A Case-Control Study of Airways Obstruction Among Construction Workers

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Background *While smoking is the major cause of chronic obstructive pulmonary disease (COPD), occupational exposures to vapors, gases, dusts, and fumes (VGDF) increase COPD risk. This case-control study estimated the risk of COPD attributable to occupational exposures among construction workers.*

Methods *The study population included 834 cases and 1243 controls participating in a national medical screening program for older construction workers between 1997 and 2013. Qualitative exposure indices were developed based on lifetime work and exposure histories.*

Results *Approximately 18% (95%CI = 2–24%) of COPD risk can be attributed to construction-related exposures, which are additive to the risk contributed by smoking. A measure of all VGDF exposures combined was a strong predictor of COPD risk.*

Conclusions *Construction workers are at increased risk of COPD as a result of broad and complex effects of many exposures acting independently or interactively. Control methods should be implemented to prevent worker exposures, and smoking cessation should be promoted.* Am. J. Ind. Med. 58:1083–1097, 2015. © 2015 The Authors. *American Journal of Industrial Medicine* Published by Wiley Periodicals, Inc.

KEY WORDS: COPD; construction workers; occupational risks; vapors; gasses; dusts; fumes; smoking; attributable risk

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder that includes chronic bronchitis and emphysema [Pistolesi, 2009] and more than 13 million people in the U.S. have physician diagnosed COPD [Ford et al., 2013a; NHLBI, 2014]. The prevalence of obstructive impairment determined by spirometry ($FEV_1/FVC < 0.70$) was estimated to be 13.7% during 2007–2010 among adults [Ford et al., 2013b]. COPD ranked as the third leading cause of death in 2010 [Ford et al., 2013a; Johnson et al., 2014]. Currently available treatments for COPD are minimally effective with regard to disease progression, making prevention critically important [Eisner et al., 2010].

The etiology of COPD is complex and the biology of COPD is still poorly understood. Although tobacco smoking is the major risk factor for COPD with an estimated population attributable fraction (PAF) of 80–90% [ATS, 1995a], only 15–20% of smokers develop COPD [Barr et al.,

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2002; Mannino et al., 2002]. A significant fraction of all COPD cases and COPD-related mortality occurs among non-smokers [Whittemore et al., 1995; Mannino et al., 2002; Behrendt, 2005; Eisner et al., 2010]. An estimated 15–30% of COPD cases are attributable to occupational exposures; the PAF may be as high as 53% among never smokers [Hnizdo, 2002; Balmes et al., 2003; Balmes, 2005; Eisner et al., 2010; Mehta et al., 2012; Toren and Jarvholm, 2014].

Occupational exposures to particulates, and possibly to ambient particulates, are associated with COPD [Eisner et al., 2010; Andersen et al., 2011; Omland et al., 2014]. Increased COPD risk, and increased COPD mortality, has been observed among workers exposed to "vapors, gases, dusts, and fumes" (VGDF) [Oxman et al., 1993; Hendrick, 1996; ATS, 2003; Trupin et al., 2003; Bergdahl et al., 2004; Balmes, 2005; Weinmann et al., 2008; Blanc et al., 2009a,b; Mehta et al., 2012; GOLD, 2014; Omland et al., 2014; Toren and Jarvholm, 2014]. Both large and small airway effects of VGDF exposures are suggested in the literature [Churg and Wright, 2002; de Jong et al., 2014a].

Increased COPD risk has been associated with some specific occupational exposure agents, including: **coal dust** [Becklake, 1989; NIOSH, 1995; Hendrick, 1996; Henneberger and Attfield, 1996; Coggon and Newman Taylor, 1998]; **asbestos** [Glencross et al., 1997; ATS, 2004; Dement et al., 2010]; **silica** [Hnizdo and Vallyathan, 2003; Oliver and Miracle-McMahill, 2006; Rushton, 2007b; Tse et al., 2007; Dement et al., 2010]; **welding and cutting gases and fumes** [Hunting and Welch, 1993; Bradshaw et al., 1998; Mastrangelo et al., 2003; Balmes, 2005; Dement et al., 2010; Szram et al., 2013; Koh et al., 2015]; **cement dust** [Abrons et al., 1988; Mwaiselage et al., 2004; Rushton, 2007a; Dement et al., 2010; Fell et al., 2010]; **diesel exhausts** [Tuchsen and Hannerz, 2000; Ulvestad et al., 2000; Hart et al., 2006; Weinmann et al., 2008; Hart et al., 2009]; **spray painting** [Glindmeyer et al., 2004; Hammond et al., 2005; Pronk et al., 2007]; **organic solvents** [Heederik et al., 1989; Post et al., 1994; Melville et al., 2010]; and **possibly man-made mineral fibers** [Kilburn et al., 1992; Clausen et al., 1993; Hughes et al., 1993; Hunting and Welch, 1993; Hansen et al., 1999].

Construction workers experience a wide spectrum of exposures and are at increased risk for COPD and COPD-related mortality [Glencross et al., 1997; Hnizdo, 2002; Dement et al., 2009; NIOSH, 2014; Ringen et al., 2015; Welch et al., 2015]. Increased COPD risk among construction workers has been associated with exposures to inorganic dusts, gases and irritants, and fumes [Bergdahl et al., 2004; Toren and Jarvholm, 2014].

We have previously reported results of a cross-sectional study of airways obstruction among 7579 construction and trade workers employed at U.S. Department of Energy (DOE) sites and participating in the Building Trades National Medical Screening Program (BTMED) (https://www.btmed.org) [Dement et al., 2010]. The overall prevalence of spirometry defined airways obstruction was 13.3% and was highest among cement masons, brick masons, and plasterers (24%). Cumulative exposures to asbestos, welding/cutting, silica, cement dusts, and some tasks resulting in exposures to solvents and paints were associated with the risk of airway obstruction in sub-analyses restricted to workers with less than five years of construction work outside of DOE sites.

Our prior study using BTMED data had two primary limitations. First, because the BTMED exposure assessment was primarily designed to identify exposures on DOE sites for selection of medical surveillance tests, the exposure questions were not optimal for assessment of COPD risk factors. Secondly, even though BTMED participants have worked a great deal outside DOE facilities, the BTMED exposure assessment was largely restricted to exposures on DOE sites and did not take into account exposures from work outside DOE employment. We now report results of a case-control study among construction workers which assessed lifetime exposures.

MATERIALS AND METHODS

Identification of Cases and Controls

Cases and controls for this study were identified using medical examination results from the BTMED program through December 2013. Prior reports describe the work history and medical components of the BTMED program [Dement et al., 2003, 2009, 2010; Welch et al., 2004, 2013]. Briefly, BTMED medical examinations are performed by local medical providers who meet credentialing requirements and adhere to a detailed protocol. The respiratory examination includes: a respiratory history and symptom questionnaire; a posterior-anterior (P-A) chest radiograph, classified by a B-reader according to International Labour Office (ILO) Classification of Radiographs of Pneumoconiosis [ILO, 1980, 2002]; and spirometry. The respiratory history and symptom questionnaire was adapted from the American Thoracic Society (ATS) DLD-78 questionnaire [Ferris, 1978]. All participating medical facilities agreed to obtain spirometry according to ATS standards and quality control procedures were in place for all medical data [Dement et al., 2010].

Workers completing at least one BTMED examination with spirometry through December 2013 formed the study base for selection of cases and controls if: (i) not missing key demographic data (age, race, sex, height, and BMI); and (ii) had spirometry meeting inclusion criteria of a minimum of three recorded expiratory efforts and repeatability of FVC and FEV1 of 0.2 liters or less [ATS, 1995b]. We chose the ATS 1995 criteria as these were in effect at the start of the BTMED program in 1996, and many participants were screened prior to

publication of the new ATS recommendation in 2005. The most recent examination was selected for each worker.

In this manuscript we use the term COPD to describe airways obstruction based on an epidemiologic rather than clinical case definition. In clinical practice COPD is diagnosed based on a combination of symptoms and pulmonary function, often including post-bronchodilator spirometry. However, prior studies have used the term COPD based on spirometry without bronchodilation to describe an epidemiologic case definition [Hnizdo, 2002; Behrendt, 2005; Weinmann et al., 2008]. The ATS/ERS Task Force [ATS/ERS, 2005] recommends identification of air obstruction based on an FEV_1/FVC ratio below the lower limit of normal (LLN) to avoid age-related misclassification associated with use of a fixed FEV_1/FVC ratio [Hnizdo et al., 2006; Hansen et al., 2007; Enright et al., 2008; Swanney et al., 2008]. On this basis, COPD was defined as a FEV_1/FVC ratio below the LLN using the prediction equations of Hankinson et al. [1999] without use of bronchodilation. Workers not classified as having airways obstruction by this definition but meeting all other inclusion criteria were eligible as controls.

All available cases were frequency matched to controls based on sex, race, age, and DOE site by random sampling. We oversampled controls to increase statistical power. Frequency matching by DOE site allowed some degree of control for location specific non-occupational exposures.

Exposure Assessment

A telephone questionnaire obtained a lifetime occupational and exposure history through the date of the qualifying BTMED examination, obtaining information concerning jobs held for more than six months as well a qualitative assessment of frequency (none to daily) of doing 90 specific construction-related tasks known to generate VGDF exposures (e.g., cutting concrete, insulation installation, wood sanding, etc.). Frequency of VGDF exposures were also assessed for non-construction jobs, jobs performed while in military service, and for bystander exposures. The questionnaire included a qualitative assessment of exposure frequency for other materials previously associated with respiratory disease. These agents included: coal dust; formaldehyde; beryllium; mercury; polyvinyl chloride fumes (heating or cutting PVC); isocyanates; pesticides, insecticides, or herbicides; diesel or gasoline engine exhaust; grain dusts; and animal feed or fodder. Details concerning the questionnaire can be found in the supplemental materials.

Questionnaire data were used to develop qualitative cumulative exposure indices for an a priori list of 15 common construction-related exposures (Table I). The category "particulates not otherwise regulated" (PNOR) included all mineral and inorganic "inert or nuisance dusts" without specific individual U.S. Occupational Safety and Health Administration Permissible Exposure Limits (PEL) [NIOSH, 2015; OSHA, 2015]. A VGDF index was constructed as the sum of exposure indices of a priori interest plus the PNOR exposure index.

TABLE I. Exposures with Cumulative Lifetime Exposure Assessments

Agent or exposure	Reference concentration for intensity scoring
Asbestos	2 f/cc
Silica	0.1 mg/m^3 respirable
Cement dust	5 mg/m^3 respirable
Man-made-mineral-fibers	1 f/cc
Engine exhausts	100 μg/m^3 respirable elemental carbon
Acids	Ceiling 5 ppm as HCL
Caustics	Ceiling 2 mg/m^3 as sodium hydroxide
Welding, thermal cutting, soldering, or brazing	5 mg/m^3 as total aerosol
Metal cutting, grinding, and machining aerosol	5 mg/m^3 as total aerosol
Paint-related aerosols	1 mg/m^3 as total aerosol
Isocyanates	0.02 ppm
Organic solvents	100 ppm as toluene
Wood dust	1 mg/m^3 as total aerosol
Molds and spores	Exposure above typical background
Particulates not otherwise regulated (PNOR)	10 mg/m^3 as total aerosol

Cumulative exposure indices were developed for each exposure in Table I based on the product of task frequency, job duration, work hours per week, and task exposure intensity scoring by industrial hygienists. Indices were calculated for each exposure scenario (construction, non-construction, military, and bystander) and summed to arrive at an overall cumulative exposure index for each exposure. Greater detail concerning the cumulative exposure indices can be found in the supplemental materials.

Many of the cumulative exposure indices were correlated. Principal component analysis (PCA) was used to identify independent factors that explained the maximum amount of mutual correlation of the individual task exposure indices and to derive combined cumulative exposure indices [Burstyn, 2004; Vermeulen et al., 2004; Dement et al., 2010]. Inputs to the PCA analyses were the estimated cumulative exposure indices for each agent found to be significantly associated with COPD in the individual logistic models. The output of principal component analyses was a set of weights or 'loadings' that were then multiplied by each worker's exposure index to derive a summary score for each principal component. Choice of principal components for logistic regression analyses was based on eigenvalues greater than one or where scree plots indicated a significant contribution to

explaining the multiple correlations among the exposure indices.

Case-Control Analyses

Cases and controls were compared for demographic characteristics, health status variables, spirometry, and chest x-ray readings by ILO criteria using analysis of variance (ANOVA), Wilcoxon rank-sum tests, or χ^2 test of general association as appropriate. In all tests P values of 0.05 or less were considered statistically significant.

Our primary analytical tool was unconditional logistic regression and we first developed a baseline model prior to inclusion of occupational exposures. Age, race/ethnicity, sex, and cigarette smoking (status and pack-years) are known risk factors for COPD and were included in a baseline model a priori. Univariate logistic regression was used to evaluate other analytical variables (BMI category, blood relative with COPD, history of having lived with a smoker, history of childhood pneumonia, and volunteer/hobby-related activities potentially associated with VGDF exposures) as candidates for inclusion. Body mass index (BMI) was categorized (underweight = BMI $<$ 18.5; normal = BMI 18.5–24.9; overweight = BMI 25.0–29.9; and obese = BMI $\geq$ 30). Volunteer/hobby-related activities included: gardening, stained glass work, silk screening, house painting or paint removal, model plane/car building, ceramics, melting of metals, volunteer firefighter, woodworking, jewelry making, mimeographing, furniture refinishing, hunting or indoor firing range practice, boat, auto or motorcycle racing, use of chain saws or other gasoline powered equipment, and operating farm equipment. Each volunteer/hobby-related activity was considered individually for inclusion in the baseline logistic model and a summary index based on the sum of positive participation responses also was considered.

We used a moderate level of statistical significance (P-value $<$0.25) for initial retention of parameters in the main effects logistic model [Hosmer and Lemeshow, 1989] and retained all a priori covariates as well as other covariates that were biologically plausible and having a reasonable degree of statistical significance (P-value $<$0.10). After the baseline logistic model was developed main effects models for the 15 exposures of a priori interest (Table I) and our overall measure of VGDF exposures were explored. We modeled each exposure separately followed by modeling of the summary scores from the principal component analyses. Cumulative exposure indices were standardized by dividing each worker's cumulative exposure by a value representing an exposure at the upper 95th percentile of the range for all workers. Exposures were thus expressed as a fraction of the upper 95th percentile of the exposure distribution which allowed more directed comparison of exposure-response patterns across the exposures of a priori interest. Cumulative exposures were entered as continuous variables to avoid loss of statistical power caused by categorization of continuous variables [Greenland, 1995a,b; Altman and Royston, 2006; Royston et al., 2006]. We examined the possibility of a non-linear relationship between cumulative exposure indices and COPD odds-ratios non-parametrically with restricted cubic splines [Durrleman and Simon, 1989; Ruifeng et al., 2011]. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. The proportion of workers with no reported exposure was high for acids and caustics combined and for isocyanates. For these exposures two parameters were entered into the models with one being dichotomous and indicating zero versus non-zero exposure and the other representing the value of the continuous exposure index [Robertson et al., 1994].

The joint effects of exposure agents and smoking were evaluated for departure from additive. Assessment of interaction on an additive scale is often more meaningful than an assessment on a multiplicative scale [Knol et al., 2007; Rothman et al., 2007; Richardson and Kaufman, 2009]. Departure from additivity was evaluated based on calculation of the relative excess risk due to interaction (RERI); which represents the increased risk for smoking and the exposure of interest combined relative to the risk estimated for the sum of these two factors, with a value greater than 1.0 representing some degree of interaction [Richardson and Kaufman, 2009].

Assessment of potential confounding associated with exposures not included in the task-based exposure assessments was based on the questionnaire data concerning the frequency of exposure to a list of materials (previously described) associated with COPD in the literature. For each agent, a cumulative index was developed by multiplying duration and assigned exposure days per months based reported exposure frequency. Potential confounding was evaluated in the final logistic model for VGDF exposures.

We calculated the population attributable fraction (PAF) for our overall VGDF exposure index. Very few cases or controls had a VGDF exposure index value of zero; however, many were estimated to have low cumulative VGDF exposures. In order to achieve stability in the PAF estimates workers at or below the cut point for lowest quartile of the VGDF exposure distribution for controls were classified as "unexposed." The VGDF attributable fraction point estimate was calculated as described by Benichou [2001] as well as approximate 95% confidence intervals [Greenland and Drescher, 1993; Brady, 1998]

Our COPD case definition was not based on post-bronchiolar spirometry so may include some individuals with asthma and not COPD. The possibility also exists that some individuals with airway obstruction and taking long-acting bronchodilator medications might have spirometry improvement sufficient to change their classification from case to control. We conducted sensitivity analyses to address potential misclassification on disease status based on these

two issues. Individuals with an $FEV_1 < 65\%$ of predicted are less likely to have fully reversible airway obstruction; therefore, we restricted the logistic regression model for VGDF exposure to cases with an $FEV_1 < 65\%$ of predicted. Controls were required to have a $FEV_1 \geq 70\%$ of predicted for inclusion to reduce the probability of misclassifying COPD cases using long acting bronchodilators.

SAS Version 9.3 [SAS, 2011] or STATA Version 11.1 [STATA, 2009] were used for all analysis presented in this report.

Human Subjects Protection

Participants were contacted by mail before the telephone interview and were provided information concerning the study. At the start of the telephone interviews, the interviewers administered verbal consent using a written script and study subjects gave oral informed consent before beginning the work history questionnaire. All study procedures and materials were reviewed and approved by the Central DOE Institutional Review Board and the CPWR Institutional Review Board. All data received by Duke University investigators were stripped of personal identifiers under provisions approved by the Duke University Health System Institutional Review Board.

RESULTS

Case and Control Demographic Characteristics

A total of 3741 frequency matched COPD cases and controls were identified (Table II). Of the 3741 potential study participants 1332 could not be contacted by telephone; 375 were deceased and 957 could not be contacted due to bad address or telephone information or lack of response. Among workers not deceased the overall participation rate was 60.6% among cases and 62.5% among controls. Of those contacted by telephone, 2079 (86.3%) participated. Participating controls were slightly older than non-participants and slightly fewer female cases participated. The percent predicted FEV_1 was slightly higher among participating cases as was the FEV_1/FVC ratio. No differences in smoking pack-years were observed. Of the 2079 study participants, only 572 (248 cases and 324 controls) were included in our prior cross-sectional study of exposures experienced while working on DOE sites [Dement et al., 2010].

Demographic and clinical characteristics of cases and controls are compared in Table III. Detailed data concerning the distribution of cases and controls by DOE site and trade can be found in the supplemental materials (Tables SI and SII).

TABLE II. Study Participation Summary and Comparison by Participation Status

Participation measure	Cases		Controls	
Sent invitation letters	1612		2129	
Contacted, completed interview	834		1245	
Contacted, declined interview	130		200	
Not contacted	648		684	
Reasons for no contact				
Deceased	238		137	
No telephone contact[a]	410		547	
Overall participation rate among living	60.6%		62.5%	
Overall participation rate among those contacted	86.5%		86.3%	
Demographic variable[b]	Participants (n = 834)	Non-participants (n = 778)	Participants (n = 1245)	Non-participants (n = 884)
Mean age (Std Err)	62.3 (0.37)	62.0 (0.48)	62.7 (0.30)	60.2 (0.44)[c]
Male sex (%)	764 (91.6)	734 (94.3)[c]	1153 (92.6)	823 (93.1)
Non-white race or hispanic ethnicity (%)	94 (11.3)	87 (11.2)	142 (11.4)	124 (14.1)
Spirometry, mean (Std Err)				
% Predicted FVC	81.3 (0.70)	79.4 (0.76)	87.7 (0.46)	87.0 (0.54)
% Predicted FEV_1	62.9 (0.67)	60.3 (0.75)[c]	89.7 (0.49)	88.8 (0.57)
FEV_1/FVC ratio	0.58 (0.003)	0.56 (0.004)[c]	0.77 (0.002)	0.77 (0.002)
Mean cigarette pack-years (Std Err)	31.3 (0.88)	32.8 (1.04)	15.6 (0.56)	16.7 (0.76)

[a]Includes those with bad address or telephone information and those who did not respond after two reminder letters and up to six telephone contact attempts.
[b]Continuous data expressed as means and standard errors. Categorical data expressed as number and percent.
[c]Parameter significantly different for participants compared to non-participants, $P < 0.05$.

TABLE III. Demographic and Clinical Characteristics of Cases and Controls by Cigarette Smoking Status

	Current or Former		Never Smokers		All Subjects	
Characteristic[a]	**Cases (n = 698)**	**Controls (n = 770)**	**Cases (n = 136)**	**Controls (n = 473)**	**Cases (n = 834)**	**Controls (n = 1243)[b]**
Mean age (Std Err)	62.8 (0.39)	63.8 (0.36)	59.4 (0.98)	60.7 (0.53)	62.3 (0.37)	62.7 (0.30)
Male sex (%)	641 (91.8)[e]	730 (94.8)	123 (90.4)	422 (89.2)	764 (91.6)	1152 (92.7)
Non-white race or Hispanic ethnicity (%)	50 (7.2)	67 (8.7)	26 (19.1)d	51 (10.8)	76 (9.1)	118 (9.5)
Respiratory history (%)						
Asthma (N = 2076)	155 (22.2)[e]	61 (7.9)	37 (27.2)[e]	53 (11.2)	192 (23.1)[e]	114 (9.2)
Chronic bronchitis (N = 2076)	155 (22.2)[e]	77 (10.0)	14 (10.3)[e]	26 (5.5)	169 (20.3)[e]	103 (8.3)
Emphysema (N = 2076)	180 (25.8)[e]	39 (5.1)	5 (3.7)	10 (2.1)	185 (22.2)[e]	49 (3.9)
Pneumonia (N = 2076)	219 (31.4)[e]	158 (20.5)	23 (16.9)	83 (17.6)	242 (29.1)[e]	241 (19.4)
Respiratory symptoms (%)						
Cough (N = 2074)	375 (53.8)[e]	232 (30.2)	43 (31.6)	121 (25.6)	418 (50.1)[e]	353 (28.4)
Phlegm (N = 2074)	350 (50.2)[e]	238 (31.0)	43 (31.6)[e]	99 (20.9)	393 (47.1)[e]	337 (27.2)
Dyspnea (N = 2074)	422 (60.6)[e]	258 (33.6)	47 (34.6)	128 (27.1)	469 (56.3)[e]	386 (31.1)
Spirometry, mean (Std Err)						
% Predicted FVC	80.0 (0.74)[e]	86.5 (0.60)	87.7 (1.80)	89.6 (0.73)	81.3 (0.70)[e]	87.7 (0.46)
% Predicted FEV_1	61.2 (0.71)[e]	88.3 (0.64)	71.4 (1.71)[e]	92.1 (0.76)	62.9 (0.67)[e]	89.7 (0.49)
FEV_1/FVC ratio	0.57 (0.003)[e]	0.77 (0.002)	0.62 (0.006)[e]	0.78 (0.003)	0.58 (0.003)[e]	0.77 (0.002)
FEV_1/FVC < LLN & FEV_1 < 65% pred. (%)	393 (56.3)	–	45 (33.1)	–	438 (52.5)	–
Chest X-ray B-Reader prevalence (%)[c,d]						
Pleural changes only	105 (15.2)	116 (15.2)	15 (11.3)	63 (13.4)	120 (14.6)	179 (14.5)
Parenchymal changes only (Profusion ≥ 1/0)	17 (2.5)	19 (2.5)	3 (2.3)	4 (0.85)	20 (2.4)	23 (1.9)
Both Pleural and Parenchymal	22 (3.2)	24 (3.1)	1 (0.75)	4 (0.85)	23 (2.8)	28 (2.3)
History of hypertension (%) (N = 2076)	223 (32.0)[e]	207 (26.9)	39 (28.6)	124 (26.2)	262 (31.5)e	331 (26.6)
History of congestive heart disease (%) (N = 2074)	21 (3.0)[e]	13 (1.7)	2 (1.5)	13 (2.8)	27 (2.8)	23 (2.1)
History of severe childhood pneumonia (%)	27 (3.9)	31 (4.0)	4 (2.9)	16 (3.4)	31 (3.7)	47 (3.8)
Cigarette smoking status at exam (%)[d]						
Current smoker	236 (33.8)	138 (17.9)	–	–	236 (28.3)[e]	138 (11.1)
Past smoker	462 (66.2)	632 (82.1)	–	–	462 (55.4)	632 (50.8)
Never smoker	0 (0.0)	0 (0.0)	136 (100)	473 (100)	136 (16.3)	473 (38.1)
Mean cigarette pack-years (Std Err)	37.4 (0.88)	25.2 (0.71)[e]	–	–	31.3 (0.88)[e]	15.6 (0.56)
Mean body mass index (Std Err)	29.0 (0.21)	30.5 (0.19)[e]	29.9 (0.56)	30.6 (0.25)	29.2 (0.20)[e]	30.5 (0.15)
Blood relative with COPD (%)	181 (25.9)[e]	139 (18.1)	31 (22.8)	91 (19.4)	212 (25.4)[e]	230 (15.5)
History of living with a smoker (%)	78 (11.2)	85 (11.0)	13 (9.7)	28 (5.9)	91 (10.9)	113 (9.1)
Childhood history of pneumonia (%)	27 (3.9)	31 (4.0)	4 (2.9)	16 (3.4)	31 (3.7)	47 (3.8)

[a]Continuous data expressed as means and standard errors. Categorical data expressed as number and percent.
[b]Two controls were dropped from the analyses due to missing smoking pack years or BMI.
[c]B-reader data was available for 2057 workers.
[d]Smoking and chest X-ray categories compared using an overall chi square measure of association.
[e]Parameter significantly different for cases compared to controls, $P < 0.05$.

The final analytic sample included 834 cases and 1243 controls; two workers missing data were excluded. Overall, there were no statistically significant differences between participating cases and controls for the frequency matching variables (age, gender, race/ethnicity, and DOE site). Cases were significantly more likely to report a history of physician diagnosed respiratory conditions (asthma, chronic bronchitis, emphysema, and pneumonia), prevalent respiratory symptoms (cough, phlegm, and dyspnea), hypertension, and having a blood relative with COPD. Cases were significantly more likely to have smoked and had a significantly higher mean pack-year smoking history. No significant differences were

observed in prevalence of B-reader chest x-ray findings, history of childhood pneumonia, or history of having lived with a smoker. Cases and controls were significantly different by job or trade distribution (Supplemental Materials Table SII). Among the COPD cases 52.5% had an $FEV_1 < 65\%$ of predicted, indicative of clinically significant airway obstruction.

Exposure Assessment

Detailed results of the industrial hygienists' ratings for task exposure intensity can be found in the supplemental materials (Table SIII). Multi-rater kappa values ranged from 0.41 to 0.82. In general, kappa values below 0.40 represent poor agreement and values greater than 0.75 represent excellent agreement [Fleiss et al., 2003]. Based on these criteria, good to excellent agreement was achieved for all exposures of interest except the heterogeneous category "particulates not otherwise regulated" (PNOR) where the overall kappa was 0.41.

A detailed presentation of each cumulative exposure index by case status can be found in the supplemental materials (Table SIV). Except for exposure indices for acids/caustics and isocyanates, both cases and controls had a high probability of exposure for the exposure agents of a priori interest, with cases having a higher probability of any exposure for all agents. Differences in exposures between cases and controls tended to be greatest in the highest exposure tertile.

Multivariate Baseline Logistic Model

The baseline model included age, gender, race/ethnicity, and cigarette smoking history a priori. Both cigarette smoking status and pack-years of smoking were strong predictors of COPD risk ($P = 0.0011$ and <0.0001, respectively). Having a blood relative with COPD and having lived with a smoker were highly correlated ($\chi^2 = 10.05$, $P < 0.0015$); however, only a having a blood relative with COPD was significantly associated with COPD and retained in the baseline model. A history of childhood pneumonia was not significantly associated with COPD after adjustment for demographic variables and smoking. BMI category was retained because it was significantly associated with COPD risk, with elevated risk for those underweight and a moderate protective effect among those overweight or obese.

Dichotomous covariates for the volunteer/hobby activities were evaluated separately and collectively for inclusion in the baseline model. No volunteer/hobby activity demonstrated a significant positive relationship with COPD risk whereas gardening and working with wood showed significant negative associations ($P < 0.05$). A categorical summary measure based on the sum of volunteer/hobby-related activities was negatively associated with COPD risk in the baseline model ($P < 0.001$). However, model fit based on AIC criterion was negatively impacted by inclusion of this covariate and inclusion slightly inflated the effects of occupational exposures; therefore, volunteer/hobby-related exposures were not included in the baseline model but were considered in sensitivity analyses.

Cumulative Exposure Indices and COPD Risk

Final logistic regression model results for the exposures of a priori interest are summarized in Table IV. Acids and caustics were grouped together as these exposures occurred with low frequency and their mode of action (e.g., respiratory irritation) is likely similar. Significant associations were observed for all exposures except man-made-mineral-fibers and painting aerosols. The associations were best described as a linear function in the logistic models for all exposures except wood dust where the restricted cubic spline provided a better model fit. At the upper 95th percentile of the exposure distribution for each exposure the odds-ratios for the exposure indices ranged from 1.17 for wood dust to 2.15 for PNOR. The exposure index for all VGDF combined demonstrated a relatively strong association with COPD risk ranging from 1.19 at the lower range of exposures to 2.03 among those with exposures at the upper 95th percentile. Wood dust demonstrated a non-linear relationship with evidence of flattening of the exposure–response relationship at higher cumulative exposures. The exposure–response relationship for acids and caustics was largely influenced by the dichotomous variable indicating exposure compared to no exposure.

In a separate model (not shown) we investigated the time period of first employment in construction (before or after 1980) as a predictor of COPD associated with VGDF exposures. Calendar year 1980 reflects the implementation of many permissible exposure limits by the US Occupational Safety and Health Administration (OSHA) and studies have shown declines in asbestos-related respiratory diseases among workers first employed in this timeframe [Welch et al., 2007]. After adjustment for all model parameters including VGDF exposures, the dichotomous covariate for pre versus post 1980 first employment was not significant ($P = 0.6459$), suggesting continued risk among workers first employed in construction after 1980.

Potential confounding by exposure to other materials associated with COPD was assessed in the final model for VGDF exposures. Only exposures indices for pesticides/herbicides and grain dust were significantly associated with

TABLE IV. COPD Odds-Ratios by Cumulative Exposure Index

Cumulative exposure index[a]	Restricted cubic spline *P*-value[b]	Exposure index *P*-value[c]	Odds-ratio (95%CI) by fraction of upper 95th percentile[d] 0.25	0.50	0.75	1.00
Asbestos	0.1157	0.0038	1.15 (1.05–1.26)	1.31 (1.09–1.58)	1.50 (1.14–2.00)	1.72 (1.19–2.48)
Silica	0.5963	<0.0001	1.21 (1.11–1.32)	1.46 (1.23–1.74)	1.77 (1.36–2.30)	2.13 (1.50–3.03)
Cement dust	0.4216	0.0017	1.16 (1.05–1.25)	1.31 (1.11–1.56)	1.51 (1.17–1.94)	1.73 (1.23–2.43)
Man-made-mineral-fibers	0.1764	0.1829	1.06 (0.97–1.16)	1.13 (0.94–1.35)	1.20 (0.92–1.57)	1.28 (0.89–1.82)
Engine exhausts	0.1577	0.0021	1.15 (1.05–1.26)	1.33 (1.11–1.74)	1.53 (1.17–2.00)	1.76 (1.23–2.52)
Acids and caustics[f]	0.2281	<0.0001	1.46 (0.91–2.32)	1.49 (1.09–2.04)	1.51 (1.16–1.98)	1.54 (1.07–2.22)
Welding, thermal cutting, soldering, brazing	0.2015	0.0254	1.11 (1.01–1.21)	1.23 (1.03–1.46)	1.36 (1.04–1.77)	1.50 (1.05–2.14)
Metal cutting, grinding, and machining aerosol	0.1869	0.0364	1.09 (1.00–1.19)	1.20 (1.01–1.42)	1.31 (1.02–1.68)	1.43 (1.02–2.00)
Paint-related aerosols	0.1436	0.2873	1.05 (0.96–1.15)	1.10 (0.92–1.31)	1.15 (0.89–1.50)	1.21 (0.85–1.72)
Isocyanates[f]	0.5335	<0.0001	1.09 (0.83–1.42)	1.22 (0.97–1.52)	1.36 (1.03–1.80)	1.52 (1.04–2.23)
Organic solvents	0.1869	0.0008	1.16 (1.07–1.26)	1.34 (1.13–1.59)	1.55 (1.20–2.01)	1.80 (1.28–2.53)
Wood dust[g]	0.0434	0.0420	1.36 (1.07–1.74)	1.46 (1.10–2.00)	1.36 (1.02–1.80)	1.17 (0.80–1.69)
Molds and spores	0.3965	0.0018	1.12 (10.3–1.22)	1.25 (1.05–1.49)	1.40 (1.08–1.82)	1.57 (1.11–2.23)
Particulates not otherwise regulated (PNOR)	0.6489	<0.0001	1.21 (1.11–1.32)	1.47 (1.23–1.74)	1.78 (1.37–2.30)	2.15 (1.52–4.04)
All VGDF[e]	0.9148	<0.0001	1.19 (1.09–1.30)	1.42 (1.20–1.69)	1.70 (1.31–2.20)	2.03 (1.43–2.87)

[a]Cumulative exposure indices generated as function of task frequency, exposure intensity, and duration. Each index summed exposures from construction and non-construction work, bystander exposures, and military exposures. The fraction represents the proportion of the upper 95 percentile for each exposure.
[b]Likelihood ratio test for non-linearity of the exposure index comparing the adjusted model with only the linear term to the adjusted model with the linear and the cubic spline terms.
[c]Likelihood ratio *P*-values for the cumulative exposure indices.
[d]Increase in the COPD odds-ratio for an exposure at each proportion of the maximum for the exposure index compared to those unexposed. Logistic regression model adjusted for age, gender, race/ethnicity, smoking status (Current, Past, Never), cigarette pack-years, blood relative with COPD, and BMI.
[e]VGDF is an overall measure for all vapors, gasses, dusts, and fumes combined.
[f]Many workers reported no exposures to acids and caustics and isocyanates; therefore, models for acids and caustics and isocyanates included two exposures variables as described in the text. The p-value represents the change in the -2 log likelihood with these two parameters in the model.
[g]The restricted cubic spline model provided a better fit for wood dust and was retained as the final model.

the risk of COPD ($P = 0.0154$ and 0.0336, respectively). Inclusion of these covariates changed the risk estimates for VGDF exposures negligibly, suggesting independent effects of these exposures rather than confounding of the construction-related VGDF risk estimates.

A detailed presentation of analyses of the interaction between cigarette smoking and the cumulative exposures of interest can be found in the supplemental materials (Table SV). While most values for the relative excess risk due to interaction (RERI) were slightly greater than 1.0, indicating some degree of smoking–exposure interaction, only the interaction between smoking and exposures to molds and spores was of borderline statistical significance (RERI = 1.07, 95%CI = 1.00–1.16). Overall, the analyses support the conclusion that the effects of smoking and the occupational exposures studied did not depart significantly from additivity.

Analyses of Combined Exposures

Cumulative exposure indices found to be significantly associated with COPD in the logistic models were included in the principal component analyses. The first four components were retained based on selection criteria, accounting for 78% of the total exposure index variance and 63 to 93 percent of the variance of the individual cumulative exposure indices (Table V). The first three components were significant predictors of COPD risk and component four was of borderline significance. The first component was heavily loaded by welding and thermal cutting exposures as well as metal cutting, grinding, and machining exposures. Asbestos, cement dust, silica, and solvent exposures also contributed to component one. Component two was heavily loaded by exposures to wood dust as well as molds and spores, with lesser loading for

TABLE V. Principal Component Analysis Rotated Factor Pattern, Final Communality Estimates, and Logistic Model Results

	Principal component number[a]				
Cumulative exposure index	**#1**	**#2**	**#3**	**#4**	**Final communality estimates[b]**
Metal cutting, grinding, and machining aerosol	**0.89**	0.17	0.07	0.06	0.84
Welding, thermal cutting, soldering, brazing	**0.88**	0.12	0.07	0.02	0.79
Particulates not otherwise regulated (PNOR)	**0.69**	**0.56**	0.37	0.13	0.93
Silica	**0.67**	**0.59**	0.28	0.15	0.89
Cement dust	**0.60**	**0.63**	0.10	0.13	0.78
Asbestos	**0.53**	**0.65**	0.14	0.08	0.73
Organic solvents	**0.44**	0.25	**0.71**	0.13	0.77
Molds and spores	0.31	**0.74**	0.17	−0.10	0.68
Engine exhausts	0.15	0.18	**0.77**	−0.18	0.68
Acids and caustics	0.13	0.11	0.09	**0.90**	0.91
Wood dust	0.00	**0.77**	0.12	0.15	0.63
Isocyanates	-0.07	0.07	**0.82**	0.24	0.74
Component proportion of total variance	0.50	0.12	0.08	0.08	
Logistic regression model *P*-value[c]	0.0211	0.0381	0.0045	0.0536	

[a]Exposures with a rotated factor loading $\geq$0.40 are shown in bold.
[b]Communality refers to the percent of variance in a given cumulative exposure index that was accounted for by the four retained principal components.
[c]Type 3 Wald *P*-values for principal components in a logistic regression model that adjusted for age, gender, race/ethnicity, smoking status (Current, Past, Never), cigarette pack-years, blood relative with COPD, BMI and all selected principal components.

asbestos, cement dust, and silica. PNOR exposures were loaded on components one and two. Isocyanates, engine exhausts, and organic solvents loaded component three while only acids and caustics loaded component four.

Occupational-Attributable COPD

The overall PAF due to occupational VGDF exposures was estimated to be 18% (95%CI = 2–24%) based on a model adjusted odds-ratio of 1.29 (95%CI = 1.02–1.63) and a case VGDF exposure fraction of 0.784. In a logistic model restricted to never smokers (136 cases and 473 controls) a PAF of 32% (95%CI = 6–42%) was estimated based on a model adjusted odds-ratio of 1.72 (95%CI = 1.05–2.83) and a case VGDF exposure fraction of 0.772. It should be noted that for PAF calculations, workers in the lowest quartile of the entire distribution of VGDF exposures were classified as unexposed whereas results in Table IV were derived based on continuous exposure variables and standardized to a proportion of the upper 95th percentile of the VGDF distribution.

Sensitivity Analyses

Sensitivity analyses that restricted cases and controls based on percent predicted FEV_1 demonstrated negligible changes in the exposure-response pattern for VGDF exposures. VGDF exposures were significantly associated with COPD in these sub-analyses ($P = 0.0030$) and the slope parameter differed from the overall study results by less than five percent.

Hobby-related VGDF exposures were not included in the final logistic regression models. Sensitivity analyses which included the hobby-related exposure index in the final model for VGDF exposures did not change risk estimates for occupational VGDF exposures in any meaningful way.

DISCUSSION

This study supports the general hypothesis that COPD is strongly associated with occupational exposures during construction work and confirmed the increased COPD risk associated with exposures to asbestos, welding, silica, and cement dust observed in our prior cross-sectional study [Dement et al., 2010]. Other agents significantly associated with the risk of COPD included engine exhausts, acids/caustics, metal cutting and grinding aerosols, isocyanates, organic solvents, wood dust, and molds/spores.

We observed an association between COPD risk and exposure to cement dusts. Prior studies of cement dust exposures have largely involved workers producing Portland cement whereas construction workers are exposed primarily through tasks such as cutting, grinding, and drilling of concrete and masonry materials resulting in high exposure levels to mixed dusts of cured Portland cement and silica [Croteau et al., 2002; Flanagan et al., 2003; OSHA, 2009].

Exposure to cement dust has been shown to be associated with airway irritation [Fell et al., 2010].

Exposure to paint-related aerosols was not associated with COPD risk in this study. Our exposure metric included surface preparation and cleaning tasks as well as spray painting. Painting also results in exposures to organic solvents and isocyanates and indices for both of these components of paints were associated with the risk of COPD in our study. Prior studies associating risk of COPD with painting exposures have included workers using paints containing isocyanates [Glindmeyer et al., 2004; Hammond et al., 2005; Pronk et al., 2007]. Additionally, exposure to organic solvents has been associated with COPD and/or chronic bronchitis in some studies [Heederik et al., 1989; Post et al., 1994; Suadicani et al., 2001; Valcin et al., 2007; Ebbehoj et al., 2008; Melville et al., 2010]. The current study results are reasonably consistent with the published literature.

The construction work environment is complex resulting in multiple and mixed exposures to many agents. A strong relationship between COPD risk and all VGDF was observed, consistent with the published literature [Omland et al., 2014]. The current study adds to prior research in finding a nearly uniform exposure-response pattern for various a priori exposures and COPD. The principal component analyses provide further support for consideration of all VGDF exposures collectively in assessing the risk of COPD among construction workers. The VGDF exposure metric is a reasonable exposure measure for assessment of COPD risk in complex exposure environments.

In addition to risks for all VGDF combined we observed increased risk for PNOR exposures, which are currently regulated by OSHA as 'inert or nuisance dusts' with a very high PEL of 15 mg/m^3 as total dust. PNOR exposures result from many different construction tasks such drywall work, demolition, work with insulation materials, and cutting, drilling, or grinding concrete. While a reasonably strong gradient in COPD risk with increasing PNOR exposures was observed, the PNOR exposure index was correlated with several exposure indices including asbestos, cement dust, and silica making determination of the independent contribution of PNOR problematic. None-the-less, our data suggests increased COPD risk associated with materials considered 'inert or nuisance dusts'. Others have recommended that use of the term "nuisance dust" should be discontinued in scientific and regulatory contexts [Christiani, 2005] and our findings support this recommendation.

We observed associations between COPD and exposures to pesticides/herbicides and grain dusts. These results are consistent with the published literature showing associations between chronic bronchitis and/or COPD and exposures to these agents [Dosman et al., 1980; Christiani, 1996; Post et al., 1998; Salameh et al., 2006; Hoppin et al., 2007; Valcin et al., 2007; Ye et al., 2013; de Jong et al., 2014b, c; Hansell et al., 2014].

Our study population was relatively old (mean age at entry was about 62 years), and we conducted analyses to determine if the risks for COPD were the result of exposures prior to the 1980 when occupational safety and health precautions were weaker than in subsequent years. Statistical models that adjusted for all model parameters including VGDF exposures found that workers first employed in construction after 1980 continued to experience increased COPD risk.

Reporting a blood relative with COPD was significantly associated with COPD risk in this study. We hypothesized that our measure of familial aggregation was acting as a surrogate measure of common household and/or environmental exposures, including environmental tobacco smoke (ETS), rather than an indication of a genetic influence [Eisner et al., 2010]. We have no data to directly test this hypothesis; however, we did observe a high degree of correlation between variables for having lived with a smoker and reporting a blood relative with COPD. Our hypothesis seems plausible as a family history of obstructive lung disease was not a risk factor for incident COPD in a large longitudinal study [Lindberg et al., 2005] and prior research has shown ETS exposure to increase COPD risk [Eisner et al., 2010; Hagstad et al., 2014].

We observed an inverse relationship between COPD risk and increasing BMI. While BMI was associated with COPD risk it did not confound the association between VGDF and COPD, as risk estimates for VGDF exposures changed little with or without BMI in the final logistic model. The finding of increased COPD risk among those underweight is consistent with other published data [Harik-Khan et al., 2002; Johannessen et al., 2005; Collins et al., 2015].

Our overall estimated PAF for occupational VGDF exposures of 18% is within the range observed in other studies [Balmes, 2005; Eisner et al., 2010]. Other studies have observed a higher occupational PAF with an upper range of approximately 30% [Balmes, 2005; Blanc et al., 2009b; Weinmann et al., 2008]. The PAF of 32% among workers who never smoked also is similar to some prior estimates [Hnizdo, 2002] but lower than found in other studies where a PAF as high as 53% has been observed among never smokers [Toren and Jarvholm, 2014]. Our PAF estimates are likely conservative as workers in lowest quartile of the VGDF exposure distribution were classified as "unexposed" in the PAF calculations.

Analyses of interactions between occupational exposures and cigarette smoking in this study suggested that the effects of smoking and the exposures studied did not depart significantly from additivity. A recent COPD incidence study also found an additive effect [Pallasaho et al., 2014]. The level of interaction between occupational VGDF exposures and cigarette smoking has been variable in the literature, ranging from additive to greater than additive [Humerfelt et al., 1993; Trupin et al., 2003; de Meer et al., 2004; Boggia et al., 2008; Blanc et al., 2009b].

Sensitivity analyses which addressed possible disease misclassification due to use of spirometry without bronchodilation and possible use of long-acting bronchodilators did not show study results to be sensitive to exclusion of cases and controls based on the percent predicted FEV_1. Although research has demonstrated that airway obstruction prevalence based on spirometry post bronchodilator may be 25–35% lower than found without use of bronchodilators [Tilert et al., 2013], this effect is stronger in younger individuals, decreases in individuals between 60 and 74 years of age [Johannessen et al., 2005], and decreases in high risk populations. A recent study among individuals with a high risk for COPD found that only 9% had some reversal of airway obstruction with bronchodilators, and 60% of those still had an $FEV_1 < 70\%$ (the definition used in that specific study) [Kjeldgaard et al., 2015]. Our results are also consistent with other studies that found COPD risk factors to be consistent with or without post bronchodilator testing [Johannessen et al., 2005].

STRENGTHS AND LIMITATIONS

This study has several strengths: an objective COPD case definition based on spirometry, inclusion of a large number of COPD cases and controls, and assessment of lifetime occupational exposures for jobs held more than six months. Additionally, the qualitative cumulative exposure indices were task-based and incorporated the dimensions of task frequency, duration, and exposure intensity. The assessment of cumulative exposures was comprehensive, including construction and non-construction work, bystander exposures, and exposures while serving in the military. This study also benefitted from a wealth of clinical, medical, and exposure history data derived from BTMED examinations, allowing for assessment and control of important confounders.

This study also has a number of limitations. Our results were not based on post-bronchodilator spirometry; however, sensitivity analyses found study results to be robust with respect to potential disease misclassification. Occupational exposures and cigarette smoking histories were self-reported and undoubtedly resulted in exposure misclassification. Assessment of exposures to health hazards in construction is extraordinarily difficult, because these exposures occur in an uncontrolled environment where job tasks are subject to frequently unique work situations, including the work practices of each worker and type and model of tools used. Over a working life, construction workers are exposed to a myriad of hazards, either as part of the work tasks they perform or as bystanders to work tasks performed by other workers.

An additional limitation is lack of unexposed reference population due to the nature of construction-related exposures. However, a broad spectrum of construction crafts as well as security and administrative workers were included in this study, which allowed reasonable exposure contrasts for most specific exposures. Nonetheless, effects of occupational exposures are likely to be underestimated due to exposure misclassification and absence of a non-exposed referent group.

CONCLUSIONS

We estimate that approximately 18% of COPD risk among construction workers can be attributed to occupational exposures; the fraction among those who never smoked may be as high as 32%. The risks contributed by occupational exposures add to the smoking-related risk. All VGDF exposures combined were a strong and consistent predictor of COPD risk. Increased COPD risk persisted among those first employed in construction after 1980. Appropriate control methods should be implemented to prevent worker exposures to VGDF as a whole. In this study, although only 13.2% of all subjects were current smokers, 28.3% of workers with COPD were current smokers, and they would greatly benefit from smoking cessation advice and support.

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