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REVIEW ARTICLE

Tobacco and tuberculosis: a qualitative systematic review and meta-analysis

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SUMMARY

OBJECTIVES: To assess the strength of evidence in published articles for an association between smoking and passive exposure to tobacco smoke and various manifestations and outcomes of tuberculosis (TB). Clinicians and public health workers working to fight TB may not see a role for themselves in tobacco control because the association between tobacco and TB has not been widely accepted. A qualitative review and meta-analysis was therefore undertaken.

METHODS: Reference lists, PubMed, the database of the International Union Against Tuberculosis and Lung Disease and Google Scholar were searched for a final inclusion of 42 articles in English containing 53 outcomes for data extraction. A quality score was attributed to each study to classify the strength of evidence according to each TB outcome. A meta-analysis was then performed on results from included studies.

RESULTS: Despite the limitations in the data available, the evidence was rated as strong for an association between smoking and TB disease, moderate for the association between second-hand smoke exposure and TB disease and between smoking and retreatment TB disease, and limited for the association between smoking and tuberculous infection and between smoking and TB mortality. There was insufficient evidence to support an association of smoking and delay, default, slower smear conversion, greater severity of disease or drug-resistant TB or of second-hand tobacco smoke exposure and infection.

CONCLUSIONS: The association between smoking and TB disease appears to be causal. Smoking can have an important impact on many aspects of TB. Clinicians can confidently advise patients that quitting smoking and avoiding exposure to others' tobacco smoke are important measures in TB control.

KEY WORDS: tuberculosis; smoking; second-hand smoke; risk factors

A HIGH PREVALENCE of tobacco use has been noted since 1918 in studies looking at risk factors for tuberculosis (TB).[1] However, the association between smoking and TB has rarely been highlighted, and clinical case management of TB does not emphasise this association. Reluctance to attribute causality to tobacco exposure is based on methodological issues, such as lack of adjustment for important confounders or misclassification of patients due to poor standards for establishing TB outcomes,[2,3] and this has led to an assumption that appropriate care for TB does not require action related to tobacco use. Tobacco control experts have noted the poor quality or absence of assessment of tobacco exposure in investigations of risk factors for TB outcomes. A systematic review was therefore undertaken to weigh the strength and quality of the evidence of a causal association between exposure to tobacco smoke and various manifestations and outcomes of TB.

METHODOLOGY FOR THE SYSTEMATIC REVIEW*

Selection of articles

Two researchers independently examined titles of published English language journal articles on tobacco exposure and TB in PubMed for all years from 1954 to July 2005, using the key words 'tuberculosis' and 'smoking', 'tobacco' or 'cigarettes'. A database of over 14 000 articles about TB from 1918 to July 2005 developed for staff of the International Union Against Tuberculosis and Lung Disease (The Union) was then searched using the database classification key words 'smoking', 'risk factors', 'predictors', 'case management', 'death', 'defaulters', 'definitions', 'delay' and 'indicators'. Reference lists from publications were

* A report of the full systematic review is available from the WHO Stop TB programme.

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examined for other relevant titles, and Google Scholar was then consulted under the terms 'TB and smoking'. Identified citations were then more fully examined if the title or abstract indicated possible relevance, and their full texts were screened for inclusion according to pre-established criteria. Each article chosen for inclusion was reviewed for data extraction by three independent reviewers.

Inclusion criteria

Articles in all languages were collected and examined for coherence with English language studies, but only published journal articles in the English language were included. Cohort, case-control or cross-sectional studies providing effect estimates of exposure to tobacco smoke in relation to TB outcomes were selected for inclusion. The TB outcomes of interest were infection, TB disease, recurrent TB, treatment outcome indicators (delay, default, slower smear conversion, severity of disease, drug-resistant TB), TB death during or after treatment and TB mortality. Selected articles were reviewed for information on the country of study, sample size, population source, age and sex.

Definitions

The following definitions were determined by the reviewers based on their experience and knowledge of best practice.

Tobacco exposure

Tobacco smoke exposure was measured according to one or more of the following: type of exposure (active and/or passive), current and past exposure, duration and frequency of exposure and age at initial exposure. The best measures for determining reported tobacco use were defined as biochemical validation of self-report for active smoking: exhaled carbon monoxide >8 parts per million or cotinine unless nicotine replacement medication was used, and cotinine for passive exposure. Self- or family-reported exposure was considered an acceptable measure. A failure to provide an explanation of how exposure to tobacco was determined was considered unacceptable and led to a lower quality score.

Outcome measures

Tuberculin skin test reaction at a specified cut-off of induration size was considered the best measure for tuberculous infection. Sputum smear positive for acid-fast bacilli and/or culture positive for *Mycobacterium tuberculosis* was considered the best measure for TB disease. An acceptable measure included clinical, radiological or histological diagnosis in addition to an appropriate response to anti-tuberculosis treatment. Retreatment TB was defined as the retreatment of active TB in a patient who was previously demonstrated to be cured of the disease. An acceptable measure of TB death during or after treatment was defined as dying with verified TB, as defined above. For mortality studies, death certificate notification, medical records or family interviews were considered acceptable sources of information. Their designation as 'acceptable' rather than 'best' measures was due to clear evidence of substantial error in routine reports of Vital Statistics Registers concerning mortality designated as being due to TB.[4–6]

Procedures

A steering committee* was invited to oversee the protocol and the final report, and to approve the procedure for review and the criteria for quality assessment. Each article received three independent reviews.

Each article was rated for quality on the 25 items presented in Table 1. All items were judged either to be present, or, if they were unreported or badly reported, to be absent. If unsure, the reviewer was to mark absent. Quality items that could not be provided according to the study design (e.g., follow-up in cross-sectional studies) were considered 'not applicable' for assessment. In all cases, a majority assessment was obtained. Quality scores were determined by the proportion of items that were present from all those applicable. The articles whose scores were above the mean of scores were considered to be high quality.

Strength of evidence for each TB outcome was determined according to the following criteria:

- Strong evidence: consistent findings in at least two high-quality cohort studies and in multiple case-control studies
- Moderate evidence: consistent findings in one high-quality cohort study and two high-quality case control studies or three or more high-quality case control studies
- Limited evidence: consistent findings in a single high-quality cohort study or two high-quality case-control studies or at least three high-quality cross-sectional studies
- Not enough evidence: the above conditions are not met
- Conflicting evidence: less than 75% of the studies report consistent findings.

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Table 1 Items for quality assessment

1 Study population
  a. Cases and controls were drawn from the same population.
  b. Covariates were designated.
  c. Eligibility criteria were specified.
  d. Attrition rate was similar in each group in cohorts.
2 Assessment of exposure to tobacco smoke
  a. Smoking status was defined.
  b. Smoking status was validated by more than self-report.
  c. Quantity consumed was measured.
  d. Duration of use was measured.
  e. Those who assessed smoking status did not know the TB outcome.
3 Assessment of passive smoking
  a. Passive smoking exposure was clearly defined.
  b. A valid measurement was used to determine passive exposure.
  c. Non-exposure was unlikely to be misclassified.
4 Assessment of TB outcome
  a. A valid definition was used for the TB outcome.
  b. Assessment of the outcome was reproducible.
  c. A valid measurement of the TB outcome was used.
  d. Those who assessed the TB outcome did not know the individual's tobacco use history.
5 Study design
  a. The design was adequate to measure an association.
  b. Information was given about those lost to follow-up.
  c. Effect of co-variables was measured.
  d. Follow-up was long enough for outcomes to occur.
  e. Results were consistent with data.
6 Analysis and data presentation
  a. Appropriate analysis was performed.
  b. Dose-effect calculations were made.
  c. Adjustment for confounders was presented.
  d. Importance of loss to follow-up on outcomes was described.

TB = tuberculosis.

RESULTS OF THE QUALITATIVE REVIEW

The search for articles in PubMed yielded 718 articles. The search of the Union database of TB articles found 959 articles, of which 202 were duplicates of those already identified, for a total of 1475 published articles. Google Scholar yielded over 9000 entries, including many duplicates and unusable entries; from that search and from reference lists, 388 interesting titles were added, for a final list of 1863 references. From that list, the full texts of 192 articles were chosen and screened for inclusion according to inclusion criteria. A final selection of 42 articles contained 53 studies for data extraction.

Associations

None of the studies showed a protective effect of active or passive smoking on TB outcomes. Forty-six (87%) of the studies included in the systematic review showed a significant effect of tobacco smoke exposure on a TB outcome: 8/8 studies showed increased risk for infection, 22/24 for disease, 2/3 for retreatment TB, 1/2 for patient delay, 2/2 for default, 1/3 for smear conversion, 2/2 for drug-resistant TB, 1/2 for death during or after treatment and 5/5 for mortality. Among all 53 studies, 14 found a dose-effect relationship, 19 found a coherent effect and 13 found limited or partial effects. Seven of the 53 studies found no significant effect. Table 2 provides summarised effects based on the qualitative analysis. Table 3 gives an overview of the studies and effect ratios found.

Tuberculous infection

All of the studies of infection found significant effects of exposure to tobacco,[7–14] seven for smoking and one for second-hand exposure to tobacco smoke. The high-quality studies were also considered to have used the best measure for assessing infection.[7–9,12,13] None of the studies used best measures for assessing exposure to tobacco smoke.

Tuberculosis disease

Twenty-two of the 24 studies looking at new and/or retreatment TB disease found a significant relationship between exposure to tobacco smoke and disease.[15–36] Nineteen studies of new disease found significant associations with active exposure.[15–18,20–28,30–35] Of the four studies of new disease with significant effects for passive exposure,[19,20,28,29] odds ratios (ORs) ranged from 2.3 (95% confidence interval [CI] 1.3–4.2) to

Table 2 Significant associations between active and passive tobacco smoke exposure and TB outcomes by study type

			Studies that show a significant association							
				Cohort studies		Case-control studies		Cross-sectional studies		
TB outcome	Tobacco smoke exposure	Total number of studies	*n*	High quality	Other	High quality	Other	High quality	Other	Strength of evidence
Infection	Active	7	7	—	—	1	—	3	3	Limited
	Passive	1	1	—	—	—	—	1	—	Not enough
TB disease	Active	19	18	2	1	6	6	2	1	Strong
	Passive	5	4	—	—	3	1	—	—	Moderate
Retreatment TB	Active	3	2	2	—	—	—	—	—	Moderate
Treatment delay	Active	2	1	—	—	—	—	—	1	Not enough
Default	Active	2	2	—	—	1	1	—	—	Not enough
Smear conversion	Active	3	1	—	—	—	—	—	1	Not enough
Severity of TB	Active	2	2	—	—	1	1	—	—	Not enough
Drug-resistant TB	Active	2	2	—	—	—	1	1	—	Not enough
Death after treatment	Active	2	1	1	—	—	—	—	—	Not enough
TB mortality	Active	5	5	—	1	2	2	—	—	Limited

Table 3 Overview of studies

Reference, author, year	Country, setting	Study design	High quality (x = yes)	Adjusted tobacco effect ratio[1]	(95%CI)	Sample size *n*	Age range years	Male participants %
Tuberculous infection and active smoking								
7 Anderson et al., 1997	USA, prisons	Case-control	x	>15 years' smoking	OR 2.12 (1.03–4.36)	233	7–57	95
				Current smoking	OR 1.78 (0.98–3.21)*			
8 Den Boon et al., 2005	South Africa, high-risk urban community	Cross-sectional	x	<5 p-y smoked	OR 1.77 (1.33–2.35)*	2 347	⩾15	38
				5–15 p-y smoked	OR 1.77 (1.25–2.5)			
				>15 p-y smoked	OR 1.90 (1.28–2.81)			
9 Hussain et al., 2003	Pakistan, prisons	Cross-sectional	x	1–5 cigarettes/day	OR 2.6 (1.6–4.4)	425	18–60	100
				6–10 cigarettes/day	OR 2.8 (1.6–5.2)*			
				>10 cigarettes/day	OR 3.2 (1.3–8.2)			
10 McCurdy et al., 1997	USA, migrant farm workers	Cross-sectional		Current smoker	OR 1.87 (0.73–4.8)*	269	All ages	41
				Ex-smoker	OR 3.11 (1.20–8.09)			
11 Nisar et al., 1993	UK, nursing home	Cross-sectional		Unadjusted	OR 1.59	2 635	22–104	25
12 Plant et al., 2002	Australia, Vietnamese immigrants	Cross-sectional	x	Ever-smokers	OR 1.53 (1.13–2.09)*	1 395	16–81	24
14 Solsona et al., 2001	Spain, homeless persons	Cross-sectional			OR 1.72 (1.02–2.86)	447	14–69	88
Tuberculous infection and passive smoking								
13 Singh et al., 2005	India, children of parents with TB	Cross-sectional	x		OR 2.68 (1.52–4.71)	28	<5	54
TB disease and active smoking								
15 Chang et al., 2001	Hong Kong, China, silicotics	Cohort	x	Pack-years	RR 1.012 (1.005–1.019) $p = 0.019$	707	29–84	99
16 Hnizdo and Murray, 1998	South Africa, white goldminers	Cohort		Pack-years	OR 1.02 (1.01–1.03)	115	45–83	100
17 Leung et al., 2004	Hong Kong, China, elderly persons	Cohort	x	Current	HR 2.87 (2.00–4.11)*	42 659	⩾65	73
				Ex	HR 1.39 (0.98–1.97)*			
18 Alcaide et al., 1996	Spain, young adults exposed to TB	Case-control	x		OR 3.6 (1.5–2.2)*	92	15–24	52
				Daily and passive	OR 5.6 (2.1–15.1)			
20 Ariyothai et al., 2004	Thailand, adults	Case-control	x	Current	OR 2.70 (1.04–6.97)*	128	⩾15	63
				Ex	OR 2.88 (0.85–9.78)*			
21 Buskin et al., 1994	USA, adults	Case-control	x	>30 years' smoking	OR 2.6 (1.1–5.9)	696	⩾17	~50
				Current	OR 1.3 (0.8–2.1)			
				Ex	OR 1.4 (0.8–2.5)			
22 Crampin et al., 2004	Malawi, adults	Case-control	x	1–4 cigarettes/day	OR 0.9 (0.5–1.7)	606	⩾15	46
				5+ cigarettes/day	OR 1.3 (0.7–2.4)*			
				Ex	OR 1.6 (0.7–3.2) (2nd adjust.)*			
				Ex	OR 1.9 (1.1–3.5) (1st adjust.)			
23 Kolappan and Gopi, 2002	India, adult villagers	Case-control	x		OR 2.24 (1.27–3.94)*	544	20–50	100
24 Leung et al., 2003	Hong Kong, China, adults	Case-control		Age <65 years	OR 2.13 (1.46–3.11)*	8 686	⩾15	50
25 Lienhardt et al., 2005	Guinée, Guinea Bissau, Gambia, adults	Case-control		Current	OR 2.03 (1.22–3.39)*	1 376	⩾15	56
				Ex	OR 1.53 (1.11–2.10)*			
26 Miguez-Burbano et al., 2003	USA, HIV+ patients	Cross-sectional		>20 years' smoking	3x (OR 3)	39	32–54	58
27 Perez-Padilla et al., 2001	Mexico, health care	Case-control			OR 1.5 (1.0–2.3)*	833	Adults	52
28 Tekkel et al., 2002	Estonia, adults	Case-control		Current	OR 4.62 (2.44–8.73)*	492	⩾15	72
				Ex	OR 2.27 (1.00–5.14)*			
30 Tocque et al., 2001	UK, adults	Case-control	x	⩾30 years' smoking	OR 2.3 (1.2–4.2)	310	Adults	55
				Current	OR 2.33 (1.40–3.88)*			
31 Toledo et al., 2000	Brazil, HIV+ patients	Case-control			Unadjusted OR 1.3 (1.0–1.6)*	477	16–61	91
32 Adelstein and Rimington, 1967	UK, mass X-ray volunteers	Cross-sectional	x	⩾20 cigarettes/day	OR 6.26 (3.04–12.89)	73 287	⩾15	57
				Current (vs. never)	OR 4.55 (2.4–8.64)*			
				Ex (vs. never)	OR 2.34 (0.95–5.76)*			
				Ever (vs. never)	OR 4.13 (2.18–7.82)*			
				Current (vs. not)	OR 3.40 (2.06–5.63)			

33 Gajalakshmi et al., 2003	India, adults	Cross-sectional			RR 2.9 (2.6–3.3)	235 101	35–65	100
34 Shah et al., 2003	Pakistan, young adults in prison	Cross-sectional			OR 1.59 (0.44–5.37)*	75	15–23	100
35 Yu et al., 1988	China, adult sanitary workers	Cross-sectional	x		OR 2.17 (1.29–3.63)*	30 289	⩽30–⩾50	57
TB disease and passive smoking								
18 Alcaide et al., 1996	Spain, young exposed to TB	Case-control	x		OR 2.5 (1.0–6.2)*	92	15–24	52
19 Altet et al., 1996	Spain, children exposed to TB	Case-control	x		OR 5.21 (2.31–12.62)*	188	0–14	51
20 Ariyothai et al., 2004	Thailand, adults	Case-control	x		OR 2.37 (0.94–6.01)*	128	⩾15	63
				>3 times/week	OR 4.26 (1.47–14.51)			
28 Tekkel et al., 2002	Estonia, adults	Case-control			OR 2.31 (1.25–4.24)	492	⩾15	72
29 Tipayamongkholgul et al., 2005	Thailand, children + BCG	Case-control	x		OR 9.31 (3.14–27.58)	260	<15	Matched for sex
Recurrent TB and active smoking								
36 Thomas et al., 2005	India, PTB patients	Cohort	x		OR 3.1 (1.6–6.0)	503	<45; ⩾45	76
17 Leung et al., 2004	Hong Kong, elderly	Cohort	x		OR 2.48 (1.04–5.89)	42 659	⩾65	73
24 Leung et al., 2003	Hong Kong, adults	Case-control		ns		8 686	⩾15	50
Delay and active smoking								
37 Altet-Gomez et al., 2005	Spain, TB patients	Case-control	x	ns		13 038	⩾14	68
38 dos Santos et al., 2005	Brazil, TB patients	Cross-sectional		Stopped smoking	OR 0.58 (0.43–0.79)	1 105	⩾18	67
Severity of TB disease and active smoking								
24 Leung et al., 2003	Hong Kong, adults	Case-control			OR 1.76 (1.18–2.63)	8 686	⩾15	50
37 Altet-Gomez et al., 2005	Spain, TB patients	Case-control	x		OR 1.9 (1.6–2.3)	13 038	⩾14	68
Smear conversion and active smoking								
39 Abal et al., 2005	Kuwait, TB patients	Cohort			OR 0.47 (0.21–1.06)	339	All ages	79
24 Leung et al., 2003	Hong Kong, adults	Case-control			OR 0.89 (0.21–3.77)	8 686	⩾15	50
40 Durban Immunotherapy Trial Group, 1999	TB patients	Cross-sectional		Smoking	HR 0.58 (0.40–0.84)	347	18–65	70
Drug-resistant tuberculosis disease and active smoking								
41 Barosso et al., 2003	Brazil, TB patients	Case-control			OR 3.01 (1.4–7.1)	319	$\bar{x}$ = 40, 41	62
42 Ruddy et al., 2005	Russia, MDR-TB patients	Cross-sectional	x	Resistance to H	OR 3.3 (1.2–9.2)	600	⩾18	93
Default and active smoking								
43 Chang et al., 2004	Hong Kong, China, TB patients	Case-control	x	Current	OR 3.44 (1.81–6.53)*	408	15–90	86
				Ex	OR 2.48 (1.09–5.64)*			
44 Salami et al., 2003	Nigeria, TB patients	Cross-sectional			Unadjusted OR 1.61 (1.31–1.98)	1 530	⩾15	52
Death during or after treatment for TB disease and active smoking								
17 Leung et al., 2004	Hong Kong, elderly	Cohort	x	Men	OR 4.66 (1.20–18.0)	42 659	⩾65	73
37 Altet-Gomez et al., 2005	Spain, TB patients	Cohort		ns		13 038	⩾14	68
Tuberculosis mortality and active smoking								
45 Doll, UK, 1999	British male doctors' mortality	Cohort		>25 cigarettes/day	RR 5.0	34 000	⩾35	100
33 Gajalakshmi et al., 2003	India, mortality records	Case-control		Urban	OR 4.5 (4.0–5.0)*	78 000	⩾25	100
				Rural	OR 4.2 (3.7–4.8)*			
46 Lam et al., 1998	China, mortality reports	Case-control	x	Men 35–69 years	OR 2.54 (1.24–5.22)*	40 561	⩾35	47
47 Liu et al., 1999	China, mortality reports	Case-control	x	Urban	OR 1.42 (1.33–1.52)*	275 616	35–69	61
				Rural	OR 1.1 (1.09–1.25)*			
48 Sitas et al., 2004	South Africa, death certificate	Case-control			OR 1.61 (1.23–2.11)*	5 341	⩾25	55

* Selected example, OR used in exposed vs. non-exposed meta-analysis.
CI = confidence interval; OR = odds ratio; p-y = pack-years; TB = tuberculosis; RR = relative risk; HR = hazard ratio; HIV = human immunodeficiency virus; BCG = bacille Calmette-Guérin; PTB = pulmonary tuberculosis; ns = non-significant; MDR-TB = multidrug-resistant tuberculosis; H = isoniazid.

9.3 (95%CI 3.14–27.58). Best measures of new disease were used to assess TB in eight studies.[15,17–20,22,23,25] Twelve studies were considered to be of high quality.[15,17–23,29,30,32,35] Two high-quality studies found significant associations of retreatment TB with active smoking.[17,36] No studies used best measures to assess exposure to tobacco.

TB characteristics and case management

There were not enough studies of treatment characteristics and case management to be considered to show evidence of an association. Of the 11 studies examined,[24,37–42] seven found significant association with tobacco use. Three of the four high-quality studies: diagnostic and treatment delay,[37] severity,[37] drug resistance[42] and default,[43] found significant associations with tobacco use, and two of the three studies that used best measures for identifying TB outcomes[39,40,44] found significant associations. None of the studies used best measures for assessing exposure to tobacco.

Death during and after treatment and mortality

One high-quality study of death during or after treatment found an association,[17] and another did not.[37] Five studies investigated the role of exposure to tobacco smoke and TB mortality in large data sets.[33,45–48] All of the studies showed strong associations between smoking and TB mortality. None of the studies used either best measure of disease or best measure to assess exposure to tobacco.

Potential confounders

Alcohol and tobacco

Two studies of tuberculous infection[7,14] and 10 studies of TB disease[17,20–22,24–26,28,30,31] measured both tobacco use and alcohol use; three of these studies did not evaluate alcohol as a risk factor for disease,[17,24,26] but one adjusted for alcohol use in determining the significant effect of tobacco.[17] Both of the studies of infection found a significant effect for alcohol use. One did not control for alcohol in the adjusted rate for tobacco,[7] and the other found an effect for tobacco but no effect for alcohol in multivariate analysis.[14] In the studies of disease, all 10 studies that measured alcohol found an unadjusted association between tobacco use and TB disease, and the association remained significant in nine studies (90%) after adjustment for other variables,[17,20–22,24–26,28,30] although in one study, the effect of tobacco did not remain in a second adjustment for the human immunodeficiency virus (HIV).[22] Three of the seven studies that investigated alcohol use as a risk factor for TB disease did not find a significant effect in univariate analysis,[21,25,31] while another found a significant association in univariate analysis but the significance was lost in multivariate analysis.[30] All four studies that adjusted for alcohol[17,20,21,30] found a significant adjusted effect for tobacco.

Tobacco and poverty

Level of education or income were the most frequent indicators of socio-economic class, but other indicators measured included type of residence, ownership and number of persons per room. Twenty-one studies in this review which found an independent effect for exposure to tobacco smoke also examined the independent effect of at least one measure of socio-economic status; 15 studies adjusted for the socio-economic measure that was significantly related to the TB outcome.[9,17–20,25–30,33,35,46,48] The other six studies did not show a significant adjusted effect for the socio-economic measure investigated.[8,10,12,21,22,32]

Tobacco and sex

Five studies included only men.[16,23,33,34,45] Another six studies had samples matched,[28,29,43] stratified[24] or standardised on sex.[21,48] In 10 populations studied, male sex was found to be a risk factor for the TB outcome measured.[7,8,11,12,14,25,35,37,42,44] In 14 other studies, sex was not found to be a risk factor for the TB outcome.[10,13,15,18,19,21,22,27,30,31,36,38,40,41] Of the studies that adjusted for sex on the TB outcome, 20 found significant excess risks for tobacco use.[7,8,10,14,15,17,18,19,24,26–28,30,32,35,37(severity),43,40–42] Seven of the studies reported the impact of tobacco on the TB outcome according to sex,[17,24,32,35,46–48] and five of them found excess risks for both men and women.[24,32,35,47,48]

Tobacco and human immunodeficiency virus

Eleven studies measured HIV status as a risk factor,[7,20–22,25,37,38,41–44] and of the three that found an increased risk from HIV, two found that tobacco use had an independent risk after adjustment for HIV.[25,42] Two other studies investigated only HIV-infected cases, both of which found a significant effect for smoking.[26,31]

Quality assessment for determining levels of evidence

Results of quality assessment are presented in Table 2. The range of possible scores is 0–100. The mean score for studies of infection was 76.3, for studies of disease 76.5, for studies of death or mortality 74.1 and for disease characteristics and case management issues 66.7. Using the quality assessment procedure, the conditions are met for the following levels of evidence of a causal relationship between active smoking or passive exposure to tobacco smoke and the measured TB outcomes. Table 2 summarises the following results.

Strong evidence

- Smoking and TB disease: two high-quality cohort studies, six high-quality case-control studies and two high-quality cross-sectional studies each show at least one statistically significant relationship between TB disease and active exposure to tobacco smoke; six of the above studies show a dose effect.

Eight of nine other studies also show significant effects.

Moderate evidence

- Second-hand exposure to tobacco smoke and TB disease: three high-quality and one other case control study found significant associations between passive exposure to tobacco smoke and TB disease.
- Smoking and retreatment TB: two high-quality cohort studies found an effect of smoking on relapse and retreatment. One other study did not identify an association.

Limited evidence

- Smoking and infection: one high-quality case-control study and three high-quality cross-sectional studies show high ORs for infection among those exposed actively to tobacco smoke. Three other studies also show an effect.
- Smoking and mortality: two high-quality case-control studies show significant ORs for smokers compared to non-smokers of mortality from TB, as do the three other studies looking at the issue of mortality.

Not enough evidence

According to pre-established criteria, there is insufficient evidence from the material reviewed for measuring an effect of passive smoking on infection or active tobacco smoking on the following outcomes:

- Default: two studies showed a significant association
- Drug-resistant TB: two studies showed significant effects
- Severity of disease: two studies showed significant effects
- Diagnosis and treatment delay: one study showed a significant association, the other high-quality study did not
- Smear conversion: one study showed significant effects, but two others did not
- Death during or after treatment: one high-quality cohort study found a significant effect of tobacco use on death after treatment among men, but not among women. The other study did not find a significant effect.

META-ANALYSIS

Adjusted effects from studies on the association between tobacco exposure and tuberculous infection, TB disease and TB mortality included in the qualitative review were pooled for meta-analysis. Of the 28 studies used to estimate the increased risk in the meta-analysis, 27 presented ORs and one hazard ratios.[17] Relevant information was independently extracted from each study and compared with values extracted as part of the larger literature review as an accuracy check. When 95%CIs were not provided, they were computed using standard error values (where OR is the estimated odds ratio and se_{OR} is the standard error of the effect estimator):

$$95\%\text{CI} = e^{*}[1n(\text{OR}) \pm 1.96(se_{OR}/\text{OR})]$$

Data were transferred to Stata Version 8.1 (Stata Corporation, College Station, TX, USA), where analysis was conducted for fixed and random-effects meta-analysis.* Standard plots were also generated using the meta-analysis programme and are described in more detail in the results section. For each TB outcome, a pooled estimate of the OR was computed for exposed compared to non-exposed individuals, where exposure to active smoke was specified in each study. Studies included in the meta-analysis for tuberculous infection defined infection as induration of $\geqslant$10 mm. Those included in the meta-analysis for TB disease and smoking consider only pulmonary TB.

The pooled estimate was computed again, restricting the group of included studies to only those rated as high quality. Finally, when there was variation in the definitions of the exposed and non-exposed groups between studies, a pooled estimate was calculated for each possible definition (e.g., ever vs. never-smokers, current vs. non-current smokers, current vs. never smokers and ex- vs. never-smokers). The purpose of this breakdown is to facilitate the pooling of the most similar results, as the risk of negative TB outcomes appears to be different by average quantity smoked and duration of smoking. For each pooled result, a χ^2 test for statistical heterogeneity was conducted. Because so few studies were pooled in each meta-analysis, the power of this test was low and the cut-off for rejection was raised from $P = 0.05$ to $P = 0.1$. If the test was not significant, it was assumed that the individual risk estimates belonged to the same distribution, and a fixed effects model could be used to calculate the pooled estimate. However, if the test for heterogeneity was significant, a random effects model was used to compute the pooled estimate.

Results of the meta-analysis

Table 3 provides information about the studies and the effect ratios used in the meta-analysis, and identifies high-quality studies. Table 4 provides the pooled estimates based on meta-analysis for high-quality and all studies looking at TB infection, disease and mortality. The Figure presents standard plots for the three TB outcomes (infection, disease, mortality) corresponding to the exposed vs. non-exposed meta-analysis. Each graph shows the effect ratios included in the analysis, the pooled estimate and corresponding 95%CIs. Boxes represent weights used in the meta-analysis for each study (proportional to the inverse of each standard

* The meta-analysis programme for fixed and random effects was written by Stephen Sharp and Jonathan Sterne (www.stata.com).

Table 4 Meta-analysis results

	Pooled estimate	95%CI	Method	Test for heterogeneity *P* value	Populations included *n*	Individuals included *n*
Pooled estimate for OR of being infected with TB according to tobacco smoke exposure						
All definitions of active exposure vs. non-exposure						
High-quality only	1.757	1.458–2.118	Fixed	0.364	4	4460
Overall	1.762	1.467–2.116	Fixed	0.525	5	4729
Study specific definitions: ever vs. never-smoker						
High-quality only	1.655	1.343–2.039	Fixed	0.495	2	3742
Overall	1.664	1.357–2.041	Fixed	0.769	3	4011
Current vs. non-current						
High quality/overall*	2.236	1.472–3.396	Fixed	0.288	2	718
Pooled estimate for odds ratio of developing pulmonary tuberculosis disease according to tobacco smoke exposure						
All definitions of active exposure vs. non-exposure						
High-quality only	2.641	2.066–3.378	Random	0.035	8	147 915
Overall	2.284	1.765–2.954	Random	<0.001	14	159 854
Study-specific definitions: ever vs. never-smokers						
High-quality only	2.856	2.035–4.007	Random	0.030	5	116 772
Overall	2.335	1.683–3.241	Random	<0.001	10	128 636
Current vs. not current						
High-quality/overall*	2.592	1.931–3.479	Fixed	0.419	3	103 576
Current vs. never						
High-quality only	2.605	1.589–4.269	Random	0.045	4	116 680
Overall	2.721	1.884–3.930	Random	0.035	6	118 548
Ex vs. never						
High-quality only	1.561	1.167–2.087	Fixed	0.538	4	116 680
Overall	1.586	1.288–1.952	Fixed	0.705	6	118 548
Passively exposed vs. not (never-active smokers only)*						
Overall	3.353	2.028–5.543	Fixed	0.315	3	480
Pooled estimate for OR of mortality from TB according to tobacco smoke exposure						
All definitions of active exposure vs. non-exposure						
High-quality only	1.347	1.107–1.638	Random	<0.001	3	31 582
Overall	2.236	1.340–3.732	Random	<0.001	6	67 168
Study-specific definitions: Ever vs. never-smokers						
High-quality only	1.347	1.107–1.638	Random	<0.001	3	31 582
Overall	2.390	1.347–4.242	Random	<0.001	5	64 802

* All studies included in this category are rated high-quality.
CI = confidence interval; OR = odds ratio; TB = tuberculosis.

error estimate). Studies from the qualitative study were excluded because neither CI nor standard error was available[11,45] or because of inconsistent definitions of TB outcomes (an inconsistent cut-off for infection;[14] or include all rather than just pulmonary TB[21,33]) or exposure (effect ratio by pack-year smoked rather than for smokers overall[15,16]). Studies that compare different degrees of exposure but do not compare against non-exposure are also excluded.[26,28(passive smoking)]

Tuberculous infection

The meta-analysis for tuberculous infection of high-quality studies found a pooled OR of 1.8 (95%CI 1.5–2.1) for active smoking.

TB disease

The meta-analysis for high-quality studies of the association between smoking and pulmonary TB disease found a pooled OR of 2.6 (95%CI 2.1–3.4). Furthermore, current smokers were found to be 2.6 (95%CI 1.6–4.3) times more likely to develop pulmonary disease compared to never smokers, whereas former smokers were 1.6 (95%CI 1.2–2.1) times more likely.

Of the three high-quality studies of the association with passive exposure, the pooled OR was 3.4 (95% CI 2.0–5.5).

Meta-analysis was not performed for retreatment TB.

TB mortality

Meta-analysis for high-quality studies on the associations between smoking and TB mortality showed a pooled OR of 1.3 (95%CI 1.1–1.6).

DISCUSSION

Principal findings

This systematic review used pre-defined methods to identify the available evidence regarding the association between tobacco exposure and TB. Active smoking was found to be significantly associated with tuberculous infection, and both active and passive smoking with TB disease. Active smoking was significantly asso-

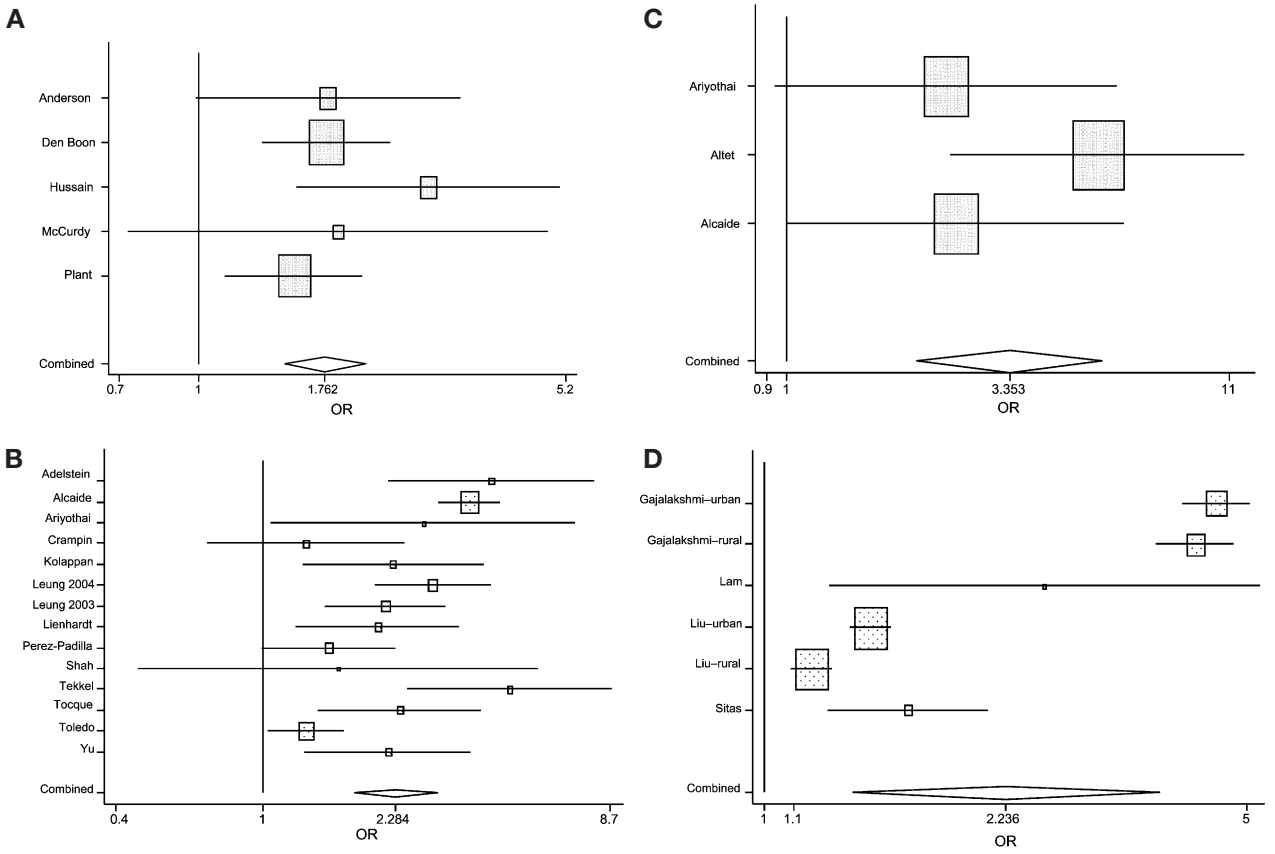

Figure Standard plots for main meta-analyses outcomes. For each study, the included effect estimates are graphed on the x-axis and the first author's last name is on the y-axis. Horizontal lines represent 95% confidence intervals and boxes represent the weight placed on each study (proportional to the inverse of the standard error of each estimate). The dotted vertical line represents odds ratio (OR) = 1, while the diamond shows the pooled estimate of each OR and its 95% confidence interval. **A.** OR of being infected for ever- vs. never-smokers. **B.** OR of developing TB disease for ever- vs. never-smokers (Note: the study by Leung 2004 estimates a hazard ratio; all others are odds ratios). **C.** OR of developing TB disease for passively-exposed individuals compared to those not. **D.** OR of TB mortality for ever- vs. never-smokers.

ciated with retreatment TB and with TB mortality. These effects appear to be independent of the effects of alcohol use, socio-economic status and a large number of other potential confounders. Although none of the studies used biological validation of reported exposure to tobacco smoke, significant associations with TB outcomes were found in all but six studies. The results showed a dose-effect in two studies of infection, nine studies of disease and three studies of mortality.

The majority of the studies measured active smoking of cigarettes. There are few available studies looking at the impact of exposure to passive smoking. Investigating the effects of passive smoking is fraught with difficulty in clearly identifying non-exposed individuals.[49] Because they stay at home more often, infants and children are probably less likely than adults to be at risk of misclassification in exposure to second-hand tobacco smoke. It is therefore notable that the studies of children show strong excess risk of tuberculous infection or TB disease through exposure to others' tobacco smoke. In this review, five out of six studies[13,19,20,28,29] found significant differences in risk between those not exposed and those exposed to passive smoking. The higher pooled OR for passive smoking than for active smoking may relate to the smaller number of studies used, but a hypothesis that merits study is that passive smoking exposure among non-smokers may be contaminating results on the effects of active smoking. As the higher estimates of risk associated with passive smoking are found in studies of children and young adults, it is also possible that children are more sensitive to the effects of exposure to second-hand smoke.

It has been noted in some countries that the differences in TB disease rates by sex begin to be seen in age cohorts when young men start smoking. A recent article presents evidence for the hypothesis that the differences in TB rates among men and women are influenced by the sex differences in tobacco use, in terms of prevalence of use, shorter duration of use or lower frequency of use.[50] Although two studies from China found excess risk for men but not for women according to smoking status,[17,46] other studies from China,[24,35,47] South Africa[48] and the UK[32] found excess risk for both men and women.

Limitations of existing original studies

The results described here are tempered by the methodological limitations of the included studies. There were no cohort studies of tuberculous infection. There were few studies that specifically identified transition from infection to disease in relation to tobacco smoke exposure. Most studies provided a detailed account of the criteria used to determine the TB outcome, but the best measures of TB disease were assessed to be present in only 19 studies. The tobacco smoke exposure measures were often weak: many studies defined smoking as simply present or absent, with no dose measures (consumption, duration of use), and some studies did not indicate the procedure undertaken for assessing smoking status. When duration and consumption rates were measured, they were often collapsed into pack-years, which may mask a dose effect. None of the studies used biochemical validation, even though a certain percentage of individuals may not provide accurate information about their tobacco use status.[51] Only one of the studies in this review noted that they may not have adequately measured the true extent of active smoking in the chosen population.[10] Many studies missed the opportunity to investigate exposure to others' tobacco smoke, even in populations where close proximity to smokers would be expected to subject them to high levels of passive smoking.

Limitations of the review process

This systematic review has limitations that warrant discussion. Although we collected non-English language studies that showed significant effects of smoking or passive exposure to tobacco smoke on TB outcomes (e.g., [52,53]), the review did not include these papers due to funding restrictions. Nevertheless, the evidence of an association between tobacco smoke exposure and disease is unlikely to be altered in any meaningful way by the inclusion of such studies.

Our understanding of the relationship between exposure to tobacco and TB treatment and case management is limited by the inclusion criteria but can be strengthened by new cohort and case-control trials.

We also acknowledge the limits of this review concerning mortality. Nine studies (five were included in the review, the others did not meet inclusion criteria) are known to us to provide significant effects ratios of exposure to tobacco smoke with TB mortality rates;[34,45–48,54–57] these results are not well represented in this systematic review.

Limitations of the meta-analysis

The main limitation of the meta-analysis is the inconsistency in the definitions of both tobacco smoke exposure and TB outcomes. For tobacco exposure, because there is such a significant dose-response relationship (in terms of both consumption and duration of smoking), there is likely also to be a risk reduction conferred on quitters. As such, effect estimation for current vs. non-current smokers is likely to be different from the effect estimation for ever vs. never smokers. This shortcoming requires either the pooling of slightly inconsistent results or effect estimation that is based on a more limited number of studies (results obtained in both of these ways are presented here; future studies should define smoking in a more consistent way).

Another limitation involves variation in the potential confounding variables addressed in each study. Most studies address important confounding variables in some way (age, sex and socio-economic status in most cases; alcohol consumption in some) by specifying inclusion criteria, matching in the study design or controlling directly in analysis. Adjusted results are pooled in the meta-analysis, to estimate the impact of tobacco exposure on TB outcomes as accurately as possible. Because quality ratings are assigned in part due to how well each study addresses potential confounding variables, the pooled results for high-quality studies only can be assumed to better approximate the true impact of smoking. Potentially confounding variables should be included consistently in future research.

Recommendations for research

There is sufficient evidence to indicate that studies of risk factors for TB outcomes should include the type of tobacco product, measures of dose and duration of smoking and passive exposure to tobacco smoke, and validation of self-reported exposures. New studies should use cohort and case-control designs to examine the association of passive or active smoking with excess rates of tuberculous infection, increased severity of disease, slower smear conversion, relapse and other treatment outcomes. While there are numerous studies about TB disease, few focus on smear- or culture-positive TB or specifically the transition to disease from infection.

Researchers looking at the effects of exposure to tobacco smoke need to be attuned to the criteria for identifying TB and to seek an approach to validate the precision of reported TB mortality from large population surveys where the possibility of misclassification may be large.

Recommendations for case management policy

While clinicians are implementing the DOTS strategy:

- Smoking status (and any tobacco exposure) should be recorded during patient registration as a TB case.
- Patients should be warned that continued smoking will compromise the effectiveness of the treatment and should be advised to quit all tobacco use and avoid tobacco smoke exposure.
- Patients should be counselled on how to quit smoking when starting TB treatment. If they do not stop, they should be told to avoid exposing others to their tobacco smoke.

- Monitoring of patients should include follow-up and support for smoking cessation.
- Cured patients should be warned that resuming smoking poses a risk of re-infection and disease.

CONCLUSIONS

The relationship between smoking and TB is important knowledge for clinicians dealing with patients. This association, which has been shown to exist in individual studies and reviews, has not received the attention it merits in terms of TB care standards and research. This systematic review attempts to remedy this situation.

Clinicians' knowledge about a patient's smoking status or exposure to passive smoking can help them to better manage treatment by providing counselling about stopping smoking. The results of this study show that smokers have greater risks for TB disease and retreatment and some evidence of higher risks for infection and TB disease severity. These results indicate that a clinician can confidently advise TB patients to stop smoking and remain non-smokers or to avoid exposure to others' smoke in the context of good case management.

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RÉSUMÉ

OBJECTIFS : Les cliniciens actifs dans la lutte antituberculeuse peuvent ne pas considérer qu'ils ont un rôle à jouer dans la lutte contre le tabagisme, car l'association entre le tabac et la tuberculose (TB) n'a pas été acceptée de manière générale. Une étude qualitative ainsi qu'une méta-analyse ont été entreprises pour évaluer dans la littérature publiée la puissance des preuves d'une association entre le tabagisme actif ou passif et diverses manifestations et résultats de la TB.

MÉTHODES : On a recherché les listes de référence, PubMed, la base de données de L'Union et Google Scholar pour inclure finalement 42 articles en anglais comportant 53 résultats en vue de l'extraction des données. Un score de qualité a été attribué à chaque étude pour classifier la puissance des preuves concernant chacun des résultats en matière de TB. On a pratiqué ensuite une méta-analyse sur les résultats des études inclues.

RÉSULTATS : Malgré des limitations des données disponibles, l'évidence a été classée comme puissante pour une association entre le tabagisme actif et la maladie tuberculeuse, comme modérée pour l'association entre le tabagisme passif et la maladie tuberculeuse et entre le tabagisme et les rechutes de TB, et finalement comme limitée pour l'association entre le tabagisme et l'infection tuberculeuse et entre la tabagisme et la mortalité par TB. Les preuves sont insuffisantes pour confirmer une association entre tabagisme et délai, abandon, négativation plus lente des frottis, gravité plus marquée de la maladie ou TB à germes résistants ou encore entre exposition à la fumée de tabac environnementale et infection.

CONCLUSIONS : L'association entre le tabagisme et la maladie tuberculeuse est du type causal. Le tabagisme peut avoir un impact important sur de nombreux aspects de la TB. Les cliniciens peuvent en toute confiance donner à leurs patients l'information que cesser de fumer et éviter l'exposition à la fumée passive sont des mesures importantes dans la lutte contre la TB.

RESUMEN

OBJETIVOS : Es posible que los médicos que trabajan en el control de la tuberculosis (TB) no reconozcan para sí mismos una función en la lucha contra el tabaquismo, pues la asociación entre tabaco y TB no se acepta ampliamente. Se emprendió una reseña cualitativa y un metanálisis con el fin de evaluar la potencia de los datos probatorios publicados en los artículos científicos en favor de una asociación entre tabaquismo activo y pasivo y las diversas manifestaciones y desenlaces clínicos de la TB.
MÉTODOS : Después de consultar listas de referencias, las bases de datos PubMed, de La Unión y el motor de búsqueda Google Scholar se tomaron 42 artículos en inglés con 53 desenlaces, de los cuales se extrajeron datos. Se atribuyó a cada estudio una puntuación de calidad, con el fin de clasificar la potencia de los datos probatorios para cada desenlace clínico de la TB. Se realizó luego un metanálisis de los resultados de los casos estudiados.
RESULTADOS : Pese a las limitaciones de los datos obtenidos, se calificó como fuerte la evidencia de una asociación entre tabaquismo y enfermedad tuberculosa ; la evidencia fue moderada para la asociación entre tabaquismo pasivo y enfermedad tuberculosa y entre tabaquismo y enfermedad tuberculosa recurrente y restringida para aquella entre tabaquismo e infección tuberculosa y entre tabaquismo y mortalidad por TB. No hubo suficientes pruebas en favor de una asociación entre tabaquismo y retraso diagnóstico, abandono, lentitud en la negativación de la baciloscopia, mayor gravedad de la enfermedad o TB farmacorresistente ni entre tabaquismo pasivo e infección tuberculosa.
CONCLUSIONES : La asociación entre tabaquismo y enfermedad tuberculosa parece ser de tipo causal. El tabaquismo puede tener una repercusión considerable sobre diversos aspectos de la TB. Los médicos pueden confiar en la pertinencia de aconsejar a sus pacientes el abandono del tabaco y la evitación de la exposición al humo del tabaco de los demás, como medidas importantes en la lucha contra la TB.