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Prevalence of Restricted Spirometry within Two Eastern Kentucky Counties A Cross Sectional Study

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Prevalence of Restricted Spirometry within Two Eastern Kentucky Counties

A Cross Sectional Study

CAPSTONE PROJECT PAPER

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Abstract (or Executive Summary)

Objective: This study examines the prevalence of restrictive spirometry in Eastern Kentucky and its association among men and women with various demographic and exposure (occupational and environmental) factors.

Methods: A cross sectional, cluster sample (N = 685) of participants from Letcher and Harlan Counties, aged 21 and over, answered a questionnaire focused on risk factors for respiratory health outcomes including questions on demographic, health, occupational, and environmental exposures variables. Pulmonary function tests were administered to all participants with no significant cardiovascular or cerebrovascular events within the past 30 days. Log-binomial regression was used to calculate prevalence ratios (PRs) adjusted for multiple covariates.

Results: The prevalence of restricted spirometric pattern (RSP) among men and women was 24.3% and 30.6%, respectively. RSP prevalence was particularly high among men and women with comorbidities. Significant associations for restricted spirometry among women included **$\mathbf{Age_{35\text{-}64}}$**: adjusted prevalence (PR: 5.49, 95% CI 1.69 to 17.8, p=0.005), **$\mathbf{Age_{\geq 65}}$** (PR:7.23, 95% CI 2.20 to 23.7, p=0.001), **widowed, single or divorced women** (PR: 1.78, 95% CI 1.02 to 3.10, p=0.043), **one comorbidity** (PR: 1.79, 95% CI: 1.14 to 2.80) and **obesity** (PR: 2.21, 95% CI 1.05 to 4.64, p=0.036). Significant associations for restricted spirometry among men was **obesity** (PR: 2.68, 95% CI 1.05 to 6.80, p=0.039).

Conclusions: The prevalence of RSP in Central Appalachia is substantially higher when compared with previous literature. Increased RSP in our cohort is multifactorial but may be due to higher prevalence of obesity and comorbid conditions, which is in line with previous studies. Occupational and environmental exposures did not show association with RSP despite many participants living in proximity to coal mines and mining activities.

Keywords: pulmonary disease; restricted spirometry; restrictive spirometric pattern

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Introduction

Restrictive lung disease may be broadly defined as "reduced lung expansion expressed as a decreased total lung capacity (TLC)."[1] When the TLC is not available, one can look at the restrictive spirometric patterns. These non-obstructive patterns are characterized by deficits in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), with FEV_1/FVC ratios that are within normal limits.[2] Collectively, these patterns may be referred to as restrictive spirometric patterns, preserved ratio-impaired spirometry (PRiSM), GOLD-unclassified, restrictive lung disease (RLD) patterns, or nonspecific patterns (when accompanied by a normal TLC).[1-3] Receiver operating characteristics' (ROC) curves best cut-off point for FVC detection of restrictive spirometric patterns is approximately 70%.[4]

Restrictive spirometric patterns are associated with several risk factors, including defects in the chest wall, changes in the lung parenchyma, diseases of the pleura, adverse reaction to certain drugs or neuromuscular disorders, and cardiovascular risk factors such as obesity, diabetes, systemic arterial hypertension, smoking, and physical inactivity.[3,5] Besides airflow obstruction, restrictive spirometry has also been associated with congestive heart failure.[6]

Chest wall pathology may play a major role in restrictive spirometry as it is a critical part of the respiratory pump, responsible for the expansion and contraction of the lungs and causing air to flow from the atmosphere to the alveoli and back out. Some diseases of the chest wall include congenital and childhood abnormalities, kyphosis and scoliosis, ankylosing spondylitis, traumatic and iatrogenic processes, and morbid obesity.[7]

Abnormal changes in lung parenchyma comprise of interstitial lung diseases (ILDs) and are a heterogeneous group of disorders with similar pathologic, clinical, imaging, and physiologic findings. These abnormalities can have either known or unknown etiologies. The most identifiable known cause and risk factors of ILD are exposure to occupational and environmental agents, which include inorganic or organic dusts, drug-induced pulmonary toxicity, and radiation-induced lung injury. Unexplained causes for ILD include cryptogenic organizing pneumonia, sarcoidosis, and idiopathic interstitial pneumonias.[8]

Occupational exposure to inorganic dust such as respirable crystalline silica is particularly important as it known to cause several lung diseases in susceptible hosts, including classic pneumoconiosis (silicosis), nodular interstitial lung disease of coal workers' pneumoconiosis (CWP), and lung cancer. Crystalline silica has also been associated with other lung pathology not commonly recognized with restricted spirometry, such as chronic obstructive pulmonary disease (COPD).[9,10] In regards to silicosis, the risk of disease appears to be higher with exposure to the more toxic, clean, silica dioxide (SiO_2) tetrahedral form.[11] Exposure to respirable crystalline silica occurs in a vast array of occupations and industries. It is estimated that over two million workers are exposed to crystalline silica with jobs in foundry, brick making, and abrasive blasting operations; paint, glass, china dishes, pottery, and plumbing fixture manufacturing; and in many construction activities such as highway repair, masonry, concrete work, rock drilling, and tuck pointing.[9]

Previous epidemiological studies indicate the prevalence of disease among silica exposed workers. One cohort study comprised of 2342 individuals employed at a diatomaceous earth mining facility reported substantially increased standardized mortality ratios (SMR) for lung cancer mortality (RR: 2.15; 95% CI 1.08 to 4.28) for 15-year lagged exposure and non-malignant respiratory disease (SMR: 5.35; 95% CI 2.23 to 12.8).[10] A population-based case only study of 6521 individuals with lung cancer had a weighted prevalence of exposure to crystalline silica of 25.7% (95% CI 24.7 to 26.8) across all histological types of lung cancer.[12]

Occupational exposure to respirable coal mine dust can lead to the development of restrictive or obstructive lung disease. Respirable coal dust causes coal mine dust lung disease (CMDLD), which encompasses mixed dust pneumoconiosis with coexistent silica exposure, chronic bronchitis, emphysema, and dust-related diffuse fibrosis, in addition to classical CWP and the severe form, complicated or progressive massive fibrosis (PMF).[13] A study of 5605 active coal miners outside of Central Appalachia, regardless of tenure, found a prevalence of restrictive lung disease via spirometric analysis in three different regions. The highest prevalence (6.3%) was among 213 coal miners in the Eastern region from Alabama, Maryland, Ohio, Pennsylvania and Tennessee.[14] In Kentucky from January 2015 through August 2016, 60 active or former coal miners were found to have radiographic findings consistent with PMF; 56 of them (93%) were residents of four contiguous counties: Floyd, Knott, Letcher and Pike, which are all a part of the central Appalachian coalfield.[15]

Pleural diseases, which can also cause restrictive spirometric patterns, affects the pleural space and the parietal pleura, which covers the chest wall, diaphragm, and the mediastinum. Almost 1.5 million people in the United States per year develop pleural effusions primarily due to congestive heart failure, pneumonia, and cancer.[16] Asbestosis is one of more common pleural diseases caused by inhaling asbestos fibers and is characterized by slowly progressive, diffuse pulmonary fibrosis.[17] Asbestosis is also a form of interstitial lung disease that is indiscernible from idiopathic pulmonary fibrosis (IPF).[18] Involvement of the pleura (pleural effusion or pleural plaques) is considered a hallmark sign of asbestos exposure and is unusual in other interstitial lung disorders.[17] It demonstrates restrictive ventilatory patterns with decreased lung volumes on pulmonary function testing.

Jobs with potential exposure to asbestosis include electrical workers, power plant employees, aircraft mechanics and manufacturers, telephone lineman, shipyard workers, building supply manufacturers, operational navy and coast guard personnel, power plant employees, railroad and sheet metal workers, and asbestosis mining and transport.[19,20] Prevalence of asbestos exposure is demonstrated in a population-based case only study of 6521 individuals with lung cancer by El Zoghbi et al[12], where they reported a weighted prevalence of exposure to asbestos of 33.9% (95% CI: 32.8 to 35.1), according to histological types of lung cancer. There was no statistically significant difference in the weighted prevalence of exposure when looking at the different types of histological lung cancer.

Adverse reactions to certain drugs or physical agents are another potential cause of restrictive spirometry. Farmers were found them to have a substantial reduction in FVC and FEV_1 with normal FEV_1/FVC ratios on pulmonary function tests after occupational exposure to low levels of organophosphates.[21] Drugs potentially linked to restrictive lung disease include--but are not limited to--amiodarone, methotrexate, and nitrofurantoin.[3]

Heavy metals may also be linked to restrictive spirometry. A cross sectional study of 2460 individuals examined the association of spirometric parameters, RLD, obstructive lung disease (OLD) and spirometric defined COPD, with the urinary levels of 23 nutrient elements and heavy metals. They found urinary zinc (Zn) to be dose-dependently associated with increased RLD risk after adjusting for age, gender, height, smoking status, pack-years of smoking, alcohol status, body mass index (BMI), exercise and urinary creatinine. Individuals with urinary copper (Cu) levels in the highest quartile (>10.86 µg/L), had significantly increased RLD risk (OR: 1.4; 95% CI 1.018 to 1.909) compared with those in the lowest quartile (<5.2 µg/L), after adjusting for the aforementioned confounders, but there was a lack of a dose-response trend.[22] Beryllium is also linked with restricted spirometry as it causes granulomas in the lung and diminished diffusing capacity for CO (DL_{CO}).[23]

Neuromuscular disorders may lead to significant disability and progressive respiratory failure as a consequence of resultant functional limitations.[24] For example, Duchenne's muscular dystrophy is characterized by progressive loss of muscle function with the inevitable respiratory muscle weakness causing ineffective cough and decreased ventilation. This leads to atelectasis, and respiratory insufficiency and patients often progress to musculoskeletal deformities such as kyphosis, which is also associated with restricted spirometry.[25]

Several large studies have identified the prevalence of restrictive spirometry. A longitudinal population study of 5542 individuals found restrictive spirometric patterns among 8.8% of the men and 9.6% of the women.[26] Another longitudinal population study of 15,440 individuals found a prevalence of restrictive spirometry of 7.1% among all participants.[27] A cross-sectional study of 121,965 French adults presenting for regular evaluations found a prevalence of 4.6% among all participants.[28]

Studies have shown that within the general population, between 7% to 13% of adults have FVCs <80% of expected for their gender, age, and height in the presence of normal FEV_1/FVC ratios, indicating a restrictive spirometric pattern. Individuals showing restricted spirometry have increased risk for all-cause, and cardiovascular mortality.[29] Restrictive spirometric patterns have also been shown to be associated with various comorbid conditions including diabetes, metabolic syndrome, hypertension, stroke, and cardiovascular disease.[29] Metabolic syndrome specifically, is characterized by a constellation of metabolically related cardiovascular risk factors, including insulin resistance, hyperlipidemia, hypertension, and central obesity. Low FVC is substantially associated with increasing prevalence of metabolic syndrome along with increasing mortality.[2,30]

Restrictive spirometry is particularly important to individuals who live and work in the central Appalachian regions of Eastern Kentucky. After adaptation of the Coal Workers' Health Surveillance Program (CWHSP) in the late 1960s, which was used to identify coal worker pneumoconiosis (CWP) and prevent its progression, the rate of CWP amongst coal miners dropped sharply in the 1970s.[31] By the 1990s, the prevalence of CWP and PMF had fallen to 5% and 0.5%, respectively, compared to a prevalence of CWP and PMF in the 1970s among long tenured (≥ 25 years) underground coal miners of 30% and 3.5%.[31] However, during the 2000s, there has been a resurgence of CWP in central Appalachian regions in Kentucky, Virginia, and West Virginia. By 2015, the prevalence of PMF among long tenured miners had reached 5% in central Appalachia, which was the highest percentage ever recorded.[31] Increases in this prevalence has been linked to increased coal mine dust levels, longer working hours, especially at the face of the mine, increased exposure to silica, and employment in smaller mines.[13] These individuals face a future of severe and disabling disease.[31]

The objectives of this cross-sectional study were to assess the prevalence of restrictive spirometry among residents of two Eastern Kentucky counties and evaluate how the prevalence differs by men and women across various demographic factors, and by occupation and environmental exposure differences. Understanding how various exposure parameters may be associated with the prevalence of restrictive spirometry, may guide implementation of preventive measures to reduce the prevalence of disease and associated morbidity and mortality.

Methods

The Mountain Air Project (MAP) is a cross-sectional epidemiologic study with a primary goal of applying an environmental public health action strategy (EPHAS) to address community priorities regarding respiratory health. The project enhanced the identification of persons with respiratory disease and obtained a wide range of information regarding community-identified exposures of concern. The study was also designed to obtain individual-level exposure data to assess the association between putative mining and environmental exposures and respiratory health outcomes which had been reported in previous ecologic studies.

Study Area and Population

Our study focused on two Appalachian Kentucky counties (Letcher and Harlan) with long histories of coal mining and economic disadvantage. This area has the nation's highest burden of respiratory disease, as well as environmental justice concerns stemming from air-borne contaminant exposures. The study area was selected based on the presence of extractive industries, marked disparities in respiratory disease, community concerns regarding the health impacts of mining, and infrastructure for mobilizing the project from previous community-based health research. Community stakeholders suggested using "hollows" as the most relevant geographic unit for defining "neighborhoods" for the cross-sectional study and for ambient air sampling. This approach is discussed further in a previous publication by May et al.[32] The study was approved by the University of Kentucky Institutional Review Board and written informed consent was obtained from all participants.

Eligibility

Inclusion criteria included non-institutionalized, English-speaking adults age 21 or older, of any race or ethnicity, residing within an eligible household in either Letcher or Harlan counties. Eligible households consisted of single-family residences, apartment housing, or mobile homes. One adult participant was recruited per household. If an adult in the household reported having asthma, COPD, black lung or other respiratory health condition, he or she was encouraged to serve as the participant for that household. If the person with respiratory disease declined to participate and another adult household member without a respiratory condition was eligible, then that person was recruited for the study.

Geographic Site and Enrollment of Study Participants

We used an adaptive stratified cluster sampling technique to select small geographic areas in Harlan and Letcher counties to be the sampling units. We defined

candidate ‘hollows’ using GIS map layers representing the boundaries of 14-digit hydrologic unit codes (HUCs). These are the smallest hydrologic units available and often coincide with residential development patterns in the study region, since streets and homes are often ordered in linear fashion along narrow valleys. We calculated the following metrics to characterize each HUC in ArcGIS: 1) surface mining, as a percent of HUC total surface area; 2) underground mining, as a percent of HUC total surface area; 3) road miles per square mile; 4) coal haul route miles per square mile; and 5) oil and gas wells per square mile. We then summed these ordinal values to create an index of overall environmental risk to respiratory health. The index was divided into tertiles of high, medium, and low presumptive exposure levels to the five sources of airborne particulates above. The final set of around 30 HUCs (hollows) was selected in each county.
Homes were enumerated on-the-ground within the HUCs by field staff. Within each hollow, homes were sampled by dividing the total number of homes by an appropriate fraction to yield at least 10 homes per hollow for the study. Eligible homes were selected using a random starting point and systematic sample of every n^{th} home. Each selected home had its GPS coordinates logged using a QStarz GPS data logger. The GPS data were linked with the household survey data and the environmental sampling data so that we were able to develop maps and integrate other datasets with the final epidemiologic files.

HUCs with insufficient residences to yield at least 10 eligible households were eliminated from the sample and randomly selected replacement HUCs were provided to the field staff. Nine replacement HUCs were identified through a two-step process that included random selection followed by rooftop survey using Google satellite imagery.

Data Collection

Community Health Workers (CHW), most with previous experience in community-based research, were hired for recruiting and data collection. CHWs recruited selected households for the study. Household contact forms which collected demographic information and respiratory health status for each member of the household were entered into a database for tracking of response and participation rates. Details of the field operations for the MAP study are described in May et al.[32] One CHW was responsible for recruiting, obtaining informed consent, and using GPS to locate the home. Others were assigned to recruited households to administer the questionnaire and collect spirometry. Data were collected on iPads using the Redcap survey software. Participants received $40 for survey completion. Interviewers used REDCap for all data collection. The REDCap database, stored and backed up on servers, was exported to SAS datasets.

The survey, which took approximately 40 minutes to administer, focused on established and potential risk factors for respiratory health outcomes, and obtained data on current and past symptoms of respiratory health over the past 2 to 12 months before the survey. Questions were drawn primarily from established questionnaires, including the ISAAC questionnaire on wheezing and asthma, the Medical Research Council symptom-based questionnaire, and the Seattle Healthy Homes I baseline questionnaire.[33-37] Family history of respiratory disease, allergies, chronic conditions, and eczema was obtained. We assessed chemical and biological environmental triggers, focusing on environmental tobacco smoke (ETS), pesticides, VOCs, dust mites, molds, rodent and cockroach feces, and animal dander; home heating (wood, coal, gas, space heaters, etc.), home cooking (electric, wood, gas, oil), indoor smoking, pets, molds, and dampness. Detailed information was obtained on demographic and lifestyle factors (education, marital status, employment status, occupational exposures, dietary intake, alcohol consumption, and tobacco use). At the time of the interview, pulmonary function tests were also administered to all participants who did not report a stroke or myocardial infarction in the past 30 days. At a later date, a convenience subsample of 72 participants received indoor air quality and exposure assessment to quantify fine particulates and record in-home and outdoor exposure sources. For the analysis in this paper, we deleted the subjects with obstructed spirometry, defined as the presence of an FEV1/FVC ratio less than 0.70.

Spirometry testing was completed for all participants using the Easy On PC® Spirometer, ndd Medical Technologies Inc., Andover, MA. NHANES prediction equations, which are programmed into the Easy On PC spirometers (ndd), were used to calculate the percent predicted lung function levels. These require the input of age, height, and race/ethnicity (White, Black, Hispanic). Spirometry results were sent for central review for quality control assurance and adjudication of results. Study participants performed three to eight efforts, with appropriate coaching by the research coordinators. Every spirometric effort was assessed and the initial quality assessment was over read by the central reader. Only results with quality grades of A, B, C, and D were used in the data analysis. Importantly, the presence of obstruction on spirometry was determined by the presence of an FEV1/FVC ratio less than 0.70. Presence of restriction was determined by the presence of an FEV1/FVC ratio greater than or equal to 0.70 with an FEV1 less than 80% of the predicted value.

Statistical Analysis

Frequency distributions of the demographic characteristics of our sample of respondents were calculated using SAS v9.6 (SAS Institute, Inc.). The health outcome variable, restricted spirometry, was highly prevalent (>10%) in our sample. Consequently, log-binomial regression, a generalized linear method with a link function, to calculate prevalence ratios (PRs) adjusted for multiple covariates.

Results

Table 1 shows the prevalence of restricted spirometric pattern by selected characteristics of the study participants stratified by gender. A total of 685 individuals participated in the study comprising 424 women and 261 men with a prevalence in restricted spirometry of 24.3% and 30.6%, respectively. Age appears to be a factor significantly affecting the prevalence of restricted spirometry for both men and women. Hence, the prevalence of restricted spirometry among women age 35 to 64 was 23.9%, and there was a 65% increase in the prevalence (PR: 1.65, 95% CI: 1.20-2.29) of restricted spirometry compared to women aged 18 to 34 years. The prevalence of restricted spirometry among men age 35 to 64 years was 31.4%, and there was greater than 2.5-fold increase in the prevalence (PR: 2.52, 95% CI 1.06 to 5.95) of restricted spirometry compared to men aged 18 to 34 years. Age group ≥65 continued to be significant for restricted spirometry risk for both genders, but much more significant for women as the prevalence (PR: 10.9, 95% CI 3.5 to 33.9) increased more than 10-fold with a 39.5% prevalence compared to women 18 to 34 years.

Marriage or living as married appeared to be protective for women having restricted spirometry, but no such association was seen for men. In this population, there was no strong association between socioeconomic factors such as education level or household annual income, although lower prevalences were observed among the more highly educated. Obesity (BMI: 30+ kg/m^2) appears to be significantly associated with restricted spirometry risk for both women (PR: 2.91, 95% CI 1.47 to 5.76) and men (PR: 3.04, 95% CI 1.30 to 7.12) when compared to people in the normal BMI ranges. Several comorbidities, such as coronary artery disease (CAD) or ever having a heart attack, were also significantly related to having restricted spirometry for both men and women. Particularly with women, two or more comorbid conditions appear to be significant for restricted spirometry risk as the prevalence (PR: 2.62, 95% CI 1.74 to 3.94) increased 360% when compared to women who had no comorbidities. Other characteristics in Table 1 did not appear to have any statistically significant effect with restricted spirometry.

Table 2 shows the effect of environmental and occupational factors on restricted spirometry prevalence. Women and men who were disabled had the highest prevalence of restricted spirometry at 48.0% and 37.9%, respectively. The prevalence of restricted lung dysfunction of women who spent no time outside the home each day was 37.2%, and there was a 3.5-fold increase in the prevalence (PR: 3.42, 95% CI 1.93 to 5.99) compared to women who spent ≥ 8 hrs outside the home each day. In addition, the prevalence of restricted lung dysfunction of women who spent 1 to 3 hours outside the home each day was 30.4% and there was a 1.8 fold increase in the prevalence (PR: 2.77, 95% CI 1.59 to 4.84) compared to women who spent ≥ 8 hrs outside the home each day.

The prevalence of restricted spirometry was elevated amongst women who had a history of working in underground and surface coal mining. Although only four women had ever worked as underground coal miners, three of them had restricted spirometry, a prevalence of 75% (PR: 3.15, 95% CI 1.74 to 5.68). The prevalence of restricted spirometry among the very few women who had ever worked in logging, roadway construction, and building was also increased, significantly so for the 2 out of 3 women who had worked in roadway construction. However, the prevalence of restricted spirometry was actually decreased for men who had worked in these trades.

Overall, there was no significant association with the environmental parameters studied and restricted spirometry, except for men in the middle quartile of abandoned underground mining, % HUC area, who had a prevalence of 39.6% with a prevalence ratio of 1.72 (95% CI 1.09 to 2.73) when compared to the lowest quartile of abandoned underground mining, % HUC area.

Table 3 shows the adjusted restricted spirometry prevalence by selected variables. Among women age 35-64, there was more than a 5-fold increase in the adjusted prevalence (PR: 5.49, 1.69 to 17.8, p=0.005) for restrictive spirometry compared to women age 18 – 34 years. With women over age 65, there was more than a 7-fold increase in the adjusted prevalence (PR: 7.23, 2.20 to 23.7, p=0.001) for restricted spirometry compared to women age 18 – 34 years. There was no statistically significant difference in the prevalence for men cross the three age groups. With single, widowed, or divorced women, there was 1.8 times increase in the adjusted prevalence (PR: 1.78, 95% CI 1.02 to 3.10, p=0.043) for restrictive spirometry, but there was no association for this variable in men. In the adjusted model, obesity continued to show significance with restricted spirometry for both women and men. Obese women had over a two-fold increase in the adjusted prevalence ratio (women PR: 2.21, 95% CI 1.05 to 4.64, p=0.036) of restricted spirometry compared to women with normal. Obese men had a 1.7-fold increase in the adjusted prevalence ratio

(PR: 2.68, 95% CI 1.05 to 6.80, p=0.039) of restricted spirometry compared to men with normal BMI. One and two or more comorbidities in women continued to be significant for restrictive spirometry, but not in men. There were no strong associations between occupation or environmental exposure categories, for either men or women, and restrictive spirometry. Table 4 provides the final adjusted model for the most important variables associated with restricted spirometry.

Discussion

This is the first known study that primarily focuses on determining the prevalence of restricted spirometry patterns in Appalachian regions of eastern Kentucky and evaluates how the prevalence differs in gender by various demographic, occupational, and environmental exposure factors. Nearly 1000 people participated in this cross-sectional study (n=972), which was the target population size, but a larger cohort would have provided greater power to evaluate associations between respiratory patterns and occupational and environmental exposure categories. The number of participants in this paper was 685 however, because persons with obstructed spirometry patterns were deleted and the subject of a separate manuscript.

This study found a high prevalence (26.7%) of restricted spirometry among the participants in this study, who were drawn from the Appalachian region of eastern Kentucky which is noted to have among the highest prevalence of lung disease in the U.S. This prevalence of restricted spirometry may be compared to the Burden of Lung Disease (BOLD) cross sectional study by Mannino et al[38] which found a restricted spirometry prevalence of 11.7% in men (546/4664) and 16.4% in women (836/5098). Another cross sectional study by Eriksson et al[39] with a comparable sample size (n=642), also found a restricted spirometry prevalence of only 3.1% in men (10/321) and 2.8% in women (9/321). Other aforementioned epidemiological studies that assessed restricted spirometry prevalence also had substantially lower prevalence among men and women.[12,13]

The reason for the much higher restricted spirometry prevalence in eastern Appalachian regions is likely multifactorial. In our study, participants also had high prevalence of cardiovascular disease, diabetes, and obesity. As the literature indicates, these conditions are strongly associated with restricted spirometry patterns.[38,40] The etiology of cardiovascular diseases leading to restricted spirometry may be associated with inflammatory conditions that cause endothelial dysfunction with reduced airflow in the lung and lung capacity. An association between restricted spirometry patterns and diabetes may be associated with its association with obesity, vascular disease, and neuromuscular weakness. Increased waist circumference from large amounts of visceral and subcutaneous fat around the central body region can decrease lung volume by reducing diaphragm and thoracic cage mobility.[40] However, in the Third National Health and Nutrition to Examination Survey (NHANES), only 9% of individuals in the obese category (BMI: 30+ kg/m^2) were found to have restricted spirometry.[41] Therefore, the increased prevalence of restricted spirometry patterns in this population from two counties in Eastern Kentucky is likely to be due at least in part to the high prevalence of obesity, and comorbid conditions. Individuals age 35 – 64 and ≥ 65 years were more likely to have an increased restricted spirometry prevalence compared with individuals age 18 – 34 years of age. Although, results were only statistically significant for women age 35 - 64 and ≥ 65, they reflect previous literature.[38,42] Women married or living as married served as a protective factor for restricted spirometry and was statistically significant. We suspect that being married may be associated with better overall health outcomes or better controlled risk factors associated with restricted spirometry. This suspicion is supported by Waldrone et al[43] who reported lower morbidity and mortality rates among married couples, along with better physical and mental health compared with individuals who were not married.

Higher educational attainment also served as a protective factor for restricted spirometry in both women and men which has been found in other studies.[5,42] In NHANES 1988 – 1994, individuals who had at least some college education were significantly less likely to have a restricted spirometry pattern (OR: 0.62, 95% CI: 0.42 to 0.90).[42] Sperandio et al[5] also reported a substantially lower prevalence of respiratory lung disease in individuals with restrictive patterns on spirometry who reported yes to higher education completion compared with individuals with restrictive patterns on spirometry who reported no to higher education completion. We suspect individuals with higher educational attainment are less likely to have the potential risk factors (e.g., CVD, obesity, hazardous occupational exposure, etc.) that may be associated with restricted spirometry.

One of our more compelling findings was that smoking did not have a strong effect on restricted spirometry prevalence; this finding is not congruent with the literature. For example, current smokers from NHANES 1988 -1994 were 31% more likely to have a restricted spirometry pattern compared to never smokers (OR: 1.31, 95% CI: 1.04 – 1.65).[42] In addition, current smokers from NHANES 1998 – 1994 were 89% more likely to have moderate to more severe restrictive patterns (FVC < lower limits of normal (LLN), FEV_1/FVC > LLN, FEV_1 < 70%) compared to never smokers from 1988 – 1994 (OR: 1.89, 95% CI: 1.24 – 2.86).[42] Schoenberg et al[44] reported women and men from Appalachian Kentucky smoke cigarettes at rates 1.8 times and 1.6 times higher, respectively, compared to their national counterparts. Therefore, we would expect a higher restricted spirometry prevalence in Letcher and Harlan counties associated with a higher prevalence of cigarette smoking.

Importantly, our study is subject to limitations. Selection bias was introduced into our study when we encouraged individuals with underlying respiratory disease (e.g., asthma etc.) to serve as the participants representing the household. So, our cohort may not be representative of Letcher or Harlan County as it may undermine external validity. It may have also overestimated RSP prevalence. Spirometry is a useful test in occupational health evaluations to rule out restrictive lung patterns with acceptable accuracy.[4] However, it is incapable of determining TLC which is performed by lung plethysmography and known to be the gold standard for determining RSPs.[4]

The primary hypotheses in our study were that the prevalence of lung diseases among participants in these two Eastern Kentucky counties would be associated with environmental exposures, mainly living near coal mines or mining activities. However, no statistically significant associations with either selected environmental, or occupational, exposure factors with restricted spirometry prevalence was found. Regarding our occupational exposure factors, this in line with previous literature. The NHANES 2007 – 2010 also found no statistically significant associations between occupational exposure factors and restricted lung disease prevalence (OR:1.05, 95% CI: 0.81 – 1.35).[42] The lack of low adjusted RSP prevalence mean estimates in our study with occupational and environmental factors may reflect employers, health officials, and workers in Appalachian Kentucky adopting and adhering to appropriate preventative measures (e.g., strict compliance of OSHA safety and health standards, appropriate personal protective equipment etc.). Further research looking at occupational and environmental factors are needed to further classify their relationship with RSP.

Table 1: Characteristics study participants by gender in prevalence of restricted spirometry in the Mountain Air Project

	Restricted Lung Function – Women Total = 424				Restricted Lung Function – Men Total = 261			
	Number	%	PR*	95% CI	Number	%	PR*	95% CI
All participants	103	24.3	---		80	30.6	---	
Age group								
18-34	3	3.6	Ref.	-----	5	12.5	Ref.	-----
35-64	53	23.9	1.65	1.20 – 2.29	39	31.4	2.52	1.06 – 5.95
≥65	47	39.5	10.9	3.5 – 33.9	36	37.1	2.97	1.26 – 7.02
Marital Status								
Married or living as married	49	20.3	Ref.	------	56	32.6	Ref.	-----
Single, Widowed, Divorced	54	29.5	1.45	1.04 – 2.03	24	27.0	0.83	0.55 – 1.24
Educational attainment								
<High School	27	33.8	1.43	0.98 – 2.08	24	32.4	1.00	0.67 - 1.49
High school or some college	65	23.6	Ref.	-----	51	32.5	Ref.	-----
College Graduate+	11	16.2	0.69	0.38 – 1.23	5	16.7	0.51	0.22 - 1.18
Annual household income								
<$25K	52	27.5	1.84	0.99 – 3.42	37	32.2	1.09	0.66 - 1.81
$25-$50K	8	13.8	0.92	0.39 – 2.19	10	27.8	0.94	0.48 - 1.86
$50K+	10	14.9	Ref.	-----	15	29.4	Ref.	-----
Missing	33	30.0	0.50	0.26 – 0.94	18	30.5	1.04	0.58 - 1.84
Type of dwelling								
Single family house	57	21.6	Ref.	-----	55	31.8	Ref.	-----
Mobile home	37	28.0	1.30	0.91 – 1.86	22	27.9	0.88	0.58 - 1.32
Multi-unit housing	9	32.1	1.49	0.83 – 2.67	3	33.3	1.05	0.41 – 2.71
Body mass index (BMI) (kg/m^2)								
Underweight (<18.5)	3	27.3	2.56	0.80 – 8.21	1	16.7	1.33	0.19 - 9.54
Normal (18.5-24.9)	8	10.7	Ref.	-----	5	12.5	Ref.	-----
Overweight (25.0-29.9)	19	18.5	1.73	0.80 – 3.74	28	29.8	2.38	0.99 – 5.73
Obese (30.0+)	73	31.1	2.91	1.47 – 5.76	46	38.0	3.04	1.30 – 7.12
Smoking status								
Current	35	27.6	1.37	0.94 – 2.03	17	25.0	0.73	0.45 – 1.17
Former	24	31.2	1.56	1.02 – 2.38	21	29.6	0.86	0.56 – 1.33
Never	44	20.0	Ref.	-----	42	34.4	Ref.	-----
Smoking Level								
High >20 packyears	39	45.4	2.29	1/61 – 3.25	27	34.6	1.01	0.68 – 1.49
Low 1 to 20 packyears	20	17.2	0.87	0.54 – 1.40	11	18.6	0.54	0.30 – 0.97
Non-Smoker	44	19.8	Ref.	----	42	34.4	Ref.	-----

Currently Lives Smoker								
Yes	70	28.2	1.51	1.04 – 2.17	46	29.5	0.91	0.63 – 1.32
No	33	18.8	Ref.	-----	34	32.4	Ref.	-----
Lived with Smoker as a Child								
Yes	71	24.5	1.03	0.71 – 1.47	57	30.6	0.99	0.67 – 1.50
No	32	23.9	Ref.	-----	23	30.7	Ref.	-----
Physical Activity or Exercise Past Month								
Yes	51	22.8	1.14	0.82 – 1.60	42	26.8	0.73	0.51 – 1.05
No	52	26.0	Ref.	-----	38	36.5	Ref.	-----
Have Diabetes								
Yes	35	41.7	2.08	1.49 – 2.89	15	41.7	1.44	0.93 – 2.23
No	68	20.1	Ref.	-----	65	28.9	Ref.	-----
Ever Had a Heart Attack								
Yes	13	48.2	2.12	1.38 – 3.26	14	45.2	1.57	1.01 - 2.43
No	90	22.7	Ref.	-----	66	28.8	Ref.	-----
Have Coronary Heart Disease								
Yes	20	37.0	1.65	1.11 – 2.45	21	42.0	1.50	1.01 – 2.22
No	83	22.5	Ref.	-----	59	28.0	Ref.	-----
Ever Had a Stroke								
Yes	10	43.5	1.87	1.14 – 3.08	5	45.5	1.51	0.77 – 2.96
No	93	23.3	Ref.	-----	75	30.1	Ref.	-----
Have Kidney Disease								
Yes	5	25.0	1.03	0.47 – 2.24	7	41.2	1.37	0.75 – 2.50
No	98	24.3	Ref.	-----	73	30.0	Ref.	-----
Number of Comorbid Conditions								
≥2	22	75.9	2.62	1.74 – 3.94	16	41.0	1.56	0.99 – 2.45
1	34	39.1	2.36	1.63 – 3.43	19	39.6	1.50	0.97 – 2.31
0	47	16.5	Ref.	-----	45	26.3	Ref.	-----

* PR = Prevalence Ratio

Table 2: Univariate analysis of normal and restricted spirometry by occupational and environmental exposure variables in the Mountain Air Project

	Restricted Lung Function – Women Total = 424				Restricted Lung Function – Men Total = 261			
	N	%	PR*	95% CI	n	%	PR*	95% CI
Employment Status								
Employed	18	13.1	Ref.	-----	22	25.3	Ref.	-----
Not Employed	43	23.6	1.80	1.09 – 2.98	10	22.2	0.88	0.46 – 1.69
Retired	18	32.7	2.49	1.40 – 4.42	26	36.6	1.45	0.90 – 2.33
Disabled	24	48.0	3.65	2.18 – 6.13	22	37.9	1.50	0.92 – 2.45
Hours Spent Outside the Home Each Day								
0	32	37.2	3.42	1.93 – 5.99	15	30.0	0.99	0.60 – 1.67
1 to 3	41	30.4	2.77	1.59 – 4.84	23	40.4	1.34	0.87 – 2.06
4 to <8	16	21.3	1.95	1.01 – 3.77	11	21.6	0.72	0.39 – 1.31
≥ 8	14	10.9	Ref.	-----	31	30.1	Ref.	-----
Ever Worked as an Underground Coal Miner								
Yes	3	75.0	3.15	1.74 – 5.68	42	35.3	1.32	0.92 – 1.90
No	100	23.8	Ref.	-----	38	26.8	Ref.	-----
Years a Underground Coal Miner								
≥ 15	0	0.0	0	-----	21	36.2	1.35	0.87 – 2.09
1 to <15	3	100.0	4.20	3.54 – 4.98	21	34.4	1.29	0.83 – 2.00
0	100	23.8	Ref.	-----	38	26.8	Ref.	-----
Ever Worked as a Surface Coal Miner								
Yes	3	33.3	1.38	0.54 – 3.54	33	30.6	0.99	0.69 – 1.44
No	100	24.1	Ref.	-----	47	30.7	Ref.	-----
Ever Worked in the Logging-Timber-Wood Milling Industry								
Yes	1	33.3	1.38	0.28 – 6.88	8	21.1	0.65	0.34 – 1.24
No	102	24.23	Ref.	-----	72	32.3	Ref.	-----
Ever Worked in Roadway Construction								
Yes	2	66.7	2.78	1.23 – 6.30	5	17.2	0.53	0.23 – 1.21
No	101	24.0	Ref.	-----	75	32.3	Ref.	-----
Ever Worked in Home or Building Construction								
Yes	4	36.4	1.52	0.68 – 3.38	21	26.6	0.82	0.53 – 1.25
No	99	24.0	Ref.	-----	59	32.4	Ref.	-----
Roadway Miles/sq. mi. within HUC								
Lowest Tertile (0.19-1.89)	41	28.3	Ref.	-----	28	31.8	Ref.	-----
Middle Tertile (1.891-2.76)	37	23.1	1.10	0.70 – 1.72	21	27.6	0.87	0.54 – 1.40
Highest Tertile (2.77-6.003)	25	21.0	1.35	0.87 – 2.08	31	32.0	1.00	0.66 – 1.53

Coal Haulage Miles/sq. mi. within HUC								
Zero (32%)	30	23.6	Ref.	-----	26	30.9	Ref.	-----
Middle Tertile (0.004-0.50)	33	21.0	0.89	0.57 – 1.38	29	30.8	0.99	0.64 – 1.55
Highest Tertile (0.51-1.27)	40	28.6	1.21	0.80 – 1.82	25	30.1	0.97	0.62 – 1.54
Oil/Gas Wells/sq. mi. within HUC								
Zero (25%)	28	26.7	Ref.	-----	19	29.2	Ref.	-----
Middle 37.5% (0.34-0.85)	40	22.6	0.85	0.56 – 1.29	38	36.2	1.24	0.79 – 1.95
Highest 37.5% (0.86-8.44)	35	24.7	0.92	0.60 – 1.42	23	25.3	0.86	0.52 – 1.45
Abandoned Surface Mining, % HUC Area								
Zero (40%)	45	27.8	Ref.	-----	31	29.5	Ref.	-----
Middle 30%	32	22.9	0.82	0.56 – 1.22	28	34.1	1.16	0.76 – 1.76
Highest 30%	26	21.3	0.77	0.50 – 1.17	21	28.4	0.96	0.60 – 1.53
Active Surface Mining, % HUC Area								
Zero (78%)	80	24.5	Ref.	-----	61	29.9	Ref.	-----
Greater than Zero	23	23.7	0.97	0.65 – 1.45	19	33.3	1.11	0.73 – 1.70
Abandoned Underground Mining, % HUC Area								
Lowest Tertile	43	27.6	Ref.	-----	20	23.0	Ref.	-----
Middle Tertile	29	21.0	0.76	0.51 – 1.15	36	39.6	1.72	1.09 – 2.73
Highest Tertile	31	23.9	0.87	0.58 – 1.29	24	28.9	1.25	0.75 – 2.10
Active Underground Mining, % HUC Area								
Zero (62%)	69	27.3	Ref.	-----	48	29.6	Ref.	-----
Greater than Zero	34	19.9	0.73	0.51 – 1.05	32	33.3	1.09	0.75 – 1.58
Abandoned Mining, % HUC Area								
Lowest Tertile (0 – 0.1)	42	27.1	Ref.	-----	21	24.4	Ref.	-----
Middle Tertile (0.12 – 0.5)	30	21.6	0.80	0.53 – 1.20	35	38.0	1.55	1.00 – 2.45
Highest Tertile (0.51 – 1.96)	31	23.9	0.88	0.59 – 1.31	24	28.9	1.18	0.71 – 1.96
Active mining, % HUC Area								
Zero (50%)	54	28.0	Ref.	-----	35	27.8	Ref.	-----
Middle (25%)	28	19.2	0.69	0.46 – 1.03	28	40.0	1.44	0.96 – 2.15
Highest 25%	21	24.7	0.88	0.57 – 1.36	17	26.2	0.94	0.57 – 1.55

Table 3: Adjusted Restricted Spirometry Prevalence by Selected Variables – Mountain Air Project – Restricted Lung Disease Analyses

	Women			Men		
Variable	Mean Est.	95% CI	p	Mean Est.	95% CI	p
Age Groups						
Age: 18 – 34 yrs	1.00	Ref.	-----	1.00	Ref.	-----
Age: 35 – 64 yrs	5.49	1.69 – 17.8	0.005	2.13	0.83 – 5.48	0.116
Age: ≥65 yrs	7.23	2.20 – 23.7	0.001	2.26	0.85 – 6.02	0.103
Marital Status						
Married or Living as Married	1.00	Ref.	-----	Not an important variable for men		
Single, Widowed, Divorced	1.78	1.02 – 3.10	0.043			
Smoking Categories						
NonSmoker	1.00	Ref.	-----	1.00	Ref.	-----
Smoker	1.34	0.89 – 2.01	0.160	0.93	0.59 – 1.45	0.741
Body Mass Index (BMI)						
Lean	1.93	0.51 – 7.28	0.333	1.56	0.18 – 13.5	0.686
Normal	1.00	Ref.	-----	1.00	Ref.	-----
Overweight	1.41	0.61 – 3.24	0.418	2.21	0.85 – 5.75	0.105
Obese	2.21	1.05 – 4.64	0.036	2.68	1.05 – 6.80	0.039
Number of Comorbidities						
0	1.00	Ref.	-----	1.00	Ref.	-----
1	1.79	1.14 – 2.80	0.011	1.25	0.71 – 2.20	0.430
≥2	1.50	0.89 – 2.55	0.129	1.36	0.74 – 2.49	0.317
Number of Years Worked as an Underground Coal Miner						
No Worker as UG Miner	Only 4 women ever worked as an underground coal miner; 3 of them had restricted lung function			1.00	Ref.	-----
UG Miner 1 – 15 yrs				1.28	0.73 – 2.26	0.387
UGMiner >15 yrs				1.18	0.65 – 2.13	0.587
Number of Years Worked as a Surface Miner						
0 Years Worked as Surface Miner	Only 9 women ever worked as a surface coal miner; 3 of them had restricted lung function			1.00	Ref.	-----
Surface Miner 1 – 15 yrs				0.78	0.43 – 1.44	0.434
Surface Miner >15 yrs				1.10	0.64 – 1.89	0.739
Number of Roadway Miles per Square Mile within HUC						
Lowest Tertile (0.19-1.89)	1.00	Ref.	-----	1.00	Ref.	-----
Middle Tertile (1.891-2.76)	1.01	0.64 – 1.58	0.969	0.83	0.46 – 1.48	0.525
Highest Tertile (2.77-6.00)	0.85	0.52 – 1.41	0.538	1.00	0.59 – 1.71	0.993
Number of Coal Haulage Miles per Square Mile within HUC						
Zero (32%)	1.00	Ref.	-----	1.00	Ref.	-----
Middle Tertile (0.004-0.50)	0.71	0.45 – 1.13	0.015	1.06	0.62 – 1.82	0.832
Highest Tertile (0.51-1.27)	0.75	0.47 – 1.21	1.21	1.01	0.58 – 1.75	0.982
Number of Oil and Gas Wells per Square Mile within HUC						
Zero (25%)	1.00	Ref.	-----	1.00	Ref.	-----
Mid Tertile 37.5% (0.34-0.85)	1.01	0.64 – 1.59	0.975	1.25	0.71 – 2.18	0.437
Highest 37.5% (0.86-8.44)	1.05	0.64 – 1.71	0.852	0.85	0.46 – 1.58	0.612
Abandoned Surface Mines, % of Area within HUC						
Zero (40%)	1.00	Ref.	-----	1.00	Ref.	-----
Middle 30%	0.84	0.49 – 1.44	0.532	1.11	0.66 – 1.86	0.690
Highest 30%	1.25	0.76 – 2.04	0.376	0.90	0.51 – 1.57	0.670
Active Surface Mines, % of Area within HUC						
Zero (78%)	1.00	Ref.	-----	1.00	Ref.	-----
Greater than Zero	1.07	0.67 – 1.72	0.764	1.03	0.61 – 1.74	0.926
Abandoned Underground Mines, % of Area within HUC						
Lowest Tertile 30.6% (0.07)	1.00	Ref.	-----	1.00	Ref.	-----
Mid Tertile 32.6% (0.07-0.4)	1.14	0.68 – 1.91	0.630	1.55	0.89 – 2.70	0.121
Highest Tertile 36.8% (>0.4)	1.22	0.76 – 1.94	0.415	1.17	0.64 – 2.12	0.614
Active Underground Mines, % of Area within HUC						
Zero (62%)	1.00	Ref.	-----	1.00	Ref.	-----
Greater than Zero	0.90	0.59 – 1.36	0.607	1.07	0.68 – 1.69	0.769

Table 4: Modeling Comparison – Mountain Air Project – Restricted Spirometry Analyses

	Women			Men		
Variable	**Mean Est.**	**95% CI**	**p**	**Mean Est.**	**95% CI**	**p**
Age Groups						
Age: 18 – 34 yrs	1.00	Ref.	-----	1.00	Ref.	-----
Age: 35 – 64 yrs	5.49	1.69 – 17.8	0.005	1.93	0.74 – 5.03	0.181
Age: ≥65 yrs	7.23	2.20 – 23.7	0.001	1.77	0.61 – 5.13	0.295
Smoking Categories						
NonSmoker	1.00	Ref.	-----	1.00	Ref.	-----
Smoker	1.34	0.89 – 2.01	0.160	0.88	0.67 – 1.39	0.576
Marital Status						
Married	1.00	Ref.	-----	1.00	Ref.	-----
Unmarried	1.78	1.02 – 3.10	0.043	1.31	0.75 – 2.29	0.334
Body Mass Index (BMI)						
Lean	1.93	0.51 – 7.28	0.333	1.69	0.19 – 14.7	0.636
Normal	1.00	Ref.	-----	1.00	Ref.	-----
Overweight	1.41	0.61 – 3.24	0.418	2.29	0.87 – 5.98	0.092
Obese	2.21	1.05 – 4.64	0.036	2.85	1.11 – 7.33	0.029
Number of Comorbidities						
0	1.00	Ref.	-----	1.00	Ref.	-----
1	1.79	1.14 – 2.80	0.011	1.19	0.67 – 2.10	0.550
≥2	1.50	0.89 – 2.55	0.129	1.38	0.74 – 2.57	0.310
Number of Years Worked as an Underground Coal Miner						
No Worker as UG Miner				1.00	Ref.	-----
UG Miner 1 – 15 yrs				1.29	0.73 – 2.28	0.380
UGMiner >15 yrs				1.18	0.65 – 2.12	0.591

References

1. Backman H, Eriksson B, Hedman L, et al. Restrictive spirometric pattern in the general adult population: Methods of defining the condition and consequences on prevalence. *Respiratory Medicine.* 2016;120:116-123.
2. Godfrey MS, Jankowich MD. The Vital Capacity Is Vital: Epidemiology and Clinical Significance of the Restrictive Spirometry Pattern: Epidemiology and Clinical Significance of the Restrictive Spirometry Pattern. *Chest.* 2016;149(1):238-251.
3. Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. *American family physician.* 2014;89(5):359-366.
4. Mehrparvar AH, Sakhvidi MJZ, Mostaghaci M, Davari MH, Hashemi SH, Zare Z. Spirometry values for detecting a restrictive pattern in occupational health settings. *TANAFFOS - Journal of Respiratory Disease, Thoracic Surgery, Intensive Care and Tuberculosis.* 2014;13(2):27-34.
5. Sperandio EF, Arantes RL, Matheus AC, et al. Restrictive pattern on spirometry: association with cardiovascular risk and level of physical activity in asymptomatic adults. *Jornal Brasileiro de Pneumologia.* 2016;42(1):22-28.
6. Jankowich M, Elston B, Liu Q, et al. Restrictive Spirometry Pattern, Cardiac Structure and Function, and Incident Heart Failure in African Americans. The Jackson Heart Study. *Annals of the American Thoracic Society.* 2018;15(10):1186-1196.
7. Scwartzstein RM. *Chest wall diseases and restrictive physiology.* Waltham, Massachusetts: UpToDate; 2019.
8. King TE. *Approach to the adult with interstitial lung disease: Clinical evaluation.* Waltham, Massachusetts: UpToDate; 2019.
9. Cohen RAC, Patel AHY, Green FHY. Lung Disease Caused by Exposure to Coal Mine and Silica Dust. *Seminars In Respiratory And Critical Care Medicine.* 2008;29(6):651-661.
10. Checkoway H, Heyer NJ, Seixas NS, et al. Dose-response associations of silica with nonmalignant respiratory disease and lung cancer mortality in the diatomaceous earth industry. *American journal of epidemiology.* 1997;145(8):680-688.
11. Schatzel SJ. Identifying sources of respirable quartz and silica dust in underground coal mines in southern West Virginia, western Virginia, and eastern Kentucky. *International journal of coal geology.* 2009;78(2):110-118.
12. El Zoghbi M, Salameh P, Stücker I, et al. Prevalence of occupational exposure to asbestos and crystalline silica according to phenotypes of lung cancer from the CaProMat study: A case ‐ only study. *American Journal of Industrial Medicine.* 2018;61(1):85-99.
13. Perret JL, Plush B, Lachapelle P, et al. Coal mine dust lung disease in the modern era. In*.* Vol 22. Chichester, UK2017:662-670.
14. Reynolds LE, Blackley DJ, Laney AS, Halldin CN. Respiratory morbidity among U.S. coal miners in states outside of central Appalachia. *American Journal of Industrial Medicine.* 2017;60(6):513-517.

15. Blackley DJ. Resurgence of progressive massive fibrosis in coal miners—Eastern Kentucky, 2016. *Morbidity and mortality weekly report : MMWR /.* 2016;65(49):1385.
16. Ingelfinger JR, Feller-Kopman D, Light R. Pleural Disease. *The New England Journal of Medicine.* 2018;378(8):740-751.
17. King TE. *Asbestos-related pleuropulmonary disease.* Waltham, MA: UpToDate; 2020.
18. Gulati AM, Redlich AC. Asbestosis and environmental causes of usual interstitial pneumonia. *Current Opinion in Pulmonary Medicine.* 2015;21(2):193-200.
19. Lazarus AA, Philip A. Asbestosis. *Dm Disease-A-Month.* 2011;57(1):14-26.
20. O'Reilly K, McLaughlin A, Beckett W, Sime P. Asbestos-Related Lung Disease. *American Family Physician.* 2007;75(5):683-690.
21. Peiris-John RJ, Ruberu DK, Wickremasinghe AR, van-Der-Hoek W. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. *Respiratory Medicine.* 2005;99(10):1319-1324.
22. Feng W, Huang X, Zhang C, et al. The dose-response association of urinary metals with altered pulmonary function and risks of restrictive and obstructive lung diseases: a population-based study in China. *BMJ open.* 2015;5(5):e007643.
23. Newman LS, Maier LA. *Chronic beryllium disease (berylliosis).* Waltham, MA: UpToDate; 2020.
24. Gartman EJ. Pulmonary Function Testing in Neuromuscular and Chest Wall Disorders. *Clinics in Chest Medicine.* 2018;39(2):325-334.
25. Sharma GD. Pulmonary function testing in neuromuscular disorders. *Pediatrics.* 2009;123 suppl 4(Supplement 4):S219-S221.
26. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax.* 2003;58(5):388.
27. Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respiratory Medicine.* 2006;100(1):115-122.
28. Leone N, Courbon D, Thomas F, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *American journal of respiratory and critical care medicine.* 2009;179(6):509.
29. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax.* 2010;65(6):499.
30. Lee HM, Chung SJ, Lopez VA, Wong ND. Association of FVC and Total Mortality in US Adults With Metabolic Syndrome and Diabetes. *Chest.* 2009;136(1):171-176.
31. Blackley DJ, Halldin CN, Laney AS. Continued Increase in Prevalence of Coal Workers' Pneumoconiosis in the United States, 1970-2017. *American journal of public health.* 2018;108(9):1220.

32. May BA, Cardarelli KM, Silver R, Christian WJ, Schoenberg NE, Browning SR. Hollows as sampling units for community-based participatory research in appalachia: The mountain air project. *Progress in Community Health Partnerships: Research, Education, and Action.* 2019;13(4):401-410.
33. Krieger J, Takaro TK, Song L, Beaudet N, Edwards K. A randomized controlled trial of asthma self-management support comparing clinic-based nurses and in-home community health workers: the Seattle-King County Healthy Homes II Project. *Arch Pediatr Adolesc Med.* 2009;163(2):141-149.
34. Krieger JK, Takaro TK, Allen C, et al. The Seattle-King County healthy homes project: implementation of a comprehensive approach to improving indoor environmental quality for low-income children with asthma. *Environ Health Perspect.* 2002;110 Suppl 2:311-322.
35. Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: a randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. *Am J Public Health.* 2005;95(4):652-659.
36. Braun-Fahrlander C, Gassner M, Grize L, et al. Comparison of responses to an asthma symptom questionnaire (ISAAC core questions) completed by adolescents and their parents. SCARPOL-Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with respect to Air Pollution. *Pediatr Pulmonol.* 1998;25(3):159-166.
37. Valle SO, Kuschnir FC, Sole D, Silva MA, Silva RI, Da Cunha AJ. Validity and reproducibility of the asthma core International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire obtained by telephone survey. *J Asthma.* 2012;49(4):390-394.
38. Mannino DM. Restricted spirometry in the Burden of Lung Disease Study. *The International Journal of Tuberculosis and Lung Disease.* 2012;16(10):1405-1411.
39. Eriksson B, Lindberg A, Müllerova H, Rönmark E, Lundbäck B. Association of heart diseases with COPD and restrictive lung function – Results from a population survey. *Respiratory Medicine.* 2013;107(1):98-106.
40. Kurth L, Hnizdo E. Change in prevalence of restrictive lung impairment in the U.S. population and associated risk factors: the National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 2007-2010. *Multidisciplinary respiratory medicine.* 2015;10(1):7-7.
41. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the third national health and nutrition examination. *The American Journal of Medicine.* 2003;114(9):758-762.
42. Kurth L, Hnizdo E. Change in prevalence of restrictive lung impairment in the U.S. population and associated risk factors: the National Health and Nutrition Examination Survey (NHANES) 1988–1994 and 2007–2010. *Multidisciplinary Respiratory Medicine.* 2015;10(1).
43. Waldron I, Hughes ME, Brooks TL. Marriage protection and marriage selection—Prospective evidence for reciprocal effects of marital status and health. *Social Science & Medicine.* 1996;43(1):113-123.

44. Schoenberg EN, Huang CB, Seshadri CS, Tucker CT. Trends in Cigarette Smoking and Obesity in Appalachian Kentucky. *Southern Medical Journal.* 2015;108(3):170-177.