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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