

Morbidity and Mortality among Underground Coal Miners

JUDITH MARIE-ANNA GRABER
B.S., UNIVERSITY OF WISCONSIN MADISON, 1981
M.S., UNIVERSITY OF ILLINOIS AT CHICAGO, 1991

THESIS

Submitted as partial fulfillment of the requirements
for the degree of
Doctor of Philosophy in Public Health Sciences (Epidemiology)
in the Graduate College of the
University of Illinois at Chicago, 2012

Defense Committee:

Leslie Stayner, Chair and Advisor
Robert Cohen
Lorraine Conroy
Richard Campbell
Michael Attfield, National Institute for Occupational Safety and Health

UMI Number: 3551418

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



UMI 3551418

Published by ProQuest LLC (2013). Copyright in the Dissertation held by the Author.

Microform Edition © ProQuest LLC.

All rights reserved. This work is protected against unauthorized copying under Title 17, United States Code



ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

DEDICATION

This work is dedicated to the coal miners who participated in the research projects in which these studies are based, and to those who continue to participate in public health research, surveillance, and prevention activities.

This work is also dedicated to my husband and son, Paul and Evan Kuehnert, without whose love, laughter, and support it would not have been possible. Evan, may you follow your passion and may your passion be your life's work.

ACKNOWLEDGMENTS

I would like to thank the members of my dissertation committee for their guidance and insights: Leslie T. Stayner, PhD, who set the bar high but never completely out of reach; Michael D. Attfield, PhD, for his attention to detail without losing sight of the larger issues; Robert A. Cohen, MD, FCCP, for his clinical and social insights regarding coal miners; Richard T. Campbell, PhD, for his statistical guidance; and Lorraine Conroy, PhD, for lending her expertise in exposure estimation. I would also like to thank Daniel Hryhorczuk, MD, MPH, for providing the early direction to conduct research on this important topic and support throughout.

Public health research is a collaborative endeavor, and innumerable people contributed to the completion of this thesis whose efforts I would like to acknowledge, including in Ukraine: Alexander Zvinchuk, MS, and coworkers at the University of Illinois at Chicago (UIC) Data Management Center in Kyiv for their dedication and close attention to detail; Angela Basanets, PhD, and Yuri Kundiev, MD, of the Institute of Occupational Health, Kyiv; Vladimir Mukhin, MD, of the Research Institute for Medico-Ecological Problems of Donbass and Coal Industry, Donetsk; and Olga Lysenko, MD, City Hospital No. 25. Donetsk.

In the United States, I would like to thank the many people in governmental agencies who helped with data access and linkage, including Janet Hale, National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC); Robert Bilgrad and Michelle Goodier, National Center for Health Statistics, CDC; Brenda South, Social Security Administration; George Niewiadomski, Mine Safety and Health Administration, Department of Labor (DOL); and Lorraine Lewis, United Mine Workers of America Health and Retirement Funds.

ACKNOWLEDGEMENTS (continued)

Finally, I gratefully acknowledge my fellow doctoral students – Caryn Peterson, MS, and Abigail Silva, MPH – who were never more than a phone call away and who helped me understand my strengths and work with my weaknesses.

The researchers and research conducted with the Study of Occupational Lung Disease in Ukrainian Coal Miners were supported, in part, by National Institutes of Health Research Grant #D43 TW00653 funded by the Fogarty International Center, National Institutes on Environmental Health Services, NIOSH, and the Agency for Toxic Substances and Disease Registry, NIOSH Grant #T42 CCT510424-8, the American International Health Alliance/USAID, and DOL.

The researchers and research conducted with the National Study of Coal Worker's Pneumoconiosis was supported in part by NIOSH training grant #T42/OH008672.

JMG

TABLE OF CONTENTS

<u>CHAPTER</u>	<u>PAGE</u>
I. PROJECT SUMMARY AND SPECIFIC AIMS	1
II. BACKGROUND AND SIGNIFICANCE	3
A. COAL-MINE DUST AND NONMALIGNANT RESPIRATORY DISEASE	3
1. COAL WORKERS' PNEUMOCONIOSIS	4
2. CHRONIC OBSTRUCTIVE PULMONARY DISEASE	8
B. COAL-MINE DUST EXPOSURE AND MORTALITY	10
1. MORTALITY FROM NONMALIGNANT RESPIRATORY DISEASE	10
2. MORTALITY FROM LUNG CANCER	13
C. SELECTION BIASES – THE HEALTHY WORKER EFFECT	16
1. HEALTHY WORKER EFFECT: DEFINITIONS	17
2. CONTROLLING FOR THE HEALTHY WORKER SURVIVOR EFFECT	19
a. CONTROLLING FOR THE HEALTHY WORKER SURVIVOR EFFECT BY ADJUSTING FOR WORK STATUS	20
b. CONDITIONING TIME-RELATED FACTORS	22
c. THE HEALTHY WORKER SURVIVOR EFFECT AS A CONFOUNDER AND/OR A MEDIATING FACTOR	27
3. WORK STATUS AND HEALTH OUTCOMES AMONG COAL MINERS	30
III. MORTALITY DUE TO NONMALIGNANT CAUSES AMONG U.S. COAL MINERS: RESULTS AFTER 37 YEARS OF FOLLOW-UP	35
A. INTRODUCTION	35
B. METHODS	37
1. STUDY COHORT	37
2. VITAL STATUS AND CAUSE OF DEATH DETERMINATION	37
3. COAL-RANK REGIONS	39
4. CUMULATIVE EXPOSURE ESTIMATES	39
5. TERMINATION OF EMPLOYMENT	40
6. MODIFIED LIFE TABLE ANALYSIS	40
7. COX PROPORTIONAL HAZARDS ANALYSIS	41
8. SENSITIVITY ANALYSIS	42
9. HUMAN SUBJECTS' PROTECTION	43
C. RESULTS	44
1. STUDY PARTICIPATION AND INCLUSION	44
2. DESCRIPTIVE STATISTICS	44
3. MODIFIED LIFE TABLE ANALYSIS	46
4. COX PROPORTIONAL HAZARDS ANALYSIS	49
a. CHRONIC OBSTRUCTIVE LUNG DISEASE	49
b. PNEUMOCONIOSIS	57
5. SENSITIVITY ANALYSIS	57

TABLE OF CONTENTS (CONTINUED)

<u>CHAPTER</u>	<u>PAGE</u>
D. DISCUSSION	62
1. CHRONIC OBSTRUCTIVE LUNG DISEASE	62
2. PNEUMOCONIOSIS.....	64
3. LIMITATIONS.....	65
E. CONCLUSION	66
 IV. MORTALITY DUE TO LUNG CANCER AND OTHER MALIGNANCIES AMONG U.S. COAL MINERS: RESULTS AFTER 37 YEARS OF FOLLOW-UP	 67
A. INTRODUCTION.....	67
B. METHODS	69
1. THE COHORT.....	69
2. STATISTICAL METHODS	70
3. SENSITIVITY ANALYSIS	73
4. HUMAN SUBJECTS' PROTECTION	74
C. RESULTS	74
1. STUDY PARTICIPATION AND DESCRIPTIVE STATISTICS.....	74
2. MODIFIED LIFE TABLE ANALYSIS.....	78
3. COX PROPORTIONAL HAZARDS ANALYSIS.....	79
a. LUNG CANCER	79
i. SENSITIVITY ANALYSIS – EXTENDED EXPOSURE ESTIMATES	81
ii. SENSITIVITY ANALYSIS – ROUND 4	81
iii. TIME-VARYING COVARIATES	89
b. OTHER CANCER SITES	93
D. DISCUSSION	95
1. LUNG CANCER	95
2. OTHER CANCERS.....	100
3. SENSITIVITY ANALYSIS	100
4. LIMITATIONS.....	101
E. CONCLUSION	101
 V. PREVALENCE AND PREDICTORS OF RESPIRATORY SYMPTOMS AMONG UKRAINIAN COAL MINERS	 102
A. INTRODUCTION.....	102
B. METHOD	104
1. THE COLLABORATION: GOALS AND APPROACH.....	104
2. STUDY LOCATION	104
3. STUDY DESIGN AND SAMPLING STRATEGY	105
4. DATA COLLECTION.....	106
5. DEFINITIONS OF SYMPTOM AND ILLNESS	106

TABLE OF CONTENTS (CONTINUED)

<u>CHAPTER</u>	<u>PAGE</u>
6. PREVALENCE OF RESPIRATORY SYMPTOMS AND SAMPLE WEIGHTS	107
7. MULTIVARIATE ANALYSIS OF PREVALENCE AND RISK FACTORS	108
8. EVALUATION OF REASON FOR LEAVING WORK	109
9. HUMAN SUBJECTS' PROTECTION	109
C. RESULTS	109
1. ACCOMPLISHMENTS AND LESSONS LEARNED FROM THE COLLABORATION	109
2. STUDY ENROLLMENT	110
3. PREVALENCE OF RESPIRATORY SYMPTOMS	110
4. MULTIVARIATE ANALYSIS OF PREVALENCE AND RISK FACTORS	115
5. REASON FOR LEAVING WORK	117
D. DISCUSSION	119
1. STUDY RESULTS: PREVALENCE OF RESPIRATORY SYMPTOMS	119
2. STUDY RESULTS: POTENTIAL SOURCES OF SELECTION BIAS	120
3. STUDY RESULTS: POTENTIAL SOURCES OF INFORMATION BIAS	122
4. STUDY RESULTS: OTHER FINDINGS	123
5. STUDY RESULTS: OTHER METHODOLOGICAL CONSIDERATIONS	124
VI. CONCLUSIONS	125
APPENDICES	128
APPENDIX I: HUMAN SUBJECTS APPROVAL: AIM 1 AND 2	129
APPENDIX II: HUMAN SUBJECTS APPROVAL: AIM 3	131
CITED LITERATURE	133
VITA	142

LIST OF TABLES

<u>TABLE</u>		<u>PAGE</u>
I.	CLASSIFICATION OF UNDERLYING AND CONTRIBUTING CAUSES OF DEATH BY INTERNATIONAL CLASSIFICATION OF DISEASES (ICD) VERSION FOR SELECT CAUSES OF DEATH	38
II.	DEMOGRAPHIC INFORMATION AT ENROLLMENT AMONG THE 8,829 COAL MINERS INCLUDED IN THE STUDY	45
III.	STANDARDIZED MORTALITY RATIOS (SMRs) FOR SELECTED UNDERLYING CAUSE OF MORTALITY AMONG DECEASED COAL MINERS	47
IV.	STRATIFIED STANDARDIZED MORTALITY RATIOS (SMRS) FOR SELECTED UNDERLYING CAUSES OF DEATH AND PERCENTAGE OF EVER SMOKERS, MEAN CUMULATIVE COAL-MINE DUST AND RESPIRABLE SILICA EXPOSURE CATEGORY BY COAL-RANK REGION, RADIOGRAPHIC STATUS AT ENROLLMENT, RACE, AND CALENDAR YEAR	48
V.	HAZARD RATIOS (HRs) FOR MORTALITY DUE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AS THE UNDERLYING CAUSE OF DEATH (309 DEATHS) ESTIMATED IN SINGLE- AND DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH	50
VI.	HAZARD RATIOS (HRs) FOR MORTALITY DUE TO CHRONIC AIRWAYS OBSTRUCTION (A SUBSET OF COPD) AS THE UNDERLYING CAUSE OF DEATH (293 DEATHS) ESTIMATED IN SINGLE- AND DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH	53
VII.	HAZARD RATIOS (HRs) FOR MORTALITY DUE TO CHRONIC BRONCHITIS AND EMPHYSEMA (A SUBSET OF COPD) AS THE UNDERLYING CAUSE OF DEATH (N=69 DEATHS) ESTIMATED IN SINGLE- AND DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH	55
VIII.	HAZARD RATIOS (HRs) FOR MORTALITY DUE TO CHRONIC OBSTRUCTIVE DISEASES AND THE COMPONENTS THEREOF, AS THE UNDERLYING CAUSE OR CONTRIBUTING CAUSES OF DEATH IN DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS, CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH, SMOKING STATUS AND PACK-YEARS SMOKED AT STUDY ENTRY, REGION, AND RACE	56
IX.	HAZARD RATIOS (HRs) FOR MORTALITY DUE TO PNEUMOCONIOSIS AS THE UNDERLYING CAUSE OF DEATH (403 DEATHS) ESTIMATED IN COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AND YEAR OF BIRTH	59

LIST OF TABLES (continued)

<u>TABLE</u>		<u>PAGE</u>
X.	RESULTS OF SENSITIVITY ANALYSIS AMONG COHORT MEMBERS WITH KNOWN TERMINATION OF EMPLOYMENT DATE (N=7,397) COMPARING ESTIMATED HAZARD RATIOS (HRs) FOR MORTALITY DUE TO PNEUMOCONIOSIS AS THE UNDERLYING CAUSE OF DEATH USING ORIGINAL AND EXTENDED CUMULATIVE DUST EXPOSURE ESTIMATES	61
XI.	DISTRIBUTION OF KEY CHARACTERISTICS FOR ALL DEATHS FROM ALL AND SELECTED MALIGNANT UNDERLYING CAUSES OF DEATH	76
XII.	STANDARDIZED MORTALITY RATIOS FOR ALL CAUSE AND MALIGNANT UNDERLYING CAUSES OF DEATH, WITH >25 OBSERVED DEATHS AMONG DECEASED COAL MINERS (N=5,907).....	77
XIII.	STANDARDIZED MORTALITY RATIOS FOR SELECTED UNDERLYING CAUSES OF DEATH AND PERCENTAGE OF EVER SMOKERS AT ENROLLMENT (AMONG THE DECEASED, N=5,907) BY REGION, RACE, RADIOGRAPHIC STATUS AT ENROLLMENT, AND CALENDAR YEAR OF DEATH	80
XIV.	HAZARD RATIOS FOR MORTALITY DUE TO LUNG CANCER MORTALITY (583 DEATHS) ESTIMATED IN COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH	83
XV.	RESULTS OF SENSITIVITY ANALYSIS AMONG MINERS WITH KNOWN LAST DATE OF EMPLOYMENT (N=7,397) COMPARING ESTIMATED HAZARD RATIOS (HRs) FOR LUNG CANCER MORTALITY (490 DEATHS) USING ORIGINAL AND EXTENDED EXPOSURE ESTIMATES	85
XVI.	DISTRIBUTION OF KEY CHARACTERISTICS FOR MINERS ORIGINALLY ENROLLED IN ROUND 1 AND INCLUDED IN THE ROUND 4 SENSITIVITY ANALYSIS (N=1,503)	87
XVII.	RESULTS OF SENSITIVITY ANALYSIS AMONG PARTICIPANTS ENROLLED IN ROUND 4 WITH A KNOWN LAST DATE OF EMPLOYMENT (N=1,503; 58 LUNG CANCER DEATHS) COMPARING ESTIMATED HAZARD RATIOS FOR MORTALITY DUE TO LUNG CANCER USING CMD ESTIMATES DEVELOPED FOR ROUND 4 AND EXTENDED CMD ESTIMATES DEVELOPED FOR ROUND 1	88
XVIII.	HAZARD RATIOS (HRs) FOR MORTALITY DUE TO LUNG CANCER AS THE UNDERLYING CAUSE OF DEATH, STRATIFYING ON CALENDAR TIME (FOLLOW-UP TIME), ESTIMATED IN SINGLE-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH IN MODELS	90

LIST OF TABLES (continued)

<u>TABLE</u>		<u>PAGE</u>
XIX.	HAZARD RATIOS FOR MORTALITY DUE TO LUNG CANCER AS THE UNDERLYING CAUSE OF DEATH STRATIFYING ON TIME SINCE FIRST EXPOSURE (TSFE), ESTIMATED IN SINGLE-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH	91
XX.	HAZARD RATIOS FOR MORTALITY DUE TO LUNG CANCER AS THE UNDERLYING CAUSE OF DEATH, CONTROLLING FOR AND STRATIFYING ON TIME SINCE LAST EXPOSURE (TSLE), AMONG THE 7,397 MINERS FOR WHOM TERMINATION OF EMPLOYMENT DATE WAS OBTAINED, ESTIMATED IN SINGLE-EXPOSURE COX PROPORTIONAL HAZARDS MODELS	92
XXI.	HAZARD RATIOS FOR MORTALITY DUE TO GASTRIC CANCER ESTIMATED IN A COX PROPORTIONAL HAZARDS MODEL CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH.....	93
XXII.	ESTIMATED HAZARD RATIOS FOR MORTALITY DUE TO MULTIPLE MYELOMA AS THE UNDERLYING CAUSE OF DEATH (N=28) AS ESTIMATED IN A COX PROPORTIONAL HAZARDS MODEL	94
XXIII.	COMPARISON OF SMOKING STATUS AND FREQUENCY BETWEEN MEN ENROLLED IN ROUND 1 OF THE NSCWP BETWEEN 1969 AND 1971, AND THAT OF THE GENERAL U.S. MALE POPULATION IN 1970, AS ESTIMATED BY THE NATIONAL HOUSEHOLD INTERVIEW SURVEY	99
XXIV.	CHARACTERISTICS OF MINERS WHO COMPLETED THE SURVEY BY EMPLOYMENT STATUS	112
XXV.	PREVALENCE OF RESPIRATORY SYMPTOMS OF CURRENT AND FORMER MINERS WITHIN LEVELS OF DEMOGRAPHIC, WORK, AND SMOKING CHARACTERISTICS.....	113
XXVI.	PREVALENCE RATIOS (PRs) FOR RESPIRATORY SYMPTOMS ESTIMATED FOR PREDICTOR VARIABLES IN BINOMIAL MULTIVARIATE MODELS AMONG FORMER UNDERGROUND UKRAINIAN COAL MINERS WITH AND WITHOUT A HISTORY OF WORK IN ANOTHER DUSTY INDUSTRY	116
XXVII.	THE EFFECT OF REASON FOR LEAVING WORK AS A COAL MINER ON THE EXPOSURE RESPONSE ASSOCIATION BETWEEN RESPIRATORY SYMPTOMS AND YEARS WORKING AS A COAL MINER AMONG FORMER MINERS AGED 65 AND YOUNGER WITH NO PREVIOUS WORK IN A DUSTY INDUSTRY (N=340)	118

LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BMI	Body mass index
BOM	U.S. Bureau of Mines
CDC	Centers for Disease Control and Prevention
CI	95% confidence interval
CMD	Coal-mine dust
COPD	Chronic obstructive pulmonary disease
CWP	Coal workers' pneumoconiosis
CWXSP	Coal Workers' X-ray Surveillance Program
CYP1A1	Cytochrome P450, family 1, subfamily A, polypeptide 1
DOL	Department of Labor (United States)
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
HHE	Healthy hire effect
HWE	Healthy worker effect
HR	Hazard ratio
HWSE	Healthy worker survivor effect
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
UICC	International Union Against Cancer
ILO	International Labor Organization
LTAS	NIOSH Life Table Analysis System
LRT	Likelihood ratio test
MSHA	Mine Safety and Health Administration
MSHAct	Federal Coal Mine Health and Safety Act of 1969
NDI	National Death Index
NIOSH	National Institute for Occupational Safety and Health
NMRD	Nonmalignant respiratory disease
NSCWP	National Study of Coal Workers' Pneumoconiosis
PEL	Permissible exposure limit
PFR	Pneumoconiosis Field Research (United Kingdom)
PFTs	Pulmonary function tests
PMF	Pulmonary massive fibrosis
POR	Prevalence odds ratio
OR	Odds ratio
RR	Relative risk
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
SMRs	Standardized mortality ratios
SSA	Social Security Administration
SSN	Social Security number
SRRs	Standardized rate ratios

LIST OF ABBREVIATIONS (continued)

SOB	Shortness of breath
TSFE	Time since last exposure
TSLE	Time since last exposure
UIC	University of Illinois at Chicago
UMWA Funds	United Mine Workers of America Health and Retirement Funds
USAID	United States Agency for International Development

SUMMARY

The goals of this research were to examine the contributions of coal-mine dust (CMD) and silica exposure to respiratory disease and mortality among underground coal miners in the United States and describe the prevalence of, and risk factors for, respiratory disease among Ukrainian coal miners.

In the U.S., vital status and cause of death were assessed among 9,033 miners after an average of 37 years of follow-up. Mortality was evaluated with life-table analysis; associations with dust exposures were examined using Cox proportional hazard regression. Among 5,925 deaths, excess mortality was seen for chronic obstructive pulmonary disease (standard mortality ratio [SMR] = 1.11; 95% confidence interval [CI] 0.99, 1.24), pneumoconiosis (SMR=77.68; 95% CI 70.24, 85.69), and lung cancer (SMR=1.08; 95% CI 1.00, 1.18). CMD exposure was a significant predictor of lung cancer mortality (hazard ratio (HR) for mean cumulative exposure (CMD 64.6 mg-year/m³) = 1.70; 95% CI 1.02, 2.83).

In Ukraine, a cross-sectional survey was conducted among a stratified random sample of working and former underground coal miners. Demographic, work, and health information were gathered using a standardized questionnaire. The weighted prevalence of respiratory symptoms was higher among former compared with current miners (shortness of breath: 35.6% vs. 5.1%; chronic bronchitis: 18.1% vs. 13.9%). A significant exposure-response relationship was seen with respiratory symptoms in former miners with years mining and among current miners with years working at the face.

Our findings expand upon previous results showing that work as a coal miner puts miners at increased risk for morbidity and mortality from respiratory disease as well as lung cancer, the latter in contrast with some previous studies. The findings on disease occurrence in Ukrainian miners are the first published in the Western literature. A healthy worker effect was seen in each of our studies, which may have downwardly biased our estimates of disease prevalence, relative mortality, and exposure-response associations with CMD and respirable silica.

I. PROJECT SUMMARY AND SPECIFIC AIMS

The deleterious effects of coal mining on respiratory health were described as early as the mid-17th-century. Since that time, occupational exposure to coal-mine dust (CMD) has been shown to cause a variety of nonmalignant respiratory diseases, including coal workers' pneumoconiosis (CWP) and the most insidious form, complicated CWP, also known as pulmonary massive fibrosis (PMF). Occupational exposure to CMD has also been causally associated with chronic obstructive pulmonary disease (COPD). A causal association with any malignant disease, including respiratory system cancers, has not been convincingly demonstrated.

While often hidden from the public's view, morbidity and mortality from coal mining remain important occupational health issues both in the United States and internationally. In the U.S., coal production has increased during the past decade (U.S. Department of Energy, [http://www.eia.doe.gov/oiaf/ieo/pdf/0484\(2009\).pdf](http://www.eia.doe.gov/oiaf/ieo/pdf/0484(2009).pdf), accessed 2/14/2010), as has the prevalence of CWP among U.S. coal miners (Antao et al. 2005; Laney and Attfield 2010). A number of factors may be contributing to this increase, including the mining of coal from thinner seams, which makes dust suppression more difficult and potentially increases exposure to silica dust, as well as the increasing length of work shifts and hours worked per week.

The overarching theme of this proposal is the estimation of respiratory morbidity and mortality rates among underground coal miners (henceforth referred to as "coal miners").

The analyses will be conducted using data from two sources: 1) The National Study of Coal Worker Pneumoconiosis (NSCWP), a prospective epidemiologic study in the United States, and 2) The Occupational Lung Disease in Ukrainian Coal Miners Study, a cross-sectional study of active and former miners in the Donetsk region of Ukraine.

The specific aims of this thesis were:

1. To examine the mortality experience from non-malignant respiratory diseases, including the contributions of CMD and respirable silica exposure, among underground coal miners of U.S. coal miners using an updated follow-up of the NSCWP.
2. To examine the mortality experience of U.S. coal miners from malignant diseases, including lung and stomach cancer, and the contributions of CMD and respirable silica exposure, using an updated follow-up of the NSCWP.
3. To examine and compare the prevalence of respiratory disease among active and former Ukrainian coal miners, and to assess the role of work status and reason for leaving work in the association between coal mine dust exposure and prevalence of respiratory symptoms.

II. BACKGROUND AND SIGNIFICANCE

A. Coal-Mine Dust and Nonmalignant Respiratory Disease

The causal relationship between occupational exposure to CMD and nonmalignant respiratory disease (NMRD) is well established including CWP and COPD (Cohen, Patel, and Green 2008; NIOSH, 1995). An extensive review of this topic was published in 1995 by NIOSH as part of the “Criteria for a Recommended Standard: Occupational Exposure to Respirable Coal-Mine Dust” (NIOSH, 1995). That document relied heavily on studies which used standardized methods of disease classification and had extensive exposure monitoring data that could be used to investigate relationships between cumulative CMD exposure and disease incidence, prevalence and/or mortality. This includes findings from large cohort studies of coal miners in the U.S. and U.K. as well as from U.S. surveillance data.

Results from both the British and U.S. cohorts are discussed and cited throughout the following literature review. To provide context for readers not familiar with these studies, the next few paragraphs give a brief summary of their methods.

The British Pneumoconiosis Field Research (PFR) project was a large prospective study established to study the health of British coal miners (Love and Miller 1982). Approximately 25,000 miners were enrolled from 24 British coal mines between 1953 and 1958; follow-up continued among 18,000 miners from 10 mines. The participation rate was about 90%.

Data collection for the PFR included regular health questionnaires, pulmonary function tests, and chest radiographs. Detailed exposure estimates of both respirable coal and quartz dust were based on a sampling of respirable CMD with static samplers under a sampling strategy designed to estimate exposure under a wide range of mining jobs and working conditions. Cumulative exposure estimates

were constructed for all participants based on detailed work histories at each visit. The exposure estimates are among the best available for mining studies to date.

Methods for the NSCWP (a prospective epidemiologic study in the United States) are described in detail in a later section of this proposal, since this is one of the primary studies that will be examined in this proposal (See section IV. A). In brief, the NSCWP included three cross sectional studies of U.S. coal miners from 1969 through 1981, known as Round 1, Round 2 and Round 3 (Attfield 1983). Men were recruited from mines selected to be representative of all U.S. coal fields in the continental U.S. A morbidity follow-up study was conducted from 1985 through 1989. This study, known as Round 4, enrolled current and former miners from Round 1 or Round 2 who were aged 58 or less at the time. The later restriction was intended to enroll men who were age-eligible for work. The methods for collection health status for the NSCWP were similar to those used by the PFR. Cumulative CMD exposure was estimated for each enrollee.

1. **Coal workers' pneumoconiosis**

CWP is the accumulation of CMD in miners' lungs and the resulting tissue's reaction to its presence (NIOSH. 1995). It is diagnosed in living miners by chest radiograph. Simple CWP is differentiated from PMF by the shape, size, profusion, and extent of opacities.

CWP is diagnosed when the findings are of small radiographic opacities of less than 10mm in diameter combined with a history of working as a coal mining for ten or more years. The profusion of small opacities is characterized into major categories 1, 2, or 3 which reflect increasing severity of

disease. PMF is diagnosed by the presence of large opacities; the finding of one or more opacity of greater than 10 mm is considered to be indicative of PMF. PMF is classified into categories of increasing severity labeled A, B, and C. PMF is a progressive disease and predictive of mortality (Cohen, Patel, and Green 2008; Wiener et al. 2004).

The mechanisms by which PMF develops from CWP are not fully understood. Hypothesized mechanisms include that: the dust clearance processes are unable to remove excessive dust loads; the presence of high levels of silica may intensify the disease process; and, that atypical reactions to *M. tuberculosis* may occur (Wiener et al. 2004).

Prospective studies in the U.S., the U.K. and Germany have all demonstrated a definitive positive exposure-response relationship between cumulative CMD exposure and risk of CWP and PMF (Miller and MacCalman 2010; Attfield and Kuempel 2008). The presence and stage of CWP as well as the progression of PMF have also been associated with the proportion of respirable silica in the CMD, coal rank, bioactivity of the CMD, individual immunological factors and tuberculosis (Ross and Murray 2004). Of note, silica levels tended to vary inversely with coal rank (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans and International Agency for Research on Cancer. 1997).

In the U.S., dust concentrations in coal mines have changed over time. Dust levels were likely highest after the introduction of mechanized mining techniques in the 1950's. Levels remained high until the Federal Coal Mine Health and Safety Act of 1969 (the MSHA Act). The MSHA Act codified CWP as a compensable disease of coal miners, enacted monitoring programs, and set a permissible exposure limit (PEL) of 3 mg/m³. The PEL was reduced to 2 mg/m³ in 1972, this remains the current standard despite a 1977 amendment to the Act. Based on the findings in the criteria document, in 1995 NIOSH recommend that the PEL be cut in half to 1 mg/m³; the current NIOSH recommended exposure level.

Before 1970, most underground miners were likely exposed to CMD at levels above the current PEL. Some jobs, particularly those working at the coal face were estimated to have been exposed to levels as high as 6 mg/m^3 . After the passage of the MSHAct, CMD levels have fallen as did the reported rate of CWP and PMF. There is however concern that the current system, whereby coal mine operators are primarily responsible for monitoring dust levels in their mines, may result in frequent exceedances of the PEL and underreporting of dust levels (Weeks 2003).

Studies of coal miners who began work after the passage of the MSHAct indicate that despite the PEL, not all miners are protected against lung disease. A study of 3,194 underground bituminous coal miners and ex-miners predicted that 1.4% (95% confidence interval (CI) 0.7, 2.7%) of miners working for 40 years at the current exposure limit of 2 mg/m^3 would develop PMF (Attfield and Seixas 1995). Higher prevalence was predicted for less severe categories of CWP. The exposure-response curve for CMD and CWP was similar in miners employed before and after 1970, indicating no change in the basic relationship as a function of decreased exposure levels. Whether ongoing disease under the current PEL is a function of the PEL being insufficient to protect all miners against lung disease or an issue of inadequate enforcement remains unclear.

In the U.S., prevalence of CWP is monitored by NIOSH's Coal Workers' X-ray Surveillance Program (CWXSP). A steady decline was observed in tenure-specific prevalence of CWP and PMF from 1970 until 1995 (CDC, 2003) in the CWXSP data. However, the prevalence began to increase in 1995, and this increase was accompanied by high rates of rapidly progressive CWP, PMF and silicosis (Antao et al. 2005; Laney and Attfield 2009). An investigation by Antao et. al. [2005] found that new cases of CWP were occurring among miners in the U.S. whose working life in coal mining had all occurred after the 2 mg/m^3 standard was enacted. They also looked at risk factors which predicted rapidly progressive CWP compared to classical CWP. They reported that risk factors associated with rapidly progressive CWP

included more time working at the coal face, younger age, and working at mines which employed 50 or fewer employees. Reasons for the increases may also include higher silica exposure due to mining of narrower coal seams and/or longer working shifts and days per week reducing miners' ability to adequately clear dust from their respiratory tract between shifts.

The risk of CWP and PMF increases with increasing coal rank. Coal rank is a classification of coal ranked according to the relative percentages of fixed carbon they contain, a result of geological alteration from the original plant materials to coal (coalification). The three major categories of coal rank from lowest to highest rank are lignite, bituminous and anthracite. The categories correspond to the physical characteristics of the coal including percent fixed carbon, volatile matter and heating value. In the U.S., coal rank varies geographically, with the highest rank found in the mines of Eastern Pennsylvania (i.e. anthracitic coal) with decreasing rank to the south and west. Studies from the NSCWP have consistently shown that a higher risk of CWP category 2 or greater and PMF is positively associated with mining higher rank coal (Suarthana et al. 2011; Antao et al. 2005). A recent study by found that the prevalence of CWP in seven coal mine regions correlated with levels of bioavailable iron and not with coal rank (Huang et al. 2005). However the findings, based on small numbers, were not statistically significant.

Findings from the PFR include that the risk of PMF increases with increasing severity of CWP at study enrollment (Hurley et al. 1987). Among British coal miners with CWP category 0, 1, 2, and 3, who worked from 1952 to 1977, the 5-year incidences of PMF were 0.2%, 4.4%, 12.5%, and 13.9%, respectively. Even though the prevalence of PMF was low among those with category 0 (no radiological evidence of CWP), this category included most of the miners and so it accounted for 20% of total cases of PMF observed in the study. The risk of PMF among miners with category 0 CWP increased with exposure to respirable CMD. An important limitation to this and other studies looking at progression of

disease is that chest X-rays may give false negative results regarding detection of early stages of CWP(Ruckley et al. 1984). Another limitation is that CWP is likely to be along the causal pathway to PMF; hence the risk of PMF may be underestimated if CWP is controlled for.

A number of studies in the U.S. and U.K. have developed predicted prevalences for both CWP and PMF. Estimates for exposure to the current PEL of CMD (2 mg/m³ during a 40-year work life) are between 7.0 and 8.9 cases of PMF and between 65 and 316 cases of CWP (category 1 or greater) per 1,000 coal miners by the age of 58. The ranges reflect the variation in risk by coal rank and other variations in the studied populations(NIOSH. 1995). Higher rates of CWP have been observed among former coal miners compared to current miners with the same years of mining experience.¹

2. **Chronic obstructive pulmonary disease**

COPD is a progressive disease characterized by chronic obstruction of the flow of air through the airways. People with COPD may have chronic bronchitis, airway obstruction, and/or emphysema(Wiener et al. 2004). For epidemiologic studies, chronic bronchitis is typically assessed by symptoms using a survey and/or medical examination, airway obstruction is typically measured by pulmonary function tests (PFTs), and emphysema is typically assessed by pathology.

Symptoms of COPD are a result of reduced lung function and include wheezing, cough with mucus, shortness of breath that worsens with mild activity, and frequent respiratory infections. Major risk factors include cigarette smoking and airborne occupational exposures (e.g., silica, CMD).

An exposure-response relationship between cumulative CMD exposure and chronic bronchitis has been demonstrated in cross sectional and longitudinal studies from the U.S. and the U.K.(Rae,

¹ This phenomenon has been observed consistently across studies and is discussed in more detail below; see section titled "Work status and health outcomes among coal miners"

Walker, and Attfield 1970; Kibelstis et al. 1973; Marine, Gurr, and Jacobsen 1988; Seixas et al. 1992; Henneberger and Attfield 1997). Exposure-response relationships between respirable CMD and deficits in lung function have also been observed in several cross-sectional and prospective cohort studies (Seixas et al. 1993; Attfield and Hodous 1992; Dimich-Ward and Bates 1994; Love and Miller 1982). Predicted declines in lung function during a working life at the current PEL are basically consistent across studies. For non-smokers, the number of cases of severe pulmonary function deficit (defined as <65% of predicted forced expiratory volume in one second (FEV₁) for men aged 58 who have worked as coal miners for 40 years is predicted to be between 16 and 63 per 1,000 population (Marine, Gurr, and Jacobsen 1988). Deficits in pulmonary function including FEV₁ and forced vital capacity (FVC) have been associated with cumulative CMD exposure even in the presence of normal radiographic findings (Attfield and Hodous 1992).

Longitudinal studies have shown that the relationship between the rate of decline of FEV₁ and CMD exposure is not linear. The greatest reduction in lung function occurs in the first few years of coal mining and the slope of the decline is less steep in subsequent years. A study of coal miners employed since 1970 from the second of the NSCWP cross-sectional studies found that rapid loss of lung function associated with cumulative exposure to respirable CMD occurred during the first five or fewer years of coal mining. The decline was similar both for FVC and FEV₁, about 30 milliliters for each milligram per meter cubed per year (mg/m³-year) of exposure. During the subsequent 10 to 14 years, while lung function declined for the group as a whole, with age, declines in FEV₁, or FVC were not associated with continued coal dust exposure (Seixas et al. 1993). A French study showed that the rate of decline in retired coal miners increased among smokers but slowed among miners who had never smoked (Dimich-Ward and Bates 1994).

Emphysema is also associated with exposure to CMD. The contribution of smoking and CMD exposure to emphysema has been investigated in a number of autopsy studies. Ruckley et al. (1984) reported that the prevalence of emphysema rose with increasing category of CWP and PMF. A study from Australia reported that among smokers the extent of emphysema was significantly associated with age as well as CMD content of the lungs (Leigh et al. 1994). A recent autopsy study in the U.S. specifically sought to investigate whether there was an effect of CMD exposure or lung burden of coal dust on emphysema in coal miners (Kuempel et al. 2009). The study included 722 individuals, 106 of which were non-coal miners from West Virginia and Vermont whom died during the same time period. They found that the mean emphysema severity index was significantly higher among miners compared with non-miners. The largest difference in severity was between miners and non-miners who never smoked. Among coal miners, emphysema severity was significantly elevated both among ever- and never-smokers ($p < 0.0001$). In weighted least-squares regression models, which adjusted for cigarette smoking, age at death, and race, cumulative exposure to respirable CMD and CMD retained in the lungs were significant predictors of emphysema severity ($p < 0.0001$). Cigarette smoking, age at death, and race were also significant predictors of emphysema in each of the models (p -value range 0.002 - < 0.0002).

B. **Coal-mine dust exposure and mortality**

1. **Mortality from nonmalignant respiratory disease**

Longitudinal studies in the United Kingdom (Miller and MacCalman 2010) and the U.S. (Attfield and Kuempel 2008) have reported excess mortality among coal miners compared to the general population from occupational respiratory diseases including PMF and chronic bronchitis or emphysema, as well as from accidental deaths. Higher mortality rates for NMRD were observed in

regions with higher coal rank. Cumulative exposure to CMD was associated with all non-violent causes of death and specifically with mortality from pneumoconiosis and chronic bronchitis and emphysema.

The most recent follow-up from the PFR was through 2006 and followed 17,820 coal miners with almost 11,000 confirmed deaths (Miller and MacCalman 2010). Standardized mortality ratios (SMRs) comparing observed mortality in the cohort were presented in 15-year intervals beginning in 1959; the reference population was males from the geographic area where the coal mines were located. In general, SMRs increased in later time periods for non-malignant respiratory disease. An analysis using Cox proportional hazards regression found a strong positive exposure-response relationship between both CMD and quartz exposure and pneumoconiosis mortality, with a 15-year lag providing an improved model fit. Smoking was not found to contribute to the model and was not included in the analysis of CWP. For COPD, chronic bronchitis alone and all NMRD excluding pneumoconiosis had the same positive relationship with CMD and quartz with a 15-year lag when including smoking as an independent predictor. For COPD, the effect was modified by smoking with a significant effect of exposure only within the non-smokers (relative risk for lagged dust exposure was 1.21)

The most recent mortality follow-up of the NSCWP was through December 31, 1993; 8,899 miners were followed and 3,213 deaths observed (Attfield and Kuempel 2008). The findings were similar to those from the U.K., but more subset analyses were presented. For the external analyses, comparisons were made with the U.S. male population. A statistically significant increase was seen for NMRD (SMR 1.95, CI 1.07- 2.14), with a threefold increase from pneumoconiosis and other respiratory diseases (SMR 3.08, CI 2.78-3.41). A positive trend was seen in SMRs for NMRD with increasing category of radiographic abnormality at baseline (SMR 1.52, 95% CI 1.35, 1.70 to 8.74 95% CI 6.88, 1.09). SMRs were also stratified by coal rank, as defined by geographic region. A statistically significant increase for

NMRD was seen ranging from 1.26 (95% CI 1.07, 1.46) in West Appalachia to 7.88 (95% CI 0.67, 0.92) in the Anthracite region of Western Pennsylvania.

Cumulative dust exposure was modeled both as a categorical and continuous variable in Cox proportional hazard models. In the analysis of the continuous exposure variable, a linear relationship was observed between NMRD and CMD exposure (relative risk (RR)=1.007 per mg-year/m³; 95% CI 1.0046, 1.0096). The effect was somewhat modified by smoking status, after controlling for age and coal rank, the HR in the never smoker subgroup was 1.013 per mg-year/m³ (95% CI 1.008, 1.0183). When modeling CMD as a continuous variable, significant positive relationships were seen between CMD exposure and pneumoconiosis (RR=1.009; 95% CI 1.005, 1.012) and with chronic airways obstruction (RR=1.008; 95% CI 1.003, 1.014). A significant association was not observed with bronchitis and/or emphysema as an underlying cause, but this was based on only 38 deaths.

Additional analyses were conducted for deaths from NMRD using underlying cause of mortality, which increased the number of deaths for all categories. Findings were similar for all outcomes. A total of 257 miners were reported to have chronic airways obstruction but not pneumoconiosis; for these men, a significant exposure-response relationship was observed with cumulative dust exposure (RR = 1.004, 95% confidence interval (95% CI) 1.001, 1.008). While there was some evidence of higher risk for chronic bronchitis/emphysema in the highest compared with the lowest exposure categories, no exposure-response relationship was observed. However, miners with a report of COPD as well as pneumoconiosis did show an increasing risk with increasing exposure category that was stronger than the trend for miners with pneumoconiosis alone.

Excess mortality among coal miners who had severe declines in lung function was observed in studies from the follow-up portion of the NSCWP (Round 4) as well as in a Dutch cohort study (Meijers, Swaen, and Slangen 1997; Beeckman et al. 2001; Sircar et al. 2007). A NSCWP study looked at 1,730 coal

miners who had performed two PFTs an average of 13 years apart and were followed for an additional 12 years(Sircar et al. 2007). Cox proportional hazard models were used to estimate the risk of death at three cut-off points for rate of decline 30, 60, and ≥ 90 ml/. Elevated hazard ratios (HRs) were found for the two highest categories (60 to ≥ 90 ml/year and ≥ 90 ml/year) compared with the referent category of < 30 ml/year (RR=1.39, CI 0.99 - 1.97, and RR=1.90, CI 1.32 - 2.76, respectively).

Findings from a study of mortality among a cohort of Dutch coal miners of whom 89% (n=3,367) had radiologic manifestations of CWP, included a significantly increased SMR for COPD of 2.12 (CI 1.74, 2.48) among miners with diminished lung function as measured by FEV₁, but no such excess was seen among men with normal lung function(Meijers, Swaen, and Slangen 1997).

2. **Mortality from lung cancer**

Lung cancer has been examined extensively in the coal-related epidemiologic literature. Most studies do not find a positive relationship. This finding is surprising since coal miners are exposed to a number of substances classified by the International Agency for Research on Cancer (IARC) as human lung carcinogens, including silica and radon(IARC Working Group on the Evaluation of Carcinogenic Risks to Humans and International Agency for Research on Cancer. 1997; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., International Agency for Research on Cancer., and National Cancer Institute (U.S.) 1988). In addition, an association between COPD and lung cancer has been observed in several studies(Sundar et al. 2011). Evidence suggests that chronic silica exposure causes COPD(Hnizdo and Vallyathan 2003). Excess lung cancer among coal miners, however, has generally not been observed in cohort studies. While most cohort studies published in the past four decades have shown a deficit in lung cancer in coal miners,(Atuhaire et al. 1986; Liddell 1973; Costello, Ortmeier, and Morgan 1974; Kuempel et al. 1995) there have been some notable exceptions(Enterline

1972; Rockette 1977; Une et al. 1995; Attfield and Kuempel 2008; Miller and MacCalman 2010; Goldman 1965). A small to moderate excess of lung cancer has also been reported in at least two population based case-control studies (Swanson, Lin, and Burns 1993; Morabia et al. 1992). One explanation regarding the lack of consistency of findings between studies is that coal miners cannot smoke cigarettes underground, which greatly reduces their exposure to the primary population risk factor for lung cancer. Whether the lack of an association between coal dust exposure and lung cancer is due to less frequent smoking or whether methodologic problems in study design and analysis might be masking an association is yet to be determined (Stayner and Graber 2011).

IARC conducted a comprehensive review of the data on coal dust carcinogenicity in 1997 and concluded that “coal dust cannot be classified as to its carcinogenicity to humans (Group 3).” The reviewers found that the evidence from occupational cohort studies for an association between CMD and lung cancer has not been consistent and that overall the evidence in both humans and animals was inadequate to determine carcinogenicity (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans and International Agency for Research on Cancer. 1997).

In 1955 James observed the apparent discrepancy between consistent reports of lung cancer associated with silicosis, but not with coal-related pneumoconiosis (James 1955). Among the epidemiologic studies in the 1970s and 1980s that compared cause-specific mortality rates among occupational groups to those of the general population using SMRs, most (Goldman 1965; Liddell 1973; Atuhaire et al. 1986; Costello, Ortmeyer, and Morgan 1974), but not all (Enterline 1972; Rockette 1977), found lower than expected rates of lung cancer mortality. Some of these studies, as well as autopsy studies (Mc 1949; Vallyathan et al. 1985; Rooke et al. 1979), have reported an inverse relationship between severity of pneumoconiosis and lung cancer occurrence.

The findings from the large cohort studies remain mixed. While initial findings from the NSCWP reported no association between cumulative CMD exposure and lung cancer mortality (Kuempel et al. 1995), the more recent follow-up was more nuanced (Attfield and Kuempel 2008). An excess of lung cancer was reported but it was predominantly among smokers and in miners with negative radiological results at baseline. They also reported a decreasing trend in lung cancer deaths with increasing category of pneumoconiosis, the SMR in category 0 was 1.13 (CI 1.01, 1.26) and was protective in categories 1 through 4 (SMRs 0.89 [n=23], 0.53 [n=6], 0.33 [n=1], and 0.69 [n=7], respectively). The authors speculate that this finding may indicate a failure to detect lung cancer in patients with CWP or possibly competing pathological pathways. An important limitation of this study in the evaluation of lung cancer mortality is the lack of exposure measurements for silica.

Results from the most recent follow-up of the PFR, found no overall excess death from lung cancer (SMR 0.99, CI 0.93- 1.05), SMRs did increase by decade of follow-up, as might be expected from a diminishing healthy worker hire effect (Miller and MacCalman 2010). However a statistically significant excess of lung cancer was observed in the most recent follow-up period (SMR 1.16, 95% CI 1.05, 1.28). Analyses of cumulative dust exposure controlling for smoking found an exposure -response relationship between cumulative silica dust and lung cancer, but no such relationship with CMD.

Two other large prospective studies also examined lung cancer in coal miners, one in Poland (Starzynski et al. 1996, 1995) and Japan (Une et al. 1995). The Polish cohort was comprised of coal miners from the National Register of Occupational Diseases diagnosed with CWP between 1970 and 1975. The cohort was followed through to the end of 1991 and was published in a series of papers (Starzynski et al. 1996, 1995). In 1995 they reported an elevated SMR for lung cancer compared to the general male Polish population (SMR 1.16, $P < 0.01$) (Starzynski et al. 1995). Based on a comparison between smoking prevalence in the cohort with that in the reference population, the authors concluded

that smoking was responsible for the excess of lung cancer deaths. A subsequent paper in 1996 reported no excess of lung cancer mortality either for the cohort as a whole or for categories of coal miners with varying levels of CWP(Starzynski et al. 1996).

Results from a retrospective Japanese cohort included an elevated but not statistically significant increased risk for lung cancer(Une et al. 1995). The authors used a mail survey in a former coal-mining area in Japan, to enroll 1,796 coal miners and 4,022 non-coal miners. Controlling for age and tobacco use, the relative risk for lung cancer was 1.6 (CI 0.8, 3.4). However among men who had worked 15 years or more as a coal miner the risk was two and a half times higher for miners compared to non-miners, and was statistically significant (RR 2.4, CI 1.1, 5.3). The response rate on the survey to enroll the cohort was 58%, suggesting selection factors may have biased the resulting estimates.

While counterintuitive, the hypothesis that CMD may play a role in preventing lung cancer is consistent with recent experimental evidence that exposure to CMD may inhibit the expression and activity of CYP1A1 (Cytochrome P450, family 1, subfamily A, polypeptide 1) in the lung(Ghanem et al. 2004). CYP1A1 is a gene involved in lung carcinogenesis by promoting the metabolic activation of aromatic hydrocarbons in cigarette smoke to reactive intermediates. This work raises the possibility that CMD might negatively modify the effect of tobacco smoke on lung cancer risk. To explore this hypothesis in humans will require studies of coal miners that include detailed measurements of smoking histories as well as history of exposure to CMD and silica.

C. **Selection biases – the healthy worker effect**

While there is extensive literature on the adverse effect of coal mining on miners' health, like most occupational epidemiology the results are generally limited by exposure measurement and the inability to account for well described risk factors and biases. The latter includes selection biases, most

notably the healthy worker effect (HWE), but also failure to account for competing exposures or factors which may be along the causal path. This section will focus on describing potential bias due to the HWE.

1. **Healthy worker effect: definitions**

The HWE is a term used to describe selection biases associated with employment status. The concepts of the HWE evolved from the observation that people who are hired and those who remain working are generally healthier than those who are not. The impact of selection and survival forces on occupational cohorts was first described in the literature by William Ogle in 1885. Ogle described two factors contributing to errors in the calculation of death rates for specific industries. In the timeline of employment, the first of these he described was: “some occupations may repel, while others attract, the unfit at the age of starting work, and, conversely some occupations may be of necessity recruited from men of supernormal physical condition” (Fox and Collier 1976). This phenomenon, that healthier individuals in a population are more likely than those less healthy to both seek and gain employment has been termed the healthy-hire effect (HHE) (Arrighi and Hertz-Picciotto 1994).

The other aspect of the HWE which Ogle described is now known as the HWSE and refers to the phenomenon of healthier individuals being more likely to remain in jobs, while those less healthy are more likely to either leave employment or move to a position with lower levels of exposure (Fox and Collier 1976).

The impact of the HWE is not uniform across study designs, demographic groups, health outcomes or types of work places (Checkoway, Pearce, and Kriebel 2004; Howe, Chiarelli, and Lindsay 1988). The HHE may be stronger among non-whites and older worker as well as among jobs requiring more physical labor.

Bias from the HHE is often evident when workers' health is compared to that of the general population, for example when indirect standardization (i.e. SMR analyses) is used for the analysis. In contrast, internal analysis, which compares workers to other workers by exposure level, adequately controls for this bias. Because the HHE is easily dealt with in analysis, this review will primarily be concerned with the HWSE.

The HWSE cannot be fully controlled by internal analysis because it accumulates throughout the duration of a working lifetime. Like the HHE, the bias from the HWSE tends to attenuate any relationship between exposure and disease. Even in the absence of an effect of cumulative exposure and disease a negative association between the two can be observed in occupational studies due to the HWSE (Steenland et al. 1996). So despite high cumulative exposure, long-term employees often comprise a uniquely healthy group of workers. Long term employment may have numerous beneficial effects including income, access to health insurance,² physical exercise, and social support (McMichael 1976; Checkoway, Pearce, and Kriebel 2004). Disease and mortality rates are usually lower among actively employed workers compared to those who are not working, a reflection of the HWE.

The HWSE may be stronger among non-fatal chronic-diseases such as COPD or musculo-skeletal injuries than among more rapidly fatal outcomes such as lung cancer. Cross-sectional studies conducted at work places are especially prone to the attenuation due to the HWSE as those most sensitive to the effects of exposure are disproportionately likely to transfer to a lower-exposure job or leave (Checkoway, Pearce, and Kriebel 2004).

Howe and his colleagues (1988) described components of the HWSE, including time since hire. The study used data from three Canadian occupational cohorts: atomic energy workers, uranium mine workers, and a 10% sample of all Canadian workers. Each cohort was linked with the Canadian Human

² This is a phenomena primarily in the US where health insurance coverage is closely linked to employment status.

Mortality Database to ascertain vital status, date of death and underlying cause of death for cohort members. The HWE was considered to be biasing study findings when SMRs declined with increasing follow-up time, as one would expect to observe for the HHE. Results for all-cause mortality indicated that the HWE was strongest in the study that followed employees since hire (i.e. nuclear energy industry) and was stronger among female workers. SMRs decreased with age in two of the cohorts; however, among atomic energy workers, the SMRs increased with age. For cause-specific mortality, the HWE was strongest for deaths from circulatory diseases and weakest for deaths from lung cancer. A sub-analysis of atomic energy workers found that those who left employment had higher all-cause mortality rates than those still employed. The authors hypothesized that differences among atomic energy and other workers may have been due to different selection factors. However, it is also possible that differences may have been due to the differential follow-up between the industries. Atomic energy workers were followed from first employment in the industry, while in the other studies they were not. The authors conclude that when possible, internal comparisons will reduce bias from the HWE, but such analyses should take into account time since hire and continued employment if those factors differ among the exposed and non-exposed cohort members.

2. Controlling for the healthy worker survivor effect

Many approaches have been proposed to control for the HWSE. Most apply traditional epidemiologic analytic techniques including controlling for work status (Gilbert and Marks 1979; Fox, Goldblatt, and Adelstein 1982; McMichael 1976; Howe, Chiarelli, and Lindsay 1988; Steenland and Stayner 1991), using an exposure lag, (Gilbert 1982) stratifying on time since-end-of work or for time since-first hire (Richardson et al. 2004; Arrighi and Hertz-Picciotto 1995), and stratifying (or restricting) by date of hire (Applebaum, Malloy, and Eisen 2007). Robins postulated that traditional epidemiologic

methods are not appropriate to control for the HWSE if it is acting as an intermediate variable (i.e. along the causal pathway)(Robins et al. 1992; Robins 1987). Steenland and coauthors have since empirically demonstrated this effect in occupational cohorts. Robins and colleagues have proposed a number of analytical techniques including G-estimation and structural nested models to get accurate measures of disease-response relationships under these conditions(Hernan, Brumback, and Robins 2000; Robins et al. 1992). Each of these approaches used for describing and controlling the HWSE is discussed in more detail below.

a. **Controlling for the healthy worker survivor effect by adjusting for work status**

Since work status is a key component of the HWSE, many proposed methods to control for the HWSE include using traditional epidemiologic methods to condition on this variable. In their seminal 1976 paper, Fox and Collier (1976) discussed the lack of satisfactory solutions to account for selection effects. The authors described the difficulties in measuring the HWSE that is “continuously altered by the dynamic movements within and out of the industry.” This dynamic is complicated because workers change jobs or leave the work force for a multitude of reasons, some unknown fraction of which is related to the workers’ health. They noted that in 1975 Enterline proposed the use of internal comparisons, a technique now accepted to be sufficient to address bias from the HHE but not from the HWSE.

Fox and Collier (1976) proposed stratifying by time since hire within age groups as well as restricting the analysis to workers with at least 15 years of exposure. They examined mortality rates among men who had worked in the vinyl chloride industry in England for a minimum of 15 years and found, as expected, that the SMRs among men who had left the industry were 50% higher than those who remained in the industry (SMR 1.08, CI 0.92, 1.26 vs. SMR 0.74, CI 0.58, 0.93, respectively). This

effect was observed in all age groups. However, the greatest differences between former and current workers were found among younger men. The SMR among men age 25-44 who were currently employed (SMR 0.49, CI 0.13, 1.28) was over two and half times smaller of that for past employees (SMR 1.81, CI 0.90, 3.26). Examining time since hire, SMRs increased with length of time in the industry. The greatest disease-specific difference reported was for lung cancer and respiratory disease. They concluded that mortality rates depend upon selection into the workforce, continued employment, the length of time studied, and the disease outcome.

In his 1976 discussion of the healthy worker effect, McMichael also noted the need to stratify by employment status. He described a process wherein younger workers who develop symptomatic disease from their working conditions will, if possible, leave for another working environment. He observed that while the survival advantage of work increases with length of employment (and hence age), this advantage disappears after termination of employment. Hence one sees the strongest survival effect in longer employed workers accompanied by higher rates of illness and death among those recently leaving work. McMichael's article was primarily about the need to be cautious regarding summary measures of association because the impact of the healthy worker effect differs between subgroups. Such subgroups include not only work-status but also age group, race, cause of death, and length of follow-up.

Gilbert and Marks proposed that in addition to controlling for the HWE by adjusting for work status, analyses should be restricted to workers with two or more years of exposure, and that employment should be lagged for 2 years (Gilbert and Marks 1979). They theorized that lagging (i.e. ignoring) the most recent exposures would control for the HWSE because the most recent exposures would be incurred among the healthiest employees, and would therefore eliminate the association between exposure and survival. In the case of the mortality study in the nuclear energy industry, the

authors proposed that “workers would have less potential for occupational exposure to radiation during the year or two before death than workers who survive.”

In a subsequent paper, Gilbert (1982) explored these approaches to controlling bias from the HWE as well as exploring other time-related variables including calendar year, length of employment, and date of initial hire. In contrast to most previous studies which used SMRs, she employed primarily internal comparisons using Mantel Haenszel techniques. Her results were consistent with previous findings that mortality increased in the years immediately following termination of employment. She restated the recommendation that lagging exposure would control for bias due to the HWSE in analysis of mortality studies because workers will likely cease employment for at least the year or two preceding death. While she recommended using a lag of at least two years, she also recommended considering using lags of different lengths of time for different diseases, for example, for chronic diseases and some malignancies which would manifest their symptoms over a longer period would require longer lag times.

b. Conditioning on time-related factors

Authors have proposed and debated the appropriateness of stratifying by many time-related factors, including using time since hire and time since termination of employment, to control for the different components of the HWE.

Flanders and colleagues (1993) proposed that controlling for time since hire using traditional epidemiologic methods eliminated the HWE in mortality studies. The authors suggested this approach to the extent that time since hire is correlated with both cumulative exposure and mortality. They noted the need to let enough time elapse to be able to observe any effects of exposure that would be both apparent and measurable. They therefore endorsed the previous approach used by Fox and Collier

[1976] of restricting the analysis to workers who had been employed for many years before the start of the follow-up period. They noted in their discussion that this approach would be applicable only to bias from the HHE.

Steenland and Stayner [1991] investigated the effects of employment status in 10 large cohort studies previously conducted by NIOSH. All of the studies included had negative findings, that is, SMRs were not elevated and no strong positive trends with duration of exposure for any major category of death were observed. The outcomes considered were all-cause mortality, mortality from all cancers and mortality from ischemic heart disease. Person-years were categorized as those accumulated while working in the study industry (active) or after termination of work in the industry (inactive), ignoring gaps in work. Findings for all causes of death included that SMRs among inactive workers were all protective, between 0.27 (CI 0.21, 0.34) and 0.61 (CI 0.51, 0.72) while those among active workers ranged from 0.91 (CI 0.84, 0.98) to 1.26 (CI 1.23, 1.30). Stratification of SMRs by year since employment ended showed that the highest SMRs occurred in the first two years immediately following termination of employment. The authors concluded that researchers should evaluate the effects of employment status when comparing results across cohorts or interpreting rate ratios within a given cohort. They also pointed out the need to carefully consider the potential for effect modification by time since first hired or time since first exposure on any exposure-disease relationship. In doing so, the authors were in part pointing to the intertwined nature of the relationship between the HHE and HWSE.

In a subsequent article, Steenland and colleagues (Steenland et al. 1996) used the same data set to further investigate how the potential for negative bias from the HWSE may impact estimates of exposure-response trends by work status. They noted that the observed mortality rates were higher for inactive workers because some of these workers left work due to illness. These workers therefore had lower cumulative exposure resulting in a higher percentage of inactive relative to active person time

among workers with lower cumulative exposure. The result is that employment status acted as a negative confounder of exposure-response trends. Steenland et al. showed that adjusting for time since hire without accounting for work status may result in a positive bias. They also showed that adjustment for employment status removes negative bias unless employment status is acting as an intermediate variable between cumulative exposure and death. Their findings included that when cumulative exposure was not associated with disease incidence, mortality, or leaving rates then employment status acted as a negative confounder of exposure-response trends, and, as expected, traditional adjustment eliminated the confounding. However, when cumulative exposure was associated with disease incidence, mortality, or rates of leaving, then adjustment for employment status was not sufficient to remove the bias. Hence, they concluded that traditional epidemiologic approaches that adjust for employment status will not remove bias from the HWSE when employment status is simultaneously a confounder and intermediate variable.

A study by Arrighi and Hertz- Picciotto (1995) further explored time-related factors and the HWSE. The authors reported that adjusting for time since hire and/or time since start of follow-up had little effect on the disease-exposure relationship. The study was conducted within two occupational cohorts for which death from respiratory tract cancer was the outcome of interest. The first was a cohort of copper smelter workers for which previous analysis had demonstrated a strong relationship between cumulative arsenic exposure and respiratory tract cancer. The second was a cohort of workers exposed to external ionizing radiation among which only a small adverse dose-response effect of exposure was found for lung cancer. In both of these cohorts there was substantial variability in time since first exposure and time since follow-up and both of these variables were independently associated with the outcome of interest. In modeling the dose-response relationships the addition of time since hire did not contribute significantly to the models which already controlled for age, calendar year and

work status, nor did it improve precision. In both cohorts there was some evidence of confounding by time since hire, with controlling for time since hire resulting in up to a 9% change in the effect estimate. However there was no evidence observed for confounding by time since start of follow-up. The authors attributed the lack of significant difference between models that did and didn't include time since hire and follow-up to the strong and linear correlation between these factors and age, which was tightly controlled in the models.

The above approaches all include controlling for or describing the effects of the HWSE by conditioning on work status and time-since end of employment, but noted the limitations of enrolling workers after exposure began, as is the case with many occupational mortality studies. In their study of lung cancer mortality Applebaum et al. (2007) applied a novel approach which addressed some of the previous limitations. In a prospective cohort of Vermont granite workers, the authors classified workers as either "incident" or "prevalent" hires. "Incident" hires described workers hired after follow-up began and "prevalent hires" described those hired before study enrollment. The authors treated this categorization of hiring as an effect modifier and analyzed incident and prevalent hires separately. The analysis of the incident cohort was limited by a considerable loss in power – only 56 (26%) of the 213 lung cancer cases developed in the incident group, which was also limited by a more restricted exposure range. Among incident hires, there was no difference in cases and non-cases by silica exposure status (0.3 mg-year/m^3), while among prevalent hires the mean was higher among non-cases compared with cases ($3.7 \text{ vs. } 2.9 \text{ mg-year/m}^3$, respectively). Despite these limitations they found that restricting the analysis to incident hires reduced bias assumed to be associated with the HWSE. Among prevalent hires the maximum mortality rate ratio was 1.97 (CI 1.52, 2.56) while among incident hires it was 2.19 (CI 1.27, 3.76). The authors reported that adjusting for work status did not change the overall estimate of cumulative exposure on lung cancer mortality.

Applebaum et al. also noted that a limitation of their study was that they did not have smoking information on the study participants. Smoking status can play a complex role in many occupational studies because while it is clearly causally related to many outcomes of interest and so can act as a positive confounder, it can also be causally related to termination of employment and in that capacity act as a negative confounder. Additionally, one can postulate that smoking may be a marker for lack of susceptibility to dusty conditions and so may also be independently associated with exposure. Unfortunately, the approach used by Applebaum et al. cannot be applied to occupational mortality studies which enroll subjects using cross-sectional sampling, such as the NSCWP.

Time since-termination of employment was also explored by Richardson et al(2004). The authors used both simulated and empirical data to evaluate whether temporal variations in mortality rates that occur following termination of employment are an aspect of the HWSE. They also assessed whether and how that variation is correlated with cumulative exposure. The analysis included a comparison of controlling for work status as a binary variable with controlling for time since-last worked as a categorical variable analyzed in 1 year increments (i.e. <1, 2, 3, ..., ≥ 10). They found, as expected, that workers with more active years tended to accumulate higher levels of exposure and also observed that cancer mortality rates were relatively low during the years of active employment. A positive association was observed between cumulative exposure and cancer in the post-employment period (relative rate per decade =1.56, CI 1.04 to 1.65) whereas only a weak association was seen during the period of active employment (relative rate per decade=1.05, CI 0.99- 1.11).

Using simulated data, Richardson et al. further demonstrated that controlling for time since-leaving work reduced bias in estimates of cumulative-exposure-mortality trends more effectively than the commonly-used method of adjusting for a binary indicator of employment status. The discussion noted that the results apply to the specific study conditions which included an incidence cohort and

assessed an outcome with relatively short survival time following diagnosis, such as lung cancer. These findings may not be generalizable when these specific conditions are not met. For example if the time between disease onset and mortality is extended, as is the case with NSCWP, then the authors hypothesize that controlling for a binary indicator of work status would have the same control on bias from the HWSE as controlling for time since termination of employment.

c. **The healthy worker survivor effect as a confounder and/or a mediating factor**

Mediator or intermediate effects refer to variables that are along the causal sequence between two other variables. Conditioning on a mediating factor, including treating a mediator as either a confounder or an effect modifier, in an analysis will introduce bias toward the null hypothesis (Weinberg 1993). Robins (1986) postulated that the HWSE may be both a confounder as well as a mediator (i.e. along the causal pathway). He pointed out that time since-leaving work may assert effects as either a confounder or mediating variable at any point in the follow-up period and as such is a time-varying factor. He described three possible impacts of employment status: 1) as an independent predictor of mortality, 2) as a predictor of subsequent exposure status, and 3) as being partially determined by previous exposure. He notes that when these three conditions are met, standard methods of analysis produce biased estimates whether or not employment status is adjusted for. Whether a factor such as employment status is acting as a confounder or intermediate variable cannot be empirically determined. Robins proposed the use of the g-null test, g-estimation and structural nested failure time to address this problem. These procedures adjust for the HWSE by tightly controlling for work status as a time-varying factor. He also demonstrated that they are robust even when unmeasured factors, such as smoking, are predictive of work status. All of these methods longitudinal

cohort data with information on exposure, health status and work status determined at repeated points (ideally six-month intervals) throughout duration of the study for all cohort members.

The G-null test is conducted using a nested case-control design with density sampling. Cases are additionally matched to non-cases by employment status and work history. At each observation point, exposure status of the case is compared to that of the control set using a log-rank-trend statistic.

The more powerful modified G-null test algorithm can be used if the probability of exposure is dependent only upon employment status and exposure history. The disadvantage of this method is that a measure of effect equivalent to that usually obtained from traditional epidemiologic analyses (e.g. a hazard ratio, (HR)) is not obtained, only a measure of statistical significance. However, a test for trend is produced and can give some indication of direction of the relationship (Arrighi and Hertz-Picciotto 1996). The advantages of the method include that it can control for both fixed and dynamic variables in matched analysis and that employment status is treated simultaneously as a confounder and an intermediate variable.

Structural nested failure time models differ from the models commonly used to explore exposure-outcome relationships in epidemiologic analysis in that they predict exposure status. Specifically they predict dichotomous exposure status at each observation time (ideally every six months throughout the duration of study follow-up), modeled as a function of past employment history, exposure history, other time-dependent variables and the time to observed death. The exposure-disease association is evaluated by a score test of the hypothesis that the coefficient for the observed death time as a predictor of the outcome is zero. Hence the approach is anchored on defining a counterfactual outcome (time to death if no exposure). The model results in an estimate of effect between the exposure and outcome (Hernan et al. 2005).

There are substantial challenges to applying Robin's methods, not the least of which is the conceptually challenging nature of the model. More concretely however, structural nested failure time models have not been successfully generalized to occupational cohorts, where some time periods and individuals may have no exposure for all or some time under observation. While g-estimation techniques can be applied to occupational cohorts, Steenland and colleagues (1996) point out, one of the limitations of these methods is that they are not robust when all workers have been exposed when follow-up begins, which is so often the case in occupational cohort studies.

In a study published in 1994 which did have ideal data for Robin's methods, Arrighi and Hertz-Picciotto (1994) compared four methods for controlling the HWSE:

- i. Restricting the analysis to survivors of 10, 15, and 20 years,
- ii. Lagging exposure by 10, 15, and 20 years
- iii. Controlling for a work status in Poisson regression models (where the observation unit is person time), and
- iv. Using both the G-null test and modified g-null test procedures.

The analysis was conducted in the aforementioned cohort of copper smelter workers in Tacoma, Washington. The study considered the potential impact of the HWSE on the shape and magnitude of the observed non-linear relationship between arsenic exposure and respiratory cancer mortality. Their findings for the four analyses were:

- i. Rate ratios did not differ among groups restricted to 10 and 15 year survivors. Rates were higher among 20 year survivors but they were unstable due to the loss of person years (a 53% reduction) and cases (a 16% reduction).
- ii. The 10 and 15-year lag increased rate ratios at all exposure levels.

- iii. Adjustment for employment status increased the rate ratios and did not alter the shape of the exposure-response curve.
- iv. Both the G-null and the modified g-null test procedures resulted in significant chi squared tests and tests for trend.

In their discussion, the authors noted the importance of not equating time-working-with-no exposure with time-off work, as the latter may be a function of health and/or exposure status. They also noted that this distinction is made by only two of the four methods used, controlling for work status and the G-null approach. As well, they observed that the shape of the exposure-response curve was similar for all analyses and concluded that the HWSE was not responsible for the non-linear shape of the curve. This observation was further explored and confirmed in a more in depth study of the impact of the HWSE on the shape and magnitude of the exposure-response curve.

3. **Work status and health outcomes among coal miners**

Work status has been explored in a number of studies of coal miners, including the NSCWP(Petersen and Attfield 1981; Henneberger and Attfield 1996) and the PFR(Soutar and Hurley 1986) as well as a small study conducted among coal miners in South Africa(Naidoo et al. 2005). As expected, these studies have found higher rates of symptoms and disease among former miners compared with current miners, consistent with a HWSE.

A study from the PFR examined the relationship between cumulative CMD exposure and lung function among 1,867 current and 2,192 former miners after approximately 22 years of follow-up(Soutar and Hurley 1986). Occupational histories were used to determine job status. Former miners were classified based on reason for having left coal mining as either retired, left to take another job, or “made redundant”, i.e. involuntary termination of employment. Concerning former miners, the authors

reported that both younger (age ≤ 64) and older former miners had poorer average lung function than currently working miners. As well, former miners had a different response to CMD than those who remained in the industry. While dust exposure was associated with reduced lung-function levels among all miners with chronic bronchitis, this finding was most severe among former miners aged 65 and under. This effect was particularly high among the small group of ex-miners (age 65 and under with chronic bronchitis) who had taken other jobs. The authors noted that these findings may still be biased by the HWSE since men were excluded if they had less than ten years mining experience, had PMF, were lost-to follow-up or had died (34% by the time of the follow-up).

Studies exploring health status of former compared to current miners have also been conducted within the NSCWP. The first was an early descriptive study exploring potential biases in the NSCWP among men who enrolled in both the first and second rounds of that study (Petersen and Attfield 1981). Three groups were studied: 1) participants from the first rounds ($n=4,360$), 2) those who left mining after round 1, called leavers ($n=2,039$), and, 3) those who were eligible but did not participate in the second round, called non-participants ($n=972$). Higher rates of PMF were found among leavers compared to the other two groups ($P<0.01$). However similar rates of simple CWP were found among leavers and non-leavers. Interestingly, rates of simple CWP were lowest among non-participants ($P<0.01$). Higher prevalence of disease symptoms were observed among leavers than non-leavers. As well, for each lung function characteristic analyzed, leavers showed more decline with years of exposure than repeaters. The authors also reported that men with lower levels of education at baseline may be more likely to leave work due to health status than men with more education. A limitation of this study was that it was conducted before cumulative CMD exposure had been estimated for the NSCWP participants.

A later study from the NSCWP investigated the prevalence of respiratory symptoms and lung function outcomes in 1,866 coal miners who had been enrolled in the follow-up study in 1985 (Henneberger and Attfield 1996). The study goal was to investigate whether respiratory symptoms were associated with lowered CMD levels mandated by the 1969 U.S. Coal Mine Health and Safety Act. The authors reported that almost half (48.1%) the men enrolled in Round 1 had left mining by the follow-up study. Regarding pulmonary function, decline in FEV₁ was principally associated with exposures occurring before 1969. Logistic regression models were used to assess the relationship between cumulative CMD exposure and respiratory symptoms controlling for smoking status and age. Findings included that termination of mining employment by 1985 was associated with increased risk of chronic bronchitis, shortness of breath and wheezing (odds ratio (OR)= 1.6, CI 1.3-1.9; for chronic bronchitis and shortness of breath; OR= 1.7, CI 1.4-2.1 for wheezing). A previous analysis of the follow-up data found a decline in FEV₁ of 60ml associated with leaving mining.

A similar analysis of 3,194 miners and ex-miners enrolled in the NSCWP follow-up examined radiographic evidence of CWP (Attfield and Seixas 1995). Only men who were age-eligible for work (defined as age 58 or less) qualified for enrollment. A total of 3,280 men were enrolled, of which 53% were currently employed as miners, 33% had left mining for work-related reasons (mostly laid off) and 14% had left for health-related reasons. The prevalence of CWP was found to be higher among the 456 men who reported that they had left mining for health reasons than in the other two groups. While the primary goal of the study was to estimate prevalence of PMF and simple CWP among men exposed to the PEL for a working life, the authors did graphically present CWP prevalence by work status, these were: ~21% among current miners; ~24% among miners who had left mining for job related reasons; and, ~39% among miners who had left mining for health-related reasons. The authors noted the need to consider ex-miners in studies of occupational disease prevalence and incidence.

Other studies of coal miners conducted in the U.S. and Europe have examined various aspects of the HWE. Petsonk et al. (1995) examined the potential bias introduced by self-selection over time and whether data on airway hyperresponsiveness could improve accuracy in estimating occupational risks. Between May 1985 and July 1987 miners were recruited from three large central Appalachian underground bituminous coal mines. Non-mining subjects were recruited from nine employers in the same region with no recognized current adverse respiratory exposures. They reported that compared with miners who had never worked at the coal face miners with the longest duration of work at the face had a low prevalence of methacholine responsiveness, (39% v 12% $P < 0.01$). They also reported that miners who responded to methacholine were consistently less likely to have worked in dusty jobs than non-responders. The authors conclude that their results provide evidence for health related job selection among coal miners. They conclude that studies of workers in dusty jobs may underestimate the effects of dust exposure on respiratory health. While air responsiveness data may help clarify these effects, due to the expense and technical expertise required, these data are rarely collected in such studies.

A study by Wang et al. (1999) looked at factors beyond occupational exposure which may predict clinically relevant loss in pulmonary function in a cohort of coal miners in Jiangsu province, China. The study was conducted with 264 coal miners whose lung function had been followed up for an average of 11 years and was compared to that of a smaller group who were student miners at baseline. At baseline, the average age of the miners was 21 (range 16 to 35), compared to 17 for the students. The authors reported that excessive declines in FEV_1 were associated with specific work tasks including roof bolting and exposures including exposure to explosive blasting, and to spraying water (for dust control) that had been stored in holding tanks. Non-work related factors found to be significantly associated with declines in pulmonary function included smoking, weight gain, body mass, history of

childhood pneumonia, and childhood exposure in the home to passive tobacco smoke. No longer working as a miner was also associated with excessive decline in FEV₁.

In another of the few studies of coal mining and work status conducted outside of the U.S. and Western Europe, Naidoo et. (2006) examined the relationship between CMD exposure and respiratory health outcomes by work status in a study of South African coal miners. They recruited current (n = 684) and former (n = 212) coal miners from three bituminous mines in Mpumalanga province, South Africa. The mines were selected in part because of the availability of reliable historical environmental monitoring data. Participants were drawn from a sampling frame of current and former miners constructed from mining records and from information on former miners collected by field workers from the communities surrounding the mines. Detailed work and smoking histories were collected as well as respiratory symptoms and job histories were supplemented by a review of mine records. All participants underwent pulmonary function testing conducted according to the American Thoracic Society (ATS) criteria (Standards of spirometry 1979). The prediction equations used were based on a population of South African non-smoking males. Cumulative exposure was estimated using historical monitoring data as well as additional sampling conducted by the research team in each mine. Exposure matrices were derived for specific zones (e.g. face) within each mine. All symptoms, as well as physician diagnosed acute bronchitis and asthma, were more frequent among former than current miners (5.4% vs 1.4% for chronic bronchitis; 6.3% vs 1.2% for asthma). There were no differences for chronic bronchitis or emphysema. While among current miners there was no association between symptoms and lung function, among former miners the presence of symptoms was significantly associated with lower mean FEV₁. Logistic regression models including an interaction term for employment status showed that former miners had consistently higher rates of symptoms compared to current miners (p<0.0005, ORs were not presented). Also among the findings was that former miners had on average

worked fewer years as coalminers and were more likely to be smokers than current miners. In a related paper, the authors reported that in a model controlling for smoking status and pack-years and TB status, former miners had lower mean percent predicted lung function than currently working miners, and this was found for each level of cumulative CMD exposure. The authors noted that the degree to which the enrolled former miners were representative of the population of former miners is unknown.

III. MORTALITY DUE TO NONMALIGNANT OUTCOMES AMONG U.S. COAL MINERS: RESULTS

AFTER 37 YEARS OF FOLLOW-UP

A. Introduction

Mortality from nonmalignant respiratory diseases (NMRDs) remains an important occupational hazard among coal miners. Dozens of publications have reported an association between coal-mine dust (CMD) exposure and NMRD-related mortality. Until the 1990s, these studies typically examined standardized mortality ratios by occupation, work tenure, and health status, finding excess all-cause mortality as well as mortality due to NMRD – the latter largely driven by coal workers' pneumoconiosis (CWP). Excess mortality from CWP was often associated with proxies for cumulative dust exposure, including mining tenure and radiographic evidence of CWP and complicated CWP (also known as progressive massive fibrosis, or PMF).

The causal relationship between occupational exposure to CMD and NMRD-associated mortality is now well established, including that from CWP and chronic obstructive pulmonary disease (COPD) [Cohen, et al. 2008; NIOSH 1995; NIOSH 2011]. The first research program that included estimates of cumulative CMD exposure was the British Pneumoconiosis Field Research (PFR) project. Workers were recruited from 24 British coal mines between 1953 and 1958 [Miller and Jacobsen 1985]. Follow-up has continued among 18,000 miners from 10 mines. In the latest mortality follow-up, evidence of an association between increased risks of pneumoconiosis and COPD with exposure to coal dust and respirable quartz dust were observed in internal analysis [Miller and MacCalman 2010].

In the U.S., enrollment in a similar study, the National Study of Coal Workers' Pneumoconiosis (NSCWP), began in 1969. The most recent mortality follow-up conducted after an average of 23 years

found statistically significant relationships between cumulative exposure to CMD (before 1969) and mortality from pneumoconiosis and COPD after controlling for age, smoking, and coal rank. A relationship was also observed between increasing coal rank (as determined by geographic region) and mortality from pneumoconiosis [Attfield and Kuempel 2008].

During the past decade, coal production has increased in the U.S. with the demand for energy [U.S. Department of Energy, <http://www.eia.doe.gov/oiaf/ieo/pdf/0484.pdf> (2009), accessed 2/14/2010]. After years of decline, the prevalence of CWP among U.S. coal miners has increased since 1995 [Antao, et al. 2005; Laney and Attfield 2010] despite the institution of mandated dust-control levels in 1969 with the passage of the Federal Coal Mine Safety and Health Act (MSHAAct).

The current study is a further follow-up of the NSCWP, extended to an average of 37 years. For the first time in this cohort, cumulative silica exposure was estimated and used to explore NMRD mortality. Also, for a large portion of the cohort, employment termination date was obtained and used to estimate exposures after the initiation of the study in 1969. The larger number of deaths allows for both the confirmation of previous findings as well as the exploration of outcomes and analyses previously limited by small numbers.

B. Methods

1. Study cohort

Between 1969 and 1971, 9,078 working underground coal miners were enrolled from 31 mines selected to be representative of major U.S. coalfields [Attfield and Castellan 1992]. Detailed information on respiratory symptoms, work history, smoking history, and demographics were collected using a standardized questionnaire. Participants received full-format posterior-anterior chest

radiographs taken in accordance with the International Labour Organization criteria, and pulmonary function tests in accordance with the American Thoracic Society guidelines. The readings were made using The International Union Against Cancer (UICC)/Cincinnati classification of pneumoconiosis [Bohlig H 1970] and tabulated by major category (0–3) of small opacities of simple CWP or PMF.

2. Vital status and cause of death determination

The cohort was followed up to December 31, 2007. Records of the 5,636 participants alive at the end of the previous follow-up (through December 31, 1993) were submitted to the Social Security Administration to determine vital status. Of these, 3,081 records identified as deceased or with unknown vital status were submitted to the National Death Index (NDI) to confirm vital status and obtain cause of death. NDI conducted a probabilistic linkage based on subject's last name, first name, middle initial, Social Security number, birth year, birth month, and birth day, and assigned each study record a score of 1 through 5 (1 indicated a true match and 5 a non-match). Manual review of records coded with a score other than 1 or 5 was conducted by a coauthor (MDA) to determine their acceptability as matches.

Cause of death was assigned using the NIOSH Life Table Analysis System (LTAS) mortality program using either the 8th, 9th, or 10th revision of the International Classification of Diseases (ICD) depending on the date of the miner's death as recorded on the death certificate (see Table I for ICD code mapping) [Schubauer-Berigan, et al. 2011]. For all analyses, pneumoconioses included deaths categorized as "other pneumoconiosis" (n=399) and "silicosis" (n=4) by LTAS.

TABLE I
 CLASSIFICATION OF UNDERLYING AND CONTRIBUTING CAUSES OF DEATH BY INTERNATIONAL
 CLASSIFICATION OF DISEASES (ICD) VERSION FOR SELECT CAUSES OF DEATH

Cause of Death	8th Revision 1968–1978	9th Revision 1979–1998	10th Revision 1999–Present
Pneumoconioses	515.1, 515.9, 516.0	500, 503, 505	J60, J63-J64
Chronic obstructive pulmonary disease (COPD)	490-492, 519.3	490-492, 496	J40-J44
Chronic airways obstruction (COA)	519.3	496	J44.9
Chronic bronchitis or emphysema (CBE)	490-492	490-492	J40, J41, J42, J43
Other respiratory diseases	500-514, 516.1-516.2, 517-519.2, 519.4-519.9	470-478, 494-495, 504, 506-519	J30-J33, J34.1-J34.8, J35-J39, J47, J66- J95, J98-J99, R09.1
Ischemic heart disease	410-414	410-414, 429.2	I20-I22, I24-I25, I51.3, I51.6
Cerebrovascular disease	430-438	430-438	G45.0-G45.2, G45.4- G45.9, I60-I69
Conductive heart disorders	427.2-427.9	426-427	I44-I49, R00.1, R00.8

3. **Coal-rank regions**

Coal rank is a measure of the percentage of fixed carbon in the coal. Higher rank coal is older and denser and has a greater propensity to cause pneumoconiosis compared with lower rank coal [NIOSH. 1995]. The highest coal rank is anthracite, which, in the U.S., is found almost exclusively in Eastern Pennsylvania. As with previous analyses of this cohort, regions were defined in descending order of coal rank as follows: Eastern Pennsylvania, Eastern Appalachia (Central Pennsylvania and Eastern West Virginia), Western Appalachia (Western Pennsylvania, rest of West Virginia, Eastern Ohio, Western Virginia, Eastern Kentucky, Tennessee, and Alabama), Midwest (Western Kentucky, Illinois, and Indiana), and West (Colorado and Utah).

4. **Cumulative exposure estimates**

Cumulative exposure to respirable CMD was estimated for each individual for all coal-mining jobs through study enrollment (1969–1971), as described previously by Attfield and Moring [1992]. Briefly, detailed job histories were obtained through the questionnaire. Job-specific exposure estimates were derived using one of two data sources: (1) U.S. Bureau of Mines (BOM) sampling data including approximately 4,300 gravimetric samples of airborne respirable dust obtained between 1968 and 1969 from 29 underground coal mines (17 were included in NSCWP), and (2) mine operators' samples collected from 1970 through 1972. A ratio of the BOM/Mine Safety and Health Administration (MSHA) estimates was derived using data for jobs having both sets of information. The common ratio was then applied to all of the MSHA job means to give adjusted means for the pre-1970 period. Individual cumulative exposures were estimated by multiplying the exposure intensity assigned to each job category by the duration of employment in that job, and these products were summed over all jobs for each miner.

Estimates of respirable quartz dust exposure were constructed using MSHA compliance data from 1982–2002. Mean percent silica was estimated for each Lainhart job grouping [Lainhart 1969] for underground (face, transportation, maintenance, and miscellaneous activities) and surface (transportation, maintenance, tibble, strip mining, and miscellaneous activities) mining jobs within each of the coal-rank regions. Job-specific silica estimates were calculated by multiplying the region and job category-specific estimates of percent respirable silica by the mean CMD estimate for each job within the respective job grouping and region. The individual cumulative silica exposure estimate was then calculated by multiplying the number of years at each job by the corresponding job-specific silica exposure estimate for each miner, and summing those products.

5. **Termination of employment**

Date of last employment as a coal miner was sought for cohort members from two sources: the United Mine Workers of America Health and Retirement Funds (UMWA Funds) and the Department of Labor (DOL), Office of Workers' Compensation Programs, which administers the Black Lung Benefits Act. Individual data-sharing agreements were established between both agencies and NIOSH that stipulated conditions for maintaining data security and confidentiality of research participants. Deterministic linkages were conducted by based on Social Security number and name. When conflicting dates were provided, the DOL date was used, as it was believed to be more reliable. Termination dates within one year of death were recoded to date of death; those greater than one year after death were considered missing and excluded from any analysis using this variable.

6. **Modified life table analysis**

Analyses of underlying causes of death were conducted using the LTAS program [Schubauer-Berigan, et al. 2011]. Person-days were calculated from the date of enrollment (1969–1971)

until date of death or end of follow-up (December 31, 2007), whichever occurred first. Expected deaths for each cause of death were calculated by applying the age-, race-, and calendar year-specific mortality rates for all males in the U.S. population to the person-years in each corresponding exposure stratum of the study population. SMRs were calculated as the ratio of the observed and the expected numbers of deaths for selected underlying causes of death. SMRs were stratified by coal-rank region, race, chest X-ray status at study enrollment, and calendar year for death due to all nonviolent causes, pneumoconioses, COPD, and conductive heart disorder.

7. **Cox proportional hazards analysis**

The associations between CMD and respirable silica exposure with selected underlying, as well as underlying and contributing, causes of death were explored using Cox proportional hazards regression models. Causes of death examined included pneumoconiosis and COPD. Additionally, the two major components of COPD, chronic airways obstruction (CAO) and chronic bronchitis and/or emphysema (CBE), were modeled as separate outcomes. The time dimension used in these models was follow-up time (i.e., time from study enrollment until date of death or censoring). All models included age at enrollment and birth year. Smoking status and pack-years, coal-rank region, race, year of birth, and calendar year were also investigated as risk factors and potential effect modifiers of the associations with the two exposures. CMD and silica exposures were analyzed in separate models (i.e., single-exposure models) as well as in the same model (i.e., dual-exposure model).

Alternative parameterizations of the continuous exposure variables (e.g. log-linear, log transformed and the addition of a quadratic term) were evaluated for the best model fit of the exposure-response relationships using the likelihood ratio test (LRT) while including all potential covariates in the model. Exposures were also analyzed as categorical variables constructed by grouping the data into quartiles among the deceased. Categorical covariates were entered into the models using

the following indicator variables, where the last level listed was the reference group: smoking (ever, former, or never); coal-rank region (Eastern Pennsylvania, Eastern Appalachia, Western Appalachia, Midwest, and West); and race (black or white). Continuous covariates were modeled in the best fitting form as described previously.

Hazard ratios (HRs) for continuous exposure were calculated for the change in the HR for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³). Effect modification with the exposure terms was evaluated by including a cross-product term of each covariate with the exposure, and considered to be present if the *p*-value for the product term was statistically significant at the alpha level of <0.05. Covariates or combinations of covariates were included in the model if their addition resulted in a change of greater than 10% in the HR estimate for CMD or silica exposure or if the model fit was significantly improved as demonstrated by the LRT. The validity of the proportional hazards assumption (i.e., that the HR does not vary significantly over time) was tested by assessing whether there was a statistically significant interaction between follow-up time and cumulative exposure to each of the two exposures.

Proportional hazards analyses were conducted using SAS® 9.2 (PROC PHREG).

8. **Sensitivity analysis**

As with previous mortality follow-ups of this cohort, the potential for exposure misclassification exists, as any exposure after study enrollment was not included in the original cumulative exposure estimates. For the previous two mortality follow-ups, it was proposed that any such misclassification may be minimal because these miners likely accumulated most of their exposure before enrollment, which coincided with the implementation of mandatory dust controls in U.S. coal mines in 1969. Also, the average age of the cohort at enrollment was 45 years, well into the working life

of most miners. To explore the robustness of these assumptions after 37 years of follow-up, a sensitivity analysis was conducted among the 83% of miners with a known date of employment termination.

We developed extended exposure estimates by assuming that miners remained at their last known job (at time of study enrollment) through the end of their employment as a coal miner. The dust concentration associated with the last known job was multiplied by the number of years from enrollment to end of employment. That quantity was added to the previously estimated cumulative exposure at enrollment and became the extended exposure estimate. The associations between the original and extended exposures were then assessed in Cox proportional hazards models (as described previously) for pneumoconiosis and COPD cancer as the underlying causes of death.

9. **Human subjects' protection**

Human subjects' review was conducted and the study protocol was approved by Institutional Review Boards at CDC-NIOSH and the UIC. All participants were administered and signed informed consent.

C. Results

1. Study participation and inclusion

The study enrollment rate was 90%. At the last follow-up (through December 31, 1993), vital status had been determined for 9,033 of the original 9,078 cohort members [Attfield and Kuempel 2008]. Of those 9,033 participants, 137 records were excluded from the current study due to missing or invalid data (dust exposure [n=24], smoking [n=81], radiograph result [n=31], and birthdate [n=1]); 67 were excluded because they were not matched with either NDI or the Social Security Administration (SSA). Because of the small percentage of missing data (1.5%), records with incomplete data for key analytical variables were excluded from the analysis. Only one miner had race recorded as other than black or white, and this record was recoded to the majority category, white (95.2%).

2. Descriptive statistics

Of the 8,829 miners included in the analysis, 5,907 (67%) had died by the end of the follow-up period (December 31, 2007). The mean age of participants at enrollment was 45 years and the majority of participants were current (54%) or former (26%) smokers (Table II). The largest group of coal miners came from Western Appalachia (55%) and the smallest group came from the Eastern Pennsylvania mines (6%). At enrollment, the average tenure in coal mining was 21 years, with an average of nine years working at the coal face. The mean cumulative exposure prior to enrollment was 64.6 mg-year/m³ for CMD and 2.6 mg-year/m³ for respirable silica.

TABLE II
 DEMOGRAPHIC INFORMATION AT ENROLLMENT AMONG THE 8,829 COAL MINERS INCLUDED IN THE
 STUDY

Baseline Categorical Characteristic	N (Percent)
Smoking status at enrollment	
Current smoker	4,770 (54.3)
Former smoker	2,257 (25.6)
Never smoked	1,802 (20.4)
Region	
Eastern Pennsylvania	513 (5.8)
Eastern Appalachia	1,335 (15.1)
Western Appalachia	4,838 (54.8)
Midwest	1,198 (13.6)
West	945 (10.7)
Race	
White	8,403 (95.2)
Black	426 (4.8)
Baseline Continuous Characteristic	Mean (SD)
Age (years) at start of follow-up	44.6 (11.9)
Years coal mining	20.8 (13.2)
Years underground	17.6 (13.7)
Years at the coal face	8.7 (11.2)
Cumulative coal-mine dust exposure (mg-year/m ³)	64.6 (46.4)
Cumulative respirable silica exposure (mg-year/m ³)	2.6 (1.0)

3. Modified life table analysis

No difference was observed between the overall mortality experience of the cohort and the U.S. male population (SMR=1.00; 95% CI 0.97, 1.02; Table III).

A small but statistically significant deficit was seen for all nonviolent causes of death (SMR=0.96; 95% CI 0.94, 0.99). SMRs increased with increasing length of follow-up for deaths from all nonviolent cause mortality (Table IV) and from west to east by region. A stronger deficit of mortality was observed among black compared with white miners for all nonviolent causes of death (SMR_{WHITE}=0.97; 95% CI 0.94, 0.99; SMR_{BLACK}=0.88; 95% CI 0.77, 0.96, respectively) possibly indicating a stronger healthy worker effect (HWE) among black miners.

A nearly twofold excess in mortality from all NMRD was observed (SMR=1.79; 95% CI 1.67, 1.91; Table III), largely driven by pneumoconiosis-related mortality (SMR=79.7; 95% CI 72.1, 87.67). Excess mortality from COPD (SMR=1.11; 95% CI 0.99, 1.24) and “other respiratory diseases” (SMR=1.25; 95% CI 1.00, 1.53) was also observed. Stratified SMRs for COPD and pneumoconiosis had the same temporal pattern as nonviolent cause mortality; for COPD the only significant SMR was among deaths in the most recent years (SMR₂₀₀₀₋₂₀₀₇=1.26; 95% CI 1.03, 1.50; Table IV). Significant excess mortality was seen only in the Midwest for COPD; in contrast, SMRs for pneumoconiosis were lowest in the Midwest and dramatically higher in the highest coal-rank region, Eastern Pennsylvania, which also had the highest mean cumulative CMD values.

A significant deficit in mortality was observed for all categories of heart and circulatory diseases, with the exception of conductive heart disorders (SMR=1.67; 95% CI 1.42, 1.95; Table III). Mortality associated with conductive heart disorders was significantly elevated in both Appalachian regions, while the SMR was highest in the most recent decade of follow-up.

TABLE III.
STANDARDIZED MORTALITY RATIOS (SMRS) FOR SELECTED UNDERLYING CAUSE OF MORTALITY AMONG
DECEASED COAL MINERS (N=5,907)

Cause	Obs.	SMR (95% CI)
All causes	5,907	1.00 (0.97, 1.02)
Nonviolent causes	5,588	0.96 ^b (0.94, 0.99)
Respiratory tuberculosis	6	0.72 (0.26, 1.56)
All cancers	1,442	0.96 (0.91, 1.01)
Stomach cancer	45	0.96 (0.70, 1.28)
All respiratory cancers	583	1.06 (0.98, 1.15)
Lung, trachea, and bronchus cancers	568	1.08 (1.00, 1.18)
Lymphatic and hematopoietic cancer	127	0.89 (0.74, 1.06)
Non-Hodgkin's lymphoma	51	0.93 (0.69, 1.23)
Multiple myeloma	28	1.11 (0.74, 1.60)
Leukemia	47	0.85 (0.63, 1.13)
Heart diseases	2,043	0.95 ^a (0.91, 1.00)
Ischemic heart disease	1,637	0.92 ^a (0.88, 0.97)
Conductive disorder	155	1.67 ^b (1.42, 1.95)
Cerebrovascular disease	249	0.78 ^b (0.68, 0.88)
Diseases of the respiratory system	934	1.79 ^b (1.67, 1.91)
Pneumonia	123	0.82 ^a (0.68, 0.98)
COPD	309	1.11 (0.99, 1.24)
Pneumoconioses	403	79.70 ^b (72.11, 87.67)
Other respiratory diseases	91	1.25 ^a (1.00, 1.53)
All injuries	319	0.87 ^b (0.79, 0.97)
Transportation injuries	73	0.63 ^b (0.49, 0.79)
Falls	22	0.59 ^b (0.37, 0.89)
Other injury	120	1.30 (1.07, 1.55)
Violence	104	0.87 (0.71, 1.06)

TABLE IV

STRATIFIED STANDARDIZED MORTALITY RATIOS (SMRS) FOR SELECTED UNDERLYING CAUSES OF DEATH AND PERCENTAGE OF EVER SMOKERS, MEAN CUMULATIVE COAL-MINE DUST AND RESPIRABLE SILICA EXPOSURE CATEGORY BY COAL-RANK REGION, RADIOGRAPHIC STATUS AT ENROLLMENT, RACE, AND CALENDAR YEAR

Category	All Nonviolent Causes		Pneumo- conioses		COPD		Conductive Heart Disorders		Ever Smoked at Enrollment	Mean Cumulative Exposure ^a	
	Obs.	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR	Percent	Coal-Mine Dust mg-year/m ³	Respirable Silica mg-year/m ³
Total	5,588	0.96 ^a	403	79.7 ^a	309	1.11	155	1.67 ^a	79.6	81.0	3.2
Region											
Eastern Pennsylvania	457	1.21 ^a	181	365.29 ^a	11	0.61	6	1.06	77.0	97.7	2.6
Eastern Appalachia	873	1.04	65	86.91 ^a	48	1.26	27	2.05 ^a	82.4	77.4	2.8
Western Appalachia	3217	1.00	101	38.21 ^a	157	1.05	91	1.80 ^a	82.3	82.3	3.8
Midwest	774	1.00	14	17.38 ^a	53	1.44 ^b	19	1.59	86.7	72.8	2.7
West	586	0.80 ^c	42	53.74 ^a	40	1.10	12	1.02	81.7	77.5	2.5
Race											
White	5578	0.97 ^a	385	67.44 ^a	293	1.09	136	1.59 ^a	82.5	80.4	3.3
Black	329	0.88 ^b	14	129.84 ^a	16	1.60	19	2.63 ^a	78.1	90.4	3.8
Baseline radiograph											
Category 0	4,712	0.95 ^b	237	48.50 ^a	250	1.06	132	1.67 ^a	83.0	76.4	3.2
Category 1	506	1.00	56	92.67 ^a	29	1.15	15	1.86 ^b	78.9	99.3	3.6
Category 2	261	0.99	65	192.82 ^a	24	1.85 ^b	5	1.17	75.7	113.0	3.6
Category 3	109	1.22 ^b	43	409.78 ^a	6	1.39	3	2.17	82.5	122.0	3.6
Calendar year											
1970–1989	2234	0.92 ^a	179	63.25 ^a	85	0.86	67	1.59 ^a	83.60		
1990–1999	1922	1.14 ^a	139	106.20 ^a	118	1.19	48	1.57 ^a	81.90		n/a
2000–2007	1431	1.21 ^a	81	127.59 ^a	106	1.26 ^b	40	1.87 ^a	80.90		

a. Statistically significant at $p \leq 0.01$;

b. Statistically significant at $p \leq 0.05$

4. Cox proportional hazards analysis

As expected, CMD and silica exposures were significantly correlated but the correlation was only moderately strong (Pearson's correlation coefficients = 0.29, $p < 0.01$). In all models, estimates of the association between the exposure and outcomes were stronger in the single-exposure models compared with the dual-exposure model. Unless otherwise specified, presented results are from single-exposure models.

5. Chronic obstructive lung disease

The exposure-response relationship between CMD exposure and COPD was modified by smoking status at enrollment ($p = 0.02$; Table V). The association was significant and positive among never and former smokers ($HR_{\text{Mean CMD exposure: } 64.6 \text{ mg-year/m}^3} = 1.93$; 95% CI 1.12, 3.34; and $HR_{\text{Mean CMD exposure: } 64.6 \text{ mg-year/m}^3} = 1.61$; 95% CI 1.06, 2.44, for never and former smokers, respectively), and there was no evidence of increased risk among current smokers ($HR_{\text{Mean CMD exposure: } 64.6 \text{ mg-year/m}^3} = 1.04$; 95% CI 0.81, 1.34). Cumulative respirable silica exposure was best fit as a log-transformed variable. Silica exposure was significantly and positively associated with COPD mortality ($HR_{\text{Mean silica exposure: } 2.6 \text{ mg-year/m}^3} = 1.23$; 95% CI 1.00, 1.52). In the model with silica exposure alone, being a current smoker at enrollment was a significant predictor of COPD mortality ($HR_{\text{Current smoker vs. former or never smoker}} = 1.23$; 95% CI 1.00, 1.52). A significant exposure-response association with pack-years of smoking was also seen ($HR_{10 \text{ pack-years of smoking}} = 1.12$; 95% CI 1.04, 1.20). Neither coal-rank region nor race was a significant predictor of COPD mortality.

TABLE V

HAZARD RATIOS (HRS) FOR MORTALITY DUE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AS THE UNDERLYING CAUSE OF DEATH (309 DEATHS) ESTIMATED IN SINGLE- AND DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH

Variables	Single-Exposure Models				Dual-Exposure Model	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff	HR (95% CI)	<i>B</i> coeff	HR (95% CI)
Cumulative exposures (mg-year/m³)						
CMD modified by smoking at enrollment ^c						
Never	0.0102	1.93 (1.12, 3.34)			0.0095	1.84 (1.05, 3.22)
Former	0.0074	1.61 (1.06, 2.44)			0.0065	1.52 (0.98, 2.34)
Current	0.0007	1.04 (0.81, 1.34)			-0.0009	0.99 (0.76, 1.29)
Respirable silica						
Continuous			0.0798	1.23 (1.00, 1.52)	0.0438	1.12 (0.88, 1.42)
Categorical						
<2.22			Ref.		Ref.	
2.22–<3.30			0.2839	1.33 (0.95, 1.85)	0.2541	1.29 (0.92, 1.81)
3.30–<4.13			0.4258	1.53 (1.10, 2.13)	0.3684	1.45 (1.02, 2.06)
≥4.13			0.4317	1.54 (1.09, 2.19)	0.3463	1.41 (0.95, 2.10)
Coal-rank region						
Eastern Pennsylvania	-0.3595	0.70 (0.35, 1.40)	-0.4146	0.66 (0.33, 1.33)	-0.3455	0.71 (0.35, 1.41)
Eastern Appalachia	0.2348	1.27 (0.79, 2.01)	0.2086	1.23 (0.77, 1.97)	0.2378	1.27 (0.79, 2.03)
Western Appalachia	0.0014	1.00 (0.69, 1.45)	-0.0899	0.91 (0.63, 1.34)	-0.0317	0.97 (0.66, 1.42)
Midwest	-0.0961	1.28 (0.85, 1.94)	0.2162	1.24 (0.82, 1.88)	0.2528	1.29 (0.85, 1.94)
West	Ref.		Ref.		Ref.	

TABLE V (continued)

Variables	Single-Exposure Models				Dual-Exposure Model	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff	HR (95% CI)	<i>B</i> coeff	HR (95% CI)
Race						
White	Ref.		Ref.		Ref.	
Black	-0.0961	0.91 (0.54, 1.52)	-0.0396	0.96 (0.57, 1.61)	-0.1059	0.90 (0.54, 1.51)
Smoking at enrollment ^c						
Never			Ref.			
Former			-0.0099	0.99 (0.62, 1.59)		
Current			1.2380	3.45 (2.25, 5.30)		
Pack-years			0.0111	1.12 (1.04, 1.20)		

a. The interaction terms for cumulative coal-mine dust exposure and smoking status had a *p*-value of 0.0046 for COPD and 0.0179 for CAO.

b. Hazard ratios for continuous exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

c. Hazard ratios pack-years of smoking were calculated for the change in the hazard ratio for 10 units of exposure.

Records coded with COPD as the underlying cause of death were further subdivided into those coded as chronic airways obstruction (CAO; n=293) and CBE (n=69) and analyzed separately. Six records coded as COPD-NOS (not otherwise specified) were not included in these analyses. As with overall COPD mortality, that attributed to CAO was moderated by smoking status, with a significant exposure-response association among current and former smokers (p -value for interaction = 0.02; HR=2.08; 95% CI 1.14, 3.80; and HR=1.72; 95% CI 1.07, 2.75 for current and former smokers, respectively; Table IV). Mortality attributed to CBE was not moderated by smoking status ($p=0.58$) and there was no significant association with either CMD or respirable silica (HR=1.05; 95% CI 0.66, 1.69; and HR=1.18; 95% CI 0.71, 1.95; Table VI). With the addition of deaths from all contributing causes of death, the results of analysis for all COPD and CAO were similar to those for underlying cause alone (Table VII). However, with the additional deaths attributed to CBE (n=292; 45 among smokers, 69 among former smokers), a significant interaction was observed with smoking status at enrollment ($p=0.02$) such that there was a significant exposure-response association among never smokers (HR=1.95; 95% CI 1.17, 3.24; Table VIII).

TABLE VI

HAZARD RATIOS (HRS) FOR MORTALITY DUE TO CHRONIC AIRWAYS OBSTRUCTION (A SUBSET OF COPD) AS THE UNDERLYING CAUSE OF DEATH (293 DEATHS) ESTIMATED IN SINGLE- AND DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS, CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH

Variables	Single-Exposure Models				Dual-Exposure Model	
	B coeff.	HR (95% CI)	B coeff.	HR (95% CI)	B coeff.	HR (95% CI)
Cumulative exposures (mg-year/m ³)						
CMD modified by smoking at enrollment ^{a,b}						
Never	0.0114	2.08 (1.14, 3.80)			0.0107	2.00 (1.08, 3.69)
Former	0.0084	1.72 (1.07, 2.75)			0.0077	1.64 (1.01, 2.67)
Current	0.0013	1.09 (0.82, 1.44)			0.0007	1.04 (0.77, 1.42)
Respirable silica ^b						
Continuous			0.0896	1.24 (0.98, 1.56)	0.0377	1.10 (0.84, 1.51)
Categorical						
<2.22			Ref.		Ref.	
2.22–<3.30			0.3160	1.37 (0.93, 2.02)	0.2541	1.29 (0.92, 1.81)
3.30–<4.13			0.5491	1.73 (1.18, 2.54)	0.3684	1.45 (1.02, 2.06)
≥4.13			0.4527	1.70 (1.14, 2.54)	0.3463	1.41 (0.95, 2.10)
Coal-rank region						
Eastern Pennsylvania	–0.8433	0.43 (0.16, 1.13)	–0.8579	0.40 (0.16, 1.08)	–0.8319	0.44 (0.17, 1.14)
Eastern Appalachia	0.4116	1.51 (0.90, 2.52)	0.3847	1.47 (0.87, 2.46)	0.4146	1.51 (0.91, 2.53)
Western Appalachia	0.0378	1.04 (0.68, 1.58)	–0.0515	0.95 (0.62, 1.54)	0.0098	1.01 (0.66, 1.54)
Midwest	0.0525	1.05 (0.65, 1.71)	0.0159	1.02 (0.63, 1.65)	0.0529	1.05 (0.65, 1.71)
West	Ref.		Ref.		Ref.	

TABLE VI (continued)

Variables	SINGLE EXPOSURE MODELS				DUAL EXPOSURE MODEL	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)
Race						
White	Ref.		Ref.		Ref.	
Black	-0.1874	0.83 (0.46, 1.50)	-0.1331	0.87 (0.48, 1.59)	-0.1958	0.82 (0.45, 1.49)
Smoking at enrollment ^c						
Never			Ref.			
Former			-0.0610	0.94 (0.55, 1.60)		
Current			1.1559	3.18 (1.98, 5.11)		
Pack-years			0.0113	1.12 (1.03, 1.21)		

a. The interaction terms for cumulative CMD exposure and smoking status had a *p*-value of 0.0179.

b. Hazard ratios for continuous exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

c. Hazard ratios pack-years of smoking were calculated for the change in the hazard ratio for 10 units of exposure.

TABLE VII

HAZARD RATIOS (HRS) FOR MORTALITY DUE TO CHRONIC BRONCHITIS AND EMPHYSEMA (A SUBSET OF COPD) AS THE UNDERLYING CAUSE OF DEATH (N=69 DEATHS) ESTIMATED IN SINGLE- AND DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS, CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH

Variables	Single-Exposure Models				Dual-Exposure Model	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)
Cumulative exposures (mg-year/m ³) ^a						
Coal-mine dust	0.0008	1.05 (0.66, 1.69)			0.98 (0.58, 1.64)	
Respirable silica			0.0629	1.18 (0.71, 1.95)	0.0659	1.19 (0.68, 2.06)
Coal-rank region						
Eastern Pennsylvania	0.3797	1.46 (0.45, 4.79)	0.3988	1.49 (0.46, 4.86)	0.4020	1.50 (0.46, 4.90)
Eastern Appalachia	-0.5220	0.59 (0.17, 2.06)	-0.5177	0.60 (0.17, 2.07)	-0.5166	0.60 (0.17, 2.08)
Western Appalachia	-0.2055	0.81 (0.33, 1.99)	-0.2532	0.78 (0.31, 1.92)	-0.2534	0.78 (0.31, 1.92)
Midwest	0.7904	2.20 (0.91, 5.31)	0.7963	2.22 (0.92, 5.34)	0.7972	2.22 (0.92, 5.35)
West	Ref.		Ref.		Ref.	
Race						
White	Ref.		Ref.		Ref.	
Black	0.1365	5.14 (0.34, 3.78)	0.1231	1.13 (0.34, 3.73)	0.1220	1.13 (0.34, 3.73)
Smoking at enrollment ^b						
Never	Ref.		Ref.		Ref.	
Former	0.0186	1.02 (0.32, 3.24)	0.0135	1.01 (0.32, 3.22)	0.0143	1.01 (0.32, 3.22)
Current	1.4342	4.20 (1.50, 11.77)	1.4232	4.15 (1.48, 11.65)	1.4238	4.15 (1.48, 11.66)
Pack-years	0.0111	1.12 (0.96, 1.30)	0.0113	1.12 (0.96, 1.30)	0.0143	1.12 (0.96, 1.30)

a. Hazard ratios for continuous exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

b. Hazard ratios pack-years of smoking were calculated for the change in the hazard ratio for 10 units of exposure.

TABLE VIII

HAZARD RATIOS (HRS) FOR MORTALITY DUE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE^A AND THEREOF, AS THE UNDERLYING CAUSE OR CONTRIBUTING CAUSES OF DEATH IN DUAL-EXPOSURE COX PROPORTIONAL HAZARDS MODELS, CONTROLLING FOR AGE AT STUDY ENTRY AND YEAR OF BIRTH, SMOKING STATUS AND PACK-YEARS SMOKED AT STUDY ENTRY, REGION, AND RACE

Cumulative exposures (mg-year/m ³) ^a	COPD (1,240 deaths)		CAO (954 deaths)		CBE (292 deaths)	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff	HR (95% CI)	<i>B</i> coeff	HR (95% CI)
CMD modified by smoking status at enrollment ^b						
Never	0.0105	1.97 (1.50, 2.59)	0.0100	1.90 (1.38, 2.64)	0.0104	1.95 (1.17, 3.24)
Former	0.0052	1.40 (1.13, 1.73)	0.0060	1.47 (1.15, 1.88)	0.0026	1.18 (0.77, 1.79)
Current	0.0015	1.10 (0.95, 1.27)	0.0022	1.15 (0.98, 1.36)	0.0001	1.00 (0.74, 1.37)
Respirable silica ^b						
Continuous	0.0178	1.04 (0.92, 1.19)	0.0237	1.06 (0.92, 1.22)	0.9780	0.98 (0.73, 1.31)
Categorical						
<2.22	Ref.		Ref.		Ref.	
2.22–<3.30	0.1876	1.21 (0.97, 1.50)	0.2198	1.25 (0.96, 1.60)	0.1358	1.15 (0.72, 1.82)
3.30–<4.13	0.3267	1.39 (1.03, 1.87)	0.3503	1.42 (1.01, 1.97)	0.1765	1.19 (0.62, 2.30)
≥4.13	0.3549	1.43 (0.92, 2.22)	0.4105	1.51 (0.92, 2.47)	–0.0738	0.92 (0.34, 2.56)

a. Hazard ratios for continuous exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

b. The interaction terms for cumulative coal-mine dust exposure and smoking status had a *p*-value of <0.0001 for COPD, 0.0179 for CAO, and 0.0107 for CBE.

6. Pneumoconiosis

The exposure-response relationship between cumulative CMD exposure and pneumoconiosis as an underlying cause of mortality was modified by region ($p=0.03$; Table IX). The strongest associations were seen in the Eastern Pennsylvania (highest rank; HR=1.93; 95% CI 1.49, 2.51) and Eastern Appalachia (next highest rank; HR=2.66; 95% CI 1.88, 3.77) regions. The weakest association was seen in the West (HR=1.24; 95% CI 0.80, 1.91). No significant interactions were observed between silica exposure and any covariates. Silica was best fit as a log-transformed continuous variable with which there was a positive and significant association with pneumoconiosis-related mortality (HR=1.75; 95% CI 1.43, 2.13).

7. Sensitivity analysis

Overall, 7,397 (83.8%) miners were included in this analysis; 1,432 were excluded due to missing termination dates, and 13 were excluded because the termination dates provided were a year or more after the date of death. The DOL and UMWA Funds identified employment termination dates for 5,749 (65.1%) and 6,458 (73.2%) miners, respectively. There was a strong correlation for year of termination between the two data sources (Pearson's correlation coefficient = 0.77, $p<0.01$).

Compared with the 1,432 miners not included in the sensitivity analysis, those included were older (mean age = 44.9 (SD=11.0) vs. 42.5 (SD=13.5) years, $p<0.01$), had a higher mean cumulative CMD exposure at enrollment (66.9 mg-year/m³ [SD=45.9] vs. 52.9 mg-year/m³ [SD=47.0], $p<0.01$), included a higher percentage from the Eastern Pennsylvania (13.6% vs. 4.3%) and a lower percentage from the Eastern Appalachia region (11.5% vs. 15.8%), had a higher percentage of black miners (5.1% vs. 3.6% white, $p=0.02$), and had a lower rate of overall mortality from pneumoconiosis (5.8% vs. 4.3%, $p=0.01$). The groups did not differ significantly by radiographic status at enrollment ($p=0.17$) or percent ever smoked ($p=0.46$).

The mean extended cumulative CMD and respirable silica exposure estimates were 83.0 mg-year/m³ (SD=41.3) and 4.1 mg-year/m³ (SD=1.8), respectively, an average increase over the estimates at enrollment of 28% for CMD and 52% for silica. The coefficients for the exposure-response relationships with both COPD and pneumoconiosis were generally slightly lower for the extended compared with the original estimates (Table X).

TABLE IX
HAZARD RATIOS (HRS) FOR MORTALITY DUE TO PNEUMOCONIOSIS AS THE UNDERLYING CAUSE OF DEATH (403 DEATHS) ESTIMATED IN COX PROPORTIONAL HAZARDS MODELS, CONTROLLING FOR AGE AND YEAR OF BIRTH

Variables	Single-Exposure Models		Dual-Exposure Model	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)
Cumulative exposure (mg-year/m ³)				
Coal-mine dust modified by coal-rank region ^{a,b}				
Eastern Pennsylvania	0.0102	1.93 (1.49, 2.51)		0.0099 1.89 (1.44, 2.50)
Eastern Appalachia	0.0152	2.66 (1.88, 3.77)		0.0142 2.50 (1.73, 3.60)
Western Appalachia	0.0079	1.66 (1.21, 2.28)		0.0057 1.45 (1.03, 2.03)
Midwest	0.0096	1.85 (0.89, 3.86)		0.0080 1.68 (0.81, 3.49)
West	0.0033	1.24 (0.80, 1.91)		0.0023 1.16 (0.74, 1.80)
Respirable silica ^b				
Continuous (log)			0.5832	1.75 (1.43, 2.13)
Categorical				
<2.22			Ref.	Ref.
2.22–<3.30			0.2833	1.33 (1.01, 1.74)
3.30–<4.13			0.3691	1.45 (1.09, 1.92)
≥4.13			0.6740	1.96 (1.44, 2.67)
Covariates				
Coal-rank region				
Eastern Pennsylvania			2.0782	7.99 (5.46, 11.70)
Eastern Appalachia			0.2628	1.30 (0.84, 2.02)
Western Appalachia			–0.7609	0.47 (0.31, 0.70)
Midwest			–1.1089	0.33 (0.18, 0.61)
West				

TABLE IX (continued)

Variables	Single-Exposure Models				Dual-Exposure Model	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)
Race						
White	Ref.		Ref.		Ref.	
Black	-0.0528	0.95 (0.55, 1.65)	-0.0653	0.94 (0.54, 1.63)	-0.0699	0.93 (0.54, 1.62)
Smoking at enrollment ^c						
Never						
Former	0.1888	1.21 (0.87, 1.68)			0.1839	1.20 (0.86, 1.67)
Current	0.5361	1.71 (1.23, 2.37)			0.5374	1.71 (1.23, 2.38)
Pack-years	0.0007	1.01 (0.94, 1.07)	0.0062	1.01 (0.94, 1.07)	0.0007	1.01 (0.94, 1.07)

a. The interaction terms for cumulative coal-mine dust exposure and coal-rank region had a *p*-value of 0.0295.

b. Hazard ratios for continuous exposures were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.7 mg-year/m³).

c. Hazard ratios for pack-years of smoking were calculated for the change in the hazard ratio for 10 units of exposure.

TABLE X

RESULTS OF SENSITIVITY ANALYSIS AMONG COHORT MEMBERS WITH KNOWN TERMINATION OF EMPLOYMENT DATE (N=7,397) COMPARING ESTIMATED HAZARD RATIOS (HRS) FOR MORTALITY DUE TO PNEUMOCONIOSIS AS THE UNDERLYING CAUSE OF DEATH, USING ORIGINAL AND EXTENDED CUMULATIVE DUST EXPOSURE ESTIMATES

Cumulative exposure (mg-year/m ³)	Pneumoconiosis (320 Deaths)			
	Original Estimates		Extended Estimates	
	B coeff.	HR (95% CI)	B coeff	HR (95% CI)
Coal-mine dust exposure modified by coal-rank region ^{a,b}				
Eastern Pennsylvania	0.0096	1.85 (1.32, 2.60)	0.0090	1.79 (1.27, 2.52)
Eastern Appalachia	0.0155	2.73 (1.88, 3.93)	0.0130	2.33 (1.57, 3.42)
Western Appalachia	0.0076	1.64 (1.05, 2.33)	0.0062	1.49 (1.03, 2.12)
Midwest	0.0112	2.01 (0.94, 4.54)	0.0112	2.06 (0.86, 4.90)
West	0.0025	1.17 (0.74, 1.85)	0.0016	1.11 (0.69, 1.77)
Respirable silica ^{a,b}				
Continuous (log)	0.3121	1.35 (0.89, 2.04)	0.0735	1.07 (0.80, 1.44)
		COPD^b (282 Deaths)		
Coal-mine dust exposure modified by coal-rank region ^{b,c}				
Never	0.0076	1.64 (0.92, 2.94)	0.0052	1.42 (0.77, 2.53)
Former	0.0068	1.55 (0.98, 2.47)	0.0060	1.47 (0.92, 2.34)
Current	-0.0002	0.99 (0.74, 1.30)	-0.0016	0.90 (0.68, 1.18)
Respirable silica ^{b,c}				
Continuous	0.0421	1.04 (0.94, 1.14)	0.0054	1.01 (0.93, 1.09)

a. Controlling for smoking status and pack-years and age at enrollment, race, and birth year; continuous silica exposure was log transformed.

b. Hazard ratios for continuous exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

c. Controlling for region, age at enrollment, race, and birth year

D. Discussion

This mortality follow-up, extended to almost four decades, confirms previous findings on NMRD deaths in U.S. coal miners. Additional insights into the relationship between cumulative exposure to CMD and respirable silica were also explored. This is the first time exposure to respirable silica has been included in analyses of this cohort, making a significant contribution to our understanding of mortality in U.S. coal miners.

Studies conducted in Scottish coal mines by the PRF have demonstrated the complexity of the relationship between silica and disease progression. In particular, one mine where unusually high levels of quartz dust occurred in the 1970s has been intensely studied. An early finding was that miners exposed to low levels of CMD with a high level of quartz showed unexpectedly rapid progression to pneumoconiosis [Seaton, et al. 1981]. Another study modeled silica dust exposure to account for differential response with exposure intensity and length of residence (time). Risk of profusion of radiographic abnormalities category 2/1+ increased with long-term exposure to low quartz concentrations (e.g., 0.1 mg/m³), but also with short-term exposure to high concentrations (e.g., 2 mg/m³), and the latter at an exaggerated rate. While our study could not explore high-intensity, short-duration silica exposures, our finding that the highest levels of silica exposure were associated with both COPD and CWP mortality are consistent with a complex profile of silica-associated mortality.

1. Chronic obstructive lung disease

The finding that silica exposure is strongly and significantly associated with mortality from COPD is consistent with findings observed in the latest follow-up of the British cohort (HR=1.08; 95% CI 1.03, 1.13) [Miller and MacCalman 2010]. There is also consistent evidence suggesting that chronic exposure to silica dust causes chronic bronchitis and emphysema, even in the absence of radiological silicosis [Hnizdo and Vallyathan 2003]. The finding of increased mortality associated with

silica exposure in U.S. mines is particularly disturbing, as there is a concern that silicosis may be becoming more frequent among coal miners[Laney, et al. 2010]. Silica exposure in U.S. coal mines may be increasing as coal reserves become more difficult to mine and coal is extracted from increasingly narrower seams, resulting in more rock cut in the process of mining and, hence, increasing respirable silica exposure.

The positive exposure-response relationships between cumulative CMD exposure and COPD observed among never and former smokers but not among current smokers was also consistent with the latest findings from the U.K. In the British cohort the inclusion of an interaction term between CMD and smoking status at study enrollment significantly improved model fit. The estimated coefficients showed a significant effect of exposure only within the nonsmokers, among whom the relative risk for lagged dust exposure was 1.21 rather than 1.17, the unstratified estimate from the model without the interaction term(Miller and MacCalman 2010). The finding is also consistent with a related observation made in this cohort in a study exploring the relationship between cumulative dust exposure and measures of pulmonary function. In that study, the authors reported that the relationship between Forced Expiratory Volume in one second (FEV1) and dust exposure was more severe in never and former smokers (-0.73 and -1.0 ml/gh/m³, respectively) compared with current smokers (-0.44 ml/gh/m³) [Attfield and Hodous 1992]. However, the deleterious effects of CMD exposure on pulmonary function have been found both among smokers and nonsmokers at autopsy [Kuempel, et al. 2009]. The current observed significant effect among former and never smokers may be due in part to selection effects (i.e., smokers with more severe lung deficits may have left coal mining earlier in their work life than nonsmokers of the same age and, hence, were not available for recruitment into our study). This potential selection bias is probable given the old age of this cohort at enrollment (average age 45 years) resulting in most cohort members being well into their working lives (average 21 years).

A clear HWE was observed in the SMR analysis, such that there was a deficit in mortality among men during the first 2 decades of follow-up followed by an excess in mortality among those in the following decades. For all non-violent cause mortality the deficit in mortality was stronger among black, compared with white miners. This finding may be a function of the selection forces at the time of hiring, which can be stronger among nonwhite people [Checkoway, et al. 2004]. Black miners were primarily enrolled from the Western Appalachian region (70% of 426 black miners), so any difference by race may be attributable to unmeasured regional factors including behavioral, social, and/or environmental factors.

2. Pneumoconiosis

The strong positive exposure-response relationship between CMD and pneumoconiosis-related mortality is consistent with previous analyses of this and other cohorts of coal miners [Miller and MacCalman 2010, Attfield and Kuempel 2008, Kuempel, et al. 1995]. However, in our study the strength of that relationship varied by region, generally declining from east to west (i.e., with declining coal rank). The magnitude of the association we observed within each region was similar to that observed in the last follow-up of this cohort, which also observed coal-rank region as a strong risk factor [Attfield and Kuempel 2008].

We saw a strong effect of increased mortality from pneumoconiosis with increasing silica exposure, in contrast with the latest follow-up of the PFR, where such an association was not observed [Miller and MacCalman 2010]. Our findings are generally supportive of recent concerns that increasing prevalence and severity of pneumoconiosis in U.S. miners may be due, at least in part, to increasing silica exposure [Laney and Attfield 2009, Cohen 2010].

3. Limitations

There were a number of limitations to this study, particularly related to exposure estimation. Perhaps of greatest concern is the lack of job histories on which to base exposure estimates after study enrollment. In previous studies of this cohort, it was proposed that exposure misclassification may be minimal because the miners were enrolled at an average age of 45 years and after an average of more than two decades working as a miner. Hence, it was felt that most of the miners' exposure was likely accumulated before enrollment. Also supporting this idea is the fact that most of the cohort's exposures occurred before mandatory dust control in U.S. coal mines was implemented in 1969 and thus CMD exposures were likely much higher prior to the time of study enrollment. Our sensitivity analysis to test these assumptions found no meaningful differences between the exposure-response relationships for death from NMRD using the original and extended estimates for either CMD or silica exposure, lending empirical support to the aforementioned assumptions.

Another potential limitation of this study was misclassification of the outcomes. Misclassification of cause of death has long been recognized as a source of potential bias in occupational studies [Selikoff and Seidman 1992]. In this and other studies of coal miners, it is conceivable, if not likely, that CWP is favored as the underlying cause of death as opposed to other NMRDs. This hypothesis is supported by exploring other NMRDs as contributing causes of death among miners for whom pneumoconiosis was assigned as the underlying cause. Overall, 49% of these miners had COPD as a contributing cause of death, but the proportion varied by smoking status. Among miners who smoked at enrollment, the proportion of deaths with COPD as a contributing cause was 58% and among never smokers at enrollment it was 40% ($p < 0.01$). However, smoking should not impact CWP, as smoking does not cause CWP. Hence, these findings may lend support to the possibility that CWP was overdiagnosed and COPD was underdiagnosed as the underlying cause of death. Another possible explanation of this finding is that smoking may exacerbate the disease process initiated by CWP. If this is the case, then

miners with both diseases, CWP from dust and COPD from smoking and/or dust, may die at a younger age than those with CWP alone.

Another possible source of bias in our analysis was the inability to analyze silicosis as a unique cause of death, as only four death certificates were coded with silicosis as the underlying cause of death, and only five were coded with silicosis as a contributing cause. As with COPD, it is quite possible that silicosis was underreported in this cohort, as any pneumoconiosis-related death in a coal worker may be likely to be classified as CWP. The regression analysis predicting pneumoconiosis as the underlying cause of death was rerun without the four deaths attributed to silicosis. As one would expect given the small number of deaths attributed to silicosis, the resulting exposure-response estimates for the association between both CMD and silica were largely unchanged.

Another limitation of the sensitivity analysis was the assumption that miners continued to work in the same job after study enrollment until termination of employment, and at the same level of exposure. We have no empirical way to test this assumption. However, if systemic change in exposure over time did occur due to job changes, it seems most likely that it would be due to workers moving to lower exposure jobs. If this were the case, our extended estimates would be an overestimation of total cumulative exposure, and our exposure-response relationships weakened.

D. **Conclusion**

Our findings show elevations in NMRD mortality in association with both cumulative CMD and silica dust exposure. While an excess of mortality was observed from conductive heart disorders, it was not associated with dust exposures. A strong HWE was present as evidenced by an increase in excess mortality in later follow-up periods. This HWE likely exerted a negative bias on the exposure-response relationships we observed. Our findings add to the accumulated evidence that occupational CMD and silica dust exposure lead to nonmalignant lung diseases including pneumoconioses and COPD.

IV. MORTALITY DUE TO LUNG CANCER AND OTHER MALIGNANCIES AMONG U.S. COAL MINERS: RESULTS AFTER 37 YEARS OF FOLLOW-UP

A. Introduction

A causal relationship between occupational exposure to coal-mine dust (CMD) and mortality from nonmalignant respiratory disease (NMRD) has been clearly demonstrated (Miller and MacCalman 2010; Attfield and Kuempel 2008; NIOSH. 1995). However, whether a causal relationship exists between CMD exposure and death from lung cancer or other malignant disorders remains unclear.

Lung cancer mortality among coal miners has been intensely studied since Kenaway and Kenaway reported a deficit of lung cancer mortality among coal miners compared with British men in other occupations (Kennaway EL 1936; Kennaway EL 1947). Most subsequent cohort studies also found a significant deficit of lung cancer mortality in coal miners (Atuhaire et al. 1986; Liddell 1973; Costello, Ortmeyer, and Morgan 1974; Kuempel et al. 1995), but some have not (Enterline 1972; Rockette 1977; Miyazaki 2001). Most of these studies did not include smoking histories and may have been negatively biased from smoking bans in the mines and by the healthy worker effect (HWE) (Stayner and Graber 2011). These findings are surprising because, in addition to coal dust, miners are exposed to other substances that are widely recognized to cause respiratory cancer in humans, most notably silica but also diesel exhaust and radon gas.

The most recent mortality follow-up from a large cohort of British coal miners, which included individual estimates of cumulative coal mine and silica dust exposure, reported an excess of lung cancer mortality in the most recent 15 years of follow-up (1990–2005) but not in previous time periods (1959–1974 and 1975–1989). Internal analyses found evidence of an increased risk of lung cancer with increased quartz exposure, particularly with a 15-year lag, but not with increased CMD exposure (Miller and MacCalman 2010). The findings on lung cancer mortality from previous follow-ups of a cohort of

U.S. coal miners, the National Study of Coal Workers' Pneumoconiosis (NSCWP), also suggests an excess of lung cancer mortality with increasing follow-up. After an average of eight years of follow-up, a deficit of lung cancer was observed (standardized mortality ratio [SMR] = 0.77; 95% confidence interval [CI] 0.60, 98.51 (Kuempel et al. 1995)); however, after an average of 23 years of follow-up, there was a small and statistically non-significant excess of lung cancer mortality (SMR=1.07; 95% CI 0.95, 1.19; (Attfield and Kuempel 2008)). These findings suggest that the previously reported deficit in lung cancer mortality may be reversed with extended follow-up. This finding may be explained by a very strong HWE in the early follow-up period, in part because the health benefits from smoking bans in the mines would diminish with time as workers leave work.

In contrast to lung cancer mortality, an excess of gastric cancer mortality has been reported from most studies of coal miners. Results from the most recent mortality follow-up of the British cohort observed an excess of gastric cancer mortality, but no exposure-response association with either cumulative coal mine or quartz dust exposure and gastric cancer (RR 0.96 95% CI 0.87, 1.07; RR 1.00 95% CI 0.91, 1.09 for lifetime cumulative exposures of 100 ghm^{-3} , respectively). The most recent follow-up of the NSCWP reported an SMR of 0.75 (95% CI 0.46, 1.14) for gastric cancer based on only 21 cases.

The findings reported in this study are from an extended follow-up of the NSCWP to an average of 37 years. The larger number of deaths in this study allowed for the exploration of malignant outcomes that were previously limited by small numbers, including gastric cancer. Two data elements have been added to specifically explore lung cancer mortality: individual estimates of cumulative respirable silica exposure and the termination date of employment as a coal miner.

B. Methods

1. The cohort

Methods for analysis of this cohort are described in detail in the companion paper reporting findings on mortality from NMRD causes. In brief, 9,078 working underground coal miners were enrolled from 31 U.S. mines between 1969 and 1971 (Attfield and Castellan 1992). Participants received full-format posterior-anterior chest radiographs, and a questionnaire was administered to all participants to collect information on respiratory symptoms, work history, smoking history, and demographics. Records of the 5,636 participants alive at the end of the previous follow-up (December 31, 1993) were submitted to the Social Security Administration (SSA) and the National Death Index (NDI) for vital status determination; NDI also provided cause of death.

The cohort was followed up to December 31, 2007. Underlying cause of death was assigned for analysis using the National Institute for Occupational Safety and Health (NIOSH) Life Table Analysis System (LTAS) mortality program as follows: cancers of the trachea, bronchus, and lung (henceforth, “lung cancer”): 8th and 9th revisions of the International Classification of Diseases (ICD) code 162 or the 10th revision of the ICD (ICD-10) codes C33-C34 (excludes mesothelioma); stomach cancer: 8th or 9th ICD revision code 151 or ICD-10 revision code C16; multiple myeloma: 8th or 9th ICD revision code 203 or ICD-10 revision codes C88.7, C88.9, and C90.

Regional groups were designed as a proxy for coal rank, a measure of the coal’s carbonaceous. Higher rank coal is denser and has greater propensity than lower rank coals to cause NMRD (NIOSH. 1995; Schubauer-Berigan et al. 2011). In the U.S., the highest rank coal (anthracite) is found almost exclusively in Eastern Pennsylvania, and rank generally declines from east to west. As with previous analyses of this cohort, regions were defined in decreasing rank order as follows: Eastern Pennsylvania, Eastern Appalachia (Central Pennsylvania and Eastern West Virginia), Western Appalachia (Western

Pennsylvania, the rest of West Virginia, Eastern Ohio, Western Virginia, Eastern Kentucky, Tennessee, and Alabama), Midwest (Western Kentucky, Illinois, and Indiana), and West (Colorado and Utah).

Cumulative CMD exposure for each miner was calculated as the summation of the product of each job-specific dust concentration by the duration of time worked at that job, as developed by Attfield and Moring (Attfield and Moring 1992). Estimates of respirable quartz dust exposure were constructed for this analysis using Mine Safety and Health Administration (MSHA) compliance data from 1982–2002. Mean percent silica was estimated for Lainhart job grouping, as first described in 1969 (Lainhart), for underground (face, transportation, maintenance, and miscellaneous activities) and surface (transportation, maintenance, tipple, strip mining, and miscellaneous activities) mining jobs within each of the five coal-rank regions. Job-specific silica estimates were made by multiplying the percentage of respirable silica for each region and job category (e.g., face, transportation) by the mean CMD estimate for each job within the region. An individual cumulative silica exposure estimate was then assigned to each study participant by summing the product of the number of years at each job by the corresponding region and job group-specific silica exposure estimate.

Date of last employment as a coal miner was sought for cohort members from two sources, the United Mine Workers of America Health and Retirement Funds (UMWA Funds) and the Department of Labor (DOL), Office of Workers' Compensation Programs. When conflicting dates were provided, the DOL date was used because it was considered more reliable.

2. **Statistical methods**

Modified life table analysis of causes of death was conducted using the LTAS program (Schubauer-Berigan et al. 2011). Person-days were calculated from the date of enrollment (1969–1971) until date of death or end of follow-up (December 31, 2007), whichever occurred first. The number of expected deaths was calculated for each cause of death by applying the age-, race-, and calendar year-

specific mortality rates for all males in the U.S. population to the corresponding person-years in each corresponding exposure stratum of the study population. SMRs (the ratio of the observed and the expected number of deaths) and 95% CIs were calculated for all underlying causes of deaths and for specific malignancies for which 25 or more deaths were observed.

The associations between cumulative CMD as well as respirable silica exposure and lung cancer, stomach cancer, and multiple myeloma (the latter was included based on findings from the life table analysis) were explored using Cox proportional hazards regression models. The time dimension used was follow-up time; all models included age at enrollment and birth year. Other covariates were explored as risk factors and potential effect modifiers of the associations with the two exposures. Alternative functional forms of the continuous CMD and silica exposure variables were assessed for the best model fit (e.g., log-linear, log-transformed, quadratic) using the likelihood ratio test (LRT) while including all potential covariates in the model. Exposures were also analyzed as four-level categorical exposure variables, based on quartiles of exposure among the deceased. For lung cancer, categorical variables were entered into the models using the following levels, the last listed being the reference group: smoking (ever, former, and never); region (Eastern Pennsylvania, Eastern Appalachia, Western Appalachia, Midwest, and West); race (black and white); and body mass index (BMI) (<25.0 kg/m² [normal], 25.0 – 29.9 kg/m² [overweight], and ≥ 30.0 kg/m² [obese]). Because of the relatively small number of cases, models predicting gastric cancer ($n=45$) and multiple myeloma ($n=28$) used a two-level parameterization of region, East (Eastern Pennsylvania, Eastern and Western Appalachia) vs. West (Midwest and West).

The associations between CMD and silica exposure and lung cancer mortality were further explored by stratifying on three time-varying factors: follow-up time, time since first exposure (TSFE), and time since last exposure (TSLE). Follow-up time (in this study, equivalent to calendar year) was grouped as 1970–1989, 1990–1999, and 2000–2007. TSFE was calculated as the total time worked in all

jobs (mining and non-mining) plus follow-up time. TSFE was categorized as <35, 35–44, 45–49, and ≥50 years. The lower cutoff (35 years) was chosen because it provided sufficient lung cancer deaths for a stable estimate (n=26); the remaining records were grouped so as to have an approximately even number of deaths from lung cancer. Due to invalid or missing data, 134 records were excluded from the analysis of TSFE.

TSLE was assessed in the subgroup of miners for whom termination of employment date was obtained. TSLE was calculated as the time since last worked as a coal miner until end of time on the study. TSLE was categorized with the reference category as ≤1 year and then approximate tertiles among the lung cancer deaths within the remaining records: ≤10, >11–18, and >18 years. This analysis was repeated using the outcome gastrointestinal cancer (excluding stomach cancers) as the underlying cause of death. This outcome has not previously been associated with CMD exposure and was included to evaluate if any findings might be attributable to the effect of ending employment rather than the exposure(s).

Single- and dual-exposure models were explored for all analyses unless otherwise specified. Hazard ratios (HRs) for continuous cumulative exposure were calculated for mean exposure (CMD = 64.6 mg-year/m³, silica = 2.7 mg-year/m³) and for pack-years of smoking for a 10-unit change.

Interaction with each exposure was evaluated by including cross-product terms of each covariate with each exposure. Interaction was considered present if the *p*-value for that term was statistically significant (*p*<0.05, two-tailed). Covariates were included in the model if their addition resulted in a change of greater than 10% in the resulting HR or if the model fit was significantly improved as demonstrated by the LRT. The validity of the proportional hazards assumption (i.e., that the HR does not vary significantly over time) was tested by assessing whether there was a statistically significant interaction between follow-up time and cumulative exposure.

All regression analyses were conducted using SAS[®] 9.2 (PROC PHREG).

align were previously estimated up to study enrollment; hence, there is the potential for underestimating exposure, as any exposure accumulated thereafter was not included. To explore the robustness of using the original exposure estimates, two sensitivity analyses were conducted among miners with a last known date of employment (83%):

- Extended exposure estimates: We developed extended exposure estimates by assuming that miners remained at their last known job (at time of study enrollment) through the end of their employment as a coal miner. The dust concentration associated with the last known job was multiplied by the number of years from enrollment to end of employment. That quantity was added to the previously estimated cumulative exposure at enrollment and became the extended exposure estimate. The associations between the original and extended exposures were then assessed in Cox proportional hazards models (as described previously) for pneumoconiosis and COPD as the underlying causes of death.
- Round 4 exposure estimates: Beginning in September 1985, miners who had participated in Round 1 (1969–1971, the subjects of the current study) or Round 2 (1972–1975) of the NSCWP, and who were aged 58 years or younger at the time, were eligible to participate in a follow-up study, known as Round 4³. The age restriction was intended to enroll men who were age-eligible for work; however, both working and former miners were enrolled. Cumulative CMD exposure was estimated for each miner according to a job-exposure matrix developed by Seixas and colleagues [1990]. Among Round 4 participants who had originally enrolled in Round 1 (1,770) and who had a date of employment termination available (85%, n=1,504), Cox

³ Round 3 was conducted from 1977–1981; however, the participation rate was only 52% and these miners were not included as eligible for Round 4.

proportional hazards regression was conducted with lung cancer mortality as the outcome using the CMD estimates developed for Round 4. The analysis was repeated substituting the extended CMD exposure estimates developed for the current study, and the results were compared. For both models, the extended silica estimates from Round 1 were used. Given the small sample size, categorical levels of exposure were not assessed.

3. **Human subjects' protection**

Human subject's review was conducted and the study protocol was approved by the Institutional Review Boards at the Centers for Disease Control and Prevention (CDC)/NIOSH and the UIC. All participants were administered and signed informed consent.

C. **Results**

1. **Study participation and descriptive statistics**

The study enrollment rate was 90%. Of 9,033 participants with known vital status at last follow-up, 8,829 miners were included in the current study; 137 records were excluded due to missing or invalid data and 67 records were excluded because the subjects were not matched with either NDI or SSA. The mean age at enrollment was 44.6 years (standard deviation [SD] = 11.9). The vast majority of participants were white (95.2%); one record with race recorded as "other" was recoded to white. The average tenure in coal mining was 20.8 years (SD=13.2) and duration at the coal face was 8.7 years (SD=11.2). Prior to enrollment, the mean cumulative CMD exposure was 64.6 mg-year/m³ (SD=46.4) and mean respirable silica exposure was 2.6 mg-year/m³ (SD=1.0).

By the end of the follow-up period, 66.9% (5,907) of participants had died. At enrollment, the majority of participants were current (54.3%) or former (25.6%) smokers (Table XI). Not surprisingly, a

higher percentage of lung cancer deaths occurred among current smokers (81%) (Table XII), with only 2.5% (n=14) among never smokers. Miners were unevenly distributed across regions, with the smallest proportion from Eastern Pennsylvania (predominantly anthracitic coal, 5.8%) and the largest proportion from Western Appalachia (predominantly bituminous coal, 54.8%).

TABLE XI
 DISTRIBUTION OF KEY CHARACTERISTICS FOR ALL DEATHS FROM ALL AND SELECTED MALIGNANT UNDERLYING CAUSES OF DEATH

Variable	All Participants		All Deaths		Lung Cancer		Stomach Cancer		Multiple Myeloma	
	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent
Total	8,829		5,907		568		45		28	
Region										
Eastern Pennsylvania	513	5.8	457	8.2	26	4.6	1	2.2	0	0.0
Eastern Appalachia	1,335	15.1	873	15.6	77	13.6	10	22.2	6	21.4
Western Appalachia	4,838	54.8	3,217	57.5	334	58.8	23	51.1	16	57.1
Midwest	1,198	13.6	774	13.8	101	17.8	4	8.9	3	10.7
West	945	10.7	586	10.5	30	5.3	7	15.6	3	10.7
Smoking status at enrollment										
Never	1,802	20.4	1,048	18.7	14	2.5	6	13.3	6	21.4
Former	2,257	25.6	1,572	28.1	95	16.7	17	37.8	12	42.9
Current	4,770	54.3	3,287	58.8	459	80.8	22	48.9	10	35.7
Race										
White	8,403	95.2	5,578	99.8	26	4.6	1	2.2	6	21.4
Black	426	4.8	329	5.9	542	95.4	44	97.8	22	78.6
Body mass index										
Normal	3,850	43.6	2,408	43.1	292	51.4	18	40.0	7	25.0
Overweight	3,902	44.2	2,695	48.2	236	41.5	20	44.4	15	53.6
Obese	1,077	12.2	804	14.4	40	7.0	7	15.6	6	21.4

TABLE XII
 STANDARDIZED MORTALITY RATIOS (SMRS) FOR ALL CAUSE AND MALIGNANT UNDERLYING CAUSES OF
 DEATH WITH >25 OBSERVED DEATHS AMONG DECEASED COAL MINERS (N=5,907)

Cause	Observed	SMR (95% CI)
All causes	5,907	1.00 (0.97, 1.02)
All cancers	1,442	0.96 (0.91, 1.01)
Cancers of the digestive system and peritoneum		
Esophagus	43	1.01 (0.73, 1.36)
Stomach	45	0.96 (0.70, 1.28)
Intestine	125	0.95 (0.79, 1.13)
Biliary, liver, gall bladder	27	0.70 (0.46, 1.02)
Pancreas	66	0.88 (0.68, 1.11)
Cancers of the respiratory system		
Trachea, bronchus, lung	568	1.08 ^a (1.00, 1.18)
Cancers of the male genital organs		
Prostate	152	1.04 (0.88, 1.22)
Cancers of the urinary tract		
Kidney	28	0.76 (0.50, 1.09)
Bladder and other urinary site	40	0.94 (0.67, 1.28)
Cancers of the brain and other nervous	25	0.70 (0.45, 1.04)
Lymphatic and hematopoietic cancers		
Non-Hodgkin's lymphoma	51	0.93 (0.69, 1.23)
Multiple myeloma	28	1.11 (0.74, 1.60)
Leukemia	47	0.85 (0.63, 1.13)

a. $p=0.064$

2. Modified life table analysis

No significant difference was observed between the overall mortality experience of the cohort and the U.S. male population (SMR=1.00; 95% CI 0.97, 1.02) or with mortality from any specific cancer site (Table XII). A borderline significant deficit was observed for mortality from all cancers (SMR=0.96; 95% CI 0.91, 1.01; $p=0.10$), and a borderline significant excess was observed for lung cancer (SMR=1.08; 95% CI 1.00, 1.18; $p=0.06$). For lung cancer, SMRs were highest and significant among deaths occurring in later years of follow-up (SMR₁₉₇₀₋₁₉₈₉=0.95; 95% CI 0.83, 1.08; SMR₁₉₉₀₋₁₉₉₉=1.31; 95% CI 1.13, 1.49; SMR₂₀₀₀₋₂₀₀₇=1.23; 95% CI 1.02, 1.45; Table XIII).

SMRs for lung cancer varied by region, with significantly elevated risk in Western Appalachia and the Midwest. These findings may be partially confounded by smoking, the single strongest known risk factor for lung cancer, as the largest proportion of ever smokers was in the Midwest (82.9%) and the lowest proportion was in the West (77.0%). However, the percentage of ever smokers in Eastern Appalachia (79.3%) was not very different than the percentage in Western Appalachia (79.6%), where no excess lung cancer mortality was observed. A significant excess of lung cancer (SMR=1.13; 95% CI 1.04, 1.24) was observed among workers who had no evidence of pneumoconiosis at baseline, and there appeared to be a decreasing trend in SMRs for lung cancer with increasing evidence of pneumoconiosis based on radiograph at the start of follow-up (Table XIII).

Consistent with the previous follow-ups of this cohort, an overall excess of mortality was not observed for gastric cancer (SMR=0.96; 95% CI 0.70, 1.28; Table XII); however, a nonsignificant excess was observed in the last eight years of follow-up (SMR₂₀₀₀₋₂₀₀₇=1.53; 95% CI 0.93, 2.36; Table XIII).

A statistically elevated SMR was observed for multiple myeloma among black (SMR=2.84; 95% CI 1.08, 6.40) but not white (SMR=0.93; 95% CI 0.59, 1.43) miners, but this finding was based on only six cases among black miners.

3. Cox proportional hazards analysis

a. Lung cancer

Continuous CMD exposure was log-transformed, as it provided the best model fit (LRT Chi-square = 3.12, with no additional parameters). CMD exposure was positively and significantly associated with lung cancer mortality in both the dual-exposure model (including silica; HR=1.71; 95% CI 1.03, 2.85) and the single-exposure model (HR=1.70; 95% CI 1.02, 2.83; Table XIV). The association with untransformed (log linear) continuous CMD exposure was positive but not significant (coefficient from dual-exposure model = 0.0010, standard error [SE] = 0.0013). In contrast, respirable silica was not a significant predictor of lung cancer mortality in either the single- (HR=1.05; 95% CI 0.90, 1.23) or dual- (HR=0.99; 95% CI 0.84, 1.18) exposure models. As expected, the silica and CMD estimates were significantly but not strongly correlated (Pearson's correlation coefficient = 0.2919, $p < 0.01$.)

All measures of smoking were strong predictors of lung cancer mortality (pack-years: HR_{10 UNIT CHANGE}=1.24; 95% CI 1.18, 1.30; current smoking: HR_{FORMER VS. NEVER}=2.68; 95% CI 1.50, 4.79; HR_{CURRENT VS. NEVER}=9.20; 95% CI 5.30, 15.98). The risk of lung cancer mortality was over twice as high in the Eastern Appalachian, Western Appalachian, and Midwestern regions compared with the West (Table XIV).

Consistent with most other studies (Nonemaker et al. 2009; Kollarova et al. 2008; Calle et al. 2003; Whitlock et al. 2009; Leung et al. 2011), the risk of lung cancer declined across increasing levels of BMI (HR_{OVERWEIGHT VS. NORMAL}=0.84; 95% CI 0.70, 1.00; HR_{OBESE VS. NORMAL}=0.59; 95% CI 0.42, 0.82).

TABLE XIII

STANDARDIZED MORTALITY RATIOS (SMRS) FOR SELECTED UNDERLYING CAUSES OF DEATH AND PERCENTAGE OF EVER SMOKERS AT ENROLLMENT (AMONG THE DECEASED, N=5,907), BY REGION, RACE, RADIOGRAPHIC STATUS AT ENROLLMENT, AND CALENDAR YEAR OF DEATH

Category	Lung, Trachea, and Bronchus Cancers			Stomach Cancer			Ever Smoked at Enrollment	
	Obs.	SMR	(95% CI)	Obs.	SMR	(95% CI)	Percent	(95% CI)
All	568	1.08	(1.00, 1.18)	45	0.96	(0.70, 1.28)	79.6	(78.8, 80.3)
Region								
Eastern Pennsylvania	26	0.79	(0.51, 1.15)	1	0.33	(0.65, 1.82)	77.0	(73.8, 81.0)
Eastern Appalachia	77	1.01	(0.80, 1.26)	10	1.46	(0.70, 2.68)	79.3	(77.5, 80.1)
Western Appalachia	334	1.17 ^b	(1.05, 1.31)	23	0.89	(0.57, 1.34)	79.6	(78.4, 80.1)
Midwest	101	1.47 ^b	(1.19, 1.78)	4	0.68	(0.18, 1.78)	82.9	(80.7, 84.9)
West	30	0.49 ^b	(0.33, 0.69)	7	1.30	(0.52, 0.69)	77.0	(74.3, 79.6)
Race								
White	542	1.09 ^a	(1.00, 1.19)	44	1.05	(0.76, 1.41)	79.7	(78.9, 80.6)
Black	26	0.88	(0.58, 1.29)	1	0.20	(0.01, 1.12)	76.8	(72.6, 80.6)
Baseline radiograph								
Category 0	510	1.13 ^b	(1.04, 1.24)	35	0.88	(0.61, 1.22)	79.7	(78.9, 80.7)
Category 1	39	0.89	(0.63, 1.22)	4	1.00	(0.27, 2.56)	78.9	(75.6, 82.0)
Category 2	14	0.62	(0.34, 1.03)	4	1.80	(0.49, 4.60)	75.8	(70.8, 80.4)
Category 3	5	0.61	(0.20, 1.41)	2	2.51	(0.30, 9.05)	82.5	(73.7, 87.5)
Calendar year								
1970–1989	233	0.95	(0.83, 1.08)	9	0.73	(0.33, 1.38)		
1990–1999	208	1.31 ^b	(1.13, 1.49)	16	0.79	(0.45, 1.20)		
2000–2007	127	1.23 ^a	(1.02, 1.45)	20	1.53	(0.93, 2.36)		

a. Statistically significant at $p \leq 0.05$

b. Statistically significant at $p \leq 0.01$

i. **Sensitivity analysis – extended exposure estimates**

The mean extended cumulative CMD and respirable silica exposure estimates were 83.0 mg-year/m³ (SD=41.3) and 4.1 mg-year/m³ (SD=1.8), respectively. A 13% increase was seen in the coefficient for the exposure-response relationship for CMD and lung cancer for the extended estimates compared with the original estimates (0.1803 and 0.1600, respectively; Table XV). The coefficient for the association with silica exposure was positive but not statistically significant using the original estimates, and negative but not significant using the extended exposure estimates, possibly indicating exposure misclassification in the original estimates.

ii. **Sensitivity analysis – Round 4**

The mean cumulative CMD exposure for the 1,504 miners included in the sensitivity analysis was 51.1 mg-year/m³ (SD=37.7) using the estimates developed for Round 4, and 60.2 mg-year/m³ (SD=32.1; Table XVI) using the extended estimates developed for Round 1.

In this subset analysis with 58 lung cancer deaths, the log-transformed CMD variable did not improve the model, and the sensitivity analysis was conducted using the untransformed (log-linear) continuous CMD exposure variable. Both models (that using the Round 4 CMD exposure estimates and that using the extended Round 1 CMD exposure estimates) yielded similar findings, and there was no indication of a significant exposure-response association between CMD exposure and lung cancer, as both coefficients were close to zero (−0.0005 and 0.0001; Table XVII).

TABLE XIV

HAZARD RATIOS (HRS) FOR MORTALITY DUE TO LUNG CANCER MORTALITY (583 DEATHS) ESTIMATED IN COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH

Variables	Single-Exposure Models				Dual-Exposure Model	
	B coeff.	HR (95% CI)	B coeff.	HR ^a (95% CI)	B coeff.	HR (95% CI)
Exposures (mg-year/m ³)						
Cumulative						
Coal-mine dust (log) ^{a,b}	0.1271	1.70 (1.02, 2.83)			0.1290	1.71 (1.03, 2.85)
Respirable silica ^b			0.0191	1.05 (0.90, 1.23)	-0.0028	0.99 (0.84, 1.18)
Categorical						
Coal-mine dust						
<52.4		Ref.				Ref.
52.4–80.7	0.1354	1.15 (0.90, 1.47)			0.1062	1.11 (0.87, 1.43)
80.8–97.7	0.0356	1.04 (0.80, 1.36)			-0.0214	0.98 (0.73, 1.31)
≥99.7 [0.1831	1.20 (0.89, 1.62)			0.0959	1.10 (0.79, 1.53)
Respirable silica						
<2.22				Ref.		Ref.
2.22–3.30			0.0769	1.08 (0.85, 1.37)	0.0711	1.07 (0.84, 1.37)
3.31–4.12			0.1845	1.20 (0.95, 1.52)	0.1735	1.19 (0.93, 1.52)
≥4.13			0.1590	1.17 (0.92, 1.50)	0.1463	1.16 (0.88, 1.52)
Covariates						
Smoking status at enrollment						
Never		Ref.				Ref.
Former	0.9872	2.68 (1.50, 4.79)	0.9948	2.70 (1.51, 4.83)	0.9874	2.68 (1.50, 4.79)
Current	2.2190	9.20 (5.30, 15.98)	2.2268	9.27 (5.33, 16.11)	2.2195	9.20 (5.30, 16.00)
Pack-years at enrollment ^c	0.0213	1.24 (1.18, 1.30)	0.0212	1.23 (1.17, 1.30)	0.0213	1.24 (1.18, 1.30)

TABLE XIV (continued)

Variables	Single-Exposure Models				Dual-Exposure Model	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR ^a (95% CI)	<i>B</i> coeff.	HR (95% CI)
Region						
Eastern Pennsylvania	0.5029	1.65 (0.96, 2.86)	0.5407	1.72 (0.99, 3.00)	0.5018	1.65 (0.95, 2.86)
Eastern Appalachia	0.7547	2.13 (1.36, 3.33)	0.7907	2.20 (1.41, 3.45)	0.7538	2.13 (1.40, 3.32)
Western Appalachia	0.8224	2.28 (1.55, 3.35)	0.8212	2.32 (1.57, 3.42)	0.8242	2.28 (1.54, 3.36)
Midwest	0.9753	2.65 (1.76, 4.00)	0.9845	2.67 (1.77, 4.03)	0.9750	2.65 (1.76, 3.99)
West	Ref.				Ref.	
BMI						
Normal	Ref.				Ref.	
Overweight	-0.1771	0.84 (0.70, 1.00)	-0.1678	0.85 (0.71, 1.01)	-0.1776	0.84 (0.70, 1.00)
Obese	-0.5265	0.59 (0.42, 0.82)	-0.5185	0.60 (0.43, 0.83)	-0.5265	0.59 (0.42, 0.82)

a. Continuous CMD exposure was log-transformed.

b. Hazard ratios for continuous exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

c. Hazard ratios for pack-years of smoking were calculated for 10-unit change.

TABLE XV
 RESULTS OF SENSITIVITY ANALYSIS AMONG MINERS WITH KNOWN LAST DATE OF EMPLOYMENT
 (N=7,397) COMPARING ESTIMATED HAZARD RATIOS (HR) FOR LUNG CANCER MORTALITY (490 DEATHS)
 USING ORIGINAL AND EXTENDED EXPOSURE ESTIMATES^a

Variables	Original Estimates		Extended Estimates ^a	
	B coeff.	HR (95% CI)	B coeff.	HR (95% CI)
Exposure (mg-year/m ³)				
Cumulative exposure				
Coal-mine dust ^b (log)	0.1600	1.95 (1.17, 3.24)	0.1803	2.12 (1.16, 3.89)
Respirable silica	0.0165	1.04 (0.87, 1.26)	-0.0115	0.97 (0.83, 1.13)
Categorical exposure ^e				
Coal-mine dust				
Lowest quartile	Ref.			
Second quartile	0.0609	1.06, (0.81, 1.39)	-0.1793	0.84 (0.64, 1.09)
Third quartile	-0.0271	0.97 (0.72, 1.32)	-0.1253	0.88 (0.67, 1.17)
Highest quartile	0.0401	1.04 (0.74, 1.48)	-0.0642	0.94 (0.68, 1.29)
Respirable silica				
Lowest quartile	Ref.			
Second quartile	0.1514	1.16 (0.89, 1.52)	-0.0947	0.91 (0.69, 1.20)
Third quartile	0.3187	1.38 (1.05, 1.80)	0.3072	1.36 (1.04, 1.78)
Highest quartile	0.2365	1.27 (0.94, 1.71)	0.1269	1.14 (0.84, 1.54)
Covariates				
Smoking status at enrollment				
Never	Ref.		Ref.	
Former	1.0848	2.96 (1.55, 5.66)	1.0870	2.97 (1.55, 5.68)
Current	2.3468	10.45 (5.62, 19.44)	2.3508	10.49 (5.64, 19.52)
Pack-years at enrollment ^d	0.0207	1.23 (1.17, 1.30)	0.0207	1.23 (1.17, 1.30)
Region				
Eastern Pennsylvania	0.5270	1.69 (0.92, 3.13)	0.5109	1.67 (0.90, 3.08)
Eastern Appalachia	0.7326	2.08 (1.30, 3.34)	0.7237	2.06 (1.29, 3.31)
Western Appalachia	0.7112	2.04 (1.35, 3.08)	0.7321	2.08 (1.38, 3.14)
Midwest	0.9051	2.47 (1.60, 3.81)	0.9011	2.46 (1.59, 3.80)
West	Ref.		Ref.	

TABLE XV (continued)

Variables	Original Estimates		Extended Estimates ^a	
	B coeff.	HR (95% CI)	B coeff.	HR (95% CI)
BMI				
Normal	Ref.		Ref.	
Overweight	-0.1425	0.87 (0.72, 1.05)	-0.1463	0.86 (0.72, 1.04)
Obese	-0.5855	0.56 (0.38, 0.81)	-0.5841	0.56 (0.39, 0.81)

a. Estimated in Cox proportional hazards models controlling for age at study entry, race, and year of birth.

b. Continuous CMD exposure was log-transformed.

c. Categorical exposure was defined as quartiles among the deceased; upper boundaries of the first three quartiles are as follows: original CMD = 55.01, 83.05, and 110.14; extended CMD = 66.13, 92.02, and 120.87; original silica = 2.86, 3.33, and 4.18; extended silica = 2.67, 3.82, and 4.95.

d. Hazard ratios for pack-years of smoking were calculated for 10-unit change.

TABLE XVI
 DISTRIBUTION OF KEY CHARACTERISTICS FOR MINERS ORIGINALLY ENROLLED IN ROUND 1 AND
 INCLUDED IN THE ROUND 4 SENSITIVITY ANALYSIS (N=1,503)

Baseline Characteristic	N (Percent)
Race	
White	1,415 (94.2)
Black	88 (5.9)
Smoking status at enrollment	
Never	366 (24.4)
Former	584 (38.9)
Current	553 (36.8)
Region	
Anthracite [Authornote: Eastern Pennsylvania?]	0 (0.0)
Eastern Appalachia	259 (17.2)
Western Appalachia	894 (59.5)
Midwest	151 (10.1)
West	199 (13.2)
Body Mass Index	
Normal	350 (23.4)
Overweight	747 (49.7)
Obese	406 (27.0)
Baseline characteristic	Mean (SD)
Age (years) at start of follow-up	33.4 (7.5)
Years coal mining	9.2 (8.3)
Years underground	7.6 (8.0)
Years at the coal face	5.6 (7.8)
Cumulative exposure estimates (mg-year/m ³)	
Coal-mine dust	
Round 4	51.1 (37.8)
Original Round 1	30.3 (29.8)
Extended Round 1	60.2 (32.1)
Respirable silica (extended Round 1)	4.5 (2.2)

TABLE XVII

RESULTS OF SENSITIVITY ANALYSIS AMONG PARTICIPANTS ENROLLED IN ROUND 4 WITH A KNOWN LAST DATE OF EMPLOYMENT (N=1,503; 58 LUNG CANCER DEATHS) COMPARING ESTIMATED HAZARD RATIOS (HRS) FOR MORTALITY DUE TO LUNG CANCER USING CMD ESTIMATES DEVELOPED FOR ROUND 4 AND EXTENDED CMD ESTIMATES DEVELOPED FOR ROUND 1

Variable	Source of CMD Exposure Estimates			
	Round 4		Round 1 (Extended)	
	<i>B</i> coeff.	HR (95% CI)	<i>B</i> coeff.	HR (95% CI)
Exposures (mg-year/m ³)				
Cumulative				
Coal-mine dust (log) ^{a,b}	0.0001	1.01 (0.60, 1.68)	-0.0005	0.97 (0.52, 1.81)
Respirable silica ^{b,c}	0.0074	1.02 (0.68, 1.73)	-0.0064	0.98 (0.66, 1.47)
Smoking status at enrollment				
Never	Ref.		Ref.	
Former	0.7716	2.16, (0.78, 6.02)	0.7745	2.17 (0.78, 6.04)
Current	1.5108	4.53 (1.64, 12.51)	1.5156	4.55 (1.65, 12.56)
Pack-years at enrollment ^d	0.0124	1.13 (0.93, 1.38)	0.0123	1.13 (0.93, 1.37)
Region				
Eastern (Eastern Pennsylvania and Eastern Appalachia)	-0.0866	0.92 (0.48, 1.75)	-0.0762	0.93 (0.49, 1.77)
Midwest and West	Ref.		Ref.	

- a. Hazard ratios for cumulative exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³), controlling for age at study entry, race, and year of birth.
- b. Categorical exposure was defined as tertiles among the deceased; upper boundaries of the first two quartiles are as follows: both CMD estimates: 55.00 and 83.00; original silica: 2.60 and 3.90; and extended silica estimates: 3.50 and 5.10.
- c. Round 1 extended estimates were used for respirable silica.
- d. Hazard ratio for pack-years of smoking was calculated for the change in the hazard ratio for 10 units of exposure.

iii. **Time-varying covariates**

When stratified by follow-up time, the exposure-response associations between both CMD and silica and lung cancer mortality were positive and significant in the most recent follow-up period only (CMD $HR_{2000-2007}=1.41$; 95% CI 1.19, 1.67; and silica $HR_{2000-2007}=1.17$; 95% CI 1.11, 1.23; Table XVIII), which is consistent with both the long latency of this cancer and the mitigation of the HWE over time. Also consistent with the long latency of lung cancer were the results of stratifying by TSFE. The exposure-response associations between CMD and lung cancer mortality were positive and only significant in the 36-40 and the 41-50 years since first exposure-strata ($HR_{36-40YRS}=1.94$; 95% CI 1.61, 2.34; $HR_{<41-50YRS}=1.90$; 95% CI 1.47, 2.46; Table XIX). A similar pattern was observed for silica exposure however none the associations with silica exposure were significant within any level of TSFE.

In the analysis stratifying by TSLE groups, the exposure-response relationships between CMD and silica exposure with lung cancer mortality declined monotonically with increasing time after exposure ceased (Table XX). For both exposures, positive and significant associations were observed in the twelve years after exposure ended. In all models the addition of TSLE significantly improved the model fit and increased the estimate of the HR. In the model which included log-transformed CMD exposure the HR increased 20% with the addition of TSLE ($HR_{WITHOUT\ TSLE}$ 1.20, 95% 1.04, 1.39, and $HR_{WITH\ TSLE}$ 1.44, 95% CI 1.24, 1.91). In the model which included the continuous untransformed CMD exposure the HR increased 10% and became significant with the addition of TSLE ($HR_{WITHOUT\ TSLE}$ 1.13, 95% 0.95, 1.92, and $HR_{WITH\ TSLE}$ 1.26 95% CI 1.05, 1.51). In the model which included continuous respirable silica exposure the HR increased 13% with the addition of TSLE ($HR_{WITHOUT\ TSLE}$ 1.11, 95% 0.94, 1.32, and $HR_{WITH\ TSLE}$ 1.27, 95% CI 1.07, 1.51).

TABLE XVIII
HAZARD RATIOS (HRS) FOR MORTALITY DUE TO LUNG CANCER AS THE UNDERLYING CAUSE OF DEATH, STRATIFYING ON CALENDAR TIME (FOLLOW-UP TIME), ESTIMATED IN SINGLE-EXPOSURE COX PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH IN MODELS

Variables	B coeff.	HR ^b (95% CI)	B coeff.	HR ^b (95% CI)
	Coal-mine dust (log) ^a		Respirable silica	
Cumulative exposure (mg-year/m ³) by follow-up time				
Coal-mine dust (log) ^a				
1970–1989 (233 deaths)	0.0357	1.04 (0.82, 1.22)		
1990–1999 (208 deaths)	–0.0070	0.99 (0.85, 1.18)		
2000–2007 (127 deaths)	0.3445	1.41 (1.19, 1.67)		
Respirable silica				
1970–1989 (233 deaths)			0.0010	1.00 (0.77, 1.31)
1990–1999 (208 deaths)			–0.0214	0.94 (0.72, 1.24)
2000–2007 (127 deaths)			0.0156	1.17 (1.11, 1.23)
Covariates				
Smoking status at enrollment				
Never	Ref.		Ref.	
Former	1.2082	3.35 (1.88, 5.97)	1.2269	3.41 (1.91, 6.09)
Current	2.0462	7.74 (4.47, 13.5)	2.0666	7.89 (4.54, 13.7)
Pack-years at enrollment ^b	0.0156	1.17 (1.11, 1.23)	0.0156	1.17 (1.11, 1.23)
Region				
Eastern Pennsylvania	0.2239	1.25 (0.72, 2.17)	0.2380	1.27 (0.73, 2.20)
Eastern Appalachia	0.5262	1.69 (1.08, 2.66)	0.5852	1.80 (1.45, 2.81)
Western Appalachia	0.6633	1.94 (1.31, 2.87)	0.6893	1.99 (1.35, 2.95)
Midwest	0.7645	2.15 (1.42, 3.24)	0.7798	2.18 (1.45, 3.29)
West	Ref.		Ref.	
Body Mass Index				
Normal	Ref.		Ref.	
Overweight	–0.1504	0.86 (0.72, 1.02)	–0.1331	0.88 (0.74, 1.04)
Obese	–0.5650	0.57 (0.41, 0.79)	–0.5481	0.41 (0.41, 0.81)

a. CMD exposure was log-transformed.

b. Hazard ratios for pack-years of smoking were calculated for 10-unit change.

TABLE XIX
HAZARD RATIOS (HRS) FOR MORTALITY DUE TO LUNG CANCER AS THE UNDERLYING CAUSE OF DEATH
STRATIFYING ON TIME SINCE FIRST EXPOSURE (TSFE), ESTIMATED IN SINGLE-EXPOSURE COX
PROPORTIONAL HAZARDS MODELS CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF
BIRTH

Variables	B coeff	HR (95% CI)	B coeff	HR (95% CI)
Cumulative exposure (mg-year/m ³) stratified by TSFE				
Coal-mine dust (log) ^{a,b}				
≤35 years (33 deaths)	-0.1146	0.89 (0.67, 1.19)		
36–40 years (140 deaths)	0.6621	1.94 (1.61, 2.34)		
41–49 years (111 deaths)	0.6408	1.90 (1.47, 2.46)		
≥50 years (280 deaths)	0.1422	1.15 (0.95, 1.41)		
Respirable silica ^b				
≤35 years (33 deaths)			-0.3739	0.38 (0.18, 0.77)
36–40 years (140 deaths)			0.0463	1.13 (0.83, 1.53)
41–49 years (111 deaths)			0.0783	1.23 (0.83, 1.53)
≥50 years (280 deaths)			0.0479	1.13 (0.91, 1.41)
Covariates				
Smoking status at enrollment				
Never	Ref.		Ref.	
Former	1.0108	2.75 (1.54, 4.91)	1.0606	2.89 (1.62, 5.16)
Current	2.0693	8.14 (4.67, 14.17)	2.1639	8.71 (5.00, 15.15)
Pack-years at enrollment ^c	0.0205	1.23 (1.17, 1.29)	0.0199	1.21 (1.16, 1.28)
Region				
Eastern Pennsylvania	0.2772	1.32 (0.76, 2.30)	0.4404	1.55 (0.89, 2.71)
Eastern Appalachia	0.7240	2.06 (1.31, 3.25)	0.8230	2.28 (1.45, 3.58)
Western Appalachia	0.8152	2.26 (1.52, 3.35)	0.8985	2.46 (1.65, 3.64)
Midwest	0.8972	2.45 (1.62, 3.72)	0.9145	2.50 (1.65, 3.79)
West	Ref.		Ref.	
Body Mass Index				
Normal	Ref.		Ref.	
Overweight	-0.1360	0.87 (0.73, 1.04)	-0.1259	0.88 (0.74, 1.05)
Obese	-0.4635	0.63 (0.45, 0.88)	0.4588	0.63 (0.45, 0.88)

a. CMD exposure was log-transformed.

b. Hazard ratios for cumulative exposures were calculated for the change in the hazard ratio for mean exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

c. Hazard ratios for pack-years of smoking were calculated for 10-unit change.

TABLE XX

HAZARD RATIOS (HRS) FOR MORTALITY DUE TO LUNG CANCER AS THE UNDERLYING CAUSE OF DEATH, CONTROLLING FOR AND STRATIFYING ON TIME SINCE LAST EXPOSURE (TSLE), AMONG THE 7,397 MINERS FOR WHOM TERMINATION OF EMPLOYMENT DATE WAS OBTAINED, ESTIMATED IN SINGLE-EXPOSURE COX PROPORTIONAL HAZARDS MODELS

Cumulative Exposure (mg-year/m ³)	Coal-Mine Dust (Log) ^b			Respirable Silica ^{b,c}	
	Deaths	B coeff.	HR ^b (95% CI)	B coeff.	HR ^b (95% CI)
Stratifying by TSLE					
<5 years	85	0.9113	2.49 (1.87, 3.21)	0.1836	1.61 (1.10, 2.37)
5–11 years	121	0.6452	1.91 (1.46, 2.48)	0.1355	1.42 (1.02, 2.00)
12–18 years	138	0.1241	1.13 (0.91, 1.40)	0.0372	1.10 (0.79, 1.53)
>18 years	144	−0.3032	0.74 (0.60, 0.91)	0.0650	1.18 (0.89, 1.57)
Controlling for TSLE					
Without controlling for TSLE	490	0.1848	1.20 (1.04, 1.39)	0.0423	1.11 (0.94, 1.32)
Controlling for TSLE ^a	490	0.3622	1.44 (1.24, 1.91)	0.0928	1.27 (1.07, 1.51)
Coal-mine dust – without log transformation					
	Deaths	B coeff.	HR ^b (95% CI)		
Without controlling for TSLE	490	0.0020	1.13 (0.95, 1.92)		
Controlling for TSLE ^a	490	0.0036	1.26 (1.05, 1.51)		

- TSLE was included in the model as a continuous variable. The models also controlled for age at study entry, smoking status and pack-years at enrollment, coal-rank region, obesity, race, and year of birth.
- Continuous CMD exposure was log-transformed.
- Hazard ratios for cumulative exposures were calculated for the change in the hazard ratio for mean exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).

b. **Other cancer sites**

Cumulative CMD was not found to be associated with gastric cancer mortality (HR=0.82; 95% CI 0.44, 1.53; $p=0.55$). A positive but not significant association was seen between respirable silica exposure and gastric cancer mortality (HR=1.47; 95% CI 0.84, 2.56; $p=0.17$; Table XXI). The risk of gastric cancer mortality was more than two and a half times higher among former smokers compared with never smokers (HR=2.40; 95% CI 0.86, 6.74).

TABLE XXI
HAZARD RATIOS (HRS) FOR MORTALITY DUE TO GASTRIC CANCER ESTIMATED IN A COX PROPORTIONAL HAZARDS MODEL CONTROLLING FOR AGE AT STUDY ENTRY, RACE, AND YEAR OF BIRTH

Variable	Gastric Cancer (45 Deaths)	
	<i>B</i> coeff.	HR (95% CI)
Cumulative exposure (mg-year/m ³)		
Coal-mine dust ^a	-0.0029	0.82 (0.44, 1.53)
Respirable silica ^a	0.1425	1.47 (0.84, 2.26)
Smoking status at enrollment		
Never	Ref.	
Former	0.8769	2.40 (0.86, 6.74)
Current	0.9515	2.59 (0.91, 7.37)
Pack-years at enrollment ^a	-0.0083	0.92 (0.74, 1.14)
Region		
Eastern Pennsylvania, Eastern Appalachia	0.0096	1.01 (0.46, 2.22)
Midwest, West	Ref.	

- a. Hazard ratios for cumulative exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³).
- b. Hazard ratios for pack-years of smoking were calculated for 10-unit change.

In the most parsimonious model for multiple myeloma mortality, the relationship with CMD exposure was modified by race (p -value for interaction <0.01) such that the association was significant among black but not white miners. However, the numbers of deaths in each group were small ($HR_{\text{WHITE}}=1.56$; 95% CI 0.61, 3.99; $n=22$; $HR_{\text{BLACK}}=10.51$; 95% CI 2.93, 37.65; $n=6$; Table XXII). There was no evidence of a significant association between multiple myeloma and cumulative silica exposure.

TABLE XXII
ESTIMATED HAZARD RATIOS (HRS) FOR MORTALITY DUE TO MULTIPLE MYELOMA AS THE UNDERLYING CAUSE OF DEATH (N=28) AS ESTIMATED IN A COX PROPORTIONAL HAZARDS MODEL

Variable	B coeff.	HR (95% CI) ^a
Cumulative exposure (mg-year/m ³)		
Coal-mine dust modified by race ^b		
White (n=22 cases)	0.0069	1.56 (0.61, 3.99)
Black (n=6 cases)	0.0364	10.51 (2.93, 37.65)
Respirable silica exposure	-0.1988	0.58 (0.24, 1.38)
Smoking status at enrollment		
Never	Ref.	
Former	1.1407	3.13 (1.02, 9.57)
Current	0.7112	2.04 (0.61, 6.81)
Pack-years at enrollment	-0.0328	0.83 (0.50, 1.03)
Age	0.0642	1.89 (1.03, 3.50)

a. P -value for interaction between cumulative coal-mine dust exposure and race = 0.007.

b. Hazard ratios for cumulative exposure were calculated for the change in the hazard ratio for mean cumulative exposure (CMD = 64.6 mg-year/m³; silica = 2.6 mg-year/m³),

c. Hazard ratios for pack-years of smoking and age were calculated for 10-unit change.

D. Discussion

This is the first in-depth exploration of mortality from lung cancer and other cancers in the NSCWP. Our exploration of the association between lung cancer and CMD exposure was enhanced by the extended follow-up period to 37 years, the addition of cumulative silica exposure estimates, and the investigation of time-varying cofactors including follow-up time, TSFE, and TSLE. The additional number of deaths accumulated in the extended follow-up also allowed for the analysis of less common cancers, including stomach cancer and multiple myeloma. We also conducted a sensitivity analysis to assess the robustness of our exposure estimates, which were previously only derived up to time of study enrollment.

1. Lung cancer

Lung cancer is the leading cause of cancer mortality among U.S. males; in 2003–2007, the annual age-adjusted mortality rate was 68.8/10,000(ACS 2011). We observed an overall excess of lung cancer mortality (SMR=1.08; 95% CI 1.00, 1.18) in this cohort. In contrast, many earlier studies have reported a strong deficit in lung cancer mortality among coal miners (Liddell 1973; Costello, Ortmeyer, and Morgan 1974; Rooke et al. 1979; Atuhaire et al. 1986). When stratified by calendar time, only the SMR for lung cancer in the last follow-up period (2000–2007) was significant. This finding is consistent with the long latency period for lung cancer. It may also be that competing causes of death resulted in underdiagnoses of lung cancer, especially in the earlier years of this cohort, when dust exposures were at their highest. Miners with lung cancer and NMRD, both of which are caused by dust exposures, may

have been more likely to die from the NMRD before neoplastic process of lung cancer could progress to the point of diagnosis.

We observed an inverse trend with lung cancer mortality and CWP, which could be viewed as a marker of CMD exposure, has similarly been reported to be inversely related to lung cancer mortality in several cohorts [James 1955, Liddell 1973, Rooke, et al. 1979]. In the current study, the findings for CWP are likely attributable, at least in part, to selection biases, which may have occurred because this study relied on a cross-sectional sampling of coal miners, many of whom were well into both their work and smoking experience when enrolled. Downward bias from the healthy worker survivor effect (HWSE) may have occurred if miners who smoked or had higher dust exposures and were at increased risk of lung cancer were more likely to leave work before other men their age and, therefore, were not eligible for enrollment. It is also possible that men with more advanced CWP are more likely to cease or reduce cigarette smoking and, hence, be afforded some protection from lung cancer.

In sharp contrast to other studies, we saw a strong and significant association with cumulative CMD exposure and lung cancer. This association with CMD was present in models with and without silica exposure, and in all models the coefficients for CMD were larger than those for silica exposure. In the current study, we saw significant associations between both CMD and respirable silica exposure with lung cancer mortality in the most recent follow-up period only, 2000–2007. This observation is consistent with the long latency of lung cancer, the mitigation of the HWE over time, and the possibility of competing causes of mortality, especially from NMRD in the earlier years of this cohort, as described previously. In the most recent follow-up of the British cohort, an overall significant exposure-response relationship was observed with silica but not CMD exposure (Miller and MacCalman 2010). The British cohort had a longer follow-up time than our study (1959–2005 and 1969–2007, respectively) and,

therefore, accumulated a higher percentage of cases in the later follow-up period compared with our study (44% vs. 22%). As such, the summary HRs reflected the case distribution. The greater weight of the earlier follow-up periods in our study may have contributed to the overall nonsignificant effect estimate for silica in our study.

In the analysis of TSLE, conducted among the 83% of the cohort for whom termination of employment date was known, both CMD (log-transformed) and silica were significant predictors of lung cancer in the early time period. In all single-exposure models, including CMD as a log-transformed variable, untransformed CMD, and respirable silica, the addition of TSLE significantly improved the model fit and increased the estimate of the HR, clearly demonstrating that in this study controlling for TSLE can reduce at least some bias from the HWSE. The inability of this and other occupational studies to fully control for this selection force can lead to downward bias in the overall effect estimates. Robins and Hernán have proposed methods to more completely adjust for this effect, but such methods have not been successfully extended to occupational studies (Hernan, Brumback, and Robins 2000; Robins et al. 1992)

The analysis of TSLE also provided some insights into how mortality rates vary by work status. The risk of death from lung cancer associated with CMD declined with time after leaving work. The same pattern was seen for the association between CMD and gastrointestinal cancer (excluding gastric cancers) mortality (data not shown). Hence, the observations may, at least in part, reflect the tendency for mortality rates to rise in the time period immediately following leaving work. This tendency was previously described by Richardson and colleagues (2004), who proposed that such a trend likely reflects aspects of selection due to the HWSE (i.e., selection correlated with exposure whereby workers with symptoms and advanced disease leave work before other workers their age).

Coal dust is classified as a Group 3 carcinogen (not classifiable as a human carcinogen) by the International Agency for Research on Cancer (IARC) (1997). Inhaled crystalline silica is classified as a Group 1 lung carcinogen by IARC (1997) based on evidence from both epidemiologic and toxicologic studies. This conclusion was supported by a meta-analysis of the evidence from 1996 to 2005, which found a pooled relative risk from cohort studies of lung cancer due to silica exposure of 1.34 (95% CI 1.25, 1.45; n=28 studies) using random effects models (Pelucchi et al. 2006).

The observed deficit of lung cancer among coal miners, which has been reported from other studies, has been attributed to the prohibition against smoking in underground mines (Miller and MacCalman 2010) as well as the theory that clay particles may partially detoxify silica by coating it, thereby potentially rendering it less carcinogenic among coal miners (Harrison J. 1997). These factors may downwardly bias estimates from our and other studies in coal miners.

Smoking is the single strongest risk factor for lung cancer incidence. U.S. male smokers are about 23 times more likely to develop lung cancer than nonsmokers (ACS 2011). In our models, all measures of smoking at enrollment were strong predictors of lung cancer mortality. At enrollment, approximately 80% of our study participants were current or former smokers. Compared with the general U.S. male population in 1970, the miners in our study were more likely to be current smokers but on average smoked fewer cigarettes per day (Table XXIII). The reduced amount of cigarette consumption may be explained, by the prohibition on smoking in the mines. Whatever other factors may contribute to lung cancer incidence and mortality in this population, interventions to reduce smoking and smoking initiation among miners and their communities should be investigated.

Our finding that obesity was protective for lung cancer mortality is consistent with other studies' findings of an inverse association between increased BMI and lung cancer risk (Kollarova et al.

2008), survival (Yang et al. 2011), and mortality (Nonemaker et al. 2009; Whitlock et al. 2009; Leung et al. 2011). The protective effect of BMI on lung cancer mortality could be due to lower BMI among smokers and, therefore, to inadequate control for smoking. The protective effect of increased BMI was stronger among smokers than nonsmokers for lung cancer survival and mortality in two U.S. studies (Calle et al. 2003; Yang et al. 2009) but not in a Chinese study (Leung et al. 2011).

While BMI has an inverse relationship with lung cancer mortality, the opposite is true for most other cancers (Calle et al. 2003). In our study, BMI was not a significant risk factor for death from other cancers examined, including stomach cancer.

TABLE XXIII

COMPARISON OF SMOKING STATUS AND FREQUENCY BETWEEN MEN ENROLLED IN ROUND 1 OF THE NSCWP (BETWEEN 1969 AND 1971), AND THAT OF THE GENERAL U.S. MALE POPULATION IN 1970, AS ESTIMATED BY THE NATIONAL HOUSEHOLD INTERVIEW SURVEY

Variable	NSCWP		Percent	NHIS	
	Percent	(95% CI)		(95% CI)	
<u>Smoking status</u>					
Current	54.0	(53.0, 55.0)	44.1	(43.3, 44.9)	
Former	25.6	(24.7, 26.5)	26.3	(25.6, 27.1)	
Never	20.4	(19.6, 21.2)	29.6	(29.0, 30.2)	
<u>Smoking frequency: cigarettes per day</u>					
≤14	31.8	(30.8, 32.8)	27.3	(26.3, 28.3)	
15–24	55.8	(54.8, 56.9)	44.7	(43.7, 45.7)	
≥25	12.4	(11.7, 13.1)	28.0	(27.0, 29.0)	

2. Other cancers

Among black but not white miners, we observed both a significant excess risk of multiple myeloma and a significant positive exposure-response association with CMD exposure and mortality due to multiple myeloma. To our knowledge, excess mortality from multiple myeloma has not been previously reported among coal miners. Multiple myeloma is a cancer of the plasma cells that has higher incidence and mortality rates among African Americans in the U.S. (Alexander et al. 2007). Our findings of a race-specific excess risk, while intriguing, were based on only eight cases among black miners and, hence, may be an area for further research.

Unlike most other studies of mortality among coal miners, we did not observe an overall excess of stomach cancer. Consistent with the most recent follow-up of the British cohort (Miller and MacCalman 2010), we did not see a significant exposure-response relationship for either CMD or silica dust exposure with stomach cancer mortality.

align the previously published decision to omit post-1969 exposures (Attfield and Kuempel 2008). The analysis of the original and extended estimates indicated that there may have been some additional contribution of CMD exposure to lung cancer deaths after enrollment, but the majority of the contribution appeared to have occurred in pre-enrollment exposure. A limitation in this analysis was the assumption that a miner continued work in the same job and at the same level of exposure. If systemic change in exposure over time due to change in job had occurred, it seems most likely that it would be due to workers moving to lower exposure jobs over time. If this were the case, our extended estimates could be an overestimation of total cumulative exposure.

3. Limitations

This study had a number of limitations, particularly related to exposure estimation. Perhaps of greatest concern is the lack of job histories after study enrollment, on which exposure estimates were based. In previous studies of this cohort, it was proposed that exposure misclassification may have been minimal because the miners were enrolled at an average age of 45 years and after an average of 20 years working as a miner; as such, most of their exposure was likely accumulated before enrollment. Also, most of the cohort's heavy exposures occurred before mandatory dust control in U.S. coal mines was implemented in 1969. Our sensitivity analysis to test these assumptions found no meaningful differences between the exposure-response relationships for lung cancer mortality using the original and extended estimates for either CMD or silica exposure; these findings lend empirical support to the aforementioned assumptions.

Our silica estimates were based on MSHA compliance data from 1982–2002, more removed in time than the sampling data used to develop the CMD estimates. An assumption made in our estimation was that the proportion of silica in the dust during this time period would be the same as that in earlier time periods. This assumption, as well as our application of job group-based estimates to specific jobs, may have caused exposure misclassification.

E. **Conclusion**

Our findings provide evidence that coal miners are at increased risk for lung cancer. These findings are in stark contrast with those from earlier studies. The increased lung cancer mortality was observed to increase with cumulative CMD, a finding not previously reported. Our findings suggest a need for a reevaluation of the carcinogenicity of CMD exposure, which has been classified by the IARC as group 3 (unlikely). They also suggest a need for continued investigation of lung cancer mortality and incidence among coal miners, especially in the modern-day mining industry, where the prevalence of CWP has been increasing (Laney and Attfield 2010).

V. PREVALENCE AND PREDICTORS OF RESPIRATORY SYMPTOMS AMONG UKRAINIAN COAL MINERS

A. Introduction

Occupational exposure to CMD continues to cause respiratory disease including pneumoconiosis, lung function impairment and increased frequency of respiratory symptoms worldwide (Cohen, Patel, and Green 2008; NIOSH. 1995). There are over 300,000 workers employed in the coal mining industry in Ukraine (<http://www.euracoal.be/pages/layout1sp.php?idpage=269>, accessed May 20, 2011). Ukraine's current energy plan, "Energy Strategy to 2030," proposes a significant increase in coal production by the year 2015. However there is a paucity of information on the burden of respiratory disease among Ukrainian coal miners.

This study was conducted through a Fogarty International Center-supported collaboration between researchers at the Great Lakes Centers of the UIC-School of Public Health (UIC) and the Institute of Occupational Medicine (IOM) in Kyiv, Ukraine. The UIC Fogarty grant for "International Training and Research in Environmental and Occupational Health" (ITREOH) supported the research training of Ukrainian investigators in epidemiologic methods, exposure assessment, pulmonary function testing, and standardized reading of pneumoconiosis chest X-rays. The specific aim of this study was to estimate the prevalence of, and risk factors for, respiratory symptoms and disease among Ukrainian underground coal miners.

An exposure-response relationship between cumulative CMD exposure and chronic bronchitis has been demonstrated in cross sectional and longitudinal studies from the United States and the United

Kingdom (Seixas et al. 1992; Henneberger and Attfield 1997; Lewis et al. 1996; Marine, Gurr, and Jacobsen 1988; Kibelstis et al. 1973). An excess of respiratory symptoms has been observed even among U.S. miners who had the majority of their exposure after the enactment of the current permissible exposure limit of 2 mg/m^3 (Seixas et al. 1992). The deleterious effects of CMD exposure on pulmonary function have been found both among smokers and non-smokers. In an autopsy study including lung sections from 722 U.S. coal miners, coal mine dust accumulation significantly predicted emphysema after adjusting for smoking, age at death and race (Kuempel et al. 2009).

Our study of Ukrainian coal miners employed a cross-sectional design. In occupational settings, cross-sectional studies of diseases with long latencies, such as chronic respiratory illness, are especially prone to downward selection bias from the healthy worker survivor effect (HWSE) (Checkoway, Pearce, and Kriebel 2004). The HWSE may result when workers who are more susceptible to the effects of work-related exposures either leave employment or move to jobs with lower levels of exposure more frequently than workers who are not as susceptible to the exposure effects. Employment status is a key component of the HWSE (Fox and Collier 1976; McMichael 1976) hence we studied both current and former coal miners, and from the latter group collected information on reason for leaving work as a coal miner.

We present the lessons learned from our collaboration and the results from our study of the respiratory status of Ukrainian coal miners.

B. **Methods**

1. **The collaboration: goals and approach**

This study was the result of a capacity-building collaboration started by the American International Health Alliance (AIHA), a grantee of the United States Agency for International Development (USAID). The collaboration was developed between Hospital #25, which is the large primary care hospital and clinic in the city of Donetsk, Ukraine and U.S. partners that included the Magee Women's Hospital, the University of Pittsburgh School of Public Health, the University of Pittsburgh Medical Center Department of Family Medicine and Clinical Epidemiology, the UIC School of Public Health, and the health and safety department of the United Mine Workers of America. The goal of this collaboration was to develop sustainable infrastructure for coal miner's health clinics including proper medical surveillance for respiratory disease. Staff members from Hospital #25 completed NIOSH certification in spirometry, B-reading training, and training in questionnaire development. Relationships were fostered between the scientists from IOM, UIC, and personnel from Hospital #25. The research training was further supported by the Fogarty ITREOH grant.

2. **Study location**

The study was conducted in the heart of the Ukrainian coal-mine industry, the Donbass, within the city of Donetsk. Three coal mines were selected for the study based on their long standing association with City Hospital #25 where the mandatory annual medical surveillance examinations were conducted. The selected mines were deep-shaft anthracite coal mines typical of the region; they ranged in depth from 800 to 1500 meters. All three mines used long-wall mining, Mine 2 also used conventional

mining techniques, including drilling and blasting to create tunnels; Mine 3 used a combination of conventional and modern mining methods.

An assessment of CMD levels was conducted in concert with the health survey and found that respirable dust exposures in the three mines were high compared to those in the U.S.: 75% of all samples exceeded the current U.S. permissible exposure level (PEL) of 2 mg/m³ and 37% of samples exceeded the PEL for quartz. During mining activities no significant differences in CMD levels were observed at different locations within the mines. However, in Mine 2 total dust concentrations were significantly lower during mining activities and concentrations of quartz were significantly lower during development activities (such as digging tunnels) compared to the other two mines. Production levels, reported by mine management, were also lower for Mine 2 compared with the other two mines. The sampling did not include enough job categories or conditions to facilitate estimation of exposure for the study miners [Written communication, Kathleen Kennedy MPH, Chicago, 2002].

3. **Study design and sampling strategy**

Separate cross-sectional surveys of working and former underground coal miners were conducted in 2000 and 2002, respectively. Personnel departments at each study mine provided lists of current and former miners.

Miners age 30 or older were eligible for enrollment into the study of currently working underground coal miners (current miners). Older miners were oversample to ensure that stable estimates of disease rates could be obtained for that group. The population of miners was stratified by mine and then by the following age tertiles: 30-45, 46 - 61, and ≥ 62 - 72 years. A random sample was drawn from each mine-age strata so as to have an approximately equal number of potential participants

from each stratum. For former miners, the sampling was designed to ensure stable estimates of symptom prevalence within each of 3 inclusive categories of the reason for employment termination: pensioned, disabled, or other (included any other reason for employment termination). A random sample was drawn from each strata of reason for leaving work.

4. **Data collection**

A survey modeled on the American Thoracic Society and the U.S. National Institute for Occupational Safety and Health (NIOSH) instruments was administered to participants by trained interviewers. The survey collected information on demographics, respiratory symptoms and illnesses, work histories, history of tobacco use, and among former miners, reason for leaving work. Study participants underwent spirometry testing and received chest x-rays, results of which will be reported elsewhere.

5. **Definitions of symptom and illness**

Chronic bronchitis was defined as having both usual cough and phlegm, defined thusly:

- **Usual cough**: Having a cough on most days of the week for 3 consecutive months or more during the year, and having one or more of the following: coughing as much as 4-6 times a day; usually coughing at all on getting up; or, any usual coughing during the rest of the day.
- **Usual phlegm**: Bring up phlegm on most days of the week for 3 consecutive months or more during the year, as well as one or more of the following: usually bringing up phlegm as much as twice a day; usually bringing up phlegm at all on getting up; or, usually bringing up phlegm at all during the rest of the day.

- Shortness of Breath (SOB): Being “troubled by shortness of breath when hurrying on the level or walking up a slight hill” and one or more of the following: having to walk slower than people of your age on the level because of breathless; having to stop for breath after walking about 100 yards on the level; or, being too breathless to leave the house or breathless on dressing or undressing.

Statistical methods

Overall study response rates were calculated as the percentage of miners who completed a survey among those whom were selected to participate, as well as within major sampling strata (i.e. by mine for current miners and by reason for leaving work for former miners).

6. **Prevalence of respiratory symptoms and sample weights**

Characteristics of study miners including demographics, mining history, and smoking were described for current and former miners. Weighted prevalence rates and 95% confidence intervals were calculated for chronic bronchitis and SOB among former and current miners alone and within levels of demographic, work, and smoking characteristics. Because a stratified sampling design had been used, relative sample weights were developed and assigned to each observation and used for all analyses. These sample weights were used in order to present estimates of population characteristics (rather than sample characteristics) and to obtain correct standard errors for statistical testing. The population weights were calculated by taking the inverse of the selection probability for the sampling strata. Relative weights were then obtained by dividing the population weight by the average population weight (Kalton 1983).

Current miners lacked data on smoking quantity, so for that group years-of smoking was used for analysis rather than pack-years of smoking. Missing data values represented less than 3% of any one

variable; they were recoded to the most prevalent level for categorical variables and the median for continuous variables by employment status.

7. **Multivariate analysis of prevalence and risk factors**

Because of the cross-sectional study design, binomial regression was used to assess the exposure-response association between duration of coal mining and chronic bronchitis and SOB and to evaluate risk factors. Since there were no reliable estimates of CMD levels from the study mines, duration of mining was used as a proxy for CMD exposure. Because exposures are generally highest at the coal face, the relationship between duration of mining at the coal face and respiratory symptoms was also explored. Different forms of the exposure-response relationship (e.g. categorical, log-linear, adding a quadratic term) were assessed while including all covariates in the model. Best model fit was determined using the likelihood ratio test (LRT). Effect modification with the exposure terms was evaluated by including a cross-product term of each covariate with the exposure and considered present if the associated P-value was significant at the alpha level of <0.10 . Covariates or combinations of covariates were included in the model if their addition resulted in a change of greater than 10% in the estimate of the prevalence ratio (PR) or if the model fit was improved as demonstrated by the LRT. A priori all models included age and smoking. In multivariate models, prevalence ratios are presented for a ten-year increase in exposure duration.

8. **Evaluation of reason for leaving work**

The role of reason for leaving work was explored as a potential confounder or effect modifier of the exposure-response relationship observed between years mining and respiratory

symptoms. This analysis included former miners aged 65 and younger and excluded the subgroup of miners who reported previously working in another dusty industry.

9. **Human subject's protection**

The study was approved by the UIC, Institutional Review Board (protocol #2000-0578.) and by the Scientific Council of the IOM, Academy of Medical Sciences of Ukraine through a Single Project Assurance (SPA# S-022277-01). All participants were administered and signed informed consent.

C. **Results**

1. **Accomplishments and lessons learned from the collaboration**

The team of U.S. and Ukrainian investigators was able to successfully leverage the modest resources provided through the AIHA USAID grant and Fogarty ITREOH grant to establish a research program that addressed public health and scientific issues of importance for both countries. The key success factors were the individual investigators' commitment to promoting the health and safety of coal miners; the high-level endorsement of the research program by Ukrainian IOM and the Ukrainian Academy of Medical Sciences; the significantly lower cost for scientific manpower in Ukraine; and the strategic investment in research training that could support a long-term research program. Salary support for Ukrainian collaborators was provided in large part by the Ukrainian Ministry of Health and Academy of Medical Sciences and, in part, through the Fogarty ITREOH grant.

The partnership developed during this work transformed the surveillance examinations performed for coal miners. Spirometry testing was improved from use of a non-recording Wright type

spirometer to the standards recommended by the ATS and the European Respiratory Society. Chest radiography was improved from mass miniature x-ray screening to full size 14 X 17 inch PA chest radiographs, read using ILO standards. Standardized respiratory questionnaires were developed based on NIOSH and ATS standards. These techniques were incorporated into the routine medical examinations for coal miners conducted by Hospital #25.

Data management for the study was done by the UIC Data Management Center in Kyiv. This research collaboration model on coal miners' health was officially adopted as a part of the work plan of the World Health Organization network of Collaborating Centers in Occupational Health.

2. **Study enrollment**

Potential participants included 1,061 current and 1,124 former miners of whom 53.9% (n=592) and 42.1% (n=473), respectively, completed the survey. Response rates varied by sampling strata: among active miners the rates were highest from Mine 1 (68.9%) and lowest among enrollees from Mine 3 (47.3%); among former miners response rates were 33.0% among retired miners and 44% among miners who left work because of disability or for another reason.

3. **Prevalence of respiratory symptoms**

As expected, current miners were on average younger than former miners (mean age 47.1, range 30 to 72 years, and mean 56.7 years range 29 to 81, respectively; Table XXIV). The two groups were otherwise similar in terms of smoking habits, nationality and by average years mined and worked at the coal face. The similar tenure in the current and former miners may, in part, be due to the

latter having a relatively high proportion of miners (38%) who left work before being pensioned and hence presumably accumulated less tenure.

The prevalence of SOB was seven times higher among former compared to current miners, while the prevalence of chronic bronchitis was similar (Table XXV). Respiratory symptoms increased with age and years mining. Interestingly among men who worked at the coal face a bimodal distribution was observed, with the highest prevalence rates among miners who had worked at the face for less than ten and greater than 25 years. Rates of respiratory symptoms were lowest among miners who had left work for a reason other being pensioned or disabled.

TABLE XXIV
CHARACTERISTICS OF MINERS WHO COMPLETED THE SURVEY BY EMPLOYMENT STATUS

	Current Miners (n=592)		Former Miners (n=473)	
<i>Variable (unit = years)</i>	Weighted Mean^a	(Std. Dev.)	Weighted Mean^a	(Std. Dev.)
Age at survey	47.1	(9.3)	56.7	(11.2)
Duration of work as a coal miner	22.6	(9.5)	20.6	(10.6)
Duration of work at the coal face	8.1	(11.0)	7.7	(12.0)
Cigarette smoking	19.6	(13.8)	26.3	(17.2)

Variable	Weighted Percent^a	(Count)	Weighted Percent^a	(Count)
Smoking status				
Current	64.0	(351)	64.9	(313)
Former	15.1	(108)	18.5	(83)
Never	20.9	(133)	16.6	(77)
Mine				
Mine 1	39.4	(258)	31.8	(128)
Mine 2	31.9	(117)	28.3	(144)
Mine 3	28.6	(217)	40.0	(201)
Nationality				
Ukrainian	53.1	(332)	53.8	(248)
Russian	42.2	(231)	39.2	(196)
Other	4.7	(29)	7.0	(29)
Worked in other dusty industry				
Yes	11.1	(62)	6.3	(30)
Reason left work				
Disabled			7.4	(137)
Pensioned			31.9	(157)
Other ^b		n/a	60.7	(179)

- a. All analyses used relative sample weights, i.e. the population sample weight (the inverse of the selection probability for the sampling strata) divided by the average population weight.
- b. Other reasons for leaving work, which included voluntary termination (quitting) or involuntary termination (being laid-off or fired)

TABLE XXV
PREVALENCE OF RESPIRATORY SYMPTOMS OF CURRENT AND FORMER MINERS WITHIN LEVELS OF DEMOGRAPHIC, WORK, AND SMOKING CHARACTERISTICS

Variables	CURRENT COAL MINERS (n=592)								FORMER COAL MINERS (n=473)							
	CHRONIC BRONCHITIS				SHORTNESS OF BREATH				CHRONIC BRONCHITIS				SHORTNESS OF BREATH			
	N	% ^a	(SE) ^b	P-value ^c	n	%	(SE)	P-value	n	%	(SE)	P-value	n	%	(SE)	P-value
Respiratory symptoms																
Chronic bronchitis	69	13.9	(1.9)						90	18.1	(2.1)					
Shortness of breath					36	5.1	(1.2)						174	35.6	(2.6)	
Age at survey																
<=45	28	14.6	(3.0)		7	3.8	(1.7)		13	12.3	(3.8)		16	9.4	(3.0)	
46 - 55	17	14.5	(3.3)		8	6.1	(2.2)		29	21.2	(4.1)		35	26.0	(4.4)	
56 - 65	13	10.1	(3.1)		11	4.6	(1.8)		21	18.3	(4.6)		48	42.1	(6.1)	
65+	11	22.0	(6.0)	0.3175	10	17.0	(5.3)	0.0161	27	18.4	(3.7)	0.5177	75	51.9	(4.9)	<.0001
Years mined																
5 - 14	8	10.7	(4.1)		1	1.0	(0.9)		17	6.5	(2.0)		39	19.2	(3.6)	
15 - 24	26	14.2	(2.9)		11	5.6	(2.0)		35	20.0	(3.6)		59	30.5	(4.2)	
25 - 34	15	16.2	(4.2)		5	4.5	(2.2)		20	27.5	(6.0)		40	54.4	(6.7)	
>=35	20	14.8	(3.7)	0.7955	19	9.8	(2.8)	0.0621	16	23.8	(5.9)	0.0019	36	54.2	(7.0)	<.0001
Years working at the face																
None	27	9.6	(2.1)		7	1.9	(1.1)		37	15.1	(2.6)		82	32.6	(3.5)	
>0 - 10	12	24.4	(7.2)		7	11.0	(5.4)		14	23.3	(6.4)		27	42.2	(7.1)	
11 - 20	13	17.5	(5.0)		6	4.9	(2.2)		14	14.3	(5.0)		18	21.8	(6.5)	
>20	17	19.9	(4.0)	0.0703	16	8.5	(3.3)	0.0246	25	23.3	(4.9)	0.2868	47	45.2	(5.9)	0.0544
Smoking status																
Current	48	16.9	(2.5)		18	5.8	(1.6)		65	19.9	(2.6)		103	32.9	(3.2)	
Former	13	10.7	(3.3)		11	4.9	(1.7)		11	14.8	(4.8)		36	43.9	(6.4)	
Never	8	7.4	(3.2)	0.0653	7	2.9	(1.2)	0.3387	14	14.4	(4.6)	<.0001	35	37.0	(6.7)	<.0001

TABLE XXV (continued)

Variables	CURRENT COAL MINERS (n=592)							FORMER COAL MINERS (n=473)								
	CHRONIC BRONCHITIS				SHORTNESS OF BREATH			CHRONIC BRONCHITIS				SHORTNESS OF BREATH				
	N	% ^a	(SE) ^b	P>z ^c	n	% ^a	(SE) ^b	P>z ^c	n	% ^a	(SE) ^b	P>z ^c	n	% ^a	(SE) ^b	P>z ^c
Years smoked																
None	8	7.4	(3.2)		7	2.9	(1.9)		14	14.1	(4.5)		36	38.0	(6.7)	
<=20	13	6.7	(1.9)		7	2.2	(1.0)		6	9.7	(5.1)		14	17.6	(6.0)	
21 - 30	27	24.7	(4.7)		12	9.6	(3.2)		19	15.4	(3.8)		29	22.9	(4.6)	
>30	21	16.1	(3.7)	0.0005	10	5.0	(1.9)	0.0372	51	22.8	(3.3)	0.0202	95	45.4	(4.0)	0.0147
Mine																
Mine 1	23	8.7	(1.8)		5	1.6	(0.7)		23	18.2	(3.9)		40	32.1	(4.7)	
Mine 2	28	25.2	(4.2)		15	9.7	(3.1)		46	17.0	(3.7)		67	47.7	(5.1)	
Mine 3	18	8.6	(2.1)	<.0001	16	4.8	(1.4)	0.0012	41	18.7	(3.3)	0.3286	67	29.8	(3.9)	<.0001
Nationality																
Ukrainian	37	12.2	(2.2)		30	7.7	(1.7)		41	15.2	(2.6)		95	38.7	(3.7)	
Russian	27	14.8	(3.0)		4	2.1	(1.4)		38	19.4	(3.5)		68	30.3	(4.0)	
Other	5	26.0	(10.9)	0.2797	2	2.5	(1.6)	0.0243	11	32.8	(9.9)	0.1007	11	41.7	(10.9)	0.2774
Reason left work																
Disabled									28	22.2	(3.7)		63	50.0	(4.4)	
Pensioned									37	22.4	(3.7)		67	43.7	(4.0)	
Other ^d					n/a				25	15.2	(2.9)	0.1043	44	29.6	(3.7)	0.0011

a. All analyses used relative sample weights, i.e. the population sample weight (the inverse of the selection probability for the sampling strata) divided by the average population weight.

b. Standard errors of the weighted percentage, calculated using relative sample weights

c. The p-value for nominal variables is associated with the Rao-Scott chi-square statistic, it was computed from the Pearson chi-square statistic with a design correction based on the design effects of the proportions; the p-value for ordinal variables is associated with the chi-square test for nonzero correlation with a design correction and can be interpreted as a test for trend

d. Other reasons for leaving work included voluntary termination (quitting) or involuntary termination (laid-off or fired)

4. **Multivariate analysis of prevalence and risk factors**

Duration of working at the coal face was a strong predictor of chronic bronchitis among current miners while duration of work in coal mines was not. The associations between SOB and the two exposures were of borderline significance. Age, years of smoking and working in Mine 2 were each positively associated both outcomes; being of other than Ukrainian or Russian descent was positively associated with the prevalence of chronic bronchitis (data not shown).

A history of work in another dusty industry was found to be a significant modifier of the exposure-response association between years of working as a coal-miner and chronic bronchitis ($p=0.009$). Among the 443 men without prior work in a dusty industry the association was positive and significant; among the 30 miners with prior work in a dusty-industry no association was observed, although this latter observation may be due to small numbers. In the best fitting model among men without prior work in a dusty industry, age, pack years of smoking and being a nationality other than Ukrainian or Russian were positive predictors of chronic bronchitis ($p=0.0080$, <0.0001 and 0.0140 , respectively, data not shown).

Prior work in a dusty industry was also found to modify the association between years mined and SOB, but the interaction was not as strong as for that observed with chronic bronchitis ($p=0.0470$). Among men without prior work in a dusty industry, increased years of mining at the coal face was a significant predictor of SOB (Table XXVI) as were age and pack-years-of smoking ($p=0.0020$ and 0.0360 , respectively, data not shown).

TABLE XXVI
 PREVALENCE RATIOS (PRS) FOR RESPIRATORY SYMPTOMS ESTIMATED FOR PREDICTOR VARIABLES IN BINOMIAL MULTIVARIATE MODELS
 AMONG FORMER UNDERGROUND UKRAINIAN COAL MINERS WITH AND WITHOUT A HISTORY OF
 WORK IN ANOTHER DUSTY INDUSTRY^a

Current Miners(n=592)^b	PR^c	Std. Err.	95% CI	P>z				
Chronic Bronchitis								
Year of coal-mine dust exposure	1.30	0.31	(0.94 - 1.93)	0.3350				
Years working at the coal face	1.12	0.46	(1.03 - 1.21)	0.0070				
Shortness of breath								
Year of coal-mine dust exposure	2.01	0.46	(1.35 – 3.20)	0.1330				
Years working at the coal face	1.10	0.063	(0.99 - 1.23)	0.0970				
Former Miners(n=473)²	Without a History of Previous Work in a Dusty Industry (n=443)				With a History of Previous Work in a Dusty Industry (n=30)			
	PR^c	Std. Err.	95% CI	P>z	PR^c	Std. Err.	95% CI	P>z
Chronic Bronchitis								
Year of coal-mine dust exposure	1.96	0.32	(1.41 – 2.70)	<0.0001	0.77	0.65	(0.15 – 4.00)	0.7580
Years working at the coal face	1.10	0.13	(0.84 - 1.37)	0.6220	0.76	0.55	(0.18 - 3.12)	0.7040
Shortness of breath								
Year of coal-mine dust exposure	1.55	0.24	(1.11 – 2.04)	0.0050	0.86	1.10	(0.06 - 10.77)	0.9060
Years working at the coal face	0.95	0.10	(0.77 - 1.17)	0.6680	0.72	1.17	(0.46 – 11.4)	0.1570

a. All analyses used relative sample weights, i.e. the population sample weight (the inverse of the selection probability for the sampling strata) divided by the average population weight.

b. All models controlled for age pack-years smoking, nationality and mine

c. The prevalence ratio (PR) represents an increase in the prevalence of the outcome for every 10 years of exposure, adjusted for all other variables in the model (age pack-years smoking, nationality and mine)

5. **Reason for leaving work**

Reason for leaving work was not a confounder or a significant effect modifier of the exposure-response relationship between duration of coal mining work with either chronic bronchitis or with shortness of breath. However for both outcomes when stratifying on reason for leaving work, a log-linear statistically significant exposure-response relationship was only observed among miners who terminated employment for a reason other than being pensioned or disabled (Table XXVII).

TABLE XXVII

THE EFFECT OF REASON FOR LEAVING WORK AS A COAL MINER ON THE EXPOSURE-RESPONSE ASSOCIATION BETWEEN RESPIRATORY SYMPTOMS AND YEARS WORKING AS A COAL MINER AMONG FORMER MINERS AGED 65 AND YOUNGER WITH NO PREVIOUS WORK IN A DUSTY INDUSTRY (N=340)^A

Model structure and covariates ^b	Chronic Bronchitis				Shortness of Breath			
	PR ^c	Standard Error	95% Confidence Interval	P-value	PR ^c	Standard Error	95% Confidence Interval	P-value
Without conditioning on reason for leaving work	1.57	0.24	(1.16 - 2.12)	0.0040	2.07	0.46	(1.35 - 3.18)	0.0010
Controlling for reason left work	1.74	0.35	(1.16 - 2.59)	0.0060	2.08	0.46	(1.35 - 3.22)	0.0010
Stratifying by reason left work								
Pensioned (n=103)	1.33	0.39	(0.74 - 2.35)	0.3390	1.61	0.47	(0.91 - 2.87)	0.1030
Disabled (n=98)	0.95	0.47	(0.36 - 2.50)	0.9210	0.72	0.22	(0.40 - 1.32)	0.2980
Other^d (n=139)	2.41	0.92	(1.13 - 5.12)	0.0220	3.00	1.35	(1.22 - 7.26)	0.0160

a. All analyses used relative sample weights, i.e. the population sample weight (the inverse of the selection probability for the sampling strata) divided by the average population weight

b. Models controlled for years mined at the coal face, pack years of smoking, and mine

c. The prevalence ratio (PR) represents an increase in the prevalence of the outcome for every 10 years of exposure adjusted for all other variables in the model

d. Other reasons for leaving work included voluntary termination (quitting) or involuntary termination (laid-off or fired)

D. **Discussion**

This successful research collaboration was due in part to the research training supported by the Fogarty ITREOH grant. The scale of the research program required substantial in-kind contributions from the Ukrainian Institute of Occupational Medicine as well as leveraging the capacity-building provided by USAID through the International Health Alliance. The ITREOH-supported Data Management Center provided coordination of field research activities as well as state-of-the-art data management.

1. **Study results: prevalence of respiratory symptoms**

To the best of our knowledge, this study is the first study to report on the burden of respiratory symptoms among Ukrainian coal miners in the western literature. The study will help to establish a baseline of disease prevalence in this population from which collaborative prevention efforts can be planned and evaluated. Our study also elucidates some of the challenges of accurately estimating disease rates in working population, including the tendency to underestimate disease rates.

Two studies from the U.S. National Study of Coal Workers' Pneumoconiosis (NSCWP) have reported prevalence rates of respiratory symptoms. The corresponding rate among former miners for chronic bronchitis from our study (18.1%) was lower than those reported from either of those studies, and that for shortness of breath (35.6%) was midway between the U.S. study estimates. These studies enrolled current and former miners aged 58 or less from previous rounds of the NSCWP. Our study did not restrict enrollment by an upper age limit. The study populations differed in that Seixas et al. [1992] reported symptom prevalence rates from miners whose average age was 40 years and average cumulative dust exposure was 16 mg/m³-yr (Seixas et al. 1992). The report by Hennenberger and Attfield [1997] included a group of miners whose average age was 49.9 and average cumulative dust exposure level was 52 mg/m³-yr. The prevalence rates for chronic bronchitis from these studies were 21.0% and 34.8%, respectively; for shortness of breath the corresponding rates were 22.3% and 43.0%.

The rates we observed among currently working miners (chronic bronchitis=13.9%; shortness of breath=5.1%) were considerably lower than the prevalence of chronic bronchitis among British coal miners with 10 or more years of working at the coal face which ranged from 9.7% among non-smokers with no CMD exposure to 41.2% among smokers with an intermediate-level of exposure (Marine, Gurr, and Jacobsen 1988). A 1970 study from the U.K. reported an overall rate of 38.7% (Rae, Walker, and Attfield 1970). A survey of South African coal miners reported a lower prevalence of chronic bronchitis (6%) than we observed among current miners, and a higher prevalence than we observed among former miners (46%) (Naidoo et al. 2006).

A number of factors may account for the lower prevalence rates of respiratory symptoms which we observed. However, dust exposures were high in the three study mines so we do not believe that lower dust exposure is responsible for the lower disease rates in our sample of miners. Rather many factors, including bias from both selection and measurement issues, likely contributed to a strong downward bias in the estimation of prevalence rates in our sample.

2. **Study results: potential sources of selection bias**

Participation rates for both surveys were low. Among former miners the reasons for not participating in the study were collected and included being too sick (n=52, 5.6%), lost to follow-up (n=259, 27.7%), and having died (n=303, 32.4%). Hence miners who enrolled in our study may have been healthier than those who did not enroll.

A small study of 478 miners from the first round of the NSCWP examined the potential bias introduced by self-selection. The authors reported that miners with the longest duration of work at the face had a lower prevalence of airway hyper-responsiveness than those who never worked at the face, (39% v 12% $P < 0.01$) (Petsonk et al. 1995). They also reported that miners with greater bronchial hyper-reactivity were less likely to have worked in dusty jobs than those who were less hyper-reactive. Their

results provided some evidence for health-related job selection among coal miners and support the hypothesis that studies of workers in dusty jobs may underestimate the effects of dust exposure on respiratory health. These findings may also imply that the higher than anticipated proportion of symptoms observed among miners with lower tenure at the coal face observed in the current study may, in part, represent a hyper-responsive subgroup.

Cross-sectional study designs may be strongly impacted by the healthy worker effect (HWE), a term used to describe selection biases associated with employment status. The healthy-hire effect (HHE) describes the bias attributable to healthier individuals in a population being more likely to both seek and gain employment (Arrighi and Hertz-Picciotto 1993). The HHE is sufficiently controlled in analyses such as ours which use an internal reference for exposure. Our exclusion of miners with less than 5 years of mining tenure (or younger than age 30 as a proxy for tenure among current miners) was also an attempt to reduce this potential bias.

The phenomenon that healthier individuals may be more likely to remain in jobs, while those less healthy may be more likely to leave employment or move to a position with lower levels of exposure, is referred to as the HWSE. This bias accumulates and varies over time. Because components of this bias such as employment status can be both confounders or intermediate variables, there is no agreed upon solution for its full control in most observational studies (Robins 1987; Robins et al. 1992).

Observations from our analysis which supported an influence of the HWSE include: the low prevalence rates of respiratory illness among current compared to former miners, the lack of statistically significant exposure-response associations between duration of mining and respiratory symptoms in current miners in multivariate analysis, and our findings from the analysis of work status, specifically the observation of an exposure-response association between respiratory symptoms and mining tenure only within the subgroup of men who left mining for reasons other than disability or retirement.

Our finding of higher rates of respiratory symptoms among former compared with current miners is consistent with those from other occupational studies, including cohort studies of coalminers in the U.S.(Henneberger and Attfield 1996; Petersen and Attfield 1981) and the U.K.,(Soutar and Hurley 1986) and a cross-sectional study from South Africa(Naidoo et al. 2006).

Another factor possibly related to selection bias is that Ukrainian miners undergo mandatory annual health screening. While the policy of the mining administration was not to use the results of those examinations for employment decisions, it is plausible that the examination resulted in either voluntary or involuntary termination of work for men with signs of disease. We also speculated that it is possible that fear of termination due to disease status may have resulted in lower enrollment rates among symptomatic working miners.

3. **Study results: potential sources of information bias**

A strength of our study was that we collected information on why former miners left work as coal miner. A limitation of our approach however was that the category “left for another reason” was heterogeneous, possibly including men who had left work voluntary or involuntary, either of which may have been related to health or exposure status. A study from the NSCWP reported higher rates of respiratory symptoms among former miners who left for health, rather than non-health related reasons(Attfield and Seixas 1995). A related consideration is that miners who were disabled because of injury were likely to have had a different exposure and outcome profile than those who were disabled as the result of respiratory illness.

There were also a number of potential measurement issues concerning both the exposure and outcomes which may have reduced the accuracy or precision of our findings. The lack of CMD measurements is a significant limitation to this research; duration of mining and duration of mining at the coal face were a crude substitute for estimates of cumulative CMD exposure. However the dust

sampling conducted in 2001 did not include enough job categories or conditions to make them suitable for exposure estimates. While there are historical compliance monitoring data from Ukraine, the poor validity and reliability of those data also rendered them unsuitable for estimating historic exposures.

4. **Study results: other findings**

An unexpected finding was that both current and former miners who were ethnic minorities (ethnicity other than Ukrainian or Russian) had higher prevalence rates of chronic bronchitis than the majority populations, after controlling for age and smoking. This was a heterogeneous group comprised of men mainly of Belarusian and Moldavian descent. Among current miners, statistical testing found no differences between these miners and those of Ukrainian or Russian descent in terms of age, smoking, mine at time of enrollment, or prior work in a dusty industry (data not shown), but the small number of ethnic minorities (n=29) may have limited our ability to detect differences. Among former miners, those who were ethnic minorities were on average older than other miners (61.9 years, 95% CI 58.8, 64.9 vs. 56.7 years old, 95% CI 55.6, 57.7) and less likely to be current smokers (44.8%, 95% CI 26.6, 63.0; n=13) than their Ukrainian and Russian counterparts (67.6%, 95% CI 63.2, 71.9; n=300). The former finding may reflect changes in smoking subsequent to symptom onset. Hence, it is unclear if the findings were due to differential work exposures, underlying health status, or some other unmeasured factor such as differences in culture or language. Given these findings, the burden of disease among ethnic minorities in Ukrainian coal mines may warrant further investigation.

Another intriguing finding was the higher rates of respiratory symptoms among current miners in Mine 2 compared with workers from the other two mines. While the analysis controlled for age and years mining, miners enrolled from Mine 2 were on average older than other miners (mean age 49.0 vs. 46.1, respectively; p-value [T-Test] = 0.0006) and had longer tenure as miners (24.4 vs. 21.6 years, respectively, p-value for [T-test] = 0.0002), hence there may have been residual confounding in

the analysis. Other unmeasured factors such as selective enrollment or differential work practices at the mines may also have contributed to this finding.

5. **Study results: other methodological considerations**

A strength of our analysis was the use of prevalence ratios rather than prevalence odds ratios. This decision was made for two reasons. Firstly when disease prevalence is over 10% the odds ratio may substantially over estimate the relative risk(Thompson, Myers, and Kriebel 1998). Secondly and as discussed previously, in cross sectional studies of chronic disease the average duration of observable disease likely differs by exposure status and is typically shorter for more highly exposed miners. In such conditions, the prevalence odds ratio is also likely inflated compare to the prevalence ratio.

VI. CONCLUSIONS

Our study added significantly to previous explorations of mortality in the NSCWP cohort in two ways. First the inclusion of respirable silica exposure, which -by-weight is more toxic than CMD, allowed us to understand the contribution of this exposure to mortality. Secondly, the addition of date of employment termination for most of the cohort permitted us to validate past assumptions that the majority of this cohorts' dust exposures occurred prior to study enrollment and to explore time-varying aspects of lung cancer mortality.

Our findings expand upon previous results showing that work as a coal miner puts miners at increased risk for morbidity and mortality from NMRD. What is more novel is our finding of an increased risk of lung cancer mortality in coal miners and that the risk increased with cumulative CMD exposure. While this finding may appear to be in conflict with those from earlier studies, it appears that this may be explained by the longer follow-up of our cohort than that of most of the earlier studies. Our findings of an excess of lung cancer are consistent with the observation of a lung cancer excess in the most recent follow-up period of the British cohort (Miller and MacCalman 2010). Given our findings and those from the British study a reevaluation of the carcinogenicity of CMD exposure (which has been classified by the IARC as group 3) is warranted. Our findings also support the need for continued follow-up and investigation of lung cancer mortality and incidence among coal miners.

Our observations of an association between silica and mortality form NMRD, including COPD and pneumoconiosis, are disturbing given that exposure to silica appears to be increasing in both the US and UK(Laney, Petsonk, and Attfield 2010; Cohen 2010). While further work to both better characterize current exposures of coal miners is warranted, there is adequate evidence to warrant improved efforts to control and reduce exposure to respirable silica in US coal mines.

The findings on disease occurrence in Ukrainian miners are, to the best of our knowledge, the first published in the Western literature. These findings help to establish a baseline of disease prevalence in this population from which prevention efforts can be planned and evaluated. The Ukrainian coal mining industry is expanding in order to meet that country's growing need for energy and exportable goods. Measures should be taken to: monitor and characterize dust exposure in Ukrainian coal mines; reduce dust exposures in the mines to levels that protect workers' health; and to better characterize the health status of current and former miners in Ukraine.

APPENDICES

APPENDIX I: HUMAN SUBJECTS APPROVAL: AIM 1 AND 2

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7342

**Approval Notice
Continuing Review**

June 9, 2011

Judith M. Graber, MS
Epidemiology and Biostatistics
Dept. of Epidemiology/Biostatistics
9th Fl. SPH-PI, 1603 W. Taylor St., M/C 923
Chicago, IL 60612
Phone: (207) 441-3862

RE: Protocol # 2009-0535
“Cancer Mortality Among Coal Miners -- a 35 Year Follow-up”

Dear Dr. Graber:

Your Continuing Review was reviewed and approved by the Expedited review process on June 8, 2011. You may now continue your research.

Please note the following information about your approved research protocol:

<u>Protocol Approval Period:</u>	June 8, 2011 - June 6, 2012
<u>Approved Subject Enrollment #:</u>	Research limited to data analysis of 8,988 NIOSH subjects
<u>Additional Determinations for Research Involving Minors:</u> These determinations have not been made for this study since it has not been approved for enrollment of minors.	
<u>Performance Sites:</u>	UIC, NIOSH
<u>Sponsor:</u>	National Institute for Occupational Safety and Health
<u>PAF#:</u>	2008-00688
<u>Grant/Contract No:</u>	Not available
<u>Grant/Contract Title:</u>	Safety and Health, ERC, University of Illinois at Chicago

Research Protocol(s):

- a) Cancer mortality among coal miners -- a 35 year follow-up, Version 4, 09/01/2010

APPENDIX I (continued)

Informed Consent(s):

- a) Informed consent was originally obtained during enrollment into the NIOSH study

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific category:

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
06/06/2011	Continuing Review	Expedited	06/08/2011	Approved

Please remember to:

→ Use your **research protocol number** (2009-0535) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-7323. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jennifer Joaquin, MPH
 IRB Coordinator, IRB # 1

Office for the Protection of Research Subjects

Enclosure(s): **UIC Investigator Responsibilities, Protection of Human Research Subjects**

APPENDIX II: HUMAN SUBJECTS APPROVAL: AIM 3

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7342

**Approval Notice
Continuing Review (Response To Modifications)**

Robert Cohen, MD
Medicine
2121 W. Taylor Street
335 S.P.H.W., M/C 922
Chicago, IL 60612
Phone: (312) 996-5804 / Fax: (312) 413-8485

**RE: Protocol # 2000-0578
“Occupational Lung Disease in Ukrainian Coal Miners”**

Dear Dr. Cohen:

Your Continuing Review (Response To Modifications) was reviewed and approved by Members of IRB #1 by the Expedited review process on November 3, 2006. You may now continue your research.

Please note the following information about your approved research protocol:

<u>Protocol Approval Period:</u>	November 3, 2006 - November 2, 2007
<u>Approved Subject Enrollment #:</u>	1500 (1234 subjects enrolled; enrollment closed)
<u>Performance Sites:</u>	UIC, John H. Stroger Jr. Hospital of Cook County,
Occupational Health Institute of Ukraine	
<u>Sponsor:</u>	Fogarty International Center
<u>Research Protocol(s):</u>	
b) PI Grant Application: Occupational Lung Disease in Ukrainian Coal Miners: Application for second year of funding 2001-2002	
<u>Recruitment Material(s):</u>	N/A – Research closed to accrual.
<u>Informed Consent(s):</u>	N/A – Research closed to accrual.

Your research continues to meet the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific category:

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

APPENDIX II (continued)**Please note the Review History of this submission:**

Receipt Date	Submission Type	Review Process	Review Date	Review Action
10/16/2006	Continuing Review	Expedited	10/18/2006	Modifications Required
11/01/2006	Response To Modifications	Expedited	11/03/2006	Approved

Please remember to:

→ Use your **research protocol number** (2000-0578) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-2939. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jewell Hamilton, MSW

IRB Coordinator, IRB # 1

Office for the Protection of Research Subjects

Enclosure(s):

- 1. UIC Investigator Responsibilities, Protection of Human Research Subjects**
- 2. Form 310 - Protection of Human Subjects, Assurance**

CITED LITERATURE

- ACS. 2011. Cancer Facts & Figures 2011. edited by A. C. Society. Atlanta.
- Alexander, D. D., P. J. Mink, H. O. Adami, P. Cole, J. S. Mandel, M. M. Oken, and D. Trichopoulos. 2007. Multiple myeloma: a review of the epidemiologic literature. Int. J Cancer 120 Suppl 12:40-61.
- Antao, V. C., E. L. Petsonk, L. Z. Sokolow, A. L. Wolfe, G. A. Pinheiro, J. M. Hale, and M. D. Attfield. 2005. Rapidly progressive coal workers' pneumoconiosis in the United States: geographic clustering and other factors. Occup. Environ. Med. 62 (10):670-4.
- Applebaum, K. M., E. J. Malloy, and E. A. Eisen. 2007. Reducing healthy worker survivor bias by restricting date of hire in a cohort study of Vermont granite workers. Occup. Environ. Med. 64 (10):681-7.
- Arrighi, H. M., and I. Hertz-Picciotto. 1993. Definitions, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. J. Occup. Med. 35 (9):890-2.
- Arrighi, H. M., and I. Hertz-Picciotto. 1994. The evolving concept of the healthy worker survivor effect. Epidemiology 5 (2):189-96.
- Arrighi, H. M., and I. Hertz-Picciotto. 1995. Controlling for time-since-hire in occupational studies using internal comparisons and cumulative exposure. Epidemiology 6 (4):415-8.
- Arrighi, H. M., and I. Hertz-Picciotto. 1996. Controlling the healthy worker survivor effect: an example of arsenic exposure and respiratory cancer. Occup. Environ. Med. 53 (7):455-62.
- Attfield, M. D. 1983. Pneumoconiosis in coal miners: NIOSH research and surveillance. Morb. Mortal. Wkly. Rep. Surveill. Summ. 32 (1):39SS-42SS.
- Attfield, M. D., and R. M. Castellan. 1992. Epidemiological data on US coal miners' pneumoconiosis, 1960 to 1988. Am. J. Public Health 82 (7):964-70.
- Attfield, M. D., and T. K. Hodous. 1992. Pulmonary function of U.S. coal miners related to dust exposure estimates. Am. Rev. Respir. Dis. 145 (3):605-9.
- Attfield, M. D., and K. Moring. 1992. The derivation of estimated dust exposures for U.S. coal miners working before 1970. Am. Ind. Hyg. Assoc. J. 53 (4):248-55.
- Attfield, M. D., and E. D. Kuempel. 2008. Mortality among U.S. underground coal miners: a 23-year follow-up. Am. J. Ind. Med. 51 (4):231-45.

- Attfield, M. D., and N. S. Seixas. 1995. Prevalence of pneumoconiosis and its relationship to dust exposure in a cohort of U.S. bituminous coal miners and ex-miners. *Am. J. Ind. Med.* 27 (1):137-51.
- Attfield, M. D., and E. D. Kuempel. 2008. Mortality among U.S. underground coal miners: a 23-year follow-up. *Am. J. Ind. Med.* 51 (4):231-45.
- Atuhaire, L. K., M. J. Campbell, A. L. Cochrane, M. Jones, and F. Moore. 1986. Specific causes of death in miners and ex-miners of the Rhondda Fach 1950-80. *Br. J. Ind. Med.* 43 (7):497-9.
- Beeckman, L. A., M. L. Wang, E. L. Petsonk, and G. R. Wagner. 2001. Rapid declines in FEV1 and subsequent respiratory symptoms, illnesses, and mortality in coal miners in the United States. *Am. J. Respir. Crit. Care. Med.* 163 (3 Pt 1):633-9.
- Calle, E. E., C. Rodriguez, K. Walker-Thurmond, and M. J. Thun. 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N. Engl. J. Med.* 348 (17):1625-38.
- Checkoway, Harvey, Neil Pearce, and David Kriebel. 2004. *Research methods in occupational Epidemiology* 2nd ed, *Monographs in epidemiology and biostatistics*. New York: Oxford University Press.
- Cohen, R. A., A. Patel, and F. H. Green. 2008. Lung disease caused by exposure to coal mine and silica dust. *Semin. Respir. Crit. Care. Med.* 29 (6):651-61.
- Cohen, R. A. 2010. Is the increasing prevalence and severity of coal workers' pneumoconiosis in the United States due to increasing silica exposure? *Occup. Environ. Med.* 67 (10):649-50.
- Costello, J., C. E. Ortmeyer, and W. K. Morgan. 1974. Mortality from lung cancer in U.S. coal miners. *Am. J. Public Health.* 64 (3):222-4.
- Dimich-Ward, H., and D. V. Bates. 1994. Reanalysis of a longitudinal study of pulmonary function in coal miners in Lorraine, France. *Am. J. Ind. Med.* 25 (5):613-23.
- Enterline, P. E. 1972. A review of mortality data for American coal miners. *Ann N Y Acad Sci* 200:260-72.
- Flanders, W. D., V. M. Cardenas, and H. Austin. 1993. Confounding by time since hire in internal comparisons of cumulative exposure in occupational cohort studies. *Epidemiology* 4 (4):336-41.
- Fox, A. J., and P. F. Collier. 1976. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. *Br. J. Prev. Soc. Med.* 30 (4):225-30.
- Fox, A. J., P. O. Goldblatt, and A. M. Adelstein. 1982. Selection and mortality differentials. *J Epidemiol Community Health.* 36 (2):69-79.

- Ghanem, M. M., D. Porter, L. A. Battelli, V. Vallyathan, M. L. Kashon, J. Y. Ma, M. W. Barger, J. Nath, V. Castranova, and A. F. Hubbs. 2004. Respirable coal dust particles modify cytochrome P4501A1 (CYP1A1) expression in rat alveolar cells. Am J Respir Cell Mol Biol. 31 (2):171-83.
- Gilbert, E. S. 1982. Some confounding factors in the study of mortality and occupational exposures. Am. J. Epidemiology 116 (1):177-88.
- Gilbert, E. S., and S. Marks. 1979. An analysis of the mortality of workers in a nuclear facility. Radiat. Res. 79 (1):122-48.
- Goldman, K. P. 1965. Mortality of Coal-Miners from Carcinoma of the Lung. Br. J. Ind. Med. 22:72-7.
- Harrison J., Brower P., Attfield M., Doak C., Keane M., Grayson R., Wallace W.E. 1997. Surface composition of respirable silica particles in a set of US anthracite and bituminous coal mine dusts. J. Aerosol. Sci. 28:8.
- Henneberger, P. K., and M. D. Attfield. 1996. Coal mine dust exposure and spirometry in experienced miners. Am. J. Respir. Crit. Care. Med. 153 (5):1560-6.
- Henneberger, P. K., and M. D. Attfield. 1997. Respiratory symptoms and spirometry in experienced coal miners: effects of both distant and recent coal mine dust exposures. Am. J. Ind. Med. 32 (3):268-74.
- Hernan, M. A., B. Brumback, and J. M. Robins. 2000. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 11 (5):561-70.
- Hernan, M. A., S. R. Cole, J. Margolick, M. Cohen, and J. M. Robins. 2005. Structural accelerated failure time models for survival analysis in studies with time-varying treatments. Pharmacoepidemiol Drug Saf. 14 (7):477-91.
- Hnizdo, E., and V. Vallyathan. 2003. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occup. Environ. Med. 60 (4):237-43.
- Howe, G. R., A. M. Chiarelli, and J. P. Lindsay. 1988. Components and modifiers of the healthy worker effect: evidence from three occupational cohorts and implications for industrial compensation. Am. J. Epidemiol. 128 (6):1364-75.
- Huang, X., W. Li, M. D. Attfield, A. Nadas, K. Frenkel, and R. B. Finkelman. 2005. Mapping and prediction of coal workers' pneumoconiosis with bioavailable iron content in the bituminous coals. Environ. Health Perspect. 113 (8):964-8.

- Hurley, J. F., W. P. Alexander, D. J. Hazledine, M. Jacobsen, and W. M. Maclaren. 1987. Exposure to respirable coalmine dust and incidence of progressive massive fibrosis. Br. J. Ind. Med. 44 (10):661-72.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, and International Agency for Research on Cancer. 1997. Silica, some silicates, coal dust, and para-aramid fibrils, IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France Geneva: IARC;World Health Organization Distribution and Sales.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans., International Agency for Research on Cancer., and National Cancer Institute (U.S.). 1988. Man-made mineral fibres and radon, IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: World Health Organization, International Agency for Research on Cancer ; Geneva, Switzerland : Distributed for the International Agency for Research on Cancer by the Secretariat of the World Health Organization.
- James, W. R. 1955. Primary lung cancer in South Wales coal-workers with pneumoconiosis. Br. J. Ind. Med. 12 (2):87-91.
- Kalton, Graham. 1983. Introduction to survey sampling, Sage university papers series Quantitative applications in the social sciences. Beverly Hills: Sage Publications.
- Kennaway EL, Kennaway NM. 1936. A study of the incidence of cancer of the lung and larynx. J Hyg (Lond). 36 (2):31.
- Kennaway EL, Kennaway NM. . 1947. A further study of the incidence of cancer of the lung and larynx. Br. J. Cancer 1 (3):38.
- Kibelstis, J. A., E. J. Morgan, R. Reger, N. L. Lapp, A. Seaton, and W. K. Morgan. 1973. Prevalence of bronchitis and airway obstruction in American bituminous coal miners. Am. Rev. Respir. Dis. 108 (4):886-93.
- Kollarova, H., L. Machova, D. Horakova, L. Cizek, G. Janoutova, and V. Janout. 2008. Is obesity a preventive factor for lung cancer? Neoplasma 55 (1):71-3.
- Kuempel, E. D., L. T. Stayner, M. D. Attfield, and C. R. Buncher. 1995. Exposure-response analysis of mortality among coal miners in the United States. Am. J. Ind. Med. 28 (2):167-84.
- Kuempel, E. D., M. W. Wheeler, R. J. Smith, V. Vallyathan, and F. H. Green. 2009. Contributions of dust exposure and cigarette smoking to emphysema severity in coal miners in the United States. Am. J. Respir. Crit. Care. Med. 180 (3):257-64.
- Lainhart, W. S. 1969. Roentgenographic evidence of coal workers' pneumoconiosis in three geographic areas in the United States. J. Occup. Med. 11 (8):399-408.

- Laney, A. S., and M. D. Attfield. 2009. Quartz exposure can cause pneumoconiosis in coal workers. J. Occup. Environ. Med. 51 (8):867; author reply 868.
- Laney, A. S., and M. D. Attfield. 2010. Coal workers' pneumoconiosis and progressive massive fibrosis are increasingly more prevalent among workers in small underground coal mines in the United States. Occup. Environ. Med. 67 (6):428-31.
- Laney, A. S., E. L. Peterson, and M. D. Attfield. 2010. Pneumoconiosis among underground bituminous coal miners in the United States: is silicosis becoming more frequent? Occup. Environ. Med. 67 (10):652-6.
- Leigh, J., T. R. Driscoll, B. D. Cole, R. W. Beck, B. P. Hull, and J. Yang. 1994. Quantitative relation between emphysema and lung mineral content in coalworkers. Occup. Environ. Med. 51 (6):400-7.
- Leung, C. C., T. H. Lam, W. W. Yew, W. M. Chan, W. S. Law, and C. M. Tam. 2011. Lower lung cancer mortality in obesity. Int. J. Epidemiol. 40 (1):174-82.
- Lewis, S., J. Bennett, K. Richards, and J. Britton. 1996. A cross sectional study of the independent effect of occupation on lung function in British coal miners. Occup. Environ. Med. 53 (2):125-8.
- Liddell, F. D. 1973. Morbidity of British coal miners in 1961-62. Br. J. Ind. Med. 30 (1):1-14.
- Love, R. G., and B. G. Miller. 1982. Longitudinal study of lung function in coal-miners. Thorax 37 (3):193-7.
- Marine, W. M., D. Gurr, and M. Jacobsen. 1988. Clinically important respiratory effects of dust exposure and smoking in British coal miners. Am. Rev. Respir. Dis. 137 (1):106-12.
- McVittie Jc. 1949. Pneumoconiosis in coal miners. Postgrad Med J 25 (290):618-31, illust.
- McMichael, A. J. 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J. Occup. Med. 18 (3):165-8.
- Meijers, J. M., G. M. Swaen, and J. J. Slangen. 1997. Mortality of Dutch coal miners in relation to pneumoconiosis, chronic obstructive pulmonary disease, and lung function. Occup. Environ. Med. 54 (10):708-13.
- Miller, B. G., and L. MacCalman. 2010. Cause-specific mortality in British coal workers and exposure to respirable dust and quartz. Occup. Environ. Med. 67 (4):270-6.
- Miyazaki, M. and Une, H. 2001. Risk of lung cancer among Japanese coal miners on hazard risk and interaction between smoking and coal mining. J. Occup Health 43:6.

- Morabia, A., S. Markowitz, K. Garibaldi, and E. L. Wynder. 1992. Lung cancer and occupation: results of a multicentre case-control study. *Br. J. Ind. Med.* 49 (10):721-7.
- Naidoo, R. N., T. G. Robins, N. Seixas, U. G. Lalloo, and M. Becklake. 2005. Differential respirable dust related lung function effects between current and former South African coal miners. *Int. Arch. Occup. Environ. Health* 78 (4):293-302.
- Naidoo, R. N., T. G. Robins, N. Seixas, U. G. Lalloo, and M. Becklake. 2006. Respirable coal dust exposure and respiratory symptoms in South-African coal miners: a comparison of current and ex-miners. *J. Occup. Environ. Med.* 48 (6):581-90.
- NIOSH. 1995. Occupational exposure to respirable coal mine dust, Criteria for a recommended standard. Cincinnati, Ohio Washington, D.C.: U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health For sale by the Supt. of Docs., U.S. G.P.O.
- Nonemaker, J. M., E. Garrett-Mayer, M. J. Carpenter, M. E. Ford, G. Silvestri, D. T. Lackland, and A. J. Alberg. 2009. The risk of dying from lung cancer by race: a prospective cohort study in a biracial cohort in Charleston, South Carolina. *Epidemiol* 19 (5):304-10.
- Pelucchi, C., E. Pira, G. Piolatto, M. Coggiola, P. Carta, and C. La Vecchia. 2006. Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996-2005. *Ann. Oncol.* 17 (7):1039-50.
- Petersen, M., and M. Attfield. 1981. Estimates of bias in a longitudinal coal study. *J. Occup. Med.* 23 (1):44-8.
- Petsonk, E. L., E. M. Daniloff, D. M. Mannino, M. L. Wang, S. R. Short, and G. R. Wagner. 1995. Airway responsiveness and job selection: a study in coal miners and non-mining controls. *Occup. Environ. Med.* 52 (11):745-9.
- Rae, S., D. D. Walker, and M. D. Attfield. 1970. Chronic bronchitis and dust exposure in British coalminers. *Inhaled Part.* 2:883-96.
- Richardson, D., S. Wing, K. Steenland, and W. McKelvey. 2004. Time-related aspects of the healthy worker survivor effect. *Ann. Epidemiol.* 14 (9):633-9.
- Robins, J. 1986. A new approach to causal inference in mortality studies with a sustained exposure period – application to control of the healthy worker survivor effect. *Mathematical Modeling* 7:119.
- Robins, J. 1987. A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *J. Chronic Dis.* 40 Suppl 2:139S-161S.

- Robins, J. M., D. Blevins, G. Ritter, and M. Wulfsohn. 1992. G-estimation of the effect of prophylaxis therapy for *Pneumocystis carinii* pneumonia on the survival of AIDS patients. Epidemiology 3 (4):319-36.
- Rockette, H. E. 1977. Cause specific mortality of coal miners. J. Occup. Med. 19 (12):795-801.
- Rooke, G. B., F. G. Ward, A. N. Dempsey, J. B. Dowler, and C. J. Whitaker. 1979. Carcinoma of the lung in Lancashire coalminers. Thorax 34 (2):229-33.
- Ross, M. H., and J. Murray. 2004. Occupational respiratory disease in mining. Occup. Med. (Lond) 54 (5):304-10.
- Ruckley, V. A., S. J. Gauld, J. S. Chapman, J. M. Davis, A. N. Douglas, J. M. Fernie, M. Jacobsen, and D. Lamb. 1984. Emphysema and dust exposure in a group of coal workers. Am. Rev. Respir. Dis. 129 (4):528-32.
- Schubauer-Berigan, M. K., M. J. Hein, W. M. Raudabaugh, A. M. Ruder, S. R. Silver, S. Spaeth, K. Steenland, M. R. Petersen, and K. M. Waters. 2011. Update of the NIOSH life table analysis system: A person-years analysis program for the windows computing environment. Am. J. Ind. Med. 54 (12):915-24.
- Seixas, N. S., T. G. Robins, M. D. Attfield, and L. H. Moulton. 1992. Exposure-response relationships for coal mine dust and obstructive lung disease following enactment of the Federal Coal Mine Health and Safety Act of 1969. Am. J. Ind. Med. 21 (5):715-34.
- Seixas, N. S., T. G. Robins, M. D. Attfield, and L. H. Moulton. 1993. Longitudinal and cross sectional analyses of exposure to coal mine dust and pulmonary function in new miners. Br. J. Ind. Med. 50 (10):929-37.
- Sircar, K., E. Hnizdo, E. Petsonk, and M. Attfield. 2007. Decline in lung function and mortality: implications for medical monitoring. Occup. Environ. Med. 64 (7):461-6.
- Soutar, C. A., and J. F. Hurley. 1986. Relation between dust exposure and lung function in miners and ex-miners. Br. J. Ind. Med. 43 (5):307-20.
- Standards of spirometry. 1979. Am. Rev. Respir. Dis. American Thoracic Society
- Starzynski, Z., K. Marek, A. Kujawska, and W. Szymczak. 1995. Mortality pattern in men with pneumoconiosis in Poland. Int J. Occup. Med. Environ Health 8 (3):223-9.
- Starzynski, Z., K. Marek, A. Kujawska, and W. Szymczak. 1996. Mortality among coal miners with pneumoconiosis in Poland. Int J. Occup. Med. Environ Health 9 (4):279-89.

- Stayner, L. T., and J. M. Graber. 2011. Does exposure to coal dust prevent or cause lung cancer? Occup. Environ. Med. 68 (3):167-8.
- Steenland, K., J. Deddens, A. Salvan, and L. Stayner. 1996. Negative bias in exposure-response trends in occupational studies: modeling the healthy workers survivor effect. Am. J. Epidemiol. 143 (2):202-10.
- Steenland, K., and L. Stayner. 1991. The importance of employment status in occupational cohort mortality studies. Epidemiology 2 (6):418-23.
- Suarthana, E., A. S. Laney, E. Storey, J. M. Hale, and M. D. Attfield. 2011. Coal workers' pneumoconiosis in the United States: regional differences 40 years after implementation of the 1969 Federal Coal Mine Health and Safety Act. Occup. Environ. Med. .
- Sundar, I. K., N. Mullapudi, H. Yao, S. D. Spivack, and I. Rahman. 2011. Lung cancer and its association with chronic obstructive pulmonary disease: update on nexus of epigenetics. Curr. Opin. Pulm. Med. 17 (4):279-85.
- Swanson, G. M., C. S. Lin, and P. B. Burns. 1993. Diversity in the association between occupation and lung cancer among black and white men. Cancer Epidemiol. Biomarkers Prev. 2 (4):313-20.
- Thompson, M. L., J. E. Myers, and D. Kriebel. 1998. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? Occup. Environ. Med. 55 (4):272-7.
- Une, H., H. Esaki, K. Osajima, H. Ikui, K. Kodama, and K. Hatada. 1995. A prospective study on mortality among Japanese coal miners. Ind. Health 33 (2):67-76.
- Vallyathan, V., F. H. Green, N. F. Rodman, C. B. Boyd, and R. Althouse. 1985. Lung carcinoma by histologic type in coal miners. Arch. Pathol. Lab. Med. 109 (5):419-23.
- Wang, M. L., E. L. Petsonk, L. A. Beeckman, and G. R. Wagner. 1999. Clinically important FEV1 declines among coal miners: an exploration of previously unrecognised determinants. Occup. Environ. Med. 56 (12):837-44.
- Weeks, J. L. 2003. The fox guarding the chicken coop: monitoring exposure to respirable coal mine dust, 1969-2000. Am. J. Public Health 93 (8):1236-44.
- Weinberg, C. R. 1993. Toward a clearer definition of confounding. Am. J. Epidemiol. 137 (1):1-8.
- Whitlock, G., S. Lewington, P. Sherliker, R. Clarke, J. Emberson, J. Halsey, N. Qizilbash, R. Collins, and R. Peto. 2009. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 373 (9669):1083-96.

Wiener, Charles M., Philip J. Nivatpumin, Cynthia D. Brown, Anna R. Hemnes, and Tinsley Randolph Harrison. 2004. Harrison's principles of internal medicine : self-assessment and board review. 16th ed. New York: McGraw-Hill, Medical Pub. Division.

Yang, L., G. Yang, M. Zhou, M. Smith, H. Ge, J. Boreham, Y. Hu, R. Peto, J. Wang, and Z. Chen. 2009. Body mass index and mortality from lung cancer in smokers and nonsmokers: a nationally representative prospective study of 220,000 men in China. Int. J. Cancer 125 (9):2136-43.

Yang, R., M. C. Cheung, F. E. Pedroso, M. M. Byrne, L. G. Koniaris, and T. A. Zimmers. 2011. Obesity and weight loss at presentation of lung cancer are associated with opposite effects on survival. J. Surg. Res. 170 (1):e75-83.

VITA

NAME: Judith Marie-Anna Graber

EDUCATION: B.S.: Agricultural Sciences, University of Wisconsin, Madison Wisconsin, 1981
M.S., Epidemiology, University of Illinois at Chicago, Chicago Illinois, 1991
Ph.D., Epidemiology, University of Illinois at Chicago, Chicago Illinois, 2012

TEACHING: Undergraduate Honors College, University of Illinois at Chicago, Public Health and the Study of Disease and Epidemics, 2012

Department OF Epidemiology and Biostatistics, University of Illinois at Chicago, Introduction to Epidemiology: Principals and Methods, Teaching Assistant, 2009

Department OF Epidemiology and Biostatistics, University of Illinois at Chicago, Intermediate Epidemiology Methods, Teaching Assistant, 2009

Intermediate Epidemiology Methods, Teaching Assistant, 2008

Department OF Epidemiology and Biostatistics, University of Illinois at Chicago, Advanced Quantitative Methods in Epidemiology, Teaching Assistant, 2007

HONORS: National Institute of Occupational Safety and Health Trainee, 2008-2012

PROFESSIONAL MEMBERSHIP: American Public Health Association
American Society of Epidemiology

SELECTED ABSTRACTS: Graber JM, Attfield MD, Stayner LT Results from 37 years of mortality experience among U.S. Underground Coal Miners. Plenary presentation - 2011 Annual Meeting of the Scientific Committee on Epidemiology in Occupational Health (EPICOH), Oxford, UK. 2011

Graber, JM, Stayner, LT, Basanets, A, Kundiev, Y, Hryhorczuk D, Cohen, R.A. Do prevalence and predictors of respiratory symptoms among Ukrainian ex-coal miners vary by reason for leaving mining? 2010 Annual Meeting of the Scientific Committee on Epidemiology in Occupational Health (EPICOH), Taipei, Taiwan, 2010

Graber, JM, The National Carbon Monoxide Surveillance Work Group. Carbon Monoxide as an Environmental Public Health Indicator; Progress to Date. Environmental Public Health Tracking Workshop, 2007.

VITA (CONTINUED)

- PUBLICATIONS: Graber JM, Cohen RA, Basanets A, Stayner LT, Kundiev Y, Conroy L, Mukhin VV, Lysenko O, Zvinchuk A, Hryhorczuk D. Prevalence and predictors of respiratory symptoms among Ukrainian coal miners. Am. J. Ind. Med. *Accepted for publication*
- Stayner LT, Graber JM. Does exposure to coal dust prevent or cause lung cancer? Occup. Environ. Med. 68(3);167-8. 2011.
- Graber JM, Smith AE. Results from a state-based surveillance system for carbon monoxide poisoning. Public Health Rep. 122(2):145-54. 2007.
- Graber JM, Macdonald SC, Kass DE, Smith AE, Anderson HA. Carbon Monoxide: The Case for Environmental Public Health Surveillance. Public Health Rep122(2):138-44.2007.
- Graber JM, Corkum BE, Sonnenfeld N, PhD, Kuehnert PL. Underestimation of cardiovascular disease mortality among Maine American Indians: The role of procedural and data errors. Am. J. Public Health 95(5):827-30.2005.
- Graber JM, Corkum BE, Sonnenfeld N, PhD, Kuehnert PL. Underestimation of cardiovascular disease mortality among Maine American Indians: The role of procedural and data errors. *Authors reply.* Am. J. Public. Health 10:1674. 2005.
- Solomon L, Cannon MJ, Reyes M, Graber JM, Wetherall NT, Reeves WC; Task Force on HSV Resistance. Epidemiology of recurrent genital herpes simplex virus types 1 and 2. Sex. Transm. Infect. 2003 79(6):456-9.
- Reyes M, Shaik NS, Graber JM, Nisenbaum R, Wetherall NT, Fukuda K, Reeves WC; Task Force on HSV Resistance. Acyclovir-resistant genital herpes among persons attending sexually transmitted disease and human immunodeficiency virus clinics. Arch. Intern. Med. 163(1):76-80. 2003.
- Zeitz PS, Graber JM, Voorhees RS, Kioski C, Shands LA, Ksiazek TG, Jenison S, Khabbaz RF. Assessment of occupational risk for Hantavirus infection in Arizona and New Mexico. J. Occup. Environ. Med. 39:463-7. 1997.
- CDC (*Graber JM, Bauer S*). Hantavirus Pulmonary syndrome -- Virginia, 1993 Morb. Mortal. Wkly. Rep. 43:876-7. 1994.
- Woods TC, Graber J, Hershov RC, Khabbaz RF, Kaplan JE, Heneine W: Investigation of HTLV-II proviral load infected individuals. AIDS and Human Retrovirol. 11(10):1235-9. 1995.

VITA (CONTINUED)

Tappero JW, Khan AS, Pinner RW, Wenger JD, Graber JM, Armstrong LR, Holman RC, Ksiazek TG, Khabbaz RF. Hantavirus Pulmonary Syndrome, 1993: results from an emergency, telephone-based national surveillance system. JAMA 275:398-400. 1996.

Pinner RW, Tuetsch SM, Simonsen L, Klug LA, Graber J, Clarke MJ, Berkelman RL. Trends in infectious disease mortality in the United States. JAMA 257:189-93. 1996.

Khan AS, Khabbaz RF, Armstrong, LR, Holman RC, Bauer S, Graber JM, et.al. Hantavirus Pulmonary Syndrome: The First 100 U.S. Cases. J. Infect. Dis. 173:1297-303. 1996.

Hershow RC, Galai N, Fukuda K, Graber J, Vlahov D, et. al. The effect of coinfection with Human T-lymphotrophic Virus type II (HTLV-II) on decline of CD4 lymphocytes and disease progression after HIV-seroconversion in injecting drug users. J. Infect. Dis. 174:309-17. 1996.

**GRANT
FUNDING:**

US National Institute of Occupational Safety and Health, Education and Research Center, University of Illinois at Chicago T42/OH008672. Title: Results from 37 years of mortality experience among U.S. Underground Coal Miners. Total funding: \$17,956.11