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Assessment of relationships between blood-lead concentrations in children and toxic effects

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Abstract
During the period 1978-2007 we analysed lead in blood (B-Pb) from a total of 3,680 children (the majority aged 7-8) living in or around the cities Landskrona and Trelleborg in the south of Sweden. The mean B-Pb was as low as 37.1 (median 33, range 5.6-244) µg/L, with a six-fold decrease over the time period.

There were statistically significant negative associations between later school performance in grade 9 (at age 16), 8-9 after the blood sampling (grades up to 1992/93: r_S=-0.209; P<0.0001; school merits 1992/93-2007: r_S=-0.152; P<0.0001), on the one hand, and B-Pb in early childhood, on the other.

There were a significant negative associations between cognitive functions (IQ; Stanine points; (r_S=-0.093; P=0.002), height (r_S=-0.107; P<0.0001) and weight r_S=-0.138; P<0.001) at examination of men for military service (age 18-19), 11-12 years after blood sampling, on the one hand, and B-Pb in young childhood, on the other.

Hence, the present, crude analyses confirm earlier findings of toxic effects of Pb at very low exposures (B-Pb <50 µg/L). Of particular interest is that the effects remained as much as 8-12 years after the exposure assessment. However, firm conclusions must await more advanced statistical modelling, taking into account potential confounding factors.

Background
Lead (Pb) is neurotoxic (Skerfving 2005; Skerfving and Bergdahl, 2007). In particular, effects of the central nervous system (CNS; cognitive functions and hearing) of fetuses and children is a major problem. There are also toxic effects of Pb on the growth of children.

Recent studies have shown discrete effects on cognitive functions at low exposures, as reflected by low blood-Pb (B-Pb), and without any clear threshold (Lanphear et al., 2005). Such effects have limited importance for the individual, since they are influenced by many conditions, and since the fraction of the total variance that is explained by Pb is limited. However, they are of major importance for the society. Thus, the potential effects at very low needs further clarification.

In Sweden, the exposure to Pb has always been low, as compared to most other areas of the world. However, studies of B-Pb in children before (during a gradual decrease) and after the prohibition of Pb 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 wide variation, but still in the low range.

The aim of the present study is to describe measures of cognitive functions and anthropometrics as a function of the B-Pb of the children.

Subjects and methods
Subjects
During the period 1978-2007 blood was sampled from a total of 3,680 children (age 3-17; only one aged 3, three aged 17) 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 of about 100 boys and girls. The participation rate was each year was about 60%.

Landskrona has a secondary Pb smelter, while Trelleborg has no Pb-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 Committee at Lund University.

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 Pb.

Blood-lead determinations

Blood was drawn from the cubital vein into evacuated, heparinised tubes (Venoject® VT-100SH; Terumo Europé, Leuven, Belgium).

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

Quality control was strict during the whole period, and in particular at the changes of methods. The detection limits were always $\leq$0.5 μg/L and the unprecision <5% (coefficient of variation at duplicate determinations). 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 assembled data on performance arat the end of grade 9 (end of 9-year compulsory school, usually at age 16).

The system has changed during the period. In 1978-1992, a 5-grade system of 1-5 was applied, with 5 as the highest. 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 adding the grades and dividing it with the number of grades, obtaining a number between 1 and 5.

In 1992-2007 a 4-grade system (here denoted "school merits") was used, with three passing grades (G, VG, MVG, with increasing performance) and one non-passing (U). 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.

This information was available at Statistics Sweden.

Cognitive functions

Apart from 2007 on, all Swedish men aged 18-19 (about 50,00 per year) have been summoned to undergo military enrolment tests. However, men in institutions have been excluded (1,500-2,000 per year, depending of the size of the age group). Since 2001, the number of recruits has decreased, due to lowering of the military budget. Therefore, a number of diagnoses have been accepted as valid for not undergoing the tests (4,300 in 2001; 5,200 in 2001; 7,700 in 2003, 7,800 in 2004; 8,400 in 2005; 2,900 in 2006; including persons in institutions). From 2007 on, only 17,000-25,000 (men and some women) have undergone the military enrolment tests. A last enrolment tests before the end of obligatory military service was in spring of 2010.

We used the score of the military enrolment cognitive ability test of men as a measure of cognitive functions. The overall score is based on a number of sub-tests of logical, verbal and spatial abilities, as well as test of the person's technical understanding.

The IQ score had been transformed into Stanine points (Standard Nine; top score is 9); 1 corresponds to IQ <-3 standard deviations (SD; 0.13% of the population), 2=-3 to -2SD (2.14%), 3=-2 to -1SD

(13.59%), 4=-1 to IQ 100 (34.13%), 5= IQ 100 to +1SD (34.13%), 6=+1 to +2SD (13.59%), 7=+2 to +3SD (2.14%), and 8=>+3SD (0.13%).

Data was received from the National Service Administration and the Military Archives.

Anthropometrics
We used the measurements of height and weight of the military enrolment examination.

Data was received from the National Service Administration and the Military Archives.

Statistics
Differences in B-Pb between groups were tested by Mann-Whitney U-test. Associations between effects and B-Pb were assessed by Spearman´s rank correlation (with correction for shared ranks). At this stage, no adjustments for potential confounding factors were made

Results
Blood-lead concentration
The mean B-Pb was 37.1 (median 33, range 5.6-244) µg/L (**Figure 1**). B-Pb decreased 1978-2007 (**Figure 2**). There was no over-all age-trend for B-Pb (**Figure 3**). Boys (N=1,858) had higher levels than girls (N=1,829), medians 39.5 (range 6.6-250) *vs* 31.7 (5.7-156) µg/L (P<0.0001).

There were differences between children living in different geographical areas; those living near the smelter in Landskrona had higher levels than those in other parts of the urban area, who were, in turn, higher than the rural children (**Table 1**). Similarly, in Trelleborg, urban children where higher than rural ones.

Children born in Sweden had lower B-Pb than those (very few) born in Nordic countries outside Sweden, but higher than children born in other parts of the world (**Table 2**).

School performance
The distribution of average school performance in grade 9 (up to 1992/93) is shown in **Figure 4**. There was a significant negative association between these and B-Pb (**Figure 5**; r_S=-0.209; P<0.0001).

The distribution of school merits 1992/93-2007 is shown in **Figure 6**. There was a significant negative association between these and B-Pb (**Figure 7**; r_S=-0.152; P<0.0001).

Cognitive function
The distribution of IQ at military enrolment is shown in **Figure 8**. There was a significant association between IQ and B-Pb (**Figure 9**; r_S=-0.093; P=0.002).

Anthropometrics
The distribution of heights at military enrolment is shown in **Figure 10**. There was a significant negative association between height and B-Pb (**Figure 11**; r_S=-0.107; P<0.0001).

The distribution of weight at enrolment to military service in men is shown in **Figure 12**. There was a significant negative association between weight and B-Pb (**Figure 13**; r_S=-0.138; P<0.001).

Discussion
The present data indicate that B-Pb in early childhood (the major part at age 7-8) is correlated with average school performance in grade 9 (16 years) in girls and boys, as well as cognitive ability, height and weight in boys at recruitment to military service (at age 18-19).

The strength of the present material is the large number of children, the good quality of the determinations of B-Pb, the almost complete follow-up in registers by use of the unique identification number and the good registers of school performance and findings of cognitive functions and anthropometrics at the scrutinizing of boys for military service. In particular, the lag between the assessment of Pb exposure and potential toxic effects is of interest, since there is very limited data of late follow-up of early exposure, which is of importance for the interpretation of its life-long importance.

Limitations are the relatively low participation rate at the baseline examination, the availability of only one B-Pb value for each child, the lack of detailed later examination of girls in the same manner as boys, and the use over time of different scales for effect parameters. Also, after having been an almost complete examination of all boys for military service, there has been a decrease in the fraction assessed in the last years, which, however, only marginally affects the present results. Also, there have been minor changes of the cognitive tests over time and the normalization of the results, but that should only have a marginal effect on our results. Also, as to the anthropometric measures, one has to consider the fact that both height and weight have increased over time.

This, report is a first, descriptive one. Thus, we have not yet made a detailed analysis by potential confounding factors. However, it will be possible to do more advanced modelling, since we have information on the calendar year, fathers′ cognitive function, hearing, height and weight at his recruitment for military service. Also, we have obtained register information on several socioeconomic factors, to be included in the models. Such modelling is under way (Skerfving et al., to be published).

The present association between B-Pb and school performance is in accordance with an earlier, ecological study, which showed association between moss levels of Pb in all Swedish communities and the school performance (Nilsson, 2009). Interestingly, there was a good correlation between Pb in moss in areas of Landskrona and B-Pb in children (Nilsson et al., to be published).

B-Pbs in children from Landskrona and Trelleborg has decreased by a factor six in the period 1978-2007. The levels have always been low in an international perspective, and has continued to be so (Skerfving and Bergdahl, 2007; Hruba et al., submitted).

Also, the present results are in accordance with a U.S. study, in which the B-Pb at age 30 months (mean 42 μg/L) were associated with developmental, behavioural and educational outcomes at age 7-8 (Chandramouli et al., 2009), though we both sampled blood and assessed effects later.

The present data are in accordance with the results of several prospective studies in U.S. and former Yugoslavia, in which there was an association between IQ and concurrent B-Pbs <5 μg/L, without any defined threshold (Lanphear et al., 2005). SWe have not yet analysed whether our data are in accordance with a threshold.

The present results show closer relationships for school performance than for IQ at examination for enrolment in military service. This is not surprising, since the lag time between blood sampling and effect assessment is shorter (and thus the influence of other factors), and since the IQ assessment only included men, the school performance both sexes. Also, the cognitive testing of the young men was designed only to assess the usefulness in military service.

Earlier studies effects on height and weight have shown associations with B-Pb (Skerfving, 2005; Skerfving and Bergdahl, 2007), but the present results indicate effects at lower B-Pbs than have been reported earlier.

In the present report, we have not included the available information on hearing, which has previously been shown to be associated with B-Pb (Skerfving, 2005; Skerfving and Bergdahl, 2007), since this needs further analyses, particularly because our B-Pbs are lower than those reported to be oto-toxic.

The present toxic effects are of minor importance for the individual, since they are of limited size, and since many other factors affect the school performance, cognitive functions and anthropometrics sizes.

However, on a population basis, the effects are important; e.g., it has been estimated that a decrease of I U on the IQ scale means a life-time cost of 15,000 Euros.

Acknowledgments
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Dr. Peter Nilsson, PhD, gave valuable advice as regards the planning of the follow-up study.

References
Chandramouli K, Steer M, Emond AM. Effects of early childhood lead exposure on academic performance and behaviour of school age children. Arch Dis Child 2009; 94:844-848.

Hruba F, Strömberg U, Cerna M, Chunying C, Harari F, Harari R, Horvat M, Josko O, Koppova K, Kos A, Lundh T, Lundström N-G, Löfmark L, Lyoussi B, Laamech J, Mladen K, Pawlas K, Pawlas N, Rentschler G, Spevackova V, Spiric′Z, Yu-Feng L, Skerfving S, Bergdahl I A. Blood cadmium, mercury, and lead in city children from Croatie, Czech Republic, Poland, Slovakia, Slovenia, Sweden, China, Ecuador, and Morocco. Submitted.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, Roberts R. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect. 2005;113:894-9.

Nilsson P. Essay 1: The Long-term effects of early childhood lead exposure:
evidence from the phase-out of leaded gasoline. In: Essays on social interactions and the long-term effects of early-life conditions. Department of Economics, Uppsala University, 2009, pp. 23-80. ISBN 978-91-85519-27-9. ISSN 0283-7668.

Skerfving S. Inorganic lead – an update 1991-2004. Criteria Document for Swedish Occupational Standards. Arbete och Hälsa 2005:3, 119 pp.

Skerfving S, Bergdahl IA. Chapter 31. Lead. In: Nordberg GF, Fowler BA, Nordberg M, Friberg LT. Handbook on the Toxicology of Metals, Academic Press, Elsevier, 2007, p.599-643. ISBN 978-0-369413-3.

Strömberg U, Lundh T, Skerfving S. Yearly measurements of blood lead in Swedish children since 1978: The declining trend continues in the petrol-lead-free period 1995-2007. Environ Res 2008;107:332-335. DOI:10.1016/j.envres.2008-03-007.

Stroh E, Lundh T, Oudin A, Skerfving, Strömberg U. Geographical patterns in blood lead in relation to industrial emissions and traffic in Swedish children, 1978-2007. BMC Public Health 2009;9:225, sid 1-14. doi:10.1186/1471-2458-9-225.

Table 1. Blood lead concentrations (B-Pb) in children living in different geographical areas in and around Landskrona (where there is a secondary smelter) and Trellborg.

	Near smelter			Urban			Rural		
		B-Pb (µg/L)			B-Pb (µg/L)			B-Pb (µg/L)	
City	N	Md	(range)	N	Md	(range)	N	Md	(range)
Landskrona	582	38.0	(6.6-210)	871	33.0	(5.9-250)	918	29.4	(5.7-182)
Trelleborg	-			582	34.0	(6.9-162)	734	30.0	(6.1-116)

Table 2. Blood lead concentrations (B-Pb) in children born in different parts of the world.

Country	N	B-Pb (µg/L) Md	(range)
Sweden	3,387	33.0	(5.7-250)
Other Nordic countries	57	41.0[1]	(10.4-102)
Other	243	29.0[2]	(9.2-106)

[1] Higher than Swedish (P=0.002).
[2] Not different from Swedish (P=0.44).

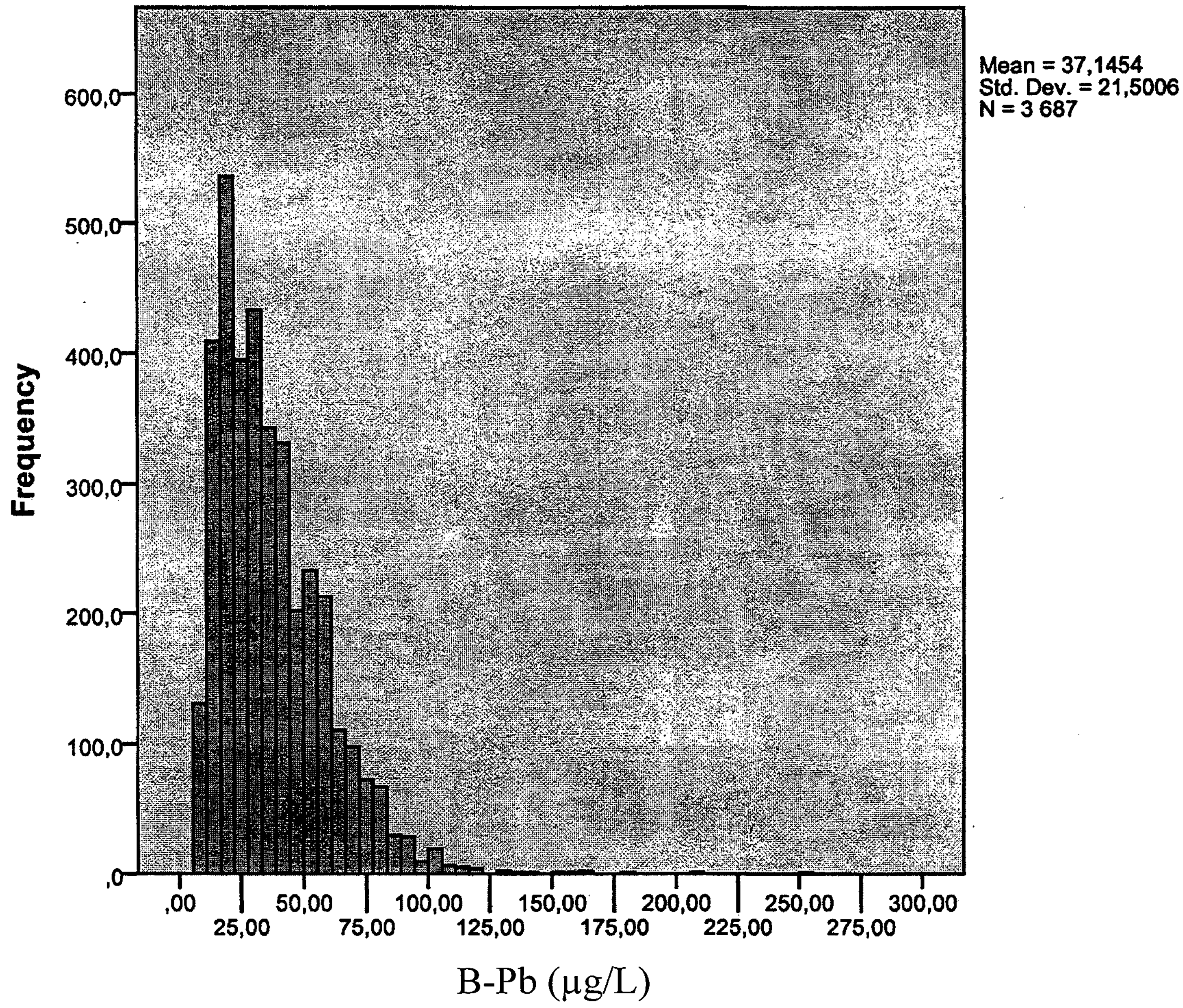

Figure 1. Distribution of blood-lead concentrations (B-Pb) in 3,680 children from Landskrona and Trellborg sampled 1978-2007.

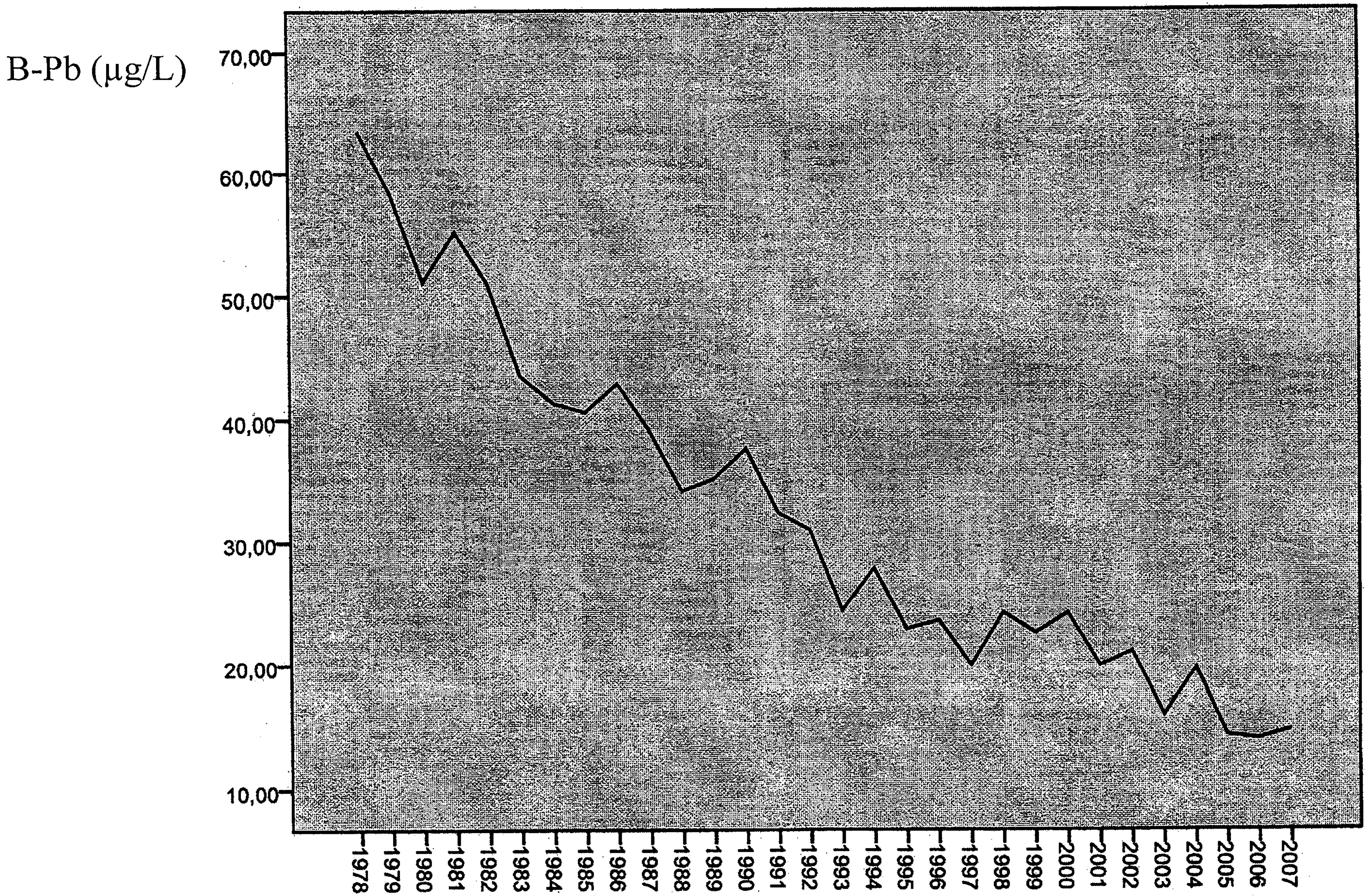

Figure 2. Yearly means of blood-lead concentrations (B-Pb) in 3,680 children from Landskrona and Trellborg sampled 1978-2007.

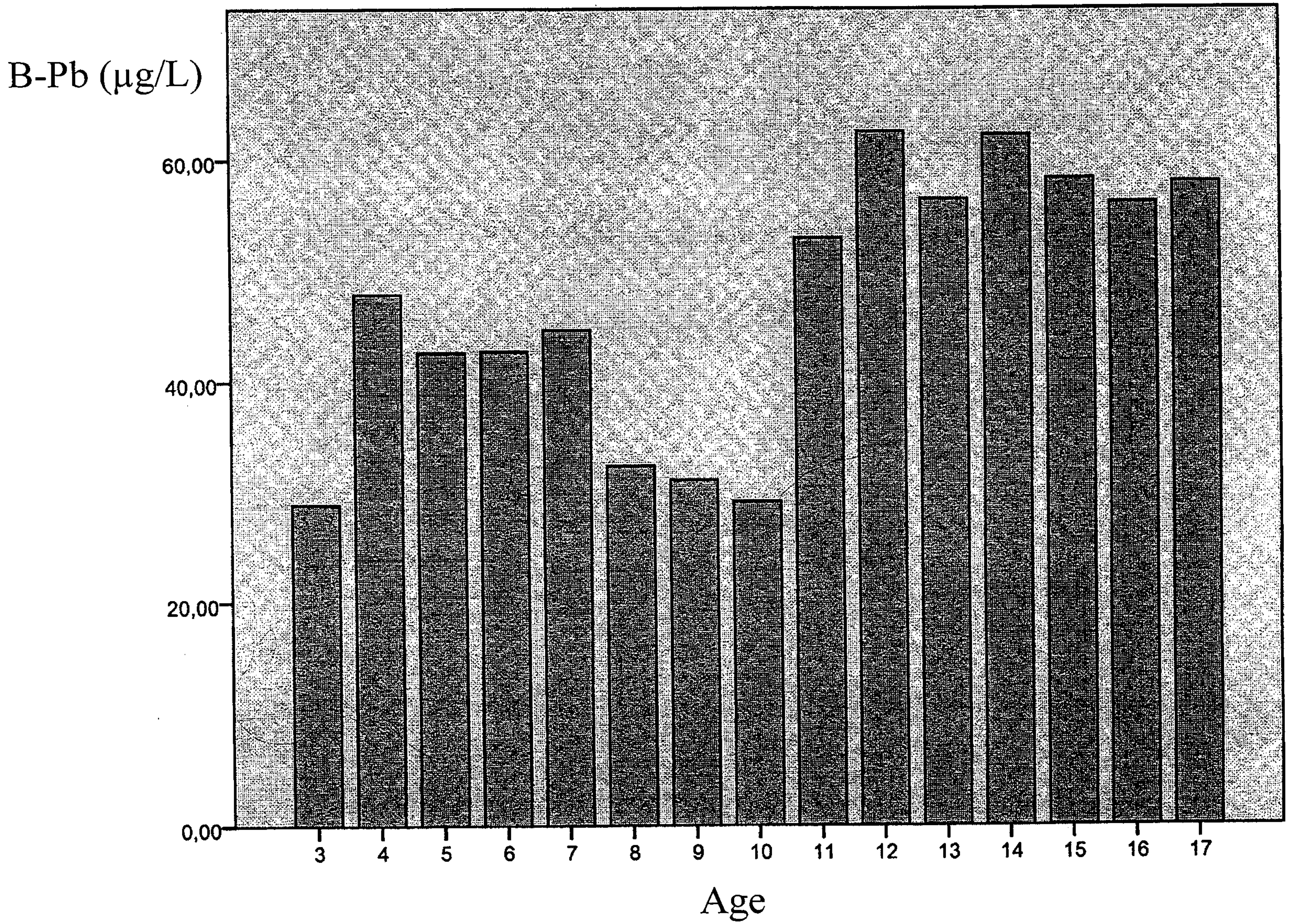

Figure 3. Age distribution of medians of blood-lead concentrations (B-Pb) in 3.680 children from Landskrona and Trellborg sampled 1978-2007.
N.B: that there was only one 3-year old child, and only three 17-year old; the other age groups were much more prevalent.

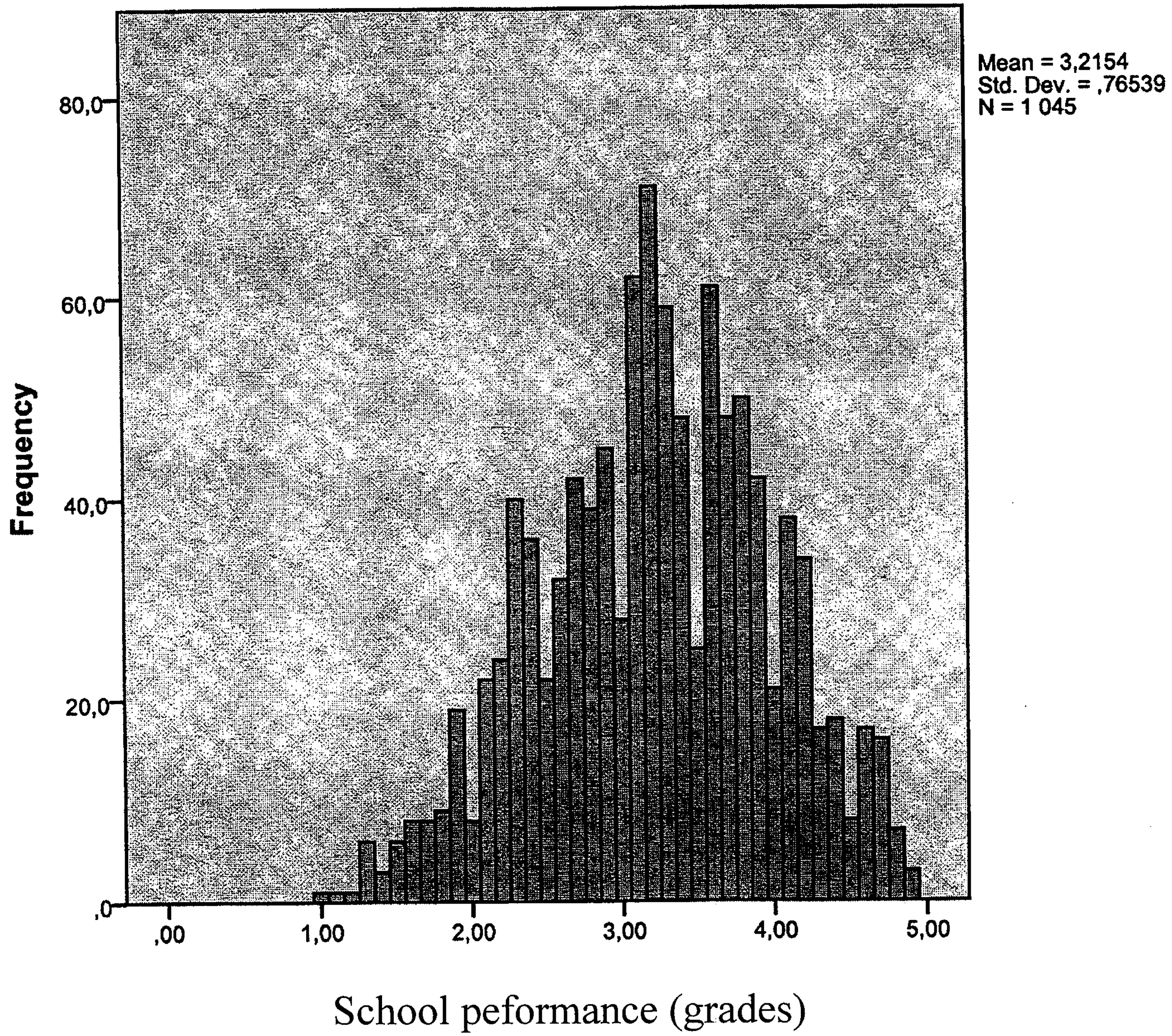

Figure 4. Distribution of average school performance in grade 9 in 1,045 children from Landskrona and Trellborg.

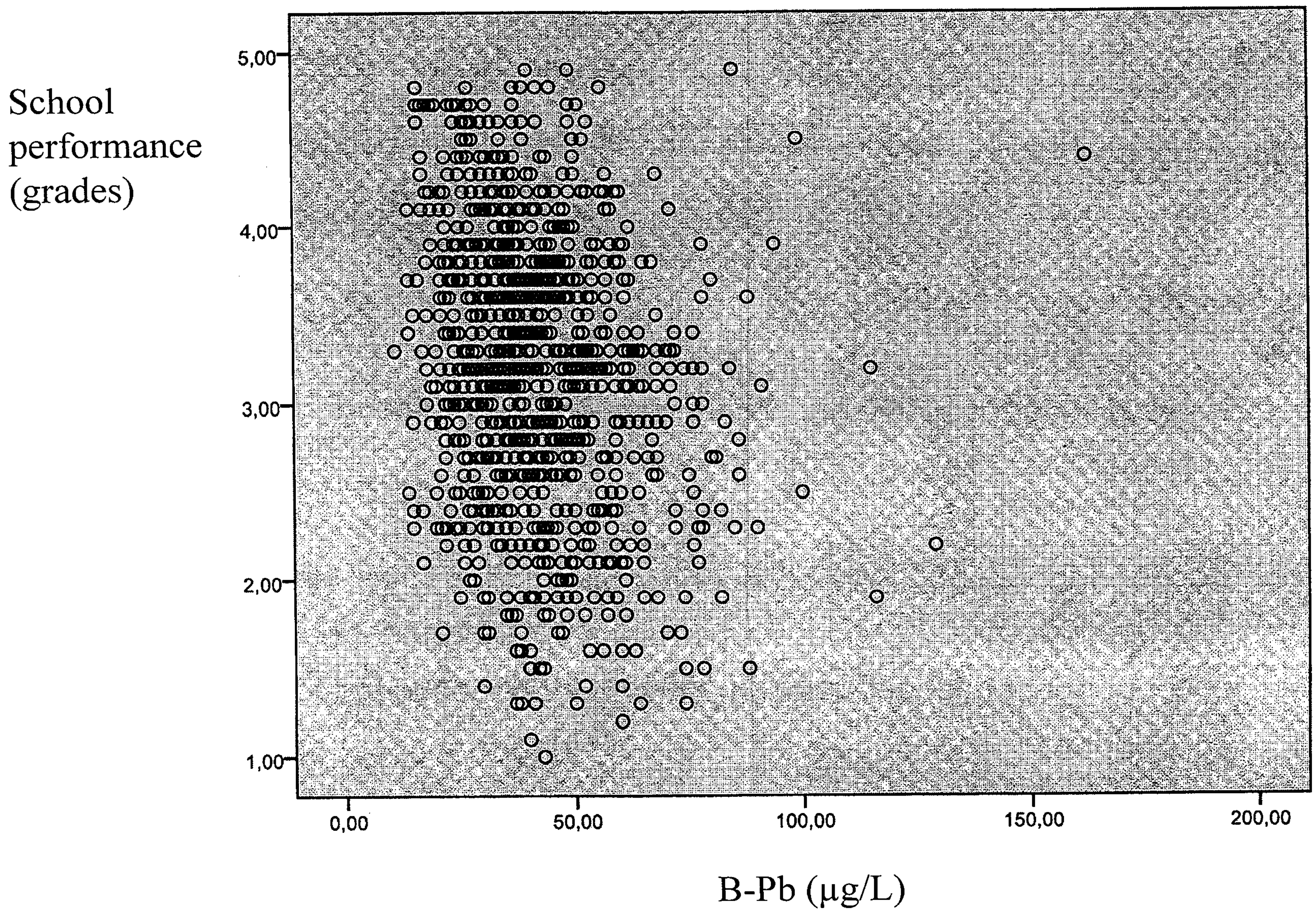

Figure 5. Association between blood lead concentrations (B-Pb) and average school performance in grade 9 in 1,045 children from Landskrona and Trellborg sampled 1978-2007 ($r_S=-0.209$; $P<0.0001$). The box encloses 25th to 75th percentiles and has the median in the centre.

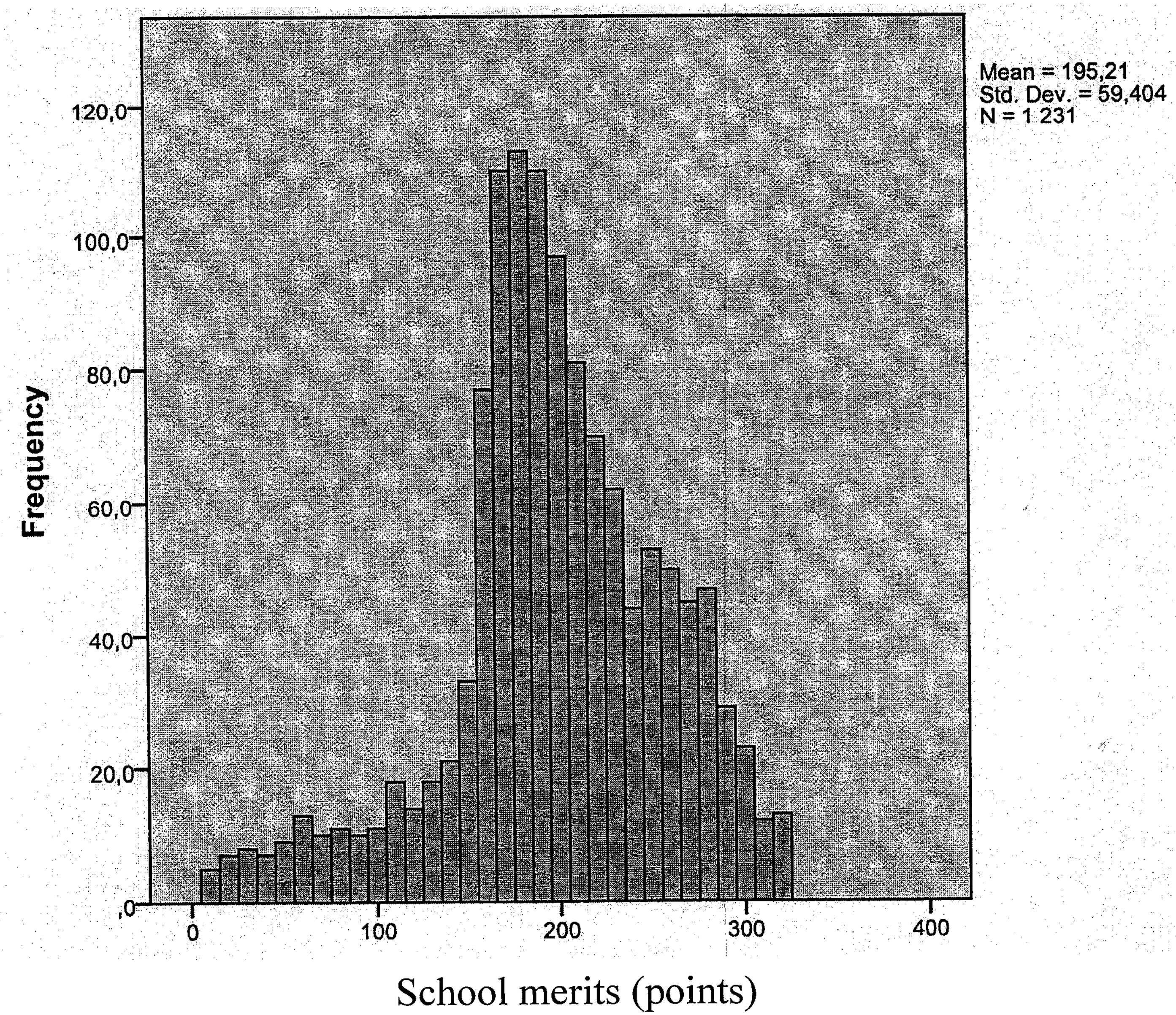

Figure 6. Distribution of school merits in 1.231 children from Landskrona and Trellborg.

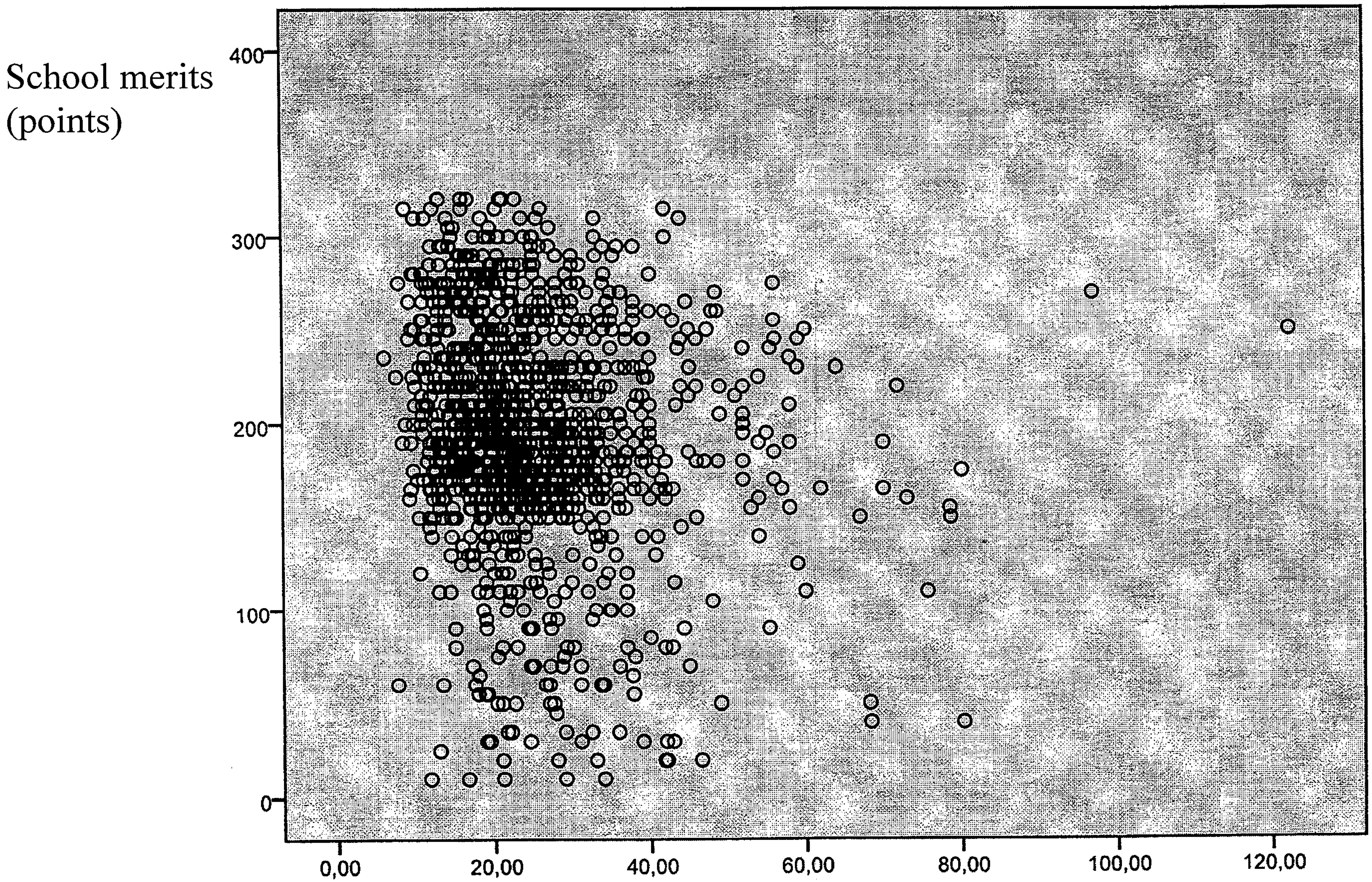

Figure 7. Association between blood lead concentrations (B-Pb) and school merits in 1,231 children from Landskrona and Trellborg sampled 1978-2007 (rS=-0.152; P<0.0001).

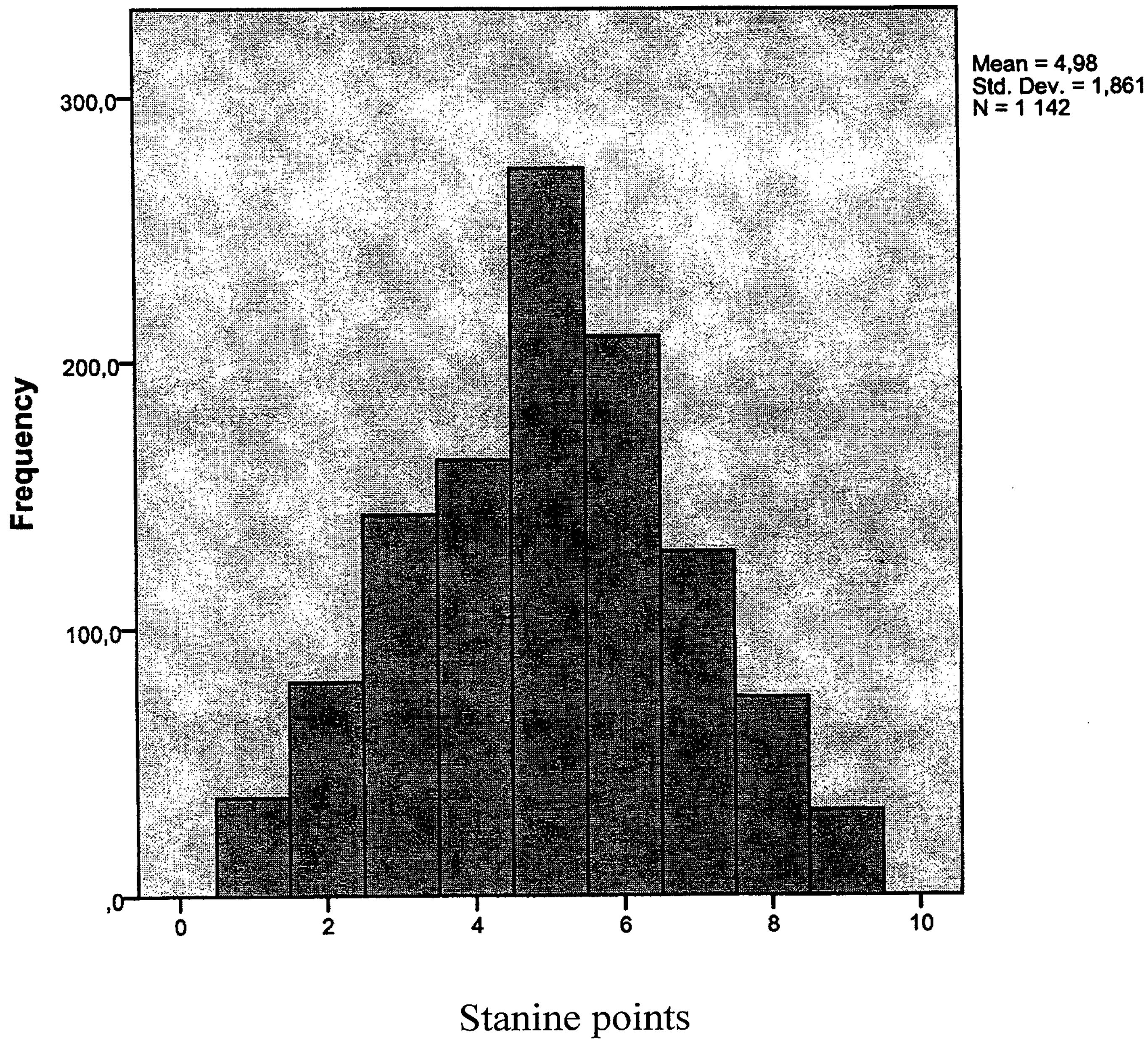

Figure 8. Distribution of IQ (Stanine points) at enrolment to military service in 1.069 men from Landskrona and Trellborg.

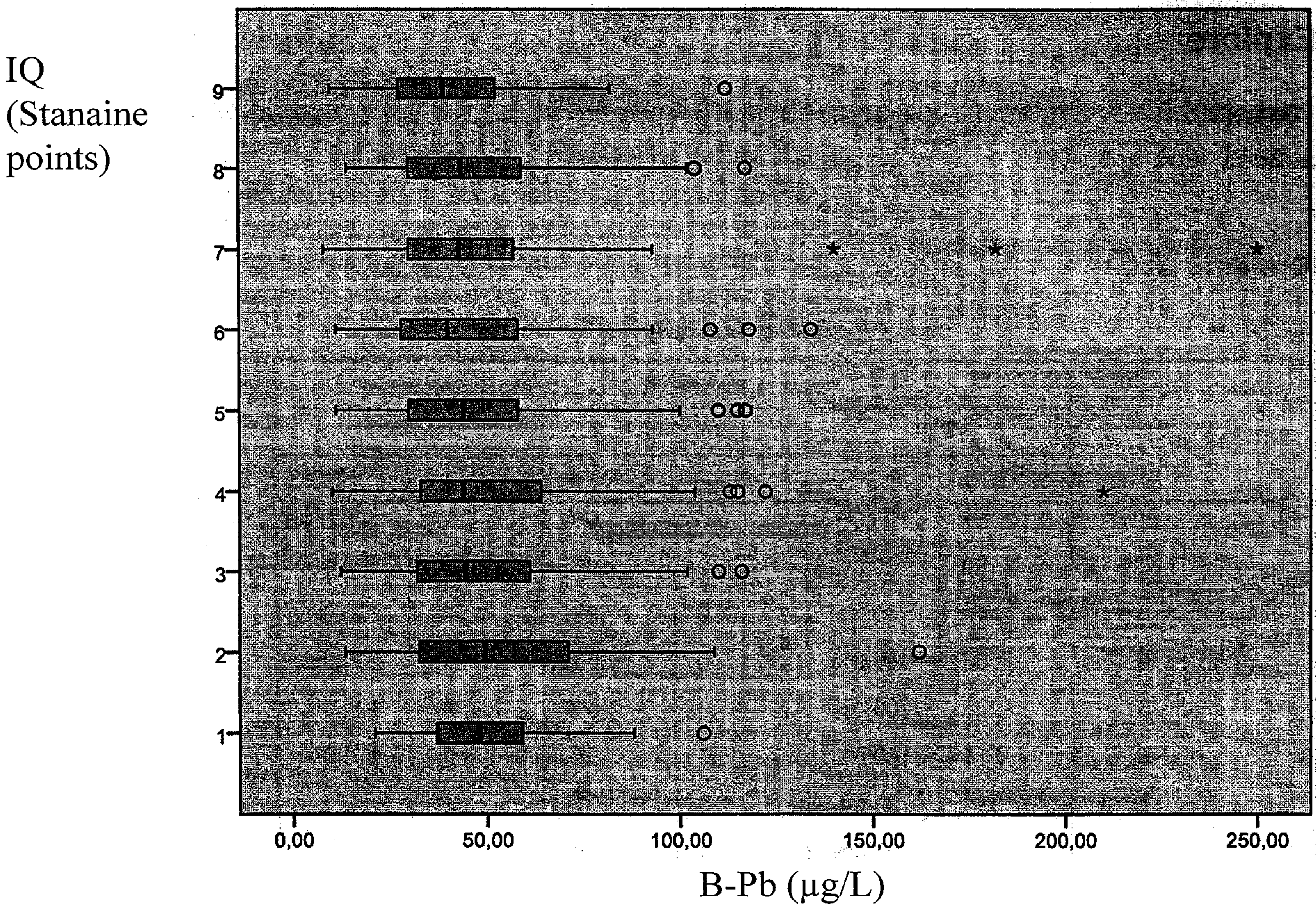

Figure 9. Association between blood-lead concentrations (B-Pb) and IQ at enrolment to military service in 1,069 men from Landskrona and Trellborg blood ampled 1978-2007 (rS=-0.093; P=0.002).

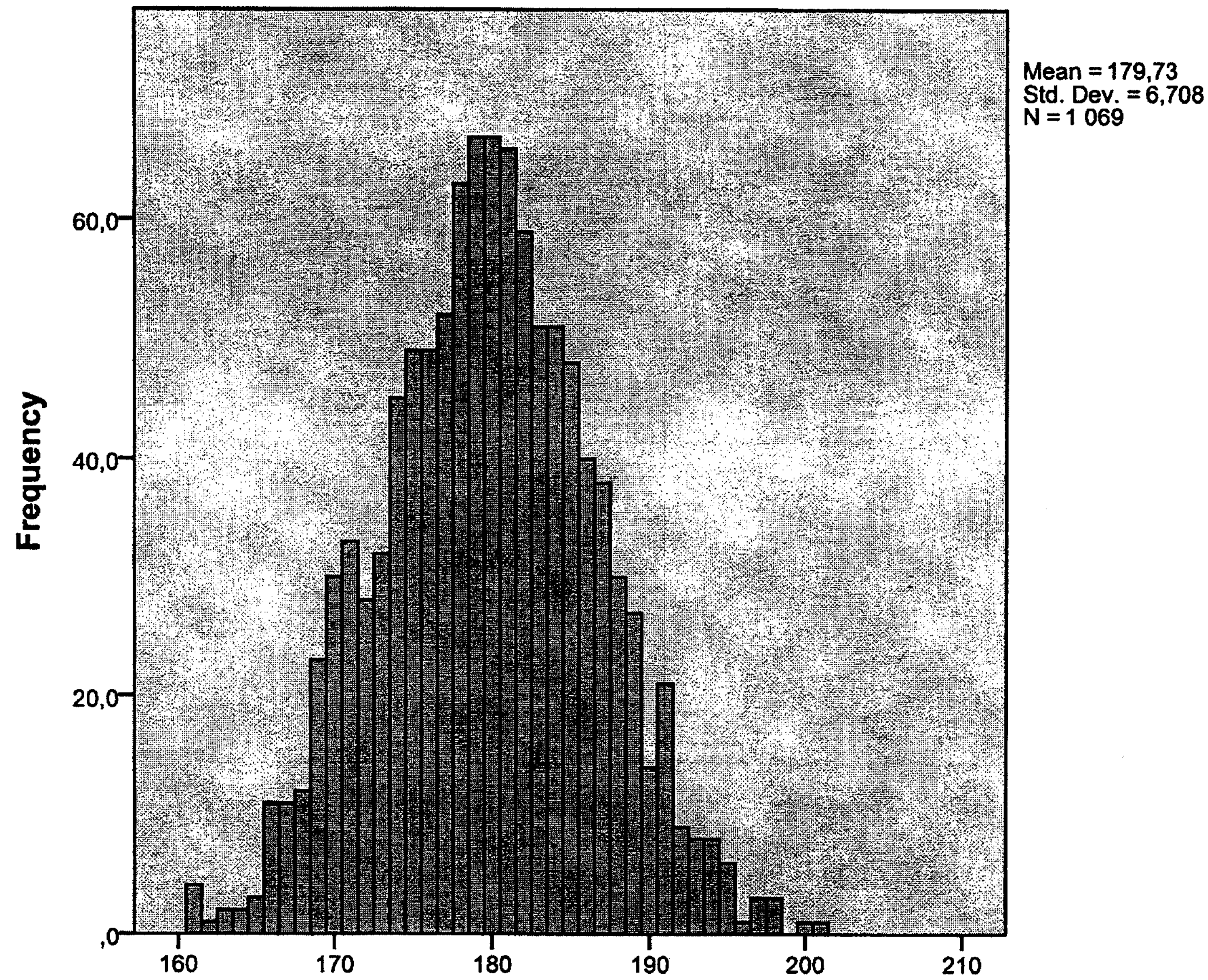

Figure 10. Distribution of height at enrolment to military service in 1,069 men from Landskrona and Trellborg.

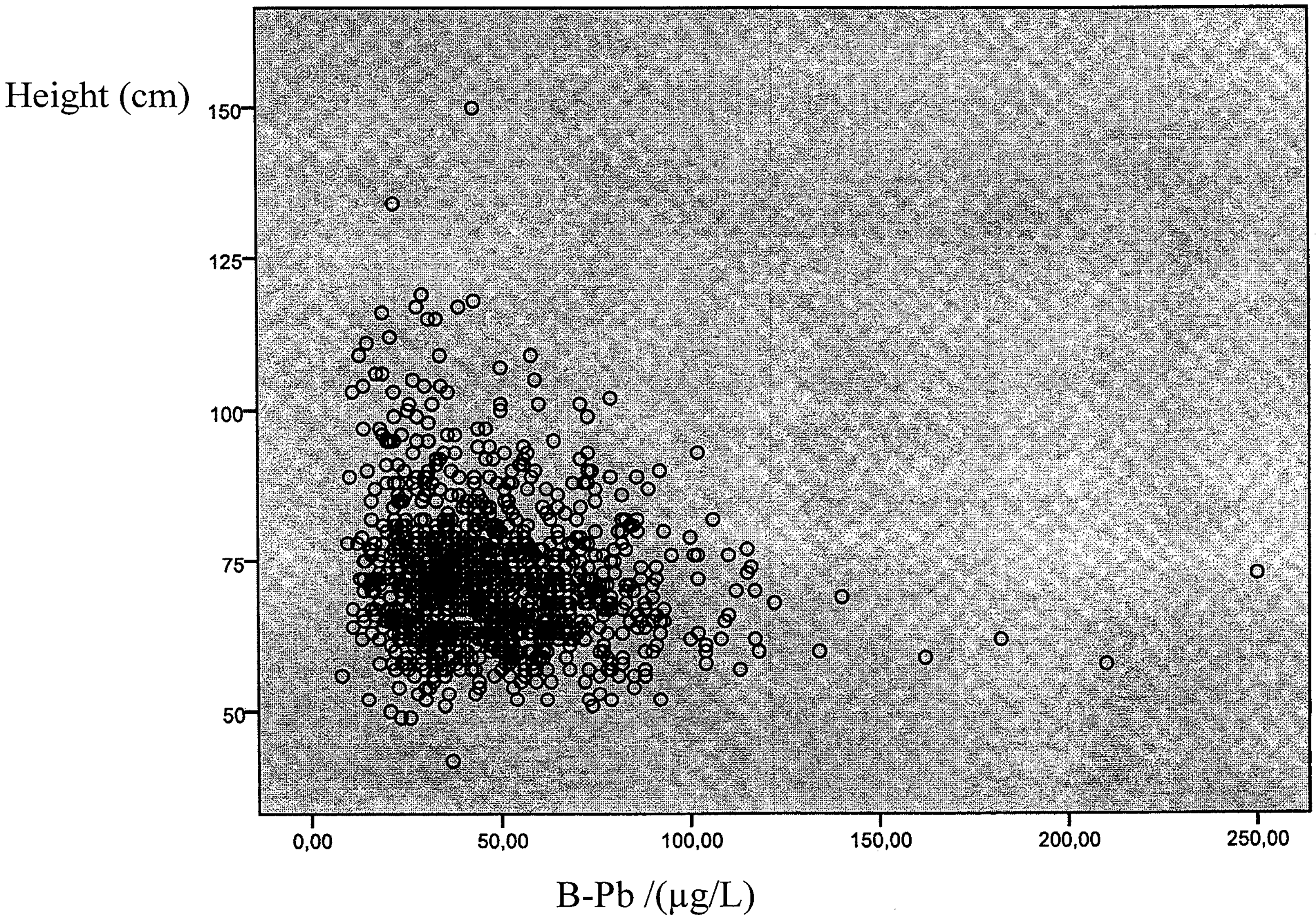

Figure 11. Association between blood-lead concentrations (B-Pb) and height at enrolment to military service in 1,069 men from Landskrona and Trellborg blood sampled 1978-2007 ($r_S=-0.107$; $P<0.0001$).

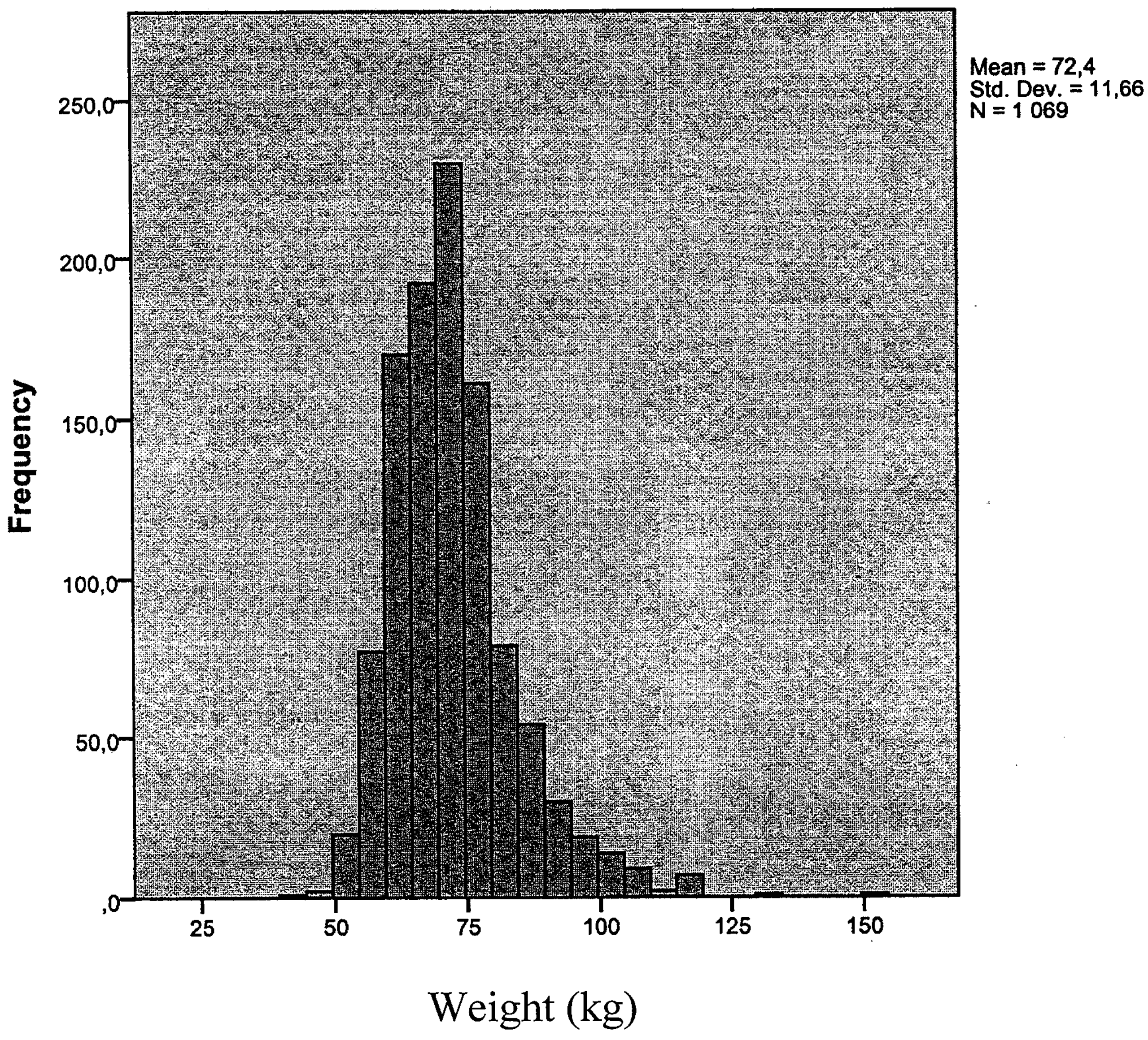

Figure 13. Association between blood lead concentrations (B-Pb) and weight at enrolment to military service in 1.069 men from Landskrona and Trellborg blood sampled 1978-2007 ($r_S=-0.138$; $P<0.0001$).

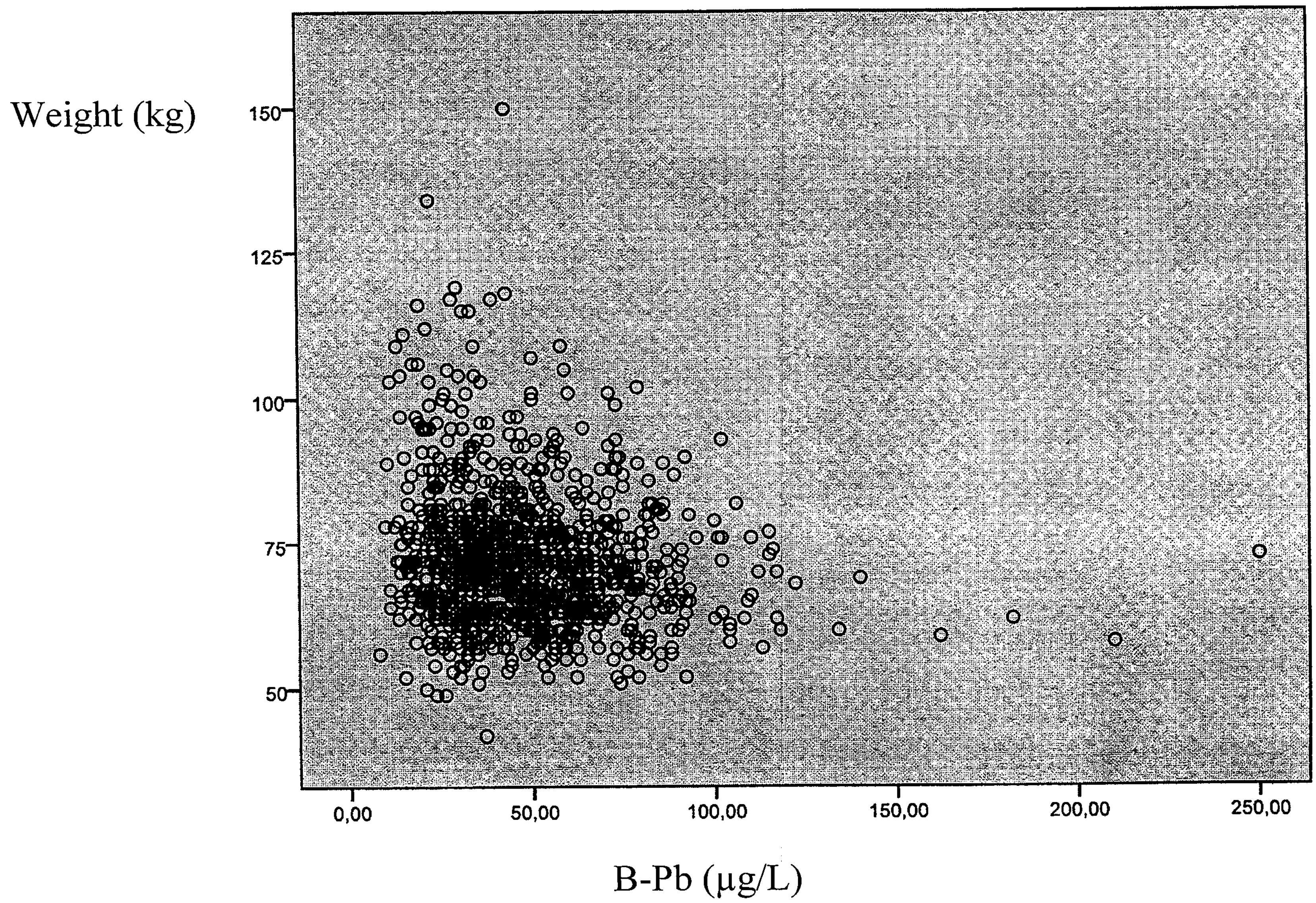

Figure 13. Association between blood lead concentrations (B-Pb) and weight at enrolment to military service in 1.069 men from Landskrona and Trellborg blood sampled 1978-2007 (rS=-0.138; P<0.0001).

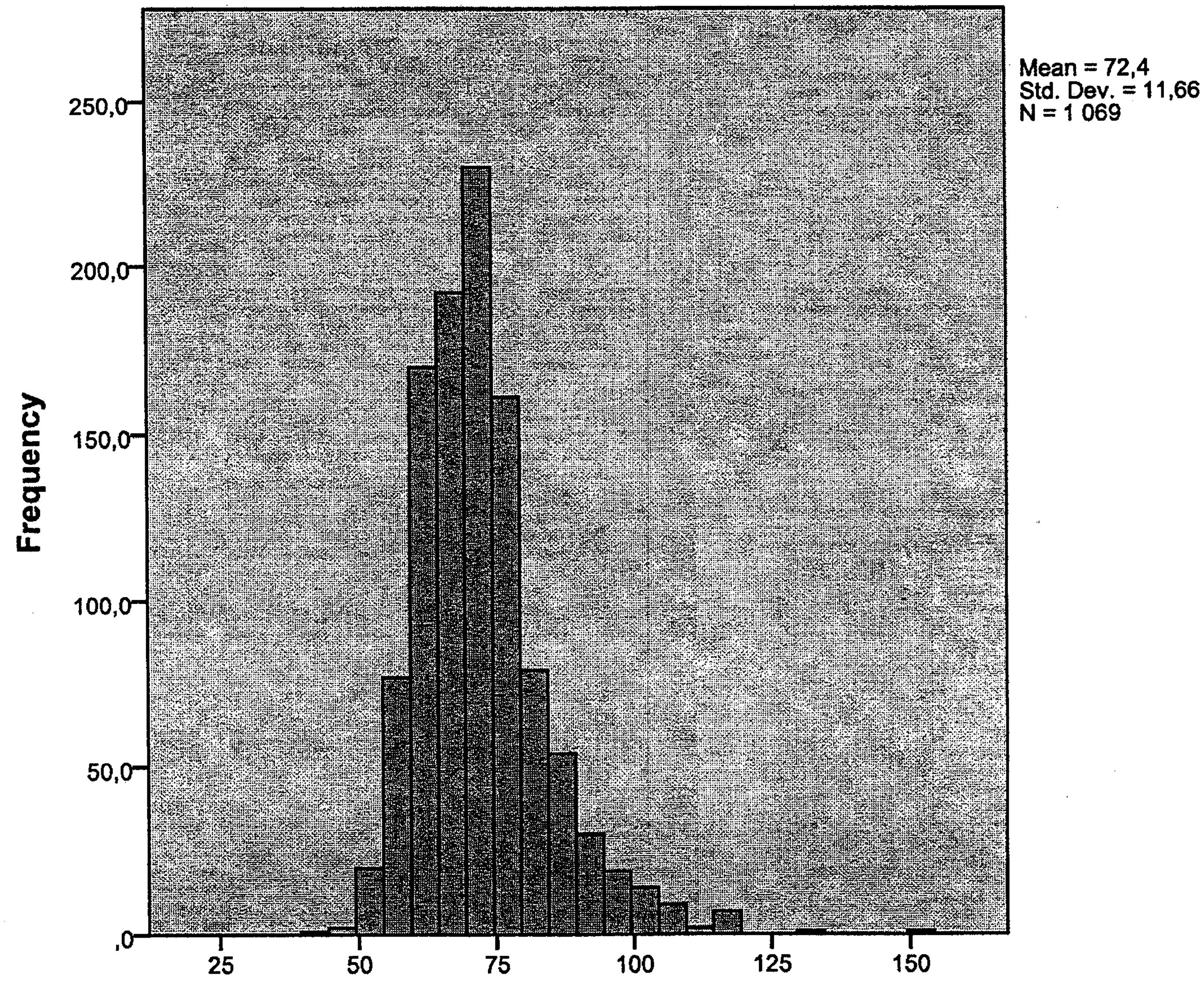

Figure 12. Distribution of weight at enrolment to military service in 1,069 men from Landskrona and Trellborg.