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Cumulative lead exposure is associated with reduced olfactory recognition performance in elderly men: The Normative Aging Study

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ABSTRACT

Introduction: Olfactory dysfunction has been identified as an early warning sign for Alzheimer's disease, Parkinson's disease, dementia and more. A few occupational and environmental exposures have also been associated with reduced olfactory function, although the effects of long term environmental exposure to lead on olfactory dysfunction have not been explored. Here we performed olfactory recognition testing in elderly men in a community-dwelling cohort and examined the association with cumulative lead exposure, as assessed by lead in tibial and patellar bone.

Methods: Olfactory recognition was measured in 165 men from the Normative Aging Study (NAS) who had previously taken part in bone lead measurements using K-X-ray fluorescence (KXRF). Olfactory recognition was measured using the University of Pennsylvania Smell Identification Test (UPSIT). Associations between olfactory recognition, global cognition and cumulative lead exposure were estimated using linear regression, with additional adjustment for age, smoking, and functional polymorphism status for hemochromatosis (*HFE*), transferrin (*TfC2*), glutathione-s-transferase Pi1 (*GSTP1*) and apolipoprotein E (*APOE*) genotypes. Sensitivity analyses explored olfactory recognition in men with high global cognitive function as measured using the Mini-Mental Status Exam (MMSE).

Results: The average age of the NAS participants at the time of olfactory recognition testing was 80.3 (standard deviation or SD = 5.7) years. Mean tibia lead was 16.3 (SD = 12.0) μg/g bone, mean patella lead was 22.4 (SD = 14.4) μg/g bone, and mean UPSIT score was 26.9 out of 40 (SD = 7.0). Consistent with previous findings, age at olfaction testing was negatively associated with UPSIT score. Tibia (but not patella) bone lead was negatively associated with olfaction recognition (per 15 μg/g tibia lead: $\beta = -1.57$; 95% CI: −2.93, −0.22; $p = 0.02$) in models adjusted for smoking and age. Additional adjustment for education did not significantly change results. Of all the genes explored, only the presence of one or more HFE variant alleles was significantly associated with olfaction recognition (HFE $\beta = 2.26$; 95% CI: 0.09, 4.43; $p = 0.04$). In a model containing the HFE term and a lead term, the tibia lead parameter estimate dropped by 21% (per 15 μg/g tibia lead: $\beta = -1.25$; 95% CI: −2.64, 0.14; $p = 0.08$) while the HFE term dropped 15% ($\beta = 1.91$; 95% CI: −0.28, 4.10; $p = 0.09$). None of the other gene terms were associated with olfactory recognition in this cohort, nor were any gene–lead interaction terms significant. Additional sensitivity analysis in men with MMSE scores of 25 or higher ($n = 149$) showed a similar but slightly attenuated association between lead and olfactory recognition (per 15 μg/g tibia lead $\beta = -1.39$; 95% CI: −3.00, 0.22; $p = 0.09$).

Conclusion: Cumulative exposure to lead is associated with reduced olfactory recognition in a cohort of elderly men. The association was similar but not significant in men with better cognitive function as measured by the MMSE. Iron metabolism gene status may also affect olfactory function.

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1. Introduction

Olfactory dysfunction is regarded as an early warning sign of Parkinson's disease (Louis et al., 2008; Mollenhauer et al., 2013; Ross et al., 2012), Alzheimer's Disease (Murphy et al., 1990; Thompson et al., 1998; Wang et al., 2010), and cognitive decline (Royall et al., 2002; Seo et al., 2009; Sohrabi et al., 2012; Swan and Carmelli, 2002). Given that lead, pesticides like DDT and other environmental exposures also show associations with these diseases (Richardson et al., 2009, 2014; Weisskopf et al., 2010), and are known to be rhinotoxic in occupationally exposed populations and animal models (Sunderman, 2001), it is plausible that environmental exposures such as lead could also be related to olfactory dysfunction.

Occupational exposures including cadmium (Rose et al., 1992; Sulkowski et al., 2000), solvents (Schwartz et al., 1990), pesticides (Dick et al., 2001), industrial chemicals (Schwartz et al., 1989) and manganese (Antunes et al., 2007) have been associated with decrements in olfactory function. An Italian occupational study found significant associations between lead measured via air sampling and performance on an olfactory threshold task (Caruso et al., 2007), while two other studies on occupational lead exposure found detrimental but not significant associations with performance on an odor identification task (Bolla et al., 1995; Schwartz et al., 1993). Environmental manganese emitted from a ferroalloy plant was associated with reduced performance on an olfactory task in Italian adolescents (Lucchini et al., 2012), and reduced olfactory scores were associated with air pollution exposure in children and young adults in Mexico (Calderon-Garciduenas et al., 2010).

While environmental lead exposure's effect on olfactory function has yet to be investigated, cumulative lead exposure has been previously shown to be associated with multiple types of cognitive dysfunction in adults (Bandeen-Roche et al., 2009; Schwartz et al., 1993; Shih et al., 2006; van Wijngaarden et al., 2009). Specifically among men in the Normative Aging Study (NAS), bone lead measured in either the tibia or patella has been shown to be associated with impaired visuomotor skills (Payton et al., 1998), increased rate of cognitive decline (Weisskopf et al., 2004, 2007), lower scores on the Mini-Mental Status Exam (Wright et al., 2003), reduced associative learning (Grashow et al., 2013a), and poorer hand-eye coordination (Grashow et al., 2013b).

A number of genes related to metal ion transport (TfC2) and absorption (HFE) have been shown to affect how lead is processed and stored in the body. Lead exposure may interfere with iron metabolism (Eaton and Qian, 2002; Samson and Nelson, 2000) and be associated with toxic levels of non-transferrin bound iron in plasma leading to neurodegenerative disease (Huang et al., 2004; Todorich and Connor, 2004). The hemochromatosis gene encodes a protein that is in part responsible for iron sensing and regulation and HFE variant homozygosity results in clinical hemochromatosis, which is characterized by iron overload. The presence of one or more polymorphism of the HFE gene (either H63D or C282Y) has been shown to exacerbate the detrimental effects of lead on cognitive function in elderly men (Wang et al., 2007), and has been associated with increased susceptibility to neurodegenerative disease (Eum et al., 2014; Mariani et al., 2013; Nandar and Connor, 2011). Interestingly, variant HFE gene expression has also been associated with lower blood and bone lead in the NAS cohort (Wright et al., 2004). Based on this finding, we hypothesized that carriers of any HFE variant would have reduced circulating blood and bone lead and therefore reduced effects on olfactory recognition performance.

Other genes, such as the ApoE gene, may also play a role in age-related cognitive function and olfaction. ApoE is a polymorphic gene that encodes a protein regulating transport of cholesterol, lipids, and fat-soluble vitamins. Certain ApoE polymorphisms such as ApoE-ε4 have been found to predispose individuals to neurodegenerative diseases like Alzheimer's (Poirier et al., 2014; Teter et al., 2002). Recently, it was shown that metals may be involved in the regulation of Alzheimer's related proteins, and that aberrant metal ions concentrations are more likely to occur in AD-diagnosed patients (Xu et al., 2014). ApoE is expressed in olfactory brain structures, and those with the ApoE-ε4 variant allele show reduced odor identification (Olofsson et al., 2010) and altered brain responses to olfactory stimuli (Green et al., 2013).

Glutathione-s-transferase Pi1(GSTP1) has been shown to reduce the effects of oxidative stress through free radical clearance (Hayes and Strange, 2000), and may modify the relationship between lead and cognitive function in the elderly (Eum et al., 2013) and inflammatory markers in adult males (Sirivarasai et al., 2013). Finally, the gene TfC2 encodes the transferrin protein that is responsible for iron transport, and interacts with HFE (Namekata et al., 1997). We therefore examined the association between cumulative lead exposure as measured in bone and olfactory recognition in a population of elderly men in the Boston, MA area, with additional analysis of associations with HFE, GSTP1, TfC2 and ApoE polymorphism status. Additional analyses explored associations between olfactory identification and lead in men with higher MMSE scores.

2. Methods

2.1. Study population

The Normative Aging Study (NAS) began recruiting men from the Boston area community beginning in the 1960s. Since that time, NAS subjects have been encouraged to return every 3–5 years for medical examinations (Bell et al., 1966; Hu et al., 1996; Weisskopf et al., 2007). Current NAS participants are elderly and are mostly Caucasian. Starting in 1991, subjects were invited to participate in bone lead testing using K-shell X-ray fluorescence (KXRF). 68% (876 participants) agreed to bone lead testing. Two hundred and forty-three NAS subjects participated in olfactory recognition testing between January of 2009 and March of 2012, with 231 completing the entire olfactory recognition test (12 subjects did not complete all questions). Of those with completed tests, 165 had participated in bone lead testing. None of the men participating in the olfactory recognition testing reported diagnosis of Alzheimer's disease or Parkinson's disease. Approval from the Institutional Review Boards at the VA Boston Healthcare System, Brigham and Women's Hospital and the Harvard School of Public Health was obtained prior to study commencement. All subjects provided written informed consent before participating.

2.2. KXRF measurement of bone lead

Lead concentrations in tibial and patellar bone are considered to be markers of cumulative lead exposure: patella lead reflects exposure over the previous 8–10 years, while tibial shaft bone represents exposure occurring over decades (Wilker et al., 2011). For this study, KXRF was used to measure bone lead concentrations at the patella and midtibial shaft using either an ABIOMED KXRF prototype or upgraded system (ABIOMED, Danvers, MA). As previously explained (Weuve et al., 2009), a linear relationship was established between the two instrument types, and data used in this study adjust for the linear difference between the two machines. Additional detail on the testing protocol has been previously described (Aro et al., 1994; Chettle et al., 2003; Hu et al., 1998). Bone lead concentration is measured in μg of lead per gram of bone.