Diesel Exhaust, Respirable Dust, and Ischemic Heart Disease: An Application of the Parametric g-formula

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Background: Although general population studies of air pollution suggest that particulate matter—diesel exhaust emissions in particular—is a potential risk factor for cardiovascular disease, direct evidence from occupational cohorts using quantitative metrics of exposure is limited. In this study, we assess counterfactual risk of ischemic heart disease (IHD) mortality under hypothetical scenarios limiting exposure levels of diesel exhaust and of respirable mine/ore dust in the Diesel Exhaust in Miners Study cohort.

Methods: We analyzed data on 10,779 male miners from 8 nonmetal, noncoal mines—hired after diesel equipment was introduced in the respective facilities—and followed from 1948 to 1997, with 297 observed IHD deaths in this sample. We applied the parametric g-formula to assess risk under hypothetical scenarios with various limits for respirable elemental carbon (a surrogate for diesel exhaust), and respirable dust, separately and jointly.

Results: The risk ratio comparing the observed risk to cumulative IHD mortality risk at age 80 under a hypothetical scenario where exposures to elemental carbon and respirable dust are eliminated was 0.79 (95% confidence interval [CI]: 0.64, 0.97). The corresponding risk difference was -3.0% (95% CI: -5.7, -0.3).

Conclusion: Our findings, based on data from a cohort of nonmetal miners, are consistent with the hypothesis that interventions to eliminate exposures to diesel exhaust and respirable dust would reduce IHD mortality risk.

Keywords: Diesel; Ischemic heart disease; g-formula; Healthy worker survivor effect

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Diesel exhaust is an important source of fine and ultrafine particles in the ambient environment and a major contributor to traffic-related elemental carbon (EC).[1] Fine and ultrafine particles from diesel sources have been associated with increased risk of ischemic heart disease (IHD) mortality,[2] and EC in particular has been reported to be associated with higher hazard ratios of IHD mortality than fine particulate mass in general.[3] Furthermore, controlled inhalation studies of diesel exhaust have shown associations with outcomes related to risk of cardiovascular disease including inflammation, thrombosis, and vascular dysfunction.[4–7]

Cohort studies of diesel exhaust exposures in certain occupational settings have linked quantitative levels of EC, a key surrogate for diesel exhaust, to increased risk of lung cancer.[8–13] There has been less focus on occupational diesel exposures and adverse cardiovascular outcomes; available studies have typically used job titles to characterize exposures of interest, rather than quantitative exposures metrics.[14–16] Workers in the mining industry may also be exposed to high concentrations of respirable dust from mining ore. Studies of the association of respirable coal dust and IHD mortality in miners exist,[17,18] but studies involving occupational exposures to other types of respirable dust are rare.[19]

The Diesel Exhaust in Miners Study (DEMS) is a mortality study among noncoal, nonmetal miners regularly exposed to diesel exhaust.[9,10] Workers in the mining industry can experience high levels of diesel exhaust, generated from diesel-powered mining and transport equipment used in the mines.[20] In the current study, we seek to address the healthy worker survivor effect and competing risks while estimating risk reductions in IHD mortality associated with limiting exposure levels. Controlling for time-varying confounders affected by prior exposure,

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Requestors interested in the data supporting the Diesel Exhaust in Miners Study (DEMS) can access these data through the Research Data Center (RDC) at the National Center for Health Statistics by following the standard RDC procedures for accessing non-NCHS Restricted Data (https://www.cdc.gov/rdc/b1datatype/dt130.htm). For questions regarding code please contact the corresponding author.

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such as the case of healthy worker survivor bias in a standard regression framework, would result in collider bias as the confounder is also on the causal pathway from past exposure.[21,22] The parametric g-formula permits adjustment for time-varying confounding without introducing this type of bias.[23] We leverage the DEMS data and apply the parametric g-formula to estimate the counterfactual risk of IHD mortality under enforcement of hypothetical exposure limits for respirable elemental carbon (REC) and respirable dust in the mining industry.

METHODS

Study Population

DEMS was conducted jointly by the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health. Details about the cohort are provided elsewhere.[9] Briefly, investigators selected eight nonmetal mining facilities (three potash, three trona, one limestone, and one salt) because of their extensive use of diesel-powered equipment over long periods of time and their low levels of co-exposures to known occupational lung carcinogens (radon, asbestos, and silica). The cohort consisted of 12,315 workers employed in a blue-collar job at one of these mines for at least 1 year after dieselization. Follow-up of the cohort began 1 year after dieselization at each mine, ranging from 1948 to 1968, and continued until 31 December 1997. The current study was approved by the University of California, Berkeley, and NCI institutional review boards.

Outcome Assessment and Covariates

Information on job titles and work dates as well as sex, date of birth, and race (when available) was obtained through work records. Vital status was ascertained via. matching with the National Death Index (NDI-plus) and Social Security Administration (SSA) death files. The investigators censored 111 participants who could not be matched to either of these files after their last observed date in the work history files. Cause of death was obtained from NDI-plus from 1979 through 1997 and before that from death certificates coded by a certified nosologist. There were 29 deaths identified through SSA or other non-NDI-Plus sources for which a death certificate could not be located, so no specific cause of death was assigned. Cases were defined based on international classification of diseases (ICD) codes for IHD (ICD-7: 420, ICD-8 & 9:410–414). All identified cases except 2 were male, so 498 female cohort members were excluded from analyses. We further restricted the study sample to the inception cohort of 10,779 (corresponding to 297 IHD mortality cases) male workers hired after dieselization. In this restricted dataset, potential occupational exposures to both diesel exhaust and respirable dust in the participating facilities could only occur during follow-up.

Exposure Assessment

Details of the exposure assessment in DEMS are described elsewhere.[24–28] Briefly, REC exposure values were estimated from personal air samples collected during the 1998–2001 DEMS industrial hygiene surveys. Modeled historical trends in carbon monoxide concentration levels based on horsepower use and exhaust ventilation airflow were used to adjust REC measurements from 1998 to 2001 back through time to estimate historical average daily REC exposures over each year.[27] Surface jobs were assigned to one of three job groups based on 1998–2001 DEMS REC measurement data and proximity to diesel-powered equipment, as well as its size and frequency of use.[24] Exposure estimates were derived for all jobs by year and mine facility from dieselization in each facility to the end of follow-up.

Exposure estimates of average daily respirable dust concentrations were developed for each facility, job group, and decade as a potential confounder for previous analysis of lung cancer mortality. No personal measurements for respirable dust were collected during the 1998–2001 DEMS surveys. Estimates were assigned based on previously collected personal measurements available from the US Mine Safety and Health Administration (MSHA) and other government and company sources. Underground and surface jobs were each classified into one of three groups based on tasks and locations, and each measurement was then assigned to the appropriate group. Each job was assigned the facility–job group-specific mean of measurements over each decade as the average daily exposure over all years within that decade. Machine-generated mine dust was the primary contributor to respirable dust in the mines, but diesel exhaust would have contributed to respirable dust levels in jobs where diesel-powered equipment was present.[26]

Statistical Analyses

The directed acyclic graph in Figure 1 depicts the assumed associations between REC exposure, employment status, and the outcome of interest. In a previous study, exposure to REC in this cohort was found to be associated with earlier termination of employment ($A_{k-1} \rightarrow W_k$ in Figure 1).[29] Since the association between employment status and exposure ($W_k \rightarrow A_k$ for all k) exists by definition (only the actively employed have nonzero probabilities of exposure in the participating facilities), an additional association between employment status and IHD mortality, if present, would imply that the relationship of interest between REC exposures and IHD mortality is subject to time-varying confounding affected by previous exposure. To assess whether employment status was also associated with IHD mortality ($W \rightarrow Y$ or $W \leftarrow U \rightarrow Y$), we used a Cox proportional hazards model with age as the time scale and duration of employment as the exposure of interest, conditional on year of birth, and cumulative exposures to REC and respirable dust, stratified by state.

In this study, we applied the parametric g-formula to assess the risk of IHD mortality under a simulated natural course (i.e., what was observed) and under various hypothetical scenarios reducing exposures.[30] The method is, in essence,

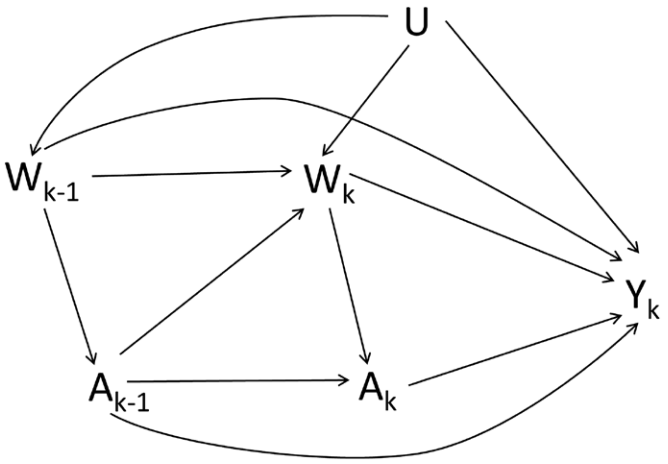

FIGURE 1. Directed acyclic graph depicting the assumed relationships between respirable elemental carbon exposure (A), active employment status (W), and ischemic heart disease mortality (Y). Unmeasured covariates are represented by U while subscripts denote years (k).

an extension of standardization to a time-varying framework[31] and allows estimation of population average risk under hypothetical exposure scenarios that may differ from the ones observed (counterfactuals). Counterfactual risk was estimated under the natural course and a series of hypothetical scenarios setting over each year the maximum average daily REC exposure levels, including the current MSHA permissible exposure limit (PEL) of 160 μg/m^3 of total carbon (TC), measured as an 8-hour time-weighted average.[32] 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 exposure measured on the submicron particulate matter fraction[33,34]), as well as a scenario eliminating diesel exposures entirely. To obtain REC values corresponding to these limits, we used internal exposure assessment data[26] to convert the TC limit to the appropriate EC value, and the EC value to REC. We also converted the submicron level to the appropriate REC fraction. The ratio of average EC to TC on the submicron level was ~0.51, while the ratio of submicron EC to REC was ~0.77. The hypothetical REC limits examined were a) 106 μg/m^3 (corresponding to the current MSHA PEL), b) 25 μg/m^3 (corresponding to the ACGIH recommendation) and c) 0 μg/m^3 (always unexposed to REC). The REC equivalent of the current MSHA PEL in this study (106 μg/m^3) corresponded to the 72nd percentile of the observed REC exposure distribution, while the equivalent of the former ACGIH recommended value (25 μg/m^3) corresponded to the 58th percentile.

We estimated counterfactual risk under scenarios setting average REC and respirable dust maximum exposure limits, separately and also jointly. Relevant regulatory limits for respirable dust in this industry, that is, the MSHA PEL for nuisance dust (PEL of 10 mg/m^3 for total particulate matter, no PEL for the respirable fraction) and the ACGIH recommendation for occupational respirable dust exposure of 3 mg/m^3,[35] are much higher than most of the observed exposures in the study; hypothetical scenarios based on these limits would result in very few workers' exposures being impacted. We instead estimated counterfactual risk under scenarios using hypothetical maximum exposure levels of respirable dust equal to the 72nd and 58th percentiles of exposure distributions during actively employed person time. These quantiles were chosen to match the quantiles of REC that corresponded to the hypothetical REC limits listed above. The respirable dust hypothetical limits set were 1.69 mg/m^3, 1.15 mg/m^3, and 0 mg/m^3. The joint interventions were for maximum limits of: a) 106 μg/m^3 REC and 1.69 mg/m^3 respirable dust b) 25 μg/m^3 REC and 1.15 mg/m^3 respirable dust and c) 0 REC and respirable dust.

Details on the parametric g-formula in general can be found elsewhere,[29–31] and in eAppendix 1; http://links.lww.com/EDE/B440 specifically for its application in the current study. Briefly, we fitted parametric models for the outcome (IHD mortality), competing events (non-IHD mortality) and time-varying covariates (employment status, job location) and exposures (REC, respirable dust), conditional on prior exposure and covariate histories as well as baseline covariates (age, calendar year, race, and state). Models were fit in a pooled dataset on the person–year level. Average daily exposure estimates over the year were entered in all models for both exposures, while the outcome and censoring models also included terms for cumulative exposure up to the prior year. We used cubic splines for REC exposure variables as predictors, because analyses based on conditional Cox proportional hazards models indicated nonlinearity of the exposure–response,[36] with a decreasing trend at lower exposures and an increasing trend at moderate to high exposures. We used simple linear covariate terms for respirable dust exposure variables and considered cubic spline terms in a sensitivity analysis.

Based on the observed distributions of the baseline covariates, we then generated a large pseudo-sample (n = 100,000). In this pseudo-sample, we simulated exposure, covariate, and outcome values at each age ≤ 80 using the parameters of the models above. For predicting the natural course, the simulation uses values for the exposure and time-varying covariates that are predicted from the models and then predicts the risk under those covariate and exposure histories. These predicted values of the outcome and covariates were contrasted with observed values to assess the validity of the simulation process. For alternative hypothetical exposure scenarios, the exposure values were changed from the predicted values according to a specific limit. For example, under a maximum hypothetical limit for REC exposure of 106 μg/m^3, all predicted REC values above 106 μg/m^3 were replaced with 106 μg/m^3; otherwise, they remained unchanged. Values for all covariates at the subsequent time point, including probabilities of death due to competing risks and to IHD, were then

predicted using the assigned exposure and covariate values at each age and the parameters from the covariate, outcome, and competing risks models. The results for single interventions on REC exposure are adjusted for respirable dust as a time-varying covariate and conversely, results for single interventions on respirable dust are adjusted for REC.

Cumulative incidence (or risk, defined as the probability that a person has died due to the outcome of interest by the time t[37]) of IHD was calculated for each exposure scenario using an estimator for the subdistribution of the outcome of interest in the presence of competing risks,[38] with age as the time scale. We thus estimate the population-average risk of a particular cause of death, analogous to the proportion of a hypothetical closed-cohort that dies from the cause of interest, assuming no loss to follow-up and that death from multiple causes is possible. We estimated counterfactual risk under each hypothetical exposure scenario and compared it to the risk under the natural course on the ratio and difference scales. The standard deviation (SD) of estimates from 200 bootstrap samples was used as an estimate of the standard error to generate 95% confidence intervals (CI).[39] All analyses were carried out in SAS (SAS version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Table 1 summarizes demographic information of male participants in DEMS. The mean ± SD follow-up time was 22.1 ± 10.3 years, while the mean ± SD duration of employment at the participating facilities was 12.6 ± 10.0 years. Density plots for the exposure distribution for REC and respirable dust among actively employed person–time are depicted in Figure 2, with indicators for the percentile of the exposure distribution corresponding to the maximum exposure levels used in the hypothetical exposure scenarios. The two distributions were correlated (Spearman's rank correlation coefficient = 0.68).

Duration of employment was protective for the risk of IHD mortality with a hazard ratio of 0.96 (95% CI: 0.95–0.98) for every 1-year increase in duration of employment in the participating facilities. Coupled with earlier findings indicating that REC exposure is associated with earlier termination of employment,[29] this suggests the presence of time-varying confounding affected by previous exposure for the overall relationship between exposure and outcome of interest in the current study.

Figure 3 displays comparisons of observed IHD mortality cumulative risk over age, and employment status over follow-up time, with the corresponding simulated values for the natural course designed to reproduce the observed course of events. Simulated values closely approximated the observed data. For the predicted natural course, the mean simulated average daily REC exposure levels when employed was 65.6 μg/m^3 (interquartile range [IQR]: 0.8, 108.5), compared with the observed 66.4 μg/m^3 (IQR: 0.9, 109.8). The corresponding values for respirable dust were 1.29 mg/m^3 (IQR: 0.44, 1.98) and 1.25 mg/m^3 (IQR: 0.49, 1.73) respectively.

Hypothetical limits on REC exposures resulted in reduced risk of IHD mortality (Table 2). The risk ratio (RR) comparing the cumulative IHD mortality risk at age 80 under the hypothetical exposure scenario, setting a maximum REC exposure limit of 106 μg/m^3 to the risk under the natural course, was 0.90 (95% CI: 0.83, 0.98), while the RR comparing always unexposed to REC with the natural course was 0.86 (95% CI: 0.66, 1.1). The corresponding risk difference was -2.0% (95% CI: -5.5, 1.5). The greatest risk reduction for REC was achieved under an exposure limit of 25 μg/m^3 as opposed to completely unexposed. The greatest risk reduction for respirable dust, by comparison, was achieved when setting exposure to zero (RR: 0.89 [95% CI: 0.75, 1.1], risk difference: -1.6 % [95% CI: -3.8, 0.6]). Results using cubic spline terms for respirable dust exposure variables resulted in similar findings.

The RR comparing risk under a joint intervention setting both exposures to zero was 0.79 (95% CI: 0.64, 0.97). The corresponding risk difference for this joint intervention was -3.0% (95% CI: -5.7, -0.3). Joint interventions on REC and respirable dust resulted in greater reductions in risk compared with interventions on REC or respirable dust alone. A cumulative incidence graph under the natural course and under the hypothetical scenario setting REC and respirable dust to zero is depicted in Figure 4.

TABLE 1. Characteristics of Male Miners in the Diesel Exhaust in Miners Study, Hired After Dieselization and Followed for Mortality From 1948 Through 1997

Characteristics	N	%	Mean	SD
No. participants	10,779			
White and/or Hispanic	10,693	99		
Mine type/state				
Limestone/Missouri	1,298	12.0		
Potash/New Mexico	4,034	37		
Salt/Ohio	518	5		
Trona/Wyoming	4,929	46		
Age at baseline (y)			29.5	9.0
Age of IHD cases (y)			61.2	10.8

IHD, ischemic heart disease; SD, standard deviation.

DISCUSSION

We assessed IHD mortality risk with respect to occupational diesel exhaust and respirable dust exposures in a subcohort of male miners from the DEMS, using the parametric g-formula to account for potential healthy worker survivor bias. Our results suggest that IHD mortality may be associated with both these exposures. We estimated the possible reduction in cumulative IHD mortality risk under exposure scenarios in which historical exposures in this cohort comply with hypothetical exposure limits, including current/past regulations/guidelines for occupational diesel exhaust exposures.

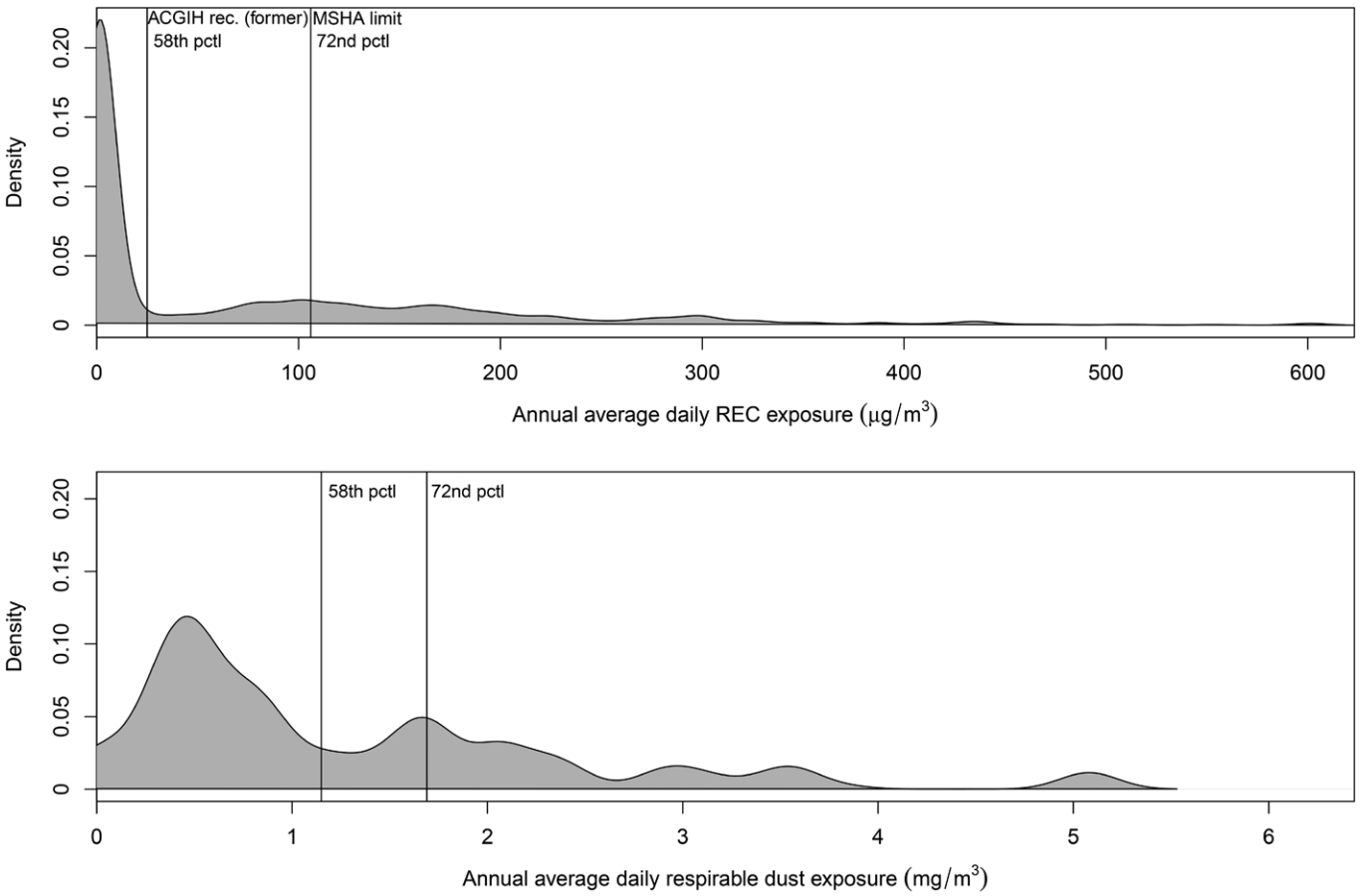

FIGURE 2. Density plots for the exposure distributions of average daily respirable elemental carbon (REC, in μg/m^3) and respirable dust (in mg/m^3) exposure rates over the year during active employment in a cohort of US male miners in the Diesel Exhaust in Miners Study (DEMS), 1946–1997. Vertical lines represent values of maximum limits set in hypothetical interventions assessed in this study.

We observed risk reductions associated with separate limits on REC and on respirable dust. Setting limits jointly to both exposures resulted in greater risk reduction than individual limits, though risk differences appeared subadditive compared with the sum of risk difference from individual exposure limits. REC contributes to respirable dust concentrations, which may partially explain this subadditive nature of risk reduction from joint interventions.

Our findings are not consistent with a monotonic exposure–response over the entire range of REC exposures, as the estimated risk reduction under a hypothetical exposure limit of 25 μg/m^3 was slightly greater than when everyone was set to be unexposed to REC. Absence of a monotonic exposure–response for REC exposures was also observed in conditional analysis using Cox proportional hazards models.[36]

It should be noted that there may be greater exposure misclassification for respirable dust exposures than REC in DEMS. Estimates of personal respirable dust exposure in DEMS were based on less than 500 measurements in eight facilities over 30 years, and all jobs were categorized into only six facility-specific job groups by decade.[24] By comparison, exposure assessment for REC was based on thousands of measurements and a much more detailed protocol for modeled historical annual exposure levels for each facility-specific job.[24,25,27] Although REC exposures are still subject to exposure misclassification, they are likely more accurate than respirable dust exposures. Exposure misclassification for both exposures is expected to be nondifferential with respect to the outcome and thus generally expected to bias associations towards the null.

Our counterfactual risk estimates are not only a function of the exposure–response observed in DEMS, but also a function of the distribution of the exposure variables in the DEMS cohort. Even though we chose percentile values for maximum exposure levels that would result in roughly the same proportion of person–time intervened upon, the shapes of the two exposure distributions were quite different (Figure 1). The more skewed distribution of REC exposures would result in greater relative reductions in exposure for those more highly exposed compared with respirable dust exposures, thus theoretically

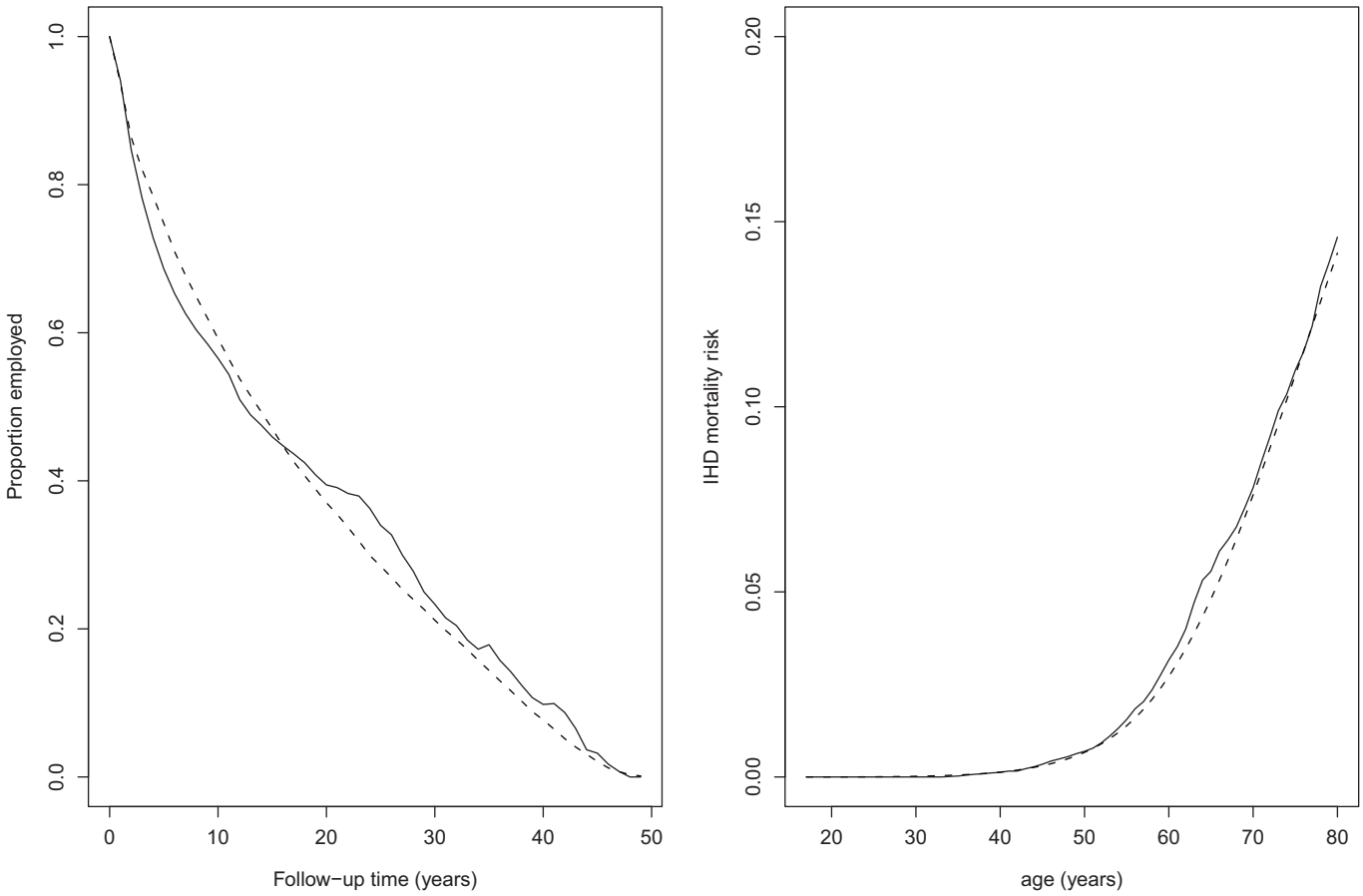

FIGURE 3. Observed (solid lines) cumulative risk of ischemic heart disease mortality over age, and employment status over follow-up time, in a cohort of US male miners in the Diesel Exhaust in Miners Study (DEMS), 1946–1997, compared with simulated values (dashed lines) for the natural course.

resulting in greater risk reduction among the workers heavily exposed to REC if their respective exposure–response relationships had been similar.

For the same reasons, quantitative generalizations to other settings may not be appropriate. The estimated impact would differ for populations with lower or higher exposures and different distributions of other risk factors, as the miners in question were selected to be low in some risk factors, and were restricted to males. For example, hypothetically setting REC exposure under a maximum corresponding to the existing MSHA limit would have resulted in lowering exposures in only 28% of actively employed person–time in the cohort, leaving the rest of the person–time unaffected. The same intervention in a different population with a greater percentage of highly exposed person–time may have resulted in greater reduction in risk.

The parametric g-formula is one of several "g-methods," which (under certain assumptions) allow us to adequately control for time-varying confounding affected by exposure, a signature of healthy worker survivor bias.[40] Under assumptions of conditional exchangeability, consistency, no information bias, and correct model specification, g-methods can allow estimation of causal effects of time-varying exposures.[21] These features of the parametric g-formula render it particularly useful for analyses of risk in occupational epidemiology, where it has recently been applied in other studies,[41–43] including another application in the DEMS cohort.[29]

The assumption of conditional exchangeability (or no unmeasured confounding) requires that counterfactual outcomes are statistically independent of observed exposures, given measured covariates. A potential limitation pertaining to this assumption was the lack of information on smoking and potential employment outside the participating facilities for the cohort, which prevented us from accounting for smoking and other high-risk occupations as potential confounders. Results from the DEMS nested lung cancer case–control study adjusting for these variables, however, indicated that the net confounding effect from smoking and other considered potential confounders in the case of lung cancer mortality was negative, that is, the effect estimates from the case–control study were actually stronger in magnitude.[10] If the directions of associations are the same for IHD mortality, then associations may actually be stronger than those reported.

TABLE 2. Cumulative Risk of IHD Mortality at Age 80 Under the Natural Course and Under Hypothetical Exposure Scenarios for REC and Respirable Dust Exposures in US Male Miners in the Diesel Exhaust in Miners Study Hired After the Beginning of Dieselization (n = 10,779), 1946–1997

Intervention	IHD Risk (%)	Risk Ratio	95% CI	Risk Difference (%)	95% CI
Natural course (no intervention)	14.2	1.00		0.0	
REC scenarios					
REC ≤ 106 μg/m^3	12.8	0.90	0.83, 0.98	-1.4	-2.6, -0.2
REC ≤ 25 μg/m^3	12.0	0.85	0.71, 1.0	-2.2	-4.6, 0.2
REC = 0 μg/m^3	12.2	0.86	0.66, 1.1	-2.0	-5.5, 1.5
Respirable dust scenarios					
Respirable dust ≤ 1.69 mg/m^3	13.6	0.96	0.90, 1.0	-0.6	-1.2., 0.2
Respirable dust ≤ 1.15 mg/m^3	13.2	0.94	0.87, 1.0	-0.9	-1.8, 0.1
Respirable dust = 0 mg/m^3	12.6	0.89	0.75, 1.1	-1.6	-3.8, 0.6
Joint scenarios for REC and respirable dust					
REC ≤ 106 μg/m^3 and respirable dust ≤ 1.69 mg/m^3	12.5	0.88	0.81, 0.95	-1.7	-2.9, -0.5
REC ≤ 25 μg/m^3 and respirable dust ≤ 1.15 mg/m^3	11.4	0.81	0.70, 0.94	-2.8	-4.8, -0.8
REC = 0 and respirable dust = 0 mg/m^3	11.2	0.79	0.64, 0.97	-3.0	-5.7, -0.3

CI, confidence interval; IHD, ischemic heart disease; REC, respirable elemental carbon.

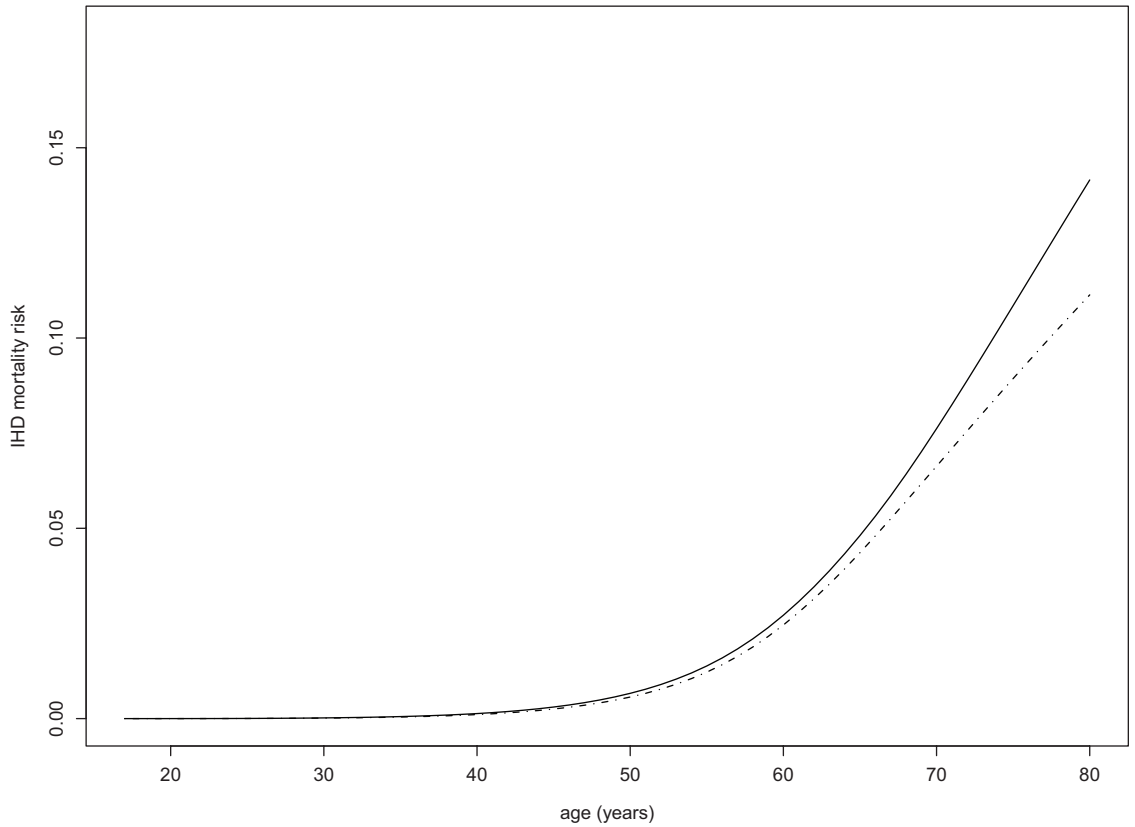

FIGURE 4. Cumulative incidence of ischemic heart disease mortality in a cohort of US male miners in the Diesel Exhaust in Miners Study (DEMS), 1946–1997, under the natural course (solid line) and a hypothetical exposure scenario setting respirable elemental carbon and respirable dust exposures to zero (dashed line).

Regarding the counterfactual risk estimates in the current study, we assumed that risk prediction based on the observed exposure ranges is representative of the risk that would occur under exposure scenarios with lower exposures achieved through some intervention. However, the type of intervention by which exposures would be lowered would likely

affect the exposure distributions differently. For example, introduction of improved ventilation may reduce exposures for all those workers spending time in areas where ventilation was improved, potentially also affecting workers who already have low exposures. An intervention relying on protective equipment only affects those wearing the equipment and would also depend on compliance. In the current study, we assessed risk under exposure scenarios with the least change compared with the observed to be within a given maximum limit, thus allowing us to estimate a lower bound for risk reduction that could be achieved while in compliance with the hypothetical limit. Lastly, while we considered an intervention where everyone was always unexposed to occupational REC to be theoretically feasible (e.g., substituting electric powered engines for diesel engines), the same is probably not true in this cohort for respirable dust, since dust exposures would probably always exist in this occupational setting. Analyses for interventions setting exposures to zero may also suffer from nonpositivity (the assumption of positivity refers to exposure being possible for every combination of covariates) as very little actively employed person–time was unexposed to REC and no actively exposed person–time was unexposed to respirable dust so we must rely on extrapolation from the models.

Correct model specification is a strong assumption: the parametric g-formula in the current study relies on multiple parametric models (one each for outcome, competing events, time-varying exposures and covariates). Incorrect specification of one or more of these models or failure of any of the other assumptions could lead to bias that is propagated over long follow-up time.[31] Although this does not guarantee correct model specification, our predicted estimates for the natural course were very close to the observed, as were probabilities of active employment over time and predicted exposures.

In this occupational setting, we assessed exposure scenarios in which a) participants were potentially exposed only when at work at the participating facilities, and b) termination of employment at these facilities (without any subsequent occupational exposures) were possible. Although the contrasts reported here are not traditional etiologic comparisons of "exposed vs unexposed," they are representative of real-world settings (where people leave the workforce) and are thus of direct relevance to public health. They are also less prone to violations of positivity unlike scenarios of the nature "always exposed."[44] In occupational settings, there typically is structural nonpositivity as those who are not employed cannot be occupationally exposed.

In summary, we calculated risk of IHD mortality under hypothetical exposure scenarios setting limits on REC and respirable dust exposures, in a cohort of male nonmetal miners exposed to diesel exhaust and respirable dust. We estimated reductions in risk under these scenarios, suggesting that there may be an excess IHD mortality risk associated with these occupational exposures in this cohort. There are, however, questions remaining about the shape of the exposure–response relationship and about the relative contributions to excess risk of each of the exposures considered in this setting that merit further investigation.

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