# A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults

**Dissertation by**

**Dr Brian Allwood**



**For the degree**

**Masters in Public Health (Clinical Research)**

**University of Cape Town**

# Table of Contents

## Section 1: 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 (TB) as a cause of COPD is debated, with some, but not all evidence suggesting an association between the two conditions.

**Aim:**

To systematically review evidence for the association between pulmonary tuberculosis and the development of chronic obstructive pulmonary disease.

**Methods:**

We performed a systematic review of original English language, peer-reviewed literature using the PUBMED/MEDLINE database. Chronic Airflow Obstruction was defined on spirometric data ($FEV_1$: FVC Ratio < 0.70; or $FEV_1$: FVC Ratio < lower limit of normal for age, with or without bronchodilator use).

**Results:**

Only 15 studies met eligibility criteria (1 case series, 2 case-control studies, 3 cohort studies, 6 single-centre cross-sectional studies and 3 multi-centre cross-sectional studies). All studies except 2, showed evidence of a positive~~n~~ association between pulmonary tuberculosis and chronic airflow obstruction. Four large population based surveys were included (n = 4291 to 8066). Three of these showed a significant association between TB and Chronic Airflow Obstruction (OR 1.37 – 2.94), with only the BOLD Study failing to demonstrate an association. We were unable to perform a meta-analysis, due to marked heterogeneity among the studies.

**Conclusions:**

Our systematic review of the peer-reviewed literature shows evidence for an association between a past history of tuberculosis and the presence of COPD. This association is independent of cigarette smoking. Causality is likely but cannot be assumed.

# Section 2: PROTOCOL

## i. Title

Systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adult patients.

## ii. Background

Chronic obstructive pulmonary disease (COPD) is estimated to affect 64 million people worldwide in 2004. The Global Initiative for Obstructive Lung Diseases defines COPD (1) as a preventable and treatable disease, which is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (2). COPD is a major public health concern, with approximately 3 million people worldwide dying of the condition annually. It is estimated that 90% of these deaths arise in low- and middle-income countries.(1) Further, COPD is projected to become the 3$^{th}$ leading cause of death worldwide by 2030.

The major risk factors for the development of COPD have long been considered to be smoking and air pollution from the burning of wood and other biomass fuels. (2) However, there is growing interest in additional risk factors for the development of COPD. Pulmonary tuberculosis is increasingly being recognised as a risk factor in high prevalence countries (4), and recent cross-sectional surveys performed in low and middle-income countries have highlighted this relationship.
The burden of pulmonary tuberculosis is particularly high in low- and middle-income countries. In 2009, there were 9.4 million new cases of TB worldwide with 1.7 million deaths. In South Africa, during the same period, the WHO estimated 490 000 new cases of tuberculosis, which ranks third only behind China and India with their very much larger populations.(5).

To date there have been limited analyses of the magnitude of the contribution of TB to the worldwide increasing prevalence of COPD. However, given the high prevalence of TB in some regions, this is likely to be high. This is a public health issue of potentially great significance.

I propose to perform a systematic review of publications on the association between COPD and tuberculosis, and the potential causative role of tuberculosis with due consideration of the potential of confounding presented by smoking, exposure to biomass fuel and other factors.

## iii. Aim

To review evidence for the association between pulmonary tuberculosis and the development of Chronic Obstructive Pulmonary Disease.

iv. **Methods**

This will be a systematic review involving a systematic search of the PUBMED / MEDLINE database. Additional hand searching will be performed, of references in major reviews and other publications.

The PUBMED search will be made using the following search terms for Chronic Airflow Obstruction:

| | |
|---|---|
| Lung Diseases, Obstructive | [MeSH Major Topic] |
| Airway Obstruction | [MeSH Major Topic] |
| Airways Obstruction | |
| Obstructive Airway Disease | |
| Obstructive Airways Disease | |
| Pulmonary Emphysema | |
| Emphysema | |

The following search terms will be excluded from the above:

| | | |
|---|---|---|
| Asthma* | (wild card) | only if present in the article title |

The PUBMED search will be made using the following search term for Tuberculosis:

| | | |
|---|---|---|
| Tubercul* | (wild card) | only if present in the article title or abstract |

The PUBMED search will be limited to:

Articles in English
Adult subjects (older than 19years)
Human subjects

The search results will be subjected to the following steps:

1. Papers with titles that do not suggest a link with the research question will be eliminated.

2. The abstracts of all remaining papers will be screened for relevance, and only those satisfying this requirement will be considered further. Where there is no abstract but the paper suggests relevance, the publication will be included.

A hand-search will be conducted to ensure that publications that pre-dated Pubmed or were not captured in the initial search, will be included. This search will involve a review of references of seminal papers on the association of tuberculosis and COPD. Titles and abstracts relevant to the question will be added.

## v. Eligibility Criteria for Study Inclusion

The review will include original research into the association between TB and COPD. It is predicted that the majority papers will be observational in nature; cross-sectional, cohort and case-control studies. Case series will also be considered.

Papers containing non-original work will not be included (e.g. review articles, editorials etc).

## vi. Conduct of the Systematic Review.

A data extraction form containing all relevant fields will be created to ensure that all potentially relevant data is recorded from the papers reviewed.

The following will be evaluated and recorded on each paper

**a.** General aspects:

- **i.** Study design

**b.** Selection Bias

- **i.** Study Population and setting
- **ii.** Selection of participants and controls (if appropriate)
- **iii.** Nature and number of exclusions
- **iv.** Nature of controls (if appropriate)

**c.** Measurement Bias

- **i.** Definition and measurement of airflow obstruction
- **ii.** Definition and diagnosis of “tuberculosis”
- **iii.** Presence or absence of blinding (where applicable).

**d.** Assessment of confounders

Adequately account for the measurement and magnitude of the recognised causes of COPD, especially

- **i.** Smoking (cigarette, cannabis, pipe-tobacco etc)
- **ii.** Biomass fuel

**e.** Statistical analysis

- **i.** Techniques of data analysis
- **ii.** Nature and Statistical strength of association of reported findings

## vii. Research Ethic Committee approval

This dissertation is a systematic review, involving analysis of data in the public domain. There will be no patient contact, and no new data will be generated. Research Ethics Committee approval is therefore not required.

## viii. Outputs

The findings of the systematic review will form the basis of a paper of between 3000 and 4000 words to be submitted for publication in an appropriate peer reviewed journal, and will be submitted as a dissertation, forming part of the requirements for a Masters in Public Health degree through the School of Public Health at the University of Cape Town.



## References:


1. WHO. Chronic obstructive pulmonary disease (COPD) Fact sheet N°315 February 2011 [Internet]. 2011 ;[cited 2011 Apr 7] Available from: http://www.who.int/mediacentre/factsheets/fs315/en
2. Global Initiative for Chronic Obstructed Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of COPD [Internet]. 2010. [cited 2011 Apr 7] Available from: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
3. WHO. The global burden of disease: 2004 update [Internet]. 2011 ;[cited 2011 Apr 7] Available from: http://www.who.int/mediacentre/factsheets/fs315/en/index.html
4. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. [Internet]. Lancet. 2009 Aug ;374(9691):733-43.[cited 2011 Mar 2] Available from: http://www.ncbi.nlm.nih.gov/pubmed/19716966
5. Global tuberculosis control report 2010 [Internet]. 2010 ;[cited 2011 Apr 7] Available from: http://www.afro.who.int/en/clusters-a-programmes/dpc/tuberculosis/features/2622-global-tuberculosis-control-2010.html

## Section 3: DISSERTATION

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is estimated to affect 80 million people worldwide. It is currently the fifth leading cause of death, accounting for approximately 3 million deaths annually. Ninety percent of these deaths are in low- and middle-income countries. COPD is projected to become the third leading cause of death by 2030, with a 30% increase in total death rate in the next 10 years. (1)

The traditional risk factors for COPD are a cigarette smoking, exposure to dust and biomass fuel, as well as childhood respiratory illnesses. More recently, tuberculosis has been identified as a cause of COPD.

Tuberculosis is a major cause of mortality worldwide and results in approximately 1.7 million deaths annually. In 2009, there were 9.4 million new cases of tuberculosis globally, affecting predominantly low- and middle-income countries.(2) Many tuberculosis survivors have chronically damaged or destroyed lungs, and others have minimal long-term sequelae.

The nature of the relationship between tuberculosis and the subsequent development of chronic airflow obstruction has not been well defined. If there is an association, the potential impact of tuberculosis on the global prevalence of COPD could be large. In addition, there is increasing awareness of the heterogeneity of conditions that have been labelled as COPD. A significant proportion of COPD cases have never smoked, representing from 25% to 45% in different surveys (3), and it is often unclear what aetiological factors apply in these cases. Non-smoking risk factors appear to be especially important in developing countries, and it is likely that tuberculosis accounts for a significant number of these cases. The existence of tuberculosis-associated COPD is debated, as well as how the pathophysiology and response to treatment compare with smoking related COPD.

The aim of this study is to systematically review peer-reviewed literature on the presence and magnitude of the association between pulmonary tuberculosis and the subsequent development of chronic airflow obstruction in adults.



## METHODS

We made a systematic search of the PUBMED/MEDLINE database and used the following search strategy:

A search was conducted for *Chronic Airflow Obstruction,* the following search terms being used: “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”.

We excluded “Asthma*” (wild card) only if present in the title, in order to limit our search to irreversible airflow obstruction.

We then added a search for *Tuberculosis* using the term: “AND Tubercul*” (wild card), only if present in title or abstract.

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

Papers with titles that did not suggest a link with the research question were eliminated. The abstracts of all remaining papers were screened for relevance, and only those satisfying this requirement were considered further.

An additional hand search was performed of references contained in seminal papers and publications to find reference to 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 of either methodology or results to assess the validity of findings. Additionally, articles were excluded if they evaluated patients while on treatment for active tuberculosis, without post-treatment follow-up. Where there was doubt about whether an article should be included, the article was discussed and consensus was reached among the authors.

A flexible definition of *Chronic Airflow Obstruction* was used for papers dated before 1975. This was due to the changing definitions of airflow obstruction prior to this date. However, later articles were excluded if they used non-standard definitions of airflow obstruction (e.g. $FEV_1$ only; or $FEV_1$: FVC Ratio <0.80 rather than 0.70). In keeping with recommendation in current guidelines and recent papers, Chronic Airflow Obstruction was defined as $FEV_1$: FVC Ratio < 0.70; or $FEV_1$: FVC Ratio < lower limit of normal for age. Use of bronchodilators prior to spirometry was noted, however studies without bronchodilators were not excluded. ~~.~~



## RESULTS

The PUBMED/MEDLINE search revealed 419 articles from 1966 until 2011 that met the initial search criteria. On review of their titles, 44 of these articles appeared relevant to the research question, but after review of their abstracts, a further 15 were excluded. Of the remaining 29 articles, 10 met inclusion criteria. A hand search identified an additional 20 potential articles, dating from 1955 until 2011. However, only 5 of these met eligibility criteria, and were included. (*See Figure 1*)

Reasons for exclusion after abstract review, were: Review article (5); only active tuberculosis assessed (9); Insufficient information provided to assess association (7); Non-standard measures of obstruction used e.g. only $FEV_1$ (8); Letter to editor (2); Case report (1); Study not relevant to research question (2). (*See Appendix C*)

The fifteen studies included, originated from 25 countries, and included 1 case series, 2 case-control studies, 3 cohort studies, 6 single-centre cross-sectional studies and 3 multi-centre cross-sectional studies. Study size varied from 43 to 8,066 subjects. Of these studies, four were population based, four were in outpatient or primary care-settings, six were conducted in a hospital setting, and one was conducted in retrenched mine workers. Publication dates ranged from 1971 to 2011, 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 of the included studies.



Case Series

In the Case Series of 47 patients, Baig et al (4) showed the prevalence of obstruction to be 55.3% with mixed restriction/obstruction in an additional 14.8%. However this was a highly selected population, selected on the basis of having dyspnoea, previous tuberculosis and residual Chest X-Ray (CXR) changes of tuberculosis. They were all never-smokers, without a history of recognised occupational exposure.

Case Control Studies

The two case control studies included in the analysis showed discrepant results.

In a cohort of 289 patients with previous pulmonary tuberculosis from Hong Kong and 289 matched controls, Chang-Yeung et al, found no association between chronic airflow obstruction and previous tuberculosis on multivariate analysis.(5) In this series, previous tuberculosis status was defined by a positive response (self-reported) to questions about previous tuberculosis on questionnaire. The background prevalence of tuberculosis in the community was not reported. By contrast, Pasipanodya et al (U.S.A.) found obstruction in 15% of cases (compared with 3% in controls) and mixed obstruction/restriction in 13% (compared with 1% in controls).(6) All cases in this study had been TB culture positive and completed at least 20 weeks of treatment, while controls were adults with latent tuberculosis infection presenting for assessment. In both studies smoking status was measured and included in multivariate analysis.

Cohort Studies

All three of the Cohort studies meeting inclusion criteria, showed an association between tuberculosis and the development of obstruction.

Vargha followed up 99 patients from 1958/1959 to 1974 (15 years), after discharge from hospital.(7) At the time of discharge, 47.5% of medically

treated patients (28 of 59) had airflow obstruction. After 15 years 52% (25 of 48) were found to have airflow obstruction, 34.8% without initial obstruction having developed airflow obstruction, while in 12,0% the obstruction had resolved. However 18.6% of patients were lost to follow-up in the medically treated group, which may have influenced the results. Smoking status was measured but not quantified or adjusted for.

Similarly, in a retrospective cohort, Willcox *et al,* found obstruction in 68% of the 71 patients followed up for a mean of 5.6 years.(8) In a subset analysis, patients younger than 45 years, were matched with controls, and found to have a significantly lower $FEV_1$/FVC ratio and a higher RV/TLC ratio. This matched comparison of younger subjects was an attempt to minimise the confounding effect of long-term smoking that may occur in older smokers. Potential candidates for this study had been successfully treated at a tuberculosis clinic, and those responding to a letter of invitation to return to the clinic, were included. The selection process may have affected results by either over-estimation ("healthy worker effect") or underestimation of disease (sicker patients died, or were unable to participate).

In agreement with these studies, Plit *et al* conducted a prospective cohort study of hospitalised patients during their first episode of tuberculosis. (9) They found airflow obstruction in 28% of patients (21 of 74), after completion of 6 months of TB therapy. Of these, 62% (13 of 21) did not have airflow obstruction on commencement of treatment.

None of the three cohort studies reported whether values for lung function were pre- or post-bronchodilator. If pre-bronchodilator, the results might have overestimated airflow obstruction. Small improvements in FEV1 might have resulted in fewer with obstruction (i.e. lower FEV1: FVC ratio), and others with reversible airflow obstruction (including any with asthma) would be considered as COPD.



Cross-sectional Studies – single institution

Four of five cross-sectional surveys were hospital based and showed a high prevalence of airflow obstruction. The patient populations however, varied markedly between the studies, ranging from subjects treated as inpatients, to patients referred as outpatients to specialist centres, to patients selected retrospectively based on hospital tuberculosis culture results. This heterogeneity again prohibited summation of effects observed in the studies.

Between 1964 – 1966, Snider et al, assessed 1403 patients at medical discharge from a tuberculosis sanatorium. He found a reduced $FEV_1$: FVC ratio in 42% of patients (23% with obstruction, and 19% with mixed obstruction/restriction). Obstruction was associated with age, severity of tuberculosis on CXR, and heavier smoking. In this population, only 16.9% were non-smokers, and prevalence of airflow obstruction within the subgroups tended to correspond with the prevalence of smoking. (10)

Some 40 years later, Ramos *et al* (2006) published a cross-sectional study of 50 patients attending a tertiary referral clinic, whom had completed TB treatment. Patients with other respiratory condition were excluded from the analysis. Although 54% were never-smokers, they found airflow obstruction in 24% of subjects, with 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 co-morbidity and lack of lung function testing. (11)

Gothi *et al* also published a prospective cross-sectional study from a tertiary referral centre. They investigated 268 consecutive patients referred with airflow obstruction, 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 i) irreversible airflow obstruction ii) reduced $FEV_1$ iii) exclusion of another cause of airflow obstruction (e.g. asthma, emphysema, bronchiectasis). The diagnosis was confirmed by finding expiratory mosaic attenuation on HRCT scan. They attributed the obliterative bronchiolitis to past tuberculosis in 77.8% (n=28) of these cases. (12)

Chung *et al* ref, also in a tertiary referral hospital setting, reported an even higher association between tuberculosis and airflow limitation than in the above studies. They retrospectively examined the case notes of all patients who had had positive TB cultures and had completed treatment for tuberculosis at their institution. Only 7.6% (213 of 2789) of culture positive patients had had 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.(13)

In a non-hospital based study, Girdler-Brown *et al* studied 610 retrenched Basotho Gold miners. They found a high prevalence of COPD despite a relatively young population group with a light smoking history. The prevalence of airflow obstruction was 13.5%, in a population of men with an average age of 49 years. Among current smokers (34.8%), the median smoking history was only 4 cigarettes/day. Among the patients with COPD a large proportion had a history of previous tuberculosis (45%). However, the high overall prevalence of silicosis (24.6%) makes it difficult to isolate the association between tuberculosis and airflow obstruction, as multivariate analysis was not performed.(14)



Cross-sectional Studies – population based

Four cross-sectional studies examined the association between tuberculosis and chronic airflow obstruction in the general population, providing the most generalizable assessment of the association.

In the largest study of 8,066 subjects, Lam *et al* used chest radiographs with changes attributable to previous tuberculosis to estimate the risk of airflow obstruction after tuberculosis infection. They found an odds ratio of 1.37 (95% C.I., 1.13 – 1.67). This association remained after adjusting for age, sex, smoking, passive smoking, biomass fuel and dust. The study was conducted in a high tuberculosis setting, with a prevalence of past tuberculosis (on CXR) of 24.2%. However only pre-bronchodilator lung functions were performed.(15)

The multi-centre PLATINO (Proyeto Latinamericano de Investigacion en Obstruccion Pulmonar)(16) and PREPOCOL (Prevalencia de EPOC en Colombia) (17) cross-sectional studies performed in Latin America also found an association between previous tuberculosis and chronic airflow obstruction. Both studies were conducted in non-institutionalised general populations, and

assessed tuberculosis status by means of a questionnaire. Lung function tests were performed after bronchodilators.

The PLATINO Study was conducted in five Latin American countries with 5571 subjects, and estimated the adjusted odds ratio of association to be 2.33 (95% C.I., 1.50 – 3.62), with the association being stronger in men. The prevalence of reported previous tuberculosis was 2.4%. The PREPOCOL Study was conducted in five Colombian cities, with 5539 subjects. They found an adjusted odds ratio of 2.94 (95% C.I., 1.58 – 5.49), with 25.8% of people with a history of tuberculosis having obstruction. This association was greater than the association with obstruction for either smoking (OR 2.56; 95% C.I., 1.89-3.46) or wood smoke exposure (OR 1.50; 95% C.I., 1.22–1.86). The prevalence of a previous history of tuberculosis was 1.3% in this population, while 30% of all subjects with chronic airflow obstruction had never smoked.

In contrast, to these three population-based cross-sectional studies, the BOLD (Burden of Obstructive Lung Disease) investigators found no association between airflow obstruction and a previous history of tuberculosis. (18) This study involved 14 countries, and in order to assess non-smoking risk factors for obstructive lung disease, they assessed all 4,291 never smokers, from their original sample population of 10,000 subjects (42.9%). On multivariate analysis the association for women, was OR 1.47 (95% C.I., 0.69-3.12; p=0.323) and for men was OR 1.65 (95% C.I., 0.43-6.34). The prevalence of previous tuberculosis in this never-smoking population was 3.2%.

All three 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.



## DISCUSSION

This systematic review of the literature shows evidence of an association between the presence of chronic airflow obstruction on pulmonary function testing, and a previous history of tuberculosis. From the literature available, it appears that tuberculosis is likely to be causal. However, the lack of population based cohort studies prevents definite conclusions in this regard. The argument for causation can be strengthened by considering the temporal nature of the association, confounders and plausible mechanisms of disease.

### Consistency of Evidence for Association

The strongest body of evidence comes from three large population-based, cross-sectional studies that showed a statistically significant association between previous tuberculosis and COPD. The PLATINO Study (n=5571) showed an adjusted odds ratio of 2.33 (95% CI: 1.50 – 3.62)(16), the PREPOCOL Study (n=5539) an adjusted odds ratio of 2.94 (95% CI: 1.58-5.49)(17), and Lam *et al* (n=8066) estimated an adjusted odds ratio of 1.37 (95% CI: 1.13-1.67)(15). The PREPOCOL study showed the association between tuberculosis and COPD to be greater in magnitude than that of both

cigarette smoking or wood smoke exposure. Additionally, the PLATINO Study found that a history of tuberculosis was associated with more severe grades of obstruction. These findings are supported by the other smaller cross-sectional, cohort and case-control studies.

In contrast to these studies, the BOLD investigators were unable to find an association between the presence of COPD and a history of tuberculosis, even when they assessed airflow obstruction in never-smokers (n=4291). (19)(18) However, the median prevalence for tuberculosis (using 2009 figures) among the fourteen countries participating in the BOLD Study was only 10.45 / 100,000 population (range: 2.4 – 782 / 100,000), compared to the global prevalence of 201/100,000 during the same time period. (20) In this study, only 2 countries had a prevalence of tuberculosis that was higher than the global average. Thus the BOLD study was predominantly performed in countries with a low burden of tuberculosis. By averaging the odds ratios between sites, the combined measure of association is likely to tend towards the null, thereby underestimating the association. This could have resulted in the dilution of effects from the high prevalence sites. For example, in the South African arm of the study (the site with the highest prevalence of both tuberculosis and COPD), Jithoo *et al* found a strong association between chronic airflow obstruction and a history of previous tuberculosis. For people with mild COPD (GOLD Stage I/II), the odds ratio was 2.6 (95% CI: 1.5-4.6). The association was even stronger for people with GOLD Stage III/IV disease. (OR 8.9; 95% CI: 4.2-18.9) (21) (22)

A further reason for the differences in the associations observed in different studies, is the basis on which previous tuberculosis was diagnosed. Self-reporting by subjects, using questionnaires may result in an underestimation of the burden of disease. This was noted by Lam *et al* found the prevalence of previous tuberculosis to be 2.9% when using questionnaires, and 24.2% when assessed using chest x-rays, in the same population. (15) These investigators suggest that, in their population, stigmatisation might be a reason for the under-reporting on questionnaire. If this finding holds true in other population groups, it may cause significant underestimation of the burden of COPD associated with tuberculosis by questionnaire-based studies.

Eight studies were omitted from this review because of non-standard measures of airflow obstruction (e.g. $FEV_1$ only; or $FEV_1$: FVC Ratio <0.80 rather than 0.70), and could not be used to address the review hypothesis. However, the findings within these studies were not inconsistent with the overall findings of this review.

Temporal relationship

Causality cannot be based on cross-sectional studies alone, but is strengthened when evidence of a temporal relationship is found between pulmonary tuberculosis and the subsequent development of chronic airflow obstruction. Relevant questions are whether the obstruction develops during active tuberculosis; during treatment; or during the subsequent years as part of the healing process.

Obstruction during active pulmonary tuberculosis:

Several studies have shown that airflow obstruction occurs in many patients during the active phase of tuberculosis. As early as 1955, Anno & Tomashefski, showed active tuberculosis to be associated with emphysema in their case series (n=25). They defined emphysema as a raised RV/TLC ratio. (23) This limitation in airflow has been confirmed in numerous studies, with the prevalence of airflow obstruction ranging from 11% - 50.8% (24), (25), (26), (27), (28), (29), (30), (9). Additionally the incidence of combined airflow obstruction and restriction (defined as a $FEV_1$: FVC ratio <70% and FVC < 80% predicted) appears high.

Obstruction on completion of treatment:

There is a relative paucity of data on the progression (or resolution) of obstruction after completion of medical treatment. Plit *et al,* studied a hospitalised cohort of patients during their first episode of tuberculosis (n=74). (9) During the course of treatment, restrictive defects became less prevalent, while airflow obstruction developed in some. The prevalence of restriction declined from 57% at diagnosis and commencement of treatment, to 24% after treatment completion (usually at 6 months). In contrast, airflow obstruction increased from 11% (n=8) at diagnosis, to 28% (n=21) on treatment completion. Thus 62% of post-treatment airflow obstruction developed while on treatment.

Obstruction following successful treatment

Evidence from longer-term follow-up studies after completion of medical therapy for tuberculosis is inconclusive regarding the role of pulmonary tuberculosis in the pathogenesis of COPD. Vargha followed up 99 patients after discharge from hospital.(7) He found high initial rates of airflow obstruction (47.5%). After 15 years of follow-up, 34.8% of the medically treated patients had developed new airflow obstruction, while in 12,0% the airflow limitation had resolved. Unfortunately, in this study, smoking (as a confounder) was not adequately adjusted for, limiting the conclusions made.

In a retrospective review of 115 patients (162 lung function tests) who had completed tuberculosis treatment and undergone lung function testing, Chung *et al* found a gradual decline in pulmonary function (both $FEV_1$: FVC ratio and $FEV_1$) until about 18months after completion of treatment, with some subsequent improvement thereafter. (13)

Hnizdo *et al*, in a retrospective review of data from a cohort of 27,660 gold miners, reported that loss of lung function was highest 6 months after tuberculosis diagnosis, and stabilised after 12 months. However, their conclusions were based on $FEV_1$ alone rather than on FEV1: FVC ratio, and was therefore not able to distinguish between restrictive and obstructive lung disease. (31)

All the above findings, although inconclusive, suggest that the active phase of disease associated with the post pneumonic changes may be more restrictive in nature or restriction might mask obstruction, the latter appearing as the former resolves as a result of treatment. Further, during the healing

phase chronic airflow obstruction may appear and/or progress over months, or perhaps even years. The deterioration may additionally have two phases, with an initial more rapid deterioration, followed by a period of stabilization.

Confounding by smoking

When assigning causality, it is important to consider potential confounders in the observed association between tuberculosis and COPD. Cigarette smoking undoubtedly has the potential to act as a confounder. Smoking is the major risk factor worldwide for the development of COPD. (32) There is also good evidence of an association between smoking and tuberculosis, with smokers being twice as likely to develop tuberculosis. (33) This association was also noted by Lam *et al.* These investigators found smoking to be more common among people with radiological evidence of tuberculosis, compared to those with a normal chest X-ray (31.9% vs. 19.7%; p<0.001). (15)

But smoking alone in insufficient to explain the association between tuberculosis and COPD. Vargha noted that 32.5% of patients with airflow obstruction after TB treatment were non-smokers. (7) Willcox and Ferguson also found evidence of increased airflow obstruction in patients treated for tuberculosis, when compared to smoking matched controls. (8) Additionally, both the large PLATINO (16) and PREPOCOL studies (17) adjusted for smoking (and biomass fuel) and still found a significant association between previous tuberculosis and COPD. Lam *et al* confirmed this association in non-smokers, (OR 1.30; 95% CI: 1.02-1.66), even though the association was noted to be greater in smoking subjects (OR 1.47; 95%CI: 1.04-2.08). (15)

Smoking therefore, cannot account for the association between tuberculosis and COPD on the basis of confounding. However, it is highly likely that smoking has an effect-modifying role in tuberculosis patients who develop COPD. Although not proven, it is probable that the pathological processes that occur during tuberculosis resulting in airflow obstruction are compounded and exacerbated by the inflammatory effects of smoking.

Hypotheses of pathogenesis

The mechanism through which tuberculosis causes chronic airflow obstruction is largely speculative, and several hypotheses have been previously suggested.(10) It is useful to consider these potential mechanisms as either involving the bronchial tree, small airways or the lung parenchyma per se.

Hypothesis of bronchial tree involvement

Tuberculosis is well known to involve the bronchial tree. Long *et al*, using CT scanning, found virtually all cases of active tuberculosis (n=25), to have endobronchial disease. They defined endobronchial disease as the presence of centrilobular nodules, branching linear structures, “tree-in-bud” appearance, or poorly defined nodules. (30) This submucosal infection and inflammation of the airways in the acute phase, may subsequently progress to peribronchial fibrosis resulting in fixed airflow limitation in the chronic phase.

Chronic airflow obstruction following tuberculosis may also result from the development of post-tuberculous bronchiectasis. The abnormal, permanent dilation of the bronchi that defines bronchiectasis can arise through a number of mechanisms. Endobronchial tuberculosis can result in damage to the bronchi with subsequent fibrosis and stenosis. This leads to distal dilation and bronchiectasis. Enlarged lymph nodes have also been implicated as a cause of bronchiectasis, through obstruction and dilation of bronchi. Additionally bronchi in areas of parenchymal fibrosis and scarring may become distorted and dilated, with resultant bronchiectatic change. (10)

It is also possible that the residual destructive fibro-cavitatory changes that are common after tuberculosis, may lead of airflow obstruction *per se*. This has not been well studied, however, Lee *et al* examined 11 patients with extensive residual damage on chest x-ray following tuberculosis, who exhibited airflow obstruction. They found high airway resistance, and raised residual volumes in these subjects, despite low FVC and $FEV_1$. (34) It is possible that the observed traction and distortion, causes increased airway resistance or premature closure of the airways during expiration, resulting in the observed obstruction. Alternatively, premature airway closure with air trapping could be due to loss of elastin in the tissues, with consequent inability to maintain airway patency during expiration. Further research is needed to confirm and elucidate this theory.

Several authors have tried to correlate the extent of tuberculosis on chest x-ray, with lung function test results, in an attempt to link structure to function, Their findings show consistent evidence of an inverse relationship between extent of disease on initial CXR and $FEV_1$ following treatment.(8,9,13,35) However the data relating chest x-ray damage to airflow obstruction (i.e. $FEV_1$: FVC ratio) is less convincing. Snider *et al,* showed an association of disease extent with the presence of airflow obstruction (10), while Willcox *et al*, found only a non-significant trend between original chest x-ray score and the extent of airflow obstruction. (8)

Furthermore, it appears likely that profusion of disease based on chest x-ray alone, does not determine the severity of airflow obstruction. For example, Plit *et al* found, that despite a highly significant radiological improvement on treatment for their cohort, 13 of 74 patients developed new airflow obstruction.(9)

Hypothesis of small airways disease

Small airways involvement by is another potentially important mechanism producing airflow obstruction. Bronchiolitis Obliterans can develop as a result of inflammation, fibrosis or distortion, of airways that do not contain cartilage (usually <2mm in diameter). In the correct clinical context, and after exclusion of other conditions, Bronchiolitis Obliterans can be diagnosed by finding airflow obstruction on lung function testing, with suggestive features on HRCT. These HRCT features include mosaic attenuation on expiratory scans, providing indirect evidence of gas trapping. Both Gothi *et al* and Long *et al* have showed a strong association with a mosaic pattern on HRCT and tuberculosis. (12,30) Long *et al*, found that 14 of 20 patients had a mosaic

pattern of attenuation at diagnosis of tuberculosis. These mosaic patterns were strongly (but not exclusively) associated with cavitatory disease, and persisted despite completion of treatment. Although mosaic attenuation in the context of tuberculosis, may be due to vascular injury or hypoxic vasoconstriction, it is more likely to be due to gas trapping. This is supported by Gothi *et al*, who found Obliterative Bronchiolitis, defined by mosaic attenuation on HRCT, to be the third leading cause of chronic airflow limitation after Asthma and COPD (n=268). Seventy-eight percent (77.7%) of these cases were associated with previous tuberculosis.

Hypothesis of Inflammatory Parenchymal Destruction

Another possible mechanism for the observed airflow obstruction is development of abnormal, permanent dilation of airspaces distal to the terminal bronchioles (emphysema), similar to the damage caused by smoking. It is plausible that the inflammatory environment established during acute tuberculosis infection may persist after treatment, and result in pathological changes similar to that observed in emphysema related to smoking. There is evidence of some similarity and overlap in the two disease processes. For example, matrix metalloproteinases (MMPs), responsible for digestion of collagens and gelatins (specifically, MMP-1 & MMP-9), are raised in both tuberculosis and emphysema. (36)

In smoking related emphysema, the inflammatory milieu and progression of emphysema can persist long after the cessation of smoking.(37) It is possible, that a similar process is established with tuberculosis resulting in ongoing lung destruction long after the acute episode. This may, in part, account for observed deterioration of lung function that appears after treatment completion.

What is less clear is to what extent emphysematous changes contribute to the observed post-tuberculous airflow obstruction. In 1968, Martin *et al*, performed a small autopsy study of patients who had active tuberculosis. (38) Of those where lung function were measured, 65% had Diffuse Obstructive Pulmonary Syndrome. He found that, despite high rates of abnormal expiratory flow, there was no difference in the type and extent of Emphysema, and no difference in measures of Chronic Bronchitis, when compared with controls. In this study, controls were only matched by sex, and smoking was not measured in either cases or controls. Therefore, the contribution of smoking to emphysema in the individual groups of this study could not be adequately assessed. Additionally all cases had active tuberculosis, making it difficult to draw conclusions about post-tuberculous emphysema.

In emphysema, the diffusion capacity of carbon monoxide ($DL_{CO}$) is frequently reduced, due to loss of alveolar-capillary surface area. However, Lee *et al* found that in a small group of patients with post-tuberculosis airflow limitation (n=11), the mean $DL_{CO}$ was not low, suggesting a lack of emphysema. (34)

Because of the paucity of data, and lack of HRCT imaging studies assessing emphysema scores, we are unable to exclude emphysema as a cause of the airflow obstruction following tuberculosis.

It is probable that no single mechanism of pathogenesis proposed above is solely responsible for the development of post-tuberculous airflow obstruction in all patients. But the relative contribution of each disease mechanism to disease burden is not known, and further research is warranted.

Treatment response

There is little data on the physiological response of post-tuberculous airflow obstruction to bronchodilators. Lee *et al* found bronchodilator response rates to be lower in post-tuberculous airflow limitation, compared with COPD controls (n=11).(34) While Ramos *et al* found only 6% (3 of 50) of patients had reversibility when given a bronchodilator.(11) These findings need further confirmation, and further studies need to be performed to assess possible treatment options.

Limitation of Review

This systematic review has several limitations. Firstly, like all systematic reviews, there is the potential for publication bias. Studies showing negative findings are more likely not to be published, and therefore affect our findings.

Secondly, there was marked heterogeneity among the studies found, both in terms of study design and subject selection. It was therefore, not possible to perform a meta-analysis on these studies, and thus difficult to determine the true magnitude of the association. Additionally, it may not be advisable to perform a meta-analysis using data from population groups with vastly different prevalence rates of tuberculosis. For example, many of the large population based studies were performed in developed nations, where TB prevalence is low, and smoking common. Therefore it would be difficult to study the effect of tuberculosis independent of smoking, and conclusions are therefore likely to tend towards the null hypothesis.

Thirdly, it is not possible to accurately measure the true proportion of COPD that is attributable to tuberculosis from the available published literature. There is a notable lack of prospective, community based cohort studies, needed to assess the lifetime risk of developing COPD after an episode of tuberculosis. Many of the studies published were not prospective, and were performed on highly selected populations. This may lead to an overestimation of the association in these studies.

Fourthly, as only English language articles were reviewed, it is possible that results of studies published in other languages that have bearing on the research question were overlooked.

Finally, on the available literature, causality is strongly suggested but not definitively proven. The evidence for causality includes a strong association, temporality and several plausible mechanisms for pathogenesis.

## CONCLUSION

Our systematic review of the peer-reviewed literature shows evidence of an association between a past history of tuberculosis and the presence of COPD.

This association is independent of cigarette smoking and biomass fuel exposure. The development of airflow obstruction continues in some subjects after treatment completion, with an initial deterioration followed by stabilisation. The pathogenesis of the airflow obstruction is unclear, and may include structural changes in airways ranging from large airways to bronchioles, the latter possibly including obliterative bronchiolitis. To date, no studies have attempted to examine the generation of airways responsible for the airflow limitation associated with healed pulmonary tuberculosis. With modern imaging techniques and refined tests for examining small airways disease, structure/ function analysis of these patients should be informative and cast light upon the pathogenesis of airflow limitation. In addition, there is a need for further longitudinal cohort studies in high tuberculosis prevalence areas to provide data on changes in lung function from baseline screening through an episode of pulmonary tuberculosis, with follow-up continuing for years after the event. Longitudinal studies of this nature have commenced in patients being treated for HIV infections, but their results will not be generalisable to non-HIV infected persons. Questions that remain to be answered are whether tuberculosis-associated COPD is progressive and deteriorates more rapidly than usual forms, whether tobacco smoking and pulmonary tuberculosis are simply additive in causing airflow obstruction, or whether there is evidence for a synergistic relationship between these risk factors. Finally, whether tuberculosis-associated COPD responds to the treatments recommended for the usual form of COPD, or whether other approaches must be developed. Further, whether treatments directed at limiting airway damage, and particularly endobronchial fibrosis might be effective. This might include the use of anti-inflammatory or even anti-fibrotic agents.

The size of the tuberculosis problem worldwide, and particularly in areas where tobacco smoking is also increasing, provides conditions for a dramatic increase in cases of COPD. Clinical case series attest to the morbidity, mortality and burden placed on health services associated with COPD. This should spur attempts to better understand and develop effective prevention and management strategies for tuberculosis-associated COPD.

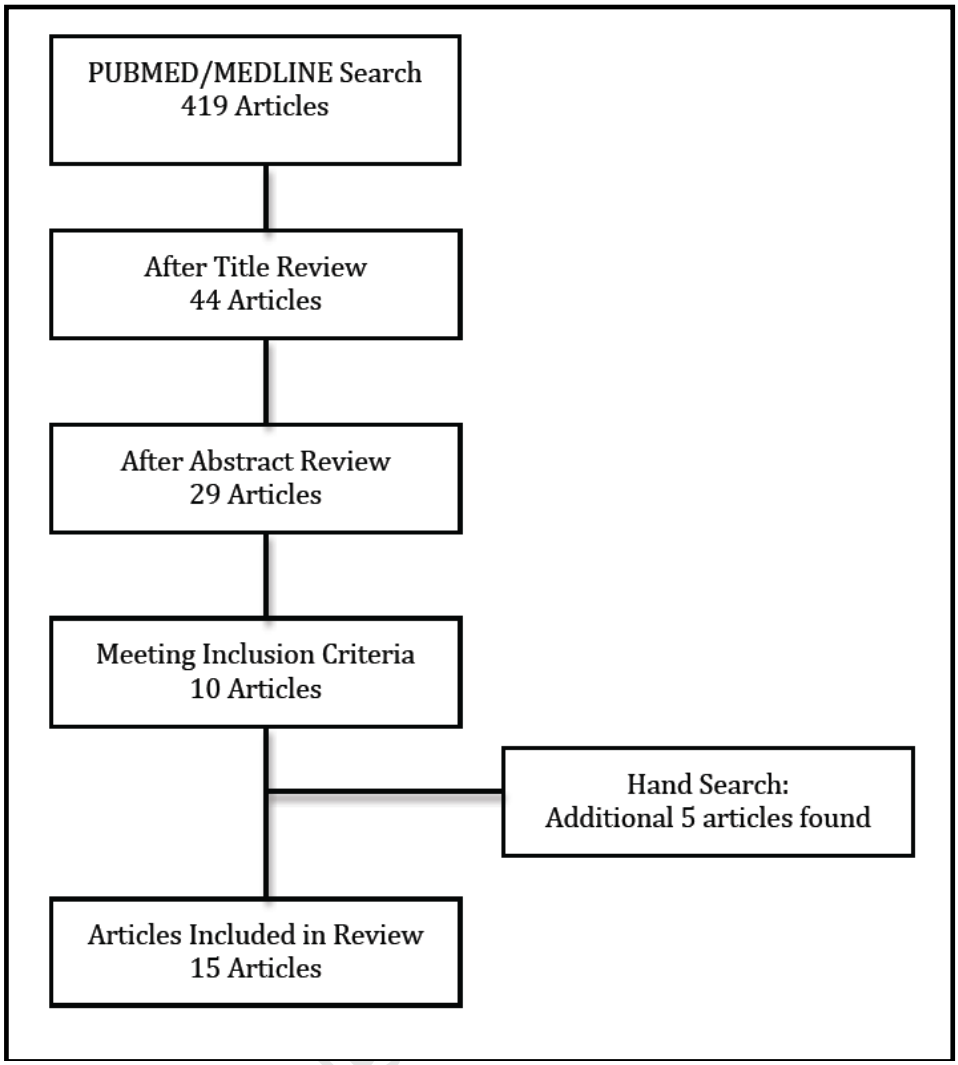


**Figure 1 Results of Search Strategy**

| Author | Year | Country | Study Design | (n) | Setting | Selection criteria | Comparison group (Y/N) | Confounders measured | Measure of Obstruction | Measure of TB | Association | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Case Series** | | | | | | | | | | | | |
| Baig *et al* (4) | 2010 | Pakistan | Case-Series | 47 | Referral Hospital | Patients referred with Past TB, CXR changes and SOB | N | Only non-smokers included | Post BD $FEV_1$: FVC Ratio | Patient history, CXR changes | 55.3% had obstruction<br>14.8% mixed obstruction/restriction | Highly selected group |
| **Case-Control** | | | | | | | | | | | | |
| Chang-Yeung *et al* (5) | 2007 | Hong Kong | Case-Control | 289 (cases) | Seven (Hospital) outpatient clinics | Consecutively diagnosed COPD patients | Y<br>Matched population based (n=289) | Smoking | Post BD $FEV_1$: FVC Ratio | Patient questionnaire | No association on multivariate analysis | Population TB prevalence not stated. Potential bias in control selection |
| Pasipanodya *et al* (6) | 2007 | USA | Prospective Case-Control | 121 (Cases) | County Public Health Department | Culture positive TB patients who had completed 20wks treatment | Latent TB Infected subjects (n = 218) | Smoking, Occupational Dust, Asbestos, HIV | Pre BD $FEV_1$: FVC Ratio | TB culture | Cases: 15% had obstruction, 13% mixed PFTs<br>Controls: 3% had obstruction, 1% mixed PFTs | Higher rates of obstruction in smokers |
| **Cohort** | | | | | | | | | | | | |
| Vargha (7) | 1983 | Hungary | Cohort (15 yr follow-up) | 99 | Outpatient clinic | Patients discharged as cured in 1958/59 | N | Smoking | $FEV_1$: FVC Ratio | Hospital records | After 15 years in medically treated patients:<br>52% had obstruction.<br>(34.8% without initial obstruction developed new obstruction; and 12% with initial obstruction normalised PFTs) | Loss to follow-up (in medically treated patients) was 18% |
| Willcox *et al* (8) | 1989 | South Africa | Retrospective cohort (Mean follow-up of 5.6 years) | 71 | Primary care clinic | All patients treated for TB by clinic | Y<br>Young patients matched to controls | Smoking | $FEV_1$: FVC Ratio &/or RV>120% predicted | Clinic records, CXR | Overall 68% had obstruction.<br>Young patients had significantly lower $FEV_1$: FVC Ratio and higher RV, compared with matched controls | Potential bias in selection of cohort. |
| Plit *et al* (9) | 1998 | South Africa | Prospective cohort (Follow-up = 6 months) | 74 | Tuberculosis Hospital | Consecutive inpatients, with first episode TB | N | Smoking, HIV | $FEV_1$: FVC Ratio | Hospital records | After treatment completion 28% (n=21) had obstruction. Of these 62% (13) were new. | Exclusion of MDR-TB, Previous TB and Co-existing pathology |
| **Cross-Sectional – Single Institution** | | | | | | | | | | | | |
| Snider *et al* (10) | 1971 | USA | Cross-sectional (single centre) | 1403 | Tuberculosis Sanatorium | Patients at medical discharge | N | Smoking | $FEV_1$: FVC Ratio | Hospital records | Obstruction in 23%, Mixed obstruction/ restriction in 19% | Very high rates of smoking (84%) |
| Ramos *et al* (11) | 2006 | Brazil | Cross-sectional (single centre) | 43 | Referral Hospital | Complex TB cases referred, who had PFTs | N | Smoking | Not defined | Patient records | 24% had obstruction. 34% had mixed obstruction/restriction | Severity of PFT matched CXR changes. Highly selected population. (54% never smokers) |
| Chung *et al* (13) | 2011 | Taiwan | Cross-sectional (single centre) | 115 | University Hospital | Patients with positive TB cultures, who underwent PFTs after TB treatment. | N | Smoking | $FEV_1$: FVC Ratio | TB culture | Obstruction in 48.6%; Mixed obstruction/ restriction in 9.3% | Median follow-up of 16 months.<br>Only 7.6% of culture positive TB had PFTs.<br>NTMs isolated in 26.4% of isolates. |
| Gothi *et al* (12) | 2007 | India | Cross-sectional (single centre) | 268 | Referral Centre | Patients referred for investigation of chronic airflow-obstruction | N | Smoking | Post BD $FEV_1$: FVC Ratio | Patient history and records | 77.7% of Obliterative Bronchiolitis was due to past TB | Obliterative Bronchiolitis accounted for 13% of PFT obstruction |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Girdler Brown *et al* (14) | 2008 | Lesotho | Cross-sectional (single centre) | 610 | Mine workers | Retrenched workers | N | Smoking, HIV, Silicosis | Pre BD $FEV_1$: FVC Ratio | Patient history | Of patients with COPD, 45% had past/current TB | Not corrected for smoking, no post BD spirometry |
| **Cross-Sectional – Population** | | | | | | | | | | | | |
| Lam *et al* (15) | 2010 | China | Cross-sectional (single centre) | 8,066 | Population | Guangzhou Biobank Cohort Study Population | N | Smoking, Dust, Socio-economic status (education) | Pre BD $FEV_1$: FVC Ratio & LLN | CXR & questionnaire | OR 1.37 (1.13-1.67) | Only Pre BD values. Large difference between self-reported previous TB and CXR changes of previous TB |
| Menezes *et al* (16) | 2007 | 5 Latin American Countries (PLATINO Study) | Cross-sectional (multi-centre) | 5571 | Population | Multistage sampling | N | Smoking, work dust, fossil fuel, childhood illness | Post BD $FEV_1$: FVC Ratio | Patient questionnaire | OR 2.33 (1.50-3.62) | 132 had past TB<br>TB history associated with more severe COPD. |
| Cabarello *et al* (17) | 2008 | Colombia (PREPOCOL Study) | Cross-sectional (multi-centre) | 5539 | Population | Multistage cluster sampling | N | Smoking, Biomass, SES | Post BD $FEV_1$: FVC Ratio | Patient questionnaire | OR 2.94 (1.58 – 5.49) | 72 had past TB<br>25.8% of past-TB had COPD. |
| Lamprecht *et al* (18) | 2011 | 14 Countries (BOLD Study) | Cross-sectional (multi-centre) | 4291 | Population | Population based sampling. Only Non-smokers. | N | Smoking, Dust, Childhood illness, Biomass fuels, Education, Medical conditions, BMI | Post BD $FEV_1$: FVC Ratio (& LLN) | Questionnaire | Women: OR 1.47 (0.69-3.12)<br>Men: OR 1.65 (0.43-6.34) | Only "never smokers" included. |

## Table 1. Studies included in Systematic Review

*Abbreviations: TB – tuberculosis; BD – bronchodilator; CXR – Chest Xray; wks – weeks; PFT – Pulmonary function test; RV – Residual volume; MDR-TB – Multidrug resistant tuberculosis; NTM – Non-tuberculous Mycobacterium, LLB – lower limit of normal; SES – Socio-economic status; BMI – Body mass index*

## REFERENCES


1. WHO. Burden of Chronic Obstructive Pulmonary Disease [Internet]. [cited 2011 Aug 29];Available from: http://www.who.int/respiratory/copd/burden/en/index.html
2. WHO. Tuberculosis. Fact sheet No. 104 [Internet]. [cited 2011 Aug 31];Available from: http://www.who.int/mediacentre/factsheets/fs104/en/index.html
3. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009 Aug;374(9691):733-43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19716966
4. Baig IM, Saeed W, Khalil KF. Post-Tuberculous Chronic Obstructive Pulmonary Disease. Journal of the College of Physicians and Surgeons of Pakistan. 2010;20(8):542-544.
5. Chan-Yeung M, Ho A, Cheung A, Liu R, Yee W, Sin K, et al. Determinants of chronic obstructive pulmonary disease in Chinese patients in Hong Kong. The International Journal of Tuberculosis and Lung Disease. 2007;11(5):502–507.
6. Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, et al. Pulmonary Impairment After Tuberculosis *. Chest. 2007;131(6):1817.
7. Vargha G. Fifteen Year Follow-up of Lung Function in Obstructive and Non-Obstructive Pulmonary Tuberculosis. Acta Medica Hungarica. 1983;40(4):271-276.
8. Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. Respiratory Medicine. 1989;83:195-198.
9. Plit ML, Anderson R, Van Rensburg CEJ, Page-Shipp L, Blott JA, Fresen JL, et al. Influence of antimicrobial chemotherapy on spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis. European Respiratory Journal. 1998;12:351-356.
10. Snider GL, Doctor L, Demas TA, Shae AR. Obstructive Airway Disease in Patients with Treated Pulmonary Tuberculosis. American Review of Respiratory Disease. 1971;103:625-640.
11. Ramos LMM, Sulmonett N, Ferreira CS, Henriques JF, DeMiranda SSDE. Functional profile of patients with tuberculosis sequelae in a university hospital*. J Bras Pneumol. 2006;32(January 2005):43-47.
12. Gothi D, Shah DV, Joshi JM. Clinical profile of diseases causing chronic airflow limitation in a tertiary care centre in India. The Journal of the Association of Physicians of India. 2007 Aug;55:551-5.
13. Chung K-P, Chen J-Y, Lee C-H, Wu H-D, Wang J-Y, Lee L-N, et al. Trends and predictors of changes in pulmonary function after treatment for pulmonary tuberculosis. Clinical Science. 2011;66(4):549-556.
14. Girdler-Brown BV, White NW, Ehrlich RI, Churchyard GJ. The burden of silicosis, pulmonary tuberculosis and COPD among former Basotho goldminers. American journal of industrial medicine. 2008;51(9):640–647.

15. Lam KB, Jiang CQ, Jordan RE, Miller MR, Zhang WS, Cheng KK, et al. Prior TB, Smoking, and Airflow Obstruction□: A Cross-Sectional Analysis of the Guangzhou Biobank Cohort Study. Chest. 2010;137(3):593–600.
16. Menezes AMB, Hallal PC, Perez-Padilla R, Jardim J, Muino A, Lopez M, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. European Respiratory Journal. 2007;30(6):1180-1185.
17. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al. Prevalence of COPD in Five Colombian Cities Situated at Low, Medium, and High Altitude (PREPOCOL Study)•. Chest. 2008;133(2):343-349.
18. Lamprecht B, Mcburnie MA, Vollmer WM, Welte T, Nizankowska-mogilnicka E, Bateman E, et al. COPD in Never Smokers□: Results From the Population-Based Burden of Obstructive Lung Disease Study. Chest. 2011;139(4):752-763.
19. Buist a S, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007 Sep;370(9589):741-50.
20. WHO. Global tuberculosis control report 2010. Available from: http://www.afro.who.int/en/clusters-a-programmes/dpc/tuberculosis/features/2622-global-tuberculosis-control-2010.html
21. Jithoo A. Respiratory symptoms and chronic obstructive pulmonary disease. Prevalence and risk factor in a predominantly low-income urban area of Cape Town, South Africa. PhD thesis. 2006;1-284.
22. Ehrlich RI, Adams S, Baatjies R, Jeebhay MF. Chronic airflow obstruction and respiratory symptoms following tuberculosis: a review of South African studies. The international journal of tuberculosis and lung disease□: the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(7):886-91.
23. Anno H, Tomashefski JF. Studies on the Impairment of Respiratory Function in Pulmonary Tuberculosis. American Review of Tuberculosis and Pulmonary Disease. 1955;71(3):333-48.
24. Kawoos MY, Khanna BK. A study of airway obstruction in pulmonary tuberculosis. The Indian Journal of Chest Diseases & Allied Sciences. 1979;21(1):18-23.
25. Birath G, Caro J, Malmberg R, Simonsson BG. Airways Obstruction in Pulmonary Tuberculosis. Scand. J. Resp. Dis. 1966;47:27-36.
26. Lancaster JF, Tomashefski JF. Tuberculosis--a cause of emphysema. The American review of respiratory disease [Internet]. 1963;87:435-7.
27. Gaesnsler EA, Lindgren I. Chronic bronchitis as an etiologic factor in obstructive emphysema; preliminary report. The American Review of Respiratory Disease. 1959;80(1, Part 2):185-93.
28. Hallett WY, Martin CJ. The diffuse obstructive pulmonary syndrome in a tuberculosis sanatorium. I. Etiologic factors. Annals of internal medicine. 1961;54:1146-55.

29. Martin CJ, Hallett WY. The diffuse obstructive pulmonary syndrome in a tuberculosis sanatorium. II. Incidence and symptoms. Annals of internal medicine. 1961;54:1156-64.
30. Long R, Maycher B, Dhar A, Manfreda J, Hershfield E, Anthonisen N. Pulmonary tuberculosis treated with directly observed therapy: serial changes in lung structure and function. Chest. 1998;113(4):933-43.
31. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax. 2000;55:32-38.
32. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of COPD [Internet]. 2010 [cited 2011 Apr 7]. Available from: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
33. van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. European Respiratory Journal. 2010;35(1):27-33.
34. Lee JH, Chang JH. Lung function in patients with chronic airflow obstruction due to tuberculous destroyed lung. Respiratory Medicine. 2003 Nov;97(11):1237-1242.
35. Krishna K, Bond S, Artvinli M, Reid KDG, McHardy GJR, Crofton JW. Pulmonary Function in Treated Tuberculosis; A Long Term Follow-Up. American Review of Respiratory Disease. 1977;15:402.
36. Elkington PTG, Friedland JS. Matrix metalloproteinases in destructive pulmonary pathology. Thorax. 2006;61:259-266.
37. Miller M, Cho JY, Pham A, Friedman PJ, Ramsdell J, Broide DH. Persistent airway inflammation and emphysema progression on CT scan in ex-smokers observed for 4 years. Chest. 2011;139(6):1380-7.
38. Martin CJ, Cochran TH, Katsura S. Tuberculosis, emphysema, and bronchitis. American Review of Respiratory Disease. 1968;97:1089-1094.

# Section 4: APPENDICES

## a. ACKNOWLEDGEMENTS

I wish to acknowledge the help given to me by Prof E Bateman, my supervisor, and Prof L. Myers, my co-supervisor. Their guidance, help and encouragement have been invaluable in the preparation of this dissertation.

Additionally I would like to acknowledge my Father in heaven, without whom, none of this would have been possible.

## b. DATA EXTRACTION FORM

| Date Reviewed | | Study Number |
|---|---|---|
| | **DATA Extraction Form** | |

| | | | |
|---|---|---|---|
| First Author, Year | | Study Group Name | |
| Country | | Journal | |

### 1. METHODS

| Study Design | Duration | Setting (Hospital, Clinic etc), Socio-economic status |
|---|---|---|
| | | |

**A. Selection of Participants**

| Diagnosis of TB | Notes |
|---|---|
| ☐ Patient History? n= ……<br>☐ Case Records? n= ……<br>☐ Microbiology? n= ……<br>☐ CXR? n=……<br>☐ CT Scan? n=……<br>☐ PPD? n=……<br>☐ (Other?) n=…… | Potential for Bias? (comment)<br>Y ☐ N ☐ |

| Diagnosis of Airflow Obstruction | | | | | Notes |
|---|---|---|---|---|---|
| Definition | | | | | |
| Machines used | | | | | |
| No of operators | | Good training? | | Q.C.? | |
| Grading of OLD? Y ☐ N ☐ | | Grading system used? GOLD ☐ OTHER ☐ | | | Potential for Bias? (comment) |
| Description of Grading System: | | | | | Y ☐ N ☐ |

**B. Selection of Controls / Non-exposed**

| Case-Control Study | | Cohort Study | | Other Study |
|---|---|---|---|---|
| Matched? | Y ☐ N ☐ | Matched? | Y ☐ N ☐ | Comment: |
| Similar population? | Y ☐ N ☐ | Similar Population? | Y ☐ N ☐ | |
| Confounders matched? | Y ☐ N ☐ | Confounders matched? | Y ☐ N ☐ | |
| Characteristics similar? | Y ☐ N ☐ | Characteristics similar? | Y ☐ N ☐ | |
| Major concerns? | Y ☐ N ☐ | Major concerns? | Y ☐ N ☐ | |
| Potential for Bias (comment) | | Potential for Bias (comment) | | Potential for Bias (comment) |
| Y ☐ N ☐ | | Y ☐ N ☐ | | Y ☐ N ☐ |

## 2. STUDY DETAILS

**A. Numbers**

| | Enrol | Exclusions | LTFU | Final | Age-mean | Age - Range | Male | Female | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total | | | | | | | | | | |
| TB Group | | | | | | | | | | |
| Non-TB | | | | | | | | | | |
| Major differences in groups? | | | | | | | | | | |
| Potential for Bias? Y ☐N☐ | | | | | | | | | | |

**B. Confounders**

| Measured confonders | Measured by? | Differences between groups? (describe) |
|---|---|---|
| ☐Smoking<br>☐Cannabis<br>☐Other Drugs<br>☐Fossil Fuels<br>☐Other | | |
| Potential for Confounding? Y ☐N☐ | | |

## 3. RESULTS

**TB Group**

| Number of episodes: Range:<br>Time from 1st episode: Range: | Comment: |
|---|---|

| | Average FEV1/FVC | Ratio Range | Other Measure | % with OLD | GOLD1 | GOLD2 | GOLD3 | GOLD4 | |
|---|---|---|---|---|---|---|---|---|---|
| TB group | | | | | | | | | |
| Control | | | | | | | | | |
| Total | | | | | | | | | |
| Comment | | | | | | | | | |

| Relative Risk (95% CI, p-value) | Odds Ratio (95% CI, p-value) | Statistical Analysis ok? Y ☐N☐ |
|---|---|---|

Can be used in Meta-Analysis? Y ☐N☐

## 4. COMMENTS

| | | | | |
|---|---|---|---|---|
| | Additional comments: | | | |
| | Points to clarify: | | | |
| Tick (√) | Included ☐ | Excluded ☐ | Uncertain ☐ | Awaiting further information ☐ |
| Reason(s) for exclusion: | | | | |

## c. SUMMARY OF ALL ARTICLES REVIEWED

| Number | First Author | Journal | (Reference) | Included? | Reason for exclusion |
|---|---|---|---|---|---|
| 1 | Baig | J Coll Physician Surg Pak | 2010; 20(8):542-544 | Y | - |
| 2 | Jordan | Respirology | 2010; 15: 623-628 | N | Review article |
| 3 | Park | Am J Ind Med | 2009; 52: 901-908 | N | Study not relevant to reasearch question |
| 4 | Lindoso | Rev Saude Publica | 2008; 42 (5): 1-7 | N | Study not relevant to reasearch question |
| 5 | Girdler Brown | Am J Ind Med | 2008; 51: 640-647 | Y | - |
| 6 | Buist | Int J Tuberc Lung Dis | 2008; 12(7):703-708 | N | Insufficient detail |
| 7 | Caballero | Chest | 2008; 133: 343-349 | Y | - |
| 8 | Menezes | Eur Respir J | 2007; 30:1180-1185 | Y | - |
| 9 | Majumdar | J Indian Med Assoc | 2007; 105(10): 565-580 | N | Insufficient detail |
| 10 | Gothi | J Assoc Physicians India | 2007; 55: 551-555 | Y | - |
| 11 | Chan-Yeung | Int J Tuberc Lung Dis | 2007; 8(1): 2-14 | N | Review article |
| 12 | Chakrabarti | Int J Chronic Obstruct Pulmon Dis | 2007; 2(3): 263-272 | N | Review article |
| 13 | Ait-Khaled | Int J Chronic Obstruct Pulmon Dis | 2007; 2(2): 141-150 | N | Review article |
| 14 | Ramos | J Bras Pneumol | 2006; 32(1): 43-47 | Y | - |
| 15 | Hassan | Saudi Med J | 2005; 26(7): 1155-1157 | N | Insufficient detail |
| 16 | de Valliere | Int J Tuberc Lung Dis | 2004; 8(6): 767-771 | N | Non-standard measure of obstruction |
| 17 | Chan-Yeung | Int J Tuberc Lung Dis | 2004; 11(5): 502-507 | Y | - |
| 18 | Lee | Respir Med | 2003; 97: 1237-1242 | N | Non-standard measure of obstruction |
| 19 | Hnizdo | Thorax | 2000; 55: 32-38 | N | Non-standard measure of obstruction |
| 20 | Wiley | N Eng J Med | 1996; 334(26): 1749 | N | Letter to editor |
| 21 | Couderc | N Eng J Med | 1996; 334(26): 1748 | N | Letter to editor |
| 22 | Willcox | Respir Med | 1989; 83: 195-198 | Y | - |
| 23 | Vargha | Acta Med Hung | 1983; 40(4): 271-276 | Y | - |
| 24 | Seiden | Can Med Assoc J | 1981; 124: 165-169 | N | Case Report |
| 25 | Schaeffer | Can Med Assoc J | 1980; 123: 997-1004 | N | Insufficient detail |
| 26 | Kawoos | Indian J Chest Dis Allied Sci | 1979; 21(1): 18-23 | N | Active tuberculosis |
| 27 | Snider | Am Rev Respir Dis | 1971; 103: 625-640 | Y | - |
| 28 | Martin | Am Rev Respir Dis | 1968; 97: 1089-1094 | N | Active tiberculosis, Pathology study |
| 29 | Birath | Scand J Respir Dis | 1966; 47: 27-36 | N | Active tuberculosis |
| 30 | Lancaster | Am Rev Respir Dis | 1963: 87: 435-437 | N | Active tuberculosis |
| 31 | Gaensler | Am Rev Respir Dis | 1959; 261(1): 10-8 | N | Active tuberculosis |
| 32 | Hallet | Ann Intern Med | 1961; 54: 1146-55 | N | Active tuberculosis |
| 33 | Martin | Ann Intern Med | 1961; 54: 1156-64 | N | Active tuberculosis |
| 34 | Anno | Am Rev Tuberc | 1955; 71: 333-48 | N | Active tuberculosis |
| 35 | Simpson | Am Rev Respir Dis | 1963; 87: 1-16 | N | Active tuberculosis |
| 36 | Krishna | Am Rev Respir Dis | 1977; 15: 402 | N | Insufficient detail |
| 37 | Long | Chest | 1998; 113: 933-43 | N | Insufficient detail |
| 38 | Plit | Eur Respir J | 1998; 12: 351-356 | Y | - |
| 39 | Buist | Lancet | 2007; 370: 741-50 | N | Insufficient detail |
| 40 | Lam | Chest | 2010; 137(3): 593-600 | Y | - |
| 41 | Chung | Clinics | 2011; 66(4): 549-556 | Y | - |
| 42 | Pasipanodya | Chest | 2007; 131: 1817-1824 | Y | - |
| 43 | Ehrlich | Int J Tuberc Lung Dis | 2011; 15(7): 886-891 | N | Review article |
| 44 | Lamprecht | Chest | 2011; 139(4): 752-763 | Y | - |
| 45 | Cowie | Chest | 1998; 113: 340-43 | N | Non-standard measure of obstruction |
| 46 | Baatjies | Eur Respir J | 2009; 34: 825-833 | N | Non-standard measure of obstruction, Asthma study |
| 47 | Ehrlich | Occup Environ Med | 2011: 68(2): 96-101 | N | Non-standard measure of obstruction |
| 48 | Ross | Thorax | 2010; 65(11): 1010-5 | N | Non-standard measure of obstruction |
| 49 | Naidoo | Int Arch Occup Environ Health | 2005; 78(4): 293-302 | N | Non-standard measure of obstruction |