SHORT REPORT

Chronic renal disease among lead-exposed workers

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ABSTRACT

Background Very high exposure to inorganic lead causes serious kidney damage. We have studied workers with occupational exposure and data on blood lead.

Methods We extended follow-up for 7 more years, for a previously studied cohort of 58 307 male workers who were part of a surveillance programme in 11 different states. Mortality was assessed using the National Death Index, and end-stage renal disease (ESRD) incidence was assessed using the US Renal Data System. We conducted internal analyses via Cox regression adjusting for age, calendar time and race.

Results The cohort was followed for a median of 18 years and had 524 cases of ESRD and 6527 deaths. Average maximum blood lead was 26 µg/dL; the mean year of first blood lead test was 1997. No trends by lead level were seen overall or when restricting to those with 15+ years follow-up. Among non-Caucasians with >15 years of follow-up, there was a positive but inconsistent trend (Rate ratios (RRs) 1.00, 2.10, 1.33, 2.20 and 2.76 for maximum blood lead categories of <20 µg/dL, 20–29 µg/dL, 30 to <40 µg/dL, 40 to ≤50 µg/dL and >50 µg/dL, respectively (p for linear trend 0.26). Those with >15 years of follow-up and birth year <1941 showed a positive trend with increased blood lead (RRs 1.00, 1.14, 1.18, 1.46, 1.66, p trend=0.26).

Conclusions We found no association between higher lead exposure and ESRD. There were positive but not statistically significant trends of increased risk for non-Caucasians with >15 years of follow-up and for older men with >15 years of follow-up.

Key messages

What is already known about this subject?

- There are few studies of incident kidney failure among workers with measured blood lead, and results are contradictory.

What are the new findings?

- We followed 58 000 men in the USA with measured blood lead, for an average of 18 years, and found 524 cases of end-stage renal disease (ESRD). We did not find a positive trend of increased ESRD with higher blood lead measurement. There was some suggestion of a positive trend among non-Caucasians with longer follow-up, who are known to have higher levels of hypertension.

How might it impact on policy or clinical practice in the foreseeable future?

- Currently recommended blood lead levels for exposed workers may be too high for non-Caucasian workers prone to hypertension.

INTRODUCTION

Although environmental exposure to lead in the USA has decreased substantially since the 1970s, there remain substantial numbers of US workers exposed (an estimated 1.6 million, https://www.osha.gov/SLTC/lead/). Current US Occupational Safety and Health Administration standards require workers be removed from lead exposure when their blood lead level reaches 50–60 µg/dL, but there is concern that current standards are outdated and do not adequately protect workers' health.[1]

Very high exposure is known to result in severe kidney damage.[2] However, evidence is relatively sparse regarding occupational lead exposure and chronic kidney disease (CKD). There are only two prospective studies, not subjected to reverse causality which can affect cross-sectional studies. Harari *et al*[3] studied 2600 adults with median blood lead of 25 µg/dL in the early 1990s, followed through 2012 (185 cases of CKD). The HR was 1.49 (1.07–2.08) for the top quartile of blood lead versus the bottom three quartiles. Evans *et al*[4] prospectively studied end-stage renal disease (ESRD) in 10 000 lead workers with blood leads in a surveillance programme in Sweden, with only 30 cases. No trends were observed between ESRD and lead. The National Toxicology Program (NTP)[5] has concluded that there is sufficient evidence of kidney damage among adults from blood lead levels of <10 µg/dL). However, many of studies reviewed by NTP were cross-sectional studies kidney function rather than clinical disease.

We previously followed a large cohort of lead-exposed workers for renal disease incidence over 12 years and found a positive trend of renal disease for those with >5 years of follow-up.[6] Now we here report the results of extending the follow-up of this cohort for 7 years.

METHODS

Data sources/study participants

The NIOSH Adult Blood Lead Epidemiology and Surveillance (ABLES) programme started collecting state-level data on blood lead exposure in 1987.[7] Blood lead tests were primarily due to occupational exposure.

We obtained data from 11 state ABLES programs through 2008 which had the most subjects and went back the farthest in time. We excluded everyone first tested after 2005. For subjects with more than one blood lead test (51%), blood lead category was defined as the highest category ever achieved. We chose maximum blood lead, because we believed

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that biologically it was most likely to correlate with cumulative blood lead, which we have previously shown to be the case, using bone lead tests, among a sample of 200 members of this cohort.[8]

We restricted our analytic cohort to men, because women represented only 15% of the cohort and were largely in the lowest blood lead category, suggesting they may have been non-occupational exposures (eg, pregnant women). We further excluded all people restricted to those tested between 18 and 70 years of age. The final analytic data set was 58 307.

Matching with the National Death Index (NDI) was done to determine vital status (https://www.cdc.gov/nchs/ndi/index.htm). We used first name, last name, date of birth, gender, race (when available) and Social Security Number (SSN) (when available) to match with the NDI through 2017. Previous work has indicated good sensitivity and specificity when matching to NDI in general and when using only name and date of birth.[9 10] We used the same matching variables as we did for NDI for US Renal Data System (USRDS) matching, through 2017 (https://www.usrds.org/). As per the USRDS website 'all ESRD patients, regardless of insurance coverage and age, are included in the USRDS database' (https://www.usrds.org/faq.aspx) .

Adjustment for missing race

The majority of our cohort was missing data on race (69%). US non-Caucasians have much higher ESRD rates than whites, presumably due in part to the higher prevalence of hypertension in this group, primarily composed of African-Americans (https://www.usrds.org/reference.aspx). While race was not associated with lead level among those with known or imputed race, and therefore would not be expected to act as confounder in internal analyses, we wanted to have data on race to assess possible effect modification. Hence, we imputed race for those missing race (although not for the 524 ESRD cases in the total cohort, for whom we had data on race) via multiple imputation. The percentage of non-Caucasian race in the imputed data was 19, similar to the 21 in the US male population aged 18–64 years in 2010 (www.census.gov/popest/data/national/asrh/2012/index.html). The imputation model, based on data with known race, resulted in correct prediction of race for 69% of the observations, incorrect for 30% and 'tied' data for 2% of observations (area under the receiver operating characteristic curve was 0.69).

Analyses

We conducted internal analyses via Cox regression using SAS PHREG (https://www.sas.com/en_us/software/stat.html). The time variable was age. Follow-up began at the time of first blood test and ended at death, ESRD incidence or end of follow-up. Covariates in the model were age at first blood test, decade of birth and race. Trend tests were conducted using the maximum level of blood test as a continuous variable. We categorised each blood lead level reading into one of five categories: <20 µg/dL, 20–29 µg/dL, 30 to <40 µg/dL, 40 to ≤50 µg/dL and >50 µg/dL. Proportional hazard assumptions were tested and were fulfilled for all models presented in results. In analyses stratified by follow-up time, those with 15+ years had their person-time begin after they reached 15 years of follow-up, and those with <15 years had their follow-up end at 15 years.

RESULTS

Median year of birth was 1959 (range 1914–1993 years). Mean age at first blood test was 39, and the mean year was 1997. Median follow-up for the cohort was 19 years. There were 6527 deaths (11%) and 524 incident ESRD cases. Half of the cohort (49%) had only one blood lead test. The mean level of maximum blood lead was 25.9 µg/dL.

Table 1 gives the results of ESRD incidence rate ratios by blood lead category, with the lowest category as referent, as well as a trend test. There is no trend among those with known race.

For the larger cohort (imputed race), there is also no trend, whether across all follow-up time, or by strata of follow-up. Among those with >15 years of follow-up (184 cases), there was a suggestion of an interaction between race and lead (p=0.12). Non-Caucasians had an increasing but inconsistent trend of ESRD incidence by blood lead, with RRs of 1.00, 2.10, 1.33, 2.20 and 2.76, across maximum blood lead categories of <20 µg/dL, 20–29 µg/dL, 30 to <40 µg/dL, 40 to ≤50 µg/dL and >50 µg/dL, respectively, and a positive linear trend with maximum blood lead (p=0.26) or log maximum blood lead (p=0.12). Combining the categories above the referent (ie, >20 µg/dL), the RR was 2.04 (1.10–3.78). Among those with at least 15 years of follow-up, we also found some suggestion of effect modification by age (year of birth) (p=0.15), indicating greater risk with increasing lead for those who were older. When we restricted analyses for those with 15 years of follow-up to the oldest cases born before 1940 (51 cases), we

Table 1 HRs* and 95% CIs for ESRD by lead category and follow-up time, imputed race

Follow-up time	Highest lead category achieved										
	<20 µg/dL		20 to <30 µg/dL		30 to <40 µg/dL		40 to <50 µg/dL		≥50 µg/dL		
	n with ESRD	HR	n with ESRD	HR (95% CI)	n with ESRD	HR (95% CI)	n with ESRD	HR (95% CI)	n with ESRD	HR (95% CI)	P-value for trend†
Known race‡	36	1.00	28	0.66 (0.40-1.08)	38	0.64 (0.40–1.02)	34	0.77 (0.47–1.24)	44	1.03 (0.65–1.63)	0.91
Imputed race											
Overall	192	1.00	93	0.77 (0.60–0.99)	99	0.73 (0.57–0.94)	67	0.78 (0.59–1.04)	73	1.04 (0.79–1.37)	0.55
≤15 years	166	1.00	54	0.72 (0.53–1.00)	52	0.70 (0.50–0.97)	28	0.69 (0.44–1.05)	40	1.26 (0.86–1.87)	0.93
>15 years	26	1.00	39	1.02 (0.61–1.71)	47	0.92 (0.55–1.52)	39	0.98 (0.56–1.706)	33	0.95 (0.53–1.70)	0.50
>15 years Caucasians	22	1.00	30	0.84 (0.47–1.50)	39	0.82 (0.47–1.44)	29	0.78 (0.41–1.45)	21	0.67 (0.33–1.31)	0.14
>15 years non-Caucasians	4	1.00	9	2.10 (0.63–7.02)	8	1.33 (0.38–4.68)	10	2.21 (0.63–7.71)	12	2.76 (0.78–9.68)	0.26

*Proportional hazards regression models adjusted for calendar time period (10-year categories) of first blood test, and imputed race (Caucasians vs non-Caucasians) with age as timescale.
†From proportional hazards regression model with continuous maximum blood lead as exposure (adjusted for calendar time period and race with age as time).
‡31% of the cohort had known race; there were 180 cases.
ESRD, end-stage renal disease.

found an increasing but not statistically significant trend by increased blood lead category (RR=1.00, 1.19, 1.33, 1.83, 2.08, p for linear trend=0.07).

DISCUSSION

Overall, with extended follow-up, we found little evidence of increased ESRD incidence in this lead exposed cohort. Given other evidence of effects of much lower blood lead levels on both glomerular function[8] and blood pressure (a contributor to kidney disease),[11] it is somewhat surprising that high occupational lead levels did not lead to higher ESRD incidence in this cohort.

There was a suggestion of a positive trend in ESRD among non-Caucasians with longer follow-up, and among older men with longer follow-up. Non-Caucasians are known to have higher levels of hypertension, which can damage the kidney and lead to ESRD. Age-adjusted prevalence of high blood pressure is 41% among US African-Americans versus 27% among non-Hispanic whites (https://www.cdc.gov/nchs/data/databriefs/db289.pdf). It is not surprising that ESRD might be higher in those with longer follow-up, as ESRD is a chronic disease which might be expected to occur only with more follow-up time. Similarly, as ESRD is a disease which primarily occurs at ages over 65 (https://www.usrds.org/2018/view/v2_01.aspx), it may be that any effects of lead exposure would be most evident at older ages. It is possible that further follow-up of this relatively young cohort (median age of 58 years at the end of follow-up in 2017) will reveal trends of increased ESRD by increased lead levels which are not apparent now.

A limitation of our data is that we do not have a measure of cumulative exposure, combining intensity with duration of exposure, although we have previously shown that shown that bone lead, a surrogate for cumulative lead exposure, is well correlated with our maximum bone lead measure in a sample of our cohort.[8] Other limitations include the relatively few number of ESRD cases in some subcategories, as well as the fact that ESRD itself often occurs at the end of chronic renal disease, is a less sensitive endpoint than incident disease, and will be affected by death from other causes before ESRD incidence.

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