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ORIGINAL ARTICLE

Occupational Exposures Are Associated with Worse Morbidity in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Links between occupational exposures and morbidity in individuals with established chronic obstructive pulmonary disease (COPD) remain unclear.

Objectives: To determine the impact of occupational exposures on COPD morbidity.

Methods: A job exposure matrix (JEM) determined occupational exposure likelihood based on longest job in current/former smokers (n = 1,075) recruited as part of the Subpopulations and Intermediate Outcomes in COPD Study, of whom 721 had established COPD. Bivariate and multivariate linear regression models estimated the association of occupational exposure with COPD, and among those with established disease, the occupational exposure associations with 6-minute-walk distance (6MWD), the Modified Medical Research Council Dyspnea Scale (mMRC), the COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), 12-item Short-Form Physical Component (SF-12), and COPD exacerbations requiring health care utilization, adjusting for demographics, current smoking status, and cumulative pack-years.

Measurements and Main Results: An intermediate/high risk of occupational exposure by JEM was found in 38% of participants. In multivariate analysis, those with job exposures had higher odds of COPD (odds ratio, 1.44; 95% confidence interval, 1.04–1.97). Among those with COPD, job exposures were associated with shorter 6MWDs (−26.0 m; $P = 0.006$); worse scores for mMRC (0.23; $P = 0.004$), CAT (1.8; $P = 0.003$), SGRQ (4.5; $P = 0.003$), and SF-12 Physical (−3.3; $P < 0.0001$); and greater odds of exacerbation requiring health care utilization (odds ratio, 1.55; $P = 0.03$).

Conclusions: Accounting for smoking, occupational exposure was associated with COPD risk and, for those with established disease, shorter walk distance, greater breathlessness, worse quality of life, and increased exacerbation risk. Clinicians should obtain occupational histories from patients with COPD because work-related exposures may influence disease burden.

Keywords: chronic obstructive pulmonary disease; occupational exposure; work-related; quality of life; job exposure matrix

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At a Glance Commentary

Scientific Knowledge on the Subject: Although smoking remains the predominant risk factor for chronic obstructive pulmonary disease (COPD), this condition has also been associated with occupational exposures. Less is known of how occupational exposures affect the morbidity of individuals with established COPD.

What This Study Adds to the Field: The present study addresses a significant gap in the current evidence base by examining the role of occupational exposures in health status in established COPD, including health-related quality of life, disease severity, and exacerbations. Based on a multicenter sample of adults with COPD, occupational exposures are associated with worse COPD outcomes even after accounting for significant smoking histories. These results suggest that clinicians should anticipate worse disease in patients with COPD with histories of occupational exposure.

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, and global COPD burden is projected to increase as the population ages (1). Direct cigarette smoking remains the predominant risk factor for disease, but inhaled particulates and gases from other sources can also lead to COPD development. Occupational exposures have been implicated in COPD causation even in populations with concurrent smoking (2–4). Systematic reviews have estimated that 15% of COPD may be attributed to workplace exposures (5, 6).

Once established, the severity of COPD is primarily defined by the degree of airflow limitation, the impact of the disease on health status, and the risk of future exacerbations (7). Factors believed to contribute to worse outcomes include prior history of exacerbations, current smoking status, and respiratory infection (8, 9). Despite the strong evidence linking occupational exposures to COPD prevalence, the potential relationship between work-related exposures and outcomes among patients with established disease has not been well delineated. Understanding the burden of occupational exposures on COPD outcomes has been limited by small cohort sizes and by the challenges of estimating the effects of multiple risk factors, in particular concomitant smoking. These limitations may explain the heterogeneous findings on the role of occupational exposures in COPD outcomes in the limited number of studies addressing this question (10–15).

The goal of the present study was to assess the association of occupational exposures with COPD disease status in current and former smokers in a United States–based observational cohort and COPD morbidity across a range of outcomes. Morbidity was assessed using validated measures of disease severity, symptom burden, and health-related quality of life (HRQOL) in a population of former and current smokers with well-defined COPD. We used data from the multicenter Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS), which comprehensively assessed occupational exposures in a well-characterized cohort of current and former smokers with varying degrees of lung function decline. Some of the results of these studies have been previously reported in the form of an abstract (16).

Methods

Study Population

SPIROMICS is a multicenter cohort study including current and former smokers with and without COPD. Participants with COPD were 40 to 80 years old and had a $\geqslant$20 pack-year smoking history and post-bronchodilator FEV_1/FVC of less than 0.70. Smokers without COPD had an FEV_1/FVC of less than 0.70 and an FVC below the lower limit of normal (17). The study and exclusion criteria have been previously described (18). The current study is a cross-sectional analysis of baseline data from the first 1,075 smoking participants in SPIROMICS who had complete occupational exposure data. Smoking history was determined by current smoking status, defined as whether the participant reported smoking within the last month, and lifetime cumulative pack-years of smoking.

COPD Status and Outcomes

Validated questionnaires assessed HRQOL using respiratory-specific (St. George's Respiratory Questionnaire [SGRQ] total score) and generic (Short-Form Health Survey [SF-12] physical component scale) instruments (19, 20). COPD health-related status was assessed using the COPD Assessment Test (CAT) (21), and dyspnea was assessed using the Modified Medical Research Council Dyspnea Scale (mMRC) (22). COPD exacerbations were defined by (*1*) worsening respiratory symptoms requiring antibiotics or steroids or (*2*) those requiring health care utilization (HCU). Participants were dichotomized by exacerbation status, with "yes" defined as any exacerbation over the past 12 months. Spirometry, including pre- and post-bronchodilator FEV_1% predicted, and the 6-minute-walk test were performed according to standard procedures (17, 23, 24).

Occupational Exposure

The longest-held job was ascertained based on free text entries, was assigned a 2000 Census code by a single reviewer, and, if unclear, was reviewed by two separate authors and adjudicated by a third. The likelihood of occupational exposures relevant to COPD was assigned using a job exposure matrix (JEM) (jobs classified as not exposed, intermediate, or high exposure likelihood) (2). Independent of the JEM assignment, self-reported exposure to vapors, gas, dust, or fumes (VGDF) was ascertained by the following questionnaire item: "Did this [longest held] job expose you to vapors, gas, dust or fumes?"

Statistical Analysis

Because there were no significant differences in outcomes between those with intermediate or high risk of occupational exposures, these groups were combined, creating a dichotomous JEM variable (intermediate/high vs. low risk of exposure), as was done previously (25). Secondary analyses used participant-reported exposure to VGDF as the metric of occupational exposure. Multiple logistic regression analysis was used to determine the association between occupational exposures and the odds of COPD among smokers. Among participants with

established COPD, we used multiple linear and logistic regression analyses, as appropriate, to estimate the associations between occupational exposure and outcomes. All multivariate models included adjustment for age, race, sex, current smoking within the last month (yes/no), and total pack-years as a continuous variable. Adjustment for medication use and comorbid disease using a comorbidity score (26) was included in secondary analyses. In addition, mediation analyses separately included FEV_1% predicted and income as covariates in the multivariate models. Additional analyses were conducted that defined COPD as FEV_1/FVC ratio less than the lower limit of normal (LLN) (17). Interaction terms were tested to assess whether sex or smoking status significantly modified the effect of occupational exposures on outcomes. Additional analyses were stratified by sex and smoking status (current vs, former smoker; above vs. below median pack-years). All analyses were performed with StataMP statistical software, version 12.1 (StataCorp, College Station, TX). Statistical significance was defined as $P < 0.05$. Further details are provided in the online supplement.

Results

Participant Characteristics

The majority of participants (n = 1,075) were male (55%) and white (77%); the mean age was 65 years, and approximately 38% of participants were current smokers at study enrollment. The median smoking history was 45 pack-years, reflecting a cohort with overall heavy smoking exposure. Participants worked an average of 26 years (SD = 12 yr) at their longest job, and over a third of participants (38%) had intermediate or high risk of occupational exposures based on JEM assignment. The most common job classifications among those with occupational exposures were factory work/machine operations, truck driving, construction/general contracting, and food industry jobs, altogether accounting for 45% of the jobs in the exposed group. Compared with those without COPD, those with disease were older; more likely to be male, to be white, and to have self-reported coronary artery disease; had a greater number of pack-years; and were less likely to be current smokers (Table 1).

Among those with COPD (n = 721), the mean age was 67 years, with a median smoking history of 49.5 pack-years. Participants worked an average of 27 years (SD = 11) at their longest job. Thirty-nine percent had intermediate or high risk of occupational exposures based on the JEM; participants with such job exposures were more likely to be male, younger, nonwhite, and current smokers and to have self-reported diabetes mellitus compared with those with low risk for job exposure. There was no statistically significant difference in medication use (long-acting inhaled bronchodilators, inhaled corticosteroids, or oral corticosteroids) or cumulative smoking in pack-years by job exposure (Table 2).

The Association of Occupational Exposures as Defined by JEM with COPD

Although there was a trend toward an association between occupational exposure with COPD, it was not statistically significant (odds ratio [OR], 1.20; 95% confidence interval [CI], 0.92–1.56) in bivariate analysis; however, after adjustment for potential confounders, including smoking, occupational exposure was associated with a higher point-estimated odds of COPD, which was statistically significant (OR, 1.44; 95% CI, 1.04–1.97). Occupational exposures were associated with greater odds of COPD among former smokers as compared with current smokers (OR, 1.75; 95% CI, 1.15–2.66 vs. OR, 1.09; 95% CI, 0.66–1.82; smoking-exposure interaction, $P = 0.06$) and among those with fewer versus more pack-years of smoking (OR, 1.97; 95% CI, 1.27–3.05 vs. OR, 1.02; 95% CI, 0.64–1.61; pack-years–exposure interaction, $P = 0.05$). There was no substantive difference between male and female smokers and the odds of COPD (men: OR, 1.44; 95% CI, 0.95–2.17 vs. women: OR, 1.41; 95% CI, 0.85–2.31; sex–exposure interaction, $P = 0.74$).

When defining COPD using LLN criteria (n = 595), there was an association between occupational exposures and COPD in bivariate (OR,1.44; 95% CI, 1.12–1.85) and multivariate (OR = 1.57; 95% CI, 1.18–2.10) analyses.

Table 1. Participant Characteristics among Smokers with and without Chronic Obstructive Pulmonary Disease

	All Smokers (*n = 1,075*)	Smokers without COPD (*n = 354*)	Smokers with COPD (*n = 721*)	*P* Value
Age, yr; mean (SD)	65.0 (8.8)	61.7 (10.0)	66.7 (7.6)	<0.0001
Sex, n (% male)	591 (55.0)	193 (54.5)	430 (59.6)	<0.0001
Race, n (%)				
White	828 (77.0)	238 (67.2)	590 (81.8)	<0.0001
Black	194 (18.0)	99 (28.0)	95 (13.2)	
Other	53 (4.8)	17 (4.8)	36 (5.0)	
Hispanic ethnicity, n (%)	45 (4.2)	16 (4.5)	29 (4.0)	0.70
Income, n (%)				
<$15,000	177 (16.8)	76 (21.5)	101 (14.0)	0.002
$15,000–$34,999	206 (19.6)	57 (16.1)	149 (20.7)	
$35,000–$49,999	131 (12.1)	31 (8.8)	100 (13.9)	
>$50,000	341 (32.4)	104 (29.4)	237 (32.9)	
Declined answer	198 (18.8)	75 (21.2)	123 (17.1)	
Comorbidities, n (%)				
Coronary artery disease	95 (8.8)	15 (4.3)	80 (11.1)	<0.0001
Diabetes mellitus	147 (13.7)	46 (13.0)	101 (14.0)	0.78
Pack-years cigarette smoking, median (25th, 75th percentile)	45 (33, 60)	37.5 (30, 50)	49.5 (37.5, 66)	<0.0001
Current smoking, n (%)	405 (38.4)	167 (47.6)	238 (33.9)	<0.0001
Currently employed, n (%)	141 (13.1)	56 (15.8)	85 (11.8)	<0.0001

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Table 2. Participant Characteristics by Occupational Exposure Status among Current or Former Smokers with Chronic Obstructive Pulmonary Disease

	JEM Low Exposure Risk (*n* = *438*)	JEM Intermediate/High Exposure Risk (*n* = *283*)	*P* Value
Age, yr; mean (SD)	67.9 (7.1)	64.9 (8.1)	<0.0001
Sex, n (% male)	212 (48.4)	218 (77.0)	<0.0001
Race, n (%)			
White	375 (85.6)	215 (76.0)	<0.0001
Black	39 (8.9)	56 (19.8)	
Other	24 (5.5)	12 (4.2)	
Hispanic ethnicity, n (%)	10 (2.3)	19 (6.7)	0.003
Income, n (%)			<0.0001
<$15,000	39 (8.9)	62 (21.9)	
$15,000–$34,999	84 (19.2)	65 (23.0)	
$35,000–$49,999	67 (15.3)	33 (11.7)	
>$50,000	162 (37.0)	75 (26.5)	
Declined answer	82 (18.7)	41 (14.5)	
Comorbidities, n (%)			
Coronary artery disease	46 (10.5)	34 (12.0)	0.52
Diabetes mellitus	52 (11.9)	49 (17.3)	0.04
Medications within last 3 mo, n (%)			
Long-acting bronchodilators	175 (40.0)	116 (41.0)	0.68
Inhaled corticosteroids	190 (43.3)	118 (41.7)	0.70
Current use of oral steroids, n (%)	16 (3.7)	12 (4.2)	0.73
Pack-years cigarette smoking, median (25th, 75th percentile)	50 (38, 66)	46 (37, 66)	0.47
Current smoking, n (%)	130 (30.4)	108 (39.1)	0.02
Currently employed, n (%)	63 (14.4)	22 (7.8)	<0.0001

Definition of abbreviation: JEM = job exposure matrix.

The Association of Occupational Exposures as Defined by JEM with Health Outcomes among Those with COPD

Among those with COPD, participants with a greater likelihood of occupational exposure by JEM compared with a lower likelihood reported worse respiratory-specific and generic HRQOL (SGRQ, 38.7 vs. 33.2; $P = 0.0002$) and SF-12 physical component scale (25.2 vs. 28.4; $P = 0.0001$). They also manifested poorer functional status (CAT, 15.8 vs. 13.8; $P = 0.001$) and had worse dyspnea (mMRC, 1.3 vs. 1.1; $P = 0.01$). There was a significantly higher proportion of individuals reporting COPD exacerbations requiring HCU in those with occupational exposures compared with those without (0.49 vs. 0.33; $P = 0.01$). There was no statistical difference, however, in the number of individuals reporting exacerbations defined by medication use. Those with greater occupational exposures also tended to have worse dyspnea, lower FEV_1, and shorter 6MWD compared with those without exposure, although in bivariate analyses these differences were not statistically significant (Table 3).

After adjustment for potential confounders including smoking, the associations between occupational exposure and worse COPD morbidity remained (Table 4). Specifically, occupationally exposed participants reported worse quality of life and worse symptom burden, as evidenced by higher SGRQ scores ($\beta = 4.5$; $P = 0.003$), lower SF-12 physical component scores ($\beta = -3.3$; $P < 0.0001$), higher mMRC dyspnea scores ($\beta = 0.23$; $P = 0.004$), and higher CAT scores ($\beta = 1.8$; $P = 0.003$). In addition, those with occupational exposure manifested statistically significant shorter 6MWDs ($\beta = -26.0$ m; $P = 0.006$). Although exposure was negatively associated with FEV_1% predicted, this effect was not statistically significant ($\beta = -2.6\%$; $P = 0.20$).

The point estimates of the associations between occupational exposures and health outcomes were minimally affected after including FEV_1 in the multivariate models, suggesting that the effects of occupational exposure on COPD morbidity is not strongly mediated by its effect on lung function (Table 4). Similarly, the addition of income to the model slightly attenuated the point estimates and significance but did not meaningfully alter the association between occupational exposure and health outcomes (data not shown). Adjustment for inhaled corticosteroid or long-acting bronchodilator use within the past 3 months did not significantly change the association between occupational exposure and observed outcomes (data not shown). Consideration of comorbid disease did not meaningfully change outcomes (*see* Table E1 in the online supplement). When using the LLN definition of COPD, we found that the results were similar to those of our main analysis, although the effect of occupational exposures on dyspnea and exacerbations requiring HCU no longer reached statistical significance (Table E2).

Effect Modification by Smoking Status and Sex

Occupational exposure had a greater effect on FEV_1% predicted among former smokers compared with current smokers ($\beta = -6.4\%$ in former vs. 5.1% in current smokers; interaction $P = 0.007$). Occupational exposures also tended to have a larger impact in former compared with current smokers on other health outcomes, including worse quality of life (QOL), worse CAT scores, and higher odds of exacerbations requiring HCU, although interaction terms were not statistically significant (Table 5). There were no statistically significant interactions between pack-years of smoking and occupational exposures, although occupational exposure tended to have a greater impact on some health outcomes, such as lung function and 6MWD, among those with the heaviest tobacco exposure (Table 5).

Occupational exposures were also associated with an increased risk of severe exacerbations requiring HCU (OR, 1.53; $P = 0.03$), although the association was weaker for exacerbation defined by medication use (Figure 1). When stratified by sex, occupational exposure was more strongly associated with risk of COPD exacerbations among men by both definitions but not among women. A sex × occupational exposure interaction

Table 3. Chronic Obstructive Pulmonary Disease Outcome Measures among Subjects with Chronic Obstructive Pulmonary Disease with Intermediate/High Risk and Low Risk of Occupational Exposure

	All Smokers with COPD (*n* = 721)	JEM Low Risk of Exposure (*n* = 438)	JEM Intermediate/High Risk of Exposure (*n* = 283)	*P* Value
COPD severity				
6MWD, m; mean (SD)	392.2 (112.3)	396.8 (110.9)	385.0 (114.4)	0.18
Post-bronchodilator FEV_1% predicted, mean (SD)	61.2 (23.4)	62.5 (23.6)	59.2 (22.9)	0.08
mMRC, mean (SD)	1.2 (1.0)	1.1 (0.9)	1.3 (1.0)	0.01
CAT, mean (SD)	14.6 (7.6)	13.8 (7.3)	15.8 (7.8)	0.001
HRQOL				
SGRQ, mean (SD)	35.5 (18.9)	33.2 (18.2)	38.7 (19.6)	0.0002
SF-12 Physical, mean (SD)	27.1 (10.5)	28.4 (10.3)	25.2 (10.5)	0.0001
COPD exacerbation over past 12 mo, n (% reporting)				
Requiring HCU	180 (25.0)	95 (21.7)	85 (30.1)	0.01
Requiring meds	171 (23.8)	98 (22.4)	73 (25.9)	0.28

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; HCU = health care utilization; HRQOL = health-related quality of life; JEM = job exposure matrix; mMRC = modified Medical Research Council Dyspnea Scale; SF-12 Physical = Short-Form Health Survey physical component scale; SGRQ = St. George's Respiratory Questionnaire; 6MWD = 6-minute-walk distance.

term was statistically significant ($P < 0.05$) for HCU by both measures. There were no significant sex interactions for the other outcomes (data not shown).

The Association of Occupational Exposures as Defined by VGDF with COPD and Health Outcomes among Those with COPD

Almost half (43%) of participants reported exposure to VGDF at their longest job. The sensitivity of self-reported exposure to VGDF when compared with the gold standard JEM was 70.7%, and its specificity was 73.1%. Participants who reported exposure to VGDF had increased odds of COPD (in the bivariate model: OR, 1.16, 95% CI, 0.90–1.50; in the multivariate model: OR, 1.37; 95% CI, 1.02–1.85). Among participants with COPD, results using self-reported exposure to VGDF in place of the JEM yielded similar results overall (Table E3).

Discussion

The results from this cross-sectional analysis expand on the findings of other investigations, indicating that occupational exposures are associated with increased odds of COPD (2–6), in particular through

Table 4. Multivariate Analyses of Effect of Occupational Exposure on Chronic Obstructive Pulmonary Disease Health Outcomes

	Multivariate Model*			Addition of Post-bronchodilator FEV_1% Predicted to Model†		
	β	95% CI	*P* Value	β	95% CI	*P* Value
Severity						
6MWD, m	−26.0	−44.4 to 7.7	0.006	−25.4	−42.6 to −8.2	0.006
Post-bronchodilator FEV_1% predicted	−2.6	−6.5 to 1.4	0.20	−2.6	−6.5 to 1.4	0.20
mMRC	0.23	0.07 to 0.38	0.004	0.19	0.04 to 0.34	0.01
CAT	1.8	0.6 to 3.0	0.003	1.6	0.4 to 2.7	0.01
HRQOL						
SGRQ	4.5	1.5 to 7.4	0.003	3.9	1.2 to 6.5	0.004
SF-12 Physical	−3.3	−4.9 to −1.6	<0.0001	−2.8	−4.4 to −1.2	0.001
	OR	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Exacerbations						
Requiring HCU	1.53	1.04 to 2.25	0.03	1.49	0.98 to 2.25	0.06
Requiring meds	1.24	0.83 to 1.84	0.29	1.44	0.75 to 1.75	0.54

Definition of abbreviations: CAT = COPD Assessment Test; CI = confidence interval; HCU = health care utilization; HRQOL = health-related quality of life; mMRC = Modified Medical Research Council Dyspnea Scale; OR = odds ratio; SGRQ = St. George's Respiratory Questionnaire; SF-12 Physical = Short-Form Health Survey physical component scale; 6MWD = 6-minute-walk distance.

*Model adjusted for age, sex, race, current smoking status, and pack-years smoking.

†Model adjusted for age, sex, race, current smoking status, pack years smoking, and post-bronchodilator FEV_1% predicted. Post-bronchodilator FEV_1% predicted is not included in the model predicting lung function.

Table 5. Multivariate Analyses of Effect of Occupational Exposure on Chronic Obstructive Pulmonary Disease Health Outcomes, Stratified by Smoking Status

	Current Smoking*					Pack-Years Smoking History†				
	Yes (*n* = 238)		No (*n* = 465)		*P* Value for Interaction	High (*n* = 369)		Low (*n* = 352)		*P* Value for Interaction
	β	*P* Value	β	*P* Value		β	*P* Value	β	*P* Value	
Severity										
6MWD, m	−9.8	0.52	−32.7	0.006	0.27	−33.2	0.008	−18.0	0.20	0.21
Post-bronchodilator FEV_1% predicted	5.1	0.11	−6.4	0.01	0.007	−4.6	0.09	−0.4	0.89	0.22
mMRC	0.21	0.14	0.23	0.02	0.83	0.21	0.06	0.24	0.03	0.61
CAT	1.2	0.34	2.1	0.003	0.69	1.9	0.02	1.8	0.04	0.86
HRQOL										
SGRQ	1.42	0.61	5.6	0.002	0.42	5.7	0.007	3.2	0.13	0.44
SF-12 Physical	−2.3	0.13	−3.6	<0.0001	0.50	−3.1	0.01	−3.5	0.004	0.75
	OR	***P* Value**	**OR**	***P* Value**	***P* Value for Interaction**	**OR**	***P* Value**	**OR**	***P* Value**	***P* Value for Interaction**
Exacerbations										
Requiring HCU	0.99	0.97	1.84	0.01	0.18	1.77	0.04	1.38	0.26	0.33
Requiring meds	0.96	0.91	1.37	0.20	0.40	1.40	0.25	1.15	0.64	0.43

Definition of abbreviations: CAT = COPD Assessment Test; HCU = health care utilization; HRQOL = health-related quality of life; mMRC = Modified Medical Research Council Dyspnea Scale; OR = odds ratio; SF-12 Physical = Short-Form Health Survey physical component scale; SGRQ = St. George's Respiratory Questionnaire; 6MWD = 6-minute-walk distance.
*Model adjusted for age, sex, race, and pack-years smoking history.
†Model adjusted for age, sex, race, and current smoking status.

reconfirming that occupational exposures increase the odds of COPD even among heavy smokers. Building on that observation, we also show here that occupational exposures are linked to worse morbidity in patients with well-established COPD. Job exposures were associated with adverse outcomes across multiple validated indices of morbidity, representing a significant risk of impairment among patients with COPD. Our study benefitted from an exceptionally well-phenotyped cohort recruited from seven sites in the United States, the use of validated symptom-based respiratory and COPD-specific questionnaires, and objective measures of functional status collected by trained staff as part of the SPIROMICS study. Our results highlight the important contribution of occupational exposures to COPD morbidity across a diverse COPD population.

Our study addresses a knowledge gap by investigating the role of occupational exposure in contributing to COPD morbidity among those with already-established disease and significant smoking histories. Occupational exposures were associated with worse HRQOL, as demonstrated by a clinically significant 4.5-point increase in SGRQ (27). In addition, occupational exposures were linked to an increase in CAT score, nearing the minimum clinically important difference (28), and lower SF-12 physical scores, reflecting worse COPD-related

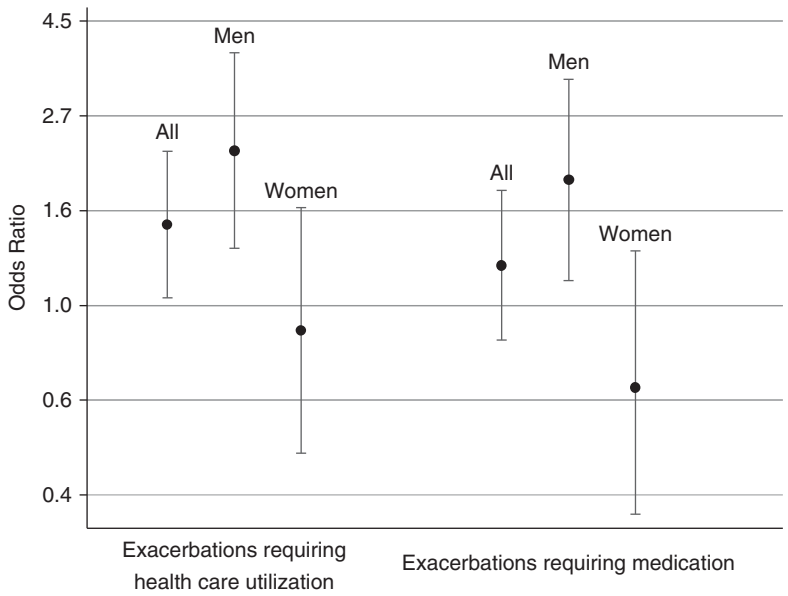

Figure 1. Effect of occupational exposure (Job Exposure Matrix longest job) on chronic obstructive pulmonary disease exacerbations. Visual representation of the impact of occupational exposure on the odds of exacerbations requiring medications and exacerbations requiring health care utilization for the entire sample, for men, and for women, respectively. *Bars* surrounding point estimates represent 95% confidence intervals. Model for all participants adjusted for age, sex, race, current smoking status, and pack-years smoking history; models for men and women adjusted for age, race, current smoking status, and pack-years smoking history.

and general health status. Individuals with occupational exposures had worse dyspnea and objective clinical outcomes, including a clinically significant worsening in 6MWD (29). Furthermore, patients with COPD were 53% more likely to report exacerbations requiring HCU within the past year, representing a potentially heavy burden on the health care system. These results do not appear to be explained by decreased lung function as the mediator of an occupational effect given that adjustment for the former resulted in only mild attenuation of the effect size of job exposure on indices of morbidity.

Similar to our results linking occupational exposure to worse QOL, Blanc and colleagues (10) showed that, among 386 participants with self-reported COPD, VGDF exposure was associated with worse SF-12 physical component and SGRQ scores, with a magnitude of effect similar to that in our study. Few published studies have evaluated the effect of occupational exposures on other measures of respiratory morbidity in patients with established COPD, and the limited work that does exist is inconsistent. Caillaud and colleagues, in a cross-sectional study of COPD (n = 591), showed that reported exposure to VGDF at any point in the occupational history, compared with no exposure, was associated with increased likelihood of lifetime wheeze (71.9 vs. 61.1%; $P = 0.04$) but observed no exposure-related differences in dyspnea or HRQOL (13). In a cross-sectional study of male outpatients with COPD (n = 185), Rodriguez and colleagues found that patients reporting exposure to occupational dust, gas, or fumes at any point in their occupational history were more likely to report sputum production (OR, 2.8; 95% CI. 1.2–6.6), but there were no significant exposure-related differences in dyspnea, cough, or wheeze or risk of COPD hospitalizations (12).

Our results may differ from these studies, in part, because defining exposure based on events at any point in a job history (as opposed to longest-held job as in our analysis) can lead to exposure misclassification arising out of very short-duration jobs. In addition, our primary analyses were based on a validated JEM-derived assessment, as opposed to self-reported exposure to VGDF. The JEM method of determining risk of occupational exposures is a benchmark to which other exposure methods (including self-reported exposure to VGDF) are often compared (30). Although self-reported VGDF was also associated with worse health outcomes (*see* the online supplement), use of the JEM exposure variable predicted larger differences in symptom, QOL, and exacerbation outcomes.

Our results add to available evidence by evaluating the effect of occupational exposure on several COPD-related health outcomes in a larger study population with spirometry-confirmed COPD. Because of our relatively large sample size, we were able to examine whether sex and smoking history modified the effect of occupational exposures on COPD morbidity. Current smokers appeared to be less affected by occupational exposures compared with ex-smokers. Although the mechanism for this interaction is unclear, it may be due in part to the fact that individuals who quit smoking may have an increased susceptibility to the respiratory effects of cigarette smoke (31); correspondingly, these individuals may be more susceptible to the effects of prior occupational exposures. This finding suggests that clinical counseling on modifying exposure risks must extend beyond smoking cessation and should include targeted discussions about modifying occupational exposures among the currently exposed—even among those who have already quit smoking. In addition, occupational exposure had an adverse impact even among subjects with COPD with the greatest tobacco exposure, highlighting the importance for clinicians to look for other sources of exposure that may contribute to disease morbidity even in individuals with substantial smoking histories.

We also noted that occupational exposures were linked to increased risk of COPD exacerbations in men but not in women even though there were no differences by sex in other indices of morbidity. Although the use of subgroup analyses limits definitive conclusions, there are several potential explanations for this observed difference. Sex-related physiologic differences may explain this finding (3, 32, 33), but it is also important to note that job duties and exposures can differ by sex even within the same occupation (34), a nuance that would not be captured by the JEM approach.

Our study has several limitations. Because our analysis was cross-sectional, we cannot determine causality, and we are unable to determine if prior or current exposures are associated with worse outcomes over time. We also lacked sufficient numbers of high- versus intermediate-risk JEM-defined exposures to explore potential gradients of effect. In addition, because exposure was based on the longest-held job, it is unknown whether or not a current or more recent job, even if shorter term, might have contributed additional exposure risks. Given that so few subjects were currently employed, we did not study the impact of current job exposure on COPD outcomes. Furthermore, actual exposures may vary among different positions within the same job industry, leading to some degree of misclassification. However, these limitations would have been likely to bias results toward the null, and thus the actual association between work exposure and COPD morbidity may be stronger than those we report in the study. Because socioeconomic factors and occupational exposures may lie on the same causal pathway leading to health outcomes, similar to prior studies assessing occupational exposure on health outcomes (2, 11, 12, 25, 35), we did not include income or education in our primary models. In addition, as part of the SPIROMICS study design, inclusion criteria for those with COPD included a greater than 20 pack-year smoking history. As such, we are unable to comment on the role of occupational exposures in a population of individuals with COPD without substantial smoking histories. Because JEM determination of exposure is based on expert opinion of risk associated with the occupation of the participant, the degree of recall bias associated with querying participants about exposures related to disease is minimal using the JEM method (25). However, some degree of uncertainty remains because validation of job history, detailed information about job responsibilities, use of personal protective equipment, and workplace environmental monitoring results were not available, making conclusions about exact job exposures difficult. In addition, we did not find a significant decrease in lung

function in the group with occupational exposures; this may suggest that the poorer symptomatic and functional outcomes observed may be via a mechanism other than the effect on large airways.

In summary, we found that, in addition to occupational exposures being linked to increased odds of COPD, occupational exposures are associated with increased morbidity in patients with established COPD. This effect is seen even in those with significant smoking histories and in patients who have already quit smoking. Occupational histories should be obtained on all patients with COPD; clinicians should anticipate more severe disease in patients who report occupational exposures and accordingly should expect more symptoms and possibly increased utilization of health care resources in this population. Because the majority of the subjects with COPD were no longer working, the association appears to be driven by employment that occurred in the past rather than ongoing exposure, highlighting that past occupational exposures affect current symptoms even in individuals who have retired. Targeted measures to reduce exposure to potentially harmful agents should be a part of workplace controls for all employees; additional protective measures may be required of those with known COPD. These results suggest that job history plays a large role in the global impact of COPD and point to the need to address occupational exposures as an important contributor to COPD morbidity worldwide. ■

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