# Contributions of Dust Exposure and Cigarette Smoking to Emphysema Severity in Coal Miners in the United States

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***Rationale*: Previous studies have shown associations between dust exposure or lung burden and emphysema in coal miners, although the separate contributions of various predictors have not been clearly demonstrated.**

***Objectives*: To quantitatively evaluate the relationship between cumulative exposure to respirable coal mine dust, cigarette smoking, and other factors on emphysema severity.**

***Methods*: The study group included 722 autopsied coal miners and nonminers in the United States. Data on work history, smoking, race, and age at death were obtained from medical records and questionnaire completed by next-of-kin. Emphysema was classified and graded using a standardized schema. Job-specific mean concentrations of respirable coal mine dust were matched with work histories to estimate cumulative exposure. Relationships between various metrics of dust exposure (including cumulative exposure and lung dust burden) and emphysema severity were investigated in weighted least squares regression models.**

***Measurements and Main Results*: Emphysema severity was significantly elevated in coal miners compared with nonminers among ever- and never-smokers ($P < 0.0001$). Cumulative exposure to respirable coal mine dust or coal dust retained in the lungs were significant predictors of emphysema severity ($P < 0.0001$) after accounting for cigarette smoking, age at death, and race. The contributions of coal mine dust exposure and cigarette smoking were similar in predicting emphysema severity averaged over this cohort.**

***Conclusions*: Coal dust exposure, cigarette smoking, age, and race are significant and additive predictors of emphysema severity in this study.**

**Keywords:** occupational exposure; regression analysis; chronic obstructive lung disease; autopsy; severity of illness index

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Cumulative dust exposure is a significant predictor of emphysema severity in coal miners after accounting for cigarette smoking, age at death, and race. Coal mine dust exposure and cigarette smoking had similar additive effects on emphysema severity in these models.

### What This Study Adds to the Field

Quantitative estimates of the contributions of smoking and dust exposure on emphysema severity in coal miners support the role of occupational dust exposure in chronic obstructive pulmonary disease.

The relative contribution of occupational dust exposure and smoking to chronic lung disease is relevant to occupational and environmental lung diseases generally and to coal mining specifically. A perception that chronic obstructive pulmonary disease (COPD), including emphysema, is caused primarily by smoking has hindered opportunities for primary prevention, diagnosis, and treatment of these diseases (1). This perception persists despite a number of studies in the past several decades demonstrating that work in dusty jobs is associated with obstructive respiratory disease and functional deficiency (2, 3) and that dust-related lung function deficits can be severe enough to cause clinically significant impairment even in the absence of chest X-ray evidence of pneumoconiosis (4–7).

Several studies have shown that coal miners are at increased risk of developing COPD, including emphysema relative to nonminers (8–11). Increased mortality from COPD has been associated with cumulative exposure to respirable coal mine dust after accounting for smoking history (12, 13). A significant negative relationship between emphysema severity at autopsy and $FEV_1$ during life was shown in gold miners from South Africa (14) and in a subset of miners in this study (15). In a case-control analysis of coal miners in the United States, emphysema was one of the respiratory diseases or conditions that was elevated among miners with rapid decline in $FEV_1$ (at least 60 ml/yr greater than that of referent miners matched on age, height, smoking status, and initial $FEV_1$) (16).

Chronic airflow limitation, which is characteristic of COPD, is caused by a mixture of large airway disease (chronic bronchitis) and small airway disease (obstructive bronchiolitis) as well as parenchymal destruction (emphysema) (17). Some of the difficulty in determining the role of coal mine dust exposure, smoking, and other factors on COPD is due to the diagnostic challenge of distinguishing the various causes of airway obstruction because they are all associated with deficits in $FEV_1$. Although a definitive diagnosis of emphysema is based on anatomic criteria evaluated by pathologic observation of whole lung sections (18), it can also be seen on standard chest radiographs and graded by computerized tomography (19, 20).

Few studies have had the quantitative data to ascertain the relationships between occupational dust exposure, cigarette smoking, and emphysema severity (9, 10, 21). In the current study, miners' job-specific working lifetime cumulative exposures to respirable coal mine dust are estimated using individual miners' work history data and job-specific estimates of airborne mean dust concentration. These data are used in multivariate

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analyses to examine whether dust exposure experienced by coal miners is associated with emphysema severity after accounting for nonoccupational factors including cigarette smoking. Earlier studies of emphysema were reported for a subset of this coal miner population in an abstract and conference proceedings (21–23) before developing the cumulative dust exposure estimates. An analysis of emphysema and pulmonary impairment based on these data was reported at a recent conference (15).

## METHODS

### Study Description

The study group consists of 722 autopsied individuals, including 616 coal miners from southern West Virginia and 106 nonminers from West Virginia (n = 56) and Vermont (n = 50) who died during the period from 1957 to 1978. Lungs from West Virginia were collected from consecutive autopsies from 1957 to 1973 at the Beckley Southern Appalachian Regional Hospital by the late Dr. W. Laqueur as part of a black lung study funded by Occupational Safety and Health through the Public Health Service. All miners who died during the period of the study were identified, and their families were contacted about the study and invited to participate. No other selection criteria were applied, and all miners had an equal opportunity to be included in the study without regard to cause of death, respiratory disease status, or any other factor. Autopsy consent was obtained using the standard Beckley Hospital consent form. Autopsies of nonminers at the same hospital were requested by the physicians for their own diagnostic purposes, and the next-of-kin were also contacted for participation in the study. Left lungs of miners and nonminers were inflated for the study. The lungs from Vermont were processed in a similar manner from consecutive autopsies at the University of Vermont during 1972 to 1978 in a population of Medical Examiner deaths of individuals who died suddenly (as a result of accident, suicide, or acute medical problems) (24). No other selection criteria were applied to these autopsies, although nonminers who had a history of work in dusty jobs were excluded (24). Participation rates are not known, although the greater number of coal miners than nonminers was due to the focused study of coal miners, compared with routine hospital autopsies or medical examiner cases of nonminers.

Data were available for most individuals (n = 719) on the miner/nonminer status, age at death, and race. Most (90%) of the nonwhite miners were African American. Smoking data were obtained from medical records or questionnaire completed by next-of-kin, including cigarette smoking status, duration of smoking, number of packs of cigarettes smoked per day, and other tobacco use. Cigarette smoking status (ever/never) was available for 520 individuals (n = 405 ever; n = 115 never). Among ever-smokers, pack-year (packs/d $\times$ yr) data were available for 232 individuals.

### Cumulative Exposure Estimates

Individual work history data were used to estimate cumulative dust exposure for each miner using a method described by Attfield and Morring (25). Job-specific dust exposure estimates (airborne concentration of respirable coal mine dust) were obtained by gravimetric sampling during the U.S. Bureau of Mines environmental surveys of 1968 and 1969 in 29 underground coal mines across the United States. For surface coal mine jobs, data were collected from 1970 to 1972 by mine operators as part of the Federal Coal Mine Safety and Health Act (26). Exposures were adjusted by Attfield and Morring (25) to account for the reduction in the allowable airborne concentration that occurred in 1970 (3 mg/m$^3$ from 1970 to 1972, then 2 mg/m$^3$ afterwards [27]). The validity of their method was shown by the consistent trend between the U.S. Bureau of Mines data and subsequent Mine Safety and Health Administration data (25). Cumulative exposure to respirable coal mine dust (mg/m$^3$ $\times$ yr) was estimated for each miner by summing the products of the mean airborne respirable dust concentration (mg/m$^3$) for each mining job and the years worked in that job. For nonminers, who had no documented occupational history to coal mine dust exposure, cumulative exposure to respirable coal mine dust was assumed to be zero.

Among miners, the coal mining tenure records varied in detail and quality. The minimal data required to estimate cumulative dust exposure included a record of being a miner and the total mining tenure (recorded from next-of-kin or computed from dates in the miners' work history). Of the 616 miners, 549 had data on the duration in mining. Complete work history data (with job titles for all years in mining) were available for 391 miners, 70 miners had some missing work history data, and 88 miners had minimal work history data (i.e., record of being a coal miner and the total duration in mining but no specific job titles). Inconsistencies in the work histories were resolved where possible by checking the original records. When a miner's job title was not recorded for a given time period during his recorded mining tenure, the coal dust exposure for the unknown job time period was assumed to be the time-weighted average of the worker's exposure for his recorded job history. For miners with data on mining duration but no specific job title, a general miner category was assigned as reported by Attfield and Morring (25).

A work history quality variable was created for miners and nonminers for use in the sensitivity analysis of the modeling results. Miners were assigned to one of three levels based on the quality of their work history data, as described above, including (*1*) complete (n = 391), (*2*) some missing (n = 70), and (*3*) minimal work history data available (n = 88). An additional 67 miners had unknown mining tenure and were assigned to a fourth group, which was removed from all analyses that required duration in mining or cumulative exposure. For nonminers, the archived records were rechecked to verify the original designation as nonminer without dusty jobs. Nonminer data quality level designations include: (*1*) job history available indicating nonminer for men (n = 55); for women without specific job history, the original nonminer designation was accepted (n = 24); (*2*) job history suggested possible dust exposure, although without sufficient evidence to exclude (e.g., mention of construction or automotive repair) (n = 21); and (*3*) inability to verify the original nonminer classification and male gender (n = 6). Sensitivity analyses of the final models were performed based on the following subsets of the data: Subset 1: keep the best data (i.e., keep miner level 1 and nonminer level 1), and Subset 2: drop the poorest data (i.e., keep miner levels 1 and 2 and nonminer levels 1 and 2).

### Pathologic Evaluation for Emphysema

Two pathologists (F.H.Y.G. and V.V.) reviewed three or more whole lung sections prepared from sagittal slices of the left lung (21, 23). Emphysema was classified by type (23), and all types were included in the quantitative grading. Emphysema severity was graded using photographic standards prepared by Thurlbeck and colleagues (28) in conjunction with a 10-segment grid (29). The standards covered the full range of abnormalities seen in human lungs, producing an incremental scale. The method has been shown to be rapid and highly reproducible (29). Each of the 10 lung zones was graded for emphysema severity up to a maximum score of 100 for each zone, for a possible maximum score of 1,000. The total emphysema severity index/10 is equivalent to the percentage of the total lung tissue affected. Figure 1 illustrates the 10-segment grid (29) used in grading emphysema severity in sagittal slices of whole lungs and shows different grades of emphysema in miners' lungs.

### Lung Dust Analysis

For a subgroup of 141 miners, a 1.5-cm slice of lung adjacent to the whole lung section was analyzed gravimetrically for total dust, coal dust, total mineral dust, and free silica, as described previously (23, 30, 31). The percentage of dust (by weight) in 100 g of dry tissue was converted to mass of dust (g) per whole lung by assuming a ratio of 1/5 for dry/wet tissue and a mass of 1,000 g per human lung (left and right) at autopsy.

### Statistical Analyses

Statistical analyses were performed using the 9.1 Windows Version of SAS (32), and all tests were performed at the 0.05 level of significance. Tests for significant differences in values of variables by group (e.g., miner/nonminer; ever/never-smoker) were performed using the Wilcoxon rank-sum or Fishers exact test in SAS. Evaluations of intra- and inter-individual agreement were performed based on data of 20 autopsied lungs evaluated independently by two readers (F.H.Y.G., V.V.) on two different occasions several months apart. For each reader, the emphy-

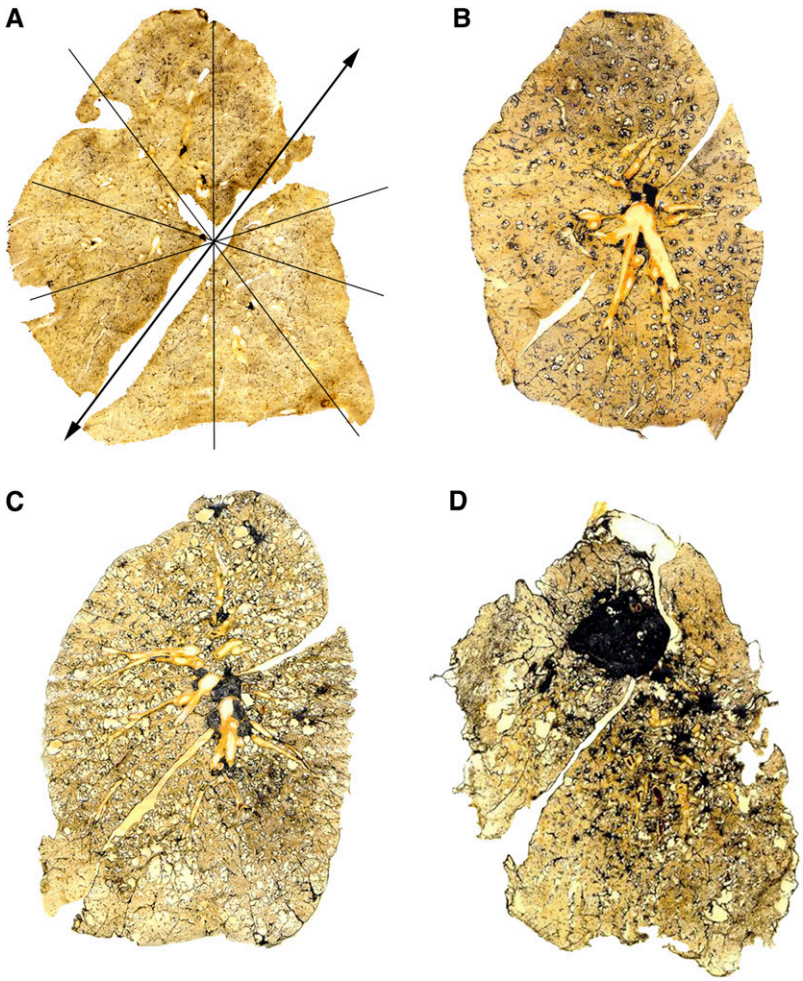


***Figure 1.*** (*A*) Whole lung section from a never-smoker, white, nonminer (age at death, 62 y) showing minor senile emphysema with a severity score of 50. Overlaid is the 10-segment grid used to evaluate emphysema severity (29). The grid is placed with its axis (*arrows*) along the oblique fissure separating the upper and lower lobes of the left lung (upper and middle lobes for a right lung). Each segment is graded on a scale from 0 to 100 such that the total maximum emphysema score for a lung is 1,000. Each segment corresponds to an anatomical lung compartment, allowing analysis by lung lobe, zone, and segment. (*B*) Whole lung section from a 78-year-old, never-smoker, white, coal miner (43 y of mining) showing mild macular coal workers' pneumoconiosis with associated centriacinar (focal) emphysema. The emphysema score for this case was 235. (*C*) Whole lung section from a 73-year-old, never-smoker, African American, coal miner (28 y of mining) showing simple macular and nodular coal worker's pneumoconiosis against a background of severe emphysema, predominantly of centriacinar type. Scar emphysema is seen adjacent to the macronodules. The emphysema score for this case was 750. (*D*) Whole lung section from a 67-year-old, never-smoker, African American, coal miner (36 y of mining) with progressive massive fibrosis. The lung also shows moderately severe emphysema of centriacinar, scar, and bullous types. The emphysema score for this case was 490.

sema scores of the 20 lungs were grouped into intervals based on the cut points of 100, 200, . . . , 900, and each cut point was the largest value of its interval. Square two-way frequency tables of the grouped scores of the two readers were formed, and agreement was assessed using a weighted generalization of the Kappa statistic so that smaller disagreements were penalized less than larger ones (32). The agreement between the two readers (interreader) was based on the average of the two scores assigned by each reader. The agreement within each reader (intrareader) over the two occasions of scoring was assessed for each reader separately and with a combined weighted Kappa statistic controlling for reader.

The relationship between emphysema severity index and predictor variables was investigated using weighted least squares modeling (33). The weights were computed as the reciprocal of the variance of the residuals for fixed levels of the predicted values of emphysema computed from an unweighted least squares fit. The weighted model was required because of observed heteroscedasticity in the response (i.e., the variability in the emphysema index increased as the mean increased). Variables of *a priori* interest as predictors of emphysema index included smoking, mining, and age at death. These variables were included in the initial models. Cigarette smoking variables examined were ever/never-smoker, duration of smoking, and pack-years of smoking. Mining variables examined were miner/nonminer, years worked in mining, cumulative exposure to respirable coal mine dust, and coal dust lung burden. The additional variables of race and retirement years—as well as two-way interactions between the main variables and quadratic terms for age at death, coal mining tenure, and cumulative exposure—were tested for inclusion in the model using a forward stepwise selection approach.

Hierarchical tests for significance of variables (main effects and interactions) were performed in a weighted linear regression model in which the full model criteria were used in the reduced or nested model. Joint tests of a main effect and its interaction were performed based on an $F$ statistic. The 95% confidence intervals (CIs) were based on linear combinations of the coefficients in the model (33). *Post hoc* sensitivity analyses were performed to examine whether the findings were sensitive to the underlying model (weighted least squares) or to specific groups (e.g., by work history quality, miner, or smoker group).

## RESULTS

### Population Characteristics

Table 1 shows the characteristics of the study population, including the full dataset, miners, and nonminers. Compared with the miners, nonminers on average died at a younger age (56 vs. 66 yr), smoked more (among smokers, 48 vs. 41 pack-years), and were more likely to be never-smokers (25 vs. 21%) and white (84 vs. 70%). Although age at death and race were significantly different among miners versus nonminers ($P < 0.04$), ever/never and pack-years of smoking were not ($P > 0.2$).

### Intra- and Interreader Variability

The interreader weighted Kappa statistic was 0.80, and the intrareader weighted Kappa statistics of the two readers and combined were 0.85, 0.86, and 0.86, respectively. These results indicate good agreement of the emphysema severity scores within and between readers.

### Emphysema Severity in Miner and Smoker Groups

The mean emphysema severity index was significantly greater in miners versus nonminers among ever-smokers or never-smokers

**TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION**

| Variable | Full Data (*n* = 722)* | All Miners (*n* = 616) | Nonminers (*n* = 106) |
|---|---|---|---|
| Characteristics, mean (SD) | | | |
| Age at death, years | 64.6 (12.1) | 66.2 (10.2) | 55.7 (17.2) |
| Tenure in mining, years† | 28.8 (15.6) | 34.3 (10) | 0 |
| Cumulative coal mine dust exposure, mg/m$^3$ × year† | 86.7 (53.3) | 103 (40.6) | 0 |
| Pack-years smoked, packs/day × years‡ | 42.4 (30.9) | 41.3 (28.2) | 48.2 (41.6) |
| Duration smoked, year‡ | 35.4 (14.1) | 36.4 (13.9) | 30.1 (14.0) |
| Cigarette smoking group§, % (n) | | | |
| Ever | 77.9 (405) | 78.4 (351) | 75.0 (54) |
| Never | 22.1 (115) | 21.6 (97) | 25.0 (18) |
| Race, % (n) | | | |
| White | 72.3 (522) | 70.3 (433) | 85.0 (89) |
| Nonwhite | 27.6 (199) | 29.7 (183) | 15.0 (16) |

* Number of observations in full data with missing values for age at death (n = 3), race (n = 1), years in mining and cumulative exposure (n = 67), and cigarette smoking status (n = 202).

† Assumed zero for nonminers.

‡ Among ever-smokers (n = 405) (observations missing: years smoked, 151; pack-years, 173).

§ Percentage among those with data (omits observations with missing values, as noted *).

($P < 0.0001$) (Table 2). A significantly greater emphysema severity index was also observed in ever- versus never-smokers among miners or nonminers ($P \leq 0.005$). The largest difference in emphysema severity index (nearly sixfold) was between miners and nonminers among the never-smokers (302 vs. 54, respectively).

The distributions of emphysema severity scores for miners and nonminers in this study (n = 722) were skewed among ever- or never-smokers (Figure 2). Among miners, the distribution was clearly shifted toward the higher scores, illustrating the increased severity of emphysema among miners compared with nonminers in the never-smoker or the ever-smoker group.

### Emphysema Severity and Cumulative Dust Exposure or Lung Burden

Cumulative exposure to respirable coal mine dust was a highly significant predictor of emphysema severity ($P < 0.0001$) (Table 3) after accounting for cigarette smoking (pack-years), age at death, and race (nonwhite). Figure 3 illustrates the results of this model. Emphysema severity is predicted to increase with cumulative exposure to respirable coal mine dust (range, 0–282; mean, 103 mg/m$^3$ × yr among miners). Plots based on the studentized residuals and the predicted means suggested that the estimated weights adequately accounted for the heteroscedasticity of the data (not shown).

In this model, the effect of smoking on the emphysema severity depends on age, due to the significant interaction between pack-years of smoking and age at death (Table 3). Although the main coefficient of smoking is negative, the overall effect of smoking on emphysema severity is determined by the sum of the smoking and smoking–age interaction terms. According to this model, cumulative coal mine dust exposure has a greater effect on emphysema severity than does cigarette smoking, assuming the mean values of cumulative exposure (103 mg/m$^3$ × yr), cigarette smoking (42.4 pack-year), and age at death (64.6 y) in this study population. Emphysema severity is also predicted to be higher among nonwhites at any given cumulative exposure. For example, in whites, the mean cumulative dust exposure contributes 113 units (95% CI, 74–152) to the predicted emphysema severity index, whereas the mean pack-years of cigarette smoking contributes 67 units (95% CI, 38–97). In nonwhites, the mean emphysema severity index is predicted to be an additional 152 units (95% CI, 88–214) at the same age of death.

**TABLE 2. EMPHYSEMA SEVERITY INDEX BY MINING AND SMOKING STATUS**

| | Nonminers | | Miners | | |
|---|---|---|---|---|---|
| | Mean (SD) | n | Mean (SD) | n | *P* Value* |
| Never-smokers | 54 (66) | 18 | 302 (248) | 97 | <0.0001 |
| Ever-smokers | 141 (126) | 54 | 377 (252) | 351 | <0.0001 |
| *P* value* | 0.005 | | 0.004 | | |

* Wilcoxon scores (rank sums), two-sample, two-sided test (*t* approximation).

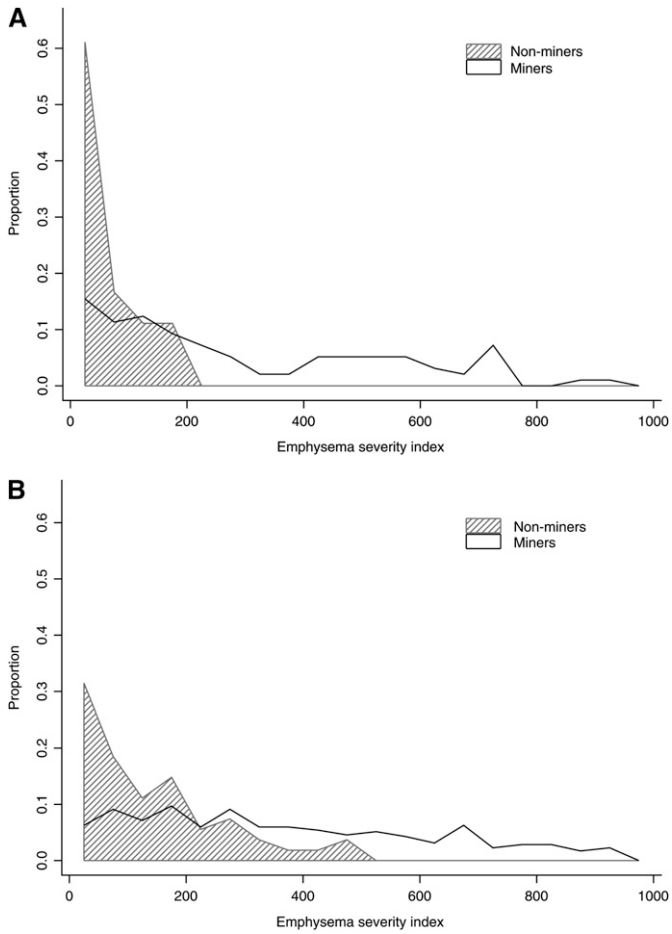


***Figure 2.*** Distribution of emphysema severity index among miners and nonminers by cigarette smoking status (proportions are within smoking group). (*A*) Proportions for never-smokers. (*B*) proportions for smokers.

In the subset of 141 miners with lung dust burden data, the mean coal dust lung burden was 9.2 g (SD, 7.2). The mean silica dust lung burden was 0.37 g (SD, 0.22) in the 119 miners with those data. Coal dust retained in the lungs was a highly significant predictor of emphysema severity ($P \leq 0.0001$) (Table 4) after accounting for cigarette smoking (ever/never), age at death, and race. The estimated effect of ever smoking was 178 units (95% CI, 85.7–269), compared with 117 units (95% CI, 67.1–167) at the average coal dust lung burden (Table 4). In a model with pack-years of cigarette smoking, the smoking effect was 98.8 units (95% CI, 36.0–162) at the average pack-

**TABLE 3. WEIGHTED LEAST SQUARES REGRESSION MODEL: RELATIONSHIP BETWEEN EMPHYSEMA SEVERITY INDEX AND CUMULATIVE EXPOSURE TO RESPIRABLE COAL MINE DUST*†**

| Parameter | Estimated Coefficient | Standard Error | *P* Value |
|---|---|---|---|
| Intercept | −48.4 | 23.6 | 0.04 |
| Cumulative exposure, mg/m$^3$ × years | 1.10 | 0.19 | <0.0001 |
| Cigarette smoking, packs/d × years | −3.21 | 1.05 | 0.002 |
| Age at death, years | 2.62 | 0.56 | <0.0001 |
| Race (nonwhite), n | 152 | 32.1 | <0.0001 |
| Interaction: cigarette smoking × age | 0.074 | 0.019 | 0.0002 |

* Weights for predicted value of emphysema index: 0–100, 101–200, 201–300, 301–400, 401–500, and >500, respectively, with number in parentheses: $6.59 \times 10^{-4}$ (25), $1.57 \times 10^{-4}$ (40), $2.27 \times 10^{-5}$ (89), $1.54 \times 10^{-5}$ (99), $1.32 \times 10^{-5}$ (66), and $1.34 \times 10^{-5}$ (22).

† N = 342 miners and nonminers. *F* value = 72.4 (5 df); $P < 0.0001$; $R^2 = 0.52$.

years, compared with 109 units (95% CI, 41.0–177) at the average coal dust lung burden. Silica dust retained in the lungs was not a significant predictor of emphysema severity ($P > 0.1$).

All predictor variables tested in these regression models were linearly related to the emphysema severity index. The only significant interaction was between smoking and age at death (Table 3). The race and dust exposure interaction term was not significant, although the coefficient was positive and the standard error was large. None of the quadratic terms were significant. Other models with continuous variables for duration of dust exposure and cigarette smoking or categorical variables for miner and smoking status (as well as race and age at death) were also significant predictors of emphysema severity (results not shown).

### Sensitivity Analyses

The effect of smoking on emphysema severity (i.e., the sum of smoking main effect and smoking–age interaction terms) was positive and significant at age of death greater than 43 years. This smoking effect was negative and significant at ages of death 29 years or less; however, this significance disappeared when the analysis was limited to the highest-quality data based on work history (subset 1). Furthermore, only 1% of the individuals in this study had an age of death from 20 to 29 years (nonminers only, including ever- and never-smokers). In a model fit to only miners, the smoking–age interaction was not significant ($P > 0.4$), and omitting this interaction term resulted in a significant and positive main effect of smoking (the quantitative effects of dust exposure and smoking were similar in the miners-only model, contributing 83 and 86 emphysema severity units, respectively, at the cohort average values).

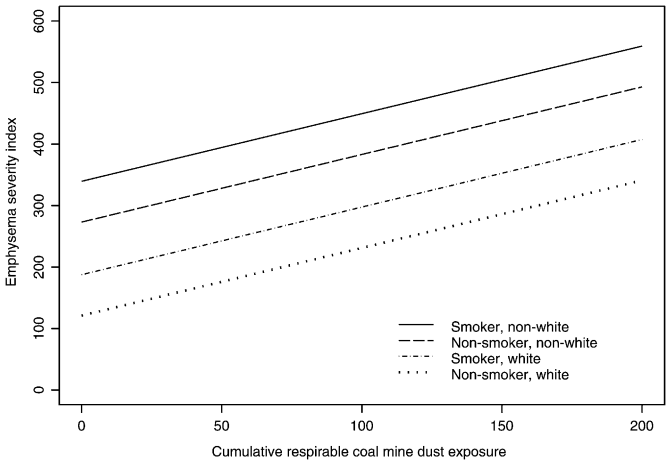


***Figure 3.*** Relationship between cumulative exposure to respirable coal mine dust (mg/m$^3$ × yr) and predicted emphysema severity index, by smoking status and race, assuming mean pack-years of smoking (among smokers; 0 for nonsmokers) and cohort mean age of death, based on weighted least squares regression model in Table 3.

**TABLE 4. WEIGHTED LEAST SQUARES REGRESSION MODEL: RELATIONSHIP BETWEEN EMPHYSEMA SEVERITY INDEX AND COAL DUST LUNG BURDEN*†**

| Parameter | Estimated Coefficient | Standard Error | *P* Value |
|---|---|---|---|
| Intercept | −473 | 128 | 0.0004 |
| Coal dust in lungs, g in whole lungs | 12.7 | 2.71 | <0.0001 |
| Cigarette smoker (ever) | 178 | 46.4 | 0.0002 |
| Age at death, yr | 7.84 | 1.79 | <0.0001 |
| Race (nonwhite) | 162 | 44.7 | <0.0004 |

* Weights for predicted value of emphysema index: 0–200, 201–300, 301–400, 401–500, and > 500, respectively, with number in parentheses (lowest two categories combined due to low n): $1.21 \times 10^{-4}$ (9), $2.45 \times 10^{-5}$ (32), $1.88 \times 10^{-5}$ (32), $2.83 \times 10^{-5}$ (23), and $1.60 \times 10^{-5}$ (24).

† N = 120 miners. $F = 23.1$ (4 df); $P < 0.0001$; $R^2 = 0.44$.

The sensitivity analyses based on the *a priori* data quality criteria for the work histories gave the same qualitative results as those in the full data (Table 3), including consistent significance and direction of the main effects and interaction terms. The quantitative results were also similar (i.e., changes in the coefficients were generally < 10 to 20%, including slight increases in the cumulative exposure coefficient), and the largest changes were 26 and 31% (i.e., decreases in pack-years and age at death coefficients, respectively, in subset 1).

*Post hoc* sensitivity analyses showed that the main findings are consistent across different subsets of the data and regression models. Nonminer status (indicator variable) did not contribute significant information ($P > 0.9$) to the prediction of emphysema severity reported in Table 3. Fitting separate models by smoking status (ever- or never-smoker) gave similar results for the effect of cumulative exposure, which decreased 6% among ever-smokers and increased 25% among never-smokers.

Sensitivity to the modeling of regression errors as being normally distributed was examined by fitting generalized linear models (GLMs) using the γ distribution (34) because histograms of the studentized residuals showed some evidence of positive skewness in the weighted least squares model (Tables 3 and 4). The GLM model analogous to Table 3 also departed from a γ distribution, whereas the GLM model analogous to Table 4 appeared similar to a γ distribution. The GLM model results were consistent with those of the weighted least squares models in that the significance and direction of the regression coefficients were preserved in all cases. Quantitative changes in the coefficients indicated some sensitivity to the assumed distribution (e.g., 25% increase in cumulative dust exposure and 25% decrease in coal dust lung burden coefficients and standard error increases of 29 and 63%, respectively).

## DISCUSSION

In this study, we show that cumulative exposure to respirable coal mine dust, cigarette smoking, age at death, and race are significant predictors of emphysema severity in a group of autopsied coal miners from the Unites States. Emphysema and other chronic obstructive lung diseases are associated with occupational and nonoccupational factors, including smoking,

outdoor and indoor air pollution, and workplace exposures (3, 17, 35). Coal mine dust as a cause of COPD including emphysema is now well established in the scientific literature (2–13, 16, 36). However, there is need for greater understanding of the roles of the various factors, including cigarette smoking and dust exposure, in causing pulmonary impairment. Better recognition of the key disease predictors may enhance opportunities for the primary prevention, diagnosis, and medical management of occupational dust-related lung diseases (1). This is the first study of autopsied coal miners from the United States to address these issues with high-quality pathology data from whole lung sections, detailed smoking histories, and work histories with sufficient detail to reconstruct cumulative coal mine dust exposures.

### Comparison to Previous Studies

Previously, Cockcroft and colleagues (8) found that emphysema was significantly more frequent in coal miners than in nonminers after accounting for age and smoking. Leigh and colleagues (10) observed a significant relationship between the coal dust lung burden, the amount smoked, and the age at death in a multiple linear regression model of emphysema severity in 264 deceased Australian coal miners. Among the 40 nonsmokers in their study, the effect of coal dust lung burden increased by 25%, and the model provided improved fit compared with the model with all miners. Naidoo and colleagues (11) reported that duration of coal dust exposure was a significant predictor of moderate/marked emphysema (defined as $\geqslant$ 35% lung tissue affected) among 725 South African coal miners after adjusting for smoking but not after adjusting for age at death.

Emphysema develops in coal miners in association with pneumoconiosis (9, 10, 21). Leigh and colleagues (36) found that emphysema severity was significantly higher among individuals with pneumoconiosis compared with those with minimal or no pneumoconiosis (36). Ruckley and colleagues (9) showed positive associations between coal dust lung burden and the presence of emphysema in miners at autopsy, which increased with the severity of pneumoconiosis but achieved significance only among those with progressive massive fibrosis. Consistent with Leigh and colleagues (10), silica dust lung burden was not a significant predictor of emphysema severity in our study. This may reflect the relatively low proportion of silica compared with total lung dust or the ability of coal dust to modulate the toxicity of quartz (37).

A relationship between emphysema and pneumoconiosis is also consistent with the pathological definition of simple coal workers' pneumoconiosis, which includes centriacinar (focal) emphysema as a component of the coal dust macule (18). As reported elsewhere (39), a majority of the miners in this study had some degree of pneumoconiosis at autopsy: 95% had at least mild simple macular coal workers' pneumoconiosis, 65% had micronodules (25% silicotic), and 23% had progressive massive fibrosis. Among miners with chest radiographic data (n = 428), 69% had small rounded opacity profusions of category 0/1 or greater. The extent of pneumoconiosis by chest radiograph was significantly but weakly correlated with the emphysema severity at autopsy in these miners (Spearman correlation coefficient, 0.29; $P < 0.0001$). Although pneumoconiosis and emphysema may develop in lungs with a sufficient dust burden, pathologically these are distinct disease processes. Pneumoconiosis involves the formation of fibrotic scar tissue in the lungs, whereas emphysema involves the destruction and loss of lung tissue (38, 40). Pneumoconiosis is associated primarily with a restrictive pattern of lung impairment, whereas emphysema is an obstructive lung disease. Epidemiological and clinical studies show that pneumoconiosis and emphysema may be expressed to different degrees in individual miners (5), often with a poor relationship between lung function and radiographic category (4). These distinctions are important for physicians to bear in mind when evaluating an individual miner.

### Strengths and Limitations

Several features of this study provided the opportunity to quantitatively assess the contributions of key predictors of emphysema severity. The pathological disease classification used is systematic, quantitative, sensitive, and specific. Sensitivity analyses of the regression models and data subsets show similar results to the main analyses and full data. The collection of the material and data in this study (1960s to early 1970s) occurred at a time when smoking was not a contentious issue and before Federal compensation programs were introduced (27). Smoking rates did not appear to change substantially (e.g., >70% ever-smokers among coal miners medically examined in the 1980s), and the workforce continues to be primarily male (16, 41). We consider our models and findings to be relevant to current miner populations.

Potential limitations of this study include possible selection bias of miners or nonminers in this study, unmeasured predictors of emphysema, or misclassification of dust exposure and/or smoking histories. Although autopsy data can be subject to selection bias, this is less likely in this study because of the systematic collection of lungs from consecutive autopsies of miners and nonminers (21, 24). Bias could have been introduced from an unknown (but presumably low) proportion of miners who were eligible for study but were not included (e.g., if relatives were less likely to agree to an autopsy if the deceased miner did not have respiratory problems). As expected with a chronic progressive disease, the distribution of emphysema severity in this autopsy population may be shifted toward higher disease severity compared with the distribution in a population of living individuals. The lower mean age of death in nonminers was due to a higher proportion of accidental or other sudden deaths compared with more chronic disease-related deaths in miners.

### Occupational and Nonoccupational Predictors of Emphysema

In this study, we have shown that coal mine dust exposure is a significant predictor of emphysema severity. Coal mine dust exposure and cigarette smoking had similar effects at the cohort average values. The estimated effect of race exceeded that of coal mine dust exposure or cigarette smoking when evaluated at the cohort mean values, with nonwhites predicted to have a higher emphysema index. We could find no differences in any exposure metric between the racial groups to explain this effect. Average ages at retirement and death were similar among white and nonwhite miners. The higher emphysema severity among nonwhites could be due in part to unmeasured factors associated with race. We dismissed misclassification in the cumulative exposure estimates as an explanation because of the significant effect of race in the coal dust lung burden model (Table 4). Our findings appear to be at variance with data from health and vital statistics from the United States that have long established higher prevalence rates (42) and attributable mortality (43) of COPD and emphysema in whites compared with African Americans (44). This discrepancy between the mortality statistics and our findings may be due to inaccuracies in cause of death reported on death certificates (45), including by race (46). Recent studies have reported that African Americans are more susceptible to the effects of tobacco smoke than whites, with adverse effects occurring at a younger age and with lower pack-years of smoking (44, 47). Our results suggest that this susceptibility may extend to an occupational dust.

The unexplained variability in prediction of emphysema in these models may be due in part to interindividual variability in response, including genetic susceptibility. One well-recognized genetic susceptibility factor for emphysema is $\alpha_1$-antitrypsin deficiency. Although homozygosity for $\alpha_1$-antitrypsin is relatively rare (1:2,000) in the general population, the heterozygous state is more common (1:50) and has been shown to be a risk factor for accelerated declines in lung function in nonsmokers and smokers exposed to dusts and fumes in the workplace (48).

The data in this study were collected on miners who worked in the mines before the enforcement of the Federal 2 mg/m$^3$ standard in 1972 (49). However, exposures at the current United States standard for a full working lifetime would produce a cumulative exposure similar to the mean for these miners. That is, miners working for 45 years (e.g., age 20–65 yr) at 2 mg/m$^3$ would experience a cumulative dust exposure of 90 mg/m$^3$ $\times$ years. Based on the weighted least squares regression in Table 3, this cumulative exposure would increase the average emphysema severity index by 99 points, providing additional evidence of the need to reduce exposures to respirable coal mine dust to 1 mg/m$^3$ or less, as recommended by NIOSH (27). Furthermore, miners in many developing countries may be faced with exposure levels in excess of those reported here. Thus, the effects of dust that we report are relevant to current conditions in many countries, including in the United States, where an increase in rapidly progressive pneumoconiosis has recently been observed (50).

As Dr. Rasmussen, a pulmonary physician in West Virginia, observed years ago before many current coal miners began their careers, "overemphasis on coal workers' pneumoconiosis *per se*, especially when related to roentgenographic findings, leads to too narrow a view of respiratory disease in coal miners" (2). This and other seminal studies have demonstrated the importance of medical evaluation of lung physiology and function, in addition to radiological changes, to ascertain the full risk of occupational lung diseases in coal miners and other dust-exposed workers (3–6). Prevention of work-related respiratory conditions is important because once the disease process has begun, workers are at risk of developing chronic disease even many years after exposure ceases (17). Primary prevention of dust-related COPD includes limiting exposures through effective standards, dust controls, and personal protective equipment; secondary measures include early diagnosis and management. Improving disease surveillance and awareness among health-care professionals about the occupational components of COPD including emphysema can increase the effective detection and management of these diseases.

## Conclusion

Cumulative coal mine dust exposure or coal dust lung burden, cigarette smoking, age at death, and race were statistically significant predictors of emphysema severity in this study of autopsied miners and nonminers in the United States. Coal dust exposure and cigarette smoking had similar additive effects on emphysema severity in these models at cohort average values. The role of dust exposure on emphysema severity in coal miners is relevant to regulatory decision-making and medical determinations.

***Conflict of Interest Statement***: E.D.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.W.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.J.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. V.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.H.Y.G. has provided expert medical opinion on autopsied coal miners relating to claims for Black Lung benefits; some of these cases had COPD in addition to pneumoconiosis. The amount earned for these reports has ranged from 8 to $11,000 per year for the past 3 years.

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