ERJ Express. **Published on November 14, 2008 as doi: 10.1183/09031936.00118808**

Occupational Exposures and COPD: An Ecological Analysis of International Data

Paul D. Blanc[a]

Ana Maria B. Menezes[b]

Estel Plana[c,d,e]

David M. Mannino[f]

Pedro C. Hallal[b]

Kjell Toren[g]

Mark D. Eisner[a]

Jan-Paul Zock[c,d,e]

[a]Division of Occupational and Environmental Medicine University of California San Francisco

[b]Federal University of Pelotas, Pelotas, Brazil

[c]Centre for Research in Environmental Epidemiology, (CREAL), Barcelona, Spain

[d]Municipal Institute of Medical Research (IMIM-Hospital del Mar), Barcelona, Spain

[e]CIBER Epidemiología y Salud Pública (CIBERESP), Spain

[f]University of Kentucky, Lexington, KY, USA

[g]Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

Correspondence to: Prof PD Blanc paul.blanc@ucsf.edu

Word count: Abstract 310, Body of Text, 3351

Although the three international studies from which these data were drawn had multiple sources of funding, this ecological analysis was not supported through extramural mechanisms.

Abstract

The occupational contribution to chronic obstructive pulmonary disease (COPD) has yet to be put in a global perspective. We used an ecological approach to this question, analyzing group-level data from 90 gender-specific strata from 45 sites of the Burden of Obstructive Lung Disease (BOLD) study; the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO); and the European Community Respiratory Health Survey follow-up (ECRHS II). We used these data to study the association between occupational exposures and COPD Stage II or above (Global Obstructive Lung Disease [GOLD]). We regressed the gender-specific group-level prevalence rates of COPD at each site against the prevalence of occupational exposure and ever smoking, taking into account mean smoking pack years and mean age by site, gender, study cohort, and sample size. For the entire data set, the prevalence of exposures predicted COPD prevalence (0.8% increase in COPD prevalence per 10% increase in exposure prevalence, p=0.003). By comparison, for every 10% increase in the proportion of the ever smoking population, the prevalence of COPD GOLD Stage II or above increased by 1.3% ($p<0.0001$). Given the observed median population COPD prevalence of 3.4%, the model predicts that a 20% relative reduction in the disease burden (i.e., to a COPD prevalence of 2.7%) could be achieved by a 5.4% reduction in overall smoking rates or an 8.8% reduction in the prevalence of occupational exposures. When the data set was analyzed by sex-specific site data , among men, the occupational effect was a 0.8% COPD prevalence increase per 10% change in exposure prevalence (p=0.004); among women, a 1.0% increase in COPD per 10% change in exposure prevalence (p=0.03). Within the limitations of an ecological analysis, these findings support a worldwide association between dusty trades and COPD for both women and men, placing this within the context of the dominant role of cigarette smoking in COPD causation.

Multiple studies of occupation and COPD risk at the individual level have addressed the association between work-related exposure and disease. These investigations consistently have observed a smoking-adjusted excess risk of COPD associated with occupational exposures (e.g., vapors gas dust or fumes).[1,2] As critical as such individual-level studies are, they do not capture population-level effects that may be important contributors to exposure prevalence and disease risk. For example, a high prevalence of individually-reported workplace exposures may indicate generally poor employment conditions even for those who may not report it, leading to imprecision of personal-level estimates of the workplace contribution to COPD and more accurate measures in grouped data. Moreover, since any intervention to improve working conditions is likely occur at the group level (i.e., through regulation), examining exposure and disease across groups can provide key insights for public health policy makers.

For these reasons, we intentionally undertook an "ecological" approach to this question, analyzing morbidity at the population level in order to gain a better understanding of the role that workplace factors play in the burden of COPD internationally. Two recent population-based studies have addressed the prevalence of COPD on an international scale, focusing on the primary role of cigarette smoking as the dominant individual-level risk factor for disease, although occupational exposure was considered as a potential co-variate.[3,4] A third international study has been principally concerned with asthma risk in adults, including the individual-level effects of occupational exposures.[5-6] Although a relatively young cohort, follow-up has extended into an age range where COPD endpoints can also be studied.[7,8]

We used grouped data from all three of these studies combined together to assess the ecological associations among the prevalence rates for occupational exposures, cigarette smoking, and the COPD. We wished to test whether the frequency of adverse working conditions predicted COPD prevalence rates at a population-level, taking into account group-level smoking data, thus providing a global context for potential public health interventions.

Methods

Overview

This is an ecological analysis using group-level data from three separate cohort studies of COPD involving 45 different sites, each yielding results stratified by gender. Thus, 90 separate sets of observations were available for analysis, each providing frequency data at the group level for the independent predictor variables of study interest (occupational and smoking data and mean age of each site by gender) and the prevalence of COPD (the dependent variable). The overall analytic strategy was designed to estimate the association between the population frequency of occupational exposures and prevalence of COPD, taking into account potential clustering by study cohort and the potential confounding effects of smoking and age at the group level, studying these relationships among men and women together and separately.

Study Design

We used data from three large studies, each with international, random population sample designs: the Burden of Obstructive Lung Disease (BOLD) study; The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO); and the European Community Respiratory Health Survey follow-up study (ECRHS II). Studying occupational factors in COPD was not a primary goal of any of these studies, but each did collect data relevant to this question. Representatives from each study group participated in this analysis.

For BOLD, we extracted study site-level, gender stratified data as it appeared in published tables.[3] For that analysis we used as study site weights the number of participants with acceptable spirometry data (total n=8775) in lieu of the somewhat larger total study population (n=9425). For PLATINO, we used study site-level data paralleling tabular data as previously published, but further stratified by gender and with additional data on years of occupational exposure.[4] Stratified data were provided by PLATINO study investigators who participated in the current analysis (co-authors A.M.B.M. and P.C.H.). Site-level gender-stratified data from the ECRHS II were provided by that study (co-authors of this study, E. P. and J-P. Z.).

Because the ECRHS II recruited a younger age range population at baseline, the data set was limited to persons from the population-based sampling frame aged 40 or older who completed spirometric measurements at follow-up, in order to exclude younger subjects unlikely to have yet manifest COPD even if exposed to risk factors..

Definition of Occupational Exposure

Occupational exposure was defined using differing but comparable protocols among the studies. For BOLD and PLATINO, occupational exposure was based on self-report of exposure to "dusty work" for *at least but not limited to* one year or more at any point in time.[3,4] For the ECHRS II analysis, exposure was based on baseline interview (ECHRS I) self-report of "vapors, gas, dusts or fume" at the current or any previous job and/or (at ECHRS II follow-up) any interval employment for *at least but not limited to* three months in an occupation with a high likelihood of exposure to dust (biologic or inorganic), or gases or fumes based on a job exposure matrix.[6,8] We also analyzed site and gender specific duration of adverse working conditions at each study as another measure of occupational exposure.

Definition of COPD

We defined COPD consistent with the Global Obstructive Lung Disease (GOLD) cut-off criteria of Stage II or greater disease: a forced expiratory volume in one second (FEV_1) less than 80% height, age, and gender predicted and a ratio of FEV_1 to forced vital capacity (FVC) of less than 70%.[9] Use of the GOLD Stage II cut-off is consistent with recent analysis of international COPD prevalence in the BOLD study.[3]

Although all spirometry was performed in a manner consistent with ATS criteria, there were differences in how data were obtained in each study. BOLD measured lung function post-bronchodilator using an EasyOne spirometer (nnd Medical technologies, Andover, MA, USA) and calculated predicted FEV_1 values using equations for white men and women from the third US National Health and Nutrition Survey.[3] PLATINO also measured lung function post-

bronchodilator using an EasyOne spirometer, but calculated predicted FEV_1 values using internally generated equations.[4,10] ECHRS II measured pre-bronchodilator lung function with most, but not all, centers using a Biomedin water sealed bell spriometer (Biomedin, Padova, Italy) and calculated predicted FEV_1 using the formulae of Quanjer.[11,12]

Statistical Analysis

All analyses utilized SAS software (Cary, North Carolina, U.S.). Differences in the site-gender stratum prevalence of occupational exposure, ever smoking, and COPD Stage II or greater among the three study cohorts were tested using the Kruskall-Wallis test for non-parametric data; differences in duration of occupational exposure and pack years of smoking were tested by Anova. Differences by gender were tested by the Wilcoxon rank sum test or the t-test. The associations among occupational exposure, smoking, and COPD prevalence by gender-site stratum were estimated using the Spearman rank correlation.

The ecological associations among occupation, smoking, and COPD were tested in mixed effects multiple linear regression models. Regression diagnostics supported the validity of linear regression modeling. The prevalence of COPD GOLD Stage II or greater was the dependent variable. The proportion of the population with occupational exposure and the prevalence of ever smoking were independent variables. The independent covariates included were gender of the gender-stratified site, the mean age and the mean pack years of smoking (for ever smokers) for each site stratum and the study cohort (BOLD, ECHRS II, or PLATINO), which was included as a random effect. Parameter estimates were weighted based on the sample size of each stratum. In order to test the potential effect of clustering at the study site level, the model was also re-estimated adding an additional level for study site as a random effect. We repeated theses analyses stratified by gender. To assess the effect of exposure duration, we carried out additional analyses adding mean duration of occupational exposure among those exposed (by study site by gender) to the models previously tested.

In order to evaluate potential cigarette smoking-occupational interactions at the group level, we evaluated the feasibility of including in our models a simple cross-product term of smoking and occupational exposure. This interaction term was highly collinear with both cigarette smoking (r=0.72) and occupational exposure (r=0.93). We therefore took an alternative approach, dividing the study sites into 4 categories: above the gender-specific median values for both smoking and occupational exposure (n=18; 20% of 90 observations); above median for smoking only (n=26; 29%); above the median for occupational exposure (24; 27%) and below the median for both (22; 24%). We tested a mixed model including the former three categories as indicator variables (with lower occupational exposure and lower smoking being the referent), while including all of the other covariates as previously described.

Results

For the three studies included in the analysis, data were available representing 19,094 study participants (8,627 men and 10,467 women) from 17 countries on six continents. Table 1 presents, for each of the three cohorts and for all subjects combined, study site-specific data for sample size and the mean age of participants, stratified by gender. Overall, subject numbers per site were smaller and participants younger within the ECHRS II cohort (limited in this analysis to persons above age 40 at follow-up), compared to the BOLD and PLATINO.

Table 2 provides the distributions of site-gender stratum data for occupational exposure as a percent prevalence and the mean years of exposure among those exposed and ever smoking (current or past cigarette use) as a percent prevalence and the mean pack years of smoking among ever smokers. Among the 90 gender-site strata overall, the median prevalence of occupational exposures in dusty or related adverse job conditions was 41 percent (inter-quartile range [IQR] 29 to 62%), with an absolute range of 7 to 85% (the latter not shown in Table). The proportions of exposures by site-gender strata did not differ statistically by cohort (Kruskal-Wallis p=0.23). The mean duration of occupational exposure among those exposed

was 13.0±4.8 years. Duration of exposure did differ overall by cohort (Anova p<0.0001); the only statistically significant pair-wise comparison was between the BOLD and ECRHS cohorts (difference 4.6 %; 95% CI 2.1-7.1%). Exposure duration was significantly greater at the group level among men than women (mean difference 4.1 years; 95% CI 2.3-5.9 years).

The median prevalence of ever smokers overall was 61 percent (IQR 50-70%), with an absolute range of 6 to 83% among all the site-gender strata. As with occupational exposures, the cigarette smoking prevalence distribution did not differ significantly among the three study cohorts (Kruskal-Wallis p=0.60). Smoking intensity-duration among ever smokers was highest in the BOLD and lowest in the PLATINO cohorts and, in each cohort, lower among women than men. Mean pack years per site-gender stratum did not differ significantly by cohort (Kruskal-Wallis p=0.11).

Table 2 also includes the distribution for proportion of COPD of severity GOLD II or higher for each site-gender stratum. For all 90 site-gender strata, the median proportion was 3.4% (IQR 1.4-6.8%). The proportions for COPD were highest in the BOLD study sites and lowest in the ECHRS II data set. There were 15 gender-site strata in the ECHRSII with no COPD GOLD II or above. The differences in COPD proportions among differed significantly among the three study cohorts (Kuskal-Wallis p<0.001).

Figure 1 presents the scatter plots and correlations between occupational exposure prevalence and the prevalence of COPD GOLD II or higher for each study cohort separately. Occupational exposure and COPD prevalence were correlated within the BOLD cohort (Spearman r=0.48; p=0.02), the ECHRS II (Spearman r=0.26; p=0.06), and the PLATINO study (Spearman r=0.63; p=0.05).

The correlations between the prevalence of ever smoking and COPD by strata (not shown in Figure) were, respectively, r=0.58 (p=0.003); r=0.27 (p=0.04); and r=0.55 (p=0.10). The population prevalence of occupational exposure and cigarette smoking by gender-site

stratum proportion was inter-correlated overall (Spearman r=0.49; p< 0.001). The inter-correlations were highest in two of the cohorts (BOLD r=0.65, p<0.001; PLATINO r=0.86, p=.001) and less so in the ECHRS II (r=0.37; p=0.005).

The results of mixed effects multiple linear regression modeling are presented in Table 3. The model including all strata takes into account study cohort as a random effect variable and adjusts for the gender, mean age, and mean pack years of smoking among ever smokers in each stratum. Both the proportions of dusty/dirty jobs and of ever smoking were independently associated with the prevalence of COPD. Based on this ecological estimate, for every 10% increase in the frequency of dusty employment and related exposures, the prevalence of COPD is increased by 0.8%. By comparison, for every 10% increase in the proportion of the ever smoking population, the prevalence of COPD GOLD Stage II or above is increased by 1.3 %. Based on the observed IQR for occupational exposure prevalence (33%), the model predicts a 2.6% shift in COPD Stage II and above prevalence over this range; based on the IQR in smoking prevalence (25%), the model predicts a 3.3% shift in COPD. Put in terms of public health actions, given the observed median population COPD prevalence of 3.4%, the model predicts that a 20% relative reduction in the disease burden (i.e., to a COPD prevalence of 2.7%) could be achieved by a 5.4% reduction in overall smoking rates or an 8.8% reduction in the prevalence of occupational exposures.

The mixed multivariate model, as noted, also included sex, age, and pack years of smoking as independent predictors. In this model, women compared to men had a 3.2% higher predicted prevalence of COPD (p=0.005) while mean age and pack years among smokers were not statistically significant predictors of COPD prevalence. Re-estimating the effect adding a random term for study site yielded similar findings for smoking (1.2% increase in COPD per 10% change) and occupation (0.7% increase per 10% change) (p<0.05 for both). Because of the inter-correlation between the prevalence of smoking and occupational exposure noted above,

we also examined the potential impact on the parameter estimate and standard error term for smoking when the model excluded occupational exposure variable, comparing this to the final model. Inclusion of occupational exposure had little substantive impact on the smoking term, indicating that collinearity between these two variables was not impacting the performance of the model. We also tested another additional model that included mean years of occupational exposure which yielded similar results.

Stratifying by gender yielded similar estimates for the sex-specific ecological associations between the occupational exposures and smoking and COPD (Table 3). The ecological association between dusty trades and COPD among males was consistent with a 0.8% increase per 10% change in prevalence; among females the estimate was a 1.0% increase in COPD for every 10% increase in prevalence of job exposures. Among women pack years among smokers was positively associated with COPD prevalence (p=0.02), but mean age was not. Among men in the stratified analysis both pack years among smokers (p=0.006) and mean age (p=0.04) were statistically associated with COPD, but in a negative direction, that is, taking ever smoking and occupational exposure into account, sites with younger mean age and less pack years of smoking intensity manifest a higher prevalence of disease.

We assessed the potential for a smoking-occupational exposure interaction by analyzing the effect of conjoint prevalence of risk at the group level. Sites with a higher combined prevalence of smoking and occupational exposure were associated with a 2.8% higher COPD prevalence relative to sites with both lower smoking and exposure (p=0.003). There was no significant difference associated with higher smoking or occupational exposure alone, relative to neither. The same pattern was seen when the sites were stratified by gender, with a higher COPD prevalence associated with combined higher smoking and occupational exposure of 3.3% among women (p=0.01) and 3.0% among men (p=0.008).

Discussion

The individual-level association between occupational exposure and COPD has been documented in a rapidly accumulating literature on this subject.[1,2,13-18] The findings of this ecological analysis are consistent with those studies, but also add another important dimension by assessing this question from a population perspective. Moreover, association between adverse working conditions and COPD that we report here carries significance as a global finding, applicable to both men and women. This observation places the occupational burden in COPD squarely in the public health context, alongside the well appreciated and critical contribution of cigarette smoking to disease prevalence.

It is paramount to keep in view the inherent the limitations, as well as the advantages, of an ecological group-level analytic approach. [19,20] For example, the overall prevalence of smoking we included in our model is an imprecise surrogate of individual-level, direct cigarette exposure. Yet, conversely, this group-level smoking measure has the advantage of also subsuming the likelihood of secondhand smoke exposure in the population in addition to direct personal smoking. Indeed, data from the ECRHS has suggested an ecological association between personal and workplace secondhand smoking.[21] Lifetime secondhand cigarette smoke exposure has been implicated as a risk factor for COPD and can be difficult to accurately measure at the individual level using standard survey methods.[22,23] Similarly, the prevalence of *in utero* cigarette smoking exposure, which may be a risk factor for COPD through low birth weight or other mechanisms, is also likely to correlate with female population smoking rates and is difficult to ascertain at the individual level.[24] Smoking intensity-duration at the population level, which we also included in our models, may reflect secondhand smoke exposure intensity as well. This measure, however, is complicated by potential inter-relationships with the distributions of population age and age at smoking initiation and cessation. This may account for the paradoxical association we observed between COPD and age and pack years in the male

stratum. On balance, although ecological measures of smoking imperfectly estimate individual personal smoking, such measures do have the advantage of capturing elements secondhand smoke exposure that may otherwise not be assessed.

As with cigarette smoking, population-level rates of adverse occupational exposures provide a measure that is more than simply a surrogate of individually-assessed employment conditions and thus at risk of ecological bias.[25] Although the ECHRS measure of occupational risk included assigned exposure likelihood using a job exposure matrix, a key measure in all three cohorts is self-reported exposure. Such self-reports theoretically can introduce bias in exposure assessment, but the actual impact of this remains open to question, with heterogeneous estimates of such impact in different studies internaitonally.[26-28] In areas with generally poorer workplace conditions, some subjects may be more likely to under-report exposure because, relative to other sites, they minimize their individual on-the-job condition; in situations of overall excellent hygiene, even trivial exposures may lead to report a vapors gas dust of fumes: both tendencies would lead to measurement “noise” that is dampened in group-level analysis. The confounding effect of recall bias systematically linking exposure to disease can also be mitigated by analysis at the population level. Finally, to the extent that workplaces are indeed widely contaminated, there is increased likelihood of local neighborhood and wider ambient air pollution exposure from site sources that can be captured with a group-level analysis.

Several individual-level analyses suggest that there is smoking-occupational exposure interaction that is a more than additive for increased COPD risk.[29-31] In our analysis, sites with smoking and occupational exposure above the gender-specific median had a significantly higher prevalence of COPD, an observation that could be consistent with such an interaction. More fully teasing out the nuanced inter-relationships between occupation and smoking in COPD, including the potential associations between second hand smoke in youth and later exposure-

ridden employment, may require multi-level analyses that simultaneously take into account both individual-level and population-level exposures, thus balancing potential biases present in individual-level and ecological approaches.[18] Going forward, it also will be important to analyze through longitudinal study associations with specific occupations or occupational groups with COPD while taking into account temporal changes in the occupational contribution to COPD that might come from improved or deteriorating working conditions. Such changes may modify the role that vapors, gas, dust and fumes play in the burden of disease. By the same token, it is important to recognize as well that reductions in direct and secondhand cigarette smoke exposure resulting from successful public health efforts may increase the proportion of disease attributable to occupational factors. Smoking remains critical in COPD causation, but the contribution of occupational exposures must not be ignored. This is true not only at the population level, but also in the prevention of disease initiation and progression at the one-on-one level of clinical practice.

References

1. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et. al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med. 2003;167:787-97.

2. Blanc PD, Torén K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis. 2007; 11:251-7.

3. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et. al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370: 741-9.

4. Menezes AMB, Perez-Padillo R, Jardim JRB, Muiño A, Valdivia G, Montes de Oca M, et. al. Chronic obstructive pulmonary disease m five Latin American cities (the PLATINO study): a prevalence study. Lancet 2005; 366:1875-81

5. Kogevinas M, Antó JM, Sunyer J, Tobias A, Kromhout H, Burney P. Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. Lancet. 1999;353:1750-4. Erratum in: Lancet 1999; 354:166.

6. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). Lancet. 2007;370:336-41.

7. Zock JP, Sunyer J, Kogevinas M, Kromhout H, Burney P, Antó JM. Occupation, chronic bronchitis and lung function in young adults: An international study. Am J Respir Crit Care Med 2001; 163: 1572-7.

8. Sunyer J, Zock JP Kromhout H, Garcia-Esteban R, Radon K, Jarvis D, et al. Lung function decline, chronic bronchitis, and occupational exposures in young adults. Am J Repsir Crit Care Med 2005; 172: 1139-45.

9. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2006. http://goldcopd.org

10. Pérez-Padilla R, Valdivia G, Muiño A, et al. [Spirometric reference values in 5 large Latin American cities for subjects aged 40 years or over.]. Arch Bronconeumol 2006;42:317–325

11. Chinn S, Jarvis D, Melotti R, Luczynska C, Ackermann-Liebrich U, Antó JM, at. al. Smoking cessation, lung function, and weight gain: a follow-up study. Lancet 2005; 365:1629-35.

12. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Resp J Suppl 1993; 16:5-40.

13. Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 1989; 140: S85-S91.

14. Hendrick DJ. Occupation and chronic obstructive pulmonary disease (COPD). Eur Respir J 1994; 7: 1032-1034.

15. Burge PS. Occupation and COPD. Eur Respir Rev 2002; 12(86/87): 293-294.

16. Viegi G, Di Pede C. Chronic obstructive lung diseases and occupational exposure. Curr Opin Clin Immunol 2002; 2: 115-121.

17. Meldrum M, Rawbone R, Curran AD, Fishwick D. The role of occupation in the development of chronic obstructive pulmonary disease (COPD). Occup Environ Med 2005; 62: 212-214.

18. Toren K, Balmes J. Chronic obstructive pulmonary disease. Does occupation matter? Am J respire Crit Care Med 2007; 176:951-3.

19. Pearce N. The ecological fallacy strikes back. J Epidemiol Community Health 2000; 54:326-7.

20. Diez Roux AV. The study of group-level factors in epidemiology: rethinking variables, study designs, and analytical approaches. Epidemiol Rev 2004; 26:104-11.

21. Janson C, Chinn S, Jarvis D, Zock JP, Torén K, Burney P, on the behalf of the European Community Respiratory Health Survey. Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function and total serum IgE in the European Community Respiratory Health Survey. Lancet 2001; 358: 2103-9.

22. Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Environ Health. 2005 4:715.

23. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, et. al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet. 2007;370:751-7.

24. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007; 357:1946-55.

25. Lin RT, Takahashi K, Karjalainen A, Hoshuyama T, Wilson D, Kameda T, Chan CC, Wen CP, Furuya S, Higashi T, Chien LC, Ohtaki M. Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis. Lancet. 2007; 369:844-9.

26. De Vocht F, Zock JP, Kromhout H, Sunyer J, Antó JM, Burney P, Kogevinas M. Comparison of self-reported occupational exposure with a job exposure matrix in an international community-based study on asthma. Am J Ind Med 2005; 47: 434-42.

27. Blanc PD, Eisner MD, Balmes J, Trupin L, Yelin EH, Katz PP. Exposure to vapors, gas, dust, or fumes: assessment by a single survey item compared to a detailed exposure battery and a job exposure matrix. Am J Ind Med 2005; 48:110-117.

28. Quinlan PJ., Earnest G, Eisner MD, Yelin EH, Katz PP, Blames JR, Blanc PD. Performance of self-reported occupational exposure compared to a job exposure matrix approach in asthma and chronic rhinitis. Occup Environ Med (In Press)

29. Trupin L, Earnest G, San Pedro M, Balmes JR, Eisner MD, Yelin E, Katz PP, Blanc PD. The occupational burden of chronic obstruction pulmonary disease. Eur Respir J 2003; 22:462-9.

30. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of Smoking and Occupational Exposure on Etiology of Chronic Obstructive Pulmonary Disease in Workers of Southern Italy. J Occup Environ Med 2008; 50:366-370.

31. Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD. Occupational exposures and the risk of COPD: dusty trades revisited. Thorax (In Press).

Table 1. International studies included in analysis: geographic distribution and study size						
Study Cohort (n)	Nations Included	Study Sites	Study Subject Number per Site		Mean Age in Years by Site	
			Men	Women	Men	Women
	n	n	Med (Range)	Med (Range)	Med (Range)	Med (Range)
BOLD (8775)	12	12	334 (206-685)	343 (237-435)	56.4 (52.1-58.6)	57.5 (53.4-60.1)
ECRHS II (4648)	14	28	70.5 (30-179)	78.5 (35-79)	47.5 (44.9-57.2)	47.2 (45.2-50.2)
PLATINO (5671)	5	5	442 (380-474)	632 (558-983)	56.0 (54.9-59.3)	55.5 (55.0-61.0)
All (19094)	21*	45*	111 (65-324)	108 (72 -334)	48.9 (44.9-59.3)	48.3 (45.2-61.0)

Med = Median value among observed n or means of age by study site

BOLD=Burden of Obstructive Lung Disease

ECHRS II= European Community Respiratory Health Survey Follow-up Survey

PLATINO=Poyecto Latinoamericano de Investigación en Obstrucción Pulmonar

*Of total 19094 study participants, data for 8627 men and 10467 women are included. Taking into account duplicated countries between BOLD and ECRHS II (Iceland, Norway, U.S.A., and Australia) 17 different countries are included among the three cohorts; Reykjavik (Iceland) and Bergen (Norway) served as study sites in both BOLD and ECHRS II, 43 distinct sites are represented.

Table 2. Occupational exposure, cigarette smoking, and COPD prevalence by study cohort and sex					
Cohort	Dusty/Dirty Jobs		Cigarette Smoking		COPD ≥ GOLD II
	Prevalence of Dirty Jobs	Exposure Years*	Prevalence of Ever Smoking	Pack Years in Smokers	
Stratum (n)	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
BOLD					
Men (n=12)	48% (39-75%)	16.8±3.6	69% (60-80%)	27.8±6.8	10.7% (9.3-14.4)
Women (n=12)	28.5% (20-35.5%)	15.2±4.7	46.5% (36.5-55.5%)	19.0±6.1	8.0% (6.0-11.6%)
Total (n=24)	38% (28.5-48%)	16.0± 4.2	58.5% (46.5-69%)	23.4±7.8	9.4% (7.8-13.0%)
ECRHS II					
Men (n=28)	64.5% (51-78.5%)	13.9±2.6	68% (62-74.5%)	24.1±6.4	2.5% (0.5-4.1%)
Women (n=28)	27% (22-37.5%)	8.8±4.7	56% (49-62.5%)	16.0±4.7	1.6% (0-2.8%)
Total (n=56)	44% (27-64.5%)	11.4±4.6	62.5% (55-69.5%)	20.0±6.9	2.0% (0-3.4%)
PLATINO					
Men (n=5)	63% (61-64%)	17.0±2.3	74% (73-77%)	22.5±8.3	5.4% (4.9-6.6%)
Women (n=5)	40% (33-45%)	12.9±2.1	44% (44-50%)	14.4±4.2	4.9% (4.5-5.3%)
Total (n=10)	46% (40-63%)	14.9±3.0	65% (44-74%)	18.5±7.5	5.1% (4.5-5.4%)
All Combined					
Men (n=45)	62% (49-75%)	15.0±3.1	70% (63-77%)	24.9±6.8	4.1% (2.2-9.1%)
Women (n=45)	30% (22-39%)	11.0±5.3	53% (44-60%)	16.6±5.2	2.9% (1.3-5.4%)
Total (n=90)	41% (29-62%)	13.0±4.8	61% (50-75%)	22.8±7.3	3.4% (1.4-6.8%)

COPD=Chronic Obstructive Pulmonary Disease, ≥Stage II GOLD: (FEV_1/FVC <70%; FEV_1 <80% predicted)

IQR=Interquartile range

*Exposure years among those with any exposure

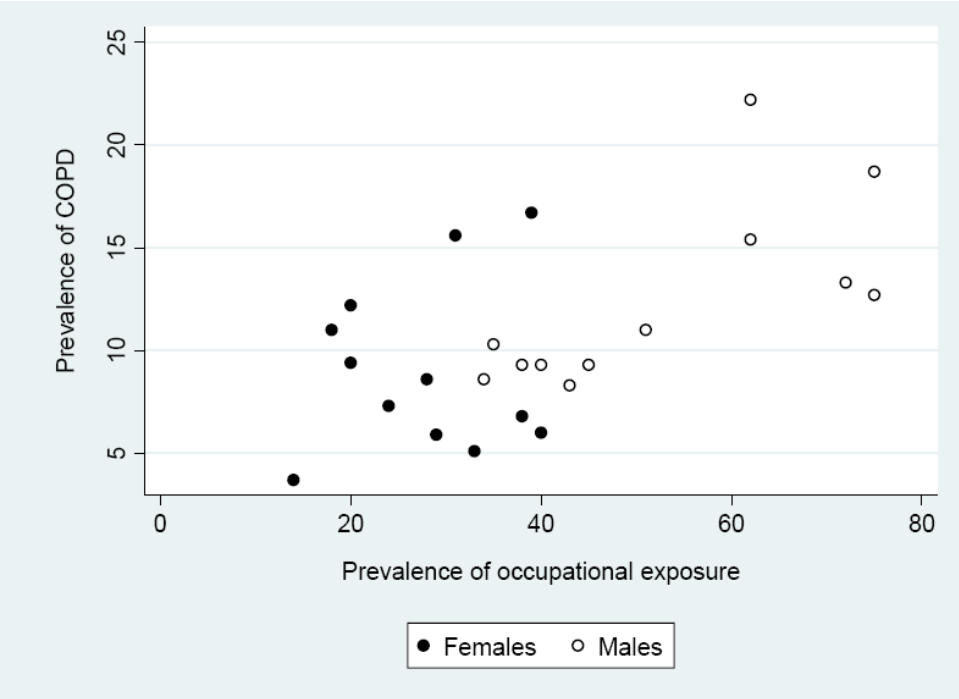
Table 3. Population prevalence of occupational exposure and cigarette smoking as independent predictors of COPD prevalence: multiple linear regression analysis		
Independent Variables	↑ COPD prevalence per 10% ↑ exposure	P value
All Observations (n=90 strata)*		
% Dusty/Dirty jobs	0.8% (0.3 - 1.3%)	0.003
% Cigarette ever smokers	1.3% (0.7 - 1.8%)	<0.0001
Men only (n=45 strata)†		
% Dusty/Dirty jobs	0.8% (0.3 -1.3%)	0.004
% Cigarette ever smokers	0.9% (0.1 -1.8%)	0.04
Women only (n=45 strata)†		
% Dusty/ Dirty jobs	1.0% (0.1-11.9%)	0.03
% Cigarette ever smokers	1.1% (0.4 - 1.8%)	0.005

*Mixed model also includes gender, mean age per stratum and mean pack years among ever smokers per stratum as fixed effect variables and study cohort as a random variable; analysis weighted for study number per gender stratum per site

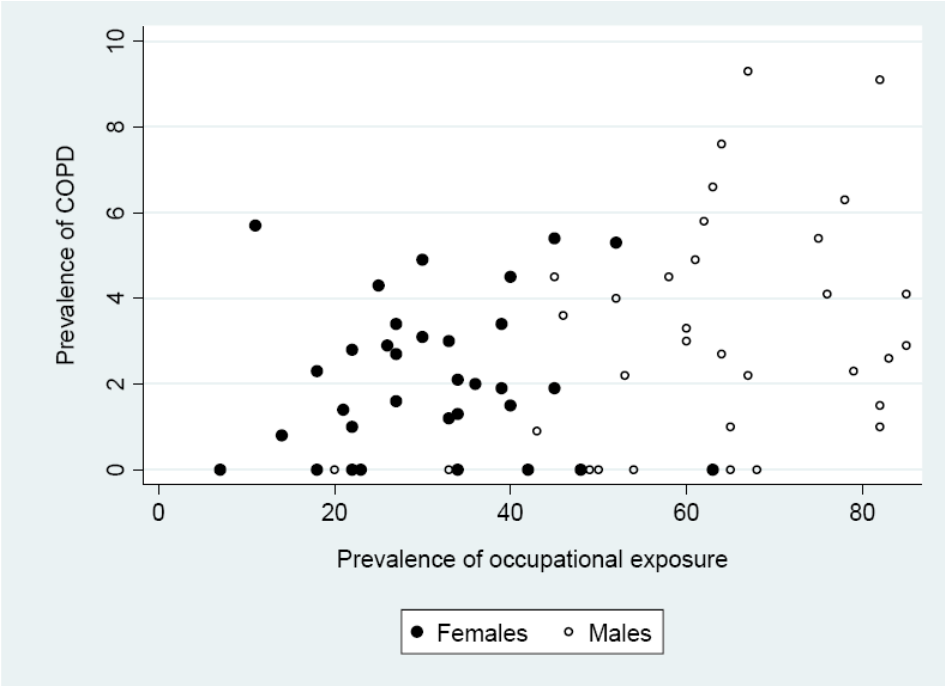
†Mixed model including mean age per stratum and mean pack years among ever smokers per stratum as fixed effect variables and study cohort as a random variable; analysis weighted for study number per site

Figure 1: Prevalence of occupational exposure against the prevalence of COPD stage GOLD II or higher by study cohort and for all the site-gender strata combined. Panel A. BOLD cohort: Spearman correlation r=0.48 (p=0.02). Panel B. ECHRS II cohort: Spearman correlation r=0.26 (p=0.06). Panel C. PLATINO study: Spearman correlation r=0.63 (p=0.05).

PANEL A


Prevalence of COPD
5
10
15
20
25
0
20
40
60
80
Prevalence of occupational exposure
Females
Males

PANEL B



PANEL C