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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)

significant. We used SAS software (Version 9.3, SAS Institute Inc., Cary, NC) for all statistical analyses.

3. Results

Most of the men were former smokers (55.8%), reported between 12 and 16 years of education (51.9%), exhibited overweight or obesity (79.7%), and were Caucasian (95%). Additional characteristics at baseline by subgroups and bone levels are shown in Table 2. Lower levels of lead were observed in younger, more educated men and in those who had computer experience (Table 2). At least one ε4 allele was observed in 23.0% of men and the ε4ε4 haplotype was observed in 2.7% (Table 3), concordant with frequencies observed worldwide (Komurcu-Bayrak et al., 2011). Haplotype ε1ε2 was observed in only 2 individuals and included in the 'None' ε4 allele group for analysis. No differences in tibia lead levels were observed among *APOE* haplotypes (p=0.27 for analysis of variance of tibia lead levels between allelic groups; p=0.09 for haplotypes).

We did not observe association between *APOE* haplotype or *APOE* ε4 allele status on cognitive change (Supp. Table 1). However, in analysis including all individuals, an increase of one interquartile range (IQR: 14.23 μg/g) in tibia lead concentration was associated with a 0.06 (95% confidence interval (95%CI): −0.11 to −0.01) lower point total cognition z-score (Table 4). Additive models of *APOE* ε4 allele status showed that in carriers of both *APOE* ε4 alleles, one IQR increase in tibia lead was associated with 0.57 (95%CI: −0.97 to −0.16) lower point total cognition z-score. In the presence of only one *APOE* ε4 allele, a borderline association was observed (Estimate effect per 1-IQR increase: −0.11, 95%CI: −0.22, 0.01). When *APOE* ε4 allele was absent, there was little evidence of an association between lead and cognition (Estimate effect per 1-IQR increase: −0.04, 95%CI: −0.09 to 0.02) (Table 4). In analyses considering *APOE* haplotypes, ε4ε4 carriers had a 0.57 lower points total cognition z-score (95%CI: −0.97 to −0.16) for each IQR increase in tibia lead. Also, ε4ε4 showed an interaction in the association between tibia lead and total cognition z-score (p-value for interaction=0.010) (Table 4). A borderline effect was observed in those individuals carrying one *APOE* ε4 allele (Estimate effect per 1-IQR increase in tibia lead for ε3ε4: −0.10, 95%CI −0.21 to 0.02; for ε4ε1: −0.43, 95%CI: −0.91, 0.05). We did not observe association among those individuals lacking *APOE* ε4 allele (Estimate per 1-IQR increase for ε3ε3: −0.03, 95%CI: −0.09 to 0.03; Estimate per 1-IQR increase for ε2ε3: −0.06, 95%CI: −0.18 to 0.06) with a likelihood ratio test (LRT) for the interaction of

Table 2
Demographic characteristics of VA-Normative Aging Study men at the initial examination of cognitive function (N=489).

Variable	n	%	Tibia lead (μg/g)	
			Median	IQR
Age, years				
< 60	285	58.3%	17	(5–29)
60–69	176	36.0%	21	(6–36)
> 70	28	5.7%	26	(6–45)
Education				
6–11 yrs	143	29.3%	23	(8–38)
12–16 yrs	254	51.9%	18	(6–30)
> 16 yrs	92	18.8%	14	(3–25)
Smoking status				
Never	158	32.3%	18	(2–34)
Former	273	55.8%	20.5	(4–36)
Current	58	11.9%	19	(7–31)
Alcohol consumption				
Yes	95	19.4%	19	(6–32)
No	394	80.6%	19	(4–34)
History of diabetes[a]				
Yes	34	6.9%	21.5	(5–37)
No	455	93.1%	19	(5–33)
Computer experience				
Yes	275	56.2%	17	(4–30)
No	214	43.8%	20	(4–36)
English as first language				
Yes	487	99.6%	19	(5–33)
Body mass index				
≤25	99	20.3%	18	(5–31)
>25	390	79.7%	19	(4–34)
Physical activity (MET-hr)				
< 12	272	55.6%	19	(3–35)
12–30	131	26.8%	19	(8–30)
> 30	86	17.6%	18	(3–33)

MET-hr: metabolic equivalent hours.

[a] History of diabetes defined as reporting a diagnosis of diabetes or having fasting glucose above 126 mg/dl. IQR=Interquartile range.

Table 3
APOE-epsilon ε4 allele and haplotypes frequencies, and tibia lead levels in the VA-Normative Aging Study (N=489).

Variable	n	%	Tibia lead (μg/g)	
			Median	IQR
ε4 Allele frequencies				
None	364	74.3	19	(13–28)
One ε4 allele	112	23.0	20	(13–26)
Both ε4 alleles	13	2.7	13	(11–18)
Haplotype frequencies[a]				
ε3ε3	305	62.4	19	(5–33)
ε3ε4	105	21.5	20	(7–33)
ε2ε3	57	11.7	20	(6–34)
ε4ε4	13	2.7	13	(6–20)
ε1ε4	7	1.4	14	(0–31)

[a] Haplotype ε1ε2 was observed in only 2 individuals, and included in the 'None' ε4 allele group for analysis. Haplotypes ε1ε1, and ε2ε4 were not observed. VA: Veterans Affairs – Normative Aging Study.

Table 4
Difference in global cognitive z-score per an interquartile range (14.23 μg/g) increase in tibia lead biomarker in the VA-Normative Aging Study (N=489).

	Effect estimate	95% Confidence interval	p-Value	p-Value for interaction
All individuals	−0.058	(−0.107, −0.011)	0.018	
By *APOE* allele				
None	−0.036	(−0.090, 0.019)	0.197	.
One ε4 allele	−0.105	(−0.216, 0.007)	0.066	0.336
Both ε4 alleles	−0.565	(−0.973, −0.157)	0.007	0.010
LRT[a]				0.030
By *APOE* haplotype				
ε3ε3	−0.032	(−0.094, 0.030)	0.308	.
ε3ε4	−0.098	(−0.213, 0.017)	0.094	0.462
ε2ε3	−0.062	(−0.183, 0.059)	0.313	0.865
ε4ε4	−0.565	(−0.973, −0.157)	0.007	0.010
ε1ε4	−0.431	(−0.911, 0.049)	0.081	0.250
LRT[b]				0.093

Adjusted for age, education, computer experience, physical activity, census tract percentage of the participants that is are non-white, census tract percentage of the participants with a college degree, and diabetes mellitus. LRT=Likelihood ratio test.

[a] LRT for the interaction of allele.

[b] LRT for the interaction of haplotypes. VA: Veterans Affairs – Normative Aging Study.

haplotypes = 0.09 (Table 4).

Cross-sectional analysis —using only the first cognitive assessment— to determine the impact on global cognition, showed a lack of effect of lead on cognitive performance (Estimate effect per 1-IQR increase = 0.004, 95%CI −0.058 to 0.067). A borderline effect on carriers of both *APOE* ε4 alleles was observed (Estimate effect per 1-IQR increase = −1.14, 95%CI −2.29 to 0.01). No association was found in the presence of only one or in absence of *APOE* ε4 allele (Supp. Table 2). We also tested the role of age in the interaction observed for *APOE* ε4 allele, but no significant association was observed (Supp. Table 3).

4. Discussion

In this cohort of aging men, we found that the association of bone lead with age-related cognitive decline was stronger in *APOE* ε4 allele carriers, with the strongest statistically significant association in those with two copies of the allele. To the best of our knowledge, this is the first report of a potential interaction of *APOE* ε4 allele with environmental lead exposure in relation to cognitive decline in elderly individuals.

Several studies have associated cognitive impairment with low-level lead exposure (Weisskopf et al., 2004). One previous cross-sectional analysis in former organolead workers found interaction ($p < 0.05$) of *APOE* ε4 in three out of 20 cognitive tests (Stewart et al., 2002). This study was also cross sectional and the interaction between *APOE* ε4 and lead for cognitive decline was not assessed. The mechanisms linking lead and cognitive function are unknown; however, neural dysfunction has been attributed to lead's ability to substitute for calcium, which plays a central role in synapsis, mitochondria function, among other cellular processes (White et al., 2007). *APOE* ε4 genetic variants have been repeatedly associated with impaired cognition in the elderly and individuals with *APOE* genetic susceptibility show more pronounced age-related reduction in hippocampal volume (Lind et al., 2006), decreased antioxidant capacity (Miyata and Smith, 1996), and altered use of nutrients (Reiman et al., 2004). All those characteristics may make *APOE* ε4 carriers more susceptible to lead-induced neuroinflammation. Previous studies have found that other genetic susceptibilities may also modify the rate of lead-related cognitive decline (Wilker et al., 2011). In our study, we also found the presence of haplotypes showing the ε1 allele (haplotypes ε1ε2 and ε1ε4). Scientific literature is full of data claiming that *APOE* ε1 allele is a very rare allele, even to the point of considering it almost as 'inexistent' in the clinical practice. However, this comment is related to the ε1ε1 condition, which was not observed in our population (Steinmetz et al., 1990). We did not find haplotype ε2ε4, which has also been reported in very low frequencies in similar epidemiological studies (Koopal et al., 2016).

Our study has several limitations: the study participants are male Caucasians and our results may not apply to other ethnic groups, e.g. *APOE* ε4 have showed an attenuated effect in Hispanics (Farrer et al., 1997). Also, although most evidence suggests APOE ε4 effect is stronger in women, (Ungar et al., 2014) the *APOE*-gender interaction remains controversial (Qiu et al., 2004). Also, non-differential misclassification of cognitive status is likely, but reduced by our use of all available cognitive data as a measure of age-related cognitive decline. Also, the number of individuals with *APOE* ε4ε4 haplotype is small (N = 13), and it could bias our finding and give rise to the possibility of type-1 error. However, very few cohorts worldwide have determined concomitantly bone lead, APOE genotype, and have assessed cognitive function longitudinally during aging, and including several variables involved in cognitive performance during aging.

5. Conclusions

In summary, elderly men with two copies of the *APOE* ε4 allele showed greater cognitive decline associated with lead exposure. Based on the long retention of lead in the body, the rapid growth of older populations in modern societies and the special susceptibility to chronic low-levels of lead exposure in some minorities and socioeconomically disadvantaged groups, our findings stress the need to control lead to protect cognitive function in the elderly.

Conflict of interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.07.034.

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