

# Diesel Exhaust Exposure and Cause-Specific Mortality in the Diesel Exhaust in Miners Study II (DEMS II) Cohort

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**BACKGROUND:** With the exception of lung cancer, the health effects associated with diesel exhaust for other cancers and nonmalignant health outcomes are not well understood.

**OBJECTIVES:** We extended the mortality follow-up of the Diesel Exhaust in Miners Study, a cohort study of 12,315 workers, by 18 y (ending 31 December 2015), more than doubling the number of observed deaths to  $n = 4,887$ , to evaluate associations between mortality and diesel exhaust exposure.

**METHODS:** Quantitative estimates of historical exposure to respirable elemental carbon (REC), a surrogate for diesel exhaust, were created for all jobs, by year and facility, using measurements collected from each mine, as well as historical measurements. Standardized mortality ratios (SMRs) and hazard ratios (HRs) were estimated for the entire cohort and by worker location (surface, underground).

**RESULTS:** We observed an excess of death for cancers of the lung, trachea, and bronchus ( $n = 409$ ; SMR = 1.24; 95% CI: 1.13, 1.37). Among workers who ever worked underground, where the majority of diesel exposure occurred, excess deaths were evident for lung, trachea, and bronchus cancers ( $n = 266$ ; SMR = 1.26; 95% CI: 1.11, 1.42). Several nonmalignant diseases were associated with excess mortality among workers ever-employed underground, including ischemic heart disease (SMR = 1.08; 95% CI: 1.00, 1.16), cerebrovascular disease (SMR = 1.22; 95% CI: 1.04, 1.43), and nonmalignant diseases of the respiratory system (SMR = 1.13; 95% CI: 1.01, 1.26). Continuous 15-y lagged cumulative REC exposure  $< 1,280 \mu\text{g}/\text{m}^3\text{-y}$  was associated with increased lung cancer risk (HR = 1.93; 95% CI: 1.24, 3.03), but the risk declined at the highest exposures (HR = 1.29; 95% CI: 0.74, 2.26). We also observed a significant trend in non-Hodgkin lymphoma (NHL) risk with increasing 20-y lagged cumulative REC (HR<sub>Tertile3 vs. Tertile1</sub> = 3.12; 95% CI: 1.00, 9.79;  $p$ -trend = 0.031).

**DISCUSSION:** Increased risks of lung cancer mortality observed in the original study were sustained. Observed associations between diesel exposure and risk of death from NHL and the excesses in deaths for diseases of the respiratory and cardiovascular system, including ischemic heart disease and cerebrovascular disease, warrant further study and provide evidence of the potential widespread public health impact of diesel exposure. <https://doi.org/10.1289/EHP12840>

## Introduction

Studies in animals and in humans have demonstrated that diesel engine exhaust causes lung cancer [International Agency for Research on Cancer (IARC), Group 1 “carcinogenic to humans” designation].<sup>1</sup> Although there is also suggestive evidence for a positive association between diesel exhaust and bladder cancer,<sup>1,2</sup> studies of other cancer sites [esophagus, larynx, pancreatic, kidney,<sup>3</sup> colorectal,<sup>4</sup> and prostate cancer,<sup>5</sup> as well as multiple myeloma and non-Hodgkin lymphoma (NHL), including lymphoid leukemia and myeloid leukemia]<sup>1</sup> remain limited because of their assessment of exposure and small numbers of exposed cases. Several nonmalignant health outcomes have been linked to traffic-related air pollution (e.g.,

respiratory disease, heart disease),<sup>6–10</sup> and by extension, are suspected to be related to diesel exhaust exposure.

Millions of workers are occupationally exposed to diesel engine exhaust in various workplace settings, including mining, truck driving, railroad work, and other occupations that involve heavy equipment operation.<sup>11</sup> Some of the most compelling epidemiologic studies of diesel exhaust and cancer risk have been conducted in high-exposure occupational settings. In 2012, results were published from the Diesel Exhaust in Miners Study (DEMS), a retrospective cohort study of 12,315 workers exposed to diesel exhaust at eight U.S. nonmetal mining facilities.<sup>12,13</sup> In both the analysis of the mortality experience of the cohort<sup>13</sup> and the companion nested case–control study,<sup>12</sup> increasing quantitative estimates of respirable elemental carbon (REC), a surrogate for diesel exhaust exposure, were associated with increasing lung cancer mortality. The cohort study also found some evidence of a suggestive association between diesel exhaust and esophageal cancer,<sup>13</sup> but the numbers of observed deaths for this and other cancer sites were small.

Here, we extended the mortality follow-up of this cohort by 18 y (ending on 31 December 2015), more than doubling the number of observed deaths, to further evaluate associations between mortality and diesel exhaust exposure in DEMS (hereafter this extended follow-up is referred to as DEMS II).

## Methods

### Study Population and Exposure Assessment

The DEMS study population has been previously described.<sup>13</sup> Briefly, the study population includes 12,315 workers exposed to

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diesel engine exhaust at eight U.S. nonmetal mining facilities. The eight facilities included one limestone, three potash, one salt, and three trona mines located in Missouri, New Mexico, Ohio, and Wyoming, respectively. All workers who were ever employed in a blue-collar job (excluding solely administrative or management positions) for at least 1 y after dieselization (1947–1967, depending on the facility) were eligible for the study. Information on demographics and work history records (1947–1999) were abstracted from employer personnel files. For this extended follow-up, we matched individuals who were alive or who had an unknown vital status at the end of 1997 (the previous cut off of mortality follow-up) to the National Death Index (NDI-Plus) through 31 December 2015. Underlying causes of death were coded according to the *International Classification of Diseases* (ICD) revision in effect at the time of death (ICD-7,<sup>14</sup> ICD-8,<sup>15</sup> ICD-9,<sup>16</sup> and ICD-10<sup>17</sup>). DEMS II also consists of an extended nested case–control study of lung cancer mortality with detailed information for smoking and other confounders not available for the entire cohort.<sup>18</sup> The DEMS II study protocol was approved by the institutional review board of the National Cancer Institute.

In DEMS II, no changes were made to the original DEMS job coding or to the exposure estimates developed previously (through 31 December 1997). For six facilities, additional work history record information was available (maximum through 31 December 1999); the seventh facility had job records collected only through 1997, and the eighth facility had closed in 1993. Using previously collected exposure determinant information,<sup>19,20</sup> updated diesel exhaust exposure estimates were created for the additional job records.

Quantitative estimates of historical exposure to REC were created for all jobs, by year and facility by DEMS exposure assessors.<sup>19–23</sup> Briefly, estimates were developed from arithmetic means of REC measurements collected during an industrial hygiene survey conducted at each facility from 1998 to 2001. For underground jobs, facility-specific historical temporal changes in these 1998–2001 estimates were modeled back to 1947–1967 using diesel engine horsepower and ventilation rates and calibrated based on historical trends in measurements of carbon monoxide. For surface jobs, exposure was assigned based on proximity to diesel-powered equipment. Estimates of exposure to silica, radon, asbestos, nondiesel exhaust polycyclic aromatic hydrocarbons (PAHs), and respirable dust were also developed for each facility, job, and year; these were not updated.

### Statistical Analysis

Standardized mortality ratios (SMRs) were calculated comparing the cohort's mortality to state-specific mortality rates with stratification by 5-y age and 5-y calendar-time, race, and sex using the National Institute for Occupational Safety and Health (NIOSH) Life Table Analysis System (LTAS; version 4.0; <https://www.cdc.gov/niosh/ltras/>). Confidence intervals (CIs) for the SMRs were calculated according to the formula described by Breslow and Day.<sup>24</sup> Individuals who worked at multiple facilities were assigned to the facility where they worked the longest but assigned the appropriate estimates of each facility. Person-years at risk began at the time that state-based death rates became available (1960). The accumulation of person-years ceased when an individual died or on 31 December 2015, whichever occurred first. SMRs were calculated for outcomes with at least 10 reported deaths (overall). Additional stratification using worker location was also assessed (ever-underground workers and surface-only workers). The NIOSH-119 underlying cause of death groups (using the LTAS)<sup>52</sup> were used to define all outcomes evaluated. To accommodate the change in definition of NHL<sup>25</sup> over time, NHL was defined according to the Surveillance, Epidemiology, and End Results (SEER) Program Cause of Death Recode ([\[seer.cancer.gov/coderecode/1950\\\_d04152002/index.html\]\(https://seer.cancer.gov/coderecode/1950\_d04152002/index.html\)\), which resulted in the inclusion of chronic lymphocytic leukemia \(CLL\) with NHL. Subsequent analyses for NHL with and without CLL were evaluated. SMRs for NHL including CLL were calculated using the SEER\\*Stat Multiple Primary–Standardized Incidence Ratio \(MP-SIR\) to allow for rates associated with the updated coding of NHL.](https://</a></p></div><div data-bbox=)

To assess the relationship between average REC intensity and cumulative REC and cancer-specific mortality, we used Cox proportional hazard models [PROC PHREG from the SAS software (version 9.3; SAS Institute)]. Person-years at risk began at the date of dieselization (facility-dependent) and accumulated through 31 December 2015. Hazard ratios (HRs) and 95% CIs for time-dependent diesel exposure metrics [i.e., cumulative REC exposure (in micrograms per meter cubed-year), duration of exposure (in years), and average REC intensity (in micrograms per meter cubed)] were calculated for each cancer-specific outcome using attained age as the time metric with adjustment for race and ethnicity (abstracted from facility personnel records), sex, and birth year. Models of lung cancer included race and ethnicity as Black vs. non-Hispanic White or Hispanic because of known variation in lung cancer incidence among racial/ethnic groups by U.S. Census region showing a higher incidence among Black populations compared with other racial groups.<sup>26</sup> Analyses were stratified by state (facility location) and were calculated with a time-dependent dichotomous variable representing worker location; analyses were also presented separately, by worker location. Exposure to silica, asbestos, nondiesel exhaust PAHs, radon, and respirable dust were also developed from measurement data<sup>19,20,23</sup> and examined as potential confounders. Covariates included in the final model were outcome dependent and were retained if they resulted in a 10% change in parameter estimates using forward stepwise selection. The proportional hazards assumption was tested by evaluating the impact of an interaction term between exposure and age and was not violated for any models.

Cut points for exposure categories were based on the outcome-specific distribution of deaths for outcomes with  $\geq 25$  exposed deaths; for outcomes with  $< 25$  deaths, HRs were calculated considering only continuous exposure. Similar to prior analysis, we also explored expanded cut points (representing a doubling in exposure with each increasing category) for analyses of lung cancer to explore the full range of the exposure–response relationship. Continuous log-transformed cumulative REC exposure  $< 1,280 \mu\text{g}/\text{m}^3\text{-y}$  was also modeled to assess the exposure–response relationship among workers with low-to-moderate diesel exposure for lung cancer as in Attfield et al.<sup>13</sup> Tests for linear trend in categorical analyses were calculated using the median value for each exposure category as continuous. Statistical tests were two-sided and based on a  $\chi^2$  Wald test, with  $p < 0.05$  considered statistically significant. Consistent with the prior follow-up, to account for an observed differential mortality pattern in short-term workers, those with  $< 5$ -y tenure were excluded from the final analyses, although sensitivity analyses were conducted to evaluate risk with and without this tenure exclusion, as well as with the addition of outcome-specific deaths noted as a contributing cause. Lagged estimates of exposure were used for the evaluation of exposure–response relationships to eliminate the effect of recent exposures unlikely related to cancer death. The Akaike information criteria (AIC) was used to determine which lagged estimates provided the best fit for a given outcome.

### Results

Characteristics of the study population and the facilities have been reported previously.<sup>13</sup> This cohort of miners was predominantly male and non-Hispanic White.

**Table 1.** Observed numbers of deaths and standardized mortality ratios (SMRs) for selected causes of death, in the DEMS II (USA, 1960–2015) total cohort and by worker location.

Cause of death	Total cohort Person-years <sup>a</sup> = 422,343		Ever-underground Person-years <sup>a</sup> = 282,840		Surface-only Person-years <sup>a</sup> = 139,503	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All causes of death	4,887	1.02 (1.00, 1.05)	3,259	1.06 (1.03, 1.10)*	1,628	0.95 (0.91, 1.00)
All malignant neoplasms	1,251	1.12 (1.06, 1.18)*	824	1.14 (1.07, 1.22)*	427	1.07 (0.97, 1.18)
Esophagus	53	1.40 (1.05, 1.83)*	36	1.44 (1.01, 2.00)*	17	1.31 (0.76, 2.10)
Stomach	40	1.25 (0.89, 1.70)	28	1.36 (0.90, 1.96)	12	1.05 (0.54, 1.84)
Intestine	91	1.00 (0.81, 1.23)	67	1.15 (0.89, 1.46)	24	0.74 (0.47, 1.10)
Rectum	16	0.75 (0.43, 1.22)	11	0.80 (0.40, 1.43)	5	0.67 (0.22, 1.57)
Biliary, liver, and gall bladder	43	0.99 (0.72, 1.34)	28	0.97 (0.65, 1.41)	15	1.03 (0.58, 1.70)
Pancreas	67	1.04 (0.81, 1.32)	43	1.03 (0.74, 1.39)	24	1.07 (0.68, 1.59)
Lung, trachea, and bronchus	409	1.24 (1.13, 1.37)*	266	1.26 (1.11, 1.42)*	143	1.22 (1.03, 1.43)*
Larynx	15	1.35 (0.76, 2.23)	11	1.53 (0.76, 2.74)	4	1.02 (0.28, 2.61)
Prostate	92	0.90 (0.73, 1.11)	60	0.94 (0.71, 1.20)	32	0.85 (0.58, 1.20)
Urinary	74	1.14 (0.90, 1.44)	46	1.10 (0.80, 1.47)	28	1.22 (0.81, 1.77)
Kidney	34	1.02 (0.71, 1.43)	23	1.05 (0.67, 1.58)	11	0.96 (0.48, 1.71)
Bladder and other urinary	40	1.27 (0.91, 1.73)	23	1.15 (0.73, 1.72)	17	1.49 (0.87, 2.39)
Melanoma	29	1.29 (0.87, 1.86)	21	1.43 (0.88, 2.18)	8	1.04 (0.45, 2.05)
Mesothelioma <sup>b</sup>	13	2.71 (1.44, 4.64)*	7	2.24 (0.90, 4.61)	6	3.61 (1.32, 7.85)*
Brain and other nervous	45	1.41 (1.03, 1.88)*	33*	1.57 (1.08, 2.20)*	12	1.10 (0.57, 1.92)
Lymphatic and hematopoietic	121	1.07 (0.88, 1.27)	73	1.00 (0.78, 1.25)	48	1.19 (0.88, 1.58)
Non-Hodgkin lymphoma with CLL <sup>c</sup>	61	1.22 (0.94, 1.57)	39	1.21 (0.86, 1.66)	22	1.25 (0.78, 1.89)
Multiple myeloma	17	0.81 (0.47, 1.29)	9	0.66 (0.30, 1.26)	8	1.07 (0.46, 2.12)
Leukemia <sup>d</sup>	51	1.09 (0.81, 1.43)	31	1.03 (0.70, 1.46)	20	1.19 (0.73, 1.84)
Diabetes mellitus	123	0.98 (0.81, 1.17)	93	1.12 (0.91, 1.38)	30	0.70 (0.47, 1.00)
Diseases of the heart	1,362	1.03 (0.98, 1.09)	877	1.06 (0.99, 1.13)	485	1.00 (0.91, 1.09)
Ischemic heart disease	1,103	1.06 (1.00, 1.12)	710	1.08 (1.00, 1.16)*	393	1.02 (0.92, 1.12)
Other diseases of circulatory system	331	0.97 (0.87, 1.08)	226	1.07 (0.94, 1.22)	105	0.81 (0.66, 0.98)*
Cerebrovascular disease	217	1.04 (0.91, 1.19)	156	1.22 (1.04, 1.43)*	61	0.76 (0.58, 0.97)*
Diseases of respiratory system	470	1.03 (0.94, 1.13)	325	1.13 (1.01, 1.26)*	145	0.85 (0.72, 1.01)
Chronic obstructive pulmonary disease	284	1.04 (0.92, 1.16)	194	1.12 (0.97, 1.29)	90	0.89 (0.71, 1.09)
Other pneumoconioses	25	10.66 (6.90, 15.74)*	19	12.93 (7.78, 20.20)*	6	6.86 (2.52, 14.92)*

Note: Rate definitions taken directly from LTAS rate file MCO119 1960–2014. CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; ICD, *International Classification of Diseases*; LTAS, Life Table Analysis System; MCO119, Multiple Cause-of-Death (mortality data); SEER\*Stat, Surveillance, Epidemiology, and End Results statistical software.

\* $p < 0.05$ .

<sup>a</sup>Person-years based on 12,272 individuals, which is the number in the study from 1960 to 2015, the period when state rates available.

<sup>b</sup>Starting with ICD-10<sup>17</sup> in 1999.

<sup>c</sup>SMR for non-Hodgkin lymphoma grouped with chronic lymphocytic leukemia (CLL); rates calculated using SEER\*Stat.

<sup>d</sup>ICD-7<sup>14</sup> code 204; ICD-8<sup>15</sup> codes 204–207; ICD-9<sup>16</sup> codes 204–208; ICD-10<sup>17</sup> codes C91.0–C91.3, C91.5–C91.9, and C92–C95.

During the period for which state rates were available, 1960 through the end of extended follow-up, we observed  $n = 4,887$  deaths (prior total  $n = 2,185$ ), more than doubling the number of observed deaths. Observed numbers and SMRs for cancers with at least 10 reported deaths overall were included, as well as major groups of nonmalignant conditions previously associated with diesel exhaust exposure, are presented in Table 1. An excess of all-cause mortality was observed with extended mortality follow-up (SMR = 1.02; 95% CI: 1.00, 1.05) primarily driven by significant excess deaths observed in ever-underground workers (SMR = 1.06; 95% CI: 1.03, 1.10). Lower than expected all-cause mortality was observed among surface-only workers (SMR = 0.95; 95% CI: 0.91, 1.00). There was an excess of death for all malignant cancers combined ( $n = 1,251$ ), specifically for cancers of the lung, trachea, and bronchus ( $n = 409$ ; SMR = 1.24; 95% CI: 1.13, 1.37), esophagus ( $n = 53$ ; SMR = 1.40; 95% CI: 1.05, 1.83), brain/other nervous system ( $n = 45$ ; SMR = 1.41; 95% CI: 1.03, 1.88), and for mesothelioma ( $n = 13$  since 1999, the start of ICD-10<sup>17</sup> coding for mesothelioma; SMR = 2.71; 95% CI: 1.44, 4.64). When considering workers who ever worked underground, where the majority of diesel exhaust exposure occurred, excess deaths were evident for lung, trachea, and bronchus (SMR = 1.26; 95% CI: 1.11, 1.42), esophagus (SMR = 1.44; 95% CI: 1.01, 2.00), and brain/other nervous system (SMR = 1.57; 95% CI: 1.08, 2.20) cancers.

Several nonmalignant diseases showed an excess of death among workers ever-underground including ischemic heart disease (IHD) (SMR = 1.08; 95% CI: 1.00, 1.16), cerebrovascular

disease (SMR = 1.22; 95% CI: 1.04, 1.43), and diseases of the respiratory system (SMR = 1.13; 95% CI: 1.01, 1.26), the last driven mainly by excess mortality from chronic obstructive pulmonary disease (COPD; SMR = 1.12; 95% CI: 0.97, 1.29) and other pneumoconioses (SMR = 12.93; 95% CI: 7.78, 20.20). A deficit of deaths was observed among surface-only workers for cerebrovascular disease (SMR = 0.76; 95% CI: 0.58, 0.97). Observed numbers of deaths and SMRs in the total cohort for causes of death not shown in Table 1 are presented in Table S1.

HRs for lung cancer mortality for 15-y lagged (the best fitting model) REC cumulative exposure and average intensity in the total cohort and by worker location are presented in Table 2. Quintiles, as well as the expanded categories, of cumulative REC exposure showed a significant increase in risk of lung cancer, followed by a plateau in risk at the higher levels of exposure (above  $\geq 1,280 \mu\text{g}/\text{m}^3\text{-y}$  in expanded categories). In the range of  $< 1,280 \mu\text{g}/\text{m}^3\text{-y}$ , the HR for continuous cumulative REC exposure ( $\log \mu\text{g}/\text{m}^3\text{-y}$ ) was associated with significantly elevated lung cancer risk overall (HR = 1.93; 95% CI: 1.24, 3.03) and among ever-underground workers (HR = 1.95; 95% CI: 1.21, 3.14). Average REC intensity was not significantly associated with elevated lung cancer risk in quintile categories or across the range of exposure (except for two HRs:  $> 4$  to  $< 8$ , and  $> 32$  to  $< 64 \mu\text{g}/\text{m}^3$ ) for all workers combined or for ever-underground workers. The HR for continuous average REC intensity ( $\log \mu\text{g}/\text{m}^3$ ) among surface-only workers was statistically significant (HR = 2.22; 95% CI: 1.15, 4.29). Side-by-side results

**Table 2.** Hazard ratios and 95% confidence intervals for lung cancer mortality for 15-y lagged REC cumulative exposure and average intensity in the DEMS II (USA, 1947–2015) total cohort ( $N = 12,315$ ) and by worker location: expanded categories and continuous modeling results.

Total cohort Person-years <sup>a</sup> = 279,050			Ever-underground Person-years <sup>a</sup> = 182,142			Surface-only Person-years <sup>a</sup> = 96,908		
Exposure metric	Deaths (n)	HR (95% CI) <sup>b</sup>	Exposure metric	Deaths (n)	HR (95% CI) <sup>c</sup>	Exposure metric	Deaths (n)	HR (95% CI) <sup>c</sup>
<b>Cumulative REC (<math>\mu\text{g}/\text{m}^3\text{-y}</math>)</b>								
0 to <11.17	59	1.0	0 to <147.81	40	1.0	0 to <2.31	20	1.0
11.17 to <67.49	59	0.83 (0.55, 1.23)	147.81 to <536.44	39	1.11 (0.69, 1.77)	2.31 to <7.69	20	0.76 (0.37, 1.55)
67.49 to <536.10	59	1.30 (0.77, 2.17)	536.44 to <978.36	39	1.70 (1.04, 2.78)	7.69 to <17.12	20	0.64 (0.30, 1.36)
536.10 to <1,242.30	59	2.02 (1.18, 3.46)	978.36 to <1,813.87	39	1.57 (0.96, 2.59)	17.12 to <34.43	20	0.68 (0.30, 1.55)
$\geq 1,242.30$	59	1.17 (0.66, 2.07)	$\geq 1,813.87$	39	0.97 (0.57, 1.63)	$\geq 34.43$	19	0.97 (0.38, 2.46)
<b>0 to &lt;20</b>								
0 to <20	78	1.0	0 to <20	10	1.0	0 to <20	68	1.0
20 to <40	20	0.74 (0.44, 1.24)	20 to <40	6	1.65 (0.59, 4.66)	20 to <40	14	0.69 (0.37, 1.30)
40 to <80	23	1.31 (0.78, 2.20)	40 to <80	8	1.88 (0.72, 4.96)	40 to <80	15	1.50 (0.74, 3.06)
80 to <160	19	1.86 (1.01, 3.43)	80 to <160	17	2.73 (1.19, 6.26)	80 to <160	2	1.26 (0.27, 5.89)
160 to <320	22	1.85 (1.00, 3.41)	160 to <320	22	2.67 (1.20, 5.96)	160 to <320	—	—
320 to <640	29	1.47 (0.82, 2.62)	320 to <640	29	2.19 (1.00, 4.78)	320 to <640	—	—
640 to <1,280	48	2.18 (1.27, 3.74)	640 to <1,280	48	3.19 (1.50, 6.79)	640 to <1,280	—	—
$\geq 1,280$	56	1.29 (0.74, 2.26)	$\geq 1,280$	56	1.88 (0.86, 4.10)	$\geq 1,280$	—	—
Continuous (per 1,000 $\mu\text{g}/\text{m}^3\text{-y}$ )	—	0.99 (0.89, 1.09)	—	—	0.98 (0.88, 1.08)	—	—	1.00 (0.99, 1.01)
Continuous (<1,280 $\mu\text{g}/\text{m}^3\text{-y}$ )	—	1.93 (1.24, 3.03)	—	—	1.95 (1.21, 3.14)	—	—	NA
<b>Average REC (<math>\mu\text{g}/\text{m}^3</math>)</b>								
0 to <0.91	61	1.0	0 to <9.39	40	1.0	0 to <0.63	20	1.0
0.91 to <4.41	57	0.94 (0.63, 1.40)	9.39 to <47.91	39	1.18 (0.74, 1.90)	0.63 to <0.88	20	1.37 (0.66, 2.86)
4.41 to <47.39	59	1.68 (0.97, 2.89)	47.91 to <86.11	39	1.49 (0.91, 2.44)	0.88 to <1.06	20	1.17 (0.52, 2.63)
47.39 to <123.97	59	1.66 (0.94, 2.94)	86.11 to <159.32	39	1.05 (0.63, 1.76)	1.06 to <2.11	20	1.46 (0.62, 3.42)
$\geq 123.97$	59	1.50 (0.84, 2.71)	$\geq 159.32$	39	1.21 (0.71, 2.06)	$\geq 2.11$	19	1.92 (0.80, 4.61)
0 to <2	90	1.0	0 to <2	14	1.0	0 to <2	76	1.0
<b>2 to &lt;4</b>								
2 to <4	26	1.31 (0.83, 2.07)	2 to <4	7	1.56 (0.61, 4.03)	2 to <4	19	1.36 (0.78, 2.37)
<b>4 to &lt;8</b>								
4 to <8	18	2.04 (1.11, 3.74)	4 to <8	14	1.81 (0.83, 3.95)	4 to <8	4	3.03 (1.00, 9.21)
<b>8 to &lt;16</b>								
8 to <16	14	1.79 (0.91, 3.53)	8 to <16	14	1.78 (0.82, 3.84)	8 to <16	—	—
<b>16 to &lt;32</b>								
16 to <32	13	1.37 (0.68, 2.76)	16 to <32	13	1.43 (0.65, 3.13)	16 to <32	—	—
<b>32 to &lt;64</b>								
32 to <64	40	2.08 (1.21, 3.56)	32 to <64	40	2.19 (1.15, 4.19)	32 to <64	—	—
<b>64 to &lt;128</b>								
64 to <128	38	1.42 (0.81, 2.47)	64 to <128	38	1.47 (0.75, 2.88)	64 to <128	—	—
$\geq 128$	56	1.50 (0.88, 2.58)	$\geq 128$	56	1.58 (0.81, 3.06)	$\geq 128$	—	—
Continuous (log $\mu\text{g}/\text{m}^3$ )	—	1.06 (0.96, 1.17)	—	—	1.06 (0.95, 1.18)	—	—	2.22 (1.15, 4.29)

Note: —, not applicable; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; HR, hazard ratio; NA, not available; REC, respirable elemental carbon.

<sup>a</sup>Person-time reflects tenure exclusion.

<sup>b</sup>Models adjusted for race/ethnicity, sex, birth year, and worker location; stratified by state. Excluding individuals with <5-y tenure.

<sup>c</sup>Models adjusted for race/ethnicity, sex, and birth year; stratified by state. Excluding individuals with <5-y tenure.

for lung cancer from DEMS I<sup>13</sup> and for DEMS II are provided in Table S2 for comparison.

REC exposure and risk of NHL with CLL ( $n = 46$ ) results are presented in Table 3. AIC values indicated that a 20-y lagged average REC intensity and cumulative REC exposure was the best fitting model. Statistically significant elevated HRs for continuous cumulative REC exposure (in log  $\mu\text{g}/\text{m}^3\text{-y}$ ) were observed for the total cohort (HR = 1.25; 95% CI: 1.00, 1.54), with a significant trend in risk (HR<sub>Tertile3 vs. Tertile1</sub> = 3.12; 95% CI: 1.00, 9.79;  $p_{\text{Trend}} = 0.031$ ); continuous cumulative REC exposure was significantly elevated in ever-underground workers as well (HR = 1.34; 95% CI: 1.03, 1.74). Similar patterns were observed in the total cohort for average REC intensity, for example, HR<sub>Tertile3 vs. Tertile1</sub> = 4.45; 95% CI: 1.32, 14.98;  $p_{\text{Trend}} = 0.032$  and for continuous exposure = 1.29; 95% CI: 0.99, 1.69. Results considering NHL without CLL (Table S3), the addition of contributing causes of death, deaths including workers with <5-y tenure, and after adjustment for radon were similar (Table S4).

Continuous and categorical exposure-response modeling results for site-specific cancer mortality showed few additional positive associations (Table 4). Continuous cumulative REC lagged 15-y was significantly associated with multiple myeloma (MM; HR = 1.87; 95% CI: 1.11, 3.15), as was average REC intensity (HR lagged 15-y = 2.12; 95% CI: 1.06, 4.25). A significant HR in the second tertile of cumulative REC lagged 15-y was observed for kidney cancer, but no monotonic pattern in the HRs was observed with

increasing exposure ( $p_{\text{Trend}} = 0.768$ ). A positive monotonic pattern in the HRs was observed for bladder cancer (cumulative REC lagged 15-y; HR<sub>Tertile2</sub> = 1.82, HR<sub>Tertile3</sub> = 3.31); however, these HRs were not statistically significant at the 0.05 level, nor was the test for linear trend in the categorical data ( $p = 0.242$ ). Although there was an observed excess of brain and esophageal cancers, as well as mesothelioma in the external analysis (Table 1 SMRs), internal exposure-response analyses did not show any positive associations between cumulative REC or average REC intensity exposure and risk for these outcomes (Table 4). Further evaluation of other cancer outcomes by worker location also showed no additional notable increases in risk (Table S5).

## Discussion

In this extended mortality follow-up, we provide additional data characterizing the adverse health effects associated with exposure to diesel engine exhaust based on quantitative levels of historical exposure estimates. The excess of lung cancer observed in the original study, and the exposure-response relationships,<sup>13</sup> were sustained after a doubling in the observed number of lung cancer deaths accrued with 18 y of extended follow-up. We observed an exposure-response relationship between diesel exhaust and risk of death from NHL. Excesses in deaths were also observed for cardiovascular events, including IHD, cerebrovascular disease, and nonmalignant respiratory disease, primarily for those working underground where exposures were the highest.

**Table 3.** Hazard ratios and 95% confidence intervals for non-Hodgkin lymphoma with chronic lymphocytic leukemia for 20-y lagged cumulative REC exposure and average REC intensity in the DEMS II cohort (USA, N = 12,315, 1947–2015).

Total cohort Person-years = 279,050			Ever-underground Person-years = 182,142			Surface-only Person-years = 96,908		
Exposure metric	Deaths (n)	HR (95% CI) <sup>a</sup>	Exposure metric	Deaths (n)	HR (95% CI) <sup>b</sup>	Exposure metric	Deaths (n)	HR (95% CI) <sup>b</sup>
<b>Cumulative REC (µg/m<sup>3</sup>-y)</b>								
0 to <32.52	17	1.0	0 to <837.67	13	1.0	0 to <12.71	10	1.0
35.52 to <1,558.19	17	1.41 (0.57, 3.51)	837.67 to <2,844.08	12	1.84 (0.78, 4.34)	12.71 to <22.26	4	0.97 (0.28, 3.35)
≥1,558.19	12	3.12 (1.00, 9.79)*	≤2,844.08	4	1.73 (0.51, 5.91)	≥22.26	3	0.41 (0.10, 1.69)
<i>p</i> <sub>Trend</sub> -Value <sup>c</sup>	—	0.031*	—	—	0.307	—	—	0.216
Continuous <sup>d</sup>	46	1.25 (1.00, 1.54)*	Continuous <sup>d</sup>	29	1.34 (1.03, 1.74)*	Continuous <sup>d</sup>	17	0.72 (0.42, 1.23)
<b>Average REC (µg/m<sup>3</sup>)</b>								
0 to <2.50	17	1.0	0 to <58.61	10	1.0	0 to <0.87	9	1.0
2.50 to <91.98	13	2.33 (0.81, 6.65)	58.61 to <143.48	8	1.51 (0.55, 4.14)	0.87 to <1.39	5	0.98 (0.29, 3.29)
≥91.98	16	4.45 (1.32, 14.98)*	≥143.48	11	2.51 (0.94, 6.71)	≥1.39	3	0.50 (0.12, 2.10)
<i>p</i> <sub>Trend</sub> -Value <sup>c</sup>	—	0.032*	—	—	0.066	—	—	0.311
Continuous <sup>e</sup>	46	1.29 (0.99, 1.69)	Continuous <sup>e</sup>	29	1.29 (0.97, 1.72)	Continuous <sup>e</sup>	17	0.43 (0.08, 2.28)

Note: —, not applicable; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; HR, hazard ratio; REC, respirable elemental carbon.

<sup>a</sup>Models adjusted for birth year and worker location. Excluding individuals with <5-y tenure.

<sup>b</sup>Models adjusted for birth year. Excluding individuals with <5-y tenure.

<sup>c</sup>Tests for linear trend were calculated using the median value (provided in Table S6) for each exposure category as continuous.

<sup>d</sup>Log µg/m<sup>3</sup>-y.

<sup>e</sup>Log µg/m<sup>3</sup>.

There is sufficient evidence that diesel engine exhaust causes cancer of the lung in humans; however, the evidence supporting a link between diesel exhaust and NHL is equivocal based on few studies.<sup>1</sup> In DEMS II, we found elevated HRs for continuous cumulative REC exposure for the total cohort for NHL, with elevated HRs being driven by ever-underground workers; exposure-response associations showed a tripling of risk in the top tertile of

exposure and a significant trend. Interestingly, although numbers of deaths were small, we also observed statistically significant HRs for both cumulative and average exposure for another lymphoid malignancy, MM. Animal studies have shown some increases in lymphoma incidence after diesel exposure, but these studies were small and, in some instances, the noted increases were not statistically significant.<sup>27–30</sup> Some human studies have

**Table 4.** Hazard ratios and 95% confidence intervals for cancer site-specific mortality for 15-y lagged REC cumulative exposure and average intensity in the DEMS II (USA, 1947–2015) total cohort (N = 12,315): categorical and continuous modeling results.

Cancer site	REC metric	Cases (n)	Continuous [HR (95% CI)] <sup>a</sup>	Tertile [HR (95% CI)] <sup>b</sup>			<i>p</i> <sub>Trend</sub> -Value <sup>b,c</sup>
				1	2	3	
Prostate	Cumulative	73	0.91 (0.78, 1.07)	1.0	0.83 (0.42, 1.64)	0.55 (0.24, 1.26)	0.143
	Average	73	0.92 (0.75, 1.11)	1.0	1.45 (0.70, 2.99)	0.91 (0.38, 2.13)	0.194
Pancreas	Cumulative	44	1.00 (0.83, 1.22)	1.0	0.57 (0.24, 1.34)	0.49 (0.17, 1.44)	0.558
	Average	44	0.97 (0.77, 1.23)	1.0	0.86 (0.36, 2.04)	0.77 (0.26, 2.25)	0.732
Leukemia	Cumulative	41	0.93 (0.76, 1.14)	1.0	0.52 (0.22, 1.21)	0.33 (0.11, 1.01)	0.202
	Average	41	0.98 (0.75, 1.27)	1.0	1.89 (0.82, 4.38)	0.94 (0.31, 2.83)	0.240
Brain	Cumulative	34	0.97 (0.79, 1.18)	1.0	0.64 (0.24, 1.69)	0.50 (0.15, 1.62)	0.440
	Average	34	0.96 (0.74, 1.24)	1.0	0.93 (0.34, 2.57)	0.96 (0.29, 3.16)	0.975
Esophagus	Cumulative	32	1.09 (0.86, 1.39)	1.0	1.75 (0.61, 4.99)	1.19 (0.33, 4.34)	0.632
	Average	32	1.10 (0.81, 1.48)	1.0	0.66 (0.24, 1.81)	0.51 (0.15, 1.80)	0.505
Stomach	Cumulative	31	1.10 (0.87, 1.40)	1.0	1.18 (0.42, 3.30)	1.28 (0.33, 4.91)	0.821
	Average	31	1.16 (0.86, 1.56)	1.0	2.23 (0.82, 6.04)	1.45 (0.40, 5.27)	0.673
Liver	Cumulative	31	1.20 (0.92, 1.57)	1.0	2.00 (0.66, 6.01)	1.90 (0.48, 7.43)	0.772
	Average	31	1.16 (0.84, 1.60)	1.0	0.83 (0.29, 2.38)	0.95 (0.26, 3.56)	0.831
Bladder urinary	Cumulative	27	1.25 (0.89, 1.74)	1.0	1.82 (0.63, 5.27)	3.31 (0.69, 15.92)	0.242
	Average	27	1.24 (0.82, 1.89)	1.0	1.07 (0.38, 2.97)	1.33 (0.29, 6.14)	0.713
Kidney	Cumulative	25	1.28 (0.96, 1.72)	1.0	7.16 (1.58, 32.49)*	2.81 (0.53, 14.85)	0.768
	Average	25	1.21 (0.86, 1.70)	1.0	5.20 (0.84, 32.16)	4.31 (0.63, 29.4)	0.492
Melanoma <sup>d</sup>	Cumulative	23	0.89 (0.70, 1.13)	—	—	—	—
	Average	23	0.89 (0.65, 1.22)	—	—	—	—
Multiple myeloma <sup>d</sup>	Cumulative	16	1.87 (1.11, 3.15)*	—	—	—	—
	Average	16	2.12 (1.06, 4.25)*	—	—	—	—
Buccal pharynx <sup>d</sup>	Cumulative	15	1.24 (0.85, 1.80)	—	—	—	—
	Average	15	1.42 (0.86, 2.35)	—	—	—	—
Mesothelioma <sup>d,e</sup>	Cumulative	11	1.04 (0.62, 1.77)	—	—	—	—
	Average	11	0.71 (0.41, 1.25)	—	—	—	—

Note: —, not applicable; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; HR, hazard ratio; ICD, *International Classification of Diseases*; REC, respirable elemental carbon. \**p* < 0.05.

<sup>a</sup>Models adjusted for birth year and worker location. Excluding individuals with <5-y tenure. Total person-years = 279,050. Cumulative unit is log µg/m<sup>3</sup>-y, average unit is log µg/m<sup>3</sup>.

<sup>b</sup>Values for tertile cut points are provided in Table S7.

<sup>c</sup>Tests for linear trend were calculated using the median value (Table S7) for each exposure category as continuous.

<sup>d</sup>Hazard ratio for categories (tertiles) not calculated for sites with <25 deaths.

<sup>e</sup>Starting with ICD-10<sup>17</sup> in 1999. Additionally adjusted for asbestos exposure.

shown a positive association between exposure to diesel exhaust and NHL<sup>31</sup> or CLL<sup>32</sup> separately, although others have not.<sup>1</sup> Positive associations between occupational exposure to diesel exhaust and risk of MM,<sup>33</sup> including in construction workers<sup>34</sup> and railroad workers,<sup>35</sup> have been observed. Existing studies, however, have not examined risk by quantitative estimates of diesel exposure. Studies of environmental air pollution, typically containing emissions from diesel engines, also provide some relevant information about diesel exhaust and cancer risk. Two recent studies have evaluated the impact of exposure to PM<sub>2.5</sub> and its constituents and found positive associations between incidence<sup>36</sup> and death<sup>37</sup> due to NHL. It is worth noting that the gaseous components of diesel exhaust include several known and suspected lymphomagens including 1,3-butadiene (with sufficient evidence for NHL and MM),<sup>38</sup> benzene and ethylene oxide (with limited evidence for NHL and MM)<sup>38,39</sup>; however, it is unclear if these components are related to the observed increased risk associated with diesel exhaust. Additional studies are needed to examine the relationship between diesel exhaust exposure and lymphoid malignancies, as well as the precise components of diesel exhaust responsible for the observed risks. Particular attention should be given to exploring incident NHL (not just mortality) given its favorable prognosis and to evaluating diesel exhaust exposure and risk of specific subtypes of NHL, which are etiologically heterogeneous.<sup>40</sup>

DEMS II SMR analyses showed excess mortality for lung, esophageal, and brain cancer, as well as for mesothelioma. Consistent with prior results, exposure-response associations between REC and lung cancer were evident in both the cohort and the companion nested case-control study,<sup>18</sup> which provided adjustment for smoking and other lifestyle factors. For brain and esophageal cancers and for mesothelioma, internal analyses of cumulative or average REC exposure did not reveal any positive association in the total cohort or by worker location. The only cancer site that showed a suggestive monotonic trend in the HRs was bladder cancer, a site that has been linked to diesel exhaust in previous studies,<sup>2,41–46</sup> although bladder cancer trends did not reach statistical significance at the  $p = 0.05$  level. The numbers of deaths for cancer sites other than the lung is small, and additional follow-up is needed with better statistical power to explore these effects, particularly for bladder cancer, where characterization of incident cancer is needed given the favorable survival rate that results in a small number of bladder cancer deaths relative to incident cases.<sup>47</sup>

We also observed significant excess mortality associated with IHD and cerebrovascular disease. In both instances, these excesses were observed in ever-underground workers, whereas no excess mortality (i.e., for IHD) or a deficit in mortality (i.e., for cerebrovascular disease) was observed for surface-only workers. Fine particles from diesel exhaust and other sources have been associated with these and other cardiovascular disease outcomes.<sup>6</sup> In a pooled analysis from six population-based cohorts in Europe, fine particulate matter [PM  $\leq 2.5$   $\mu\text{m}$  in aerodynamic diameter (PM<sub>2.5</sub>)] was associated with increased risk of cerebrovascular accident (or stroke) mortality.<sup>10</sup> In the California Teacher's Study, PM<sub>2.5</sub> and ultrafine particles from diesel sources were significantly associated with IHD mortality<sup>9</sup>; similar increased risks for IHD mortality were also observed in the American Cancer Society cohort<sup>8</sup> and in a large study of >2 million people in Canada.<sup>48</sup> In the original DEMS, exposure to diesel exhaust, as well as respirable dust, was also linked to increased IHD mortality.<sup>7</sup> Further exploration of the exposure-response profile for both IHD and cerebrovascular disease in relation to REC exposure will be pursued in a separate DEMS II analysis.

DEMS II is one of the largest cohort studies based on historical, quantitative exposure estimation of diesel exhaust. Detailed

work histories were available and used to assign exposure for all jobs, by year and facility. For the extended follow-up, work history information and additional estimation of exposure beyond 1997–1999 (depending on the facility) was not available for the entire cohort, resulting in an  $\sim 15$ -y period of unavailable exposure information. This was unlikely to have impacted our results, however, because the analyses for NHL and lung cancer identified a minimum of 15 y as the preferred lag period owing to the long latency for most cancers. For the exposure estimates that were available, it is likely that some misclassification may have occurred; such misclassification probably was nondifferential, given that it tends to dilute observed HRs. Further, we cannot rule out the impact of the healthy worker survivor bias<sup>49</sup> (see also Silverman et al.<sup>18</sup>) for some outcomes (e.g., IHD, chronic obstructive lung disease), which will tend to lead to downward bias. In addition, the cohort study did not collect information on potential confounders, such as smoking. For lung cancer, the companion nested case-control study showed that smoking was inversely associated with REC underground; smoking adjustment resulted in estimates of risk for lung cancer slightly larger than those observed without adjustment. Thus, it may be expected that the same would occur for the entire cohort. The risk estimates reported by Silverman et al.<sup>18</sup> represent the most comprehensive assessment of the relationship between diesel exhaust and lung cancer after multivariable adjustment and should be used for downstream risk assessment for lung cancer.

Our findings suggest associations for NHL and possibly for MM. The nonmetal mines in the present study were selected because of their low levels of exposure to potential confounders (e.g., radon, silica, asbestos).<sup>12,13,50</sup> In the nested case-control study (Silverman et al.<sup>18</sup>), these low levels were not associated with lung cancer. Radon (given the associations between radiation and lymphoid malignancies)<sup>31,51</sup> was not associated with NHL in the analyses of the cohort (Table S4). Other risk factors for lymphoid malignancies (e.g., infections, body weight) were not available in the cohort and thus could not be evaluated as confounders. Ultimately, the results observed for the lymphoid malignancies require cautious interpretation because the numbers of observed deaths are small, which increases the likelihood of a chance finding. The observed elevated risks underground and response relationships (for NHL), however, support an association with diesel exhaust exposure.

In conclusion, based on the extended follow-up of the DEMS II cohort, increased risks for lung cancer associated with diesel engine exhaust exposure are observed for nonmetal miners. Observed associations between diesel exhaust exposure and risk of death from NHL and the excesses in deaths for diseases of the respiratory and cardiovascular system, including IHD and cerebrovascular disease, warrant further study and provide evidence of the potential widespread public health impact of diesel exposure.

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