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APOE ε4 allele modifies the association of lead exposure with age-related cognitive decline in older individuals

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ABSTRACT

Background: Continuing chronic and sporadic high-level of lead exposure in some regions in the U.S. has directed public attention to the effects of lead on human health. Long-term lead exposure has been associated with faster cognitive decline in older individuals; however, genetic susceptibility to lead-related cognitive decline during aging has been poorly studied.
Methods: We determined the interaction of *APOE*-epsilon variants and environmental lead exposure in relation to age-related cognitive decline. We measured tibia bone lead by K-shell-x-ray fluorescence, *APOE*-epsilon variants by multiplex PCR and global cognitive z-scores in 489 men from the VA-Normative Aging Study. To determine global cognitive z-scores we incorporated multiple cognitive assessments, including word list memory task, digit span backwards, verbal fluency test, sum of drawings, and pattern comparison task, which were assessed at multiple visits. We used linear mixed-effect models with random intercepts for individual and for cognitive test.
Results: An interquartile range (IQR:14.23 μg/g) increase in tibia lead concentration was associated with a 0.06 (95% confidence interval [95%CI]: −0.11 to −0.01) lower global cognition z-score. In the presence of both ε4 alleles, one IQR increase in tibia lead was associated with 0.57 (95%CI: −0.97 to −0.16; p-value for interaction: 0.03) lower total cognition z-score. A borderline association was observed in presence of one ε4 allele (Estimate-effect per 1-IQR increase: −0.11, 95%CI: −0.22, 0.01) as well as lack of association in individuals without *APOE* ε4 allele.
Conclusions: Our findings suggest that individuals carrying both ε4 alleles are more susceptible to lead impact on global cognitive decline during aging.

1. Introduction

By 2020 as many as 42 million individuals worldwide will suffer from dementia, and that number is expected to double by 2040 (Rizzi et al., 2014). Although lead exposure has reduced in the last decades, a very recent state of emergency has been declared in Flint, Michigan, U.S. because of high-levels of lead in drinking water, which has highlighted the importance of lead exposure in public health (Wang, 2015). Lead has been repeatedly associated with adverse cognitive effects both in children and older individuals (Koller et al., 2004; Wright et al., 2003), due to occupational (ATSDR, 2007) and environmental exposures (Weisskopf et al., 2007). However, very few susceptibility biomarkers are available to predict the impact of environmental toxicants, including lead exposure, on age-related cognitive decline. Availability of such biomarkers is critical to design targeted preventive strategies on those at risk, and to reduce the burden of

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cognitive impairment during aging. Apolipoprotein E (*APOE*) epsilon-4 allele (ε4), is one of the best known genetic risk markers for cognitive function impairment and Alzheimer's disease (Liu et al., 2013). Few studies have evaluated the role of genetic susceptibility in the cognitive effects of environmental lead exposures (Wang et al., 2007), and while a prior study addressed occupational lead exposure (Stewart et al., 2002), no previous environmental study has evaluated the role of the *APOE* ε4 allele. In this study, we evaluated whether the *APOE* epsilon alleles modified the association between tibia bone lead and global cognitive function in a cohort of male participants aged 41–77 years (mean: 58.58, SD: 6.52 yrs) at baseline in the Veterans Affairs (VA) - Normative Aging Study (NAS).

2. Material and methods

2.1. Participants

The present analysis was conducted on 489 elderly men from the VA – NAS (Bell et al., 1966). NAS was approved by the Institutional Review Boards (IRB) at participating institutions and participants have provided written informed consent at each visit.

2.2. Bone lead measurements and APOE ε4 genotyping

We focused our analysis in tibia lead (cortical bone) as its half-life estimates may reach up to 20 years (Hu et al., 1998). Tibia lead measurements were performed on average 1.6 times per participant (SD: 0.74, min = 1, max = 4) at the mid-tibial shaft by K-shell x-ray fluorescence with an ABIOMED KXRF, and we used the closest measurement to cognitive evaluation for analysis. *APOE* epsilon variants were determined as previously described (Prada et al., 2014).

2.3. Neuropsychological testing

For cognitive performance, we evaluated "total" cognitive function integrating multiple cognitive tests (Table 1) (Power et al., 2014; 2013). Cognitive data were collected at multiple visits approximately 3.6 years apart, with nearly 2.7 visits (min = 1, max = 7) per subject and 3566 visits in total were included, from 1993 to 2004.

2.4. Data analysis

We assessed the association between tibia lead and "total" cognitive function by incorporating the multiple cognitive assessments at multiple visits, and treating each cognitive score as a repeat measure of underlying overall cognition. We used linear mixed-effect models with random intercepts for individual and for cognitive test, determining association with global cognitive decline. Also, to determine the effect of lead on overall cognition as well as the interaction of *APOE* epsilon variants, we explored the association using only the first cognitive assessment. To determine effect modification by *APOE* epsilon variants in the association of tibia lead with overall cognitive change, we added multiplicative interaction terms. We adjusted for age at cognitive assessments, education 6-11, 12-16, > 16 years of education), first language (English, not English), computer experience (yes, no), smoking status (never, current, former), physical activity (< 12, 12–30, and > 30 metabolic equivalent hours) (Jetté et al., 1990), alcohol intake (< 2 or ≥ 2 drinks/day), diabetes (self-reported or having fasting glucose above 126 mg/dl) and census tract percentages of the participants that are non-white and with at least a college degree. All tests were two-sided and p-values < 0.05 were considered

Table 1
Description of cognitive tests in the VA-Normative Aging Study.

Cognitive test	Subtest	Description of the test	Battery	Core Cognitive Domain	Reference
Word list memory task	Immediate recall	10 words presented. Recall them. One point for each recall. Three trials.	Consortium to Establish a Registry for Alzheimer disease, CERAD	Recent memory	(Fillenbaum et al., 2008)
	Delayed recall	Recall of the 10 words presented after 5–10 min delay. One trial.			
Digit span backwards	Numbers recall (Standard score)	Repeat from 3 to 8 digits in reverse orally. The maximum number of digits correctly repeated is the score.	Wechsler Adult Intelligence Scale-Revised, WAIS-R	Executive function	(Wechsler, 1981)
Verbal fluency test	Total number of animals named	Say as many words as possible from a category (animals) in 60".	Consortium to Establish a Registry for Alzheimer Disease, CERAD	Language	(Fillenbaum et al., 2008)
Sum of drawings	Sum of drawings	Copy circle, rectangles, diamond, and cube. Accuracy of copied forms.	Consortium to Establish a Registry for Alzheimer Disease, CERAD	Visospatial ability	(Fillenbaum et al., 2008)
Pattern comparison task	Mean response time Number correct	Discern whether two sided pictures are the same or not.	Neurobehavioral Evaluation System 2, NES2	Executive function	(Letz, 1991)