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Mortality of Lead Smelter Workers: A Follow-Up Study With Exposure Assessment

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Abstract

Background—Lead exposure has been linked to impaired renal function and kidney failure. High lead exposures have been associated with increased mortality from certain cancers, hypertension, cardiovascular disease, and amyotrophic lateral sclerosis (ALS).

Methods—We extended vital status follow-up on a cohort of 1,990 lead smelter workers by 25 years and computed standardized mortality ratios and rate ratios (RR) stratified by cumulative lead exposure.

Results—The update added 13,823 person-years at risk and 721 deaths. Increased risk of mortality was observed for the a priori outcomes of lung cancer, cardiovascular disease (including cerebrovascular disease), chronic kidney disease, and ALS. However, of these outcomes, only cardiovascular, cerebrovascular, and chronic kidney diseases were associated with a positive exposure-response in RR analyses.

Conclusions—This study reaffirms the association of lead exposure with cardiovascular and kidney diseases; however, increased mortality observed for certain cancers is not likely to be due to lead exposure.

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AUTHORS' CONTRIBUTIONS

BSJ performed statistical analysis and drafted the manuscript. LEJ submitted paperwork for updating the cohort and initially drafted the manuscript. WSJ assisted in the exposure assessment and the creation of the JEM. HMJ provided statistical consultation and assisted in interpretation of results.

HUMAN SUBJECTS REVIEW

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The authors declares no conflicts of interest.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Keywords

mortality cohort study; lead exposure

INTRODUCTION

Lead is a well-established nephrotoxin and high exposures can result in impaired renal function and kidney failure [Ekong et al., 2006]. Other chronic effects of lead exposure are less clear. For many years lead has been variously implicated to increased morbidity and mortality from other chronic diseases including certain cancers [Steenland and Bofetta, 2000], and hypertension and cardiovascular disease [Navas-Acien et al., 2007]. In addition, a recent meta-analysis of studies examining the association between occupational exposure to lead and amyotrophic lateral sclerosis (ALS) reported that workers exposed to lead had an 81% increased risk of developing ALS [Wang et al., 2014].

Two previous studies of a cohort of lead smelter workers in Idaho [Selevan et al., 1985; Steenland et al., 1992] observed excess mortality from chronic kidney disease, cerebrovascular diseases, nonmalignant respiratory diseases, kidney cancer, and accidents. However, the authors noted the excesses of nonmalignant respiratory disease and accidents were likely due to the large number of workers that also worked in the mining industry and not lead exposure.

The purpose of this paper is to: (i) update the mortality experience of this cohort and (ii) evaluate associations between mortality and cumulative lead exposure using a more refined job exposure matrix based on lead exposure measurements taken at the lead smelter plant that were not previously considered. The a priori outcomes of interest in this update are: cancers of the lung, kidney, and stomach; cardiovascular diseases (including cerebrovascular disease and hypertension); renal diseases; and ALS.

METHODS

Cohort

The cohort definition includes all white male hourly workers employed for at least 1 year at an Idaho lead smelter plant with at least 1 day of employment between 1940 and 1965 at the smelter. The cohort, followed initially through 1977 [Selevan et al., 1985] and subsequently through 1988 [Steenland et al., 1992] has been previously described. Details of the cohort demographics and work history can be found in Table I.

Mortality

Names of cohort members considered alive as of 1988, or deceased for whom we did not have a cause of death, were submitted to the National Death Index (NDI) for determination of vital status through 2013. NDI Plus provided underlying and contributing causes of death for deceased workers identified by the NDI. All deaths were coded according to the revision of the International Classification of Diseases (ICD) in effect at the time of death. Workers were considered to be alive as of the study end date of December 31, 2013 as long as they

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were confirmed alive on January 1, 1979, had a valid (within assigned range) Social Security number, and were not shown to be deceased by the NDI. Those not confirmed alive on January 1, 1979, with invalid Social Security numbers, and thus not able to be matched with the NDI were considered lost to follow-up.

Exposure Assessment

Work history records included beginning and ending dates of employment in 14 lead exposed departments (Table II). Records were collected in 1975 and are therefore incomplete for 159 workers who were still actively employed in 1975. As a result, these individuals work histories were assigned to end on 12/31/1975. The lead smelter ceased operations in 1982.

The lead exposure assessment described in the original cohort study was based on exposure data collected by the National Institute for Occupational Safety and Health (NIOSH) in 1975 where a total of 69 lead samples were collected with all 14 departments represented. For analysis purposes, exposure was defined at the department level for lead and other heavy metal exposures. Two strata were created: high lead and low lead. The high lead stratum included nine departments in which average airborne lead concentrations exceeded the existing Occupational Safety and Health Administration (OSHA) standard (200 μg/m^3 in 1975) or in which at least 50% of jobs had average levels more than twice the existing standard.

For this update, additional exposure records from OSHA were used to develop a more refined exposure assessment. These records included air sampling data from four compliance surveys conducted by OSHA at the site from 1973 to 1980. Data included reported/calculated 8-hr time-weighted average (TWA) and lead concentrations (mg/m^3) for personal and area samples by department and operator codes. The exposure assessment for this study was based on 143 OSHA samples of personal air lead concentrations. Descriptive statistics were generated for each department by averaging each job title (within each department) and then taking the average of the job title averages over the department (Table II). Overall, the exposure assignments were refinements of the previous high/low lead strata, with the exception of the maintenance department. Maintenance was categorized as high lead exposure in the previous study; however, maintenance exposure levels were consistently lower than the other high lead departments in the current exposure assessment. For departments that were not sampled, a value of 0.06 mg/m^3 was assigned since this was the lowest value measured and these departments were previously identified as having low exposure to lead. Cumulative lead exposure was calculated for each subject by multiplying the assigned exposure level by duration of employment within the department and summing over all jobs worked.

Exposures other than lead were also evaluated during the NIOSH 1975 visit. Workers in two departments (cadmium refinery and charge preparation) were determined to be highly exposed to cadmium; in particular, workers in the cadmium refinery had cadmium exposures well above the OSHA standard at the time. Person-time with 1 day or more of exposure in either of the two cadmium exposed departments was flagged for sensitivity analyses to control for possible confounding by cadmium.

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Statistical Analysis

Standardized mortality ratio (SMR) analyses comparing the mortality experience of the cohort to that of several referent populations were conducted using the NIOSH Life Table Analysis System for Windows, LTAS.net [Schubauer-Berigan et al., 2011]. Person-time at risk began at the latest of the following dates: (i) 1 year after the first date of employment; (ii) the first day of employment 1940–1965; and (iii) the date the referent rate file began. Person-time ended at the earliest of the following dates: (i) the worker's date of death for the deceased members of the cohort; (ii) the date last observed for those lost to follow-up; and (iii) December 31, 2013. Person-time at risk was stratified by age and calendar period (in 5-year intervals) and multiplied by the corresponding rate in the reference population to generate expected numbers of deaths. The SMR was defined as the ratio of the observed to the expected number of deaths and were indirectly standardized based on age and calendar period. Reference rates were based on death rates for white males in the US population (1940–2011) for 92 cause-of-death categories [Robinson et al., 2006]. Because cancer and cardiovascular disease rates are lower in Idaho [CDC, 2016], and the smelter was located in Idaho and a large number of deaths occurred in Idaho (43%), we also considered death rates for the state of Idaho available for 119 cause-of-death categories (1960–2007). Multiple cause of death reference rates (1960–2011) that consider all causes listed on the death certificate were considered, especially for renal diseases and hypertension since these outcomes tend to appear on death certificates but not commonly as the underlying cause of death [Steenland et al., 1992]. Mortality from ALS was evaluated using underlying and multiple cause death rates for white males (1960–2009). For all rate files, the last calculated calendar-specific rate was used for all years after the last year of rate data.

Rate ratios (RR) were also calculated to internally compare the mortality experience of the cohort by exposure. For each outcome, the cohort was further stratified by cumulative lead exposure (0–<209 mg/m^3-days; 209–<757 mg/m^3-days; and 757+ mg/m^3-days) and Poisson regression was performed controlling for age and calendar period with the 5 year categories. Exposure cut-points were selected so that approximately equal numbers of deaths occurred within each stratum. Due to the long latency of cancer mortality, exposures were lagged by 10 years for cancer outcome analyses [Checkoway et al., 1990]. In all analyses, 95% confidence intervals (CIs) were calculated and for the RR analyses, a linear trend was performed by assigning the midpoint of the exposure categories and 1.5× the lower bound for the highest category. All analyses were also rerun excluding person-time with 1 day or more of exposure in two cadmium exposed departments to investigate possible confounding by cadmium. Results of this sensitivity analyses are presented in an on-line appendix (Appendix Tables S I and S II).

RESULTS

The cohort definition provided a study population of 1,990 white male hourly workers who contributed a total of 73,296 person-years at risk (Table I). By the end of the study follow-up period (December 31, 2013), 225 workers were alive (11%), 1,749 were deceased (88%), and only 16 (1%) were lost to follow-up. Analyses based on rate files beginning in 1960 included 53,175 person-years at risk after January 1st, 1960 and excluded 198 deaths prior to

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1960 and 10 workers with a date last observed prior to 1960. The 25 additional years of follow-up added 721 new deaths and cause of death information was available for over 97% of the known deaths.

Mortality results compared to the US (underlying and multiple cause) and Idaho (underlying only) populations are described in Table III for selected outcomes of interest. Table IV internally compares death rates across increasing strata of lead exposure.

There was a significant excess of lung cancer mortality (e.g., ID SMR = 1.94, CI: 1.64, 2.27); however, lung cancer rates did not increase with estimated cumulative lead exposure. In addition, there were non-significant excesses of both stomach and kidney cancer mortality, but neither showed a positive exposure-response relation (in fact, stomach cancer and lung cancer rates ratios decreased with estimated cumulative lead exposure).

Mortality from cardiovascular disease and the subcategory cerebrovascular disease were found to be significantly elevated when compared to the Idaho referent population; in internal analyses, rate ratios for cardiovascular disease and cerebrovascular disease increased with estimated cumulative lead exposure. Mortality from hypertension without heart disease was elevated, particularly compared to the Idaho referent population (10 deaths, SMR = 2.09, CI: 1.00, 3.84), and was in significant excess compared to the US referent population based on the multiple cause of death analysis (82 deaths, SMR = 1.34, CI: 1.06, 1.66); however, rate ratios for hypertension without heart disease did not increase with estimated cumulative lead exposure.

Renal disease was also more likely to be listed as a contributing cause on the death certificate with three underlying and 11 multiple-cause acute kidney disease deaths and 20 underlying and 64 multiple-cause chronic kidney disease deaths. Mortality from acute kidney disease was not in excess. Mortality from chronic kidney disease (multiple cause analysis) was not elevated compared to the US referent population; however, rate ratios for chronic kidney disease increased with estimated cumulative lead exposure. This association disappeared in the sensitivity analysis excluding cadmium-exposed person-time (Appendix Table S II).

Only three ALS deaths were observed in the cohort with one additional death identified using contributing causes of death. ALS mortality was not elevated and due to the small number of deaths, an exposure-response analysis could not be performed.

Several outcomes not of a priori interest were elevated in the cohort. Suicide mortality was elevated (US SMR = 1.68 CI: 1.18, 2.33) as was both accidental falls and transportation accidents (ID SMR = 1.72, CI: 1.04, 2.69; ID SMR = 1.18, CI: 0.82, 1.65; respectively). In addition, an excess of nonmalignant respiratory diseases was found (ID SMR = 1.29, CI: 1.11, 1.50), mostly due to the subcategory chronic obstructive pulmonary disease (COPD) (ID SMR = 1.43, CI: 1.18, 1.72) and pneumoconiosis and other respiratory diseases (ID SMR = 1.11 CI: 0.68, 1.72). However, neither nonmalignant respiratory diseases nor the subcategory COPD displayed a significant positive exposure-response, but pneumoconiosis and other respiratory diseases rates did increase with increasing exposure.

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DISCUSSION

Much of the research on the health effects of lead has historically focused on the acute effects of recent lead exposure, most notably cognitive impairment and acute kidney diseases. As lead exposure levels have declined, recent research has shifted focus to the longer-term, long-latency health effects from occupational exposure to lead [Schwartz and Hu, 2007].

In this update, using the new refined exposure assessment, analyses revealed significant positive trends in standardized rates for several causes of death. Specifically, increasing incremental levels of lead exposure were associated with higher rates of three a priori outcomes of interest: cardiovascular disease, cerebrovascular disease, and chronic kidney disease. Additionally, transportation accidents and pneumoconiosis and other respiratory diseases were found to be positively associated with increasing lead exposure.

The new refined exposure assessment also highlighted outcomes that had significantly higher overall rates when compared to the national and Idaho population rates but were not likely due to lead exposure. For example, there was a significant elevation of lung cancer deaths in this cohort, however, when lung cancer deaths were stratified by lead exposure, the exposure-response was found to be negative. Therefore, it is likely that the excess in lung cancer deaths observed is due to some potential confounder.

Potential confounders, such as arsenic, cadmium, and smoking were not controlled for in the previous follow-up of this study. Measurements taken during the NIOSH 1975 survey found that exposure to cadmium and arsenic were generally minor [Steenland et al., 1992], with the exception of two departments that were highly exposed to cadmium, one of which was a cadmium refinery. Sensitivity analyses removing person-time in these two cadmium departments did not change the results overall, with the exception of chronic kidney disease. Chronic kidney disease rates were no longer elevated and no longer increased with increasing exposure; however, RRs were elevated when compared to the lowest exposed referent group.

Smoking data on a sample of this cohort was collected for 173 of the 395 current workers in a cross-sectional survey conducted in May, 1976 where all departments were represented. An internal NIOSH reports indicate that at the time of the survey, 56.6% of the male workers were current smokers and 27.7% were former smokers. In comparison, the national male current smoking rate for 1974–1985 ranged between 33.5% and 43.4% [Fiore et al., 1989]. While no reliable smoking rates are available for Idaho for 1976, a 1985 population survey found Idaho to have the fourth lowest smoking rate in the US [Marcus et al., 1989]. The higher smoking rates of this cohort may explain some of the excess mortality figures from smoking-related causes of death, in particular the cancer outcomes, COPD and the cardiovascular diseases. Furthermore, the lack of a positive exposure response for the cancer outcomes and COPD indicates that excesses were for these outcomes were likely not due to lead exposure. In addition, while other studies have suggested a relationship between lead exposure and lung and stomach cancer, these findings were not consistent across studies [Steenland and Boffetta, 2000]. Also, reports by the DHHS [2007] and EPA [2006] based on

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comprehensive reviews of the body of scientific literature essentially arrived at the same conclusion that even though many studies have reported low to moderate elevations in lung cancer mortality, the results are susceptible to confounding by smoking and other occupational exposures.

The kidney cancer results are consistent with a meta-analysis that examined cancer mortality/morbidity among eight highly lead-exposed cohorts (combined RR = 1.01; CI: 0.72–1.42) [Steenland and Bofetta, 2000]. Few studies have supported a connection between lead exposure and kidney cancer, although two earlier case studies have observed renal tumors in workers with prolonged exposure to lead [Baker et al., 1980; Lilis, 1981].

Mortality from COPD was elevated when compared to both the national and Idaho rates; however, no trends in relation to levels of exposure were noted. Smoking is a significant risk factor for COPD, additionally, some of this cohort worked in underground mining prior to working at the smelter; underground mining is also a notable COPD risk factor [Selevan et al., 1985].

The kidney disease results are consistent with the significant body of research on lead nephrotoxicity, especially at high exposure levels in occupational settings [ATDSR, 2007]. Additionally, a study using population-based data reported increasing prevalence of chronic kidney disease with increasing blood lead levels (BLLs) in individuals with hypertension [Muntner et al., 2003].

Cardiovascular disease, hypertension, and cerebrovascular disease are also of particular interest because a cross-sectional population study found an exposure-response between lead and circulatory diseases [Lustberg and Silbergeld, 2002]. In adults, long-term exposure to lead has also been associated with an increased risk from hypertension and cerebrovascular disease, even at relatively low levels of lead exposure [Pirkle et al., 1985]. A meta-analysis of BLLs and blood pressure analyzing 31 diverse studies from a wide range of populations indicated mostly positive effects; blood lead was significantly associated with both higher systolic and diastolic blood pressure [Nawrot et al., 2002]. Similar results using meta-analysis were found by Schwartz [1995] and [Staessen et al., 1994]. This is consistent with our cardiovascular and cerebrovascular disease results, and to a lesser extent our hypertension without heart disease results where mortality was elevated but did not demonstrate an exposure response. However, it is possible these results are confounded by smoking.

ALS was found to be elevated in previous studies of lead exposed individuals [Kamel et al., 2002; Fang et al., 2009; Wang et al., 2014] with Wang [2009] noting an 81% increase in mortality. This cohort saw a slight excess in ALS deaths, however, due to the rarity of this outcome, this estimate was very imprecise.

While the previous follow-up also found excesses of accidents, the authors noted this was likely confounded by the high number of workers in the cohort who worked in the mining industry where accidents are more prevalent and not likely due to lead exposure. However, lead is a known neurotoxin and, in a population study, Min et al. [2012] found an association with blood lead and cadmium levels and balance dysfunction. In addition to an excess in

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accidents, an excess in suicides was observed in this update; however, this excess was not associated with an exposure response.

Lastly, in addition to the limitations stated above regarding lack of control for potential confounders, it is important to also note the lack of complete work history information for 159 individuals who were still employed when work histories were collected in 1975. This lack of complete information would result in potential exposure misclassification for these individuals. However, since the smelter ceased operation in 1982, at worst, exposure information is missing for 7 years for all 159 individuals resulting in 1,113 person-years of employment which would constitute less than 5% of all employed person-years.

In conclusion, this study observed an overall elevated mortality risk for the a priori causes of death of lung cancer, cardiovascular disease, cerebrovascular disease, and chronic kidney disease as well as for nonmalignant respiratory diseases, including COPD, accidental falls and transportation accidents. However, it is likely the excess in lung cancer, COPD and accidental falls were not due to lead exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE I

Lead Smelter Cohort Characteristics

Cohort size	1,990
Vital status (through12/31/2013)	
Deceased	1,749 (88%)
Alive	225 (11%)
Lost to follow-up	16 (1%)
Person years at risk (begin1/1/1940)	73,296
Year of birth, mean (range)	1916 (1867–1946)
Decade of first employment	
1900–1909	5 (<1%)
1910–1919	53 (3%)
1920–1929	162 (8%)
1930–1939	264 (13%)
1940–1949	873 (44%)
1950–1959	510 (26%)
1960–1969	123 (6%)
Duration of employment (years)	
1–<5	681 (34%)
5–<10	419 (21%)
10–<15	229 (12%)
15–<20	189 (9%)
20–<25	139 (7%)
25–<30	108 (5%)
30+	225 (11%)

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TABLE II

Lead Exposure Assessment

	NIOSH (1975)	OSHA sampling (1973–1980)		
Department	**Original lead exposure assessment**	**No. samples**	**No. unique job titles sampled**	**Average lead TWA (mg/m^3)[a]**
Sinter plant, Lurgi	High	13	6	2.34
Charge preparation	High	26	11	1.68
Blast furnace	High	23	8	1.25
Slag fuming furnace	High	21	8	0.68
Lead refinery	High	17	8	0.55
Cadmium refinery	High	4	2	0.49
Silver refinery	High	12	4	0.28
Materials recovery	High	7	2	0.10
Concentrator	Low	0	0	0.06[b]
Casting and loading	Low	9	3	0.06
Electric furnace (hard lead)	Low	0	0	0.06[b]
Quality control	Low	0	0	0.06[b]
Maintenance	High	11	4	0.06
Yard crew, labor pool, bull gang	Low	0	0	0.06[b]
Total		143	56	

[a] Samples were first averaged over each unique job title, then the job title averages were again averaged within each department.

[b] The concentrator, electric furnace, and quality control departments as well as the yard crew, labor pool, bull gang department were not sampled and so a value of 0.06 mg/m^3 was assigned since this was the average level sampled for the casting and loading department and these departments were previously grouped together in the low grouping.

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TABLE III

Mortality for the Lead Smelter Cohort Based on Underlying and Multiple Cause-of-death Referent Rates for Selected Causes of Death[a]

	US underlying cause		US multiple cause		Idaho underlying cause	
Cause of death	**OBS**	**SMR (95%CI)**	**OBS**	**SMR (95%CI)**	**OBS**	**SMR (95%CI)**
All causes	1749	1.11 (1.05, 1.16)	3702	1.02 (0.99, 1.06)	1551	1.23 (1.17, 1.29)
All cancers	387	1.09 (0.98, 1.20)	535	1.08 (0.99, 1.18)	355	1.29 (1.16, 1.43)
MN trachea, bronchus, lung	162	1.43 (1.22, 1.67)	162	1.37 (1.17, 1.60)	154	1.94 (1.64, 2.27)
MN stomach	19	1.29 (0.77, 2.01)	13	1.10 (0.59, 1.88)	12	1.31 (0.67, 2.28)
MN kidney	14	1.64 (0.89, 2.75)	11	1.17 (0.58, 2.09)	11	1.56 (0.78, 2.79)
Cardiovascular disease	782	1.02 (0.95, 1.09)	1573	0.97 (0.92, 1.02)	703	1.22 (1.13, 1.31)
Diseases of the heart	579	0.95 (0.87, 1.03)	1102	0.91 (0.86, 0.97)	515	1.16 (1.06, 1.26)
Ischemic heart disease	472	0.93 (0.85, 1.02)	609	0.88 (0.81, 0.95)	428	1.18 (1.07, 1.30)
Hypertension with heart disease	16	0.82 (0.47, 1.33)	14	0.80 (0.44, 1.35)	8	1.00 (0.43, 1.96)
Other diseases of the circulatory system	203	1.29 (1.12, 1.48)	471	1.14 (1.04, 1.25)	188	1.40 (1.20, 1.61)
Hypertension without heart disease	10	1.42 (0.68, 2.61)	82	1.34 (1.06, 1.66)	10	2.09 (1.00, 3.84)
Cerebrovascular disease	132	1.24 (1.03, 1.46)	189	1.07 (0.93, 1.24)	119	1.32 (1.10, 1.58)
Diseases of the respiratory system	191	1.41 (1.21, 1.62)	471	1.21 (1.10, 1.32)	175	1.29 (1.11, 1.50)
Chronic obstructive pulmonary disease	115	1.73 (1.43, 2.08)	219	1.40 (1.22, 1.60)	112	1.43 (1.18, 1.72)
Pneumoconiosis and other respiratory diseases	27	1.31 (0.86, 1.91)	109	1.16 (0.95, 1.40)	20	1.11 (0.68, 1.72)
Diseases of the genitourinary system	31	1.07 (0.73, 1.52)	110	0.94 (0.77, 1.13)	28	1.43 (0.95, 2.06)
Acute glomerulonephritis and renal failure	3	1.11 (0.23, 3.24)	11	0.72 (0.36, 1.28)	3	1.95 (0.40, 5.70)
Chronic and unspecified nephritis and renal failure	20	1.40 (0.85, 2.16)	64	1.10 (0.84, 1.40)	17	1.83 (1.06, 2.93)
Accidents	106	1.69 (1.39, 2.05)	135	1.63 (1.36, 1.93)	77	2.22 (1.75, 2.77)
Transportation accidents	49	1.73 (1.28, 2.29)	34	1.94 (1.34, 2.71)	34	1.18 (0.82, 1.65)
Accidental falls	25	2.05 (1.33, 3.03)	21	1.33 (0.82, 2.03)	19	1.72 (1.04, 2.69)
Violence	38	1.46 (1.03, 2.01)	32	1.57 (1.07, 2.21)	32	1.33 (0.91, 1.88)
Suicide	36	1.68 (1.18, 2.33)	30	1.83 (1.23, 2.61)	30	1.40 (0.95, 2.00)
Homicide	2	0.44 (0.05, 1.57)	2	0.50 (0.06, 1.80)	2	0.77 (0.09, 2.79)
Amyotrophic lateral sclerosis	3	1.22 (0.25, 3.58)	4	1.36 (0.37, 3.49)		NA

OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; MN, malignant neoplasm; NA, not available.

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[a] Referent rates based on data 1940–2011 for US underlying cause analyses (1960–2009 for ALS), 1960–2011 for US multiple cause analyses (1960–2009 for ALS1960), and 1960–2007 for Idaho underlying cause analyses. Person-time at risk and observed deaths enumerated for the cohort 1940–2013 for US underlying cause analyses (1960–2013 for ALS), 1960–2013 for US multiple cause analyses (1960–2013 for ALS), and 1960–2013 for Idaho underlying cause analyses.

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TABLE IV

Rate Ratios by Cumulative Lead Exposure for Selected Underlying Causes of Death (1940–2013) in the Lead Smelter Cohort

	Cumulative lead exposure (mg/m^3-days)						
	0–<209		209–<757		757+		Trend
Cause of death	**OBS**	**RR**	**OBS**	**RR (95%CI)**	**OBS**	**RR (95%CI)**	***P*-value**
All causes	578	1 (ref)	576	1.02 (0.91, 1.14)	595	1.14 (1.02, 1.28)	0.02
All cancers[a]	149	1 (ref)	130	1.05 (0.83, 1.33)	108	0.99 (0.77, 1.27)	0.90
MN trachea, bronchus, lung[a]	70	1 (ref)	49	0.85 (0.59, 1.22)	43	0.84 (0.58, 1.23)	0.39
MN stomach[a]	11	1 (ref)	5	0.65 (0.22, 1.91)	3	0.44 (0.12, 1.61)	0.21
MN kidney[a]	5	1 (ref)	6	1.57 (0.48, 5.20)	3	0.90 (0.21, 3.82)	0.87
Cardiovascular disease	241	1 (ref)	264	1.06 (0.89, 1.26)	276	1.19 (1.00, 1.42)	0.04
Diseases of the heart	178	1 (ref)	198	1.08 (0.88, 1.32)	203	1.20 (0.98, 1.46)	0.08
Ischemic heart disease	151	1 (ref)	156	1.02 (0.81, 1.27)	165	1.16 (0.93, 1.45)	0.17
Hypertension with heart disease	2	1 (ref)	7	2.37 (0.48, 11.6)	7	2.82 (0.58, 13.8)	0.24
Other diseases of the circulatory system	63	1 (ref)	67	1.00 (0.71, 1.41)	73	1.19 (0.84, 1.67)	0.28
Hypertension without heart disease[b]	32	1 (ref)	25	0.84 (0.50, 1.42)	25	0.93 (0.55, 1.58)	0.84
Cerebrovascular disease	37	1 (ref)	45	1.13 (0.73, 1.75)	50	1.38 (0.90, 2.12)	0.13
Diseases of the respiratory system	69	1 (ref)	55	0.82 (0.57, 1.17)	67	1.09 (0.78, 1.53)	0.48
Chronic obstructive pulmonary disease	51	1 (ref)	30	0.63 (0.40, 0.99)	34	0.78 (0.51, 1.21)	0.33
Pneumoconiosis and other respiratory diseases	7	1 (ref)	9	1.14 (0.42, 3.09)	11	1.54 (0.59, 4.02)	0.35
Diseases of the genitourinary system	9	1 (ref)	8	0.94 (0.36, 2.44)	14	1.76 (0.76, 4.09)	0.14
Acute glomerulonephritis and renal failure[b]	3	1 (ref)	4	1.48 (0.33, 6.68)	4	1.63 (0.36, 7.33)	0.55
Chronic and unspecified nephritis and renal failure[b]	19	1 (ref)	22	1.28 (0.69, 2.37)	23	1.43 (0.78, 2.63)	0.27
Accidents	39	1 (ref)	27	0.87 (0.53, 1.42)	40	1.39 (0.89, 2.17)	0.11
Transportation accidents	18	1 (ref)	13	0.96 (0.47, 1.98)	18	1.42 (0.74, 2.76)	0.26
Accidental falls	12	1 (ref)	6	0.45 (0.17, 1.21)	7	0.61 (0.24, 1.57)	0.36
Violence	11	1 (ref)	18	1.88 (0.88, 4.00)	9	1.04 (0.43, 2.52)	0.93
Suicide	10	1 (ref)	17	1.97 (0.90, 4.32)	9	1.14 (0.46, 2.82)	0.93

OBS, observed deaths; RR, rate ratio (reference: <209 mg/m^3-days of cumulative lead exposure); MN, malignant neoplasm; CI, confidence interval.

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[a] Cumulative exposure was lagged by10 years for cancer outcomes.

[b] Results for hypertension without heart disease, acute glomerulonephritis and renal failure (AKD), and chronic and unspecified nephritis and renal failure (CKD) consider all causes listed on the death certificate (i.e., a multiple cause of death analysis).