 as being nearer to the mean age across all studies. Because of differences in analytical techniques and the portion of the tooth analysed, direct comparisons between lead exposure in different tooth lead studies is not easy. However, the available blood lead data also suggest that exposure levels were generally higher in the Boston sample than in the three studies situated in areas with lead related industry. Boston is also the oldest of the studies (1979) and this may reflect the decline in lead exposure that has tended to occur in many populations over the last two decades. The Boston and London studies had a stratified design based on specifically selected samples of children with high and low tooth lead (also a mid group in London). Original results were in terms of mean IQ differences, but regression analyses have been presented since.[28 33 34] Three of these tooth lead studies—Port Pirie, Edinburgh, and Sassuolo (Modena)—relate to subsamples of children from blood lead studies already reported in tables I and II.

Overall, these tooth lead studies gave greater attention to potential confounders than many of the cross sectional blood lead studies. However, the studies in Christchurch, Dusseldorf, and Sassuolo did not include parental IQ as a covariate. Also, in Sassuolo we obtained only the unadjusted regression coefficient, though we do know that adjustment had negligible effect on the P value. Otherwise the coefficient and standard error from the most fully adjusted analysis was used to derive the estimated change in full scale IQ for an increase in tooth lead from 5 to 10 μg/g, a doubling around the middle of the tooth lead distribution in most studies. The results are shown in figure 3.

All seven studies indicate an observed inverse association between tooth lead and full scale IQ, but only in Boston and Sassuolo was this significant.

ADJUSTMENT FOR POTENTIAL CONFOUNDERS

It is generally recognised that the scientific worth and credibility of observational studies of risk relation are enhanced by taking account of potential confounders (covariates), but it is relevant to consider just how much this matters in the studies of lead and IQ. Focusing on those studies that made extensive use of parental and social factors in their main analyses, table IV compares the magnitudes of association with and without adjustment for such covariates. Not all such studies presented the unadjusted results, but this table is as complete as we could make it. For simplicity, only the "two year" blood lead results are shown for the prospective studies.

TABLE IV—*Influence of adjustment for covariates on association of lead and IQ*

Study	Estimated change in IQ (SE) for increase from 10 to 20 μg/dl in blood lead (or 5 to 10 μg/g increase in tooth lead)	
	Unadjusted	Adjusted
Prospective:		
Port Pirie (years 0 to 3)	−8·5 (1·5)	−3·3 (1·6)
Cincinnati (year 3)	−2·6 (0·9)	−1·3 (0·9)
Cleveland (2 years)	−12·1 (2·4)	−1·1 (0·9)
Sydney (1-2 years)	0·0 (?)	0·39 (2·0)
Boston (2 years)	−7·1 (2·5)	−5·8 (2·1)
Cross sectional blood lead:		
Lavrion	−3·8 (0·8)	−2·7 (0·7)
Edinburgh	−3·8 (1·1)	−2·6 (1·0)
Cross sectional tooth lead:		
London	−1·84 (0·60)	−0·65 (0·54)

In every study the unadjusted results indicated stronger evidence of an inverse association than did the more informative results after adjustment for confounders. For most studies the impact of adjustment was not great—the estimate was reduced by less than 1·5 points and the standard error was affected only slightly. In the Port Pirie blood lead study, the estimate fell by over five IQ points, which suggests that the family and home environment was indeed an important confounder. In Cleveland, adjustment had an even more dramatic effect: a 10 point IQ reduction in estimated effect and a much reduced standard error. This suggests that in the Cleveland study the parental and social factors had a more precise ability to predict child IQ and were also strongly associated with blood lead, features which perhaps relate to the rather unusual choice of cohort (over half were alcoholic mothers).

META-ANALYSIS

It is common practice to proceed one step further in a systematic review by formally combining the evidence from the different studies into a single overall estimate of association. In undertaking such a formal meta-analysis it is important to separate the different main types of study design (prospective or cross sectional; blood lead or tooth lead). In addition, it is

TABLE III—*Main features of cross sectional tooth lead studies*

Location	Nature of sample	No of children	Measurement: Age (mean age) (years)	Measurement: Mean full scale score	Lead measurement: Mean blood lead μg/dl	Lead measurement: Mean blood lead μmol/l	Lead measurement: Mean tooth lead (μg/g)	Statistical analysis: Covariates	Statistical analysis: Log transform
Christchurch[15] (New Zealand)	Middle class suburban	724	8	103			~6	8, including parental education (no parent IQ)	Yes
London[16] (UK)	Mixed suburban and inner city	402	6-7	106	12·8 (n=91)	0·62	5·1*	10, including mother's IQ, parental interest and socioeconomic status	Yes
Port Pirie[17] (Australia)	Smelter town and rural surroundings	262	7-8	108	17·0* (postnatal average)	0·82*	8·6*	HOME, mother's IQ+11 others	Yes
Edinburgh[18] (Scotland)	Mixed urban	259	6·9	112	11·5*		9·3*	33, including mother's IQ	Yes
Boston[19] (USA)	Middle class suburban	218	6-9	105	27·1 (n=81, age 2-4 years)	1·31	12·7	Parent IQ, socioeconomic status, and other parental factors	No
Dusseldorf[20] (Germany)	Smelter town	115	(9·4)	116	14·3* (n=83)	0·69*	6·2*	Socioeconomic status, age, gender, and perinatal factors (no parent IQ)	Yes
Sassuolo[21] (Italy)	Near ceramics industry	115	7-8½	119	11·6	0·56	6·1	Age and socioeconomic status	Yes

HOME=score of caregiving environment assessed by home observation for the measurement of the environment inventory.
*Geometric mean.

TABLE V—*Meta-analysis of all studies of association between lead and IQ*

	No of studies	No of children	Mean (SE) estimated change in IQ for specific doubling of body burden of lead	Test for heterogeneity χ^2	df	P value
Prospective studies:						
Around birth	5	1166	0·18 (0·62)	1,2	4	0·9
Around 2 years	5	1197	−1·85 (0·51)	7,8	4	0·1
Postnatal mean	5	1260	−0·88 (0·58)	5,2	4	0·3
Cross sectional blood lead studies*	14	3499	−2·53 (0·41)	45,6	13	0·001
Cross sectional tooth lead studies	7	2095	−0·95 (0·25)	5,3	6	0·5

*Excluding Shanghai, estimated mean (SE) is −1·74 (0·43) IQ points and heterogeneity $\chi^2_{12} = 14·2$; P=0·3.

essential to note the substantial heterogeneity of design and reporting features within each broad category (for example, differing selection procedures, communities, exposure levels, extent of allowance for confounders). Thus, it is appropriate to recognise the potentially false illusion of precision in the meta-analytic technique and to exercise caution when interpreting results of meta-analysis.[35]

Table V presents the combined estimates of association (and their standard errors) for each of the sets of studies shown in figures 1-3. A fixed effect method has been used,[35] and in addition a test for statistical heterogeneity between studies is given.

For the prospective studies this meta-analysis confirms the lack of association with blood lead around birth and the inconclusiveness of the findings for the mean postnatal blood lead concentrations. However, the collective results for blood lead around 2 years show stronger evidence for an inverse association, the estimated mean change being −1·85 IQ points for a change in blood lead from 10 to 20 μg/dl (95% confidence interval −0·85 to −2·85 IQ points). Note that the fixed effect method weights studies inversely according to the square of the standard error. This usually gives the larger studies greater weight, but curiously the Cleveland study (n=149) and the Cincinnati study (n=212) get considerably more weight than the Port Pirie study (n=494). We have not corrected for this anomaly, but it casts doubt on the validity of this overall estimate.

Also, for Port Pirie and Cincinnati alternative choices of intervals for blood lead were the mean of years 0 to 2 (instead of 0 to 3) and the mean of year 2 (instead of year 3) respectively. With these replacements the overall estimated IQ deficit is reduced to −1·17 IQ points. Again this illustrates the fragility of the meta-analysis estimate in the face of such a multiplicity of different analyses, both within and between studies. However, none of these analyses revealed significant statistical heterogeneity between the studies.

In contrast, the 14 cross sectional studies of blood lead showed great heterogeneity in estimated associations with IQ (P<0·01). This is largely due to the Shanghai study's extreme value, since its exclusion reduces the heterogeneity to non-significance. The combined estimate for mean change in IQ for a change in blood lead from 10 to 20 μg/dl is −2·53 IQ points (−1·76 IQ points if Shanghai is excluded). However, these estimates are hard to interpret given the lack of adequate allowance for confounders in many of these studies.

The seven cross sectional studies of tooth lead showed a greater consistency in their results. The combined estimate for mean change in IQ for a change in tooth lead from 5 to 10 μg/g was −1·03 (−0·50 to −1·56) IQ points. Again, there is something of an anomaly in the weightings since the Boston study (n=218) has more weight than the much larger studies in Christchurch (n=724) and London (n=402), probably because its estimate is based on selected groups with high and low tooth lead.

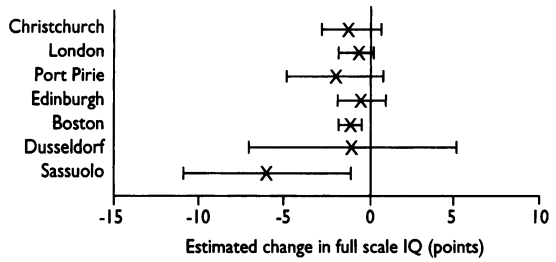

FIG 3—*Cross sectional tooth lead studies: estimated change in full scale IQ (and 95% confidence interval) for an increase in tooth lead from 5 to 10 μg/g*

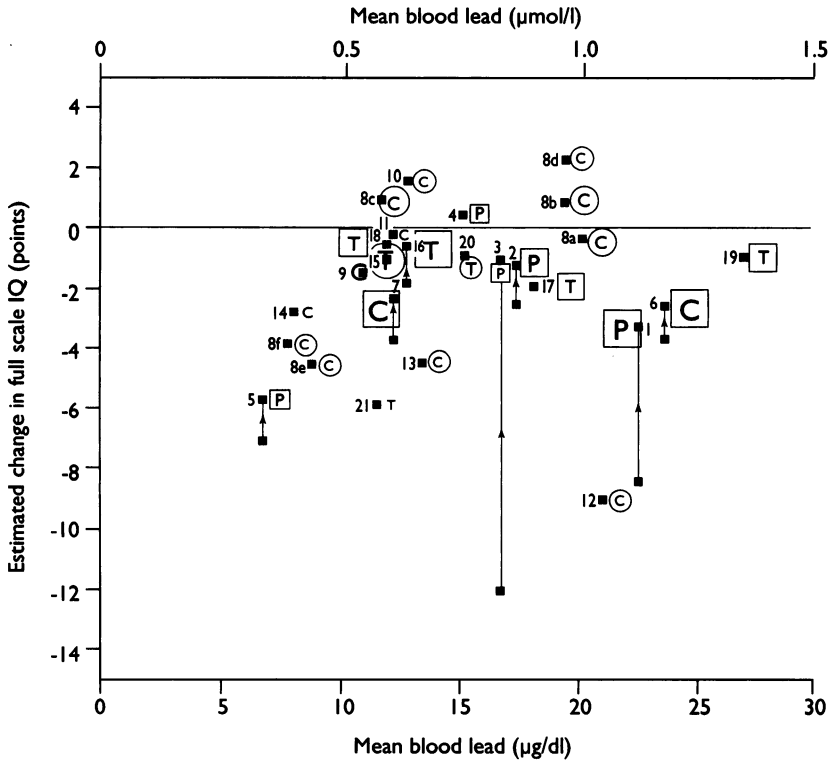

FIG 4—*Overall synthesis of 26 studies relating lead concentrations to IQ. For each study the estimated change in IQ for a specific doubling of body lead burden (10 to 20 μg/dl blood lead or 5 to 10 μg/g tooth lead) is plotted against the study's mean blood lead concentration. Study types: P=prospective, C=cross sectional blood lead, T=cross sectional tooth lead. Three sizes of letter represent the size of the study (>400, 200-400, or <200 children). Substantial or partial adjustment for confounders is indicated by a square or circle respectively; the influence of substantial adjustment is shown by the arrowed lines. The number of each point identifies the study's reference (see tables)*

AN OVERALL SYNTHESIS

So far we have considered results separately for the three types of study. As a final overview of the evidence we now consider a single display of the estimated associations of lead and IQ for all 26 studies simultaneously. The rather complex graph in figure 4 represents each study by a single letter: P for prospective, C for cross sectional blood lead, and T for cross sectional tooth lead studies. The size of this letter (large, medium or small) reflects the size of the study (>400, 200-400, or <200 children, respectively). The position of each study is determined horizontally by its mean blood lead and vertically by its estimated reduction in IQ for a specific doubling of body burden of lead (from 10 to 20 μg/dl blood lead or 5 to 10 μg/g tooth lead). The identifying number next to each point corresponds to the study's reference in tables I to III. For the prospective studies the association with blood lead around age 2 years has been chosen. For some of the tooth lead studies, mean blood lead is measured on a subsample only. Geometric means have been increased by 7% to correct for their lower values compared with arithmetic means.

The extent to which each study has adjusted for potential confounders is indicated as follows: a square surrounds the letter for substantial adjustment, (including mother's IQ), a circle surrounds the letter

for partial adjustment, and the letter is unadorned if no adjustment was done. Lastly, for seven of the principal studies with substantial adjustment we are able to display by vertical lines with arrows the magnitude of change in estimates going from the unadjusted analysis to the adjusted analysis.

This display in figure 4 reveals an interesting pattern. The great majority of studies have an inverse association between lead and IQ (points below the line). Also, all the larger studies (>400 children) show a reduction in full scale IQ of around 0·5 to 3 IQ points for the specific doubling of blood lead or tooth lead. However, the two largest studies, in Christchurch and Dunedin, might have produced estimates closer to zero if they had had fuller adjustment for confounders, including parental IQ.

There is no striking relation between the studies' mean blood lead and the magnitude of the lead-IQ association, except that the three studies with highest mean blood lead (Boston, Lavrion, and Port Pirie) had highly significant associations.

Discussion

This systematic review provides clearer insight into the magnitude of the association between body burden of lead in the early years of life and the intellectual performance of children from age 5 onwards than has previously been possible. The key question is the extent to which such observational results provide evidence that children's intake of lead as commonly experienced in the general population is causing small but important deficits in intellectual attainment. In this discussion we consider the sufficiency of the available epidemiological evidence to answer this question.

Firstly, let us summarise the emerging picture regarding the pattern of association found. The prospective studies of birth cohorts were undertaken so that the time sequence of lead exposure followed by possible intellectual deficit could be explored longitudinally. One prior hypothesis was that very early exposure in the fetus or around birth might be particularly important, but in fact no such evidence has emerged (fig 1a). The prospective studies have a plethora of measures and summary statistics for postnatal blood lead concentrations, which can pose problems of overinterpretation from multiple hypothesis. Hence we focused on two main issues: blood lead around the time of peak exposure (age 2 years) and an overall mean of postnatal blood lead over several years. The former showed more convincing evidence of an inverse lead-IQ association (fig 1b, table V) but even with over 1000 children the precise magnitude was still not clear, given that studies had used different summaries of blood lead around age 2 years.

The larger body of evidence from cross sectional studies of blood lead (3499 children in all) poses greater problems of interpretation. While the studies do show overall signs of a clear and highly significant inverse association, especially in Edinburgh and Lavrion, there is also substantial heterogeneity between studies. However, the greatest difficulty is in deciding what the blood lead measured close to the time of IQ assessment actually represents. It is implausible that moderate increases in blood lead at age 6 or more cause a rapid change in full scale IQ. Instead current blood lead is meant as a marker for longer term or past exposure. It is therefore curious that these cross sectional studies produced a stronger magnitude of association than the prospective studies (table V), an issue considered below.

The six cross sectional studies of tooth lead show consistent overall evidence of an inverse association with full scale IQ, although the magnitude is quite small, around one IQ point deficit for a typical doubling of tooth lead from 5 to 10 μg/g. Tooth lead is used as a marker of cumulative body lead burden, although it is uncertain exactly how it reflects lead exposure over time.

Our overall synthesis of the evidence in all 26 studies (table V and figure 4) strongly supports an inverse association between body lead burden and child IQ. Such a disparate collection of studies should not be reduced to a single figure, but it seems plausible to state that for a "typical" doubling of body lead burden (from 10 to 20 μg/dl blood lead or 5 to 10 μg/g tooth lead) there is an average deficit in IQ of the order of 1 or 2 IQ points.

POSSIBLE EXPLANATIONS

We need now to consider in turn all the possible reasons for this finding: chance; that lead causes an IQ deficit; that published studies are not representative; inadequate allowance made for confounders; other selection biases; or that children of lower IQ have increased lead uptake (reverse causality).

Chance can be readily dismissed as an explanation. The collective evidence is highly significant.

The hypothesis that low level lead exposure causes a small IQ deficit is highly plausible. Animal studies have shown neuropsychological deficits at similar exposure levels, but of course animal models can provide only indirect support. One problem is whether full scale IQ is an appropriate measure of the kind of neuropsychological performance that might be impaired by lead, but we are constrained by the fact that no other measures have been consistently investigated to any extent.

It is well recognised that systematic reviews and meta-analyses are prone to publication bias in that studies with negative findings are less likely to appear.[36] We are confident that all prospective studies are represented in this review, but we do know of one large "negative" cross sectional study of blood lead (in Leeds) that has not been published. It is possible that other cross sectional studies are also missing.

The allowance for confounding factors can never be fully satisfactory since one can never hope to measure all the complex of parental, social, and environmental factors (other than lead) that influence a child's intellectual attainment. While many of the more recent studies have made substantial efforts to account for potential confounders, it must remain a matter of judgment as to how successful they have really been in this regard. Specifically, many studies have allowed for mother's IQ (unfortunately not usually measured in full) but another important factor, father's IQ, has not been considered.

Alongside imperfect measurement of confounders is the fact that any single measure of blood lead or tooth lead must inevitably be an imperfect marker for the true underlying body burden of lead. These two "measurement errors" are competing forces: the former will inflate the observed lead-IQ association while the latter will underestimate it, so that the true impact is indeterminable.[37]

Other selection biases might be present in any particular study. For instance, all studies depend on children donating the appropriate sample, whether it is blood or teeth, and one may question whether such cooperative children are representative of their communities. Similarly, the prospective studies experience some dropouts in follow up from birth to the age of IQ assessment, which again may leave a biased sample. However, it is difficult to conjecture whether (and in which direction) such selection bias could influence the observed lead-IQ association.

The possibility of reverse causality also needs serious consideration: could children of lower IQ be more

prone to behaviour patterns that would enhance their uptake of lead? Furthermore, to what extent would these need to occur in order to account for the observed associations presented here? This can be measured as follows. An IQ deficit of around 1 to 2 IQ points corresponds to a partial correlation coefficient between IQ and blood lead (or tooth lead) of around −0·05 to −0·1. Given knowledge of the standard deviations for log (blood lead) and IQ one can back calculate the regression of log (blood lead) on IQ for a typical study. The end result is that every 10 point decrease in IQ corresponds to a 1·5-3% increase in blood lead (or tooth lead), a very small but crucially important effect were it to occur. Observational epidemiology cannot distinguish between this direction of effect and the more important issue, "does lead cause a deficit in IQ?" However, this review provides some implicit evidence that reverse causality is plausible. Current IQ at age 5 or more is more likely to relate to current, lead related behaviour than earlier behaviour, say at age 2 years. This may explain why the cross sectional studies of current blood lead (a marker of recent intake) show an overall stronger association than either the prospective studies or the tooth lead studies (see table V).

It is impossible to determine the relative importance of all the above explanations for the lead-IQ association. The observational evidence is inconclusive on the causal role of low level lead exposure but one cannot dismiss the possibility that current body burden of lead in children may continue to have a small but important influence on intellectual attainment.

SHAPE OF THE RELATION

For those who do accept this evidence as causal, the next key question concerns the shape of the dose-response relation; specifically, is there a threshold of blood lead (or tooth lead) below which there is negligible influence on IQ? No single study has been large enough to investigate such issues, and quite contradictory patterns can be observed, which are plausibly due to the play of chance. For instance, the Lavrion study shows a steeper gradient at higher blood lead levels, above 25 μg/dl, while the Edinburgh study shows associations continuing below 10 μg/dl. As long as the data from each study are analysed separately we see little scope for clarification. Instead, we propose that investigators collaborate by combining their databases[38] so that a meta-analysis of the raw data on individual subjects can be undertaken.

CONCLUSIONS

The public health implications of low level lead exposure in children continue to provoke widespread concern in many countries. Our systematic review of the overall evidence shows a small but potentially important deficit in full scale IQ among children with raised body lead burden. However, the inherent limitations of observational epidemiology in pinpointing the reasons for this association mean that uncertainty remains as to the real impact that lead makes on children's neuropsychological development. In the face of this doubt, the priority that should be devoted to detection and intervention on children with moderately increased blood lead, compared with other social influences on childhood development, is open to debate.

We are indebted to the WHO International Program on Chemical Safety Task Group for Environmental Health Criteria on Inorganic Lead, whose meeting in February 1993 stimulated us to undertake this research. We thank authors of several of the reviewed articles for providing us with extra unpublished results. We appreciate the help from Rebecca Hardy and Paul Seed in the analysis and presentation of results.

Public health implications

- Early (neonatal) lead exposure seems not to affect child IQ in the general population
- Blood lead and tooth lead measures during the first few years of life show a weak, but highly significant, inverse association with child IQ at ages 5 upwards
- At face value, it seems that a typical doubling of body lead burden is linked to a loss of 1-2 IQ points
- Given that these are observational studies, the extent to which lead actually causes an IQ deficit in the general population of children inevitably remains open to debate
- This overall quantification of the lead-IQ association will help in determining public health policy in limiting children's exposure to environmental lead

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Wartime evacuation and mortality from childhood leukaemia in England and Wales in 1945-9

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Abstract

***Objective*—To discover whether the wartime government evacuation of children from London and other population centres to rural districts was associated with any increase in childhood leukaemia.**

***Design*—Observational study of mortality from leukaemia among the childhood population of England and Wales in relation to the unique population movements during the second world war. The 476 rural districts of England and Wales were ranked according to the ratio of government evacuees (two thirds of them children) to local children in September 1941. The districts were divided into three categories, each with similar numbers of children in 1947 but with different ratios of evacuees to local children ("low," "intermediate," "high"). Mortality from childhood leukaemia was examined in these three rural categories in 1945-9. Urban areas were also examined according to their exposure to evacuees.**

***Setting*—Local authority areas of England and Wales.**

***Subjects*—Children aged under 15.**

***Results*—47% excess of leukaemia at ages 0-14 years occurred in 1945-9 in the rural "high" category for evacuees relative to the "low" category, with a significant trend across the three categories. There were increases in both the 0-4 and 5-14 year age groups, but these were larger in the older age group. Rates 25% lower than average occurred in rural areas with few evacuees.**

***Conclusion*—These findings suggest that wartime evacuation increased the incidence of childhood leukaemia in rural areas and that other forms of population mixing may have contributed to the increases in past decades. Overall, they add to the appreciable evidence for an infective basis in childhood leukaemia.**

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Introduction

The mixing of rural and urban groups of people has been associated with significant increases in childhood leukaemia.[1-6] This is consistent with the disease having an infective basis. Such mixing is conducive to an epidemic by promoting some critical level of contacts between susceptible and infected people, people who are susceptible being more prevalent in rural areas. During the second world war the evacuation by the government of large numbers of children from London and other population centres to safer areas produced urban-rural mixing. We therefore investigated the possible effects of such evacuation on mortality from childhood leukaemia with particular reference to the rural parts of England and Wales.

Subjects and methods

EVACUATION AND POPULATION DETAILS

Before the second world war the fear of aerial bombardment of civilians led the British government to prepare a scheme for evacuation. Under this scheme London and many towns were designated as evacuation areas, many other local authority districts being designated as "reception areas," and the remainder being declared "neutral."[7 8] These categories applied to children and certain other special groups in the (voluntary) official scheme, and people were free to make their own arrangements to move into neutral or reception areas if they wished. Most rural districts in England and Wales were designated as reception areas for government evacuees.

The numbers of people billeted away from their home areas under the government scheme fluctuated appreciably during the war[7] (see table I). However, only one billeting schedule could be traced in the Public Records Office. This gave the numbers of unaccompanied and accompanied children, mothers, and other evacuated adults (including teachers and helpers) present in each local authority area in September 1941 (Public Records Office, file RG26/76).

The ratio of the number of evacuated people (as given in the billeting schedule) to the number of local children (below age 15)—the "evacuee index"—in each district of England and Wales in 1941 was taken as a crude measure of the intensity of exposure of local children in each area to evacuees. The numbers of local children in each district in 1941 were estimated by adjusting those recorded in 1947[9] by factors that related the national populations in each age group in 1941[10] to those in 1947. That year (1947) was the only year between 1931 and 1951 for which age specific populations of children were known for each local authority district, the details being derived from national registration records.[9]

The availability of local population details of children by age group in 1947 was also useful because it was the central year of the study (1945-9) and therefore provided a convenient set of denominators in the mortality analyses. The relative populations of three