Further Exploration of the Links between Occupational Exposure and Chronic Obstructive Pulmonary Disease

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Abstract

Objective—To examine occupational risk for COPD.

Methods—We randomly recruited 233 subjects aged 55-75 reporting a physician's diagnosis of COPD, emphysema or chronic bronchitis. Interviews assessed cigarette smoking and longest-held job, identifying exposure to vapors, gas, dust, or fumes (VGDF). Lung function was assessed in n=138. Comparison data were derived from a sample of referents without COPD.

Results—VGDF was reported by 123 (53%) of 233 cases vs. 577 (34%) of 1709 referents. VGDF was associated with COPD (Odds Ratio [OR] 2.5; 95% CI 1.9 to 3.4); the population attributable fraction [PAF] was 32%. In the lung function subset, the FEV_1/FVC was <70% in 79 (57%); 35 (44%) reported VGDF associated with an OR=1.6 (95% CI 0.99 to 2.6) and PAF 17%.

Conclusions—These data support an important role for occupational exposures in COPD.

Keywords

COPD; chronic bronchitis; occupation; attributable fraction

A growing body of evidence supports the link between occupational exposures and COPD. Historically, key evidence to support this association has been industry specific, in particular analyses of dust-years of exposure in coal or gold mining in relation to airflow obstruction.[1,2] In more recent years, however, a growing number of investigations has addressed the risk of COPD from work-related exposures across multiple industries and occupations. This approach, frequently defining risk as survey-based reports of exposure to vapors, gas, dust, or fumes

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(VGDF), has allowed the estimation of risk from a population-based perspective, quantified as the population attributable fraction (PAF). Two systematic reviews of the epidemiological literature have found the PAF for the occupational exposure contribution to the population burden of COPD is approximately 15%.[3,4] A recent international ecological analysis of this question indicated that the association between occupational exposure and COPD prevalence is a global phenomenon with an impact on women and men in countries with both more-developed and less-developed economies.[5]

Risk estimates of occupational exposure have taken into account the concomitant effect of cigarette smoking on population health, which is by far the dominant risk factor for COPD, with an estimated PAF of 80-90%. At the same time, evidence is emerging that the combined effects of occupational exposures and smoking are may be more than additive. In two previous analyses in separate cohorts, we found combined occupational exposure and smoking markedly increased the odds ratios (OR's) for COPD to 18-fold risk compared to non-exposed non-smokers, a modestly supra-additive effect.[6,7] Using a recently recruited, community-based cohort of adults with COPD, we re-assessed the relationship between occupational exposure and COPD, including potential combined effects with smoking. We wished to see whether our findings would be consistent with other recent estimates of occupational risk for COPD risk, further supporting a causal interpretation of this association.

Methods

Subjects with COPD

Subjects with COPD were newly recruited in 2006 to supplement an ongoing cohort study of airway disease.[8] Random digit dialing identified households with at least one person aged 55-75 with self-report of a physician-reported diagnosis of COPD, emphysema, chronic bronchitis, or asthma. Sampling was limited to residential land line telephones (cellular phones excluded) in northern California. Of 701 potentially eligible households, 375 (53%) completed initial interviews. Of these, 291 reported at least one of three COPD-defining physician's diagnoses: COPD, emphysema, or chronic bronchitis. The diagnoses could be overlapping, that is, multiple COPD-defining diagnoses could be reported (e.g., COPD and chronic bronchitis). Although asthma could also be reported, those reporting only a physician's diagnosis of asthma alone and not a COPD-defining condition were excluded from this analysis. We did not ascertain other respiratory diagnoses associated with obstruction (e.g., bronchiectasis or bronchiolitis obliterans). Of the 291 cases with one of the three COPD-defining diagnoses, 233 (80%) were successfully re-interviewed one year later (2007) when the occupational exposure data were obtained.

Home Assessments in COPD

COPD subjects were eligible for home-based evaluations conducted by a trained staff team (completed by 138 [59%] of those with COPD). Home visits were randomized to occur after the baseline or first follow-up interview and were approximately 2 hours in duration, including lung function testing. Spirometry was performed using an EasyOne™ spirometer (ndd Medical Technologies, Chelmsford, MA, USA) that met American Thoracic Society (ATS) 1994 spirometry standards and a standard protocol that conformed to ATS performance guidelines.[13,14] Subjects used their normal inhaler medications as scheduled on the day of the home visit; additional bronchodilators were not systematically administered prior to testing. Percent predicted values were calculated using the race-ethnicity specific predictive equations derived from NHANES III.[15] The protocol was approved by institutional review for research on human subjects.

Subjects without COPD

Referents without COPD had been previously studied; they were recruited initially in 2001. Random digit dialing was used to identify households with adults aged 55-75 not reporting a COPD-defining diagnosis, an approach similar to that used for the cases described above. Referent recruitment, however, was not restricted to northern California, but rather carried out throughout the 48 contiguous U.S. states, also including over-sampling from areas with increased COPD mortality rates. The results of this initial recruitment (overall participation rate 53% among households with an eligible respondent present) have been previously reported.[6]

Interviews

At recruitment for cases and referents and, for cases, at one year follow-up, subjects participated in structured interviews performed by trained personnel using computer-assisted telephone interviewing (CATI) software. Essentially the same interview protocol was used both for those with COPD newly interviewed in 2006-2007 and the referents who had been interviewed 5 to 6 years previously. Interviews, approximately 35 minutes long, included socio-demographics, smoking, and condition-related symptoms and medications. Standard items defined ongoing chronic bronchitis (three months of productive cough for each of the last 2 years). The baseline interviews for referents and the follow-up interview for the COPD group included an occupational exposure history battery. Those with any history of labor force participation were asked to identify the occupation, industry and typical duties of their longest-held job. This was asked using open-ended questions with narrative responses that were reviewed and classified using 2000 Census codes.[9]

Measurement of Occupational Exposure

We ascertained exposure in each subject's longest-held job using two approaches, separately and combined. We asked, "Does/did this job expose you to vapors, gas, dust, or fumes?" (VGDF).[10] This survey item does not provide specific examples of occupations, industries, or exposures as interviewing prompts, allowing for potentially broad interpretation on the part of respondents. In addition to self-reported VGDF exposure, we also classified jobs according to their inherent exposure risk using a job exposure matrix (JEM). To create the JEM, we adapted a classification originally used to analyze data from the Swedish component of the European Community Respiratory Health Survey.[11] The initial classification was based on 3-digit occupational code, which provides a moderate level of detail (for example, biological technicians are differentiated from chemical technicians and agricultural and food science technicians; technicians in all cases are coded differently than managers). The JEM, linked to each code, classified each subject as being of low, intermediate, or high probability of having had a COPD-related exposure on the longest-held job. Next, we used an expert review approach to modify the JEM assignment if it appeared to be inconsistent with the specific details of the job contained in the open-ended narrative of job duties that was elicited from respondents.[10,12] For example, the classification "Managers, All Other" (Code 043), which would have been assigned a default low exposure category was upgraded to "intermediate" on the basis of open-ended text indicating the subject worked as a manager of coal mine. Additional details of the JEM protocol are available form the authors.

Finally, we also created a more conservative definition of exposure based on both report of VGDF and JEM assignment in the high likelihood of exposure category.

Data Analysis

We used the chi square or chi square test for trend to assess differences between subjects with COPD based on report of a physician's diagnosis and referents. We used the same approach to

test the differences between subjects who did and did not participate in the homes visits and between subjects defined as having COPD based on report of a COPD diagnosis and the confirmatory findings of either spirometry showing airflow obstruction (Forced Expiratory Volume in one second percent [FEV_1] over Forced Vital Capacity [FVC] <70% (consistent with the Global Initiative for Chronic Lung Disease (GOLD) Stage I or greater categorization[16]) or a questionnaire-based diagnosis symptomatic chronic bronchitis (productive cough for three month's duration in two consecutive years), compared to all other subjects with neither characteristic. We used multiple logistic regression analysis to estimate the association between occupational exposure and COPD, taking into account age, sex, race-ethnicity, and smoking status (current smokers and former smokers as two indicator variables). We tested three separate models defining exposure as reported VDGF, as exposure likelihood by JEM (moderate and high exposure as two indicator variables), and combined VGDF-JEM high exposure likelihood (versus any other exposure status). In addition to the OR, we estimated the PAF associated with these occupational exposure factors.[17] These multiple logistic regression analyses were carried out using increasingly more conservative definitions of disease: all COPD (n=233 cases); after excluding chronic bronchitis alone (n=133 cases); after excluding those without obstruction by spirometry or ongoing chronic bronchitis by questionnaire (n=99 cases); and finally, excluding those with ongoing chronic bronchitis alone (n=79 cases). Using the latter two conservative definitions of disease, as well as a further restricted definition of COPD based on FEV1/FVC <70% and FEV1 % predicted less than 80% (i.e., consistent with GOLD Stage II COPD or greater). In these analyses we assessed the potential interaction of smoking and VGDF exposure for COPD by categorizing subjects into four potential groups: up to 10 pack-years smoking without VGDF exposure (the referent category); up to 10 pack-years with VGDF exposure; ≥10 pack-years without VGDF exposure; and both ≥10 pack-years smoking and VGDF exposure. The latter three indicator variables were tested in a multiple logistic regression analysis that also included age, sex, and race-ethnicity.

Results

Diagnoses, Demographics, and Exposure

Of 233 cases included, the conditions reported were: COPD (84; 36%) emphysema (89; 38%), and chronic bronchitis 161 (69%). Among the cases there were 99 (42%) who reported chronic bronchitis as their sole COPD-defining condition. Among 134 (58%) reporting COPD or emphysema, COPD was reported by 84 (63% of 134) and emphysema by 89 (66% of 134); both diagnoses were reported by39 (29% of 134) Among the 134, 62 (46%) reported concomitant chronic bronchitis.

Half of the cases were in the 66-75 year age range at the time of recruitment; this age distribution was older than that of the 1709 referents included in the analysis (Table 1). The proportion of females among the cases was also higher than among referents; race-ethnicity did not differ statistically by case status. There were more persons with a history of smoking among the cases of COPD (76%) than among referents (56%). Self-reported VGDF exposure was higher among cases compared to referents (53% v. 34%; p<0.001), while exposure likelihood based on a JEM approach did not differ significantly.

COPD Risk, All Cases vs. Referents

The magnitude of occupationally-associated COPD risk varied in relation to the metric used to quantify risk and the definition of disease (Table 2). Using a definition of disease including physician diagnosis of chronic bronchitis, VGDF was associated with more than a doubling of the odds of COPD (OR = 2.5; 95% CI 1.9 to 3.4) and accounted for almost a third of the cases (PAF= 32%). Although JEM-based exposure alone was not associated with significantly

increased odds of disease, when exposure was defined conservatively by both VGDF and high-exposure likelihood JEM, this was associated with elevated COPD risk (OR = 1.8; 95% CI 1.1 to 3.1) and an estimated PAF = 5%. Re-analysis following exclusion of cases with chronic bronchitis alone is shown in the bottom half of Table 2. In that analysis, VGDF remained associated with COPD (OR = 2.1; PAF = 25%), but none of the JEM-based exposures was associated with a statistically significant increased odds of disease.

COPD Risk for Cases Defined by Spirometry and Symptoms

There were 138 of 233 cases studied (59%) who participated in home visits. Differences between these two groups are shown in Table 3. There were no significant differences in demographic, diagnostic, or exposure parameters by home visit status. Of 138 cases with home visit spirometry data, 79 manifested airflow obstruction (FEV1/FVC < 70%); another 20 subjects who did not meet this cut-off did meet standard criteria for active chronic bronchitis based on their structured interview responses, for a total of 99 subjects with COPD by one of these measures. The differences between these 99 cases and the remaining 134 cases are also presented in Table 3. The group defined by lung function or ongoing symptoms were older and more likely to report a physician's diagnosis of COPD or emphysema.

For the 99 cases of COPD defined by airflow obstruction or active chronic bronchitis symptoms, VGDF was associated with a doubling of the odds of disease (OR = 2.1; 95% CI 1.3 to 3.2); the estimated PAF was 25% (95% CI 8 to 39%). Exclusion of those with current chronic bronchitis only but not obstruction (retained case n=79) yielded a lower point estimate of risk with wider confidence intervals that did not exclude the no effect level (OR = 1.6; 95% CI 0.99 to 2.6); the estimated PAF was 17% (95% CI -3 to 32%). The odds of COPD associated with JEM-based exposure based this case definition were marginally elevated and not statistically significant (data not shown).

Combined Exposure and Cigarette Smoking

We defined four categories of combined occupational exposure (based on VGDF) and cigarette smoking (based on a cut-off of 10 pack years). There was one case and 57 referents with a history of smoking lacking data for cumulative pack-years of exposure. Among 98 cases (Table 4), VGDF alone was associated with elevated risk of COPD, with a point estimate was similar to that of smoking alone (OR = 3.2 compared to OR = 3.3). Combined exposure was associated with a modest step-up in risk (OR = 5.6), but less than the cross-product of the component main effect OR's (i.e., somewhat less than additive and not multiplicative). Limiting the analysis to the 78 cases with airflow obstruction (GOLD ≥ Stage I) and smoking intensity data or further limiting the analysis to the 67 cases with more severe COPD (GOLD ≥ Stage II) also yielded findings that were somewhat less than additive for combined occupational and smoking exposure.

Discussion

These data are consistent with a previous analysis we carried out using interview data from the same referent population use in a study with an entirely different group of COPD cases whose occupational exposures had been similarly characterized. In that previous investigation, VGDF was associated with a doubling of the odds of COPD (OR = 2.0) and a PAF of 20%.[6] The current analysis also complements the results we reported from another, clinically- and spirometrically-defined COPD cohort in which the VGDF-related risk also was doubled (OR= 2.1) and the PAF was 31%.[7] Moreover, the current study fits in well with summary data generated through systematic reviews of multiple studies of occupational exposures in COPD; two such reviews have both concluded that approximately 15% of COPD is attributed to workplace factors.[3,4]

In both of the previous studies alluded to above, however, there was evidence that combined occupational exposure and smoking manifest an effect that was more than additive[6,7] whereas we observed a somewhat less than additive effect. The current analysis, however, differs methodologically from those studies by combining never smokers with light smokers (<10 pack-years) as the referent category. This was necessitated by limited numbers of never-smokers with disease. This is a relatively small study, with a further reduction in study numbers for the subset with spirometry that was obtained through home visits. The limited number of cases limits study power to examine certain questions, especially disease among non-smokers, as noted, or the ability to reliably carry out analyses stratified by sex or age groups. Although the small study numbers contribute to the wide confidence intervals for certain estimates, this should not have led to the positive findings that were observed in terms of statistical significance (alpha error).

Another limitation is the national sampling basis of the referents compared to the regional (northern California) derivation of the cases, along with the temporal lag in sampling of more than five years. This may have accounted for the relatively weak JEM-based associations that we observed, given the narrower range and different distribution of occupations likely on a regional compared to national basis (although migration to California after a longest-held job would have blunted this effect). Certainly, the geographic factor may limit the ability to generalize these findings to other locations. Moreover, since the referents were interviewed earlier in time and were somewhat younger, (although like the cases, the referents were approaching or past the age typical of retirement), they might have gone on to receive a COPD diagnosis after the date at which they were studied. This could have led to systematic misclassification of cases as referents, biasing our findings toward the null. We do not have follow-up data that would allow us to analyze this further. In addition, we did not analyze years of employment at the longest held job as a modifying factor or separately analyze broad classes of occupation (for example blue collar trades) of industry of employment.

Reporting bias is another consideration when using subject-reported VGDF exposure. We have previously analyzed this question in depth, using data from a different cohort study of adults with asthma.[18] We found that self-reported VGDF was fairly sensitive measured against JEM-defined exposure as the gold standard. More importantly, compared to asthma, rhinitis (a less severe condition) was more likely to lead to over-reporting of VGDF, arguing against reporting bias driven by disease severity. In a previous analysis of data from the COPD cohort, based on the original baseline survey, we showed that the single VGDF item performs well (sensitivity 69%; specificity 88%) against a checklist of 16 specific exposures including subsets of irritant exposures, and organic and inorganic dusts and fumes.[10]

We did not have medical records from which to verify the reported physician diagnosis. We addressed this limitation, in part, through our analysis of the subset of cases defined either by airflow obstruction by spirometry or the standard questionnaire criterion for chronic bronchitis.

In summary, these findings add yet another positive study to a growing body of evidence indicating that occupational exposures are indeed a risk factor for COPD. A number of questions arise out of this central observation, including whether or not there is a different pattern of risk for chronic bronchitis as compared to airflow obstruction and the role that sex, duration and type of exposure and other co-factors may play in modifying occupational risks. In particular, the potential interplay between active smoking, which is by far the dominant risk factor in COPD causation, and occupational exposure remains to be more fully explored. This is important for improved prevention efforts, clinical diagnosis, management, and, from a societal point of view, attribution of cause and apportionment of the costs of preventing and treating illness.

Acknowledgments

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Table 1

Demographics, Smoking and Occupational Exposure among Cases and Referents

Subject Characteristics	COPD (n=233) N (%)	Referents (n=1709) N (%)	P value
Age			0.001[*]
55-60 years	59 (25%)	612 (36%)	
61-65 years	59 (25%)	416 (24%)	
66-75	115 (50%)	681 (40%)	
Female	148 (64%)	951 (56%)	0.03
White, Non-Hispanic	204 (88%)	1433 (84%)	0.17
Smoking Status			<0.001
Never smoker	55 (24%)	748 (44%)	
Current smoker	40 (17%)	279 (16%)	
Past smoker	138 (59%)	682 (40%)	
Exposure on Longest-Held Job			
Self-reported VGDF	123 (53%)	577 (34%)	<0.001
Exposure Likelihood by Job Exposure Matrix			0.12
Low	169 (72%)	1189 (70%)	
Moderate	39 (17%)	376 (22%)	
High	25 (11%)	144 (8%)	
VGDF and High JEM Exposure	23 (10%)	115 (7%)	0.10

Of those with COPD, reported physicians diagnoses (could be multiple) were COPD 84 (36%); emphysema 89 (38%), and chronic bronchitis 123 (53%). Chronic bronchitis alone was reported by 99 subjects.

[*] Chi square test for trend.

Table 2

Occupational Risk of COPD using Differing Exposure Metrics

Exposure	Occupational Risk of COPD	
	OR (95% CI)	Population Attributable Fraction [PAF] (95% CI)
All Cases (n=233)		
Exposure Measures		
Model 1: VGDF	2.5 (1.9 to 3.4)	32% (21 to 41%)
Model 2: JEM		
Low	1.0 (Referent)	--
Moderate	0.8 (0.5 to 1.1)	0
High	1.5 (0.9 to 2.4)	3% (-2 to 9%)
Model 3: VGDF and High JEM	1.8 (1.1 to 3.1)	5% (0 to 9%)
COPD Alone[*] (n=134)		
Exposure Measures		
Model 1: VGDF	2.1 (1.4 to 3.0)	25% (11 to 38%)
Model 2: JEM		
Low	1.0 (Referent)	--
Moderate	0.7 (0.4 to 1.1)	0
High	1.2 (0.6 to 2.3)	4% (-7 to 9%)
Model 3: VGDF and High JEM	1.6 (0.8 to 3.1)	4% (-3 to11%)

[*] Excludes 99 cases with physician reported chronic bronchitis without concomitant COPD or emphysema

All models include age, sex, race-ethnicity, and smoking status consistent with classifications as shown in Table 1.

Table 3

Demographic, Airway Disease and Exposure for Cases with and without Home Visits and with or without Disease defined by Airflow Obstruction by Spirometry or Chronic Bronchitis Symptoms by Survey

	Home Visit (n=138)	No Home Visit (n=95)	P value	FEV$_1$/FVC<0.70 or CB (n=99)	All Others* (n=134)	P value
Age			0.48			0.01
55-60 years	31(22%)	28(29%)		17 (17%)	42 (31%)	
61-65 years	36 (26%)	23 (24%)		22 (22%)	37 (28%)	
66-75	71 (51%)	44(46%)		60 (61%)	55 (41%)	
Female	86(62%)	62 (65%)	0.75	60 (61%)	88 (66%)	0.51
White, Non-Hispanic	120 (87%)	84 (88%)	0.90	88 (89%)	116 (87%)	0.74
Smoking Status			0.21			0.06
Never smoker	32 (23%)	23 (24%)		20 (20%)	35 (26%)	
Current smoker	19 (14%)	21 (22%)		12 (12%)	28 (21%)	
Past smoker	87 (63%)	51 (54%)		67 (68%)	71 (53%)	
Diagnosis						
COPD	49 (36%)	35 (37%)	0.94	41 (41%)	43 (32%)	0.18
Emphysema	55 (40%)	34 (36%)	0.62	50 (51%)	39 (29%)	0.001
Chronic Bronchitis	92 (67%)	69 (73%)	0.41	60 (61%)	101 (75%)	0.02
Exposure						
Self-reported VGDF	69 (50%)	54 (57%)	0.37	48 (48%)	75 (56%)	0.32
JEM Assignment			0.77			0.48
Low	99 (72%)	70 (74%)		69 (70%)	100 (75%)	
Moderate	25 (18%)	14 (15%)		20 (20%)	19 (14%)	
High	14 (10%)	11 (12%)		10 (10%)	15 (11%)	
VGDF + High JEM	13 (9%)	10 (11%)	0.96	9 (9%)	14 (10%)	0.90

*
95 did not participate in the home visit and thus were without lung function data and 39 did complete home visits but met neither of the two criteria: airflow obstruction (FEV$_1$/FVC ≥ 0.70) or productive cough for three months in row over the previous two years by questionnaire (CB).

Table 4

Combined Cigarette Smoking and Occupational Risk

Cigarette Smoking and Occupational Exposure Categories [case number]	OR (95% CI)
Model I: Cases = COPD by Spirometry ≥ GOLD I or Current Chronic Bronchitis	Risk of COPD or Bronchitis (Cases=98; Referents=1652)
Minimal Smoking (Never up to 10 Pack Years), No Exposure [n=18 cases]	1.0 (Referent)
Minimal Smoking; VGDF Exposure [n=20 cases]	3.2 (1.6 to 6.2)
Smoker (> 10 Pack years); No VGDF Exposure [n=32 cases]	3.3 (1.8 to 5.9)
Smoker and VGDF Exposure [n=28 cases]	5.6 (2.9 to 5.6)
Model 2: Cases = COPD by Spirometry ≥ GOLD I	Risk of COPD[*] (Cases=78; Referents=1652)
Minimal Smoking (Never up to 10 Pack Years), No Exposure [n=14 cases]	1.0 (Referent)
Minimal Smoking; VGDF Exposure [n=10 cases]	2.0 (0.9 to 4.6)
Smoker (> 10 Pack years); No VGDF Exposure [n=29 cases]	3.7 (1.9 to 7.1)
Smoker and VGDF Exposure [n=25 cases]	5.9 (2.9 to 12.0)
Model 3: Cases = COPD by Spirometry ≥ GOLD II	Risk of COPD[†] (Cases-67; Referents =1652)
Minimal Smoking (Never up to 10 Pack Years), No Exposure [n=10 cases]	1.0 (Referent)
Minimal Smoking; VGDF Exposure [n=7 cases]	2.1 (0.8 to 5.5)
Smoker (> 10 Pack years); No VGDF Exposure [n=27 cases]	4.9 (2.3 to 10.4)
Smoker and VGDF Exposure [n=23 cases]	8.5 (3.8 to 18.8)

[*] Excludes 20 cases who did not have obstruction (≥ GOLD I stage of COPD = FEV1/FVC <0.70)

[†] Excludes 32 cases who did not have obstruction (≥ GOLD II stage of COPD = FEV_1/FVC <0.70 and FEV_1 % predicted <0.80)

Models adjusted for Age, Gender and Race Status. Light Smoker (10 or less Pack years) and no VGDF Exposure referent. Data for smoking intensity-duration are missing for one of the cases and 57 referents.