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Tuberculosis associates with both airflow obstruction and low lung function: BOLD results

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Abstract

Background—In small studies and cases series, a history of tuberculosis has been associated with both airflow obstruction, which is characteristic of chronic obstructive pulmonary disease, and restrictive patterns on spirometry.

Objective—To assess the association between a history of tuberculosis and airflow obstruction and spirometric abnormalities in adults.

Methods—The study was performed in adults, aged 40 and above, who took part in the multicentre cross-sectional, general population-based, Burden of Obstructive Lung Disease study, had provided acceptable post-bronchodilator spirometry measurements and information on a history of tuberculosis.

The associations between a history of tuberculosis and airflow obstruction and spirometric restriction were assessed within each participating centre, and estimates combined using meta-analysis. These estimates were stratified by high and low/middle income countries, according to gross national income.

Results—A self-reported history of tuberculosis was associated with airflow obstruction (adjusted odds ratio = 2.51, 95% confidence interval 1.83-3.42) and spirometric restriction (adjusted odds ratio = 2.13, 95% confidence interval 1.42-3.19).

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Conclusion—A history of tuberculosis was associated with both airflow obstruction and spirometric restriction, and should be considered as a potentially important cause of obstructive disease and low lung function, particularly where tuberculosis is common.

Keywords

Tuberculosis; airflow obstruction; chronic obstructive pulmonary disease; spirometric restriction

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Introduction

In 2012, there were an estimated 8.6 million new cases of tuberculosis worldwide (1), with South-East Asia, Western Pacific Regions, and Africa accounting for more than 75% of the toll. More than 30% of the world population may have latent tuberculosis, but only 5-20% of them develop active tuberculosis at some point in their lifetime (1, 2). Those who survive it usually show post-treatment sequelae in the lung that may contribute to reduced quality of life and disability (3-5).

Airflow obstruction is characteristic of chronic obstructive pulmonary disease (COPD), and its main risk factor is tobacco smoking (6, 7). However, more than 20% of patients satisfying the criteria for COPD do not have a history of tobacco smoking (8, 9). Among other potential risk factors, a history of tuberculosis has been suggested by several studies as a strong predictor of chronic airflow obstruction that could explain COPD among non-smokers (9-11). With some exceptions, most of these studies were small ($n < 1000$), not population-based (i.e. participants not randomly selected from general population) and limited to a single centre or country, and several used pre-bronchodilator instead of post-bronchodilator spirometric measurements (11).

Spirometric restriction is characteristic of restrictive lung diseases and has been reported as a consequence of tuberculosis since the late 1910s (12, 13). More recent epidemiological studies with South African miners and hospital-based cases have suggested that a history of tuberculosis and increasing number of events of this disease may lead to a deficit in lung function (14-18). However, population data to support the association between a history of tuberculosis and spirometric restriction is lacking.

The aim of the present analysis was to assess the association of airflow obstruction and spirometric restriction with a history of tuberculosis in the large international, population-based, Burden of Obstructive Lung Disease (BOLD) study.

Methods

Participants

The design and rationale for the BOLD study have been reported elsewhere (19). Non-institutionalised adults aged 40 years and older were sampled and invited to take part in the study. Sampling plans designed to randomly recruit a representative sample of the population at all study sites were used.

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Of the 21,962 participants who responded to the core questionnaire, 18,669 had acceptable post-bronchodilator spirometry, and of these 18,664 answered a question on history of tuberculosis. Data were available from 27 sites, but Australia (Sydney), India (Mumbai, Srinagar), Malaysia (Penang), Nigeria (Ife), Norway (Bergen), Tunisia (Sousse), Turkey (Adana), which each contained less than five participants with history of tuberculosis, were excluded; therefore the present study population consists of 14,050 participants from 19 sites. The countries and sites represented in this analysis are: Albania (Tirana), Algeria (Annaba), Austria (Salzburg), Canada (Vancouver), China (Guangzhou), England (London), Estonia (Tartu), Germany (Hannover), Iceland (Reykjavik), India (Pune), Morocco (Fes), Netherlands (Maastricht), Philippines (Manila, Nampicuan & Talugtug), Poland (Krakow), Portugal (Lisbon), South Africa (Cape Town), Sweden (Uppsala), and USA (Lexington). All sites received approval from their local ethics committee, and participants provided written informed consent.

History of tuberculosis

Face-to-face interviews were conducted by trained and certified staff in the native language of the participant in order to collect information on respiratory symptoms, health status, and exposure to risk factors. A history of tuberculosis was defined as a positive answer to the question: “Has a doctor or other health care provider ever told you that you have tuberculosis?” Participants who were on treatment for tuberculosis at the time of the study were excluded from participation.

Outcome measures

Lung function, including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), was measured using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland), before and 15 minutes after administration of salbutamol (200 μg) from a metered dose inhaler through a spacer. The BOLD Pulmonary Function Reading Centre reviewed each spirogram and assigned them a quality score based on acceptability and reproducibility criteria from the American Thoracic Society (ATS) and European Respiratory Society (ERS) (20). 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: i) airflow obstruction, defined as a post-bronchodilator FEV1/FVC ratio below the low limit of normal (LLN) for age and sex (21), based on reference equations for Caucasians derived from the third US National Health and Nutrition Examination Survey (NHANES) (22); and ii) spirometric restriction, defined as a post-bronchodilator FVC below the LLN for height, age and sex, based on the same reference population.

Statistical analysis

To assess the association of airflow obstruction and spirometric restriction with history of tuberculosis, multivariable logistic regression models were fitted and adjusted for age (years), sex, body mass index (underweight: <18.5, normal: 18.5 to <24, overweight: 24 to <30, obese: 30+ kg/m^2), and pack-years of smoking. Additional variables were considered as potential confounders: education (years of schooling complete), passive smoking (yes,

no), and cumulative exposure to dust in the workplace (years). The association with a history of tuberculosis was estimated for each site using probability weights to allow for the sampling design at each site and then combined in a random effects meta-analysis. The meta-analyses were stratified by gross national income, i.e. high vs low/middle income countries. The level of heterogeneity was summarised using the I^2 statistic. We also regressed FEV1/FVC and FVC (L) as continuous variables against the same independent variables as above. Sensitivity analyses were conducted excluding participants presenting with both airflow obstruction and spirometric restriction. In another set of sensitivity analyses, the association of a history of tuberculosis with airflow obstruction, spirometric restriction, FEV1/FVC, and FVC was assessed omitting all sites with a cooperation rate below 60%. All analyses were conducted using Stata/IC V.12.1 (StataCorp LP, College Station, TX, USA).

Results

The characteristics of the 14,050 participants with acceptable post-bronchodilator spirometry, who responded to the core questionnaire and answered the question on history of tuberculosis are presented, by site, in table 1. There were slightly more females than males, and the overall age ranged from 52.3 to 59.6 across sites. Cumulative smoking exposure, i.e. pack-years, and passive smoking varied widely across sites. The prevalence of a history of tuberculosis [0.7% in Albania (Tirana) to 15.4% in South Africa (Cape Town)] as well as the prevalence of airflow obstruction [6.1% in Estonia (Tartu) and India (Pune) to 19.5% in South Africa (Cape Town)] and spirometric restriction [8.5% in Canada (Vancouver) and Estonia (Tartu) to 66.1% in India (Pune)] also varied across sites (Tables 1 and 2).

The unadjusted odds ratio (OR), and 95% confidence interval (CI), for the association between airflow obstruction and history of tuberculosis was 3.33 (2.54-4.37). Figure 1 shows adjusted ORs, and 95% CIs, for this association, by gross national income group and site. Overall, the risk of airflow obstruction in people with a history of tuberculosis was more than twice as much as that of people without such a history (aOR = 2.51, 95% CI 1.83-3.42). This association was stronger in low/middle income sites (aOR = 3.11, 95% CI 2.30-4.21) and showed no evidence of heterogeneity (I^2 = 0%, P = 0.55).

The unadjusted OR, and 95% CI, for the association between spirometric restriction and history of tuberculosis was 2.02 (1.42-2.86). Figure 2 shows adjusted ORs, and 95% CIs, by gross national income group and site for this association. The overall pooled aOR was 2.13 (95% CI 1.42-3.19), and significant heterogeneity across sites was recorded (I^2 = 62.4%, P < 0.001). In high income sites there was no evidence of heterogeneity (I^2 = 0%; p=0.72) but the risk was low and not significant (aOR = 1.43, 95% CI 0.93, 2.18). In low income countries, although the risk was higher and significant (aOR = 3.19; 95% CI 1.70, 5.99) there was a marked and unexplained heterogeneity in the risk estimates (I^2 = 79.1%; p<0.001). In both figures 1 and 2, ORs are adjusted for age, sex, body mass index, and pack-years. Adjustment for education, passive smoking, and cumulative exposure to dust in the workplace did not materially change the estimates for the effect of tuberculosis. Poland (Krakow) was excluded from the analyses due to insufficient number of participants with

both history of tuberculosis and either airflow obstruction (n = 0) or spirometric restriction (n = 2).

A history of tuberculosis was also associated with both decreased FEV1/FVC (beta = −3.43, 95% CI −5.05 to −1.80; I^2 = 65.3%, P < 0.001) and decreased FVC (beta = −0.15, 95% CI −0.23 to −0.06; I^2 = 48.6%, P = 0.01) (supplementary figures 1 and 2).

Sensitivity analyses, excluding 482 participants who had both FEV1/FVC<LLN and FVC<LLN, showed that the magnitude of the effects of tuberculosis reduced slightly but remained statistically significant (aOR for airflow obstruction = 2.13, 95% CI 1.40-3.23; aOR for spirometric restriction = 2.11, 95% CI 1.31-3.38), suggesting that these effects are largely independent of each other.

The omission of sites with a cooperation rate below 60% did not materially change the results (supplementary figures 3-6).

Discussion

In this population-based study of adults aged 40 years and over, a history of tuberculosis was associated with increased risk of airflow obstruction. A history of tuberculosis was also associated with spirometric restriction, but mainly in sites in low/middle income countries. The strengths of the present study are: i) its large population-based sample and the inclusion of a great number of sites; ii) the use of a standardised questionnaire for collection of data on risk factors and protocol for spirometry across sites; and iii) the use of post- instead of pre-bronchodilator spirometric measurements. The most convincing effect relates to obstruction in low/middle income countries where the odds ratio was high (OR = 3.11) and the results were consistent between sites (I^2 = 0%).

Our study also has some limitations. One is its cross-sectional nature, which impedes us from drawing conclusions in terms of temporality and makes us consider the possibility of reverse causation. Tuberculosis is more common in people with some restrictive diseases such as silicosis, but these are relatively very rare. Tuberculosis may also be reactivated in those who take corticosteroids, and particularly inhaled corticosteroid treatment recommended in chronic airway disease. However, their use is rare in this population and even rarer in the low/middle income countries where the association between tuberculosis and airflow obstruction is most pronounced. In some sites response rates were lower than desirable, but when we omitted all sites with a cooperation rate below 60% results did not materially change. Another limitation is the use of data on a self-reported history of tuberculosis, which may suffer from under-reporting due to stigmatisation of the diagnosis. However, differential under-reporting due to stigmatisation between people with and without airflow obstruction or spirometric restriction seems unlikely. It is also possible that several participants have suffered from tuberculosis and healed without any treatment and thus tuberculosis infection may be underestimated. However, in a study in China, the magnitude of the association of airflow obstruction with tuberculosis was similar between self-reports and radiological confirmation (23). According to ATS/ERS (24), pulmonary restriction is defined by a total lung capacity (TLC) less than the fifth percentile of the predicted value.

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This implies measuring TLC by plethysmography or helium dilution, which is unrealistic in large-scale epidemiological studies, such as this, and especially at centres in low/middle income countries. We are mindful that our choice of FVC as a surrogate of TLC may lead to false positive findings in those with increased residual volumes, but outside the clinical environment the prevalence of this is very low. We are also aware that the use of the NHANES reference equations in our spirometry measurements may overemphasize lung function abnormality in some study sites, but the effect of this is unlikely to be differential as the analyses were done within each site (the sites are ethnically fairly homogeneous) and only then were meta-analysed. In addition, the results from the binary outcomes (FEV1/FVC < LLN, and FVC < LLN) are supported by those of the continuous outcomes (FEV1/FVC, and FVC), which are independent of reference equations.

Our findings add to existing knowledge and support the majority of previous smaller studies that have reported an association between airflow obstruction and a history of tuberculosis (10, 11, 25). We also confirm findings from the few occupational and small hospital-based studies that have observed a decline in lung function associated with both history of and radiographically-confirmed tuberculosis (14-18).

Although it is widely accepted that tuberculosis and the healing process the lung undergoes during and after treatment can cause scarring that leads to loss of parenchymal tissue and restrictive spirometry, it is not clear what mechanisms explain airflow obstruction associated with tuberculosis. The finding that tuberculosis is associated with airflow obstruction, and not only with spirometric restriction, suggests that this is not solely the result of parenchymal scarring. One possibility is that this is caused by bronchiectasis and bronchial stenosis, which can occur as a result of tuberculosis (26). Another possibility is that this is caused by a dysregulation of macrophages arising from latent intracellular infection (27). Macrophages in the lung act primarily to kill bacteria or to facilitate wound healing and resolution (28), and it is widely accepted that they play a central role in the remodelling that causes chronic airflow obstruction. It is possible that latent mycobacteria in lung macrophages could lead to maintenance of inflammation in the lung and more aggressive remodelling of the airways (28, 29).

In summary, a history of tuberculosis was associated with both airflow obstruction and spirometric restriction. Nevertheless, large longitudinal studies with post-bronchodilator spirometry are recommended to confirm or refute these findings. With the continuing spread of tuberculosis in developing countries, an increasing incidence of multi-drug resistant disease, and an aging world population, it is important to improve our understanding of the mechanisms that link tuberculosis to airflow obstruction and COPD, and to devise effective strategies to limit this problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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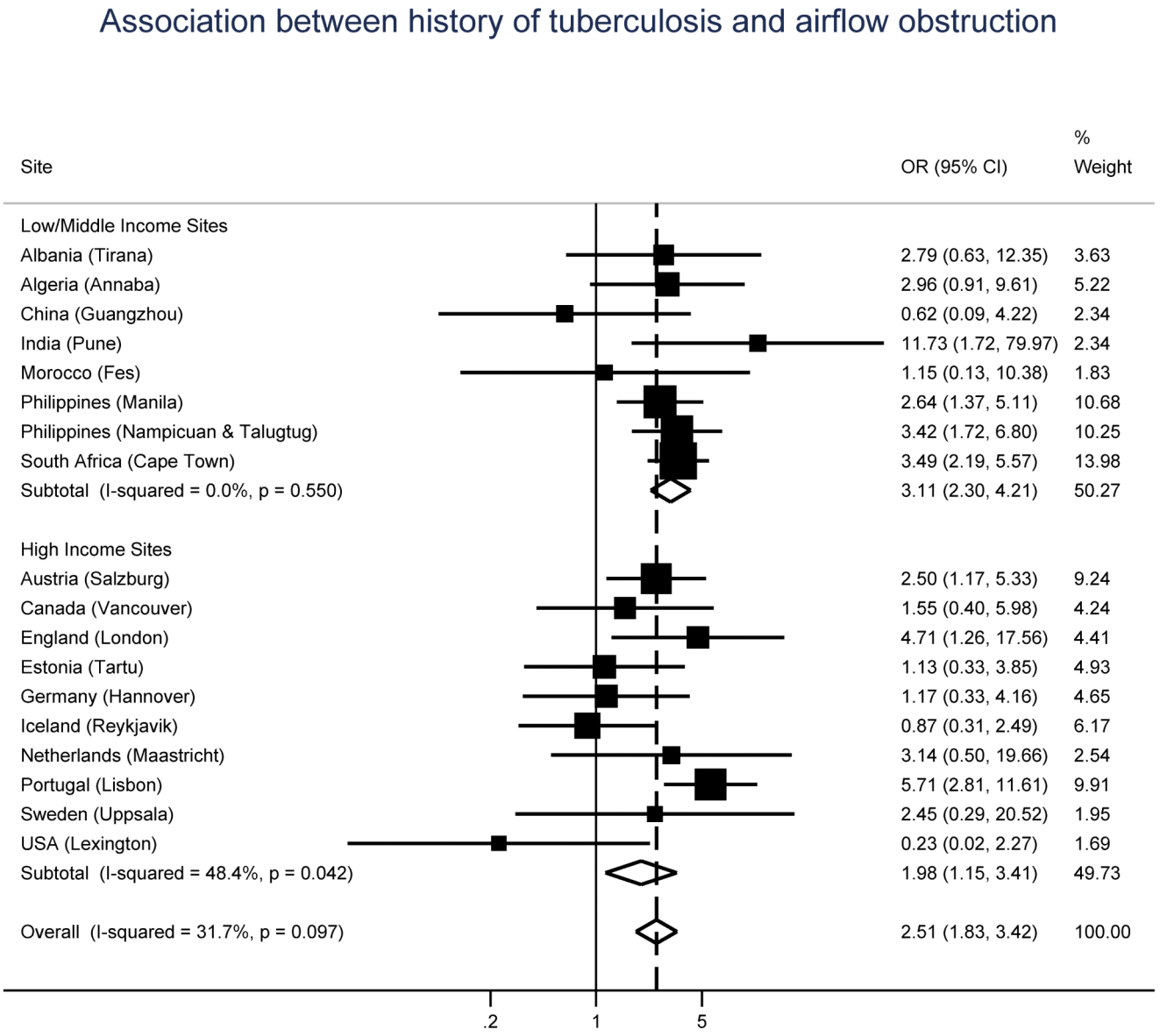

Figure 1.

Odds ratios of airflow obstruction for a history of tuberculosis, by gross national income group (low/middle vs high) and site. All models were adjusted for age, sex, body mass index, and pack-years of smoking.

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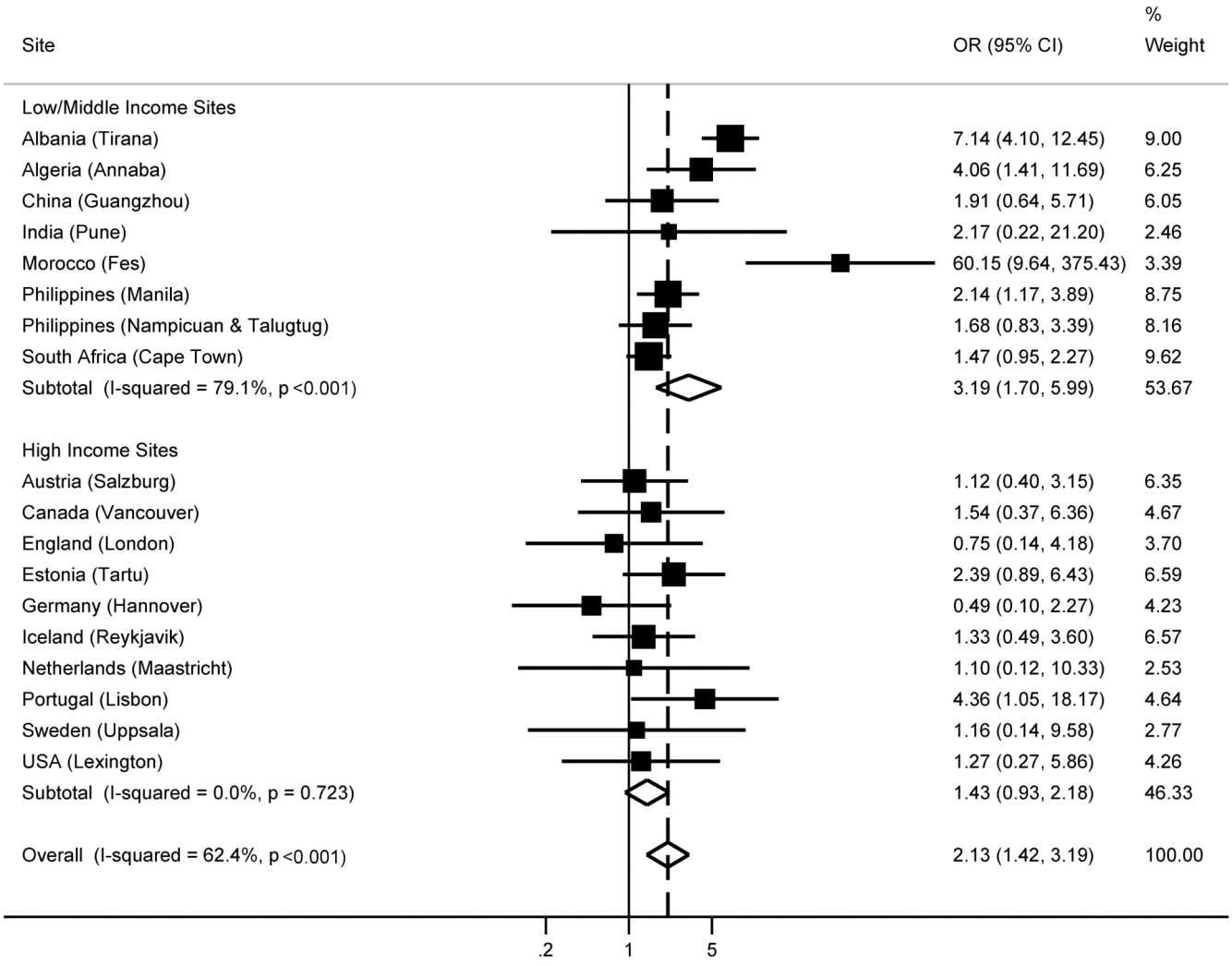

Figure 2.

Odds ratios of spirometric restriction for a history of tuberculosis, by gross national income group (low/middle vs high) and site. All models were adjusted for age, sex, body mass index, and pack-years of smoking.

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Table 1

Characteristics of participants from 19 sites of the Burden of Obstructive Lung Disease (BOLD) study with good quality spirometry and data on history of tuberculosis (at least 5 cases).

	Albania (Tirana)	Algeria (Annaba)	Austria (Salzburg)	Canada (Vancouver)	China (Guangzhou)	England (London)	Estonia (Tartu)	Germany (Hannover)	Iceland (Reykjavik)	India (Pune)	Morocco (Fes)	Netherlands (Maastricht)	Philippines (Manila)	Philippines (Nampicuan & Talugtug)	Poland (Krakow)	Portugal (Lisbon)	South Africa (Cape Town)	Sweden (Uppsala)	USA (Lexington)
N	939	890	1253	827	461	675	613	680	757	845	768	590	892	722	526	711	846	547	500
Age (yrs), mean (SD)	55.4 (11.7)	53.5 (10.9)	59.2 (12.2)	56.8 (12.7)	54.0 (10.6)	58.0 (12.4)	59.6 (12.2)	57.7 (11.1)	57.0 (12.0)	52.3 (10.0)	54.2 (11.9)	58.5 (12.0)	52.7 (11.1)	54.2 (10.6)	56.2 (11.8)	58.5 (12.0)	53.5 (10.5)	58.9 (11.4)	57.0 (11.6)
Males (%)	48.9	49.9	46.1	47.3	52.0	46.2	39.1	45.4	51.3	59.8	52.2	46.8	47.5	49.4	49.6	45.3	43.8	47.1	46.4
BMI (kg/m^2), mean (SD) *	28.0 (4.6)	28.2 (5.6)	26.4 (4.3)	26.7 (5.1)	23.3 (3.2)	27.3 (5.2)	28.4 (5.4)	27.1 (4.6)	27.9 (5.0)	22.1 (3.9)	27.5 (5.2)	27.5 (4.6)	24.4 (4.7)	21.6 (4.1)	27.8 (4.7)	27.9 (4.7)	27.5 (7.3)	26.9 (4.4)	30.6 (6.5)
Pack-years, mean (SD) **	11.5 (19.3)	10.4 (18.3)	12.7 (20.7)	12.1 (21.4)	11.8 (17.7)	17.5 (27.4)	7.4 (13.0)	14.6 (20.4)	12.9 (24.9)	0.7 (3.6)	6.6 (14.9)	14.5 (19.0)	10.6 (18.6)	12.9 (18.4)	15.8 (25.5)	13.1 (25.0)	11.9 (16.1)	10.4 (16.2)	24.4 (34.7)
Passive smoking (%)	37.4	10.9	21.8	5.7	23.6	16.6	15.6	18.6	16.8	11.1	11.4	17.7	48.8	47.3	39.3	18.7	50.6	5.8	29.6
Education (yrs), mean (SD) †	10.0 (4.6)	7.7 (5.4)	9.8 (2.2)	15.4 (3.4)	8.4 (3.9)	13.6 (3.6)	13.5 (3.8)	10.3 (2.2)	13.2 (4.4)	4.3 (4.3)	4.2 (5.3)	14.9 (5.1)	9.4 (3.6)	7.8 (3.6)	10.4 (3.4)	8.5 (4.9)	7.8 (3.3)	12.8 (4.0)	12.8 (3.3)
Cumulative exposure to dust in workplace (yrs), mean (SD) ‡	15.0 (14.1)	5.6 (10.3)	5.2 (11.7)	3.1 (7.5)	6.9 (11.6)	4.0 (9.7)	5.0 (10.1)	3.3 (8.7)	4.2 (9.6)	1.8 (5.5)	8.5 (12.8)	3.3 (8.8)	7.1 (10.8)	6.1 (11.8)	10.5 (13.4)	10.6 (14.3)	6.8 (10.3)	5.5 (11.3)	8.3 (12.1)
PB-FEV1 (l/s), mean (SD)	2.8 (0.8)	2.7 (0.8)	2.9 (0.9)	3.0 (0.9)	2.4 (0.7)	2.7 (0.9)	2.9 (0.9)	3.0 (0.8)	3.0 (0.9)	2.2 (0.6)	2.7 (0.7)	2.9 (0.9)	2.1 (0.6)	2.1 (0.7)	2.9 (0.9)	2.7 (0.9)	2.3 (0.7)	3.0 (0.9)	2.7 (0.9)
PB-FVC (l), mean (SD)	3.5 (0.9)	3.4 (0.9)	3.9 (1.0)	4.0 (1.1)	3.1 (0.8)	3.6 (1.1)	3.8 (1.1)	3.9 (1.0)	4.0 (1.0)	2.7 (0.7)	3.4 (0.9)	3.8 (1.1)	2.6 (0.7)	2.7 (0.8)	3.8 (1.0)	3.4 (1.1)	3.0 (0.9)	3.9 (1.1)	3.5 (1.1)
History of tuberculosis (%)	0.7	2.2	2.0	3.2	3.5	2.1	7.0	3.6	4.0	0.9	1.4	1.4	10.8	3.6	2.8	4.5	15.4	1.1	1.9

SD, standard deviation. BMI, body mass index. PB-FEV1, post-bronchodilator forced expiratory volume in 1 second. PB-FVC, post-bronchodilator forced vital capacity. Education, years of schooling complete.

* Missing: 3 in Poland (Krakow); 2 in South Africa (Cape Town); and 1 in USA (Lexington).

** Missing: 7 in Philippines (Manila); 3 in Philippines (Nampicuan & Talugtug) and Poland (Krakow); 2 in Canada (Vancouver), South Africa (Cape Town) and Netherlands (Maasstricht); and 1 in Iceland (Reykjavik), Morocco (Fes) and Sweden (Uppsala).

† Missing: 7 in Philippines (Nampicuan & Talugtug); 5 in England (London); and 1 in Estonia (Tartu), Morocco (Fes), Portugal (Lisbon) and South Africa (Cape Town).

‡ Missing: 4 in Netherlands (Maasstricht).

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Table 2

Estimated population prevalence of airflow obstruction and spirometric restriction in 19 sites of the Burden of Obstructive Lung Disease (BOLD) study with good quality spirometry and data on history of tuberculosis (at least 5 cases).

	Albania (Tirana)	Algeria (Annaba)	Austria (Salzburg)	Canada (Vancouver)	China (Guangzhou)	England (London)	Estonia (Tartu)	Germany (Hannover)	Iceland (Reykjavik)	India (Pune)	Morocco (Fes)	Netherlands (Maastricht)	Philippines (Manila)	Philippines (Nampicuan & Talugtug)	Poland (Krakow)	Portugal (Lisbon)	South Africa (Cape Town)	Sweden (Uppsala)	USA (Lexington)
N	939	890	1253	827	461	675	613	680	757	845	768	590	892	722	526	711	846	547	508
Airflow obstruction (%)	8.9	6.4	17.4	13.5	7.6	17.6	6.1	8.2	11.3	6.1	8.9	18.8	9.4	15.2	13.5	8.3	19.5	9.6	14.4
Spirometric restriction (%)	16.1	26.5	9.3	8.5	29.9	17.8	8.5	9.0	12.5	66.1	19.3	10.1	62.7	56.7	10.1	10.7	46.7	10.2	26.2
Response rate (%) *	82.3	94.6	65.0	26.0	87.0	17.0	49.0	59.0	81.0	97.0	98.0	46.0	58.0	85.5	78.0	10.0	63.0	61.0	14.0
Cooperation rate (%) **	84.0	94.6	67.0	51.0	87.0	37.0	70.0	61.0	84.0	97.0	98.0	55.0	58.0	86.2	79.0	27.0	68.0	63.0	27.0

Airflow obstruction, FEV1/FVC < LLN. Spirometric restriction, FVC < LLN.

* Denominator comprises people of unknown eligibility status who could not be contacted. Only known participants considered ineligible were excluded.

** Denominator comprises only participants who were contacted and eligible.