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Low-level exposure to lead, blood pressure, and hypertension in a population-based cohort

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ABSTRACT

Background: Environmental lead exposure is a possible causative factor for increased blood pressure and hypertension, but large studies at low-level exposure are scarce, and results inconsistent.
Objective: We aimed to examine the effects of environmental exposure to lead in a large population-based sample.
Methods: We assessed associations between blood lead and systolic/diastolic blood pressure and hypertension in 4452 individuals (46–67 years) living in Malmö, Sweden, in 1991–1994. Blood pressure was measured using a mercury sphygmomanometer after 10 min supine rest. Hypertension was defined as high systolic ($\geq$ 140 mmHg) or diastolic ($\geq$ 90 mmHg) blood pressure and/or current use of antihypertensive medication. Blood lead was calculated from lead in erythrocytes and haematocrit. Multivariable associations between blood lead and blood pressure or hypertension were assessed by linear and logistic regression. Two-thirds of the cohort was re-examined 16 years later.
Results: At baseline, mean blood pressure was 141/87 mmHg, 16% used antihypertensive medication, 63% had hypertension, and mean blood lead was 28 μg/L. Blood lead in the fourth quartile was associated with significantly higher systolic and diastolic blood pressure (point estimates: 1–2 mmHg) and increased prevalence of hypertension (odds ratio: 1.3, 95% confidence interval: 1.1–1.5) versus the other quartiles after adjustment for sex, age, smoking, alcohol, waist circumference, and education. Associations were also significant with blood lead as a continuous variable. Blood lead at baseline, having a half-life of about one month, was not associated with antihypertensive treatment at the 16-year follow-up.
Conclusions: Low-level lead exposure increases blood pressure and may increase the risk of hypertension.

1. Introduction

Environmental exposure to lead is ubiquitous. This poses a common public health problem, particularly in terms of effects on the central nervous system in children. In adults, exposure to lead has been evaluated as a possible causative factor of increased blood pressure (BP) or hypertension, in occupationally exposed individuals as well as in the general population (WHO, 2011; NTP Monograph on Health Effects of Low-level Lead, 2012). The most common biomarker of lead exposure is lead in blood (B-Pb); however, this mainly reflects recent exposure, since the half-life of lead in blood and soft tissue is about a month, while lead in bone

Abbreviations: B-Cd, blood cadmium; BP, blood pressure; B-Pb, blood lead; DBP, diastolic blood pressure; Ery-Pb, lead in erythrocytes; MDCS-CC, the cardiovascular cohort of the Malmö Diet and Cancer Study; NHANES, National Health and Nutritional Examination Survey; NTP, National Toxicology Program; OR, odds ratio; Pb, lead; SBP, systolic blood pressure

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is a measure of long-term exposure and body burden (Barbosa et al., 2005). In adults, >90% of body lead is located in the skeleton, and the half-life is about 5 years in trabecular bone and 10–20 years in cortical bone (EFSA, 2010; Skerfving and Bergdahl, 2015).

Two meta-analyses have been performed regarding lead exposure and increased BP or hypertension. One used lead in bone as an indicator of lead exposure, (Navas-Acien et al., 2008) and the other used B-Pb (Nawrot et al., 2002). The strongest association with BP was seen with lead in bone, but the meta-analysis using B-Pb as indicator also found a significant association between lead and BP. However, the effect size in the latter case was limited, with a two-fold increase in B-Pb producing an increase of 1.0 (95% confidence interval [CI]: 0.5–1.4) mmHg in systolic BP (SBP), and an increase of 0.6 (95% CI: 0.4–0.8) mmHg in diastolic BP (DBP).

A recent review by the United States of America National Toxicology Program (NTP) (NTP Monograph on Health Effects of Low-level Lead, 2012) found that the available epidemiological studies and animal studies provide sufficient evidence that lead exposure is associated with increased BP, but not for low-level exposure (<50 μg/L).

The studies reviewed by the NTP (NTP Monograph on Health Effects of Low-level Lead, 2012) included only three large (>1000 participants) cross-sectional studies, and no prospective study in adults (apart from pregnant women) with average B-Pb <50 μg/L, and the results from these were inconsistent. An English study (Bost et al., 1999) showed an association between B-Pb and diastolic but not systolic BP in men, but no associations in women. Studies using data from the National Health and Nutritional Examination Survey (NHANES) III (Den Hond et al., 2002) showed significant associations between B-Pb and SBP in black men and women, and DBP in black women, but in white men there was a significant *decrease* in DBP with increasing B-Pb. NHANES data from 1999 to 2002 showed that the odds ratios (ORs) for hypertension increased with increasing B-Pb, and that the trend was nearly significant in non-Hispanic blacks and Mexican Americans but not in non-Hispanic whites (Muntner et al., 2005). After the publication of the NTP review (NTP Monograph on Health Effects of Low-level Lead, 2012), another study based on NHANES (2003–2010) found significant associations between B-Pb and systolic and diastolic BP among men and women, although there were no significant associations in white men or women (Hara et al., 2010). There was no significantly increased risk for hypertension in any group.

The aim of the present study was to examine associations between lead exposure and BP and hypertension in a large cross-sectional study from Sweden, in a population-based sample with on average low (mean <50 μg/L) B-Pb levels. Two-thirds of the cohort was re-examined after 16 years.

2. Methods

2.1. Study population

Our study is based on the cardiovascular cohort in the Malmö Diet and Cancer Study (MDCS-CC). This cohort includes 6103 individuals living in Malmö, Sweden, aged 46–67 years, and examined in 1991–1994 (Rosvall et al., 2000). It is a random sample of the larger population-based Malmö Diet and Cancer Study (MDCS) (Berglund et al., 1993). Under the inclusion criterion of having data available on both B-Pb and BP, 4452 individuals were eligible for the present study, and 2904 of these (65%) could be re-examined in 2007–2012. Of those who could not be followed up, 44% had died, while the others were sick or unwilling to attend, had emigrated, or could not be traced (Rosvall et al., 2015).

The study complies with the Declaration of Helsinki. All participants provided written informed consent, and the study was approved by the regional ethics committee.

2.2. Blood pressure and cardiovascular risk factors

The participants completed established self-administered questionnaires concerning lifestyle, socioeconomic status, health, and medication, and underwent medical examination (Rosvall et al., 2000). Blood pressure was measured by a study nurse using a standard mercury sphygmomanometer with a 14 cm cuff after supine rest for 10 min at baseline and at follow-up. Hypertension was defined as an average SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and/or current use of antihypertensive medication prescribed by a physician (Mancia et al., 2013).

At baseline, participants were categorized into never, former, or current smokers. Pack-years of smoking were calculated as the product of the number of years of smoking and the number of cigarettes smoked daily, divided by 20. Data on pack-years were available for 1208 current smokers, 815 ex-smokers, and all non-smokers (n=1915), who were given the value of zero (in total n=3938). Daily alcohol intake was calculated in grams per day. Leisure time physical activity was a composite measure of 18 different leisure time activities during the preceding year (Li et al., 2009). Low physical activity was defined as the lowest quartile of the summary score. Educational level was classified as low if participants had completed less than 12 years of education (i.e. had not completed secondary education). Height, weight, and waist circumference were measured, and body mass index (BMI) was calculated.

2.3. Lead and cadmium analyses

Peripheral blood samples were obtained at baseline by venepuncture after overnight fast. In whole blood, lead (Pb) is located in red blood cells with only marginal levels in plasma (EFSA, 2010; Skerfving and Bergdahl, 2015). Since an association between cadmium (Cd) and hypertension has been described in the literature, we also analysed Cd, which like Pb is localized in the red blood cells (Akerstrom et al., 2013). Pb and Cd in whole blood were calculated from haematocrit and erythrocyte concentrations of Pb and Cd, respectively, using erythrocytes which had been kept frozen at −80 °C since the baseline examination. The analysis of Pb and Cd in erythrocytes was performed by inductively coupled plasma mass spectrometry operating in the helium collision cell mode as described previously (Fagerberg et al., 2015). Samples were diluted 20 times with a basic diluent containing 1-butanol (2% w/v), ethylenediamine tetraacetic acid (0.05% w/v), Triton X-100 (0.05% w/v), and ammonium hydroxide (1% w/v). None of the samples were below the limits of detection, which were 0.16 μg/L for Pb and 0.02 μg/L for Cd. External quality control samples with a low Pb level (Seronorm Trace Elements Whole Blood L-1, Lot no. 1103128; Sero AS, Billingstad, Norway) were included in all analytical rounds (N=38), and showed satisfactory results (mean 10.3 μg/L, SD 0.5 μg/L versus recommended limits of 6–14 μg/L). The imprecision (coefficient of variation) was 5.1% for Pb and 7.1% for Cd, as calculated for 38 duplicate samples of the L-1 quality control sample.

2.4. Data analyses

2.4.1. Cross-sectional analyses

Data were available on BP, smoking, and levels of Pb and Cd in blood for 4552 individuals. Since we suspected a non-linear effect of Pb and Cd, B-Pb and B-Cd were classified in quartiles.

Descriptive statistics were calculated, and BP and prevalence of

hypertension were first compared by quartiles of B-Pb. Blood lead levels were generally low, and so our a priori hypothesis was that any effect of B-Pb on BP and/or hypertension would have a threshold and would mainly be found in the highest B-Pb quartile.

Differences in outcomes or in cardiovascular risk factors between the fourth B-Pb quartile and the other quartiles were tested using a *t*-test or a chi-squared test. Associations between single variables and B-Pb as a continuous variable were assessed with the Spearman correlation coefficient (r_s) or a *t*-test.

Multivariable associations between B-Pb (in quartiles) and systolic and diastolic BP were examined using multiple linear regression analysis. Apart from crude analyses (Model 1), we used two multivariable models: Model 2 included B-Pb, age, and those variables associated with both B-Pb and blood pressure (sex, alcohol intake, smoking habits, waist circumference, and educational level), while Model 3 also included B-Cd (in quartiles). Multivariable associations between B-Pb (in quartiles) and hypertension were examined using multiple logistic regression analysis with the same models as for BP.

In order to assess whether B-Pb was associated with BP at low levels of B-Pb, we also excluded individuals with the highest B-Pb in the fourth quartile. In a sensitivity analysis, we replaced B-Pb with lead in erythrocytes (Ery-Pb) in quartiles. We also repeated the linear and logistic regression analyses with B-Pb as a continuous variable using the same models as above for quartiles of B-Pb. Finally, in Model 3, we assessed a possible association between B-Cd and BP and hypertension.

(P-value)s refer to two-tailed tests.

Table 2
Systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension (HT) versus blood lead (B-Pb) (quartile 4 versus quartiles 1–3) with and without adjustment for other factors.

	SBP β coefficient (*p*-value)	**DBP** β coefficient (*p*-value)	**HT** OR (95% CI) (*p*-value)
Model			
1. B-Pb only (Q4 versus Q1–3)	2.6 <0.001	2.1 <0.001	1.4 (1.2–1.6) <0.001
2. B-Pb, sex, age, smoking, alcohol, waist, education	1.8 0.006	1.4 <0.001	1.3 (1.1–1.5) 0.002
3. B-Pb, sex, age, smoking, alcohol, waist, education, and B-Cd	1.7 0.01	1.3 <0.001	1.3 (1.1–1.5) 0.004

2.4.2. Analyses based on individuals examined at follow-up

Since antihypertensive treatment was common at follow-up (58%), we used antihypertensive treatment as outcome in the longitudinal analysis. We also studied hypertension at follow-up

Table 1
Characteristics of 4452 participants in the cardiovascular cohort of the Malmö Diet and Cancer Study (MDCS-CC) by quartiles (Q1–Q4) of lead in blood (B-Pb). Mean (range) or %.

	Blood-lead quartile (μg/L)					
	N	All 4452	Q1 1113	Q2 1113	Q3 1113	Q4 1113	(P-value) Q4 versus Q1–3
B-Pb (μg/L)		28 (1.5–258)	15 (1.5–19)	22 (19–25)	28 (25–33)	47 (33–258)	
Sex (women %)		66	78	66	54	41	<0.001
Age (years)		57 (46–67)	57 (46–67)	58 (46–67)	57 (46–67)	57 (46–67)	0.51
Smoking							P<0.001
Never (%)		40	51	46	35	29	
Former smokers (%)		34	32	30	38	35	
Current smokers (%)		26	17	24	27	37	
BMI (kg/m^2)		26 (16–51)	26 (17–51)	26 (17–43)	26 (16–41)	26 (16–43)	P=0.34
Waist (cm)		83 (54–152)	81 (59–152)	82 (59–134)	84 (54–135)	86 (56–138)	p<0.001
SBP (mmHg)		141 (98–220)	140 (98–210)	140 (98–220)	140 (105–210)	143 (98–210)	P<0.001
DBP (mmHg)		87 (58–130)	86 (60–118)	86 (58–126)	87 (60–130)	89 (62–120)	P<0.001
Hypertension (%) [a]		63	63	60	49	69	P<0.001
Antihypertensive medication (%)		16	17	14	16	17	P=0.28
Low education (%)		47	48	49	45	44	P=0.07
Low physical activity (%)		23	23	24	22	25	P=0.27
B-Cd (μg/L)		0.48 (0.03–5.1)	0.35 (0.04–4.4)	0.42 (0.06–4.3)	0.50 (0.04–4.8)	0.63 (0.03–5.1)	P<0.001

[a] Systolic blood pressure ≥140 or diastolic blood pressure ≥90 or antihypertensive medication.

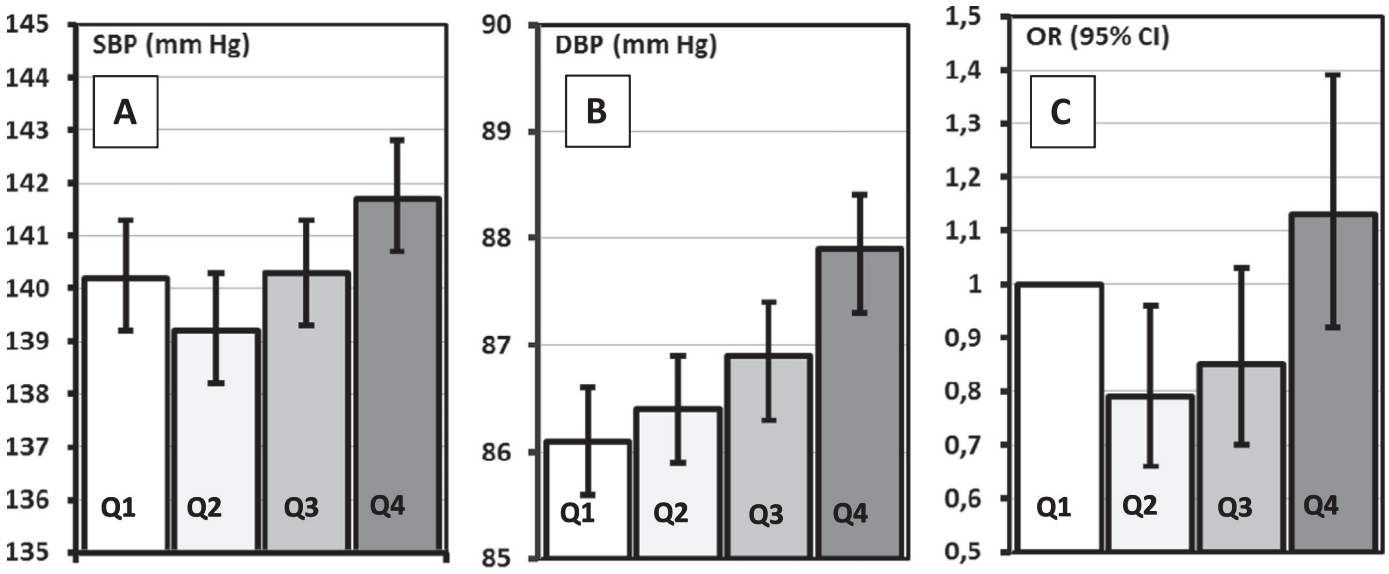

Fig. 1. Panel A: Systolic blood pressure (SBP) with 95% confidence interval versus blood lead in quartiles (Q1–Q4) at baseline, adjusted for sex, age, smoking, alcohol intake, waist circumference, and educational level. Panel B: Diastolic blood pressure (DBP) with 95% confidence interval versus blood lead in quartiles (Q1–Q4) at baseline, adjusted as in Panel A. Panel C: Odds ratio (with 95% confidence interval) for hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or current use of antihypertensive medication) adjusted for covariates as in panel A.

Table 3
Systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension (HT) versus B-Pb, stratified by sex, age, and smoking. The models are adjusted for sex, age, smoking, alcohol, waist, and education (Model 2 in Table 2, except for the stratification variable). β coefficients, odds ratios, and (*p*-value)s refer to the comparison of quartile 4 versus quartiles 1–3 combined.

	SBP	DBP	HT
	β coefficient (p-value)	β coefficient (p-value)	OR (95% CI)
Sex (P for interaction)	0.30	0.30	0.60
Men	2.1 (0.02)	1.7 (0.001)	1.2 (0.96–1.5)
Women	1.5 (0.12)	1.1 (0.02)	1.4 (1.1–1.7)
Smoking (P for interaction)	< 0.001	0.10	0.007
Ever-smokers	3.0 (< 0.001)	1.6 (< 0.001)	1.5 (1.2–1.8)
Never-smokers	0.6 (0.58)	1.1 (0.06)	0.96 (0.7–1.3)
Age (P for interaction)	0.15	0.65	0.04
≤ 57 years	2.4 (< 0.001)	1.4 (< 0.001)	1.5 (1.2–1.9)
> 57 years	1.3 (0.17)	1.5 (< 0.001)	1.3 (0.9–1.4)

using the same definition as for the baseline examination. Multivariable associations between B-Pb at baseline and risk of hypertension at follow-up were examined using multiple logistic regression analysis with Model 2 from the analyses of baseline data (i.e. B-Pb in quartiles, age, sex, alcohol intake, smoking habits, waist circumference, and educational level, all at baseline). Since individuals examined at follow-up were not representative of all individuals examined at baseline, we also repeated the baseline analyses for this subgroup (N = 2904).

3. Results

3.1. Cross-sectional analyses

At the beginning of the 1990s, the mean blood pressure in this general population sample aged 46–67 years was 141/87 mmHg (Table 1). Based on today's criteria (Mancia et al., 2013), hypertension was present in 63% of the sample (68% of the women and 59% of the men), even though only 16% used antihypertensive medication. Mean B-Pb was higher in men (32 μg/L) than in women (25 μg/L).

When the participants were stratified in B-Pb quartiles, systolic and diastolic BP were significantly higher in the fourth quartile than in the other three quartiles combined (Table 1). The prevalence of hypertension was also higher in the fourth quartile. Current smoking and high B-Cd were more frequent in the fourth B-Pb quartile, and the individuals in this quartile also had a tendency toward having higher education.

Multivariable analyses showed that the associations between B-Pb and BP persisted after adjustment for sex, age, smoking habits, alcohol intake, waist circumference, and educational level. The point estimate was 1–2 mmHg increase of SBP and DBP in the fourth quartile versus the other three quartiles combined (Table 2, Model 2, and Fig. 1). Additional adjustment for B-Cd changed the estimates only marginally. There was an association between B-Pb and prevalence of hypertension with an OR of 1.3 (95% CI: 1.1–1.5) in the fourth quartile. However, antihypertensive medication (16%) was not significantly associated with B-Pb (OR: 1.1, 95% CI: 0.9–1.3).

Mean B-Pb was 32 μg/L among current smokers, 28 μg/L among ex-smokers, and 25 μg/L among never-smokers (P < 0.001 for all comparisons). The corresponding mean levels for B-Cd were 1.06, 0.29, and 0.23 μg/L. In ex-smokers who had quit smoking > 20 years before recruitment (N = 484), B-Pb and B-Cd were the same as in never-smokers. There was a significant interaction between smoking (ever versus never) and B-Pb for both BP and prevalence of hypertension (Model 2, Table 3). Associations with B-Pb were statistically significant in ever-smokers but not in never-smokers. In the combined group of never-smokers and ex-smokers who had quit smoking > 20 years before recruitment, the results were similar to those for never-smokers, but the positive association between B-Pb and DBP was now statistically significant (beta 1.2 mmHg, P = 0.01). There was also a tendency towards stronger associations with B-Pb in participants ≤ 57 years compared with older participants. There were no significant gender differences regarding the associations between B-Pb and BP or hypertension, and there were no interactions between B-Pb and waist

circumference for BP or hypertension.

The association between B-Pb and BP was still significant when B-Pb was treated as a continuous variable in the models; the beta coefficients for a 20 μg/L increase in B-Pb were 1.2 mmHg for SBP (P=0.002) and 1.0 mmHg for DBP (P < 0.001). The adjusted (Model 2) OR for hypertension was 1.1 for a 20 μg/L increase in B-Pb (P=0.04).

When repeating all data analyses using lead in erythrocytes (Ery-Pb) instead of B-Pb, the results were essentially the same regarding associations between Ery-Pb and BP and hypertension (data not shown). Results were also unchanged if we included menopausal status in the adjusted models.

We also repeated the multivariable models for SBP and DBP after exclusion of all individuals on antihypertensive medication. The associations with B-Pb were still statistically significant, and the point estimates in Table 2 were similar (data not shown).

In order to assess whether the associations between B-Pb and BP and hypertension were driven by the individuals with the highest B-Pb levels (i.e. those in the fourth quartile), the analyses were repeated excluding individuals with B-Pb > 100 μg/L (N=20); the beta coefficients and ORs in Model 2 were essentially the same, and the associations were still statistically significant. When excluding all individuals with B-Pb > 50 μg/L, the beta coefficient for SBP decreased from 1.8 (Table 2) to 0.8 and was no longer statistically significant. The beta coefficient for DBP decreased from 1.4 to 1.0 (P=0.005), and the OR for hypertension decreased from 1.3 (Tables 2) to 1.2 (P=0.048).

There were no associations between B-Cd and BP or hypertension (data not shown).

3.2. Analyses based on individuals examined at follow-up

The mean age of individuals examined at follow-up was 73 years. Their mean age at baseline was 56 years, versus 59 years for those who could not be examined at follow-up, reflecting the higher risk of dying or drop-out for other reasons in the oldest individuals. The mean SBP and DBP at follow-up were 143 and 83 mmHg. The mean baseline SBP, DBP, and prevalence of antihypertensive medication were all significantly higher (P < 0.001) among individuals who could not be followed up. There was no increased risk of antihypertensive medication at follow-up in individuals in the highest B-Pb quartile at baseline (OR: 1.0, 95% CI: 0.8–1.2), and the result was similar (OR: 1.0, 95% CI: 0.7–1.3) if we included individuals with high BP at follow-up but no antihypertensive medication.

The analysis of baseline data for this sub-cohort showed weaker associations between B-Pb and outcomes at baseline than in participants lost to follow-up. The point estimate for SBP was 1.5 mmHg increase in the fourth quartile versus the other three quartiles combined among individuals examined at follow-up, and 2.2 mmHg in individuals lost to follow-up. For DBP, the corresponding figures were 1.1 mmHg and 2.0 mmHg. The OR for hypertension at baseline was 1.3 (1.04–1.5) among those examined at follow-up, and 1.4 (1.05–2.0) among those lost to follow-up.

4. Discussion

In this population-based study conducted in Sweden in the 1990s, both systolic and diastolic blood pressures were higher in the fourth quartile of blood lead, even after adjustment for potential confounders such as age, sex, smoking habits, alcohol intake, waist circumference, and educational level. The association with B-Pb was also present for hypertension, with a significantly increased OR of 1.3 in the fourth quartile of B-Pb. Hypertension was defined as a high blood pressure (SBP ≥ 140 or DBP ≥ 90) at baseline or treatment for hypertension. Under this definition, 63% of individuals had hypertension at baseline, but only 16% of them used antihypertensive medication.

There was, however, no association between B-Pb at baseline and antihypertensive medication at follow-up 16 years later. This is not a surprising finding, given that blood lead has a half-life of one month. Bone lead has a much longer half-life, and as previously summarized, significant associations with BP are more consistently found with bone Pb as a measure of exposure than with blood Pb (NTP Monograph on Health Effects of Low-level Lead, 2012). Hence, a reasonable interpretation is that blood lead is associated with an increase in BP in cross-sectional terms, but not with the long-term risk of hypertension, given our results, low B-Pb levels and insufficient representativity of total body burden of lead exposure. An alternative explanation is that there was a differential loss of individuals with hypertension caused by lead exposure, as the majority of the individuals who could not be followed up had died or were sick, and they had higher BP and a higher prevalence of hypertension at baseline. This suggestion is supported by the fact that individuals lost to follow-up had stronger associations between B-Pb and BP at baseline. At follow-up, we focused on antihypertensive medication as an outcome, since we found it less meaningful to test associations between B-Pb at baseline and BP 16 years later. Regarding antihypertensive medication, it should be noted that some of these drugs are also prescribed for conditions other than hypertension.

Our results are in agreement with the results of the meta-analysis conducted by Nawrot et al. (2002), which demonstrated an association between BP and B-Pb. However, that meta-analysis included many studies with much higher B-Pb levels than are common today, as well as studies of occupationally-exposed workers.

The present study shows stronger effects of B-Pb on BP and hypertension than those found in previous studies in the general population with low B-Pb levels. An analysis of NHANES III (1988–1994) found an increase in BP with increasing B-Pb in black but not white participants (Den Hond et al., 2002), and in peri- and post-menopausal women (Nash et al., 2003). A combined analysis of NHANES III and NHANES 1999–2002 (Muntner et al., 2005) showed associations between B-Pb and the risk of hypertension in Mexican Americans and black participants, but not in white participants. The latest NHANES study showed overall associations between B-Pb and BP, but for white participants this held true only for DBP, and there were no significant associations between B-Pb and hypertension (Hara et al., 2010). For men, our results are in agreement with those of Bost et al. (1999); however, the latter found no significant association between BP and B-Pb in women. Our results are partly in agreement with the NHANES studies, but we found stronger associations between B-Pb and BP in our (white) participants, and we also found associations between B-Pb and hypertension. Aside from those mentioned above, we are aware of no other large studies incorporating longitudinal follow-up of individuals with low B-Pb.

The pathophysiology of lead-induced hypertension has been examined in several studies. Proposed mechanisms, as reviewed by Vaziri (2008), include dysregulation of the renin-angiotensin-aldosterone system, direct effects on the endothelium and vascular smooth muscle, and stimulation of the sympathetic nervous system due to elevated production of catecholamines. Several of these effects may be mediated by oxidative stress, which may be produced directly by lead ions or by binding of lead to glutathione, thereby disturbing one of the defence mechanisms against reactive oxygen species. The effect on endothelium is caused by binding and inhibition of endothelial nitric oxide synthase, which decreases nitric oxide production and thus compromises vasodilatation (Solenkova et al., 2014). Lead has been shown to promote

endothelial release of endothelin; to elevate serum levels of norepinephrine, angiotensin-converting enzyme, and thromboxane; and to decrease production of prostacyclin (Solenkova et al., 2014). These changes will promote vasoconstriction.

Animal studies provide strong evidence that low-level exposure to lead contributes to onset of hypertension (NTP Monograph on Health Effects of Low-level Lead, 2012). However, experimental studies show a non-monotonic relationship between levels of lead exposure and BP, which could partially explain the inconsistencies observed in human studies (NTP Monograph on Health Effects of Low-level Lead, 2012).

The mean BP at baseline was high (141/87) according to today's criteria for hypertension (SBP $\geq$ 140 or DBP $\geq$ 90). This is, however, in agreement with several other studies in Swedish people around 60 years of age in the early 1990s; for example, in 1990, Wilhelmsen et al. (1997) found a mean BP of 140/87 in men and 141/84 in women (N=436). It should be noted, however, that BP measurements performed on one occasion only may result in overestimation of BP for some individuals. The reason why only 16% were on antihypertensive treatment is that in the period before 1991–1994 (baseline for the present study) the criteria for start of antihypertensive medication in Sweden (and many other countries) were less strict than today.

The associations between B-Pb and BP were statistically significant, and the effect size was small but not negligible. The beta coefficients for an increase in B-Pb of 20 μg/L were 1.8 and 1.4 mmHg for SBP and DBP respectively, which was equal to the difference between the 80th and 20th percentiles of the distribution. For SBP, this was equivalent to an increase of 2 years of age or 5 cm of waist circumference, while for DBP it was equivalent to an increase of 9 years of age or 6 cm of waist circumference.

In the present study, blood lead was used as indicator of exposure. Although $>$90% of lead in blood is found in the erythrocytes, lead in whole blood is the most commonly used biomarker. In adults, the lead pool in blood constitutes less than 1% of the body burden (EFSA, 2010; Skerfving and Bergdahl, 2015). The half-life of lead in blood is about one month, but there is a continuous exchange between lead in erythrocytes, plasma, and the skeleton (Skerfving and Bergdahl, 2015), and so B-Pb reflects not only recent exposure, but partly also the body burden. It is therefore to be expected that a long-term effect of lead exposure on blood pressure should be more easily demonstrated in studies using bone lead compared to studies using blood lead as exposure indicator (Navas-Acien et al., 2008).

It is not clear from previous studies whether there is a threshold for associations between B-Pb and BP. The associations between lead and BP were found in the fourth quartile, and the mean B-Pb in this group was 47 μg/L. The sensitivity analyses suggest that if there is a threshold, it is below 50 μg/L.

Blood lead levels have decreased over time in Sweden, as in most countries. The fact that there was no association between age and B-Pb in the present study indicates that ongoing exposure was more important for B-Pb levels than a slow mobilization of lead from bone. However, the age distribution was relatively narrow; all individuals were 47–67 years of age. The association between B-Pb and BP seemed slightly weaker among individuals above the median age (57 years), which might reflect the increasing importance of other factors, overshadowing a possible impact of lead exposure. The fact that B-Pb has decreased over time is important for evaluation of the exposure-response relationship. Time trends for B-Pb in children in a city close to the city of the present study showed a decrease from about 42 μg/L in 1983 to 23 μg/L in 1993. Mean B-Pb levels were 30–50 μg/L in Swedish adults in the 1980s (Elinder et al., 1986; Vahter et al., 1991). Thus, if there is a lasting effect of B-Pb on BP, the associations found in the present study could reflect previous higher exposure levels.

It is well known that smoking causes slightly higher B-Pb levels (Skerfving and Bergdahl, 2015). The association between hypertension and B-Pb was significant only among smokers. Smokers on average have more atherosclerosis and stiffer blood vessels than non-smokers, which may make them more sensitive to the effects of lead on BP. However, in the NHANES III study no significant interaction was found between smoking and lead regarding the association with BP (Nash et al., 2003). Ever-smokers had higher SBP and DBP than never-smokers, but there was no association between smoking and risk of hypertension. The association between smoking and BP is complex (Omvik, 1996). BP increases immediately during smoking, due to the effect of nicotine, but when measured in smoking-free intervals, it is often lower, and it usually increases after smoking cessation (Omvik, 1996; Janzon et al., 2004).

We found no significant interaction with sex. Previous studies of low-level lead exposure have shown mixed results regarding possible differences between men and women (Bost et al., 1999; Den Hond et al., 2002; Nash et al., 2003; Muntner et al., 2005; Hara et al., 2010).

There was no association between B-Cd and either BP or hypertension. Previous studies have not been consistent; however, a meta-analysis suggested a positive association between blood cadmium and BP in women, but no such association for urinary cadmium, and none between cadmium exposure and hypertension (Gallagher and Meliker, 2010).

The present population-based study is one of the few studies including a large population with low B-Pb levels. A limitation is that we did not adjust for family history of hypertension, sodium intake and kidney function, which are potential confounders. Although the cross-sectional design does not allow causal inference, the significant associations between B-Pb and BP are in agreement with previous studies at higher lead levels, several of which had a prospective design. We therefore find it likely that the associations are also causal at these low levels of B-Pb.

In conclusion, the present study suggests that blood lead levels as low as 20–30 μg/L increase blood pressure and possibly also the risk of hypertension. Continued efforts to reduce lead exposure are warranted.

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Ethics review

All participants provided written informed consent, and the study was approved by the regional ethics committee.

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