



Tobacco and Tuberculosis:

Risk and Interventions

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Presentation Outline

- Evidence for tobacco as a risk factor for:
 - TB infection, TB disease, TB mortality
- Tobacco and TB treatment outcomes
- Tobacco cessation interventions

TB AND SMOKING TOBACCO: A Deadly Combination

more than
10 MILLION
people around the world
became sick with TB disease
in 2015.

more than
1.8 MILLION
people died from
TB disease in 2015.

more than
1 BILLION
people smoke tobacco
worldwide.



more than
6 MILLION
people die from tobacco
use each year worldwide.

Tobacco smoking and TB disproportionately affect people in low- and middle-income countries.



Nearly **1 in 4** people worldwide are infected with TB.



1 in 5 cases of TB disease around the world are attributable to tobacco smoking.

PEOPLE WHO SMOKE TOBACCO...

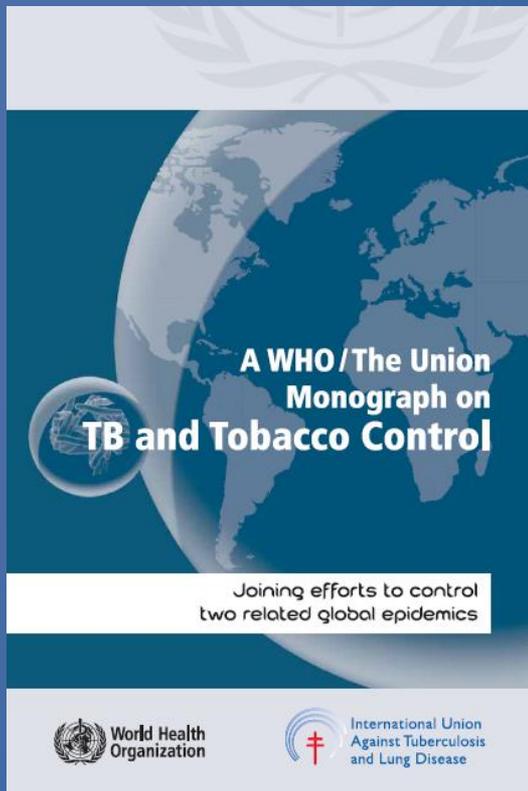


have a **GREATER** risk of developing TB and are less likely to be cured of the disease.



have a **GREATER** risk of dying from TB disease.

Evidence continues to grow



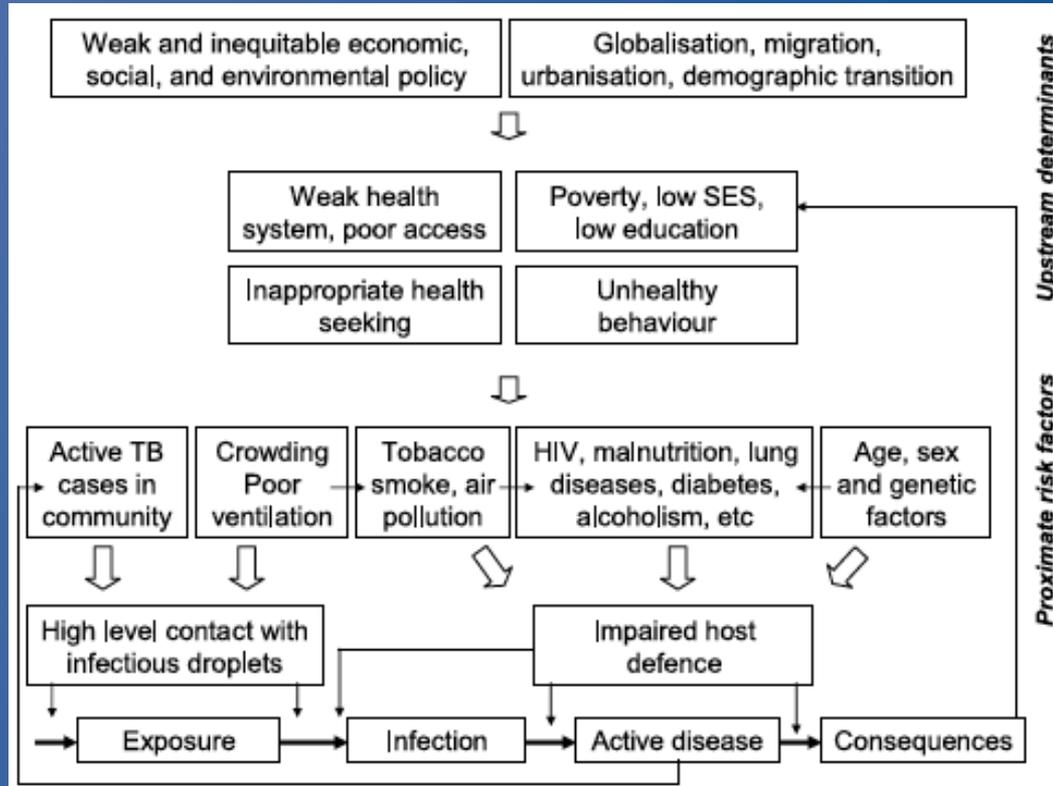
- “This review indicates that passive or active exposure to tobacco smoke is significantly associated with **tuberculosis infection** and **tuberculosis disease**. Active smoking is significantly associated with **recurrent tuberculosis** and tuberculosis **mortality**. These effects appear to be independent of the effects of alcohol use, socioeconomic status and a large number of other potential confounders.”
- At least 8 systematic reviews/meta-analyses over the past 10 years

Smoking prevalence among TB patients

	South Africa	Republic of Georgia	Pakistan
TB incidence	834/100,000	116/100,000	510/100,000
Population smoking estimate	7% females 29% males	6% females 52% males	4% females 23% males
Prevalence among TB patients	11% females 43% males	14% females 55% males	3% females 23% males

* Smoking estimates ALWAYS greater when include smoking at time TB symptoms began

TB Risk Factors

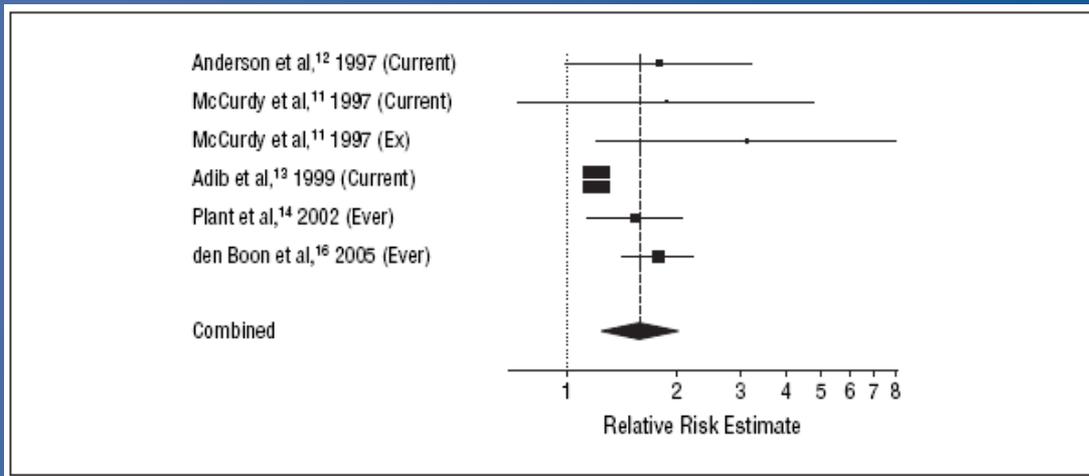


Active Smoking as a RF for Tuberculosis Infection

- Smokers are at risk for bacterial and viral infections (Arcavi 2004)
- Tobacco smoke causes mechanical disruption of cilia function in the airways, thus permitting an easier pathway for *M. tuberculosis* to reach the alveoli where infection begins (Arcavi 2004; Atlet 1996)
- Is smoking an independent risk factor for tuberculosis infection?

Active Smoking as a RF for Tuberculosis Infection (2)

- Limited studies looking at active smoking and TB infection
- Temporality very difficult to establish

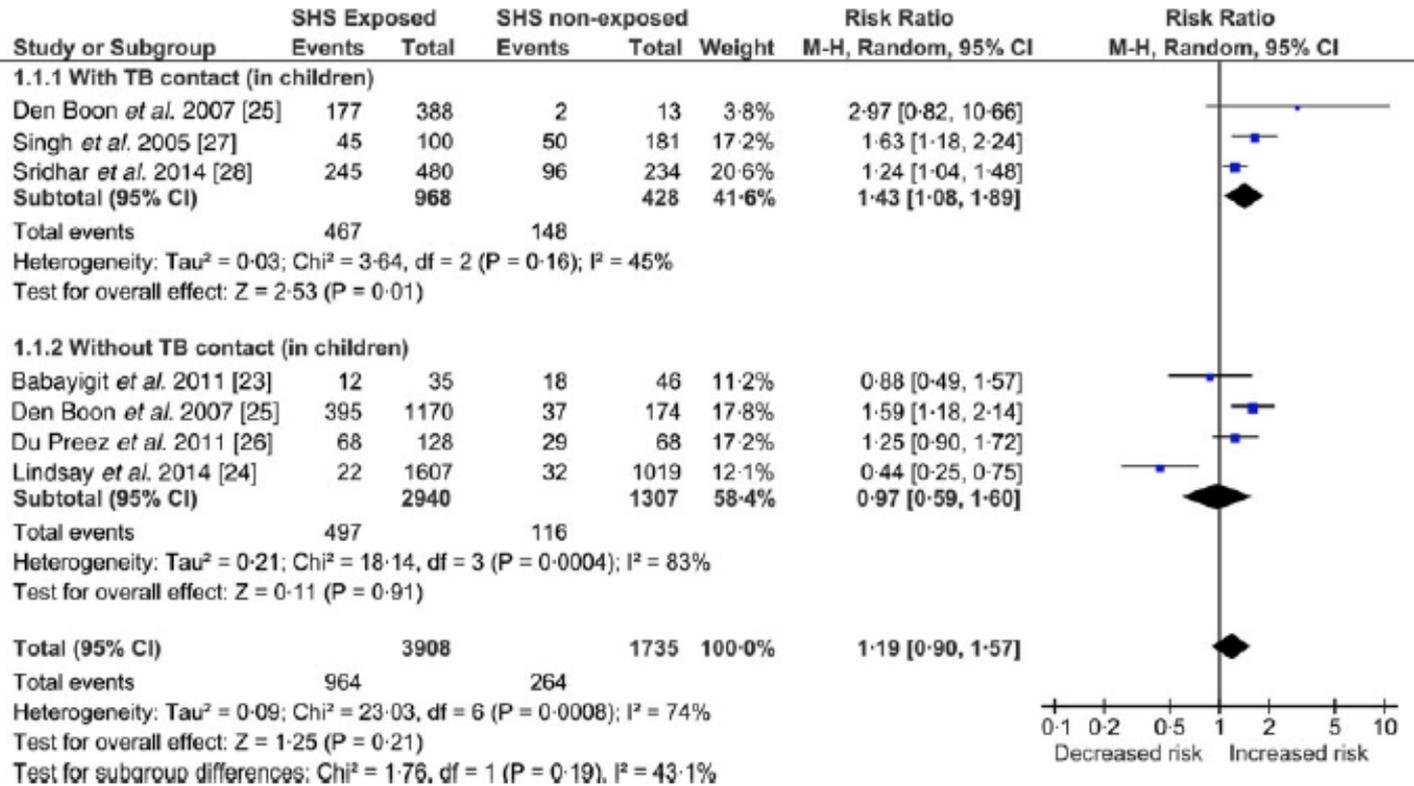


Pooled RR ~1.7 (1.5-2.0)

Passive Smoking as a RF for Tuberculosis Infection

- Passive exposure investigated among children (children recently infected)
- Children living in households of TWO parents who smoke twice as likely to be latently infected (Kuemmerer and Comstock 1967)
 - No adjustment for potential confounders
- Children of sputum smear positive TB patients who smoked were ~3 times as likely to be infected compared to children of sputum smear positive patients who did NOT smoke (Singh 2005)
- Children exposed to passive smoke and living with an active TB case reported over a 4-fold risk of latent infection (den Boon 2007)
 - Only in households with a TB case – smokers may have delayed diagnosis

Passive Smoking as a RF for Tuberculosis Infection

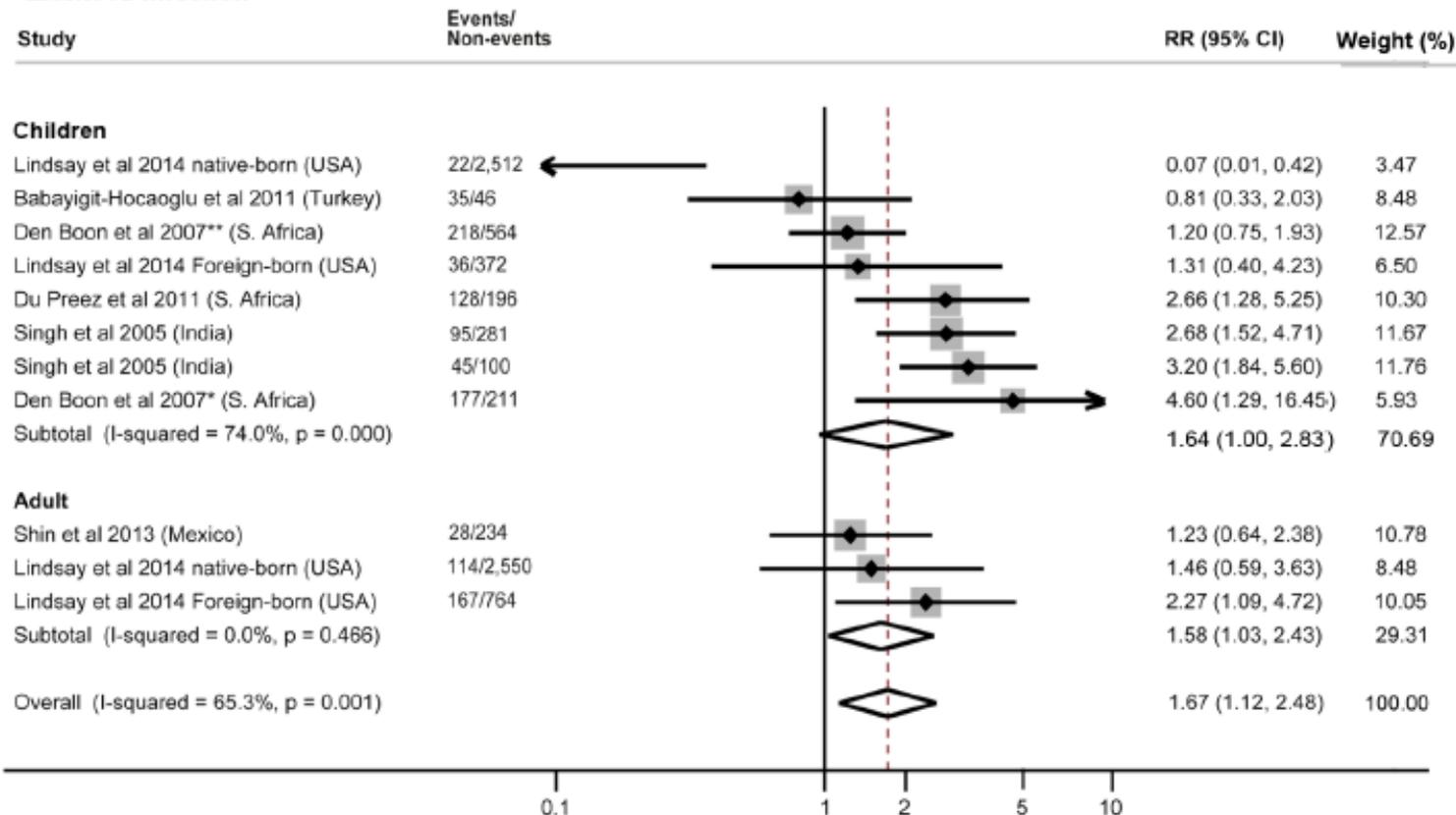


Pooled RR for children with TB contact = 1.43 (1.08-1.89)

Pooled RR for children without TB contact = 0.97 (0.59-1.60)

Passive Smoking as a RF for Tuberculosis Infection

A Latent TB infection



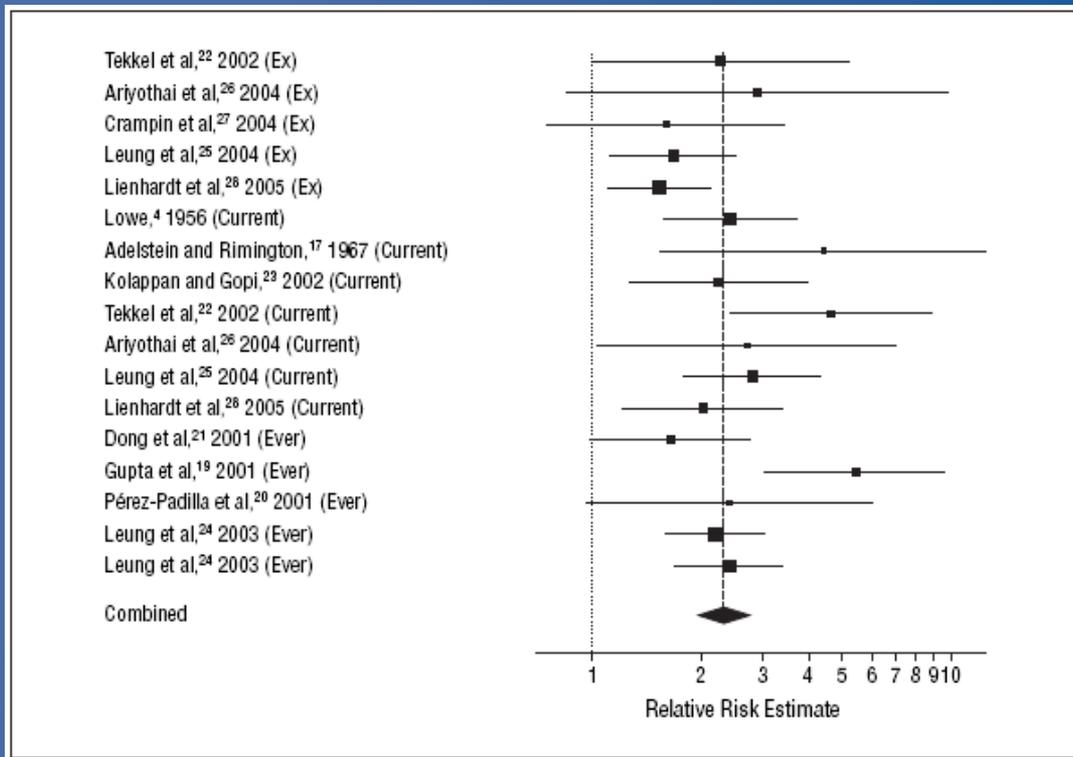
Pooled RR for
Children =
1.64 (1.00-2.83)

Adults =
1.58 (1.03-2.43)

Active Smoking as a RF for Tuberculosis Disease

- Where does smoking fit in?
 - Smoking has widespread effects on lung structure and function and affects host defenses both in the lung and systemically
 - Nicotine/tobacco smoke disrupts function of macrophages – key defenders against TB
- Strongest evidence for an association
 - Prospective cohort studies from Hong Kong, Taiwan, Korea
 - More adjustment for potential confounders

Active Smoking as a RF for Tuberculosis Disease (2)

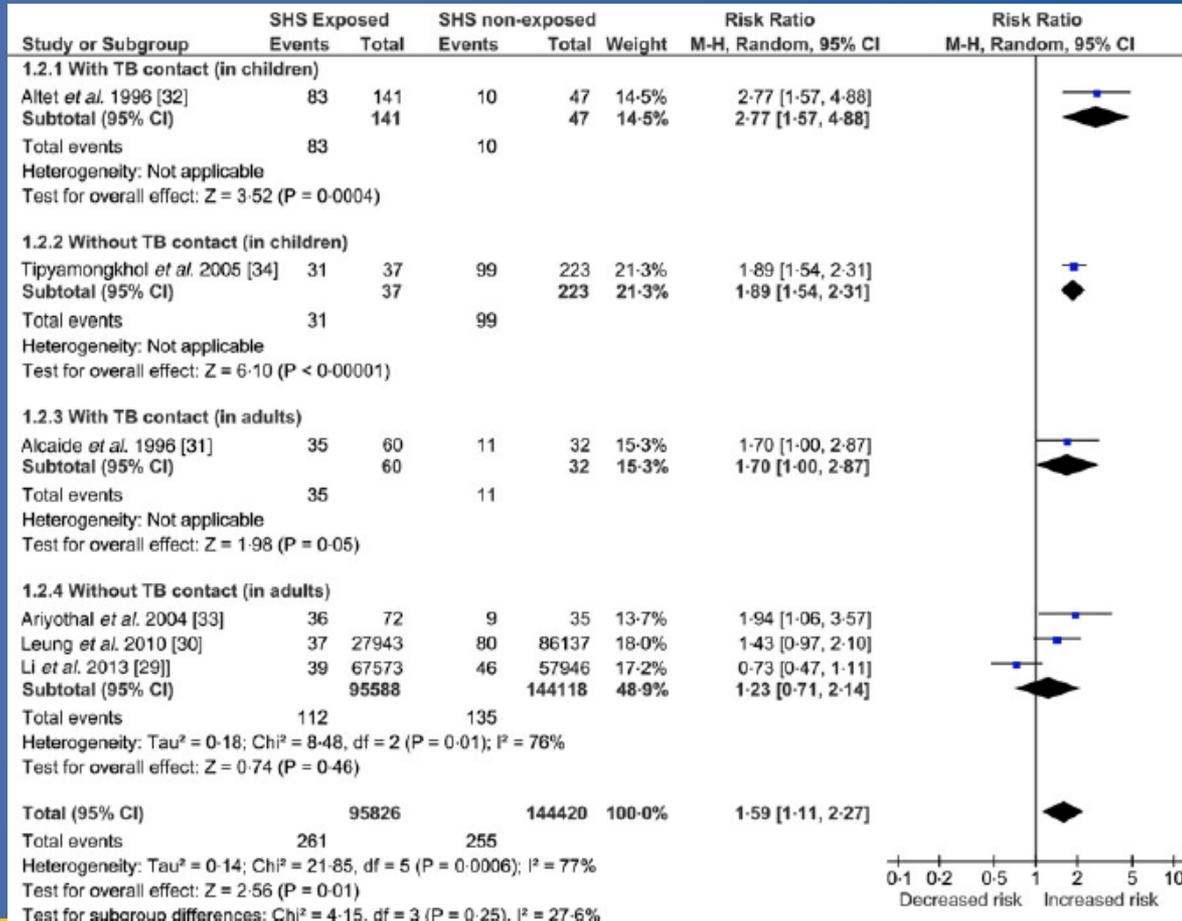


Pooled RR ~ 2.3 (2.0-2.8)

Passive Smoking as a RF for Tuberculosis Disease

- Very few studies: Spain, Thailand, Estonia, Hong Kong
 - Children and Adults → predominantly case-control
 - Strong risk estimates
- Prospective study directly assessed this relationship in adults (Leung 2010)
 - Never smoking females age 65-74 living with their surviving husbands were linked with TB notification and death registries
 - Passive exposure to secondhand smoke in household independently associated:
 - Active TB during follow-up (HR=1.49, 1.01-2.19)
 - Culture confirmed TB (HR=1.70, 1.04-2.80)
 - Passive smoking accounted for 14% of active TB, 19% culture-positive TB

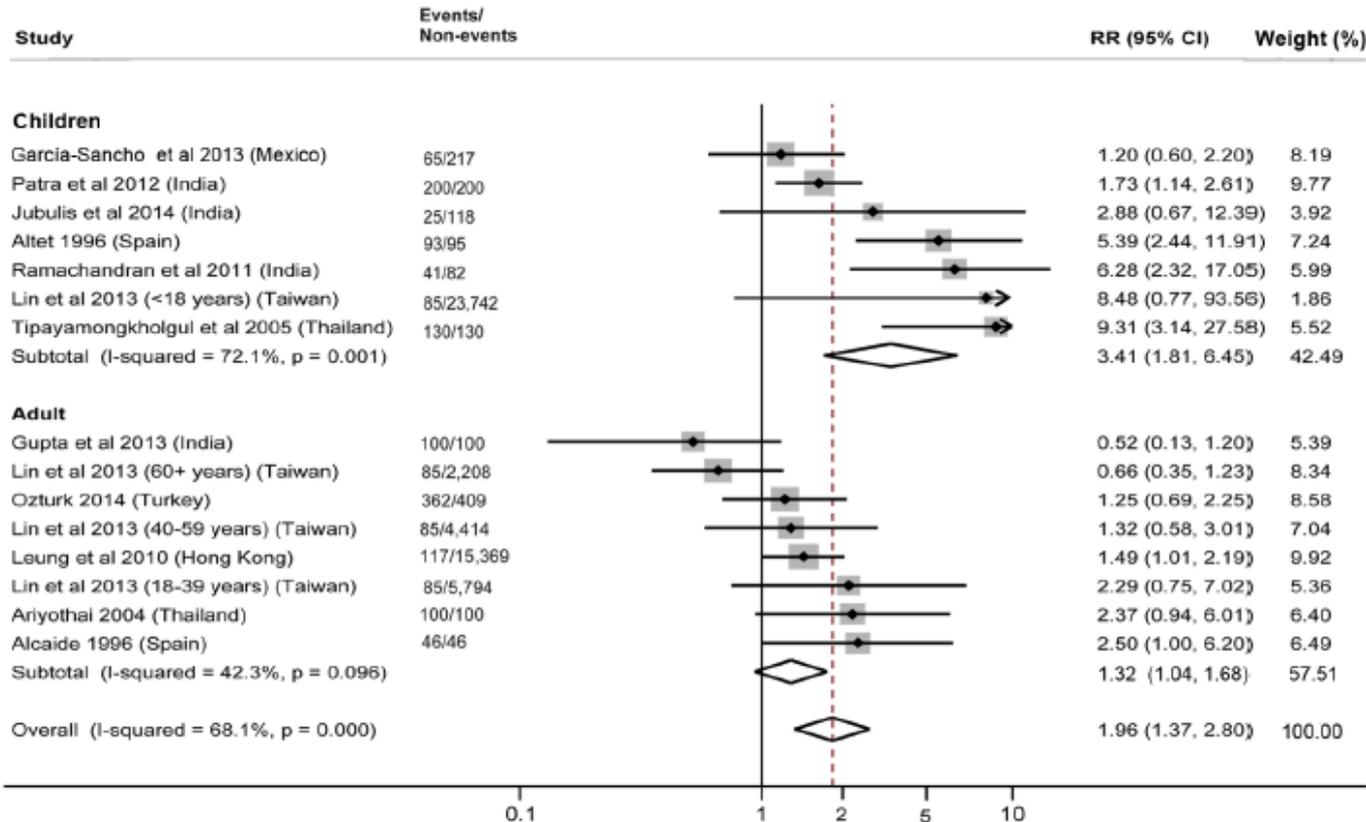
Passive Smoking as a RF for Tuberculosis Disease (2)



- Heterogeneity explained by age
- Lin (2013) found no association in large Taiwan study of general population

Passive Smoking as a RF for Tuberculosis Disease (3)

B Active TB disease



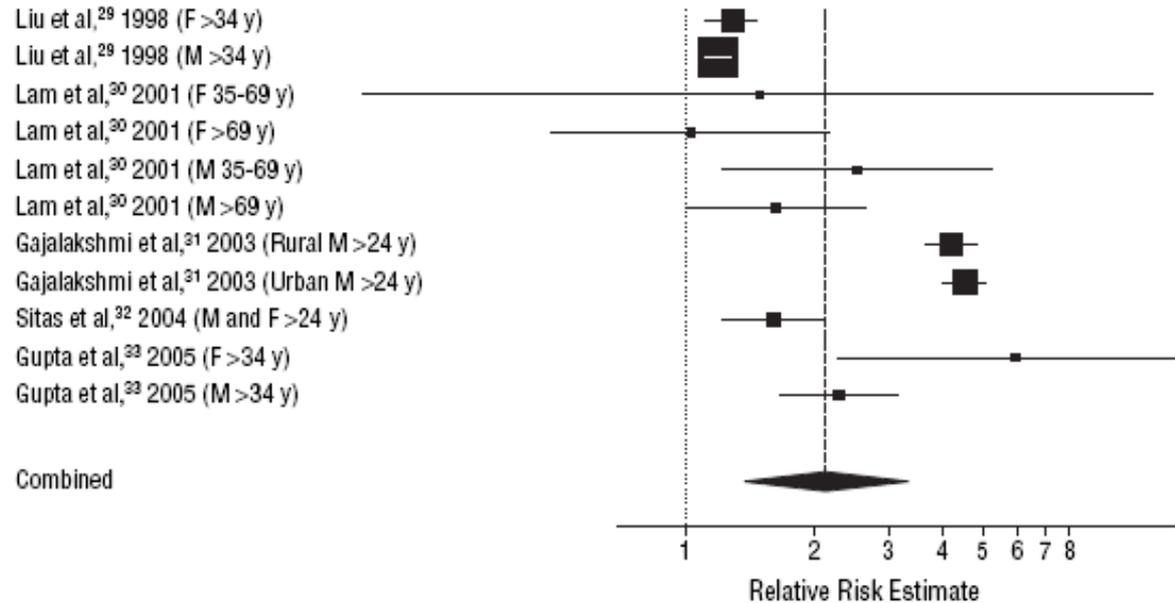
Pooled RR for children =
3.41 (1.81-6.45)

Pooled RR for adults =
1.32 (1.04-1.68)

Active Smoking as a RF for Tuberculosis Mortality

- Evidence less than for TB disease, and few studies account for potential confounders; UK, China, India, Hong Kong, Korea, South Africa
- British Doctor's Study (Doll 1954-1999)
 - Deaths due to pulmonary TB one of 25 diseases linked to cigarette smoking

Active Smoking as a RF for Tuberculosis Mortality



Pooled RR ~ 2.1 (1.4-3.4)



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Original Contribution

Smoking and Risk of Tuberculosis Incidence, Mortality, and Recurrence in South Korean Men and Women

Sun Ha Jee, Jonathan E. Golub, Jaeseong Jo, Il Su Park, Heechoul Ohrr*, and Jonathan M. Samet

- 14 year prospective study (1992-2006) among 1.3 million South Koreans
- Adjusted for age, alcohol use and stratified by sex
 - Current smokers – 58% among men; 4% among women

Table 4. Effect of Smoking and Alcohol Drinking on Incident Tuberculosis in Men and Women, Korean Cancer Prevention Study, 2001–2005

	Men					Women				
	No. of Cases	Model 1 ^a		Model 2 ^b		No. of Cases	Model 1 ^a		Model 2 ^b	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Smoking status										
Nonsmoker	1,451	1.0		1.0		4,179	1.0		1.0	
Ex-smoker	2,112	1.2	1.1, 1.3	1.2	1.1, 1.3	155	1.1	0.9, 1.3	1.1	0.9, 1.3
Current smoker	5,094	1.4	1.3, 1.5	1.2	1.2, 1.3	275	1.1	1.0, 1.2	1.0	0.9, 1.1
Amount of smoking^c (among current smokers), cigarettes/day										
1–9	1,064	1.2	1.1, 1.3	1.1	1.0, 1.2				No data	
10–19	2,497	1.4	1.3, 1.5	1.2	1.2, 1.3				No data	
≥20	1,527	1.5	1.4, 1.6	1.4	1.3, 1.5				No data	
Alcohol drinking, g/day										
Nondrinker	2,045	1.0		1.0		3,829	1.0		1.0	
<25	5,087	0.9	0.9, 1.0	1.0	0.9, 1.1	778	1.0	0.9, 1.1	1.0	1.0, 1.1
25–49.9	722	1.0	0.9, 1.1	1.1	1.0, 1.2				No data	
50–99.9	607	1.2	1.1, 1.3	1.3	1.2, 1.4	2	0.6	0.2, 2.5	0.6	0.2, 2.5
≥100.0	196	1.5	1.3, 1.7	1.6	1.4, 1.9				No data	

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Results were adjusted for age and age squared.

^b Results were adjusted for age, age squared, and body mass index.

^c Six cases among men had missing information on amount of smoking.

- Smoking increased TB incidence in men

Table 5. Effect of Smoking and Alcohol Drinking on Risk of Recurrent Tuberculosis in Men and Women, Korean Cancer Prevention Study, 2001–2005

	Men					Women				
	No. of Cases	Model 1 ^a		Model 2 ^b		No. of Cases	Model 1 ^a		Model 2 ^b	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Smoking status										
Nonsmoker	720	1.0		1.0		942	1.0		1.0	
Ex-smoker	1,400	1.3	1.1, 1.4	1.3	1.2, 1.4	34	1.2	0.9, 1.8	1.2	0.9, 1.8
Current smoker	2,409	1.3	1.2, 1.4	1.2	1.1, 1.3	41	1.2	0.8, 1.6	1.0	0.7, 1.4
Amount of smoking^c (among current smokers), cigarettes/day										
1–9	571	1.3	1.2, 1.5	1.2	1.1, 1.4	22	1.1	0.7, 1.7	0.9	0.6, 1.4
10–19	1,188	1.3	1.2, 1.4	1.2	1.1, 1.3	12	1.1	0.6, 2.0	0.8	0.5, 1.6
≥20	645	1.4	1.2, 1.5	1.3	1.2, 1.5	6	1.6	0.7, 3.6	1.4	0.6, 3.2
Alcohol drinking, g/day										
Nondrinker	1,139	1.0		1.0		843	1.0		1.0	
<50	3,008	0.9	0.9, 1.0	1.0	0.9, 1.1	174	1.0	0.8, 1.2	1.0	0.9, 1.2
≥50	382	1.2	1.0, 1.3	1.3	1.1, 1.4					No data

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Results were adjusted for age and age squared.

^b Results were adjusted for age, age squared, and body mass index.

^c Five cases among men and 1 case among women had missing information on amount of smoking.

- Smoking increased TB recurrence in men but not women

Table 3. Effect of Smoking and Alcohol Drinking on Mortality From Tuberculosis, Korean Cancer Prevention Study, 1993–2006

	Men					Women				
	No. of Cases	Model 1 ^a		Model 2 ^b		No. of Cases	Model 1 ^a		Model 2 ^b	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Smoking status										
Nonsmoker	107	1.0		1.0		119	1.0		1.0	
Ex-smoker	188	1.45	1.14, 1.85	1.37	1.07, 1.75	22	2.16	1.35, 3.46	1.98	1.21, 3.24
Current smoker	364	1.58	1.27, 1.97	1.21	0.96, 1.51	27	1.55	1.00, 2.41	1.08	0.67, 1.74
Amount of smoking (among current smokers), cigarettes/day										
1–9	119	1.55	1.19, 2.00	1.17	0.89, 1.53	13	1.34	0.75, 2.41	1.02	0.55, 1.88
10–19	149	1.62	1.26, 2.08	1.24	0.96, 1.60	11	1.93	1.00, 3.70	1.10	0.50, 2.38
≥20	96	1.59	1.20, 2.10	1.22	0.91, 1.62	3	1.59	0.50, 5.02	1.33	0.42, 4.21
Alcohol drinking, g/day										
Nondrinker	262	1.0		1.0		147	1.0		1.0	
<50	370	0.83	0.70, 0.97	0.91	0.77, 1.08	21	0.72	0.45, 1.15	0.78	0.48, 1.26
≥50	27	1.00	0.66, 1.51	1.31	0.86, 1.97					No data

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Results were adjusted for age and age squared.

^b Results were adjusted for age, age squared, and body mass index.

Smoking
 increased TB
 mortality in men
 and women

Summary of Pooled Data: Causality?

Meta-analysis	Pooled relative risk (95% CI)		
	TB infection	TB disease	TB mortality
Studies n	~6	~15	~5
SLAMA [2]	~1.8 (1.5–2.1)	~2.3 (1.8–3.0)	~2.2 (1.3–3.7)
LIN [3]	1.7–2.2 (1.5–2.8)	~2.0 (1.6–2.6)	~2.0 (1.1–3.5)
BATES [4]	~1.7 (1.5–2.0)	~2.3 (2.0–2.8)	~2.1 (1.4–3.4)

van Zyl Smit 2010

Temporality	No	Yes	Yes
Consistency	Yes	Yes	Yes
Strength of association	Moderate	Moderate	Moderate
Dose-response	No	Yes	Yes
Biological Plausibility	Yes	Yes	Yes
Other factors considered	Weak	Yes	Weak
Specificity	No	No	No

Evidence Summary (Surgeon General's Report)

TB Outcome	Tobacco Exposure	Evidence
TB Infection	Passive	Weak
	Active	Weak
TB Disease	Passive	Moderate
	Active	Strong
TB Mortality	Passive	NA
	Active	Moderate

Confounders and Other Factors to Consider

- Alcohol
 - Most significant confounder
 - For TB infection and TB disease, smoking effect does not disappear with inclusion of alcohol, but is reduced
- SES
 - For active TB disease, adjustment for SES does not greatly reduce smoking effect
- Gender
 - Males smoke more, males have more TB
 - Smoking may account for some of the gender gap in TB rates
- Co-morbidities
 - Diabetes increases TB mortality among smokers (Reed 2013; Korea)
 - PLWH who are smokers have higher risk of TB (Bronner 2016; South Africa)
- Reverse causation
 - Former/Ex/Quitters sometimes reported to have equal/greater risk than current smokers
 - Likely due to the misclassification of “former/ex” → likely quit upon developing TB symptoms and self-reported non-smoker at time of TB diagnosis

Tobacco impact on TB treatment outcomes

- Delays sputum and culture conversion
- Increases relapse and recurrence

Tobacco impact on TB treatment outcomes

Table 2. **Smoking status and treatment outcomes among adults with tuberculosis, Georgia, 2011–2012**

Treatment outcome ^a	No. (%)		
	Never smokers (<i>n</i> = 122)	Past smokers (<i>n</i> = 159)	Current smokers (<i>n</i> = 243)
Favourable	101 (82.8)	132 (83.0)	163 (67.1)
Cured	42 (34.4)	69 (43.4)	81 (33.3)
Completed treatment	59 (48.4)	63 (39.6)	82 (33.7)
Poor	21 (17.2)	27 (17.0)	80 (32.9)
Defaulted treatment	16 (13.1)	22 (13.8)	61 (25.1)
Failed treatment	1 (0.8)	3 (1.9)	7 (2.9)
Died	4 (3.3)	2 (1.3)	12 (4.9)

Smoking cessation among TB patients

- “Teaching Moment”
- Captive audience
- Decrease treatment default
- Decrease mortality
- Decrease recurrence
- Increase long-term cessation?
- Cochrane review 2016 – “Empty”



Reducing the number of people who smoke tobacco can reduce the number of people who get infected or have TB disease, and the number who die of the disease.

People with TB infection or disease have frequent visits with a health care provider for diagnosis and ongoing treatment.

Health care providers should ask their patients with TB infection or disease about tobacco smoking, and if they use tobacco, help them quit.



Review on Smoking Cessation Interventions: Methods

Search Engines	PubMed, Embase, Scopus, CINAHL, Web of Science, and Cochrane Review
Hand Searching	Reference lists of identified articles and bibliographies
Search Terms	Tuberculosis, Smoking Cessation, and medications (e.g. Bupropion)
Inclusion Criteria	<ul style="list-style-type: none">• Smoking Cessation Intervention with presumed or confirmed TB patients• All ages and genders• Any location (although results were all LMICs)• English, Spanish, French, Portuguese, or Korean
Exclusion Criteria	<ul style="list-style-type: none">• No data on outcome of smoking cessation intervention• Study protocols

Review on Smoking Cessation Interventions: Results

- From 1645 articles, 14 studies identified (13 interventions)
- 11 different countries (e.g. Indonesia, Sudan, Pakistan, South Africa)
- Study Designs
 - Randomized controlled trials (n=3)
 - Cluster randomized trials (n=2)
 - Non-randomized interventions (n=3)
 - Prospective cohort studies (n=5)
- Smoking abstinence & cessation operationalized differently (i.e. smoking a puff in the last 3 months, in the last 2 weeks, or at the time of TB diagnosis)
- All based on The Union or WHO smoking cessation guidelines

Summary of components by intervention type

Type of intervention	Possible components	Who delivered intervention	Time required
Brief advice	<ul style="list-style-type: none"> -Open ended questions -Information on the benefits and risk of smoking -Refer to smoking cessation counselor within facility (TB or Primary Healthcare Center) -Advice on making homes smoke-free -Encouragement to speak with their families for understanding and support of quitting -No smoking sign for home 	Nurse, CHW, Physician, DOT provider	<ul style="list-style-type: none"> -Typically 5-10 minutes (up to 20 minutes) -Treatment initiation -Follow-up visits varied from none to every TB visit
Behavioral counseling	<ul style="list-style-type: none"> -Motivational interview assessment and solution development -Behavioral change technique based on 5 A's such as envisioning person as non-smoker -Identify specific situations likely to be difficult and develop coping strategies -Follow-up on the set quit date to review progress 	CHW, DOT provider	<ul style="list-style-type: none"> -15-30 minute initial session -Shorter follow-up sessions
Medication	<ul style="list-style-type: none"> -Nicotine replacement therapy -Bupropion (7-9 weeks) 	Physician	Consult for initial prescription and follow-up to monitor for side effects
Community based care	<ul style="list-style-type: none"> -Information on the benefits and risk of smoking -Proactive support to quit and maintain abstinence including smoke-free home 	CHW, Family members	<ul style="list-style-type: none"> -With community health visits weekly or monthly -Ongoing with family member including post-TB treatment

CHW: Community Health worker; DOT: Direct observed therapy

Results: Randomized Controlled Trials

Author/Year	Intervention Type, Provider & Dosing	Key Findings
Aryanpur et al., 2016; Iran	Behavioral counseling + medication / Physician 4 sessions + 9 wks of med	Smoking abstinence at 6 months was 71.7% BSS+, 33.9% BSS and 9.8% CG (p<0.001). Behavioral counseling increased smoked cessation (OR=7.1, 95% CI 2.7-18.7) and medication increased the effect (OR=35.3, 95% 13.8-90.3).
Kumar et al., 2017; India	Brief advice Physician; 1 session	There was no difference between MD and counselor (RR=1.2, 95% CI 0.8-18). Among TB patients, 40.5% quit from CG and 44.4% from IG (p=0.735).
Louwagie et al., 2014; South Africa	Motivational Interviewing CHW 1 session + f/u surveys	Self-reported 6 months sustained abstinence was 21.5% for IG and 9.3% for CG (RR=2.29, 95% CI 1.4-3.92).
Nichter et al., 2016; Indonesia	Brief advice plus family Physician or family member Every TB visit	No difference between the interventions (73% I-MD, 71% IG-family , X ² >0.05).
Siddiqi et al., 2013; Pakistan	Behavioral counseling + medication DOT facilitator & physician 2 sessions + 7 wks of meds	Behavioral support with and without medications reduced smoking (BSS RR=8.5, 95% CI 3.7-19.6; BSS+ RR=9.3 95% CI 4.0-21.6). 6-month smoking abstinence was 8.5% CG, 41.0% BSS, & 41.5% BSS+. There was no added benefit to medications for quit rates (RR=1.1 95% CI 0.5-2.3).
Dogar et al., 2014; Pakistan (Analysis of Siddiqi et al 2013)	Behavioral counseling + medication / DOT/physician 2 sessions + 7 wks of meds	Intervention had greater impact on cigarette smokers OR=5.8 , 95% CI 4.0-8.5; BSS+ OR=6.6, 95% CI 4.6-9.6) than hookah smokers (OR=2.2 , 95% CI 1.3-.38; BSS + OR =2.5 95% CI 1.3-4.7)

Results: Non-randomized Interventions

Author/Year	Intervention Type, Provider & Dosing	Key Findings
Awaisu et al., 2011; Malaysia	Behavioral counseling + nicotine replacement therapy Nurse/Physician 11 sessions + medication	Patients were enrolled into IG based on motivation to quit. The intervention increased smoking abstinence (4-week abstinence at month 6): 77.5% IG vs 8.7% CG , $p < 0.001$).
Campbell et al., 2014; Nepal	Brief advice Healthcare worker 3 sessions	Simple brief advice lead to 39% quit rate compared with 0% in the control group ($p < 0.0001$) over 6 months within the NTP program using existing staff.
El Sony et al., 2007; Sudan	Brief Advice Medical Assistant 4 sessions	Quit rate was 56.3% compared with 14.3% at the control centers.

Results: Prospective Cohort Studies

Author/Year	Intervention Type, Provider & Dosing	Key Findings
Bam et al., 2015, Indonesia,	Brief advice Healthcare worker Every TB visit	The intervention led to high quit rates (41.4% at month 1 & 66.8% at month 6) , greater awareness of second hand smoke risk, and more smoke-free homes.
Kaur et al., 2013, India,	Brief advice Healthcare worker 1 session + follow-ups	The intervention was feasible in existing programming with minimal financial resources and infrastructure. Among smokers, 67.3% quit tobacco, 18.2% relapsed and 14.5% were lost to follow-up at the end of treatment.
Lin et al., 2015, China,	Brief advice Healthcare worker 1 session	Smokers with TB were willing to quit (96%) with a 66.7% cessation rate at 6 months . Only 3% of patients (n=7) relapsed at 6 months.
Sereno et al., 2012, Brazil,	Brief advice Nurse 1 session	Smoking cessation was feasible but modified from 5As to AAR (ask, advise, refer) by providers to help with intervention adherence. 15% (3 out of 28 smokers) reported quitting after 3 months.
Siddiqi et al., 2013, Bangladesh,	Brief advice + community follow-up HCW & community volunteer 1 session + biweekly visits at home	Modified ABC's for brief advice is feasible and effective, with 82% smoking reduction by month 6 . High nicotine dependence and extra-pulmonary TB decreased likelihood of cessation. Community volunteers may have contributed to high quit rates.

Review on Smoking Cessation Interventions: Discussion

- Practice
 - Any healthcare worker can intervene with smoking cessation
 - Involvement of family members may increase and sustain the effect
 - Training and supervision of staff on smoking cessation messages specific to TB and counseling methods is needed
 - The added benefit of medications needs to be further explored
 - Mobile technology could assist with smoking cessation messaging
- Research
 - Further research is needed to determine what interventions work best for which patients (e.g. adaptive trials, qualitative work)
 - Standardize definitions of smoking and cessation will improve comparisons across studies and national TB programs
 - Follow patients beyond TB treatment to understand smokers who resume
 - Include cost-effectiveness analysis

Review on Smoking Cessation Interventions: Discussion (cont.)

- Policy Implication/Recommendations
 - Include standardized smoking indicators in TB clinical documentation and TB program evaluations to allow for comparisons across programs
 - Support the necessary training and supervision required to integrate smoking cessation messages/programs
 - Consider the integration of non-communicable (e.g. tobacco control) and infectious disease programming to share resources and strengthen programs

Impact of smoking cessation

- Among persons at risk of TB
 - Does risk revert after quitting?
 - Very few studies
 - Wen et al (2010) report mortality risk declines 65% among quitters compared to non-quitters (similar risk as never smokers)
- Among persons diagnosed with TB
 - Are treatment outcomes better among patients who quit?
 - Treatment adherence
 - Treatment completion
 - Culture conversion
 - Relapse/Recurrence
 - Mortality

Impact of smoking cessation

■ Among persons at risk of TB (Lin 2007)

