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CHRONIC OBSTRUCTIVE PULMONARY DISEASE: OCCURRENCE AND ASSOCIATIONS WITH OCCUPATIONAL EXPOSURES AND SMOKING

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Presently COPD is the fourth leading cause of death, responsible for more than 3 million deaths in 2012 and accounting for 6% of all deaths globally. It is projected that by 2020 COPD will be the third leading cause of death.[1] With regard to Ontario, Statistics Canada estimated in 2014 that 4.3% of Ontarians live with COPD, with estimates ranging as high as 12%.[2]

Diseases of the airways include bronchitis affecting the large airways, small airways disease (SAD), asthma, and COPD. Bronchitis manifests clinically as cough and sputum production. SAD manifests clinically as decreased air flow in the small airways of the lung, with reduced FEF_{25-75} and FEF_{75}. Asthma is airway hyperreactivity with reversible airway obstruction; symptoms are cough, wheeze, chest tightness, and shortness of breath. The basic mechanism for each of these diseases is inflammation. COPD is chronic irreversible airway obstruction with respiratory symptoms similar to those of asthma, with the exception of chest tightness which tends to be less prominent with COPD. Chronic bronchitis, chronic asthma, and SAD are associated pathophysiologically with development of COPD, as is emphysema, a disease of the alveoli or air sacs in the lung.

Smoking is the most common cause of COPD. As Agusti and Hogg stated in their update of the pathogenesis of COPD, "For almost 50 years, since Fletcher and Peto reported their seminal observation in young working men in London, COPD has been widely accepted as a self-inflicted condition caused by tobacco smoking."[3,4] But we now know that non-smokers are diagnosed with COPD, and that COPD is a multi-factorial disease.

The U.S Department of Health and Human Services/Centers for Disease Control and Prevention (CDC) recently estimated that 24% of adults with COPD have never smoked.[5] Population-attributable fractions (PAF) for smoking range from 9.7 to 97.9%, with the majority of PAF estimates being less than 80%.[6] Variability in prevalence is related to gender and age of the study population, the proportion of smokers, diagnostic criteria used, and differences in methods used to calculate PAF. The prevalence of COPD is higher in industrialized countries than in developing countries. Published data indicate that factors other than smoking, or in addition to smoking, are important contributors to the development of COPD. These factors include genes; chronic asthma; air pollution; second-hand smoke; occupational exposures to vapors, gases, dusts, and fumes (VGDF); exposure to wood smoke and biomass fuels used in heating and cooking; and frequent pulmonary infections in childhood.[2,6] COPD is associated with a number of co-morbidities and is believed to contribute independently (of smoking) and causally to increase in risk for lung cancer.

The purpose of this paper is to review COPD and etiologic factors that have been shown to be important to development of disease. COPD is a preventable disease. Understanding etiologic factors is necessary for reducing risk for disease and improving prognosis once COPD has been diagnosed. The impact of Interactions between occupational exposures and smoking on risk for disease will be examined. A companion piece will explore dose-response relationships between dust exposures and risk for COPD.

DEFINITION

The Science Committee of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in its 2018 Report defined COPD as "a common, preventable and treatable disease that is characterized by persistent airway symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1] The American Thoracic Society (ATS) in its examination of published epidemiologic evidence in order to assess the global burden of COPD and novel risk factors used three broad definitions of COPD: spirometry-based (e.g., GOLD FEV1/FVC < 0.70); symptom-based, specifically chronic bronchitis (cough and sputum production for $\geq$ 3 months/year for $\geq$ 2 consecutive years); and self-reported physician diagnosis of chronic bronchitis, emphysema, or COPD.[6] The weight given to each study depended on the definition of COPD, with greatest weight being given to those studies that used spirometry-based definitions and the least to those studies reliant upon self-report.

Chronic bronchitis and emphysema have been used clinically in the past to indicate obstructive airways disease. Diagnosis of the former is symptom-based and of the latter, pathology-based. Timens et al in *Spencer's Pathology of the Lung* describe three pathologic components of COPD.[7] These are chronic bronchitis and bronchiolitis, affecting the large and small airways, respectively, and emphysema. Anatomy and clinical characteristics of these conditions vary. The basic mechanism, inflammation, does not. The importance of external exposures to the development of COPD is clear from the anatomical relationship between the respiratory tract and the external environment. The airways are in open communication with the environment and lead directly to the alveoli. Inhaled particulate and gaseous matter cause inflammatory changes in the airways, the alveoli, or both depending on particle size and solubility.

The ATS in its Public Policy Statement of 2010 recognizes the heterogeneity of COPD, noting chronic airflow obstruction as the single common denominator.[6] The criterion used by GOLD, the ATS, and the British Thoracic Society to define airflow obstruction is post-bronchodilator FEV1/FVC < 0.70.[1,6,8] The basic pathophysiologic mechanism is inflammation. Disease of the small airways occurs early-on and predicts progression of COPD and functional decline in FEV1.[9-11] SAD manifests physiologically as decreased airflow at 25-50% and 75% of vital capacity (FEF_{25-50} and FEF_{75}) on spirometry.[1] Because these findings are nonspecific and will likely precede the development of obstruction defined as FEV1/FVC < 0.70, they are often overlooked or ignored. The significance of SAD has been considered somewhat controversial in the past.[11] As we are becoming better able to detect, measure, and monitor SAD using physiologic, tomographic, and other tools, it may emerge as an important component of the definition of obstruction and therefore of COPD.[10,11] At the very least, in the context of exposure to cigarette smoke and/or occupational exposure to VGDF, evidence of SAD may provide an opportunity for prevention of COPD as currently defined.

DIAGNOSIS

Diagnosis of COPD depends upon suspecting the diagnosis. Guidelines recommended by the British Thoracic Society state that breathlessness, chronic cough, sputum production, "frequent winter bronchitis", and wheeze suggest COPD in at-risk individuals over the age of 35 years.[8] GOLD advises that COPD should be considered in those with typical respiratory symptoms and/or risk factors for disease. Warning signs are persistent dyspnea, progressive over time and worse with exertion; chronic cough; chronic sputum production; and recurrent wheeze.[1] A history of frequent respiratory tract infections

may be an indicator. Risk factors include host factors such as positive family history, tobacco smoke, smoke from home cooking and heating fuels such as biomass, and occupational exposure to VGDF. The greater the number of variables present, the greater the likelihood of disease. Risk factors on their own may be sufficient to warrant further investigation.

A diagnosis of COPD must be confirmed with objective measurements.[1,8] Because physical evidence of disease is generally not present until disease is in advanced stages, physical examination may provide support for a suspected diagnosis, but it is not confirmatory. There is consensus that spirometry is "the most reproducible and objective measurement of airflow limitation."[1]

Confirmation of the diagnosis of COPD is based upon post-bronchodilator FEV1/FVC < 0.70.[1,6,8] Asthma can mimic COPD, and vice versa, so that the magnitude of the bronchodilator response should be taken into account in diagnostic considerations and treatment decisions. It is important to note that improvement in the FEV1/FVC ratio to > 0.70 does not equate with resolution of disease.[12] Such a transition may be attributable to decline in FVC, as Guillamet et al point out, or to successful treatment with medication and/or removal from toxic exposures.

The recommendation of the use of an absolute ratio as the criterion for diagnosis of COPD is based upon its simplicity, its freedom from reference values, and its common use in epidemiologic studies that provide basis for existing guidelines.[1] However, the use of a fixed threshold has been called into question. There are epidemiologic data to support the use of lower and upper limits of normal (LLN and ULN, respectively) to define the normal range. Clinically obstruction is often defined as FEV1/FVC < LLN. The LLN for spirometric parameters is based upon the 95% confidence interval around a mean value determined on the basis of epidemiologic studies of representative populations. Age, gender, race, and ethnicity are variables used in developing prediction equations for absolute predicted values.[13] Socioeconomic factors have also been taken into account. For example, predicted values more relevant to workers have been derived from studies of blue-collar workers.[14]

The clinical validity of the use of a fixed FEV1/FVC threshold of < 0.70 to define COPD was reaffirmed in a cohort study by Bhatt et al of 24,207 participants enrolled in the National Heart, Lung, and Blood Institute Pooled Cohorts Study from 1987 to 2000 and followed to 2016.**[15]** The outcome of interest was the predictive value of different definitions of obstruction for COPD hospitalizations and COPD mortality. COPD was defined by fixed thresholds ranging from 0.75 to 0.65 and by FEV1/FVC less than the LLN. Seventy-seven percent (n=11,077) achieved complete 15-year follow-up. A fixed threshold of < 0.70 for FEV1/FVC was as effective or more effective than other fixed thresholds and LLN in discrimination of COPD-related hospitalizations and death. The authors concluded that their findings support the use of FEV1/FVC < 0.70 to identify individuals at risk for clinically significant COPD.

To be reliable, pulmonary function test results must be reproducible and acceptable using criteria set forth by the ATS and the European Respiratory Society.[1,16,17] A comment on patient effort by the pulmonary technician performing the lung function tests is helpful to assessment of reliability of test results. However, test results that are not reproducible should not be attributed automatically to poor effort as epidemiologic studies have shown that participants with respiratory disease are less likely to perform spirometry reproducibly.[18] The exclusion of these participants on the basis that they are not giving full effort is likely to bias results toward the null (i.e., there is no association with exposures such as VGDF or cigarette smoke).

Spirometry is used not only to diagnose COPD and but also to determine severity.[1] The algorithm recommended by GOLD is as follows: GOLD 1: mild, FEV1 $\geq$ 80% predicted; GOLD 2: moderate, 50% $\leq$ FEV1 < 80% predicted; severe GOLD 3: 30% $\leq$ FEV1 < 50% predicted; GOLD 4: very severe FEV1 < 30% predicted. Lung volumes and single breath diffusing capacity for carbon monoxide (DLCO) are important to further characterizing the nature and severity of disease in an objective manner. For example, increase in lung volumes outside the normal range (> 120% predicted or > ULN) indicate air trapping that may be the consequence of SAD and/or emphysema. A normal total lung capacity in the presence of reduced FEV1/FVC, or with other indicators of obstruction but normal FEV1/FVC, may indicate co-existent restriction. Reduction in DLCO in the presence of obstruction indicates impaired gas exchange likely due to emphysema, in the absence of other causes of impairment in gas exchange.

COPD is a complex chronic condition. In some cases, its diagnosis is straightforward and clear-cut. In other cases it is complicated by other or co-existent disease such as asthma or a restrictive ventilatory deficit caused by interstitial fibrosis. It is associated with a number of co-morbidities that may obscure the clinical picture and make COPD diagnosis more difficult. These include heart disease, pulmonary hypertension, musculoskeletal dysfunction, and metabolic syndrome. COPD is a risk factor for lung cancer independent of co-existent exposures to lung carcinogens such as cigarette smoke.[19] Early diagnosis and determination of causal attribution is key because it provides the opportunity to prevent worsening of respiratory symptoms and lung function.

ETIOLOGY: OCCUPATIONAL EXPOSURES

Epidemiologic Studies of General Populations and Exposures

As Naidoo reminds us in his editorial entitled "Occupational exposures and chronic obstructive pulmonary disease: incontrovertible evidence for causality?", it was in 1984 that the U.S. Surgeon General published a report arguing that up to 90% of cases of COPD were caused by smoking. And only one year later that Margaret Becklake published an article describing the relationship between chronic airflow limitation and work in the dusty trades.[20-22] In 1989 Becklake authored a review setting forth evidence for a causal association between occupational exposures and the development of COPD.[23] She reviewed the published scientific literature on respiratory health effects of occupational exposure to airborne dusts, vapors, and fumes, with a focus on chronic obstructive airway disease. Becklake concludes "This evidence, reviewed here according to accepted criteria for establishing causality, leaves little doubt that occupational exposure to dust and/or to dust and fumes may be causally implicated in the genesis of COPD."

Over time, evidence supporting such an association has grown substantially. An Official Statement of the ATS and the European Respiratory Society published in June, 2019 examines "The Occupational Burden of Nonmalignant Respiratory Diseases."[24] The authors conducted an exhaustive review of published population-based studies of the occupational burden of COPD; chronic bronchitis; asthma; idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases; hypersensitivity pneumonitis and other granulomatous lung diseases such as sarcoidosis; and tuberculosis and community-acquired pneumonia. For classic occupational pneumoconiosis, a PAF of 100% was assumed. For COPD, PAF was estimated based on the reported PAF or derived from case-control and cohort studies. COPD was defined on the basis of spirometry vs. self-report, using LLN where possible; exposure was determined based on job-exposure matrix (JEM) vs. self-report where possible. Where

data were stratified by smoking status, separate pooled-analyses were carried out for ever-smokers and for never-smokers. Twenty-six studies were reviewed to estimate pooled PAF for occupational contribution to COPD burden. The overall pooled PAF adjusting for smoking was 14% (95% CI 10-18%). For never-smokers, the pooled PAF for never-smokers was 31% (95% CI 18-43%), similar to that observed by Hnizdo et al in their examination of COPD and occupation/industry in the U.S. using data from the Third National Health and Nutrition Examination Survey (NHANES III).[25]

GOLD in its 2001 report identified both host and environmental risk factors for the development of COPD.[26] Environmental risk factors included tobacco smoke and occupational dusts and chemicals. With regard to the latter, the Scientific Committee wrote "When the exposures are sufficiently intense or prolonged, occupational dusts and chemicals (vapors, irritants, fumes) can cause COPD independently of cigarette smoking and increase the risk of the disease in the presence of concurrent cigarette smoking."

In 2003 the ATS published an Official Statement on "Occupational contribution to the burden of airway disease."[27] In preparing this document, a committee of the ATS conducted an extensive review of existing published literature, including case reports and cross-sectional, case-control, and cohort studies, in order to quantify the contribution of workplace exposures to the burden of asthma and COPD. Among the difficulties encountered for COPD was the historic lack of a standardized definition. The committee concluded that a reasonable estimate of population-attributable risk (PAR) for occupational exposures in the case of COPD was 15%, similar to the 14% observed in a more-recently published analysis.[24]

The importance of SAD in the development of COPD is discussed above.[9-11] In their review of the epidemiology and pathology of COPD caused by occupational exposure to silica dust, Hnizdo et al discuss SAD attributable to mineral dust exposure (MDAD) more generally.[28] SAD is detectable physiologically and pathologically. Physiologically SAD manifests as decreased airflow in the small airways of the lung (FEF_{25-75}, FEF_{75}). Pathologically the disease affects the respiratory bronchioles and alveolar ducts, with the respiratory bronchioles being affected first. In the case of MDAD, described early on by Churg et al, peribronchiolar fibrosis and pigment changes are common.[29] Compared to SAD in smokers, MDAD is characterized by marked thickening and fibrosis of the wall of the respiratory bronchiole and the presence of golden iron and/or black carbon pigment *vs.* thinner bronchiolar walls and a relative paucity of pigment seen in smokers.

Of 53 dust-exposed workers evaluated by Churg et al, 25% (n=13) had evidence of MDAD compared to 0.8% (1 of 121) non-mineral-dust exposed subjects.[29] Pathologic changes affected not only the respiratory bronchioles but also the membranous bronchioles. Compared to 53 unexposed subjects, significant declines in FEV_{25-75}, FEV1, FVC, and DLCO were observed in the exposed group with MDAD, as was increase in RV/TLC consistent with obstruction and air trapping. Age and smoking habits of the two groups were similar. These findings are particularly significant given the likely etiologic importance of SAD and MDAD in the development of COPD.

The ATS in its 2010 Public Policy Statement concludes that existing evidence supports a causal association between occupational exposures to VGDF and the development of COPD.[6] The stated bases for its conclusion are several. The data were obtained from "high quality" epidemiologic studies, using variable definitions of COPD: respiratory symptoms, spirometric evidence of obstruction, physician diagnosis, and mortality. The evidence includes demonstrated dose-response relationships and

temporal associations. Experimental studies in animals have shown development of pathologic changes consistent with chronic bronchitis and/or emphysema following exposure to agents shown to be associated with COPD in epidemiologic studies of humans.

A case-control study of COPD and occupational exposures was carried out by Weinmann et al in adult members of Kaiser Permanente Northwest (KPNW), a large managed care organization.[30] Cases were selected on the basis of lung function test results that met criteria for obstruction defined as FEV1/FVC < LLN using prediction equations from the NHANES III survey.[25] A telephone interview survey was then conducted of cases (n=388) and controls (n=356). Experienced certified industrial hygienists from KPNW and the National Institute of Occupational Safety and Health (NIOSH) assessed and categorized workplace exposure histories.

Study results revealed increased OR's among all subjects for *mineral dust* (odds ratio (OR) 1.7, 95% confidence interval (CI) 1.1-2.7), *irritant gases and vapors* (OR 1.6, 95% CI 1.2-2.2), *diesel exhaust* (OR 1.9, 95% CI 1.3-3.0), *irritant gases or vapors* (OR 1.6, 95% CI 1.2-2.2), and the *sensitizers/organic solvents* (GVSS) (OR 1.7, 95% CI 1.2-2.4).[30] When examined by smoking status, in the group of never smokers (n=100), significant or borderline-significant increases in ORs were observed for mineral dust (OR 3.5, 95% CI 0.94-13.3), diesel exhaust (OR 6.4, 95% CI 1.3-31.6), GVSS (OR 2.3, 95% CI 0.96-5.6), and any dust, GVSS or diesel exhaust (OR 2.4, 95% CI 0.99-5.6).

When data were examined by level of exposure (low vs. high), at high levels ORs among smokers were significantly elevated for the following exposures: metal dust, mineral dust, gases/vapors, dust composite, and dust/GVSS/diesel. At low-level exposure, ORs were significantly elevated for diesel exhaust and GVSS. Consistent with the recognition of chronic asthma as a novel risk factor for COPD, personal history of asthma was significantly associated with COPD in both ever and never smokers in the current study ($p<0.05$).[6,30]

Omland et al conducted a systematic search of the published scientific literature for peer-reviewed epidemiologic studies of occupational exposures and COPD.[31] Of 4,528 citations found, the authors selected 147 for review. Criteria for selection included pulmonary function testing, sufficient occupational history, and use of external or internal referents. Ten panel members who conducted the review included occupational physicians, pulmonary physicians, and experts in respiratory physiology from five different countries. Occupational exposures to the general category VGDF and more specifically to inorganic and mineral dusts and to organic and biologic dusts were examined. Of the studies reviewed, only two were studies of coal and gold miners. These were not included in the general analysis because of potentially confounding factors such as co-existent pneumoconiosis and/or tuberculosis.

Despite the heterogeneity of study populations and study designs, the authors found consistency of association between occupational exposures and COPD. Exposure preceded the development of disease, satisfying Sir Austin Bradford Hill's criterion of *temporal association* for causation.[32] Dose-response relationships were observed in more recently-conducted studies. Despite limitations introduced by variability in determination of definition of "COPD", the authors concluded that there was "strong evidence" of a causal association between occupational exposures and development of COPD.

The Collegium Ramazzini, an international organization of 180 occupational and environmental health professionals, issued a position statement in 2016 entitled "A New Approach to the Control of Chronic Obstructive Pulmonary Disease (COPD)."[33] The Collegium committee reviewed published epidemiologic and experimental studies of relationships between exposure to vapors, gases, dusts, and fumes and development of COPD, as well as existing regulatory standards for workplace exposures. The Collegium advised the use of a new paradigm to improve recognition and regulation of risks associated with occupational exposures to VGDF. The suggested paradigm is the recognition and regulation of *mixtures* of agents rather than a single agent at a time, as such mixed exposures are the reality for most workers. Similarly, the Collegium advised recognition and consideration of combined risks from tobacco smoke, occupational exposures, and environmental exposures as etiologically important in development of COPD and in its prevention.

Epidemiologic Studies of Specific Populations and Exposures

Epidemiologic studies of work and COPD have revealed significant associations with specific occupations and occupational exposures. Using data from NHANES III collected during the period 1988 to 1994, Hnizdo et al estimated that 19% of cases of COPD in the United States are attributable to workplace exposures.[25] NHANES surveys are conducted on a continuous basis and released in two-year cycles. The surveys consist of a detailed in-home telephone interview and a subsequent physical examination that includes spirometry. In the Hnizdo study COPD was defined by spirometry as FEV1/FVC < 0.70 and FEV1 < 80% predicted; the GOLD criteria in use at that time. Among nonsmokers, the PAR was 31%. Among all subjects with COPD, there was a 20% increase in risk for the occupational category of laborer or other construction trades worker (OR 1.2, 95% CI 0.6-2.5); for nonsmokers, observed OR was 3.4 (95% CI 1.1-10.5). For the occupational grouping that included laborers or other construction workers, there was increasing risk with increasing duration of work at the trade: for 1-14 years, OR 1.4 (95% CI 1.0-1.9); for $\geq$ 15 years, OR 1.5 (95% CI 1.2-2.0).

In 2019 Kurth et al reported the results of their examination of airflow obstruction and work in the U.S. using data from three NHANES surveys: 2007-2008, 2009-2010, and 2011-2012.[34] Data were obtained and analyzed for ever-employed U.S. adults ages 18 to 79 years by industry and occupation. Airflow obstruction was defined on the basis of spirometry: pre-bronchodilator values showing FEV1/FVC < LLN; when FEV1 was < 70% of predicted, additional analysis was undertaken to determine severity of obstruction. Employment history was based on the longest-held job.

The number of participants was 13,044. Prevalence of airflow obstruction was 7.15% among never smokers and 18.47%% among ever smokers. By industry, the highest prevalence was observed for *mining* where prevalence of airflow obstruction was 22.66% (95% CI 10.78-34.54); and a twofold increase in prevalence odds ratio (POR) was observed (POR 2.04, 95% CI 1.05-3.97). Significant increases in POR were also observed for workers employed in the *manufacture of motor vehicles and motor vehicle equipment* (POR 1.66, 95% CI 1.20-2.30), *construction* (POR 1.64, 95% CI 1.26-2.13), and *services to buildings, landscaping, and waste management* (POR 1.57, 95% CI 1.08-2.27). POR was adjusted for age, gender, race/Hispanic origin, and smoking status. By occupation, the highest prevalence was observed for extraction at 34.49%, with POR 3.82, 95% CI 1.55-9.43. Significant increases in POR were also observed for *bookbinders and printers* (POR 3.14, 95% CI 1.56-6.30); *installation, maintenance, and repair* (POR 3.11, 95% CI 1.48-6.55); and *construction laborers and construction trades helpers* (POR 1.94, 95% CI 1.28-2.94). Potential occupational exposures cited for miners and extraction workers were

diesel exhaust; volatile organic compounds; polycyclic aromatic hydrocarbons; fumes; dusts such as silica, coal dust, and metallic compounds; as well as "other chemicals."

Using the same NHANES dataset, Doney et al examined associations between self-reported occupational exposures and airflow obstruction and self-reported COPD.[35] Airflow obstruction was determined on the basis of spirometry showing FEV1/FVC < LLN. Self-reported COPD was defined as a positive response to the questions have you ever been told by a physician or other health care professional that you have chronic bronchitis and that you still have chronic bronchitis, or that you have emphysema. Occupational exposure information was obtained for any job and for number of years of exposure. In addition to specific self-reported workplace exposures, a COPD-job exposure matrix (JEM) previously constructed by the National Institute of Occupational Safety and Health (NIOSH) was used to assign level of exposure (low, medium, high).

POR for self-reported occupational exposure to organic dust was significantly elevated for airflow obstruction and for self-reported COPD at POR 1.23, 95% CI 1.05-1.44 and POR 1.64, 95% CI 1.29-2.08, respectively. For self-reported COPD, POR's were significantly elevated for the following: mineral dust (POR 1.62, 95% CI 1.19-2.21); exhaust fumes (POR 2.01, 95% CI 1.48-2.74); other gases/vapors/fumes (POR 1.47, 95% CI 1.20-1.79); and ever dust and/or fumes (POR 2.04, 95% CI 1.64-2.53). Elevation in POR for exhaust fumes was borderline significant (POR 1.13, 95% CI 0.97-1.31). Among ever smokers and never smokers, prevalence of occupational exposures overall and of the following specific exposures was elevated: mineral dust, organic dust, exhaust fumes, other gases/vapors/fumes, and ever dust and/or fumes. Prevalence was higher among ever smokers. The authors concluded that in a nationally-representative study, airflow obstruction and self-reported COPD were associated with workplace exposures determined both by self-report and JEM-assignment.

Mabila et al used data from the U.S. National Health Interview Survey (NHIS) conducted 2006-2015 to examine risk for obstructive airways disease in mining occupations, stratified by dust exposure level.[36] The NHIS is a cross-sectional telephone-interview survey of non-institutionalized adults in the U.S. conducted on an annual basis by the National Center for Health Statistics. Participants with the industry code of "mining" were classified as miners. The type of mine was not specified. Chronic bronchitis, emphysema, and asthma were each defined as positive responses to the questions "During the past 12 months have you been told by a doctor or other health professional that you have" chronic bronchitis, emphysema, or asthma, respectively. COPD was determined on the basis of positive response to the question for either chronic bronchitis or emphysema. Mine dust exposures were categorized as low, moderate, high, and very high. Very high exposure levels were assigned to extraction workers defined as *drillers, blast/explosive technicians, long wall operators, and roof bolters*.

The number of mining workers who participated in the NHIS surveys during the period in question was 1,531. Of these, 44.3% gave mining as their occupation of longest duration; 44.7% were never smokers. In multivariate analysis controlling for age, gender, race, and smoking status, significant increases in ORs were observed in the very-highly exposed group for the following outcomes, using the low exposure group as a referent: chronic bronchitis (OR 2.18, 95% CI 1.02-4.64), emphysema (OR 7.85, 95% CI 1.70-36.27), and COPD (OR 2.56, 95% CI 1.29-5.12). The finding of significant increase in OR for these disease outcomes, while taking into account smoking status (never, former, current), provided support for the independent association between exposure to respirable mineral dust and development of COPD, in the stated view of Mabila et al.

Using data from the NHIS survey 2013-2017, Syamlal et al examined the prevalence of COPD by industry and occupation in a representative sample of never-smoking adults age 18 or older.[5] Definition of COPD was a positive response to one or more of the following questions: 1) "Have you ever been told by a doctor or other health professional that you had chronic obstructive pulmonary disease, also called COPD?" 2) "Have you ever been told by a doctor or other health professional that you had emphysema?" 3) During the past 12 months, have you been told by a doctor or other health professional that you had chronic bronchitis?" Respondents were considered never smokers if they had never smoked or if they had smoked less than 100 cigarettes in their lifetime.

In a representative sample of the estimated population of 164 million adults in the U.S. working at any time during the 12 months preceding the interview, among ever-smokers COPD prevalence was 6.0% (n=3.4 million) and among never-smokers, 2.2% (n=2.4 million).[5] Prevalence varied by age, gender, self-perceived health, and industry and occupation. For each of these variables, prevalence was uniformly higher among women than men. Among adults overall age $\geq$ 65 years, prevalence was 4.6% (95% CI 3.8-5.4). For those who self-reported poor/fair health, prevalence was 7.8% (95% CI 6.4-9.2) among women and 5.3% (95% CI 3.9-6.7) among men.

With regard to industry, significant elevation in COPD prevalence were observed for women but not men for *wholesale trade, transportation and warehousing, and information*. With regard to occupational groups, the highest COPD prevalence was observed among women for the following: office and administrative support (4.0%, 95% CI 3.3-4.6), production (4.4%, 95% CI 2.0-6.8), and transportation and material moving (4.5%, 95% CI 2.1-6.8).

In this survey, 35% of respondents were ever smokers and 65%, never smokers. Among ever smokers, 3.8% reported chronic bronchitis, while 1.1% and 2.5% reported emphysema and COPD, respectively. For never smokers 1.9% reported chronic bronchitis and 0.1% and 0.4% emphysema and COPD, respectively. Thus, chronic bronchitis was reported 3.5 times more frequently than emphysema by ever smokers, and 19 times more frequently by never smokers, suggesting that COPD is more often caused by chronic bronchitis among never smokers compared to ever smokers.

Railroad workers exposed to diesel exhaust, silica, and asbestos dust have been shown to be at increased risk for COPD mortality. In a case-control study of railroad workers exposed to diesel exhaust, Hart et al observed a significant increase in risk for COPD mortality among railroad engineers and conductors, taking smoking into account.[37] For those with $\geq$ 16 years of work for the railroad, OR 1.67 (95% CI 1.17-2.39) was observed. Test for trend (increasing risk for COPD mortality with increasing years of work for the railroad) was significant (p=0.01). A similar increase in risk for COPD mortality was observed by Hart el al in a cohort study of railroad workers followed from 1959 to 1996.[38] For engineers and brakemen hired after 1945 with $\geq$ 20 years of work for the railroad, HR 1.67 3.3, 95% CI 1.03-2.71, was observed, controlling for smoking.

On March 25, 2016, the U.S. Occupational Safety and Health Administration (OSHA) promulgated its silica standard: *Occupational Exposure to Respirable Crystalline Silica; Final Rule*.[39] The current silica standard reduces the permissible exposure limit (PEL) for respirable crystalline silica from 100 µgm/m3 to 50 µgm/m3. Among the bases cited by OSHA for its regulatory decision to decrease the PEL was the increase in risk for non-malignant respiratory disease (NMRD) shown to be associated with occupational exposure to respirable crystalline silica. OSHA concluded that there is a dose-response relationship between respirable crystalline silica and risk for NMRD, exclusive of silicosis. These NMRDs

are primarily COPD, chronic bronchitis, and emphysema. OSHA further concluded that "the risk is strongly influenced by smoking and opined that the effects of smoking and silica exposure may be synergistic" (p.16310).

OCCUPATIONAL EXPOSURES: LONGITUDINAL EFFECT ON LUNG FUNCTION

A number of investigators have examined the effect of ongoing occupational exposures to VGDF on lung function over time.[40-44]

Risk factors for incidence of COPD and increased rate of decline in FEV1 were examined by Krzyzanowski et al in a 13-year follow-up study of a cohort of randomly selected residents of Cracow.[40] Examinations consisting of questionnaires administered by trained interviewers, and spirometry, were conducted at baseline in 1968 and at follow-up in 1981. Respiratory symptoms, smoking habits, and occupational exposure to dusts and chemicals were queried. Results are described here for male participants in both surveys (n=759). COPD was defined as FEV1 < 65% of predicted. Those considered at risk at baseline were those without evidence of obstruction (FEV1 $\geq$ 70% of predicted (n=731)).

Although respiratory symptoms were associated with lower baseline FEV1, none was significantly associated with rate of decline in FEV1. Self-reported occupational exposure to dusts and/or to chemicals was not associated with baseline FEV1. Each exposure was associated with excessive rate of decline in FEV1 over the 13-year period of the study for the exposed group compared to the unexposed group. For the group with exposure to dusts, baseline FEV1 was 3.99 L and rate of FEV1 decline, 61.1 ml/yr, $0.01<p<0.05$. For the group with exposure to chemicals, baseline FEV1 was 4.06 L and rate of FEV1 decline, 61.3 ml/yr, $0.01<p<0.05$. Occupational exposure to dusts and/or chemicals did not emerge as a significant predictor of COPD incidence as defined; although for dust exposure, incidence was higher in those exposed vs. unexposed (10.7% vs. 7.7%, $p<0.10$).

Humerfelt et al conducted a cohort study of 1,933 Norwegian men randomly selected from the Population Registry of Bergen.[41] The purpose of the study was to assess the relationship between smoking and occupational exposures on rate of decline in FEV1 over the period of recruitment in 1965-1970 to follow-up in 1988-1990. The examination consisted of self-administered questionnaires and spirometry. "Airflow limitation" was defined as FEV1/FVC < 0.65. Smoking was defined on the basis of smoking status and number of cigarettes/day: < 10 and $\geq$ 10. Occupational exposures of interest were the following: mineral dusts (asbestos, quartz), gases (ammonia, chlorine, nitrous oxide, ozone, sulfur dioxide), vapors and fume (aldehydes, anhydrides, diisocyanates), and metals (chromium, nickel, platinum).

A total of 951 men participated in both surveys. Mean baseline FEV1 was normal in the total group and in the group participating in both surveys at 99.7% predicted and 100.3% predicted, respectively. Distribution by smoking status was 66% current smokers, 16% former smokers, and 18% never smokers. The proportion without known occupational exposure was 56.9%. For this group, annual decline in FEV1 was 51.9 ($\pm$0.8) ml; 10% had airflow limitation at follow-up. Compared to the unexposed group, exposure to sulfur dioxide and metals was associated with significant decline in FEV1 at 58.7 ($\pm$2.7) and 56.8 ($\pm$1.9) ml/yr, respectively, $p<0.05$. Age, height, and smoking were also significantly associated with rate of decline ($p<0.01$). Twenty-eight percent of those with asbestos exposure had airflow limitation at follow-up ($p<0.05$). For the remaining occupational agents, the proportion with airflow limitation at the end of the follow-up period was not significantly different from

the referent group. Test for trend for increasing decline in annual FEV1 with exposure to increasing numbers of occupational agents was significant ($p<0.01$). In multiple regression analysis controlling for age, height, and smoking, the decline in FEV1 ml/yr per occupational exposure agent was statistically significant ($p=0.01$).

Humerfelt et al concluded that their findings demonstrate a dose-response relationship between occupational exposure to an increasing number of irritant agents and accelerated decline in FEV1 in men. For those reporting occupational exposure to six or more agents, the adjusted annual decline in FEV1 was 61 ml. These findings provide support for the paradigm suggested by the Collegium Ramazzini in their 2016 position paper, namely assess and regulate mixtures of agents rather than a single agent at a time.

The population-based studies of Krzyzanowski et al and Humerfelt et al reveal longitudinal declines in FEV1 that are remarkably similar to each other and to those observed by Kauffmann et al in an earlier study of 556 male factory workers in and around Paris.[40-42] Men aged 30 to 54 working in 11 factories in the Paris area were recruited in 1960-1961 and re-examined in 1972-1973. The examination consisted of personal interviews to obtain information about respiratory symptoms, smoking habits, and workplace exposures, and spirometry. Factory types were metallurgy, chemistry, printing, and flour/milling.

At the time of the initial survey, engineers and "industrial" physicians visited each of the factories to ascertain, qualify, and roughly quantify physical and chemical exposures. Heat and work out of doors were identified as physical hazards; and mineral and organic dusts, and vapors and gases, as chemical hazards. Among the mineral dusts identified were silica, coal, iron, and other metal and mineral dusts. Gases included chlorine, sulfur dioxide, ammonia, halogenated hydrocarbons, and phenol and plastics. Dust exposure was graded as slight or noticeable degrees 1, 2, or 3 depending on intensity. Gas exposure was graded as low or high, with high being defined as exposure without respiratory protection for > 1 hour/week. Heat was judged as none, low, or high.

FEV1 and FVC were determined at baseline and follow-up, and decline in FEV1 and FVC at follow-up in ml/yr. Job changes occurred for 59% of the study population during the study period. To adjust for these changes and the possible impact on FEV1 slope (change over time), the authors used the average of the initial and follow-up $FEV1/H^3$ to determine the FEV1 and FVC slopes. Age range in 1960 was 37 to 43 years. FEV1 slope adjusted for age, smoking, and $FEV1/H^3$ varied by factory type and ranged from 31 to 65 ml/yr. Greater loss was observed for work in flour/milling. Variability by specific exposure was also observed, with significant decline in FEV1 being associated with exposure to dusts as a whole and silica, abrasives, iron, other mineral dusts, and plant dusts specifically; to oil of turpentine, resins, and varnishes; and to heat, $p\leq0.01$. For exposure to noticeable dust degree 3, observed adjusted declines in FEV1 and FVC were 61 and 60 ml/yr, respectively. This annual FEV1 decline is virtually identical to annual loss in FEV1 observed by Krzyanowski et al and Humerfelt et al in different populations of occupationally-exposed workers.

Ulvestad et al conducted an 8-year longitudinal follow-up study of lung function in underground tunnel workers (TW) in heavy construction in Norway.[43] Excluded from the study were workers $\geq$ 55 years of age in 1991 and those with physician-diagnosed asthma or COPD at baseline.

Ninety-six TWs, 178 outdoor construction workers, and 71 white-collar employees were examined in 1991 and again in 1999. Exposures of interest were total dust, respirable dust, α-quartz, oil mist, and NO2. Smoking was defined by pack-years of cigarettes and status: current, former, never. Outcomes of interest were respiratory symptoms (any, morning cough, cough during the day, shortness of breath with exertion, attacks of dyspnea, and wheeze), FEV1, FVC, and FEF25-75. Age and height were similar in the three groups. Fewer white- collar employees were current smokers (31% vs. 52%). Duration of employment was 19 (±8), 16 (±8), and 18 (±9), respectively.

TWs were subdivided on the basis of job description into drillers (n=79) and shotcreters (n=17). Drillers perform conventional drilling and blast operations; shotcreters spray concrete on tunnel walls. Shotcreters experienced higher mean cumulative exposure to respirable dust (25.4 (±0.9) mg.y/m3 vs. 9.6 (±0.2) mg.y/m3) than drillers, while drillers were more highly exposed to α-quartz (0.35 (±0.01) mg.y/m3 vs. 0.13 (±0.01) mg.y/m3). Cumulative exposures were adjusted for sick leave and other longer periods of absence.

Baseline FEV1, FVC, and FEF25-75 were normal and similar in drillers, shotcreters, and the referent group as a whole. Statistically significant differences were observed among the groups with regard to decline in FEV1 over the study period: drillers, 430 (± 40) ml; shotcreters, 540 (± 100) ml; and referents 260 (± 20) ml, $p<0.001$. Significant associations were observed between decline in FEV1 and cumulative exposure to respirable dust ($p<0.001$) and α-quartz ($p=0.02$). Significant declines in FEF25-75 were also observed for shotcreters compared to the referent group ($p=0.006$). The groups did not differ with regard to change in FVC over the eight-year period of the study. For a TW 40 years of age, the regression model predicted annual declines in FEV1 as follows: unexposed non-smoker, 25 ml/yr; unexposed smoker, 35 ml/yr; non-smoking driller, 50 ml/yr; and non-smoking shotcreter, 63 ml/yr. Regression models were adjusted for age and pack-years of smoking.

Significant ORs were observed for TWs and any respiratory symptom (OR 3.8, 95% CI 2.3-6.4) and for each of the specific respiratory symptoms of interest. The associations with cumulative respirable dust exposure were also statistically significant for any respiratory symptom (OR 2.9, 95% CI 1.9-4.5) and for each specific symptom.

Ulvestad et al concluded that cumulative occupational exposure to respirable dust and α-quartz are significant risk factors for airflow limitation in underground heavy construction workers, with cumulative respirable dust exposure being a major risk factor for respiratory symptoms as well.

Harber et al conducted a longitudinal follow-up study of the effect of occupational exposures on lung function in 5,724 participants in the Lung Health Study (LHS).[44] The LHS is a multicentre study of smoking cessation and anticholinergic bronchodilator administration in subjects with early COPD in the U.S. and Canada. Early COPD was defined as FEV1/FVC < 0.70 and FEV1 55-90% predicted. Subjects were recruited beginning in 1986 and followed for five years with annual examinations. At baseline, occupational and smoking histories were obtained; and spirometry (pre- and post-bronchodilator (BD)) and methacholine challenge testing (MCT) were performed, the latter to determine airway hyper-responsiveness. At each annual exam, exposure and smoking histories were updated and spirometry performed. Work history included employment status; current, prior, and usual job; and self-reported exposure to dust or fume or "mask use" at current job. Cigarette use was defined at baseline as number of cigarettes/day and thereafter, as smoking status and categorically by number of cigarettes per day, e.g., 0, 1-15, 16-25, etc.

Among 3,592 male participants, baseline and 5-year average post-BD FEV1 was 78.4 (±9.2) % predicted and 75.0 (±12.0) % predicted, respectively. FEV1/FVC was 0.65 (±.06) and 0.62 (±.08) at baseline and follow-up, respectively. Ninety-one percent were employed at baseline; 77.8% at 5-year follow-up. At baseline 13.9% (n=499) reported workplace exposure to both dust and fume; five years later, 20.6% (n=690) reported exposure to both. At 5-year follow-up, occupational exposure to fume but not dust was associated with a significant decline in post-BD FEV1 of 0.25% predicted per year in the five mixed-effect regression models in which it was tested (range -0.218 (p=0.038) to -0.263 (p=0.011)). The mixed-effect models used controlled for baseline FEV1 and airway hyper-responsiveness, and allowed separation of effect of cumulative exposure as measured by baseline post-BD FEV1 and effect of exposures over time. Smoking status was also associated with significant decline in % predicted (p<0.0001). Continuing fume exposure was not associated with decline in FVC.

In an editorial accompanying the article by Harber et al, Toren and Balmes remind us that the annual decline in FEV1 of 0.25% predicted amounts to about 10 ml/yr and is in addition to any loss having been experienced at baseline and/or attributable to cigarette smoking.[45] Over a 30-year working lifetime with fume exposure, the cumulative loss would be 300 ml, or about 7.5% of predicted FEV1 on average. A loss of this magnitude could well be associated with respiratory disability. In a prospective cohort study of adults with COPD, Blanc et al observed a twofold increase in risk for respiratory disability (OR 1.9, 95% CI 1.0-3.6) among 234 subjects with occupational exposure to VGDF, taking smoking, age, gender, and race into account.[46] For those with work disability and history of VGDF exposure, significant increased risk for restricted activity and one or more related hospitalizations was observed: OR 3.9, 95% CI 1.1-13.6 and OR 6.3, 95% CI 1.2-33.0, respectively. Concomitant respiratory disability and VGDF exposure was associated with even greater risk.

ETIOLOGY: OCCUPATIONAL EXPOSURES AND SMOKING

Independent effects of VGDF on risk for COPD in smokers have been acknowledged by GOLD and observed and reported by Mabila.[26,36] Others have shown not only independent and additive effects of smoking and occupational exposure to VGDF on risk for COPD, but also an interactive effect such that the joint effect is greater than additive (i.e., synergistic) - in a manner similar to that of smoking and asbestos on risk for lung cancer.

Hnizdo et al examined the impact of combined silica dust exposure and smoking on airflow obstruction in published studies of Canadian and U.S. hard rock miners exposed to silica.[28] Different patterns of pulmonary function were observed in non-smokers compared to smokers. In non-smokers, observed ventilatory deficits were suggestive of restriction, with reduction in residual lung capacity. Smokers, on the other hand, had findings more consistent with obstruction, with reduction in FEV1, FVC, FEV1/FVC, and maximal expiratory airflow rates, and increase in residual lung capacity. Physiologic abnormalities increased with increasing silica dust exposure levels.

In an earlier study of 2,209 South African gold miners, Hnizdo et al examined effects of increasing silica dust exposure and smoking on lung function.[47] Spirometry was performed and an abnormal test result defined as a value < LLN. Air flow rates, FEV1/FVC, and FVC were measured. The following ventilatory deficits were defined: minimal obstruction, moderate obstruction, marked obstruction, marked combined obstruction/restriction, and restriction. Respiratory impairment was examined by smoking status (nonsmoker, ex-smoker, current smoker) and by dust exposure at levels up to 52,000 particle-years. The effect of increasing dust exposure up to 40,000 particle-years on decline in

lung function was greatest for the small airways (FEF_{25-75}) in current smokers. With regard to ventilatory deficits, a trend for increasing prevalence with increasing dust exposure was observed for ex- and current smokers with moderate obstruction and for current smokers with marked obstruction and marked obstruction/restriction. A similar trend was not observed for nonsmokers. Among those with marked obstruction or marked combined obstruction/restriction, risk was highest for heavy smokers at higher dust exposures (OR 10.4 (95% CI 5.6-19.4)). The PAF for silica dust alone was 8%; for smoking alone, 42%; and for the combination of the two, 40%. These findings indicate a higher prevalence of more severe obstruction among occupationally-exposed miners who smoke than among miners who do not smoke, and support an interactive effect of occupational exposure to silica dust and smoking on risk for COPD.

Trupin et al conducted a telephone interview survey of 2,061 randomly-selected U.S. residents ages 55-75 years.[48] Respiratory health (chronic bronchitis, emphysema, COPD, and asthma), general health, and occupational exposures were queried. Those reporting chronic bronchitis alone were subsequently excluded from data analysis. Information about occupational exposures was obtained using a question from the European Community Respiratory Health Survey (ECHRHS). Based upon self-reported occupational exposures, a job-exposure matrix (JEM) created for the ECHRHS was applied. Both self-reported exposures and the JEM were applied in data analysis.

Associations between COPD or emphysema and occupational exposures to VGDF and cigarette smoke were examined. Adjusted OR for exposure to VGDF alone was 2.4 (95% CI 0.9-6.1); for smoking alone, 7.0 (95% CI 3.6-13.7). For the two together, adjusted OR was 18.4 (95% CI 9.3-36.4), indicating that the effect of both together was greater than either alone, with the numbers suggesting a multiplicative effect. The authors concluded "In the present analysis, evidence was found for an interaction between smoking and occupational exposures, such that current or former smokers reporting job exposure were at particularly high risk of COPD."

Blanc et al conducted a nested case-control analysis of data obtained as part of a prospective cohort study of COPD in adult members of a managed health care organization.[49] One of the purposes of the analysis was to examine separate and combined effects of smoking and occupational exposure to VGDF on risk for COPD. Cases were chosen on the basis of meeting both a healthcare-utilization criterion and a medication-prescribing criterion. Required to meet the healthcare-utilization criterion was one or more ambulatory visits or emergency department visits or hospitalizations with a principal ICD-9 diagnostic code for chronic bronchitis, emphysema, or COPD during the preceding 12 months. Required to meet the medication-prescribing criterion was two or more prescriptions for COPD-related medication during the preceding 12 months. Occupational exposure information and smoking history were obtained from structured telephone interviews and, for occupational exposures, a JEM. Blanc et al observed a twofold increase in risk of COPD among cases (OR 2.11, 95% CI 1.59-2.82) for self-reported occupational exposure to VGDF during the longest-held job, adjusting for smoking, age, gender, and race. Estimated PAR was 31%.

Analysis of joint associations between smoking and occupational exposure to VGDF on COPD risk for the group as a whole revealed adjusted OR 1.98 (95% CI 1.26-3.09) for occupational exposures alone and OR 6.71 (95% CI 4.58-9.82) for cigarette smoking alone. For the two together, an OR of 14.1 (95% CI 9.33-21.2) was observed, a finding consistent with that of Trupin et al (2003) and suggestive of a multiplicative effect. For those with GOLD II COPD (FEV1/FVC < 0.70, 50% $\leq$ FEV1 < 80% predicted)

results were similar, with OR 1.69 (95% CI 0.96-2.97) for occupational exposure alone; OR 8.31 (95% CI 5.27-13.1) for smoking alone; and OR 18.7 (95% CI 11.6-30.0) for both together.

Boggia et al examined associations between COPD and occupational exposure to "welder smokes, gases, or chemical irritants for the airway" and cigarette smoking in a group of 2,019 workers in different sectors in Southern Italy.[50] Exposure information was obtained from the workers themselves. Smoking was defined as follows: non-smoker – never smoker or "quit smoking for more than 10 years at the baseline"; smokers – smoked > 5 cigarettes/d for > 5 years. COPD was defined on the basis of respiratory symptoms consistent with the standardized definition of chronic bronchitis (cough and phlegm on most days for three months or more per year for at least two consecutive years) and spirometry (FEV1/FVC < 0.70 and FEV1 < 80% predicted). Based on workplace exposures and smoking, participants were divided into four groups: group 1: non-smoker without professional occupational exposures as defined (n=261, 12.9%); group 2: smoker without professional occupational exposures (n=676, 33.5%); group 3: non-smoker with professional occupational exposures (n=242, 12%); and group 4: smokers with professional occupational exposures (n=838, 41.5%).

Prevalence of COPD varied by group at baseline in 1995, at first follow-up in 2000, and at second follow-up in 2005, with groups 3 and 4 having the highest prevalence at each of the three examinations. For group 1, the referent group, COPD prevalence was 3.1% at baseline; 4.0% at second exam; and 5.2% at the third exam. Prevalence for group 2 was 6.7%, 7.9%, and 11%, respectively; for group 3, 9.1%, 11.5%, and 16.3% for the respective time periods. For group 4, the group with combined occupational and cigarette smoke exposures, prevalence of COPD was 13.8%, 18.3%, and 23.4% for the respective time periods. Chi-square for difference in prevalence among the four groups was statistically significant at baseline and at each follow-up. Significant ORs (Exp(β)) were observed for cigarette smoking (OR 1.75, 95% CI 1.27-2.41), for occupational exposures (OR 2.62, 95% CI 2.02-3.41), and for the interactive effect of cigarette smoking-occupational exposures (OR 2.51, 95% CI 1.97-3.20), respectively. These findings support the independent and positive effect of occupational exposure to VGDF on risk for COPD. In this study, prevalence data and logistic regression analysis indicate a risk for COPD from workplace exposures alone that is greater than the risk from smoking alone.

Darby et al examined the relationship between occupational exposures and risk for COPD in Sheffield, UK, an industrialized area in the northern part of the country.[51] Iron and steel foundries populated the area at one time. A population-based cross-sectional study of subjects randomly-selected (n=4,000), and of hospital-based subjects (n=209) selected on the basis of pulmonary function test results consistent with COPD GOLD category 1 or greater, was conducted. Probable diagnosis of COPD in the population-based sample was made on the basis of self-report of physician-diagnosed COPD (including emphysema, chronic bronchitis), or asthma, or respiratory symptoms of grade 3 dyspnea using the Medical Research Council (MRC) questionnaire and at least one other respiratory symptom.[52] This information, smoking history, and exposure history were obtained from a self-administered questionnaire mailed to potential participants over 55 years of age whose names were obtained from health records. Occupational exposure information was assessed in three ways: self-report of exposure to VGDF; use of a specific exposure checklist; and a JEM based on job history. Occupational exposures included combustion by-products, inorganic dusts or fumes, and organic dusts.

Fifty percent of subjects randomly-selected from the population and 29% of subjects selected on the basis of COPD demonstrated by spirometry returned questionnaires. For the population sample,

responders were somewhat younger than non-responders and similar with regard to gender. Smoking history was not available for non-responders. Any COPD exclusive of chronic bronchitis was reported by 8% (n=165) of population respondents. Of these subjects, 21.8% were current smokers; 67.3% former smokers; and 10.9% never smokers. Strength of association of COPD with occupational exposure adjusted for age, gender, and pack-years of smoking was stronger for self-reported VGDF vs. JEM: OR 3.66, 95% CI 2.31-5.79 and OR for JEM high exposure 1.55, 95% CI 0.94-2.54, respectively. Using unexposed never smokers as the referent group, the following age- and gender-adjusted ORs were observed: for never smokers with VGDF exposure, OR 5.47, 95% CI 1.85-16.16; for low pack-years and no VGDF exposure, OR 3.50, 95% CI 1.10-11.18; for low pack-years and VGDF exposure, OR 15.93, 95% CI 5.85-43.34; for high pack-years and no VGDF exposure OR 16.47, 95% CI 6.07-44.74; and for high pack-years and VGDF exposure, OR 54.11, 95% CI 20.94-139.87). These data indicate a relationship between smoking and VDGF exposures on risk for COPD that is synergistic.

Potential weaknesses in the Darby study are the low response rates in the study groups, the lack of information on smoking among population-based non-responders, possible confounding by foundry-related environmental air pollution, and the fact that the group with COPD exclusive of chronic bronchitis may have contained subjects with concomitant asthma (not subjects with asthma only). Despite these potential weaknesses, Darby et al show increased risk for COPD associated with occupational exposures defined by self-report and JEM, taking into account smoking. Their findings also support those of Trupin and Blanc showing a synergistic relationship between occupational exposures and smoking in increasing risk for COPD.

CONCLUSIONS

COPD is a global public health problem. By 2020 it is expected to constitute the third leading cause of morbidity and mortality worldwide. In Ontario, COPD is a significant contributor to respiratory morbidity and mortality.

In the past, COPD has been attributed almost exclusively to cigarette smoking. Thanks in large part to Becklake and her illuminating review published in 1989, the paradigm has shifted.[23] We have learned that while smoking remains the predominant cause of COPD, a substantial proportion of the burden of COPD is attributable to occupational exposures to VGDF. The ATS has concluded that "The evidence is sufficient to infer a causal relationship between occupational exposures and development of COPD."[6] Multiple epidemiologic studies published in peer-reviewed journals have demonstrated associations that are statistically significant and consistent using different definitions of COPD and across different industries and occupations. Where measured, dose-response relationships have been observed. Experimental studies in animals have demonstrated biologic plausibility.

Published studies have also shown that occupational exposures act additively to synergistically with cigarette smoke in current or former smokers to increase the risk for COPD. NHANES data and other published studies indicate that certain industries and certain occupational exposures are associated with a significant increase in risk for COPD. At-risk occupations include mining, manufacture of motor vehicles and motor vehicle equipment, and construction.[26] Occupational exposures include mineral dusts, organic dusts, diesel exhaust, and other fumes.[50] In the same way that workplace exposures to VGDF and smoking interact to increase COPD risk over and above that associated with either exposure alone, it is likely that there is an interaction between single agents in the workplace on risk for COPD that is at least additive, although research remains to be done in this regard.[33,41]

Jaakkola in her editorial entitled "Smoke and dust get in your eyes: what does it mean in the workplace?" addresses an important clinical issue: the diagnosis of *occupational* COPD in current or former smokers.[53] Too often the fact of smoking precludes a determination that COPD is work-related. Either the physician fails to move beyond the smoking history to an occupational history in someone with COPD, or dismisses the occupational history as relatively unimportant in a smoker. As published data show and as the current paper describes, occupational exposures are an important and preventable cause of COPD in their own right. As Jaakkola correctly states: "It seems clear that being a smoker can no more mean that the individual does not have occupational COPD, as smokers appear to be at an even higher risk of developing work-related COPD than non-smokers." Smoking and exposure to VGDF in the workplace are separate risk factors for COPD and when combined there appears to be a synergistic effect. Along with the diagnosis come related issues of disability and compensation for work-related COPD.

COPD is a preventable disease. As with all preventable diseases, recognition of the cause(s) is the first step toward reducing exposure to potentially toxic agents in order to prevent disease altogether, or to prevent worsening of disease in those already affected. Not only must we work to stop smoking, we must also work to maintain a safe and healthy workplace through substitution of non-toxic agents for toxic agents and where this is not possible, provision of adequate ventilation and proper respiratory protection.

Respectfully submitted,

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