

International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study



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Summary

Background Chronic obstructive pulmonary disease (COPD) is a growing cause of morbidity and mortality worldwide, and accurate estimates of the prevalence of this disease are needed to anticipate the future burden of COPD, target key risk factors, and plan for providing COPD-related health services. We aimed to measure the prevalence of COPD and its risk factors and investigate variation across countries by age, sex, and smoking status.

Methods Participants from 12 sites (n=9425) completed postbronchodilator spirometry testing plus questionnaires about respiratory symptoms, health status, and exposure to COPD risk factors. COPD prevalence estimates based on the Global Initiative for Chronic Obstructive Lung Disease staging criteria were adjusted for the target population. Logistic regression was used to estimate adjusted odds ratios (ORs) for COPD associated with 10-year age increments and 10-pack-year (defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years that the participant smoked) increments. Meta-analyses provided pooled estimates for these risk factors.

Findings The prevalence of stage II or higher COPD was 10·1% (SE 4·8) overall, 11·8% (7·9) for men, and 8·5% (5·8) for women. The ORs for 10-year age increments were much the same across sites and for women and men. The overall pooled estimate was 1·94 (95% CI 1·80–2·10) per 10-year increment. Site-specific pack-year ORs varied significantly in women (pooled OR=1·28, 95% CI 1·15–1·42, p=0·012), but not in men (1·16, 1·12–1·21, p=0·743).

Interpretation This worldwide study showed higher levels and more advanced staging of spirometrically confirmed COPD than have typically been reported. However, although age and smoking are strong contributors to COPD, they do not fully explain variations in disease prevalence—other factors also seem to be important. Although smoking cessation is becoming an increasingly urgent objective for an ageing worldwide population, a better understanding of other factors that contribute to COPD is crucial to assist local public-health officials in developing the best possible primary and secondary prevention policies for their regions.

Introduction

Chronic obstructive pulmonary disease (COPD) is an important and growing cause of morbidity and mortality worldwide.^{1–3} The WHO Global Burden of Disease Project^{1,2} estimated that COPD was the fifth leading cause of death worldwide in 2001 and will be the third leading cause by 2020. The growing burden of COPD is partly due to the ageing of the world's population and partly to the continued use of tobacco, which is the most important risk factor for this disease.^{2,3}

WHO estimates of the burden of COPD are based on the little data available for both COPD and present patterns of cigarette smoking. Available information about COPD has not been obtained by consistent methods, and evidence suggests that rates of disease are generally underestimated.^{4,5} Accurate estimates of the prevalence of COPD and its risk factors would help guide future projections of the worldwide burden of this disease and assist public-health officials in planning to meet the growing demand for services that rising COPD rates will create.

The Burden Of Obstructive Lung Disease (BOLD) Initiative⁶ developed standardised methods for estimating COPD prevalence and for obtaining information about risk factors. These methods can be

used in countries at all levels of development and were developed in conjunction with The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO),⁷ which was undertaken in five Latin American countries.

Our aim was to measure the worldwide prevalence of COPD and its risk factors in adults aged 40 years and older and to investigate variation in prevalence across countries by age, sex, and smoking status.

Methods

Study design and participants

A description of the design and rationale for the BOLD initiative has been published elsewhere.⁶ Participants were recruited with use of population-based sampling plans. Questionnaires were used to obtain information about respiratory symptoms, health status, exposure to risk factors, and economic data for the burden of COPD. Prebronchodilator and postbronchodilator spirometry testing was also done for all participants. Data were entered into a secure web platform maintained by the BOLD Operations Center, which provided centralised training, standardised materials, data management, quality control, and data analysis.

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See [Editorial](#) page 713

See [Comment](#) page 715

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	Sampling design	Strata	Number of clusters	Number of respondents*	Response rate†	Cooperation rate‡
Guangzhou, China	Stratified random sample	Sex	1	602	87%	87%
Adana, Turkey	Stratified cluster sample	Urban versus rural	45	875	82%	85%
Salzburg, Austria	Stratified random sample	Sex	1	1349	65%	67%
Cape Town, South Africa	Cluster sample§	None	852	896	63%	68%
Reykjavik, Iceland	Simple random sample	None	1	758	81%	84%
Hannover, Germany	Stratified random sample	Administrative area and sex	1	713	59%	61%
Krakow, Poland	Stratified random sample	Administrative area and sex	1	603	78%	79%
Bergen, Norway	Stratified random sample§	Previous responders and non-responders	1	707	68%	71%
Vancouver, Canada	Random-digit dialling	None	1	856	26%	51%
Lexington, USA	Random-digit dialling	None	1	563	14%	27%
Manila, Philippines	Cluster sample	Administrative districts	95	918	58%	58%
Sydney, Australia	Stratified random sample	Sex	1	585	25%	33%

Sites are ordered in chronological order of completion. *Participants with core questionnaire and any postbronchodilator spirometry. The total number of respondents was 9425. †Denominator includes people of unknown eligibility status who could not be contacted. Only known ineligible participants were excluded. ‡Denominator includes only participants who were contacted and eligible. §The sample was derived from a previously studied population-based sample.

Table 1: Summary of sampling designs by site

As of Dec 31, 2006, 12 sites had completed data collection and are included in this report. Table 1 shows locations of the clinical centres for these sites. (Data from one site have been published separately,⁸ but are included in this analysis for completeness and as part of our cross-site comparisons). Participating sites agreed to recruit a population-based sample of at least 600 adults (300 men and 300 women) who were not institutionalised, were aged 40 years and older, and who were living in a well-defined administrative area in which the total population exceeded 150 000. These target populations, as well as the sampling plans, were approved in advance by the Operations Center. Every site had to obtain approval from its local ethical committee and written informed consent from every participant. Table 1 provides a summary of the sampling designs used by all sites. Further details about every site's target population are included in the webappendix.

See Online for webappendix

The minimum sample size requirement was designed to provide an acceptable degree of precision for estimates of prevalence at any specific site assuming simple random sampling and to allow for the reduced precision that might result from alternative sampling designs. For example, with a sample size of 600 participants, an estimated prevalence of 15%, and a gender-stratified simple random sampling design, a 95% CI for each sex would be 15% (11–19%), whereas the comparable CI for the sample as a whole (assuming equal prevalences for men and women) would be about 15% (12–18%).

Questionnaire data were obtained by face-to-face interviews with trained and certified staff in the participant's native language. A core questionnaire based on standardised instruments⁶ was completed for

all individuals and included questions about respiratory health and symptoms, smoking history, quality of life, respiratory-related health care use, and limitation of activities. The questions about cigarette smoking, in particular, derive from the 1978 American Thoracic Society (ATS)—the Division of Lung Disease's Epidemiology Standardization Project.⁹ Translation of questionnaires into the sites' local languages followed Mapi Institute (Lyon, France) guidelines.¹⁰

Lung function data were obtained at all BOLD sites with use of the ndd EasyOne Spirometer (nnd Medical Technologies, Andover, MA, USA), which is a hand-held, battery-operated device chosen for its level of accuracy and portability.¹¹ Lung function was measured before and 15 min after 200 µg of salbutamol was given. All spirometrys were reviewed by the BOLD Pulmonary Function Reading Center (PFRC) and assigned a quality score based on acceptability and reproducibility criteria from the ATS and European Respiratory Society (ERS).¹² Spirometry technicians were certified before the start of data collection and received regular feedback about the quality of their performance.

As part of the quality control review process, all volume-time and flow-volume graphs were simultaneously displayed and examined by staff at the PFRC. Data for forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were deemed usable and included in this analysis if they fully met ATS acceptability criteria and were reproducible to within 200 mL.

With the rare exception of participants for whom spirometry was contraindicated (eg, chest or abdominal surgery, heart attack or admission for a heart disorder, detached retina or eye surgery, last trimester of

	Guangzhou, China	Adana, Turkey	Salzburg, Austria	Cape Town, South Africa	Reykjavik, Iceland	Hannover, Germany	Krakow, Poland	Bergen, Norway	Vancouver, Canada	Lexington, USA	Manila, Philippines	Sydney, Australia
Men												
Total	291 (48%)	425 (49%)	736 (55%)	335 (37%)	403 (53%)	367 (51%)	302 (50%)	348 (49%)	363 (42%)	236 (42%)	385 (42%)	291 (50%)
Age (years)	54.2 (0.7)	53.6 (0.7)	58.6 (0.5)	52.7 (0.6)	56.4 (0.6)	58.5 (0.6)	55.7 (0.8)	57.4 (0.7)	56.4 (0.7)	56.6 (0.9)	52.1 (1.3)	57.6 (0.7)
Number of pack years*	27.2 (1.2)	34.1 (1.7)	28.7 (1.2)	18.3 (1.1)	24.1 (1.6)	27.8 (1.6)	29.6 (1.6)	21.4 (1.0)	28.4 (2.5)	44.9 (2.6)	23.5 (2.2)	25.9 (2.4)
Number of years in dusty job†	19.3 (1.2)	22.8 (1.4)	19.9 (1.0)	14.8 (0.8)	15.7 (1.0)	15.4 (1.3)	19.6 (0.8)	19.1 (1.0)	9.4 (0.9)	17.3 (1.0)	13.9 (0.7)	14.9 (1.1)
BMI (kg/m ²)	22.9 (0.2)	27.5 (0.2)	26.6 (0.1)	24.6 (0.3)	28.3 (0.2)	27.7 (0.2)	27.3 (0.2)	26.9 (0.2)	27.2 (0.2)	30.5 (0.4)	23.7 (0.6)	28.0 (0.3)
Number of years in education	9.2 (0.2)	6.7 (0.7)	9.8 (0.8)	8.1 (0.2)	13.9 (0.2)	10.5 (0.1)	10.7 (0.2)	12.9 (0.2)	15.8 (0.2)	12.8 (0.2)	9.6 (0.2)	11.6 (0.2)
Current smoker	2.9 (54%)	49.6% (3.0)	16.9% (1.4)	56.9% (2.9)	15.4% (1.8)	21.0% (2.3)	34.0% (2.7)	26.8% (2.5)	15.5% (1.9)	27.4% (3.0)	52.5% (1.9)	14.1% (2.1)
Ever smoker	79.7% (2.4)	80.2% (2.6)	59.4% (1.8)	83.0% (2.2)	61.4% (0.2)	70.0% (2.5)	78.1% (2.3)	67.5% (2.6)	58.3% (2.6)	67.9% (3.2)	81.5% (3.1)	54.3% (2.9)
History of TB	3.8% (1.1)	2.8% (0.8)	2.7% (0.6)	19.2% (2.3)	4.0% (1.0)	3.6% (1.1)	4.5% (1.2)	0.5% (0.3)	2.9% (0.9)	1.5% (0.9)	14.3% (1.6)	1.0% (0.6)
≥1 year in dusty job	39.5% (2.9)	61.6% (2.6)	35.3% (1.8)	61.9% (2.9)	42.5% (2.5)	33.9% (2.6)	71.6% (2.6)	51.1% (2.7)	38.1% (2.6)	75.2% (2.9)	75.2% (2.3)	45.3% (2.9)
Women												
Total	311 (52%)	450 (51%)	613 (45%)	561 (63%)	355 (47%)	346 (49%)	301 (50%)	359 (51%)	493 (58%)	327 (58%)	533 (58%)	294 (50%)
Age (years)	53.9 (0.6)	53.9 (0.6)	60.1 (0.6)	54.2 (0.5)	57.7 (0.7)	57.3 (0.7)	58.0 (0.10)	59.3 (0.7)	57.5 (0.65)	57.5 (0.8)	53.4 (0.6)	59.9 (0.8)
Number of pack years*	17.3 (3.0)	16.4 (2.1)	20.3 (1.3)	15.1 (0.9)	16.5 (1.0)	20.4 (1.5)	18.9 (2.2)	17.3 (1.1)	18.5 (1.1)	35.5 (2.1)	9.3 (0.9)	22.7 (2.0)
Number of years in dusty job†	18.4 (1.1)	23.3 (1.8)	19.8 (1.4)	12.9 (0.7)	8.1 (1.1)	13.0 (1.7)	22.2 (1.6)	14.3 (1.0)	11.3 (1.1)	13.2 (1.4)	11.2 (1.2)	14.6 (1.6)
BMI (kg/m ²)	23.3 (0.2)	31.3 (0.3)	26.2 (0.2)	29.5 (0.4)	27.5 (0.3)	26.5 (0.3)	28.0 (0.3)	26.2 (0.3)	26.3 (0.3)	30.8 (0.4)	24.9 (0.3)	27.8 (0.4)
Number of years in education	7.7 (0.2)	5.8 (1.2)	9.7 (0.9)	8.1 (0.4)	12.5 (0.2)	10.3 (0.1)	10.1 (0.2)	12.2 (0.2)	15.1 (0.2)	12.6 (0.2)	9.3 (0.2)	10.9 (0.1)
Current smoker	4.8% (1.2)	19.8% (2.1)	19.3% (1.6)	40.6% (2.3)	20.8% (2.1)	21.4% (2.5)	21.9% (2.2)	27.3% (2.5)	11.6% (1.5)	25.5% (2.6)	19.0% (2.1)	13.9% (2.0)
Ever smoker	6.1% (1.4)	29.8% (2.6)	41.4% (2.1)	59.0% (2.3)	60.1% (2.6)	52.6% (3.0)	42.1% (2.6)	58.2% (2.7)	48.4% (2.3)	50.0% (3.0)	31.5% (3.0)	45.0% (2.9)
History of TB	2.6% (1.4)	2.0% (0.7)	3.4% (0.8)	11.9% (1.5)	6.0% (1.3)	3.7% (1.1)	2.4% (1.0)	0	3.3% (0.8)	2.1% (0.9)	8.0% (1.9)	0.3% (0.3)
≥1 year in dusty job	32.8% (2.7)	40.0% (3.3)	18.2% (1.6)	38.8% (2.1)	19.8% (2.1)	14.1% (2.0)	28.2% (2.6)	28.7% (2.5)	23.7% (1.9)	31.4% (2.8)	37.7% (2.1)	20.0% (2.3)

Data are number (%), mean (SE), or % (SE). BMI=body-mass index. TB=tuberculosis. *Among ever-smokers. †Among those with a year or more in a dusty job.

Table 2: Estimated population demographics and risk factors of sites

pregnancy, resting pulse rate greater than 120, or positive for or taking drugs for tuberculosis), sites attempted to collect prebronchodilator and post-bronchodilator spirometry for all participants.

Definition of COPD

BOLD uses the Global Initiative for Chronic Obstructive Lung Disease (GOLD) lung function criteria for defining and staging COPD.³ The GOLD definition is consistent with ATS and ERS standards.¹³ BOLD follows standard practice in the published work, and bases the COPD diagnosis strictly on the lung function criteria^{5,14,15} without requiring documented exposure to a known causative agent.

Because of the low frequency of occurrence of stage IV COPD in these population-based samples, stages III and IV are combined in this paper. BOLD uses the prediction equations for white men and women derived from the third US National Health and Nutrition Examination Survey¹⁶ to compute percentage predicted FEV₁ (FEV₁%).

Statistical analysis

Participants at every site were assigned an analysis weight, which was computed as the product of a pure sampling weight times adjustment factors. Where applicable, weighting class adjustments¹⁷ were used to directly adjust for non-response within age-sex specific strata. When this adjustment was not possible, we used adjustment after stratification¹⁷ to ensure that the age-sex distribution of the weighted sample matched that of the target population. Both adjustments were used in sites with sampling protocols that were especially difficult.

Response rates (table 1) were defined as the number of responders (those who completed the core questionnaire and postbronchodilator spirometry), divided by the total number of individuals contacted, less those known to be ineligible. Cooperation rates were defined as the number of responders divided by the total number of responders plus active refusers. Standard methods were used to adjust these rates for multistage sampling designs and, for random-digit-dialling sites, to estimate the proportion of

	Guangzhou, China	Adana, Turkey	Salzburg, Austria	Cape Town, South Africa	Reykjavik, Iceland	Hannover, Germany	Krakow, Poland	Bergen, Norway	Vancouver, Canada	Lexington, USA	Manila, Philippines	Sydney, Australia
Men												
n	236	389	685	315	402	349	266	324	344	206	378	265
No airflow obstruction	84.7% (2.3)	71.5% (2.0)	73.4% (1.7)	71.3% (2.7)	81.8% (2.0)	81.9% (2.2)	72.3% (2.4)	77.4% (2.3)	78.0% (2.4)	81.9% (2.7)	80.4% (1.7)	81.1% (2.4)
Stage I	5.9% (1.5)	13.1% (1.7)	16.3% (1.4)	6.5% (1.5)	9.7% (1.5)	9.4% (1.7)	14.4% (2.1)	11.6% (1.7)	12.7% (1.9)	5.4% (1.6)	0.9% (0.4)	9.6% (1.8)
Stage II	7.6% (1.7)	13.1% (1.5)	9.3% (1.1)	14.2% (2.1)	6.7% (1.3)	7.5% (1.5)	10.3% (1.7)	9.4% (1.6)	9.3% (1.7)	7.1% (1.6)	11.3% (1.4)	7.2% (1.6)
Stage III-IV	1.7% (0.8)	2.3% (0.9)	1.0% (0.4)	8.0% (1.6)	1.9% (0.7)	1.1% (0.6)	3.0% (1.0)	1.6% (0.6)	0	5.6% (1.7)	7.4% (1.2)	2.1% (0.9)
Women												
n	237	417	573	532	353	334	260	334	483	302	515	276
No airflow obstruction	92.4% (1.7)	89.7% (1.9)	74.3% (2.0)	80.0% (1.9)	82.5% (2.1)	90.7% (1.6)	83.4% (2.2)	84.6% (1.9)	83.2% (1.8)	79.2% (2.7)	91.4% (1.4)	80.5% (2.5)
Stage I	2.5% (1.0)	4.3% (1.1)	14.7% (1.6)	3.3% (1.0)	8.1% (1.5)	5.6% (1.3)	8.1% (1.7)	9.5% (1.6)	9.5% (1.4)	5.2% (1.5)	1.8% (0.9)	7.3% (1.6)
Stage II	3.4% (1.2)	5.3% (1.1)	9.2% (1.4)	11.0% (1.4)	7.4% (1.4)	3.1% (1.0)	7.8% (1.7)	5.0% (1.1)	5.5% (1.1)	12.6% (2.2)	4.0% (0.8)	11.4% (2.0)
Stage III-IV	1.7% (0.8)	0.7% (0.4)	1.8% (0.7)	5.7% (1.1)	2.0% (0.7)	0.6% (0.5)	0.8% (0.6)	0.9% (0.5)	1.8% (0.6)	3.0% (1.0)	2.8% (0.8)	0.8% (0.6)
Overall												
n	473	806	1258	847	755	683	526	658	827	508	893	541
No airflow obstruction	88.6% (1.5)	80.9% (1.5)	73.9% (1.3)	76.2% (1.6)	82.1% (1.4)	86.7% (1.3)	77.9% (1.6)	81.2% (1.5)	80.7% (1.5)	80.4% (1.9)	86.2% (1.1)	80.8% (1.7)
Stage I	4.2% (0.9)	8.6% (1.0)	15.5% (1.1)	4.7% (0.9)	8.9% (1.1)	7.3% (1.0)	11.2% (2.3)	10.5% (1.2)	11.1% (1.2)	5.3% (1.1)	1.4% (0.6)	8.4% (1.2)
Stage II	5.5% (1.0)	9.1% (0.9)	9.2% (0.9)	12.4% (1.1)	7.0% (0.9)	5.1% (0.9)	9.0% (1.2)	7.1% (1.0)	7.3% (1.0)	10.1% (1.4)	7.5% (0.8)	9.4% (1.2)
Stage III-IV	1.7% (0.6)	1.5% (0.4)	1.4% (0.4)	6.7% (0.9)	1.9% (0.5)	0.8% (0.3)	1.9% (0.6)	1.2% (0.4)	0.9% (0.3)	4.2% (1.0)	5.0% (0.7)	1.4% (0.5)

Data are % (SE).

Table 3: Estimated population prevalence of COPD according to GOLD stage

individuals with uncertain eligibility who were likely to have been eligible.¹⁸ Data describing population demographics include all responders. For estimation of COPD prevalences, however, the population is restricted to responders who had usable spirometry. We did not report prevalence estimates if there were fewer than 20 participants in a specific category.

The term pack-years was defined as the number of cigarettes smoked per day divided by 20 and multiplied

by the number of years that the participant smoked. This variable was winsorised¹⁹ by setting all pack-year estimates greater than 200 to 200.

Stata survey analysis facilities (version 9.2 [Stata Corp, College Station, TX, USA]) were used to obtain point estimates and standard errors that show the sampling designs used at every site. For sites that used multistage cluster sampling, only the highest level of clustering was modelled. The adjusted Wald test was used to test hypotheses comparing prevalences and risk factors across subgroups. Logistic regression models incorporating cluster, strata, and weighting information were generated for every site to estimate odds ratios (and 95% CIs) of COPD for 10-year intervals of pack-years and for 10-year age increments. Models were adjusted for age, years of education, and smoking status (current, former, never). Random effects meta-analysis models were used to estimate pooled prevalence estimates and odds ratios, and to assess heterogeneity across sites and sex with use of the I² measure.²⁰

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

At the 12 study sites, 9425 study participants completed core questionnaires and postbronchodilator spirometry

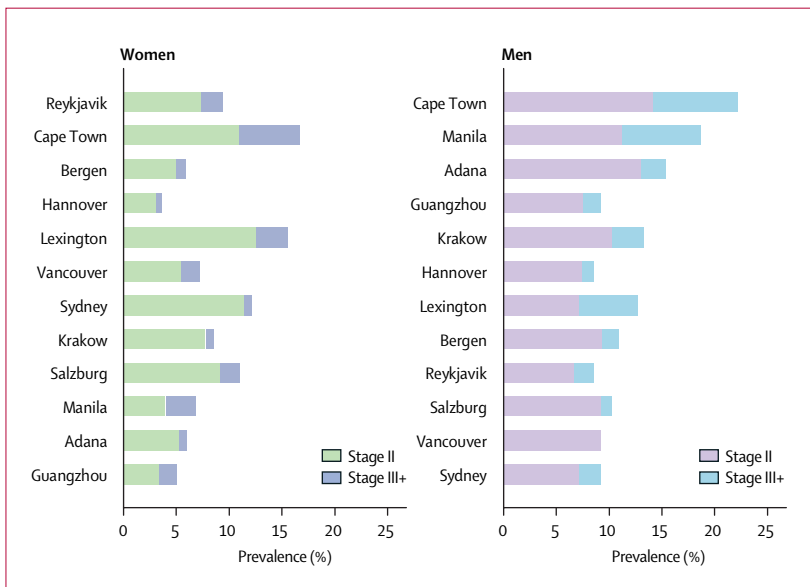


Figure 1: Prevalence of stage II and stage III or greater COPD by sex and site, ordered by (descending) prevalence of ever-smoking

(table 1). Cooperation rates were slightly higher than were response rates, which ranged from 14% to 87%. The lowest response and cooperation rates were in the random-digit-dialling sites (Vancouver and Kentucky; table 1), which reflect the large number of phone numbers for which either no contact was made or the respondent hung up before eligibility was confirmed.

Usable spirometry measures (ie, those that met ATS acceptability criteria and were reproducible to within 200 mL) were obtained from 8775 (93%) participants overall, with ten of 12 sites obtaining usable spirometry for 90% or more of their participants. The lowest proportion of usable manoeuvres was 79%, which was primarily due to early truncation of manoeuvres after the curve plateaued. This problem arose at one of the two pilot sites and was not corrected since that site did not send its spirometry files to the Operations Center until after data were obtained.

The age of male participants ranged from 52–58 years across sites and 53–60 years for female participants (table 2). Patterns of cigarette smoking varied widely across sites and between men and women. Sex-related differences in smoking patterns (especially in the ever-smoked group) were recorded for almost all sites,

and mean pack-years were consistently higher for men than for women.

The prevalence of COPD that was GOLD stage I or higher (postbronchodilator $FEV_1/FVC < 0.7$) varied significantly across sites ($p < 0.0001$) and was generally greater in men than in women (table 3). These variations tended to track the differences in smoking prevalence between sexes. Much the same sex-related differences were seen for GOLD stage II or higher disease.

The prevalence of stage II or higher COPD was 10.1% (SE 4.8) overall, 11.8% (7.9) for men, and 8.5% (5.8) for women. Figure 1 shows the prevalence of stage II and higher disease for men and women at every site. Within each sex, the sites are ordered by decreasing prevalence of ever smoking. Despite a slight trend in male participants, this crude ecological analysis suggests that factors other than smoking also affect prevalence of COPD.

Generally, the prevalence of COPD that is GOLD stage II or higher increased steadily with age for men and women in every site (table 4); disease that was GOLD stage II or higher was usually less than 5% in individuals aged 40–49 years. For those aged 70 years

	Guangzhou, China	Adana, Turkey	Salzburg, Austria	Cape Town, South Africa	Reykjavik, Iceland	Hannover, Germany	Krakow, Poland	Bergen, Norway	Vancouver, Canada	Lexington, USA	Manila, Philippines	Sydney, Australia
Men												
n	236	389	685	315	402	349	266	324	344	206	378	265
Overall	9.3% (1.9)	15.4% (1.5)	10.3 (1.2)	22.2 (2.4)	8.5 (1.4)	8.7 (1.6)	13.3 (1.9)	11 (1.7)	9.3 (1.7)	12.7 (2.3)	18.8 (1.7)	9.3 (1.8)
Age (years)												
40–49	0.9% (0.9)	10.8% (2.3)	1.5% (0.9)	17.5% (3.6)	2% (1.2)	0% (0)	2.1% (1.5)	4.5% (2.2)	2.8% (1.4)	1.8% (1.8)	11.5% (3.1)	2.7% (1.9)
50–59	6.7% (3.2)	14.5% (3.3)	8.3% (2)	20.8% (4.3)	3.3% (1.6)	10.7% (3.4)	10.4% (3.4)	11.2% (3.3)	6.4% (2.3)	17.9% (4.5)	15% (3.5)	4.1% (2.3)
60–69	23.3% (6.4)	25.7% (5.5)	11.9% (2.4)	34.8% (6.6)	12.5% (3.9)	8.9% (3)	19.9% (5.5)	12.9% (4)	12% (4.6)	19.6% (5.6)	39.4% (6.3)	13.8% (4.5)
70+	25.9% (8.4)	18.9% (9.2)	22.3% (3.8)	28.2% (8.6)	27.4% (5.7)	19% (5.6)	40.4% (8.2)	20.5% (4.7)	26.2% (6.8)	19.2% (7.7)	46.6% (8.4)	22.4% (5.5)
Smoking exposure in pack-years												
Never smoker	4.5% (3.1)	5.3% (2.1)	4.6% (1.3)	3.1% (3)	5.4% (1.8)	4.3% (2)	3.5% (2.5)	7.4% (2.6)	4.3% (1.8)	0	9.4% (2.2)	4.3% (1.9)
0–10	0	9.4% (3.9)	7.8% (3.1)	16.2% (3.9)	3.4% (2.4)	3.4% (2.5)	3% (3)	5.9% (3.3)	7.7% (3.7)	*	11.1% (2.8)	5.7% (3.2)
10–20	4.0% (2.8)	11.6% (5)	8.2% (3.0)	30.8% (5.3)	4.7% (2.7)	3.2% (3.1)	13.9% (5.4)	13.9% (4.2)	8.6% (4.9)	*	19.4% (4.8)	6.9% (4.7)
20+	15.8% (3.4)	21.2% (2.6)	18.6% (2.6)	33.9% (5.1)	17.6% (3.6)	15.8% (3.3)	19.5% (3.3)	15.5% (3.5)	17.7% (4.2)	22.1% (3.9)	28.7% (4.6)	21.7% (4.9)
Women												
n	237	417	573	532	353	334	260	334	483	302	515	276
Overall	5.1% (1.4)	6% (1.3)	11% (1.5)	16.7% (1.7)	9.3% (1.6)	3.7% (1.1)	8.6% (1.7)	5.9% (1.2)	7.3% (1.3)	15.6% (2.4)	6.8% (1)	12.2% (2)
Age (years)												
40–49	2% (1.4)	2.2% (1)	3.5% (1.4)	7.8% (2.1)	3.2% (1.6)	2.5% (1.6)	2% (1.4)	1.3% (1.2)	1.3% (0.9)	5.1% (2.5)	2.9% (0.9)	4.9% (2.4)
50–59	1.5% (1.5)	4.9% (1.9)	9% (2.2)	19.8% (3.4)	5.1% (2.2)	2.9% (1.9)	6.1% (2.9)	3.1% (1.7)	1.3% (0.9)	11% (2.9)	3.9% (1.5)	6.8% (3)
60–69	9.3% (3.9)	12.7% (4.1)	6.6% (2)	23.4% (4.3)	17.2% (4.7)	4.4% (2.2)	15.3% (4.4)	6.5% (2.9)	10.8% (3.2)	25.6% (4.9)	13% (4.6)	13.8% (4.5)
70+	20% (8.9)	14.3% (4.8)	25% (4.7)	32.7% (6.9)	17.9% (4.7)	6.2% (3.7)	15.8% (5.3)	15.1% (3.9)	20.7% (4.3)	29.6% (8.8)	20.5% (5.6)	23.8% (5.4)
Smoking exposure in pack-years												
Never smoker	4.1% (1.3)	5.9% (1.4)	8.6% (1.8)	8.2% (1.8)	8.3% (2.4)	2.9% (1.4)	11.2% (2.4)	3.8% (1.6)	3.2% (1.1)	6.5% (2.7)	6.9% (1.6)	10.2% (2.5)
0–10	*	0	9.3% (3.7)	22.5% (3.6)	2.1% (1.5)	0% (0)	0% (0)	1.1% (1.1)	3.7% (2.1)	9.7% (7.1)	6.5% (4)	2.5% (2.4)
10–20	*	12.5% (6.5)	14.1% (5.1)	19.4% (4.6)	6.6% (3.7)	3.5% (2)	12.4% (5.8)	6.3% (3.1)	11% (4.7)	19.7% (8.2)	7.6% (4.3)	8.8% (6)
20+	*	13.5% (6.1)	18.9% (4.2)	26.1% (5.1)	21.5% (4.8)	7.9% (3.4)	2.7% (2.7)	14.6% (4.2)	20% (4.5)	29.7% (5)	4.3% (3.3)	28.2% (6.4)

Data are % (SE). *Due to small number (<20), prevalence estimates are not reported for these cells. †Stage II or higher defined as $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$.

Table 4: Estimated population prevalence of GOLD stage II or higher COPD, separated by age and smoking exposure†

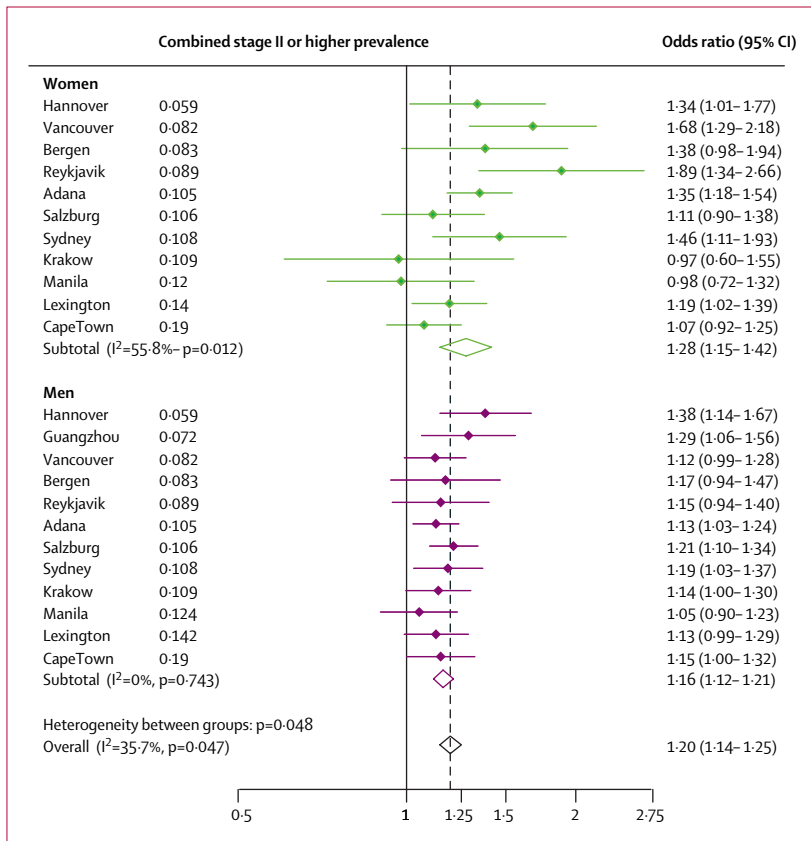


Figure 2: Odds ratios of stage II or more COPD for an increase of 10 pack-years in ever-smokers, by sex and site
 All models except that for men from Lexington were adjusted for age, years of education, and smoking status (current, former, never). The model for men from Lexington was adjusted only for years of education since there were no cases of stage II or more COPD in the reference group for smoking status (never-smoker), on which the age estimate depends. The model for women from Lexington is adjusted as other groups. Women from Guangzhou are excluded from this analysis because of their very low smoking prevalence.

and older, the prevalence was 19–47% for men and 6–33% for women. However, the relation between COPD that was GOLD stage II or higher and pack-years was less clear, partly because of confounding by age. Generally, the prevalence increased with increasing pack-years, and the prevalence among participants who had never smoked tended to be similar to that for those who had ever smoked and who had 0–10 pack-years of cigarette smoking exposure.

Figure 2 shows odds ratios (ORs) by sex and site for stage II or higher COPD associated with an increase of 10 pack-years. Data were adjusted for age, years of education, and smoking status (current, former, never), with the exception of the Lexington population, which was adjusted only for years of education. These OR estimates tended to be greater than one, indicating a strong positive association between cigarette smoking and COPD; however, in women, significant heterogeneity between sites was recorded ($p=0.012$). This variation seems to be because of smaller effects of smoking in sites with the highest prevalences of stage II or higher disease (Krakow, Manila, Lexington, and Cape

Town). Significant heterogeneity between the sexes was also noted ($p=0.047$). The pooled OR estimates were 1.28 (95% CI 1.15–1.42) for women and 1.16 (1.12–1.21) for men.

Figure 3 shows ORs for GOLD stage II or higher COPD associated with a 10-year increment in age after adjusting for years of education, smoking status (current, former, never), and pack-years. The lower CI bounds were greater than one for most OR estimates, and the tests for heterogeneity between sites and between sexes were not statistically significant. The overall pooled OR estimate was 1.94 (1.80–2.10) per 10-year increment.

Discussion

Our study has shown heterogeneity in the prevalence and staging of COPD both across sites and between men and women within sites. These differences can be at least partly explained by site and sex differences in the prevalence of cigarette smoking and other risk factors. The prevalences of COPD reported in this study tended to be greater than those typically reported in previous studies,^{4,5} but are generally similar to those reported in the PLATINO Study.⁷ PLATINO, which used similar methods to our study, reported crude rates of stage I or higher COPD between 7.8% (95% CI 5.9–9.7) and 19.7% (17.2–22.2) in samples from five Latin American countries. An absence of standardisation in previous studies has hindered cross-site comparisons. Our study implemented rigorous methods to achieve the maximum accuracy and completeness of the surveys and to obtain high-quality postbronchodilator spirometry.⁶ These methods ensured that the data were as comparable as possible across countries.

The GOLD classification of COPD severity,³ which is based on postbronchodilator spirometry, has been widely used since it was introduced in 2002. Whether GOLD stage I should be regarded as early COPD is debated,^{21,22} because the fixed FEV₁/FVC ratio falls with age in healthy individuals, resulting in substantial overdiagnosis in groups aged older than 50 years.^{23,24} This issue needs longitudinal follow-up of populations in good health to those with clinically significant disease.^{14,25} From a public-health perspective, the social and economic burden of COPD is modest in stage I and thereafter rises steadily with increasing severity of disease.^{26–28}

A recent, careful meta-analysis⁵ of surveys investigating prevalence of COPD reported a pooled prevalence estimate for people aged 40 years and older of 10.0% (95% CI 8.4–11.8) and showed the following distribution of COPD stages: stage I 6.6% (4.2–10.3), stage II 4.3% (3.7–5.0), and stage III/IV 1.2% (0.8–1.8) (Halbert R, UCLA School of Public Health, CA, USA, personal communication). Our estimates of the overall prevalence and staging of COPD are consistently higher than these figures, which accord with claims that COPD

has generally been underestimated in the past.⁴⁻⁶ In view of the acknowledged bias in prevalence of stage I disease with increasing age,^{23,24} we have shown that the prevalence of stage II and higher disease also was increased in our sites, six of which had a combined stage II or more prevalence greater than 10% (four sites for women and seven for men). In three sites (Cape Town, Manila, and Lexington), the prevalence of stage II disease was more than twice that of stage I, suggesting a much higher than usual burden of clinically significant COPD in these populations.

The high burden of COPD that we found might be the result of our choice of sites or our methods, or an indication of the changing nature of COPD worldwide, but in any case it needs attention for future health-care planning. The substantial differences in prevalences of COPD that we observed between sites question the relevance of a single, pooled estimate of COPD prevalence; the prevalence of this disease will depend on the prevalence of COPD risk factors in the population being studied as well as the age distribution.

We restricted our population samples to individuals aged 40 years and older because COPD develops over several decades of exposure to inhaled particulates. We imposed no upper age limit since age itself is an important risk factor for this disease.^{29,30} This notion is confirmed by our finding that the overall pooled adjusted OR estimate for stage II and higher COPD per 10-year age increment was almost two. The individual sites' adjusted ORs and lower 95% CIs were generally greater than one. For individuals aged 70 years or older, the prevalence of COPD that was stage II or higher exceeded 20% in nine sites for men and seven sites for women, which is a striking finding in view of projections for the ageing of the world's population.¹⁻³

We attempted to obtain information about several potential risk factors for COPD, including smoking,^{1,2} occupational exposures to dust,³¹ indoor exposure to biomass fuels used for home heating and cooking,^{1,2,32} tuberculosis,³³ and socioeconomic status.³ Although we reported crude exposure data for most of these risk factors, we focussed on the association of COPD with age, sex, and cigarette smoking. Differences in smoking patterns between men and women helped to explain much of the observed sex-related differences in prevalence of COPD. Nonetheless, several sites had high amounts of exposure to other risk factors that probably contributed to the variation in prevalence that we observed. For example, Cape Town, which had by far the highest prevalence of stage II or greater COPD, had very high reported levels of prior tuberculosis and occupational exposures in addition to high smoking rates. Adana, Krakow, Lexington, and Manila, which along with Cape Town had the highest reported occupational exposures in men, also had high prevalences of stage II or greater COPD in men. Future work will explore the effect of these and other risk factors in more detail.

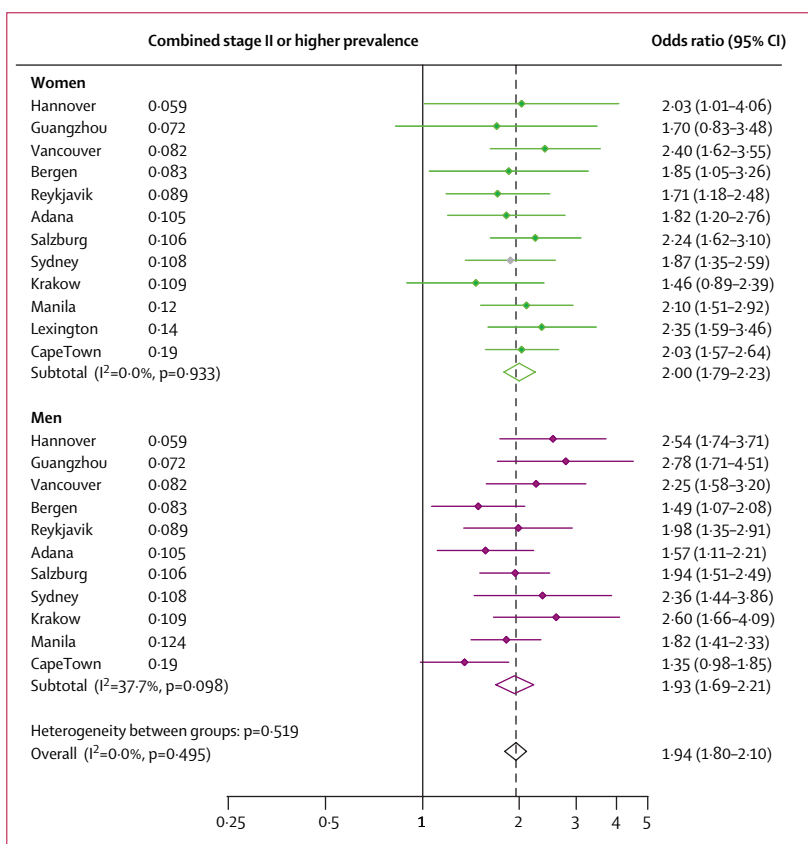


Figure 3: Odds ratios of stage II or more COPD for a 10-year increase in age, by sex and site
Models adjusted for age, years of education, and smoking status (current, former, never). Men from Lexington are excluded since age estimate is not comparable because of an absence of men who have never smoked and who have COPD of stage II or more.

The fairly high prevalence of stage II or more COPD in individuals who had never smoked and the increased risk in women raise important questions about the role of other exposures, and possibly of a greater genetic susceptibility in women. At present, COPD in those who have never smoked is poorly understood.³ In some people, the high prevalence of disease might indicate long-standing asthma with remodelling in the small airways, whereas in others it could suggest other unidentified exposures. Whether women are at greater risk for COPD than men, if they are equally exposed to smoking and other particulates, remains controversial.^{34,35}

We used the GOLD criterion of a fixed postbronchodilator ratio of FEV₁/FVC less than 0.7 as the primary indicator of irreversible airflow obstruction, despite its shortcomings,^{22,23} because it allows comparison across countries without the need for reference values and is a widely used standard that can be readily compared with other published findings. Other definitions, such as those for GOLD stage II and higher COPD, typically need the use of prediction equations to account for the age-related decrease in lung function in healthy individuals. Widely accepted reference equations for spirometric variables are available from the US

NHANES III Study¹⁶ and from large cross-sectional surveys in some other countries, but they are not available for many parts of the world. Even if they were available, whether country-specific or race-specific reference equations are appropriate to use in the context of cross-cultural comparisons is unclear, since such use might mask true differences related to exposure between countries or between racial groups within countries. Specifically, some investigators have noted that lung function is partly determined by factors associated with deprivation in early life,^{36–38} and these factors are probably as important in determining normal values of local lung function as are any genetic differences between populations. We used the NHANES III reference equations because NHANES is a large, high-quality, population-based survey. We used only the NHANES Caucasian equations for these reasons. Recognising that this issue may still be controversial, we also have developed reference equations using all the sites' healthy participants who have never smoked, and plan to assess the effect of using these reference equations, and other prediction equations, in place of the NHANES equations for future work.

Our study also has limitations. First, the BOLD protocol calls for sample sizes of at least 300 men and 300 women in every site, although sites were encouraged to recruit more individuals if they could. The minimum sample size was purposely kept small to make the surveys as affordable as possible while providing acceptable confidence limits for overall and sex-based comparisons. This strategy allows more countries to participate and permits cross-site comparisons with a sufficiently large pooled sample. The weakness of this strategy is that the absolute number of patients with COPD within any particular site is generally small, thus limiting power for specific types of within-site analyses, such as detailed subgroup analyses or analyses designed to characterise the effect or patterns of care for patients with COPD.

A second limitation is that the lower than desirable response rates at some sites could have introduced the potential for response bias. Our analysis weights were designed to show both the sampling design and non-response at every site by adjustment of prevalence estimates to the target populations; however, the representativeness of responders cannot be assessed. When sites' meta-analysis weights were adjusted by their response rates, the overall and sex-specific pooled OR estimates were similar. Also, unlike PLATINO, our study did not require that sites use entire cities as their target population, which was a practical decision driven largely by logistics and the widely different sampling frames that our sites had access to. Additionally, unlike PLATINO, we had no centralised funding for local site operations. Every site obtained its own funding, and budgetary constraints sometimes restricted the type of sampling that was feasible. Nonetheless, the protocol

requirement that every target population represents a well-defined administrative area of at least 150 000 individuals was designed to keep to a minimum the likelihood that any specific population's prevalence would be overly affected by a single, unique exposure. Caution should therefore be exercised when extrapolating any individual site's data to a broader population.

Contributors

This paper was written by the BOLD Collaborative Research Group Writing Committee. ASB, WMV, PB, DMM, AMBM, SDS, TAL, KW, and RLJ contributed to the conception and design of the study. GBM, AG, ENM, and SG acquired data or actively participated in data management activities. MAM and WMV directed the statistical analysis. ASB, WMV, SG, MAM, PB, and RLJ drafted the report, and all co-authors revised the manuscript. ASB obtained funding for the study.

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Conflict of interest statement

ASB, WMV, MAM, SG, TAL, SDS, KW, DMM, and RLJ received funding for the BOLD study operations center and/or other research from unrestricted educational grants from GlaxoSmithKline, Pfizer, Boehringer Ingelheim, AstraZeneca, ALTANA, Novartis, Merck, Chiesi, Schering Plough, and Sepracor. Several co-authors have served on advisory boards for GlaxoSmithKline (ASB, SDS, DMM), ALTANA (ASB), Schering Plough (ASB, SDS), Merck (ASB, WMV, SDS), Novartis (ASB, SDS, DMM), Pfizer (ASB, SDS, DMM), Sepracor (ASB, DMM), Ortho Biotech (DMM), and Astra-Zeneca (SDS, DMM). Several authors have participated in COPD workshops funded by AstraZeneca (ASB, SDS), GlaxoSmithKline (ASB, WMV, TAL, SDS), and Merck (WMV). RLJ has served on oversight committees for Pfizer and Eli Lilly. DMM serves on Speakers Bureaus for Dey, GlaxoSmithKline, Pfizer, and Boehringer-Ingelheim. GM received funding for the BOLD Sydney site from Air Liquide Healthcare P/L, AstraZeneca P/L, Boehringer Ingelheim P/L, GlaxoSmithKline Australia P/L, Pfizer Australia P/L. ENM received funding for the BOLD Krakow site from 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 Agropion. All other authors declare that they have no conflict of interest.

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