

## Occupational exposures and the risk of COPD: dusty trades revisited

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## ABSTRACT

**Background.** The contribution of occupational exposures to chronic obstructive pulmonary disease (COPD) and, in particular, their potential interaction with cigarette smoking remains underappreciated.

**Methods.** We used data from the FLOW study of 1,202 subjects with COPD (of which 742 had disease classified as Stage II or above by Global Obstructive Lung Disease [GOLD] criteria) and 302 referent subjects matched by age, sex, and race, recruited from a large managed care organization. Occupational exposures were assessed using two methods: self-reported exposure to vapors, gas, dust, or fumes on the longest held job (VGDF) and a job exposure matrix (JEM) for probability of exposure based on occupation. Multivariate analysis was used to control for age, sex, race, and smoking history. The odds ratio (OR) and the adjusted population attributable fraction (PAF) associated with occupational exposure were calculated.

**Results.** VGDF exposure was associated with an increased risk of COPD (OR 2.11; 95% CI 1.59-2.82) and a PAF of 31% (95% CI 22-39%). The risk associated with high probability of workplace exposure by JEM was similar (OR 2.27; 95% CI 1.46-3.52), although the PAF was lower (13%; 95% CI 8 to 18%). These estimates were not substantively different when the analysis was limited to COPD GOLD Stage II or above. Joint exposure to both smoking and occupational factors markedly increased the risk of COPD (OR 14.1; 95% CI 9.33-21.2).

**Conclusions.** Workplace exposures are strongly associated with an increased risk of COPD. On a population level, prevention of both smoking and occupational exposures, and especially both together, is needed to prevent the global burden of disease.

Occupational factors are believed to contribute to the population burden of chronic obstructive pulmonary disease (COPD). The American Thoracic Society conducted a systematic epidemiologic review and concluded that approximately 15% of COPD may be attributable to workplace exposures.<sup>1</sup> A more recent follow-up review provided similar estimates.<sup>2</sup> Despite this research, the role of the workplace in COPD causation is not widely appreciated, especially the combined effects of “dusty trades” and cigarette smoking.

Cigarette smoking is the dominant risk factor for COPD causation and must be considered in any analysis of occupational exposures. Previous estimates of the population attributable fraction (PAF) for occupational exposures and COPD risk have statistically adjusted for smoking.<sup>1,2</sup> Nonetheless, non-smokers are at risk for developing COPD. Recent analyses have estimated that the PAF for occupational exposures among non-smokers ranges from 11 to 53 percent.<sup>3-7</sup> The combined effects of smoking and occupational exposures, however, have not been well characterized, even though delineating these joint impacts could have important ramifications for the prevention and clinical management of COPD.

In a previous national survey-based study of U.S. adults, we estimated that the PAF for occupational exposure and COPD was 9 to 31 percent.<sup>8</sup> We also observed a sharp step-up in COPD risk associated with the combination of smoking and occupational exposure. Two subsequent studies also observed a potential smoking-occupational interaction for chronic bronchitis alone or chronic bronchitis plus airflow obstruction.<sup>9,10</sup> In the current study, we elucidated the separate and combined impact of smoking and occupation on the risk of COPD among persons who were recruited from a large U.S. managed care organization and underwent pulmonary function testing.

## METHODS

### Overview

The current study is a matched case-referent analysis nested within the Function, Living, Outcomes, and Work (FLOW) study of COPD, which is an ongoing prospective cohort study of adult members of an integrated health care delivery system (closed-panel managed care organization) with a physician’s diagnosis of COPD and a matched referent group without COPD. The long-term goal is to determine what factors are responsible for the development of disability in COPD. At baseline assessment, we conducted structured telephone interviews that ascertained COPD status, health status, self-reported functional limitations, and sociodemographic characteristics. Subjects then underwent a research clinic visit that included spirometry and other physical assessments. The study was approved both by the University of California, San Francisco Committee on Human Research and the Kaiser Foundation Research Institute’s institutional review board and all participants provided written informed consent.

### COPD Subject Eligibility

We studied adult members of Kaiser Permanente Medical Care Program (KPMCP), the largest non-profit managed care organization in the United States. In northern California, the KPMCP provides the full spectrum of primary-to-tertiary care to approximately 3.1 million members (25 to 30% of the regional population).<sup>11</sup> The demographic characteristics of KPMCP members are similar to the overall Northern California population, except for the extremes of income distribution.<sup>12</sup>

We identified all adult KPMCP members who were recently treated for COPD using a previously described approach.<sup>13</sup> The age range was restricted to 40-65 years because a key study outcome includes work disability.<sup>14</sup> Using KPMCP computerized databases, we identified all subjects who met each of two criteria: one based on health care utilization and the second based on medication prescribing. The health care utilization criterion was one or more ambulatory visits, emergency department visits, or hospitalizations with a principal International Classification of Disease (ICD-9) diagnosis code for COPD (chronic bronchitis [491], emphysema [492], or COPD [496] during a recent 12 month time period. The medication criterion was two or more prescriptions for a COPD-related medication during a 12 month window beginning 6 months before the index utilization date and ending 6 months after index date. The criterion medications included: inhaled anticholinergic medications, inhaled beta agonists, inhaled corticosteroids, and theophylline. Based on medical record review, we demonstrated that this algorithm is a valid method for identifying adults with COPD.<sup>14</sup> To facilitate attendance at the research clinic, we restricted the sample to persons living within a 30 mile geographic radius of the research clinic where the study examinations took place.

Persons identified by the algorithm who were no longer KPMCP members or who had moved away were considered ineligible for study. The primary care physicians for all patients were contacted and given the opportunity to decline contact of any identified patients under their care. Potential subjects were then contacted by a letter describing the study and given an opportunity to decline participation. Those not declining were then contacted by telephone to arrange an interview. At the end of the interview, subjects were invited to participate in the research clinic visit. Persons who were found at the time of interview to have severe communication difficulties attributable to advanced dementia or aphasia were excluded.

### COPD Subject Participation

A total of 5,800 subjects were initially identified using the computerized algorithm. Of these, 298 died before they could be recruited into the study. Another 1,011 did not meet study inclusion criteria or were excluded at the time of interview contact as noted above. The completion rate for structured telephone interviews was 2,310 out of a remaining eligible group of 4,419 (51%). This is comparable to our earlier cohort study of adult asthma conducted at KPMCP and compares favorably for other survey-based epidemiologic studies conducted in the U.S.<sup>15,16</sup> Among the 2,310 respondents, 112 were not eligible for the clinic visit (8 were subsequently deceased, 10 were no longer Kaiser members, 85 were physically unable to attend, and 9 moved out of the area). Of the 2,198 eligible subjects, 1,216 completed the research clinic visit (55% of those interviewed and eligible). An additional 10 subjects were excluded because they did not meet the GOLD criteria for COPD after interviews and spirometry were performed.<sup>17</sup> Four additional subjects were excluded from this analysis because they could not perform spirometry due to previous tracheostomy placement. Ultimately, there were 1,202 subjects with COPD who completed both interviews and research clinic visits.

Demographic information was available for interviewed subjects from their structured telephone interviews and non-interviewed subjects from Kaiser computerized databases. Compared to subjects who were eligible but not interviewed, interviewed subjects were slightly older (by 0.7 years on average), more likely to be female (59 vs. 51%), and more likely to be white (69 vs. 56%). In terms of race-ethnicity, the two largest minority subgroups were slightly over-represented among those who completed interviews vs. not: (Black / African American 14% vs. 11%, Hispanic 9% vs. 4%). Most of the differences in race were driven by limitations

inherent in the Kaiser computerized databases: the prevalence of unknown race was much higher among those who did not complete interviews (17% vs 0.3%).

Compared to subjects who completed interviews but not the clinic visit, clinic visit attendees were similar in age (mean difference 0.3 years), gender (58% vs. 55% female), and race-ethnicity (67 vs. 61% white). Black or Hispanic subjects were more likely to complete the research clinic visit (17% completed vs. 11% not completed and 9 vs. 5%, respectively).

### Study Referent Group

We aimed to recruit 300 referent subjects without COPD. Using recruitment methods similar to those for COPD subjects, we initially identified 373 referent subjects with no history of utilization for COPD who were matched to subjects with COPD by age, sex, and race. By design, we subsequently excluded 71 subjects who had evidence of airway obstruction ( $FEV_1/FVC < 0.70$ ) at the time of research clinic evaluation, leaving 302 referent subjects for the final analysis.

### Structured Telephone Interviews

All subjects (COPD subjects and non-COPD referents) underwent 30-40 minute structured telephone interviews facilitated with customized computer-assisted telephone interview software. Interviews ascertained a wide range of data potentially relevant to health status. These included items assessing sociodemographic characteristics, cigarette smoking, and occupational histories. As in previous studies, we defined educational attainment as high school or less, some college, or college / graduate degree.<sup>18</sup> Race-ethnicity was categorized as previously described.<sup>18</sup>

Cigarette smoking was measured using questions developed for the National Health Interview Survey and was defined as current smoking, past smoking, or never smoked and, in a secondary analysis, less than or 20 pack years or more smoking.<sup>19</sup>

Open-ended items elicited occupation, industry, and main job duties for the respondent's longest held job. Occupation was then coded using the U.S. 2000 Census codes.<sup>20</sup> Each subject was asked about self-reported exposures using a questionnaire item used in the baseline European Community Respiratory Health Survey (ECRHS I). This asks respondents whether they were exposed to vapors, gas, dust, or fumes (VGDF) on the job.<sup>21</sup>

### Job Exposure Matrix

In addition to self-reported exposure, we also assessed occupational risk using a job exposure matrix (JEM). This JEM was initially developed in an analysis of respiratory disability and later modified to use in asthma- and COPD-specific versions.<sup>8 22-24</sup> The JEM categorizes specific occupations as having a low, intermediate, or high probability of exposure to materials associated with chronic airway disease.

The COPD JEM differs from its asthma JEM counterpart in several ways. In particular, the COPD matrix classifies occupations likely to involve sensitizers (e.g., latex) as low probability for COPD, whereas these exposures are in the high risk category in the asthma-specific JEM. In addition, occupations with a high likelihood of secondhand smoke exposure (e.g., waitresses, bartenders) are defined as having a moderate COPD risk; occupations with diesel exhaust exposure (e.g., truck and heavy equipment operators) and dusty trades (e.g., most construction jobs) are defined as high risk in the COPD-specific JEM.

For this analysis we further adapted the COPD JEM using narrative open text fields of job descriptions to modify classifications otherwise assigned by occupational code alone, a so-called “expert-review” step that has been recommended to improve JEM performance.<sup>25</sup>

### Assessment of Pulmonary Function

To measure pulmonary function, we conducted spirometry according to American Thoracic Society (ATS) Guidelines.<sup>26,27</sup> We used the EasyOne™ Frontline spirometer (ndd Medical Technologies, Chelmsford, MA), which is known for its reliability, accuracy, and durability and has been widely used in epidemiologic research.<sup>28,29</sup> Although no calibration is recommended by the company, we checked the device daily using a 3 liter syringe (Hans-Rudolph, Kansas City, MO, USA). During the study period, the device was always within a range of +/-1%.

To calculate percent predicted pulmonary function values, we used predictive equations derived from NHANES III.<sup>30</sup> Based on FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio, and respiratory symptoms, COPD severity was staged based on NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (stage 0 to IV).<sup>17,31</sup> Because research clinic examinations were conducted by trained non-medical personnel, we did not administer bronchodilators for study purposes. However, 90% of subjects had taken their own short-acting bronchodilator within 4 hours of spirometry or had taken a long-acting bronchodilator earlier in the same day.

### Statistical Analysis

Statistical analysis was conducted using SAS software, version 9.1 (SAS Institute, Inc, Cary, NC) and Stata 10 (College Park, TX). Bivariate comparisons were carried out using t-test for continuous variables and the chi-square test for categorical variables. We used logistic regression analysis to examine the association between self-reported occupational VGDF exposure and the risk of COPD, controlling for age, sex, race, and smoking history (past smoking and current smoking as indicator variables). Education and income were not included in the analysis because they are determinants and consequences of occupational status, respectively, and are therefore on the causal pathway between occupation and COPD (rather than functioning as confounders).<sup>8</sup> In additional parallel analyses, we substituted JEM-assessed occupational risk for self-assessed exposure. We also reanalyzed occupational risk in the never smoking stratum of subjects and in the never smokers combined with very minimal smoking histories (< 5 pack years). In another secondary analysis we re-estimated the main models substituting <20 pack years and ≥20 pack years of smoking, in lieu of the ex-smoking and current smoking indicator variables. We also re-estimated the main models redefining smoking as cumulative pack-years, which had no substantive impact on the results (data not shown).

We calculated the population attributable fraction (also known as the population attributable risk percent or PAR%) to estimate the proportion of COPD prevalence attributable to occupational exposure (measured by self report of VGDF and, separately, by JEM) after adjusting for smoking status and other covariates. The adjusted PAF was estimated from the multivariate logistic regression analysis using the method of Greenland and Drescher.<sup>32</sup>

The interaction between smoking status and occupational VGDF exposure was explicitly evaluated. For these analyses, smoking was dichotomized as ever vs. never and occupational exposure was defined as exposure to VGDF during the longest held job vs not. Therefore, four cells were possible given each dichotomous combination, with the referent category being never smoking and no occupational exposure. We estimated the joint association between smoking and

VGDF as both excess probability of COPD and odds ratio for each smoking-VGDF category, which is modeled after our previous approach.<sup>8</sup>

To evaluate a more severe spectrum of COPD, we repeated our key analyses re-defining COPD as an FEV<sub>1</sub>/FVC ratio <0.70 and FEV<sub>1</sub> < 80% predicted (i.e., GOLD stage II or greater; consistent with the Burden of Lung Disease (BOLD) Study strategy).<sup>33</sup> In these analyses we eliminated subjects with less severe disease.

## RESULTS

### Demographic characteristics, smoking and pulmonary function

COPD cases were similar to referents in terms of age, sex, and race (p>0.20) (Table 1). Those with COPD had significantly lower educational attainment and annual household income (p<0.001). Consistent with the study design, cigarette smoking differed substantially between COPD cases and referents (87% compared to 48% ever smokers). Of 1,202 persons with COPD, 742 (42%) had GOLD Stage II or greater disease severity.

Table 1. Baseline characteristics of FLOW cohort of COPD vs. referent subjects

Characteristic	COPD (n=1,202)	Referents (n=302)	P value
Age in years, mean (SD)	58.2 (6.2)	58.5 (6.2)	0.50
Female, n (%)	691 (57.4%)	185 (61%)	0.23
Race / ethnicity, n (%)			0.96
White, non-hispanic	810 (67%)	200 (66%)	
African-American	206 (17%)	57 (19%)	
Asian / Pacific Islander	35 (3%)	8 (3%)	
Hispanic	111 (9%)	28 (9%)	
Other	40 (3%)	9 (3%)	
Educational attainment, n (%)			<0.0001
High school or less	352 (29%)	42 (14%)	
Some college	524 (44%)	95 (31%)	
College /graduate degree	326 (27%)	165 (55%)	
Household income,* n (%)			<0.0001
Low (<\$20,000)	129 (11%)	9 (3%)	
\$20,000 to \$80,000	699 (58%)	137 (45%)	
High (>\$80,000)	276 (23%)	133 (44%)	
Smoking status, n (%)			<0.0001
Never smoked	165 (13%)	158 (52%)	
Current smoker	393 (33%)	12 (4%)	
Ex-smoker	644 (54%)	132 (44%)	
Smoking in pack years, n (%)			<0.001
None	162 (13%)	158 (52%)	
<20 pack years	627 (52%)	92 (30%)	0.43 <sup>†</sup>
20 pack-years or more	410 (34%)	52 (17%)	

\*98 (8%) of COPD group and 23(8%) of referent group declined to state income

<sup>†</sup> Comparing proportions of <20 v. ≥20 pack years among ever smokers only.

## Occupational characteristics and workplace exposures

Lifetime labor force participation (i.e., ever worked) did not differ statistically between those with COPD and referents, but persons with COPD were less likely to be currently employed ( $p < 0.001$ ) (Table 2). This pattern was similar for the overall COPD group and those with GOLD Stage II and above. As shown in Table 2, occupational exposure was significantly more common in COPD, whether it was ascertained by self-report or JEM ( $p < 0.0001$  for both). Within the COPD group overall, the majority reported VGDF exposure (58%), whereas 32% were assigned to an intermediate or high exposure probability by JEM classification.

Table 2. Employment history and occupational exposures

Measure	COPD*	Referent	P value for comparison
<b>Entire COPD cohort (n=1,202)</b>			
Ever employed	299 (99%)	1194 (99%)	0.55
Currently employed	595 (50%)	190 (63%)	<0.0001
VGDF exposure during longest held job	697 (58%)	117 (39%)	<0.0001
JEM exposure probability			<0.0001
Low	817 (68%)	250 (83%)	
Intermediate	107 (9%)	20 (7%)	
High	278 (23%)	32 (11%)	
<b>GOLD Stage II or higher (n=742)</b>			
Ever employed	737 (99%)	1194 (99%)	0.59
Currently employed	343 (46%)	190 (63%)	<0.0001
VGDF exposure during longest held job	442 (60%)	117 (39%)	<0.0001
JEM exposure probability			<0.0001
Low	495 (67%)	250 (83%)	
Intermediate	70 (9%)	20 (7%)	
High	177 (24%)	32 (11%)	

VGDF = Vapors gas dust or fume on longest held job by self-report

JEM = Job Exposure Matrix for exposure likelihood on longest held job

GOLD = Global Obstructive Lung Disease initiative

\*First set of results are for the entire FLOW cohort of COPD subjects vs. referents; second set of results (lower portion of table) are for  $\geq$ GOLD Stage II COPD vs. referents

## Occupation and the risk for COPD

Adjusted for smoking and other covariates, self-reported VGDF exposure during the longest held job was associated with double the odds of COPD (OR 2.11; 95% CI 1.59-2.82) and a PAF of 31% (95% CI 22-39%) (Table 3). As shown in Table 3, the risk associated with high



probability of exposure by JEM was similar to self-assessed VGDF exposure (OR 2.27; 95% CI 1.46-3.52) although the PAF was lower (13%; 95% CI 8-18%). The lower PAF for JEM-assessed exposure reflects the lower prevalence of exposed COPD cases by this metric. These estimates were not substantively different when the analysis was limited to COPD Gold Stage II or above.

Table 3. Occupational exposures and the risk of COPD

Exposure	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	PAF (95% CI)
<b>Entire FLOW Cohort</b>			
VGDF exposure*	2.18 (1.69 to 2.83)	2.11 (1.59 to 2.82)	31% (22 to 39%)
JEM exposure probability*			
Low (referent)	1.0 (referent)	1.0 (referent)	Referent
Intermediate	1.64 (1.00 to 2.67)	1.27 (0.74 to 2.19)	2% (-2 to 6%)
High	2.66 (1.80 to 3.94)	2.27 (1.46 to 3.52)	13% (8 to 18%)
Cigarette Smoking			
Never (referent)	1.0	1.0	Referent
Current smoker	31 (17 to 58)	31 (17 to 58)	32% (30 to 33%)
Past smoker	4.67 (3.50 to 6.23)	4.52 (3.35 to 6.09)	42% (37 to 46%)
<b>GOLD Stage II or higher</b>			
VGDF exposure*	2.33 (1.77 to 3.06)	2.13 (1.55 to 2.93)	31% (21 to 41%)
JEM exposure probability*			
Low (referent)	1.0 (referent)	1.0 (referent)	Referent
Intermediate	1.77 (1.05 to 2.97)	1.58 (0.88 to 2.84)	3% (-1 to 8%)
High	2.79 (1.86 to 4.19)	2.33 (1.45 to 3.72)	14% (8 to 20%)
Cigarette Smoking			
Never (referent)	1.0	1.0	Referent
Current smoker	45 (24 to 86)	46 (24 to 88)	35% (32 to 37%)
Past smoker	7.05 (5.02 to 9.91)	6.27 (4.42 to 8.90)	46% (41 to 50%)

\*Unadjusted results are from logistic regression models with only that set of variables; adjusted results are from two separate models for exposure, one with VGDF and one with JEM, controlling for age, sex, race, and smoking. Adjusted smoking risk estimates are derived from the VGDF model; results for smoking were not substantively different in JEM model. Results are shown separately for the entire cohort and the subset of subjects GOLD Stage II or greater together with referents.

PAF = population attributable fraction, based on multivariate analysis.

Cigarette smoking was strongly associated with the risk of COPD (Table 3). The combined PAF for smoking (current and past) was 74% for the entire cohort and 81% for COPD GOLD stage II and above. Re-estimating the models using smoking duration-intensity (dichotomized as <20 and ≥20 pack years) did not substantively alter the occupational risk estimates (data not shown).

Among lifelong never smokers (n=323), VGDF exposure during the longest held job was associated with a greater risk of COPD after controlling for covariates (OR 2.0; 95% CI 1.28-3.18). The estimated PAF in this stratum was 26% (95% CI 10-40%). Although there was no

clear association between the intermediate JEM category and COPD risk (OR 0.79; 95% CI 0.29-2.20), the high JEM category appeared to be related to a higher risk of COPD (OR 1.58; 95% CI 0.72-3.50). When the non-smoker stratum was expanded to include both never smokers and also those with minimal cumulative lifetime smoking (<5 pack years) (n=618), the high JEM category was more strongly associated with the risk of COPD (OR 2.51; 95% CI 1.30-4.84 and attributable fraction 13%; 95% CI 6-19%).

### Joint influence of occupational exposures and smoking

We observed a step-up in risk associated with combined occupational and smoking exposures (Table 4). Those reporting VGDF exposure alone had double the odds of COPD compared to those with neither occupational exposures nor smoking risk (OR 1.98; 95% CI 1.26-3.09). Those with combined exposure had a 14-fold increased risk of COPD, whereas smoking alone was associated with a 7-fold increased risk. A similar magnitude of step-up was evident based on JEM exposure assessment. The excess probability analysis indicates that joint risk for smoking and occupational exposure is additive when COPD was defined as GOLD Stage II or higher and slightly less than additive in the entire FLOW cohort. Either way, the joint exposure to smoking and occupational exposures was related to a marked increase in risk of COPD.

Table 4. Joint associations between smoking and occupational exposure with COPD

Cigarette smoking status/ occupational exposure	Total number of subjects (COPD + referent)	Probability of COPD	Excess probability*	Crude OR	Adjusted OR
Entire FLOW cohort					
Never/no	178	0.44	0	1.0	1.0
Never/yes	145	0.60	0.16	1.92 (1.23 to 3.00)	1.98 (1.26 to 3.09)
Ever/no	512	0.83	0.40	6.44 (4.42 to 9.39)	6.71 (4.58 to 9.82)
Ever/yes	669	0.91	0.47	13.3 (8.90 to 19.8)	14.1 (9.33 to 21.2)
GOLD Stage II or higher					
Never/no	136	0.26	0	1.0	1.0
Never/yes	94	0.38	0.12	1.72 (0.98 to 3.03)	1.69 (0.96 to 2.97)
Ever/no	349	0.76	0.49	8.63 (5.49 to 13.6)	8.31 (5.27 to 13.1)
Ever/yes	465	0.87	0.61	19.1 (12.0 to 30.5)	18.7 (11.6 to 30.0)

\*difference in unadjusted probability of COPD compared to referent group – rounding error accounts for lack of agreement in some cells

Adjusted odds ratio controls for age, sex, and race in addition to smoking status.

Excess probability results indicate that joint risk for smoking and occupational exposure is additive when COPD was defined as GOLD Stage II or higher, whereas it is slightly less than additive in the entire FLOW cohort. For example, in the GOLD Stage II or higher group, the joint occurrence of smoking and occupational exposure (excess probability of 0.61) is equal to

the sum of smoking alone plus occupation alone (excess probabilities  $0.49 + 0.12 = 0.61$ ) which is consistent with an additive interaction.

## DISCUSSION

We found that occupational exposures were strongly associated with the risk of developing COPD. Depending on the workplace exposure metric employed, the PAF ranged between 15% and 31% after controlling for smoking and other covariates. Exposure to both smoking and occupational factors portended an especially high risk of COPD. The joint analysis of smoking and workplace exposures implies that elimination of one, but not the other risk, will not be fully effective for reducing the burden of COPD in the population.

Our study advances the field by providing important new evidence that occupational exposures contribute to the overall burden of COPD. The current results are highly similar to our previous study, which had a different sampling scheme (population-based sampling of the U.S. population vs. patients from a managed care organization) and COPD definition (self-reported diagnosis of chronic bronchitis, emphysema, or COPD itself vs. GOLD definition based on pulmonary function).<sup>8</sup> Our results are also consistent with a recent Kaiser Permanente study from the Northwestern U.S. that identified COPD cases using administrative data and used an exposure assessment method that was a hybrid between the JEM and self-reported exposure metrics that we utilized.<sup>7</sup> This study found a smoking-adjusted PAF of 24%, which is midway between our two estimates of 13% (VGDF) and 34% (JEM). Moreover, our findings are well within the range of other reports using a variety of different approaches, providing critical evidence for the coherence of the association between occupation and COPD.<sup>1-6 10</sup>

We found that the joint exposure to smoking and occupational factors combined to increase the risk of COPD. This observation extends our earlier results in a different population-based sample in which COPD was based on survey responses and not spirometry.<sup>8</sup> Two other studies have also found interaction effects between smoking and occupational exposure for the risk of chronic bronchitis or chronic bronchitis plus airway obstruction (GOLD stage II or greater).<sup>9 10</sup> In the latter study, the combination of smoking and occupational exposure was associated with a nearly five-fold increase in the risk of COPD.<sup>9</sup> Our findings further establish the joint risk of smoking and occupational exposures in a study that rigorously defined COPD based on a physician diagnosis of COPD, medical treatment for the condition, and objective evidence of airway obstruction.

A key study strength is its recruitment of a large sample of COPD patients with a broad spectrum of disease severity, ranging from mild to severe, and the examination of matched referent subjects drawn from the same source population. Availability of pulmonary function testing on all subjects also enables more robust conclusions about how much COPD is attributable to occupational exposures.

Our study is also subject to several limitations. Misclassification of COPD cases could have occurred. Mitigating this limitation, all patients were required to have health care utilization for COPD, a physician diagnosis of the condition, and medical treatment of the disease. Moreover, we previously demonstrated the validity of our approach using medical record review.<sup>14</sup> In addition, the observed lifetime smoking prevalence in our COPD group was similar to that in other population-based epidemiologic studies of COPD, further supporting the diagnosis of COPD rather than another condition.<sup>34 35</sup> Finally, when we limited the definition of COPD to more severe disease based on spirometry (GOLD Stage II or greater), the results were not substantively affected. In sum, we have a high degree of confidence that our results are not significantly affected by misclassification bias.

Recruitment from a large health plan should also help ensure that our results are applicable to patients who are treated for COPD in the general population. However, it is possible that the PAF calculated from members of a managed care organization could differ from a general population-based sample. For example, if patients with occupationally-caused COPD left the workforce and consequently lost their health plan membership, our PAF estimate could actually underestimate the true occupational burden of COPD. Although the direction and magnitude of any bias cannot be fully quantified, we believe that it is likely small because KPMCP members are highly similar to the regional population.<sup>12</sup> Nonetheless, we acknowledge the potential pitfalls of generalizing findings from a regional U.S. study to other geographic locations.

Selection bias could have been introduced by non-participation in the study. There were some differences among subjects who did and did not participate in the interviews and clinic visits, but they were modest in scope and not likely to substantively affect the relation between occupational exposure and COPD. Nonetheless, we acknowledge the potential for selection bias as a limitation of our study.

Exposure misclassification was mitigated by our dual approach using independent exposure measures (VGDF and JEM). VGDF could be affected by either non-differential misclassification, which would bias toward the null, or differential misclassification if patients with COPD were more likely to remember and report VGDF exposure than those without COPD.<sup>36</sup> The JEM is more likely to randomly misclassify exposure (i.e., non-differential) and bias toward the null. In this sense, the PAF estimates derived from JEM and VGDF comprise a realistic range for the occupational contribution to COPD risk. Assessment of occupational exposure during the longest held job helped ensure that exposure preceded COPD onset, even though we did not have detailed information about the temporal sequence of COPD incidence.<sup>37</sup> Although we examined COPD cases and referent subjects at a single point in time, longitudinal follow-up of the cohort may yield additional exposure-response insights.

More than twenty years ago, the relationship between dusty trades and COPD was highlighted by Becklake.<sup>38</sup> Our study, taken together with the earlier literature, supports the likely causal nature of that association. Moreover, the findings indicate that smoking and occupation are powerful and interacting factors for developing COPD.

These results have shared relevance both for public health advocates who focus on primary prevention of the disease and clinicians who treat patients at risk for COPD and its progression. Public health efforts to prevent and treat COPD must target both smoking cessation and the reduction of adverse workplace exposures. Addressing one without the other will not effectively ameliorate the population burden of COPD. Clinicians should be alert to high risk occupational exposures in their patients. In patients employed in high risk occupations, providers should consider targeted history taking, symptom assessment, and spirometric evaluation in order to identify early stage disease and prevent its progression by reduction of relevant workplace exposures.<sup>39</sup>

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