

Tuberculosis and smoking

Evidence of association and public health implications

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Aug 19, 2013

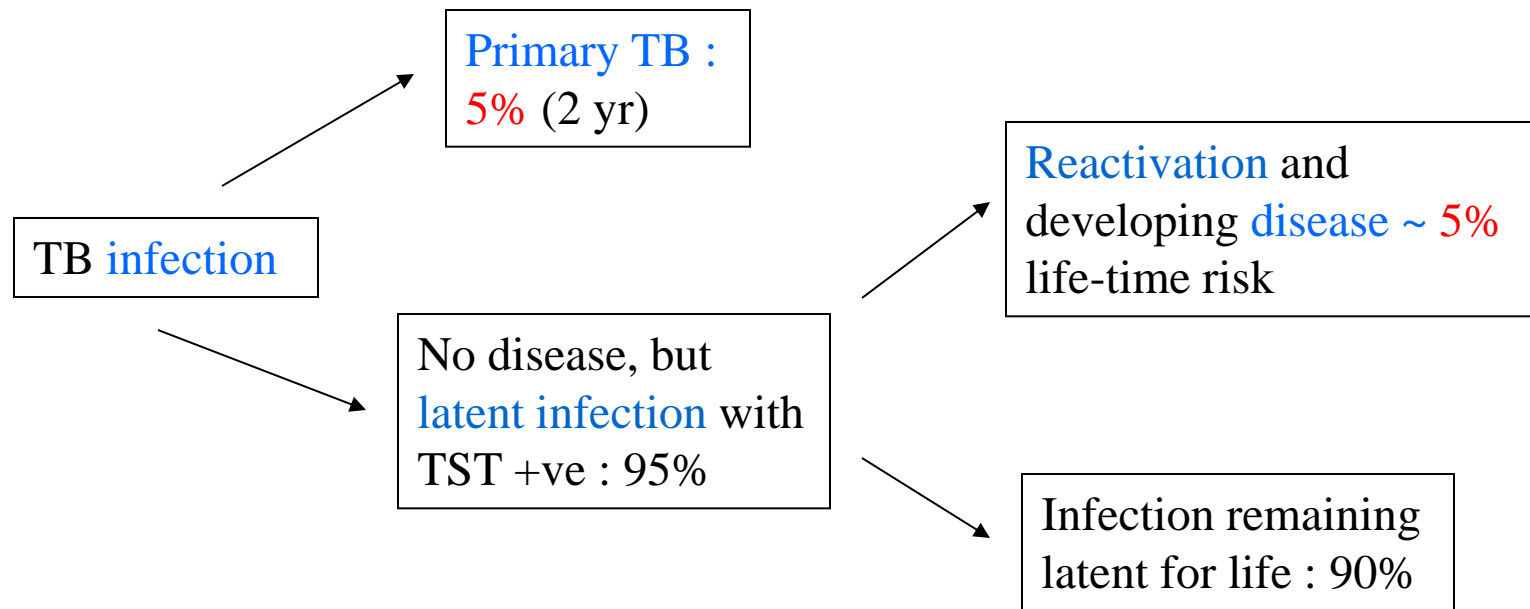


I have no conflict of interest to declare.

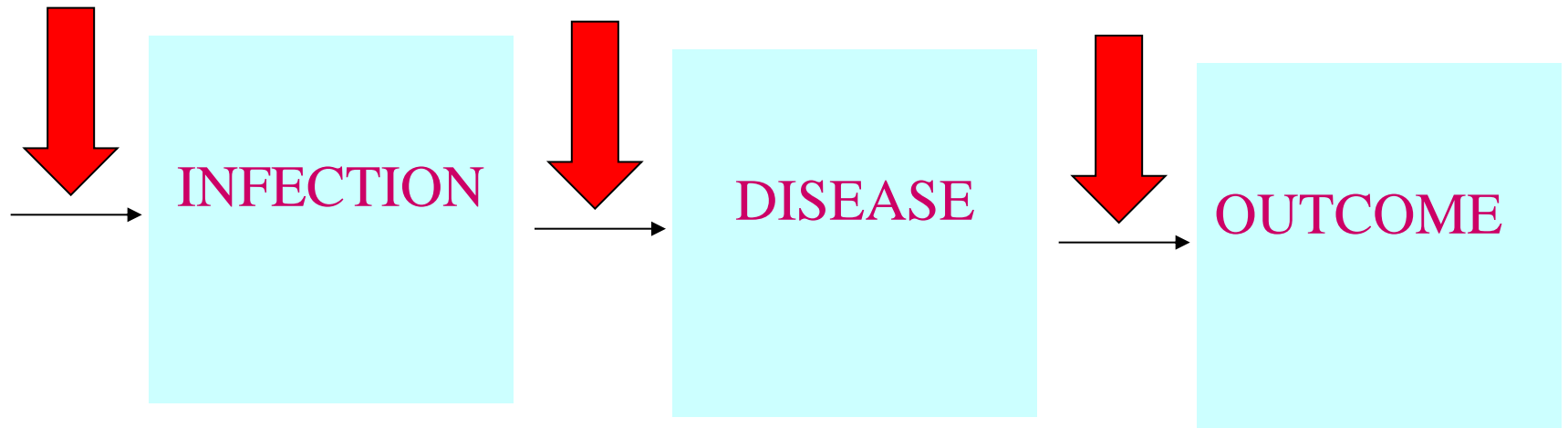


Natural history of tuberculosis

Exposure → Infection → Disease



Where can smoking act?



Smoking

- The **association** between smoking and TB has been investigated as early as **1918**.
- However, **controversies** existed for along time
 - Smoking is often associated with other **socioeconomic** factors
 - Other **substance abuses** like alcoholism, drug abuse, and **HIV** infection may also confound the observed relationship
 - Most of the previous studies were **cross-sectional or case-control** studies, and few were able to control all the potential confounders adequately



HK Elderly Cohort Study

Am J Respir Crit Care Med 2004;170:1027-33

- A cohort of **42,655 clients**
 - Registered with the **Elderly** Health Service in 2000
 - **Baseline** questionnaire + clinical assessment
 - Potential **confounders**
 - **Ex-smoker**: quitted for ≥ 1 yr
 - All **prevalent TB cases excluded**
 - Followed **prospectively**
 - through the tuberculosis **notification** and **death registry**
 - until the end of 2002 (**relatively short duration**)
 - **Cox Proportional Hazard Analysis**
 - Censored data
 - Proportional hazard assumption likely met (vs contact / treatment)

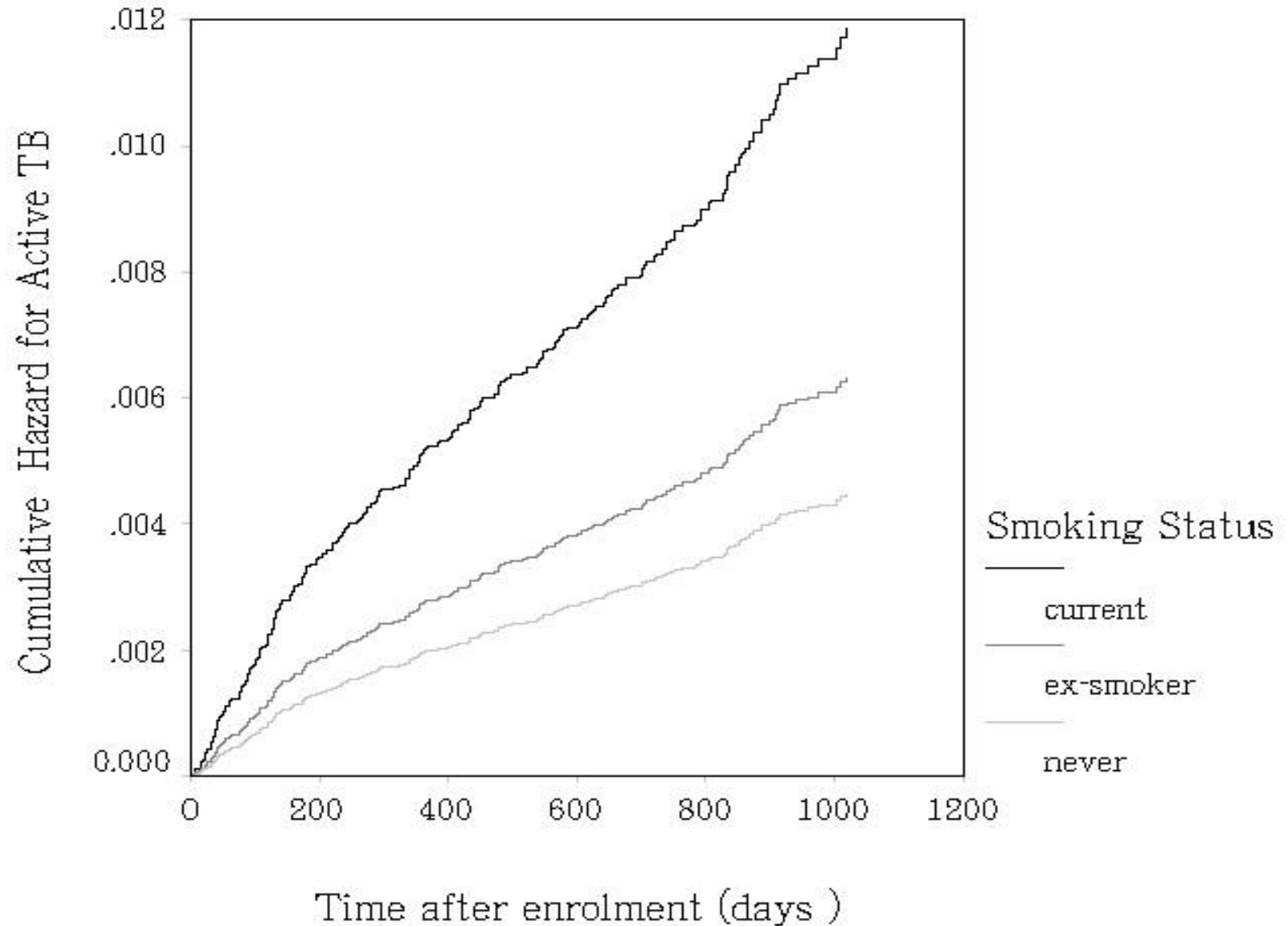


Adjusted hazard ratios of TB-related outcomes by smoking status

Outcome	Ex-smokers vs			Current smokers vs			P for trend
	Never-smokers			never-smokers			
	H. R. *	95% CI	P	H. R. *	95% CI	P	
Active TB	1.41	1.02-1.95	0.04	2.63	1.87-3.70	<0.001	<0.001
Culture-confirmed TB	1.68	1.13-2.50	0.01	2.80	1.82-4.31	<0.001	<0.001
TB > 3 month	1.48	1.04-2.10	0.03	2.39	1.63-3.50	<0.001	<0.001
Culture-confirmed TB >3m	1.73	1.13-2.67	0.01	2.36	1.45-3.86	0.001	<0.001
New TB	1.44	1.01-2.04	0.04	2.61	1.80-3.80	<0.001	<0.001
Retreatment TB cases	1.16	0.49-2.73	0.74	2.48	1.04-5.89	0.04	<0.05
Pulmonary TB	1.39	0.98-1.97	0.06	2.87	2.00-4.11	<0.001	<0.001
Extrapulmonary TB	1.32	0.57-3.05	0.52	1.04	0.33-3.30	0.95	0.79
Extrapulmonary TB only	1.77	0.72-4.35	0.22	0.73	0.16-3.46	0.70	0.86

* adjusted hazard ratio, adjusted for sex, age, alcohol use, language, marital status, education, housing, working status, public financial assistance status, monthly expenditure, participation in social activities, self-rated health status, hospital admission within 12 months, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, heart disease and cerebrovascular disease

Effect of Smoking on Active TB



Stratification by alcohol use among the males

Outcomes		Ex-smokers vs Never-smokers			Current smokers vs never-smokers		
Alcohol Use	TB cases (% [‡])	O. R.	95% CI	P	O. R.	95% CI	P
Active TB							
Regular	13 (1.0)	0.84	0.14-5.07	1.00*	2.71	0.57-12.9	0.20*
Social	34 (1.0)	1.39	0.53-3.66	0.51	3.81	1.47-9.86	0.01
Ex-drinker	42 (1.5)	2.55	0.77-8.41	0.11	3.46	0.96-12.5	0.06*
Never	86 (1.2)	1.92	1.16-3.18	0.01	3.15	1.84-5.39	<0.001
Combined [†]	175 (1.2)	1.82	1.21-2.73	0.01	3.28	2.14-5.03	<0.001
Culture-confirmed TB							
Regular	10 (0.7)	1.69	0.18-16.3	1.00*	4.06	0.49-33.9	0.25*
Social	23 (0.6)	1.71	0.45-6.45	0.55*	6.09	1.71-21.6	0.01
Ex-drinker	29 (1.1)	5.54	0.74-41.3	0.07*	6.58	0.81-53.7	0.07*
Never	59 (0.8)	2.35	1.29-4.29	0.01	2.80	1.41-5.58	0.01
Combined [†]	121 (0.8)	2.44	1.46-4.08	0.01	3.83	2.20-6.66	<0.001

* Two-sided Fisher's exact test

[†] Mantel-Haenszel stratified analysis

Dose-Response Relationship

Number of cigarettes per day	Number in cohort	Active TB		Culture-confirmed TB	
		n (%)	H.R.*	n (%)	H.R.*
=<4	734	6 (0.8)	1.00	2 (0.3)	1.00
5-9	906	11 (1.2)	1.45	9 (1.0)	3.61
10-14	1054	20 (1.9)	2.29	14 (1.3)	5.08
>=15	1171	31 (2.6)	2.80	19 (1.6)	5.32
P		0.01 [†]		0.02 [†]	

* adjusted hazard ratio, adjusted for sex, age, alcohol use, language, marital status, education, housing, working status, public financial assistance status, monthly expenditure, participation in social activities, self-rated health status, hospital admission within 12 months, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, heart disease and cerebrovascular disease,

[†] Probability for chi square for trend across categories of numbers of cigarettes smoked per day

TB risks attributable to smoking

- Males:
 - 32.8% (95% CI: 14.9 - 48.0%)
- Females:
 - 8.6% (95% CI: 3.3 - 15.1%)

Gender Difference

- Annual active TB rates
 - 486 / 100000 for males
 - 163 / 100,000 for females
- Baseline rates without smoking
 - 327 /100,000 for males
 - 149/100,000 for females
- **Smoking** accounted for
 - **44.9%** (95%CI: 20.7-64.6%)

Cross-sectional Population Study (HK)

Int J Tuberc Lung Dis. 2003;7:980-6

- 851 patients sampled from the 1996 tuberculosis notification registry
- Clinical characteristics were compared between smokers and non-smokers

Clinical Characteristics

- **Ever-smokers** were more likely to have
 - cough (O.R. 1.69)
 - dyspnea (O.R. 1.84),
 - upper zone involvement (O.R. 1.67)
 - cavity (O.R. 1.76),
 - miliary lung involvement (O.R. 2.77)
 - positive sputum culture (O.R. 1.43)
- But **less** like to have
 - isolated **extrathoracic** involvement (O.R. 0.31)

after controlling for background variables, all $P < 0.05$

Inferences

- Differing Clinical Characteristics:
 - Suggest **effect on disease development** rather than infection alone
- More **advanced pulmonary** disease with **upper zone** involvement
 - in keeping with an **airborne** insult



Independent Predictors of TST $\geq 10\text{mm}$ (Silicosis Cohort 1995-2002, HK)

Variable	O.R.	(95%CI)	P
Smoking status			0.007
Never	1.00	Ref	
Ex-smoker	1.57	(0.80-3.08)	
Current	2.72	(1.37-5.40)	
Regular Alcohol Use	2.72	(1.11-6.62)	0.028
Body mass index (per unit change)	1.08	(1.01-1.15)	0.032
Profusion of nodules (per grade)	0.96	(0.64-1.41)	0.826

Leung CC et al. Eur Respir J. 2008;31:266-72.

Smoking: Mortality Studies I

- Liu BQ, Peto R, Chen ZM, et al. Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. *BMJ*. 1998 21;317:1411-22.
- Lam TH, et al. Mortality and smoking in Hong Kong: case-control study of all adult deaths in 1998. *BMJ*. 2001;18;323:361.
- Gajalakshmi V, et al. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. *Lancet* 2003;362:507-515
- Jha P, et al. A Nationally Representative Case-Control Study of Smoking and Death in India. *N Engl J Med*. 2008;358:1137-47



Smoking: Mortality Studies II

- Most cross-sectional / case-control studies
- Major **heterogeneity** in TB mortality risks
 - Higher smoking-related TB mortality in India
 - much smaller effect observed in Hong Kong
- Hong Kong Elderly Cohort Study
 - more current smokers developed TB and subsequently died from any causes, but
 - only **1/4 of the deaths** could be **attributed directly to TB**
 - with a **case to mortality ratio of just 3.1%**
- Variation in **access to treatment**, often in association with multiple social factors, might therefore underline the heterogeneity observed across different localities.



Passive smoking and TB

- A cohort of **15486 female never-smokers** aged **65 to 74** years and living with their surviving husband were followed up prospectively.
- Passive smoking accounted for **13.7% of active tuberculosis** and **18.5% of culture-positive tuberculosis** within this cohort.

Leung CC, et al. Passive smoking and tuberculosis. Arch Intern Med. 2010 ;170:287-92.



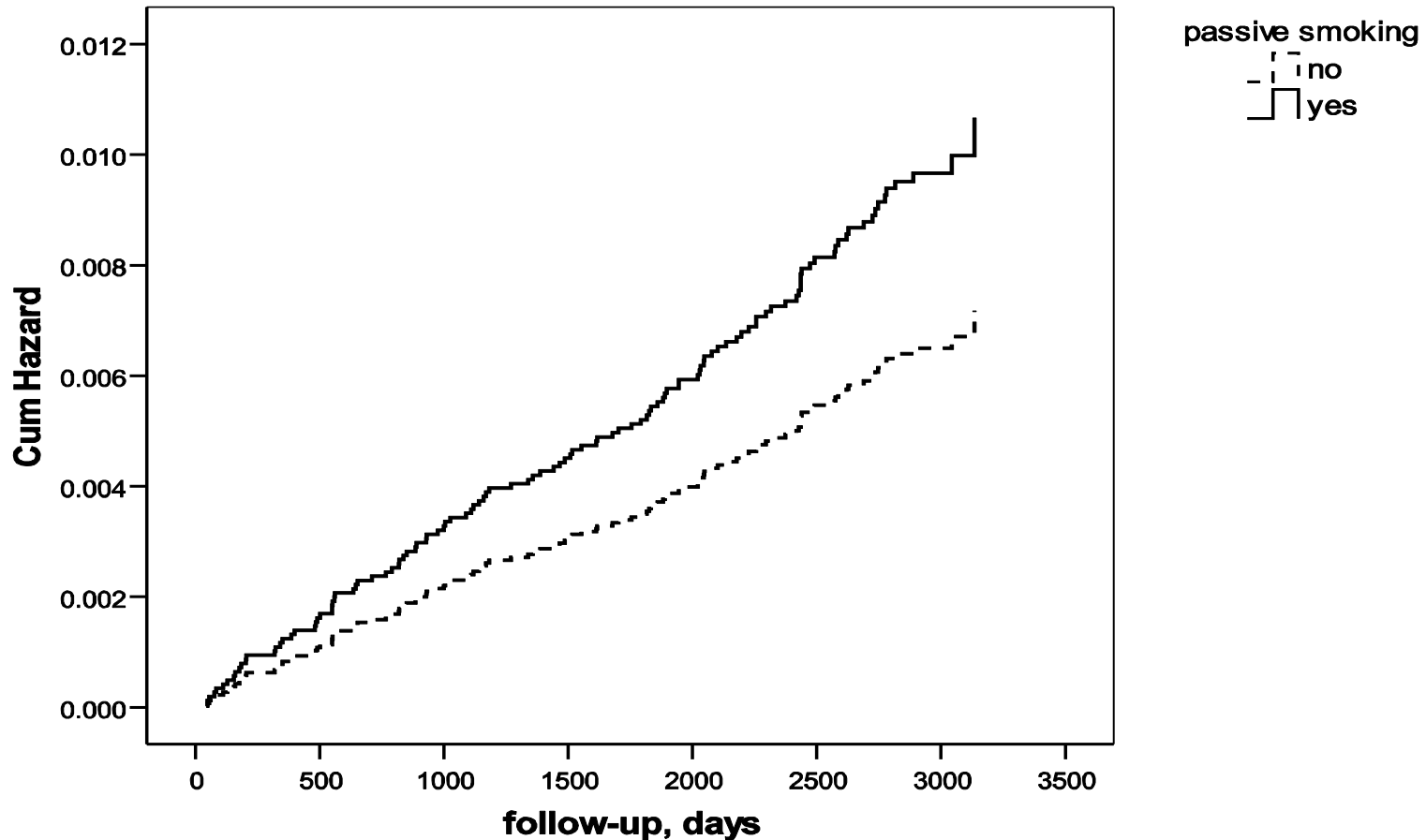
Cox proportional hazard analysis on risks of TB

Variable	Active		Culture	
	HR* (95%CI)	P	HR* (95%CI)	P
On Public Assistance	2.03(1.22-3.35)	0.006	2.52(1.38-4.63)	0.003
Passive Smoking	1.49(1.01-2.19)	0.047	1.70(1.04-2.80)	0.036
Body Mass Index	0.87(0.83-0.92)	<0.001	0.87(0.81-0.94)	<0.001
Hospital Admission	1.60(0.98-2.63)	0.060	2.06(1.14-3.72)	0.016

Passive smoking and all variables as listed in the first column of table 1 were entered as predictor variables into the initial models; under the backward conditional approach, age, Cantonese-speaking, education, housing, alcohol, obstructive lung disease, hypertension, heart disease, cerebrovascular disease, disease, and diabetes mellitus, all with a P value above 0.10, were removed.

* adjusted hazard ratio; all hazard ratios were mutually adjusted for each other

Cumulative hazards for active TB (Cox Proportional Hazards Analysis)



Smoking Prevalence

GATS Collaborative Group. Lancet 2012; 380: 668–79

- Current smokers in men ≥ 15 yrs
 - China: 52.9%
 - India: 24.3%
 - Russia: 60.2%
- Current smokers in women ≥ 15 yrs
 - China: 2.4%
 - India: 2.9%
 - Russia: 21.7%



WHO: Global TB Burden

(Fact Sheet 104)

- **2nd (to HIV) infectious disease killer worldwide**
- In 2011
 - Estimated incidence: 8.7 million
 - 310 000 MDR-TB (pulmonary), 60% in India, China, Russian Federation
 - 9% of MDR-TB cases had XDR-TB.
 - Estimated mortality: 1.4 million
 - >95% low- and middle-income countries
 - Among top three causes of death for women aged 15-44
 - Leading killer of people living with HIV: ¼ of all deaths.
- Trend
 - Incidence declining although very slowly.
 - Mortality dropped 41% between 1990 and 2011.



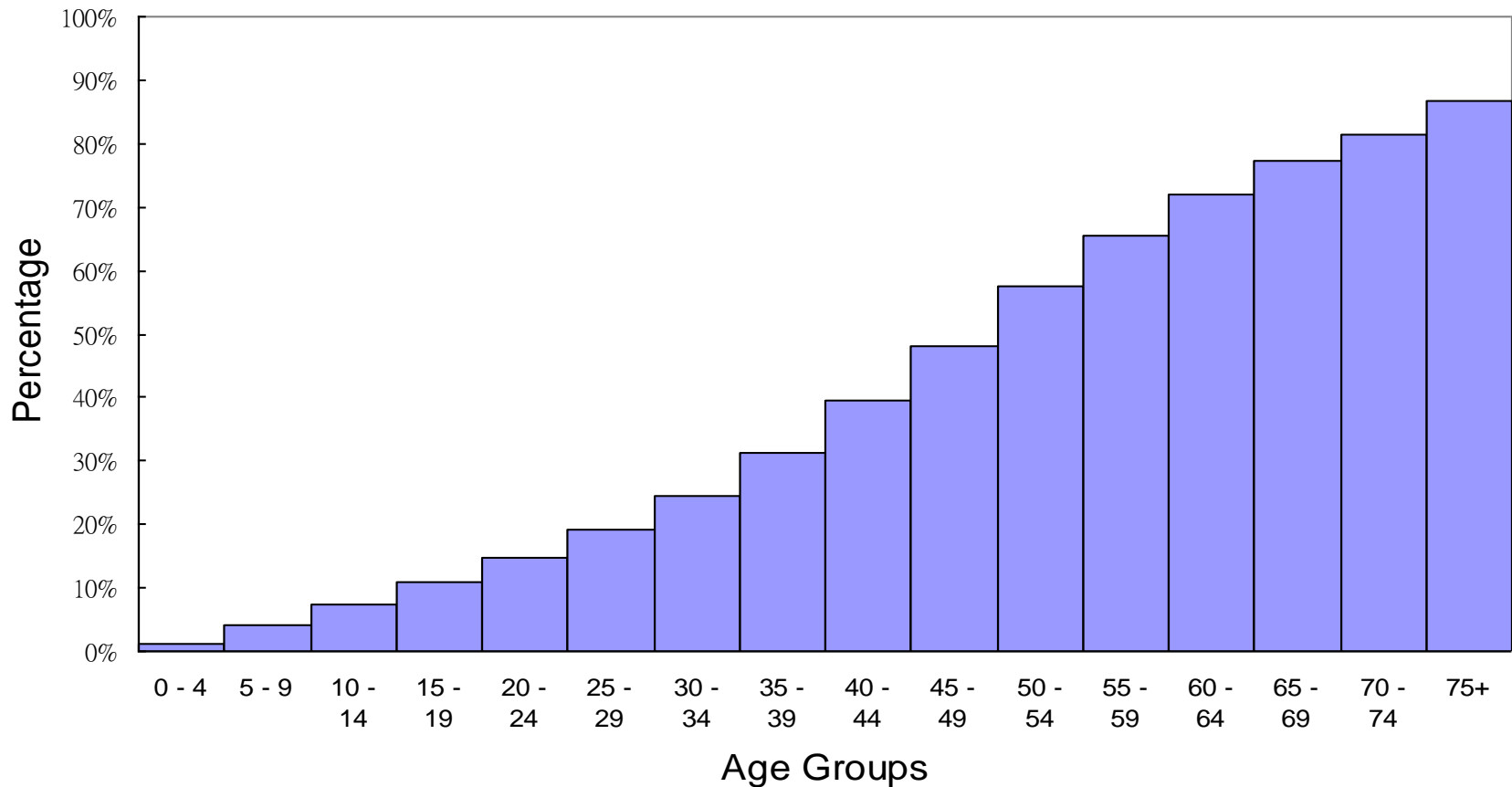
Tuberculosis Prevalence Surveys in China

TB	1979	1990	2000
	per 100000 (adjusted*)	per 100000	per 100000 (adjusted*)
Active	717 (796)	523	367 (300)
<i>Annual Decline</i>	3.7%	5.4%	
Culture-positive	-	177	160 (124)
<i>Annual Decline</i>	-	3.6%	
Smear-positive	187 (218)	134	122 (97)
<i>Annual Decline</i>	4.3%	3.2%	

*adjusted to 1990 sex / age structure

China Tuberculosis Control Collaboration. Lancet. 2004;364:417-22

Estimated Infection Rate (HK)



*Estimation based on: Incidence (smear-positive cases) = ARI * Styblo ratio

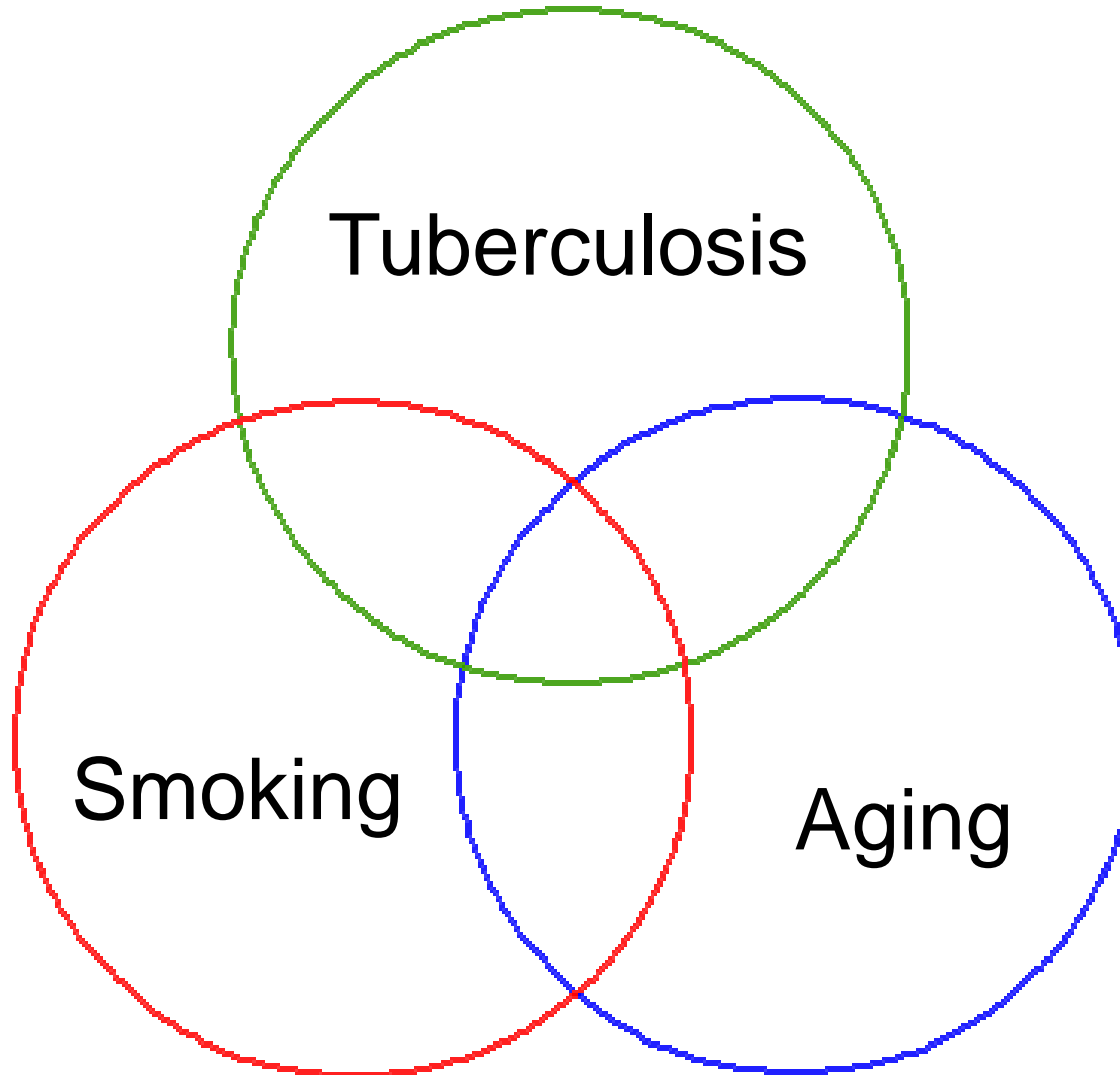
Aging of the TB Epidemic

- Treat active disease by **DOTS**
 - Control recent transmission But
 - Little impact on endogenous reactivation
- Population-based IS6110-based RFLP study
 - 24.5% (of 691 isolates) belonged to clusters
 - Recent transmission: **15 to 20%**
 - Endogenous reactivation

Chan-Yeung M, et al. *J Clin Microb* 2003;41:2706-8



Interacting Factors



China: Impact of Smoking / Solid Fuel

(Time-based, Multiple Risk Factor Modeling)

- Scenario: **Complete Cessation** of Smoking and Solid Fuel Use by 2033
- Impact: Reduce the projected annual tuberculosis incidence in 2033 by
 - **14–52%** (80% DOTS coverage)
 - **27–62%** (50% DOTS coverage)
 - **33–71%** (20% DOTS coverage)

Lin HH, et al. Lancet. 2008;372:1473-83



Tobacco Control

- Active and Passive Smoking are both hazardous
- Stop Smoking
 - Decrease infection and disease
 - Contain source and protect vulnerable contacts
 - Limit the spread of both drug-sensitive and drug-resistant TB
 - In both community and high-risk settings
- Tobacco Control Measures
 - Simple, cheap and applicable on a population scale
 - Not technology-dependent
 - Do not create more problem than they solve
- Lip Service is NOT enough, ACTION NOW !!!



Thank You

