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Mortality and Occupational Lead Exposure by Industry Type: An Analysis of a UK Lead-Exposed Cohort with Blood Lead Levels, 1975-2011

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Abstract

Mortality and Occupational Lead Exposure by Industry Type: An Analysis of a UK Lead-Exposed Cohort with Blood Lead Levels, 1975-2011

By Jennifer Liu

BACKGROUND: In 2006, the International Agency for Research on Cancer (IARC) concluded that inorganic lead is probably carcinogenic. Since then, only a few occupational worker cohorts have further examined the association between inorganic lead exposure and cancer mortality. Worker cohorts represent a unique sector of exposed individuals that can be used to assess documented lead exposure and associations with disease outcomes of interest.

OBJECTIVE: We examined the mortality of a historic cohort of workers in Great Britain using industry-defined blood lead levels (BLLs), whereby mean BLLs in an industry were assigned to all workers in that industry. We compared our results to those of McElvenny et al. (2015), which is currently the only paper published on this cohort. McElvenny et al. conducted analyses by industry categories defined by expert opinion, as well as by individual maximum BLL.

METHODS: We analyzed associations between occupational lead exposure and all-cause/cause-specific mortality among 9122 workers with measured blood lead levels from 1975 to 1979, and follow-up through 2011. Along with descriptive statistics, trends in mortality using industry-defined lead exposure and individual maximum BLLs were examined using Cox regression.

RESULTS: Mean follow-up length among the 9122 study participants was 29.2 years and 3480 deaths occurred. No consistent positive trends were found for any cause of death using industry-defined exposure. For trend tests conducted using individual maximum BLL, there were significant positive trends between increasing lead exposure and all-cause mortality ($p=<0.0001$), chronic obstructive pulmonary disease ($p=0.02$), cerebrovascular disease ($p=0.04$), and ischemic heart disease ($p=0.03$), which were generally concordant with the trend test results from McElvenny et al. which also used individual maximum BLL.

CONCLUSION: Our results were concordant with McElvenny et al. in that we found no monotonic trends using an industry-wide assignment, but we did find positive trends for lead exposure based on individual maximum BLL in all-cause mortality, chronic obstructive pulmonary disease, stroke, and ischemic heart disease. Therefore, using individual maximum BLL may be a better metric of assessing lead exposure in this cohort rather than using an industry-focused analysis. Further work is required to clarify the resulting associations and the carcinogenicity of lead.

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Introduction

Background

Lead has a half-life of about 53,000 years in soil and is a very stable compound that frequently accumulates in the environment.[3] Its properties, resistance to corrosion, density, and a low melting point, make lead a historically common metal used in a wide variety of industrial and commercial settings. In 2006, lead metal consumption worldwide was evaluated at 8 million tons, mainly for production of lead-acid batteries (71%), pigments (12%), rolled extrusions (7%), munitions (6%), and cable sheathing (3%).[9] Today, most lead found in the ambient environment is inorganic, which is typically found in old paint, soil, and leaded gasoline exhaust.[2] While many regulations have been established in industrialized countries in the Western hemisphere to limit or reduce human exposure to lead within commercial production and workplace safety, an occurrence of lead persists in the general environment and thus risk of exposure and subsequent health consequences remain.

Human exposure to lead may occur via several routes of transmission. The most common ways people are exposed to lead are by breathing dust or fumes that have been contaminated with lead or by swallowing contaminated soil or materials that contain lead.[2] Lead in dust and soil are dispersed primarily though weathering and chipping of lead-based paint from buildings, bridges, and other structures.[1] Lead that is absorbed into the body and that is not excreted is stored in the following three areas: blood, mineralized tissues such as bones and teeth, and soft tissue (liver, kidneys, lungs, brain, spleen, muscles, and heart).[9] The elimination half-lives for inorganic lead in blood and bone are approximately 30 days and 27 years, respectively.[1] Analysis of blood lead is the most common and accurate method of assessing current lead exposure in the human body. Bone lead measurements can be used to indicate cumulative exposure; urinary lead

levels have been deemed the least reliable form of biomarker measurement.[14] In the United States, a blood lead level (BLL) over 5 μg/dL is considered an elevated blood lead level in adults by the National Institute of Occupational Safety and Health (NIOSH), however no safe blood lead level in children has been identified.[17] For adults in occupational settings, the Occupational Safety and Health Association (OSHA) has set lead standards intended to maintain workers' BLLs below 40 μg/dL. While there are no clear clinical normal levels for adult blood lead. BLLs above or at 50 μg/dL indicate required medical attention.[1]

In 2006, the International Agency for Research on Cancer (IARC) concluded that inorganic lead compounds were probably carcinogenic.[9] Based on brain, lung, and stomach cancer associations identified by the IARC, the IARC has deemed inorganic lead and its links to carcinogenicity as a major research priority of the agency. In vitro, lead has not been found to be genotoxic, but there is evidence that it can increase the mutagenicity of other mutagens.[16] Animal models have found that exposure to lead compounds can cause tumors in the brain, lung, and other organs. Human studies so far provide evidence for weak associations for inorganic lead exposure with lung, stomach cancer, and, to a lesser extent, kidney and brain cancers.[12]

The epidemiologic evidence to highlight the influence of lead on cancer mortality is not well established.[7] Most of the epidemiologic studies unfortunately do not have data on dose-response relationships that could provide a better basis for inference than comparisons of exposed to non-exposed.[17] Existing studies of cancer with well-documented high exposure to lead among lead-exposed workers, which are relatively few to date, have inconsistent findings for lung, brain, kidney, and stomach cancers due to a combination of limitations in these types of studies, including heterogeneity and possible confounding.[17] Worker populations are particularly

useful for studying the effects of lead since workers generally have blood lead concentrations several times higher than the average blood lead concentration in the general population. Most occupational studies are cohort studies of workers with presumed lead exposure due to working in jobs known to involve exposure. Other studies, however, have been based on cohorts formed from lead surveillance programs, with workers who have measured blood lead levels. Such cohorts have the advantage of documented internal measures of lead exposure, but the disadvantage is a lack of complete work history, and lack of blood levels over the course of lead exposure – often workers in these cohorts have only one or two blood tests.

Goals of present study

We have been given access to data from a cohort study of UK workers in a lead surveillance program, with documented blood lead levels. Motivation for this UK lead cohort study began in England in 1972 when Sir Brian Windeyer published results indicating an urgent need for an investigation of the long-term health effects of all workers in the lead-using industries. Consequently, in 1973, the Department of Employment/Medical Council Research Working Group approved a study designed to examine the associations between lead and cancer mortality among workers. In this study, blood lead data from 9,122 UK workers were collected between 1975 and 1985, and then the cohort was follow through 2011. Many of the participants had blood lead measured at multiple points across time. A paper by McElvenny et al., published in 2015, is the first ever published analysis of this cohort. In SMR analyses using the English population as a referent, they found an excess of lung cancer, ischemic heart disease (IHD) and cardiovascular disease, however risks were not clearly associated with increasing BLLs. In

internal analyses of 10 causes of deaths, these authors found significant increasing trends for all-cause mortality, circulatory disease, and IHD.

Since blood lead, even if it is measured at several time points, estimates only current lead exposure, McElvenny et al. conducted a separate analysis that assigned lead exposure based on presumed exposure by industry. Using this method, participants' blood lead levels were not considered. Instead, exposure levels were determined by industry expert judgement informed by information from the relevant IARC monographs and European CAREX (CARcinogen Exposure) database. Experts estimated the likely proportion exposed and level of exposure using BLLs and risk assess data from the HSE National Exposure database. The exposure classification was based on the categorization of the process and industry in which workers were classified as low, medium and high exposure; experts judged industries with high exposure as those with exposure likely to be greater than 50% of the occupational exposure limit (OEL) at the time the cohort was assembled or where there was substantial risk of lead ingestion or skin absorption.[13] Internal analyses by low, medium, and high exposure categories were presented in McElvenny et al. (2015) for 6 types of cancer and 4 other causes of death (all CVD, IHD, stroke, and kidney disease). The other causes are suspected to be associated with lead because lead has been shown to increase blood pressure.[12]

Analyses by industry, rather than individual blood lead levels for each worker, might have the advantage of better capturing a worker's relative ranking in terms of long-term lead exposure. Another way to measure lead exposure based on industry is to examine the blood lead levels of individuals within an industry to calculate the average blood lead level of that industry, rather than relying on expert judgement to determine the lead level in an industry. Although each individual's blood lead level represents lead exposure at a specific time point, an average of all

the blood lead levels within an industry at various times may better represent exposure a worker receives from working in a certain industry. This paper examined exposure by industry type, with each worker assigned observed mean of mean BLLs (or median of maximum BLLs) of workers in those industries as a potentially better marker of lead exposure. The aim of this analysis was to determine whether ranking industries by low to high levels of exposure risk, based on the mean workers' average or maximum blood lead levels who worked in that industry, might describe the relationship between lead exposure and all-cause/cause-specific mortality from cancers and other diseases of interest better than using individuals' blood lead measurements. Two main hypotheses were assessed in this analysis. First, using our method of categorizing industries by exposure level, workers in higher exposed industries were hypothesized to have higher mortality risk than workers in lower exposed industries, and second, these mortality risks might be stronger than mortality risks seen in prior analyses in McElvenny et al. where industries were categorized based on expert judgement.

Methods

Study Design & Population

Data were available for each participant's mean and maximum BLL in μg/dL and the number of available measurements on which the mean was based. As per the McElvenny et al. publication, mortality data was collected from the UK records through 2011. We grouped deaths into categories in concordance with the US NIOSH definitions with corresponding International Classification of Disease (ICD) 9 and 10 codes, which described the primary cause of death in participants who had died during the study. Causes of death from cancer which we analyzed had at least 10 deaths and included bladder, brain, breast, esophageal, kidney, larynx, leukemia, lung, non-Hodgkin's lymphoma, and stomach. Other causes of death examined included chronic kidney disease (CKD), cerebrovascular disease (CVA), ischemic heart disease (IHD), and chronic obstructive pulmonary disease (COPD). These disease outcomes were also examined by McElvenny et al. except for larynx cancer, breast cancer, leukemic, non-Hodgkin's disease, and COPD. Examined mortality outcomes for this analysis were chosen if they were possibly associated with lead in previous research and were defined using ICD codes that matched U.S. cause of death definitions as defined by NIOSH. Code summaries for the mortality outcomes of interest included the following: bladder cancer (ICD-10-C67, ICD-9-188), brain cancer (ICD-10-C71, ICD-9-191), breast cancer (ICD-10-C50, ICD-9-174), esophageal cancer (ICD-10-C15, ICD-9-150), Hodgkin's disease (ICD-9-201), ischemic heart disease (ICD-10-I25, I21, ICD-9-411), kidney cancer (ICD-10-C64, ICD-9-189), larynx cancer (ICD-10-C32, ICD-9-161), leukemia (ICD-10-C92, ICD-9-205), lung cancer (ICD-10-C34, ICD-9-162), multiple myeloma (ICD-10-C90, ICD-9-203), non-Hodgkin's lymphoma (ICD-10-C82, 83, 84, 85, ICD-9-202), pharynx (ICD-9-146, 149), and stomach cancer (ICD-10-C16, ICD-9-151), chronic kidney

disease (ICD-10-N18, ICD-9-586), cerebrovascular disease ICD-10-C71, ICD-9-191, chronic obstructive pulmonary disease (ICD-10-J44, ICD-9-491,492, 496).

Industry types were classified as per McElvenny et al. using International Standard Industrial Classification (ISIC) codes for 19 EU countries. These ISIC codes described the industry sector each participant was working in at the time of recruitment into the study. UK industries with occupational lead exposure were classified as follows: badge and jewelry enameling and other vitreous enameling operations, demolition and scrap industries, glass making, lead battery, manufacture of inorganic or organic lead compounds (including lead salts of fatty acids), manufacture of pigments and colors, painting buildings and vehicles, pottery and glazes, shipbuilding repairing and breaking, smelting, refining, alloying, casting, working with metallic lead and lead containing alloys, and other processes.

Exposure classification was based on creating and categorizing industry lead exposure based on individuals' BLL measurements. All study participants had at least one BLL measurement during 1975 through 1979. Furthermore, all participants had an average BLL and a maximum BLL measurement, therefore individuals who only had a single measurement (40% of the UK cohort), the average and maximum BLLs were the same. The average blood lead in each industry for using either mean BLLs or the median of maximum individual BLLs, across all workers in an industry, were then calculated. Based on the mean (or maximum) blood lead per industry, each individual was then assigned their mean of mean (or median of maximum) industry level, and industries were classified for categorical analyses into as follows: low (<40 μg/dL), medium (40-49 μg/dL), and high ($\geq$50 μg/dL). For example, an individual who may have had an average BLL of 20 μg/dL, and worked in an industry with an average BLL was 42

μg/dL, would be assigned to the medium industry exposure category. Three-category BLL-defined industry groups were initially used based on the OSHA guidelines. We also conducted additional analyses based on four groups (<32, 32-38, 39-52, 53+ μg/dL); these cut-points were chosen so as to try to include approximately similar numbers of workers in each group.

Statistical Analysis

Cox regression models were used for internal analyses to assess whether those working in higher lead-exposed industries were at a higher mortality risk compared to those working in lower lead-exposed industries. Only study participants with information on their industry type were included in our analyses using industry-defined exposure categories, with 7657 individuals 85% of total eligible cohort) remaining. These individuals were included in analyses which had exposure levels assigned from industry averages. A model was run for each mortality outcome. Models used cause-specific mortality as the outcome, and BLL-defined industry categories (either 3 or 4 levels) as exposure, and adjusted for birth year decade and sex. Follow-up time was used as the time-scale. Time for each person began the date of their first BLL test and time ended for each person at either their date of death, date of emigration, or last day of follow-up (December 31st, 2011), whichever occurred first. Proportional hazard assumptions (via a follow-up time*industry group interactive term) were tested and found not to be violated. In addition, Cox models using the natural log of individual maximum BLLs, as either continuous (trend test) or categorical exposure variables rather than industry-defined BLLs, were also conducted to compare whether industry-defined BLL hazard ratios were similar to analyses using individual BLLs; these analyses used four categories of maximum BLL to categories workers, <20, 20-29,

30-39 40+ μg/dL. McElvenny et al. also conducted trend tests using continuous individual maximum BLL, albeit for fewer categories than our study included.

Additional survival models with nine dummy variables representing ten different industry types were ran to further examine whether any industry had higher mortality risk regardless of BLLs; the referent group for these models was assigned to the industry type that contained the lowest average mean BLL: "Badge and jewelry enameling and other vitreous enameling operations".

Further descriptive analyses were conducted to examine the proportion of those workers whose individual BLLs matched their assigned industry-defined BLL group. For these analyses, three-category BLL-defined industry groups (<40 μg/dL,40-49 μg/dL, ≥50 μg/dL) were used to assess variability of average of mean BLL and median of maximum BLL measurements.

Trend tests for all analyses were conducted to examine monotonic or quasi-monotonic positive trends between increasing lead exposure and mortality by disease outcomes of interest. P-values for trend with continuous natural log (ln) of blood lead levels were calculated. For industry-assigned analyses, a continuous blood level was assigned to each industry category using the weighted average of mean BLL in each industry type; the weighted averages were logged for trend tests. For analyses based on individual maximum BLL, the natural log of maximum BLL for each individual was used as a continuous variable.

Results

There were 9122 workers eligible for this study, based on the cohort assembled by McElvenny et al. There was a total of 267,028 number of person years contributing to the mortality analyses. All participants in the cohort had a documented birth year, however 14 individuals (0.2%) did not have available information on their day and month of birth; these individuals were kept in the cohort and included in our analyses. **Table 1** is taken from McElvenny et al. and highlights descriptive characteristics of the 9122 individuals included in the study. The average age at the start of follow-up in 1975 was 35.2 years of age (SD=13.6 years). Around half of the cohort (46%) was born before 1940, the other half (52.8%) was born between 1940 and 1959, and only 1.2% of participants were born after 1960. There were a total of 7657 participants with documented industry information who were included in the cox regression analyses using industry-defined exposure categories; 1465 workers were missing industry information. Nearly 40% of the entire cohort died during the study period, and half of those participants (50%) who died had developed at least one of the disease outcomes of interest. Only 104 individuals out of the cohort emigrated outside of the UK during the study.

Table 2, also from McElvenny et al., presents participant BLL information collected from all 9122 participants. Around 40% of the cohort (39.6%) had a single BLL measurement, 38.7% had 2-5 measurements, and less than 5% of the cohort had 10 or more. The overall mean BLL was 44.3 μg/dL and the mean maximum BLL was 52.6 μg/dL. A Pearson's correlation coefficient of 0.87 ($p<0.0001$) indicated that the mean and maximum BLLs were highly correlated.

Table 3 shows average values that were calculated for mean BLLs (mean of means) and median values for maximum BLLs for each industry type. Mean of mean BLLs were highly

positively skewed, with a larger range of measurement values due to increased number of outliers. Therefore, the median of maximum BLLs were presented in **Table 3**. The three most common industry types among cohort members were pottery, glazes, and vehicles (1315 participants), lead battery industry (1059 participants), and other processes (1054 participants).

Our own analyses of these data are presented in **Tables 4-7**. The distribution of deaths by type of death and industry can be seen in **Table 4**. Industries with the highest proportion of deaths during the study included smelting, refining, alloying, and casting (44.7%), manufacture of pigments and colours (42.3%), and other processes (41.9%). Glass making had the lowest proportion of deaths (28.3%). Disease groups with the highest number of deaths were IHD (737 individuals), lung cancer (330 individuals), CKA (213 individuals) and COPD (186 individuals). The following disease groups had 10 or less worker deaths during the study: pharynx cancer (2 individual), multiple myeloma (5 individuals), and Hodgkin's disease (1 individual); these disease groups were not included in our analyses.

The results of the mortality analyses using the BLL-defined industry categories and individual maximum BLL measurements are presented in **Table 5**. Analyses using log of maximum individual blood lead were also conducted in McElvenny et al., although we analyzed more causes of death than did McElvenny et al. The number of study participants used for our analyses using industry-defined exposure categories was confined to participants who had information on industry type 7657, while all 9122 eligible study participants were used in analyses using individual maximum BLLs in McElvenny et al. The hazard ratios and their associated p-values for our survival analyses based on either three or four different exposure categories are shown: BLL-defined industry categories using mean of mean BLLs, BLL-defined

industry categories using median of maximum BLLs (both in **Table 5a**), and individual maximum BLLs (**Table 5b**). The only significantly ($p<0.05$) raised hazard ratios (HR) from all three analyses (industry categories using mean of mean BLL, industry categories using median of maximum BLL, and individual maximum BLL) for specific causes were in kidney cancer and stomach cancer, but we found no consistent trends for these cancers of higher risk with higher exposure, regardless of the exposure metric.

P-values for trend tests that were significant for industry-assigned median of maximum BLL all-cause mortality ($p=0.04$) and chronic kidney disease ($p=0.04$) had negative effect estimates (protective trend). For trend tests conducted using individual maximum BLL, there were significant positive trends between increasing lead exposure and all-cause mortality ($p=<0.0001$), chronic obstructive pulmonary disease ($p=0.02$), cerebrovascular disease ($p=0.04$), and ischemic heart disease ($p=0.03$).

Table 6 presents a summary of the results from models using each industry type as a categorical variable (a model with 10 industries versus the referent industry, which was badge and jewelry enameling) to highlight certain industries that may be associated with specific disease outcomes. Significant associations were found in a few industries for all-cause mortality, chronic kidney disease (CKD), kidney cancer, larynx cancer, and stomach cancer, but no specific industries were identified as consistently having elevations across a number of causes.

Table 7 shows the discrepancies of participants assigned to their industry categories based on mean or maximum BLLs using 3-category groups (low, medium, high industries). For mean BLLs, 70% of individuals were correctly assigned into the low-exposed industry group, only 17% for the medium-exposed group, and 59% for the high-exposed group. Similarly, for

maximum BLLs, 59% of individuals were correctly assigned into the low-exposed industry group, only 15% for the medium-exposed group, and 67% for the high-exposed group.

Discussion

Our hypothesis initially stated that lead exposure defined by average lead exposure of all people within an industry (mean of mean or median of maximum BLLs) would represent a better marker of lead exposure than ranking individuals by their individual lead levels. However, our industry-defined lead level results did not show any significant positive trends, while individual-defined lead results showed overall strong associations for several causes of death. Regardless of whether industry mean of mean BLLs or median of maximum BLLs were used to define 3-level or 4-level industry categories as our exposure, the industry-wide analysis results yielded mostly null associations between mortality and our BLL-defined industry groups. A small number of significant elevated results for industry categories which did occur, were not found in the highest industry category, and might not have been expected given the large number of comparison we conducted. The relatively null results using industry-assignment did not differ much from the prior largely null results using industry categorizations presented for 10 causes of death in McElvenny et al., in which industries were grouped in high, medium, and low based on expert opinion. It cannot be determined from McElvenny et al. which industries were classified into which categories and therefore we cannot determine whether our method of classifying industry and referent (low, medium, high) corresponded with that of McElvenny et al. On the other hand, using individual blood lead levels like in McElvenny et al., we found significant positive trends for IHD, COPD, stroke, and all-cause mortality; McElvenny's results using trend tests with individual maximum BLLs were similar in this regard for IHD and stroke (they did not analyze all-cause mortality or COPD in internal analyses).

As mentioned before, there is currently insufficient evidence to make conclusions about the associations between lead and cancer since many studies have mixed results. Since the IARC

monograph was published in 2006 and highlighted the potential carcinogenicity of inorganic lead, only a few occupational studies have been conducted since then, including McElvenny et al. (2015), Gwini et al. (2012), and Liao et al. (2016). With less than 200 cancer deaths total, Gwini et al. had a population size that was too small to be informative.[6] Liao et al. studied cancer incidence among approximately 7000 lead-exposed men and women workers in two plans in Shanghai, comparing them to a large number of unexposed workers, and using a job-exposure matrix to classify workers into non, low, medium, and high exposure to either lead dust or fumes. Overall, Liao et al. found suggestions of excess among exposed versus non-exposed groups for brain cancer (Risk Ratio (RR)=1.8, 10 exposed cases), kidney cancer (RR 1.4, 17 exposed cases).[10] Borderline significant excess were found in high-exposed males only for lung and stomach cancer.[10] These findings were generally concordant with IARC's 2006 finding of lead to be a probably carcinogen based on lung, stomach, kidney, and brain cancer. On the contrary as noted, McElvenny et al. found no significant positive trends for cancer.

Overall, categorizing lead exposure into industry-defined groups based on observed individuals blood lead levels did not show any positive trends, while using individual blood lead levels did show positive trends. If individual lead exposure contains less misclassification than industry means assigned to all individuals in those industries, and lead is truly associated with mortality, then individual lead exposure may show an association with mortality when assigning industry-based average to individuals does not. The results from our discrepancy table highlighted the large number of people with discrepancy between their individual level and their assigned levels based on industry means, which was an expected result since our initial hypothesis assumed that individual blood lead would not necessarily reflect the mean of industry where they work. Results from our regression analyses and trend tests could not support the

prediction that industry means would classify study participants better than individual BLLs, based on the assumption that individual BLL might not reflect a participants' overall industry.

Limitations

A BLL just measures lead as a single category of exposure, and does not account for various types or forms of lead exposure. Rousseau et al. found that the category labeled "inorganic lead" is comprised of six different compounds of lead exposure resulting in a heterogeneous group of lead forms.[13] Therefore, it is difficult to evaluate the human carcinogenicity of lead given there is little to no epidemiologic evidence available for individuals forms.[13] Associations that we did find in COPD, IHD, and stroke may be due to lead exposure, but could also be due to alternative explanations such as other dust associated with lead exposure, tobacco smoking, or other co-exposures to carcinogens. Information on other potentially important confounders were also lacking in this study, including history of tobacco smoking, race, dietary habits, family history of disease, and other risk factors. McElvenny et al. tried to address the data deficits in a feasibility study, however it was found that it was not possible to extend occupational histories or to add data on smoking to this cohort in the future.[11]

The data did not provide a complete job history for its participants. Individuals in the cohort were assigned to their industry type based on the industry he or she was working in at the time of blood lead testing. Since industry was based on a single process category, our data analyses could not account for two things: 1. the length of time spent in an individual's assigned industry, 2. if in individual had moved to different industries that may have had high or lower exposure levels. It is likely that some participants in the cohort may have changed jobs between the years of 1975 and 2011. For example, a supervisory staff member may be less likely to be exposed to

high levels of lead when compared to a worker who physically removed lead paint and burns lead painted material. Furthermore, this analysis could not account for the differing processes by which workers were exposed. This uncertainty in individuals changing within or among industries could also partially account for why individuals' BLLs did not match their industry-defined lead category. Although there was data on processing operations to describe the specific processes by which individuals were exposed, the data was limited and was missing for over half of the cohort (%) and not useful for this analysis.[11] However, it may be useful for future studies to examine how the processing operation of an individual may affect their exposure level within their assigned industry. While the discrepancy table results from this paper showed that a large proportion of individuals did not "fit" into their assigned BLL-defined industry category for either mean or median, the focus of this analysis was to examine how general industry categories may be a better at assessing associations of cancer and lead than individual BLLs.

This study was limited by having incomplete BLL measurements. Instead of having data on each individual measurement, data was only provided in summary measures. Furthermore, the cohort did not have any data available on the analytical and quality control methods used to collect BLLs and measurements. For example, there was no information on the number of participating laboratories or varying methods of sample processing. While the study is limited by incomplete BLL information, the BLL measurements represent a much better metric of determining exposure levels between workers and industries than job titles alone. Generalizability of the study in recent times may also important to consider. Since lead exposure in this study represents exposure in the 1970s 1980's, it would be expected that if this study were repeated today then associations with mortality risk would be the same but there may be fewer

highly exposed participants. However, the overall decrease in BLLs in the general would not be expected to decrease the association between lead and mortality.

Conclusion

While there were a number of limitations in this study, the major strengths included size, long follow-up, and its BLL measurement data were measured and not modeled/estimated. Furthermore, this study assessed industry-level exposure using an arguably less subjective approach of categorizing industry-specific exposure levels (assigning the mean of each industry to all those in the industry) than the prior study by McElvenny et al., where classification of industries as low, medium, and high was based on expert opinion. However, we found no trend using our industry-wide assignment, similar to the null results for McElvenny using expert opinion. The fact that we did find monotonic trends for lead exposure based on individual maximum BLL in all-cause mortality, chronic obstructive pulmonary disease, stroke, and ischemic heart disease, but no such trends using our method of assigning industry-specific means to all works in specific industries, indicates that our hypothesized improvement did not occur.

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Table 1. Description of Participants, N=9122

Characteristic	Number (%)
Age at start of follow-up, mean (SD)	36.5 (13.4)
Sex	
Male	7770 (85.2)
Female	1352 (14.8)
Year of Birth	
Before 1920	903 (9.9)
1920-1929	1528 (16.8)
1930-1939	1760 (19.3)
1940-1949	2262 (24.8)
1950-1959	2557 (28.0)
1960-1969	112 (1.2)
Total industry workers in cohort	7657 (84.0)
Total participant deaths during study	3480 (38.2)
Participants who developed disease outcomes	1723 (19.0)

Table 2. Description of participant Blood Lead Level (BLL) information

Characteristic	Number (%)
Number of BLL measurements	
1	3611 (39.6)
2	1447 (15.9)
3	939 (10.3)
4	634 (7.0)
5	501 (5.5)
6-10	1401 (15.4)
11-15	421 (4.6)
16-20	109 (1.2)
21+	59 (0.6)
Total number of measurements	9122
Average number of measurements, mean (SD)	3.7 (4.0)
Mean BLL (µg/dL), mean (SD) range	44.3 (22.7) 2.3-321.5
Maximum BLL (µg/dL), mean (SD) range	52.6 (32.9) 2.1-707.9

Table 3. Mean and maximum BLLs by industry type

Industry	Total in industry	Mean of mean BLLs (µg/dL)	Median of maximum BLLs (µg/dL)
Badge and jewelry enameling and other vitreous enameling operations	479	29.1	29.0
Demolition and scrap industries	808	53.6	55.9
Glass making	212	34.8	30.0
Lead battery industry	1059	54.9	67.8
Manufacture of inorganic or organic lead compounds (including lead salts of fatty acids)	102	39.6	46.3
Manufacture of pigments and colors	971	40.3	53.0
Painting buildings and vehicles	167	31.5	35.9
Pottery, glazes, and transfers	1315	36.7	46.0
Shipbuilding, repairing and breaking	279	60.3	72.0
Smelting, refining, alloying, casting	935	56.7	66.9
Work with metallic lead and lead containing alloys	276	47.1	52.1
Other processes	1054	36.4	39.3
Missing	1465		

Table 4. Distribution of deaths by type of death and industry

Industry	Total in industry	Total number of deaths (%)	Disease Group																
			Bladder Cancer	Brain Cancer	Breast Cancer**	CKD	CKA	EC	Hodgkins Disease*	IHD	Kidney Cancer	Larynx Cancer**	Leukemia**	Lung Cancer	Multiple Myeloma*	NHL**	Pharynx Cancer*	Stomach Cancer	COPD**
Badge and jewelry enameling and other vitreous enameling operations	479	164 (34.2)	0	3	3	1	12	3	0	34	2	0	2	19	0	1	0	3	11
Demolition and scrap industries	808	317 (39.2)	2	1	0	4	19	5	0	81	3	1	2	44	0	1	0	3	20
Glass making	212	60 (28.3)	0	2	2	0	3	0	0	10	0	1	0	10	1	0	0	1	6
Lead battery industry	1059	326 (30.8)	1	2	3	0	22	7	0	84	3	1	1	33	1	3	0	4	22
Manufacture of inorganic or organic lead compounds	102	36 (35.3)	1	0	0	0	3	0	0	6	0	0	1	5	0	0	0	0	1
Manufacture of pigments and colours	971	411 (42.3)	4	4	1	2	32	8	0	104	5	2	1	43	0	2	0	7	22
Painting buildings and vehicles	167	66 (39.5)	0	1	0	2	5	1	0	17	1	1	1	4	0	0	0	1	2
Pottery, glazes, and transfers	1315	470 (35.7)	6	0	10	1	40	4	0	110	5	0	1	48	1	2	0	13	38
Shipbuilding, repairing and breaking	279	115 (41.2)	0	0	0	0	7	0	0	35	0	0	0	13	0	0	0	2	3
Smelting, refining, alloying, casting	935	418 (44.7)	4	3	1	1	30	8	0	100	7	5	2	46	1	1	1	11	24
Work with metallic lead and lead containing alloys	276	107 (38.8)	1	0	0	2	9	2	0	27	2	0	0	10	0	1	0	0	9
Other processes	1054	442 (41.9)	8	3	2	3	31	5	0	129	1	1	6	55	0	4	0	7	28
Missing	1465	1465	5	4	2	1	39	8	1	132	2	2	5	63	1	4	1	6	38
Total	9122	3480	32	23	24	17	252	51	1	869	31	14	22	393	5	19	2	58	224

Abbreviations: CKD: chronic kidney disease, CKA disease: cerebrovascular disease, EC: esophageal cancer, IHD: ischemic heart disease, NHL: non-Hodgkin's lymphoma, COPD: chronic obstructive pulmonary disease

* Diseases with less 5 or less deaths and not analyzed

**Diseases that were not included in regression analyses in McElvenny et al.

Table 5a. Cox regression analysis for disease outcomes of interest using industry-defined lead categories

	Industry Categories: Mean of Mean BLL (µg/dL)											Industry Categories: Median of Max BLL (µg/dL)									
		3-Category Group <40, 40-49, >50					4-Category Group <32, 32-38, 39-52,53+					3-Category Group <40, 40-49, >50					4-Category Group <32, 32-45, 46-60, 61+				
Disease Group	Events	Groups	P-value	HR	95% CI Lower-Upper	Trend test p-value	Groups	P-value	HR	95% CI Lower-Upper	Trend test p-value	Groups	P-value	HR	95% CI Lower-Upper	Trend test p-value	Groups	P-value	HR	95% CI Lower-Upper	Trend test p-value
All-Cause Mortality	2490	Med vs Low	0.1295	1.08	0.98-1.19	0.2602	Mid-Low vs Low	0.4345	0.96	0.86-1.06	0.0740	Med vs Low	0.1107	1.08	0.98 - 1.19	0.2676	Mid-Low vs Low	0.3846	1.04	0.95-1.13	0.0431
		High vs Low	0.8324	1.01	0.93-1.09		Mid-High vs Low	0.1872	1.07	0.97-1.18		High vs Low	0.7953	1.01	0.93-1.09		Mid-High vs Low	0.8736	1.01	0.90-1.13	
							High vs Low	0.9805	1.00	0.92-1.08							High vs Low	0.8056	0.99	0.91-1.08	
Bladder Cancer	19	Med vs Low	0.7962	0.88	0.33-2.37	0.2200	Mid-Low vs Low	0.8694	1.09	0.40-2.96	0.4744	Med vs Low	0.9476	1.03	0.41-2.62	0.2829	Mid-Low vs Low	0.6210	1.23	0.55-2.76	0.4984
		High vs Low	0.128	0.51	0.21-1.22		Mid-High vs Low	0.9138	1.06	0.40-2.79		High vs Low	0.1539	0.53	0.22-1.27		Mid-High vs Low	0.5916	0.71	0.20-2.50	
							High vs Low	0.1891	0.54	0.21-1.36							High vs Low	0.2418	0.54	0.19-1.52	
Brain Cancer	16	Med vs Low	0.9203	1.06	0.34-3.26	0.2820	Mid-Low vs Low	0.3279	0.47	0.10-2.14	0.1103	Med vs Low	0.9366	0.96	0.31-2.95	0.2716	Mid-Low vs Low	0.1969	0.48	0.16-1.47	0.0952
		High vs Low	0.3333	0.62	0.23-1.64		Mid-High vs Low	0.7353	0.82	0.26-2.58		High vs Low	0.3091	0.60	0.23-1.60		Mid-High vs Low	0.1420	0.22	0.03-1.67	
							High vs Low	0.1971	0.52	0.19-1.74							High vs Low	0.2243	0.53	0.19-1.48	
Breast Cancer	20	Med vs Low	0.7159	0.69	0.09-5.19	0.5416	Mid-Low vs Low	0.5819	1.30	0.51-3.31	0.3868	Med vs Low	0.4149	1.66	0.09-5.08	0.5467	Mid-Low vs Low	0.8933	1.06	0.44-2.57	0.5034
		High vs Low	0.4973	1.46	0.49-4.34		Mid-High vs Low	0.8237	0.79	0.09-6.46		High vs Low	0.8446	0.89	0.49-4.33		Mid-High vs Low	0.9926	0.00	0.00	
							High vs Low	0.3993	1.70	0.49-5.87							High vs Low	0.4640	1.56	0.47-5.12	
Esophageal Cancer	38	Med vs Low	0.1348	1.79	0.83-3.85	0.6521	Mid-Low vs Low	0.2513	0.52	0.17-1.59	0.9910	Med vs Low	0.2178	1.62	0.75-3.48	0.7207	Mid-Low vs Low	0.8649	1.07	0.51-2.24	0.4775
		High vs Low	0.2966	1.40	0.75-2.62		Mid-High vs Low	0.3951	1.41	0.64-3.08		High vs Low	0.3325	1.37	0.73-2.56		Mid-High vs Low	0.7636	1.15	0.47-2.78	

							High vs Low	0.6062	1.19	0.62-2.28						High vs Low	0.4915	1.28	0.64-2.57	
Kidney Cancer	28	Med vs Low	0.0574	2.57	0.97-6.81	0.8845	Mid-Low vs Low	0.4479	1.61	0.47-5.48	0.9169	Med vs Low	0.0851	2.36	0.89-6.25	0.9385	Mid-Low vs Low	0.1128	2.28	0.82-6.32	0.9248
		High vs Low	0.1167	1.95	0.85-4.51		Mid-High vs Low	0.0675	2.78	0.93-8.34		High vs Low	0.1281	1.92	0.83-4.43		Mid-High vs Low	0.1297	2.53	0.76-8.37	
							High vs Low	0.1012	2.26	0.85-6.01							High vs Low	0.0837	2.46	0.89-6.80	
Larynx Cancer	11	Med vs Low	0.6891	1.40	0.27-7.35	0.3577	Mid-Low vs Low	0.6364	0.58	0.06-5.45	0.4701	Med vs Low	0.7816	1.26	0.24-6.63	0.3778	Mid-Low vs Low	0.5338	0.59	0.11-3.08	0.5045
		High vs Low	0.266	1.95	0.60-6.30		Mid-High vs Low	0.8958	1.12	0.20-6.16		High vs Low	0.2849	1.90	0.59-6.15		Mid-High vs Low	0.5912	0.55	0.06-4.78	
							High vs Low	0.4093	1.69	0.49-5.82							High vs Low	0.4176	1.64	0.50-5.42	
Leukemia	11	Med vs Low	0.1532	0.23	0.03-1.73	0.5867	Mid-Low vs Low	0.065	0.15	0.02-1.13	0.3839	Med vs Low	0.2769	0.44	0.10-1.94	0.7539	Mid-Low vs Low	0.0610	0.30	0.09-1.06	0.3013
		High vs Low	0.1058	0.43	1.16-1.19		Mid-High vs Low	0.1459	0.33	0.07-1.47		High vs Low	0.1291	0.45	0.16-1.26		Mid-High vs Low	0.2386	0.41	0.09-1.81	
							High vs Low	0.0414	0.34	0.21-0.96							High vs Low	0.0524	0.29	0.08-1.01	
Lung Cancer	275	Med vs Low	0.636	0.93	0.68-1.26	0.7946	Mid-Low vs Low	0.8794	0.98	0.71-1.34	0.7406	Med vs Low	0.7461	0.95	0.71-1.28	0.8351	Mid-Low vs Low	0.6642	0.95	0.73-1.22	0.2637
		High vs Low	0.838	0.98	0.78-1.22		Mid-High vs Low	0.7243	0.95	0.70-1.29		High vs Low	0.8716	0.98	0.79-1.23		Mid-High vs Low	0.8259	1.04	0.76-1.42	
							High vs Low	0.8383	0.98	0.77-1.24							High vs Low	0.3736	0.89	0.68-1.15	
Stomach Cancer	45	Med vs Low	0.5516	0.78	0.34-1.78	0.2332	Mid-Low vs Low	0.0395	2.15	1.04-4.44	0.2381	Med vs Low	0.4195	0.71	0.31-1.63	0.1930	Mid-Low vs Low	0.1084	1.69	0.89-3.21	0.6529
		High vs Low	0.8073	0.93	0.53-1.65		Mid-High vs Low	0.8452	0.92	0.38-2.21		High vs Low	0.7486	0.91	0.51-1.62		Mid-High vs Low	0.2541	0.49	0.14-1.67	
							High vs Low	0.6321	1.17	0.61-2.24							High vs Low	0.3841	1.34	0.69-2.62	
COPD	158	Med vs Low	0.7178	0.93	0.62-1.68	0.1932	Mid-Low vs Low	0.7242	1.07	0.74-1.55	0.2076	Med vs Low	0.5682	0.89	0.60-1.32	0.1604	Mid-Low vs Low	0.7722	1.05	0.75-1.46	0.2285
		High vs Low	0.3377	0.86	0.64-1.17		Mid-High vs Low	0.9321	1.02	0.68-1.54		High vs Low	0.3046	0.85	0.63-1.16		Mid-High vs Low	0.7781	1.06	0.70-1.63	
							High vs Low	0.8884	0.98	0.71-1.35							High vs Low	0.4146	0.86	0.61-1.23	
CKD	13	Med vs Low	0.3521	1.79	0.53-6.08	0.3704	Mid-Low vs Low	0.2792	0.31	0.04-2.61	0.1361	Med vs Low	0.4149	1.66	0.49-5.67	0.3404	Mid-Low vs Low	0.4617	0.60	0.15-2.35	2., 0.0416

		High vs Low	0.8678	0.91	0.29-2.85		Mid-High vs Low	0.6308	1.36	0.69-4.67		High vs Low	0.8446	0.89	0.28-2.80		Mid-High vs Low	0.0701	2.78	0.91-8.45	
							High vs Low	0.5874	0.73	0.23-2.31							High vs Low	0.1318	0.20	0.02-1.62	
CVA Disease	182	Med vs Low	0.2756	1.22	0.85-1.75	0.5238	Mid-Low vs Low	0.9414	0.99	0.67-1.44	0.4688	Med vs Low	0.2144	1.25	0.88-1.77	0.5670	Mid-Low vs Low	0.3644	1.15	0.84-1.57	0.3488
		High vs Low	0.828	0.97	0.73-1.29		Mid-High vs Low	0.242	1.24	0.86-1.79		High vs Low	0.8790	0.98	0.73-1.31		Mid-High vs Low	0.8458	1.04	0.68-1.60	
							High vs Low	0.8664	0.97	0.72-1.33							High vs Low	0.9268	0.99	0.71-1.37	
IHD	608	Med vs Low	0.6557	1.05	0.86-1.27	0.9402	Mid-Low vs Low	0.548	0.94	0.75-1.16	0.6316	Med vs Low	0.8645	1.02	0.84-1.24	0.8610	Mid-Low vs Low	0.8034	1.02	0.86-1.21	0.7010
		High vs Low	0.9807	1.00	0.86-1.16		Mid-High vs Low	0.9983	1.00	0.82-1.22		High vs Low	0.9514	1.00	0.86-1.16		Mid-High vs Low	0.8899	0.99	0.79-1.23	
							High vs Low	0.7929	0.98	0.83-1.15							High vs Low	0.9037	0.99	0.83-1.18	
NHL	11	Med vs Low	0.9933	1.01	0.28-3.65	0.8961	Mid-Low vs Low	0.4116	0.52	0.11-2.50	0.9939	Med vs Low	0.8864	0.91	0.25-3.31	0.934	Mid-Low vs Low	0.5230	0.68	0.21-2.22	0.7964
		High vs Low	0.4796	0.68	0.23-1.99		Mid-High vs Low	0.7333	0.80	0.21-2.95		High vs Low	0.4532	0.66	0.23-1.94		Mid-High vs Low	0.5825	0.65	0.14-3.03	
							High vs Low	0.3323	0.58	0.19-1.74							High vs Low	0.5089	0.67	0.21-2.19	

Outcomes with less than 10 deaths were excluded from the analyses: Hodgkin's disease, multiple myeloma, pharynx cancer

Abbreviations: BLL = Blood Lead Level, Med=Medium, HR=Hazard Ratio, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, CVA disease: cerebrovascular disease, IHD: ischemic heart disease, NHL: non-Hodgkin's lymphoma

*All analyses adjusted for age and sex

Table 5b. Cox regression analysis using individual maximum BLL

Individual Max BLL (µg/dL) 4-Category Group (<20, 20-29, 30-39, 40+)						
Disease Group	**Events**	**Groups**	**P-value**	**HR**	**95% CI Lower-Upper**	**Trend test p-value**
All-Cause Mortality	2932	Mid-low vs Low	0.1733	1.12	0.95-1.30	<.0001
		Mid-High vs Low	0.0252	1.19	1.02-1.40	
		High vs Low	<.0001	1.32	1.15-1.51	
Bladder Cancer	27	Mid-low vs Low	0.3842	2.59	0.30-22.21	0.7939
		Mid-High vs Low	0.7065	1.55	0.16-14.86	
		High vs Low	0.3018	2.88	0.38-21.41	
Brain Cancer	19	Mid-low vs Low	0.1771	4.19	0.52-33.53	0.9516
		Mid-High vs Low	0.9407	1.10	0.10-12.11	
		High vs Low	0.6311	1.65	0.21-12.82	
Breast Cancer	22	Mid-low vs Low	0.1185	5.19	0.66-41	0.6004
		Mid-High vs Low	0.7821	0.68	0.04-10.86	
		High vs Low	0.1626	4.29	0.56-33.13	
Esophageal Cancer	43	Mid-low vs Low	0.5413	0.66	0.18-2.47	0.7223
		Mid-High vs Low	0.7732	0.83	0.23-2.94	
		High vs Low	0.6657	1.26	0.45-3.55	
Kidney Cancer	29	Mid-low vs Low	0.5064	0.51	0.07-3.65	0.4750
		Mid-High vs Low	0.28	0.27	0.02-2.94	
		High vs Low	0.4367	1.78	0.042-7.57	
Larynx Cancer	12	Mid-low vs Low	0.989	1.00E+06	0.00	0.4584
		Mid-High vs Low	0.9886	1.57E+06	0.00	
		High vs Low	0.9889	1.15E+06	0.00	
Leukemia	17	Mid-low vs Low	0.9902	1.02	0.09-11.21	0.4792
		Mid-High vs Low	0.1738	4.24	0.53-34.00	
		High vs Low	0.7034	1.49	0.19-11.70	
Lung Cancer	330	Mid-low vs Low	0.2765	1.29	0.82-2.03	0.5565
		Mid-High vs Low	0.1554	1.39	0.88-2.18	
		High vs Low	0.3896	1.20	0.80-1.79	
Stomach Cancer	52	Mid-low vs Low	0.3581	1.69	0.55-5.19	0.4249
		Mid-High vs Low	0.3669	0.53	0.13-2.11	
		High vs Low	0.7708	1.17	0.41-3.28	
COPD	186	Mid-low vs Low	0.2948	1.43	0.73-2.77	0.0193

		Mid-High vs Low	0.4309	1.31	0.67-2.57	
		High vs Low	0.0769	1.70	0.94-3.07	
CKD	16	Mid-low vs Low	0.1324	0.18	0.02-1.69	0.7569
		Mid-High vs Low	0.1278	0.17	0.02-1.66	
		High vs Low	0.2732	0.49	0.14-1.76	
CVA Disease	213	Mid-low vs Low	0.2216	1.45	0.80-2.61	0.0393
		Mid-High vs Low	0.1872	1.49	0.82-2.68	
		High vs Low	0.232	1.38	0.81-2.36	
IHD	737	Mid-low vs Low	0.9484	1.01	0.74-1.38	0.0326
		Mid-High vs Low	0.6919	1.07	0.78-1.46	
		High vs Low	0.0908	1.26	0.96-1.65	
NHL	15	Mid-low vs Low	0.4524	0.54	0.11-2.68	0.1876
		Mid-High vs Low	0.1509	0.19	0.02-1.83	
		High vs Low	0.406	0.58	0.16-2.08	

Outcomes with less than 10 deaths were excluded from the analyses: Hodgkin's disease, multiple myeloma, pharynx cancer
Abbreviations: BLL = Blood Lead Level, Med=Medium, HR=Hazard Ratio, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, CVA disease: cerebrovascular disease, IHD: ischemic heart disease, NHL: non-Hodgkin's lymphoma
*All analyses adjusted for age and sex

Table 6. Summary of Cox Regressions for Disease outcomes of interest using industry type as exposure

Mortality Outcome	Associated Industry Type*	HR	P-value
All-Cause Mortality			
	Manufacturing of pigments and colours	1.13	0.0381
	Painting buildings and vehicles	1.32	0.0289
CKD			
	Painting buildings and vehicles	9.13	0.0089
	Work with metallic lead and lead containing alloys	4.70	0.0666
Kidney Cancer			
	Manufacturing of pigments and colours	3.37	0.0640
	Smelting, refining, alloying, casting	4.37	0.0133
Larynx Cancer			
	Smelting, refining, alloying, casting	4.98	0.0312
Stomach Cancer			
	Pottery, glazes and transfers	2.33	0.0281

* Referent population: industry type “Badge and jewelry enameling”

Table 7. Total number of people who fit into their assigned industry category

Mean BLL	**Low Industry** (<40 µg/dL) Number (% of total)	**Medium Industry** (40-49 µg/dL) Number (% of total)	**High Industry** (>50 µg/dL) Number (% of total)
Total n	**2275**	**1247**	**3081**
N of people correctly fit	1598 (70%)	210 (17%)	1822 (59%)
N of people over range	677 (30%)	370 (30%)	
N of people under range		667 (53%)	1259 (41%)
Total missing=2519			

Max BLL	**Low Industry** (<40 µg/dL) Number (% of total)	**Medium Industry** (40-49 µg/dL) Number (% of total)	**High Industry** (>50 µg/dL) Number (% of total)
Total n	**2173**	**1349**	**3081**
N of people correctly fit	1273 (59%)	199 (15%)	2061 (67%)
N of people over range	900 (41%)	566 (42%)	
N of people under range		584 (42%)	1020 (33%)
Total missing=2519			