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Association Between Self-Reported Dyspnea and Depressive Symptoms in New Mexico Uranium Workers

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ASSOCIATION BETWEEN SELF-REPORTED DYSPNEA AND DEPRESSIVE SYMPTOMS IN NEW MEXICO URANIUM WORKERS

by

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DEDICATION

To my mother, who never wavered in her belief and support of me, through thick and thin, in my endeavor to complete the Master of Science in Clinical Research degree program.

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ABSTRACT

BACKGROUND: Uranium workers risk experiencing dyspnea, a lung disease symptom. Previous studies found associations between dyspnea and depressive symptoms in lung disease, but this requires further study in occupational cohorts.

METHODS: This study evaluated the association between dyspnea and depressive symptoms in former uranium workers screened by New Mexico Radiation Exposure Screening & Education Program. Dyspnea and depressive symptoms were evaluated through questionnaires, Modified Medical Research Council Dyspnea Scale and a modified Patient Health Questionnaire-2, respectively. Logistic regression models were applied to cross-sectional analyses. Generalized linear models were applied to longitudinal analyses.

RESULTS: Cross-sectional analyses demonstrated higher dyspnea scores were associated with higher depressive symptom scores. Longitudinal analyses failed to demonstrate association between change in dyspnea scores and concurrent change in depressive symptom scores.

CONCLUSIONS: Lower dyspnea levels were common and depressive symptoms were not commonly reported. Workers reporting higher dyspnea levels were three times more likely to endorse depressive symptoms. Further longitudinal studies are necessary to understand the mechanisms between dyspnea and depressive symptoms in occupational cohorts at risk of developing lung disease.

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Chapter 1

Introduction

Depression has long been a leading cause of disability globally (WHO, 2002) affecting 311 million people (Victora et al., 2017) and is an important cause of total disease burden (WHO, 2002). As 1 in 5 adults report significant depressive symptoms, depression is a significant American public health challenge characterized by inadequately addressed symptom management (Shim et al., 2011). Racial and ethnic minorities in the United States may be at greater risk for morbidity associated with depression as disparities exist in diagnosis and treatment (Shao et al., 2016). Highly researched and well-established risk factors for depression include female gender, family history of depression especially in biological parents, stressful life situations and events including medical illness, socioeconomic factors, and cognitive difficulties (Hammen et al., 2018). The presence of either depressed mood or anhedonia (which is a significant decrease in experiencing pleasure from the majority of one's daily activities on most days) within a two-week period is necessary to diagnose major depressive disorder (American Psychiatric Association, 2000). Examination of individual depressive symptoms may be worthwhile as the presence of certain symptoms may be suggestive of different levels of impairments in affected patients, especially based on age (García-Velázquez et al., 2019).

Occupational activity has been shown to affect health-related quality of life (HRQOL) (Shockey et al., 2017). Uncontrolled depressive symptoms have been identified as a risk factor for occupational injury (Chau et al., 2011). Inadequate treatment of depression can lead to reduced worker productivity (Fan et al., 2012). The relationship between occupational health and depression is bidirectional. Occupational injury has been identified as a risk factor for depression (Asfaw & Souza, 2012; Kim, 2013) and quick response post-occupational injury is necessary to reduce depression-associated morbidity (Kim, 2013) and financial cost (Asfaw & Souza, 2012). The cost of post-occupational injury depression as approximated only by clinic visits was $8.2 million in 2005 and this is an underestimate (Asfaw & Souza, 2012). Society as a whole, including tax-paying workers, stands to gain from further research on the relationship between occupation and depression.

Internationally, pulmonary disease secondary to occupational exposure (including dust, fumes, gases, and vapors) is an important cause of disability (Perlman & Maier, 2019). Dyspnea, the subjective report of discomfort while breathing that if severe enough can feel like suffocation (can be described as shortness of breath), has generated much research interest in its role towards pulmonary health and in validation of its measures in conjunction with clinical treatment (Parshall et al., 2011). It can be a normal finding in situations marked by heavy exertion, however when unexpected, dyspnea indicates presence of disease (Coccia et al., 2016). Dyspnea has recently been identified as a symptom that should be treated in chronic obstructive pulmonary disease (COPD) to improve linked psychological effects including anxiety and depression (Hanania & O’Donnell, 2019). Evaluation and treatment of dyspnea is challenging as its pathophysiology is complex often involving multiple organ systems, and even when the underlying cause has been identified, symptoms commonly persist despite treatment (Coccia et al., 2016).

Significance:

Behind Wyoming, New Mexico has the second largest uranium reserves in the nation and the two states collectively hold between two-thirds and three-fourths of the national uranium reserves (US Energy, 2008). Annually, 25,000 tons of uranium are responsible for an estimated 20% of domestic electricity production (Conca, 2017). Uranium mining and related activities (e.g. ore transporting and milling) date back to around 1950 when reserves were discovered in New Mexico. Despite the US Public Health Service conducting studies of radiation hazards associated with uranium exposure in 1950, over forty years passed before Congress established reparation funding for those affected by mining (including uranium) through the Radiation Energy Compensation Act (RECA) (Dawson & Madsen, 2007). The United States was the world's leader in uranium production until 1980 when falling global market prices contributed to a sharp decline in uranium-based activities. Since global prices began rising in 2001, there has been a gradual uptick in uranium mining and related activities with domestic production responsible for 7% of uranium consumed by US nuclear power plants (US Energy, 2019).

The scientific literature supports the assertion that depression is an extrapulmonary manifestation of chronic lung disease (Hung et al., 2017; Pumar et al., 2014). While numerous studies exist regarding depression in the setting of particular lung pathologies, uranium workers are at demonstrated risk of a plethora of pulmonary conditions leading to a decline in lung function (Archer et al., 1998; Bersimbaev & Bulgakova, 2015; Faa et al., 2018; Gottlieb & Husen, 1982; Kocher et al., 2016; Samet et al., 1984; Samet et al., 1991; Trapp et al., 1970; Walsh et al., 2015). Pulmonary injury occurs via two primary mechanisms: (1) radiation exposure (Bersimbaev & Bulgakova, 2015; Faa et al., 2018) and (2) inhalational exposure to dust (Kocher et al., 2016). Particular lung pathologies that uranium workers are at risk for include pneumoconiosis (including silicosis) (Kocher 2016), interstitial lung disease (ILD) (Archer et al, 1998; Kocher et al., 2016), pulmonary emboli (Shen et al, 2015a), carcinoma (Bersimbaev & Bulgakova, 2015; Faa et al., 2018), and COPD (Walsh et al., 2015). Uranium workers' pneumoconiosis, a collection of uranium mine dust-related lung diseases (Kocher et al., 2016), is associated with systemic conditions including congestive heart failure (Yen et al., 2016), peripheral arterial disease (Shen et al., 2015b), and stroke (Cheng et al., 2015), similar to other pneumonconiotic illnesses.

Uranium workers are also susceptible to depressive symptoms, partly due to risky and stressful working environments (Dawson & Madsen, 2007; Dawson & Madsen, 2011). Lung diseases have been associated with various neuropsychiatric sequelae or comorbidities (Dodd, 2015; Ryerson et al., 2012). Screening for and treatment of depression in ILD has been suggested with the goal of improvement of quality of life (Ryerson et al., 2012; Ryerson et al., 2011; Wang et al., 2008). Significant levels of depressive symptoms are associated with silicosis and may be deleterious towards quality of life (Wang et al., 2008). In a study of patients with ILD, depressive symptoms correlated with dyspnea, forced vital capacity (FVC), sleep quality, and pain (Ryerson et al., 2011). While several pulmonary function tests exist providing objective evidence in lung disease management, they are limited by their inability to take into account the patients' experiences with lung disease (Ranu et al., 2011) including subjective symptoms such as dyspnea. Additional studies of uranium workers, especially those taking into account the racial/ethnic backgrounds of the workers are warranted, due to cultural-based differences in workers' experiences with the occupational environment (Dawson & Madsen, 2011) and perceptions involving their mental health (Perini et al., 2015). Furthermore, there has been a precedence of studying dyspnea and depressive symptoms together, longitudinally, to better understand the mechanism of the association between the two (Newman et al., 2006, Schuler et al., 2018).

This project has potential ramifications towards the advancement of medical and mental health for uranium workers in a climate where domestic uranium production is likely to increase to meet national demands. It will also serve to address the historically neglected health needs of former uranium workers who deserve credit for their roles in the growth and development of the United States' radiation energy program. At its height in the 1960s, close to 4000 New Mexicans were employed annually as uranium workers. From 2003 until the present, the UNM RESEP screened cohort exhibits the following racial/ethnic breakdown: 28% Hispanic, 37% Native American, 34% Non-Hispanic Whites, and 1% African American. Most uranium mines were located in the Grants Mineral Belt, in the northwest part of the state (Brookins, 1977), either on American Indian reservations or in close proximity to them. The open-pit Jackpile Mine, the largest ever American uranium surface mine, was located on the Laguna Pueblo, and approximately 75% of the workers were Native American. Unfortunately, many entities failed to inform Native Americans of the health risk associated with uranium and they were not provided with safer work conditions, nor were they afforded the same benefits as workers of other races/ethnicities through RECA (Dawson & Madsen, 2007; Dawson & Madsen, 2011). Many individuals identifying as Navajo are part of the Mining Dust in the United States (MiDUS) cohort and the findings of this study may serve to further elucidate the biopsychosocial impacts of uranium mining upon the Navajo people as well as others engaged in this occupation.

Innovation:

The proposed research is innovative because it examines a unique occupational cohort and the potential effects of their occupational history upon their mental health. The uranium workers of New Mexico constitute an underserved and understudied occupational cohort, largely composed of racial/ethnic minorities, and this study has been developed with the intention of advancing scientific research on these workers. The occupational medicine literature asserts that healthy workers are associated with greater productivity (Polakoff & O'Rourke, 1990) as well as reduced risk of negative health outcomes (Goh et al., 2015; McCaughey et al., 2013; Lundstrom et al., 2017) and a body of evidence is emerging that associates pulmonary injury with adverse effects to the brain (Hung et al., 2017; Pumar et al., 2014). Recent research in this cohort has demonstrated that New Mexico uranium workers have greater odds of developing angina than non-uranium workers do (al Rashida et al., 2019) and that these workers have significant lung disease burden (Assad et al., 2019). Thus, the research question is one of merit that should be investigated.

Using the Modified Medical Research Council (mMRC) Dyspnea scale (Mahler & Wells, 1988), a subjective screening measure, will allow researchers to appreciate the lived experiences of uranium workers especially in conjunction with depressive symptoms. This combined overall characterization of lung function will be compared against responses to a modified PHQ-2 questionnaire (Kroenke et al., 2003) which screens for presence of two specific depressive symptoms: depressed mood and anhedonia. The PHQ-2 (Kroenke et al., 2003) has been validated in primary care settings to identify patients that are in need of further evaluation for depression.

The findings of this study will: 1) emphasize the importance of screening for depression in uranium workers; and 2) determine novel clinical markers of mental health in occupational cohorts of largely racial/ethnic minority men in New Mexico, mostly Hispanic and American Indian. The long-term impact of the study would be to help improve the screening, diagnosis, and treatment of chronic conditions in these workers. This study will provide useful preliminary data for future studies of the association between respiratory and mental health in workers and to determine the mechanism underlying this association.

Specific Aims:

The *study objective* is to better elucidate the relationship between dyspnea and depressive symptoms in a population of uranium workers enrolled in the University of New Mexico's (UNM) Radiation Exposure Screening and Education Program (NM-RESEP) component of the MiDUS cohort. The *rationale* of the study is to analyze the association between respiratory health and mental health in an occupational cohort. The *expected outcome* is that there will be positive correlations between patients' subjective reports of dyspnea and depressive symptoms. If the expected outcomes come to fruition, the *impact* of the study would be to determine novel clinical markers of mental health, which would be helpful in screening, diagnosis, and treatment of chronic conditions in these workers. The goals of the proposed study will be realized through successful completion of the following aims:

<u>Aim 1:</u> To assess the association between dyspnea and depressive symptoms in uranium workers at baseline visit (cross-sectional analysis).

Aim 1 Hypothesis: Uranium workers endorsing higher scores on the mMRC Dyspnea Scale are more likely to endorse depressive symptoms than those endorsing lower dyspnea scores at baseline visit. Regression models will be used to estimate the association between dyspnea as evaluated by the Modified Medical Research Council (mMRC) Dyspnea Scale, and depressive symptoms as evaluated by the modified Patient Health Questionnaire (PHQ-2) that screens for depression via inquiry of depressed mood and anhedonia. It is anticipated that uranium workers demonstrating higher levels of dyspnea are more likely to experience depressive symptoms.

<u>Aim 2:</u> To assess the association between change in dyspnea (from baseline to final visit) and change in depressive symptoms in uranium workers (longitudinal analysis).

Aim 2 Hypothesis: Longitudinal change in dyspnea scores between final and baseline visits is positively correlated with change in depressive symptom scores during the same timeframe in uranium workers. Regression models will used to estimate association between change in dyspnea (from baseline to final visit) as evaluated by the mMRC Dyspnea Scale and change in depressive symptoms, as evaluated by the modified PHQ-2 score, during the same time frame. It is anticipated that uranium workers demonstrating increasing severity of dyspnea are more likely to experience an increase in depressive symptom scores.

Chapter 2

Methods

Search Strategy:

PubMed is the most robust and central database for this medical research question, thus a search was performed in this database. The MeSH search option of PubMed was accessed at https://www-ncbi-nlm-nih-gov.libproxy.unm.edu/mesh. The term “Mining” was entered into the search bar yielding 3 search results. The first result “Mining” was clicked on leading to a PubMed search builder option page. The option “Restrict to MeSH Major Topic” was checked and then I clicked on “Add to Search Builder” yielding the following under the PubMed Search Builder field: “"Mining"[Majr]”. After clicking on “Search PubMed,” 10251 search results were generated. I proceeded to refine the search by adding “Depression” to the PubMed Search Builder field yielding the following search prompt: "Mining"[Majr] AND "Depression"[Mesh]. This refined the search to only 8 results. The final search query yielding 8 results was: "Mining"[Majr] AND "Depression"[Mesh]. Despite having a limited amount of results generated by the MeSH search, I applied the following search filters sequentially to ensure relevance of the generated search results: “English” (under Language) (7 results); “Humans” (under Species) (7 results); and “5 Years” (under Publication dates) (1 result). Due to the limited results generated by the application of the search filters, I made the decision not to filter by study type. The final search query yielding 1 result was: "Mining"[Majr] AND "Depression"[Mesh] AND ("2013/08/21"[PDat]: "2018/08/19"[PDat] AND "humans"[MeSH Terms] AND English[lang]). “Clear” was clicked on to remove all the added search filters and returned to the original search query yielding 8 results and proceeded to review the titles and abstracts (if available) to determine relevance to the research question.

Study Design:

Baseline and final visit evaluation data from current and former New Mexico uranium workers voluntarily enrolled between 2004 and 2017 were obtained from NM-RESEP, a federally-funded health screening and education program, located at the University of New Mexico Health Sciences Center (UNM-HSC). The research setting is NM-RESEP, which administers a majority of their surveillance examinations through the UNM Employee Occupational Health Services (EOHS) Clinic at the UNM Health Sciences Center campus in Albuquerque, New Mexico. The EOHS clinic is staffed by physicians, nurse practitioners, and physician assistants, who were adequately trained in the study protocol.

Inclusion Criteria/Exclusion Criteria:

The research participants were former uranium workers that were enrolled in NM-RESEP from 2004 to 2017 who had baseline and annual follow-up visits with documented information regarding dyspnea symptoms, as measured by the mMRC Dyspnea Scale (Mahler & Wells, 1988), and modified Patient Health Questionnaire (PHQ-2) (Kroenke et al., 2003) scores. The aforementioned data, as well as additional health information, were collected through medical history taken during the patient visits. Missing data were addressed by several statistical procedures. Mean imputation (replacement of missing values by the mean value of available data points) was used for demographic variables such as height, weight, and BMI. Missing information for demographic variables such as age or sex required manual recoding based on information obtained from other visits for the same individual. Listwise deletion was performed for individuals lacking baseline and final visit scores for the mMRC Dyspnea Scale (Mahler & Wells, 1988) and the modified PHQ-2 (Kroenke et al., 2003). Although most patients lived or worked in New Mexico, a small number originated from neighboring states and traveled to New Mexico due to non-availability of screening in their states of residence. Since the RESEP screening program is available at no charge to uranium workers, the financial status of workers did not result in selection bias.

Data Collection:

Data were obtained from a self-reported questionnaire administered by a trained interviewer (usually prior to patient visits) and then confirmed with the worker by a physician/nurse practitioner/physician assistant during patient visits. Trained interpreters were available for Spanish and American Indian languages. The questionnaire includes demographics, information on smoking and cardiovascular status, a screening questionnaire on dyspnea—the mMRC Dyspnea Scale (Mahler & Wells, 1988) and a screening questionnaire on depressive symptoms—a modified PHQ-2 (Kroenke et al., 2003)—which includes two separate items on depressed mood and anhedonia over the two-week period prior to screening. Body mass index (BMI) was calculated using measured height and weight. Percent predicted forced expiratory volume in one second (FEV_1) was determined using sex- and race/ethnicity-specific reference equations (Hankinson et al., 1999) by trained professionals using the American Thoracic

Society guidelines. The mean and median length of follow-up for workers enrolled in NM-RESEP were 4.6 and 4.0 years, respectively. Patient health information including data regarding patient visits were securely stored in locked file cabinets in the Division of Epidemiology, Biostatistics, and Preventive Medicine. Patient data obtained from these visits were de-identified and entered into a secure web-based, HIPAA-compatible Research Electronic Data Capture (REDCap) database.

Validation of mMRC Dyspnea Scale:

The seminal study evaluating the mMRC Dyspnea Scale exhibited inter-rater reliability of 98% and found associations with forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) spirometric measures, in addition to lung function and respiratory muscle strength (Mahler & Wells, 1988). Hajiro and colleagues performed a validation study involving the mMRC Dyspnea Scale (Mahler & Wells, 1988) via a cross-sectional study of Japanese patients diagnosed with chronic obstructive pulmonary disease (COPD) and found that mMRC scores moderately to strongly correlated to FEV_1, residual volume to total lung capacity ratio (RV/TLC), and maximal oxygen consumption (VO_2max) (Hajiro et al., 1998). mMRC scores highly correlate with HRQOL in patients with COPD (Henoch et al., 2016). Thus, the mMRC is valid and generalizable to a research cohort for which high clinical suspicion for pulmonary pathology exists.

Validation of PHQ-2 Questionnaire:

Querying of depressed mood has shown 85-90% sensitivity for detection of depression and addition of a second query for anhedonia, advances overall sensitivity to 95% for the PHQ-2 survey (Whooley et al., 1997). An independent structured mental health professional (MHP) interview in a sample of 580 patients in primary care and women's health settings was used to assess criterion validity and subsequent MHP re-interviews determined that PHQ-2 scores corresponding to ≥3 demonstrated sensitivity and specificity of 83% and 92% for major depression, respectively (Kroenke et al., 2003). Kroenke and colleagues assessed construct validity via the 20-item Short-Form (SF) General Health Survey, self-reported sick days and clinic visits, and symptom-related difficulty finding a correlation between increasing PHQ-2 depression severity and decrease in functional status as measured by all six SF subscales (Kroenke et al., 2003). Against the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Edition (DSM-IV-TR), the PHQ-2 had a sensitivity of 79% and specificity of 86% for any depressive disorder and demonstrated diagnostic function similar to that of longer depression instruments, as its scores were deemed to accurately reflect depressive outcomes (Löwe et al., 2005). Arroll and colleagues conducted the largest validation study of the PHQ-2 in a primary care population and found a sensitivity and specificity of 86% and 78% for diagnosing major depression, respectively (Arroll et al., 2010). Arroll et al concluded that utilization of threshold PHQ-2 scores of ≥2 led to the correct identification of larger numbers of depressed patients and that the PHQ-2 has the potential to save time with screening in the primary care setting (Arroll 2010).

A modified PHQ-2 scale (Kroenke et al., 2003) is used in the NM-RESEP. The modification is the replacement of the 0-3 depressive symptom severity scale and associated arithmetic sum cutoffs for a positive result with a binary “yes/no” response to the two-item queries regarding depressed mood and anhedonia. To date, no validation studies have examined the modified PHQ-2 as used by NM-RESEP. However, use of the PHQ-2 is acceptable given its generalizability in screening for the clinically significant symptoms of depressed mood and anhedonia and for subsequent referral for formal clinical evaluation for depressive illnesses.

Predictor and Outcome Variables:

For the cross-sectional analysis, the predictor variable was baseline dyspnea score as measured by mMRC Dyspnea Scale (Mahler & Wells, 1988), ranging from 0 to 4, signifying increasing severity of shortness of breath. 0 corresponds to shortness of breath associated with vigorous exercise. 1 corresponds to shortness of breath when walking at a brisk pace (e.g. “power” walking) or walking on a surface marked by a gentle incline. 2 is associated with walking at a slower pace than other individuals of the same age due to shortness of breath or alternatively, requiring a slower pace than one’s usual pace while walking due to shortness of breath. 3 corresponds to an individual stopping to catch breath after having ambulated approximately 100 yards or after about 3 minutes. 4 is marked by the greatest severity of dyspnea which is associated with inability to leave one’s residence, or becoming dyspneic when engaging in activities of daily living such as dressing oneself (Launois et al., 2012). For the purposes of cross-sectional statistical analyses, dyspnea scores were categorized as a binary categorical variable: 0-2 (none/mild) and 3-4 (severe dyspnea). For the longitudinal analysis, the predictor variable was the change in dyspnea scores from baseline to final visit as measured by mMRC Dyspnea Scale (Mahler & Wells, 1988), ranging from -4 to +4, where negative values suggest improving dyspnea and positive values suggest worsening dyspnea over time.

Outcomes included patient responses to the modified PHQ-2 (Kroenke et al., 2003) items on either depressive symptom, depressed mood or anhedonia. For the cross-sectional analysis, the outcome variable was the baseline modified PHQ-2 (Kroenke et al., 2003) score, ranging from 0 for no symptoms endorsed, 1 for one of two depressive symptoms endorsed, and 2 for both symptoms endorsed. For the purposes of cross-sectional statistical analyses, modified PHQ-2 (Kroenke et al., 2003) scores were categorized as a binary categorical variable: 0 (no depressive symptoms) and ≥1 (at least one depressive symptom, depressed mood or anhedonia, endorsed). For the longitudinal analysis, the outcome variable was the change in the modified PHQ-2 (Kroenke et al., 2003) scores from baseline to final visit, ranging from -2 to +2, where negative values suggest improving depressive symptoms and positive values suggest worsening depressive symptoms over time.

Covariates:

Covariates were adjusted for multivariable cross-sectional and longitudinal analyses. Potential covariates at baseline visit included age in years (continuous), race/ethnicity (Hispanic, Non-Hispanic White, Native American, Non-Hispanic Black, and Other), sex (Female, Male), highest level of completed education (9th grade or less, less than 12th grade, high school diploma or GED, some college, college graduate, post graduate, and advanced degree), BMI

(≤24.9, 25-29.9, ≥30.0 kg/m^2) based on measured height and weight, cardiovascular disease status (yes or no), smoking status (never, current, or former smoker status) and smoking pack-years, if applicable, and percent predicted prebronchodilator forced expiratory volume in one second (FEV_1). Demographic variables and previous medical history were self-reported.

For the purposes of statistical analyses, BMI was categorized as a ternary categorical variable: 0.0-24.9 (underweight and normal BMI), 25.0-29.9 (overweight), and ≥30.0 (obese). Furthermore, a positive cardiovascular disease status was defined as having had a positive history of either myocardial infarction or angina. Information regarding history of myocardial infarction and angina were obtained from administered patient history questionnaires at initial visit.

Statistical Methods:

Frequencies, percentages, means, and standard deviations in a univariate analysis were reported. Chi-Square tests were used to analyze categorical outcome variables. The Cochran–Mantel–Haenszel test was used to evaluate the association between mMRC Dyspnea Score (Mahler & Wells, 1988), a binary predictor variable, and modified PHQ-2 Depressive Symptom Score (Kroenke et al., 2003), a binary outcome variable, while taking into account the stratification of the categorical data. The Pearson coefficient was calculated to measure the linear correlation between change in dyspnea and change in depressive symptoms. The Spearman correlation coefficient was also calculated to measure correlation between change in dyspnea and change in depressive symptoms, assuming a possible nonparametric statistical dependence. Logistic regression models were applied to the cross-sectional analysis of categorical outcomes, in both univariate and multivariate analyses. Generalized linear models were applied to the longitudinal analysis of continuous outcomes, in both simple and multiple regression analyses. Data analyses were conducted using SAS 9.4 Software (SAS Institute Inc., 2013). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Alternative Approaches to Statistical Analyses:

As a covariate, BMI was analyzed as both a continuous and categorical variable. While the use of BMI as a continuous variable is a reasonable consideration, its use as a categorical variable was a better fit to understanding and describing the baseline characteristics of the uranium workers being studied. The BMI categories for underweight (<18.5 kg/m^2) and normal (18.5-24.9 kg/m^2) were combined into one category since there were too few underweight individuals. The other two BMI categories that were analyzed were overweight (25.0-29.9 kg/m^2) and obese (≥30 kg/m^2). In an ideal statistical analysis, there would be relatively equal representation of BMI categories of the uranium workers being studied.

Due to unequal distribution of mMRC scores (predictor variable), it was analyzed at baseline (cross-sectional analysis) with binary outcomes; none/mild (0-2) and severe (3-4). This is a generally acceptable approach for statistical analysis as a self-reported higher numerical grade corresponds to greater severity of dyspnea Mahler & Wells, 1988). However, for an ideal statistical analysis, there would be relatively equal representation of the five mMRC Dyspnea

Scale (Mahler & Wells, 1988) categories (0-4) in the sample of uranium workers being studied. Under an ideal scenario, the same principles would also apply for the change in dyspnea from baseline to final visit (longitudinal analysis).

As a result of the modification of the PHQ-2 questionnaire to a binary "yes/no" response in combination with the inequality in distribution of responses to both depressive symptoms, the decision was made to analyze the outcome variable at baseline (cross-sectional analysis) as a binary categorical variable: no depressive symptoms endorsed (0) or at least 1 depressive symptom, either depressed mood or anhedonia, endorsed (≥1). Ideally, the data from the sample of uranium workers being studied would have been analyzed as three separate categories, both in cross-sectional and longitudinal approaches: depressed mood only, anhedonia only, and both depressed mood and anhedonia, provided relatively equal distribution across outcome categories. It would have been more optimal had the NM-RESEP program utilized the original PHQ-2 (Kroenke et al., 2003) without modification to binary responses.

Pre-Hoc Power Calculation:

The pre-hoc sample size calculations for the study are provided in the figures below.

Figure 1: Sample Size – Proportions

Sample size – Proportions

Compare proportion with a dichotomous outcome between two samples, using the Chi-squared statistic (or z test).

Instructions: Enter parameters in the red cells. Answer will appear in the blue cells.

α (two-tailed) =	0.050	*Threshold probability for rejecting the null hypothesis. Type I error rate.*
β =	0.200	*Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate.*
q_1 =	0.500	*Proportion of subjects that are in Group 1 (exposed)*
q_0 =	0.500	*Proportion of subjects that are in Group 0 (unexposed); $1-q_1$*
P_0 =	0.0500	*Risk in Group 0 (baseline risk)*

Enter any ONE of the following three parameters (the other two will be calculated automatically):

P_1 =	0.1000	*Risk in Group 1 (exposed)*
OR =	2.111	*Odds ratio $(P_1/(1 - P_1))/(P_0/(1-P_0))$*
RR =	2.000	*Risk ratio (P_1 to P_0)*

Calculate

(UCSF Sample Size Calculators - Sample Size Proportions, n.d.)

Figure 2: Sample Size – Report

The standard normal deviate for α = Z_α = 1.960

The standard normal deviate for β = Z_β = 0.842

Pooled proportion = P = $(q_1 * P_1) + (q_0 * P_0)$ = 0.075

$A = Z_\alpha \sqrt{P(1-P)(1/q_1 + 1/q_0)}$ = 1.032

$B = Z_\beta \sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)}$ = 0.441

$C = (P_1 - P_0)^2$ = 0.003

Total group size = N = $(A+B)^2/C$ = 869

Continuity correction (added to N for Group 0) = CC = $1/(q_1 * |P_1 - P_0|)$ = 40

Sample size (with continuity correction)

	N	Outcome+	Outcome-
Group 1:	474	47	427
Group 0:	474	24	450
Total:	948	71	877

Sample size (without continuity correction)

	N	Outcome+	Outcome-
Group 1:	434	43	391
Group 0:	434	22	412
Total:	868	65	803

Note:
This calculator uses the normal distribution (with and without the continuity correction) as an approximation to the binomial distribution.

(UCSF Sample Size Calculators - Sample Size Proportions, n.d.)

P_0 = the proportion of the US male population meeting criteria for major depressive disorder that will approximate the proportion of miners with low dyspnea score endorsing depressive symptoms = 4.8% ~ 0.05 (National Institute of Mental Health, n.d.) (Figure 1).

The topic of depression (or other mental health conditions) has not been well-studied in American workers in mining industries, especially uranium. In Australia (another Westernized nation), there are approximately 150,000 workers in mining industries. A recent report has estimated over 1 in 5 Australian mining workers suffer from depression or anxiety (Mining People International, n.d.). Of note, depression and anxiety are similar and may have overlap in symptomatology. For example, poorly controlled depression may manifest as severe anxiety. To simplify the analysis for sample size/effect size, it was assumed that in the Australian mining worker population approximately 10% of mining workers are diagnosed with depression and another 10% of mining workers are diagnosed with anxiety without overlap in the two diagnoses and applied these assumptions to the study's pre-hoc power calculation. The overwhelming majority of miners tend to be male (Ndlovu et al., 2019), so another assumption made was that the above prevalence estimates were good approximations of depression and anxiety in male mining workers.

P_1 = the proportion of the US male mining worker population with high dyspnea score endorsing depressive symptoms ~ 0.10 (Figure 1).

A two-sided test at $\alpha = 0.05$ with $P_0 = 0.05$ & $P_1 = 0.10$ would require a sample size of at least 474 male miners (Figure 2).

For the above calculated needed sample size, a calculator was utilized to determine the confidence interval for the estimated proportion (0.10) of male miners endorsing depressed mood or anhedonia (UCSF Sample Size Calculators – Confidence Interval Proportions, n.d.).

95% Confidence Interval for approximated proportion, 0.10: (0.074, 0.129).

Ethical Approval and Funding:

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Chapter 3

Results

Table 1: Descriptive Characteristics at Baseline Visit

Characteristics	**N (%) or Mean (SD)**
	827 (100%)
Age (in years)	68.4 (8.7)
Race/Ethnicity	
Hispanic	256 (32.6%)
Non-Hispanic White	244 (31.1%)
Native American	278 (35.4%)
Non-Hispanic Black	2 (0.3%)
Other	5 (0.6%)
Sex	
Female	26 (3.2%)
Male	788 (96.8%)
Education	
9th Grade or less	135 (16.8%)
Less than 12th Grade	197 (24.5%)
High school diploma or GED	233 (29.0%)
Some college	163 (20.3%)
College graduate	56 (7.0%)
Post graduate	10 (1.2%)
Advanced degree	10 (1.2%)
BMI (kg/m^2)	29.4 (5.8)
BMI Categories (kg/m^2)	
0-18.5	7 (1.2%)
18.5-24.9	101 (17.4%)
25-29.9	241 (41.6%)
30-39.9	205 (35.4%)
>=40	25 (4.3%)
Pack-Years of Smoking	21.8 (27.7)
mMRC Dyspnea Score	
0	171 (21.0%)
1	139 (17.1%)
2	161 (19.8%)
3	229 (28.1%)
4	114 (14.0%)

Table 1: Descriptive Characteristics at Baseline Visit (continued)

Characteristics	N (%) or Mean (SD)
Depressive Symptoms	
No symptoms	521 (92.7%)
Depressed Mood Only	22 (3.9%)
Anhedonia Only	1 (0.2%)
Both Depressed Mood and Anhedonia	18 (3.2%)
Total with Depressed Mood	40 (7.1%)
Total with Anhedonia	19 (3.4%)
Self-Reported Cardiovascular Disease	248 (30.5%)
Smoking Status	
Never	6 (1.7%)
Former	337 (98.0%)
Current	1 (0.3%)

The subjects in the study sample were generally elderly with an average age of approximately 68 years and overwhelmingly male (~97%). The study sample was largely composed of underrepresented minority racial/ethnic groups; however, non-Hispanic Whites had a fair representation in the sample at approximately 31%. Most uranium workers in the study possessed at least a 12th grade level or GED equivalent education, but 41% did not. With a BMI of 29.4 kg/m^2, most uranium workers were overweight or obese. The preponderance of the study sample were former smokers with a mean pack-year history of under 22 years. However, there was great variability in mean pack-year history as the standard deviation was 28 years. 30% of uranium workers in the sample had a positive cardiovascular disease state (self-reported history of myocardial infarction and/or angina). At baseline visit, most individuals endorsed a mMRC dyspnea score of 3 equating to ceasing walking after 100 yards or about 3 minutes, while the least commonly reported mMRC dyspnea score was 4 meaning that a patient was essentially rendered homebound due to such severe shortness of breath (Launois et al., 2012). Approximately 21% of workers endorsed no dyspnea at their baseline visit. When viewed as a binary variable, nearly 58% of workers endorsed none to mild levels of dyspnea (0 to 2) whereas the estimated remaining 42% of workers reported more severe dyspnea (3 or 4). Most workers, just under 93%, endorsed no depressive symptoms at baseline visit. Of workers endorsing depressive symptoms, 40 endorsed depressed mood, 19 endorsed anhedonia, and 22 endorsed both depressive symptoms (Table 1).

Table 2: Cross-Sectional Analysis of Binary mMRC Dyspnea Scale Scores versus Binary PHQ-2 Depressive Symptom Scores at Baseline Visit (n=827)

mMRC Dyspnea Scale Scores	Depressive Symptoms (Depressed Mood, Anhedonia)			p-value
	0 Depressive Symptoms Endorsed	≥1 Depressive Symptom(s) Endorsed	Total	
0 to 2	318 (96.4%)	12 (3.6%)	330	<0.001
3 or 4	203 (87.5%)	29 (12.5%)	232	
Total	521	41	562	

At baseline visit, the majority of patients did not endorse any depressive symptoms. However, those workers reporting more severe levels of dyspnea (score ≥ 3) were about three times more likely to endorse at least one depressive symptom than those workers who reported low to moderate levels of dyspnea ($p<0.001$) (Table 2).

Table 3: Cross-Sectional Association Between mMRC Dyspnea Scale Scores and PHQ-2 Depressive Symptom Scores at Baseline Visit (n=827)

	PHQ-2 Depressive Symptom Score	
	Univariate (Odds Ratio and 95% CI)	**Multivariate (Odds Ratio and 95% CI)**
mMRC Dyspnea Score	3.79 (1.89, 7.59)	3.67 (1.21, 11.10)
p-value	<0.001	0.02

Univariate analysis with the Cochran–Mantel–Haenszel test demonstrated that higher dyspnea scores were associated with higher modified PHQ-2 Depressive Symptom (Kroenke et al., 2003) scores at baseline visit (OR=3.79, 95% CI: 1.89-7.59, $p<0.001$). Multivariate analysis with the Cochran–Mantel–Haenszel test demonstrated a similar finding after adjusting for various covariates (OR=3.67, 95% CI: 1.21-11.10, $p=0.02$) (Table 3). Please see below for univariate and multivariate models, respectively.

Univariate Model:
PHQ-2 Depressive Symptom Score = mMRC Dyspnea Scale Score

Multivariate Model:
PHQ-2 Depressive Symptom Score = mMRC Dyspnea Scale Score + Race/Ethnicity + Sex + BMI + Cardiovascular Disease Status + Smoking Status + Age + Smoking Pack-Years + Percent Predicted FEV_1

Table 4: Longitudinal Univariate Analyses Between Change in mMRC Dyspnea Scale Scores and PHQ-2 Depressive Symptom Scores from Baseline to Final Visit

Univariate Analyses	
Pearson, *r*	**p-value**
0.06	0.39
Spearman, ρ	**p-value**
0.05	0.47

Pearson correlation coefficient found no correlation between change in dyspnea score and concomitant change in depressive symptom scores (r=0.06, p=0.39). Spearman's rank correlation coefficient (nonparametric test) also found no correlation between change in dyspnea score and simultaneous change in depressive symptom scores (ρ=0.05, p=0.47) (Table 4).

Table 5: Longitudinal Analysis using Generalized Linear Regression Models for Change in mMRC Dyspnea Scale Score and Change in PHQ-2 Depressive Symptom Scores from Baseline to Final Visit (n= 827)

Univariate (Simple) Regression		**Multivariate (Multiple) Regression**	
Estimate, β	**p-value**	**Estimate, β**	**p-value**
0.02	0.39	-0.02	0.61

For generalized linear regression, the univariate analysis included the change in depressive symptoms as the outcome variable and the change in dyspnea scores as the predictor variable (β=0.02, p=0.39). Multiple regression analysis additionally adjusted for covariates (β=-0.02, p=0.61). Generalized linear regression failed to demonstrate an association between the change in dyspnea scores with concurrent change in depressive symptoms (Table 5). Please see below for simple and multiple linear regression models, respectively.

Univariate Linear Regression Model:
PHQ-2 Depressive Symptom Score = mMRC Dyspnea Score

Multivariate Linear Regression Model:
PHQ-2 Depressive Symptom Score = mMRC Dyspnea Score + Race/Ethnicity + Sex + BMI + Cardiovascular Disease Status + Smoking Status + Age + Smoking Pack-Years + Percent Predicted FEV_1

Chapter 4

Discussion

Summary of Results:

The uranium workers in this study were mostly male, elderly, of excess weight, from underrepresented racial/ethnic minority backgrounds, and possessed a high school level education at best. The overwhelming majority of workers were former smokers and nearly one-third had a positive history of cardiovascular disease. The most commonly reported category of dyspnea was mMRC dyspnea score of 3. However, when analyzed as a binary variable, the majority of workers reported either no or lower levels of dyspnea (mMRC dyspnea scores 0-2). At their baseline visit, the vast majority of workers did not endorse any depressive symptoms. After adjusting for covariates at baseline, higher dyspnea ratings were associated with higher modified PHQ-2 Depressive Symptom scores, and workers experiencing more severe levels of dyspnea (mMRC dyspnea scores $\geq$3) were approximately three times more likely to endorse at least one depressive symptom. Parametric and nonparametric univariate tests failed to find an association between change in dyspnea score and change in depressive symptoms. Similarly, univariate and multivariate regression models failed to detect an association between change in dyspnea score and concurrent change in depressive symptom score.

The mMRC Dyspnea Scale versus other Screening Measures for Dyspnea:

Other instruments that screen for and evaluate dyspnea exist and it is worthwhile to examine if the mMRC Dyspnea Scale was the best fit for this study. The mMRC dyspnea scale has been studied in comparison to other scales of dyspnea associated with activities of daily living (Chhabra et al., 2009; Hajiro et al., 1998; Henoch et al., 2016; Mahler & Wells, 1988). Mahler and Wells found significant correlation in dyspnea scores between the mMRC, baseline dyspnea index (BDI), and oxygen-cost diagram (OCD) ($r=0.48$-0.70, $p<0.001$) across several respiratory conditions. They also found dyspnea scores to be associated with spirometric measures in asthma ($r=0.78$, $p<0.001$), maximal respiratory pressures in COPD ($r=0.34$, $p<0.001$), maximal inspiratory mouth pressure (PIMax) in COPD ($r=0.51$, $p=0.01$), as well as FVC ($r=0.44$, $p=0.03$) in interstitial lung disease (Mahler & Wells, 1988). Mahler and Wells also concluded that while shortness of breath may be dependent upon the specific respiratory condition, dyspnea measures correlate significantly to pulmonary physiologic parameters (Mahler & Wells, 1988). The mMRC scale was completed in 30 seconds, the OCD was completed in 1-2 minutes, and the BDI was completed in 2-3 minutes (Mahler & Wells, 1988), thereby suggesting that the mMRC is an appropriate and even superior measure of dyspnea as it elicits information comparable to other scales in a shorter amount of time. This is especially applicable to this study as the majority of the workers in the sample were elderly and likely possessed lower levels health literacy as suggested by a lower average level of formal education.

Hajiro et al. conducted a study in patients with varying severity levels of COPD comparing the mMRC, BDI, and OCD dyspnea scales in addition to the Borg Scale of Perceived Exertion, which assesses dyspnea during exercise, and the St. George's Respiratory (SGRQ) and the Chronic Respiratory Disease (CRQ) questionnaires, which evaluates the effects of dyspnea on HRQOL (Hajiro et al., 1998). Factor analysis revealed that the MRC, BDI, OCD, Activity Domain of the SGRQ, and Dyspnea Domain of the CRQ, had practically the same frequency distribution and were grouped into the same factor (Hajiro et al., 1998). Additional associations between the above-mentioned scales were found with FEV_1 (r=0.31-0.48) and maximal oxygen uptake (r=0.46-0.60). Given the ease with which the mMRC is completed and comparability to the Activity Domain of the SGRQ and the Dyspnea Domain of the CRQ, it is a superior instrument for this study setting. One limitation of the mMRC is that it does not ascertain information regarding dyspnea post-exercise, which the Borg scale does, however the Borg scale was found to be of a different factor (Hajiro et al., 1998).

Chhabra and colleagues conducted a retrospective study of male patients with COPD [Global Initiative for Obstructive Lung Disease (GOLD) stages II, III and IV] using the mMRC, BDI, and OCD dyspnea scales to determine the scales' relationships with physiologic parameters assessed via spirometry (percent predicted FVC and percent predicted FEV_1), arterial blood gas (ABG) analysis, and 6 minute walk test (6MWT) (Chhabra et al., 2009). Similar to previous studies, Chhabra found interconnection between mMRC, BDI, and OCD dyspnea scales (Mahler & Wells, 1988; Hajiro et al., 1998; Chhabra et al., 2009). However, unlike the BDI and OCD measures, the mMRC did not have any associations with ABG abnormalities and the spirometric parameters of interest (Chhabra et al., 2009). None of the scales found associations with the 6MWT (Chhabra et al., 2009). While these findings reveal limitations of the mMRC scale, it is significant to recall that this study analyzed data collected as part of an occupational medicine surveillance program. In NM-RESEP, administration of the mMRC serves as the initial step to linking former workers with possible pulmonary pathology to appropriate care and likely subsequent pulmonary screening and testing.

Henoch and colleagues studied factors involved in COPD disease progression including dyspnea and HRQOL in a Swedish patient cohort (Henoch et al., 2016). Henoch et al found an association between dyspnea as measured by mMRC and HRQOL as measured by the Clinical COPD Questionnaire (CCQ) (Henoch et al., 2016). Additionally, an association between mMRC-measured dyspnea and percent predicted FEV_1 was appreciated ($r=-0.41$, $p<0.001$) (Henoch et al., 2016). Thus, the mMRC is an appropriate measure for screening dyspnea in this study as it compares well to other dyspnea scales that take longer to administer (Hajiro et al., 1998) and may cause unnecessary burden to those who are elderly with limited education levels. Depending upon the population under study, the mMRC may correlate with concurrent pulmonary physiologic changes (Mahler & Wells, 1988; Hajiro et al., 1998; Henoch et al., 2016).

<u>The PHQ-2 versus other Screening Measures for Depressive Symptoms</u>:

An examination of the PHQ-2 compared to other depressive symptom screening tools is merited to determine if the PHQ-2 was the most appropriate instrument for this study. A recent meta-analysis found that the Patient Health Questionnaire (PHQ, both versions—PHQ-2 and

PHQ-9) are the most commonly used depression screening tools in the primary care setting with sensitivity and specificity of 89.3% (95% CI: 81.5–95.1) and 75.9% (95% CI: 70.1–81.3), respectively, for the PHQ-2 (Mitchell et al., 2016). The PHQ-2 covers the first two depressive symptom items of the PHQ-9, depressed mood and anhedonia. However, this study also concluded that both versions of the PHQ should only be used for screening purposes with the intent of referring those screening positive for formal clinical evaluation—a positive screen on PHQ scales does not automatically constitute a diagnosis of a depressive disorder (Mitchell et al., 2016).

In the largest known validation study comprising 2642 patients, Arroll and colleagues sought to validate both the PHQ-2 and PHQ-9 in the primary care setting using the Composite International Diagnostic Interview (CIDI) for depression as a standard (Arroll et al., 2010). Arroll and colleagues found that at a cutoff score of ≥2 accurately identifies more patients with major depression than a cutoff score of ≥3 with good sensitivity—86%, but poor specificity—78% (Arroll et al., 2010). Improvement in specificity to 92% was noted at a cutoff score of ≥3 (Arroll et al., 2010). Given such validity in a primary care setting, use of the PHQ-2 is appropriate for this study setting as most of the clinical screening questions address primary care health issues and in clinical practice, work-up for pulmonary pathology customarily commences at the primary care level.

Arrieta and colleagues performed a cross-sectional study to determine the utility and validity of the PHQ-2 and PHQ-9 in a rural, Spanish-speaking population comprising 223 adults (Arrieta et al., 2017). In addition to screening these patients with the PHQ measure, the patients were also screened for depression using the World Health Organization Quality of Life BREF Scale (WHOQOL-BREF) as a reference standard (Arrieta et al., 2017). Arrieta et al found the PHQ-9 to exhibit a high degree internal consistency (Cronbach's alpha ≥0.8) across various population subgroups including age, gender, and literacy and confirmatory factor analysis demonstrated a reasonable 1-factor structure fit (Arrieta et al., 2017). On the basis of the PHQ-9 as the gold standard, Arrieta and colleagues determined the optimal PHQ-2 cutoff score for screening was 3 with sensitivity of 80.00% and specificity 86.88% (area under receiver operating characteristic curve = 0.89; 95% confidence interval [0.84, 0.94]) (Arrieta et al., 2017). As uranium workers are traditionally rural-living occupational cohort and many workers in this study sample are of Hispanic descent with their primary language being Spanish, Arrieta's study results support the use of the PHQ-2 as a screening tool in this study.

Liu and colleagues conducted a cross-sectional study in a cohort of 839 rural elderly Chinese adults using PHQ-9 and PHQ-2 against a reference standard of the Structured Clinical Interview for DSM Disorders (SCID-I) to diagnose major depression (Liu et al., 2016). In addition to determining validity of the PHQ instruments in this population, Liu's study sought to determine cut-off scores for the PHQ-9 and PHQ-2 instruments (Liu et al., 2016). In this study sample, the PHQ-9 (Cronbach's alpha=0.82, sensitivity=0.97, specificity=0.89) and PHQ-2 (Cronbach's alpha=0.76, sensitivity=0.90, specificity=0.90) exhibited a high degree of internal consistency in addition to sensitivity and specificity (Liu et al., 2016). Liu and colleagues concluded that the PHQ-9 (cutoff score: 8) and PHQ-2 (cutoff score: 2) are valid measures to screen elderly rural Chinese for depression (Liu et al., 2016). While there were no workers of Chinese descent in this study, the majority were elderly and living in rural areas and the PHQ-2's performance against the SCID-I supports its use.

In a study of 193 Australian patients with coronary artery disease (CAD) three months status post-discharge from admissions due to cardiac causes, the PHQ-9 and Hospital Anxiety and Depression Scale (HADS) were validated against the Mini International Neuropsychiatric Interview (MINI), a well-established research interview tool to establish psychiatric diagnoses (Stafford et al., 2007). The PHQ-9 was found to have superior positive likelihood ratios for diagnosing major depression than the HADS (Stafford et al., 2007). While Stafford and colleagues did not validate the PHQ-2 in their study population of Australian patients with CAD, it is not a stretch to believe that based on the results of other studies comparing the PHQ-9 and the PHQ-2 (Arrieta et al., 2017; Arroll et al., 2010; Liu et al., 2016; Mitchell et al., 2016), the PHQ-2 would likely be a reliable screening tool for depressive symptoms in Stafford's study. Given that 30% of former uranium workers in this study had a positive reported history of cardiovascular disease, and cardiovascular disease is associated with depression (Hare et al., 2014; Zhang et al., 2018), selection of the PHQ-2 instrument to screen for depression appears to be appropriate.

<u>Comparison with Previous Longitudinal Studies of Dyspnea and Depressive Symptoms</u>:

A longitudinal study from a sub-cohort that participated in the European Commission Respiratory Health Survey I (ECRHS I) in 1991-1992 and the follow-up, ECRHS II, eight years later, sought to determine the association between change in dyspnea and change in anxiety and depression (Neuman et al., 2006). The ECHRS featured a modified British Medical Research Council Scale to evaluate dyspnea and the HADS to measure anxiety and depression (Neuman et al., 2006). The change in dyspnea prevalence from ECHRS I to II was +1.9% and depressive symptoms were found to be independent determinants for dyspnea in ECHRS I (OR: 3.72, 95% CI: 1.51-9.17) and II (OR: 3.40, 95% CI: 1.49-7.80) (Neuman et al., 2006). Participants reporting dyspnea for the first time on ECHRS II, were at least twelve times likely to endorse depressive symptoms (OR: 12.2, 95% CI: 3.97-37.5) (Neuman et al., 2006). Neuman and colleagues postulate the existence of causation between the development of depression and anxiety and dyspnea (Neuman et al., 2006). This study of uranium workers has a somewhat similar research design to Neuman’s study, especially with regards to the longitudinal analysis, although there is a major difference as Neuman’s study did not evaluate change in depressive symptoms from ECHRS I to II.

A secondary analysis study of 590 COPD patients who underwent a 3-week pulmonary rehabilitation program suspecting causation of depression by COPD sought to determine associations between COPD symptoms (including dyspnea post-exercise via the Borg scale) and depressive symptoms via PHQ-9 (Schuler et al., 2018). COPD symptoms were predictor variables, whereas PHQ-9 individual item and sum scores were outcome variables (Schuler et al., 2018). Network analysis found that the number of occurrences of dyspnea and dyspnea-associated performance were chiefly associated with somatic depressive symptoms (e.g. anergia, insomnia) while cognitive/emotional response (as measured by SGRQ items) was predominantly related to cognitive-affective depressive symptoms (e.g. melancholic depressive symptoms including hopelessness, helplessness, and worthlessness) (Schuler et al., 2018). However, Schuler and colleagues were unable to detect any difference in strength of associations between the start and the end of the pulmonary rehabilitation program (Schuler et al., 2018).

A review paper suggests a diagnostic approach of better understanding possible mood and emotional symptoms in patients with complaints of dyspnea, as depression and anxiety have the potential to exacerbate the effects of dyspnea such that it appears excessive in comparison to objective cardiopulmonary findings and may worsen dyspnea-associated disability (Scano et al., 2013). Scano and colleagues postulate that utilization of brain imaging modalities may isolate cortical locations responsible for sensory and affective processing in response to experienced dyspnea, as well as fear and avoidance of dyspnea (Scano et al., 2013). Regardless, the literature supports a complex interplay between dyspnea and depression (Neuman et al., 2006; Scano et al., 2013; Schuler et al., 2018) and it should be further studied in various populations.

The Discrepancy between Cross-Sectional and Longitudinal Results:

A cross-sectional analysis only provides a snapshot of what association is present at a given point in time. On the other hand, a longitudinal analysis determine associations over a defined interval of time. Given the difference in timeframes, it should not be a surprise that other factors could be at play in a longitudinal analysis that may not be present in a cross-sectional analysis. Due to the employment of simple imputation methods to account for missing data, some observations that were statistically analyzed may not truly reflect the study sample. This inaccuracy could be partially responsible for driving the discrepancy between the cross-sectional and longitudinal results. The cross-sectional study sample size was 827 uranium workers and a statistical analysis of a larger sample size with a lower degree of missing data, such that imputation methods to address missing data were not necessary, may have found an association between change in dyspnea and concomitant change in depressive symptoms.

The discrepancy between the results of the cross-sectional and longitudinal analyses may be better explained by other comorbid conditions in this sample of uranium workers. In addition to uranium-associated pulmonary conditions including uranium workers pneumoconiosis (presenting as diffuse lung fibrosis or nodular pulmonary disease) (Archer et al., 1998; Kocher et al., 2016; Samet et al., 1984; Trapp et al., 1970), COPD (bronchitis, emphysema) (Walsh et al., 2015), and lung cancer (Gottlieb & Husen, 1982; Samet et al., 1991), they may be at higher risk for cardiovascular diseases compared to workers with non-uranium occupational exposures (al-Rashida et al., 2019). In this study sample, 30% of workers reported a positive history of cardiovascular disease, including myocardial infarction and angina, and downstream effects such as compromised perfusion to critical organs including the brain may play a crucial role towards the development of depressive symptoms. Al-Shair and colleagues found a positive association between the pro-inflammatory biomarker, TNF-α and depression in the setting of COPD (Al-Shair et al., 2011). Levels of inflammation are likely to wax and wane depending upon the acuity of cardiopulmonary pathology, thus providing another possible explanation for the discrepancy between cross-sectional and longitudinal findings.

Beyond pulmonary pathology, other factors, both medical and non-medical can influence the development of depressive symptoms. Suboptimal social support and stressful life situations are established risk factors for depression (Martin, 2020). Furthermore, psychological considerations such as an individual's outlook on life, how stress is processed and internalized, and finally, response to life stressors also influences risk for depression (Martin, 2020). The individuals comprising the study sample were mostly older and rural living adults. Older age is an independent risk factor for depression and is associated with the development of sleep problems (insomnia) and other conditions (hypertension, hypercholesterolemia, and diabetes) requiring medication treatment which are also risk factors for depression (Martin, 2020). Rural residing individuals suffer from unique healthcare and socioeconomic difficulties leading to a phenomenon of "rural poverty" (Weeks, 2018) which is a distinct risk factor for the individuals in this study. The healthy worker effect is a possible explanation for the relatively low prevalence of depressive symptoms in the study population (Chowdhury et al., 2017). However, this effect may possibly be minimized or even non-existent as when the workers enrolled in NM-RESEP, they were retired (some for quite some time) and elderly.

Study Implications:

Uranium has a crucial role in the American nuclear energy program including generation of electricity via nuclear reactors and the development and assembly of nuclear weapons. As historically much of uranium mining and extraction activities took place in and around American Indian reservations, studies of the potential impacts of uranium exposure will confer benefit to American Indians. This study brings additional attention to the importance of studying uranium workers from underrepresented minority backgrounds. Uranium extraction and associated activities occur on a global scale, as it affects workers in Canada, Kazakhstan, Australia, Russia, Uzbekistan, Namibia, China, Niger, and South Africa among others (US Energy, 2019). Thus, studies on uranium workers and occupational exposure hold the potential for global impact towards worker safety, health, and wellness. The mission of the National Institute of Occupational Safety and Health (NIOSH) is to cultivate occupational safety and health knowledge and to transform such knowledge into industrial and occupational practice. Workers receiving exposure to uranium are a unique and vulnerable cohort. In addition to bolstering what is currently a paucity of evidence-based literature regarding health outcomes in occupational cohorts with uranium exposure, this study will serve as an impetus for further research and more optimally designed occupational surveillance programs to track mental health outcomes, especially depression, in uranium workers.

Strengths and Limitations:

To the best of knowledge, this is the first study to examine the association of dyspnea and depressive symptoms in uranium workers. This study's strengths include that data were obtained from an occupational surveillance cohort that was prospectively followed for many years and tracks a particularly vulnerable population of rural, underrepresented racial/ethnic minorities, of largely lower socioeconomic status and education. The limitations of this study include using the modified PHQ-2, which lacks validation, to screen for depression as opposed to a traditional PHQ-2 instrument which has been validated in primary care settings (similar to the occupational surveillance setting) and in rural, elderly populations (Arrieta et al., 2017;

Arroll et al., 2010; Liu et al., 2016; Mitchell et al., 2016). There may be a phenomenon of underreporting of mental health symptoms (Call & Shafer, 2018; Salk et al., 2017) as the majority of uranium workers in this sample (and in general) tend to be males (Ndlovu et al., 2019). This may arise due to various reasons including insufficient awareness and comprehension of depression in addition to a work culture of stigmatization for self-reporting of experienced symptoms. Additionally, use of the standard PHQ-2 and DSM diagnostic criteria in American Indians may not produce reliable results due to potential cultural differences (Dawson & Madsen, 2011). Perini reported a higher absolute prevalence of depressive symptoms in patients from ethnic minorities diagnosed with "chronic nonspecific lung disease", although this finding was not based on occupational cohorts (Perini et al., 2015).

Conclusions:

In this study sample, lower levels of dyspnea were generally reported and depressed mood and anhedonia were not commonly endorsed. At baseline, workers experiencing higher levels of dyspnea were approximately three times likely to endorse depressive symptoms. Longitudinal analysis failed to determine an association between change in dyspnea and contemporaneous change in the endorsing of depressive symptoms. Additional longitudinal studies (preferably of prospective designs) of larger worker sample sizes are necessary to understand the mechanisms between dyspnea and depressive symptoms in occupational populations, including uranium workers, who are at risk of developing lung disease.

Future Directions:

This study can be improved upon by taking into account other markers of pulmonary physiologic function and health including spirometric measures (percent predicted FEV_1, percent predicted FVC, etc.) and 6MWT distance in addition to cardiac diagnostic studies such as echocardiograms (cardiac ECHO) and electrocardiograms (ECG) given that a notable percentage of uranium workers were found to have a positive history of cardiovascular disease. Performing stratified analyses based on race/ethnicity may potentially identify subpopulations at greater risk for certain health outcomes. Based on this study's findings, it is recommended that companies involved in uranium-related activities and nuclear regulatory agencies regularly (e.g. annually) screen their employees receiving occupational exposure to uranium for dyspnea (as an index of cardiopulmonary health and HRQOL) and depression to ensure optimal health for workers across their employment lifespan.

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