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The Diesel Exhaust in Miners Study (DEMS) II: Temporal Factors Related to Diesel Exhaust Exposure and Lung Cancer Mortality in the Nested Case–Control Study

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Background: The Diesel Exhaust in Miners Study (DEMS) was an important contributor to the International Agency for Research on Cancer reclassification of diesel exhaust as a Group I carcinogen and subsequent risk assessment. We extended the DEMS cohort follow-up by 18 y and the nested case–control study to include all newly identified lung cancer deaths and matched controls (DEMS II), nearly doubling the number of lung cancer deaths.

Objective: Our purpose was to characterize the exposure–response relationship with a focus on the effects of timing of exposure and exposure cessation.

Methods: We conducted a case–control study of lung cancer nested in a cohort of 12,315 workers in eight nonmetal mines (376 lung cancer deaths, 718 controls). Controls were selected from workers who were alive when the case died, individually matched on mine, sex, race/ethnicity, and birth year (within 5 y). Based on an extensive historical exposure assessment, we estimated respirable elemental carbon (REC), an index of diesel exposure, for each cohort member. Odds ratios (ORs) were estimated by conditional regression analyses controlling for smoking and other confounders. To evaluate time windows of exposure, we evaluated the joint OR patterns for cumulative REC within each of four preselected exposure time windows, <5, 5–9, 10–19, and ≥20 y prior to death/reference date, and we evaluated the interaction of cumulative exposure across time windows under additive and multiplicative forms for the joint association.

Results: ORs increased with increasing 15-y lagged cumulative exposure, peaking with a tripling of risk for exposures of ∼950 to <1,700 $\mu g/m^3$-y [OR = 3.23; 95% confidence interval (CI): 1.47, 7.10], followed by a plateau/decline among the heavily exposed (OR = 1.85; 95% CI: 0.85, 4.04). Patterns of risk by cumulative REC exposure varied across four exposure time windows ($p_{homogeneity} < 0.001$), with ORs increasing for exposures accrued primarily 10–19 y prior to death ($p_{trend} < 0.001$). Results provided little support for a waning of risk among workers whose exposures ceased for ≥20 y.

Conclusion: DEMS II findings provide insight into the exposure–response relationship between diesel exhaust and lung cancer mortality. The pronounced effect of exposures occurring in the window 10–19 y prior to death, the sustained risk 20 or more years after exposure ceases, and the plateau/decline in risk among the most heavily exposed provide direction for future research on the mechanism of diesel-induced carcinogenesis in addition to having important implications for the assessment of risk from diesel exhaust by regulatory agencies. https://doi.org/10.1289/EHP11980

Introduction

The Diesel Exhaust in Miners Study (DEMS) played a critical role in the 2012 reclassification of diesel exhaust by the International Agency for Research on Cancer (IARC) to a Group 1 carcinogen[1] and subsequent risk assessment. The study was one of the first to provide evidence of an exposure-response for diesel exhaust and lung cancer mortality based on quantitative estimates of historical diesel exposure adjusted for smoking and other confounders. To our knowledge, previous studies have not characterized the exposure–response relationship between lung cancer mortality and diesel exhaust in terms of the timing of exposure. Here we extend the mortality follow-up of the DEMS cohort of 12,315 workers through 2015, which added 18 y of follow-up and doubled the number of deaths from cancer, providing additional statistical power to characterize exposure–response relationships. We also extend the original nested case–control study of 198 lung cancer deaths and 562 controls to include all newly identified deaths from lung cancer and matched controls from the DEMS cohort of 12,315 workers. The entire study, including the extended follow-up of the cohort and the nested case–control study of lung cancer mortality, will be referred to as DEMS II (376 lung cancer deaths and 718 controls in the original and the extended follow-up nested case–control studies combined). The extended follow-up, coupled with the previous DEMS state-of-the-art exposure assessment,[2–6] afford a unique opportunity to explore several important questions regarding the carcinogenicity of diesel exhaust in the DEMS II nested case–control study of lung cancer, with adjustment for smoking and other confounders not available for the entire cohort.

Our purpose in the DEM II nested case–control study was two-fold: *a*) to further characterize the exposure–response relationship between diesel exhaust and lung cancer mortality based on a larger number of cases; and *b*) to examine the influence of temporal factors in relation to lung cancer mortality with a focus on the effect of timing of exposure and cessation of exposure. One finding from the original DEMS nested case–control study of lung cancer was an antagonistic interaction between cigarette smoking and diesel exhaust.[7] To explore smoking and other factors affecting the exposure–response relationship between diesel exhaust and lung cancer mortality in DEMS II, we repeated and extended the original analyses of the nested case–control study based on the additional follow-up, which included interviews

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The authors declare that they have nothing to disclose.

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with the next of kin of all newly identified lung cancer deaths and individually matched controls to obtain smoking histories and information on other potential confounders for adjustment in the DEMS II nested case–control analyses.

Methods

Cohort Design, Case Identification, and Control Selection

The methods used to conduct DEMS II were identical to those used to conduct the original study, which have been described in detail previously.[7,8] Briefly, the cohort comprised all blue-collar workers (excluding solely administrative workers or management) in eight nonmetal mines (three potash mines in New Mexico, three trona mines in Wyoming, one limestone mine in Missouri, and one salt mine in Ohio). These nonmetal mines were selected because of their low levels of exposure to potential occupational confounders (e.g., radon, silica, asbestos).[7–9] To be eligible for inclusion, workers had to be employed for at least 1 y after the introduction of diesel equipment into the study mine (year of introduction: 1947–1967 across the eight mines) through 31 December 1997. The DEMS II case series included all deaths from lung cancer [*International Classification of Diseases (ICD)*-9 code 162.9 and ICD-10 code C34] specified as either the underlying or contributing cause of death on the death certificate that occurred in the cohort through 31 December 2015, including those in the original study ($n = 438$). Of the 438 eligible cases identified, we interviewed 409 (93.4%) of their next of kin.

Controls were selected by incidence density sampling whereby we selected up to four controls for each lung cancer case by random sampling from among all members of the study cohort who were alive the day before the case died. Thus, controls could have served as controls for more than one case and cases could have served as controls for cases who died before the worker became a case (49 controls went on to become a case at a later point in time). Controls were individually matched to cases on study mine, gender, race and ethnicity (i.e., non-Hispanic White, Black, Hispanic, Native American, based on responses obtained at time of the interview), and birth year (within 5 y). In the analysis, all diesel exposure variables and certain potential confounders (i.e., cigarette smoking, employment in a high-risk occupation for lung cancer, and history of nonmalignant respiratory disease) for each control were truncated at the date of death of the matched case. Of the 895 eligible controls identified for interview, we interviewed 796 (88.9%) of them or their next of kin (if the subject was deceased or too ill for interview).

The Interview

As in the original study, the interview was conducted by telephone by a trained interviewer using a computerized assisted instrument. We designed the interview to obtain information on the subject's demographics, smoking history (including both active and environmental tobacco smoking), lifetime occupational history, medical history, and family medical history. The interview included information on all jobs held for at least 1 y since the age of 16 y, including those with possible exposure to diesel exhaust, asbestos, arsenic, and silica. For each job held at the study mine, we obtained the following information: use of respiratory protective equipment (i.e., respirators and masks) and the location within the mine where the subject spent most of his or her time (surface or underground). The latter was used to supplement information obtained from the subject's company employment record, particularly during the time period after the company work histories were obtained (i.e., 1 January 2000 to 31 December 2017).

Of the controls, 57% were conducted with next of kin of deceased controls and 43% were direct interviews with living controls. Data obtained from next of kin were similar to data collected from living controls. For the key confounder, cigarette smoking, the percent of direct and next-of-kin interviews by smoking history were: never smoker, 30% and 30%; occasional smoker, 3% and 2%; former smoker of less than one pack per day, 17% and 18%; former smoker of one to less than two packs per day, 30% and 24%; former smoker of 2 or more packs per day, 9% and 5%; current smoker of less than one pack per day, 2% and 4%; current smoker of one to less than two packs per day, 7% and 12%; current smoker of two or more packs per day, 2% and 5%, respectively.

The study protocol was approved by the institutional review boards of the U.S. National Cancer Institute (NCI) and Westat, Inc. All interviewees provided verbal informed consent before the interview, and next of kin of cases provided written consent to obtain medical records and pathology materials.

Diesel Exhaust Exposure Assessment

Diesel exhaust exposure occurred primarily underground at the eight study mines, with the main sources of diesel exposure occurring from ore extraction, haulage, and personnel transport vehicles. In contrast, surface workers typically had little to no diesel exposure, but some surface workers had low levels of diesel exposure from the operation (usually outdoors) of heavy equipment or diesel trucks or from working near diesel equipment at the surface.

The DEMS exposure assessors (P.S., R.V., and J.B. Coble), blinded to mortality outcomes, had developed quantitative estimates of historical exposure to respirable elemental carbon (REC) at each study mine as described previously.[2–6,9] REC is the component of diesel exhaust considered the best index of diesel exhaust in underground mining.[10] Location/job-specific exposures were estimated for each mine, by year, back to the introduction of diesel equipment at each mine. These estimates were based on measurements from 1998 to 2001 DEMS industrial hygiene surveys at each working mine, past Mine Safety and Health Administration enforcement surveys, other measurement data, and information from company records and interviews with long-term workers. REC estimates were developed for the reference year (1998 – 2001 = 100%, depending on the mine) for each mining facility/department/job based on the arithmetic means of the DEMS REC full-shift personal measurements.[5] The means were multiplied by the relative change in predicted historical carbon monoxide concentrations based on historical information on ventilation, horsepower, and other exposure determinants to derive historical estimates of REC as described in Vermeulen et al.[5] Additional detail on the diesel exhaust exposure assessment is given in the Supplementary Methods.

Statistical Analyses

Exposure estimates for all subjects were based on each subject's unique employment history. We estimated the risk of dying from lung cancer associated with three metrics of REC exposure: average intensity of exposure, cumulative exposure, and duration of exposure. Unless otherwise noted, quintile, quartile, and tertile cut points for exposure metrics were selected to achieve approximately equal numbers of cases in each category. When numbers permitted, we split the top quintile at the intra-category median to estimate risk among the most heavily exposed. Conditional logistic regression analysis was used to quantify the exposure–response relationship between lung cancer and these metrics of diesel exposure after adjustment for potential confounding factors. Statistical models included a term for exposure [e.g., quintiles of average REC intensity ($\mu g/m^3$), quintiles of cumulative REC ($\mu g/m^3$-y), or duration of REC exposure (years)]. To identify confounders, each potential confounder based on the literature (see Table 1) was entered into the conditional

logistic model along with smoking using forward stepwise selection, and those that changed the odds ratios (ORs) by more than 10% were included in the final models. The source of data for all confounders was the personal interview with each subject or their next of kin with the exception of data on exposure to radon, asbestos, silica, PAH from nondiesel sources, and respirable dust, which were based on mine-specific measurements.

Final models included terms for the following potential confounding factors: smoking status (never, former, current) and intensity (unknown or occasional smoker, <1, 1 to <2, ≥2 packs per day) by work location (surface only, ever underground); employment in a high-risk occupation for lung cancer for at least 10 y (i.e., as a miner outside the study mine, truck driver, welder, painter); history of nonmalignant respiratory disease 5 or more years before death/reference date (primarily pneumoconiosis, emphysema, chronic obstructive pulmonary disease, silicosis, tuberculosis); and body mass index (BMI) based on usual adult height and weight (<18.5, 18.5 to <25.0, 25.0 to <30.0, ≥30.0 kg/m^2).

Location worked was included in the model in combination with the smoking variables because the risk of lung cancer from cigarette smoking was different for surface and underground workers.[7] Other potential confounders [i.e., duration of cigar smoking; frequency of pipe smoking; environmental tobacco smoking; family history of lung cancer in a first-degree relative; education; leisure time physical activity; estimated cumulative exposure to radon, asbestos, silica, polycyclic aromatic hydrocarbons (PAHs) from nondiesel sources, and respirable dust in the study mine based on air measurements and other data[2]] were evaluated but had little or no impact on ORs (i.e., inclusion of these factors in the models changed the point estimates for diesel exposure by ≤10%) and were not included in the final models. Exposure to other possible confounders such as arsenic, nickel, and cadmium were not a concern; measurements from surveys at the study facilities indicated low or nondetectable levels in the study mines.[2] In categorical analyses, missing values for a covariate were included as a separate category. We examined effect modification in categorical analyses by stratifying on mine type (potash, trona, limestone, salt), use of protective equipment (yes/no), exposure to diesel exhaust in a job outside the study mine (yes/no), and cigarette smoking [smoking status (nonsmoker, former smoker, current smoker) by packs per day (<1, 1 to <2, ≥2 packs per day)].

To test for trend, a Wald test was performed, treating the median value for each level of the categorical exposure variable among the controls as continuous in the conditional logistic regression model. To test for interaction between two risk factors, whether both risk factors were categorical or one factor was categorical and the other continuous, we added a cross-product term(s) to the conditional logistic model and conducted a likelihood ratio test between the model with and without the cross-product term(s). For example, in the exposure cessation analysis, we tested for the interaction between the trends in risk for cumulative REC exposure across the medians of the categories 0 to <10, 10 to <159, 159 to <731, and ≥731 $\mu g/m^3$-y lagged 15 y and the time since exposure ceased (<20 and ≥20 y). Including an interaction term in the model, we estimated the trends in risk by <20 and ≥20 y. A Wald test was used to assess the level of significance of each trend being different from zero. All statistical tests were two-sided with a significance level of $\alpha = 0.05$.

We extended the original DEMS modeling to explore quantitative patterns in ORs and excess odds ratio (EORs; EOR = OR-1) for both continuous average REC intensity and continuous cumulative REC exposure, denoted d, by fitting various 2-parameter models including: a log-linear model, $OR(d) = \exp(\beta d + \gamma d^2)$; a power model, $OR(d) = \exp[\beta \ln(d) + \gamma \ln(d)^2]$; and a linear-exponential EOR model, $OR(d) = 1 + \beta d \exp(\gamma d)$. We evaluated both the two parameter (β, γ) and one parameter (β, $\gamma = 0$) variants. All models were adjusted for the same set of potential confounding factors as described above. We identified a preferred model based on the minimum Akaike Information Criterion (AIC), thus enabling an agnostic exploration of models without regard to level of risk.[11–13] To better evaluate OR patterns for the models shown in Figure 1 in relation to the category-specific ORs, we adjusted the continuous models to a common referent, namely the mean exposure among controls and the weighted mean of the category-specific ORs (Supplementary Methods).

We conducted two separate but related modeling analyses. First, for average REC intensity and cumulative REC exposure, we evaluated lag intervals by setting exposure occurring 0, 3, 5, . . . , 25 y (by 2-y intervals) before the death/reference date to zero and by comparing changes in model deviance to a model that omitted REC exposure. The lag interval with the largest improvement in model fit occurred for a lag between 12 and 14 y for average REC intensity and 15 and 17 y for cumulative REC exposure (Supplementary Methods and Supplementary Figure S1). For comparability, we used a 15-y lag for both exposure metrics in initial analyses. In a second modeling analysis, we considered the joint OR patterns for cumulative REC within each of four preselected exposure time windows, <5, 5–9, 10–19, and ≥20 y prior to death/reference date

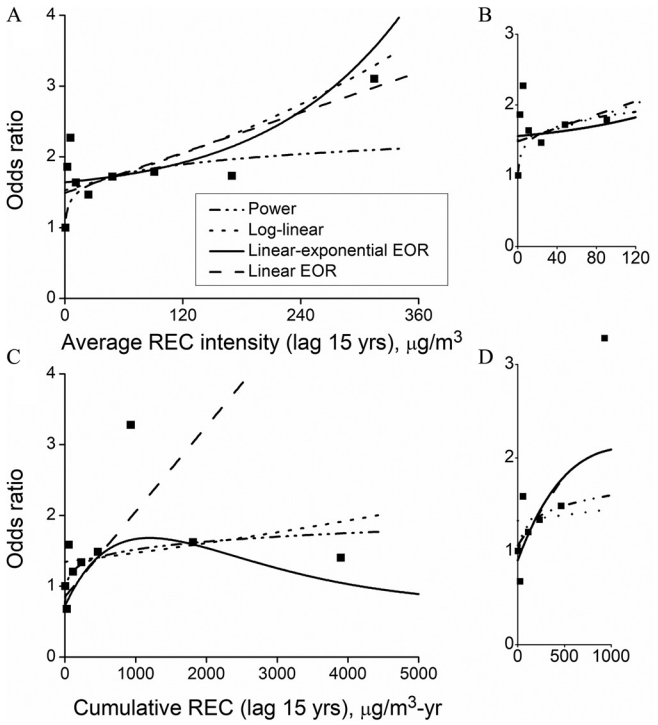

Figure 1. ORs for average REC intensity for the full range (A) and restricted range (B) and cumulative REC exposure for the full range (C) and restricted range (D) lagged 15 y by expanded categories from Table S3 (solid squares) and various fitted models for continuous exposure (d). Models include: *a*) a power model, $OR(d) = \exp[\beta \ln(d)]$ (dot-dot-dash line); *b*) a log-linear OR model, $OR(d) = \exp(\beta d)$ model (dotted line); *c*) a linear excess OR model, $OR(d) = 1 + \beta d$ (dash line); and *d*) a linear-exponential excess OR model, $OR(d) = 1 + \beta d \exp(\gamma d)$ (solid line). For each exposure metric and for the full and restricted exposure ranges, the fitted continuous models are adjusted to a common referent value, namely, the mean exposure among controls and the weighted mean of the category-specific ORs. (B) and (D) reflect common aspect ratios. DEMS II, United States, 1947–2015, 376 lung cancer deaths and 718 controls. Source data: Table S3. Note: DEMS, Diesel Exhaust in Miners Study; exp, exponential function; OR, odds ratio; REC, respirable elemental carbon.

and evaluated the interaction of cumulative exposure across time windows under additive and multiplicative forms for the joint association. An additive joint association with cumulative REC exposure within each window specified by a 1-parameter log-linear relationship, i.e., $\mathrm{OR}(d) = \sum_k \exp(\beta_k d_k) - 3$, where d_k was the cumulative REC within the kth window, $k = 1,2,3,4$, was the preferred model (Supplementary Table S7), and served as the basis for the evaluation homogeneity across exposure windows.

Of the 409 lung cancer cases and 796 controls interviewed for study, subjects were excluded for the following reasons: one case was identified as unlikely to have had lung cancer; 25 cases did not have any eligible controls (because of race and ethnicity for 23 non-White or Hispanic cases, female gender for 1 case, age for 1 case who was 88 y of age), and next of kin of 3 cases were nonresponsive; 69 controls had discordant race/ethnicity based on self-reported information obtained during interview and ultimately became ineligible for study. An additional four controls were nonresponsive. Four cases and five controls were found ineligible for inclusion in the cohort based on the company work histories.[8] The final analytic dataset included 376 cases and 718 controls (844 controls for analytic purposes because some cohort members served as controls for more than one case and some cases were controls before they became a case). All analyses pertained to the total mine (surface and underground combined) unless otherwise noted.

Categorical analyses were run using SAS 9.4, component SAS/STAT 14.2 (SAS Institute Inc.) on a Linux platform and continuous analyses were run using EPICURE 2021 software (http://epicurehelp.riskscience.com/).

Results

The analytical data set was predominantly male, with females comprising only 7 cases and 13 controls. The lung cancer risk associated with potential confounding factors is shown in Table 1. As expected, cigarette smoking was associated with a statistically significant increased risk, with risk peaking at 11.7 (95% CI: 5.9, 22.9) for current smokers of 2 or more packs per day. Surface workers experienced higher risks than underground workers for smokers of 1 to <2 and 2 or more packs per day regardless of smoking status (i.e., former or current) (Supplementary Table S1). Surface and underground nonsmokers experienced similar risks after adjustment for cumulative REC lagged 15 y (Supplementary Table S1), suggesting that the difference in risk between surface and underground workers is due to smoking. As in the original DEMS analysis,[7] because of a stronger smoking effect in surface workers, we included a term for the cross classification of work location, smoking status, and smoking intensity in all models used to estimate lung cancer risk by diesel exposure. Other potential confounders significantly associated with risk were employment in a high-risk occupation for at least 10 y, history of nonmalignant respiratory disease for at least 5 y prior to death/reference date, family history of lung cancer, environmental tobacco smoke (living with one smoker), BMI (overweight), and education (less than a high school education). Of these, only cigarette smoking cross classified by work location, employment in a high-risk occupation, a history of nonmalignant respiratory disease, and BMI were included in the final models because they impacted the estimates of risk by more than 10%. Exposure to the other potential confounders (i.e., radon, asbestos, silica, nondiesel PAHs, and respirable dust) were not associated with lung cancer risk. Levels of potential confounders such as radon, asbestos, and silica were very low at the study mines [e.g., for radon, arithmetic means were ≤0.02 Working Level (WL), which is one-fiftieth the maximum permissible concentration of 1.0 WL in U.S. mines and equal to or below the U.S. residential limit of 148 becquerels/m^3 (or 4 pico-Curies/L)].[2,9]

The Exposure–Response Relationship

We observed a statistically nonsignificant trend in risk with increasing 15-y lagged average REC intensity ($p_{trend} = 0.078$) (Table 2). Risk also increased with increasing cumulative REC lagged 15 y but peaked at exposure below the median of the top quintile (951 to <1,696 μg/m^3-y) (OR = 3.23; 95% CI: 1.47,7.10) followed by a plateau/decline in risk at exposure above the median (≥1,696 μg/m^3-y) (OR = 1.85; 95% CI: 0.85, 4.04), suggesting that the exposure–response relationship is not log-linear (see below). For duration of exposure, workers exposed for 15 or more years experienced a statistically nonsignificant increased risk (OR = 1.42; 95% CI: 0.93, 2.18), but no risk elevations were seen for those exposed <15 y.

Nearly all diesel exposure in DEMS occurred underground (average REC intensity: 1–423 μg/m^3 for underground workers and 0–8 μg/m^3 for surface workers). When we examined the exposure–response relationship only among workers who had worked underground, patterns similar to those indicated for all workers were apparent (Table 3). We observed relatively consistent trends in risk with increasing average REC intensity unlagged and lagged 15 y ($p_{trend} = 0.037$ and 0.009, respectively). In the lagged analysis, underground workers in the top quintile (≥162 μg/m^3) had a significant elevated risk (OR = 2.98; 95% CI: 1.19, 7.51). Trends for increasing cumulative REC exposures were not statistically significant ($p_{trend} = 0.134$ and 0.072 for unlagged and lagged 15 y, respectively); however, risk increased with increasing 15-y lagged exposure through the fourth quintile (675 to <1,254 μg/m^3-y) (OR = 3.83; 95% CI: 1.71, 8.55) followed by a plateau/decline at the top quintile (≥1,254 μg/m^3-y) (OR = 2.09; 95% CI: 0.94, 4.66). Subjects exposed for 15 or more years experienced an increased risk (OR = 1.77; 95% CI: 1.00, 3.11), but no significant elevations were apparent for those exposed <15 y. The trend in risk with increasing duration of exposure among underground workers was marginally significant ($p_{trend} = 0.052$). In contrast, we observed no consistent patterns in risk among surface workers, although numbers were small for those who worked exclusively at the surface (68 cases and 115 controls), and the levels of diesel exposure at the surface of the study mines were low (average REC intensity for workers at the surface was 0–8 μg/m^3) (Supplementary Table S2).

For all workers (surface and underground), we fitted various models for continuous 15-y lagged average REC intensity and cumulative REC for the full range of exposure, and a restricted range, along with an expanded number of category-specific ORs (Figure 1; Supplementary Tables S3 and S4). ORs for 15-y lagged average REC intensity exhibited a nonmonotonic increase over the full range of exposure. The pattern of ORs for average REC intensity was best explained by a 1-parameter log-linear model (dotted line), with $p = 0.057$ for the test of a null association; however, the fit of the various models differed only slightly (Supplementary Table S4). The ORs for cumulative REC exposure lagged 15 y exhibited an increasing pattern that leveled off when exposures reached 1,000 μg/m^3-y and then plateaued/declined for the most heavily exposed workers (Figure 1). The 2-parameter linear-exponential EOR model (solid line) was the preferred model for cumulative REC, with $p = 0.014$ for the test of a null association. The fitted models well characterized exposures across the full range and for the lowest exposures (Figure 1B,D).

We evaluated the overall categorical exposure–response by four potential effect modifiers—mine type, use of protective equipment, exposure to diesel exhaust in a job outside the study mine (e.g., truck mechanic), and cigarette smoking. Risk increased with increasing 15-y lagged average REC intensity and cumulative REC for workers employed in trona, potash, and limestone mines

Table 1. ORs and 95% CIs for potential risk factors for lung cancer, DEMS II, United States, 1947–2015, 376 lung cancer deaths and 718 controls.

Potential risk factor	Cases	Controls	OR (95% CI)
Smoking status/smoking intensity[a]			
Never smoker	26	232	1.00 (Ref)
Former, <1	44	125	2.97 (1.61, 5.46)
Former, 1 to <2	76	152	3.83 (2.22, 6.60)
Former, ≥2	23	41	6.91 (3.28, 14.57)
Current, <1	24	43	7.31 (3.48, 15.35)
Current, 1 to <2	100	138	9.52 (5.38, 16.86)
Current, ≥2	48	44	11.68 (5.95, 22.92)
Unknown	35	69	4.46 (2.28, 8.73)
Employment in other high-risk occupations[b,c]			
No	178	473	1.00 (Ref)
0 to <5 y	39	112	0.86 (0.55, 1.36)
5 to <10 y	15	59	0.58 (0.30, 1.13)
≥10 y	46	67	1.85 (1.17, 2.92)
Unknown	98	133	1.47 (1.01, 2.14)
p_{trend}			0.022
History of respiratory disease[b,d]			
No	153	573	1.00 (Ref)
<5 y before death/reference date	41	21	6.21 (3.30, 11.68)
≥5 y before death/reference date	41	64	2.30 (1.40, 3.80)
Unknown	141	186	2.25 (1.59, 3.19)
Family history of lung cancer[b]			
No	266	674	1.00 (Ref)
Yes	59	97	1.71 (1.14, 2.56)
Unknown	51	73	1.64 (1.05, 2.57)
Cigar smoking duration[b]			
Nonsmoker of cigars	314	690	1.00 (Ref)
<10	11	46	0.69 (0.32, 1.46)
10 to <20	8	20	1.16 (0.45, 2.99)
≥20	4	16	1.36 (0.39, 4.79)
Unknown	39	72	0.55 (0.31, 0.95)
p_{trend}			0.442
Pipe smoking (number of pipefuls/wk)[e]			
Nonsmoker of pipes	276	603	1.00 (Ref)
<10	17	45	0.77 (0.40, 1.49)
10 to <20	9	26	0.64 (0.27, 1.50)
≥20	8	40	0.52 (0.22, 1.26)
Unknown	66	130	0.91 (0.58, 1.41)
p_{trend}			0.091
Number of smokers living in participant's childhood/adult home[b]			
0 smokers	47	189	1.00 (Ref)
1 smoker	115	227	1.73 (1.13, 2.66)
≥2 smokers	152	307	1.26 (0.82, 1.94)
Unknown	62	121	0.87 (0.53, 1.44)
Body mass index[b]			
<18.5 (underweight)	0	6	
18.5 to <25.0 (normal weight = Ref)	165	319	1.00 (Ref)
25.0 to <30.0 (overweight)	119	334	0.64 (0.46, 0.89)
≥30.0 (obese)	34	84	0.71 (0.42, 1.21)
Unknown	58	101	0.51 (0.31, 0.84)
p_{trend}			0.058
Physical activity[b]			
Exercise ≥1/day	51	132	1.00 (Ref)
Exercise <1/day	262	619	1.11 (0.74, 1.67)
Unknown	63	93	0.99 (0.56, 1.76)
Education[b]			
Any college	44	128	1.00 (Ref)
Vocational school	19	45	1.56 (0.72, 3.41)
High school/GED	109	223	1.39 (0.87, 2.23)
<High school	156	361	1.72 (1.07, 2.77)
Unknown	48	87	1.20 (0.64, 2.23)
Radon [quartiles (working level months)][f,g,h]			
No exposure	124	308	1.00 (Ref)
>0 to <0.5	63	135	0.78 (0.51, 1.21)
0.5 to <1.4	63	131	1.07 (0.69, 1.65)
1.4 to <2.9	63	117	1.49 (0.97, 2.27)
≥2.9	63	153	1.05 (0.68, 1.61)
p_{trend}			0.289
Asbestos (quartiles)[b,f,i]			
No exposure	217	494	1.00 (Ref)
>0 to <1.4	38	66	0.98 (0.59, 1.64)
1.4 to <5.3	41	106	0.72 (0.45, 1.15)
5.3 to <12.6	40	105	0.73 (0.45, 1.18)
≥12.6	40	73	1.19 (0.73, 1.94)
p_{trend}			0.671
Silica (quartiles)[b,f,i]			
No exposure	89	209	1.00 (Ref)
>0 to <4.4	71	156	0.63 (0.28, 1.43)
4.4 to <11.8	72	171	0.75 (0.32, 1.76)
11.8 to <23.2	72	148	1.05 (0.45, 2.47)
≥23.2	72	160	0.84 (0.35, 2.00)
p_{trend}			0.364
PAHs from nondiesel sources (quartiles)[b,f,j]			
No exposure	215	489	1.00 (Ref)
>0 to <1.5	40	81	0.79 (0.49, 1.29)
1.5 to <4.3	40	84	0.94 (0.58, 1.53)
4.3 to <12.6	40	117	0.74 (0.47, 1.18)
≥12.6	41	73	1.20 (0.74, 1.94)
p_{trend}			0.636
Cumulative respirable dust [quartiles, (mg/m^3-y)][b,f,k]			
>0 to <5.27	94	192	1.00 (Ref)
5.27 to <13.32	94	209	1.21 (0.79, 1.85)
13.32 to <27.21	94	239	1.08 (0.69, 1.70)
≥27.21	94	204	1.32 (0.82, 2.13)
p_{trend}			0.352

Note: *p*-Values based on two-sided Wald test for linear trend. BMI, body mass index; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; GED, general equivalency diploma; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; Ref, referent; UG, underground.

[a]Adjusted for cumulative REC lagged 15 y, history of respiratory disease, history of high risk occupation, location of employment, and BMI.

[b]Adjusted for smoking status/mine location combination (surface work only/never smoker, surface work only/unknown/occasional smoker, surface work only/former smoker/<1 pack/day, surface work only/former smoker/1 to <2 packs/day, surface work only/former smoker/≥2 packs/day, surface work only/current smoker/<1 pack/day, surface work only/current smoker/1 to <2 packs/day, surface work only/current smoker/≥2 packs/day, ever UG work/never smoker, ever UG work/unknown/occasional smoker, ever UG work/former smoker/<1 pack/day, ever UG work/former smoker/1 to <2 packs/day, ever UG work/former smoker/≥2 packs/day, ever UG work/current smoker/<1 pack/day, ever UG work/current smoker/1 to <2 packs/day, ever UG work/current smoker/≥2 packs/day).

[c]Other high-risk occupations for lung cancer (i.e., a miner who worked outside the study mines, truck driver, welder, painter).

[d]History of respiratory disease excluding asthma, pneumonia, and bronchitis.

[e]Adjusted for cigarette smoking and education.

[f]Pertains only to exposures at study mines.

[g]Quartiles of cumulative radon exposure derived from estimated levels in Working Level multiplied by months at each job, summed across jobs.

[h]Adjusted for smoking status: unknown, never smoker, occasional smoker, former smoker/<1 pack/day, former smoker/1 to <2 packs/day, former smoker/≥2 packs/day, current smoker/<1 pack/day, current smoker/1 to <2 packs/day, current smoker/≥2 packs/day.

[i]Quartiles of cumulative exposure derived from intensity scores (0–3) multiplied by years at each job, summed across jobs.

[j]Quartiles of cumulative exposure derived from the presence or absence of nondiesel PAHs based on job title tasks (0,1) multiplied by years at each job, summed across jobs.

[k]Respirable dust in milligrams per cubic meter multiplied by years of exposure.

(too few workers were employed in the one salt mine to estimate risk separately) (Supplementary Table S5), with significant trends for cumulative REC in trona and potash workers ($p_{trend} = 0.025$ and $p_{trend} = 0.009$, respectively). Patterns of risk were also similar regardless of whether a subject had used protective equipment or had diesel exposure outside of that incurred at the study mines. We observed a significant trend in risk with increasing cumulative REC lagged 15 y among workers who used protective equipment (OR = 1.0 for <25 $\mu g/m^3$-y; OR = 1.98 (95% CI: 0.27, 14.28) for 25 to <475 $\mu g/m^3$-y; OR = 24.12 (95% CI: 2.21, 263.13) for ≥475 $\mu g/m^3$-y) ($p_{trend} = 0.005$) and those with no outside diesel exposure (OR = 1.0 for <25 $\mu g/m^3$-y; OR = 0.11 (95% CI: 0.01, 1.43) for 25 to <475 $\mu g/m^3$-y; OR = 5.94 (95% CI: 0.40, 87.71) for ≥475 $\mu g/m^3$-y) ($p_{trend} = 0.018$).

Table 2. ORs and 95% CIs for average and cumulative REC and total duration REC exposure DEMS II, United States, 1947–2015, 376 lung cancer deaths and 718 controls.

Exposure metric	Cases	Controls	OR (95% CI)	p_{trend}
Average REC intensity [quintiles (top quintile cut at the median); unlagged ($\mu g/m^3$)]				
0 to <2	75	175	1.00 (Ref)	0.105
2 to <8	75	198	0.77 (0.41, 1.44)	
8 to <70	75	192	0.96 (0.42, 2.18)	
70 to <142	75	148	1.09 (0.46, 2.56)	
142 to <207	38	73	1.19 (0.47, 2.99)	
≥207	38	58	1.50 (0.56, 4.03)	
Average REC intensity [quintiles (top quintile cut at the median); lagged 15 y ($\mu g/m^3$)]				
0 to <1	68	216	1.00 (Ref)	0.078
1 to <4	82	199	0.93 (0.55, 1.58)	
4 to <50	75	160	1.37 (0.70, 2.68)	
50 to <131	75	148	1.79 (0.89, 3.60)	
131 to <195	38	74	1.39 (0.64, 3.03)	
≥195	38	47	2.37 (0.99, 5.67)	
Cumulative REC [quintiles (top quintile cut at the median); unlagged ($\mu g/m^3$-y)]				
0 to <17	75	175	1.00 (Ref)	0.216
17 to <126	75	214	1.08 (0.65, 1.80)	
126 to <492	75	169	1.40 (0.68, 2.87)	
492 to <1,342	75	130	1.99 (0.94, 4.17)	
1,342 to <2,816	38	83	2.11 (0.93, 4.80)	
≥2,816	38	73	1.79 (0.77, 4.18)	
Cumulative REC [quintiles (top quintile cut at the median); lagged 15 y ($\mu g/m^3$-y)]				
0 to <6	75	209	1.00 (Ref)	0.224
6 to <55	75	225	1.07 (0.63, 1.80)	
55 to <318	75	142	1.52 (0.80, 2.90)	
318 to <951	75	150	2.33 (1.19, 4.55)	
951 to <1,696	38	54	3.23 (1.47, 7.10)	
≥1,696	38	64	1.85 (0.85, 4.04)	
Duration of REC exposure (y)				
<5	194	431	1.00 (Ref)	0.138
5 to <10	45	118	0.93 (0.58, 1.49)	
10 to <15	48	117	0.90 (0.55, 1.48)	
≥15	89	178	1.42 (0.93, 2.18)	

Note: *p*-Values based on two-sided Wald test for linear trend (Supplementary Table S8); adjusted for smoking status/mine location combination (surface work only/never smoker, surface work only/unknown/occasional smoker, surface work only/former smoker/< 1 pack/day, surface work only/former smoker/1 to <2 packs/day, surface work only/former smoker/≥ 2 packs/day, surface work only/current smoker/< 1 pack/day, surface work only/current smoker/1 to <2 packs/day, surface work only/current smoker/≥ 2 packs/day, ever UG work/never smoker, ever UG work/unknown/occasional smoker, ever UG work/former smoker/< 1 pack/day, ever UG work/former smoker/1 to <2 packs/day, ever UG work/former smoker/≥ 2 packs/day, ever UG work/current smoker/< 1 pack/day, ever UG work/current smoker/1 to <2 packs/day, ever UG work/current smoker/≥ 2 packs/day); history of respiratory disease 5 or more years before date of death/reference date; history of a high-risk job for lung cancer for at least 10 y; and BMI. BMI, body mass index; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; OR, odds ratio; REC, respirable elemental carbon; Ref, referent; UG, underground.

To follow-up on the original DEMS findings,[7] we explored the joint effects of cumulative REC and smoking (Table 4). Overall, the exposure–response relationship for cumulative REC lagged 15 y did not vary by smoking status/intensity ($p_{interaction} = 0.422$). Among nonsmokers, risk increased with cumulative REC lagged 15 y; heavily exposed (top tertile) nonsmokers had an OR of 3.79 (95% CI: 1.13, 12.64). A similar pattern was observed for all former smokers and current smokers of <1 and 1 to 2 packs per day. However, among current smokers of 2 or more packs per day (48 cases and 44 controls), risk decreased with increasing exposure. ORs across tertiles of cumulative REC lagged 15 y exhibited a 58% decline, from 31.6 (95% CI: 10.0, 99.3) to 13.3 (95% CI: 3.2, 55.4).

Timing of Exposure

We considered patterns of lung cancer risk from exposures that occurred within predefined exposure time windows: <5 y, 5–9 y, 10–19 y, and ≥20 y prior to date of death or reference date to identify risk-relevant time periods of exposure (Figure 2; Table S6). For overall cumulative REC exposure unlagged, none of the 1- or 2-parameter models significantly rejected a null association (Table S7). The preferred model with minimum AIC for cumulative REC within time windows was the additive association with exposure within each window specified by a 1-parameter log-linear relationship (Table S7). We observed significant heterogeneity in the cumulative REC-response patterns across time windows ($p < 0.001$) for the 3 degrees of freedom (df) test of homogeneity. In particular, there was a significantly increasing trend in the ORs for cumulative REC exposures accrued 10–19 y prior to death ($p < 0.01$ for the 1 df test of a null association), whereas there were no rejections from a null association for the other time windows ($p = 0.251$, $p = 0.105$, and $p = 0.924$ for tests of a null association for exposures accrued <5, 5–9, and ≥20 y prior to death, respectively). This result was consistent with the observed deviance-based lag of 15 y described above. The fitted exposure–response model for the ≥20-y time window appeared to be discrepant with the category-specific ORs. This may have been because of one highly influential OR [OR = 1.23 (95% CI: 0.65, 2.34)] among workers with exposures above 1,280 $\mu g/m^3$-y (39 cases, 59 controls); ORs were elevated for exposures below this value, with a pattern that was comparable to the 10- to 19-y time window (dashed line in Figure 2). After omission of workers in the ≥20-y time window with exposures above 1,280 $\mu g/m^3$-y, results were comparable to those in the 10- to 19-y

Table 3. ORs and 95% CIs for average and cumulative REC and total duration REC exposure for subjects who ever worked underground jobs, DEMS II, United States, 1947–2015, 252 lung cancer deaths and 471 controls.

Exposure metric	Cases[a]	Controls[a]	OR (95% CI)	p_{trend}
Average REC intensity [quintiles; unlagged ($\mu g/m^3$)]				
0 to <26	41	73	1.00 (Ref)	0.037
26 to <62	41	84	1.07 (0.52, 2.22)	
62 to <121	41	91	0.90 (0.44, 1.83)	
121 to <168	41	48	2.30 (1.02, 5.18)	
≥168	41	57	2.15 (0.88, 5.29)	
Average REC intensity [quintiles; lagged 15 y ($\mu g/m^3$)]				
0 to <7	41	87	1.00 (Ref)	0.009
7 to <47	41	76	0.82 (0.39, 1.73)	
47 to <93	41	77	1.31 (0.61, 2.82)	
93 to <162	41	63	1.40 (0.61, 3.21)	
≥162	41	50	2.98 (1.19, 7.51)	
Cumulative REC [quintiles; unlagged ($\mu g/m^3$-y)]				
0 to <198	41	81	1.00 (Ref)	0.134
198 to <469	41	74	1.08 (0.55, 2.11)	
469 to <958	41	64	1.57 (0.78, 3.18)	
958 to <2,210	41	70	1.62 (0.79, 3.31)	
≥2,210	41	64	1.72 (0.83, 3.55)	
Cumulative REC [quintiles; lagged 15 y ($\mu g/m^3$-y)]				
0 to <95	41	106	1.00 (Ref)	0.072
95 to <276	41	58	1.25 (0.59, 2.69)	
276 to <675	41	84	1.63 (0.78, 3.38)	
675 to <1,254	41	48	3.83 (1.71, 8.55)	
≥1,254	41	57	2.09 (0.94, 4.66)	
Duration of REC exposure (y)				
<5	70	132	1.00 (Ref)	0.052
5 to <10	29	54	1.20 (0.64, 2.27)	
10 to <15	37	65	1.20 (0.63, 2.27)	
15+	69	102	1.77 (1.00, 3.11)	

Note: *p*-Values based on two-sided Wald test for linear trend (Supplementary Table S8). Adjusted for smoking status (never smoker, unknown/occasional smoker, former smoker/< 1 pack/day, former smoker/1 to <2 packs/day, former smoker/≥ 2 packs/day, current smoker/< 1 pack/day, current smoker/1 to <2 packs/day, current smoker/≥ 2 packs/day); history of respiratory disease 5 or more years before date of death/reference date; history of a high-risk job for lung cancer for at least 10 y; and BMI. BMI, body mass index; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; OR, odds ratio; REC, respirable elemental carbon; Ref, referent.
[a]A total of 47 cases and 183 controls were excluded because they no longer belonged to a complete matched set after analysis was restricted to underground workers.

Table 4. ORs, 95% CIs, and numbers of cases/controls for cumulative REC lagged 15 y by smoking status/intensity, DEMS II, United States, 1947–2015, 376 lung cancer deaths and 718 controls.

Smoking status, intensity (packs per day)	Tertile 1, 0 to <26 μg/m^3-y	Tertile 2, 26 to <475 μg/m^3-y	Tertile 3, ≥475 μg/m^3-y
Nonsmoker	1.00 (Ref) 7/99	1.48 (0.43, 5.16) 7/79	3.79 (1.13, 12.64) 12/54
Former, <1 pack/day	2.78 (0.83, 9.35) 7/44	4.48 (1.39, 14.50) 14/43	10.40 (3.26, 33.12) 23/38
Former, 1 to <2 packs/day	6.14 (2.21, 17.04) 22/60	6.10 (2.12, 17.52) 26/49	10.03 (3.24, 31.08) 28/43
Former, 2+ packs/day	6.36 (1.45, 27.97) 4/15	13.82 (3.71, 51.46) 11/15	22.17 (5.24, 93.75) 8/11
Current, <1 pack/day	8.18 (2.54, 26.36) 10/24	22.28 (5.57, 89.12) 8/11	13.54 (2.94, 62.45) 6/8
Current, 1 to <2 packs/day	12.62 (4.79, 33.28) 41/68	14.91 (5.02, 44.26) 29/44	31.16 (9.60, 101.12) 30/26
Current, 2+ packs/day	31.57 (10.04, 99.31) 23/16	17.94 (5.00, 64.40) 17/17	13.27 (3.18, 55.41) 8/11
Don't know/occasional[a]	3.46 (1.04, 11.45) 10/38	8.11 (2.35, 28.04) 12/18	17.07 (4.56, 63.97) 13/13

Note: Adjusted for history of respiratory disease 5 or more years before date of death/reference date, history of a high-risk job for lung cancer for at least 10 y, mine location (surface only vs. any underground work), and BMI. p-Value for interaction between smoking status/intensity and cumulative REC lagged 15 y = 0.422. BMI, body mass index; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; OR, odds ratio; REC, respirable elemental carbon; Ref, referent.
[a]Unknown includes subjects who were smokers with unknown smoking status at death and/or unknown smoking intensity, and subjects considered occasional smokers, who smoked at least 100 cigarettes during their lifetimes, but never smoked regularly (≥1 cigarette per day for at least 6 months).

time window; homogeneity in the exposure–response patterns across time windows continued to be rejected ($p = 0.031$).

Table 5 shows the effect of cessation of cumulative REC exposure on lung cancer risk. The highest exposed workers (quartile 4) with 20 or more years since last exposure had a lower OR than those with <20 y since last exposure (cumulative REC lagged 15 y: 1.75 (95% CI: 0.64, 4.75) vs. 2.90 (95% CI: 1.34, 6.27), respectively). However, this decline in OR with time since last exposure among the most heavily exposed workers was not apparent among workers with lower exposures (quartiles 1–3). Among workers with <20 y and among those with 20 or more years of cessation, the trends in risk with increasing 15-y lagged cumulative REC were statistically significant ($p_{trend} = 0.004$ and $p_{trend} = 0.037$, respectively), and the interaction between cessation and 15-y lagged cumulative REC was not statistically significant ($p_{interaction} = 0.414$).

Discussion

DEMS II findings provide further support for the causal association between diesel exposure and lung cancer mortality. These findings align with those reported by the IARC[14] as well as positive exposure–response relationships recently observed in a pooled analysis of 14 case–control studies mainly across Europe[15] and in a case–control study in Sweden.[16] As in our original study, cumulative REC lagged 15 y, which incorporates both average REC intensity and duration of exposure, was the primary exposure metric.[7] We observed an increasing trend in risk with increasing exposure, peaking with a tripling of risk for cumulative REC exposures of about 950 to <1,700 μg/m^3-y, followed by a plateau/decline in risk among the most heavily exposed. Similarly, based on the preferred model fitted to the continuous data, we observed a statistically significant association with lung cancer mortality, with

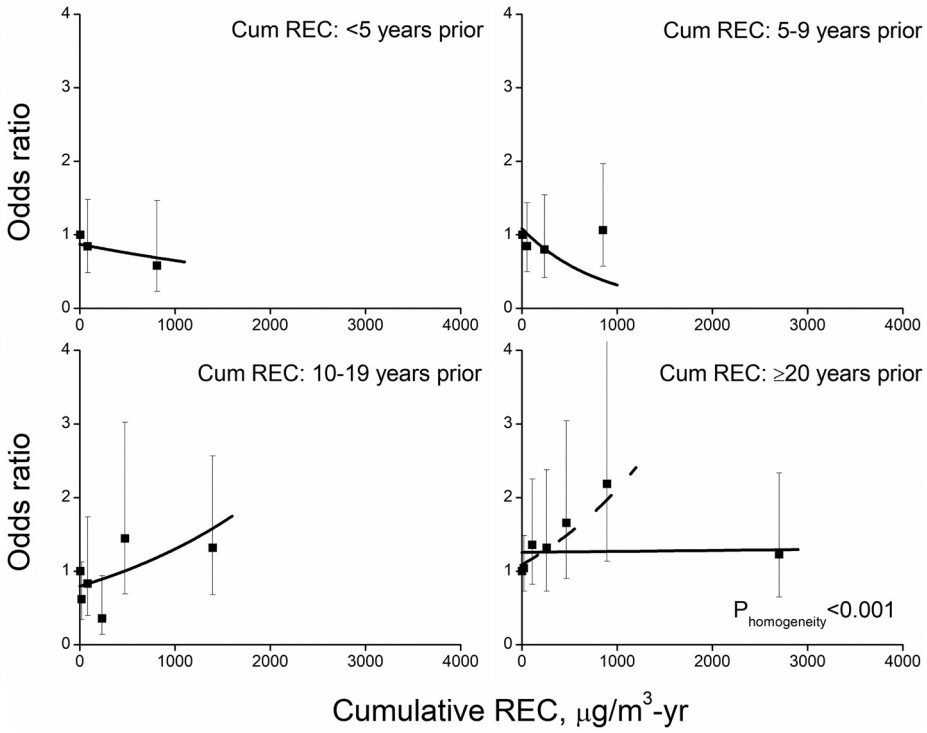

Figure 2. ORs for cumulative REC exposures (μg/m^3-y) accrued within time windows, <5, 5–9, 10–19, and ≥20 y prior to date of death/reference date by categories with 95% CIs (from Table S6) (solid squares) and a fitted continuous regression model (solid line). Dashed line in the ≥20-y window represents the fitted model omitting workers with cumulative REC ≥1,280 μg/m^3-y. The preferred model with minimum Akaike Information Criterion had an additive log-linear form, $\mathrm{OR}(d) = \sum_k \exp(\beta_k d_k) - 3$, where d_k was the cumulative REC within the kth window, $k = 1,2,3,4$. Within time window, the fitted continuous model is adjusted to a referent value defined by the mean exposure among controls and the weighted mean of the category-specific ORs. DEMS II, United States, 1947–2015, 376 lung cancer deaths and 718 controls. Source data: Table S6. Note: CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; exp, exponential function; OR, odds ratio; REC, respirable elemental carbon.

Table 5. ORs and 95% CIs for cumulative REC (15-y lag) by time since last exposure, DEMS II, United States, 1947–2015, 376 lung cancer deaths and 718 controls.

	0 to <20 y since last exposed			≥20 y since last exposed		
Exposure metric	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Cumulative REC [lag 15 y ($\mu g/m^3$-y)]						
0 to <10	60	203	1.00 (Ref)	34	57	1.02 (0.47, 2.19)
10 to <159	64	195	1.05 (0.58, 1.91)	30	53	1.55 (0.68, 3.55)
159 to <731	38	95	1.81 (0.85, 3.83)	56	93	1.93 (0.85, 4.39)
≥731	71	117	2.90 (1.34, 6.27)	23	31	1.75 (0.64, 4.75)
p_{trend}			0.004			0.037

Note: Adjusted for smoking status/mine location combination (surface work only/never smoker, surface work only/unknown/occasional smoker, surface work only/former smoker/< 1 pack/day, surface work only/former smoker/1 to <2 packs/day, surface work only/former smoker/≥ 2 packs/day, surface work only/current smoker/< 1 pack/day, surface work only/current smoker/1 to <2 packs/day, surface work only/current smoker/≥ 2 packs/day, ever UG work/never smoker, ever UG work/unknown/occasional smoker, ever UG work/former smoker/< 1 pack/day, ever UG work/former smoker/1 to <2 packs/day, ever UG work/former smoker/≥ 2 packs/day, ever UG work/current smoker/< 1 pack/day, ever UG work/current smoker/1 to <2 packs/day, ever UG work/current smoker/ ≥ 2 packs/day); history of respiratory disease 5 or more years before date of death/reference date; history of a high-risk job for lung cancer for at least 10 y; and BMI. The $p_{interaction}$ for years since last exposed and cumulative REC lagged 15 y = 0.414. *p*-Values based on two-sided Wald test for linear trend (Supplementary Table S8). BMI, body mass index; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; OR, odds ratio; REC, respirable elemental carbon; Ref, referent.

increasing risks at low-to-moderate exposures followed by a plateau/decline among the most heavily exposed workers.

The plateau/decline in risk among the heavily exposed was observed in the original study as well as in previous studies of occupational carcinogens.[17] This pattern may be due, in part, to a healthy worker survival effect.[18] It is unlikely, however, that this effect explains the entire plateau/decline because survival from lung cancer was several months for most of this cohort, which includes lung cancer deaths from 1960 to 2015. There is also some biological plausibility for this pattern because indications of a plateau/decline were observed for a 225 gene signature for diesel exhaust identified in a cross-sectional transcriptomic study in nasal epithelial cells of healthy workers exposed to a wide range of elemental carbon exposures from diesel engines.[19] Possible biological explanations for attenuation of effect among the heavily exposed include saturation of metabolic activation of carcinogens, enhanced detoxification/increased DNA repair, and threshold effects for downstream pathways identified in the diesel exhaust gene signature related to oxidative stress response, transmembrane transport, and protein modification.[7,19] Further experimental and observational research using both targeted and agnostic omic platforms is needed to evaluate the exposure–response relationship between REC and biological processes potentially important in diesel exhaust carcinogenesis to identify biological pathways that might saturate and thus not further respond at the high levels of exposure present in these workplaces.

The exposure–response relationship observed here was consistent by mine type, use of protective equipment, and potential occupational exposure to diesel exhaust outside the study mine. In contrast, heavy cigarette smoking among current smokers appeared to modify the exposure response. Among current smokers of two or more packs per day, risk decreased with increasing diesel exposure, whereas risk increased with increasing diesel exposure among nonsmokers, former smokers, and current smokers of <two packs per day. The interaction between cumulative REC and smoking was not statistically significant, however. Findings from two previous studies suggest a positive interaction between diesel exposure and cigarette smoking.[15,20] Occupational diesel exposure in these two previous studies is considerably different from that seen in the DEMS. For example, diesel exposure sustained by truck drivers from driving on highways or by heavy equipment operators outdoors is substantially different from that sustained by many underground miners in DEMS who worked in restricted spaces with diesel-powered equipment. It is also possible that the attenuation effect may have been due to chance; however, there is some evidence of biological plausibility. In the previously described transcriptomic analysis of nasal epithelial cells among workers heavily exposed to diesel exhaust,[19] the expression of several genes including CYP1A1 and CYP1B1, which are induced by nitro-polycyclic aromatic hydrocarbons,[21] showed an antagonistic interaction between diesel exhaust and cigarette smoking.[19] In addition, plasma levels of CCL2/MCP-1, a key chemokine that regulates migration of monocytes and has been linked to lung cancer risk,[22] showed an antagonistic interaction between diesel exhaust and smoking in the same study.[23] Examination of these interactions in other studies of workers who are heavily exposed to both diesel exhaust and cigarette smoking are needed to further clarify the smoking–diesel exposure interaction.

To identify risk-relevant exposure time intervals, we evaluated patterns of lung cancer risk from exposures that occurred in the following time windows: 0–4 y, 5–9 y, 10–19 y, and 20 or more years prior to death/reference date (Figure 2). We examined OR patterns for unlagged cumulative REC exposure within these predefined exposure time windows using the preferred descriptive models based on a minimum AIC criterion. We observed significant heterogeneity in the exposure–response relationship across time windows ($p < 0.001$). A statistically significant trend in risk with increasing cumulative REC was apparent 10–19 y prior to death/reference date, whereas no clear pattern in risk was apparent for the other time windows. This observation is consistent with the observed preferred lag of 15 y described above. An interesting finding is that the absence of trend in the ≥20-y time window is affected by a minimal risk among heavily exposed workers; 39 cases and 59 controls with cumulative REC ≥1,280 $\mu g/m^3$-y had an OR of 1.23 (95% CI: 0.65, 2.34). In contrast, lower exposures in the ≥20-y time window exhibited an increasing pattern of ORs comparable to the results for the 10- to 19-y window. This observation could be due to chance, but it could also suggest that some workers with extremely high exposures may experience negligible diesel-induced lung cancer risk. Taken together, these findings may provide new insight into the relevant time window for diesel-induced lung carcinogenesis.

We also evaluated the exposure–response by time since exposure ceased based on the DEMS II categorical data. Among the highest exposed workers, those whose exposures ceased for 20 or more years experienced diminished risk [15-y lagged cumulative REC: OR = 1.75 (95% CI: 0.64, 4.75)] in comparison with similarly exposed workers whose exposure ceased for <20 y [OR = 2.90 (95% CI: 1.34, 6.27)]. However, risks did not decline among workers with lower exposures. Further, the trend in risk with increasing exposure was statistically significant among workers with 20 or more years of cessation and among those with <20 y of cessation ($p_{trend} = 0.037$ and $p_{trend} = 0.004$, respectively), providing little support for a waning of risk among workers with 20 or more years since exposure ceased. This is the first study to evaluate the effect of cessation of diesel exposure on the

exposure response. Several studies of other lung carcinogens have, however, evaluated the effect of time since ceasing exposure. Reduced lung cancer risks 20 to 30 y after exposure ceased have been reported for asbestos[24] and acrylonitrile.[25]

DEMS II had several important strengths. The DEMS cohort is, to the best of our knowledge, the most heavily diesel exposed cohort in the world and workers were exposed to a wide range of diesel exposure.[2] A state-of-the-art retrospective exposure assessment based on measurement and other data was conducted at all study mines, providing the basis for estimation of quantitative levels of diesel exposure for each cohort member.[2–6] Based on nearly 400 lung cancer deaths identified over 55 y of mortality follow-up, the latency and statistical power were sufficient to detect increased lung cancer risk. To minimize confounding, nonmetal mines with low levels of radon, silica, and asbestos were selected for study. We adjusted for confounding from smoking and other potential confounders based on data obtained from interviews with next of kin with a high interview participation rate. DEMS II also had several weaknesses. REC measurement data were only available through 1998–2001, and company employment histories were only available through 2001–2003. This lack of data was unlikely to have impacted our findings for three reasons. First, the bulk of the cohort follow-up was completed by 31 December 1997, when 72% of the cohort were retired or dead and only 11% were still at our study mines working underground with diesel exposure. Second, we supplemented the work history information with data obtained from the next-of-kin interviews. Third, because follow-up was extended through 2015 and the preferred lag was 15 y, the lack of exposure data from 2000 to 2015 would not be relevant for lagged analyses pertaining to lung cancer. Another weakness was that, as in all studies where exposure is estimated for subjects over an extensive period, misclassification of exposure probably occurred. Such misclassification would have been nondifferential, likely leading to an underestimation of lung cancer risk. Last, despite the doubling in the number of lung cancer deaths in DEMS II in comparison with the original analyses, some findings from stratified analyses were based on moderate numbers of cases and thus may have been due to chance.

In conclusion, findings from DEMS II indicate that lung cancer mortality increases with increasing 15-y lagged cumulative REC exposure among low- to moderately exposed workers, followed by a plateau/decline in mortality among the most heavily exposed. DEMS II findings suggest that the exposure–response relationship is most apparent for exposures occurring within 10 to 19 y prior to the date of death, whereas risk from high exposures 20 or more years prior to death are more uncertain. Our results also provide little support for a waning of risk among workers 20 or more years after diesel exposure ceases. Diesel exhaust exposure at levels associated with increased lung cancer risk continues to be prevalent in workplaces throughout the world, underscoring the need for regulatory action.[26] DEMS II findings provide further impetus for implementation of such action, with important implications for the assessment of risk from diesel exhaust by regulatory agencies worldwide.

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