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Original Contribution

Ischemic Heart Disease Mortality and Diesel Exhaust and Respirable Dust Exposure in the Diesel Exhaust in Miners Study

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Diesel exhaust is a suggested risk factor for ischemic heart disease (IHD), but evidence from cohorts using quantitative exposure metrics is limited. We examined the impact of respirable elemental carbon (REC), a key surrogate for diesel exhaust, and respirable dust (RD) on IHD mortality, using data from the Diesel Exhaust in Miners Study in the United States. Using data from a cohort of male workers followed from 1948–1968 until 1997, we fitted Cox proportional hazards models to estimate hazard ratios for IHD mortality for cumulative and average intensity of exposure to REC and RD. Segmented linear regression models allowed for nonmonotonicity. Hazard ratios for cumulative and average REC exposure declined relative to the lowest exposure category before increasing to 0.79 and 1.25, respectively, in the highest category. Relative to the category containing the segmented regression change points, hazard ratios for the highest category were 1.69 and 1.54 for cumulative and average REC exposure, respectively. Hazard ratios for RD exposure increased across the full exposure range to 1.33 and 2.69 for cumulative and average RD exposure, respectively. Tests for trend were statistically significant for cumulative REC exposure (above the change point) and for average RD exposure. Our findings suggest excess risk of IHD mortality in relation to increased exposure to REC and RD.

cohort study; diesel exhaust; ischemic heart disease; respirable dust

Abbreviations: DEMS, Diesel Exhaust in Miners Study; IHD, ischemic heart disease; RD, respirable dust; REC, respirable elemental carbon.

Fine particulate matter from traffic-related air pollution is recognized as an important risk factor for ischemic heart disease (IHD) in the general population (1, 2). Evidence from dust storms in several major cities suggests that crustal sources of dust may also have an independent impact on cardiovascular disease (3–9). Diesel exhaust has been linked to cardiovascular disease in occupational groups that have traffic-related exposures (10), including professional drivers (11–13) and traffic police (14–17). Increased risk of cardiovascular mortality in miners has been linked with exposure to coal (18) and silica (19) dust, suggesting that respirable crustal dust may also contribute to IHD mortality. However, the exposure-response relationship between quantitative levels of diesel exhaust and respirable dust (RD) exposure and IHD mortality remains unclear.

The Diesel Exhaust in Miners Study (DEMS), originally designed to study lung cancer and diesel exhaust, offered an opportunity to examine IHD mortality in relation to exposure to diesel exhaust and respirable mine and ore dust, covering the range of diesel exhaust exposures common in the workplace and outdoor air (20). The DEMS cohort (21) and nested case-control (22) studies found that the risk of lung cancer increased with increased respirable elemental carbon (REC) exposure (the key surrogate for diesel exhaust in underground mining). Attfield et al. (21) additionally reported a standardized mortality ratio that suggested workers in the DEMS cohort were not at increased risk for IHD compared with the general population (standardized mortality ratio = 0.99, 95% CI: 0.91, 1.07). This finding, however, may have been attenuated by the healthy worker effect (i.e., workers are healthier than the general population), a problem alleviated by internal analyses. The goal of this study was to estimate the hazard ratios for IHD mortality associated with REC and RD exposure in the DEMS cohort.

METHODS

Study population

DEMS is a cohort mortality study of nonmetal, underground miners and surface workers exposed to diesel exhaust from 8 facilities in the United States (21), coupled with a nested case-control study of lung cancer (20). The facilities were located in Missouri (1 limestone mine), New Mexico (3 potash mines), Ohio (1 salt mine), and Wyoming (3 trona mines). These facilities were selected because workers had little or no exposure to known occupational lung carcinogens (particularly silica, radon, and asbestos) and included subjects with high REC exposure from diesel engine emissions underground. All workers who were ever employed in a blue-collar job for at least 1 year after dieselization were eligible. Follow-up time began at the date of dieselization at each mine, ranging from 1948 to 1968, or the date of hire, whichever came later, and continued through 1997. The DEMS cohort comprised 12,315 workers; however, the present analysis was restricted to 10,779 male workers who were hired after the start of dieselization.

Outcome and covariates

Demographic and work history information for workers in the cohort came from facility personnel records. Race/ethnicity (white/Hispanic or black) was unavailable for 64% of the cohort. Workers with unknown race were classified as white/Hispanic because 98% of those with known race/ethnicity were white or Hispanic.

Vital status was ascertained via matching with the National Death Index and Social Security Administration death files. The 111 participants who could not be matched to these databases were considered alive until their last observed date and censored afterward. Cause of death was obtained from National Death Index Plus during 1979–1997 and from death certificates coded by a certified nosologist for deaths occurring prior to 1979; 297 deaths due to IHD (*International Classification of Diseases, Seventh Revision*: 420; in the eighth and ninth revisions: 410–414) were identified.

Exposure assessment

Exposure assessment in DEMS has been described in detail elsewhere (23–27). The original exposure of interest was diesel exhaust. To estimate REC underground, 1998–2001 REC exposure levels were estimated for each job from personal air samples collected during the 1998–2001 DEMS exposure assessment surveys. Few historical REC measurements were available. Therefore 1998–2001 REC levels were back-extrapolated based on an empirical model using historical carbon monoxide (CO) concentrations relative to 1998–2001 CO levels and information on exposure determinants, including horsepower of diesel equipment used in the mines, exhaust ventilation in cubic feet per minute, job tasks, and diesel equipment characteristics. Thus, the model assumes that changes in these determinants would have affected CO and REC levels similarly. Surface jobs were categorized based on the proximity to diesel equipment and its size and frequency of use. The 1998–2001 DEMS REC measurements for surface jobs were used to calculate average REC exposures to one of 3 job groups per facility and were deemed unchanged during the period of study.

The DEMS exposure surveys collected a limited number of area mine respirable-dust measurements at each mine (total $n = 209$) (23), so personal measurements from 1976 to 1999 ($n = 442$) from the US Mine Safety and Health Administration and other government and company sources were used to evaluate RD as a possible confounder in the original lung-cancer analysis. Quantitative levels of exposure to RD were estimated by job groups, facility, and decade. Underground job groups were: 1) production and crushing; 2) haulage and travel ways; or 3) shop and office. Surface job groups were: 1) crushing and screening; 2) production and loading; or 3) maintenance and support.

Facility-specific job estimates of annual average REC exposure, as well as facility/job group and decade-specific estimates of RD exposure, were assigned to the study subjects based on their work histories. Time-varying estimates of cumulative exposure to REC (ug/m^3-years) and RD (mg/m^3-years) were calculated for each worker. Time-varying estimates of average intensity of REC and RD were calculated as the cumulative exposure divided by duration of exposure. All exposure metrics were calculated from first exposure to the time of each risk set.

Statistical methods

We used Cox proportional hazards models to estimate hazard ratios (HRs) for IHD mortality and exposures to REC and to RD, with attained age as the time variable. All analyses were stratified by the state of employment, which was synonymous with ore type.

For categorical exposure variables, we used indicator variables and the standard exponential form. For the joint association of REC and RD exposure metrics, we evaluated the multiplicative form,

$$\mathrm{HR}(x_{REC}, x_{RD}) = \mathrm{HR}(x_{REC}) \times \mathrm{HR}(x_{RD}) \qquad (1)$$

for each category of the joint cross-classification.

For the continuous exposure metrics, we initially fitted a linear model, $\mathrm{HR}(x) = 1 + \beta x$. Analyses of REC exposure revealed that a simple linear relationship did not describe hazard ratios across the full range of exposures, particularly for nonexposed and low-exposed workers. For the REC metrics, we fitted a segmented (or piecewise) linear regression model, namely,

$$\mathrm{HR}(x_{REC}) = 1 + \beta_{REC,<C} x_{REC} + \beta_{REC,\geq C}(x_{REC} - C)\,\psi(x_{REC} - C) \qquad (2)$$

where C identified the change point (i.e., the slope was $\beta_{REC,<C}$ before C and $\beta_{REC,<C} + \beta_{REC,\geq C}$ after C with the two lines meeting at C) and where $\psi(.)$ was an indicator function with a value of 1 if the argument was positive and zero otherwise. For the RD exposure metrics, the linear model fit the data well across the full exposure range.

Because reference categories included nonexposed and low-exposed workers, we included adjustment in the continuous regression models in the figures to pass through the

inverse-variance weighted mean hazard ratio across the exposure categories at the mean exposure, where the adjustment calculations used data only above the change point. The test of trend reflected the null hypothesis $\beta_{REC,<C} + \beta_{REC,\geq C} = 0$ (i.e., a zero slope beyond the change-point C).

In addition to age and state, analyses were adjusted for year of birth to handle cohort effects. Finally, workers who started employment on the surface were identified as "surface-only" workers until they transferred to an underground job, at which point they became, and remained, "ever-underground" workers.

To assess differences in the exposure-response for RD and IHD by type (composition) of dust mined, we modeled the hazard ratio relationships for each mine type separately.

Analyses used the SAS (SAS Institute, Inc., Cary, North Carolina) PHREG procedure for categorical analyses and the Epicure software package for the modeling of continuous variables (28).

The DEMS data set was publicly available, obtained under a data use agreement with the National Institute for Occupational Safety and Health and the National Cancer Institute. The data contain no direct identifiers, and the study was approved by the University of California, Berkeley, and National Cancer Institute institutional review boards.

RESULTS

The majority of the DEMS cohort comprised workers who ever worked underground (Table 1), and the majority of IHD cases occurred among those workers. REC exposures were much higher underground compared with on the surface; the median cumulative REC exposure was approximately 50 times higher and the median average intensity of REC exposure was approximately 100 times higher. In comparison, the median cumulative and average-intensity RD exposures were only approximately 2 and 3 times higher, respectively.

The moderate to strong correlation, $r = 0.60$, among cases for cumulative REC and RD exposures limited the ability of the joint analysis to disentangle the associations with IHD of the 2 cumulative exposure metrics in the same model. We therefore present joint hazard ratios for cumulative REC and average RD and for average REC and cumulative RD.

We created exposure categories that allowed for roughly comparable numbers of cases. The lowest exposure category served as the referent because there was only 1 case with zero REC exposure and no cases with zero RD exposure. Hazard ratios according to cumulative and average REC, adjusted for average and cumulative RD, respectively, showed a decreasing pattern of hazard ratios in the lowest exposure categories before increasing (Table 2). We fitted separate models among the ever-underground and surface-only workers (Tables 3–5). Using continuous metrics, fitted segmented regression models identified change points of 230 μg/m^3-years for cumulative REC and 2.0 μg/m^3 for average REC (Table 5). For exposures that exceeded the change points, hazard ratios exhibited increasing patterns with exposures (Figures 1A and 2A). The P value for the test of a zero slope beyond the change-point C was statistically significant for cumulative REC exposure ($P = 0.02$) but not average REC intensity ($P = 0.13$) (Table 5).

For the REC metrics, hazard ratios declined relative to the lowest exposure category to 0.46 for cumulative REC exposure and to 0.64 for average REC intensity before increasing to 0.79 and 1.25, respectively, in the highest category (Table 2 and Figures 1A and 2A). Using the category containing the change point as the referent, hazard ratios and 95% confidence intervals for the top category were 1.69 (95% confidence interval (CI): 1.08, 2.62) for cumulative REC and 1.54 (95% CI: 0.92, 2.57) for average REC (not shown). These were similar to fitted hazard ratios of 1.71 and 1.27 based on the segmented regression models for cumulative and average REC for the mean of the upper category (4,151 μg/m^3-years and 206 μg/m^3, respectively) relative to the mean of the categories that include the change point (368 μg/m^3-years and 2.4 μg/m^3) (not shown). Hazard ratios for RD metrics increased across the full exposure range, although patterns were not monotonic (Table 2 and Figures 1B and 2B). Hazard ratios for the highest exposure category relative to the lowest were 1.33 (95% CI: 0.83, 2.12) for cumulative RD and 2.69 (95% CI: 1.39,

Table 1. Demographic and Exposure Characteristics Among Male Workers First Employed After the Start of Dieselization in the Diesel Exhaust in Miners Study[a] Cohort, United States, Beginning During 1948–1968 and Completing Follow-up in 1997

Characteristic	Total (n = 10,779), Median (IQR)	Ever Underground (n = 7,507), Median (IQR)	Surface Only (n = 3,272), Median (IQR)
Birth year	1947 (1936–1954)	1948 (1936–1954)	1946 (1934–1954)
Duration of employment, years	9.27 (3.40–20.17)	8.81 (3.30–19.46)	10.22 (3.72–21.98)
Follow-up time since leaving work, years	12.33 (0–20.68)	12.67 (0–20.61)	10.66 (0–20.99)
Final cumulative REC μg/m^3-years	304.0 (29.8–1124.0)	666.54 (268.1–1801.1)	13.28 (4.31–29.65)
Final cumulative RD mg/m^3-years	10.15 (4.14–20.91)	13.14 (5.54–27.00)	6.00 (2.05–11.57)
Final average intensity REC μg/m^3	71.70 (2.12–151.97)	120.04 (62.69–185.45)	1.22 (0.91–2.11)
Final average intensity RD mg/m^3	1.33 (0.73–2.07)	1.69 (1.24–2.40)	0.60 (0.49–0.81)

Abbreviations: IQR, interquartile range; REC, respirable elemental carbon; RD, respirable dust.

[a] Total numbers of deaths from IHD were 297, 200, and 97 in the total, ever-underground, and surface-only cohorts, respectively.

Table 2. Hazard Ratios for Ischemic Heart Disease According to Metrics of Exposure to Respirable Elemental Carbon and to Respirable Dust, Including Cumulative Exposure and Time-Weighted Average Concentration, Among Workers First Employed After the Start of Dieselization, Diesel Exhaust in Miners Study Cohort, United States, Beginning During 1948–1968 and Completing Follow-up in 1997

Exposure	Cumulative REC			Cumulative RD			Average REC			Average RD		
	No. of Cases	HR[a]	95% CI	No. of Cases	HR[b]	95% CI	No. of Cases	HR[b]	95% CI	No. of Cases	HR[a]	95% CI
Cumulative REC, μg/m^3-year												
0–9	45	1.00	Referent									
10–19	28	0.98	0.61, 1.58									
20–39	29	0.89	0.55, 1.46									
40–159	39	0.56	0.34, 0.94									
160–639	52	0.47	0.28, 0.80									
640–1,279	29	0.46	0.25, 0.83									
1,280–2,559	38	0.68	0.38, 1.21									
≥2,560	37	0.79	0.43, 1.45									
Cumulative RD, mg/m^3-year												
0–4				62	1.00	Referent						
5–9				55	0.99	0.68, 1.43						
10–14				41	0.94	0.62, 1.42						
15–19				28	1.03	0.64, 1.64						
20–24				32	1.42	0.90, 2.25						
25–29				17	0.99	0.56, 1.74						
30–39				23	1.13	0.67, 1.90						
≥40				39	1.33	0.83, 2.12						
Average REC, μg/m^3												
0.0–0.9							44	1.00	Referent			
1.0–1.9							40	1.25	0.77, 2.02			
2.0–3.9							24	0.81	0.47, 1.41			
4.0–15.9							16	0.64	0.34, 1.20			
16.0–31.9							22	1.51	0.89, 2.56			
32.0–63.9							39	1.20	0.75, 1.93			
64.0–127.9							36	0.83	0.51, 1.34			
≥128.0							76	1.25	0.81, 1.94			
Average RD, mg/m^3												
0.0–0.49										28	1.00	Referent
0.50–0.69										31	0.88	0.51, 1.53
0.70–0.99										51	1.42	0.87, 2.30
1.00–1.49										38	1.48	0.82, 2.67
1.50–1.99										47	1.99	1.15, 3.43
2.00–2.49										35	2.00	1.05, 3.83
2.50–2.99										20	2.29	1.11, 4.71
≥3.00										47	2.69	1.39, 5.23

Abbreviations: CI, confidence interval; HR, hazard ratio; RD, respirable dust; REC, respirable elemental carbon.
[a] Model stratified on mine type, adjusted for birth year, and included cumulative REC and average RD.
[b] Model stratified on mine type, adjusted for birth year, and included average REC and cumulative RD.

5.23) for average RD. The trends were statistically significant for cumulative ($P = 0.05$) and average ($P < 0.01$) RD exposure (Table 5).

Results among the ever-underground workers (Table 3) are reflective of those of the entire cohort shown in Table 2. Among the surface-only workers (Table 4), the hazard ratios for both cumulative

Table 3. Hazard Ratios for Ischemic Heart Disease According to Metrics of Exposure to Respirable Elemental Carbon and to Respirable Dust, Including Cumulative Exposure and Time-Weighted Average Concentration, Among Workers First Employed After the Start of Dieselization and Who Ever Worked Underground, Diesel Exhaust in Miners Study Cohort, United States, Beginning During 1948–1968 and Completing Follow-up in 1997

Exposure	Cumulative REC			Cumulative RD			Average REC			Average RD		
	No. of Cases	HR[a]	95% CI	No. of Cases	HR[b]	95% CI	No. of Cases	HR[b]	95% CI	No. of Cases	HR[a]	95% CI
Cumulative REC, μg/m^3-year												
0–19	10	1.00	Referent									
20–39	10	1.46	0.60, 3.57									
40–159	25	0.75	0.34, 1.63									
160–639	51	0.58	0.28, 1.21									
640–1,279	29	0.55	0.26, 1.20									
1,280–2,559	38	0.83	0.39, 1.76									
≥2,560	37	0.93	0.42, 2.05									
Cumulative RD, mg/m^3-year												
0–4				29	1.00	Referent						
5–9				24	0.72	0.42, 1.25						
10–14				25	0.92	0.53, 1.58						
15–19				23	1.09	0.62, 1.90						
20–24				23	1.11	0.63, 1.96						
25–29				17	1.07	0.58, 2.00						
30–39				22	1.07	0.60, 1.90						
≥40				37	1.13	0.66, 1.92						
Average REC, μg/m^3												
0.0–1.9							8	1.00	Referent			
2.0–3.9							5	1.13	0.36, 3.57			
4.0–15.9							14	0.85	0.34, 2.09			
16.0–31.9							22	1.65	0.72, 3.78			
32.0–63.9							39	1.30	0.59, 2.88			
64.0–127.9							36	0.89	0.40, 1.98			
≥128.0							76	1.35	0.63, 2.92			
Average RD, mg/m^3												
0.0–0.69										12	1.00	Referent
0.70–0.99										7	0.60	0.23, 1.53
1.00–1.49										34	1.15	0.55, 2.43
1.50–1.99										45	1.70	0.86, 3.38
2.00–2.49										35	1.52	0.72, 3.23
2.50–2.99										20	1.56	0.70, 3.50
≥3.00										47	1.87	0.88, 4.00

Abbreviations: CI, confidence intervals; HR, hazard ratio; RD, respirable dust; REC, respirable elemental carbon.
[a] Model stratified on mine type, adjusted for birth year, and included cumulative REC and average RD.
[b] Model stratified on mine type, adjusted for birth year, and included average REC and cumulative RD.

and average REC in the highest exposure category were below the null. Conversely, the hazard ratios for both cumulative and average RD exposures were elevated. Additional analyses split the top average-RD-exposure group into 2 categories. The hazard ratio for the category defined as 0.70–0.84 mg/m^3 (22 cases) was 1.56 (95% CI: 0.78, 3.13) and the hazard ratio for the category defined as ≥0.85 mg/m^3 (28 cases) was 1.76 (95% CI: 0.96, 3.19).

DISCUSSION

Results of our study suggest an excess risk of IHD in relation to exposure to REC and to RD among workers in the DEMS cohort who were hired after the start of dieselization. The positive trends in the hazard ratios for cumulative REC exposure after an initial decline and for average RD exposure, both after

Table 4. Hazard Ratios for Ischemic Heart Disease According to Metrics of Exposure to Respirable Elemental Carbon and to Respirable Dust, Including Cumulative Exposure and Time-Weighted Average Concentration, Among Workers First Employed After the Start of Dieselization and Who Worked Only on the Surface, Diesel Exhaust in Miners Study Cohort, United States, Beginning During 1948–1968 and Completing Follow-up in 1997

Exposure	Cumulative REC			Cumulative RD			Average REC			Average RD		
	No. of Cases	HR[a]	95% CI	No. of Cases	HR[b]	95% CI	No. of Cases	HR[b]	95% CI	No. of Cases	HR[a]	95% CI
Cumulative REC, $\mu g/m^3$-year												
0–9	40	1.00	Referent									
10–19	23	0.88	0.51, 1.51									
20–39	19	0.68	0.37, 1.22									
≥40	15	0.43	0.19, 0.95									
Cumulative RD, mg/m^3-year												
0–4				33	1.00	Referent						
5–9				31	1.33	0.81, 2.19						
10–14				16	0.98	0.52, 1.85						
15–19				5	0.70	0.29, 2.10						
≥20				12	1.80	0.83, 3.91						
Average REC, $\mu g/m^3$												
0.0–0.9							43	1.00	Referent			
1.0–1.9							33	0.93	0.51, 1.73			
≥2.0							21	0.56	0.29, 1.09			
Average RD, mg/m^3												
0.0–0.49										26	1.00	Referent
0.50–0.69										21	0.84	0.42, 1.69
≥0.70										50	1.68	0.97, 2.92

Abbreviations: CI, confidence interval; HR, hazard ratio; RD, respirable dust; REC, respirable elemental carbon.
[a] Model stratified on mine type, adjusted for birth year, and included cumulative REC and average RD.
[b] Model stratified on mine type, adjusted for birth year, and included average REC and cumulative RD.

adjustment for the other exposure metric, were statistically significant. Our results suggest an IHD association with REC and/or with RD. It is possible that the association is actually driven by one of the exposures, but given their correlation, we could not definitively identify either as the principal risk factor.

The hazard ratios initially declined over the lower end of cumulative REC exposure range. This pattern was not observed for the average REC metric and was also absent for the dust metrics. The initial decline persisted after taking into account region, age at first exposure, age at death, average intensity, and duration. No obvious factors emerged from these analyses that could explain the downward trends seen at lower categories of REC exposure.

The trends in risk with increasing exposure were consistent with homogeneity in REC associations for surface-only and ever-underground workers. However, given the restricted range of REC exposure in surface jobs, the power to distinguish differences was minimal. The lack of power to detect association differences among surface and underground workers is particularly unfortunate given that surface workers are exposed to RD in the relative absence of REC exposure, making the surface the optimal setting to evaluate a RD association independent from that of REC.

The results presented here are not adjusted for smoking. Only the nested case-control study of lung cancer included smoking information, and those data were insufficient to adjust for smoking in the cohort analysis of IHD. Nevertheless, smoking was found to be negatively correlated with REC exposure underground (22). Similar negative confounding should also hold for IHD; thus, these unadjusted estimates may be attenuated compared with the association we would have seen had we been able to control for smoking.

The workers in this analysis included only miners who were hired after the start of follow-up (i.e., after dieselization of the mine). The restriction by hire date was done for 2 reasons. First, including exposed workers who had been employed at the facilities before follow-up began could have introduced selection bias because those workers could represent a healthier subset of all the workers eligible for the study if follow-up had started earlier (29, 30). Follow-up started in this study when dieselized equipment was introduced into each mine. Miners could not have been exposed to diesel exhaust at these facilities prior to dieselization; thus left truncation was not a potential bias for the REC results presented here or in the original study. However, the workers already employed at these facilities when diesel

Table 5. Excess Hazard Ratio for Ischemic Heart Disease According to Metrics of Exposure to Respirable Elemental Carbon and to Respirable Dust, Including Cumulative Exposure and Time-Weighted Average Concentration, Among Workers First Employed After the Start of Dieselization Diesel Exhaust in Miners Study Cohort, United States, Beginning During 1948–1968 and Completing Follow-up in 1997

Exposure and Employment Category	EHR per Unit[a]				*P* for Trend[b]
	$\beta_{REC,<C}$ or β_{rd}		$\beta_{REC,<C} + \beta_{REC,\geq C}$		
	HR	95% CI	HR	95% CI	
Cumulative REC, μg/m^3-year					
All	-2.01×10^{-3}	-2.84×10^{-3}, -7.45×10^{-4}	1.04×10^{-4}	1.83×10^{-5}, 2.29×10^{-4}	0.02
Ever worked underground	-1.81×10^{-3}	-2.80×10^{-3}, 2.76×10^{-6}	9.49×10^{-5}	5.98×10^{-6}, 2.32×10^{-4}	0.05
Worked only on the surface	-3.04×10^{-3}	-8.59×10^{-3}, 2.50×10^{-3}[c]			0.12
Cumulative RD, mg/m^3-year					
All	7.77×10^{-3}	-1.36×10^{-4}, 0.021			0.05
Ever worked underground	5.58×10^{-3}	-1.69×10^{-3}, 0.018			0.17
Worked only on the surface	7.21×10^{-3}	−0.013, 0.060			0.59
Average REC, μg/m^3					
All	−0.112	−0.271, 0.2.42	1.05×10^{-3}	-3.80×10^{-4}, 3.01×10^{-3}	0.13
Ever worked underground	0.212	−1.586, 1.971[c]	1.23×10^{-3}	-2.76×10^{-3}, 5.16×10^{-3}[c]	0.33
Worked only on the surface	−0.099	−0.194, 0.078[c]			0.13
Average RD, mg/m^3					
All	0.580	0.142, 1.900			<0.01
Ever worked underground	0.353	0.012, 2.213			0.06
Worked only on the surface	2.15	−2.930, 7.288			0.08

Abbreviations: CI, confidence interval; EHR, excess hazard ratio; HR, hazard ratio; RD, respirable dust; REC, respirable elemental carbon.

[a] For the REC metrics for all and ever underground, the estimated EHR per unit exposure for the linear parameter before $\beta_{REc,<C}$ and after $\beta_{REC,<C} + \beta_{REC,\geq C}$ the change point in the segmented regression model: 230 μg/m^3-years for cumulative REC and 2.0 μg/m^3 for average REC (see text). For RD metrics for all and for ever underground, the estimated EHR/unit for linear parameter, β_{rd}, across the full exposure range. CIs are likelihood-based. For surface-only workers, all EHRs are estimated for the parameter from a linear model.

[b] For REC metrics for all and for ever underground, *P* value for the score test of no linear trend after the change point, $\beta_{REC,<C} + \beta_{REC,\geq C} = 0$, with 230 μg/m^3-years for cumulative REC and 2.0 μg/m^3 for average REC. For RD metrics for all and ever underground, *P* value for the score test of no linear trend, $\beta_{rd} = 0$. For surface-only workers, all trend tests are estimated for the parameter from a linear model.

[c] Wald-based CI, because profile likelihood CI could not be determined.

equipment was introduced very likely had been previously exposed to respirable mine dust, so to avoid left truncation bias for RD, we excluded them. Second, exposure was assessed for RD only after dieselization. Restricting the cohort to workers hired after dieselization lessened the potential misclassification of RD exposure prior to the start of dieselization. Although these workers may have had RD exposure at previous workplaces, the chance of such exposure was likely lower than for workers employed at these facilities prior to dieselization. Sensitivity analyses of our results including workers hired before dieselization were essentially unchanged for REC and slightly attenuated for RD (results not shown).

Exposure misclassification is always a consideration in epidemiologic studies. Because few REC measurements were available prior to 1998, DEMS investigators used a large database of underground CO measurements extending back to 1975 to model the relationship of CO to diesel equipment horsepower and air exhaust from the mines to estimate exposures prior to 1975 (26). Several comparisons of the results of this modeling and of other aspects of DEMS were made with internal or external data (27). Bias was generally low (<30%), and misclassification was likely to be nondifferential, which would tend to attenuate the risk estimates toward the null. The available dust measurements were more limited in terms of coverage of jobs and years. Thus, broader job groups were developed for RD than for REC, and concentrations estimated in the 1970s were used for the years prior to the 1970s, back to the date of dieselization. This procedure would likely have resulted in overestimated exposures, given that prior to 1970, production rates were generally lower (thereby creating less dust) than after 1970. If one assumes that the lower end of exposure was estimated correctly, overestimation of exposure at the high end would attenuate the slope of the exposure-response association.

Limestone, potash, salt (halite), and trona were mined and processed at the DEMS facilities. Although it is possible that any kind of RD can cause health problems, it is worth considering the relative toxicity of each type. Limestone is inert and is recommended for use in the coal industry for rock dusting to prevent mine explosions underground (31). Potash is an irritant; the caustic mine dust can lead to perforation of the nasal septum at high levels (32) and has been linked to cardiovascular mortality (33). Trona is also an irritant and has been associated with respiratory disease (34). Halite is considered a nuisance dust with no reported adverse associations with health. To examine

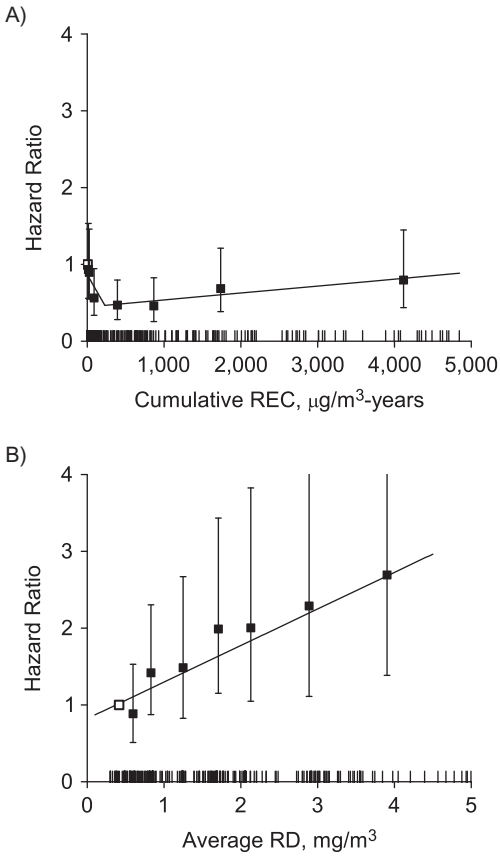

Figure 1. The shape of the exposure-response relationship between cumulative exposure to respirable elemental carbon (REC) and average intensity of respirable dust (RD) and ischemic heart disease among male workers first employed after the start of dieselization in the Diesel Exhaust in Miners Study Cohort, United States, beginning during 1948–1968 and completing follow-up in 1997. A) Hazard ratios (solid symbol) and 95% confidence intervals for categories of exposure to cumulative REC (μg/m^3-years), adjusted for time-weighted average intensity of RD (mg/m^3) and the fitted segmented linear regression model for cumulative REC (solid line). B) Hazard ratios (solid symbol) and 95% confidence intervals for categories of time-weighted average intensity of (RD (mg/m^3), adjusted for exposure to cumulative REC (μg/m^3-years) and the fitted linear regression model for average RD (solid line). Because reference categories included nonexposed and exposed workers, the regression model included adjustment to pass through the inverse-variance weighted mean hazard ratio for all categories.

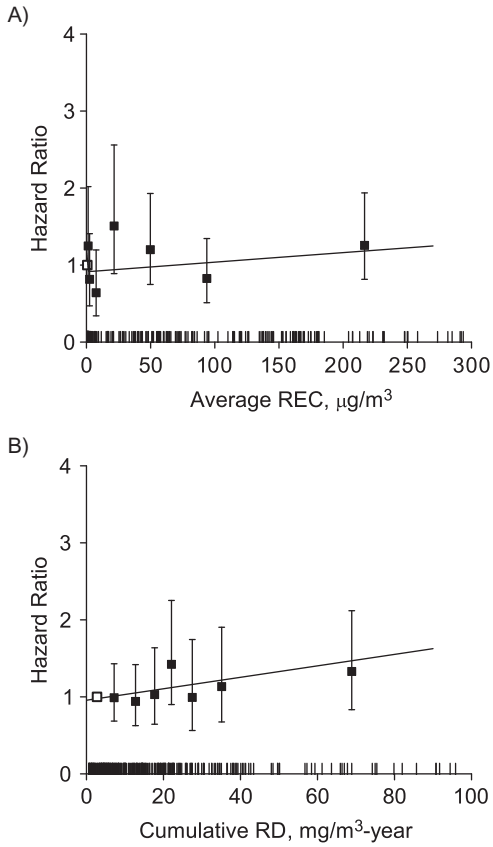

Figure 2. The shape of the exposure-response relationship between cumulative exposure to respirable dust (RD) and average intensity of respirable elemental carbon (REC) and ischemic heart disease among male workers first employed after the start of dieselization in the Diesel Exhaust in Miners Study Cohort, United States, beginning during 1948–1968 and completing follow-up in 1997. A) Hazard ratios (solid symbol) and 95% confidence intervals for categories of exposure to time-weighted average REC (μg/m^3), adjusted for cumulative RD (mg/m^3-years). B) Hazard ratios (solid symbol) and 95% confidence intervals for categories of exposure to cumulative RD (mg/m^3-years) adjusted for time-weighted average REC (μg/m^3) and the fitted linear regression model cumulative RD (solid line). Because reference categories included nonexposed and exposed workers, the regression model included adjustment to pass through the inverse-variance weighted mean hazard ratio for all categories.

the consistency of the findings by ore type, we fitted models for each type of dust. We found that the hazard ratios were systematically higher for average exposure to potash and limestone, with statistically significant tests for trend (Web Table 1, available at https://academic.oup.com/aje). Elevated hazard ratios were also observed for both potash and limestone in relation to cumulative RD exposure (Web Table 2). No associations were observed with trona or salt. Overall, however, the numbers of cases available for these ore-specific analyses were too limited for a clear analysis of differences in IHD risk by ore type.

This analysis takes full advantage of the quantitative exposure assessment by exploring the shape of the exposure-response curve using readily available proportional hazards models and cohort restriction to avoid bias. However, results presented here may have been attenuated by a healthy-worker survivor effect that could have occurred after the start of follow-up. Although this analysis does not address time-varying confounding affected by prior exposure or competing risks, future work will apply methods to handle both.

Particulate matter from crustal sources such as dust storms and mining has been found to increase heart disease risk. There is evidence of increased cardiovascular hospitalizations during storms of dust originating in the Saharan Desert (3, 5, 6). Windblown dust storms originating in the Mongolia/China desert have been associated with modest increased risk of cardiovascular disease (4, 7–9). Increased risk of cardiovascular mortality was also found during dust storms in the California desert (35) but not in British Columbia (36) or Washington State (37).

Unlike the dust exposures in DEMS, dust storm exposures are acute and can carry noncrustal particles (38); however, the levels of crustal material in the ambient environment are elevated during storms, suggesting that increased crustal material may increase risk of heart disease. Two recent studies of miners have linked increased risk of IHD mortality with coal dust (18, 39). Long-term exposure to silica dust, another crustal material, has also been linked to increased risk of cardiovascular disease mortality in miners (19). Although the workers in the present study did not mine coal, and the silica exposures were low, these workers were exposed to crustal mine dust.

There is a growing body of evidence regarding the cardiovascular health implications of fossil fuel combustion in general (40) and diesel exhaust in particular. Previous evidence suggests a possible role for the duration of diesel exhaust exposure in the etiology of ischemic heart disease among truck drivers (13). Increased risk for myocardial infarction mortality and ischemic heart disease hospitalizations were reported in Swedish (11) and Danish (12) professional drivers. Fine particulate matter from engine emissions was associated with acute cardiovascular responses in highway patrol troopers in North Carolina (14, 17). Additionally, in a recent report on 54 male workers exposed to high levels of diesel exhaust in a diesel engine manufacturing facility in China, levels of chemokine (C-C motif) ligand 15/macrophage inflammatory protein 1 delta (CCL15/MIP-1D), a marker of cardiovascular disease mortality, increased with increasing elemental carbon exposure (41). Traffic policemen in Italy had more exercise-induced electrocardiogram abnormalities compared with office workers (16), and traffic policemen in Shanghai had changes in inflammatory markers from increased exposure to fine particulate matter (15). Thus, occupational exposure to diesel exhaust and traffic-generated air pollution has been associated with markers of cardiovascular disease in a variety of settings.

Current research suggests the biologic mechanisms by which traffic-generated particulate matter may cause heart disease. These include systemic inflammatory response mechanisms, a shift in autonomic balance, and translocation of particles into the circulatory system (42). A recent review by the American Heart Association (42) determined that the mechanistic evidence was strongest for a systemic inflammatory mechanism. Diesel exhaust likely triggers cardiovascular events via vascular dysfunction (43), increased thrombotic potential (44), and increased hypertension (45), all of which have been observed in healthy exposed subjects.

Our results suggest excess risk of ischemic heart disease mortality in relation to increased exposure to REC and RD among workers in the DEMS cohort who were hired after the start of dieselization. However, because of the entanglement of these exposures in this cohort, we were unable to clearly identify if the excess is primarily driven by one or both exposures.

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