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Associations between blood lead, olfaction and fine-motor skills in elderly men: Results from the Heinz Nixdorf Recall Study

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ABSTRACT

Lead (Pb) is a recognized neurotoxin. Pb^{2+} can interfere with divalent metal transporters and ion channels and may thus affect other brain metals and cation signaling in neurons. Thereby, cognitive and sensory functions can be impaired. Whereas cognitive effects are well described less is known about olfaction and motor functions in the general population at currently lower exposure levels. The objective of this study was to evaluate the influence of Pb in blood (PbB) on odor identification and fine motor skills within the framework of the Heinz Nixdorf Recall Study (HNRS), a prospective cohort study among an elderly German population.

Data on odor identification assessed with Sniffin' sticks and fine motor test results were collected during the second follow-up of HNRS (2011–2014) in 1188 elderly men aged 55 to 86 years. PbB was determined in 1140 blood samples archived at baseline (2000–2003) and in 796 samples from the second follow-up. The association between PbB and impaired odor identification (normosmia as reference) was estimated with proportional odds ratios (PORs) with 95% confidence intervals (CI). The odds ratios (OR) of substantially impaired dexterity (tapping hits < 10th percentile, errors in aiming, line tracing, or steadiness > 90th percentile) were estimated with mixed logistic regression models for test results with both hands, where PbB was adjusted for covariates.

PbB at baseline (median 32.9 µg/L; 2.27% ≥90 µg/L) was higher than at follow-up (25.9 µg/L; 0.84% ≥90 µg/L). The individual concentrations were correlated (Spearman r_s 0.59, 95% CI 0.54 – 0.63). PORs of an impaired odor identification in men with baseline PbB ≥90 µg/L were 1.96 (95% CI 0.94–4.11) and 1.57 (95% CI 0.47–5.19) with follow-up PbB. Fine-motor tests were not affected by elevated PbB with the exception of tapping in men with follow-up PbB ≥50 µg/L (OR 2.14, 95% CI 1.09–4.23). Increasing age had strong effects on all outcomes. Low education was associated with impaired odor identification, tapping, and aiming. Also, alcohol consumption and current smoking affected the test results, particularly steadiness.

In this community-based cohort of elderly men, we could confirm indication of an influence of elevated PbB on odor identification. Small numbers of men with elevated PbB due to an on-going trend of decreasing PbB in the general population, strong covariates and multiple comparisons hamper the evaluation of adversity of these effects of PbB on olfaction and dexterity.

1. Introduction

Lead (Pb) is a major heavy metal pollutant that occurs naturally at low concentrations in the crust of the earth. Its widespread occurrence in the environment is the result of human activity. Historical sources of environmental Pb exposure were leaded gasoline and water pipes, and Pb in tableware and paints (ATSDR, 2007). High exposure to Pb was reported in several occupational settings (IARC, 2006), which can lead to an elevated body burden with Pb even years after cessation of exposure (Börjesson et al., 1996). There is a decreasing trend of body burden in the general population, for example in Germany since regulations were issued against leaded gasoline in 1971 (https://www.

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Pb in whole blood (PbB) is commonly used to assess exposure from a variety of environmental and occupational sources. The Human Biomonitoring Commission of the German Federal Environmental Agency established 90 µg/L as biological reference value for PbB in men and 70 µg/L in women each based on the 95th percentile of the distribution of PbB in the general population (Wilhelm et al., 2004). A previous analysis of metals in whole blood samples from participants of the population-based Heinz Nixdorf Recall Study (HNRS) revealed that smoking and working in the metal industries had an increased risk of presenting with elevated PbB (Bonberg et al., 2017).

Pb has long been recognized as a neurotoxin due to its ability to substitute for other divalent cations like Ca^{2+} or various metals required for proper brain functioning and thereby causing perturbations of brain metals and various neurobiological signaling pathways (Menon et al., 2016; Garza et al., 2006). Especially high exposure levels can cause neuropathological changes like white matter lesions, and affect specific brain areas such as hippocampus and frontal cortex (Khalil et al., 2009; Stewart et al., 2006). Impairment of visuomotor coordination and manual dexterity has been reported in Pb-exposed workers and vulnerable groups such as children (Mason et al., 2014). Amongst others, grooved pegboard performance and aiming were negatively affected by Pb exposure (Dorsey et al., 2006; Grashow et al., 2013; Khalil et al., 2009). In addition to ingestion, inhalation is another route of exposure to Pb. Olfactory impairment may be an essential link between metal exposure and neurotoxicity (Aschner and Dorman, 2006). A recent review and a position paper on olfactory dysfunction considered Pb as agent that may affect olfaction (Ajmani et al., 2016; Hummel et al., 2017). However, only few large and well-conducted epidemiological studies investigated the association between Pb exposure and olfactory dysfunction in the general population (Grashow et al., 2015; Noel et al., 2017).

We obtained data on PbB, odor identification, fine motor tests and potential confounders within the framework of HNRS, a prospective population-based cohort study in the Ruhr area, in order to investigate the association of elevated PbB with a potential impairment of olfaction and dexterity in elderly men from a German industrial region with a high volume of steel production.

2. Material and methods

2.1. Study population

The study used data from baseline recruitment (2000–2003) and second follow-up (2011–2014) of the HNRS. Its rationale, design, and conduct have been previously described (Schmermund et al., 2002). Lifestyle and occupational information was documented in face-to-face interviews. Testing of odor identification and dexterity at second follow-up and the determination of metals in blood samples was part of the project AeKo ("Arbeitsmedizinische Forschung in epidemiologischen Kohortenstudien" – Occupational medical research in epidemiological cohort studies) (Bonberg et al., 2017; Casjens et al., 2016; Pesch et al., 2017). The study was approved by the ethical commission of the Medical Faculty of the University Duisburg-Essen (approval number 11–4678). Written informed consent was obtained from all participants.

Starting with 1474 men with data from the second follow-up (further referred to as follow-up) we excluded seven participants with incomplete occupational history, 89 participants with incomplete olfactory testing or diseases possibly affecting this test (e.g. cold), and 238 participants with incomplete fine motor test results, missing information about handedness or with conditions known to affect motor skills (e.g. Parkinson's disease) as described for the association with Mn (Pesch et al., 2017). Hence, the dataset of this analysis consisted of 1188 men with complete data on the outcome variables and covariates. Based on questionnaire information on the participants' consumption of beer, wine, and spirit drinks we determined their alcohol consumption (g/week) at follow-up. Smoking status was assessed as never, former, or current.

2.2. Odor identification test

Olfactory dysfunction was tested with the Sniffin' sticks odor identification test at follow-up as previously described (Casjens et al., 2016). In brief, 12 odors (orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, clove, pineapple, rose, and fish) were presented in felt-tip pens. The individual pens were consecutively placed in front of both nostrils at a distance of approximately 2 cm. The participants could identify each odor as a multiple-choice task from a list of four potential answers. Men were classified as normosmic if more than 9 odors were identified, hyposmic if 7 to 9 odors were identified, and functionally anosmic if less than 7 odors were identified (Hummel et al., 2001).

2.3. Fine motor tests

The fine motor abilities of the participants were measured with the Motor Performance Series (Schuhfried, Mödling, Austria) at follow-up as previously described (Pesch et al., 2017). Four tasks (tapping, aiming, line tracing, and steadiness) were carried out with both hands separately. The tapping task measures the speed of rapid movements by tapping a stylus within 32 s as often as possible on a 1600 mm^2 plate. The number of hits was recorded. Aiming assesses the eye-hand coordination and the precision of arm-hand movements. Twenty small plates with a diameter of 5 mm standing in a line (distance 4 mm) had to be touched with a stylus as soon as possible. The number of errors (E), the duration of errors (DE) in seconds and the total time needed for this task (TT) in seconds were recorded. Line tracing examines precision of arm-hand movements by drawing a stylus through a curvy course of a groove without touching side walls or bottom. E, DE, and TT were determined. Steadiness measures the ability to maintain a precise arm-hand position by holding a stylus for 32 s in a 5.8 mm hole without touching sides or bottom. E and DE were recorded. As previously described, there are strong associations between the fine motor test results of both hands as well as between E and DE of each test (Pesch et al., 2017). Here, we evaluated the hits and errors of both hands and adjusted the statistical models by TT if time was not limited. Hits < 10th percentile and errors > 90th percentiles of the distributions of these outcomes in all men were considered as substantially impaired manual dexterity.

2.4. Determination of blood lead

PbB was determined in aliquots of whole blood archived at baseline and at follow-up by means of ICP-MS as previously described (Bonberg et al., 2017). In brief, plastic materials were used for sample preparation to prevent contamination. After thawing, 400 µL of whole blood was diluted 1:12.5 with a 0.5% solution of ammonium hydroxide and 100 µL of a 0.2% solution of Triton-X. Analysis was carried out using a 7700 ICP-MS system from Agilent Technologies in He-mode (flow rate 5 mL/min) with a collision cell to avoid interferences. Skimmer and sampler cones were made of platinum. Calibration and calculation of the PbB concentration was carried out using standards prepared in sheep blood at eight different concentrations. PbB was determined in 1140 samples at baseline and in 796 samples at follow-up, with 765 men having PbB at both time points. All measurements were above the limit of quantification.

2.5. Statistics

Median and inter-quartile range (IQR) were used to describe the distribution of continuous variables. Rank correlations between