American Journal of Epidemiology

Vol. 187, No. 6
DOI: 10.1093/aje/kwy038
Advance Access publication:
April 3, 2018

Original Contribution

Reanalysis of Diesel Engine Exhaust and Lung Cancer Mortality in the Diesel Exhaust in Miners Study Cohort Using Alternative Exposure Estimates and Radon Adjustment

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Initially submitted June 13, 2017; accepted for publication December 19, 2017.

The Diesel Exhaust in Miners Study (DEMS) (United States, 1947–1997) reported positive associations between diesel engine exhaust exposure, estimated as respirable elemental carbon (REC), and lung cancer mortality. This reanalysis of the DEMS cohort used an alternative estimate of REC exposure incorporating historical data on diesel equipment, engine horsepower, ventilation rates, and declines in particulate matter emissions per horsepower. Associations with cumulative REC and average REC intensity using the alternative REC estimate and other exposure estimates were generally attenuated compared with original DEMS REC estimates. Most findings were statistically nonsignificant; control for radon exposure substantially weakened associations with the original and alternative REC estimates. No association with original or alternative REC estimates was detected among miners who worked exclusively underground. Positive associations were detected among limestone workers, whereas no association with REC or radon was found among workers in the other 7 mines. The differences in results based on alternative exposure estimates, control for radon, and stratification by worker location or mine type highlight areas of uncertainty in the DEMS data.

cohort studies; data sharing; diesel exhaust; lung cancer; mine workers; radon; vehicle emissions

Abbreviations: ALT_REC, alternative estimate of exposure to respirable elemental carbon; CO, carbon monoxide; DEE, diesel engine exhaust; DEMS, Diesel Exhaust in Miners Study; REC, respirable elemental carbon; WLM, working level month.

The Diesel Exhaust in Miners Study (DEMS), conducted by scientists at the National Institute of Occupational Safety and Health and the National Cancer Institute, is a landmark research study of the association between diesel engine exhaust (DEE) and lung cancer mortality among 12,315 workers at 8 US nonmetal mines and related facilities, followed through 1997. In a retrospective cohort analysis (1) and a nested case-control study (2, 3) of these workers, a positive exposure-response trend between estimated exposure to respirable elemental carbon (REC), as an indicator of DEE exposure, and lung cancer mortality was observed for cumulative REC levels of <1,280 μg/m^3-years.

A critical element of DEMS was the retrospective exposure assessment that generated estimates of individual-level exposure to REC as a proxy for DEE exposure (4–8). Modeled historical trends in measured personal carbon monoxide (CO) concentrations from 1976 through 1997, along with annual mine-specific information on air ventilation rates and diesel equipment, were used to estimate past REC exposures in the original DEMS analyses. A detailed exposure survey conducted during 1998–2001, when DEMS investigators measured CO and REC levels in personal and area air samples from 7 of the 8 mines, was used as a basis for estimating annual mine- and job-specific REC exposures retrospectively from the year of introduction of diesel-powered equipment in each mine (1947–1967) through 1997.

The methodological strengths of DEMS, the substantial scientific importance and public health impact of its results, and the availability of its data for restricted access by other researchers have prompted interest in further examining these data to elucidate the relationship between DEE and lung cancer risk. Our research group has published the results of a series of alternative analyses of the DEMS data (9–12). Briefly, in the first of these studies we identified uncertainty in the assumptions and data underlying the DEMS investigators' REC estimates, and we generated substantially different (sometimes higher, sometimes lower) REC estimates when other, well-justified assumptions were used (9). We next replicated and used biologically based models to extend the original DEMS cohort analysis. We found that temporal aspects of exposure not considered in the original analysis influenced lung cancer mortality, that attained age modified the REC–lung cancer association, and that a significant exposure-response association was detected only in 1 of 4 mine types (limestone) and not among workers who worked exclusively underground (i.e., those who probably were the most highly exposed to DEE) (12). Finally, by replicating and extending the original DEMS case-control analysis, we found generally attenuated exposure-response slopes based on alternative REC exposure estimates; after additional control for confounding by radon, these slopes were flattened and statistically nonsignificant (10, 11).

In this paper, we report a reanalysis of the DEMS cohort data using the alternative REC exposure estimates generated by Crump et al. (9–11), along with control for exposure to radon, an established lung carcinogen (13), following the Cox proportional hazards regression approach originally used by the DEMS investigators (1). This analysis augments our previous cohort analysis (12) by using control for radon and alternative REC exposure estimates, which were used previously only in the case-control analysis (9–11). Due to restrictions on data access imposed after our original analyses, we were unable to use the biologically based modeling approach previously used (12). Nevertheless, this study enables a rigorous evaluation of the influence of assumptions in REC exposure assessment and confounding by radon exposure on the observed association between REC and lung cancer mortality in the DEMS cohort.

METHODS

A description of the mining operations included in DEMS is provided in the supplemental material; Table 1 shows the unique characteristics of each of the mines.

DEMS cohort

The DEMS cohort has been described in detail by Attfield et al. (1). Briefly, the cohort comprised 12,315 workers employed for at least 1 year at 8 US nonmetal mines and related facilities, including 1 limestone mine in Missouri, 3 potash mines in New Mexico, 1 salt (halite) mine in Ohio, and 3 trona mines in Wyoming. Demographic and work history information was obtained from personnel records at each facility, and follow-up for mortality was performed by linkage to the National Death Index and the Social Security Administration death files from the year of introduction of diesel-powered equipment in each facility until December 31, 1997. Among the 12,315 DEMS cohort members, 200 lung cancer deaths occurred during follow-up (Web Table 1, available at https://academic.oup.com/aje).

We accessed the original DEMS cohort data sets at the National Center for Health Statistics Research Data Center in Hyattsville, Maryland. Geographic and date variables used were state, mine ID and type, and dates of birth, hire, first exposure, last exposure, and last observation; these variables were necessary to

Table 1. Characteristics of the Mines in the Diesel Exhaust in Miners Study, United States, 1947–1997[a]

Mine	State	Ore	Ventilation	Year of First Diesel Use	Primary Mode of Operation	All Years: CO No. of Samples	All Years: CO % >LOD	All Years: Radon No. of Samples	All Years: Radon % >LOD	1982 Activity[b]: Ventilation Rate (CFM in Thousands)	1982 Activity[b]: Diesel (Adjusted HP[c])
A	Missouri	Limestone	Natural	1947	Cv/H	248	70	37	84	NA	6,862
B	New Mexico	Potash	Mechanical	1964	Cv/Con, Ct	447	62	18	44	250	852
D	New Mexico	Potash	Mechanical	1950	Cv/H, Cv/Con, Ct	323	54	61	39	360	2,326
J	New Mexico	Potash	Mechanical	1952	Cv/H, Cv/Con, Ct	178	52	13	38	240	1,421
E	Ohio	Salt	Mechanical	1959	Cv/H	207	66	39	70	233	2,804
G	Wyoming	Trona	Mechanical	1962	Cv/Con, Ct	276	50	17	24	450	638
H	Wyoming	Trona	Mechanical	1967	Cv/Con, LW, Ct	2,361	39	40	15	950	1,110
I	Wyoming	Trona	Mechanical	1956	Cv/Con, Ct, LW	2,000	54	54	20	1,630	1,493
Total						6,040	50	279	42		

Abbreviations: CFM, cubic feet per minute (ventilation rate); CO, carbon monoxide; Ct, continuous with conveyor belts; Cv/Con, conventional with conveyor belts; Cv/H, conventional with truck haulage; DEMS, Diesel Exhaust in Miners Study; HP, horsepower; LOD, limit of detection; LW, long wall with conveyor belts; NA, not applicable (mainly naturally ventilated).

[a] Data are derived from Stewart et al. (5) and the DEMS data files.

[b] Specific data for CFM and adjusted HP are shown for 1982 for illustrative purposes, because 1982 was the last year of effective exposure for workers, assuming a 15-year lag with vital status follow-up through 1997.

[c] Adjusted HP refers to diesel engine HP adjusted for the average percentage of time that the engine was used over a work shift (5).

derive attained age (the time scale for the proportional hazards regression analysis) and worker-specific time-varying exposure estimates. An alternative estimate of exposure to respirable elemental carbon (ALT_REC) and 6 other alternative exposure estimates (ALT1–ALT6), described below and in Crump et al. (9–11), were merged with the DEMS work-history data set according to job, department, mine, and year. All analyses were approved by the appropriate institutional review boards.

REC exposure estimates

For our primary analysis, we used 2 estimates of REC exposure: the CO-based estimate used by the original DEMS investigators in their main cohort and case-control analyses (referred to hereafter as "DEMS_REC") (1, 2), and an alternative estimate of REC exposure developed by Crump et al. (10) that we believed a priori to be the best-justified estimate (referred to hereafter as "ALT_REC") (Figure 1A–H). As described by Crump et al. (10) and in the supplemental material, ALT_REC was developed using detailed annual data on diesel engine horsepower and mine air-ventilation rates, without reliance on CO data, which have limited availability and suitability as a surrogate for REC. The approach underlying ALT_REC was favored by some members of the Health Effects Institute Diesel Epidemiology Panel, who described the CO-independent REC exposure assessment method as "particularly informative" and "reinforc[ing] the fact that diesel equipment utilization and ventilation are the drivers of REC concentration trends over time and between mines" (14, p. 54). We also conducted secondary analyses using 6 other alternative exposure estimates (ALT1–ALT6), previously developed and described in detail by Crump et al. (9, 11).

Statistical approach

We used the same Cox proportional hazards regression approach used in the original DEMS cohort analysis (1) and in our replication and extension of those results (12) to estimate hazard ratios with 95% confidence intervals for the association between REC exposure and lung cancer mortality. All statistical tests were 2-sided. Monthly average REC intensity and cumulative REC estimates were derived for each cohort member using each of the 8 REC estimates (DEMS_REC, ALT_REC, and ALT1–ALT6). Lagged exposure on a given date was taken from the exposure during the same month in an earlier year. If no work record existed on the earlier date, then the lagged exposure was set to zero. The strongest associations in the original DEMS analyses used a 15-year exposure lag (1, 2); hence, for a worker who died on December 31, 1997 (the end of follow-up), the last day for exposure estimates would have been December 31, 1982. Attained age was used as the time scale. Deaths from lung cancer were recorded as events, while deaths from other causes and loss to follow-up were censored at the time of occurrence.

Regression models included covariates for year of birth, sex, race, and, for analyses of the full cohort, time-dependent location (surface or underground); baseline hazards were stratified by mine type. To evaluate confounding by radon, models were constructed with and without adjustment for radon exposure, for which accurate data became available after our prior reanalysis (12). As in the original DEMS analyses (1, 2), radon exposure was expressed in continuous cumulative units of working level months (WLMs) summed across jobs.

Stratified analyses were conducted for workers who worked exclusively on the surface (surface-only workers), those who ever worked underground (ever-underground workers), and those who worked exclusively underground (underground-only workers). Based on Attfield et al. (1), we implemented a 15-year lag and restricted some analyses to workers with cumulative DEMS_REC of <1,280 μg/m^3-years and/or a minimum 5-year tenure. We conducted sensitivity analyses using models stratified by mine type and models including REC exposure duration and intensity, along with multiplicative age interactions to evaluate the validity of the proportional hazards assumption.

RESULTS

To ensure that we were working with the same data sets as the original DEMS investigators, we first confirmed that our findings matched those shown in Tables 1 and 2 of Attfield et al. (1) (results not shown). For simplicity and ease of comparison, results are shown only for DEMS_REC and ALT_REC using continuous values for cumulative REC and average REC intensity. Web Table 2 compares results between Tables 4–6 of Attfield et al. (1) and our reanalysis. Other results, including estimates of association with ALT1–ALT6 and categorical REC metrics, were similar and can be provided upon request.

Tables 2 and 3 show results replicating and extending those reported in Tables 4–6 of Attfield et al. (1) (i.e., for ever-underground workers, surface-only workers, and all workers with adjustment for worker location, respectively) and Table SI of Moolgavkar et al. (12) (i.e., for underground-only workers), using continuous measures of cumulative REC and average REC intensity based on either DEMS_REC or ALT_REC, and with or without control for radon. As expected, results using DEMS_REC and without control for radon closely matched those reported by Attfield et al. (1) and Moolgavkar et al. (12). Most associations of lung cancer mortality with ALT_REC were closer to the null than associations with DEMS_REC. The attenuated associations with ALT_REC were especially evident in analyses restricted to workers with cumulative DEMS_REC of <1,280 μg/m^3-years.

Without control for radon, several statistically significant positive exposure-response associations with cumulative REC and average REC intensity based on both DEMS_REC and ALT_REC were observed among ever-underground workers, surface-only workers, and all workers combined, but not among underground-only workers (Tables 2 and 3). Control for radon yielded substantially weaker associations with cumulative and average intensity measures of both DEMS_REC and ALT_REC among ever-underground, underground-only, and all workers (Tables 2 and 3). Nearly all significant positive associations after control for radon were found only among ever-underground and all workers after restriction to DEMS_REC of <1,280 μg/m^3-years. Positive confounding by radon was generally stronger in models using DEMS_REC than those using ALT_REC; in models using cumulative REC than those using average REC intensity; in analyses restricted to workers with cumulative DEMS_REC of <1,280 μg/m^3-years than those based on the

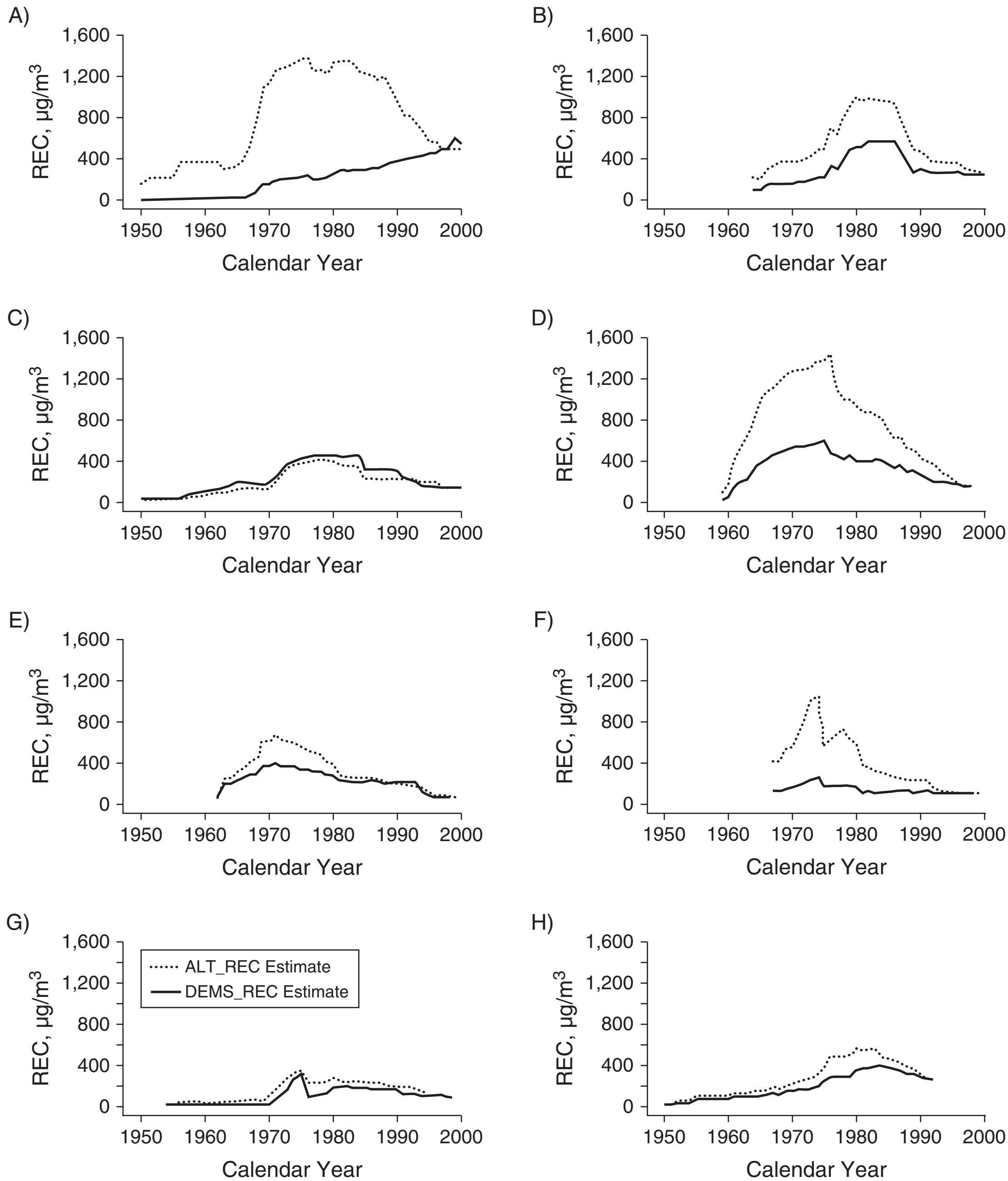

Figure 1. Respirable elemental carbon (REC) metrics, Diesel Exhaust in Miners Study (DEMS), United States, 1947–1997. The solid line shows a metric derived in part from extrapolated carbon monoxide measurements, as developed and used by Attfield et al. (1) and Silverman et al. (2) (DEMS_REC). The dashed line shows a metric derived from diesel engine horsepower and mine air ventilation, without extrapolation from carbon monoxide measurements, as developed and used by Crump et al. (10) (ALT_REC). A) Mine A, limestone; B) Mine B, potash; C) Mine D, potash; D) Mine E, salt (halite); E) Mine G, trona; F) Mine H, trona; G) Mine I, trona; H) Mine J, potash.

full exposure range; and in analyses of ever-underground and all workers than those of underground-only workers.

As shown in Table 4, which replicates and extends results shown in Table SII of Moolgavkar et al. (12), a positive association between log cumulative DEMS_REC or log cumulative ALT_REC and lung cancer mortality was driven by results in the limestone mine, and only in the absence of control for radon. No association with log cumulative DEMS_REC or ALT_REC was detected in any other mine type, with or without control for radon, or in the 7 non-limestone mines combined. After adjustment for radon, no association was observed with log cumulative DEMS_REC or ALT_REC in any mine type, including limestone and all mines combined. Likelihood ratio tests indicated that models with distinct exposure-response parameters

Table 2. Hazard Ratios for the Associations of Lung Cancer Mortality With Continuous Measures of 15-Year Lagged Cumulative Exposure to Respirable Elemental Carbon, Excluding <5-Year Tenure, Diesel Exhaust in Miners Study, United States, 1947–1997

Worker Category	Exposure Range	Exposure Unit	No. of Lung Cancer Deaths	Cumulative DEMS_REC Without Radon		Cumulative DEMS_REC With Radon		Cumulative ALT_REC Without Radon		Cumulative ALT_REC With Radon	
				HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Ever underground[b]	Full	1,000 μg/m^3-years	93	1.06	0.84, 1.34	0.76	0.54, 1.05	1.09	1.00, 1.17	1.02	0.92, 1.13
	Full	Log μg/m^3-year	93	1.20	1.04, 1.37	1.11	0.94, 1.31	1.16	1.02, 1.31	1.08	0.93, 1.24
	<1,280 μg/m^3-years	1,000 μg/m^3-years	79	4.08	2.12, 7.84	2.49	1.13, 5.46	1.34	1.17, 1.53	1.18	0.99, 1.41
Surface only[c]	Full	1 μg/m^3-year	57	1.02	1.00, 1.03	NA	NA	1.00	0.99, 1.01	NA	NA
	Full	Log μg/m^3-year	57	0.95	0.73, 1.25	NA	NA	0.98	0.79, 1.21	NA	NA
All, adjusted for location[d]	<1,280 μg/m^3-years	1,000 μg/m^3-years	136	3.57	1.97, 6.48	2.00	1.00, 4.01	1.34	1.20, 1.50	1.16	1.00, 1.35
Underground only[e]	Full	1,000 μg/m^3-years	58	0.89	0.64, 1.24	0.75	0.50, 1.14	1.03	0.91, 1.16	1.00	0.86, 1.16
	Full	Log μg/m^3-year	58	1.03	0.87, 1.21	0.99	0.82, 1.20	1.03	0.88, 1.20	1.00	0.85, 1.18
	<1,280 μg/m^3-years	1,000 μg/m^3-years	50	2.55	0.99, 6.57	2.05	0.72, 5.83	1.21	0.97, 1.50	1.13	0.87, 1.45

Abbreviations: ALT_REC, best alternative estimate of respirable elemental carbon; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; DEMS_REC, original DEMS estimate of respirable elemental carbon; HR, hazard ratio; NA, not applicable.

[a] Models adjusted for year of birth, sex, and race (and location for combined analyses), with stratification of baseline hazards by mine type, and age as the time scale.

[b] Replication and extension of Table 4 in Attfield et al. (1).

[c] Replication and extension of Table 5 in Attfield et al. (1).

[d] Replication and extension of Table 6 in Attfield et al. (1).

[e] Replication and extension of Table SI in Moolgavkar et al. (12).

Table 3. Hazard Ratios for the Associations of Lung Cancer Mortality With Continuous Measures of 15-Year Lagged Average Intensity of Exposure to Respirable Elemental Carbon, Excluding <5-Year Tenure, Diesel Exhaust in Miners Study, United States, 1947–1997

Worker Category	Exposure Range	Exposure Unit	No. Lung Cancer Deaths	DEMS_REC Intensity Without Radon		DEMS_REC Intensity With Radon		ALT_REC Intensity Without Radon		ALT_REC Intensity With Radon	
				HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Ever underground[b]	Full	100 μg/m^3	93	1.25	0.93, 1.67	1.14	0.82, 1.57	1.14	1.03, 1.27	1.12	1.00, 1.26
	Full	Log μg/m^3	93	1.26	1.07, 1.49	1.19	0.99, 1.43	1.20	1.03, 1.39	1.14	0.97, 1.34
Surface only[c]	Full	1 μg/m^3	57	1.41	1.10, 1.81	NA	NA	1.01	0.96, 1.06	NA	NA
	Full	Log μg/m^3	57	2.24	1.18, 4.27	NA	NA	1.17	0.85, 1.60	NA	NA
All, adjusted for location[d]	Full	Log μg/m^3	150	1.21	1.05, 1.38	1.13	0.97, 1.31	1.21	1.06, 1.38	1.14	0.99, 1.32
Underground only[e]	Full	100 μg/m^3	58	0.86	0.57, 1.31	0.85	0.55, 1.31	1.04	0.88, 1.23	1.04	0.88, 1.24
	Full	Log μg/m^3	58	1.01	0.81, 1.25	0.99	0.78, 1.24	1.01	0.82, 1.23	1.00	0.81, 1.23

Abbreviations: ALT_REC, best alternative estimate of respirable elemental carbon; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; DEMS_REC, original DEMS estimate of respirable elemental carbon; HR, hazard ratio; NA, not applicable.

[a] Models adjusted for year of birth, sex, and race (and location for combined analyses), with stratification of baseline hazards by mine type, and age as the time scale.

[b] Replication and extension of Table 4 in Attfield et al. (1).

[c] Replication and extension of Table 5 in Attfield et al. (1).

[d] Replication and extension of Table 6 in Attfield et al. (1).

[e] Replication and extension of Table SI in Moolgavkar et al. (12).

for the limestone mine described the data significantly better than models assuming identical parameters for all mines ($P < 0.01$ for DEMS_REC and ALT_REC, with and without radon).

Table 5 shows the results of sensitivity analyses based on multivariate models that included both REC duration and log average REC intensity, as well as with interactions of these variables with age. We replicated our previous findings that DEMS_REC duration and intensity were independent predictors of lung cancer mortality among workers with cumulative DEMS_REC of <1,280 μg/m^3-years, and that both of these covariates interacted with age (Table SIII of Moolgavkar et al. (12)). When ALT_REC was used instead as the exposure metric, however, REC duration and its interaction with age were no longer associated with lung cancer mortality, while log average REC intensity was not associated but its interaction with age was. After additional control for radon, however, only the age interaction with log average DEMS_REC intensity remained; ALT_REC duration, average ALT_REC intensity, and the interactions of these variables with age were unassociated with lung cancer mortality.

An independent positive association between cumulative radon exposure and lung cancer mortality was found in all mine types combined and in the limestone mine, but not in any other mine type or in the 7 other types of mines combined (Table 4). Additionally, we found positive associations with radon among all workers, ever-underground workers, underground-only workers, and limestone workers with a 15-year lag, and among ever-underground workers and limestone workers with no lag (Table 6).

DISCUSSION

Several prominent themes emerge from the results of our reanalysis of the DEMS cohort: 1) reasonable alternative estimates of REC—particularly an estimate based on horsepower, air ventilation rates, and temporal trends in particulate matter emissions per horsepower, without reliance on assumptions about CO—yielded generally attenuated and nonsignificant, although generally still positive, associations between REC and lung cancer mortality; 2) control for radon resulted in often substantially attenuated associations; 3) associations among underground-only workers, who would have had the highest cumulative exposure to DEE, were the weakest among all worker subgroups, whereas positive associations were detected only in the limestone mine; and 4) restriction to cumulative DEMS_REC of <1,280 μg/m^3-years remained crucial to detecting a positive exposure-response association with DEMS_REC.

The original DEMS investigators' assumptions about constant relationships between horsepower and CO and between CO and REC have been controversial (9, 14–18). In a reanalysis of the DEMS case-control study data using ALT_REC, Crump et al. (10) also found that exposure-response trends were statistically nonsignificant and attenuated, especially after control for radon, in models that controlled for smoking and other risk factors for which information was unavailable in the full cohort.

Average radon exposure levels in the DEMS cohort were low; across all mine types in the complete cohort, the mean radon exposure intensity was 0.008 WL, with mine-specific averages ranging from 0.005 to 0.014 WL. Among ever-underground workers the mean radon exposure intensity was 0.011 WL, ranging from 0.008 to 0.017 WL (1). Our findings for radon in relation to lung cancer mortality are qualitatively consistent with the results of Attfield et al. (1), who detected a significant positive association only in the limestone mine and not in the other mines. Among limestone workers, Attfield et al. (1) reported a strong positive association with radon in some models (e.g., hazard ratio = 6.2; $P = 0.020$ for exposures of 6.15–6.98 WLM among ever-underground workers with cumulative DEMS_REC of <1,280 μg/m^3-years). Excluding workers aged ≥40 years who

Table 4. Hazard Ratios for the Associations of Lung Cancer Mortality With Continuous Measures of 15-Year Lagged Cumulative Exposure to Respirable Elemental Carbon Across the Full Exposure Range Among All Workers, Adjusted for Location, Diesel Exhaust in Miners Study, United States, 1947–1997[a]

Exposure	All Mine Types			All Mine Types Except Limestone			Limestone Only		
	HR[b]	95% CI	*P* Value	HR[b]	95% CI	*P* Value	HR[b]	95% CI	*P* Value
Log cumulative DEMS_REC exposure									
REC without radon	1.09	1.01, 1.17	0.02	1.06	0.97, 1.14	0.18	1.43	1.15, 1.79	0.001
REC with radon	1.03	0.94, 1.12	0.56	1.04	0.94, 1.14	0.48	1.23	0.95, 1.59	0.11
Radon	1.01	1.00, 1.01	0.005	1.00	1.00, 1.01	0.47	1.01	1.00, 1.02	0.02
Log cumulative ALT_REC exposure									
REC without radon	1.08	1.01, 1.16	0.02	1.04	0.97, 1.11	0.31	1.49	1.16, 1.91	0.002
REC with radon	1.03	0.96, 1.11	0.40	1.02	0.94, 1.10	0.65	1.28	0.98, 1.67	0.07
Radon	1.01	1.00, 1.01	0.005	1.00	1.00, 1.01	0.31	1.01	1.00, 1.02	0.03
	Potash Only			**Salt Only**			**Trona Only**		
	HR[b]	95% CI	*P* Value	HR[b]	95% CI	*P* Value	HR[b]	95% CI	*P* Value
Log cumulative DEMS_REC exposure									
REC without radon	1.08	0.96, 1.21	0.19	1.08	0.85, 1.37	0.52	1.02	0.89, 1.16	0.78
REC with radon	1.06	0.92, 1.22	0.44	1.08	0.79, 1.47	0.64	1.01	0.86, 1.18	0.90
Radon	1.00	1.00, 1.01	0.57	1.00	0.98, 1.02	0.97	1.00	0.98, 1.02	0.84
Log cumulative ALT_REC exposure									
REC without radon	1.07	0.96, 1.19	0.20	1.07	0.87, 1.32	0.51	0.99	0.88, 1.11	0.85
REC with radon	1.05	0.93, 1.18	0.42	1.07	0.83, 1.38	0.61	0.97	0.86, 1.11	0.69
Radon	1.00	1.00, 1.01	0.46	1.00	0.98, 1.02	0.95	1.00	0.99, 1.02	0.63

Abbreviations: ALT_REC, best alternative estimate of respirable elemental carbon; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; DEMS_REC, original DEMS estimate of respirable elemental carbon; HR, hazard ratio; REC, respirable elemental carbon.

[a] Replication and extension of Table SII in Moolgavkar et al. (12).

[b] Models adjusted for year of birth, sex, race, and location, with stratification of baseline hazards by mine type for combined analyses, and age as the time scale.

were employed before 1947 removed the radon association both within the limestone facility and in the overall cohort.

In an independent analysis of potential confounding by radon in the DEMS case-control study, the Health Effects Institute (14) reported that radon appeared to confound the relationship between cumulative and average DEMS_REC and lung cancer mortality, but that after adjustment for duration of exposure, the confounding influence of radon persisted only for unlagged cumulative DEMS_REC. After adjustment for radon and/or duration, a positive association with lung cancer mortality was still detected for cumulative DEMS_REC lagged 15 years but not for average DEMS_REC intensity lagged 15 years. The Health Effects Institute (14, p. 127) concluded that it was "difficult to disentangle the effects of radon and diesel exhaust on lung cancer risk, as adjusting for duration of REC exposure may have an effect similar to that obtained by adjusting for cumulative radon."

Detailed results for associations with radon were not shown by Attfield et al. (1). Among all and ever-underground workers, we found radon-associated hazard ratios ranging from 1.002 to 1.01 per WLM. These associations are weaker than those reported by Silverman et al. (2) based on the DEMS case-control study, which yielded odds ratios of 1.08 (95% confidence interval: 0.63, 1.84) for ≥1.9 and <3.0 WLM and 1.32 (95% confidence interval: 0.76, 2.29) for ≥3.0 WLM versus no exposure.

The restriction of positive associations with both REC (without radon adjustment) and radon to the limestone mine, and the unexpected lack of an association with REC among underground-only workers, are not readily explained in the context of a positive exposure-response association between REC and lung cancer mortality. The limestone mine had the lowest average DEMS_REC and third-lowest average radon levels among ever-underground workers (1); however, it had the highest average ALT_REC levels (Figure 1A–H) and the highest proportion of detectable radon levels (Table 1 and Web Appendix 1). The high frequency of detectable radon, poor natural ventilation, and unique ore transport system requiring high-horsepower diesel equipment in the limestone mine could have contributed to a confounding influence of radon (or an unmeasured variable correlated with radon) in that mine only. The higher average ALT_REC levels in the limestone mine, as well as longer exposure due to earlier dieselization, also could have contributed to the positive associations with REC in that mine only. Ultimately, collinearity between REC and radon, resulting in mutual confounding, makes it difficult to disentangle associations of each exposure with lung cancer mortality. Attfield et al. (1, p. 881) ascribed the radon association in the limestone mine to "chance or other unknown factors affecting early older workers at that one facility." Chance seems unlikely to explain the restriction of

Table 5. Hazard Ratios for the Associations of Lung Cancer Mortality With 15-Year Lagged Intensity and Duration of Exposure to Respirable Elemental Carbon, Restricted to Cumulative Exposure of Less Than 1,280 μg/m^3-years Among All Workers, Adjusted for Location, Diesel Exhaust in Miners Study, United States, 1947–1997[a]

Covariate	Without Radon			With Radon		
	HR[b]	95% CI	*P* Value	HR[b]	95% CI	*P* Value
DEMS_REC exposure						
Birth year	1.02	1.00, 1.04	0.05	1.03	1.01, 1.04	0.005
Ever underground vs. surface only	0.36	0.19, 0.69	0.002	0.21	0.09, 0.45	<0.001
Trona vs. other mine types	0.64	0.44, 0.93	0.02	0.67	0.46, 0.97	0.04
REC duration	0.86	0.75, 0.99	0.03	0.88	0.77, 1.02	0.08
REC duration × age	1.00	1.00, 1.00	0.05	1.00	1.00, 1.00	0.16
Log average REC intensity	0.48	0.26, 0.87	0.02	0.67	0.36, 1.26	0.21
Log average REC intensity × age	1.02	1.01, 1.03	<0.001	1.01	1.00, 1.02	0.03
Radon	NA	NA	NA	1.01	1.01, 1.02	<0.001
ALT_REC exposure						
Birth year	1.02	1.00, 1.04	0.02	1.03	1.01, 1.05	0.001
Ever underground vs. surface only	0.46	0.27, 0.78	0.004	0.32	0.18, 0.56	<0.001
Trona vs. other mine types	0.55	0.37, 0.81	0.002	0.59	0.40, 0.87	0.008
REC duration	0.90	0.79, 1.03	0.13	0.92	0.80, 1.05	0.20
REC duration × age	1.00	1.00, 1.00	0.21	1.00	1.00, 1.00	0.40
Log average REC intensity	0.65	0.37, 1.13	0.13	0.85	0.47, 1.52	0.58
Log average REC intensity × age	1.01	1.00, 1.02	0.02	<1.01	1.00, 1.01	0.26
Radon	NA	NA	NA	1.01	1.00, 1.02	<0.001

Abbreviations: ALT_REC, best alternative estimate of respirable elemental carbon; CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; DEMS_REC, original DEMS estimate of respirable elemental carbon; HR, hazard ratio; NA, not applicable; REC, respirable elemental carbon.

[a] Replication and extension of Table SIII in Moolgavkar et al. (12).

[b] Models adjusted for covariates shown and sex, with age as the time scale.

both the radon association and the REC association to a single mine, but it cannot be excluded. Given the generally low concentrations of radon, the apparent confounding by radon exposure is perhaps most plausibly explained by correlated risk factors that may or may not be related to REC exposure.

Likewise, the detection of the weakest findings among underground-only workers does not comport with a straightforward positive exposure-response relationship between REC and lung cancer mortality. A related paradoxical finding is the 1,000-fold larger hazard ratios for cumulative DEMS_REC and the 100-fold larger hazard ratios for average DEMS_REC intensity among surface-only workers compared with ever-underground workers, despite substantially higher REC exposure levels in underground workers. Neophytou et al. (19) analyzed ever-underground worker data and concluded that healthy-worker survivor bias appeared to affect results in the DEMS cohort, because employment status and REC were associated. Although ultimately no clear explanations may be identified, these results contribute additional uncertainty to the results of several analyses of the DEMS data.

Finally, as in the original analysis (1) and our prior reanalysis of the DEMS cohort (Web Figure 1) (12), we found that restriction of analyses to cumulative DEMS_REC of <1,280 μg/m^3-years was critical to finding statistically significant positive associations between DEMS_REC and lung cancer mortality. After adjustment for radon, the only significant associations with continuous cumulative DEMS_REC or average DEMS_REC intensity were detected after restriction to cumulative DEMS_REC of <1,280 μg/m^3-years. No significant associations were detected with ALT_REC or ALT1–ALT6 among workers with cumulative DEMS_REC of <1,280 μg/m^3-years after adjustment for radon. Workers with cumulative DEMS_REC of ≥1,280 μg/m^3-years should have been the oldest and most highly exposed workers in the cohort, and accordingly should have been at the highest risk of lung cancer, assuming a causal relationship. Thus, the observation of positive associations only after exclusion of these workers is not congruent with a monotonic exposure-response effect of DEE, and the importance of this seemingly arbitrary cutoff is another source of uncertainty.

In our prior reanalysis (12), we found a key influence of temporal factors including duration of exposure (confirmed by the Health Effects Institute (14) in their radon analysis, as mentioned above) and timing of exposure initiation and cessation, as well as effect modification by age. In the present study, using Cox proportional hazards regression, we found that adjustment for radon reduced the influence of exposure duration and age interactions, although age continued to interact with average DEMS_REC intensity. We also found that use of ALT_REC instead of

Table 6. Hazard Ratios for the Associations of Lung Cancer Mortality With Continuous Measures of Radon Exposure, With or Without a 15-Year Lag, Diesel Exhaust in Miners Study, United States, 1947–1997

Location, Mine Type, and Lag	No. of Lung Cancer Deaths	HR[a]	95% CI	*P* Value
All workers	200			
15-year lag		1.005	1.002, 1.009	<0.001
No lag		1.002	1.000, 1.005	0.06
Ever-underground workers	122			
15-year lag		1.006	1.002, 1.010	0.001
No lag		1.003	1.000, 1.006	0.04
Underground-only workers	82			
15-year lag		1.005	1.000, 1.010	0.05
No lag		1.002	0.998, 1.006	0.39
Limestone mine	37			
15-year lag		1.010	1.005, 1.015	<0.001
No lag		1.006	1.002, 1.010	0.004
Potash mines	102			
15-year lag		1.001	0.997, 1.006	0.60
No lag		1.000	0.996, 1.004	0.98
Salt mine	12			
15-year lag		1.001	0.986, 1.017	0.86
No lag		0.996	0.985, 1.008	0.53
Trona mines	49			
15-year lag		0.999	0.985, 1.014	0.93
No lag		0.998	0.990, 1.007	0.73

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Models include radon only, with age as the time scale.

DEMS_REC diminished the roles of exposure duration and an age interaction with exposure intensity. Additionally, radon adjustment of ALT_REC models resulted in attenuated and statistically nonsignificant associations with either exposure duration or age interactions. Nevertheless, due to the focus on estimating hazard ratios and reliance on the assumption of time-invariant hazard ratios, proportional hazards regression lacks flexibility for examining the influence of temporal factors on risk. Thus, direct estimation of hazard functions, as can be conducted using biologically based multistage models of carcinogenesis as in our previous reanalysis of the DEMS cohort (12), would be more informative regarding the impact of time-related exposure factors on lung cancer mortality.

This and other reanalyses of the DEMS data (10–12, 14, 19) underscore the importance of making scientific data available to multiple investigators for independent analyses. Each group of investigators brings its own unique perspective to these analyses. Subjecting scientific data to multiple rigorous investigations can aid in realizing the potential of valuable data sets such as DEMS.

ACKNOWLEDGMENTS

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This work was funded by a coalition of trade organizations working through the Truck and Engine Manufacturers Association. Those organizations include the American Petroleum Institute, European Automobile Manufacturers Association, American Trucking Association, International Organization of Motor Vehicle Manufacturers, Alliance of Automobile Manufacturers, Association of Equipment Manufacturers, Association of American Railroads, and European Association of Internal Combustion Engine Manufacturers.

We thank the original investigators (led by Dr. Michael Attfield, Dr. Debra Silverman, and Dr. Patricia Stewart) at the National Institute of Occupational Safety and Health and the National Cancer Institute who designed and conducted the Diesel Exhaust in Miners Study project and, thus, developed the data that we analyzed. Moreover, we thank the management and workers associated with the 8 mines studied: The detailed records on mining operations and worker employment are indeed remarkable. We also thank Dr. Frances McCarty, Senior Service Fellow at the National Center for Health Statistics Research Data Center, for her generous assistance with the data analysis.

The analyses of the Diesel Exhaust in Miners Study data reported in this paper were approved by the National Center for Health Statistics Research Ethics Review Board, and the data were accessed under a confidentiality agreement with the National Center for Health Statistics Research Data Center. Only Designated Agents who completed a confidentiality agreement with the National Center for Health Statistics Research Data Center were permitted to access the raw data. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Research Data Center, the National Center for Health Statistics , the Centers for Disease Control and Prevention, the National Institute of Occupational Safety and Health, the National Cancer Institute, or the coalition that funded this research. This manuscript is exclusively the work product of the authors and was not reviewed by the study sponsors prior to journal submission.

E.T.C. and S.H.M. have provided consultation in litigation related to diesel engine exhaust exposure. S.H.M., K.S.C., and R.O.M. attended, and K.S.C. and S.H.M. were speakers at, the Health Effects Institute workshop on Diesel Exhaust, Lung Cancer and Quantitative Risk Assessment in Boston, Massachusetts, on March 6, 2014. K.S.C. participated on the National Academy of Sciences Diesel Impacts Study Committee and Panel on the Health Effects of Diesel Emissions in 1979–1980. Since the 1970s, R.O.M. has conducted scientific research, served on expert panels, and provided consultation, with and without financial compensation, to government, industry, health, and scientific agencies on the potential health effects of diesel engine exhaust exposure. He was a member of the International Agency for Research on Cancer Working Group that reviewed the carcinogenic hazard of diesel engine exhaust in 1988 and an observer at the 2012 International Agency for Research on Cancer Working Group meeting on diesel engine exhaust.

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