Association of Occupational Exposures and Chronic Obstructive Pulmonary Disease Morbidity

Jennifer S. Rous, DrPH, Peter S. J. Lees, PhD, Kirsten Koehler, PhD, Jessie P. Buckley, PhD, Lesliam Quirós-Alcalá, PhD, MeiLan K. Han, MD, Eric A. Hoffman, MD, Wassim Labaki, MD, R. Graham Barr, MD, Stephen P. Peters, MD, Robert Paine, 3rd, MD, Cheryl Pirozzi, MD, Christopher B. Cooper, MD, Mark T. Dransfield, MD, Alejandro P. Comellas, MD, Richard E. Kanner, MD, M. Bradley Drummond, MD, Nirupama Putcha, MD, Nadia N. Hansel, MD, and Laura M. Paulin, MD

Objective: The aim of the study is to determine whether aggregate measures of occupational exposures are associated with chronic obstructive pulmonary disease (COPD) outcomes in the Subpopulations and Intermediate Outcome Measures in COPD study cohort. **Methods:** Individuals were assigned to six predetermined exposure hazard categories based on self-reported employment history. Multivariable regression, adjusted for age, sex, race, current smoking status, and smoking pack-years determined the association of such exposures to odds of COPD and morbidity measures. We compared these with the results of a single summary question regarding occupational exposure. **Results:** A total of 2772 individuals were included. Some exposure estimates, including "gases and vapors" and "dust and fumes" exposures resulted in associations with effect estimates over two times the estimated effect size when compared with a single summary question. **Conclusions:** Use of occupational hazard categories can identify important associations with COPD morbidity while use of single-point measures may underestimate important differences in health risks.

Keywords: occupational history, COPD, clinical outcomes, observational study, respiratory disease

LEARNING OUTCOMES

- Discuss how different occupational exposure histories are associated with respiratory morbidity in a population of individuals with and at-risk of developing COPD
- Identify specific occupational exposure categories associated with greater COPD morbidity based on an individual's self-reported occupational history
- Describe the impact of additional years of occupational exposures on COPD morbidity based on reported occupational exposure history.

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide, affecting an estimated 216 million people every year, and represents an increasing burden for health care. [1,2] Although cigarette smoking has been identified as the leading causal risk factor of COPD in the United States, occupational exposures to vapors, gases, dusts, and fumes (VGDF) are also associated with an increased risk of development and morbidity of COPD, including increased exacerbations, worse quality of life, and greater computed tomographic (CT) markers of respiratory disease. [3–10] The population attributable fraction of workplace exposures for COPD was recently reported as 14%.[11]

Occupational exposure is often measured using a single question querying a person's exposure to VGDF, or by a job exposure

From the Region VIII, Occupational Safety and Health Administration, Department of Labor, Denver, Colorado (J.S.R.); Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (J.S.R., P.S.J.L., K.K., J.P.B., L.Q.-A.); Department of Medicine, University of Michigan, Ann Arbor, Michigan (M.K.H., W.L.); Department of Radiology, University of Iowa, Iowa City, Iowa (E.A.H.); Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York (R.G.B.); Department of Medicine, Wake Forest University, Winston-Salem, North Carolina (S.P.P.); Department of Medicine, University of Utah, Salt Lake City, Utah (R.P., C.P., R.E.K.); Department of Medicine, University of California, Los Angeles, Los Angeles, California (C.B.C.); Department of Medicine, University of Alabama, Birmingham, Alabama (M.T.D.); Department of Medicine, University of Iowa, Iowa City, Iowa (A.P.C.); Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina (M.B.D.); Department of Medicine, Johns Hopkins University, Baltimore, Maryland (N.P., N.N.H.); and Department of Medicine, Dartmouth-Hitchcock Medical Center/Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire (L.M.P.).

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Address correspondence to: Jennifer S. Rous, OSHA Region VIII, 1244 Speer Blvd, Ste 551, Denver, CO 80204 (rous.jennifer@dol.gov).

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matrix (JEM), which assigns a low, medium, or high likelihood of VGDF exposures based on self-report of occupation. Although prior research using both VGDF [12] and JEM [13] supports association between occupational exposures and COPD incidence and morbidity, these measures consolidate the complex nature and multiple hazards of many occupational exposures. Vapors, gases, dusts, and fumes by definition include compounds of varying chemical and physical characteristics that can impact their inhalation, deposition, and reaction within the lungs. Understanding if the composition of the VGDF exposure affects the odds of COPD or morbidity may offer clues toward the heterogeneity of COPD and could help inform exposure prevention efforts.

To better understand the associations between occupational exposures, mechanisms of disease, and COPD outcomes, there may be value gained in evaluating exposures individually or in more analogous groupings such as gases and vapors, biological/organic dusts, or inorganic/mineral dusts. Moreover, determining the association between duration of exposure and clinical and radiographic outcomes may inform clinical practice and identify susceptible subgroups. In the present study, we aim to evaluate the contribution of historical occupational exposure to COPD prevalence and morbidity in the SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS), a longitudinal cohort designed to identify subpopulations that may benefit from targeted, specialized therapeutic treatments.[14] In prior analyses of the same cohort, Paulin et al[9] examined the effects of occupational exposure assessed using VGDF and JEM questions on COPD morbidity and on commuted tomographic imaging characteristics [15]; our goal is to expand on the use of exposure categories, using gas and particulate classification, specific occupational exposures, and duration of such exposures, and their relationship to COPD.[16]

METHODS

Study Population

The SPIROMICS enrolled approximately 2970 participants from 12 clinical centers across the United States. Participants were enrolled in the following four strata: (1) nonsmoke-exposed persons (not included in current analysis); (2) smoke-exposed persons (hereafter referred to as smokers) with a history of at least 20 pack/years of exposure, without airways obstruction; (3) smokers with airways obstruction and a forced expiratory volume in 1 second (FEV_1) greater than or equal to 50% (≥50%) of the predicted value; and (4) smokers with obstruction and an FEV_1 less than 50% (<50%) of the predicted value. Chronic obstructive pulmonary disease was defined by airway obstruction with a postbronchodilator forced expiratory volume in 1 second over the forced vital capacity (FEV_1/FVC) of less than 0.70. The study design and exclusion criteria have been described in detail previously. [14]

Data Collection

At the baseline visit, SPIROMICS staff collected extensive demographic and clinical data from participants. Morbidity measures included St George's Respiratory Questionnaire (SGRQ),[17] 6-minute walk distance in meters (6MWD),[18] dyspnea (modified Medical Research Council questionnaire [mMRC]),[19] COPD health status (COPD assessment test [CAT]),[20] and Body Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index. [21] Current smoking was defined as report of smoking within the last month. Participants reported the total number of exacerbations in the year before the enrollment visit and were dichotomized to zero versus one or more exacerbations. Spirometry was performed according to standard procedures. [22,23] Computed tomographic measurements were undertaken at full inspiration and expiration as previously described, [24] capturing emphysema (% of total voxels in the field < −950 HU at total lung capacity), large-airway disease (measured using Pi10, a measure of airway wall thickness), and small-airway disease (% of total voxels in the field < −856 HU at residual volume). [15,24] The SPIROMICS was approved by the institutional review boards at each center and all participants provided written informed consent before any data collection.

Occupational Exposure Data

SPIROMICS staff administered a semistructured occupational questionnaire, which included questions on current and former jobs and ascertained work history through individual dichotomous (yes/no) questions about 22 occupations or trades and 16 specific hazards, as well as free form text fields for longest occupational job, along with approximate number of years exposed to each trade or hazard. Participants were also asked "if they had ever worked and if this job exposed them to VGDF." Using responses from the baseline occupational questionnaire, two separate exposure definitions were created:

1. Self-reported ever exposure (yes/no) to VGDF. This dichotomous question ascertained overall potential for exposure even to individuals who may not have worked in any of the industries, occupations, or hazards identified elsewhere in the questionnaire, hereafter referred to as "ever VGDF."

2. Assigned exposure category based on participant self-report of ever work in specific trades and/or of ever exposure to specific hazards asked in the questionnaire. We developed exposure categories defined by gases or particulates for our analysis utilizing responses to "ever worked" in the occupation and specific hazard questions from the occupational history questionnaire. Exposure categories were created for "gases and vapors" and "dusts and fumes." "Dusts and fumes" exposure category was further subdivided into "biological and organic dusts," "mineral and inorganic dusts and fumes," "metal dusts and fumes," and "agricultural dusts." For example, a person who responded as a welder was placed into exposure categories for "mineral and inorganic dusts and fumes" and "metal dusts and fumes." Assignments were not exclusive, so an individual could potentially be captured in multiple exposure categories due to reporting of multiple occupational exposures or multiple jobs. Table 1 identifies the occupations and hazards represented in the occupational history questionnaire and presents the exposure category assignments utilized.

A subset of participants (n = 2086) reported the number of years exposed to the 16 specific hazards in addition to years of asbestos exposure. Years of exposure were rounded up to the nearest year, with all reports of more than a year rounded to 1 year.

Statistical Analysis

Population and employment demographics were summarized using descriptive statistics. Logistic regression models were used to estimate crude prevalence odds ratios (PORs) and adjusted PORs (aPORs) of having COPD or having an exacerbation in the last year by occupational exposure categories. Using data from the baseline visit, crude and multivariable linear regression models were used to estimate cross-sectional associations between occupational exposure categories and COPD morbidity. In both the crude and multivariable models, the reference category used were individuals who were not included in the occupational exposure hazard category of interest. Models were adjusted a priori for age, sex, race (White vs non-White), current smoking status, and smoking pack-years. We also included body mass index (BMI; underweight, <18.5 kg/m^2; normal weight, 18.5 to <25 kg/m^2; overweight, 25 to <30 kg/m^2; obese, at least 30 kg/m^2) and examination site in our models for CT measures. In a sensitivity analysis, models were adjusted for remaining exposure hazard categories to account for multiple occupational exposures (ie, models investigating the primary exposure hazard category of gases and vapors were adjusted for dusts and fumes and models investigating the primary exposure hazard category of dusts and fumes, including all subcategories of dusts and fumes, were adjusted for gases and vapors). Results from the different occupational exposures and exposure categories were compared with the ever VGDF. In a separate sensitivity analysis, we merged the assigned

TABLE 1. Assignment Classifications for Occupational Exposures

	Gases and Vapors	Dusts and Fumes	Biological and Organic Dusts	Mineral and Inorganic Dusts and Fumes	Metal Dusts and Fumes	Agricultural Dusts
Occupation or trade identified in SPIROMICS questionnaire (n)						
Boilermaker (51)		Yes		Yes	Yes	
Carpenter (318)		Yes	Yes			
Chemical worker (120)	Yes					
Electrician (154)		Yes		Yes		
Elevator operator (29)	Yes					
Insulator (109)	Yes	Yes	Yes	Yes		
Lather (39)	Yes	Yes		Yes	Yes	
Machinist (200)	Yes	Yes		Yes	Yes	
Mechanic (229)	Yes	Yes		Yes	Yes	
Millwright (49)		Yes		Yes	Yes	
Pipefitter (78)	Yes	Yes		Yes	Yes	
Plasterer (120)		Yes		Yes		
Plumber (126)	Yes	Yes		Yes	Yes	
Sander (175)		Yes		Yes		
Sheet metal worker (120)		Yes		Yes	Yes	
Steelworker (95)		Yes		Yes	Yes	
Welder (180)		Yes		Yes	Yes	
Pig farmer (40)	Yes	Yes	Yes			Yes
Rigger (59)		Yes	Yes	Yes		
Roofer (181)	Yes	Yes		Yes		
Painter (300)	Yes					
Mason (85)		Yes		Yes		
Specific Vapor, Gas, Dust, or Fume (n)						
Irritant gases, such as chlorine or ammonia (469)	Yes					
Fire, smoke, or other combustion products (358)	Yes	Yes		Yes		
Incinerators, boilers, or oil refineries (163)	Yes	Yes		Yes	Yes	
Coal dust or powder (113)		Yes		Yes		
Silica or sand, concrete, cement, or rock dust (384)		Yes		Yes		
Indoor fuel powered motors, compressors, or engines (366)	Yes	Yes				
Diesel engine exhaust (404)	Yes	Yes				
Wheat flour or other grain dusts (104)		Yes	Yes			
Animal feed fodder (131)	Yes	Yes	Yes			Yes
Cotton dust or cotton processing (77)		Yes	Yes			Yes
Wood dust or saw dust (405)		Yes	Yes			
Cadmium fumes or batteries or silver solder (134)		Yes		Yes	Yes	
Other metal dusts or metal fumes (245)		Yes		Yes	Yes	
Welding or flame cutting (290)		Yes		Yes	Yes	
Fiberglass or other man-made mineral fibers (258)		Yes		Yes		
Explosives or blasting fumes (104)		Yes		Yes		
Total Individuals	1,247	1,291	648	1,084	739	261

exposure categories to form one composite variable representing exposure to any occupational hazard. This dichotomous (yes/no) variable was used in a separate analysis to determine the relationship between assigned exposure to COPD outcomes.

In separate analyses, we assessed effect modification by sex, race, and smoking status of the association between exposure category and our outcomes by including a single interaction term (covariate*exposure) in separate models for each potential effect modifier. Finally, in a separate analysis, crude and multivariable linear regression models were used to estimate the association between years of exposure reported by the participant and COPD status. All analyses were performed with StataIC statistical software, version 15.1 (StataCorp, College Station, TX). Statistical significance was defined as a P value less than 0.05 for main effects and effect modification. [25]

RESULTS

Study Population Characteristics

General participant demographics are provided in Table 2. Of the 2772 current or former smokers enrolled in the SPIROMICS, the average age was 63.5 years (SD, 8.9 years). Individuals with biological and organic dusts exposure were slightly younger with an average age of 61.9 years (SD, 8.9 years). Study participants were between 75% and 80% White across all exposure categories. All exposure categories had higher percentages of male participants with the highest being for metal dusts and fumes (82.5% of exposed). Smoking pack-years were 49.3 (SD, 26.9) for all participants and higher for all assigned exposure categories. More than 40% of participants were current smokers in all exposure categories. Among current smokers, mean (SD) pack-years was 46.4 (24.8); former smokers had a mean (SD) of 51.4 (28.1) pack-years. Average values for mMRC, SGRQ, CAT, 6MWD, and BODE Index were similar across all exposure categories.

As exposure categories were created by the study group using responses to trades and specific hazards, it is possible that a participant self-identified as not being exposed to ever VGDF but was still assigned as having exposure. More than 40% of participants (n = 1149) responded to "yes" to the single question "Have you ever been exposed to VGDF at work?" Of these 1149 individuals, 248 (22%) were not assigned to an exposure category based on participant self-report of ever work in specific trades and/or of ever exposure to specific hazards asked in the questionnaire. Conversely, 543 of the 1587 individuals (34%) who did not report ever VGDF exposure were assigned to an exposure category based on their work in specific trades or hazards.

TABLE 2. General Population Demographics

Demographic	All Participants (N = 2,772)	Gases and Vapors (n = 1,247)	Dusts and Fumes (n = 1,291)	Biological and Organic Dusts (n = 648)	Mineral and Inorganic Dusts and Fumes (n = 1,084)	Metal Dusts and Fumes (n = 739)	Agricultural Dusts (n = 261)	Ever VGDF[A] (n = 1,149)
Age, mean (SD), yr	63.5 (8.9)	62.4 (8.8)	62.6 (8.8)	61.9 (8.9)	62.2 (8.8)	62.5 (8.6)	63.1 (9.0)	62.3 (8.9)
White race, n (%)	2,123 (76.6)	956 (76.7)	1,004 (77.8)	514 (79.3)	838 (77.3)	566 (76.6)	209 (80.1)	852 (74.2)
Male sex, n (%)	1,498 (54.0)	877 (70.3)	968 (75.0)	489 (75.5)	851 (78.5)	610 (82.5)	172 (65.9)	758 (66.0)
Current smoker, n (%)	1,093 (40.0)	520 (42.3)	527 (41.5)	271 (42.7)	451 (42.2)	311 (42.7)	103 (40.2)	464 (40.8)
Pack years, mean (SD)	49.3 (26.9)	50.9 (27.3)	51.1 (27.5)	49.8 (25.4)	51.5 (28.2)	52.6 (29.5)	49.9 (27.4)	50.9 (25.8)
BMI, mean (SD)	27.9 (5.3)	28.1 (5.3)	28.2 (5.2)	28.0 (5.1)	28.1 (5.2)	28.1 (5.3)	28.1 (5.4)	28.2 (5.4)
Exacerbations in last year, mean (% response)	0.45 (26.4)	0.30 (29.8)	0.28 (28.3)	0.29 (29.0)	0.28 (28.3)	0.29 (28.6)	0.33 (32.6)	0.31 (31.1)
CAT score, mean (SD)	14.1 (8.3)	15.2 (8.2)	15.0 (8.2)	14.7 (7.9)	15.0 (8.3)	15.0 (8.5)	14.9 (7.9)	15.8 (8.4)
mMRC score, mean (SD)	1.08 (1.01)	1.16 (1.04)	1.15 (1.05)	1.13 (1.05)	1.15 (1.08)	1.21 (1.14)	1.21 (1.09)	1.19 (1.04)
SGRQ score, mean (SD)	33.6 (20.6)	36.8 (20.5)	36.0 (20.6)	35.9 (20.3)	36.2 (20.8)	36.9 (21.1)	37.1 (20.5)	37.9 (20.9)
6MWD, mean (SD), m	407.7 (120.6)	406.9 (120.7)	405.9 (119.8)	409.6 (118.3)	408.3 (122.4)	407.6 (125.9)	411.1 (116.8)	401.1 (123.3)
BODE Index, mean (SD)	1.53 (1.94)	1.64 (2.0)	1.64 (2.0)	1.61 (2.0)	1.66 (2.0)	1.73 (2.0)	1.65 (2.0)	1.74 (2.0)

6MWD, 6-minute walk distance; BMI, body mass index; BODE, Body Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity; CAT, COPD assessment test; mMRC, modified Medical Research Council questionnaire; SGRQ, St George's Respiratory Questionnaire; VGDF, vapors, gases, dusts, and fumes.

The number of participants who responded to each specific occupational hazard and the subset of these individuals reporting exposure duration to the specific occupational hazard are reported in Table 3. In the subset of participants who reported duration of exposure (n = 2086), those reporting asbestos exposure had the widest range of years exposed, 1–52, whereas respondents exposed to fire, smoke, or other combustion products had the highest average years of exposure 16.7 (SD, 13.7).

Occupational Exposures and COPD Morbidity Measures

Gases and Vapors

Forty-five percent of participants were assigned to the gases and vapors exposure category based on reported trades or specific exposures to gases and vapors. Gases and vapors exposure was significantly associated with increased prevalence odds of COPD (aPOR, 1.22; 95% confidence interval [95% CI], 1.02 to 1.45; P = 0.03). These results were similar to the statistically significant increased prevalence odds among those with ever VGDF exposure (aPOR, 1.18; 95% CI, 1.04 to 1.35; P = 0.01). Conversely, the associations of gas and vapors with other COPD status such as mMRC (β = 0.19; 95% CI, 0.11 to 0.27), CAT (β = 2.23; 95% CI, 1.58 to 2.88), and SGRQ (β = 6.82; 95% CI, 5.21 to 8.44) were almost double the estimated effect size using ever VGDF exposure alone as the exposure metric, values larger than the minimum clinically important difference (MCID) for these outcomes (SGRQ MCID 4 points [26]; CAT MCID 2 points [27]; Table 4). Exposure to gases and vapors was also significantly associated with increases in % emphysema (β = 0.95; 95% CI, 0.22 to 1.68) and small airways disease (β = 2.56; 95% CI, 1.06 to 4.06) (Table 4). In the sensitivity analysis adjusting for multiple exposure hazard categories, results were similar. When examining the relationship between gases and vapors and COPD morbidity, including dusts and fumes exposure as a covariate did not meaningfully change the magnitude of the observed associations, although the relationship was no longer significant for the outcomes of BODE index, 6MWD, % emphysema and small airways disease, and odds of COPD (Supplemental Digital Content Table 1a, http://links.lww.com/JOM/B322).

TABLE 3. Specific Hazard Exposure and Exposure Duration Demographics

Exposure	All Participants (N = 2,772)	Participants Reporting Exposure Duration, n	Exposure Duration, yr	
			Mean (SD)	Range*
Irritant gases, such as chlorine or ammonia	469	203	13.3 (12.3)	1–51
Wood dust or saw dust	405	187	14.2 (13.6)	0.5–51
Diesel engine exhaust	404	191	2.8 (1.7)	1–9
Silica or sand, concrete, cement, or rock dust	384	181	13.7 (13.3)	0.4–51
Indoor fuel powered motors, compressors, or engines	366	173	15.8 (14.1)	1–51
Fire, smoke or other combustion products	358	163	16.7 (13.7)	1–50
With asbestos	353	40	10.9 (11.1)	0.2–52
Welding or flame cutting	290	141	13.0 (13.6)	0.5–50
Fiberglass or other man-made mineral fibers	258	115	12.4 (12.7)	0.4–51
Other metal dusts or metal fumes	245	123	16.2 (13.5)	0.5–50
Incinerators, boilers or oil refineries	163	67	12.7 (13.6)	1–50
Cadmium fumes or batteries or silver solder	134	63	2.9 (1.9)	1–9
Animal feed fodder	131	66	2.5 (2.1)	1–9
Coal dust or powder	113	50	12.0 (12.3)	0.5–50
Wheat flour or other grain dusts	104	52	2.8 (2.0)	1–9
Explosives or blasting fumes	104	40	3.1 (2.4)	1–9
Cotton dust or cotton processing	77	36	3.0 (2.0)	1–9

*All exposure durations were rounded up to the nearest tenth of a year.

TABLE 4. Association of Gas and Vapors With COPD Status

	Ever VGDF (Yes/No)* (n = 1,149)		Gas and Vapors* (n = 1,247)	
COPD Status	**β (95% CI)**	***P*†**	**β (95% CI)**	***P***
BODE Index	**0.18 (0.07 to 0.30)**	**0.002**	**0.29 (0.13 to 0.44)**	**<0.001**
mMRC	**0.08 (0.02 to 0.14)**	**0.008**	**0.19 (0.11 to 0.27)**	**<0.001**
SGRQ	**2.86 (1.67 to 4.06)**	**<0.001**	**6.82 (5.21 to 8.44)**	**<0.001**
CAT	**1.04 (0.56 to 1.51)**	**<0.001**	**2.23 (1.58 to 2.88)**	**<0.001**
6MWD	**-8.97 (−16.01 to −1.93)**	**0.01**	**−15.25 (−24.88 to −5.62)**	**0.002**
%FEV_1	**−3.99 (−5.51 to −2.47)**	**<0.001**	**−4.94 (−7.03 to −2.85)**	**<0.001**
% Emphysema‡	**0.74 (0.21 to 1.27)**	**0.006**	**0.95 (0.22 to 1.68)**	**0.01**
Small airways disease§	**1.46 (0.37 to 2.55)**	**0.009**	**2.56 (1.06 to 4.06)**	**0.001**
Large airways disease‖	0.003 (−0.001 to 0.007)	0.10	0.002 (−0.004 to 0.007)	0.55
Odds of COPD¶	**1.18 (1.04 to 1.35)**	**0.01**	**1.22 (1.02 to 1.45)**	**0.03**
Odds of exacerbation¶	**1.25 (1.10 to 1.43)**	**0.001**	**1.60 (1.33 to 1.93)**	**<0.001**

*Adjusted for age, sex, race, current smoking status, and smoking pack-years. Body mass index and examination site were also included in CT measure models.

†$P < 0.05$ indicated in bold.

‡% Emphysema = total voxels in the field less than −950 HU at total lung capacity.

§Small airways disease = % of total voxels in the field less than −856 HU at residual volume.

‖Large airways disease = Pi10, airway wall thickness (in millimeters).

¶Odds of COPD and odds of exacerbations reported as POR.

%FEV, forced expiratory volume in 1 second; 6MWD, 6-minute walk distance; BODE, Body Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity; CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council questionnaire; SGRQ, St George's Respiratory Questionnaire; VGDF, vapors, gases, dusts, and fumes.

Dusts and Fumes

The dusts and fumes exposure category, determined from our assignments based on specific exposures or from trades where dusts and fumes exposures were common, represented approximately 47% of individuals in the study population. Dusts and fumes exposures were also significantly associated with all COPD morbidity measures with the exception of prevalence odds of COPD. For example, dusts and fumes exposures resulted in increases of exacerbations (aPOR, 1.52; 95% CI, 1.25 to 1.84; $P < 0.001$). The largest differences in effect estimates for morbidity measures as compared with the ever VGDF exposure were for 6MWD (β = −21.42; 95% CI, −31.35 to −11.49) and SGRQ (β = 6.43; 95% CI, 4.75 to 8.11), where the effect sizes were more than twice the ever VGDF value and surpassing the MCID for SGRQ. Exposure to dusts and fumes was also significantly associated with increases in CT scan measures of small airways disease (β = 2.65; 95% CI, 1.09 to 4.20) (Table 5). In the sensitivity analysis adjusting for multiple exposure hazard categories, results of the models that included gases and vapors as a covariate in the dusts and fumes analysis were largely similar, although the magnitude of the relationships was overall attenuated in many of the subcategories for several outcomes (Supplemental Digital Content Table 1b, http://links.lww.com/JOM/B323). To further examine "dusts and fumes," additional analysis was undertaken for the four subcategories (organic and biological dusts, inorganic and mineral dusts and fumes, metal dusts and fumes, and agricultural dusts.)

Organic and Biological Dusts

Organic and biological dusts exposures were observed in 23% of the participants through their report of trades or specific exposures. Although several morbidity measures were not significant with organic and biological dusts, we observed borderline statistically significant increased prevalence odds of COPD among individuals with reported exposure to organic and biological dusts (aPOR, 1.24; 95% CI, 1.00 to 1.52; $P = 0.05$) (Table 5). Increased prevalence odds were observed for increased exacerbation risk (aPOR, 1.35; 95% CI, 1.09 to 1.66; $P = 0.006$) and increases in SGRQ (β = 3.78; 95% CI, 1.88 to 5.67; $P < 0.001$), CAT (β = 0.85; 95% CI, 0.09 to 1.61; $P = 0.03$), and %FEV_1 (β = −2.67; 95% CI, −5.10 to −0.25; $P = 0.03$), although none were appreciably different than effects associated with the ever VGDF exposure. Exposure to organic and biological dusts was also significantly associated with increases in small airways disease (β = 1.86; 95% CI, 0.13 to 3.59) (Table 5). Exposures to organic and biological dusts were not associated with BODE Index, mMRC, 6MWD, and % emphysema, unlike the ever VGDF exposure (Table 5).

Inorganic and Mineral Dusts and Fumes

Analogous to dusts and fumes, we observed statistically significant results for inorganic and mineral dusts and fumes exposures across all morbidity measures with the exception of prevalence odds of COPD. Thirty-nine percent of respondents were assigned to the inorganic and mineral dusts and fumes exposure category. For example, CAT results increased by a value of 1.9 (β = 1.93; 95% CI, 1.24 to 2.62; $P < 0.001$), which approaches the MCID of 2.0. [27] The 6MWD difference (β = −18.08; 95% CI, −28.31 to −7.84) was twice the ever VGDF value (β = −8.97; 95% CI, −16.01 to −1.93). Exposure to inorganic and mineral dusts and fumes was also significantly associated with increases in small airways disease (β = 2.16; 95% CI, 0.56 to 3.75) (Table 5).

Metal Dusts and Fumes

Metal dusts and fumes represented a subcategory of both "dusts and fumes" and "mineral and inorganic dusts and fumes." Despite being a more refined assigned exposure category, 27% of subjects reported exposure to specific metal dusts and fumes or trades involving these exposures, and this exposure category resulted in statistically significant results for COPD morbidity measures comparable with both larger categories of "dusts and fumes" and "inorganic and mineral dusts and fumes." Metal dusts and fumes were associated with the highest adjusted increase (β = 0.40; 95% CI, 0.22 to 0.57; $P < 0.001$) for BODE Index. Exposure to metal dusts and fumes was also significantly associated with increases in small airways disease (β = 1.87; 95% CI, 0.16 to 3.57; $P = 0.03$) (Table 5).

Agricultural Dusts

Although representing the smallest exposure category with only 261 individuals (9% of participants) assigned from reports of specific exposures or agricultural trades, agricultural dusts exposures resulted in significant increased prevalence odds of exacerbations (aPOR, 1.50; 95% CI, 1.13 to 1.98; $P = 0.005$). Agricultural dusts exposures

TABLE 5. Association of Dusts and Fumes and Subcategories With COPD Status

COPD Status	Dusts and Fumes* (n = 1,291)		Organic and Biological Dusts* (n = 648)		Inorganic and Mineral Dusts and Fumes* (n = 1,084)		Metal Dusts and Fumes* (n = 739)		Agricultural Dusts* (n = 261)	
	β (95% CI)	P†	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
BODE Index	**0.34 (0.18 to 0.50)**	**<0.001**	0.17 (−0.01 to 0.35)	0.07	**0.36 (0.19 to 0.52)**	**<0.001**	**0.40 (0.22 to 0.57)**	**<0.001**	0.16 (−0.10 to 0.41)	0.23
mMRC	**0.19 (0.11 to 0.27)**	**<0.001**	0.09 (−0.00 to 0.18)	0.06	**0.19 (0.11 to 0.28)**	**<0.001**	**0.25 (0.16 to 0.34)**	**<0.001**	**0.17 (0.04 to 0.30)**	**0.01**
SGRQ	**6.43 (4.75 to 8.11)**	**<0.001**	**3.78 (1.88 to 5.67)**	**<0.001**	**6.08 (4.35 to 7.81)**	**<0.001**	**5.95 (4.09 to 7.82)**	**<0.001**	**4.51 (1.86 to 7.17)**	**0.001**
CAT	**2.17 (1.49 to 2.84)**	**<0.001**	**0.85 (0.09 to 1.61)**	**0.03**	**1.93 (1.24 to 2.62)**	**<0.001**	**1.65 (0.91 to 2.40)**	**<0.001**	1.02 (−0.04 to 2.08)	0.06
6MWD	**−21.42 (−31.35 to −11.49)**	**<0.001**	−10.65 (−21.78 to 0.49)	0.06	**−18.08 (−28.31 to −7.84)**	**0.001**	**−16.16 (−27.17 to −5.15)**	**0.004**	−0.68 (−16.29 to 14.94)	0.93
%FEV_1	**−4.74 (−6.90 to −2.57)**	**<0.001**	**−2.67 (−5.10 to −0.25)**	**0.03**	**−4.27 (−6.49 to −2.05)**	**<0.001**	**−3.52 (−5.91 to −1.13)**	**0.004**	−2.52 (−5.92 to 0.88)	0.15
% Emphysema‡	0.71 (−0.05 to 1.47)	0.07	0.45 (−0.39 to 1.30)	0.29	0.61 (−0.17 to 1.38)	0.13	0.79 (−0.04 to 1.62)	0.06	0.13 (−1.06 to 1.33)	0.83
Small airways disease§	**2.65 (1.09 to 4.20)**	**0.001**	**1.86 (0.13 to 3.59)**	**0.04**	**2.16 (0.56 to 3.75)**	**0.008**	**1.87 (0.16 to 3.57)**	**0.03**	0.72 (−1.72 to 3.17)	0.56
Large airways disease‖	0.004 (−0.001 to 0.010)	0.15	−0.002 (−0.009 to 0.004)	0.45	0.004 (−0.001 to 0.010)	0.13	0.005 (−0.001 to 0.012)	0.08	−0.006 (−0.015 to 0.003)	0.19
Odds of COPD¶	1.19 (0.99 to 1.43)	0.06	**1.24 (1.00 to 1.52)**	0.05	1.12 (0.93 to 1.36)	0.23	1.14 (0.93 to 1.40)	0.20	1.14 (0.85 to 1.52)	0.39
Odds of exacerbation¶	**1.52 (1.25 to 1.84)**	**<0.001**	**1.35 (1.09 to 1.66)**	**0.006**	**1.50 (1.23 to 1.83)**	**<0.001**	**1.46 (1.18 to 1.80)**	**<0.001**	**1.50 (1.13 to 1.98)**	**0.005**

*Adjusted for age, sex, race, current smoking status, and smoking pack-years. Body mass index and examination site were also included in CT measure models.
†$P < 0.05$ indicated in bold.
‡% Emphysema = total voxels in the field less than −950 HU at total lung capacity.
§Small airways disease = % of total voxels in the field less than −856 HU at residual volume.
‖Large airways disease = Pi10, airway wall thickness (in millimeters).
¶Odds of COPD and odds of exacerbations reported as POR.
%FEV, forced expiratory volume in 1 second; 6MWD, 6-minute walk distance; BODE, Body Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity; CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council questionnaire; SGRQ, St George's Respiratory Questionnaire; VGDF, vapors, gases, dusts, and fumes.

also resulted in statistically significant increases in mMRC scores (β = 0.17; 95% CI, 0.04 to 0.30; $P = 0.01$) and in statistically significant increase of SGRQ scores (β = 4.51; 95% CI, 1.86 to 7.17; $P = 0.001$), which is larger than the MCID. Both of these outcome measures were almost double the increases resulting from ever VGDF exposures. Agricultural dust exposures were not associated with significant increases in any of the CT measures (Table 5).

Composite Hazard Exposure Compared With VGDF

Using the composite assigned exposure variable in the multivariable model resulted in effect sizes that were overall similar though slightly greater than observed when using the ever VGDF variable (Supplemental Digital Content Table 2, http://links.lww.com/JOM/B324).

Effect Modification by Current Smoking Status, Race, and Sex

Current smoking status modified the exposure between gases and vapors, dust and fumes, biological and organic dusts, and ever VGDF exposure and COPD status. In general, former (noncurrent) smokers were more vulnerable to the health effects of occupational exposures as compared with current smokers. There was no significant interaction between mineral and inorganic dusts, metal dusts and fumes, or agricultural dusts and current smoking status. As examples, Figures 1A and 2A show the aPOR for COPD and adjusted difference in BODE Index respectively for current and noncurrent smokers across the occupational exposure categories.

In the main effect model, non-White race was associated with worse COPD outcomes (data not shown). There was evidence of effect modification by race for the exposure categories of gas and vapors, dust and fumes, biological and organic dusts, metal dusts and fumes, and ever VGDF exposure. In general, White participants tended to be more susceptible to the health effects of occupational exposures. There was no significant interaction between race and agricultural dusts. As examples, Figures 1B and 2B show the aPOR for COPD and BODE Index respectively for Whites and non-White participants across the exposure categories.

There was no evidence of effect modification by sex (data not shown).

Association of Duration of Exposure and COPD Status

Within the adjusted models, each additional exposure year was significantly associated with increased prevalence odds of COPD for subject reported wood dust or saw dust exposures (aPOR, 1.03; 95% CI, 1.00 to 1.06; $P = 0.02$). Each additional year of wood dust or saw dust exposure was also significantly associated with decreases in FEV1% predicted (β = −0.29; 95% CI, −0.57 to −0.02; $P = 0.04$). Among the CT measures, each additional year of exposure to wood dust resulted in greater small airways disease (β = 0.2; 95% CI, 0.0 to 0.4; $P = 0.03$). Exposure duration was not statistically significantly related to other outcomes (data not shown).

DISCUSSION

In our study of a large multicenter cohort with extensive clinical phenotyping and detailed occupational exposure questionnaire, we found that several occupational exposure categories were associated with increased respiratory morbidity measures in those with and at risk for COPD. Specific exposure categories of "gases and vapors" and "dust and fumes" exposures resulted in greater impacts on COPD morbidity than the use of self-reported ever VGDF measure. For example, SGRQ values were almost double in several exposure categories (namely gas and vapors) as compared with the ever VGDF, and reductions in 6MWD were close to two times as great for some of the exposure categories (namely, dust and fumes) as the ever VGDF. Furthermore, several occupational exposures were associated with morbidity measures

with effects > the MCID value (ie, quality of life, functional status measures), highlighting that these occupational exposures were associated with effects that are clinically meaningful in the lives of patients with and at risk of COPD. We also found that duration of occupational exposure was a valuable predictor of worse COPD morbidity. This suggests that use of summary markers of occupational exposure risk may fail to capture individuals with meaningful occupational exposures and may underestimate the impact of occupational exposures on respiratory status, while querying about exposures on a more granular level allows for capturing variability between exposures in risk and important clinical status.

Our efforts provide further support to existing research of increased risks associated with occupations as reported through examination of several National Health and Nutrition Examination Study cohorts, [28–31] as well as specific hazards including silica, [32] diesel exhaust, [33] biopersistent granular dust, [34] and pesticides. [35] Our findings for metal dusts and fumes support previously reported evidence of increased morbidity and support the need for additional quantitative exposure studies in these populations. In a case-control study, Kraïm-Leleu et al[36] reported increased COPD OR (aOR, 7.6; 95% CI, 4.5 to 12.9; $P < 0.001$) for metal dusts and fumes from foundry exposure but did not report significant increases for cotton dust from the textile industry.

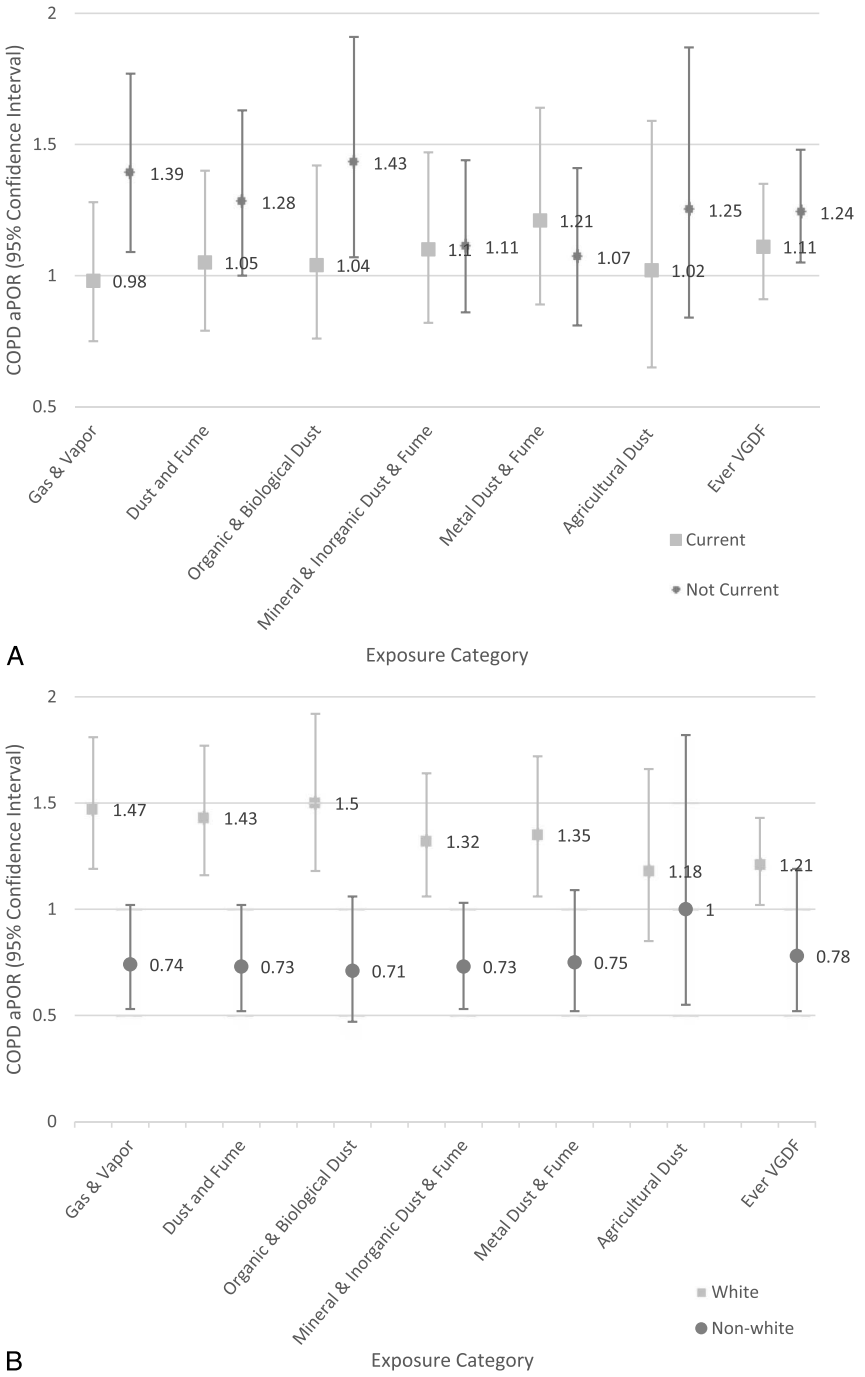

FIGURE 1. Association of occupational exposures with COPD aPOR. Effect modification by cigarette smoke exposure status (A); race (B). A, Effect modification by cigarette smoke exposure status. B, Effect modification by race.

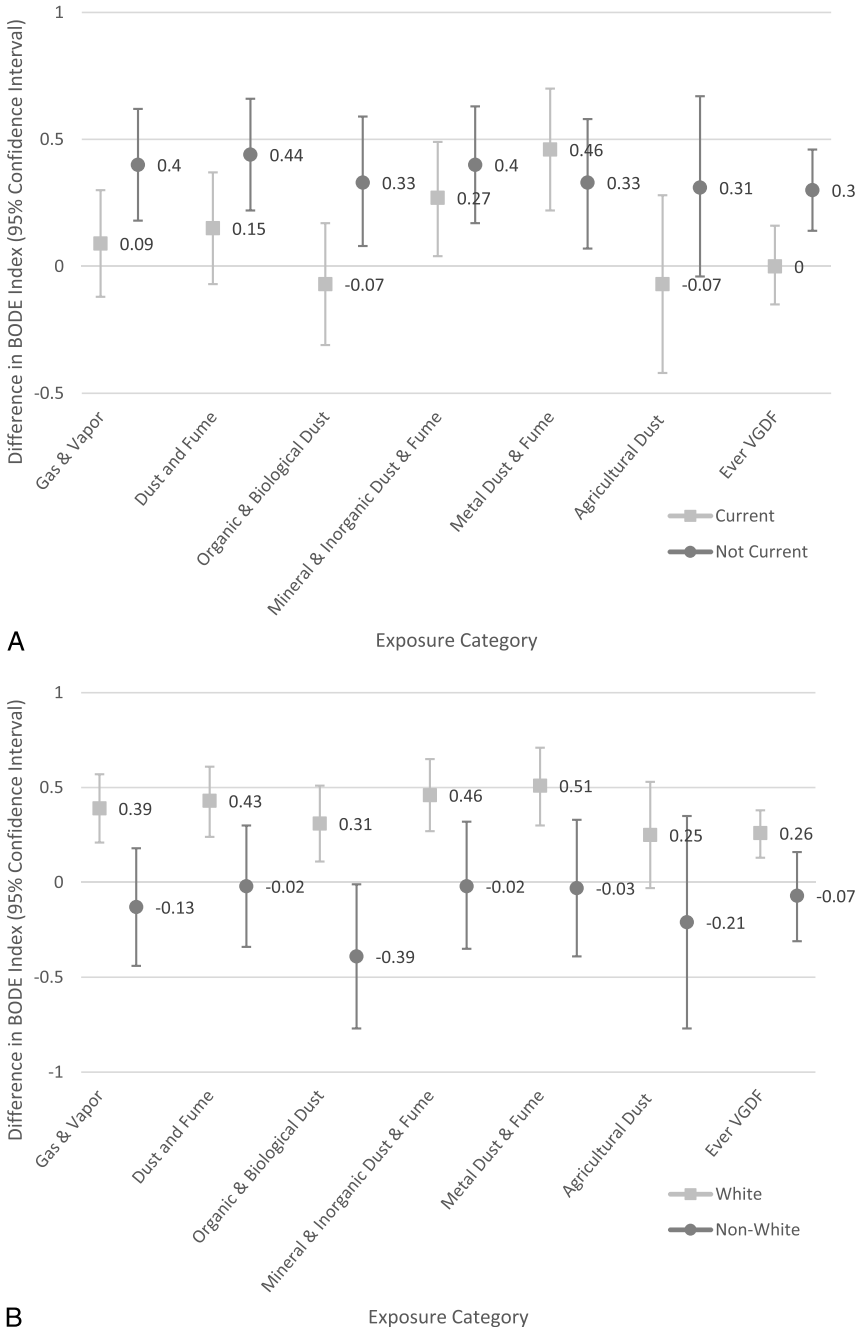

FIGURE 2. Association of occupational exposures with BODE Index. Effect modification by cigarette smoke exposure status (A); race (B). A, Effect modification by cigarette smoke exposure status. B, Effect modification by race.

Koh et al[37] also found increased COPD OR (aOR, 3.91; 95% CI, 1.36 to 13.33) for welding exposures in a cohort study of shipyard workers. Our finding of increased risk for exacerbations from biological dusts further supports Burkes et al[38] reporting of increased odds and incidence of total and severe exacerbations associated with agricultural occupation in the same cohort.

The use of CT measures to understand occupational exposure contributions to COPD is relatively novel. Galbán et al[39] reported using CT measures in the diagnosis of COPD phenotypes and disease progression and recommended their use to assist standard clinical examinations. Occupational exposures to dusts and fumes were reported to have greater % emphysema and gas trapping when compared with no exposure in both women and men. [40] Previous work by our group reported higher emphysema, greater large airways disease, and greater small airways disease with VGDF exposure. [15] As our specific exposures are subsets of the overall ever VGDF exposure, this confirms our analysis.

Current smoking status was an important modifier for morbidity measures with effects generally being larger for former (noncurrent) smokers, although this interaction was not consistently significant across all COPD morbidity measures, nor across all occupational exposure categories. Individuals who were former smokers may either have had to cease smoking due to health impacts to keep working or may have had additional workplace efforts to stop smoking. Conversely,

current smokers may have had limited occupational exposures within the same exposure category or may exhibit some resiliency against the health risks of smoke exposure. [41,42] We found no interaction with sex; this differs from previous study results reported by Paulin et al[9] and may be due to variations in exposure groupings ("ever" exposure captured in this work vs "longest job" in the prior work) and definitions of exacerbation status (any exacerbation in this work vs exacerbations requiring healthcare utilization in the prior work). While non-White race was associated with worse COPD outcomes in the main model, in the separate interaction analysis, we found that race modified the response between occupational exposure and COPD morbidity, such that Whites were more susceptible to the adverse health effects of occupational exposure compared with non-Whites. This may be influenced by actual differences in exposures by individuals reporting the same exposures (ie, carpenter vs a carpenter helper or intensity of employment environment), differences in race demographics across the industries, trades, and occupational exposures represented, selection bias, and/or unmeasured confounding. Further insight into the interactions between race, occupational exposures, and COPD is warranted and beyond the scope of this article.

This study offers two new elements in the approach to examining occupational exposure contributions to COPD. The first is focusing on different exposure classifications and specific hazards versus the more common assessment of exposure to ever VGDF. Associating exposures to occupations and specific tasks where they are understood to occur limits potential recall bias where individuals may not have understood if they had an exposure to VGDF but would remember their occupation and activities. It is also possible that individuals who provide a more granular description of exposure versus ever VGDF may have had more substantial occupational exposures and thus a stronger impact on COPD morbidity. The second, by seeking to understand if exposure duration relates to COPD characteristics, moves away from a dichotomous "exposed or not" variable toward a semiquantitative analysis. Our results of the exposure year analysis shows that exposure duration may be a helpful predictor of COPD risk and morbidity. This begins to treat occupational exposures in a manner analogous to cigarette exposures, characterized in terms of smoking pack-years. As with smoking cessation and prevention efforts, reductions in occupational exposures are the most direct way to reduce disease prevalence and improve health outcomes. The varying impacts across our exposure categories and hazards suggest that workplace exposure control efforts, in even limited areas, may have benefits toward reducing COPD morbidity. Other study strengths include detailed and objective outcome measures and information on important confounders on smoking status and smoking history. We were also able to examine effect modifiers and explore important considerations for patient care through morbidity measures.

Some limitations must be considered when extrapolating our study results. The SPIROMICS is not a population-based study and by design excluded individuals who might have reserved ratio impaired spirometry (PRISm) or other respiratory diseases. [43] Furthermore, while it is difficult to generalize results to a nonsmoking population, our results suggest that occupational exposures have potential for significant impact on clinical outcomes despite significant smoking histories. In addition, the use of exposure years is only a semiquantitative exposure measurement and does not represent airborne hazard concentrations during those years nor inhaled dose. Data on duration of exposure years are limited to a smaller subset of participants who reported information on this variable. In addition, the occupational exposure questionnaires did not seek information regarding use of any personnel protective equipment nor the presence or absence of any other workplace controls that may have impacted these exposures. Finally, knowledge of some of the specific hazard exposures may have been limited or recalled erroneously, especially those that may have occurred decades ago. Furthermore, as the researchers assigned the exposure hazard categories, there is a potential for misclassification as compared with the use of a validated JEM.

In summary, we found that differentiating prior occupational exposure into like categories of gases and vapors and dusts and fumes was associated with increased odds of COPD and worse COPD morbidity. We found prior exposure to gases and vapors and organic and biological dusts was associated with increased odds of COPD and that prior exposures to gases and vapors, mineral and inorganic dusts and fumes, and metal dusts and fumes resulted in increased COPD morbidity. We identified positive associations between select occupational exposures based on years of exposure and BODE Index, % emphysema, large airways disease, and small airways disease when carefully adjusting for important confounders. The use of more refined exposure measures captured additional individuals and allows for better determination of increased variation in risk and important clinical outcomes. Results from our study allow those in the workplace setting to prioritize exposures for control, as well as increasing the potential of earlier targeted clinical interventions for individuals with these exposures.

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