ORIGINAL ARTICLE

Mortality of a cohort of workers in Great Britain with blood lead measurements

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ABSTRACT

Objectives We examined the mortality of a historic cohort of workers in Great Britain with measured blood lead levels (BLLs).

Methods SMRs were calculated with the population of Great Britain as the external comparator. Trends in mortality with mean and maximum BLLs and assessed lead exposure were examined using Cox regression.

Results Mean follow-up length among the 9122 study participants was 29.2 years and 3466 deaths occurred. For all causes and all malignant neoplasms, the SMRs were statistically significantly raised. For disease groups of a priori interest, the SMR was significantly raised for lung cancer but not for stomach, brain, kidney, bladder or oesophageal cancers. The SMR was not increased for non-malignant kidney disease but was borderline significantly increased for circulatory diseases, for ischaemic heart disease (IHD) and cerebrovascular disease (CVD). No significant trends with exposure were observed for the cancers of interest, but for circulatory diseases and IHD, there was a statistically significant trend for increasing HR with mean and maximum BLLs.

Conclusions This study found an excess of lung cancer, although the risk was not clearly associated with increasing BLLs. It also found marginally significant excesses of IHD and CVD, the former being related to mean and maximum BLLs. The finding for IHD may have been due to lead, but could also have been due to other dust exposure associated with lead exposure and possibly tobacco smoking. Further work is required to clarify this and the carcinogenicity of lead.

What this paper adds

- Lead, in particular its inorganic compounds, is one of the research priorities identified by the International Agency for Research on Cancer for clarification with respect to its carcinogenicity.
- This cohort study found an excess of lung cancer but not a positive exposure–response relationship. It also found a borderline significant excess of circulatory diseases, for ischaemic heart disease and for cerebrovascular disease, with ischaemic heart disease risk being associated with individual mean and maximum recorded blood lead level.
- This study provides supporting evidence that occupational exposure to lead in Great Britain is associated with an increased risk of mortality from ischaemic heart disease.
- Further studies are require to confirm whether lead exposure is causally related to lung or other cancers and to understand better whether the association with circulatory disease is due to occupational lead exposure.

INTRODUCTION

The monograph working group of the International Agency for Research on Cancer (IARC) concluded in 2006 that organic lead compounds were unclassifiable as to their carcinogenicity, metallic lead was possibly carcinogenic and inorganic lead compounds were probably carcinogenic.[1] The classification for inorganic lead compounds was based on sufficient evidence of carcinogenicity in experimental animals, but limited evidence in humans.[1] The strongest evidence from human studies was for stomach cancer, with findings inconsistent for lung, brain and kidney cancers.[2]

Since the publication of the IARC monograph, a number of additional studies have been published. Significant excesses of stomach,[3] lung,[4 5] kidney[3] and brain cancer[6] have been observed. However, there are potential exposures to known or suspected occupational carcinogens other than lead in some of these study populations. Other recent epidemiological studies have not provided evidence of increased risks for these cancers.[7–10] Trends in cancer risk with increased exposure, or excess risks in the highest exposure categories, have been reported for lung cancer,[3–5 7] kidney cancer[10] and brain cancer.[11 12] In addition, positive exposure–response trends have recently been observed for bladder cancer[3] and oesophageal cancer.[6]

Occupational exposure to lead has also been found to be associated with circulatory diseases, including hypertension and mortality from cardiovascular disease, coronary heart disease and stroke[13] and with increased risk of non-malignant kidney disease.[14]

Over the past 100 years the number of workers poisoned by lead in Great Britain has decreased fairly steadily (figure 1), presumably as a consequence of better working conditions and fewer people working with lead. The removal of lead from petroleum in the 1980s has also reduced considerably the occurrence of lead in the general environment.[1] However, there remains significant potential for occupational exposures, for example in lead acid battery manufacturing and from lead

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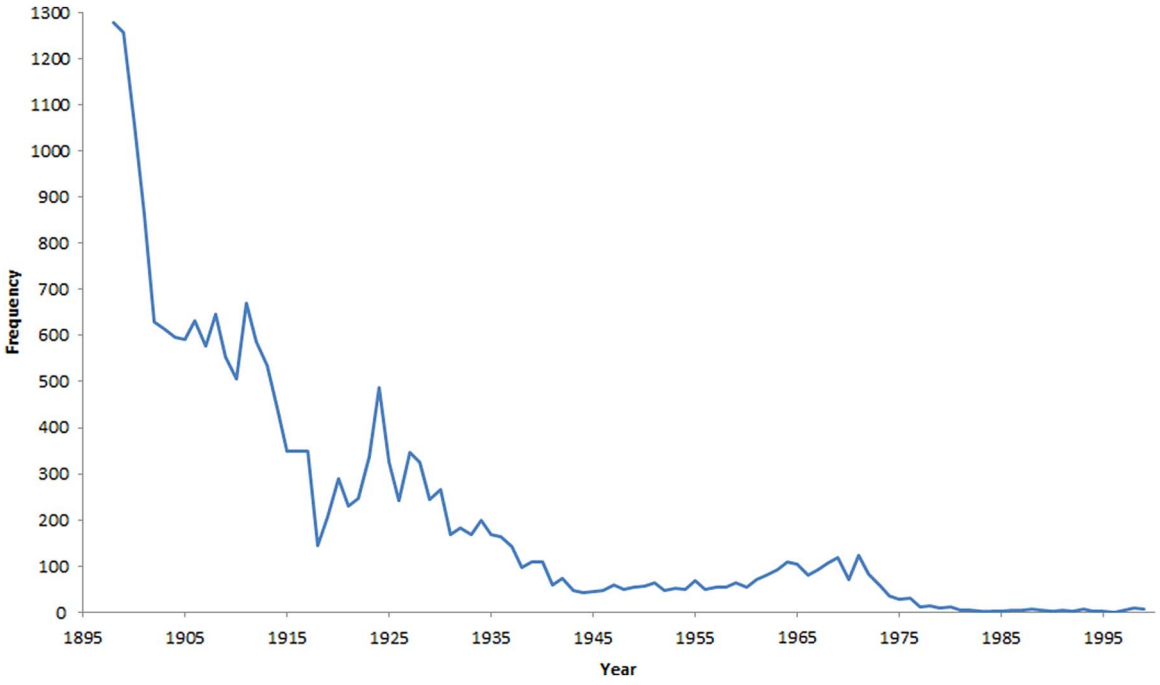

Figure 1 Lead Poisonings in Great Britain 1898–1999.[15–19]

pigments in paint[1] and also from activities such as scrap metal processing and lead smelting.

In the early 1970s, Sir Brian Windeyer published the results of an inquiry into lead poisonings at a factory in Avonmouth in England.[20] The report identified that there was an urgent need for an investigation the long-term health effects of all workers in the lead-using industries. In 1973 a Department of Employment/Medical Council Research Working Group was established and proposed that the current study be carried out.

The cohort contains a census of workers occupationally exposed to lead in the late 1970s; this is its first ever published analysis. The aim of the analysis was to investigate whether occupational exposure to lead was associated with increased mortality risks of certain a priori types of cancer and non-malignant cardiovascular and renal diseases. It is partly a response to a recent call for additional studies of new cohorts with documented lead exposure.[2]

METHODS

In 2012, the Institute of Occupational Medicine (IOM) took over the management of this study from the British Health and Safety Executive (HSE). Before the study data were released to the IOM, clearances were received from an NHS Ethics Committee and the Health Research Authority Confidentiality Advisory Group. Because part of the cohort was based in Scotland, approval to receive Scottish deaths was also obtained from the Scottish Privacy Advisory Committee. Finally, approval was obtained from the Office for National Statistics' microdata release panel and from the NHS Health and Social Care Information Centre's Data Access Advisory Group. Updated mortality data for the cohort was sought from the National Health Service Central Registers in Southport and Dumfries.

The HSE cohort data file consisted of 10 921 workers in Great Britain who had been monitored for lead via blood lead level (BLL) measurements. Two distinct exposure estimates for lead were used in the analysis. First, BLLs were used. All study participants had at least one BLL measurement during 1975–1979, and the archived data file contained each participant's mean and maximum BLL in nmol/dL (1 nmol/dL=0.207 µg/dL) and the number of available measurements on which the mean was based. In addition, the file contained for the vast majority of workers codes for the process or activity the workers undertook as well as the industry sector they were working in at the time of recruitment to the study (see online supplementary table S1). Second, risk assessment data[21] and HSE National Exposure database[22] were used develop an exposure classification based on categorisation of the process and industry in which workers were classified as high, medium or low exposure. High-exposure industries and processes were those where exposure was judged likely to be greater than 50% of the occupational exposure limit (OEL) at the time the cohort was assembled (0.15 mg/m^3 for lead and 0.1 mg/m^3 for alkyl lead) or where there was substantial risk of lead ingestion or skin absorption (which is how 'significant' exposure is defined in the current regulations). Medium and low-exposure industries and processes were those where exposure was likely to be 10–50% and <10% of the OEL, respectively. Exposure was assigned by consensus between two assessors (AS and MvT). Furthermore, known or strongly suspected carcinogens that may cause cancer at the sites of a priori interest for lead were identified using information compiled by IARC which lists carcinogenic agents both with sufficient or limited evidence in humans by cancer site.[23] Information about exposure to these carcinogens was obtained from various sources for the industries of interest in this study. The possibility of exposure (ie, yes/no) was assessed primarily using the European CAREX (CARcinogen EXposure) database, which provides an estimate of the number exposed to a particular agent by industry (classified using International Standard Industrial Classification (ISIC)[24]) for 19 EU countries.[25] CAREX Canada, which has developed profiles and estimates of occupational and environmental exposure for a number of known, probable, and possible carcinogenic agents was also used.[26]

ISIC codes were assigned to the industries or processes in the study. These were then matched with the ISIC codes in CAREX

GB and used to compile a list of agents to which there might be exposure—see online supplementary table S2. Estimates of the proportion exposed and the level of exposure for each code were derived from the British occupational cancer burden study[27] which is based on CAREX GB. Exposure was defined as significant where >5% of the population was exposed and high exposure likely. Since it was not always possible to get an exact match between the ISIC codes assigned to the industries and processes in this project and those recorded in CAREX GB, expert judgement, informed by information from the relevant IARC monographs and CAREX Canada, was used in making decisions about the likely proportion exposed and level of exposure. Exposure was assigned at group level or at process level for 'Other processes'.

SMRs were calculated using the GB population as the external comparator (with stratification by sex, 5-year age band and calendar year) and Cox regression modelling[28] was carried out using mean BLL, maximum BLL and assessed level of exposure, with adjustment for age, sex and potential co-exposure to important levels of relevant co-carcinogens. Follow-up for mortality was to the end of 2011. Analyses were carried out using Genstat,[29] R[30] and Stata.[31]

RESULTS

After matching the death data with the cohort data file, records for 9122 workers were available for analysis for this cohort. Participants could not be matched using names and date of birth between the HSE data file and death data from the National Health Service Central Registers (NHSCRs) for 1799 workers; this was mainly due to the lack of retention of study survey identifiers for the cohort on the NHSCR. Just over half the cohort were born before 1940 (25th and 75th centiles were 1929 and 1951 respectively; see table 1. All of the cohort had a birth year, but for 14 individuals (0.2%) day and month of birth were not available. The total number of person years contributing to the mortality analyses was 267 028. Results for BLL measurements were available for all study participants; nearly 40% of the cohort (39.6%) had a single BLL measurement, with just under 5% of the cohort having 10 or more measurements. The overall mean BLL was 44.3 µg/dL and the mean maximum BLL was 52.6 µg/dL—mean and maximum BLL were highly correlated (Pearson's correlation coefficient 0.87, p<0.0001). The industries with the highest mean BLLs were Shipbuilding, repairing and breaking, Smelting, refining, alloying and casting and the Lead battery industry. Apart from Badge and jewellery enamelling and other vitreous enamelling operations, the mean and maximum BLLs tended to be higher for men than for women (see table 2). The overall distribution of mean BLLs is presented in figure 2 and is highly positively skewed. The results of the exposure assessment for each industry and industry/process combination are contained in online supplementary table S2. The assessment of exposure to other potential carcinogens is contained in online supplementary table S3.

The results of the mortality analysis are presented in table 3. Overall, 3466 out of 9122 (38%) of the cohort included in the analysis had died. For all natural causes an approximate 10% increase in mortality was observed. There were statistically significant excesses for all malignant neoplasms (13%), circulatory diseases (5%), and respiratory system diseases (18%). For the diseases of a priori interest at the outset of the study, there was a significant excess of lung cancer (42%), and SMRs were raised but not statistically significant for stomach, brain and kidney cancers and for non-malignant kidney disease. The SMR for circulatory system diseases was raised (5%) and of borderline statistical significance; this also applied to ischaemic heart disease (IHD) (6%) and cerebrovascular disease (CVD) (16%). For oesophageal and bladder cancer, two cancers that became of interest because of the findings of earlier studies,[3 6] neither of the SMRs was statistically significantly raised. Of the diseases looked at that were not of a priori interest, there was a borderline significant excess of malignant neoplasms of the mesothelial and soft tissue (mainly in men), a significant excess of testicular cancer, based on only five cases and a borderline significant excess of malignant neoplasms of ill-defined and secondary sites. Also of note, in the context of the lung cancer finding, is a significant excess of non-malignant respiratory diseases.

Table 4 presents the results from our Cox regression modelling for the cancers of a priori interest plus the two additional cancer sites, IHD, CVD, and non-malignant kidney disease. The only significantly raised hazard ratios (HR) from analysis of the natural logarithm of mean BLL or maximum BLL were for circulatory diseases and IHD in particular. The HRs for log (mean BLL) and log (maximum BLL) for IHD were 1.30 (1.17 to 1.43, p<0.001) and 1.23 (1.11 to 1.34, p<0.001) respectively. The equivalent HR for mortality from CVD were 1.15 (0.83 to 1.28, p=0.314) and 1.23 (0.98 to 1.48, p=0.066) suggesting that any effect is more pronounced for IHD than CVD. The number of BLL measurements was additionally fitted to models to see if any of our findings were influenced by the volume of lead information held about an individual, but this made no difference to any of the inferences (data not shown). For non-malignant kidney disease, there was some evidence of a raised risk for exposure assessed from process and industry codes as

Table 1 Description of participants, N=9122

Characteristic	Number	Percentage
Age at start of follow-up, mean (SD)	35.2 (13.6)	
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
After 1960	112	1.2
Sex:		
Male	7770	85.2
Female	1352	14.8
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	402	4.4
7	329	3.6
8	257	2.8
9	213	2.3
10–14	564	2.2
15–19	149	1.6
20–29	65	0.7
30+	11	0.1
Total	9122	100.0
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	

BLL, blood lead level.

Table 2 Mean and maximum BLLs by industry and sex

Industry	Total in the industry	Mean of mean BLLs (µg/dL)			Mean of maximum BLLs (µg/dL)		
		Men	Women	Total	Men	Women	Total
Smelting, refining, alloying, casting	935	57.0	43.1	56.7	67.3	48.3	66.9
Lead battery industry	1059	57.1	40.7	54.9	70.4	51.4	67.8
Badge and jewellery enamelling and other vitreous enamelling operations	479	27.6	30.2	29.1	33.0	36.4	35.0
Glass making	212	40.4	26.3	34.8	46.8	28.9	39.7
Manufacture of pigments and colours	971	41.2	26.3	40.3	54.4	31.8	53.0
Pottery, glazes and transfers	1315	38.6	33.7	36.7	47.8	43.1	46.0
Manufacture of inorganic or organic lead compounds (including the lead salts of fatty acids)	102	40.2	13.0	39.6	46.9	16.6	46.3
Shipbuilding, repairing and breaking	279	60.3	–	60.3	72.0	–	72.0
Demolition and scrap industries	808	53.7	32.1	53.6	60.3	39.2	60.1
Painting buildings and vehicles	167	31.7	22.2	31.5	36.1	27.6	35.9
Work with metallic lead and lead containing alloys	276	50.0	25.1	47.1	55.6	25.4	52.1
Other processes	1054	36.8	28.9	36.4	42.3	32.2	41.9
Missing	1465	45.0	29.0	43.2	50.4	32.3	48.4

BLL, blood lead level.

medium and high compared with low and for CVD some evidence that the mortality risk was higher in high exposed versus low exposed.

DISCUSSION

Occupational cohorts often display an overall deficit in mortality, a feature often described as a healthy worker effect.[32] However, this was not evident in this cohort as all cause mortality was significantly raised, which is similar to the findings found from another UK industrial cohort who were under medical surveillance for asbestos and who were known to include many heavy smokers[33] and a recent Australian study of workers exposed to lead.[6] Here, long follow-up and a likely history of heavy smoking may have negated the appearance of any healthy worker effect. Mortality for all malignant neoplasms for sexes combined was statistically significantly raised, driven mainly by a statistically significant excess of lung cancer. The all neoplasms excess was significant only for men, whereas the risk of lung cancer was significantly raised for men and women. None of the SMRs for oesophageal cancer, stomach cancer, bladder cancer, kidney cancer or brain cancer was significantly raised, either overall or for men or women. There was also no excess of mortality from non-malignant kidney diseases.

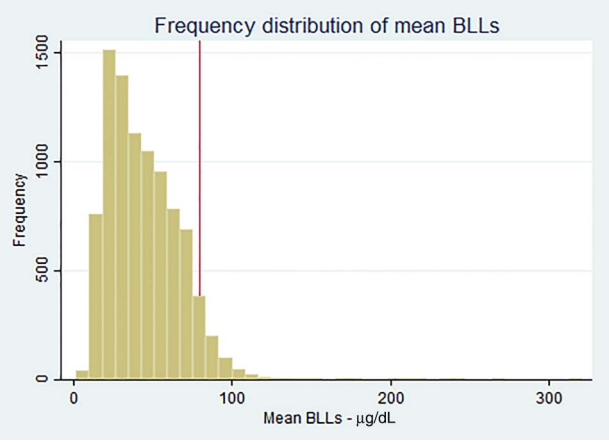

Figure 2 Mean blood lead levels for the cohort with the 1980 suspension level of 80 µg/dL. BLL, blood lead level.

Although mortality for lung cancer was significantly raised, the regression analyses showed no evidence of increased risk with increased mean BLL, nor with increasing maximum BLL. The relationship with assessed lead levels was not monotonic, showing a significant increase for medium versus low exposed, but not for high versus low exposed. It is possible that the excess for lung cancer was due to tobacco smoking, since occupational cohorts such as this are likely to have more smokers than the general population. Application of a method to assess the effect of confounding[34] by tobacco smoking removes the excess for lung cancer.

The raised SMR for circulatory system disease was of borderline statistical significance for men only and for men and women combined; similar results were seen for both IHD and CVD subcategories. All circulatory disease mortality also provided a strong exposure–response relationship with both mean and maximum BLLs, although not with exposure assessment based on industry and process. This could be due to the cruder classification of lead exposure when using this metric. Lead directly affects the haematopoietic system though restraining the synthesis of haemoglobin by inhibiting various key enzymes involved in the haeme synthesis pathway. The effect is dose-dependent and involves downregulating three key enzymes involved in the synthesis of haeme. The effect is most profound on delta-aminolevulinic acid dehydratase (ALAD) and its inhibition has been used clinically to gauge the degree of lead poisoning.[35]

As tobacco smoking is a known cause of both IHD and CVD,[36] it is possible that this could have had a role in elevating the SMRs for both of these conditions. Other risk factors for cardiovascular disease include high blood pressure, high cholesterol, obesity and diabetes mellitus.[37] There is good evidence that the exposure–response relationship for cardiovascular disease from tobacco smoking is non-linear, with the risk for light or intermittent exposure and passive smoking being almost as large as that for continuous smoking.[38] It has been proposed that lung and cardiovascular diseases from cigarette smoking are associated with exposure to inhaled particles, and that the cardiovascular effects associated with these fine particles share a common inflammatory mechanism.[39] The association between ambient particulate air pollution and cardiovascular disease is well known. A recent review concluded that for every 10 µg/m^3

Table 3 SMRs, 1975–2011

Cause of death (ICD 8 9, 10 codes)	Males			Females			Total		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
All causes (000–E999, 000–E999, A00–Y89)	3013	110	106 to 114	453	100	91 to 109	3466	109	105 to 112
All natural causes (000–899, 000–899, A00–R99)	2893	109	105 to 113	444	100	91 to 109	3337	108	104 to 111
All malignant neoplasms (140–209, 140–208, C00–C97)	953	115	108 to 122	149	106	90 to 125	1102	113	107 to 120
MNs lip, oral cavity and pharynx (140–149, 140–149, C00–C14)	12	80	46 to 141	0	–	–	12	74	42 to 130
MNs digestive organs (150–159, 150–159, C15–C26)	260	105	93 to 119	27	79	54 to 115	287	102	91 to 114
MNs oesophagus (150, 150, C15)	**46**	**104**	**78 to 138**	**5**	**118**	**49 to 283**	**51**	**105**	**78 to 138**
MNs stomach (151, 151, C16)	**53**	**111**	**85 to 146**	**5**	**106**	**44 to 256**	**58**	**111**	**86 to 143**
MNs small intestines (152, 152, C17)	0	–	–	0	–	–	0	–	–
MNs colon (153, 153, C18)	57	105	81 to 136	6	61	27 to 135	63	98	77 to 126
MNs rectum (154, 154, C20)	36	116	83 to 160	3	–	–	39	112	82 to 153
MNs pancreas (157, 157, C25)	30	82	57 to 117	4	–	–	34	79	56 to 110
MNs respiratory and intrathoracic organs (160–163, 160–165, C30–C39)	370	141	128 to 156	42	152	112 to 205	412	142	129 to 157
MNs trachea, bronchus and lung (162, 162, C33–34)	**352**	**141**	**127 to 157**	**41**	**152**	**112 to 206**	**393**	**142**	**129 to 157**
MNs bone (170, 170, C40–C41)	4	–	–	0	–	–	4	–	–
MNs of mesothelial and soft tissue (171, 171, C45–C49)	18	159	100 to 252	1	–	–	19	153	98 to 240
Melanoma and other MNs of the skin (173–173, 172–173, C43–C44)	11	93	52 to 169	2	–	–	13	96	56 to 165
MNs breast (174, 174–175, C50)	0	–	–	24	89	59 to 132	24	86	58 to 128
MNs female genital organs (180–184, 179–184, C51–C58)				20	129	77 to 186	20	129	77 to 186
MNs cervix uteri (180, 180, C53)				4	–	–	4	–	–
MNs corpus uteri (182, 182, C54)				2	–	–	2	–	–
MNs ovary (183, 183, C56)				11	117	65 to 210	11	117	65 to 210
MNs male genital organs (185–187, 185–187, C60–C63)	76	96	77 to 120				76	96	77 to 120
MNs prostate (185, 185, C61)	70	92	73 to 116				70	92	73 to 116
MNs testis (186, 186, C62)	5	329	137 to 791				5	329	137 to 791
MNs urinary tract (188–189, 188–189, C64–C68)	54	103	79 to 135	9	177	92 to 341	63	110	86 to 141
MN bladder (188, 188, C67)	**28**	**91**	**63 to 131**	**4**	**–**	**–**	**32**	**95**	**67 to 135**
MNs kidney (189, 189, C64)	**25**	**120**	**81 to 178**	**5**	**217**	**90 to 522**	**30**	**130**	**91 to 186**
MNs eye, brain and CNS (190–192, 190–192, C69–C72)	22	95	62 to 144	1	–	–	23	87	58 to 131
MNs brain (191, 191, C71)	**22**	**99**	**65 to 150**	**1**	**–**	**–**	**23**	**92**	**61 to 138**
MNs thyroid and other endocrinal glands (193–194, 193–194, C73–C75)	2	–	–	0	–	–	2	–	–
MNs ill-defined, unspecified and secondary sites (195–199, 195–199, C74A–C74B, C76–C80)	76	124	99 to 156	17	144	89 to 232	93	128	104 to 156
MNs lymphohaematopoietic system (200–209, 200–208, C81–C96)	41	67	49 to 91	6	64	29 to 142	47	66	50 to 88
Non-Hodgkin's lymphoma (200 200, 200 202–203, C82–C86)	21	65	42 to 99	3	–	–	24	64	43 to 96
Multiple myeloma (203, 203, C90.0)	4	–	–	1	–	–	5	34	14 to 82
Leukaemia (204–207, 204–208, C91–C95)	19	86	55 to 135	3	–	–	22	87	57 to 132
Circulatory system diseases (390–458, 390–459, I00–I99)	**1198**	**105**	**99 to 111**	**170**	**102**	**88 to 118**	**1368**	**105**	**99 to 110**
Ischaemic heart disease (410–414, 410–414, I20–I25)	792	106	99 to 114	82	102	82 to 127	874	106	99 to 113
Cerebrovascular disease (430–438, 430–435, I60–I69)	149	119	101 to 139	35	105	75 to 146	184	116	100 to 134
Respiratory system diseases (460–519, 460–519, J00–J99)	359	117	106 to 130	69	124	98 to 157	428	118	108 to 130
Digestive system diseases (520–579, 520–579, K00–K95)	132	122	103 to 145	17	84	52 to 135	149	116	99 to 136
Genitourinary diseases (580–629, 580–629, N00–N99)	32	102	72 to 144	5	67	28 to 160	37	95	69 to 131
Non-malignant kidney disease (590–593, 590–593, N10–N29)	**13**	**130**	**76 to 224**	**3**	**–**	**–**	**16**	**129**	**79 to 211**

–Indicates SMR and 95% CIs not presented where deaths fewer than 5.
Diseases in bold are those of a priori interest.
CNS, central nervous system; MN, malignant neoplasms; O, Observed deaths.

increase in PM2.5, the risk of death from IHD is increased by 11% (95% CI 5% to 16%).[40] However, other studies have failed to identify a clear risk of cardiovascular mortality from long-term exposure to particulate air pollutants.[41] Sjogren found some evidence from a review of the literature for an association between occupational exposure to inhaled particles and the occurrence of IHD but concluded further work was required to clarify the association.[42] More recently, a systematic review suggested a possible association between occupational exposure to particles and mortality from IHD and an increased risk of non-fatal myocardial infarction.[43] A systematic review of lead and cardiovascular disease identified a link between lead exposure and increased blood pressure, and in some cases a pattern of increasing risk with increased exposure.[13] It is therefore plausible that the excess mortality from circulatory diseases observed in the present study was caused by lead exposure or some other dust exposure associated with lead exposure. It is also possible that those more highly exposed to lead were also heavier smokers and so we cannot rule out tobacco smoking as being the cause of this association.

The exposure assessment in the current study had relied on a twin approach, with the limited objective measurement of BLL

Table 4 Cox regression analysis for the disease groups of a priori interest, with ischaemic heart disease and cerebrovascular disease

Disease Group	Analysis*,†		HR	95% CI	p Value
Oesophageal cancer	Log‡ (mean BLL)		1.09	0.65 to 1.84	0.741
	Log (maximum BLL)		1.14	0.71 to 1.82	0.590
	Assessed lead level	Medium vs low	1.38	0.67 to 2.86	0.387
		High vs low	1.75	0.79 to 3.88	0.165
Stomach cancer	Log (lean BLL)		1.15	0.70 to 1.89	0.573
	Log (maximum BLL)		1.04	0.67 to 1.61	0.866
	Assessed lead level	Medium vs low	1.57	0.81 to 3.04	0.180
		High vs low	1.74	0.82 to 3.69	0.151
Lung cancer§	Log (mean BLL)		1.10	0.89 to 1.37	0.381
	Log (maximum BLL)		1.03	0.85 to 1.24	0.796
	Assessed lead level	Medium vs low	1.40	1.06 to 1.84	0.016
		High vs low	1.03	0.73 to 1.44	0.879
Bladder cancer¶	Log (mean BLL)		1.05	0.50 to 2.20	0.904
	Log (maximum BLL)		1.02	0.53 to 1.95	0.958
	Assessed lead level	Medium vs low	1.14	0.49 to 2.66	0.769
		High vs low	0.36	0.08 to 1.70	0.198
Kidney cancer	Log (mean BLL)		1.53	0.70 to 3.36	0.286
	Log (maximum BLL)		1.31	0.67 to 2.56	0.438
	Assessed lead level	Medium vs low	0.60	0.22 to 1.59	0.303
		High vs low	0.39	0.11 to 1.41	0.151
Brain cancer**	Log (mean BLL)		0.77	0.37 to 1.62	0.498
	Log (maximum BLL)		0.75	0.38 to 1.46	0.396
	Assessed lead level	Medium vs low	2.24	0.83 to 6.01	0.109
		High vs low	0.00	0.00 to ∞	–
Circulatory diseases	Log (mean BLL)		1.30	1.17 to 1.44	<0.001
	Log (maximum BLL)		1.25	1.14 to 1.37	<0.001
	Assessed lead level	Medium vs low	1.09	0.95 to 1.24	0.229
		High vs low	1.11	0.94 to 1.30	0.218
Ischaemic heart disease	Log (mean BLL)		1.30	1.17 to 1.43	<0.001
	Log (maximum BLL)		1.23	1.11 to 1.34	<0.001
	Assessed lead level	Medium vs low	1.02	0.85 to 1.18	0.843
		High vs low	1.02	0.82 to 1.22	0.832
Cerebrovascular disease	Log (mean BLL)		1.15	0.83 to 1.28	0.314
	Log (maximum BLL)		1.23	0.98 to 1.48	0.103
	Assessed lead level	Medium vs low	1.25	0.87 to 1.62	0.247
		High vs low	1.50	1.07 to 1.93	0.066
Non-malignant kidney disease	Log (mean BLL)		1.24	0.48 to 3.21	0.664
	Log (maximum BLL)		1.05	0.46 to 2.41	0.912
	Assessed lead level	Medium vs low	4.37	1.06 to 17.97	0.041
		High vs low	3.05	0.56 to 16.54	0.195

*All analyses adjusted for age and sex.
†For some analyses there was also a significant age*sex interaction, but this had little influence on the HR of interest.
‡All logarithms were natural.
§Also adjusted for potential coexposure to arsenic, cadmium, acids, chromium VI and crystalline silica.
¶Also adjusted for potential coexposure to arsenic.
**Also adjusted for potential coexposure to arsenic and cadmium.
BLL, blood lead level.

and the estimation of exposure using a job exposure matrix. These contrasting approaches have increased the robustness of our evaluation and probably represents the best strategy given the limited information about the study participants. Our study is limited by having incomplete BLL measurements that is, only summary measures, rather than individual measurements and by the BLLs only being available for a 5-year period in the late 1970s. It is likely, given the data on poisonings in figure 1, that mean and total BLLs were much higher in this industry in the 1950s and 1960s than in the 1970s or later. Although acute lead poisonings can occur at BLLs of just over 80 µg/dL, haematological effects have occurred at much lower levels of exposure: reduction of haemoglobin concentrations (50–60 µg/dL), inhibition of iron chelation in haeme (15–30 µg/dL) and ALAD inhibition (<10 µg/dL).[1]

No data were available to the study team in terms of analytical method used, the number of participating laboratories or on other aspects of quality control for the BLLs. Nevertheless, while BLLs are incomplete and unconfirmed quality they represent a much better means of distinguishing relative exposure levels between workers than relying solely on job title. The overall mean BLL of 44.3 µg/dL is slightly higher than some other industrial cohorts[6] and this is just below the current action (50 µg/dL) and suspension (60 µg/dL) levels for general employees in the UK. Furthermore, data are available to show that BLLs in the general population decreased from the mid-1980 to the mid-1990s about threefold in adults to between 2 and 4 µg/dL. A wide range of measures were implemented in Great Britain throughout the 1980s to reduce lead exposure, including removal of lead solder from tins containing food, control of lead from paint and reduction of lead in petroleum.[44]

We also had incomplete information about work, which was based on a single process category rather than a complete job history. Although BLL are likely to be a more reliable measure of systemic lead in the body, it is not clear if this is necessarily a

more appropriate measure of exposure compared (if they had been available) to personal air samples. The study also lacks information on history of tobacco smoking. A feasibility study was undertaken to see if these data deficits might be addressed in the future, but unfortunately, it was found that it will not be possible to extend occupational histories or to add data on smoking to this study in the future. Matching death data to this old cohort was also problematic, with a substantial proportion of the cohort not being able to be matched to the data from the National Health Service Central Registers and it is therefore possible that a some errors may have been made.

The major strengths of this study were its size, long follow-up, and its BLL measurement data which had been determined independently of study outcomes.

In conclusion, this study found an overall excess of lung cancer that was not related to increased occupational lead exposure and which, at least partly, may be explained by tobacco smoking. More interesting is our finding of a borderline excess of cardiovascular diseases and an exposure–response relationship for IHD. This may be due to lead exposure, but could also be due to alternative explanations such as other dust associated with lead exposure or tobacco smoking. These results should be interpreted cautiously in the absence of data on smoking and because of incomplete occupational histories for the cohort. Although lead exposures have declined over time,[45 46] further studies of the relationship between occupational lead exposure and cancer and cardiovascular disease are warranted.

Correction notice This paper has been amended since it was published Online First. In the original version of the paper, the summary statistics for the BLL data (including those in part of Table 1, Table 2 and Figure 2) were incorrectly low by a factor of 4.83. This has now been corrected in the Tables and Figure. Note that correct exposure data were used in the regression modelling so the paper's results and conclusions are unaffected by these corrections.

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Contributors DMM and JWC led the project, oversaw the statistical analysis and had final editorial say on the manuscript. BGM and LAM carried out the statistical analysis. AS and MvT carried out the exposure assessment. KS and AJD were responsible for study design and contributed to the data management of the project. All authors contributed to the writing of the manuscript.

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Data sharing statement Provided the Office for National Statistics and the Health and Social Care Information Centre have no objection, IOM are happy to make available a pseudonymised copy of the data set to any bona fide researcher with an appropriate study protocol. Indeed these data have already been made available to the International Agency for Research on Cancer for an international pooled analysis with the permission of the aforementioned.

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Mortality of a cohort of workers in Great Britain with blood lead measurements

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