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Late Effects on School Performance and Cognitive Functions of Low Blood-Lead Concentrations in Childhood

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Short running title: Childhood lead and cognition

Abbreviations:

ADHD, Attention-deficit/hyperactivity disorder; B-Pb, blood-lead concentration; CNS, central nervous system; G, sufficient (school merits); IQ, cognitive function; full scale test; MVG, more than well sufficient (school merits); P, probability; R^2, explained variance; Stanine point, standard nine point (IQ); U, unit (IQ); U.S., United States of America; VG, well sufficient (school merits); µg/L, microgram per liter (10 µg/L = 1 µg/dL = 0.049 µmol/L).

Supplemental Material is available online…

ABSTRACT

Background: Lead is neurotoxic on cognitive functions at low blood concentrations (B-Pb), though the information is limited, as is the impact of early exposure on later function. Objectives: To assess effects of low lead exposure in early childhood on cognitive performance as teenager. Methods: 1978-2007 we analysed B-Pb (median 30 µg/L; six-fold decrease over time) in 3,176 Swedish children (age 7-12). School results in grade 9 (age 16; boys and girls) and full-scale IQ at examination for military service (age 18-19; mainly boys) were obtained from registers. In multivariate models, potential confounders (age at blood sampling, sex, parents´ education, family economy, country of birth of child and parents) and effect modifiers (socioeconomic; father´s IQ at his examination for military service) were included. Results: There were statistically significant adjusted negative associations between school performance (grades up to 1992/93: $P<0.0001$; school merits 1992/93-2007: $P<0.0001$) and IQ ($P=0.03$), on the one hand, and B-Pb, on the other. The dose-response relationships were non-linear. All effects were more pronounced for B-Pb <50 µg/L than for higher. In the B-Pb range 5-50 µg/L, the average IQ loss corresponded to about 5 IU. There was no significant effect modification by socioeconomic factors. Conclusions: Lead causes neurotoxic effects at very low exposures (B-Pb $\leq$50 µg/L). in childhood. Effects remain after many years.

Key words:

Blood

Dose-response

IQ

Lead

School performance.

1. Introduction

Lead is neurotoxic (reviews: Skerfving and Bergdahl 2007, in press; U.S. ATSDR 2007; EFSA 2010; JECFA 2011; U.S. NTP 2012). In particular, effects of the central nervous system (CNS; cognitive functions, hearing and posture) of foetuses/children are major problems. In particular, the focus has been on studies of different tests of full-scale IQ and on school/academic performance.

Recent studies have shown discrete effects on cognitive functions in children at low exposures, as reflected by low current blood-lead concentration (B-Pb; Lanphear et al. 2005). Initially, the information at very low B-Pb (<50 µg/L) was limited. However, the information is still limited.

Slight cognitive effects have limited importance for most individuals. However, they may be of major importance for subjects already in the low range because of other factors, and for the society. Thus, the potential effects at very low exposure levels need further clarification.

Another important aspect is the time perspective of any cognitive effects in childhood. It has been claimed that the effects disappear over time, so that they are no longer present later in life, either because the toxicity fades, or because they are compensated for by good socioeconomic conditions. However, the information is limited.

In Sweden, the exposure to lead has always been relatively low, as compared to most other areas of the world. However, studies of B-Pb in children in southern Sweden before (during a gradual decrease) and after the final prohibition of lead in petrol in 1994, have shown a six-

fold decrease of B-Pb (Strömberg et al. 2008). This means that we have a large material of B-Pb with a fairly wide variation, but still in the low range.

In Sweden, there are some high-quality national registries of school performance and IQ in teeagers. The aim of the present study is to analyse such measures as a function of the B-Pb of the children.

2. Materials and Methods

2.1. Index subjects

During the period 1978-2007, blood was sampled from a total of 3,176 children (age 7-12; 1,602 boys and 1,574 girls) living in or around the two cities of Landskrona and Trelleborg in the south of Sweden (Strömberg et al. 2008). Sampling was made annually in end of May/beginning of June in primary schools, each time in about 100 boys and girls. The participation rate was each year about 60%.

Landskrona has a secondary lead smelter, while Trelleborg has no lead-emitting industry. We have earlier shown that children living close to the smelter have higher B-Pb than the other children; in the beginning of the study period there was also an effect of living in the cities, as compared to the surrounding rural areas (Stroh et al. 2009).

All children had a unique personal identification number, which was linked to various national registers (see below).

The study was approved by the ethics committees at Lund University and Statistics Sweden.

2.2. Methods

Questionnaire. At the examination, each child was questioned about parents´ smoking habits, and occupations, and about hobbies, in particular such that could mean an exposure to lead.

Blood-lead determinations. Blood was drawn from the cubital vein into evacuated, heparinised metal-free tubes (Venoject® VT-100SH; Terumo Europé, Leuven, Belgium; Vacuette®; Greiner-Bio One GmbH, Frickenhausen, Germany).

In 1978-94, B-Pb was determined by flame or electrothermal atomization atomic absorption spectrometry, 1995-2007 by inductively coupled plasma mass spectrometry.

Quality control (internal and external) was strict during the whole period, and particularly so at the changes of methods. The detection limits were always $\leq$0.5 µg/L and the imprecision <5% (coefficient of variation at duplicate determinations; Schütz et al. 1985; Skerfving et al. 1986; Strömberg et al. 1995, 2003, 2008). Accuracy was checked by control blood samples (Seronorm®, SERO AS, Billingtad, Norway). We continuously produced good results in the UK National External Quality Assessment Service (Birmingham, UK).

Effects. *School performance.* To measure school performance, we collected data on performance at the end of the 9-year compulsory school (usually at age 16) from the national register at Statistics Sweden.

The system has changed during the period. In 1981-1991, there were four passing grades (2-5) and one non-passing (1). In this system, pupils were compared to each other (ranked) within

the class, and graded to achieve a normal distribution with 3 as an average. The grade point average was obtained by addition, and then division by the number of subjects of study.

In 1992-2007 a four-grade system (here denoted "merits") was used, with three passing grades (G, VG, MVG, with increasing performance) and one non-passing. The new system was goal related, in contrast to the previous group-related one. The credit value is based on the pupil's highest 16 grades, which were given different values: MVG=20, VG=15, G=10. The highest score is therefore 320.

"Over-all" IQ. Almost all Swedish men aged 18-19 (ca 50,000 each year) have been summoned to undergo military enrolment tests. Data was received from the National Service Administration and the Military Archives (14 women, others men). Men in institutions have been excluded (1,500-2,000 per year), during 2001-2006 also subjects with a number of diagnoses (2,900-8,400/year, including those in institutions). 2007-2010 and on, only 17,000-25,000 (men and some women) were tested.

The overall score is based on sub-tests of logical, verbal and spatial abilities, as well as test of technical understanding.

The IQ score had been transformed into Stanine points (standard nine; top score 9; Seashore 1955; **Supplementary material**, Fig. S3).

Other covariates. From Statistics Sweden, information on the child´s and its parents´ country of birth (Sweden, other Nordic, and other), parents´ education (primary school, high school, college/university) and family economy (total income in Swedish crowns per year) was

obtained. From the National Service Administration and the Military Archives, we received information on the full-scale IQ of the children´s fathers at their military enrolment tests; the results were transformed into Stanine points.

Statistical analysis. In the **Supplementary material**, frequency distributions of potential confounding and effect-modifying factors at time of blood sampling are summarized (age at blood sampling [Table S1]; school performance [average grades, Figures S1; merits, Figure S2]**; "**children´s" full-scale IQ **[**Figure S3**];** mothers´ and fathers´ education and family economy [Table S1]; fathers´ IQ [Figure S4], country of birth of children, mothers and fathers [Table S1], as well an overall view of the relationship between them [Table S2]).

The effects of B-Pb on cognitive functions (dependent variables), with additional consideration of the potentially explanatory variables sex, blood sample year, age at sampling, children´s country of birth, parents' country of birth and education, family economy, and fathers´ IQ were examined by generalized linear models. Except for age (which was not associated with B-Pb), only variables statistically significant ($p<0.05$) in at least one of the fully adjusted models were retained (i.e. all but parent´s country of birth; **Supplementary material,** Tables S3-S7). Also, interaction effects between B-Pb, on the one hand, and family economy, and index subject´s and his/her father´s IQ, on the other, were evaluated.

After initial data inspection and crude modeling (linear, log-linear and quadratic), we decided to model, for each dependent variable, linear associations for B-Pb <50 µg/L. We allowed for a change of the slope at B-Pb 50 µg/L, which was tested for by including an effect-modifying parameter. However, in the analysis of school performance by merits, B-Pb ≥50 µg/L were sparse.

Besides estimating the relationships between B-Pb and the dependent variables, we addressed prediction of the models. The proportion of variance in the outcome data explained by a specific model (R^2) and the individual predicted values were calculated.

SPSS for Windows (Release 11.5.1, SPSS Inc., Chicago, US) was employed for the statistical analyses.

3. Results

3.1. Blood-lead concentration

The mean B-Pb was 34.0 (median 29.7, range 6-162) µg/L (Fig. 1). B-Pb decreased dramatically 1978-2007 (Fig. 2).

3.2. Regression modelling

Effects of the potential confounding/effect-modifying factors in the final multivariate models are shown in the **Supplementary material** (Table S3). There were no statistically significant interactions (Ps>0.05) between parents´ education, family economics or index subjects´ or their fathers´ IQ on the relationship between B-Pb and any of the dependent variables.

School performance. *Grades vs B-Pb.* Among all index subjects, there were unadjusted and fully adjusted negative associations between average grades and B-Pb (Table 1; Fig. 3). There was a statistically steeper adjusted slope in subjects with B-Pb ≤50 µg/L (P<0.001) than in the higher range, where the slope was not significant. B-Pb explained 5.0% of the variance in the univariate model. For the final multivariate model, R^2 increased to 28.7%. Individual predicted and observed values are shown in **Supplementary material** (Fig. S5).

Merits vs B-Pb. Among all index subjects, there were unadjusted and fully adjusted negative associations between merits and B-Pb (Table 1; Fig. 4). In the low range (B-Pb <50 µg/L), the negative slope was more pronounced; B-Pb explained 2.3% of the variance in the univariate model, in the multivariate one 25.4%. Individual predicted and observed values are shown in **Supplementary material (**Fig. S6).

Index subjects´ IQ vs B-Pb. Among all subjects, there were unadjusted and fully adjusted negative associations between IQ and B-Pb (Table 1; Fig. 5). Though the association was present in subjects with B-Pb <50 µg/L, there was no significant difference in slope between those, and those with higher. B-Pb explained 1.5% of the variance in the univariate model (in the low range 1.2%). For the final multivariate model, R^2 was 19.3% (in the low range 20.1%). Individual predicted and observed values are shown in **Supplementary material** (Figure S7).

4. Discussion

Low B-Pb (≤50 µg/L) in childhood (age 7-12) correlated significantly with average school performance at age 16 years in girls and boys, as well as cognitive ability (IQ) in boys at age 18-19. In terms of prediction, the univariate models with B-Pb only, explained 1-5% of the variance in these outcomes, whereas the multivariate models, which included additional explanatory variables, explained 20-29%.

The strength of the present material is the large number of children, the good quality of the B-Pb determinations, the almost complete follow-up of effects in national registers by use of the unique identification number and the good registers of school performance and findings of

cognitive in young men. Of interest is that we have access to most fathers´ IQ; earlier studies have focussed on mothers´ IQ.

Limitations are the relatively low participation rate at the baseline examination, the availability of only one B-Pb value for each child, and the use of different scales for effect parameters for various parts of the cohort. We did not have a full set of all potential confounding or effect-modifying factors for all the subjects. Also, after having been an almost complete examination of all young men for military service, there has been a decrease in the fraction assessed in the last years. These limitations are most likely non-differential. Thus, there is no reason to believe that they have significantly affected the results.

As to IQ, the testing was designed mainly to assess the usefulness of young men in military service. Thus, the test is somewhat different from IQ tests for other purposes. We have focussed on the "over-all" ("full-scale") IQ, since tests of lead-induced effects on individual cognitive domains have not been conclusive (U.S. NTP 2012). We lack of examination of IQ in most girls in the same manner as boys, but considering the consistency between the sexes in effects on school performance, this should be no major problem. There have been minor changes of the cognitive tests used over time. Transformation of results into Stanine points should have taken care of this variation. Also, there has been some change of normalization of the test results over time, because of over-all improved performance, which however, if anything, would rather quench a lead effect.

Study of lead-induced cognitive effects of lead has caused extensive discussions of potential confounding factors (U.S. NTP 2012). We have included the most important ones. Usually, the focus has been on the risk of under-adjustment. However, potential confounders have

often been correlated in the same way as in the present study (**Supplementary material**; Table S2). Hence, there is also a risk of over-adjustment, causing an under-estimate of the risk

Lately, there has also been interest in effect modification. Thus, the effect of lead has been shown to be especially pronounced in children with low socioeconomic status (Bellinger 2000) and low performance (Miranda et al. 2009). We tested for such interactions, but had no significant effects, perhaps because of low B-Pb and/or a relatively homogenous population.

We describe associations between B-Pb in childhood and toxic effects 4-12 years later. Of course, we do not know whether the lead toxicity operated at the time when we measured B-Pb, since they are most likely an associated with concentrations both earlier (including *in utero*) and the first few years of life, when B-Pb peaks (U.S. NTP 2012). It has often been assumed that effects are most pronounced at early exposure. However, in the most detailed analysis published, the association was closest with concurrent B-Pb at early school age (Lanphear et al. 2005). Also, in a small study, IQ effects displayed closer association with B-Pb at age 10 than with B-Pb in cord blood, or up to age 4 (Mazumdar et al. 2011). Further, such associations have also been reported in young adults (Krieg et al. 2009). In any case, our results show that lead exposure in childhood is associated with effects that should be of importance for the whole life of the individual.

The background of the lead-effect on school performance may be cognitive impairment. However, effects on behaviour in the classroom-deficit/hyperactivity disorder; ADHD) may also contribute (U.S. NTP 2012).

The present results show somewhat higher explained variances and stronger statistical relationships for school performance than for IQ. This may not be surprising, since the lag time between blood sampling and effect assessment is shorter (and thus the influence of other factors less), and since the IQ assessment almost only included men, while school performance in the larger population of both sexes. However, it should be kept in mind that the IQ outcome data were restricted to the nine categories, which could imply statistical limitations for the fit of a generalised linear regression model.

The present association between B-Pb and school performance is in accordance with an earlier, ecological study, which showed association between levels of lead in moss in all Swedish communities and school performance (Nilsson 2009). Interestingly, there was a good correlation between lead concentrations in moss and B-Pb in different areas of Landskrona, one of the presently studied areas.

Also, the present results are in accordance with several other studies of school performance, in which B-Pbs were similar to ours (mean 34 µg/L). Thus, a U.S. study, in which the B-Pb at age 30 months (mean 42 µg/L) were associated with impaired developmental, behavioural and educational outcomes at age 7-8 (Chandramouli et al. 2009), though we both sampled blood and assessed effects later. Further, in a large cross-sectional examination of U.S. children (age 6-16), B-Pb (geometric mean 19 µg/L) was negatively correlated with an achievement test (Lanphear et al. 2000). Moreover, in another U.S. survey, as low a B-Pb as 20 µg/L at 3 months to 3 years of age was negatively associated with a decrease of reading score in the fourth grade (Miranda et al. 2007). Also, a mean B-Pb of 30 µg/L was negatively associated with IQ at age 29 (Mazumdar et al. 2011).

The present data are also in accordance with the pooled analysis of results of prospective studies in the U.S., Australia and former Yugoslavia, in which there was a supra-linear negative association between IQ and concurrent B-Pbs, even at ≤50 µg/L, without any defined threshold (Lanphear et al. 2005); however, the information at low B-Pb was limited at that time. Similar results were seen in Polish (Pawlas et al. 2012) and Italian (Lucchini et al. 2012) children. Thus, the evidence is now convincing. We did could not show significant effects (neither for IQ, nor school performance) in the fraction of our populations with higher B-Pb, probably because of lower power in a population with exposure as low as ours.

The by now well-established non-linear dose-response curve is a mystery. It may reflect two different mechanisms of toxicity, a possibility deserving further studies.

Lead accounted for only a minor fraction of the total variance of school performance and IQ. This is in accordance with earlier reports (Koller et al. 2004). Hence, genetic and socioeconomic factors are far more important. For comparison our results with others, it may be useful to express our data as a decrease of conventional IQ units. An increase of B-Pb in the low range, from 5 to 50 µg/L, would correspond to an average decrease of IQ by about 0.51 Stanine points (lower 95% confidence interval 0.07), which corresponds to about 5 IQ U. In particular when considering that our subjects were tested with a somewhat different test, this in accordance with the above-mentioned study of effects in adults of B-Pb in childhood (Mazumdat et al. 2011), as well as the pooled study of concurrent IQ and B-Pb in children (Lanphear et al. 2005), and a recent modelled risk estimate, based on the latter investigation, in which it was concluded that a B-Pb of 18 µg/l causes a decrease of 1 U of IQ (EFSA 2010).

On a population basis, even small effects are important. It has been estimated that in U.S. children, lead exposure was a slightly more important factor for IQ than exposure to organophosphate pesticides, far more significant than methylmercury (from fish), and in the range of ADHD (Bellinger 2012). In individual subjects with IQ in the low range, even the present effects are probably particularly important. Also, a small decrease may cause major costs for the individual and the society (Landrigan et al. 2002).

In the beginning of the present study period (1978), B-Pb in Swedish children was much lower than in the U.S. (Fewtrell et al. 2004). Since then, the average Swedish concentration has decreased by a factor six; it now levels with those in other parts of Europe (Hruba et al. 2012a), and also in the U.S. (U.S. CDC 2012b), which has decreased even faster. Importantly, in other parts of the world, the levels are still much higher (Hruba et al. 2012; Skerfving and Bergdahl, 2007, in press).

Hence, the present effects need serious consideration. Indeed, European Food Safety Authority (EFSA 2010) and World Health Organization/Food and Agriculture Organization (JECFA 2011) argue for a tolerable lead intake corresponding to a B-Pb of 12 µg/L Recently, a "reference value" of 50 µg/L was set for U.S. children (U.S. CDC 2012s), which seems to be high.

5. Conclusions

Lead causes neurotoxic effects at very low exposures (B-Pb $\leq$50 µg/L) in childhood. The effects remain after many years.

Conflict of interest statement

The authors declare they have no actual or potential competing financial interests.

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Figure legends

Fig. 1. Distribution of blood-lead concentration (B-Pb) in 3,176 children (age 7-12) from southern Sweden.

Fig. 2. Yearly means 1978-2007 of blood-lead concentrations (B-Pb) in 3,176 children (age 7-12) from southern Sweden.

Fig. 3. Association between blood-lead concentrations (B-Pb) in childhood (age 7-12) and school performance (average grades) at age 16 in 1,008 subjects from southern Sweden. Regression lines: B-Pb $\leq$50 µg/L (Grade=3.8 - 0.016 * B-Pb); >50 µg/L (Grade=3.07 [at 50 µg/L] – 0.0032*B-Pb).

Fig. 4. Association between blood-lead concentrations (B-Pb) in childhood (age 7-12) and school performance (merits) at age 16 in 1,211 subjects from southern Sweden (Merits=220 - 0.65 * B-Pb [µg/L]).

Fig. 5. Association between blood-lead concentrations (B-Pb) in childhood (age 7-12) and IQ at age 18-19 in 927 subjects (913 males) from southern Sweden (IQ [Stanine points]=5.5 - 0.011 * B-Pb [µg/L]).

Table 1

Relationships between blood-lead concentrations in index subjects from southern Sweden (age 7-12), on the one hand, and school performance (average grade or merits at age 16) and IQ (at age 18-19), on the other. Univariate and mutivariate models were used (see text).

		School performance					
		Grades		Merits		IQ	
Group		Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
All	N	1,008	784	1,211	903	927	815
	β (SE), U per µg/L	-	-	-0.653 (0.184)	-0.636 (0.185)	-0.0114 (0.0033)	-0.0127 (0.0042
	P -	-	<0.001	0.001	0.001	0.002	
	R^2, %	5.0[a]	28.7[b]	1.4[a]	24.7[b]	1.5[a]	19.3[2]
B-Pb	N	?	577	?	879	?	569
≤50 µg/L	β (SE), U per µg/L	-0.0155 (0.0029)	-0.0132 (0.0028)	-1.051 (0.232)	-1.09 (0.234)	-0.0208 (0.0078)	-0.0204 (0.0096)
	P	<0.001	<0.001	<0.001	<0.001	0.008	0.03
	R^2, %	-	-	2.3[a]	25.4[b]	1.2[a]	20.1[b]
B-Pb	N	?	207	-	24	-	245
>50 µg/L	β (SE), U per µg/L	-0.0032 (0.0033)	-0.0007 (0.0030)	-	-	-	-
	P	0.33	0.82	-	-	-	-

[a] By B-Pb. [b] By fully adjusted model.
Abbrevations: β = slope of the regression line, units (U) per g/L of B-Pb; SE = standard error; R^2 = explained variance.

Figure 1

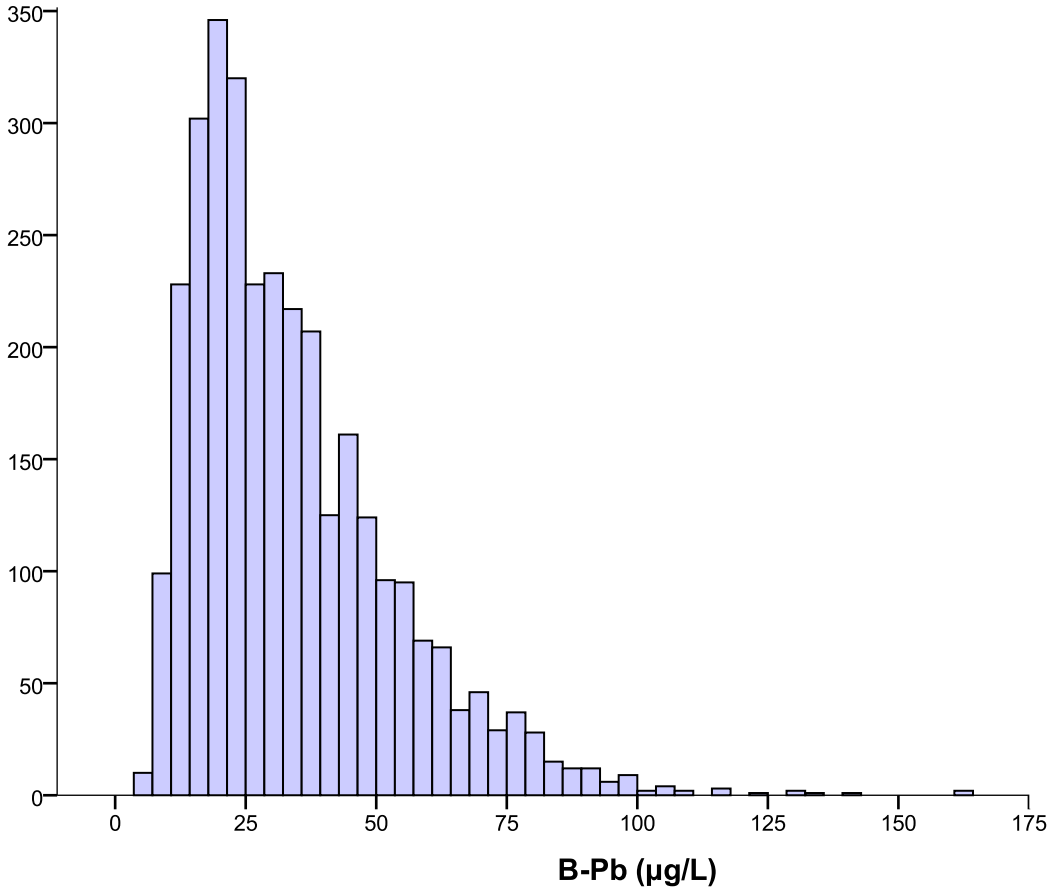

Figure 2

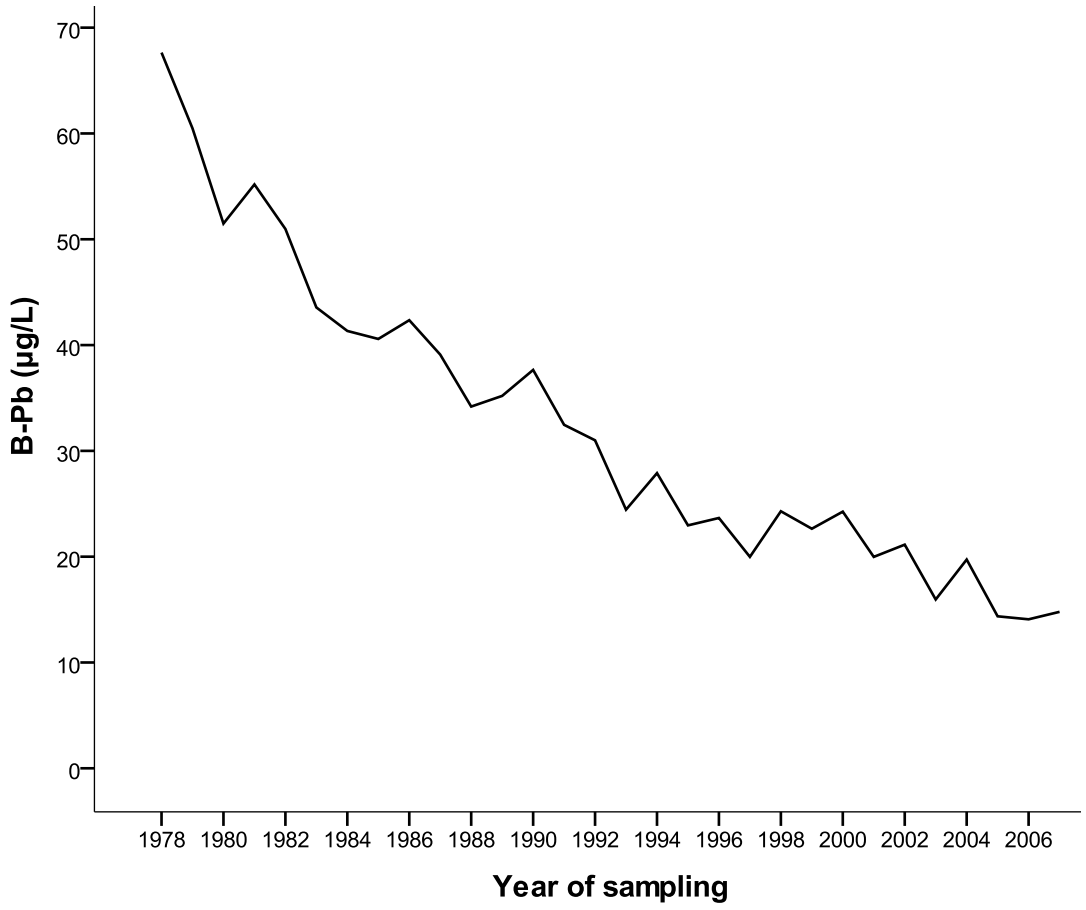
B-Pb (µg/L)
70
60
50
40
30
20
10
0
1978
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
Year of sampling

Figure 3

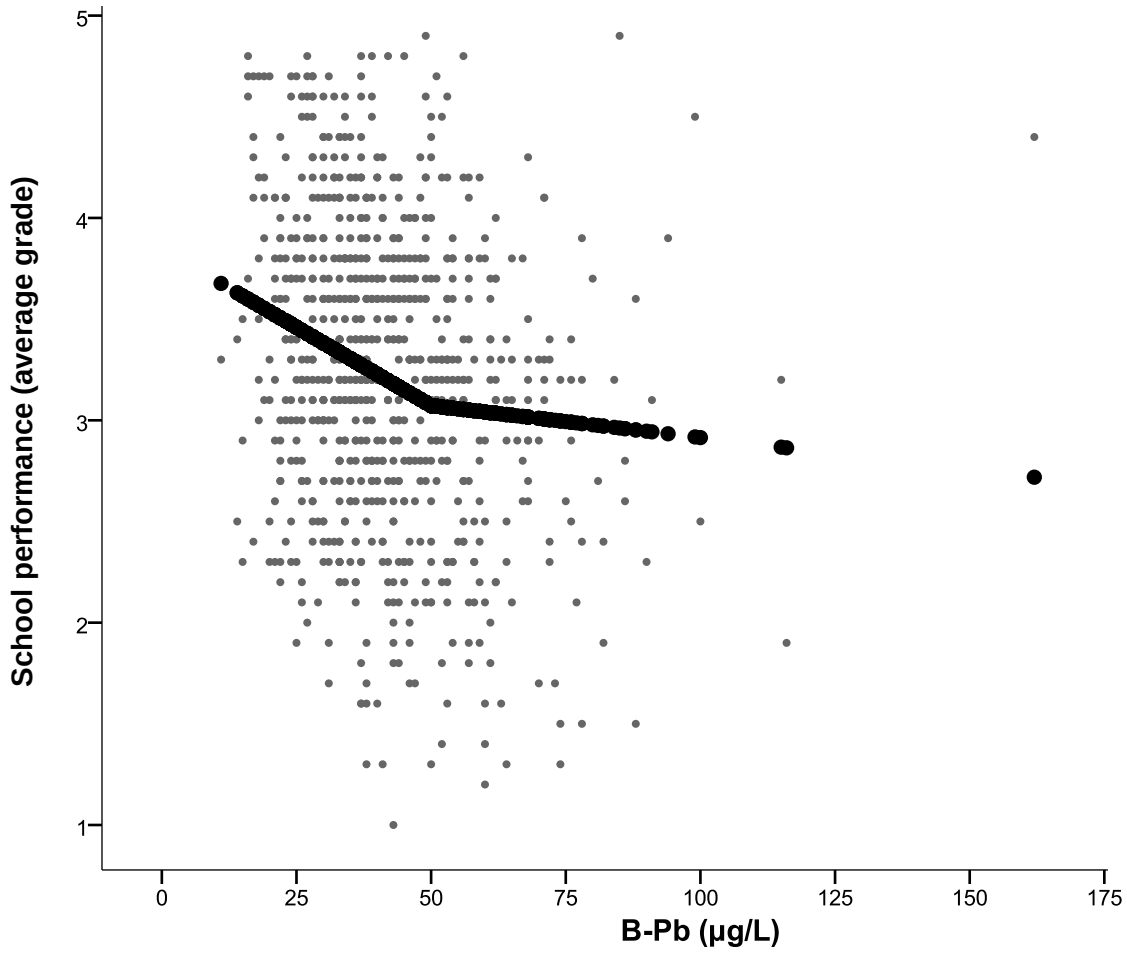
School performance (average grade)
5
4
3
2
1
0
25
50
75
100
125
150
175
B-Pb (µg/L)

Figure 4

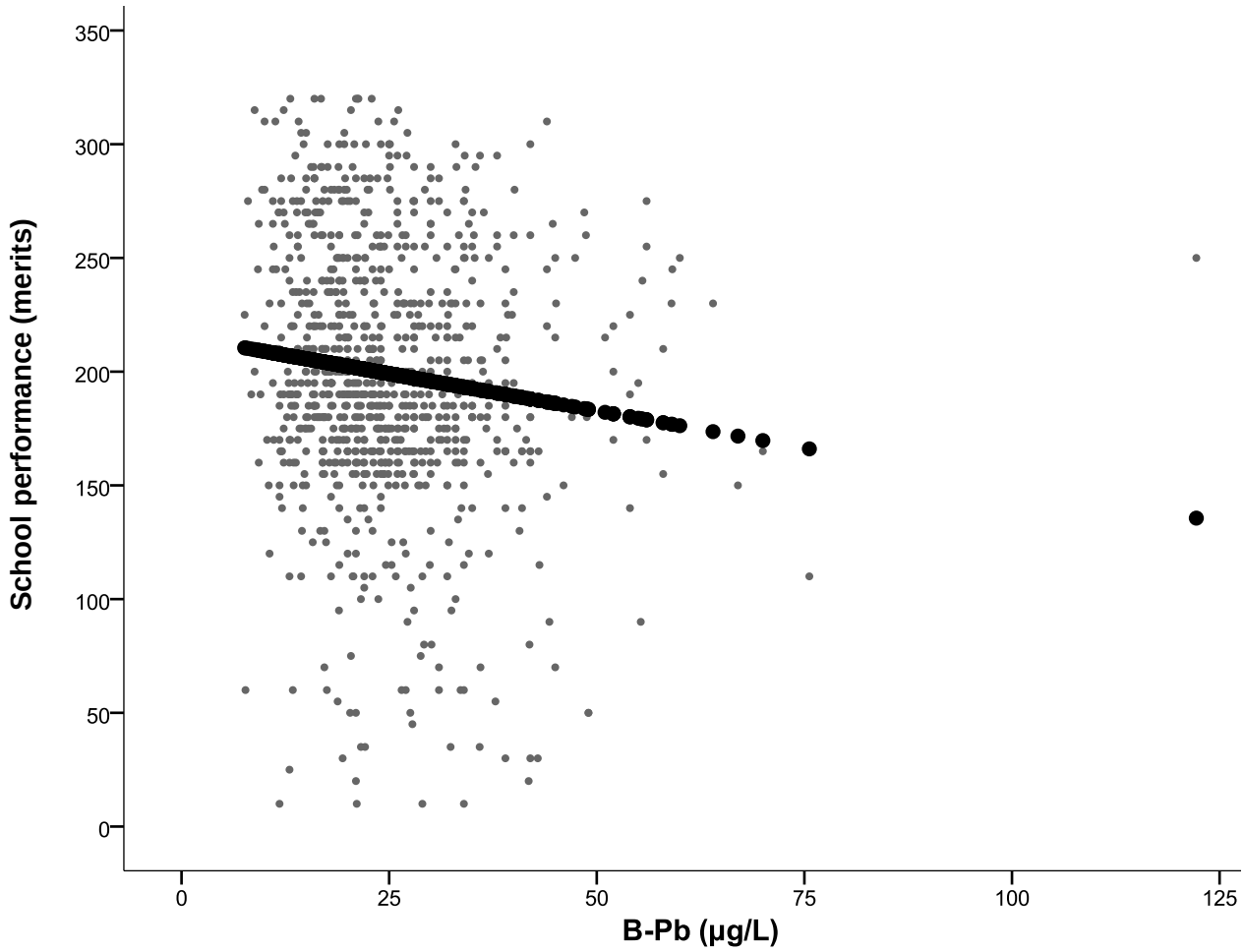
School performance (merits)
350
300
250
200
150
100
50
0
0
25
50
75
100
125
B-Pb (µg/L)

Figure 5

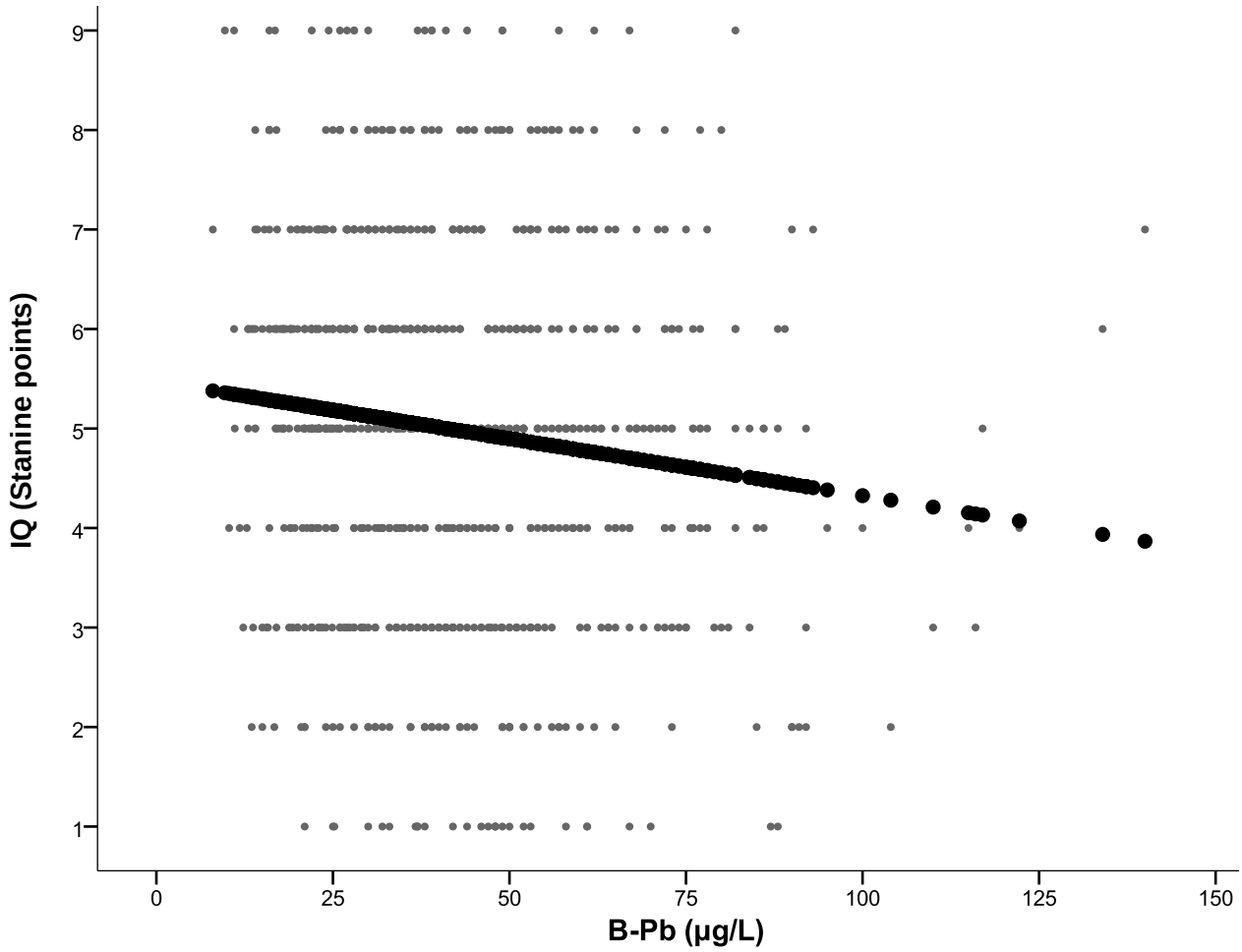

Table 1

Relationships between blood-lead concentrations in index subjects from southern Sweden (age 7-12), on the one hand, and school performance (average grade or merits at age 16) and IQ (at age 18-19), on the other. Univariate and mutivariate models were used (see text).

		School performance					
		Grades		Merits		IQ	
Group		Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
All	N	1,008	784	1,211	903	927	815
	β (SE), U per µg/L	-	-	-0.653 (0.184)	-0.636 (0.185)	-0.0114 (0.0033)	-0.0127 (0.0042
	P -	-	<0.001	0.001	0.001	0.002	
	R^2, %	5.0[a]	28.7[b]	1.4[a]	24.7[b]	1.5[a]	19.3[2]
B-Pb	N	?	577	?	879	?	569
≤50 µg/L	β (SE), U per µg/L	-0.0155 (0.0029)	-0.0132 (0.0028)	-1.051 (0.232)	-1.09 (0.234)	-0.0208 (0.0078)	-0.0204 (0.0096)
	P	<0.001	<0.001	<0.001	<0.001	0.008	0.03
	R^2, %	-	-	2.3[a]	25.4[b]	1.2[a]	20.1[b]
B-Pb	N	?	207	-	24	-	245
>50 µg/L	β (SE), U per µg/L	-0.0032 (0.0033)	-0.0007 (0.0030)	-	-	-	-
	P	0.33	0.82	-	-	-	-

[a] By B-Pb. [b] By fully adjusted model.
Abbrevations: β = slope of the regression line, units (U) per g/L of B-Pb; SE = standard error; R^2 = explained variance.

Supplementary Material

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