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Diesel exhaust and respiratory dust exposure in miners and chronic obstructive pulmonary disease (COPD) mortality in DEMS II

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Abstract

Background: Diesel exhaust and respirable dust exposures in the mining industry have not been studied in depth with respect to non-malignant respiratory disease including chronic obstructive pulmonary disease (COPD), with most available evidence coming from other settings.

Objectives: To assess the relationship between occupational diesel exhaust and respirable dust exposures and COPD mortality, while addressing issues of survivor bias in exposed miners.

Methods: The study population consisted of 11,817 male workers from the Diesel Exhaust in Miners Study II, followed from 1947 to 2015, with 279 observed COPD deaths. We fit Cox

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Andreas M. Neophytou: Conceptualization, Data curation, Methodology, Writing - original draft, Formal analysis, Writing - review & editing. **Jacqueline M. Ferguson**: Data curation, Methodology, Formal analysis, Writing - review & editing; **Sadie Costello:** Methodology, Writing - review & editing. **Sally Picciotto:** Methodology, Writing - review & editing. **John R. Balmes:** Writing review & editing. **Stella Koutros**: Conceptualization, Resources, Funding acquisition, Writing - review & editing. **Debra T. Silverman:** Conceptualization, Resources, Funding acquisition, Writing - review & editing. **Ellen A. Eisen:** Conceptualization, Methodology, Supervision, Funding acquisition, Writing - review & editing

proportional hazards models for the relationship between respirable elemental carbon (REC) and respirable dust (RD) exposure and COPD mortality. To address healthy worker survivor bias, we leveraged the parametric g-formula to assess effects of hypothetical interventions on both exposures.

Results: Cox models yielded elevated estimates for the associations between average intensity of REC and RD and COPD mortality, with hazard ratios (HR) corresponding to an interquartile range width increase in exposure of 1.46 (95% confidence interval (CI): 1.12, 1.91) and 1.20 (95% CI: 0.96, 1.49), respectively for each exposure. HRs for cumulative exposures were negative for both REC and RD. Based on results from the parametric g-formula, the risk ratio (RR) for COPD mortality comparing risk under an intervention eliminating REC to the observed risk was 0.85 (95% CI: 0.55, 1.06), equivalent to an attributable risk of 15%. The corresponding RR comparing risk under an intervention eliminating RD to the observed risk was 0.93 (95% CI: 0.56, 1.31).

Conclusions: Our findings, based on data from a cohort of nonmetal miners, are suggestive of an increased risk of COPD mortality associated with REC and RD, as well as evidence of survivor bias in this population leading to negative associations between cumulative exposures and COPD mortality in traditional regression analysis.

Keywords

diesel exhaust; respiratory dust; COPD mortality; survivor bias

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a collective term for several progressive chronic lung diseases characterized by airway obstruction, including chronic bronchitis and emphysema. COPD remains one of the leading causes of mortality in the US (Murphy et al., 2021), with an estimated five billion dollars in annual health care cost expenditures associated with it (Syamlal et al., 2020). Occupational exposures are among the leading causes of COPD after tobacco smoke (Balmes et al., 2003), with approximately 20% of cases attributable to workplace exposures to vapors, gases, dusts and fumes (Blanc et al., 2009; Lytras et al., 2018). Mitigation of respirable occupational exposures to improve worker safety and health are needed to limit the burden of COPD.

Diesel exhaust is one occupational exposure linked to increased risk of COPD, with previous evidence from studies in the construction and transportation industries, as well as from motor vehicle operations (Hart et al., 2012b, 2009, 2006; Hnizdo et al., 2002; Weinmann et al., 2008). Mining is an occupational setting with high diesel exhaust exposure as well as additional exposure to respirable dust. Diesel exhaust exposures in miners have been linked to lung cancer and ischemic heart disease mortality (Attfield et al., 2012; Costello et al., 2018; Neophytou et al., 2016; Silverman et al., 2012), but evidence for an exposure-response between diesel exhaust and COPD in this industry is limited. Occupational dust exposure has also been linked to risk of COPD (Balmes et al., 2003; Blanc et al., 2009); however, studies from the mining industry have focused specifically on coal mine dust and silica dust as opposed to dust from other sources.

The natural history of COPD, which can cause chronic health issues over many years, may also increase the potential for survivor bias in occupational settings (Picciotto et al., 2014). This type of bias, typically referred to as the healthy worker survivor effect, occurs when less healthy workers tend to leave work earlier and accrue less exposure over time compared to their healthier peers, leading to downward bias towards or even past the null for harmful exposures (Brown et al., 2017; Buckley et al., 2015). Previous findings have provided evidence that this type of bias is operating in occupational cohort studies with COPD as the outcome of interest (Chevrier et al., 2012; Hart et al., 2009).

We have previously reported results linking long-term diesel-exhaust exposure and COPD mortality in data from the Diesel Exhaust in Miners Study (DEMS). However, the original DEMS COPD analysis was limited in statistical power and had the potential for survivor bias (Ferguson et al., 2020). A better understanding of the relationship between diesel exhaust exposure and risk of COPD will enable us to quantify the overall burden of disease related to occupational exposures, as well as the general impact of diesel exhaust exposures on public health. In this study, we leverage the 18-year extended mortality follow-up in the Diesel Exhaust in Miners Study II (DEMS II) (Koutros et al., 2023; Silverman et al., 2023), to re-examine the association between long-term diesel exhaust and respiratory dust exposures with risk of COPD mortality. We further perform sensitivity analyses to assess the presence of healthy worker survivor bias that may lead to downward bias of traditional regression parameters and also examine these relationships using the parametric g-formula which is equipped to address this bias in the form of exposure-confounder feedback.

2. Methods

2.1 Study Population

The study population has been described in detail elsewhere (Koutros et al., 2023; Silverman et al., 2023). Briefly, DEMS II contains extended follow-up information from the Diesel Exhaust in Miners Study (Attfield et al., 2012; Silverman et al., 2012). The study comprised the same 12,315 non-metal miners from 8 mining facilities located in Missouri (1 limestone mine), New Mexico (3 potash mines), Ohio (1 salt mine), and Wyoming (3 trona mines). Workers employed in a blue-collar job for at least one year were eligible. Follow-up began with beginning of dieselization at each facility (varying from 1947 to 1967), after applying the one-year employment requirement for each participant. Mortality follow-up in DEMS was through 1997, with the extended mortality follow-up for DEMS II continuing through 2015. The study was approved by the Human Subjects Review Board at the University of California Berkeley.

2.2 Outcome and Covariates

Mortality and cause of death were ascertained from death records in the National Death Index (NDI). Vital status could not be ascertained for 89 participants, who we censored at their last observed date. COPD mortality was defined as death due to chronic bronchitis, emphysema, or chronic airway obstruction and identified based on codes from the International Classification of Diseases (ICD) Sixth and Seventh Revision (501–502); Eighth Revision (490–492); or Ninth Revision (490–492, 496) depending on the date of death.

We identified 284 cases with these codes listed as the underlying cause of death. Only five of the cases were among female participants, so analyses were restricted to n=279 cases among 11,817 male workers. As a sensitivity analysis we also considered an outcome definition where deaths with the same ICD codes for either the underlying or one of the first two contributing causes on the death certificate (372 cases among male miners), in accordance to previous research on COPD mortality in this setting (Ferguson et al., 2020). Work records included information on age, state where mines were located (Missouri, New Mexico, Ohio, or Wyoming each corresponding to separate mine types), date of hire (which enabled estimation of number of years as a prevalent hire), active employment status over time, job location (surface, underground, or inactive periods) and partial information on race. Smoking is considered the leading cause of COPD (Mannino et al., 2006), but smoking information was only available for the subset of participants which the DEMS nested case -control study of lung cancer (Silverman et al., 2023).

2.3 Exposure Assessment

Historical exposure to respirable elemental carbon (REC) was assessed as a surrogate for diesel exhaust exposure. REC exposure values were estimated based on personal air samples (n>1100) collected during the 1998–2001 DEMS industrial hygiene surveys. Few historical REC measurements were available and the 1998–2001 REC levels were back-extrapolated based on an empirical model to estimate underground exposures (Coble et al., 2010; Stewart et al., 2012, 2010; Vermeulen et al., 2010b, 2010a). The model relied on historical carbon monoxide (CO) concentrations based on historical area measurement (n>11,000) and information on horsepower of diesel equipment used in the mines, exhaust ventilation in cubic feet per minute, job tasks, and diesel equipment characteristics. 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 three job groups per facility and were deemed unchanged during the period of study. Respirable dust (RD) exposures were estimated based on personal measurements (n=442) from 1976 to 1999 collected by the US Mine Safety and Health Administration (MSHA) and other government and company sources (Stewart et al., 2010). Quantitative levels of exposure to RD were estimated by job groups, facility, and decade. 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. Additional information on the number and timing of samples utilized in the exposure assessment for both REC and RD can be found in Supplemental Table 1.

For the analyses in the current study, time-varying estimates of cumulative exposure to REC ($\mu g/m^3$-years) and RD (mg/m^3-years) were calculated for each worker by accumulating annual average exposures for the duration of exposure, while time-varying estimates of average intensity of REC and RD were calculated as the cumulative exposure divided by duration of exposure. Complete work history and, by extension, exposure information for both REC and RD were only available from beginning of follow-up through 1997–1999 depending on facility. Exposures were therefore not known for participants that remained employed at participating facilities after these dates, which accounted for approximately

25% of male cohort participants, while 11% of participants were actively employed un underground jobs.

2.4 Statistical Analysis

We assessed the relationship between REC and RD exposures and COPD mortality in a survival framework. We fit Cox proportional hazards models for COPD mortality and cumulative and average intensity REC and RD exposures. We mutually adjusted for two exposures of REC and RD to account for potential common causes driving exposure concentrations relating to job type/task and location. However, to reduce issues of collinearity particularly between cumulative exposures to REC and RD, two sets of models were fit: (a) with cumulative REC exposure and average intensity RD exposure included in the same model and separately, (b) with cumulative RD exposure and average intensity REC exposure included together. We also fit separate models for each of the four different metrics without any mutual adjustment as sensitivity analysis. We also considered the same models in subsets of participants limited by duration of employment, in order to assess for evidence of healthy worker survivor bias, as well as models for the relationship between duration of exposure and the outcome. In all models, attained age was the time scale of interest, while birth year, race/ethnicity (white, other or unknown), number of years employed prior to dieselization, and time-varying job location were also included; models were also stratified by state (proportional hazards assumption applies within each state). Separate models were fit with categorical and continuous exposures. In models with categorical exposures, variables were created using cut-offs based on the quartiles of the exposure distribution of the cases; a Wald test for linear trend was also performed. In addition, separate models using continuous exposures were fit using (log-)linear terms. Lastly, sensitivity analyses with models using 20-year lagged exposures were performed for both categorical and continuous exposure metrics. The lag period was chosen based on the duration of follow-up after last active employment (median duration of 20 years among the cases). Cox models were performed in Stata version 16, 2019 (Stata Corp LCC, College Station, TX, USA).

Exposure-confounder feedback in the form of a time varying confounder (active employment status) affected by prior exposure is the signature structure of the healthy worker survivor effect. In order to account for this, we estimated counterfactual risks under exposure interventions using the parametric g-formula (Robins, 1986; Taubman et al., 2009). While the approach is preferred to traditional regression approaches (including Cox proportional hazards models) due to its ability to account for exposure-confounder feedback, it comes with strong assumptions of correct model specification. The estimation process is described in detail elsewhere (Neophytou et al., 2019; Taubman et al., 2009), while a complete description of the fitted parametric models is included in the supplemental materials. Briefly, we fit separate pooled logistic models for the outcome, death by other causes as a competing event, and time-varying active employment status, as well as a multilevel logistic model for job location and linear models for annual average REC and RD exposures. We then simulated exposure, covariate, and outcome values at each age ≤ 90 years in a large pseudo-sample (n=50,000) using the baseline distribution of covariates and model parameters based on the aforementioned models. The simulation

was repeated for various hypothetical intervention scenarios setting maximum limits for REC and RD. The interventions for REC were determined based on the current MSHA permissible exposure limit (PEL) of 160 μg/m^3 of total carbon (TC), measured as an 8-hour time-weighted average (MSHA, 2001). We also estimated counterfactual risk under the EC recommendation published, but later withdrawn, by the American Conference of Governmental Industrial Hygienists (ACGIH) (20 μg/m^3 EC measured on the submicron particulate matter fraction (ACGIH, 2001; NIOSH, 2003)), as well as a scenario eliminating diesel exposures entirely. These values were converted to the respirable fraction of EC based on information for the relationship between TC, EC and REC from the exposure assessment studies, as previously described (Neophytou et al., 2019), with the MSHA PEL of 160 μg/m^3 for TC corresponding to 106 μg/m^3 REC, and the ACGIH recommended 20 μg/m^3 EC corresponding to 25 μg/m^3 REC. Corresponding PELs for RD such as the MSHA PEL for nuisance dust (10 mg/m^3 for total dust) were above the majority of the observed exposures (maximum observed annual average daily exposure for RD was 5 mg/m^3); therefore, we estimated interventions setting theoretical maximums of 0.5 mg/m^3 and 1 mg/m^3. For each intervention, at each time point, exposure values predicted to be above the hypothetical limit at each time point were replaced with the limit, while exposure values predicted to be below the hypothetical limit were allowed to remain as predicted. These replaced or predicted values were used to predict covariate and outcome values for the next time point.

Cumulative incidence (or risk, defined as the probability that a person has died due to the outcome of interest by the time t (Cole et al., 2015)) of COPD mortality was estimated for each intervention scenario using an estimator for the cumulative incidence of the outcome of interest in the presence of competing risks (Lau et al., 2009), with age as the time scale. Death from causes other than COPD was treated as the competing event in this case. Stability estimates were based on 1,000 bootstrap samples. All g-formula analyses were carried out in SAS (SAS version 9.4; SAS Institute Inc., Cary, NC) based on the gformula SAS macro available at http://www.hsph.harvard.edu/causal/software/.

3. Results

Analysis for this study was based on the male workers of the DEMS II cohort with baseline and other characteristics summarized in Table 1. Mean age at beginning of follow-up was 30.4 years (standard deviation (sd) =9.5), while the mean age at death was 68.0 (sd=14.6). Mean age at death due to COPD was 73.1 years (sd=10.5). Participants were followed for a mean of 36.2 years (sd=11.4), and the majority were white.

Average annual, time-varying cumulative exposure and average intensity of exposure distributions for REC and RD are summarized in Figure 1. The mean time-varying cumulative exposures for REC and RD were 713.6 μg/m^3-years and 13.9 mg/m^3-years, while the corresponding values for average intensity of exposure were 83.3 μg/m^3 and 1.5 mg/m^3 for REC and RD, respectively. Correlations between the different exposure metrics were moderate for average and strong for cumulative exposures (Figure S2).

Results from Cox proportional hazards models are summarized in Table 2. Models with a log-linear term for the exposure-response indicated elevated hazard ratios (HR) for average

intensity for REC, with a HR corresponding to an interquartile range width increase in exposure of 1.46 (95% confidence interval (CI): 1.12, 1.91). Results for average intensity REC using a categorical exposure were monotonic, with effect estimates increasing with increasing exposure quartiles, though CIs included the null value. The p-value for a linear trend test was 0.024. By comparison, results for average intensity of RD with categorical exposure variables yielded a HR comparing the highest exposure quartile to the lowest of 2.55 (95% CI: 1.44, 4.54). A test for linear trend yielded a p-value of 0.006; based on results from a model with log-linear term for a continuous exposure, the HR corresponding to an interquartile range width increase in average intensity of RD exposure was 1.20 (95% CI: 0.96, 1.49). Point estimates for cumulative exposures were below the null for both REC and RD regardless of how the exposure-response was modelled, an indication of healthy worker survivor bias (Table 2). Results from models where each metric was considered separately are summarized in Supplemental Table 2. Briefly, average intensity of exposure estimates were attenuated for both REC and RD without any adjustment for cumulative exposure of the respective co-exposure, but remained indicative of positive associations with the outcome. Estimates for cumulative exposures were also attenuated.

When considering subsets of participants limited based on duration of active employment, point estimates for cumulative exposures were progressively higher with decreasing duration of employment and consistent with a harmful effect for both REC and RD, though CIs included the null with the exception of cumulative REC for those with 6 years active employment or less (Table 3).

Results from sensitivity analysis using a broader definition of the outcome relying on additional contributing causes of death had a similar pattern (Supplemental Table 3), as did results using a 20-year lagged exposure, although these effect estimates tended to be attenuated compared to the unlagged analysis (Supplemental Table 4). Associations with duration of exposure were also negative for COPD mortality with a HR of 0.98 (95 CI:0.97, 0.99), for each one-year increase in duration of exposure.

Simulations from the parametric g-formula tended to overestimate the risk of COPD mortality (Figure S2a), though risk was overestimated when exposures were not considered as predictors for the outcome as well (supplemental Figure S2b), indicating that overestimation was likely due to reasons other than the modelled exposure-response. Estimates for hypothetical interventions on both exposures using the parametric g-formula are summarized in Table 4. The risk ratio (RR) comparing COPD mortality risk up to age 90 under a hypothetical intervention with a REC exposure limit of 25 $\mu g/m^3$, in which all annual average exposures above this value were replaced with 25 $\mu g/m^3$, to the risk under no intervention was 0.90 (95% CI: 0.38, 1.09) for COPD mortality by age 90. Eliminating REC exposure altogether resulted in a RR of 0.85 (95% CI: 0.55, 1.06) compared to the observed. Results from hypothetical interventions on RD resulted in smaller decreases in the risk of COPD mortality: eliminating RD exposure altogether resulted in a RR of 0.93 (95% CI: 0.56, 1.31) compared to the observed. Based on these RR point estimates, the attributable fraction of COPD deaths due to REC and RD exposures were 0.15 and 0.07 respectively. Results using a 20-year lagged exposure indicated similar effect estimates (Supplemental Table 5).

4. Discussion

Our findings, which leverage an extended mortality follow-up from DEMS II, indicate that REC and RD exposures in the mining industry are associated with elevated risk of COPD mortality, but also that there is evidence of considerable survivor bias in evaluating COPD mortality in this setting. Cumulative exposure estimates (as opposed to average intensity), as well as duration of exposure were inversely associated with risk of COPD mortality when examined in a traditional regression framework, which is indicative of healthy worker survivor bias. Analysis based on the parametric g-formula, an estimation approach equipped to address exposure-confounder feedback in the form of healthy worker survivor effect, indicated that interventions to mitigate exposure may lead to decreases in COPD mortality risk in this population, though CIs typically included the null.

Diesel generators and other diesel-powered equipment often account for the majority of energy in mining operations, due to their properties including lower combustion temperatures and lower cost compared to alternative power sources. Occupational diesel exhaust exposure, however, has been shown to be associated with increased risk of adverse outcomes, with previous findings based on the same cohort indicating that current regulatory standards (MSHA PEL of 160 $\mu g/m^3$ TC (MSHA, 2001)) may not be enough to protect worker health with respect to lung cancer and ischemic heart disease mortality (Neophytou et al., 2019, 2016; Silverman et al., 2023). Diesel exhaust exposures have also been linked to increased risk of COPD with evidence to date primarily relying on other industries (Hart et al., 2012a, 2009, 2006; Hnizdo et al., 2002; Weinmann et al., 2008). A previous study in the DEMS cohort (follow-up through 1997) indicated some evidence of an association between REC exposure and risk of COPD mortality though most CIs included the null with power and survivor bias identified as a potential limitations (Ferguson et al., 2020). Our findings leveraging the extended follow-up in DEMS II and roughly double the cases suggest that occupational diesel exhaust exposure as measured by REC concentrations in the mining industry is also associated with elevated COPD mortality, while issues of survivor bias were further documented. Overall, our findings suggest that this outcome should be taken into account in assessing the overall occupational risk of this exposure on burden of disease.

The DEMS II cohort is also exposed to respirable dust, which has been linked to increased risk of COPD (Balmes et al., 2003). In mining settings, airborne respirable dust is the result of extraction, transport and processing of the ore, stone or coal. RD exposure in this case is expected to consist primarily of the mined ore in each mining facility (limestone, potash, salt or trona). None of these substances is regulated separately, with the relevant standard being the MSHA PEL for total dust; however, they are considered irritants that may affect respiratory health. The total RD exposure in this setting, also consists of all particles in the respirable fraction including REC, PAHs and other substances common in miming settings such as asbestos and silica. Silica is an established risk factor for COPD (Gallagher et al., 2015; Hnizdo and Vallyathan, 2003; Neophytou et al., 2018). Stratified analyses by mine type were not performed due to limited power, however any RD effect would potentially be differential by mine type given the different types of ore. It should be noted that participating mines in DEMS II were originally chosen as non-coal and non-metal facilities and because of relatively low concentrations of known lung carcinogens such

as radon, asbestos, and silica (Attfield et al., 2012), The presence of both REC and RD exposures in the DEMS II study population could be of particular interest, as ineffective clearance or overload of dust particles in the lungs and airways may result in a chronic inflammatory response contributing to lung disease progression (Ling and van Eeden, 2009) and potentially exacerbate the toxicity of both exposures.

In our study, results for average intensity of exposure to REC and RD were more sensitive to the modelling of the exposure response in Cox models; in models using categorical exposure variables, associations were stronger for RD than for REC, whereas models using log-linear terms for continuous exposure resulted in stronger associations with REC than with RD. These results are likely explained by a more skewed distribution of REC exposure compared to RD and deviations from a log-linear effect (Figure 1). Effect estimates for average intensity of exposure from models that did not include cumulative metrics for the respective co-exposure were attenuated, as the cumulative co-exposure adjustment likely also acts as a proxy for a duration of exposure. Results from the g-formula were also more in line with a stronger REC effect. Mutual adjustment for REC and RD was likely more rigorous in the g-formula with flexible terms for annual average and cumulative exposures for both REC and RD added in the parametric prediction models used in the estimation. In contrast, modelling average intensity of one exposure in conjunction with cumulative exposure for the other, may have failed to fully account for the possible effect of each co-exposure in the Cox models. It should also be noted that REC is a component of the total respirable fraction of dust exposure, and adjustment for REC will have led to an underestimation of total RD risk.

Whereas average intensity of exposure measures in our study were associated with elevated effect estimates for both REC and RD exposures, cumulative exposures (a function of annual average exposures and duration of exposure) were associated with lower COPD mortality risk when examined in a traditional regression framework. Increased duration of exposure was also associated with lower COPD mortality risk indicating that those workers that were employed (and exposed) over a longer period were less likely to develop the outcome. This feature is a prime indicator of healthy worker survivor bias in occupational cohort settings, where less healthy workers, who are more likely to develop the outcome, tend to leave work earlier and accrue less exposure than their healthier peers (Brown et al., 2017). Unlike cumulative exposure metrics, average intensity of exposure did not suffer from this type of bias as it is not directly proportional to the duration of exposure.

Findings for cumulative exposure in subsets of participants with limited duration of employment were consistent with a harmful effect, which was also indicative of the presence of healthy worker survivor bias. We previously also showed that exposure is associated with termination of employment in this cohort (Neophytou et al., 2016), as would also be expected in the presence of this bias mechanism. In analysis using the parametric g-formula, an estimation approach suited to address this type of bias, the cumulative effect of hypothetical interventions limiting REC and to a lesser extent RD exposure resulted in lower risk of the outcome. Thus, while standard regression models produced an estimate of a *negative* association between cumulative exposure and the outcome, the parametric g-formula yielded effect estimates for the cumulative effect of exposure over time that were consistent with *harmful* effects of exposure. The fact that these point estimates were in a

different direction from those produced in the Cox models represents another indication of the presence of survivor bias for COPD in this cohort. CIs for g-formula analyses tended to include the null, though were much narrower compared to our prior study with more limited follow-up (Ferguson et al., 2020).

Exposure to REC has previously been found to be associated with lung cancer mortality, while both REC and RD have been reported to be associated with ischemic heart disease mortality in this cohort in both traditional regression and g-formula based analyses (Attfield et al., 2012; Costello et al., 2018; Neophytou et al., 2019, 2016; Silverman et al., 2012). Results for COPD in the current study based on the g-formula indicate a weaker association with COPD compared to these other outcomes. This could be due to a true weaker effect of exposure, or presence of survivor bias that is not as adequately addressed here. For example, g-formula simulations in the current study were not very accurate in predicting the observed risk which may have led to a less effective modelling approach. Furthermore, the use of extended follow-up meant a gap in exposure history for some participants which would have affected our ability to address time varying confounding by employment status. Results for cumulative exposure were negative in traditional regression models, which was not the case in previous studies of outcomes other than COPD (Attfield et al., 2012; Costello et al., 2018; Silverman et al., 2012). This could be because of weaker true exposure effects suffering from similar survivor bias compared to other outcomes, or potentially stronger survivor bias in the case of COPD compared to other outcomes with similar true effects in magnitude. COPD cases tend to survive longer with disease symptoms compared to other outcomes such as lung cancer, while COPD mortality tended to occur at older ages compared to other causes of death. This could in turn maximize the potential for healthier workers to continue accruing exposure while their less healthy peers (potentially due to COPD symptoms) terminate employment earlier.

Our study has important strengths, including the exposure assessment for REC as a quantitative measure for diesel exhaust exposure, and the extended duration of follow-up allowing for assessment of relationships for an outcome like COPD mortality. Our estimation approach also tackles issues of exposure-response, addresses survivor bias and yields several parameters of interest including risk (cumulative incidence) which has more direct applicability to public health compared to parameters based on the hazard or odds (Cole et al., 2015). Limitations include lack of information on potential covariates of interest such as smoking and any employment information outside of the participating facilities in the cohort. Smoking data were available in the a subset of participants which comprised the DEMS nested-case control study of lung cancer, indicating an overall prevalence of smoking (including former smokers) of about 70% (Silverman et al., 2023, 2012). Adjustment for smoking in the DEMS nested-case control study, however, led to stronger effect estimates for REC on risk of lung cancer, while results on the positive association between REC and lung cancer were consistent across different facilities with different rules about smoking though it was allowed is most facilities (Silverman et al., 2012). Given the same directions in terms of the causal relationships between exposure, smoking rates and COPD mortality we would theoretically expect any confounding by smoking in this study to result in downward bias. Misclassification of the outcome is also possible as assessment of COPD mortality from death records is expected to lead to underestimation of the true number of cases

(Jensen et al., 2006). In the current study the primary analysis was based on the underlying cause of death, though as a sensitivity analysis we considered an alternative definition of the outcome including up to three additional (contributing) causes of death, which is expected to be more sensitive, though potentially at the expense of specificity. Results using this definition of the outcome indicated similar patterns for potential exposure effects as the primary analysis in Cox models. Furthermore, it is not clear from our Cox proportional hazards analysis results if the associations between exposures and COPD mortality are a function of exposure causing the underlying disease or potentially accelerating mortality among those that already have the disease. If the latter was true then presumably we would see a diminished effect or even crossing of hazards at older ages leading to downward bias. Results from the g-formula however indicate that increased cumulative incidence continued to be associated with exposure levels even at older ages which would indicate a relationship between exposure and the underlying disease rather than mere acceleration of mortality among those with COPD. Results from the g-formula though theoretically not suffering from the same magnitude of healthy worker survivor bias, are still subject to limitations regarding the assumption of correct model specification. The large number of parametric models increases the possibility and potentially magnitude of bias that may arise from model misspecification.

As stated, complete exposure data for each participant was only available from beginning of follow-up through 1997–1999 depending on facility, with approximately 25% of the male workers in the cohort still actively employed and potentially exposed for some additional time after these dates. Cumulative exposures to REC and RD are therefore likely underestimated for these participants when exposure information is unavailable: this portion of person-time is treated as unexposed in the natural course for the parametric g-formula, thus potentially leading to underestimation of intervention effects. With mortality follow-up ending in 2015, results from the sensitivity analyses using lagged exposure values do not suffer from this limitation, though they are subject to the assumption of lagged effects of exposure. Exposure measurement error could also be a limitation, primarily in the case of RD, as the exposure assessment for RD was based on fewer samples and was overall less rigorous than REC, having relied on fewer total samples and a cruder grouping of job-title based exposures. This type of measurement error is assumed to be non-differential and likely would have resulted in bias towards the null. Lastly, although participants of this study are considered naïve to occupational REC exposure prior to dieselization at each participating facility, the same is not true for RD exposure. Participants who were already employed at the beginning of dieselization had prior RD exposures that are not included as part of the exposure of interest in this study. We adjusted for number of years as a prevalent hire in our analysis, though our population is still at least partially left-truncated with respect to RD exposure. This could potentially lead to further bias towards the null for the potential effects of RD (Applebaum et al., 2011).

In conclusion, findings from the current study suggest that occupational exposures to diesel exhaust and dust are associated with increased risk of COPD mortality in a population of miners, though results were not consistent across different estimation approaches and exposure metrics. Our findings also indicated of the presence of considerable survivor bias

in this cohort when exposure-COPD relationships were assessed in a traditional regression framework.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

ACGIH, 2001. Diesel exhaust (particulate and particulate adsorbed components), draft TLV-TWA document. American Conference of Goverment and Industrial Hygienists. Cincinnati, OH.

Applebaum KM, Malloy EJ, Eisen E a, 2011. Left truncation, susceptibility, and bias in occupational cohort studies. Epidemiology 22, 599–606. [PubMed: 21543985]

Attfield MD, Schleiff PL, Lubin JH, Blair A, Stewart PA, Vermeulen R, Coble JB, Silverman DT, 2012. The diesel exhaust in miners study: A cohort mortality study with emphasis on lung cancer. J. Natl. Cancer Inst 104, 869–883. [PubMed: 22393207]

Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G, 2003. American thoracic society statement: Occupational contribution to the burden of airway disease. Am. J. Respir. Crit. Care Med 167, 787–797. [PubMed: 12598220]

Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD, 2009. Occupational exposures and the risk of COPD: Dusty trades revisited. Thorax 64, 6–12. [PubMed: 18678700]

Brown DM, Picciotto S, Costello S, Neophytou AM, Izano MA, Ferguson JM, Eisen EA, 2017. The Healthy Worker Survivor Effect: Target Parameters and Target Populations. Curr. Environ. Heal. Reports 4, 364–372. 10.1007/s40572-017-0156-x

Buckley J, Keil A, McGrath L, Edwards J, 2015. Evolving Methods for Inference in the Presence of Healthy Worker Survivor Bias. Epidemiology 26, 204–212. [PubMed: 25536456]

Chevrier J, Picciotto S, Eisen EA, 2012. A Comparison of Standard Methods With G-estimation of Accelerated Failure-time Models to Address The Healthy-worker Survivor Effect: Application in a Cohort of Autoworkers Exposed to Metalworking Fluids. Epidemiology 23, 212. [PubMed: 22317804]

Coble JB, Stewart PA, Vermeulen R, Yereb D, Stanevich R, Blair A, Silverman DT, Attfield M, 2010. The diesel exhaust in miners study: II. Exposure monitoring surveys and development of exposure groups. Ann Occup Hyg 54, 747–761. [PubMed: 20876232]

Cole SR, Hudgens MG, Brookhart MA, Westreich D, 2015. Risk. Am. J. Epidemiol 181, 246–250. 10.1093/aje/kwv001 [PubMed: 25660080]

Costello S, Attfield MD, Lubin JH, Neophytou AM, Blair A, Brown DM, Stewart PA, Vermeulen R, Eisen EA, Silverman DT, 2018. Ischemic Heart Disease Mortality and Diesel Exhaust and Respirable Dust Exposure in the Diesel Exhaust in Miners Study. Am. J. Epidemiol

Ferguson JM, Costello S, Elser H, Neophytou AM, Picciotto S, Silverman DT, Eisen EA, 2020. Chronic obstructive pulmonary disease mortality: The Diesel Exhaust in Miners Study (DEMS). Environ. Res 180, 108876. 10.1016/j.envres.2019.108876 [PubMed: 31711661]

Gallagher LG, Park RM, Checkoway H, 2015. Extended follow-up of lung cancer and non-malignant respiratory disease mortality among California diatomaceous earth workers. Occup. Environ. Med 72, 360–365. [PubMed: 25759179]

Hart JE, Eisen E. a, Laden F, 2012a. Occupational diesel exhaust exposure as a risk factor for chronic obstructive pulmonary disease. Curr. Opin. Pulm. Med 18, 151–4. [PubMed: 22234274]

Hart JE, Eisen EA, Laden F, 2012b. Occupational diesel exhaust exposure as a risk factor for chronic obstructive pulmonary disease. Curr. Opin. Pulm. Med 18, 151–154. 10.1097/MCP.0b013e32834f0eaa [PubMed: 22234274]

Hart JE, Laden F, Eisen EA, Garshick E, 2009. Chronic obstructive pulmonary disease mortality in railroad workers. Occup. Environ. Med 66, 221–226. 10.1136/oem.2008.040493 [PubMed: 19039098]

Hart JE, Laden F, Schenker MB, Garshick E, 2006. Chronic obstructive pulmonary disease mortality in diesel-exposed railroad workers. Environ. Health Perspect 14, 1013–1017. 10.1289/ehp.8743

Hnizdo E, Sullivan PA, Bang KM, Wagner G, 2002. Association between Chronic Obstructive Pulmonary Disease and Employment by Industry and Occupation in the US Population: A Study of Data from the Third National Health and Nutrition Examination Survey. Am. J. Epidemiol 156, 738–746. 10.1093/aje/kwf105 [PubMed: 12370162]

Hnizdo E, Vallyathan V, 2003. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occup. Environ. Med 60, 237–243. 10.1136/oem.60.4.237 [PubMed: 12660371]

Jensen HH, Godtfredsen NS, Lange P, Vestbo J, 2006. Potential misclassification of causes of death from COPD. Eur. Respir. J 28, 781–785. 10.1183/09031936.06.00152205 [PubMed: 16807258]

Koutros S, Graubard B, Bassig B, Vermeulen R, Appel N, Hyer M, Stewart PA, Silverman DT, 2023. Diesel exhaust exposure and all-cause mortality in the Diesel Exhaust in Miners Study (DEMS) II cohort. Environ. Health Perspect In Press.

Lau B, Cole SR, Gange SJ, 2009. Competing risk regression models for epidemiologic data. Am J Epidemiol 170, 244–256. [PubMed: 19494242]

Ling SH, van Eeden SF, 2009. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int. J. Chron. Obstruct. Pulmon. Dis 4, 233–243. 10.2147/copd.s5098 [PubMed: 19554194]

Lytras T, Kogevinas M, Kromhout H, Carsin A-E, Antó JM, Bentouhami H, Weyler J, Heinrich J, Nowak D, Urrutia I, Martinez-Moratalla J, Gullón JA, Pereira-Vega A, Raherison-Semjen C, Pin I, Demoly P, Leynaert B, Villani S, Gislason T, Svanes C, Holm M, Forsberg B, Norbäck D, Mehta AJ, Probst-Hensch N, Benke G, Jogi R, Torén K, Sigsgaard T, Schlünssen V, Olivieri M, Blanc PD, Vermeulen R, Garcia-Aymerich J, Jarvis D, Zock J-P, 2018. Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. Thorax 73, 1008–1015. [PubMed: 29574416]

Mannino DM, Reichert MM, Davis KJ, 2006. Lung function decline and outcomes in an adult population. Am. J. Respir. Crit. Care Med 173, 985–990. [PubMed: 16439715]

MSHA, 2001. Diesel Particulate Matter Exposure of Underground Metal and Nonmetal Miners, Final Rule. 30 CFR Part 57.5060 U.S Mine Safety and Health Administration.

Murphy SL, Kochanek KD, Xu J, Arias E, 2021. Mortality in the United States, 2020.

Neophytou AM, Costello S, Picciotto S, Brown DM, Attfield MD, Blair A, Lubin JH, Stewart PA, Vermeulen R, Silverman DT, Eisen EA, 2019. Diesel Exhaust, Respirable Dust, and Ischemic Heart Disease: An Application of the Parametric g-formula. Epidemiology 30, 177–185. [PubMed: 30489348]

Neophytou AM, Picciotto S, Brown DM, Gallagher LE, Checkoway H, Eisen EA, Costello S, 2018. Estimating Counterfactual Risk Under Hypothetical Interventions in the Presence of Competing Events: Crystalline Silica Exposure and Mortality From 2 Causes of Death. Am. J. Epidemiol 187, 1942–1950. 10.1093/aje/kwy077 [PubMed: 29617927]

Neophytou AM, Picciotto S, Costello S, Eisen EA, 2016. Occupational Diesel Exposure, Duration of Employment, and Lung Cancer. Epidemiology 27, 21–28. [PubMed: 26426944]

NIOSH, 2003. Manual of Analytical Methods (NMAM). O'Connor PF, Schlecht PC, Monitoring of Diesel Particulate Exhaust in the Workplace, Chapter Q, Third Supplement to NMAM, 4th Edition, DHHS (NIOSH) Publication No. 2003–154. Cincinnati, OH.

Picciotto S, Chevrier J, Balmes J, Eisen EA, 2014. Hypothetical interventions to limit metalworking fluid exposures and their effects on COPD mortality: G-estimation within a public health framework. Epidemiology 25, 436–43. 10.1097/EDE.0000000000000082 [PubMed: 24608667]

Robins J, 1986. A new approach to causal inference in mortality studies with a sustained exposure period---application to control of the healthy worker survivor effect. Math Model 7, 1393–1512.

Silverman DT, Bassig B, Lubin J, Graubard B, Blair A, Vermeulen R, Attfield M, Appel N, Rothman N, Stewart P, Koutros S, 2023. 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. Environ. Health Perspect In Press.

Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, Coble JB, Rothman N, Schleiff PL, Travis WD, Ziegler RG, Wacholder S, Attfield MD, 2012. The diesel exhaust in miners study: A nested case-control study of lung cancer and diesel exhaust. J. Natl. Cancer Inst 104, 855–868. [PubMed: 22393209]

Stewart PA, Coble JB, Vermeulen R, Schleiff P, Blair A, Lubin J, Attfield M, Silverman DT, 2010. The diesel exhaust in miners study: I. Overview of the exposure assessment process. Ann Occup Hyg 54, 728–746. [PubMed: 20876233]

Stewart PA, Vermeulen R, Coble JB, Blair A, Schleiff P, Lubin JH, Attfield M, Silverman DT, 2012. The diesel exhaust in miners study: V. evaluation of the exposure assessment methods. Ann Occup Hyg 56, 389–400. [PubMed: 22383674]

Syamlal G, Bhattacharya A, Dodd KE, 2020. Medical expenditures attributed to asthma and chronic obstructive pulmonary disease among workers—United States, 2011–2015. Morb. Mortal. Wkly. Rep 69, 809.

Taubman SL, Robins JM, Mittleman MA, Hernán MA, 2009. Intervening on risk factors for coronary heart disease: An application of the parametric g-formula. Int. J. Epidemiol 38, 1599–1611. [PubMed: 19389875]

Vermeulen R, Coble JB, Lubin JH, Portengen L, Blair A, Attfield MD, Silverman DT, Stewart PA, 2010a. The diesel exhaust in miners study: IV. Estimating historical exposures to diesel exhaust in underground non-metal mining facilities. Ann Occup Hyg 54, 774–788. [PubMed: 20876235]

Vermeulen R, Coble JB, Yereb D, Lubin JH, Blair A, Portengen L, Stewart PA, Attfield M, Silverman DT, 2010b. The diesel exhaust in miners study: III. Interrelations between respirable elemental carbon and gaseous and particulate components of diesel exhaust derived from area sampling in underground non-metal mining facilities. Ann Occup Hyg 54, 762–773. [PubMed: 20876234]

Weinmann S, Vollmer WM, Breen V, Heumann M, Hnizdo E, Villnave J, Doney B, Graziani M, McBurnie MA, Buist AS, 2008. COPD and Occupational Exposures: A Case-Control Study. J. Occup. Environ. Med 50, 561–569. [PubMed: 18469625]

Highlights

- Average intensity of diesel exhaust and dust exposure were associated with COPD.
- Cumulative exposures were inversely related with the outcome in traditional regression.
- Survivor bias was evident in the analysis of COPD in this population of exposed miners.

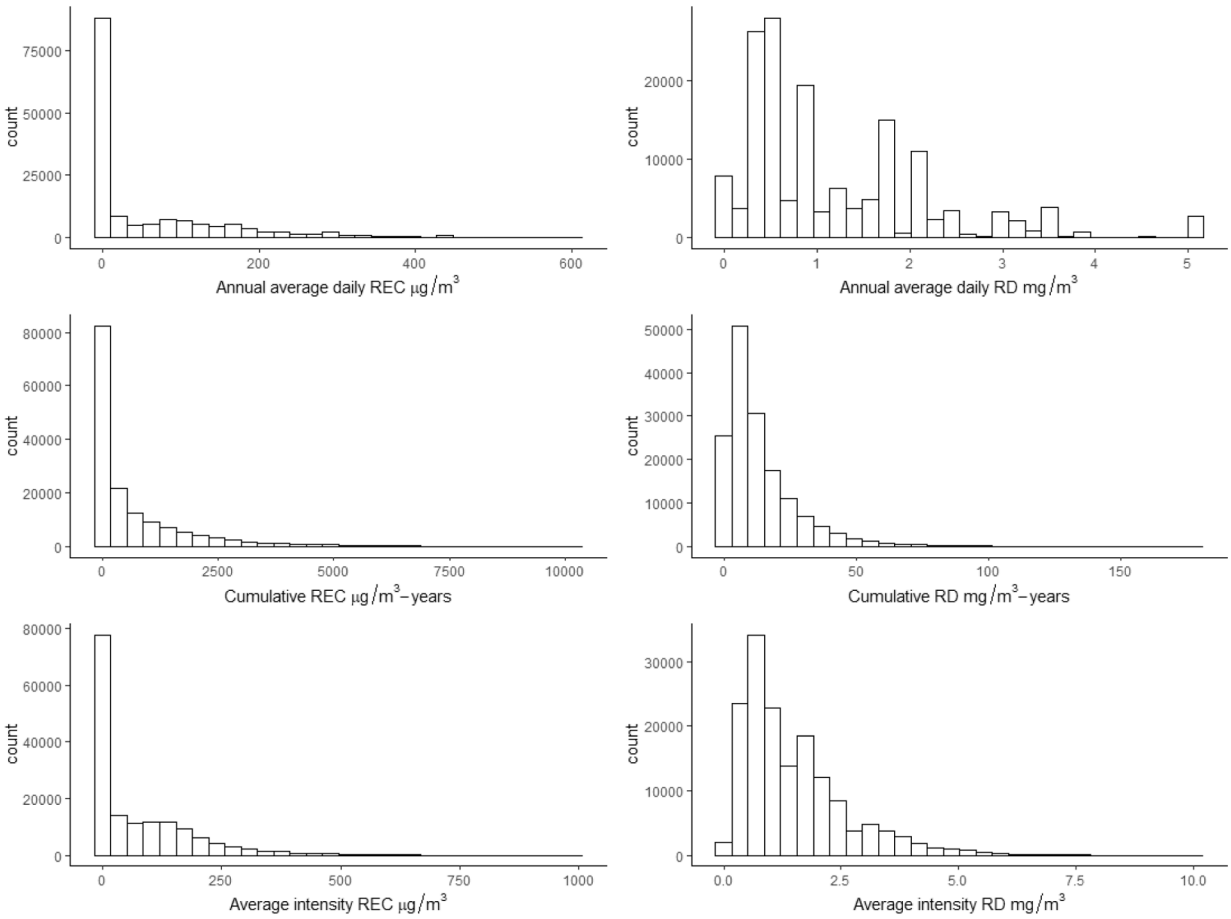

Figure 1:

Observed exposure distributions for Respirable Elemental Carbon (REC) on the right, and Respirable Dust (RD) on the left for annual average exposures (panel A), cumulative exposures (panel B) and average intensity of exposure (panel C).

Table 1:

Baseline and demographic characteristics among male participants in DEMS II, followed for mortality between 1947–2015 (n=11,817).

Variable	No (%)	Mean (sd)
Race/Ethnicity,		
White	4736 (40.1)	
Black	106 (0.9)	
Hispanic	543 (4.6)	
American Indian	118 (1.0)	
Asian/Pacific Islander	14 (0.1)	
Other	26 (0.2)	
Multiracial	1 (<0.1)	
Unknown	6273 (53.1)	
Mine type (State)		
Limestone (Missouri)	1668 (14.1)	
Potash (New Mexico)	4424 (37.4)	
Salt (Ohio)	518 (4.4)	
Trona (Wyoming)	5207 (44.1)	
Total deaths	4833 (40.9)	
COPD deaths[a]	279 (2.4)	
Age at baseline (years)		30.5 (9.5)
Age at death (years)		68.0 (14.6)
Age at COPD death (years)		73.1 (10.5)
Duration of employment (years)[b]		13.2 (10.3)
Duration of follow-up (years)		36.2 (11.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; DEMS II, diesel exhaust in miners study II;

[a]COPD mortality based only on the underlying cause of mortality. 372 cases were assessed based on a definition including the underlying and three additional causes of death.

[b]Duration of employment estimated after dieselization as this was the period where participants could have been exposure to both exposures while actively employed.

Table 2:

HRs and accompanying 95% CIs for COPD mortality associated with measures of average intensity and cumulative exposure for REC and RD exposures among male participants of the DEMS II study, followed for mortality between 1947–2015.

	N Cases	HR (95% CI)		N Cases	HR (95% CI)
Average intensity REC (μg/m^3)			**Cumulative RD (mg/m^3-years)**		
Categorical variable			Categorical variable		
≤1.80	70	1.00 (ref)	≤5.80	70	1.00 (ref)
>1.80 – ≤43.50	70	1.04 (0.70, 1.53)	> 5.80 – ≤12.90	70	0.87 (0.59, 1.27)
>43.50 – ≤136.60	70	1.20 (0.68, 2.11)	>12.90 – ≤25.90	70	0.77 (0.49, 1.20)
>136.60	69	1.70 (0.92, 3.16)	>25.90	69	0.64 (0.39, 1.03)
Log-linear term		1.46 (1.12, 1.91)[a]	Log-linear term		0.96 (0.88, 1.04)[a]
Average Intensity RD (mg/m^3)			**Cumulative REC (μg/m^3-years)**		
Categorical variable			Categorical variable		
≤0.80	70	1.00 (ref)	≤24.90	70	1.00 (ref)
>0.80 – ≤1.50	70	1.74 (1.21, 2.51)	>24.90 – ≤230.10	70	0.90 (0.64, 1.26)
>1.50 – ≤2.10	70	2.04 (1.19, 3.48)	>231.10 – ≤937.00	70	0.92 (0.65, 1.32)
>2.10	69	2.55 (1.44, 4.54)	> 937.00	69	0.78 (0.58, 1.16)
Log-linear term		1.20 (0.96, 1.49)[a]	Log-linear term		0.91 (0.83, 1.01)[a]

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DEMS II, diesel exhaust in miners study II; HR, hazard ratio; REC, respirable elemental carbon; RD, respirable dust

All models adjusted for birth year, race, location, number of years employed prior to dieselization and stratified by state. Age was the time-scale of interest. Furthermore, average intensity REC and cumulative intensity RD were mutually adjusted for each other, as were average intensity RD and cumulative REC.

[a]HRs and CIs for an interquartile range width in respective exposure

Table 3:

HRs and accompanying 95% CIs for COPD mortality associated with measures of cumulative exposure for REC and RD exposures among male participants of the DEMS II study, followed for mortality between 1947–2015, restricting by duration of employment.

Duration of Employment	N (Cases)		HR (95% CI)	
			Cumulative REC (μg/m^3-years)	Cumulative RD (mg/m^3-years)
All participants	11,817	279	0.91 (0.83, 1.01)	0.96 (0.88, 1.04)
≤15 years employment	7245	221	1.12 (0.96, 1.30)	1.13 (0.94, 1.37)
≤10 years employment	5793	150	1.25 (0.98, 1.58)	1.17 (0.85, 1.61)
≤6 years employment	4403	107	1.79 (1.21, 2.65)	1.58 (0.89, 2.80)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DEMS II, diesel exhaust in miners study II; HR, hazard ratio; REC, respirable elemental carbon; RD, respirable dust

All models adjusted for birth year, race, location, number of years employed prior to dieselization and stratified by state. Age was the time-scale of interest. The model for cumulative REC were further adjusted for average intensity RD, and similarly the model for cumulative RD was further adjusted for average intensity RD.

Table 4:

Lifetime cumulative risk of COPD mortality under the natural course and under intervention reducing REC and RD exposures in male workers of the DEMS II cohort followed for mortality between 1947 – 2015. Results based on g-computation analysis.

Intervention	Risk (%)[a]	Risk Ratio (95% CI)	Risk Difference (95% CI)
Natural course (ref.)	**7.3 (ref.)**	**1.00 (ref)**	**0.0 (ref)**
REC<=106 μg/m3	7.2	0.99 (0.94, 1.06)	−0.1 (−0.5, 0.5)
REC<=25 μg/m3	6.6	0.90 (0.38, 1.09)	−0.7 (−10.9, 0.6)
REC=0	6.2	0.85 (0.55, 1.06)	−1.1 (−4.3, 0.4)
RD<=1 mg/m3	7.3	1.00 (0.68, 1.12)	0.0 (−4.6, 0.9
RD<=0.5 mg/m3	7.2	0.99 (0.62, 1.20)	−0.1 (−5.4, 1.5)
RD=0	6.7	0.93 (0.56, 1.31)	−0.5 (−5.9, 2.3)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DEMS II, diesel exhaust in miners study II; REC, respirable elemental carbon; RD, respirable dust

[a]Predictions of COPD mortality risk (cumulative incidence) expressed as a proportion of the population that develops the outcome by age 90. The natural course represents a prediction of risk under no intervention (what happened) while all other risk estimates are based on the respective interventions on REC or RD. Analysis adjusted for age, calendar time, state, years as prevalent hire, as well as time-varying employment status and job location. REC and RD intervention estimates are each mutually adjusted for both annual average and cumulative exposures of the respective exposure not intervened.