A Systematic Review of the Association between Pulmonary Tuberculosis and the Development of Chronic Airflow Obstruction in Adults

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Conclusions: This systematic review confirms evidence for a positive association between a past history of tuberculosis and the presence of CAO. The association is independent of cigarette smoking. Causality is likely but cannot be assumed.

Introduction

Chronic obstructive pulmonary disease (COPD) is estimated to affect 65 million people worldwide. It is currently the third leading cause of death, accounting for approximately 3 million deaths annually. Ninety percent of these deaths are in low- and middle-income countries where the prevalence of pulmonary tuberculosis (PTB) remains high [1, 2]. Recognized consequences of PTB include permanent scarring, bronchiectasis and pleural fibrosis, which may be extensive and lead to respiratory disability and failure, cor pulmonale and premature death. During the treatment phase of active PTB, lung function impairment is usually restrictive; this may persist, resolve or become obstructive in nature. A relationship between PTB and the development of COPD has been suggested in several reports. However, a serious limitation in these studies is the confounding caused by concurrent exposure to risk factors such as tobacco smoking, dust and biomass fuel as well as childhood respiratory...

Key Words
Tuberculosis · Chronic obstructive pulmonary disease · Airflow obstruction

Abstract
Background: Chronic obstructive pulmonary disease (COPD) is a major public health concern, accounting for 3 million deaths annually, 90% of which occur in low- and middle-income countries. Pulmonary tuberculosis (PTB) as a contributory factor in the aetiology of COPD is under debate, with most epidemiologic evidence suggesting a positive association. Objectives: To compile a systematic review of evidence for an association between PTB and the development of chronic airflow obstruction (CAO). Methods: We performed a systematic review of original English-language, peer-reviewed literature using the PubMed/MEDLINE database. CAO was defined by spirometry (FEV 1 :FVC ratio <0.70 or <LLN (lower limit of normal) for age). Results: Nineteen studies (1 case series, 3 case-control studies, 4 cohort studies, 8 single-centre cross-sectional studies and 3 multi-centre cross-sectional studies) met the eligibility criteria. All but 2 reported a positive association between PTB and CAO. Three of 4 large population-based surveys (n = 4,291–8,066) confirmed a significant association between PTB and CAO (OR 1.37 – 2.94). A formal meta-analysis was not possible owing to marked heterogeneity between studies.

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illnesses and a lack of diagnostic precision when distinguishing COPD from other forms of structural lung disease (e.g. bronchiectasis) found in patients who have had PTB.

Both the clinical and epidemiological diagnosis of COPD – as recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and employed in the Burden of Obstructive Lung Disease (BOLD) methodology – is based on a compatible history of symptoms, exposure to risk factors (usually smoking), and the demonstration of airflow obstruction (AFO) on spirometry [3]. However, it is now evident that a significant proportion of patients with COPD defined in this manner are non-smokers, and analyses of other risk factors suggest that home and workplace exposure to dust, fumes and gases and, particularly, the combustion of biomass fuels, are significant causal factors in such patients [4]. Consistent with this, a large proportion of non-smokers with COPD are in developing countries. In this setting, assessing the significance of previous PTB, particularly as a causal factor, is challenging, but owing to the high prevalence of PTB in many developing countries this is a question of considerable public health significance.

PTB is listed as a risk factor for COPD in some COPD guidelines [3]. We report here a systematic review of peer-reviewed English-language literature of the association between PTB and chronic airflow obstruction (CAO) in adults. The purpose of this systematic search was to examine the strength of evidence for this association.

Methods

We conducted a systematic search of the PubMed/MEDLINE database, using the following search strategy:

(Lung Diseases, Obstructive [MeSH Major Topic]) OR (Airway Obstruction [MeSH Major Topic]) OR (Airways Obstruction) OR (Obstructive Airway Disease) OR (Obstructive Airways Disease) OR (Pulmonary Emphysema) OR (Emphysema) AND (tuberculosis* [Title/Abstract]) NOT (Asthma* [Title]).

Articles were limited to the English language, and adult human subjects (older than 19 years of age).

Paper titles were reviewed, and those titles that did not suggest a link with the research question were eliminated. Abstracts from the remaining papers were examined for relevance, and those not addressing the research question were removed.

An additional hand-search was performed to identify seminal papers that pre-dated PubMed or were not captured in the initial search strategy.

All remaining papers were assessed for eligibility and inclusion in the systematic review. Papers were excluded if they did not contain original research (e.g. review articles) or had insufficient detail on either methodology or results to assess the validity of the findings. They were also excluded if they evaluated patients only while on treatment for active tuberculosis (TB), without post-treatment follow-up. Where there was doubt about whether or not a paper should be included, it was discussed and consensus was reached among the authors (B.A. and L.M.).

We allowed flexibility in defining ‘airflow obstruction’ (AFO) for papers published before 1975, owing to the evolving definitions in use before this date. However, later papers were excluded if they used non-standard definitions of AFO [e.g. ‘FEV1’ only or ‘FEV1:FVC ratio <0.80’ (rather than 0.70)]. In keeping with current literature, CAO was defined as FEV1:FVC ratio <0.70 or FEV1:FVC ratio <LLN (lower limit of normal) for age. Use of bronchodilators prior to spirometry was noted; however, studies that did not use bronchodilation before spirometry were not excluded.

Results

The PubMed/MEDLINE search revealed 482 papers from 1966 until 2012 that met the initial search criteria. Upon reviewing their titles, 65 of these papers appeared relevant to the research question, but after reviewing their abstracts, 29 were excluded. Of the remaining 36 papers, 14 met the inclusion criteria. A hand-search identified an additional 20 potential papers, from dates ranging from 1955 until 2011. However, only 5 of these met the eligibility criteria and were thus included (see fig. 1). Reasons for exclusion of papers after review of the abstracts are presented in the online supplementary Appendix (for all online suppl. material, see www.karger.com/doi/10.1159/000350917).

Originating from 27 countries, 19 studies were ultimately included: 1 case series, 3 case-control studies, 4 cohort studies, 8 single-centre cross-sectional studies and 3 multi-centre cross-sectional studies. Study size varied from 40 to 8,066 subjects. Six of the studies were population-based, 6 were in outpatient or primary-care settings, 6 were in a hospital setting and 1 was conducted among retrenched mine-workers. Publication dates ranged from 1971 to 2012, with the majority published after 2000.

There was marked heterogeneity among the included studies, both in terms of study design and patient population, making meta-analysis inappropriate. The findings are presented below by study type, and table 1 provides a summary.

Case Series

In a case series of 47 patients, Baig et al. [5] showed the prevalence of obstruction to be 55.3% and mixed restriction/obstruction to be present in an additional 14.8%. However, this was a highly selected population, selected...
on the basis of having dyspnoea, previous TB and residual chest X-ray (CXR) TB changes. All were never-smokers and had no history of a recognized occupational exposure.

Case-Control Studies
The 3 case-control studies showed discrepant results. In a matched cohort of 289 patients with previous PTB from Hong Kong, multivariate analysis failed to show an association [6]. Weaknesses of the study were that previous PTB was self-reported by participants and the background prevalence of PTB in the community was not stated. By contrast, in study in the USA by Pasipanodya et al. [7], AFO was found in 15% of cases with previous PTB compared with 3% in controls, and mixed obstruction/restriction in a further 13% (compared with 1% in controls). All cases in this study had completed at least 20 weeks of treatment for culture-confirmed PTB. In a third study, conducted in an academic hospital and designed to examine the link between PTB and occupational exposure, among patients (n = 202) in South Africa presenting to a specialist pulmonary service, Govender et al. [8] found a strong independent association between COPD and a previous history of PTB. They reported odds ratios (ORs) that ranged from 7.7 to 8.1, depending on the model used. In all 3 studies, smoking status was included in multivariate analysis.

Cohort Studies
All 4 cohort studies that met the inclusion criteria showed an association between TB and the development of obstruction.

Vargha [9] followed up 99 patients for 15 years after discharge from hospital for treatment of PTB. At discharge,
## Table 1. Studies included in systematic review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>n</th>
<th>Setting</th>
<th>Setting</th>
<th>Selection criteria</th>
<th>Comparator group (Yes/No)</th>
<th>Confounders assessed</th>
<th>Measure of airflow obstruction</th>
<th>Method of TB diagnosis</th>
<th>Outcome/association</th>
<th>Comment</th>
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<tr>
<td><strong>Case series</strong></td>
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<tr>
<td>Baig et al [5]</td>
<td>2010</td>
<td>Pakistan</td>
<td>case-series</td>
<td>47</td>
<td>referral hospital</td>
<td>patients referred with past TB, CXR changes and SOB</td>
<td>No</td>
<td>all were non-smokers</td>
<td>post BD FEV₁/FVC ratio</td>
<td>questionnaire (self-reported), CXR changes (mixed)</td>
<td>55.3% obstruction, 14.8% obstruction/restriction (mixed)</td>
<td>highly selected group</td>
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<tr>
<td>Chan-Yeung et al [6]</td>
<td>2007</td>
<td>Hong Kong</td>
<td>case-control</td>
<td>289</td>
<td>(cases) outpatient clinics</td>
<td>consecutively diagnosed COPD patients</td>
<td>Yes, matched and population-based (n = 289)</td>
<td>smoking</td>
<td>post BD FEV₁/FVC ratio</td>
<td>questionnaire (self-reported)</td>
<td>no association on multivariate analysis</td>
<td>population TB prevalence not stated and potential bias in selection of controls</td>
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<tr>
<td>Pasipanodya et al [7]</td>
<td>2007</td>
<td>USA</td>
<td>prospective case-control</td>
<td>121</td>
<td>(cases) county public health department</td>
<td>culture-positive TB patients who had completed 20 weeks of treatment</td>
<td>Yes, latent TB-infected subjects (n = 218)</td>
<td>smoking, occupational dust, asbestos, HIV</td>
<td>pre BD FEV₁/FVC ratio</td>
<td>TB culture case: 15% obstruction and 13% obstruction/restriction (mixed) controls: 3% and 1%, respectively</td>
<td>higher rates of obstruction in smokers</td>
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<tr>
<td>Govender et al [8]</td>
<td>2011</td>
<td>South Africa</td>
<td>case-control</td>
<td>110</td>
<td>(cases) tertiary outpatient clinic</td>
<td>patients with COPD attending the clinic</td>
<td>Yes, controls from non-respiratory clinics at same institution (n = 102)</td>
<td>smoking occupational exposures</td>
<td>FEV₁/FVC ratio</td>
<td>questionnaire (self-reported)</td>
<td>OR range 7.7–8.1 (depending on model)</td>
<td>confidence intervals and p values not stated</td>
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<tr>
<td><strong>Cohort</strong></td>
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<tr>
<td>Vargha [9]</td>
<td>1983</td>
<td>Hungary</td>
<td>cohort</td>
<td>99</td>
<td>outpatient clinic</td>
<td>patients discharged as cured in 1958/59</td>
<td>No</td>
<td>smoking</td>
<td>hospital records</td>
<td>after 15 years in medically treated patients: 52% had obstruction, (34.8% without initial obstruction developed new obstruction and 12% with initial obstruction had normalized PFTs)</td>
<td>loss to follow-up (in medically treated patients) was 18%</td>
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<tr>
<td>Wilcox and Ferguson [10]</td>
<td>1989</td>
<td>South Africa</td>
<td>retrospective cohort</td>
<td>71</td>
<td>primary care clinic</td>
<td>all patients treated for TB by clinic</td>
<td>Yes, young patients matched to controls</td>
<td>smoking</td>
<td>clinic records, CXR</td>
<td>FEV₁/FVC ratio &amp;/or RV&gt;120% predicted</td>
<td>overall 68% had obstruction, young patients had significantly lower FEV₁/FVC ratio and higher RV compared with matched controls</td>
<td>potential bias in selection of cohort.</td>
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<tr>
<td>Plit et al [11]</td>
<td>1998</td>
<td>South Africa</td>
<td>prospective cohort</td>
<td>74</td>
<td>TB hospital</td>
<td>consecutive inpatients, with first-episode TB</td>
<td>No</td>
<td>smoking, HIV</td>
<td>FEV₁/FVC ratio</td>
<td>TB culture and CXR</td>
<td>after treatment completion, 28% (n=21) had obstruction; 62% (13) of these were new</td>
<td>exclusion of MDR-TB, previous TB and co-existing pathology</td>
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<tr>
<td>Author</td>
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<td>Radovic et al [12]</td>
<td>2011</td>
<td>Serbia</td>
<td>prospective cohort (6-month follow-up)</td>
<td>40</td>
<td>lung diseases clinic</td>
<td>newly diagnosed cavitatory TB with normal initial PFTs</td>
<td>No</td>
<td>smoking, air pollution</td>
<td>post BD FEV₁/FVC ratio</td>
<td>TB culture and CXR after treatment completion, 35% of patients developed new airflow obstruction</td>
<td>extent of CXR changes, sputum conversion rate predictive of future obstruction, selection methods not stated.</td>
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<tr>
<td>Cross-sectional, institution-based</td>
<td>Snider et al [13]</td>
<td>1971</td>
<td>USA</td>
<td>cross-sectional (single-centre)</td>
<td>1,403</td>
<td>TB sanatorium patients at medical discharge</td>
<td>No</td>
<td>smoking</td>
<td>FEV₁/FVC ratio hospital records</td>
<td>obstruction in 23% obstruction/restriction (mixed) in 19%</td>
<td>very high rates of smoking (84%)</td>
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<tr>
<td>Ramos et al [14]</td>
<td>2006</td>
<td>Brazil</td>
<td>cross-sectional (single-centre)</td>
<td>43</td>
<td>referral hospital complex TB cases referred, who had PFTs</td>
<td>No</td>
<td>smoking</td>
<td>not defined clinic records and CXR</td>
<td>24% obstruction/obstruction/restriction (mixed) in 19%</td>
<td>severity of PFT matched CXR changes highly selected population. (54% never-smokers)</td>
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<tr>
<td>Chung et al. [16]</td>
<td>2011</td>
<td>Taiwan</td>
<td>cross-sectional (single-centre)</td>
<td>115</td>
<td>university hospital patients with positive TB cultures, who underwent PFTs after TB treatment.</td>
<td>No</td>
<td>smoking</td>
<td>FEV₁/FVC ratio TB culture ratio</td>
<td>obstruction in 48.6%; obstruction/restriction (mixed) in 9.3%</td>
<td>median follow-up of 16 months only 7.6% of culture positive TB had PFT’s NTMs isolated in 26.4% of isolates.</td>
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<td>Gothi et al [15]</td>
<td>2007</td>
<td>India</td>
<td>cross-sectional (single-centre)</td>
<td>268</td>
<td>referral centre Patients referred for investigation of CAO</td>
<td>No</td>
<td>smoking</td>
<td>post-BD FEV₁/FVC ratio hospital records</td>
<td>OR 1.37 (1.13–1.67) only pre-BD values corrected for 13% of PFT obstruction</td>
<td>obliterative bronchiolitis accounted for 13% of PFT obstruction</td>
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<td>Girder-Brown et al [17]</td>
<td>2008</td>
<td>Lesotho</td>
<td>cross-sectional (single-centre)</td>
<td>610</td>
<td>mine workers retrenched workers</td>
<td>No</td>
<td>smoking, HIV, silicosis pre-BD FEV₁/FVC ratio questioned (self-reported) of patients with COPD, 45% had past/current TB</td>
<td>questionnaires</td>
<td>not corrected for smoking, no post-BD spirometry</td>
<td></td>
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<tr>
<td>Cross-sectional, population (community)-based</td>
<td>Lam et al [18]</td>
<td>2010</td>
<td>China</td>
<td>cross-sectional (single-centre)</td>
<td>8,066</td>
<td>population Guangzhou Biobank cohort study population</td>
<td>No</td>
<td>smoking, dust, socioeconomic status (education) pre-BD FEV₁/FVC ratio and LLN CXR and questionnaire (self-reported) OR 1.37 (1.13–1.67) only pre-BD values</td>
<td>large difference between self-reported previous TB and CXR changes of previous TB</td>
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Table 1. (continued)

<table>
<thead>
<tr>
<th>Author</th>
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<th>Outcome/association</th>
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<tr>
<td>Menezes et al [19]</td>
<td>2007</td>
<td>5 Latin American countries (PLATINO study)</td>
<td>cross-sectional (multi-centre)</td>
<td>5,571</td>
<td>population multi-stage sampling</td>
<td>No smoking, work dust, fossil fuel, childhood illness</td>
<td>post-BD FEV₁:FVC ratio</td>
<td>questionnaire (self-reported)</td>
<td>OR 2.33 (1.50–3.62)</td>
<td>TB history associated with more severe COPD (132 had past TB)</td>
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<tr>
<td>Caballero et al [20]</td>
<td>2008</td>
<td>Colombia (PREPOCOL study)</td>
<td>cross-sectional (multi-centre)</td>
<td>5,539</td>
<td>population multi-stage cluster sampling</td>
<td>No smoking, biomass, SES</td>
<td>post-BD FEV₁:FVC Ratio</td>
<td>questionnaire (self-reported)</td>
<td>OR 2.94 (1.58–5.49)</td>
<td>25.8% of patients with a TB history had COPD (only 72 had past TB)</td>
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<tr>
<td>Lamprecht et al [21]</td>
<td>2011</td>
<td>14 countries (BOLD study)</td>
<td>cross-sectional (multi-centre)</td>
<td>4,291</td>
<td>population-based sampling, only non-smokers</td>
<td>No smoking, dust, childhood illness, biomass fuels, education, medical conditions, BMI</td>
<td>post-BD FEV₁:FVC ratio (and LLN)</td>
<td>questionnaire (self-reported)</td>
<td>women: OR 1.47 (0.69–3.12) men: OR 1.65 (0.43–6.34)</td>
<td>only never-smokers included</td>
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<tr>
<td>Idolor et al [22]</td>
<td>2011</td>
<td>Philippines</td>
<td>cross-sectional (single-centre)</td>
<td>722</td>
<td>population multi-stage random sampling</td>
<td>No smoking, biomass, farming, dusty occupation</td>
<td>post-BD FEV₁:FVC ratio</td>
<td>questionnaire (self-reported)</td>
<td>OR 6.31 (2.67–15.0)</td>
<td>BOLD methodology used</td>
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<tr>
<td>Lee et al [23]</td>
<td>2011</td>
<td>Korea</td>
<td>cross-sectional</td>
<td>3,687</td>
<td>population stratified, multi-stage, clustered sampling</td>
<td>No smoking</td>
<td>pre-BD FEV₁:FVC ratio and LLN</td>
<td>CXR only</td>
<td>OR 2.56 (1.84–3.56)</td>
<td>TB only diagnosed on old CXR changes, no data on TB history included</td>
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BD = Bronchodilator; MDR = multidrug-resistant; NTM = non-tuberculous Mycobacterium; PFT = pulmonary function test; SOB = shortness of breath.
28 of 59 non-surgically treated patients (47.5%) had AFO, and after 15 years, this had developed in a further 34.8% but had resolved in 12.0%. However, a significant proportion (18.6%) of the cohort had been lost to follow-up and smoking status was measured but not quantified or adjusted for in the analysis.

In a retrospective cohort, Willcox and Ferguson [10] found AFO in 68% of the 71 patients followed up for a mean of 5.6 years. Their subjects had been successfully treated at a community clinic. In an attempt to account for smoking, they matched a subset of younger patients with controls, and found a significantly lower FEV₁/FVC ratio and a higher RV/TLC (residual volume/total lung capacity) ratio. This matching was an attempt to negate the confounding effect of long-term smoking.

Plit et al. [11] conducted a prospective cohort study of hospitalized patients during their first episode of TB. They found AFO in 28% of patients (21 of 74) after completion of 6 months of TB therapy. Of these, 62% (13 of 21) did not have AFO when treatment was commenced.

In a clinic-based study of similar design, Radovic et al. [12] found that 35% of their 40 patients with cavitating PTB and normal spirometry at the start of treatment had developed AFO by the end of treatment. Their method of patient selection was not described.

None of the first 3 cohort studies listed reported whether values for lung function were pre- or post-bronchodilator.

**Cross-Sectional Studies: Facility-Based**

Four of 5 cross-sectional surveys were hospital-based and showed a high prevalence of AFO. However, the patient populations varied markedly between the studies and included subjects treated as inpatients, patients referred to specialist centres and patients selected retrospectively based on hospital TB culture results. This heterogeneity prevents summation of the effects observed in these studies.

Between 1964 and 1966, Snider et al. [13] assessed 1,403 patients at discharge from a TB sanatorium. He found a reduced FEV₁/FVC ratio in 42% of patients (23% with obstruction and 19% with mixed obstruction/restriction). Obstruction was positively associated with age, severity of TB on CXR and heavier smoking. In this population, only 16.9% were non-smokers and prevalence of AFO within the sub-groups tended to correspond with the prevalence of smoking.

Some 40 years later, Ramos et al. [14] published a cross-sectional study of 50 patients attending a tertiary referral clinic, who had completed TB treatment. Although 54% were never-smokers, they found AFO in 24% of subjects and mixed obstruction/restriction in a further 34%. The findings of this study may have been affected by the complex nature of referred cases (referral bias) and the large number of exclusions (58%), primarily due to comorbidity and lack of lung function testing.

Gothi et al. [15] also published a prospective cross-sectional study from a tertiary referral centre. They investigated 268 consecutive patients referred with AFO, lung function testing and radiology. Thirty-six (13.4%) patients were considered to have obliterative bronchiolitis. Obliterative bronchiolitis was defined clinically (using Turton’s criteria) as (1) irreversible AFO, (2) reduced FEV₁ or (3) exclusion of another cause of AFO (e.g. asthma, emphysema or bronchiectasis). The diagnosis was confirmed by finding expiratory mosaic attenuation on HRCT scan. They attributed the obliterative bronchiolitis to past TB in 77.8% (n = 28) of these cases.

Chung et al. [16], also in a tertiary referral hospital setting, reported an even higher association between TB and AFO than in the above studies. They examined, retrospectively, the case notes of all patients who had had positive TB cultures and had completed treatment for TB at their institution. Only 7.6% (213 of 2,789) of culture-positive patients had had a lung function test. Patients with co-morbid lung disease were excluded, leaving 115 subjects (162 lung function tests). Of these, 48.6% had obstruction and 9.3% had mixed obstruction/restriction. Again, in this study, the process of case selection may have overestimated the effect.

In a non-hospital based study, Girdler-Brown et al. [17] studied 610 retrenched Basotho gold miners. They found a high prevalence of COPD in a relatively young population group (mean age 49 years) with a history of light smoking. The prevalence of AFO was 13.5%, in a large proportion (45%) of whom a history of previous PTB was present. However, the influence of silica exposure and the absence of a multivariate analysis make it impossible to isolate the association between PTB and AFO (the prevalence of silicosis was 24.6% in this cohort).

**Cross-Sectional Studies: Population-Based**

Six cross-sectional studies that examined the association between PTB and CAO in the general population provide the most useful assessment.

In the largest study (8,066 subjects) previous PTB was defined as chest radiograph with abnormalities attributable to healed PTB. The OR for risk of AFO after PTB was 1.37 [95% confidence interval (CI) 1.13–1.67] and
remained after adjusting for age, sex, smoking, passive smoking, biomass fuel and dust exposure. The study was conducted in a high TB setting with a prevalence of past TB on CXR of 24.2%. Only pre-bronchodilator AFO was measured, however [18].

The multi-centre PLATINO (Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar) [19] and PREPOCOL (Prevalencia de EPOC en Colombia) [20] cross-sectional studies performed in Latin America were both community-based studies using post-bronchodilator spirometry.

The PLATINO study, involving 5,571 subjects in 5 Latin American countries, provided an OR for the association of AFO with previous PTB of 2.33 (95% CI 1.50–3.62), the association being stronger in men. The prevalence of previous PTB was 2.4%. In the PREPOCOL study, conducted in five Colombian cities (5,539 subjects), the adjusted OR for this association was 2.94 (95% CI 1.58–5.49), with 25.8% of people with a history of PTB having AFO. This association was stronger than that for both smoking (OR 2.56 and 95% CI 1.84–3.46) and wood-smoke exposure (OR 1.50 and 95% CI 1.22–1.86). The prevalence of a previous history of TB was 1.3% in this population, while 30% of all subjects with AFO had never smoked.

In the combined analysis of data obtained using the BOLD methodology in 14 countries, no association between AFO and a history of previous PTB was found [21]. In a multivariate analysis of 4,291 never-smokers, the OR was 1.47 (95% CI 0.69–3.12, p = 0.323) in women and 1.65 (95% CI 0.43–6.34) in men. However, the prevalence of self-reported previous PTB in this never-smoking population was only 3.2%.

All 3 of these multi-centre studies adjusted for biomass (or wood) fuel exposure and smoking (BOLD by exclusion of ever-smokers), while the PLATINO and BOLD studies also adjusted for dusty environments and childhood illnesses.

In contrast to the pooled BOLD analysis, an analysis of 722 subjects from the rural Philippines with a high prevalence of TB revealed a risk of AFO in patients with previous PTB of 6.31 (95% CI 2.67–15.0) [22].

A positive association was also found in a population-based cohort of 3,687 subjects from Korea, in which CXR changes compatible with previous TB was used to confirm previous PTB. The OR for an association was 2.56 (95% CI 1.84–3.56). Weaknesses of this study were the use of pre- rather than post-bronchodilator spirometry and that the analysis only adjusted for smoking status [23].

### Discussion

There is increasing awareness of the heterogeneity of COPD defined according to GOLD criteria. These criteria require the presence of chronic airflow limitation that persists after use of a bronchodilator and a history of exposure to recognized risk factors for the development of AFO. Foremost among these risk factors are tobacco (cigarette) smoking, biomass exposure, childhood lung infections and occupational exposures, including exposure to dust, gases and fumes [3]. The absence of a tobacco-smoking history occurs in over 20% of patients fulfilling the criteria for COPD by spirometry and has been reported in population-based studies from many countries, thereby demanding closer examination of the role of other factors in the development of COPD [4, 21]. Whether TB should be added to the list of recognized exposures for the future development of COPD, is unclear. This systematic review of the medical literature provides evidence for a positive association between the presence of CAO and a history of PTB. The nature of CAO and mechanisms responsible for it are poorly defined. It is debatable whether TB-associated CAO should be considered as part of the COPD spectrum, a distinct phenotype of COPD (TB-associated obstructive pulmonary disease) or as an unrelated disease. However, based on the results of the few available longitudinal studies, the association of PTB with CAO appears to be causal. Although the lack of population-based cohort studies weakens the argument for causality, it is supported by analyses of the role of confounders and the plausibility, namely that several mechanisms may account for the development of CAO and even COPD after active infection with PTB. These mechanisms include the structural damage of large and small airways including bronchiectasis caused by endobronchial involvement, bronchiolar narrowing and bronchiolitis obliterans resulting from peribronchial fibrosis as well as accelerated emphysematous change caused by residual chronic or recurrent inflammation.

The strongest body of evidence comes from 3 large population-based, cross-sectional studies that showed a statistically significant association between previous PTB and COPD. These studies – PLATINO (n = 5,571) [19], PREPOCOL (n = 5,539) [20] and the study by Lam et al. [18] (n = 8,066) – provide adjusted ORs of between 1.37 and 2.94 for this association, an association greater than that with either cigarette smoking or wood-smoke exposure in the PREPOCOL study. In addition, in the PLATINO study, a history of PTB was associated with
more severe grades of obstruction. These findings are supported by the smaller cross-sectional, cohort and case-control studies.

This conclusion appears to be at variance with the results of a pooled analysis of data from 4,291 subjects from 14 countries performed using the BOLD methodology, in which a history of PTB did not appear as an independent risk factor for COPD [21, 24]. However, in that report, the median prevalence of a history of PTB was only 10.45/100,000 population (range 2.4–782/100,000) compared to the global prevalence of 201/100,000 over the same time period [25]. Only 2 participating countries had a prevalence of TB higher than the global average; in both of these, the association was positive. In the South African cohort (the site with the highest prevalence of both TB and COPD), Jithoo et al. [26] found a strong association between CAO and a history of previous TB; for subjects in COPD GOLD stage I or II, the OR was 2.6 (95% CI 1.5–4.6) and for GOLD stage III or IV, the OR was 8.9 (95% CI 4.2–18.9) [26, 27]. Similarly, a positive association was evident in data from the Philippines, the other high-prevalence country [22].

There are several other potential reasons for differences between studies. First is the basis on which the designation, previous PTB is made. The most common method used in the reviewed studies is ‘self-reporting’ by subjects, although in most, the questions asked were not recorded. Other methods include review of hospital or clinic notes for a recorded history of PTB or treatment administered for PTB, CXR features compatible with previous PTB and even bacteriologically confirmed PTB in the past. Each method has different performance characteristics and may provide different strengths of association. For the purpose of epidemiology, self-reporting of a past episode of bacteriologically confirmed PTB treated for 4 or more months (or similar) may be adequate. However, self-reporting is sensitive to patient factors such as under-reporting due to stigmatization of the diagnosis [18].

The ideal design for confirming a causal positive association between PTB and the development of COPD is a longitudinal study of a large cohort with confirmed PTB, which will confirm the temporal relationship between the PTB and the development of COPD. Short-term studies of this nature have confirmed both restriction and AFO during the treatment phase [28–34]. Two studies have reported worsening after completion of medical treatment [11, 12] and another 3 suggested continued progression of AFO in the post-treatment period [9, 16, 35].

Methodological differences in the performance and interpretation of spirometry present further reasons for the differences of results seen between studies. We omitted 9 studies from this review because of the use of non-standard measures of AFO (e.g. FEV1 only or an FEV1:FVC ratio <0.80 rather than 0.70); however, although excluded from the analysis, the findings reported were consistent with our conclusions. Secondly, in some studies, pre-bronchodilator rather than post-bronchodilator values were used. This may result in overestimation of the prevalence of COPD.

Estimates of association are further influenced by the presence of powerful confounding factors such as cigarette smoking, which predisposes to the development of both COPD and TB infection [3, 36]. However, in some of the reported studies, the influence of smoking was avoided by separate analyses in non-smokers or by excluding smokers [9, 10, 18]. In addition, in both the large PLATINO [19] and PREPOCOL studies [20], the association remained after adjusting for smoking and the use of biomass fuel. However, more complex studies of longitudinal design are necessary to establish more subtle interactions between smoking and previous PTB, as their combined effect may be more damaging than either on its own.

The mechanisms whereby PTB causes CAO are largely speculative, but several hypotheses have been put forward including peribronchial fibrosis resulting from inflammatory bronchiolitis, obstruction due to endobronchial TB and accelerated parenchymal destruction caused by persistent lower respiratory tract inflammation [13].

This systematic review has several limitations. Firstly, the potential for publication bias (failure to publish studies with negative findings), secondly, the marked heterogeneity among the studies, both in terms of study design and subject selection (preventing the performance of a formal meta-analysis), thirdly, the retrospective nature of most of the studies and lastly, the limiting of the literature review to English-language publications.

In summary, this systematic review of the peer-reviewed literature confirms an association between a past history of TB and the presence of CAO. This association is independent of cigarette smoking and biomass fuel exposure. The mechanisms underlying the development of AFO and its natural history and response to treatment require further study. AFO may progress after completion of PTB treatment. In view of the large number of patients with PTB worldwide and the rising incidence of COPD globally, the contribution of PTB as a contributory cause in the pathogenesis of COPD is important both to epidemiologists and healthcare providers.