TOBACCO SMOKING AS A POTENTIAL RISK FACTOR FOR PULMONARY TUBERCULOSIS: A META-ANALYSIS

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A research report submitted to the Faculty of Heath Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree

of

Master of Science in Medicine in the field of Tropical Diseases (Epidemiology & Biostatistics)

Johannesburg, 2001

DECLARATION

I John Benson Chipeta declare that this research report is my work. It is being submitted for the degree of Master of Science in Medicine in the field of Tropical Diseases (Epidemiology & Biostatistics) in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

29th day of December, 2001

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ABSTRACT

Objective. The aim of this paper was to systematically evaluate available evidence on tobacco smoking as a risk factor for pulmonary tuberculosis.

Methods. Relevant reports were identified by a systematic electronic search of Medline, Pubmed, Nioshtic, Toxline and Embasse. Methodological quality of all selected publications was assessed using a standardized checklist. Information was collected on all major study characteristics. Inter-study heterogeneity was examined qualitatively and statistically using the DerSimonian and Laird method.

Results. Five case-control studies and 1 cohort study were included in the systematic review. All the 6 studies revealed a relationship between tobacco smoking and pulmonary tuberculosis. Heterogeneity across studies hampered overall statistical pooling of results, however pooled risk ratios for sub-groups were determined.

Conclusion. Tobacco smoking is a potential risk factor for pulmonary tuberculosis. Confirmation would require prospective cohort studies conducted in countries with high tuberculosis incidence. Adequate sample sizes and adjustment for potential confounders including alcohol, HIV/AIDS, poverty and passive smoking are essential requirements.

ACKNOWLEDGEMENT

I would like to acknowledge Professor M.E. Edginton for all the assistance she offered. I would also thank the World Health Organization/TDR for sponsoring me to do the MSc course at the Witwatersrand University.

ABBREVIATIONS

AIDS	**Acquired immunity deficiency syndrome**
BCG	**Bacille Calmette Guerin**
CI	**Confidence Interval**
CIs	**Confidence intervals**
df	**Degrees of freedom**
HIV	**Human Immunodeficiency virus**
N/A	**Not applicable**
OR	**Odds ratio**
ORs	**Odds ratios**
PTB	**Pulmonary tuberculosis**
RR	**Risk ratio**
RRs	**Risk ratios**
SE	**Standard error**
SES	**Social Economic Status**
TB	**Tuberculosis**
Vs	**Versus**

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1. BACKGROUND

Evidence that smoking tobacco is harmful to health has been accumulating for 200 years[1]. The medical profession and the general public had nonetheless ignored the evidence on tobacco prior to 1950[1]. In 1950 case-control studies were done attributing lung cancer to tobacco smoking[1]. Large prospective and retrospective studies have shown a significant association between cigarette smoking and several cardiovascular and pulmonary diseases, in particular chronic obstructive pulmonary disease, chronic lung disease, stomach, oesophageal and liver cancers, pulmonary tuberculosis (PTB), stroke and ischaemic heart disease[2,3]. Tobacco kills 4 million people a year worldwide, and by the early 2030s the figure will increase to about 10 million. Seventy percent (70%) of these deaths will occur in developing countries[4].

TB is a global public health problem[5]. It is the leading cause of mortality among infectious diseases[5]. Worldwide the disease kills about 1.87 million a year and results in 7.96 million new cases a year[6]. The incidence of TB has increased in the majority of countries primarily due to its association with the human immunodeficiency virus (HIV) epidemic and other conditions including migration, homelessness, poverty, addictions and lack of health care resources[5,7,8].

Tobacco smoking has been cited as a risk factor for PTB but few studies worldwide have assessed the association of tobacco smoke and PTB[4]. Retrospective and prospective studies, of large numbers of subjects, that have cited the relationship between tobacco smoking and PTB, were not initially planned to test the hypothesis that tobacco smoke is related to the disease[1,3,9]. The studies aimed at assessing health hazards associated with use of tobacco in general. Case-control studies done in Spain

and USA, aimed at testing the hypothesis that tobacco smoking is a risk factor for PTB, have shown evidence of an association[10,11,12]. However, cohort studies would be strong designs to assess a potential relationship between tobacco smoking and PTB. Only one cohort study was found in the current systematic review.

1.1 AIM

The aim of this paper was to systematically evaluate available evidence on tobacco smoking as a risk factor for PTB.

1.2 JUSTIFICATION

There is a disagreement in the English literature as to whether tobacco smoking is independently associated with PTB. Systematic reviews are instrumental in resolving uncertainty when reports disagree, increasing sample sizes, hence statistical power, and estimating true effects of a risk factor[13]. A meta-analysis or review can hardly prove or disapprove causality; however it is instrumental in exploring the basis for differences among studies and in the process providing evidence bearing on causal inference[14], as well as identifying proper methods for future studies on causation.

1.3 LITERATURE REVIEW

1.3.1 ACTIVE TOBACCO SMOKING AND PTB MORTALITY

Doll et al[1] reported on findings from a prospective study of mortality in relation to smoking habits assessed over a 40 year period, from 1951 to 1991. The objective of the study was to assess hazards associated with long-term use of tobacco in a cohort of British male doctors. The study demonstrated that PTB has a moderately close relation with smoking. From 1951 to 1991, 66 subjects developed PTB. A standardized trend test indicated a significant increase in mortality from PTB with increased number of cigarettes smoked per day, $p < 0.001$. This finding is in agreement with findings by Liu et al[3] and Lam et al[9]. Liu et al[3] compared smoking habits of people who died of neoplastic, respiratory or vascular causes and a reference group who died of other causes between 1986 and 1988. The study revealed that PTB caused about 5 to 8% of all tobacco attributed deaths[3]. The study indicated that among men aged 35 to 65 there was a dose response relation between age when started smoking and the risk of dying from PTB. Lam et al[9] replicated these findings. In their study, cases were all deaths that were registered in Hong Kong in 1998. Controls were living persons suffering from diseases other than neoplastic, vascular and respiratory illnesses. This study revealed a much greater association between PTB mortality and tobacco smoking than the one done by Liu et al[3], as shown in table 1.3.1.

Table 1.3.1. RRs (95% CI) comparing PTB mortality between smokers and non-smokers, China and Hong Kong.

Study	RR (95 % CI)	
	Men aged 35-69 yrs	Women aged 35-69 yrs
Lam et al[9] (Hong Kong)	2.54(1.24-5.22)	1.49(0.18-2.57)
Liu et al[3] (China)	1.2(1.12-1.28)	1.29(1.13-1.45)

1.3.2 TOBACCO SMOKING AND DEVELOPMENT OF ACTIVE PTB

Alcaide et al[10] showed that cigarette smoking is a risk factor for PTB in young adults in a study done in 1992. They reported a dose response relationship between number of cigarettes consumed per day and risk of developing active disease. They indicated that young adult smokers who were contacts of index PTB patients were at a higher risk of disease than those not exposed to tobacco smoke, OR =3.7 (95% CI 1.5 to 9.2)[10]. This study is in agreement with results by Doll et al[1], Lam et al[9] and Liu et al[3]. Doll et al[1] observed that when TB was an important cause of mortality in Britain, mortality from PTB was strongly related to smoking[1].

If a cohort study similar to the one done by Doll[1] were done in a developing country, with high incidence of TB mortality, researchers could get more convincing results. Results of a study done in Tiruvallur district, India, in the year 2000, showed an association between tobacco smoking and PTB OR= 2.5 (95% CI 1.6 to 4.2)[15]. The ratio of cases to controls was 1:5. Only a summary of this study is available on the Internet and it seems that the study has not been published yet in international English journals. This study had an adequate number of controls and was done in a setting in which PTB is more prevalent compared to Britain and Spain. A similar study done in

King County, USA in 1990 showed that the risk of PTB among smokers of 30 years or more, is 2.6 times the risk of non-smokers[11].

1.3.3 PASSIVE SMOKING AND PTB

Cotinine, a metabolite of nicotine is the best biochemical marker for quantifying passive exposure to smoking[16]. It is specific to tobacco and has a half-life of about 20 hours and can be detected at low concentrations[16]. Cook et al[17] reported that passive smoking is a problem especially within homes. At least 50% of children, aged 5 to 7 years, included in the study done in England and Wales were exposed to tobacco smoke[17]. Cook et al[17] indicated that maternal smoking is more important than paternal smoking, despite the lower levels of smoking by mothers. They showed that children not exposed at home had a low cotinine concentration, which depended on the prevalence of smoking in the community[17]. In a study of 7-year-old children attending school in Edinburgh, Scotland, it was reported that three quarters of the children from non-smoking households had detectable salivary cotinine, suggesting that factors other than smoking by household members may be significant regarding exposure to some children[18]. Altet et al[12] assessed the effect of passive smoking within the family on the development of active PTB in children less than 15 years. The study, done in 1992, revealed that passive exposure to tobacco smoke in children was associated with an increased risk of developing active PTB, immediately following infection with *Mycobacterium tuberculosis*. Children exposed to tobacco smoke (through passive smoking) were at a higher risk of developing PTB compared to those not exposed, OR=5.4 (95% CI 2.4 to 11.9).

1.3.4 ROLE OF CONFOUNDERS IN THE ASSOCIATION BETWEEN TOBACCO SMOKING AND PTB

Studies investigating the association between tobacco and PTB are complex, as the number of potential confounders is potentially large[4]. For that reason the studies must control for confounding factors including alcohol consumption, HIV/AIDS status, intravenous drug use, malnutrition, sanitation and social status. The association between alcohol and tobacco smoking is well known[1]. In some settings persons who drink heavily and abuse tobacco are more likely to be homeless or live in squatter camps[11,19]. These are at an increased risk of exposure to *M. tuberculosis*[11]. In addition heavy drinking may increase the risk of progression to active PTB through poor eating habits and inadequate nutrition[11]. Failure to adjust for confounders will lead to false conclusions about tobacco smoking as a risk factor for PTB. Levy et al[20] observed that the roles of alcohol, HIV infection and intravenous drug use should be taken into consideration when investigating the association between tobacco and PTB. He suggested that a cohort study was needed to assess the relationship. Yach[4] also stated that results from a prospective study on the link between tobacco and PTB would be important. Cohort studies designed to assess the causal relationship between smoking and PTB should consider carefully the role of alcohol alone, smoking alone and the interaction of the two. It is also crucial to allow for the latent period of exposure to tobacco smoke, as done by Lam et al[9] and Liu et al [3,].

A matched case-control study aiming at assessing the relationship between personal behaviour (smoking and alcohol consumption) and PTB was done in Chengdu, China

in 1996, with 173 cases and 173 controls*. It showed no independent relationship between tobacco smoking and TB[21]. Univariate analysis showed that active and passive smoking were significantly associated with PTB, OR=2.12, p-value=0.006 and OR=1.55, p-value=0.04 respectively[21]. However, multivariate logistic regression analysis showed no evidence of independent associations between PTB and smoking or PTB and alcohol consumption. The study showed that smokers who took alcohol were at a higher risk of developing PTB, OR =7.73 (95% CI 1.52 to 39) [21]. The study concluded that smoking and alcohol were not independently associated with PTB[21]. This study is not in accord with studies that have shown that alcohol alone or smoking alone are risk factors for PTB [1,3,9,10,11,22].

1.3.5 INADEQUATE LITERATURE ON THE INFLUENCE OF TOBACCO SMOKING ON PTB

Yach[4] like most researchers interested in the association between smoking and PTB noted the inadequacy of studies on the topic. He pointed out that available evidence suggests that TB infection, incidence and severity, are related to tobacco use[4]. There is some clinical evidence suggesting that patients who continue to smoke after starting treatment seem to take longer to improve both clinically and bacteriologically[4]. Yach[4] believes that tobacco is likely the major cause of death among treated TB patients[4]. Further research on the relationship between tobacco and TB is needed.

* Only the abstract was available in English, full report was in Chinese

2 MATERIALS AND METHODS

2.1 SEARCH STRATEGY

Research papers were retrieved by a computerized search of Medline, Pubmed, Nioshtic, Toxline and Embasse for publications dating from 1991 to 2001. The following key words were used (MeSH headings and text words): tobacco, smoking, smoker, smoke, risk factors, cigarette, cigars, pipes, mortality, alcohol, tuberculosis, pulmonary, respiratory, addiction, environmental, pollution, case-control, cohort, passive smoking, meta-analysis and review. In addition a rigorous physical search was done in the Witwatersrand Medical School Library using references of the identified relevant studies. Papers not available in South Africa were ordered from abroad.

2.2 SELECTION CRITERIA

Studies were included in the systematic review if they met the conditions listed below:

i. Citing relationship between tobacco smoking and PTB

ii. Longitudinal in design; case-control or cohort.

iii. Full reports published in English in peer-reviewed journals.

iv. Information on risk factors for PTB available

v. Exposure assessed by interviews or questionnaires on smoking habits.

vi. Date of publication 1991 through 2001

2.3 QUALITY ASSESSMENT

Studies have differences in methodological quality. Consequently results of some are certainly more affected by bias compared to others. Quality was taken into account in assessing the potential association between smoking and PTB. A modified version of the checklist for quality appraisal used by Danielle AW Van der Windt[23] was developed. The following components of a paper; objective, selection of participants, exposure ascertainment, analysis and data presentation were scored as follows:

- Positive (+) if bias was minimal.
- Negative (-) if there was potential bias.
- Unknown (?) if information was insufficient or not available.

Details of the standardised checklist are shown in table 2.3.1. Each item shown in table 2.3.1 was scored as either positive (+), negative (-) or unknown (?) for all the studies included in this systematic review. The total number of positive scores was determined for each study. The proportion of positive scores was calculated for each study (number of positive scores divided by number of applicable items). Thereafter studies were ranked in order of methodological quality whereby a study with the largest proportion of positive scores was ranked as number 1.

Table 2.3.1. Standardised checklist for the assessment of methodological quality across studies included in this systematic review.

Item	Description of Methodological Item
	STUDY OBJECTIVE
1	Clearly stated objective
	SELECTION OF PARTICIPANTS (*applicable for case control studies)*
2	Cases and controls clearly defined
3	Cases and controls selected from the same source population
	EXPOSURE ASSESSMENT
4	Adequate* information on exposure to tobacco smoke presented
5	Major confounders adjusted for
6	Subjects categorised into exposure groups according to levels of exposure
	ANALYSIS AND DATA PRESENTATION
7	Both univariate and multivariate analysis performed
8	RRs and ORs and their 95% CI or SE displayed
9	Sample size adequate

* Adequate information include average number of cigarettes per day and duration of smoking

2.4 EXCLUDED STUDIES

Papers whose abstracts were in English but full reports were available in other languages were excluded in the systematic review. Studies that investigated the relationship between tobacco smoking and primary infection with *Mycobacterium tuberculosis* were not included. Unpublished papers were also omitted in the current systematic review.

2.5 DATA EXTRACTION AND ANALYSIS

Details for each study included in the systematic review were extracted on; study site, dates, study population, exclusion and inclusion criteria, exposure and outcome ascertainment, detection of cases, confounders and RR or OR with their 95% CIs. Pooled risk estimates were determined only when homogeneity was statistically proved in sub-groups of studies included in the current systematic review. Homogeneity in meta-analysis is constancy of exposure effect across studies or between defined strata across studies[24]. Heterogeneity may be defined as variability or differences among studies in estimates of exposure effects.

The DerSimonian and Laird random effects approach was used to assess homogeneity across studies[24,25]. A Q statistic, which has a chi-square distribution with df 1 less than the number of studies pooled, was used to test a null hypothesis of constant exposure effect across studies (Ho: homogeneity of results vs Ha: heterogeneity of results). The Mantel-Haenszel fixed effect model[26] was used to combine ORs for subgroups of studies whose results were proved to be homogeneous (see Appendix for details on the DerSimonian and Laird method).

2.6 LIMITATIONS

Limitations of this review include existence of few studies investigating the causal association between tobacco smoking and PTB, the majority of which are case-control studies. Only one prospective study was identified in the English literature. Furthermore this review only considered papers published in peer-reviewed journals. Publication bias can therefore not be ruled out. Finally, enormous heterogeneity impeded overall statistical pooling of results.

3 RESULTS

3.1 SEARCH RESULTS

The search of the computerised databases yielded 126 citations on TB and tobacco in the English literature. Only 41 studies on the causal association between tobacco smoking and TB were cited. This number was reduced to 25 when only abstracts dated 1991 to 2001 and those published in peer reviewed journals were included. After excluding publications looking at TB primary infection and reviews on TB and tobacco, only 6 studies were included in the systematic review.

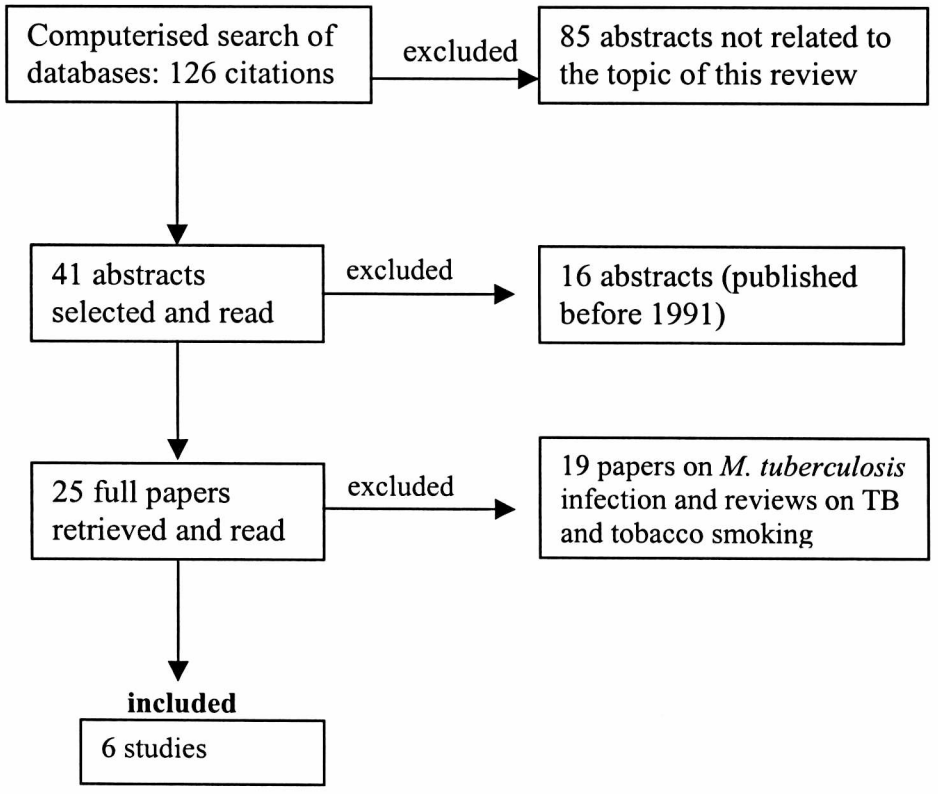


Figure 3.1.1.Flow diagram showing papers accepted and excluded for systematic review

The majority of studies reported effects of tobacco smoking on health with emphasis on cancers, heart disease, asthma and other pulmonary diseases other than TB. Similarly the majority of studies done on risk factors for TB did not assess tobacco smoking as a potential risk factor. Five cases-control studies and one cohort study were included in this systematic review.

3.2. STUDY CHARACTERISTICS

Table 3.2.1 presents a summary of study characteristics including study site, dates, population study, study design, inclusion criteria, exposure and disease ascertainment, and confounders. The table also presents multivariate RRs and ORs with 95% CIs. A wide variety of study settings across papers were observed. Differences in study characteristics are discussed in section 3.4, page 31. Exposure ascertainment was similar in all studies in such a way that questionnaires and direct interviews were administered.

Studies by Alcaide et al[10] and Altet et al[12] were similar regarding materials and methods and were all done in Barcelona, Spain. These studies were very different in design from those conducted by Liu et al[3] and Lam et al[9].

Cases in the studies by Lam et al[9] and Liu et al[3] were deaths from neoplastic, respiratory or vascular causes. These were all case control studies with large numbers of subjects.

The study by Doll et al[1] was different from the rest in design. It was a cohort study with a very long follow-up period of 40 years[1]. This study also included a large number of subjects[1] as shown in table 3.2.1. Doll et al[1] did not present an RR for PTB mortality in the paper included for this systematic review. However, Doll[27] indicated in a later review paper that the mortality ratio of PTB comparing smokers to non-smokers was 2.8 for the British male doctors cohort.

Table 3.2.1. Characteristics of studies that were included for the systematic review

Item	Case control studies					Cohort study
Author	**Altet et al[12]**	**Lam et al[9]**	**Buskin et al[11]**	**Alcaide et al[10]**	**Liu et al[3]**	**Doll et al[1]**
Site	Barcelona- Spain	Hong Kong	King County - USA	Barcelona-Spain	Mainland China	Britain
Dates	1992	1998	1988-1990	1992	1989-1991	1951-1991
Study population	Children <15 years who were contacts of index TB cases reporting to 'Centre de Prevencio i Control de la Tuberculosi' in Barcelona	Ethnic Chinese people aged above 35 years whose deaths were registered in 1998 and people who knew the dead peoples' smoking habits	King County residents aged above 17 years seeking care at King County TB Clinic	Young adults 15-24 years, who were contacts of index PTB cases reporting to 'Centre de Prevencio i Control de la Tuberculosi' in Barcelona	Chinese people aged 35 years and above	All registered British male doctors
Sample size	93 cases 95 controls	27507 cases 13054 controls	151 cases 545controls	46 cases 46 controls	0.7 million cases and 0.2 million controls	A cohort of 34 439 British male doctors
Inclusion criteria	Tuberculin test positive. Close contacts of index PTB patients seeking clinic care.	Registered deaths in 1998 and people who knew the dead peoples' smoking habits.	Residents that were mentally competent seeking clinic care at King County Clinic.	Tuberculin test positive. Close contacts of index PTB patients seeking clinic care.	People who died in 1986-88 in China. Subjects who ever smoked before 1980.	Doctors on the British medical register.
Exclusion criteria	Tuberculin test negative children were not included. Those taking isoniazid chemoprophylaxis. BCG vaccinated. Active smokers. Contacts of smear negative index PTB patients.	Non-Chinese people were not included. Wives of registered dead people not recruited as controls.	Patients <17 years of age. Those not seeking care at TB Clinic. HIV/AID patients.	Tuberculin test negative. BCG vaccinated individuals. Known previous chemoprophylaxis. Immunocompromised patients or those with other conditions associated with risk factors for TB.	Deaths before 1986 and after 1988. Smokers who started smoking after 1980. Non Chinese people.	Doctors struck off medical register. Doctors lost to follow up. Non-British doctors and female British doctors.

Author	Altet et al[12]	Lam et al[9]	Buskin et al[11]	Alcaide et al[10]	Liu et al[3]	Doll et al[1]
Exposure measurement	Questionnaires were administered to smoking family members. Urinary concentration of cotinine was determined by specific radioimmunoassay.	Questionnaires about smoking habits of the deceased were given to people registering deaths of relatives and friends.	Self administered questionnaires to all subjects.	Questionnaires were administered to subjects. Urinary concentration of cotinine was determined by specific radioimmunoassay	Interviews of surviving family members on smoking habits of the deceased.	Doctors were sent questionnaires on smoking habits. Questionnaires were sent to doctors in 1957, 1966, 1972, 1978 and 1990.
Case definition	*M. tuberculosis* culture positive or a combination of clinical evidence, radiological evidence and a positive tuberculin test.	Not specified[a]	Laboratory confirmation of *M. tuberculosis*	Culture positive or a combination of clinical and radiological evidence and a positive tuberculin test.	Not specified[a]	Not specified[b]
Case finding	Subjects were contacts of index PTB cases seeking clinical care at the TB Clinic.	Data on cases was retrieved from death registries (cases were deaths registered in 1998).	Recruitment of patients seeking care at King County Clinic.	Subjects were contacts of index PTB cases seeking clinical care at the TB Clinic.	Details about deaths were retrieved from medical records and local administration records.	Mortality information was sourced from the Office of Population Census and Surveys, BMJ and Medical Directory obituaries.
Confounders considered	Age, sex, SES, crowding and smoking habits.	Age, sex, employment, and house type.	Weight, height, age, sex, SES and alcohol.	Smoking habits, age, gender and SES.	No. of cigarettes, age when started smoking and residence (rural or urban)	Drinking habits, health history and aspirin use.
R R or OR and (95% CI)	OR = 5.39 (95% CI 2.44 – 11.91)	RR[c]= 2.54 (95% CI 1.24 –5.22)	OR =2.6 (95% CI 1.1 – 5.9)	OR=3.65 (95% CI 1.46 - 9.21)	RR[c]=1.2 (95% CI 1.12 – 1.28)	RR=2.8[d] (95% CI not given)

[a] This was a case-control study with a large number of subjects aimed at assessing different causes of mortality associated with tobacco smoking.

[b] This was a cohort study aimed at assessing all health hazards associated with long term use of tobacco.

[c] Risk ratios for smokers vs non-smokers were estimated using logistic regression.

[d] Refer to reference number 27

3.2.1 EXPOSURE TO TOBACCO SMOKE

Studies categorized exposure groups in a different way as shown in tables 3.2.2 and 3.2.3. Altet et al[12] categorized exposure as: passive smoker in homes, passive smoker both within homes and outside the home (whereby active smokers were family members) and number of cigarettes smoked by family members[12]. Alcaide et al[10] divided exposure groups into active smokers, passive and active smokers, daily smokers, occasional smokers and number of cigarettes smoked. Liu et al[3] and Doll et al[1] categorized exposure by number of cigarettes smoked per day. Altet et al[12], Buskin et al[11] and Alcaide et al[10] collected detailed information on exposure to tobacco smoke.

Table 3.2.2. Reported findings on dose response relationship between numbers of cigarettes smoked per day and risk of PTB morbidity and mortality across studies included in the current review

Cigarettes Smoked per day	Case control studies with dead cases		Case control studies with living cases			Cohort study
	Lam et al[9] RR[a]	Liu et al[3] RR (95%CI)[b]	Alcaide et al[10] OR (95% CI)	Buskin et al[11] OR (95% CI)	Altet et al[12] OR (95% CI)	Doll et al[1] (Mortality[c] per 100,000 men)
1-14	1.02					7
5-15				1.4(0.8-2.6)		
1-20		1.2(1.1-1.4)	3(1.3-7.9)		1.6(0.7-2.6)	
15-24	2.93					9
=20		1.5(1.3-1.6)				
16-29				1.9(1.1-3.4)		
>20	6.62	2.0 (1.8-2.3)	13(2.3-74)		4(1.6-9.8)	20
>30				2.9(1.2-7.2)		
>40					7.8(3.4-18)	

[a] test for trend p-value < 0.001

[b] 95% CIs determined from given standard errors of RR in the paper

[c] standardized trend test[1], has expectation zero and a standard deviation of unity values above 3.29 correspond to p-value <0.001.

Alcaide et al[10] reported that the risk of developing PTB is highest if one is both an active and passive smoker, followed by active smoking alone and then passive smoking only (see table 3.2.3).

Table 3.2.3. Dose response relationship between smoking habits and risk of developing PTB, Spanish case-control studies[10,12].

Exposure to Tobacco smoke	Alcaide et al[10] OR (95% CI)	Altet et al[12] OR (95% CI)
Passive only	2.50(1.00-6.2)	5.39(2.44-11.91)
Occasional/daily	3.6(1.5-2.2)	-
Daily	3.5(1.3-9.3)	-
Active & passive	5.6(2.1-15.1)	-

3.3 METHODOLOGICAL QUALITY RESULTS

Table 3.3.1 displays results of the assessment of methodological quality across studies. The columns in the table show scores for each methodological item, whereas the rows represent studies (names of first authors). The studies are ranked according to the proportion of positive scores.

Methodological item 5 (adjustment of major confounders) had negative scores for studies by Lam et al[9], Liu et al[3] and Alcaide et al[10]. The case-control study by Alcaide et al[10] was also scored negative for having a small sample size. The sample size of 46 cases and 46 controls was small for this study[28,29]. Studies by Altet et al[12] and Buskin et al[11] scored positive for all major methodological items. Their sample sizes were adequate and major confounding factors were controlled for. Failure to adjust for alcohol in the study by Altet et al[12] was acceptable

because the study population was children under the age of 15 years. Buskin et al[11] effectively controlled for alcohol and social economic status. Furthermore they validated their findings by using population-based data to calculate age-adjusted ORs and 95% their CIs. All studies presented RRs or ORs with CIs except Doll et al[1].

All items of the methodological checklist received equal weight. This has the disadvantage that studies with few, but important flaws may still be ranked as one of the best. As shown in table 3.3.1 the quality of the studies included in this review was high.

Table 3.3.1. Results of the assessment of methodological quality across studies included in this systematic review.

	Study (first authors)					
	Lam[9]	**Altet[12]**	**Alcaide[10]**	**Liu[3]**	**Doll[1]**	**Buskin[11]**
Year	1998	1992	1992	1989-1991	1951-1991	1988-1990
Site	HongKong	Spain	Spain	China	Britain	USA
Design[a]	cc	cc	cc	cc	ch	cc
Methodological Item*						
1. Clear objectives	+	+	+	+	+	+
2. Well defined cases/controls	+	+	+	+	N/A	+
3. Cases/controls from same population	+	+	+	+	N/A	+
4. Information on tobacco smoke exposure	+	+	+	+	+	+
5.Major confounders adjusted for	-	+	-	-	+	+
6.Smokers classified by No. of cigarettes per day	+	+	+	+	+	+
7.Multivariate analysis done	+	+	+	+	+	+
8. OR or RR with 95% CI presented	+	+	+	+	?	+
9. Sample size adequate[b]	+	+	-	+	+	+
Proportion of positive scores	0.80	1.00	0.78	0.78	0.86	1.00
Rank according to score	4	1.5	5.5	5.5	3	1.5

[a] cc = Case control study
ch = Cohort study

* methodological items listed in full in table 2.3.1. Items are scored "+" for minimal bias, "-"for potential bias, " ?" for insufficient/unavailable information and "N/A" if item not applicable.

[b] Fleiss equation for determining sample size: comparison of proportions in 2 groups[26].

3.4 SUB-GROUP POOLED ESTIMATES

Homogeneity and Heterogeneity

The terms homogeneity and heterogeneity are defined in the data extraction and analysis section (section 2.5, page 21). Studies are homogenous if they are measuring a constant exposure effect and differences in the measures of effects are only due to random error [24].

There were differences in characteristics of studies included in this systematic review regarding; age ranges of participants, definition of cases and controls, confounders considered, statistical models, exclusion and inclusion criteria as shown in table 3.2.1. Lam et al[9] and Liu et al[3] included subjects aged 35 years and above. Alcaide et al[10] enrolled participants aged between 15 and 24 years, while Altet et al[12] recruited children less than 15 years of age. Buskin et al[11] included subjects aged above 17 years. Doll et al[1] included registered British male doctors of all ages.

Studies by Lam et al[9] and Liu et al[3] defined cases as deaths due to different respiratory, neoplastic or vascular causes. But these studies had different controls. Lam et al[9] used living relatives and friends who knew the deceased's smoking habits as controls whereas Liu et al[3] defined controls as people dying of other deaths other than neoplastic, vascular and respiratory causes. These two case control studies were treated as a separate stratum in meta-analysis. Doll et al[1] also investigated respiratory, neoplastic or vascular causes related to tobacco smoking among the British male doctors cohort. This review was however only interested in deaths and cases of PTB.

The study by Doll et al[1] was the only cohort study and its data was not pooled with that from case control studies.

Alcaide et al[10], Altet et al[12] and Buskin et al[11] defined cases as PTB patients who either were culture positive, smear positive, or a combination of clinical evidence, radiological evidence and a tuberculin positive test. These used subjects without PTB as controls. In studies by Alcaide et al[10] and Altet et al[12] controls were tuberculin positive individuals.

Different inclusion and exclusion criteria were observed across studies as shown in table 3.2.1. Alcaide et al[10] excluded immuno-compromised patients or those with conditions associated with risk factors for TB (table 3.2.1, page 26). Similarly Buskin et al[11] and Altet et al[12] excluded HIV positive subjects (table 3.21, page 26). Buskin et al[11] excluded mentally incompetent patients. Alcaide et al[10] and Altet et al[12] excluded subjects who took chemoprophylaxis or received a BCG vaccine. Alcaide et al[10] and Altet et al[12] were also treated as a sub-group in meta-analysis.

Liu et al[3] and Lam et al[9] only included registered deaths. Ninety percent (90%) of all deaths are registered in China, where Liu et al[3] conducted their study. Lam et al[9] indicated that in Hong Kong where they conducted their study, death registration is a requirement by law. Bias due to exclusion of unregistered deaths was therefore minimal.

All investigators for studies included in this systematic review controlled for age, sex, social economic status and smoking habits (including number of tobacco cigarettes

smoked per day). Table 3.4.1 indicates different confounders that were controlled for and adjusted RRs and ORs. Buskin et al[11] further adjusted for alcohol, duration of smoking, weight and height. In addition to the already mentioned confounders, Liu et al[3] controlled for smoking duration and residence (rural or urban). Doll et al[1] further controlled for health history and aspirin use. Alcaide et al[10] also controlled for nature of exposure, whether active or passive tobacco smoking. In addition to confounders mentioned above Altet et al[12] further adjusted for crowding and number of smoking family members.

Table 3.4.1. Adjusted RRs and ORs determined in studies included in this systematic review and the confounders adjusted for.

Study	Confounders adjusted for	Adjusted RRs or ORs (95% CI)	Comments
Altet et al[12]	Sex, age, father's SES and cigarettes/day.	*Passive smoking vs PTB morbidity* 5.4(2.4-11.9)	Major confounders were adjusted for. HIV/AIDS patients were excluded
Alcaide et al[10]	Age, sex , number of cigarettes/day and SES.	*Active smoking vs PTB morbidity :* 3.6 (1.4-9.5) *Active and passive smoking vs PTB morbidity:* 5.7 (1.9 –17.5)	Considering age of participants (15-24yrs) should have controlled for alcohol. Immunocompromised patients were excluded
Buskin et al[11]	Age, cigarettes/day alcohol and SES.	*Active smoking for more than 30years vs PTB morbidity :* 2.6 (1.1-5.9)	Major confounders were adjusted for. HIV/AIDS patients were excluded
Lam et al[9]	Age and education	*Active smoking vs PTB mortality:* 2.54(1.24-5.22)	Alcohol was not adjusted for
Liu et al[3]	Cigarettes/day, residence, sex and age.	*Active smoking vs PTB mortality:* 1.2 (1.12 – 1.28)	Alcohol was not adjusted for
Doll et al[1]	Cigarettes/day and sex	*Active smoking vs PTB mortality:* 2.8 (CI not given)	Drinking habits were controlled for. This was a strong study design for the association under study

Differences in study characteristic were the reason for heterogeneity of results across studies included in the current systematic review. Using the DerSimonian and Laird approach as described in the data extraction and analysis section (section 2.5, page 21), heterogeneity was assessed among all the 5 case control studies included in this review. The study by Doll et al[1] was not included in the heterogeneity assessment because not all data required for the calculation of the variance for $\log_e$ OR was available. There was evidence of heterogeneity across all the 5 case control studies with a Q statistic=15, df= 4, p-value <0.01 as shown in table 3.4.2.

The Forest Plot[30] shown in figure 3.4.1 shows, at a glance, differences in exposure effect estimates across studies. The L'Abbe` plot, figure 3.4.2, one of graphical methods suggested for exploring heterogeneity of results in a systematic review,[30] graphically shows heterogeneity in results of the 5 case-control studies.

The study by Lam et al[9] had the lowest values of mortality rates, 2% among non-smoker and 4% among smokers, followed by Liu et al[3]. Alcaide et al had highest PTB morbidity rates 33% among non-smokers and 65% among smokers, followed by Altet et al. This shows that study design and age of participants played a big role in heterogeneity of results.

Results of studies by Alcaide et al[10], Altet et al[12] and Buskin et al[11] were heterogeneous as shown in table 3.4.3. However there was no evidence of heterogeneity of results in studies by Alcaide et al[10] and Buskin et al[11] Q statistic=2.2, df=1, p-value>0.1 (table 3.4.4). There was also no evidence of heterogeneity of

results between Alcaide et al[10] and Altet et al[12], Q statistic=0.4, df=1, p-value > 0.1 (table 3.4.5).

There was no evidence of heterogeneity of results between studies by Liu et al[3] and Lam et al[9], Q statistic=1.8, df=1, p-value>0.1 (table 3.4.6). Heterogeneity of results impeded pooling of results across studies. ORs of all subgroups of studies that were statistically proved to be homogeneous were pooled using the Mantel-Haenszel approach[26].

Tables 3.4.2 to 3.4.6 show results of DerSimonian and Laird heterogeneity test results. These tables also display pooled subgroup Mantel-Haenszel ORs for study subgroups that were homogeneous.

Table 3.4.2. Heterogeneity assessment in all studies included in this systematic review.

Study	Smokers	Non smokers	Wt (%)[a]	OR (95%CI)*
	PTB(yes/no)	PTB(yes/no)		
Altet et al[12]	83/58	10/37	0.93	5.3 (2.3-12.4)
Buskin et al[11]	103/300	48/245	3.82	1.75 (1.2-2.6)
Alcaide et al[10]	33/19	13/27	0.74	3.6 (1.4-9.5)
Liu et al[3]	2371/18544	1003/12165	93.3	1.55 (1.4-1.7)
Lam et al[9]	36/841	11/639	1.2	2.5 (1.2-5.2)
Doll et al[1]	-	-	-	2.8 (-)

DerSimonian and Laird Q statistic=15, df=4, p-value <0.01. **THERE IS EVIDENCE OF HETEROGENEITY**

[a] wt = % weight assigned to each study (weight =inverse of variance of $\log_e$ OR)
* See detailed results in the appendix

Table 3.4.3. Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB morbidity and tobacco smoking in subjects of all ages.

Study	Smokers	Non smokers	Wt[a] (%)	OR* (95%CI)
	PTB(yes/no)	PTB(yes/no)		
Altet et al[12]	83/58	10/37	17	5.3(2.3-12.4)
Buskin et al[11]	103/300	48/245	70	1.75 (1.2-2.6)
Alcaide et al[10]	33/19	13/27	13	3.6 (1.4-9.5)
DerSimonian and Laird Q statistic=7.4, df =2, p-value <0.05. **THERE IS EVIDENCE OF HETEROGENEITY. POOLING OF RESULTS NOT VALID**				

[a] wt = % weight assigned to each study (weight =inverse of variance of $\log_e$ OR)
* See detailed results in the appendix

Table 3.4.4. Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB morbidity and active tobacco smoking in subjects aged 17 years and above.

Study	Smokers	Non smokers	Wt (%)	OR (95%CI Fixed)
	PTB(yes/no)	PTB(yes/no)		
Buskin et al[11]	103/300	48/245	84	1.75 (1.2-2.6)
Alcaide et al[10]	33/19	13/27	16	3.6 (1.4-9.5)
		Mantel-Haenszel OR =		1.97(1.37-2.86)
DerSimonian and Laird Q statistic =2.2, df=1, p-value>0.1. **NO EVIDENCE OF HETEROGENEITY**				

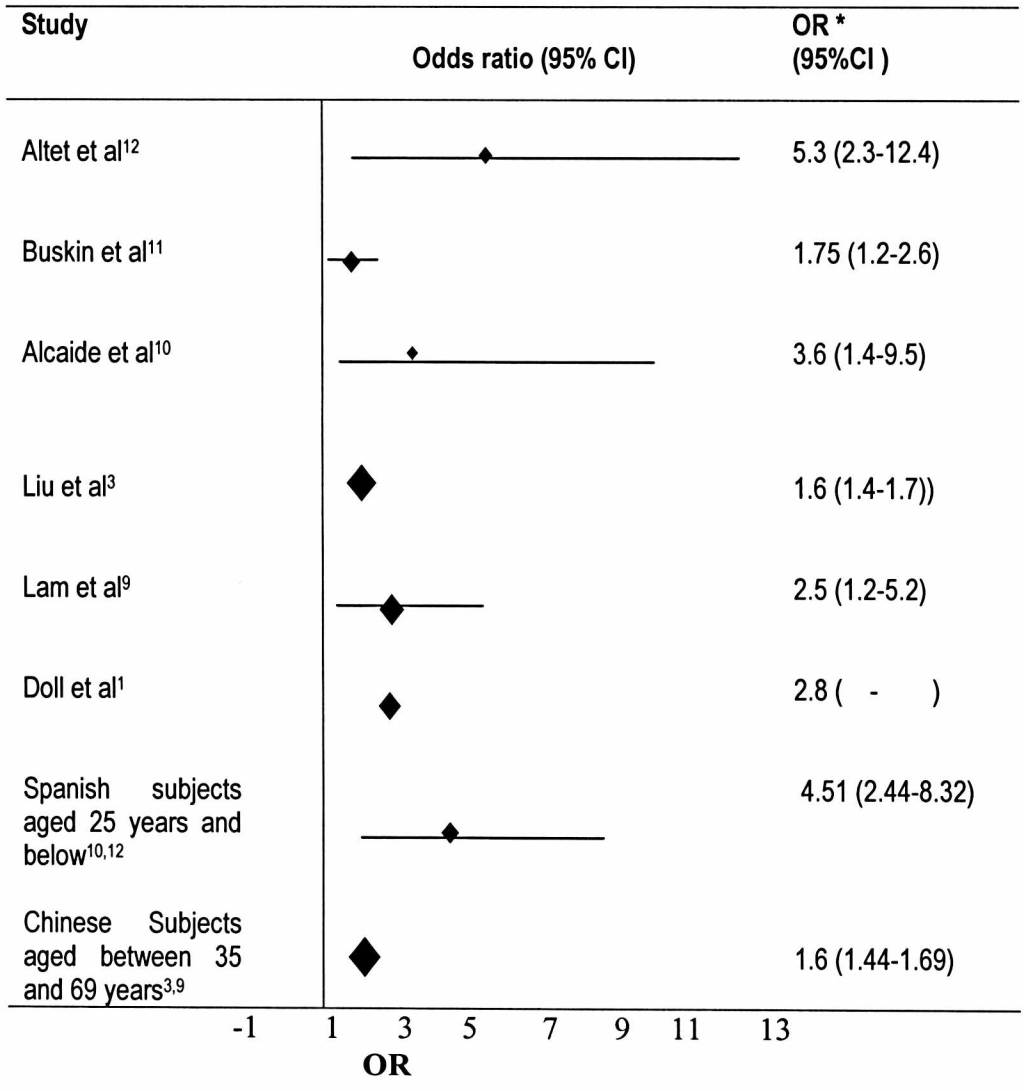
Table 3.4.5. Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB morbidity and tobacco smoking in Spanish subjects aged 25 years and below.

Study	Smokers	Non smokers	Wt (%)	OR (95%CI Fixed)
	PTB(yes/no)	PTB(yes/no)		
Altet et al[12]	83/58	10/37	56	5.3(2.3-12.4)
Alcaide et al[10]	33/19	13/27	44	3.6 (1.4-9.5)
		Mantel-Haenszel OR =		4.51 (2.44-8.32)
DerSimonian and Laird Q statistic=0.417, df=1, p-value >0.1. **THERE IS NO EVIDENCE OF HETEROGENEITY**				

Table 3.4.6 Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB mortality and tobacco smoking in Chinese subjects aged between 35 and 69 years.

Study	Smokers	Non smokers	Wt (%)	OR (95%CI Fixed)
	PTB(yes/no)	PTB(yes/no)		
Liu et al[3]	2371/18544	1003/12165	98.7	1.55 (1.4-1.7)
Lam et al[9]	36/841	11/639	1.3	2.5 (1.2-5.2)
		Mantel Haenszel OR =		1.56 (1.44-1.69)
DerSimonian and Laird Q statistic=1.81, df=1, p-value >0.1. **THERE IS NO EVIDENCE OF HETEROGENEITY**				

The Forest Plot shown in figure 3.4.1 shows differences in exposure effect estimates across studies. The diamonds represent ORs and RRs, while the lines across them represent 95% CIs. The size of each diamond roughly corresponds to the sample size in each primary study or subgroup of studies.



*The size of each diamond roughly corresponds to the sample size of each study or subgroup of studies.

Figure 3.4.1. Forest plot showing differences in exposure effect across primary studies and subgroups of studies included in the systematic review

The L'Abbe` plot in figure 3.4.2 shows heterogeneity in results of the 5 case-control studies. Each dot represents an individual study. The dotted diagonal line represents the line of equality of mortality or morbidity rates between smokers and non-smokers[30]. It can be seen that mortality or morbidity rates varied greatly among both non-smokers (2% to 33%) and smokers (4% to 65%) across studies. The study by Doll et al[1] was not included in the L'Abbe` plot because it was very different in design and was done in a very long period of time (1951 to 1991).

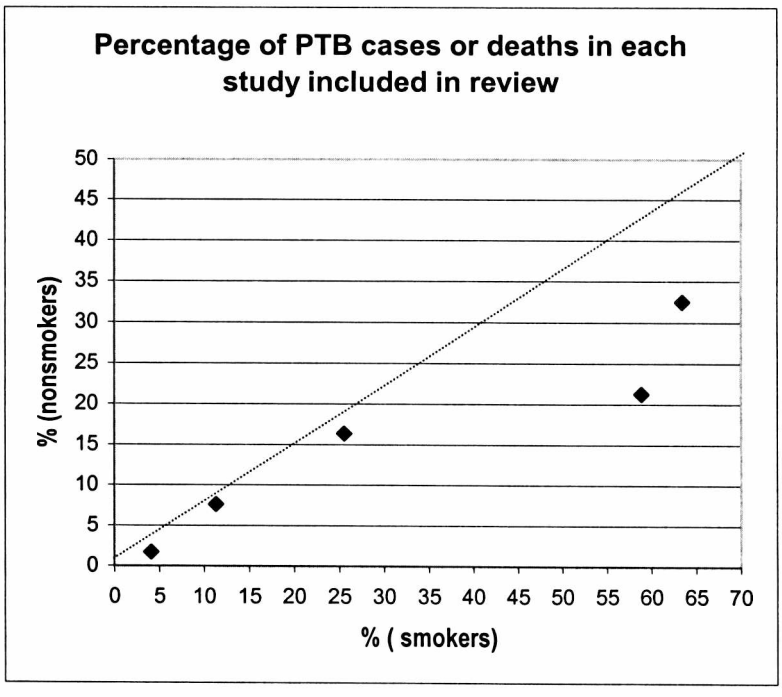


Figure 3.4.2. L'Abbe` Plot: Graphically showing heterogeneity of results across studies included in this systematic review.

4. DISCUSSION

4.1 HETEROGENEITY

This systematic review evaluated results of 6 studies, 5 case control studies and 1 cohort study on the association between tobacco smoking and PTB. The review found substantial heterogeneity across the six studies included in the systematic review. Heterogeneity across studies in estimates of exposure effect was statistical, methodological and clinical[30].

Statistical differences arose from different sample sizes and statistical models used. Studies with small samples resulted into lower precision of risk estimates as compared to those with large samples. This is evidenced by wider CIs for studies by Alcaide et al[10] and Altet et al[12] as compared to those by Liu et al[3], Lam et al[9] and Buskin et al[11], which had large numbers of subjects.

Sources of methodological heterogeneity included differences in techniques for measurement of exposure to tobacco smoke, inclusion and exclusion criteria, study design, objectives and the definition of cases and controls.

Clinical heterogeneity was a result of differences in participants' characteristics including age, race and possibly different types of tobacco.

Heterogeneity of results hampered sensible overall statistical pooling of results. As a result a qualitative summary was undertaken. However heterogeneity was further

assessed in subgroups of studies. Weighted estimates of ORs were determined in subgroups of studies using the Mantel Haenszel fixed effect model[26].

All studies in this review used different categories for levels of exposure to tobacco smoke (number of cigarettes/day or other categories). In addition, complete categorical data on exposure status for subjects of different sexes, social status groups, age groups and other confounders was not presented. This made it difficult to explore heterogeneity among studies across different strata of exposure and confounding variables. Some of exposure and confounder variable strata could be responsible for heterogeneity of results. Pooling of results could be done across exposure and confounder variable strata if these indicated no evidence of heterogeneity.

Published data was used to investigate heterogeneity of results. Age of participants, sample size, study methods, and geographical setting were some of major variables contributing to heterogeneity of results. The DerSimonian and Laird Q statistic revealed that Altet et al[12] and Alcaide et al[10] were measuring the same underlying exposure effect. Homogeneity in these studies may be explained by the similarity in methodology, study setting and a minor difference in age range.

Studies by Lam et al[9] and Liu et al[3] were also homogeneous. Reasons for this include similarity in objectives, methodology, study participants and definition of cases.

There was also no evidence of heterogeneity between studies by Busking et al[11] and Alcaide et al[10]. These studies were done in very different settings; USA and Spain,

respectively. Major similarities between these two studies were the case definition, method of recruiting controls and overlapping of age ranges of study participants.

Evidence of homogeneity across study sub-groups warranted the pooling of results. A Mantel Haenszel weighted odds ratios was determined other than calculating crude OR from pooled data to avoid treating data from individual studies as if it arose from a single study[31]. Averaging summary statistics ensured that cases and controls within each study were compared directly, and that consistency of results between studies could be investigated[31].

4.2 VALIDITY OF STUDIES INCLUDED IN THIS REVIEW

Selection Bias

Selection bias cannot be ruled out in all the case control studies in this review. The source population from where cases originated could be different from the population where controls came from. The case control study by Buskin et al[11] was clinic-based. Cases were PTB patients seeking clinic care. They enrolled patients seeking clinic care for other diseases as controls. The problem with selection of clinic-based controls is the possibility that they are not selected independently of exposure distribution in the source population[32]. Patients seeking care at the clinic could not be representative of the source population in terms of number of cigarettes smoked per day, previous exposure to tobacco smoke and duration of smoking, since they are not randomly selected[32]. Alcaide et al[10] and Altet et al[12] recruited contacts of diagnosed index PTB patients at the TB clinic as subjects for their respective studies.

Lam et al[9] and Liu et al[3] did not initially design their studies to assess the relationship between tobacco and TB, but to look at all causes of deaths attributed to tobacco. Attention in these studies was likely much focussed on selection of appropriate controls for main neoplastic and vascular diseases such as lung cancer, liver cancer, stroke and ischaemic heart disease. PTB only contributed 5 % of all causes of deaths attributed to tobacco in the study by Liu et al[3] and less than 1% in the study by Lam et al[9].

Measurement bias

Exposure misclassification is a problem in case control studies. It is likely in case control studies to get differential exposure information for cases and controls; with more accurate information gathered for cases (on smoking habits for instance). All studies in this systematic review used questionnaires and interviews to collect exposure data. In addition to use of questionnaires, Altet et al[12] and Alcaide et al[10] collected information on exposure by measuring urinary concentration of cotinine (ng/ml) in cases and controls to validate exposure data. Lam et al[9] and Liu et al[3] gathered data on smoking habits 10 years before deaths of subjects occurred. Collecting information on smoking habits practiced 10 years later could be difficult. However it is worth endeavouring so that latency of exposure is taken into account. Reporter bias might have been minimised by Lam et al[9], because informants were blinded on the variables of prime interest (smoking habits). Furthermore Lam et al[9] minimized recall bias by using living controls unlike Liu et al[3] who used dead controls. In the study by Liu et al[3] informants for patients who died of PTB are more likely to give more information on the smoking habits of the subject than those whose

relatives/friends died of other conditions such as injuries. However Liu et al[3] reported that information on smoking habits for 453 deaths in Shanghai, one of Chinese counties included in their study, was not different from that collected in a previous study despite differences in types of informants[3].

Confounding

All studies in this systematic review used multivariate analysis to determine ORs or RRs and to control for confounding variables. Univariate analysis on the association under study can be misleading since it can give false significant ORs. However in the study by Altet et al[12], crude OR=5.3 was not significantly different from an adjusted OR=5.4 (adjusted for sex, age, SES, crowding). This shows that sex, age, SES and crowding did not have significant confounding effects in this primary study. Similarly Alcaide et al[10] reported a crude OR=3.6, which was equal to an adjusted OR=3.6, whereby sex, age and SES were controlled for. Though some studies did not control for important confounders such as HIV/AIDS and alcohol consumption, findings were similar across studies, in terms of direction of the association between tobacco smoke and PTB.

Alcohol is an important risk factor for PTB and may be related to other risk factors for PTB such as poor eating habits, tobacco and homelessness[11,22]. Misclassification of this exposure could result in false associations between PTB and other factors including tobacco smoking and homelessness. Apart from studies by Buskin et al[11], Doll et al[1] and Altet et al[12] (Altet et al did not need to control for alcohol) the rest did not indicate adjusting for alcohol in the analysis. Buskin et al[11] who adjusted for alcohol indicated that tobacco was a significant risk factor for PTB in subjects who

smoked for durations of greater than 20 years[11]. However studies that did not control for alcohol indicated that tobacco smoking was a risk factor even in smokers of durations of less than 10 years[3,9,10]. This shows that differences in adequacy of controlling for major confounders across studies can lead to different results. Buskin et al[11] demonstrated that false associations might be observed between tobacco smoking and disease due to confounding. They also showed that tobacco works synergistically with alcohol in their roles as risk factors for tuberculosis; a finding also reported by Birong et al.[21.]

Since Lam et al[9], Liu et al[3] and Doll et al[1] aimed at investigating all causes of mortality attributed to tobacco, collection of data on confounders specific to PTB was minimal. Controlling for confounding in these studies was however fair because logistic regression models and stratified data analysis methods were used to adjust for age, education, gender and number of cigarettes smoked per day[1,3,9].

4.3 STRENTH OF EVIDENCE OF A CAUSAL RELATION SHIP

Study design

Apart from the British cohort study the rest of studies in this review were case-control studies, which cannot give conclusive evidence on the casual relationship between tobacco smoke and PTB. However these studies gathered information that can be improved upon, and used to conduct high quality prospective studies. Studies in this review have highlighted risk groups for exposure to passive and active tobacco smoking who are also at a potential risk of developing PTB. Prospective studies can

be done to assess the risk of PTB among cohorts of children aged between 0 to 10 years old whose both parents smoke, or whose mothers or fathers smoke. Passive smoking is an important confounder when investigating the relationship between tobacco smoking and PTB. If passive smokers are included in the non-smokers category in a study investigating the relationship between PTB and tobacco there may be a dilution effect of the risk estimate (towards the null). Cohorts of active smokers who are exposed to passive smoking and those not exposed to passive smoking also need to be followed up to compare rates of development of PTB.

This review has assessed and noted study methods that can be used to get better results. These include use of PTB patients other than deaths, recruitment of tuberculin positive subjects especially for prospective studies, use of assay by gas-liquid chromatography to detect cotinine concentrations to accurately ascertain exposure to tobacco smoke,[33] use of cohort other than case-control designs, blinding of subjects on the variables of interest during interviews or in the questionnaires, collecting data on passive smoking and adjusting for it in analysis along with other important confounders.

All studies in this review were done in average and high-income countries. Prospective studies should also be done in low-income countries, where PTB incidence is high, to get an adequate number of PTB subjects. Prospective studies to be done in developed countries should enrol subjects that are tuberculin positive other wise reference groups could be people who are not at risk of developing PTB at all.

Dose response

All studies in this review demonstrated a dose response relationship between number of cigarettes smoked per day and PTB morbidity or mortality. Liu et al[3] showed that there was a dose response relationship between age when subject started smoking and the risk of dying from PTB[3]. Altet et al[12] observed that passive exposure both within and outside the home (whereby active smokers were family members) increased the risk of development of disease. Alcaide et al[10] revealed that the effect of both active and passive tobacco smoking result into higher risk than active smoking alone and passive smoking alone.

Temporality

The impediment in case control studies is that the conviction in the results is minimal because temporality cannot be confidently established. Alcaide et al[10] and Altet et al[12] enrolled incident cases that were contacts of index PTB patients seeking care at a TB clinic. Chances are high that exposure to tobacco smoke occurred prior to occurrence of PTB among those exposed. Lam et al[9] and Liu et al[3] gave an allowance of latency of exposure by getting information on dead persons' smoking habits 10 years before the date of mortality from PTB. Again it is likely that smoking occurred prior to development of PTB for cases that were smokers.

Consistency in results and strength of association

All studies in this systematic review gave consistent results though they were done in very different settings. All the studies showed a moderate relationship between

tobacco smoking and PTB. All of them statistically proved dose response relationships. Effects of exposure were however more pronounced in specific risk groups. However Birong et al[21] whose study was available in Chinese, and only the abstract was in English, reported that tobacco and alcohol were not independently associated with PTB. They indicated that tobacco smoking and alcohol had a joint relationship with PTB as reported in section 1.3.4, page17 of this review.

Alcaide et al[10] reported a much stronger association for daily smokers who were also exposed to passive smoking, OR=5.6 (95% CI 2.07 to 15.10). Altet et al[12] indicated a very strong association in children aged 0-4, exposed to passive smoking, OR=12 (95% CI 2.3 to 43.0) seconded by those aged 5-9 years, OR =10.2 (95% CI 1.1 to 62). Among those aged between 10 and 14, OR was 3.1 (95% CI 0.83 to 11.3), comparing those exposed and those not exposed to passive smoking. These ORs were obtained after adjusting for age, sex and father's social class using multiple logistic regression analysis. Exposure to passive smoking in children was also more significant when both parents were smokers, OR=7.4 (95% CI 2.81 to 20.09).

5. CONCLUSION AND RECOMMENDATIONS

TB is a global public health problem and is the leading cause of mortality among infectious diseases. The incidence of TB has increased in the majority of countries primarily due to its association with HIV/AIDS epidemic and other conditions including migration, homelessness, and poverty. Tobacco smoking has been cited as a risk factor for TB in several studies. Tobacco kills about 4 million people a year worldwide through respiratory diseases including PTB, various neoplastic and cardiovascular diseases. Seventy percent (70%) of deaths arising from tobacco smoking will occur in developing countries by early 2030s. However few studies worldwide have assessed the association between tobacco smoke and TB and most of them were conducted in middle and high-income countries. It is therefore recommended that further studies be done on the association between TB and tobacco smoking.

Prospective cohort studies in countries with high PTB incidence (for example Sub-Saharan Africa, some parts of Asia and Eastern Europe) would show more convincing results on the association under study. Similar prospective studies done in high-income developed countries should recruit tuberculin positive subjects. Such studies must have adequate sample sizes and should control for all major confounding variables including previous exposure to tobacco, height, weight, passive smoking, duration of exposure, alcohol consumption, health history, HIV/AIDS, homelessness and SES.

This systematic review is important because it provides added weight and confidence to arguments showing that tobacco smoking is associated with PTB. Currently the issue of the relationship between tobacco smoking and PTB is not resolved in the English literature. According to findings from this systematic review, the overall association is moderate, but strong for specific risk groups in different populations. These include children under 10 years, smokers of durations greater than 20 years, children whose both parents are smokers, people exposed to both passive and active smoking, heavy smokers, smokers who take alcohol and the poor.

6. APPENDIX

The DerSimonian and Laird approach was used to assess homogeneity across subgroups of studies[24]. Using this approach studies included in this systematic review were regarded as a sample from a population of possible studies with mean effect (μ) and a population variance (Δ^2). The population variance represents the degree to which exposure effects vary across studies. Constancy of exposure effect (homogeneity) was evaluated with the DerSimonian and Laird Q statistic. The test statistic Q is the sum of squares of deviations of exposure effect for each study (y) about the weighted mean effect estimator of studies included in meta-analysis ($\check{y}_{w)}$. The weighted mean ($\check{y}_{w)}$ may be regarded as a sample mean. The squares of the deviations are each multiplied by a weight (w), which is the reciprocal of each study's sampling variance of natural log OR [24,25].

Under the null hypothesis of constant effect across studies (Ho: $\Delta^2 = 0$), Q is regarded as a chi-square statistic with k-1 degrees of freedom, where k is the number of studies. A low p-value for this statistic indicates the presence of heterogeneity, which undermines the validity of pooled risk estimates. The cut off point of α=0.05 was used. ORs were combined using the Mantel-Haenszel fixed effect model[26] for subgroups that were found to be homogeneous. This model assumes the existence of a constant effect of exposure common to all studies included in a meta-analysis[26]. Calculations were done using Epi Info version 6c and Microsoft Excel computer packages.

Full meanings of headings of column in tables 6.1 through 6.5

(Tables 6.1 to 6.5 show how the Q statistic was calculated)

rt = proportion of PTB patients among smokers

rc = proportion of PTB patients among non-smokers

y = natural logarithm of OR ($\log_e$OR). It is the estimate of exposure effect in each study

variance =variance of the OR in the logarithmic scale (var($\log_e$OR))

w_i =inverse of variance of natural log OR, it is the weight for each study

$w_i y_i$ =the product of weight and $\log_e$ OR

$\check{y}$ = weighted estimator of exposure among studies in meta-analysis

$w_i(y_i-\check{y})^2$ = product of weight and squared deviation of each study's y from the weighted estimate ($\check{y}$) of exposure effect

$w\%$ = weight percent for each study

If number of smokers in each study = n_t

And non-smokers = n_c;

Variance of $\log_e$ OR can be estimated[24] as

$$S_l^2 = [n_{ti} r_{ti}(1-r_{ti})]^{-1} + [n_{ci} r_{ci}(1-r_c)]^{-1}$$

The weighted estimator[24] of treatment effect

$$\check{y} = \Sigma w_i y_i / \Sigma w_i$$

The Q statistic = $\Sigma w(yi- \check{y}_w)^2$

Table 6.1 Heterogeneity assessment across all studies included in this systematic review

Study	Smokers		Non-smokers		Crude								
	PTB	noPTB	PTB	noPTB	OR	r_t	r_c	y_i	variance	w_i	w%	$w_i y_i$	$w(y_i - \bar{y})^2$
Altet[12]	83	58	10	37	5.29	0.59	0.21	1.667	0.156	6.4	0.928	10.663	9.2079
Alcaide[10]	33	19	13	27	3.61	0.63	0.33	1.283	0.197	5.08	0.737	6.5159	3.3814
Buskin[11]	103	300	48	245	1.75	0.26	0.16	0.561	0.038	26.3	3.823	14.78	0.2328
Liu[3]	2371	18544	1003	12165	1.55	0.11	0.08	0.439	0.002	643	93.32	282.16	0.5139
Lam[9]	36	841	11	639	2.49	0.04	0.02	0.911	0.121	8.23	1.195	7.5011	1.6228
Doll[1]	44	4	-	-	-	0.92	-	-	-	-	-	-	-
TOTAL										**689**		**321.62**	**14.959**

Table 6.2 Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB mortality and tobacco smoking in Chinese subjects aged between 35 years to 69 years.

Study	Smokers		Non-smokers		Crude								
	PTB	noPTB	PTB	noPTB	OR	r_t	r_c	y_i	variance	w_i	w%	$w_i y_i$	$w_i(y - \bar{y})^2$
Liu[3]	2371	18544	1003	12165	1.551	0.113	0.076	0.439	0.00155	643.13	98.736	282.16	0.0253
Lam[9]	36	841	11	639	2.487	0.041	0.017	0.911	0.12144	8.2345	1.2642	7.5011	1.7877
TOTAL										**651.36**		**289.66**	**1.8129**

Table 6.3 Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB morbidity and tobacco smoking in subjects of all ages

Study	Smokers		Non-smokers		Crude								
	PTB	noPTB	PTB	noPTB	OR	r_t	r_c	y_i	variance	w_i	w%	$w_i y_i$	$w_i(y - \bar{y})^2$
Altet[12]	83	58	10	37	5.29	0.59	0.21	1.6667	0.156317	6.4	17	10.66	4.3197
Alcaide[10]	33	19	13	27	3.61	0.63	0.33	1.283	0.196895	5.08	13	6.516	0.974153
Buskin[11]	103	300	48	245	1.75	0.26	0.16	0.561	0.037957	26.3	70	14.78	2.124873
TOTAL										**37.8**		**31.96**	**7.418726**

Table 6.4 Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB morbidity and active tobacco smoking in subjects aged 17 years and above.

Study	Smokers		Non-smokers		Crude								
	PTB	noPTB	PTB	noPTB	OR	r_t	r_c	y_i	variance	w_i	w%	$w_i y_i$	$w_i(y-\check{y})^2$
Alcaide[10]	33	19	13	27	3.607	0.63	0.33	1.283	0.1969	5.079	16.16	6.516	1.85872
Buskin[11]	103	300	48	245	1.752	0.26	0.16	0.561	0.038	26.35	83.84	14.78	0.36062
TOTAL										**31.42**		**21.3**	**2.21934**

Table 6.5 Heterogeneity assessment and meta-analysis of case-control studies investigating the association between PTB morbidity and tobacco smoking in Spanish subjects aged 25 years and below

Study	Smokers		Non-smokers		Crude								
	PTB	noPTB	PTB	noPTB	OR	rt	rc	y_i	variance	w_i	w%	$w_i y_i$	$w(y-\check{y})^2$
Altet[12]	83	58	10	37	5.295	0.59	0.213	1.6667	0.156	6.4	55.7	10.66	0.17784
Alcaide[10]	33	19	13	27	3.607	0.635	0.325	1.283	0.197	5.08	44.3	6.516	0.23926
TOTAL										**11.5**		**17.18**	**0.41709**

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