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Associations of cumulative Pb exposure and longitudinal changes in Mini-Mental Status Exam scores, global cognition and domains of cognition: The VA Normative Aging Study

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Abstract

Background—Lead (Pb) exposure has been associated with poorer cognitive function cross-sectionally in aging adults, however the association between cumulative Pb exposure and longitudinal changes in cognition is little characterized.

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Description of conflicts of Interest

The authors have no conflicts of interest.

Methods—In a 1993–2007 subcohort of the VA Normative Aging Study (Mini-mental status exam (MMSE) n=741; global cognition summary score n=715), we used linear mixed effects models to test associations between cumulative Pb exposure (patella or tibia bone Pb) and repeated measures of cognition (MMSE, individual cognitive tests, and global cognition summary). Cox proportional hazard modeling assessed the risk of an MMSE score falling below 25.

Results—Among men 51–98 at baseline, higher patella Pb concentration (IQR: 21 μg/g) was associated with −0.13 lower baseline MMSE (95% CI: −0.25, −0.004) and faster longitudinal MMSE decline (−0.016 units/year, 95% CI: −0.032, −0.0004) over 15 years. Each IQR increase in patella Pb was associated with increased risk of a MMSE score below 25 (HR=1.21, 95% CI: 0.99, 1.49; p=0.07). There were no significant associations between Pb and global cognition (both baseline and longitudinal change). Patella Pb was associated with faster longitudinal decline in Word List Total Recall in the language domain (0.014 units/year, 95% CI: −0.026, −0.001) and Word List Delayed Recall in the memory domain (0.014 units/year, 95% CI: −0.027, −0.002). We found weaker associations with tibia Pb.

Conclusions—Cumulative Pb exposure is associated with faster declines in MMSE and Word List Total and Delayed Recall tests. These findings support the hypothesis that Pb exposure accelerates cognitive aging.

Keywords

Cognitive decline; bone lead; longitudinal study; MMSE; aging

Introduction

Approximately 13 percent of the US population is aged 65 and older, and that demographic is expected to reach 19 percent by 2030,[1] leading to increased numbers of older adults susceptible to cognitive impairment and neurodegenerative diseases.[2,3] Worldwide, an estimated 35.6 million people were living with dementia in 2010, and this figure is expected to nearly double by 2030.[4] Cognitive impairment is part of a spectrum that deviates from normal aging, eventually leading to dementia. Dementia and mild cognitive impairment are associated with reductions in memory, visuospatial, orientation, and language domains.

Exposure to lead (Pb) adversely affects cognition, independent of age-related cognitive decline. In adults, Pb exposure from occupational or environmental sources has been inversely associated with scores on the Mini Mental Status Exam (MMSE).[5–8] Patella Pb was associated with declines in scores on the MMSE,[9] as well as measures of visuospatial and visuomotor ability,[10] indicating that a mobilized, accumulated Pb burden may impact cognition.[11] Prior research has only measured changes in MMSE or other cognitive tests over two visits. In most cognitive aging studies, mean MMSE score increases between first and second repeat tests, attributed in part to a learning effect, where subjects recognize questions from previous tests.[12,13]

This study evaluated the associations between long-term Pb exposure and longitudinal changes in cognition repeatedly measured at up to five visits over 15 years. As such, the learning effect can be accounted for over more tests per subject. Our hypothesis is that

cumulative Pb exposure as measured by bone Pb is associated with accelerated cognitive decline over 15 years, and we tested this by evaluating the following cognitive function measures: MMSE, a novel summary score termed global cognition, and domain-specific individual tests.

Methods

Study Sample

This research was conducted on a subgroup of the VA Normative Aging Study, which is a longitudinal cohort established in Massachusetts in 1963.[14] Healthy men (n=2,280), between the ages of 21–80, were recruited and participated in clinical examination and complete health and lifestyle questionnaires every 3 to 5 years depending on the age at each exam (every 5 years before age of 50 years and every 3 years after 50 years). At enrollment, men were excluded from the study if they had a past or present history of heart disease, cancer, diabetes, gout, asthma, sinusitis, bronchitis, peptic ulcer, or blood pressure greater than 140/90 mm Hg. Starting in 1993, 1131 men underwent a battery of tests to assess cognitive function (described below).

From 1991 until 1999, 876 participants had bone Pb measurements. The overlap of subjects with both patella and tibia bone lead measurement and cognitive measurement included 795 subjects. We further excluded subjects who had a patella Pb or tibia Pb measure with uncertainty greater than 15 μg/g (n=2) or 10 μg/g (n=6), respectively, and this yielded 788 subjects. Measurements with high uncertainty in bone Pb usually indicate excessive subject movement during measurement.[15] These 788 subjects contributed to a total of 2,397 cognitive function tests from 1993 through 2011. For the MMSE analysis, we excluded subjects who did not have an MMSE score (n=43), yielding 776 subjects and 2,245 observations. Finally, we excluded subjects with missing data on covariates: education level (n=30 subjects), and alcohol intake (n=8 subjects). This yielded a final number of 741 subjects with at least one MMSE assessment and full covariate data for the MMSE analysis. The sixth (n=20) and seventh assessments (n=1) for MMSE were dropped to account for influential outliers, resulting in 2,132 total observations for the 741 subjects (average number of repeated measurements=3.04; average elapsed time between cognitive tests=3.80 years (SD=1.57) (see details of study sample selection procedures in Supplementary Figure S1).

Because longitudinal regression models are subject to the learning effect in MMSE tests, we examined the binary outcome of MMSE score less than 25 at any time point after baseline using a cox proportional hazards model. In this analysis, we excluded 80 subjects with baseline MMSE scores less than 25 or 167 with only one MMSE test result. This resulted in 521 total subjects at baseline (Supplementary Figure S1).

A similar exclusion based on missing data for covariates of interest yielded 715 subjects (n=1,410 observations) with at least one measure of a global cognitive index (described below). Here, the fourth assessment was dropped to account for influential outliers, resulting in 1,365 total observations for the 715 subjects analyzed for changes in global cognition.

Exposure Assessment

Bone lead was measured using K-shell X-ray fluorescence (KXRF) spectroscopy as previously described.[10] Briefly, ^{109}Cd gamma rays excite the K-shell electrons of Pb embedded in bone, which emit an X-ray photon that can then be detected. An ABIOMED KXRF Instrument was used to measure lead at the tibia and the patella, corresponding to cortical and trabecular bone, respectively. The KXRF beam collimator was directed perpendicular to the tibial midshaft and at a 30° angle from the horizontal for the patella for 30-minute measures.[10,16–18]

Cognitive assessments

Several cognitive assessments were used for this analysis: the MMSE, NES2 (Neurobehavioral Evaluation System 2),[19] CERAD (Consortium to Establish a Registry for Alzheimer's Disease),[20] and WAIS-R (Wechsler Adult Intelligence Scale-Revised).[21] The MMSE assesses overall cognition by testing several domains including memory, visuospatial ability, attention, language, and orientation. Validated in multiple populations, the MMSE is widely used as a screening test for dementia,[22] and to assess cognitive decline in non-demented populations.[23] Declines of the MMSE over time may indicate underlying pathologies such as Alzheimer's disease, where the MMSE declines by an average of 1.8–4.2 points per year,[24–26] or normal cognitive declines associated with aging. The MMSE includes 30 questions, but the present analysis did not include "Which County are we in?" because counties in Massachusetts do not have political meaning. Thus, the maximum score was 29

We also assessed scores from 7 individual tests used in the NES2, CERAD, or WAIS-R, which have been described elsewhere.[6,27,28] Two of the tests, word list total recall and verbal fluency (both CERAD), are generally associated with language. The digit span backward sum test (WAIS-R), total number recalled for digit span test (WAIS-R), and word list delayed recall test (CERAD) assess memory. The pattern recognition test (NES2) and visual drawings summary score (CERAD) assess visuospatial ability. In addition to assessing each of these tests individually, we calculated a summary score of these tests, referred to as "global cognition", which we tested as a separate proxy for worsening cognitive impairment. To standardize comparisons in creating the summary score, we calculated z-scores for each test by subtracting the observed value for any subject at any time from the mean baseline cognitive score, and divided that value by the standard deviation of the baseline cognitive score. Overall global cognition was assessed by average z-scores of 6 of the tests (total number recalled for digit span backward was excluded due to similarity with digit span backward sum).

Other Covariates

We included age at first cognitive test, past education level and baseline smoking status, and alcohol intake as covariates in our regression model. Smoking status was assessed by questionnaire and subjects were re-categorized as "current smokers", "had smoked in the past and quit", or "had never smoked". Alcohol intake was assessed by whether a person had more than two alcoholic beverages per day. Subjects were categorized as not having finished

high school (<12 years), those who were high school graduates or completed some college (12–15 years), and college graduates (>16 years).

Data Analysis

The data used in this study were managed using SAS software (version 9.4 for Windows) and all analyses were performed using R Software version 3.1.0. We used mean and standard deviation univariate descriptive statistics to characterize our study population. We further calculated the Pearson correlation between z-score measures of cognitive domains to understand the relationships between tests. We summarized the sample size and mean values of global scores at each visit.

We used linear mixed effects models to assess the association between baseline Pb exposure and longitudinal changes, separately in each of the measures of cognition described above. This approach is robust in the analysis of unbalanced data. Our baseline model included baseline patella Pb, time from first visit, the interaction of Pb and time, and baseline covariates (age, alcohol intake, smoking, and education). Linear mixed effects modeling allows for differences in the number of repeated measures across a subject's visits. Our linear mixed effects model included random intercepts for individual as well as random slopes for time in order to account for correlations among the repeated measurements.

To account for the learning effects with MMSE and global cognition, we ran a second model, referred to as the First-test indicator model, that was the same as the basic model, with the addition of an indicator variable to adjust for whether or not a test was the subject's first assessment.[29]

Basic Model

$$\begin{aligned}\text{Cognitive test} = {} & B_0 + B_1 \times Pb + B_2 \times \text{Time}_{\text{fromVisit1}} + B_3(\text{Time}_{\text{fromVisit1}} \times Pb) + B_4 \\ & \times \text{Age}_{\text{FirstCognitiveTest}} + B_5 \times \text{Education} + B_6 \times \text{SmokingStatus} + B_7 \times \text{Alcohol}\end{aligned}$$

First-test Indicator model:

$$\begin{aligned}\text{Cognitive test} = {} & B_0 + B_1 \times Pb + B_2 \times \text{Time}_{\text{fromVisit1}} + B_3 \times (\text{Time}_{\text{fromVisit1}} \times Pb) \\ & + B_4 \times \text{Age}_{\text{FirstCognitiveTest}} + B_5 \times \text{Education} + B_6 \times \text{SmokingStatus} + B_7 \\ & \times \text{Alcohol} + B_8 \times \text{FirstTestIndicator}\end{aligned}$$

This model, similar to one employed in prior studies[30] can partially account for the learning effect by separating the change from visit 1 to visit 2, and regressing based on longitudinal changes from subsequent visits. Because MMSE is susceptible to a learning effect, as we observed in our study, we chose to report analyses based on the first-test indicator model.

Additionally, MMSE has a ceiling effect due to unequal interval scaling and may not be best modeled linearly. Ceiling effects may attenuate or inflate effect estimates in longitudinal analyses.[31] Thus, we also ran a Cox proportional hazards model in which the dichotomous outcome was whether or not a patient dropped below a cutoff score of 25 on the MMSE assessment at any point during follow-up. The longitudinal analyses of individual tests and

summary measure of global cognition were reported from the basic model only. The cutoff for MMSE score to define mild cognitive impairment or dementia has varied across the vast literature using this cognitive test.[32] Additionally, other studies have shown that people with a score of 24 or 25 are at risk for developing dementia.[33]

We chose to use the Cox model in order to conceptualize the issue as a time-to-event outcome. We are interested in the time to the first instance of crossing the threshold between cognitively normal and not cognitively normal. There are some unique situations where one might see true cognitive improvement (e.g. correction of a B vitamin deficiency) and measurement error makes the trajectory of cognitive scores slightly more variable. However, for most individuals, cognition will decline with time, with some individuals experiencing steep enough decline that they will cross the threshold into cognitive impairment. We tested the Cox proportional hazards assumption of all the predictors in the model by calculating Pearson product-moment correlation between the scaled Schoenfeld residuals and time for each covariate, and calculating a global P-value for all interactions of such a test calculated at once. Global p-value for the patella Pb model was p=0.50, and for tibia Pb model was p=0.38. These p-values suggest that the global proportionality assumption for Cox PH modeling was not violated. The individual variable for alcohol consumption seemed to violate the PH assumption, but the results remained unchanged when it was treated as strata. Supplementary table S1 demonstrates the number of subjects that dropped below a cutoff MMSE score of 25 after each visit.

The longitudinal analyses of individual tests and summary measure of global cognition were reported from the basic model only. Since there are seven individual domain measures and two global measures (MMSE and global cognition) for each of the two lead exposures (tibia and patella) it is important to consider multiple testing. Conservative Bonferroni correction across 18 tests would require a minimum p-value < 0.0028.

We performed several sensitivity analyses to test the robustness of our findings. First, there is a possibility for a selection bias related to health factors driving cohort participation in general and also the exclusion criteria at initial NAS recruitment[34]. In order to minimize this, we excluded subjects who were greater than 45 years of age at the time of NAS study enrollment because people over 45 would be more likely to exhibit health symptoms that would keep them out of the NAS and thus be more susceptible to these selection pressures. We also repeated our analyses with additional covariates including the history of a diagnosis of either hypertension, stroke, coronary artery disease, as those might be potential mechanisms by which cognitive decline is occurring and have been previously associated with Pb exposure.

Result

Descriptive Statistics

Among the 741 men with MMSE scores, mean patella Pb concentration was 30.6 μg/g (SD=19.4) and tibia Pb was 21.6 μg/g (SD=13.3) (Table 1). The average participant age was 67.8 (SD=6.8) at the time of the first cognitive assessment (range, 51.4–98.0 years). The mean MMSE score for all subjects at visit 2 was 0.4 points higher than that at visit 1,

suggestive of a learning effect (Table 2). However, we observed a subsequent decline of 0.6 points in mean scores from visit 2 to visit 5. There was a negligible increase in the z-score measure of global cognition between visits 1 and 2, and a decrease in the mean z-score by visit 3. Measures of individual cognitive domains at visit 1 were generally correlated and are reported in Supplementary Figure S2.

Lead Concentrations and Longitudinal Changes in MMSE

At baseline, an interquartile range (IQR) higher level of patella Pb (21 μg/g) was associated with 0.128 points lower MMSE score (95% confidence interval (CI): −0.251, −0.004; p=0.04) (Table 3). As expected, MMSE scores display an overall decline with time. There was a 0.10 point decrease in MMSE score per year (95% CI: −0.122, −0.077; p<0.0001). We observed a significant interaction between time and patella Pb on MMSE, indicating faster declines in MMSE scores as patella Pb levels increase. On average, MMSE scores were 0.016 points lower per IQR increase in baseline patella Pb per year of follow-up (95% CI: −0.032, −0.0004; p=0.04). This suggests that over 10 years of follow-up, MMSE scores are expected to drop by 0.16 points more per IQR increase in baseline patella Pb. We found similar but weaker associations with tibia Pb (Table 3).

Associations between Lead Concentrations and risk of having an MMSE score below 25

An IQR increase in patella Pb was borderline significantly associated with increased risk of having an MMSE score dip below the cutoff of 25 (hazard ratio (HR)=1.21, 95% CI: 0.99, 1.49; p = 0.07) (Table 4). The same analysis done with tibia Pb yields a non-significant association with MMSE score (HR=1.05, 95% CI: 0.82, 1.35).

Associations between Lead Concentrations and Global Cognition

At baseline, each IQR increase in patella Pb was borderline significantly associated with a 0.25 points lower global cognition Z-score (95% CI: −0.518, 0.019; p=0.07) (Table 5). However, the interaction between patella Pb and time was not significantly associated with global cognition Z-score. Again, we found similar but weaker associations with tibia Pb (Table 5).

Associations between Lead Concentrations and Cognitive Domains

The trajectories of each cognitive test score varied by domain (language, memory, visuospatial) (Table 6). In the language domain, there was a significant interaction between time and patella Pb on word list total recall. There was also a 0.014 point decrease in the word list total recall z-score for every IQR increase in patella Pb per year of follow-up (95% CI: −0.026, −0.001; p=0.04). The word list delayed recall test, a similar test in the memory domain, had a similar result. An IQR increase in patella Pb was associated with 0.014 point decrease in word-list delayed recall per year of follow-up (95% CI: −0.027, −0.002; p=0.03). All associations failed to reach significance when considering the conservative multiple testing corrected p-value threshold (p<0.0028). There were no associations between changes in language or memory domain tests and the interaction between tibia Pb and time of follow-up.

In the visuospatial domain, the baseline mean visual drawings summary score was associated with a 0.108 point decrease (95% CI: −0.185, −0.031) for every IQR increase in patella Pb. However, no significant positive interaction between patella Pb and time was observed on pattern recognition scores or visual drawings summary score. Tibia Pb was significantly inversely associated with baseline level but positively associated with the rate of change in visual drawing summary z-score. Every IQR increase in tibia Pb was associated with a 0.142 points lower visual drawing z-score at baseline (95% CI: −0.227, −0.057) and a 0.016 point *increase* per year change in time (95% CI: 0.001, 0.031) in the visual drawing summary z-score (Supplementary Figure S3).

Sensitivity Analyses

Our sensitivity analyses yielded similar results for the parameters of interest ($\beta_{Time\ Of\ Follow\ Up}$, β_{Pb}, $\beta_{Pb*Time\ Of\ Follow\ Up}$) found in the primary analysis. This was true for the analysis in which we excluded subjects who were >45 years of age at enrollment as well as the analysis in which we accounted for history of hypertension, stroke, coronary artery disease.

Discussion

We have further characterized the association between cognition and bone Pb over time in a 15-year subcohort of the NAS. Our data shows that faster longitudinal decline in MMSE score is associated with higher bone Pb levels, and the rate becomes steeper with time, which is consistent with previous literature. As shown in table 2, MMSE scores slightly rose from visit 1 to 2 (on average), but then declined. The decline in MMSE scores from visits 2 to 5 was consistent with trends observed previously in the NAS.[9]

A strength of the present study is the use of Pb measured in both cortical and trabecular bone, corresponding to the tibia and patella. These sites were chosen because of their differences in half-life. Reports on the half-life of Pb in bone vary by site as well as with factors such as age, prior exposure, and other conditions that modify bone turnover. Trabecular bone is reported to have an elimination half-life ($t^{1/2}$) of 8–20 years.[16,35] Cortical bone has a much longer half-life, with estimates ranging from 10–48.6 years.[16,18,35] Tibia bone Pb measures may be interpreted as the cumulative lead exposure in our population, whereas patella bone Pb serves as the predominant bone that provides Pb from bone resorption back to circulation[35]. This may explain why, in our analyses, patella Pb had a more statistically significant association with MMSE scores relative to tibia Pb.

In order to contextualize the magnitude of effect of Pb, we can compare the effect estimates for Pb to known aging risk factors for cognitive decline. For example, the magnitude of association between an IQR increase in patella Pb and MMSE score at baseline was −0.13 (95% CI: −0.25, −0.004), even greater than the per-year decline in MMSE (−0.10 points; 95% CI: −0.12, −0.077). Further, patella Pb exposure was associated with a more rapid rate of annual decline, as seen by the interaction term of $\beta_{Pb*Time\ Of\ Follow\ Up}$. The association between a 21 μg/g higher patella lead and annual change in MMSE score was 0.016 point/year. Given the widespread and cumulative nature of lead exposure, even those small associations, if causal, have large population attributable risk.

Each individual cognitive test can be assigned to a domain of cognition, although performance on each test often involves cognitive processes from multiple domains. In our analysis, the language domain included word list total recall and verbal fluency; the memory domain included digit span backward sum, total number recalled for digit span, and word list delayed recall; and the visuospatial domain included pattern recognition and visual drawings summary score. Age has varying effects on different domains and tests of cognition. For example, the individual tests of cognition that decline with age, when measured separately, have parameter estimates for $\beta_{Time\ Of\ Follow\ Up}$ that are 13–40% smaller in magnitude relative to the same parameter estimates found using global cognition measures, suggesting that aging may have a cumulative effect on overall cognition rather than each individual test.

Our findings regarding the effect of Pb on cognition are consistent with other studies. It has been established that cross-sectional cognitive test scores vary negatively with bone Pb.[6,7,9,36] Additionally, in the NAS, change in cognition was measured by the difference in MMSE scores between the first two visits only.[9] Although the previous study did not incorporate as many as five visits, it nonetheless observed a significant association between increasing Pb and decreasing MMSE (one-IQR higher patella Pb concentration associated with −0.24 point change in MMSE), which was about 1.5 times the magnitude of what was found in our present study. Our data add to these findings by assessing longitudinal repeated measures over 15 years rather than 3–4 years. The decline of scores over this longer period of time is larger than the practice effect, allowing for effective modeling. Other studies of longitudinal change in cognition have noted similar trends as well.[11,30,37] Clinical treatment for pre-clinical declines in cognition would be strengthened by effective biomarkers of dementia; this expanding area of research could also lead to longitudinal testing improvements in epidemiologic risk factor identification.[38–40]

Additionally, we noted that several individual cognitive test scores (word list recall, both delayed and total) decreased faster with higher exposure to Pb. Although we did observe a positive interaction between time and tibia Pb in our visual drawings score, the main effect of time and the main effect of Pb are still inversely associated with MMSE. As shown in supplementary figure S3, the declining MMSE trajectory for visual drawings has a steeper slope for a *lower* IQR of tibia Pb. This would paradoxically suggest that higher tibia Pb has a correcting effect on MMSE. However, this may be due to the fact that tibia Pb is more of a measure of cumulative exposure. Future studies that include repeat measures of Pb exposure would help clarify this relationship. Overall, the visuospatial and language domain had significant associations with either tibia or patella Pb and time, or the interaction of Pb and time.

It is not appropriate to convert MMSE scores to Z-scores because they are more prone to non-linear change. In other words, a decrease from an MMSE score of 28 to 27 is much less severe than a decrease from 25 to 24. Thus, we also performed a separate logistic regression analysis of MMSE scores that takes into account the non-continuous nature of the variable. Our results from that analysis supported the findings of the linear mixed effects analysis. The results of the longitudinal model suggest that the trajectory of MMSE scores over time will vary depending on Pb exposure (Table 3). The logistic analysis supplements this

finding, suggesting that patella Pb exposure may be associated with a clinically important shift in cognition.

Our study also has the possibility for selection bias due to loss to follow up. Loss to follow up may be related to comorbidities associated with Pb exposure. The subjects lost to follow-up may also have had cognitive decline that is associated with Pb exposure, but would not be included in the final analysis. In results not shown, neither patella Pb nor tibia Pb was associated with number of follow-up visits. Our sensitivity analysis excluding people with less than three visits did not affect parameter estimates. We recognize this as a limitation of our study. However, a dropout bias would skew results towards the null, so a correction for dropout bias would further support the hypothesis that Pb exposure worsens longitudinal cognitive decline. A more sophisticated analysis, such as marginal structural models with inverse probability weighting[34] may be useful to better understand this potential dropout bias. Additionally, although there were substantial correlations among the separate tests in the study, our decision to model each outcome in separate models resulted in not taking correlation or covariance structure of the various outcomes into account.

The major strength of our study is that it employs longitudinal data from up to five visits over 15 years, allowing us to observe changes in cognition over time. Additionally, bone Pb is a well-established biomarker of long-term Pb exposure. Our data employ both tibia and patella bone Pb measurements, allowing us to assess the effect of varying measures of long-term Pb exposure. Although a number of subjects have migrated over the 50 years of the study, the NAS cohort was originally selected from men have lived in a relatively homogeneous geographic area, allowing us to adjust for known confounders and mitigating the effect of unknown confounders. We used longitudinal models to measure the association of an important toxicant with changes in cognition over time. Such models can be used for future purposes to assess the role of interaction amongst exposures or between gene and environment over time.

In conclusion, we identified an association between baseline Pb and rate of change in cognition over time, spanning several measures of cognition, including MMSE. These findings further support the hypothesis that cumulative lead exposure may accelerate cognitive aging. Our results have implications for aging populations with historical Pb exposures, even when current exposure levels are low.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Grayson K, Vincent VAV. The Next Four Decades: The Older Population in the United States, 2010 to 2050. Washington,. DC. US Government Printing Office, 2008. 2008
2. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harbor perspectives in medicine. 2012; 2(8)
3. Reitz C, Mayeux R. Alzheimer disease: Epidemiology, Diagnostic Criteria, Risk Factors and Biomarkers. Biochemical pharmacology. 2014 Jan 4.
4. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2013 Jan; 9(1):63–75. e62.
5. Stokes L, Letz R, Gerr F, et al. Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. Occupational and environmental medicine. 1998 Aug; 55(8):507–516. [PubMed: 9849536]
6. Payton M, Riggs KM, Spiro A 3rd, Weiss ST, Hu H. Relations of bone and blood lead to cognitive function: the VA Normative Aging Study. Neurotoxicology and teratology. 1998 Jan-Feb;20(1):19–27. [PubMed: 9511166]
7. Wright RO, Tsaih SW, Schwartz J, et al. Lead exposure biomarkers and mini-mental status exam scores in older men. Epidemiology. 2003 Nov; 14(6):713–718. [PubMed: 14569188]
8. Hanninen H, Aitio A, Kovala T, et al. Occupational exposure to lead and neuropsychological dysfunction. Occupational and environmental medicine. 1998 Mar; 55(3):202–209. [PubMed: 9624272]
9. Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men: the VA Normative Aging Study. American journal of epidemiology. 2004 Dec 15; 160(12):1184–1193. [PubMed: 15583371]
10. Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology. 2007 Jan; 18(1):59–66. [PubMed: 17130688]
11. Schwartz BS, Stewart WF, Bolla KI, et al. Past adult lead exposure is associated with longitudinal decline in cognitive function. Neurology. 2000 Oct 24; 55(8):1144–1150. [PubMed: 11071492]
12. Karlamangla AS, Miller-Martinez D, Aneshensel CS, Seeman TE, Wight RG, Chodosh J. Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. American journal of epidemiology. 2009 Aug 1; 170(3):331–342. [PubMed: 19605514]
13. Jacqmin-Gadda H, Fabrigoule C, Commenges D, Dartigues JF. A 5-year longitudinal study of the Mini-Mental State Examination in normal aging. American journal of epidemiology. 1997 Mar 15; 145(6):498–506. [PubMed: 9063339]
14. Bell B, Rose CL, Damon A. The Veterans Administration longitudinal study of healthy aging. The Gerontologist. 1966 Dec; 6(4):179–184. [PubMed: 5342911]
15. Hu H, Aro A, Payton M, et al. The relationship of bone and blood lead to hypertension. The Normative Aging Study. Jama. 1996 Apr 17; 275(15):1171–1176. [PubMed: 8609684]
16. Kim R, Landrigan C, Mossmann P, Sparrow D, Hu H. Age and secular trends in bone lead levels in middle-aged and elderly men: three-year longitudinal follow-up in the Normative Aging Study. American journal of epidemiology. 1997 Oct 1; 146(7):586–591. [PubMed: 9326437]
17. Nie H, Sanchez BN, Wilker E, et al. Bone lead and endogenous exposure in an environmentally exposed elderly population: the normative aging study. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2009 Jul; 51(7):848–857.

18. Wilker E, Korrick S, Nie LH, et al. Longitudinal changes in bone lead levels: the VA Normative Aging Study. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2011 Aug; 53(8):850–855.
19. Letz, R. NES2 User's Manual (version 4.4). Winchester, MA: Neurobehavioral Systems, Inc; 1991.
20. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989 Sep; 39(9):1159–1165. [PubMed: 2771064]
21. Wechsler, D. Wechsler Adult Intelligence Scale-Revised. New York: Harcourt, Brace Janovich; 1981.
22. Salmon DP, Riekkinen PJ, Katzman R, Zhang MY, Jin H, Yu E. Cross-cultural studies of dementia. A comparison of mini-mental state examination performance in Finland and China. Archives of neurology. 1989 Jul; 46(7):769–772. [PubMed: 2742548]
23. Diniz BS, Yassuda MS, Nunes PV, Radanovic M, Forlenza OV. Mini-mental State Examination performance in mild cognitive impairment subtypes. International psychogeriatrics /. IPA. 2007 Aug; 19(4):647–656.
24. Morris JC, Edland S, Clark C, et al. The consortium to establish a registry for Alzheimer's disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. Neurology. 1993 Dec; 43(12):2457–2465. [PubMed: 8255439]
25. Burns A, Jacoby R, Levy R. Progression of cognitive impairment in Alzheimer's disease. Journal of the American Geriatrics Society. 1991 Jan; 39(1):39–45. [PubMed: 1987255]
26. Galasko D, Corey-Bloom J, Thal LJ. Monitoring progression in Alzheimer's disease. Journal of the American Geriatrics Society. 1991 Sep; 39(9):932–941. [PubMed: 1842209]
27. Baker EL, Letz R, Fidler A. A computer-administered neurobehavioral evaluation system for occupational and environmental epidemiology. Rationale, methodology, and pilot study results. Journal of occupational medicine. : official publication of the Industrial Medical Association. 1985 Mar; 27(3):206–212. [PubMed: 3981277]
28. Baker EL, Letz RE, Fidler AT, Shalat S, Plantamura D, Lyndon M. A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: methodology and validation studies. Neurobehavioral toxicology and teratology. 1985 Jul-Aug; 7(4):369–377. [PubMed: 4058646]
29. Vivot A, Power MC, Glymour MM, et al. Jump, Hop, or Skip: Modeling Practice Effects in Studies of Determinants of Cognitive Change in Older Adults. American journal of epidemiology. 2016 Feb 15; 183(4):302–314. [PubMed: 26825924]
30. Power MC, Korrick S, Tchetgen Tchetgen EJ, et al. Lead exposure and rate of change in cognitive function in older women. Environmental research. 2014 Feb.129:69–75. [PubMed: 24529005]
31. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015 Sep; 11(9):1098–1109.
32. Christa Maree Stephan B, Minett T, Pagett E, Siervo M, Brayne C, McKeith IG. Diagnosing Mild Cognitive Impairment (MCI) in clinical trials: a systematic review. BMJ open. 2013; 3(2)
33. Braekhus A, Laake K, Engedal K. A low, 'normal' score on the Mini-Mental State Examination predicts development of dementia after three years. Journal of the American Geriatrics Society. 1995 Jun; 43(6):656–661. [PubMed: 7775725]
34. Weisskopf MG, Sparrow D, Hu H, Power MC. Biased Exposure-Health Effect Estimates from Selection in Cohort Studies: Are Environmental Studies at Particular Risk? Environmental health perspectives. 2015 Nov; 123(11):1113–1122. [PubMed: 25956004]
35. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environmental health perspectives. 1998 Jan; 106(1):1–8. [PubMed: 9417769]
36. Shih RA, Glass TA, Bandeen-Roche K, et al. Environmental lead exposure and cognitive function in community-dwelling older adults. Neurology. 2006 Nov 14; 67(9):1556–1562. [PubMed: 16971698]
37. Bandeen-Roche K, Glass TA, Bolla KI, Todd AC, Schwartz BS. Cumulative lead dose and cognitive function in older adults. Epidemiology. 2009 Nov; 20(6):831–839. [PubMed: 19752734]

38. Mufson EJ, Ikonomovic MD, Counts SE, et al. Molecular and cellular pathophysiology of preclinical Alzheimer's disease. Behavioural brain research. 2016 Sep 15.311:54–69. [PubMed: 27185734]

39. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2016 Mar; 12(3):292–323.

40. Llorens F, Schmitz M, Ferrer I, Zerr I. CSF biomarkers in neurodegenerative and vascular dementias. Progress in neurobiology. 2016 Mar-May;138–140:36–53.

Highlights

- Cognitive data collected over 15 years was used to study how lead affects cognitive trajectories.
- Cumulative exposure to lead as measured by bone lead levels was associated with faster decline in mini-mental status exam scores.
- This suggests that exposure to lead accelerates cognitive aging, and possibly functional status.

Table 1

Baseline Study Characteristics – VA Normative Aging Study. Boston, Massachusetts.

	MMSE	Global Cognition
Number of Subjects	741	715
Mean Age in years (SD)	67.77 ± 6.82	68.43 ± 7.11
Mean Patella Pb in μg/g (SD)	30.64 ± 19.44	30.47 ± 19.65
Mean Tibia Pb in μg/g (SD)	21.62 ± 13.33	21.39 ± 13.31
Education in number of years (%)		
<12	33 (4.4)	33 (4.6)
12–15 yrs	555 (74.9)	532 (74.4)
16+	153 (20.6)	150 (21.0)
Smoking Status (%)		
Never	221 (29.8)	209 (29.2)
Former	47 (6.3)	44 (6.2)
Current	473 (63.8)	462 (64.6)
More than 2 alcoholic beverages per day? (%)		
No	585 (78.9)	560 (78.3)
Yes	156 (21.1)	152 (21.3)

Table 2

Mean Cognition Scores over time

	MMSE		Global cognition score	
Visit	**N subjects**	**Mean (±SD)**	**N subjects**	**Mean (±SD)**
1	741	26.9 ± 1.4	715	$1.5*10^{-6}$ ± 3.6
2	574	27.1 ± 1.6	452	0.0096 ± 3.8
3	415	26.7 ± 1.8	198	−0.12 ± 3.8
4	273	26.7 ± 1.8		
5	129	26.5 ± 2.0		

Table 3

Association between Pb and MMSE over time (n=741)

Patella Pb			
Parameter	**β-Estimate**	**Confidence Interval**	**p-value**
IQR change in Pb	*−0.128*	(−0.251, −0.004)	*0.04*
Time	*−0.100*	(−0.122, −0.077)	*<0.0001*
IQR change in Pb*time	*−0.016*	(−0.032, −0.0004)	*0.04*
Tibia Pb			
Parameter	**β-Estimate**	**Confidence Interval**	**p-value**
IQR change in Pb	−0.077	(−0.206, 0.052)	0.15
Time	*−0.099*	(−0.122, −0.077)	*<0.0001*
IQR change in Pb*time	−0.011	(−0.028, 0.005)	0.19

Each exposure (patella or tibia) was included as a predictor in a separate model. Covariates were baseline age, smoking status, education level, and alcohol consumption. Interpretation of parameters: Pb – baseline association of IQR change in patella Pb and MMSE; Time – change in MMSE for every IQR increase in Pb per year change in time; Pb*Time – change in MMSE for every IQR increase in Pb per year change in time. The IQR for patella Pb was 21 μg/g and for tibia Pb was 15 μg/g.

Table 4

Cox-proportional HR of having MMSE score drop below 25 in association with an IQR increase in Bone Pb Levels (n=521)

	HR	95% CI
Patella Pb (IQR=21 μg/g)	1.21	(0.99, 1.49)
Tibia Pb (IQR=15 μ/g)	1.05	(0.82, 1.35)

Adjusted for baseline age, smoking status, education level, and alcohol consumption.

Table 5

Association of Pb and Global Cognition over time (n=715)

Patella Pb			
Parameter	**β-Estimate**	**Confidence Interval**	**p-value**
IQR change in Pb	−0.250	(−0.518, 0.019)	0.07
Time	*−0.147*	(−0.187, −0.107)	*<0.0001*
IQR change in Pb*time	−0.027	(−0.069, 0.014)	0.20
Tibia Pb			
Parameter	**β-Estimate**	**Confidence Interval**	**p-value**
IQR change in Pb	−0.206	(−0.453, 0.089)	0.16
Time	*−0.148*	(−0.184, −0.106)	*<0.0001*
IQR change in Pb*time	0.002	(−0.040, 0.038)	0.93

This was modeled similarly as regression shown in Table 3. Models were adjusted for baseline age, smoking status, education level, and alcohol consumption. Global cognition was created as the average of the sum of z-scores of 6 of the individual tests.

Table 6

Association of IQR increase in Pb and individual cognitive tests over time

	Effect of Baseline Pb		*Effect of Time*		*Effect of Time*Pb Interaction*	
	Parameter	**95% CI**	**Parameter**	**95% CI**	**Parameter**	**95% CI**
Patella Pb						
Language Domain						
Word List Total Recall	0.008	(−0.065,0.081)	**−0.024**	**(−0.036,−0.011)**	**−0.014**	**(−0.026,−0.001)**
Verbal Fluency	−0.040	(−0.115,0.035)	**−0.018**	**(−0.031,−0.005)**	−0.007	(−0.020,0.006)
Memory Domain						
Digit span backward sum	−0.041	(−0.117,0.034)	0.001	(−0.013,0.016)	−0.005	(−0.019,0.010)
DSBT (total #recalled for digit span)	−0.045	(−0.121,0.031)	−0.004	(−0.018,0.010)	−0.008	(−0.022,0.006)
Word List delayed Recall	0.013	(−0.062,0.087)	**−0.030**	**(−0.043,−0.018)**	**−0.014**	**(−0.027,−0.002)**
Visuospatial Domain						
Pattern Recognition, #correct	−0.053	(−0.125,0.019)	**−0.017**	**(−0.033,−**0.002)	0.004	(−0.011,0.020)
Visual Drawings, sum	**−0.108**	**(−0.185,−0.031)**	**−0.043**	**(−0.065,0.081)**	0.007	(−0.007,0.021)
Tibia Pb						
Language Domain						
Word List Total Recall	0.040	(−0.041,0.121)	**−0.024**	**(−0.034,0.011)**	−0.006	(−0.019,0.008)
Verbal Fluency	−0.050	(−0.133,0.034)	**−0.018**	**(−0.031,−**0.005)	−0.005	(−0.019,0.009)
Memory Domain						

	Effect of Baseline Pb		*Effect of Time*		*Effect of Time*Pb Interaction*	
	Parameter	**95% CI**	**Parameter**	**95% CI**	**Parameter**	**95% CI**
Digit span backward sum	−0.039	(−0.123,0.045)	0.001	(−0.013,0.016)	−0.001	(−0.016,0.014)
DSBT (total #recalled for digit span)	−0.046	(−0.130,0.038)	−0.004	(−0.018,0.009)	−0.004	(−0.019,0.011)
Word List delayed Recall	0.076	(−0.006, 0.159)	**−0.031**	**(−0.043,−0.018)**	−0.008	(−.021,0.006)
Visuospatial Domain						
Pattern Recognition, #correct	−0.072	(−0.152,0.008)	**−0.017**	**(−0.033,−0.002)**	0.006	(−0.010,0.022)
Visual Drawings, sum	**−0.142**	**(−0.227,−0.057)**	**−0.043**	(−0.057,−0.029)	**0.016**	**(0.001,0.031)**

Models were adjusted for baseline age, smoking status, education level, and alcohol consumption.