

# Tobacco Control and Tuberculosis Control - Is there an Association?

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# Cigarette Smoking is a serious Global Public Health Concern

- Worldwide, tobacco use is estimated to kill about 5 million people annually.
- Annual tobacco deaths will rise to 10 million by 2030.
- The 21<sup>st</sup> century is likely to see 1 billion tobacco deaths, most of them in low-income countries.



# Tobacco and Tuberculosis

## A neglected issue

- High prevalence of tobacco use has been noted in studies looking at risk factors for TB since 1918.
- In England and Wales, in the period 1871-1880, mortality from pulmonary TB was similarly high for both males and females, whereas, in 1941-50, the TB mortality rate of males was much higher than that of females.
  - TB patients were more likely to be heavy smokers than control patients (Lowe CR. BMJ 1956; 10: 1081-1086.)
- Brown and Campbell in 1961 and Lewis and Chamberlain in 1963 investigated both smoking and alcohol use, and found that alcohol drinking was the major factor associated with tuberculosis.

# Tobacco and Tuberculosis

- Systematic review and meta-analysis.
  - Slama K, et al. Int J Tuberc Lung Dis 2007 (in press): include 42 papers.
  - Lin HH, et al. PLoS Med 2007;4(1): e20. doi: 10.1371/journal.pmed.004002 : include 38 papers
  - Bates M N, Arch Intern Med 2007;167:335-42: include 24 papers.
- Reviews on tobacco and TB
  - Davies PDO. Trans R Soc Trop Med Hyg 2006;100:291-8.
  - Chiang C-Y. et al Int J Tuberc Lung Dis 2007;11:258-62.
  - Pai M, et al. Expert Rev Ant Infect Ther 2007;5: 385-91



# Union's Review on Tobacco and Tuberculosis

## *Article search - inclusion and exclusion*

- Article search was performed independently by two persons at The Union using PubMed, The Union database and Google Scholar.
- Articles in English were examined for inclusion.
- Articles not providing information on the country of study, sample size, population source, age, sex and effects ratios were excluded.



# Measurement of tobacco exposure

- Tobacco exposure
  - type of exposure (active and/or passive),
  - current and past exposure,
  - duration of exposure,
  - frequency of exposure
  - amount of exposure,
  - age at initial exposure.
- Determination of exposure
  - Observational,
  - Self-report/family report,
  - Biochemical validation (Cotinine, expired CO >8ppm )



# Tuberculosis outcomes

- Infection: Tuberculin skin test positive at a specified cut-off
- Disease
  - Sputum AFB smear positive and/or culture positive for *M. Tuberculosis*
  - Clinical, radiological or histological diagnosis plus appropriate response to antituberculosis treatment



# Tuberculosis outcomes

- Tuberculosis mortality:
  - Died with verified tuberculosis as defined above
  - Death certificate, Medical records, Interview of family
- Tuberculosis characteristics and case management: delay in diagnosis, severity of disease, smear conversion, outcome, relapse, and drug resistance



# Qualitative review form

## *25 items from 6 areas*

1. Study population
2. Assessment of active exposure to tobacco
3. Assessment of passive exposure to tobacco
4. Assessment of tuberculosis outcome  
(infection, disease, mortality, tuberculosis characteristics and case management)
5. Study design
6. Analysis and presentation of data



# Study population

- Cases and controls were drawn from the same population
- Covariates were designated
- Eligibility criteria were specified
- Attrition rate was similar in each group in cohorts



# Assessment of exposure to tobacco smoke

- Smoking status was defined
- Smoking status was validated by more than self-report
- Quantity consumed was measured
- Duration of use was measured
- Those who assessed smoking status did not know the tuberculosis outcome



# Tobacco and Tuberculosis – *A qualitative systematic review*

- All articles were reviewed by three reviewers independently.
- The majority was taken in case of disagreement.
- A fourth review was done in case of three way disagreement.



# Score of article and high quality study

- The score of an article: the number of points / total possible points.
- High quality study
  - Those that have a quality score above the mean score for all articles
  - Used to assess evidence of the impact of tobacco exposure on tuberculosis.



# Levels of evidence

- **Strong evidence** is provided by consistent findings in
  - At least two high-quality cohort and two high-quality case-control studies
- **Moderate evidence** is provided by consistent findings in
  - one high-quality cohort and two or more high-quality case control studies, or
  - three or more high-quality case control studies



# Levels of evidence

- **Limited evidence** is provided by generally consistent findings in
  - A single high-quality cohort study or
  - Two high-quality case-control studies or
  - Three or more high-quality cross-sectional studies
- **Not enough evidence**



# Results of Union systematic review and meta-analysis

- A total of 1,863 references were identified.
- The full texts of 192 articles were screened for inclusion.
- A final inclusion of 42 articles containing 50 studies for data extraction.



# Results of Union systematic review and meta-analysis

Type of study	Number of studies
– cohort studies	8
– case control studies	27
– cross sectional studies	15
• Type of tobacco exposure	
– Active tobacco exposure only	44
– Passive tobacco exposure only	3
– Both active and passive exposure	3



# Tobacco smoke exposure and Tuberculosis

- None of the studies showed a protective effect of active or passive smoking on tuberculosis outcomes.
- Of the 50 studies, 44 (88%) showed a significant effect of tobacco smoke exposure on a tuberculosis outcome.
- 14 studies found a dose-effect relationship



Number of studies	Tuberculosis outcome	Tobacco smoke exposure	Significant association
7	Infection	Active	7
1		Passive	1
19	Tuberculosis Disease	Active	18
5		Passive	4
3	Retreatment TB	Active	2
2	Patient delay	Active	1
2	Default	Active	2
3	Smear conversion	Active	1
2	Severity of TB	Active	2
2	Drug resistant TB	Active	2
2	Death after treatment	Active	1
5	TB mortality	Active	5



# Levels of evidence of association

- The range of possible scores is from 0-100.
- The mean score of
  - studies of infection 76.3
  - studies of disease 76.5
  - studies of death or mortality 74.1
  - disease characteristics and case management issues 66.7



# Levels of evidence of association between tobacco smoke exposure and tuberculous infection

- Active exposure:
  - 1 high quality case-control study
  - 3 high-quality cross-sectional studies, and
  - 3 other studies
  - **Evidence of the association: Limited**
- Passive exposure:
  - One cross-sectional study
  - **Evidence of the association: not enough**



## Levels of evidence of association between tobacco smoke exposure and tuberculosis disease

- Active exposure :
  - 2 high quality cohort study,
  - 6 high quality case control studies,
  - 2 high quality cross-sectional studies
  - **Evidence of the association: Strong**
  
- Passive exposure:
  - 3 high quality case control studies
  - **Evidence of the association: Moderate**



- Levels of evidence of association between active tobacco smoke exposure and retreatment tuberculosis
  - Two high quality cohort study
  - **Evidence of the association: Moderate**
  
- Levels of evidence of association between active tobacco smoke exposure and tuberculosis mortality
  - Two high quality case control study
  - **Evidence of the association: limited**

Slama K. Int J Tuberc Lung Dis 2007 (in press)



# Not enough evidence

- Default
  - 1 high quality case control study
- Drug resistant tuberculosis
  - 1 high quality cross-sectional study
- Severity of disease
  - 1 high quality cross-sectional study
- Delay in diagnosis and treatment and smear conversion
  - No high quality study showing a positive association

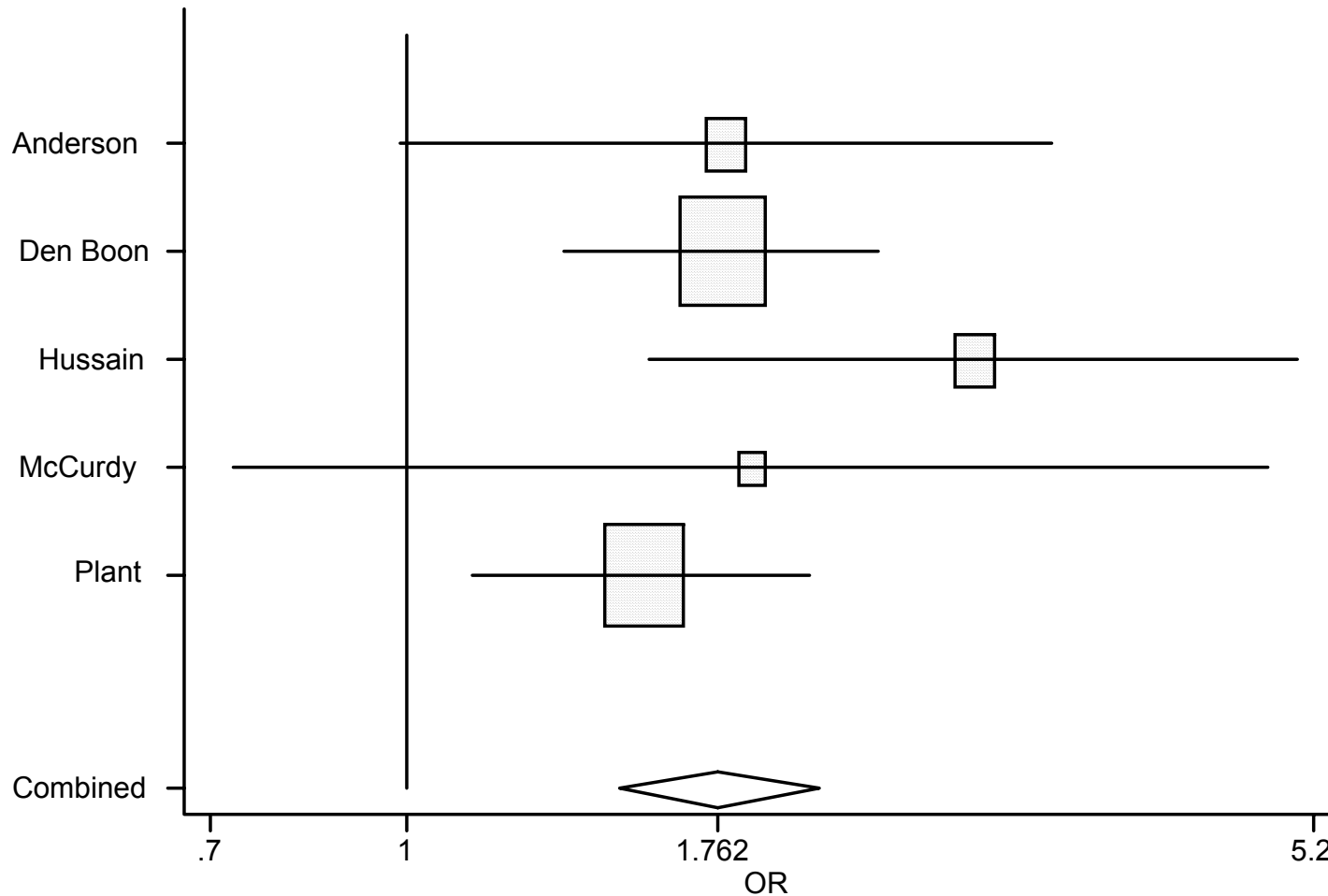


# Meta-analysis

- a pooled estimate was calculated for both high quality studies and overall
- a chi-square test for statistical heterogeneity was conducted (cutoff:  $p=0.1$ )
  - Not significant : a fixed effects model
  - Significant: random effects model



# Odds ratio of being infected for ever- versus never-smokers



Slama K. Int J Tuberc Lung Dis 2007 (in press)



## Pooled estimate for odds ratio of being infected with TB according to tobacco smoke exposure

	Pooled estimate	95% CI (Lower Upper)		Studies included
All definitions of active exposure v. non-exposure				
High quality only	1.757	(1.458	2.118)	4
Overall	1.762	(1.467	2.116)	5
Ever v. never-smoker				
High quality only	1.655	(1.343	2.039)	2
Overall	1.664	(1.357	2.041)	3
Current v. non-current				
High quality/overall <sup>1</sup>	2.236	(1.472	3.396)	2

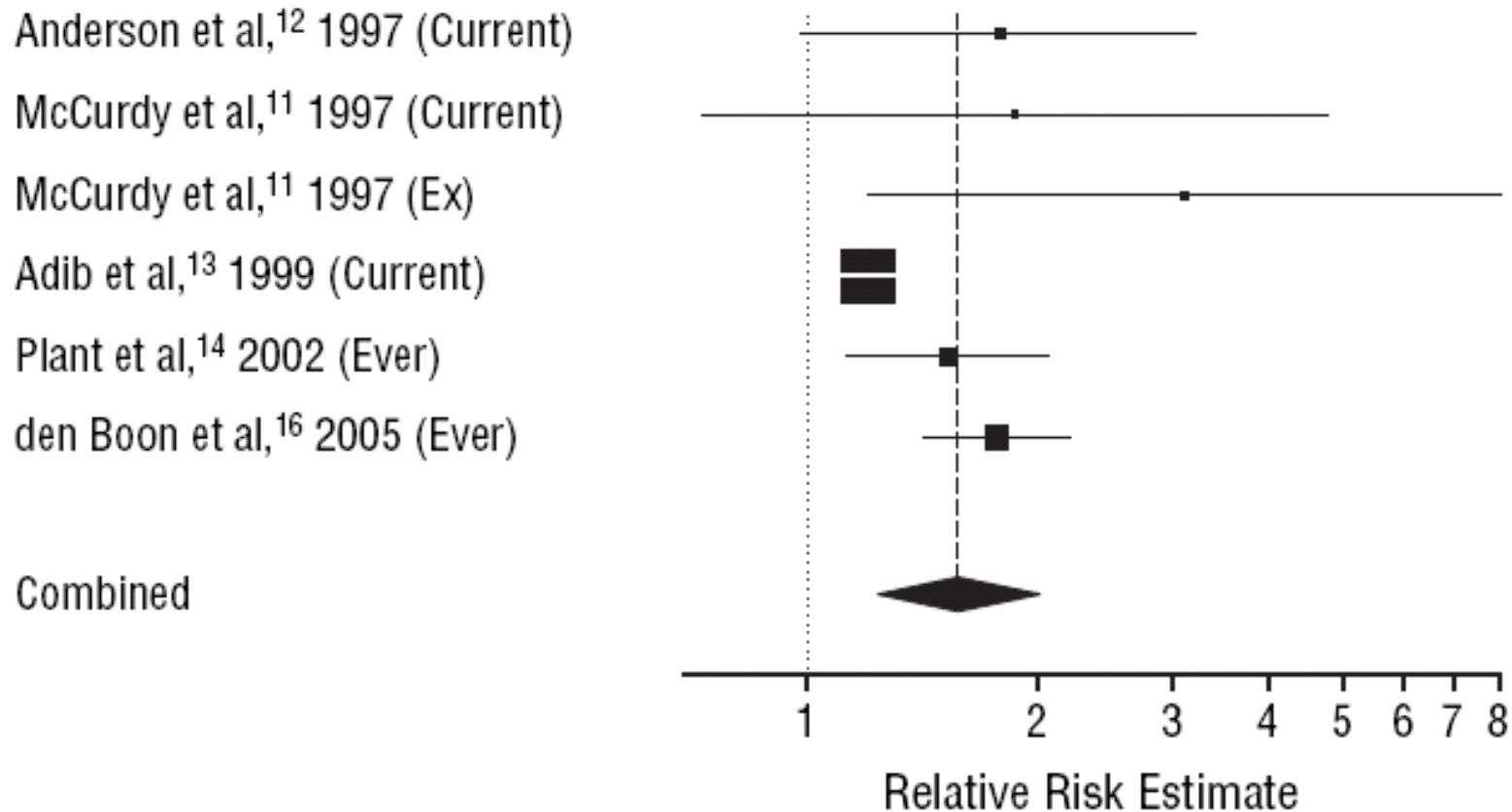


**Table 2.** Quality Assessment and Subgroup Analysis: Tobacco Smoking and Latent TB Infection

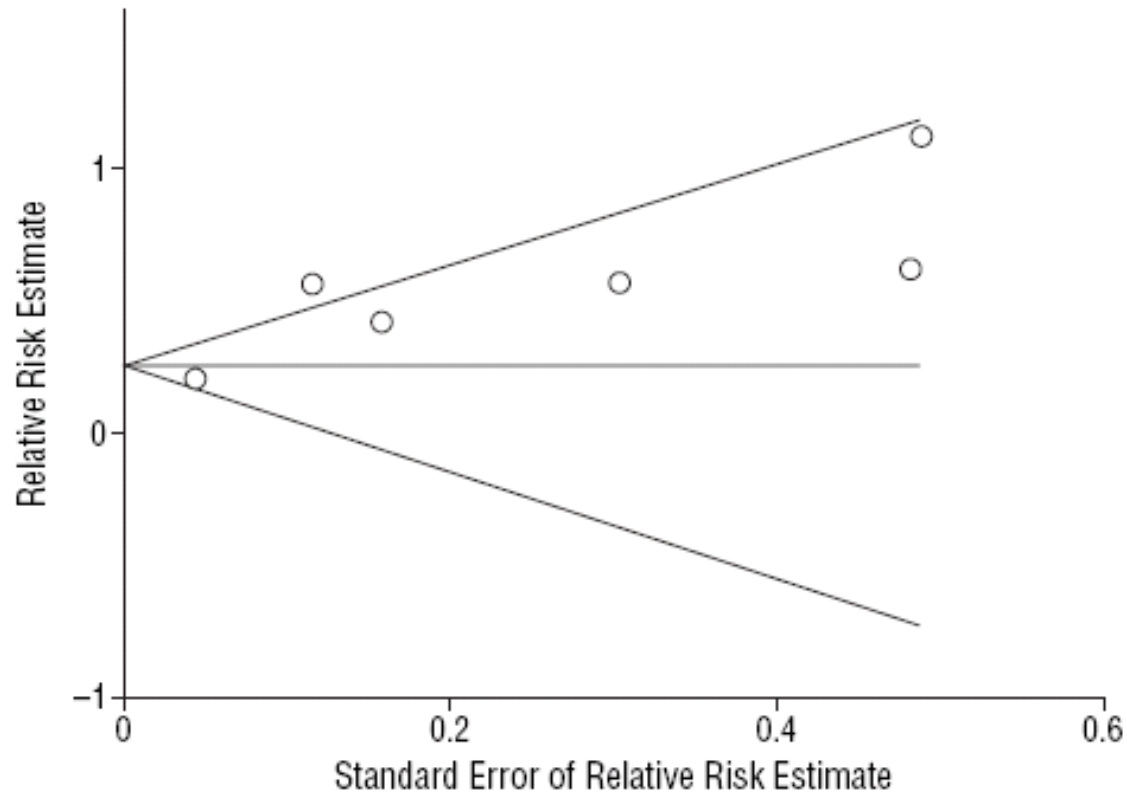
Category	Study Characteristics (Number of Studies)	Summary Estimate	95% CI	$I^2$
TST cutoff	5 mm (2)	2.08	1.53–2.83	0%
	10 mm (4)	1.83	1.49–2.23	0%
Adjustment for alcohol	Yes (2)	1.76	1.43–2.16	0%
	No (4)	2.20	1.65–2.93	0%
Adjustment for socioeconomic status	Yes (4)	1.94	1.61–2.33	0%
	No (2)	1.75	1.18–2.58	0%
Type of study	Case control (1)	1.78	0.98–3.22	NA
	Cross sectional (5)	1.91	1.60–2.27	0%
Type of smoking	Current smoking (4)	1.91	1.36–2.67	0%
	Ever smoking (2)	1.93	1.51–2.47	28.4%



# Forest plot of results of 5 studies that examined smoking and tuberculosis infection



Begg funnel plot with pseudo 95% confidence limits of results of 5 studies that examined smoking and tuberculosis infection

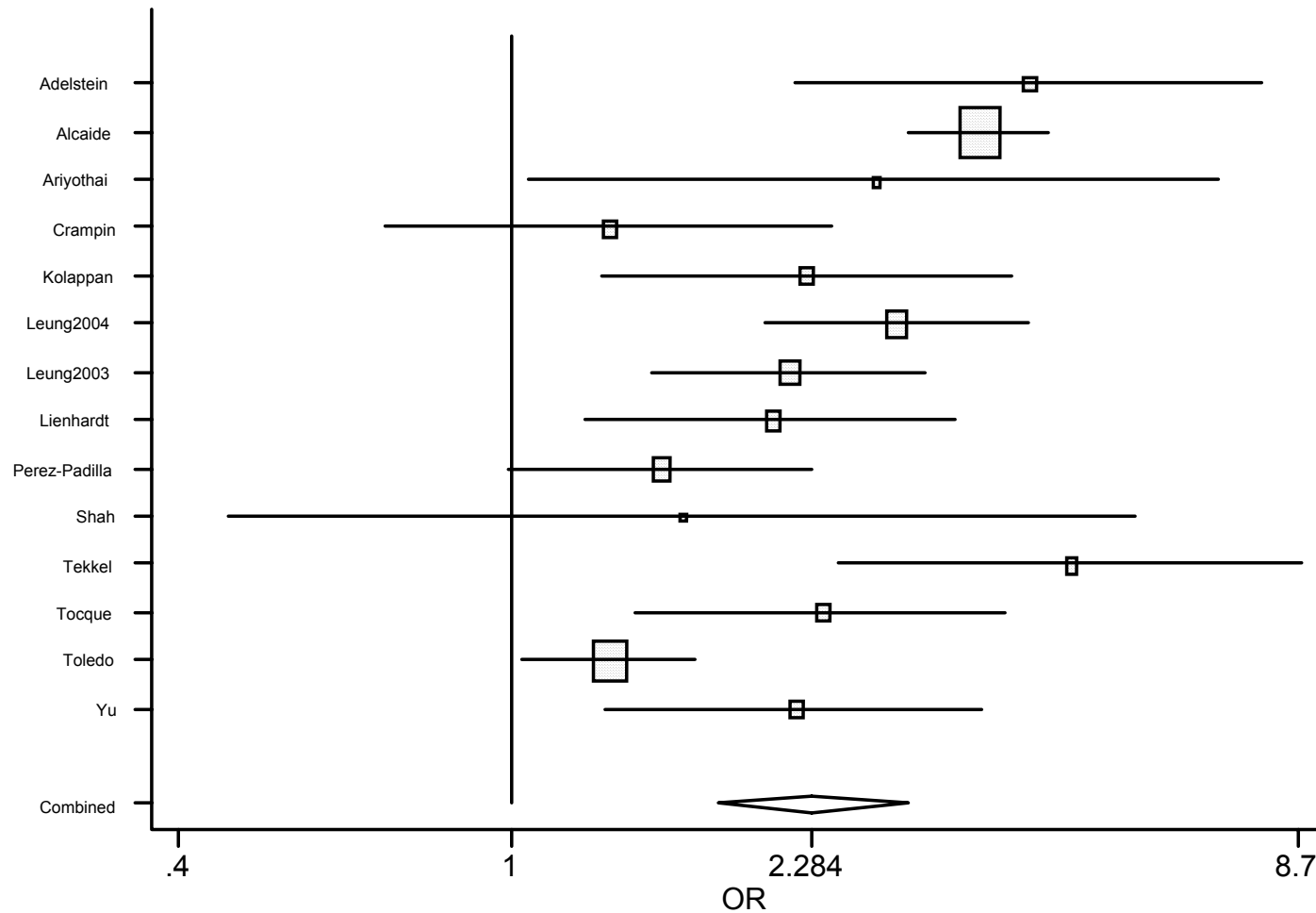


P=0.02

Bates M N, Arch Intern Med 2007;167:335-42



# Odds ratio of developing tuberculosis disease for ever- versus never-smokers



Slama K. Int J Tuberc Lung Dis 2007 (in press)



## Pooled estimate for odds ratio of pulmonary tuberculosis according to tobacco smoke exposure

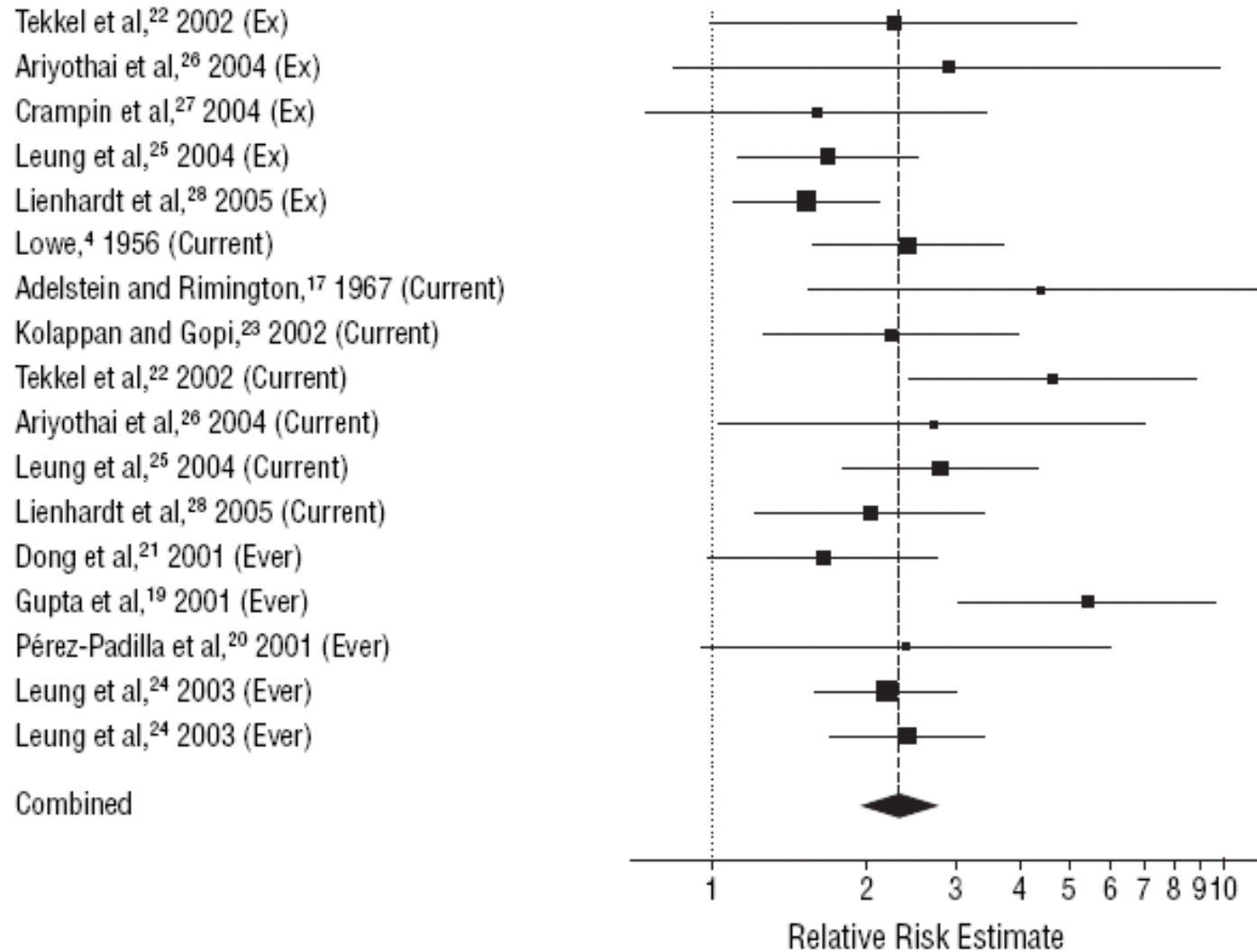
	Pooled estimate	95% CI (Lower Upper)		Studies included
All definitions of active exposure v. non-exposure:				
High quality only	2.641	(2.066	3.378)	8
Overall	2.284	(1.765	2.954)	14
Ever v. never-smokers				
High quality only	2.856	(2.035	4.007)	5
Overall	2.335	(1.683	3.241)	10
Current v. not current				
High quality/overall <sup>1</sup>	2.592	(1.931	3.479)	3

## Pooled estimate for odds ratio of pulmonary tuberculosis according to tobacco smoke exposure

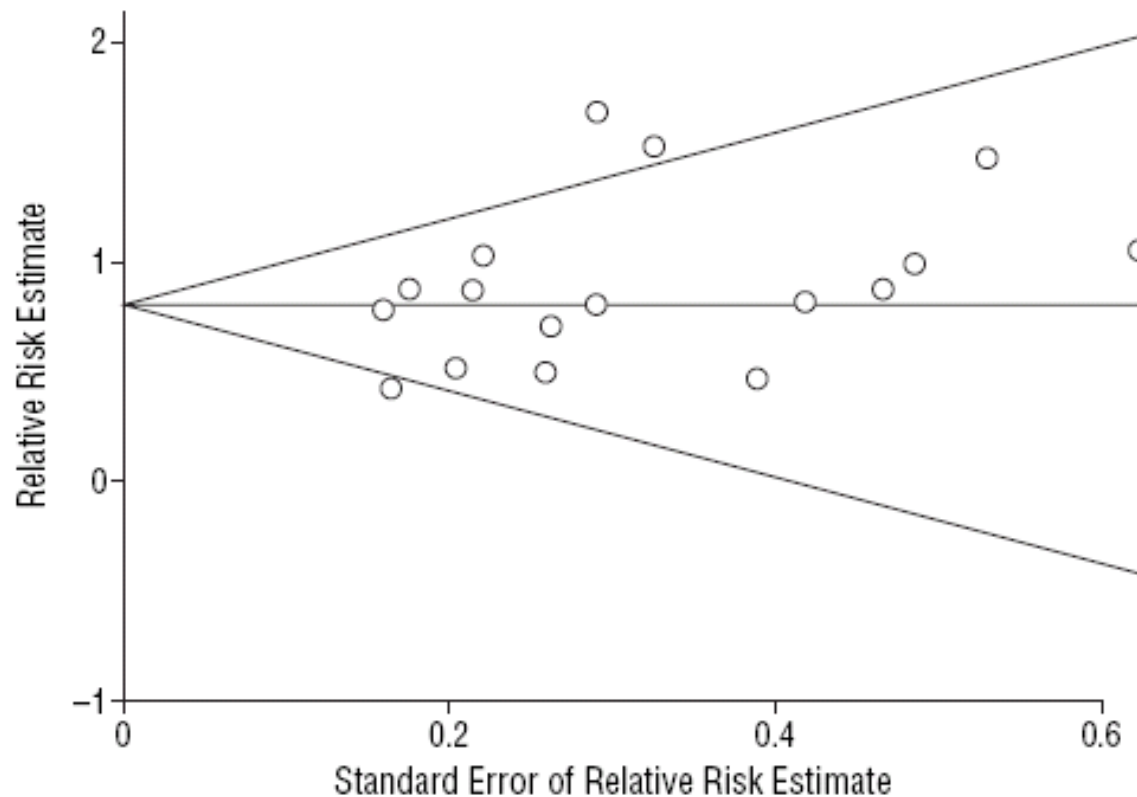
	Pooled estimate	95% CI (Lower Upper)		Studies included
Current v. never				
High quality only	2.605	(1.589	4.269)	4
Overall	2.721	(1.884	3.930)	6
Ex v. never				
High quality only	1.561	(1.167	2.087)	4
Overall	1.586	(1.288	1.952)	6
Passively exposed v. not (never-active smokers only) <sup>1</sup>				
Overall	3.353	(2.028	5.543)	3



# Forest plot of results for men only and for men and women combined in studies that examined smoking and tuberculosis disease



# Begg funnel plot with pseudo 95% confidence limits of results of studies that examined smoking and tuberculosis disease

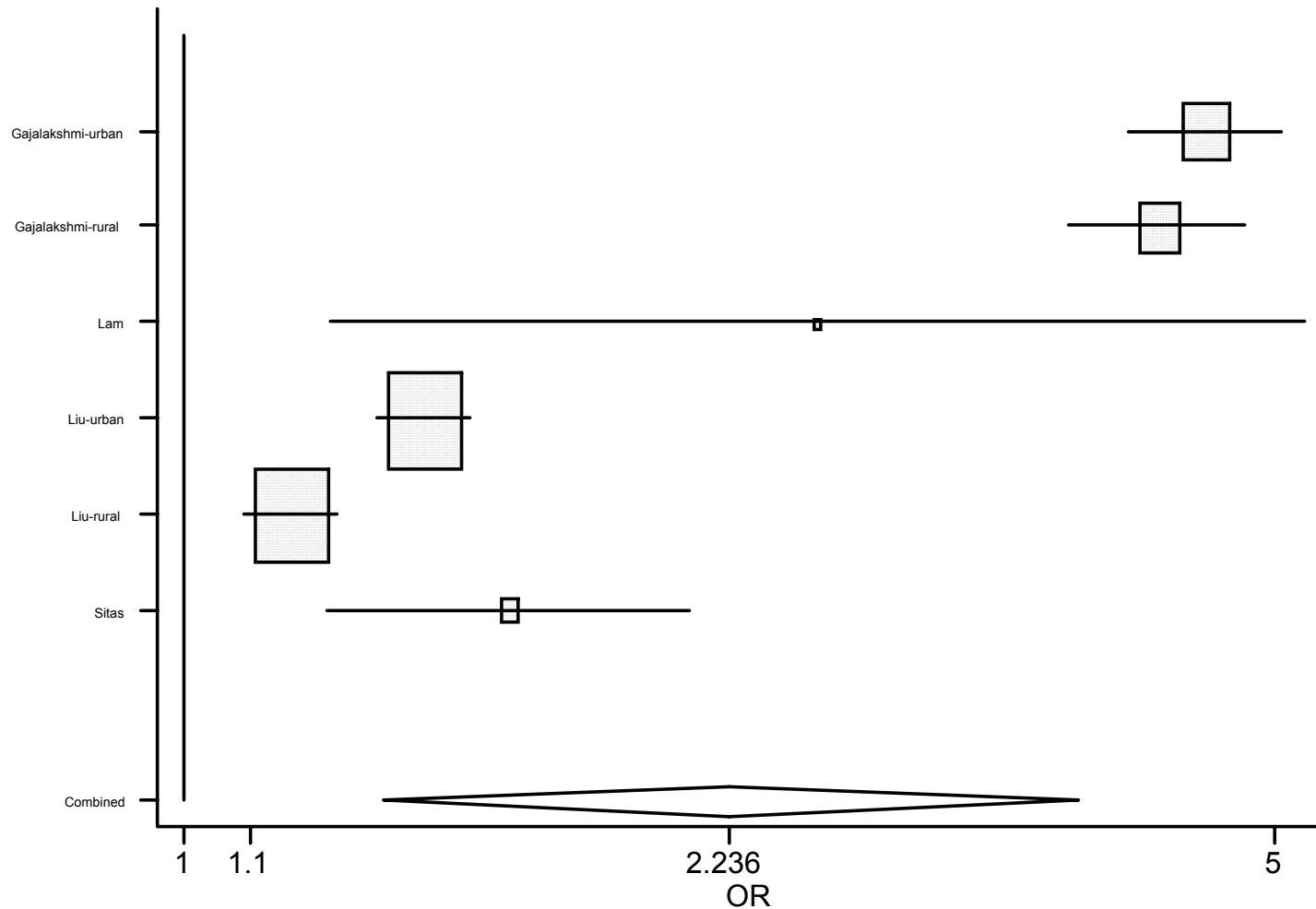


P=0.13

Bates M N, Arch Intern Med 2007;167:335-42



# Odds ratio of tuberculosis mortality for ever- versus never-smokers



Test for heterogeneity  $p < 0.001$



## Pooled estimate for odds ratio of mortality from TB according to tobacco smoke exposure

	Pooled estimate	95% CI (Lower Upper)		Studies included
All definitions of active exposure v. non-exposure				
High quality only*	1.347	(1.107	1.638)	3
Overall*	2.236	(1.340	3.732)	6
Ever v. never-smokers				
High quality only*	1.347	(1.107	1.638)	3
Overall*	2.390	(1.347	4.242)	5

\* Test for heterogeneity <0.001

# Transition of tuberculosis

- Developing tuberculosis disease involves two distinct transitions with their corresponding risk factors:
  - the transition from being exposed to being infected
  - the transition from being infected to developing disease.
- From being cured to developing recurrent tuberculosis



## Passive exposure to tobacco smoke and the transition from being infected to developing tuberculosis disease

- a case control study design on passive smoking and risk of pulmonary tuberculosis in children immediately following infection.
- Cases were 93 household contacts who became active tuberculosis cases
- Controls were 95 household contacts who were tuberculin-positive without evidence of active disease.
- Passive exposure to tobacco smoke :adjusted OR 5.4, 95%CI 2.4 – 11.9.



# Active cigarette smoking as a risk factor for tuberculosis in young adults

- Cases were patients with active pulmonary tuberculosis
- Control were persons with positive tuberculin reactions.
- In multivariate analysis, active smoking was associated with tuberculosis (adjusted OR 3.8, 95%CI 1.5-9.8)
- There was a dose-response relationship between the number of cigarettes smoked and the risk of tuberculosis



# Exposure to tobacco smoke and clinical manifestations of tuberculosis

- Smokers were more likely to have cough, dyspnea, chest radiograph appearances of upper zone involvement, cavity and miliary appearance, positive sputum culture, but were less likely to have isolated extrapulmonary involvement, as compared with non-smokers.

Leung CC, et al. Int J Tuberc Lung Dis 2003; 7:980-986

- Cigarette smoking is associated cavity or a positive smear for acid-fast bacilli

Altet-Gomez MN, et al. Int J Tuberc Lung Dis 2005; 9:430-436.



# Composition of cigarette smoke

- **Tobacco contains more than 4,500 compounds in the particulate and vapour phases.**
- **These compounds comprise five known human carcinogens and many toxic agents, including carbon monoxide, ammonia, acrolein, etc.**



# Effects of cigarette smoke on the immune system

- Cigarette smoking increases the number of alveolar macrophages, but
- Smokers' alveolar macrophages have a reduced ability to phagocytose and/or kill bacteria, such as *Staphylococcus aureus* and *Listeria monocytogenes*
- Smokers' T cells have a decreased ability to proliferate in response to T-cell mitogens, which indicates a deficient cell-mediated immune response



## Biological mechanism underlying the association between tobacco and TB

- Alveolar Macrophages and bronchial epithelial cells from smokers have reduced cell death (apoptosis).

Tomita K. Am J Respir Crit Care Med 2002;166: 724–731.

- Nicotine enhances the replication of intracellular organisms

– Matsunaga K. J Infect Dis 2002;185:229-36

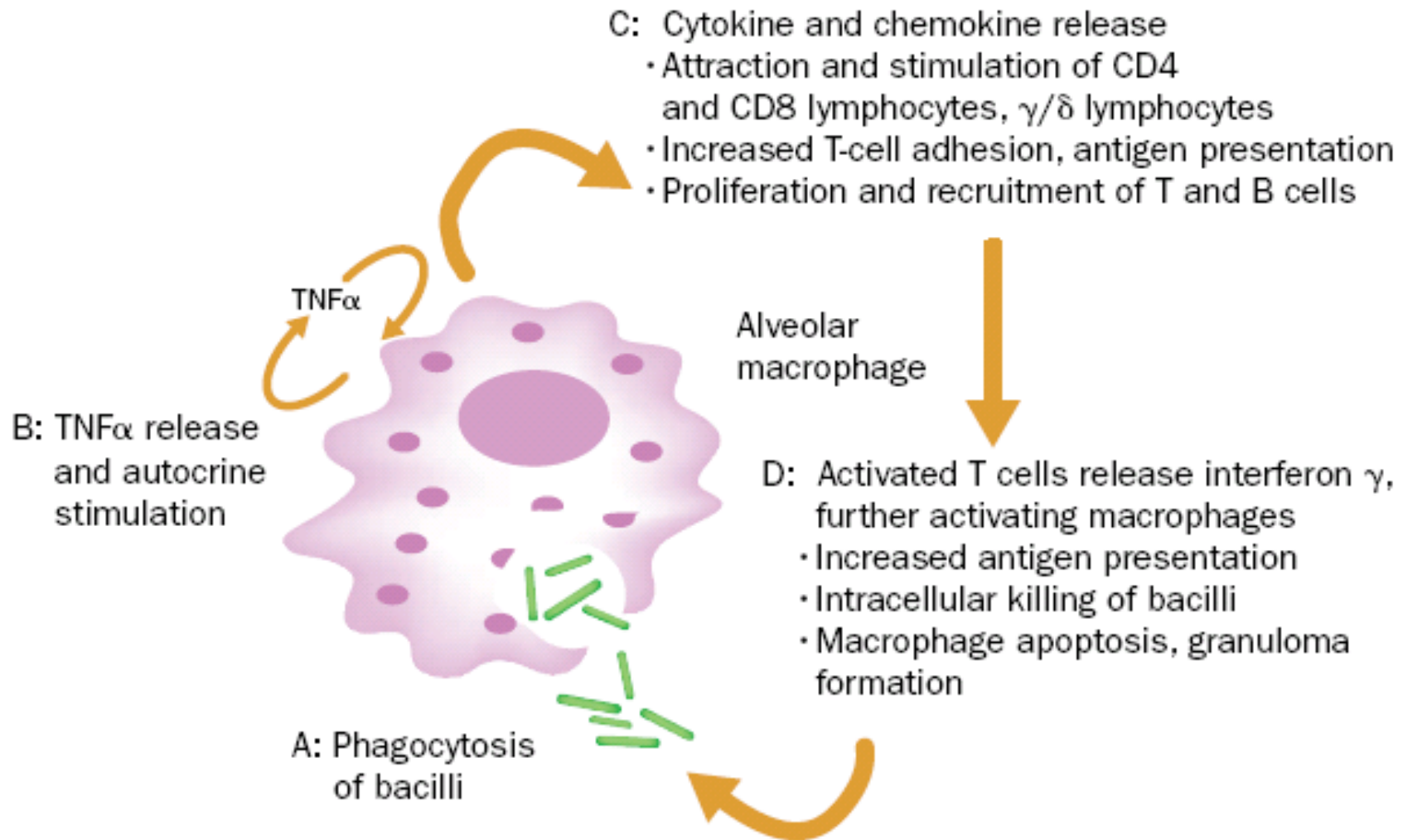


## Biological mechanism underlying the association between tobacco and TB

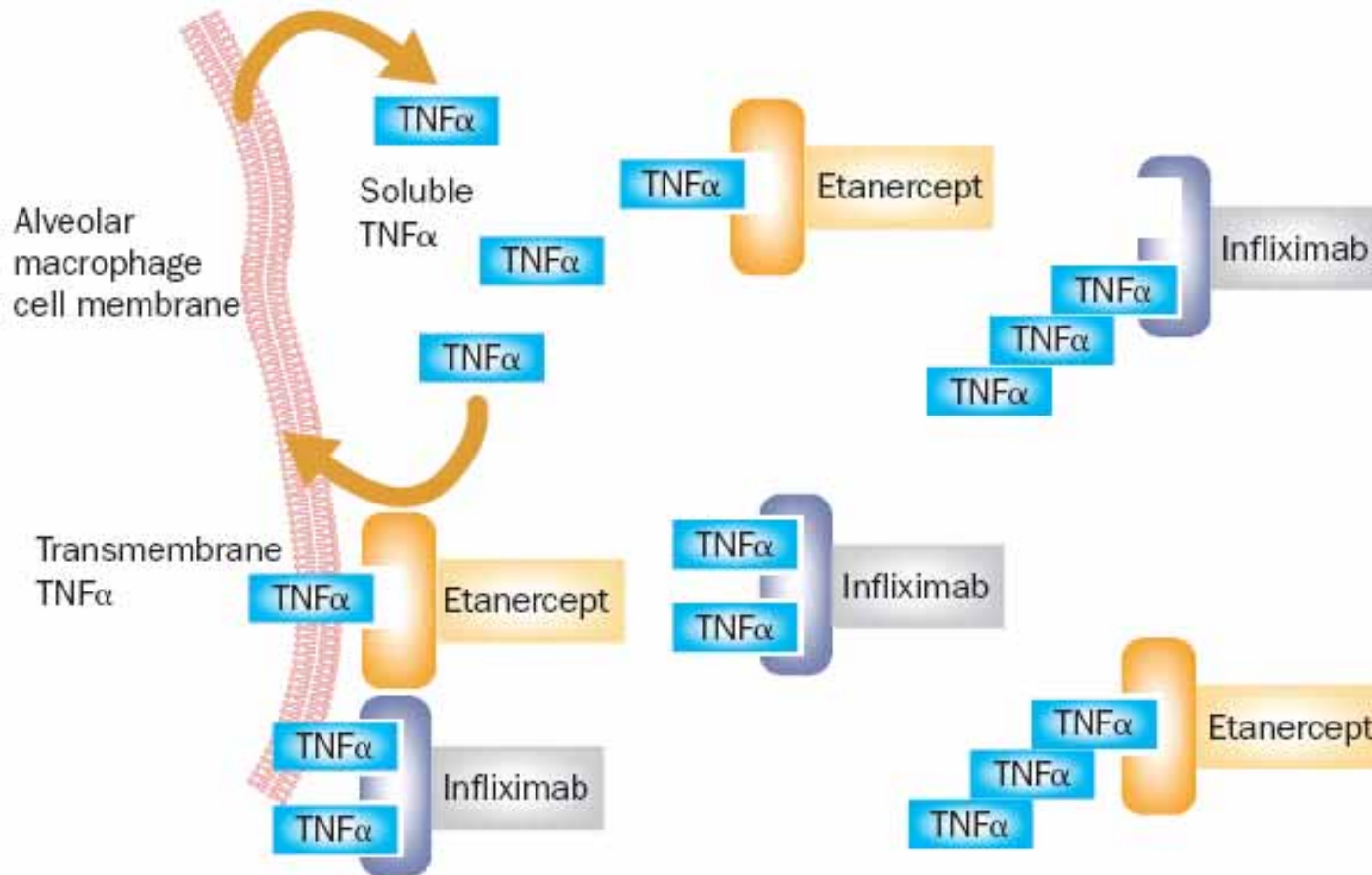
- Anti-tumour necrosis factor agents and tuberculosis
- vagus nerve and the inhibition of release of macrophage TNF
- Nicotine and the nicotinic acetylcholine receptor  $\alpha 7$  subunit



# The role of $TNF\alpha$ in the cellular immune response to *M. tuberculosis* infection.



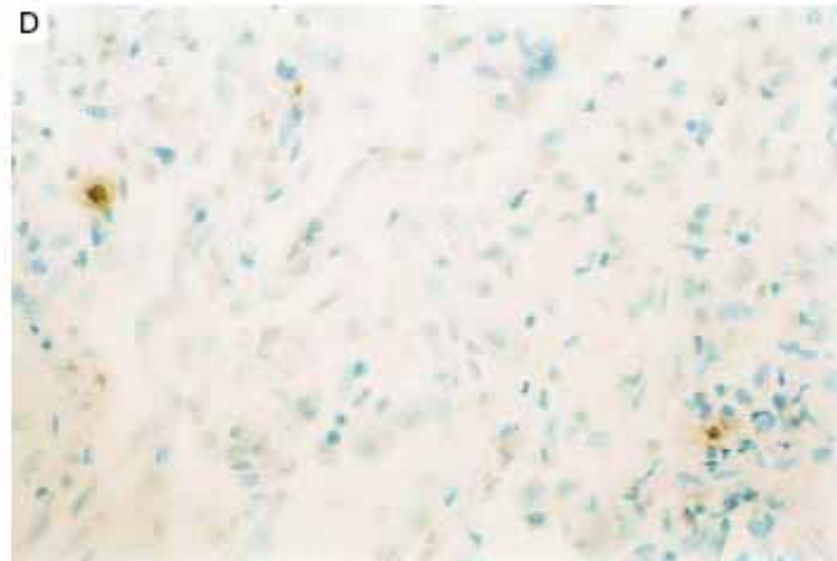
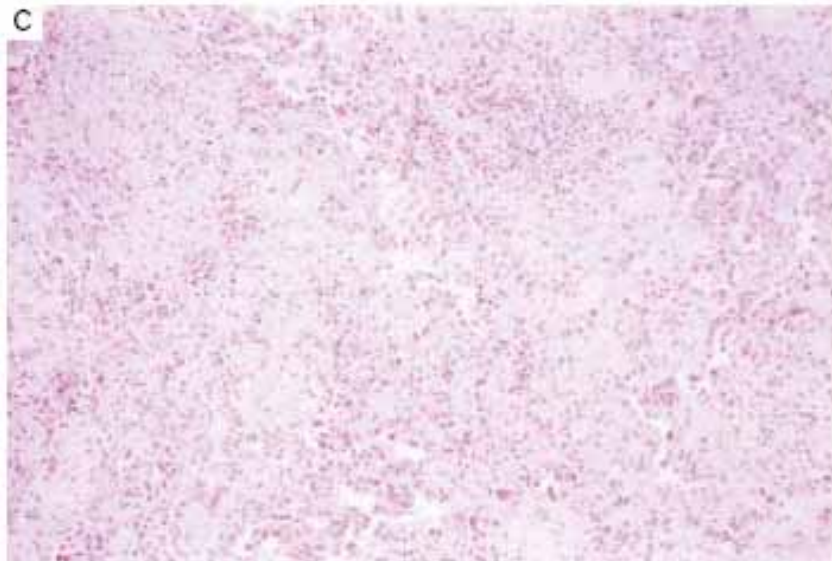
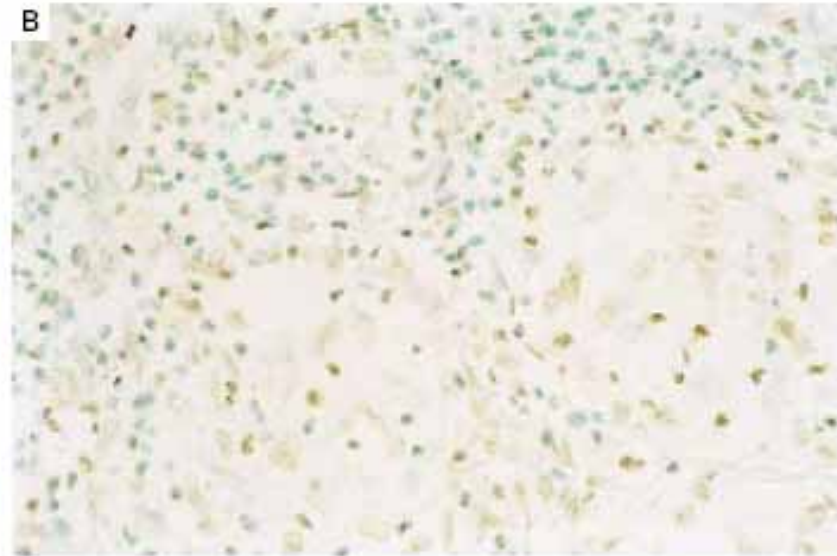
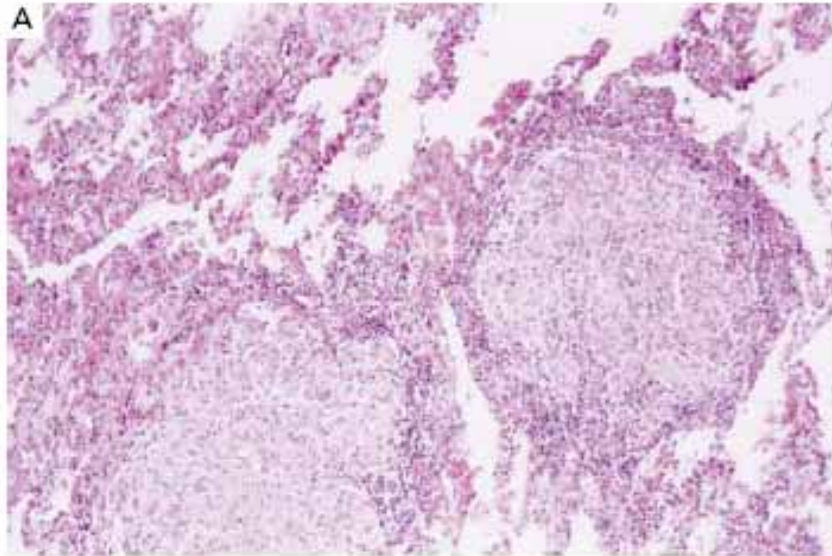
# Anti-tumour necrosis factor agents: infliximab and etanercept



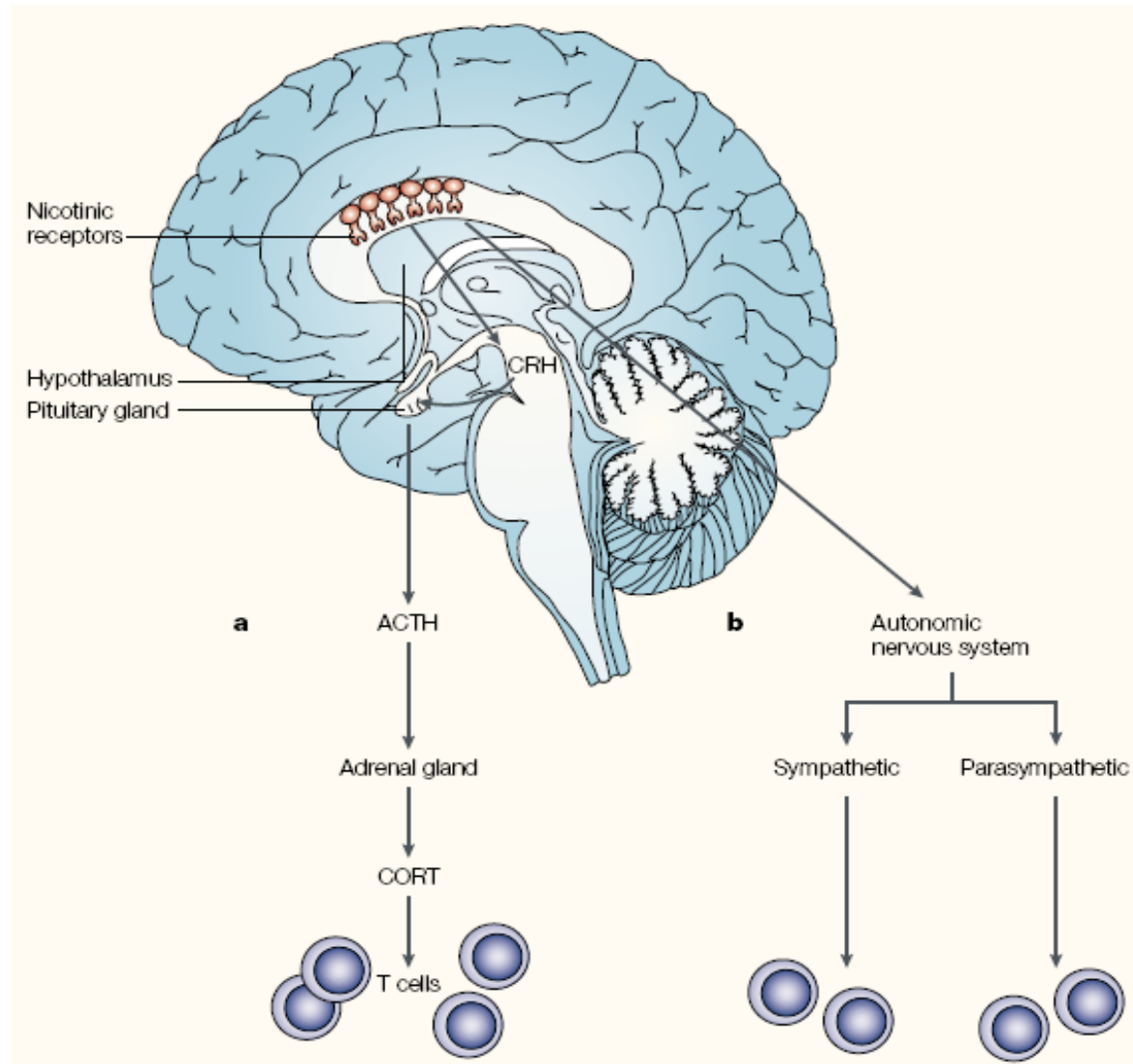
# Tuberculosis associated with infliximab, a tumor necrosis factor $\alpha$ -neutralizing agent

- There were 70 reported cases of tuberculosis after treatment with infliximab for a median of 12 weeks. In 48 patients, tuberculosis developed after three or fewer infusions.
- Forty of the patients had extrapulmonary disease (17 had disseminated disease, 11 lymph-node disease, 4 peritoneal disease, 2 pleural disease, and 1 each meningeal, enteric, paravertebral, bone, genital, and bladder disease).
- The rate of reported cases of tuberculosis among patients treated with infliximab was higher than the available background rates (24.4 per 100,000 vs 6.2 per 100,000)





A simplified schematic of possible communication between the CNS and the immune system through nicotinic acetylcholine receptors



# Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin

- A previously unrecognized, parasympathetic anti-inflammatory pathway by which the brain modulates systemic anti-inflammatory responses to endotoxin.
- Acetylcholine, the principle vagal neurotransmitter, significantly attenuated the release of cytokines (tumour necrosis factor (TNF), interleukin (IL)-1b, IL-6 and IL-18), but not IL-10, in lipopolysaccharide-stimulated human macrophage cultures.
- Direct electrical stimulation of the peripheral vagus nerve in vivo during lethal endotoxaemia in rats inhibited TNF synthesis in liver, attenuated peak serum TNF amounts, and prevented the development of shock.

Borovikova LV, et al. Nature 2000;405:458-462.



# Nicotinic acetylcholine receptor $\alpha 7$ subunit is an essential regulator of inflammation

- The nervous system, through the vagus nerve, can inhibit significantly and rapidly the release of macrophage TNF, and attenuate systemic inflammatory responses - termed the 'cholinergic anti-inflammatory pathway.
- the nicotinic acetylcholine receptor  $\alpha 7$  subunit is responsible for acetylcholine inhibition of macrophage TNF release.



# The vagus nerve, macrophages, and nicotine

- A higher rate of tuberculosis among patients using infliximab
- Nicotinic acetylcholine receptor  $\alpha 7$  subunit is specifically responsible for acetylcholine inhibition of macrophage TNF release.
- Nicotine is a potent agonist of  $\alpha 7$  nicotinic acetylcholine receptor. Smokers seems to be less likely to develop immune-mediated granulomatous diseases of the lung
- **nicotine inhibition of TNF release may reduce containment of tuberculosis and predispose to active disease.**



# Tobacco Control and Tuberculosis Control

- There appears to be enough evidence to conclude that smoking is causally associated with tuberculosis disease.
- Smoking has been found to be associated with relapse. Patients with tuberculosis need and should receive counseling and assistance in stopping smoking.
- Although tobacco use is a serious public health concern, tobacco control has so far been neglected in terms of tuberculosis control. The potential contribution of tobacco control to the fight against tuberculosis needs to be investigated.

