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Chronic obstructive pulmonary disease mortality in railroad workers

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Abstract

Background—There is little information describing the risk of non-malignant respiratory disease and occupational exposure to diesel exhaust.

Methods—US railroad workers have been exposed to diesel exhaust since diesel locomotives were introduced after World War II. In a retrospective cohort study we examined the association of chronic obstructive pulmonary disease (COPD) mortality with years of work in diesel-exposed jobs. To examine the possible confounding effects of smoking, multiple imputation was used to model smoking history. A Cox proportional hazards model was used to estimate an incidence rate ratio, adjusted for age, calendar year, and length of follow-up after leaving work (to reduce bias due to a healthy worker survivor effect).

Results—Workers in jobs with diesel exhaust exposure had an increased risk of COPD mortality relative to those in unexposed jobs. Workers hired after the introduction of diesel locomotives had a 2.5% increase in COPD mortality risk for each additional year of work in a diesel-exposed job. This risk was only slightly attenuated after adjustment for imputed smoking history.

Conclusions—These results support an association between occupational exposure to diesel exhaust and COPD mortality.

Diesel exhaust is a complex mixture of submicron particles (<1.0 μm in diameter) and combustion gases.[1] These particles have organic compounds adsorbed on an elemental carbon core that may be inhaled deep into the lung and have been shown to result in pulmonary inflammation in animal and human exposure studies.[2–8] Regulation of diesel exhaust exposure in the USA has been largely based on its potential to be a human lung carcinogen.[9] However, there is little clinical or epidemiological evidence that exposure results in non-malignant respiratory disease in humans.[10 11] Occupational exposures to dusts and fumes have been shown to contribute greatly to the burden of chronic obstructive pulmonary disease (COPD).[12–16] Previous studies, however, have had limited ability to examine the health effects of a

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specific occupational group or exposure. We recently reported in a case-control study of railroad workers that after adjusting for smoking history there was an increased risk of COPD mortality with increasing years of work in a diesel exhaust-exposed job.[17] We now assess this association in a retrospective cohort of railroad workers followed from 1959 to 1996.

MATERIALS AND METHODS

Study population

The cohort of railroad workers obtained with the assistance of the US Railroad Retirement Board (RRB) has been described elsewhere.[18–20] Briefly, the RRB has maintained computerised work records since 1959 for all railroad workers, including a yearly listing of job codes and months worked. Male workers in jobs with and without diesel exhaust exposure (see exposure assessment below) and aged 40–64 in 1959 with 10–20 years of prior railroad work were selected. Cause of death information from 1959 to 1996 was available from the National Death Index and from death certificates obtained from the RRB and state health departments, and all cases of COPD or allied causes (ICD9 490–494, 496) listed as a primary or secondary cause on the death certificate were identified. The protocol was approved by the Brigham and Women's Hospital and VA Boston Healthcare System Institutional Review Boards.

Exposure to diesel exhaust

Diesel exposure was determined based on yearly job code provided by the RRB. The US railroad industry changed from steam- to diesel-powered locomotives starting after World War II. In 1946, 10% of the locomotives in service were diesel-powered and by 1959, 95% of locomotives in use were diesel-powered.[21] Using information from an industrial hygiene survey that we conducted[22 23] and review of industry practices, each job title in the job histories was characterised as exposed or unexposed to diesel. The engineers (engineers and firemen) and conductors (conductors, brakemen, and hostlers) who worked on operating trains were determined to be "diesel exposed". Other jobs, including ticket agents, station agents, signal maintainers and other maintenance of way workers, car repair workers, and clerks, were considered "unexposed". Shop workers were determined to be a mix of diesel-exposed and -unexposed workers.

Smoking history imputation

Due to the retrospective nature of this cohort, individual-level information on smoking was not available for any individuals in the cohort. Therefore, as in our previous analysis of lung cancer,[24] to examine the potential confounding effect of cigarette smoking on the association, we used a multiple-imputation method[25 26] to assign smoking histories from a case-control study. The original railroad worker case-control study was designed as a study of lung cancer and diesel exhaust exposure.[27] Between 1 March 1981 and 28 February 1982, there were 15 059 deaths among US railroad workers eligible for benefits, and death certificates were collected in 87% of the deaths. Efforts were made to obtain cigarette-smoking histories from next of kin of 5290 deceased workers using mail questionnaires followed by a phone call. Questions about smoking included the age that the deceased first and last smoked cigarettes and the average amount smoked daily. There were 3995 individuals with complete smoking information, and percentages were similar across the case and control series. Exposure to diesel exhaust was categorised based on the exposure groups used in the retrospective cohort study.

Since smoking behaviour in the USA is highly determined by birth cohort and race,[28] we identified workers in the case-control study that were in the same birth cohort, race, and occupational categories of workers in the retrospective cohort study. There were 2470 white male workers in these categories with smoking history information available in the case-control

dataset that included workers aged 40–59 in 1959. Since smoking histories were only available on deceased workers, we limited the imputation of smoking behaviour to 39 388 workers (76% of all workers in the cohort aged 40–59 in 1959) who died through the end of follow-up in the retrospective cohort. Smoking history (age started, age stopped, and average number of cigarettes smoked daily) was assigned to each worker in the cohort with random selection from men in the case-control data of the same (a) age and birth cohort in 5-year groups (ie, aged 40–44, 45–49, 50–54, 55–59 at study entry in 1959); (b) job category (engineer, conductor, shop, clerk, or signal maintainer groups); and (c) whether the subject died of COPD or another cause. Smoking histories were available from 304 workers who died of COPD and 2166 deaths from other causes, and five datasets with imputed smoking information were created. The final analytical dataset consisted of the 30 671 workers aged 40–59 in 1959 who died before the end of follow-up, with no history of work as a shop worker, and with an imputed smoking history available.

Statistical analysis

Proportional hazards models were used to estimate the association between diesel exposure and COPD mortality in each dataset. Person–time was calculated from 1 January 1959 to the earlier of date of death or 31 December 1996. As in previous analyses,[18,24] to account for a healthy worker survivor effect,[29–31] time-varying variables for total years worked and for years off work were included in survival models. Risk sets were defined by current age in 1-year categories and separate baseline hazards were used for each calendar year. The association of COPD mortality with cumulative years of work as an engineer/brakeman was assessed using penalised splines in the Cox model to allow deviations from linearity.[32,33] The smoothing parameter was selected using Akaike's information criteria (AIC).[34] Additionally, exposure was categorised in 5-year duration categories. To examine possible effect modification by year of hire, stratified models were performed for workers hired before 1945 (the start of the conversion to diesel locomotives) and those workers hired in 1945 or later. We also conducted sensitivity analyses by creating models stratified by years of hire from 1941 to 1946.

Each worker's smoking behaviour during the analysis was imputed in a time-dependent manner between 1959 and 1981 and allowed to vary based on age of smoking initiation and smoking cessation to account for the effect of age-related changes in smoking behaviour. Because the case-control study provided smoking history information in 1981–1982, and there was no specific smoking information available, after 1981 smoking behaviour was not allowed to vary in the regression models. Variables for pack–years and years quit smoking were included as potential confounders in smoking-adjusted models. Hazard ratios were averaged across the five imputations and confidence intervals include the variability between and within imputations.[26]

RESULTS

Characteristics of the population at the start of follow-up (1959) are presented in table 1 for the whole cohort, and for cohort members stratified by date of hire. Unexposed workers tended to be slightly older at hire than engineers/brakemen, to have been hired later, and to have fewer pack–years of imputed smoking and higher years since quitting smoking. Workers hired during 1944 or earlier tended to be slightly younger when hired and older at the start of follow-up than workers hired during 1945 or later, but imputed smoking patterns were similar between the two groups.

Penalised splines for the log-hazard ratio of COPD mortality with increasing years of work as an engineer/brakeman are presented for the entire cohort (fig 1). Cohort members hired before the conversion to diesel locomotives are presented in fig 2. Cohort members hired after the conversion to diesel locomotives began are presented in fig 3. For the entire cohort and those

workers employed before the conversion to diesel locomotives, the association of COPD mortality and years of work as an engineer/brakeman was not linear. The risk of COPD mortality increased with increasing years of work, but after approximately 9 years, the risk remained steady and then declined. For workers hired after the beginning of the conversion to diesel locomotives, the association of COPD mortality and years of work as an engineer/brakeman was linear. For each additional year of work, the risk of COPD mortality increased by 2.5% (95% CI 0.9% to 4.2%). In sensitivity analyses examining different hire date cut-offs from 1941 to 1946, linear associations were only seen for cut-offs after 1944.

After adjustment for pack–years of imputed smoking and years since quitting, the results were slightly attenuated (fig 4). For example, for those hired after 1945, the age- and healthy worker survivor effect-adjusted hazard ratio for those with greater than 0 but less than 5 years of work as an engineer was 1.18 (95% CI 0.71 to 1.97), for 5 to less than 10 years was 1.34 (95% CI 0.90 to 2.00), for 10 to less than 15 years was 1.44 (95% CI 1.01 to 2.07), for 15 to less than 20 years was 1.52 (95% CI 1.09 to 2.21), and for 20 or more years was 1.85 (95% CI 1.15 to 3.00). The equivalent smoking-adjusted hazard ratios were 1.14 (95% CI 0.68 to 1.91), 1.28 (95% CI 0.85 to 1.93), 1.32 (95% CI 0.91 to 1.92), 1.38 (95% CI 0.99 to 1.94), and 1.67 (95% CI 1.03 to 2.71). For each additional year of work, in linear models, the smoking-adjusted risk of COPD mortality increased by 2.1%.

DISCUSSION

In this cohort of diesel-exposed railroad workers, work in diesel-exposed jobs was associated with higher risks of COPD mortality compared to work in unexposed jobs. These risks increased with increasing years of work, especially in those workers who were hired after the conversion to diesel locomotives. For each additional year of work as an engineer/brakeman in this group, the risk of COPD mortality increased by 2.5% (2.1% after adjustment for imputed smoking history). In our previous case-control study, we observed similar results, with a smoking-adjusted odds ratio (1.02 (95% CI 1.01 to 1.04)) for COPD mortality that also increased approximately by 2%/year for each additional year of work as an engineer/conductor.[17]

The US railroad industry converted from steam- to diesel-powered locomotives after World War II, with a rapid conversion occurring through the 1950s. First-generation diesel locomotives introduced during the 1940s and 1950s were described as "smokier" than locomotives introduced later, although historical exposure measurements are not available (A Eschenroeder, personal communication, 2004).[22,23] Locomotive emissions decreased in engines introduced in the 1960s (second generation) and decreased again in locomotives manufactured in the 1980s (third generation). In our exposure assessment conducted in the early 1980s, workers on operating trains had mean respirable particulate levels adjusted for second-hand smoke approximately 2 to 3 times that of unexposed clerical workers (71 $\mu g/m^3$ and 89 $\mu g/m^3$, of cigarette-adjusted particulate matter (PM) vs 33 $\mu g/m^3$).[22,23] These results indicate that railroad workers who are on operating trains and whose COPD mortality was assessed in this study were more exposed to diesel exhaust than workers not on operating trains.

Our results are consistent with the literature relating occupational exposures to dusts and fumes to the development of COPD, and ambient air pollution studies where exposure to PM is associated with both hospitalisations and COPD mortality.[35–37] Occupational exposures to mineral dust, welding and metal fumes, inorganic and organic dusts, and vehicle exhausts have been associated with COPD, including in non-smoking individuals.[11,12,14–16,38–46] Additionally, in the Third National Health and Nutrition Examination Study (NHANES III), 19.2% of all US COPD cases and 31.1% of non-smoking cases were attributed to work

exposures.[13] In a recent longitudinal study of men with early COPD, each year of continued fume exposure (defined by self-report from a questionnaire) was associated with a 0.25% predicted reduction in post-bronchodilator forced expiratory volume in 1 second (FEV_1)% predicted after control for smoking.[47] This suggests that occupational fume exposures may contribute to COPD progression.

Since the 1950s, researchers have shown that acute air pollution exacerbates existing COPD and asthma and also increases their incidence. This research includes panel studies and time series studies of daily variation in hospitalisations.[48–50] Furthermore, studies examining the long-term effects of air pollution exposure have consistently found increased prevalence of symptoms or diagnoses of emphysema or COPD for areas with higher levels of PM.[38,49,51–53] In residents living in areas of high air pollution, small airway fibrosis and PM deposition were noted in small airways, suggesting that chronic exposure to PM results in pathological changes in the lung.[54,55] Similar findings have been noted in workers with occupational dust exposures. [56,57] Recent studies have also implicated air pollution (and specifically traffic-related exposures) in the development of COPD, showing decreases in lung function and increases in COPD diagnoses and symptoms.[58–60]

Exposure to the organic compounds found in diesel exhaust and on the surface of the particle have also been linked to allergy, airway inflammation and changes in airway function. [3,61–63] Air toxics and other polycyclic aromatic hydrocarbon compounds found in diesel exhaust may be important in the induction of such airway inflammatory changes and possibly oxidative stress in the lung.[64] These studies, along with the evidence from occupational and environmental epidemiological studies, support the hypothesis that occupational exposure to diesel exhaust can contribute to the occurrence of COPD and COPD mortality.

There are several possible sources of limitation in this study, including classification of outcome from death certificates, classification of exposure based on job title and an industrial hygiene survey, and information on cigarette smoking from a multiple imputation. Death certificates have been shown to underestimate the true number of workers with severe COPD at death. In the Tucson Epidemiologic Study of Obstructive Airways Disease, 25% of deaths with clinically documented moderate to severe obstructive lung disease were identified using underlying cause of death only, while 81% had COPD noted as either underlying or contributing cause on the death certificate.[65] Similarly for asthma, in a cohort of persons from Olmstead County, Minnesota (that excluded persons with COPD based on detailed laboratory and clinical criteria), the specificity was 99% but the sensitivity was only 42% for detecting asthma based on death certificate diagnosis.[66] Since it would be unlikely for a physician to report obstructive lung disease based on diesel exposure category, misclassification would be non-differential and the observed hazard ratios are likely attenuated.

In any COPD study, cigarette smoking is an important potential confounder of the exposure/disease association. Due to the retrospective nature of this cohort, information on smoking status was not available. Therefore, we used a multiple-imputation method to assign smoking histories based on age, job group, and cause of death to provide the reader with a sense of the potential magnitude of confounding from smoking. There were in fact small differences in smoking rates by job title, with a slightly higher rate of smoking among the diesel-exposed workers.[67] These differences led to an attenuation of risk in smoking-adjusted models, which were similar to the attenuations seen in our previous case-control study with information available on smoking.[17]

Although we control for the healthy worker survivor effect in all models using time-varying variables for total years worked and for years off work, it is still possible that remaining bias from the healthy worker survivor effect is influencing the results of the models stratified by

year of hire. In a recent article, it was shown that prevalent hires, defined as workers already employed at the start of study follow-up, have lower risks of death than workers hired after the start of follow-up.[68] In this analysis, workers hired in 1945 or later had a higher risk of COPD mortality for each year of work as an engineer/brakeman compared to workers hired before 1945. Therefore, although we do adjust all analyses for the healthy worker survivor effect, it is possible that residual selection bias, and not diesel-locomotive-only work history, explains this finding.

In conclusion to this cohort study of railroad workers, work in jobs with exposure to diesel exhaust was associated with increased mortality from COPD. These elevations persisted after controlling for smoking and increased with increasing years of work in exposed jobs for those individuals who started work after the conversion to diesel locomotives began.

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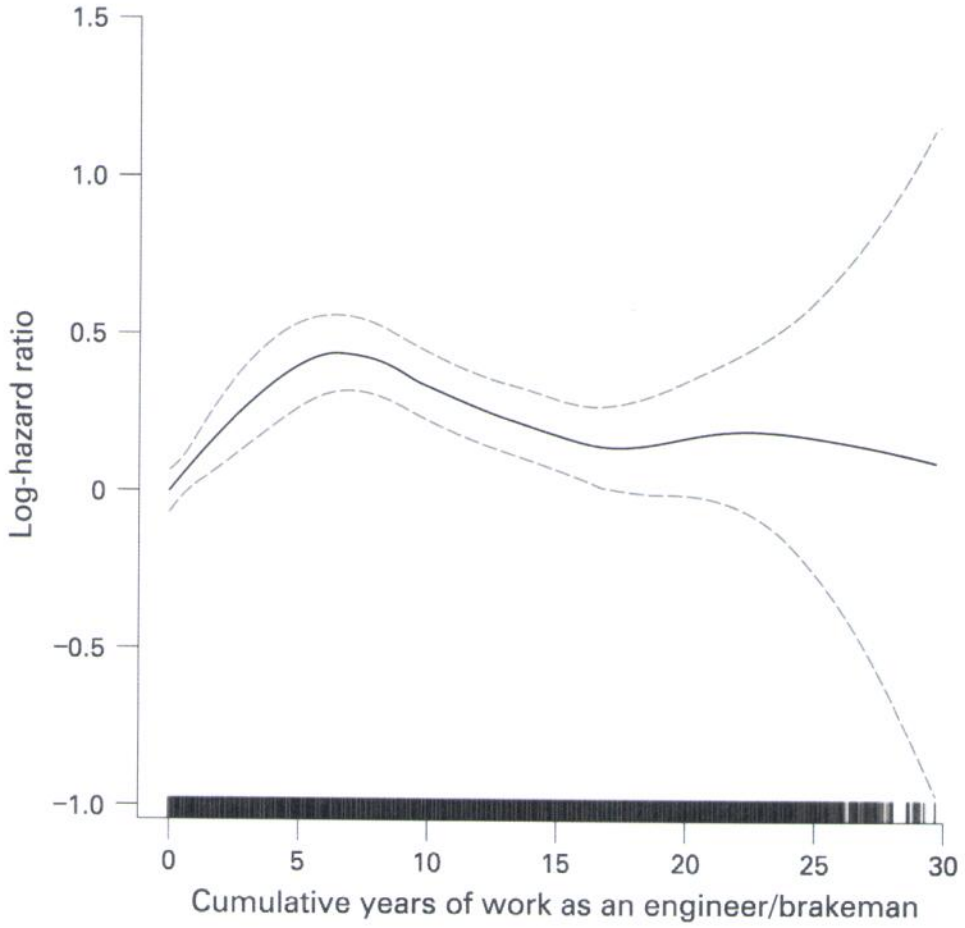

Figure 1.

Log-hazard ratio (solid curve) of chronic obstructive pulmonary disease mortality with years of work as an engineer/brakeman for the entire cohort (n=30 671). The dotted curves are the 95% confidence intervals and the histograms at the bottom of the plot indicate the distribution of years of work as an engineer/brakeman.

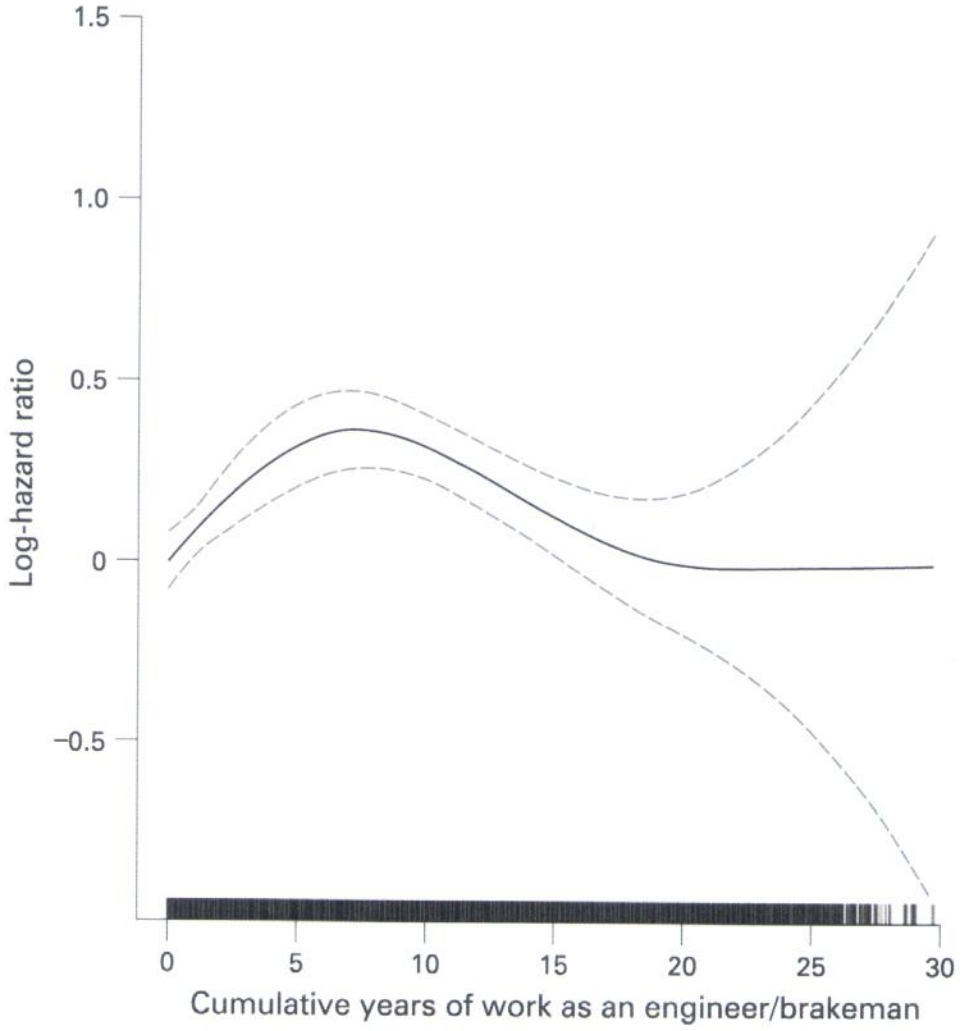

Figure 2.

Log-hazard ratio (solid curve) of chronic obstructive pulmonary disease mortality with years of work as an engineer/brakeman for members of the cohort hired before 1945 (n=24 106). The dotted curves are the 95% confidence intervals and the histograms at the bottom of the plot indicate the distribution of years of work as an engineer/brakeman.

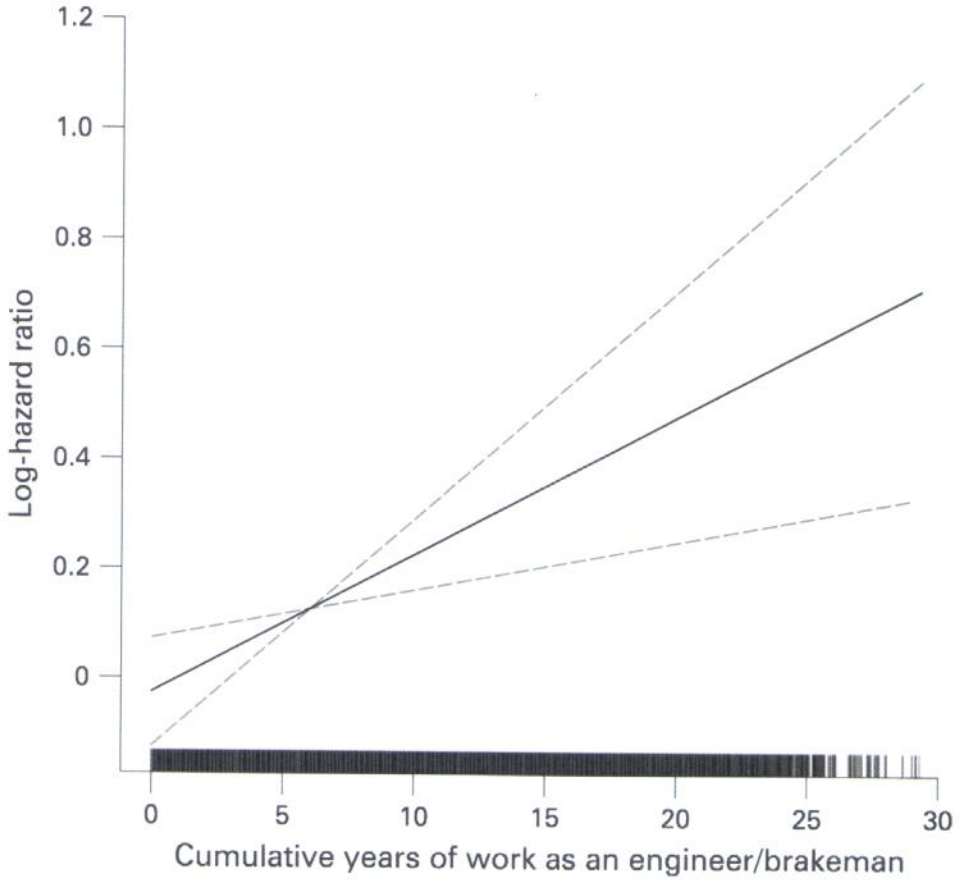

Figure 3.

Log-hazard ratio (solid curve) of chronic obstructive pulmonary disease mortality with years of work as an engineer/brakeman for members of the cohort hired during 1945 or later (n=6565). The dotted curves are the 95% confidence intervals and the histograms at the bottom of the plot indicate the distribution of years of work as an engineer/brakeman.

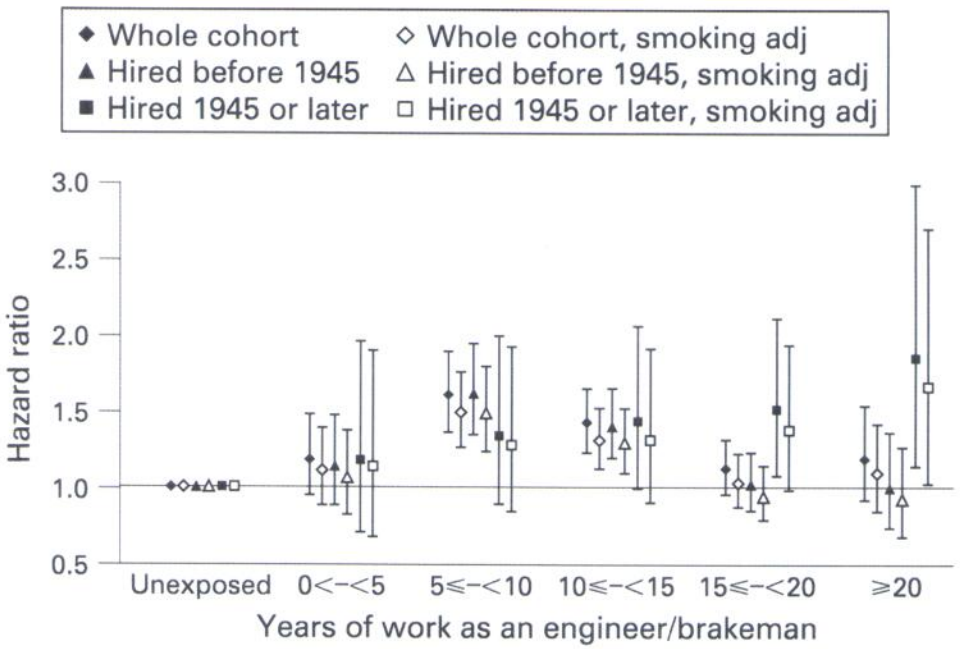

Figure 4.

Years of work as an engineer/brakeman and chronic obstructive pulmonary disease mortality risk in models adjusted and unadjusted for smoking.

Table 1

Demographics of cohort members at start of follow-up (1959)

Characteristic	Engineers/brakemen	Unexposed	Total
Whole cohort			
n	21 234	9437	30 671
Mean (SD)			
Age at hire	31.4 (5.5)	32.7 (5.9)	31.8 (5.6)
Age in 1959	47.8 (5.4)	48.7 (5.7)	48.1 (5.5)
Pack–years*	43.3 (4.1)	40.9 (3.7)	42.1 (4.1)
Cigarette smoking (%)†			
Never	2739 (12.9)	1680 (17.8)	4419 (14.4)
Current	16 329 (76.9)	6587 (69.8)	22 916 (74.7)
Former	2166 (10.2)	1170 (12.4)	3336 (10.9)
COPD deaths	1219	464	1683
Hired < 1945			
n	17 321	6785	24 106
Mean (SD)			
Age at hire	31.1 (5.5)	31.9 (5.8)	31.3 (5.6)
Age in 1959	48.1 (5.4)	49.2 (5.7)	48.4 (5.5)
Pack–years*	43.3 (4.1)	40.8 (3.8)	42.1 (4.1)
Cigarette smoking (%)†			
Never	12.9	17.5	15.2
Current	76.8	70.0	77.4
Former	10.3	12.5	11.4
COPD deaths	1002	349	1351
Hired ≥ 1945			
n	3913	2652	6565
Mean (SD)			
Age at hire	32.9 (5.1)	34.5 (5.7)	33.5 (5.5)
Age in 1959	46.4 (5.2)	47.4 (5.6)	46.8 (5.4)
Pack–years*	43.1 (4.6)	40.9 (3.8)	42.0 (4.3)
Cigarette smoking (%)†			
Never	12.9	18.4	15.7
Current	77.1	69.3	73.2
Former	10.0	12.3	11.1
COPD deaths	217	115	332

*Average of five smoking imputations among ever-smokers.

†Average of five smoking imputations.

COPD, chronic obstructive pulmonary disease.