Environmental Research 132 (2014) 100–104

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Mortality among participants in a lead surveillance program

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ARTICLE INFO

Article history:
Received 19 December 2013
Received in revised form
15 February 2014
Accepted 10 March 2014
Available online 23 April 2014

Keywords:
Mortality
Lead
Lung Cancer
Occupation

ABSTRACT

Background: There is evidence that adult lead exposure increases cancer risk. IARC has classified lead as a 'probable' carcinogen, primarily based on stomach and lung cancer associations.
Methods: We studied mortality among men in a lead surveillance program in 11 states,. categorized by their highest blood lead (BL) test (0– < 5 μg/dl, 5– < 25 μg/dl, 25– < 40 μg/dl and 40+ μg/dl).
Results: There were 58,368 men with a median 12 years of follow-up (6 to 17 years from lowest to higher BL category), and 3337 deaths. Half of the men had only one BL test. There was a strong healthy worker effect (all cause SMR=0.69, 95% CI: 0.66–0.71). The highest BL category had elevated lung and larynx cancer SMRs (1.20, 95% CI: 1.03–1.39, $n=174$, and 2.11, 95% CI: 1.05–3.77, $n=11$, respectively); there were no significant excesses of any other cause-specific SMR. Lung cancer RRs by increasing BL category were 1.0, 1.34, 1.88, and 2.79 (test for trend $p= < 0.0001$), unchanged by adjustment for follow-up time. The lung cancer SMR in the highest BL category with 20+ years follow-up was 1.35 (95% CI: 0.92–1.90).
Conclusions: We found an association of blood lead level with lung cancer mortality. Our data are limited by lack of work history (precluding analyses by duration of exposure), and smoking data, although the strong positive trend in RRs by increasing blood lead category in internal analysis is unlikely to be caused by smoking differences. Other limitations include different lengths of follow-up in different lead categories, reliance on few blood lead tests to characterize exposure, and few deaths for some causes.

1. Introduction

With the reduction of lead use in commercially available products (particularly leaded gasoline), ambient lead exposure has been reduced since the 1970s. However, occupational exposure continues to be important. The National Institute of Occupational Safety and Health (NIOSH) estimated in the 1980s that more than 3 million workers in the US were potentially exposed to lead (Staudinger and Roth 1998). More recent estimates can be made using data from NIOSH's Adult Blood Lead Surveillance (ABLES) program; data from 37 states indicated that approximately 130,000 workers had been tested for blood lead in 2005 (www.cdc.gov/niosh/topics/ABLES/pdfs/2002-2005lead_data.pdf).

The current US OSHA standard calls for workers to be removed from exposure when they have a blood lead of 50 μg/dl (construction workers), or 60 μg/dl (other workers), and to not return until their blood lead drops below 40 μg/dl (www.osha.gov/SLTC/lead/). A number of authors have called for removal of workers from exposure when blood levels reach 20 μg/dl (Hu et al. 2007, Kosnett et al., 2007, Schwartz and Hu, 2007, Spivey 2007).

Adult chronic exposure to lead has been associated with multiple outcomes, although evidence is not conclusive. Both the International Agency for Research on Cancer (IARC) and the National Toxicology Program have concluded that lead is a probable human carcinogen, based primarily on evidence of the impacts of lead exposure on lung and stomach cancers and some suggestion of an effect on kidney and brain cancer (IARC, 2006, NTP, 2004). Lead exposure has been associated with modest increases in blood pressure. A meta-analysis of 31 studies by Nawrot et al. (2002) found that most showed a positive association between blood lead and blood pressure after controlling for age; a doubling of blood lead was associated with a 1.0 mm rise in systolic pressure (95% CI 0.5–1.4), and a 0.6 mm Hg increase in diastolic pressure (95% CI 0.4–0.8). Increased blood pressure is a risk factor for stroke and heart disease, but information on these outcomes is limited in the current literature. In a review of articles concerning lead and the risk of cardiovascular disease (CVD), Navas-Acien et al.(2007) found that overall there was insufficient epidemiological data to draw conclusions.

Abbreviations: ABLES, Adult blood lead epidemiology and surveillance; NIOSH, National Institute for Occupational Safety and Health; BL, Blood lead; μg/dl, microgram/deciliter; HWE, healthy worker effect; SMR, standardized mortality ratio; RR, rate ratio

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http://dx.doi.org/10.1016/j.envres.2014.03.008
0013-9351/

Very high levels of lead in the body are known to result in kidney failure (US EPA 2005), but effects at low levels are less clear. A recent comprehensive review of lead-related nephrotoxicity concluded that lead contributes to nephrotoxicity, even at blood lead levels below 5 μg/dl, especially in people with other illnesses such as hypertension and diabetes (Ekong et al. 2006).

The objective of the current study was to evaluate the association of lead exposure and subsequent all-cause and cause-specific mortality, using data from 11 states participating in NIOSH's ABLES program.

2. Methods

2.1. Data sources/study participants

The Adult Blood Lead Surveillance program, sponsored by NIOSH, started collecting state-level data on blood lead levels in 1987 (Roscoe et al. 2002). Initially, some states gathered data only on individuals whose blood lead levels exceeded 25 μg/dl, but subsequently many states began to collect data on subjects with lower blood lead levels. Blood lead tests were conducted primarily in response to occupational exposure, but in some cases stemmed from non-occupational exposure. ABLES coverage increased from 4 states in 1987 to 41 states in 2012 (www.cdc.gov/niosh/topics/ABLES/description.html).

NIOSH has collected data on industry of employment for a limited number of ABLES subjects ($n=6999$) with blood lead levels $\geq$ 25 μg/dl (CDC, 2011). Of these 62% were in manufacturing, 10% in construction, 7% in metal mining, 1% in trade (scrap and waste materials), and 20% were in other industries or data were unavailable.

We obtained data from 11 state ABLES programs: Connecticut, California, Ohio, Minnesota, Iowa, Pennsylvania, New York, New Jersey, Wisconsin, Michigan and Massachusetts, from their year of first participation until 2005. The percentage of the cohort represented by these states was 4%, 18%, 10%, 2%, 3%, 3%, 29%, 11%, 6%, 3%, and 11% respectively. These states were chosen because they had the most subjects with blood lead data, and data which went back the farthest in time. We excluded any subjects missing information on date of birth, test date, or blood lead levels. We categorized each blood lead level reading into 1 of 4 categories, namely <5 μg/dl, 5 to <25 μg/dl, 25 to <40 μg/dl, and 40+ μg/dl. The categories <25, 25–40, and 40+ μg/dl have been traditionally used to categorize occupational blood lead levels; the lowest category of 5 μg/dl was considered equivalent to non-occupational US blood lead levels.

The data uniformly available from the states consisted of name, date of birth, gender, data of each blood test, and blood lead level for each test. Additional incomplete data was available on race (69% missing) and social security number (SSN; 74% missing). We classified those with missing race as white in our primary analyses, since 86% of subjects among those with known race were white. We also conducted sensitivity analyses using imputed race, but resulted in virtually identical results, and are not presented here. There were no data on work history or smoking. Data on type of occupation or industry were collected sporadically in only some states for limited numbers of subjects.

Data from ABLES were matched to the National Death Index (NDI) to assess mortality outcomes among the cohort. For efficiency and cost considerations, we selected a subset of the full cohort for the NDI matching process, while maintaining sufficient power to analyze the association of blood lead categories and mortality. We first selected all subjects from the states who had ever had a blood lead level in categories 3 or 4. We then randomly selected an equal number of people from categories 1 and 2 (50% from each category), stratified by state. Finally, we restricted our cohort to males, because females represented only 15% of the population, were younger than the men (few deaths), were highly concentrated in the lowest blood lead category, and were more likely to have been tested for non-occupational reasons, such as during pregnancy (personal communication, Susan Payne, California ABLES/Occupational Lead Poisoning Prevention Program (OLPPP), May 2013). We further excluded all people who were tested for the first time after the age of 70 years or before the age of 18 years, and any blood tests we considered implausible (greater than 250 μg/dl, as these values were considered implausible).

After the above exclusions and accounting for subjects with test results in multiple states (for whom data had to be merged under a single identification number), we had a final analytic dataset with 58,368 unique subjects. About half the subjects (49%) had a single blood test, while the remainder had a median of four. Considering each blood lead test an observation, we had a total of 283,270 observations. For epidemiologic analyses, blood lead category for each individual was defined as the highest category ever achieved; hence peak exposure was our variable of interest for those who had more than one blood test. It should be noted that blood levels for the majority of subjects with multiple tests were generally in the same blood lead category (see Results).

We used name, date of birth, gender, race (when available) and SSN (when available) for matching with the NDI database through the end of 2010, to obtain data on date and cause of death (underlying and multiple). Three states sent in their own data to NDI; their follow-up ended in 2009 (Massachusetts) or 2008 (Wisconsin, Michigan). To determine if a match with the NDI was a true match from amongst the multiple matches reported by NDI, we only selected those who were assigned a status code of 1 by NDI, indicating a high probability of a match. If a person's last blood lead test date was after their date of death, then the match was dropped and these subjects were considered as alive. If there were multiple matches with status code 1, we selected the one with the highest NDI probability score for a match.

2.2. Analyses

The NIOSH Life Table Analysis System (NIOSH, LTAS, Version 3.3) was used to calculate cause-specific rates of death for the cohort, and to compare these rates with those of the US population via standardized mortality ratios (SMRs), adjusted for age (five-year categories), race, sex, and five-year calendar time period (person-time at risk and observed events were categorized into strata defined by these variables) (Schubauer-Berigan et al. 2011). Overall, we had information on 92 causes of death; we present SMRs for 11 specific causes of death of *a priori* interest for lead exposure, including cancers (lung, brain, kidney, stomach, esophagus, larynx, bladder, stroke, chronic obstructive pulmonary disease (COPD), ischemic heart disease, and chronic renal disease. In the SMR calculation, US national mortality rates were used rather than those from the 11 different states, for convenience and because mortality rates in the 11 states (which represent about a third of the US population) as a whole reflect national rates. A weighted average of

Table 1
Demographics of the Cohort.

Characteristics	Highest lead category achieved				
	1 0– < 5 μg/dl	2 5– < 25 μg/dl	3 25– < 40 μg/dl	4 40+ μg/dl	Total
Total	6848 (11.7%)	18,650 (31.9%)	21,448 (36.7%)	11,422 (19.6%)	58,368
Median years of follow-up	6.4	9.9	14.2	17.1	12
Mean age at first test	40.7	39.9	37.9	38.3	38.9
Race					
White	1,448 (21%)	2356 (13%)	6246 (29%)	4339 (38%)	14,389 (26%)
Non-white	252 (4%)	558 (3%)	1673 (8%)	1200 (10%)	3683 (6%)
Missing/unknown	5148 (75%)	15,736 (84%)	13,529 (63%)	5883 (52%)	40,296 (69%)
% Non-white among known race	0.13	0.14	0.12	0.12	0.14
Median number of observations in those with > 1	2	3	4	6	4
% With single observations	6124 (89%)	12,739 (68.3%)	7786 (36.3%)	1940 (16.9%)	28,589 (48.9%)
Mean highest blood lead level	3	13	31)	52	26
% With SSN (for matching)-Overall[a]	611 (9%)	2084 (11%)	7664 (36%)	4883 (43%)	15,242 (26%)
Median year of birth	1962	1961	1959	1955	1959
Median year of death	2006	2005	2004	2003	2004
Number dead	173 (2.5%)	635 (3.4%)	1301 (6.1%)	1228 (10.8%)	3337 (5.7%)

[a] Three states, WI, MI, MA sent their own data and sent us de-identified data, without SSN; hence these percentages are underestimates.

Table 2
Standardized Mortality Ratios (SMR) and 95% confidence intervals by lead category, selected causes ($n=58,368$).

Cause of death	Highest lead category achieved									
	1 0– < 5 μg/dl		2 5– < 25 μg/dl		3 25– < 40 μg/dl		4 40+ μg/dl		Overall	
	N	SMR (95% CI)	*N*	SMR (95% CI)	*N*	SMR (95% CI)	*N*	SMR (95% CI)	*N*	SMR (95% CI)
All causes	173	0.63 (0.54, 0.73)	635	0.59 (0.55, 0.64)	1301	0.66 (0.63, 0.70)	1228	0.80 (0.75, 0.84)	3337	0.69 (0.66, 0.71)
Cancer										
Lung	10	0.42 (0.20, 0.77)	54	0.56 (0.42, 0.74)	144	0.81 (0.68, 0.95)	174	1.20 (1.03, 1.39)	382	0.86 (0.78, 0.95)
Brain	0	0.0 (0.0, 1.26)	8	0.71 (0.31, 1.40)	11	0.59 (0.30, 1.06)	11	0.83 (0.41, 1.49)	30	0.65 (0.44, 0.93)
Kidney	1	0.42 (0.01, 2.35)	9	0.96 (0.44, 1.83)	9	0.55 (0.25, 1.05)	9	0.72 (0.33, 1.37)	28	0.69 (0.46, 1.00)
Stomach	2	1.19 (0.14, 4.32)	2	0.3 (0.04, 1.08)	9	0.69 (0.31, 1.30)	10	0.92 (0.44, 1.69)	23	0.71 (0.45, 1.07)
Esophagus	2	0.59 (0.07, 2.14)	11	0.85 (0.42, 1.52)	13	0.59 (0.31, 1.01)	11	0.65 (0.32, 1.16)	37	0.67 (0.47, 0.92)
Larynx	1	1.15 (0.03, 6.40)	2	0.58 (0.07, 2.10)	2	0.31 (0.04, 1.12)	11	2.11 (1.05, 3.77)	16	1.00 (0.57, 1.63)
Bladder	0	0.00 (0.00, 2.20)	6	0.90 (0.33, 1.96)	9	0.74 (0.34, 1.41)	7	0.70 (0.28, 1.45)	22	0.72 (0.45, 1.10)
Stroke	4	0.48 (0.13, 1.24)	18	0.54 (0.32, 0.86)	54	0.79 (0.59, 1.03)	47	0.79 (0.58, 1.05)	123	0.73 (0.60, 0.87)
Chronic Obstructive Pulmonary Disease	10	1.04 (0.50, 1.92)	12	0.31 (0.16, 0.54)	45	0.61 (0.45, 0.82)	53	0.86 (0.64, 1.12)	120	0.65 (0.54, 0.78)
Ischemic Heart Disease	21	0.44 (0.27, 0.67)	95	0.49 (0.39, 0.60)	230	0.62 (0.54, 0.70)	223	0.72 (0.63, 0.82)	569	0.61 (0.56, 0.67)
Chronic Renal Disease	2	0.78 (0.09, 2.82)	3	0.31 (0.06, 0.89)	10	0.52 (0.25, 0.96)	16	1.01 (0.58, 1.64)	31	0.65 (0.44, 0.93)

the 2007 all-cause mortality rates for the 11 states in our study, with weights being the percentage of the cohort represented by each state, was 795/100,000, which is very close to the US 2007 all-cause mortality rates of 803/100,000.

Person-time at risk began at time of first blood test for each subject. For each subject, all person-years were assigned to the highest blood lead category that any of their test results were assigned. For subjects with multiple tests over time, most did not change blood lead category (see below). Lacking complete blood lead histories over time, we did not conduct more detailed analyses where subjects could change blood lead categories across time.

In internal analyses, we calculated rate ratios (RRs) using Poisson models (log person-years offset, with scaled standard errors to adjust for over-dispersion), adjusted (via stratification of person-time and observed events) for gender, race, age category, and calendar time at risk, and comparing each blood lead category (5 to < 25 μg/dl, 25 to < 40 μg/dl, and 40+ μg/dl) to the reference category (< 5 μg/dl) using SAS version 9.3 (www.sas.com). We also conducted a trend test across category-specific RRs, assigning the median blood lead level to each category.

3. Results

Table 1 provides descriptive information about the cohort. There were 58,368 male subjects, and 3337 deaths. The median years of follow-up in the cohort were 12 years (ranging from 6.4 years in lowest blood lead category to 17.1 years in highest). In general, people in the highest blood lead category compared to the lowest category had longer follow-up, higher median number of blood lead tests, more complete information on SSN and race, earlier birth year, and higher number of deaths. Among those with known race there was no indication that the percent non-white differed by blood lead level, suggesting that race was not a confounder in internal analyses.

About half of the cohort (49%) had only one blood lead test over the course of follow-up, while another 18% had more than one but did not change category. Another 24% changed category over repeated blood tests, but by only one category. Only 7% of the cohort changed blood lead category by more than one category. Considering only those who had more than one test, the standard deviation of the mean blood lead levels for each subject was 12.4 μg/dl. In comparison, the mean standard deviation of each subject's multiple tests was 5.8 μg/dl, indicating greater variation between subjects than within subjects.

Table 2 shows the SMRs for causes of *a priori* interest, as well as some smoking-related causes. A healthy worker effect (SMRs less than 1.0) is evident in this cohort, with an all cause SMR of 0.69 (95% CI: 0.66–0.71), and SMRs at or below 1.00 for all specific causes. The only significant (at the $p=0.05$ level) excesses were noted in the highest lead category (40+ μg/dl), for lung cancer (SMR=1.20, 95% CI: 1.03–1.39) and laryngeal cancer (SMR=2.11, 95% CI: 1.05–3.77). Other smoking-related causes in this blood lead category were not in excess (COPD, ischemic heart disease, esophagus, stroke). With the exception of lung cancer, the number of deaths were limited for many of the other cancer outcomes of interest with 11 or fewer cause-specific deaths in the highest blood lead category.

Table 3 shows the internal comparisons via Poisson regression for the outcomes in Table 2, with the exception of bladder and brain cancer where there were no deaths in the referent group (blood lead < 5 μg/dl). Positive linear trends were found for all causes ($p=0.0001$), lung cancer ($p<0.0001$), COPD ($p=0.02$), ischemic heart disease ($p<0.0001$), and chronic renal disease ($p=0.04$). The positive trends for renal disease and COPD, however, were not monotonically increasing. We checked whether some of these positive trends were due to the decrease in the healthy worker effect with increased follow-up time, given that follow-up time increased with higher blood lead category (Checkoway et al. 2004). Inclusion of a categorical variable for time since first blood test did not impact the categorical RRs or the positive trends across RRs for all-cause mortality, lung cancer, heart disease, or renal disease, but did decrease the positive trend for COPD ($p=0.09$).

To assess the impact of varying follow-up time (time since first blood test) in the outcomes, Table 4 shows SMRs for blood lead categories 3 and 4 (25–39 μg/dl, 40+ μg/dl), for selected outcomes with sufficient numbers of deaths, for those with more 20+ years follow-up. The healthy worker effect was weaker in this subset (SMR=0.79). The overall lung cancer SMR was 1.17, and 1.35 (95% CI: 0.92–1.90) in the highest blood lead category. There were no other elevated SMRs among the outcomes considered.

We conducted several sensitivity analyses, focused on the lung cancer finding. The lung cancer SMR for those who had SSNs (26% of the cohort, those most likely to correctly match with NDI data) was 1.17 (95% CI: 1.01–1.34; 204 deaths), and 1.42 (95% CI: 1.17–1.70; 115 deaths) for those in the highest blood lead category. Subjects with only one blood test and those with multiple tests who stayed in the same blood lead category (67% of the cohort) had an overall lung cancer SMR of 0.83 (226 deaths), and an SMR of 1.40 (95% CI: 1.08–1.79, 64 deaths) in the highest blood lead category.

4. Discussion

We found a modest excess of lung cancer mortality in the highest blood lead category compared to US national mortality

Table 3
Rate ratios and 95% confidence intervals by lead category using Poisson models.

Cause of Death[b]	Highest Lead Category Achieved								p-value for Test of Trend[a]
	1 0- < 5 μg/dl		2 5- < 25 μg/dl		3 25- < 40 μg/dl		4 40+ μg/dl		
	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	
All Causes	173	Ref	635	0.96 (0.68, 1.34)	1301	1.11 (0.81, 1.54)	1228	1.41 (1.01, 1.96)	0.0001
Cancer									
Lung	10	Ref	54	1.34 (0.79, 2.26)	144	1.88 (1.14, 3.10)	174	2.79 (1.69, 4.61)	< 0.0001
Kidney	1	Ref	9	2.41 (0.62, 9.46)	9	1.31 (0.33,5.20)	9	1.70 (0.42, 6.83)	0.62
Stomach	2	Ref	2	0.24 (0.04, 1.34)	9	0.52 (0.13, 2.04)	10	0.64 (0.16, 2.60)	0.49
Esophagus	2	Ref	11	1.54 (0.76, 3.11)	13	1.15 (0.57, 2.32)	11	1.39 (0.68, 2.85)	0.99
Larynx	1	Ref	2	0.54 (0.05, 5.97)	2	0.36 (0.03, 4.01)	11	2.96 (0.37, 23.62)	0.14
Stroke	4	Ref	18	1.12 (0.32, 3.94)	54	1.76 (0.54, 5.76)	47	1.88 (0.57, 6.28)	0.095
Chronic obstructive pulmonary disease	10	Ref	12	0.30 (0.15, 0.61)	45	0.59 (0.33, 1.05)	53	0.85 (0.47, 1.53)	0.02
Ischemic heart disease	21	Ref	95	1.13 (0.78, 1.66)	230	1.46 (1.02, 2.10)	223	1.77 (1.23, 2.56)	< 0.0001
Chronic renal disease	2	Ref	3	0.39 (0.09, 1.77)	10	0.73 (0.20, 2.64)	16	1.52 (0.43, 5.38)	0.04

[a] *P*-value is for linear trend test via Poisson regression, after assigning medians for highest blood lead in each category.
[b] Bladder cancer had too few numbers to run a trend test on and so is not reported in this table.

Table 4
Standardized Mortality Ratios and 95% Confidence Intervals for selected causes, among those with more than 20 years follow-up.

	Blood lead 25– < 40		Blood lead 40+		All	
	N	SMR (95% CI)	N	SMR (95% CI)	N	SMR (95% CI)
All causes	92	0.73 (0.59, 0.90)	213	0.83 (0.72, 0.95)	305	0.79 (0.71, 0.89)
Lung cancer	10	0.83 (0.40, 1.52)	32	1.35 (0.92, 1.90)	42	1.17 (0.84, 1.58)
Stroke	6	1.06 (0.39, 2.31)	8	0.66 (0.28, 1.30)	14	0.78 (0.43, 1.31)
Chronic obstructive pulmonary disease	3	0.43 (0.09, 1.27)	16	1.14 (0.65, 1.85)	19	0.90 (0.54, 1.41)
Ischemic heart disease	18	0.72 (0.43, 1.14)	45	0.86 (0.63, 1.16)	63	0.81 (0.63, 1.04)

rates, as well as significant positive trends in the risk of lung cancer mortality across ascending blood lead categories. There was also some suggestion of an excess of larynx cancer for those in the highest blood lead category compared to national rates, but based on small numbers. No other *a priori* cancers were in excess, although numbers were small for many of them. Furthermore, neither stroke, heart disease, nor kidney disease were in excess in the highest blood lead category when compared to the US referent population. Internal analyses showed significant positive and monotonic exposure-response trends for lung cancer and heart disease mortality.

Our results provide further support to the hypothesis that there is a causal association of lead exposure in subsequent development of lung cancer (IARC, 2006, NTP, 2004). Our finding of excess larynx cancer is novel, but based on small numbers. However, we did not observe associations of lead exposure with stomach, kidney and brain cancer, of *a priori* interest. This is possibly due to the relatively young age of the cohort, and the small number of deaths from these causes.

We found little indication of increased risk of stroke or CVD mortality in external comparisons, possibly as a result of the healthy worker effect, which particularly affects cardiovascular disease. In internal comparisons, we found a statistically significant positive trend in heart disease mortality with increased blood lead category (p-trend < 0.0001). Further, follow-up of our cohort will help clarify the heart disease findings.

In internal comparisons, we also found a significant monotonic increase in mortality due to non-malignant kidney disease (p-trend $= 0.04$), but there were no excess compared to the US population. Incidence rather than mortality data are a preferable end point for kidney disease; we have examined incident end-stage renal disease in relation to lead exposure in a separate manuscript (Chowdhury et al. 2014).

Our study has a number of limitations. One is the overall healthy worker effect in this cohort, which has relatively short follow-up, and in which only about 6% have died. This is especially true for non-malignant causes, which are more susceptible to the healthy worker effect. This may have precluded finding an excess in heart disease for those with higher exposure using the US population for a referent, for example. A further limitation is absence of work history, prohibiting analyses by duration of exposure, and by true latency (we used time since first blood lead test as a surrogate for latency). Another limitation is limited data on blood lead levels over time; for 49% of the cohort we had to rely on only one blood test to characterize exposure level. We do not know the extent to which one or a few blood lead test can accurately characterize long-term exposure, although based on data from those with multiple blood tests who did not often change blood lead category, we believe our grouping into broad exposure categories is likely to be reasonably accurate.

Additionally, we do not have data on smoking, a potential confounder for our principal findings of interest, lung cancer and larynx cancer. However, apart from lung and larynx cancer, most smoking-related diseases show no excess in the highest blood lead category (i.e., bladder cancer, heart disease, COPD, esophageal cancer), suggesting confounding by unmeasured smoking is unlikely to explain the positive associations. Furthermore, smoking differences between workers in internal analyses are unlikely to act as strong confounders, as workers with the same occupations and industries are likely to have relatively homogenous smoking habits. We found a strong positive trend of increasing lung cancer mortality by increasing exposure in internal analyses, with RRs of 1.0, 1.34, 1.88, and 2.79 (test for trend $p = < 0.0001$). It is very unlikely that high RRs such as 1.88 and 2.79 can be due to smoking differences between low exposed and high exposed workers; empirical and theoretical studies have shown that only very strong

differences in smoking habits are likely to explain RRs greater than 1.2 to 1.3 (Siemiatycki et al. 1988, Axelson and Steenland 1988, Kriebel et al. 2004).

Finally, another limitation is the lack of SSNs on 74% of our cohort, and the potential for misclassification of outcome when matching to NDI using only name, gender, and date of birth. Concerns with this may be mitigated based on previous work that has indicated good sensitivity and specificity when matching to NDI using only name and date of birth (Williams et al. 1992, Stampfer et al. 1984).

Our study has a number of strengths, the most important of which is a large study population with documented blood lead levels. Furthermore, we studied a large number of subjects with documented levels $\geq 40\ \mu g/dl$, which is the level that OSHA considers acceptably safe for workers exposed occupationally.

5. Conclusion

We found a relatively robust although modest association of blood lead level with lung cancer mortality. Lung cancer was of a priori interest since it has been elevated in prior studies of lead-exposed cohorts. Evidence was also suggestive of an increased risk of larynx cancer with higher lead exposure, but there were few larynx cancer deaths. Data were limited by reliance on one or a few blood lead tests to characterize exposure level. Data were also limited by lack of work history, no data on smoking, differential follow-up across blood lead categories, and small numbers of deaths for some causes. However, for lung cancer there were large numbers of deaths, adjustment for follow-up did not alter exposure-response trends, and internal comparisons within workers were unlikely to be strongly confounded by smoking differences. Since this is a relatively young cohort with short follow-up and few deaths, re-examination of these associations after a few years may shed more light on the chronic health effects of adult lead exposure.

Competing financial interests

The authors declare that they have no competing financial interests.

Acknowledgments

This work was supported by the National Institute of Occupational Safety and Health award R01OH00898. We would like to acknowledge the following people for their help in providing data access and matching- Susan Payne (California Dept. of Health Services), Beth Forrest (USRDS), Michele Goodier (NDI), ABLES Program: Walter Alarcon (NIOSH), Kenneth D. Rosenman (Michigan State University), Thomas St. Louis, (Connecticut Dept Health), Henry A. Anderson, MD, (Wisconsin Department of Health and Family Services), Jay Devasundaram (Pennsylvania Dept Health), Ed Socie, PhD (Ohio Dept Health), David J. Valiante, (New Jersey Department of Health and Senior Services), Alice Fletcher (New York Dept Health), Rita Gergely (Iowa Dept Health), Erik Zabel (Minn Dept Health), and Bob Nicotera (Massachusetts Dept. of Labor).

References

Axelson, O., Steenland, K., 1988. Indirect methods of assessing the effects of tobacco use in occupational studies. Am. J. Ind. Med. 13 (1), 105–118.

Centers for Disease Control and Prevention, 2011. Adult blood lead epidemiology and surveillance – United States, 2008–2009. Morbidity and Mortality Weekly Report (MMWR). CDC. U.S. Department of Health and Human Services. July 1.60 (25), pp. 841–845.

Checkoway, H., Pearce, N., Kriebel, D., 2004. Research Methods in Occupational Epidemiology. New York, Oxford University Press, New York

Chowdhury, R., Darrow, L., McClellan, W., Sarnat, S., Steenland, K., 2014. Incident ESRD among participants in a lead surveillance program. Am. J. Kidney Dis. (13), 01631–01634, http://dx.doi.org/10.1053/j.ajkd.2013.12.005 (Jan 11. pii: S0272-6386)

Ekong, E.B., Jaar, B.G., Weaver, V.M., 2006. Lead-related nephrotoxicity: a review of the epidemiologic evidence. Kidney Int. 70 (12), 2074–2084.

Hu, H., Shih, R., Rothenberg, S., Schwartz, B.S., 2007. The epidemiology of lead toxicity in adults: measuring dose and consideration of other methodologic issues. Environ. Health Perspect. 115 (3), 455–462.

International Agency for Research on Cancer, 2006. Inorganic and organic lead compounds. IARC Monogr. Eval. Carcinog. Risks Hum. 87, 1–471.

Kosnett, M., Wedeen, R., Rothenberg, S., Hipkins, K., Materna, B., Schwartz, B., Hu, H., Woolf, A., 2007. Recommendations for medical management of adult lead exposure. Environ. Health Perspect. 115 (3), 463–471.

Kriebel, D., Zeka, A., Eisen, E.A., Wegman, D.H., 2004 Oct. Quantitative evaluation of the effects of uncontrolled confounding by alcohol and tobacco in occupational cancer studies. Int. J. Epidemiol. 33 (5), 1040–1045.

National Toxicology Program, 2004. Eleventh Report on Carcinogens: Lead (CAS no 7439-92-1) and lead compounds. Research Triangle Park, NC

Navas-Acien, A., Guallar, E., Silbergeld, E., Rothenberg, S., 2007. Lead exposure and cardiovascular disease–a systematic review. Environ. Health Perspect. 115 (3), 472–482.

Nawrot, T., Thijs, S., Den Hond, E., Roels, J., Staessen, J., 2002. An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. J. Hum. Hypertens. 16 (2), 123–131.

Roscoe, R.J., Ball, W., Curran, J.J., DeLaurier, C., Falken, M.C., Fitchett, R., Fleissner, M.L., Fletcher, A.E., Garman, S.J., Gergely, R.M., Gerwel, B.T., Gostin, J.E., Keyvan-Larijani, E., Leiker, R.D., Lofgren, J.P., Nelson, D.R., Payne, S.F., Rabin, R.A., Salzman, D.L., Schaller, K.E., Sims, A.S., Smith, J.D., Socie, E.M., Stoeckel, M., Stone, R.R., Whittaker, S.G., 2002. Adult blood lead epidemiology and surveillance—United States. 1998–2001. MMWR Surveill. Summ. 51 (11), 1–10.

Schubauer-Berigan, M., Hein, M., Raudabaugh, W., Ruder, A., Silver, S., Spaeth, S., Steenland, K., Petersen, M., Waters, M., 2011. Update of the NIOSH life table analysis system: a person-years analysis program for the windows computing environment. Am. J. Ind. Med. 54 (12), 915–924.

Schwartz, B., Hu, H., 2007. Adult lead exposure: time for change. Environ. Health. Perspect. 115 (3), 451–454.

Siemiatycki, J., Wacholder, S., Dewar, R., Cardis, E., Greenwood, C., Richardson, L., 1988. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. J. Occup. Med. 30 (8), 617–625.

Spivey, A., 2007. The weight of lead. Effects add up in adults. Environ. Health Perspect. 115 (1), A30–36.

Stampfer, M., Willett, W., Speizer, F., Dysert, D., Lipnick, R., Rosner, B., Hennekens, C., 1984. Test of the national death index. Am. J. Epidemiol. 119 (5), 837–839.

Staudinger, K., Roth, V., 1998. Occupational lead poisoning. Am. Fam. Physician 719-726 (4), 731 (-712)57 719-726 (4), 731 (-712).

U.S. Environmental Protection Agency, 2005. U.S. EPA. air quality criteria for lead (First External Review Draft). USEPA. National Center for Environmental Assessment-RTP Office. Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, U.S. EPA/600/R-05/144aA-bA.

Williams, B., Demitrack, L., Fries, B., 1992. The accuracy of the national death index when personal identifiers other than social security number are used. Am. J. Publ. Health 82 (8), 1145–1147.