Eur Respir J 2012; 39: 1343–1353
DOI: 10.1183/09031936.00002711

Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD project

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is predicted to become the third most common cause of death and disability worldwide by 2020.

The prevalence of COPD defined by the lower limit of normal was estimated using high-quality spirometry in surveys of 14 populations aged ⩾40 yrs. The strength and consistency of associations were assessed using random effects meta-analysis.

Pack-years of smoking were associated with risk of COPD at each site. After adjusting for this effect, we still observed significant associations of COPD risk with age (OR 1.52 for a 10 yr age difference, 95% CI 1.35–1.71), body mass index in obese compared with normal weight (OR 0.50, 95% CI 0.37–0.67), level of education completed (OR 0.76, 95% CI 0.67–0.87), hospitalisation with a respiratory problem before age 10 yrs (OR 2.35, 95% CI 1.42–3.91), passive cigarette smoke exposure (OR 1.24, 95% CI 1.05–1.47), tuberculosis (OR 1.78, 95%CI 1.17–2.72) and a family history of COPD (OR 1.50, 95% CI 1.19–1.90).

Although smoking is the most important risk factor for COPD, other risk factors are also important. More research is required to elucidate relevant risk factors in low- and middle-income countries where the greatest impact of COPD will occur.

KEYWORDS: Age, chronic obstructive pulmonary disease, early life, risk factor, smoking, tuberculosis

Chronic obstructive pulmonary disease (COPD) is defined as airway obstruction that does not significantly decrease with bronchodilators. It is operationally defined as a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <70% [1], although it has been increasingly recognised that this ratio should be normalised for age. In this article we have used the lower limit of normal for the definition [2, 3].

The impact of COPD is predicted to increase worldwide [4]. These predictions are largely driven by current estimates of mortality and prevalence, and by predicted changes in the age structure and smoking habits of the world's population, especially in low- and middle-income countries. Data from the Burden of Obstructive Lung Disease (BOLD) study in Iceland and Norway show that COPD accounts for 0.7–1.2% of the healthcare budget, largely driven by the costs of exacerbations, and that prevalence is likely to rise over the next 10–15 yrs [5].

The strongest risk factor for COPD and an accelerated decline in adult lung function is cigarette smoking, and smoking cessation is known to slow the rate of decline of lung function [6–8]. However, cigarette smoking alone does not explain the distribution of COPD, even in economically prosperous regions [9].

Other factors that increase the burden of inhaled particulates and are associated with increased oxidative stress in the lung, including outdoor and indoor air pollution, and occupation [10, 11], are also likely to increase the risk of COPD. In addition, deaths from COPD are more strongly associated with poor social conditions than deaths from carcinoma of the bronchus, another smoking-related disease [12]. Impaired adult lung function has also been associated with

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Received:
Jan 07 2011
Accepted after revision:
Sept 19 2011
First published online:
Dec 19 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

This article has supplementary material available from www.erj.ersjournals.com

childhood poverty [13], and more specifically with two correlates of childhood poverty: low birthweight and lower respiratory tract infections in infancy [14].

The BOLD programme is an international collaboration to assess the prevalence and risk factors for COPD. This article summarises the associations between spirometrically defined COPD and its main risk factors.

METHODS

The design and rationale for the BOLD study, the characteristics of samples and the prevalence of COPD in 12 sites have been reported elsewhere [15, 16].

Lung function, including FEV_1, forced expiratory volume in 6 s (FEV_6) and FVC, was measured using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), before and 15 min after inhaled salbutamol (200 μg) by metered dose inhaler with spacer. Spirograms were reviewed by the BOLD Pulmonary Function Reading Centre, and assigned a quality score based on acceptability and reproducibility criteria from the American Thoracic Society (ATS) and European Respiratory Society [17]. Spirometry technicians at BOLD sites were certified before data collection, received regular feedback on quality and were required to maintain a pre-specified quality standard.

Outcome measures were the following. 1) A modification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I or higher COPD, defined as a post-bronchodilator FEV_1/FVC ratio below the lower limit of normal for age and sex, based on reference equations for ''Caucasians'' derived from the third US National Health and Nutrition Examination Survey (NHANES) [18]. 2) The continuous post-bronchodilator FEV_1/FVC ratio, expressed as a percentage. Prevalence of modified GOLD stage I or higher was estimated at each centre for males and females overall, and in subgroups defined by age and smoking, allowing for sampling weights and stratification or clustering in the sampling at each site.

Information on respiratory symptoms, health status and exposure to risk factors was obtained using face-to-face interviews conducted in the subject's native language by trained and certified staff. Questions about cigarette smoking were derived from the 1978 ATS Epidemiology Standardisation Project [19], and other sections of the interview were derived from the European Community Respiratory Health Study [20], the Consilio Nazionale de Ricerche (CNR) study [21] and the Obstructive Lung Disease in Northern Sweden (OLIN) study [22].

Risk factors investigated were: age; sex; body mass index (BMI; categorised as normal/underweight <25 kg·m^{-2}; overweight 25–30 kg·m^{-2} or obese >30 kg·m^{-2}), education (categorised as none, primary or middle school, secondary school, technical/vocational college or university); father's education (categorised similarly); hospitalisation for breathing problems before age 10 yrs; pack-years of smoking (number of cigarettes smoked per day divided by 20 and multiplied by years of smoking); current smoking; passive smoking (somebody else smoking in the subject's home in the last 2 weeks); doctor-diagnosed tuberculosis (ever); family history of COPD (doctor ever-diagnosed mother, father, sister or brother with emphysema, chronic bronchitis or COPD); years working in dusty jobs; regular exposure to dust in present job; regular exposure to fumes in current job; years of heating home with biomass fuel (coal, coke, peat, wood, crop residue or dung); and equivalent years of continuous exposure to cooking fires using biomass fuel (calculated by multiplying number of years over which subject was exposed by number of hours exposure per day divided by 24). Both for heating and cooking, exposures to coal, coke or peat fires, and to wood, crop residue or dung fires were recorded separately on the questionnaire. However, respondents frequently reported identical durations of exposure to each, and the distribution of time exposed in this case was similar to that of respondents who used just one type of fire. We therefore used the maximum of the two durations, rather than adding them together.

Effects of subject's and father's education were modelled as linear trends across the categories. Father's education was reported as unknown for around a quarter of participants: this was coded as no education to allow the trend effect to be estimated, and the independent effect of unknown *versus* no education was estimated as a separate covariate. The other risk factors that could be reported on the questionnaire as unknown were subject's own education, and hospitalisation for breathing problems before age 10 yrs: in the few cases where this occurred, these values were treated as missing.

We attempted to include all risk factors in the regression analyses of every centre, but in the analysis of COPD there were occasions where the exposed subgroup at a centre was small and did not include any cases of COPD. This meant that the subgroup had to be excluded from the analysis, and the effect of the factor was not estimated for this centre.

Age, pack-years of smoking, years working in dusty jobs, years exposed to biomass heating and years exposed to biomass cooking were modelled as continuous variables, but to allow for possible nonlinear effects, we first considered a model in each centre in which these variables had quadratic effects, and looked at the results of meta-analysing each quadratic term. In the case of age, years working in dusty jobs and years exposed to biomass cooking, nonlinear effects were homogeneous and nonsignificant and we, therefore, used linear effects of these variables in the final regression model. In the case of pack-years of smoking, nonlinear effects were heterogeneous and significant overall and we, therefore, retained a quadratic effect of this variable in the final regression model. Models that included quadratic effects of years exposed to biomass heating and models that divided years exposed to biomass heating into three categories did not fit the data noticeably better at any centre than models that used a linear effect of years exposed to biomass heating, according to the Hosmer–Lemeshow goodness-of-fit tests [23]. We decided, for simplicity, to model years exposed to biomass heating as a linear effect.

We tested for interactions between sex and all other risk factors in each centre. Of those interactions that could be estimated, none were statistically significant using a Simes procedure to allow for the multiple testing [24]. We did not, therefore, include any interactions in the final regression models.

Because smoking was known *a priori* to be an important risk factor for COPD, and in order to adjust for its effects as

accurately as possible, we preferred to model pack-years of smoking as a continuous variable with a nonlinear effect.

We used multiple logistic regression to estimate the effects of risk factors on COPD, and multiple linear regression to analyse the FEV1/FVC ratio. Participants with unacceptable or unreproducible post-bronchodilator spirometry, as well as those who had had part of a lung removed, were excluded. Effects of all risk factors were mutually adjusted, and estimated allowing for sampling weights and stratification or clustering in the sampling at each site. Regression models were fitted separately for each site, and results for each risk factor were pooled across sites using random effects meta-analysis [25]. Heterogeneity was summarised using the I^2 statistic [26]. Where a site did not collect information on biomass exposure, these risk factors were not included in the model for that site. p-values <0.05 are referred to as significant.

All analyses were performed using Stata 10 (Stata Corp., College Station, TX, USA).

Ethical approval was obtained by each site from the local ethics committee, and written informed consent was obtained from every subject.

RESULTS

14 sites had completed data collection by December 31, 2007. Sites were asked to provide at least 600 participants, and the number ranged from 563 to 1,349. Response rates varied from >70% at four sites to <50% in three [3].

Figure 1 shows some of the characteristics of males and females at different sites. In this figure, the sites have been ordered according to the proportion educated to college or university level. Proportions educated to college or university level ranged from 4.9% in males and 2.0% in females (Adana, Turkey) to 78.1% in males and 73.4% in females (Vancouver, Canada). Although this is a crude measure of socioeconomic status, it gives a useful ordering of sites because it is virtually independent of sex. Arranging the data in this way also helps to illustrate ecological associations. Sites with a higher level of education tended to have lower proportions of passive smokers, higher proportions hospitalised for breathing problems before the age of 10 yrs, and lower proportions exposed to biomass fires for cooking. Among males, at least, there was a tendency to have lower proportions of current and ever-smokers.

Tuberculosis was relatively commonly diagnosed in Cape Town, South Africa (19.2% in males and 12.0% in females) and Manila, Phillippines (14.3% in males and 8.0% in females), while a family history of COPD was notably prevalent in Lexington, KY, USA (35.0% in males and 44.8% in females). Current exposure to dust at work was most common in Manila (47.5% in males and 21.5% in females) as was current exposure to fumes at work (40.1% in males and 18.0% in females). Exposure to biomass fires for heating was widespread in Adana and Krakow, Poland, and was also common in Lexington and London, UK.

The prevalence of COPD (modified stage I) in males ranged from 7% in Sydney, Australia, to 23% in Cape Town (table 1). In females it ranged from 4% (Manila) to 21% (Salzburg, Austria).

We observed a significant effect of pack-years of smoking on the risk of COPD at each site ($p<0.005$ in each case). In pooled meta-analyses of multivariate models that also adjusted for pack-years of cigarette smoking, we observed significant associations between the prevalence of COPD and each of BMI, level of education, hospitalisation with a respiratory illness before the age of 10 yrs, passive cigarette smoke exposure and a family history of COPD (table 2). We found qualitatively similar results when we used the continuous FEV1/FVC ratio as our outcome. Both current smoking and a history of tuberculosis were associated with increased risk of COPD in the logistic regression analyses, but were not significantly associated with the continuous FEV1/FVC ratio measure. The opposite pattern was observed for years worked in a dusty job. Mean FEV1/FVC declined significantly with increasing age and the ratio was higher for females than for males. Increasing age was also significantly associated with increased risk of the modified GOLD stage I definition of COPD.

Table 3 provides the same information as table 2, but defines COPD stage I by the GOLD criterion of an FEV1/FVC <0.7 at all ages. As expected, the coefficients for age and sex are different from those in table 2. All other coefficients are substantively the same. Although the significance test gives a different result for years of exposure to dust, the estimates are not significantly different from each other.

Although the regression estimates in table 2 are pooled across sites, we observed statistically significant heterogeneity across sites in the effects of sex, age, BMI, hospitalisation before the age of 10 yrs and current smoking on the binary COPD outcome, and in the effects of BMI, current smoking and tuberculosis on the continuous FEV1/FVC ratio. The corresponding I^2 statistics and heterogeneity tests are also presented in figure 2. As an example, figure 2 shows the Forest plot for passive smoking.

DISCUSSION

We have found significant associations between COPD and smoking, environmental tobacco exposure, age, education, tuberculosis, hospitalisation for respiratory illness before the age of 10 yrs, a family history of COPD and the number of years worked in dusty jobs.

We have used the ratio of FEV1 to FVC to define COPD. Unlike the FEV1 and FVC individually, the ratio is not strongly related to ethnicity [27–29] and hence is a suitable measure for international comparisons. We used the lower limit of normal of the FEV1/FVC ratio to define obstruction, rather than an FEV1/FVC ratio <0.70 as recommended by GOLD, since the latter is prone to bias by age [2]. We have referred to our measure as ''modified'' GOLD stage I COPD. This is to be preferred to using the original GOLD stage II, which has the same effect [3] as it uses only the FEV1/FVC ratio and does not also include the FEV1.

Recently, it has been suggested that measuring the FEV6 would be more reliable than measuring the FVC [30]. We have re-run the analyses presented here using the FEV1/FEV6 ratio in place of the FEV1/FVC ratio and found that the heterogeneity of the risks estimated in different sites was reduced, particularly when using the binary outcome. Apart from this, we observed

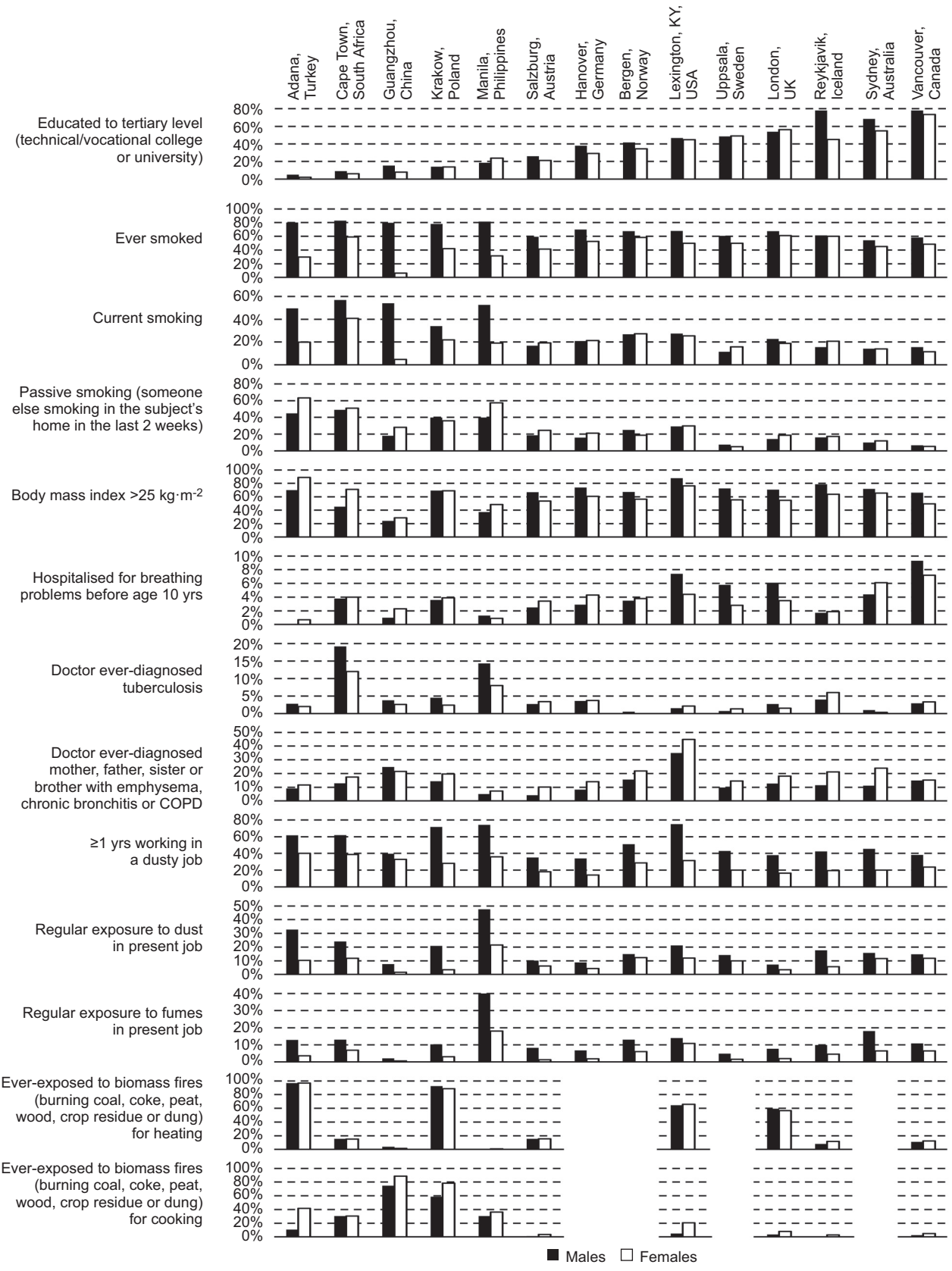

FIGURE 1. Characteristics of the populations studied at different sites (calculated using probability weights to allow for the sampling design at each site). COPD: chronic obstructive pulmonary disease.

TABLE 1 Estimated population prevalence of modified Global Initiative for Chronic Obstructive Lung Disease stage I or higher chronic obstructive pulmonary disease (COPD) in age and smoking categories[#]

	Guangzhou, China	Adana, Turkey	Lexington, KY, USA	Salzburg, Austria	Cape Town, South Africa	Reykjavik, Iceland	Krakow, Poland	Vancouver, Canada	Manila, Philippines	London, UK	Bergen, Norway	Hanover, Germany	Sydney, Australia	Uppsala, Sweden
Males														
Subjects	234	389	203	682	312	399	264	338	378	320	324	346	261	283
Overall	9.4 (1.9)	19.8 (2.0)	11.7 (2.2)	13.4 (1.3)	22.8 (2.5)	9.1 (1.5)	14.9 (2.2)	14.3 (2.0)	15.1 (2.7)	18.9 (3.1)	13.8 (1.9)	9.9 (1.7)	6.9 (1.6)	10.5 (1.9)
Age yrs														
40–49	2.9 (1.6)	15.2 (2.9)	1.8 (1.8)	7.7 (1.9)	17.8 (3.5)	2.7 (1.3)	6.0 (2.4)	7.2 (2.2)	10.8 (3.9)	9.9 (3.7)	10.5 (3.2)	2.2 (1.6)	4.0 (2.3)	6.2 (3.0)
50–59	6.7 (3.2)	20.2 (3.6)	18.7 (4.7)	14.6 (2.5)	26.0 (4.7)	7.4 (2.4)	15.9 (4.2)	8.3 (2.7)	12.1 (4.3)	12.3 (5.1)	9.0 (3.0)	11.6 (3.6)	2.7 (1.9)	4.1 (2.0)
60–69	25.6 (6.7)	30.0 (5.5)	13.8 (4.9)	8.0 (2.1)	28.0 (5.9)	11.4 (3.8)	19.1 (5.5)	16.0 (5.2)	33.1 (8.8)	26.7 (5.6)	15.8 (4.4)	10.8 93.1)	12.3 (4.4)	11.3 (3.8)
⩾70	14.8 (6.8)	18.9 (6.4)	19.2 (7.7)	25.8 (4.0)	29.2 (9.0)	23.0 (5.4)	31.6 (7.6)	39.0 (7.6)	22.9 (8.5)	36.3 (10.4)	25.4 (5.0)	17.9 (5.5)	12.5 (4.4)	26.0 (6.2)
Smoking exposure in pack-yrs														
Never-smoker	2.3 (2.2)	6.7 (2.9)	1.2 (1.2)	8.1 (1.7)	3.2 (3.1)	7.4 (2.1)	3.3 (2.3)	6.7 (2.2)	8.1 (4.7)	14.8 (5.7)	8.7 (2.8)	1.7 (1.0)	4.0 (1.8)	6.0 (2.4)
0–10	0.0 (-)	5.6 (3.1)	0.0 (-)	8.5 (3.1)	14.0 (3.7)	3.2 (2.3)	6.7 (4.6)	8.4 (4.1)	6.4 (2.8)	11.8 (5.2)	6.2 (3.5)	3.4 (2.6)	2.4 (2.3)	4.8 (2.7)
10–20	8.2 (3.9)	11.6 (4.9)	0.0 (-)	9.9 (3.3)	36.4 (5.7)	1.5 (1.5)	11.3 (4.8)	21.7 96.8)	15.1 (6.7)	2.8 (2.0)	21.8 (5.0)	7.7 (4.5)	0.0 (-)	5.0 (3.5)
>20	15.0 (3.4)	29.5 (3.1)	20.5 (3.8)	22.8 (2.8)	33.4 (5.1)	18.8 (3.7)	22.7 (3.6)	26.5 94.8)	24.9 (5.0)	28.8 (5.5)	17.9 (3.7)	19.3 (3.6)	18.5 (4.7)	25.9 (5.3)
Females														
Subjects	235	416	302	571	530	351	258	475	510	354	332	332	276	263
Overall	6.4 (1.6)	9.1 (1.4)	16.3 (2.4)	20.5 (1.8)	16.8 (1.8)	13.3 (1.8)	12.2 (2.1)	12.2 (1.5)	4.2 (1.1)	16.0 (2.8)	9.8 (1.7)	6.8 (1.5)	14.1 (2.1)	8.7 (1.8)
Age yrs														
40–49	4.1 (2.0)	5.5 (1.7)	10.2 (3.4)	16.4 (2.8)	12.1 (2.5)	10.4 (2.7)	4.0 (2.0)	8.2 (2.3)	3.8 (1.2)	10.5 (3.7)	8.1 (3.2)	6.4 (2.6)	11.0 (3.5)	3.4 (2.4)
50–59	1.5 (1.5)	9.8 (2.7)	14.5 (3.3)	19.3 (3.1)	20.8 (3.5)	7.3 (2.7)	10.7 (3.8)	5.8 (1.9)	3.1 (1.4)	9.2 (3.5)	8.2 (2.8)	4.7 (2.1)	8.2 (3.2)	5.6 (2.4)
60–69	9.4 (4.0)	15.5 (4.3)	23.0 (4.8)	16.6 (3.0)	22.3 (4.1)	20.3 (5.0)	19.8 (5.2)	18.7 (4.1)	7.5 (4.8)	25.3 (5.7)	8.3 (3.3)	6.9 (2.9)	17.2 (5.0)	11.0 (3.7)
>70	25.0 (9.7)	11.9 (5.0)	22.2 (8.0)	30.1 (5.0)	13.3 (4.6)	19.7 (4.9)	20.3 (6.3)	21.4 (4.5)	3.7 (2.5)	22.2 (8.1)	15.4 (4.0)	10.8 (4.6)	20.6 (5.1)	15.9 (5.5)
Smoking exposure in pack-yrs														
Never-smoker	4.5 (1.4)	8.3 (1.6)	6.4 (2.4)	13.5 (2.1)	6.5 (1.7)	9.0 (2.5)	13.3 (2.8)	7.7 (1.8)	3.2 (0.9)	6.5 (1.9)	4.8 (1.8)	4.3 (1.6)	9.1 (2.4)	6.7 (2.4)
0–10	20.0 (17.9)	4.5 (2.6)	0.0 (-)	27.4 (5.0)	22.2 (3.7)	6.6 (2.6)	7.5 (4.2)	5.8 (2.6)	7.2 (4.3)	11.0 (5.1)	1.9 (1.9)	1.1 (1.1)	6.2 (3.5)	3.4 (2.4)
10–20	25.0 (21.7)	16.7 (7.6)	23.0 (8.6)	30.3 (6.3)	25.1 (5.1)	6.3 (3.5)	21.2 (7.1)	21.1 (6.0)	5.6 (3.5)	19.0 (8.7)	12.9 (4.1)	9.8 (4.7)	21.0 98.4)	21.5 (7.8)
>20	50.0 (20.4)	18.9 (6.4)	34.1 (5.1)	32.3 (5.0)	25.9 (5.4)	33.9 (5.5)	5.0 (3.5)	26.3 (4.8)	4.3 (3.4)	29.7 (6.8)	25.2 (5.7)	13.8 94.3)	32.3 (6.5)	11.0 (4.3)

Data are presented as n or % (SE). The data exclude participants with unacceptable or unreproducible spirometry, and those who reported ever having had part of a lung removed. [#]: stage I or higher COPD defined as having a forced expiratory volume in 1 s/forced vital capacity ratio below the lower limit of normal given age and sex, using reference equations from the National Health and Nutrition Examination Survey.

TABLE 2 Pooled estimates of effects of risk factors on stage I or higher chronic obstructive pulmonary disease (COPD),[#] and on percentage forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio, adjusted for all risk factors in the regression model, including pack-years of smoking

	Stage I or higher COPD				% FEV_1/FVC			
	OR (95% CI)	p-value	I^2 %	p-value for heterogeneity	Regression coefficient[¶] (95% CI)	p-value	I^2 %	p-value for heterogeneity
Females	1.10 (0.85–1.43)	0.46	57	0.004	1.16 (0.70–1.57)	<0.001	39	0.069
Age per 10-yr difference	1.52 (1.35–1.71)	<0.001	60	0.002	-2.69 (-2.88– -2.49)	<0.001	26	0.17
BMI kg·m^{-2}								
<25	1.00				0.00			
25–30	0.58 (0.46– 0.72)	<0.001	43	0.045	1.87 (1.29–2.45)	<0.001	54	0.008
>30	0.50 (0.37–0.67)	<0.001	50	0.020	2.54 (1.87–3.20)	<0.001	50	0.017
Education[+]	0.76 (0.67–0.87)	<0.001	26	0.18	0.54 (0.29–0.80)	<0.001	0	0.99
Hospitalisation for breathing problems before age 10 yrs	2.35 (1.42– 3.91)	0.001	54	0.011	-1.35 (-2.44–-0.27)	0.014	32	0.12
Current smoking	1.31 (1.00–1.72)	0.049	52	0.012	-0.38 (-1.10–0.34)	0.30	55	0.007
Passive smoking[§]	1.24 (1.05–1.47)	0.012	0	0.45	-0.61 (-1.06– -0.15)	0.009	14	0.30
Doctor ever-diagnosed tuberculosis	1.78 (1.17–2.72)	0.007	41	0.070	-1.98 (-4.23–0.26)	0.083	80	<0.001
Family history of COPD[ƒ]	1.50 (1.19– 1.90)	0.001	31	0.13	-0.95 (-1.51– -0.39)	0.001	26	0.18
Years working in dusty jobs per 10-yr difference	1.04 (0.98– 1.11)	0.17	0	0.71	-0.33 (-0.50– -0.15)	<0.001	0	0.49
Regular exposure to dust in present job	0.86 (0.61– 1.21)	0.40	36	0.091	0.61 (-0.02–1.24)	0.058	28	0.16
Regular exposure to fumes in present job	0.91 (0.67–1.24)	0.55	0	0.97	0.37 (-0.22–0.97)	0.22	7	0.38
Years exposed to biomass fires per 10-yr difference[##]								
For heating	1.01 (0.94–1.10)	0.72	0	0.63	0.04 (-0.17–0.26)	0.71	0	0.47
For cooking[¶¶]	1.02 (0.68–1.54)	0.91	2	0.42	-0.20 (-2.16–1.76)	0.84	32	0.15

BMI: body mass index. See online supplementary material for more details of model fitting and coding of risk factors. The model adjusts for a quadratic effect of pack-years of smoking, which is not shown in the table because the separate coefficients of pack-years and pack-years squared are difficult to interpret. Table 1 shows how pack-years of smoking affected prevalence of COPD at different sites. [#]: stage I or higher COPD defined as having an FEV_1/FVC ratio below the lower limit of normal given age and sex, using reference equations from National Health and Nutrition Examination Survey. [¶]: a negative regression coefficient indicates a reduction in FEV_1/FVC, *i.e.* poorer lung function. [+]: effect per group, assuming a linear effect over the four groups of highest level of education, as follows: none; primary (primary or middle school); secondary (secondary school); tertiary (technical/vocational college or university). [§]: somebody else smoking in the subject's home in the last 2 weeks. [ƒ]: doctor ever-diagnosed mother, father, sister or brother with emphysema, chronic bronchitis or COPD. [##]: fires burning coal, coke, peat, wood, crop residue or dung. [¶¶]: years of equivalent continuous exposure are calculated by multiplying number of years over which subject was exposed by number of hours of exposure per day divided by 24.

TABLE 3 Pooled estimates of effects of risk factors on Global Initiative for Chronic Obstructive Lung Disease stage I or higher chronic obstructive pulmonary disease (COPD)[#] adjusted for all risk factors in the regression model, including pack-years of smoking

	OR (95% CI)	p-value	I^2 %	p-value for heterogeneity
Female	0.75 (0.64–0.89)	0.001	30	0.11
Age (per 10-yr difference)	2.14 (1.98–2.31)	<0.001	41	0.042
BMI kg·m^{-2}				
<25	1.00			
25–30	0.64 (0.51–0.79)	<0.001	58	0.002
>30	0.60 (0.47–0.76)	<0.001	53	0.006
Education[¶]	0.81 (0.74–0.89)	<0.001	0	0.62
Hospitalisation for breathing problems before age 10 yrs	2.11 (1.29–3.44)	0.003	61	0.001
Current smoking	1.34 (1.12–1.61)	0.002	30	0.11
Passive smoking[+]	1.22 (1.06–1.41)	0.006	7	0.38
Doctor ever-diagnosed tuberculosis	1.72 (1.19–2.48)	0.004	56	0.003
Family history of COPD[§]	1.38 (1.17–1.63)	<0.001	0	0.75
Years working in dusty jobs per 10-yr difference	1.08 (1.02–1.13)	0.003	1	0.44
Regular exposure to dust in present job	0.85 (0.66–1.11)	0.23	43	0.032
Regular exposure to fumes in present job	1.00 (0.79–1.26)	0.97	0	0.62
Years exposed to biomass fires per 10-yr difference[ƒ]				
For heating	1.03 (0.97–1.10)	0.33	0	0.52
For cooking[##]	0.98 (0.70–1.37)	0.91	4	0.41

BMI: body mass index. [#]: stage I or higher COPD defined as forced expiratory volume in 1 s/forced vital capacity ratio <0.7. [¶]: effect per group, assuming a linear effect over the four groups of highest level of education, as follows: none; primary (primary or middle school); secondary (secondary school); tertiary (technical/vocational college or university). [+]: somebody else smoking in the subject's home in the last 2 weeks. [§]: doctor ever-diagnosed mother, father, sister or brother with emphysema, chronic bronchitis or COPD. [ƒ]: fires burning coal, coke, peat, wood, crop residue or dung. [##]: years of equivalent continuous exposure are calculated by multiplying number of years over which subject was exposed by number of hours of exposure per day divided by 24.

only minor changes and we have kept to the more conventional measurements (FEV_1 and FEV_1/FVC) in this report.

The major effects of smoking on COPD have been extensively recorded over >40 yrs [31]. The measured association between passive smoking and COPD is strong and consistent across the sites, despite the crude assessment of exposure such as somebody else smoking in the subject's home in the last 2 weeks. Such associations have been reported before [32]. The link between passive smoking and COPD in Guangzhou, China has also been highlighted before [33].

There are reasons to believe that females may be at different risk from males because of differences in airway geometry, pattern of deposition of particles in the airway and, perhaps, hormonal differences [34]. However, dividing our samples according to sex would have increased the frequency with which small subgroups would have had to be excluded from the analysis because they predicted outcome perfectly, thus adversely affecting the accuracy of our estimates. We tested for interactions between sex and other factors in each site: none were statistically significant using a Simes procedure to allow for multiple testing [24] and, in the absence of internal evidence for differences between males and females, we chose to combine the sexes. In the PLATINO study, the prevalence of COPD was also similar between the sexes with the exception of current smokers where GOLD stage tended to be more severe among females. However, females reported more dyspnoea for a given level of ventilatory impairment [35].

Prevalence of COPD increased with age, even though our spirometric definition of COPD already takes account of the age of the participants, as does pack-years of smoking, with which it is strongly correlated. This most probably reflects the cumulative effects of many other unmeasured risks, including potentially those from air pollution [10], a poor diet [36, 37], poor social conditions and infections. The extent to which this association represents a cumulative effect across the age span and to what extent it marks an effect from early life associated with some birth cohorts is impossible to tell from these cross-sectional data.

A higher level of education was strongly and significantly associated with less disease. The effect did not show much variation across the different sites, although details of the educational system vary significantly. Educational level has previously been associated inversely with COPD and with a more rapid decline in lung function [38]. Education is inversely

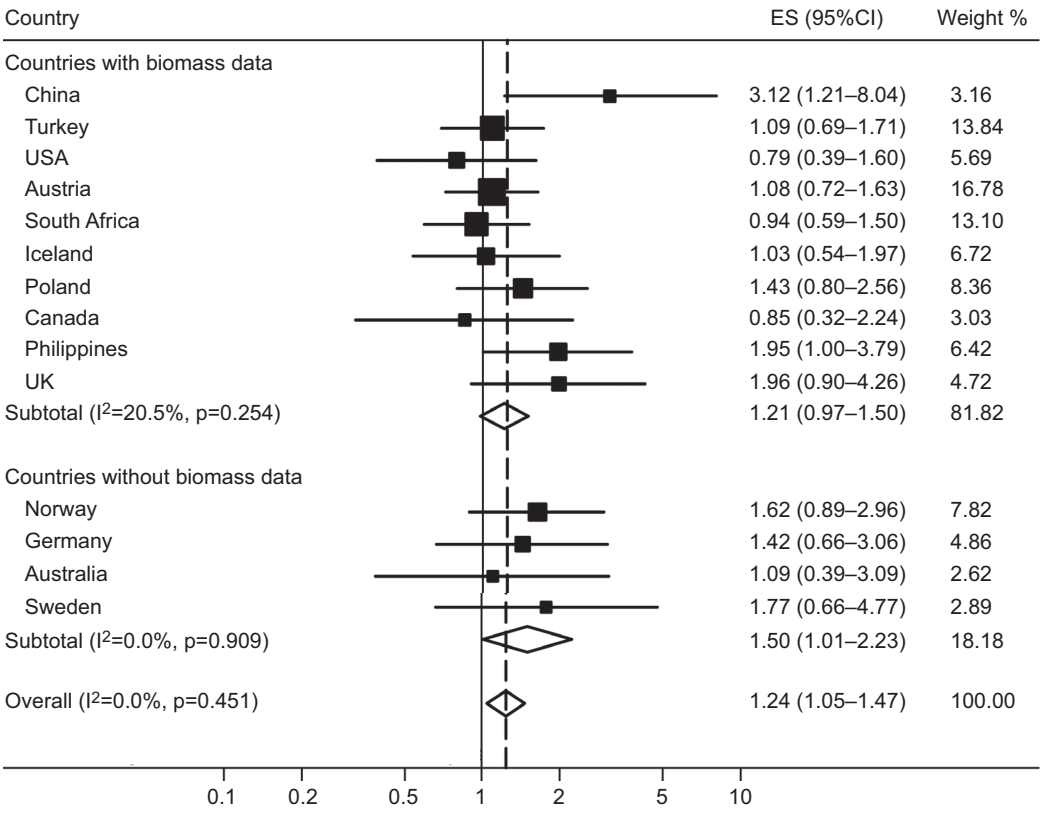

FIGURE 2. Forest plot showing associations between passive cigarette smoke exposure and modified Global Initiative for Chronic Obstructive Lung Disease stage I or higher chronic obstructive pulmonary disease. Note, weights are from random effects analysis. ES: effect size ; 95% CI: 95% confidence interval.

associated with many other risk factors such as smoking and occupation [39], which have been adjusted or partly adjusted for in this analysis. It may also be associated with other risk factors not included in this analysis, such as social conditions early in life and diet.

The lower prevalence of COPD in those with high BMI is similar to that reported by other studies [40–44]. In both a larger Chinese study using the BOLD methodology [40] and in the PLATINO study, which used substantially the same methods [43], there was a continuous increase in COPD prevalence as body mass increased, and the prevalence was particularly high in those who were ''underweight''. In our data, we are able to confirm the association with low body mass but have too few underweight subjects to add reliable information on this specific subgroup. LAMPRECHT *et al*. [44] showed an increased risk in nonsmokers with low body mass, but used less stringent methods to account for between-centre variation in effects. Paradoxically, it has been noted that when subjects give up smoking, the benefits to both FEV_1 and FVC are reduced if they also put on weight [45].

Hospitalisation for a respiratory illness before the age of 10 yrs, another recorded marker of early childhood environment or asthma, was also strongly associated with obstruction, though the size of effect was not consistent across sites. In a cross-sectional survey, this characteristic may be subject to marked recall bias. Although there is longitudinal evidence that early respiratory problems are associated with adult lung function [46], this does not exclude differential recall. In addition, hospitalisation in childhood does not have the same connotation in every site. In this study, the highest percentage of people answering positively to this question was in Vancouver, Canada, where we would not expect the worst respiratory health in early life. In the same way, the question on first degree relatives with COPD could be subject to selective recall. Because of the danger that we over-controlled our model by including early childhood hospitalisation and family history, we have checked whether excluding these variables from the model alters any of the other conclusions from the study: it does not.

A history of tuberculosis was strongly associated with the binary definition of COPD in this study and the effect was consistent across our sites. With the ratio of FEV_1 to FVC as a continuous outcome, the effect was much less consistent across sites and was not significant. A similar association was recorded previously in the PLATINO study [47]. While the association between airflow obstruction and tuberculosis was initially proposed >50 yrs ago, supporting data for this hypothesis in the interim have been lacking. Whether the obstruction is due to the pathological changes of tuberculosis or to associated risks, such as smoking and exposure to biomass fuel, is not fully resolved. However, the association is still found in this analysis after controlling for some of these risk factors.

In this article, we have looked only at more general markers of industrial exposure, but these questions appear to be as sensitive as some more elaborate methods [48]. Years worked

in a dusty job were associated with a lower FEV1/FVC ratio, although the effect was not significant when the less sensitive binary outcome was used. In contrast, we observed possible evidence of a healthy worker effect in those exposed to dust in their current jobs. A similar effect in those currently exposed to fumes was smaller and not significant.

We did not demonstrate any association between burning of biomass or solid fuels and obstruction. The odds ratios were consistently low and showed little variation across sites. Although much of the interest in indoor pollution has focused on the effects on children, there are reports of increased obstruction particularly in females exposed to indoor pollution from solid fuels. Odds ratios adjusted for age and smoking have been estimated to be ~3 for exposure to solid fuels in the home, with the effect being most clear in females [49]. In addition, mitigation of such exposures may lead to improved health [50]. In an extension of the BOLD study in China (CESCOPD), using the same instruments as reported here, ZHONG *et al.* [40] have estimated an adjusted odds ratio of 1.35 (95% CI 1.20–1.52), which is significantly greater than that reported for Guangzhou in this analysis and significantly lower than the odds ratios reported in an earlier meta-analysis [49]. The reasons for these discrepancies are unclear. Analysis of our Guangzhou data using the same model as in the paper from China produced an odds ratio of 0.90, so we do not believe it is due to differences in the methods used. The lack of an effect does not seem to be ascribable to lack of use of such fuels, as some sites reported substantial use and the lack of an effect was universal. It is likely that the ventilation of the houses and cooking areas was different, and there were important differences in the biomass fuels used across sites These findings caution against generalising the size of effects of biomass and solid fuel use on lung health without more information on how and which fuels are used and perhaps when in the lifecycle there was exposure. This said, there is an important possibility that some of the current conclusions on COPD and biomass exposure are affected by publication bias. In a recent review [51], there was a clear association between the breadth of the confidence intervals of the effects and the size of the effects, and the smallest confidence interval was associated with an odds ratio of around 1.03, very similar to the estimates given here [51].

Consistency across sites and strength of association are suggestive of true causal associations, but are neither necessary nor provide sufficient evidence. Inconsistencies across sites may be due to imprecise measurements and unresolved confounding or effect modification. A lot of the heterogeneity across sites was removed by using FEV1/FEV6 in place of FEV1/FVC. Three sites, Lexington, London and Sydney, had low response rates. This is common in several areas where there is either a low tolerance of surveys or where there is a very mobile population. Low response rates are not likely to have a large effect on estimated relative risks and are more a problem for estimates of prevalence. None of these three centres has a particular influence on the regressions and none shows an obviously different pattern from the other centres.

So far, the BOLD study has collected data largely in developed market economies. Relatively little information has been collected from low income countries and future research will be focused more on the developing economies where the main burden of the coming epidemic has been predicted. As expected, the dominant risk identified was smoking. It is increasingly emphasised that other factors are important and some of these, including factors operating in infancy (or even pre-natally), are difficult to assess in cross-sectional surveys. Other factors are hinted at by the residual association with age after using an age-adjusted measure of COPD and after pack-years of smoking has been taken into account. These findings re-emphasise the urgency of stopping the smoking epidemic and the need for better understanding of the determinants of lung health in poorer regions of the world.

SUPPORT STATEMENT

The BOLD initiative has been funded in part by unrestricted educational grants to the Operations Center (www.boldcopd.org) from ALTANA, Aventis, AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Pfizer, Schering-Plough, Sepracor, and University of Kentucky. Additional local support for BOLD clinical sites was provided by: Boehringer Ingelheim China (Guangzhou, China); Turkish Thoracic Society, Boehringer-Ingelheim, and Pfizer (Adana, Turkey); Altana, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck Sharpe & Dohme, Novartis, Salzburger Gebietskrankenkasse and Salzburg Local Government (Salzburg, Austria); Research for International Tobacco Control, the International Development Research Centre, the South African Medical Research Council, the South African Thoracic Society GlaxoSmithKline Pulmonary Research Fellowship, and the University of Cape Town Lung Institute (Cape Town, South Africa); and Landspítali-University Hospital-Scientific Fund, GlaxoSmithKline Iceland, and AstraZeneca Iceland (Reykjavik, Iceland); GlaxoSmithKline Pharmaceuticals, Polpharma, Ivax Pharma Poland, AstraZeneca Pharma Poland, ZF Altana Pharma, Pliva Kraków, Adamed, Novartis Poland, Linde Gaz Polska, Lek Polska, Tarchomińskie Zakłady Farmaceutyczne Polfa, Starostwo Proszowice, Skanska, Zasada, Agencja Mienia Wojskowego w Krakowie, Telekomunikacja Polska, Biernacki, Biogran, Amplus Bucki, Skrzydlewski, Sotwin, and Agroplon (Krakow, Poland); Boehringer-Ingelheim, and Pfizer Germany (Hanover, Germany); the Norwegian Ministry of Health's Foundation for Clinical Research, and Haukeland University Hospital's Medical Research Foundation for Thoracic Medicine (Bergen, Norway); AstraZeneca, Boehringer-Ingelheim, Pfizer, and GlaxoSmithKline (Vancouver, Canada); Marty Driesler Cancer Project (Lexington, KY, USA); Altana, Boehringer Ingelheim (Phil), GlaxoSmithKline, Pfizer, Philippine College of Chest Physicians, Philippine College of Physicians, and United Laboratories (Phil) (Manila, Philippines); Air Liquide Healthcare P/L, AstraZeneca P/L, Boehringer Ingelheim P/L, GlaxoSmithKline Australia P/L, Pfizer Australia P/L (Sydney, Australia); UK Department of Health's Policy Research Programme (London, UK); and Swedish Heart-Lung Foundation, the Swedish Heart and Lung Association and GlaxoSmithKline (Uppsala, Sweden).

STATEMENT OF INTEREST

Statements of interest for R. Hooper, P. Burney, W.M. Vollmer, M.A. McBurnie, T. Gislason, W.C. Tan, A. Jithoo, T. Welte and A.S. Buist, and the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

ACKNOWLEDGEMENTS

BOLD wishes to acknowledge the contributions of G. Harnoncourt of the ndd Corp., and P. Enright (University of Arizona, Tucson, AZ, USA), R. Crapo and R. Jenson (both Latter Day Saints Hospital, Salt Lake City, UT, USA) for their assistance with spirometry training and quality control during the study.

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