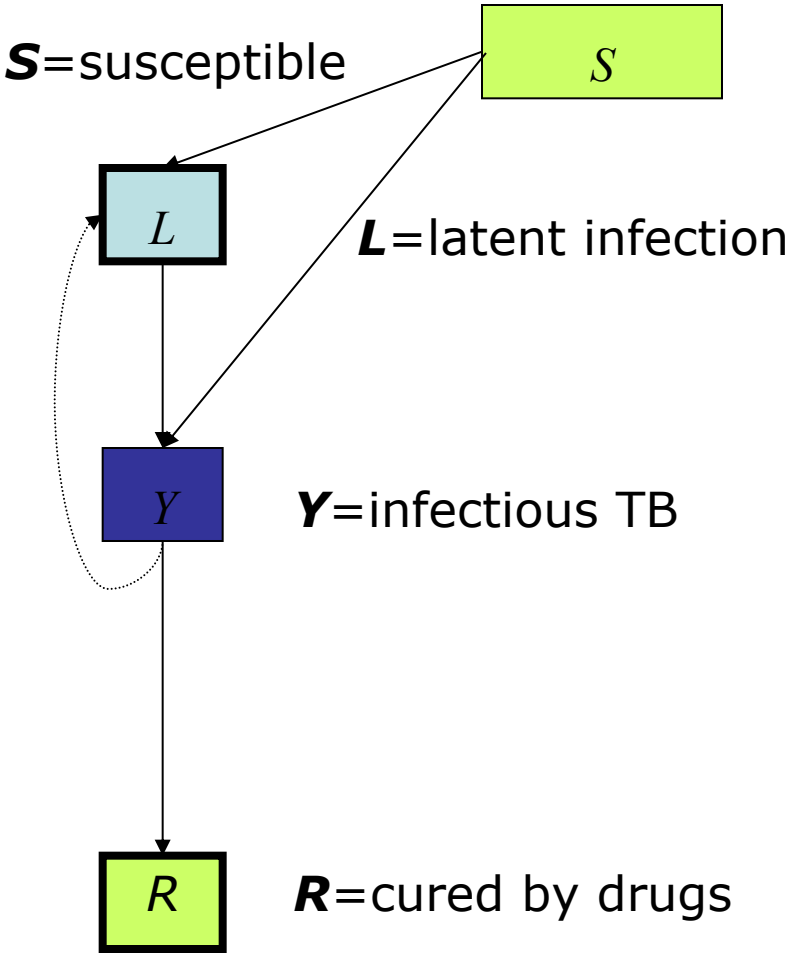
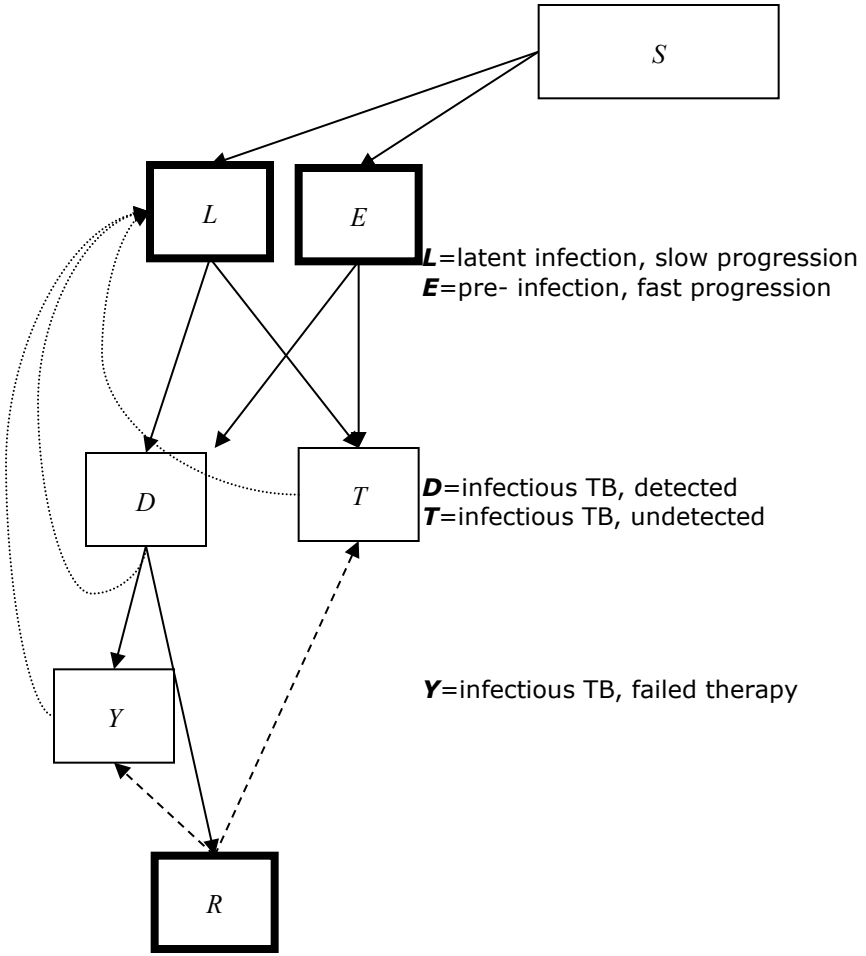
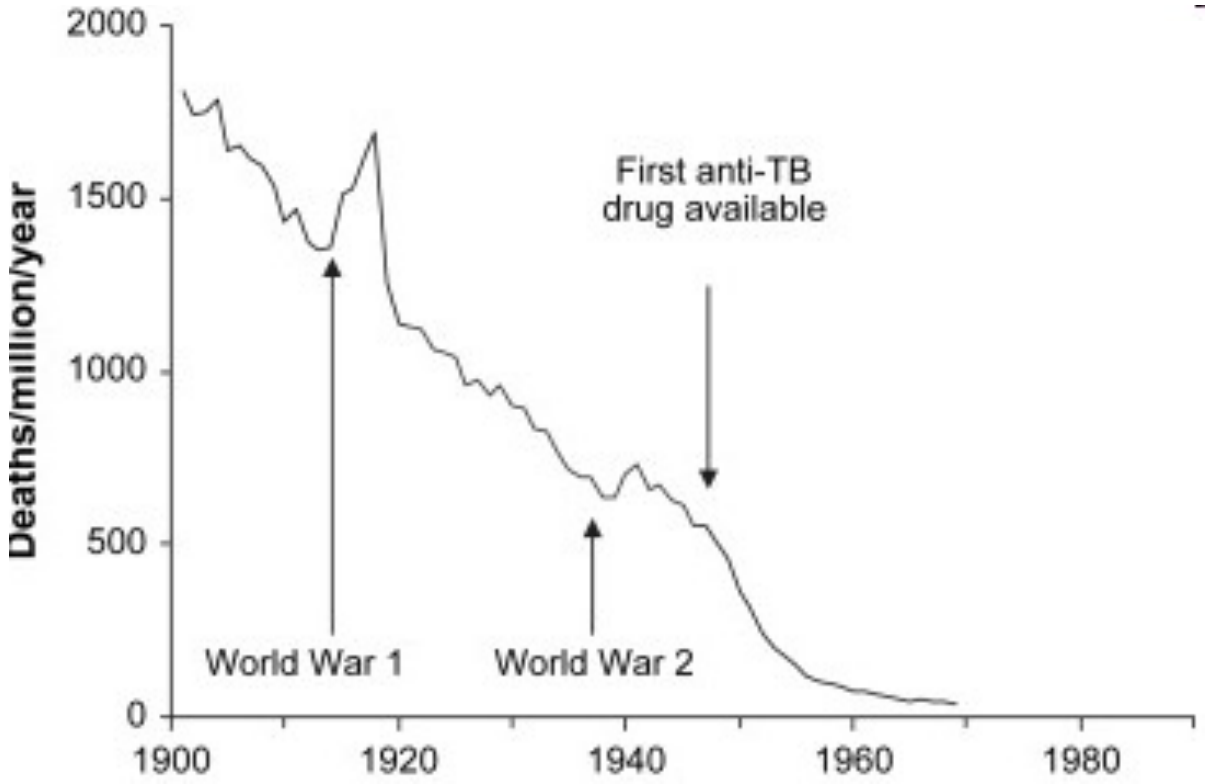
Mathematical model based on natural history of tuberculosis

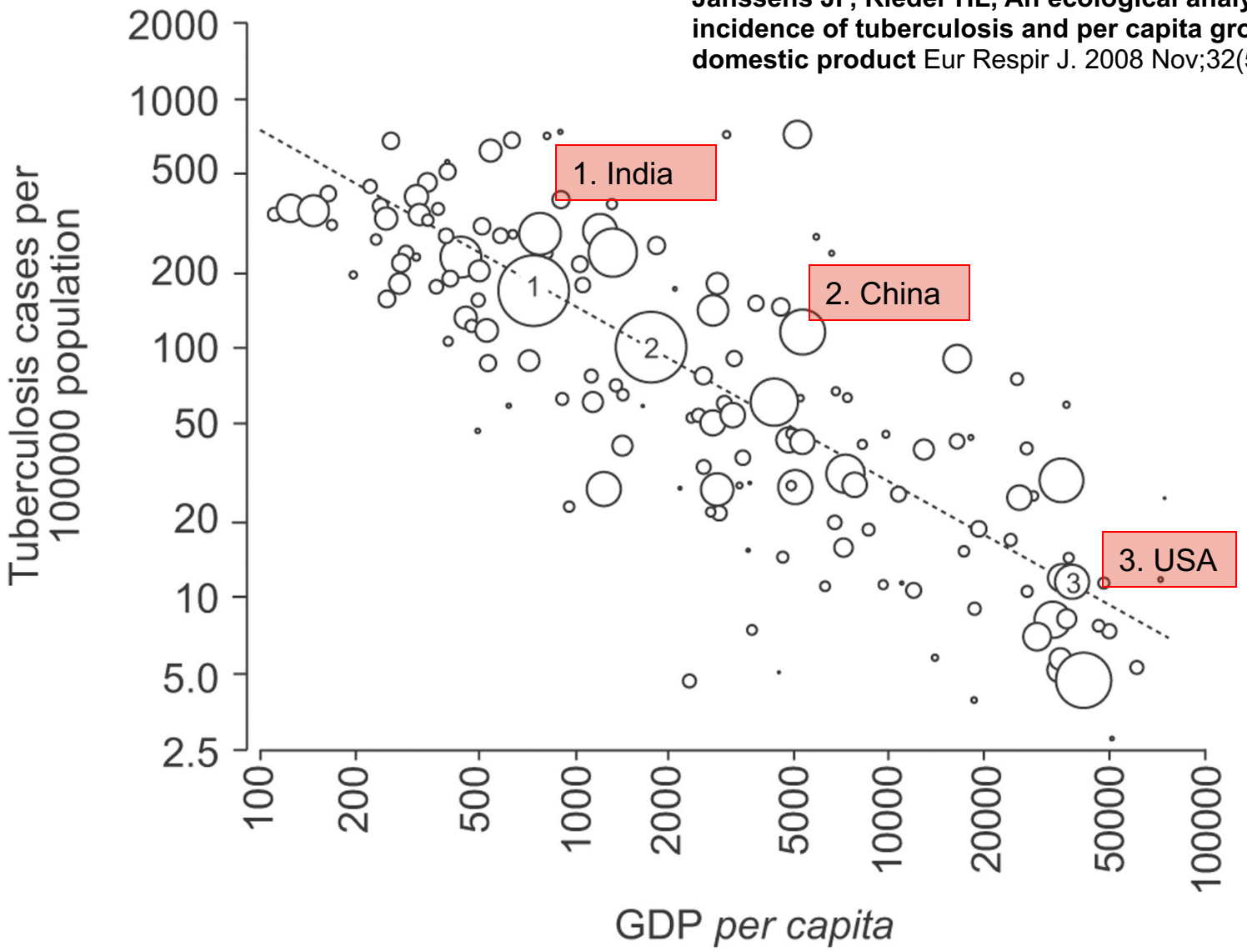






Decline in TB mortality in England and Wales, and its association in time with the two World Wars, and the introduction of chemotherapy against TB.

Janssens JP, Rieder HL, An ecological analysis of incidence of tuberculosis and per capita gross domestic product Eur Respir J. 2008 Nov;32(5):1415-6.



Comparative poverty indices: TB notification 2006 by index

Index	R2	P-value
GDP	.10	<.001
Gini	.23	<.001
Proportion <1$ day	.19	<.001
Proportion <2$ day	.21	<.001
U5 mortality	.17	<.001
Human development index	.21	<.001
Total health exp by GDP	.003	.448

Trends in TB incidence: By Human Development Index

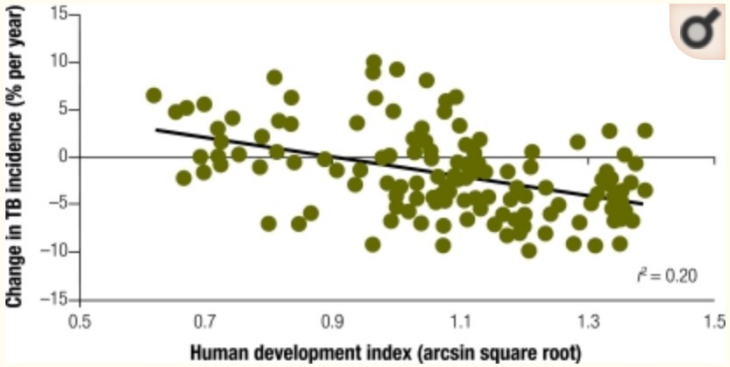


Fig. 3

Human development: a statistically significant correlate of trends in TB incidence rate across six groups of countries over 1997–2006, as judged by univariate linear regression (fitted line)[a]

Dye C, Lönnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. Bull World Health Organ. 2009 Sep;87(9):683-91.

Trends in TB incidence: By Under 5 Mortality

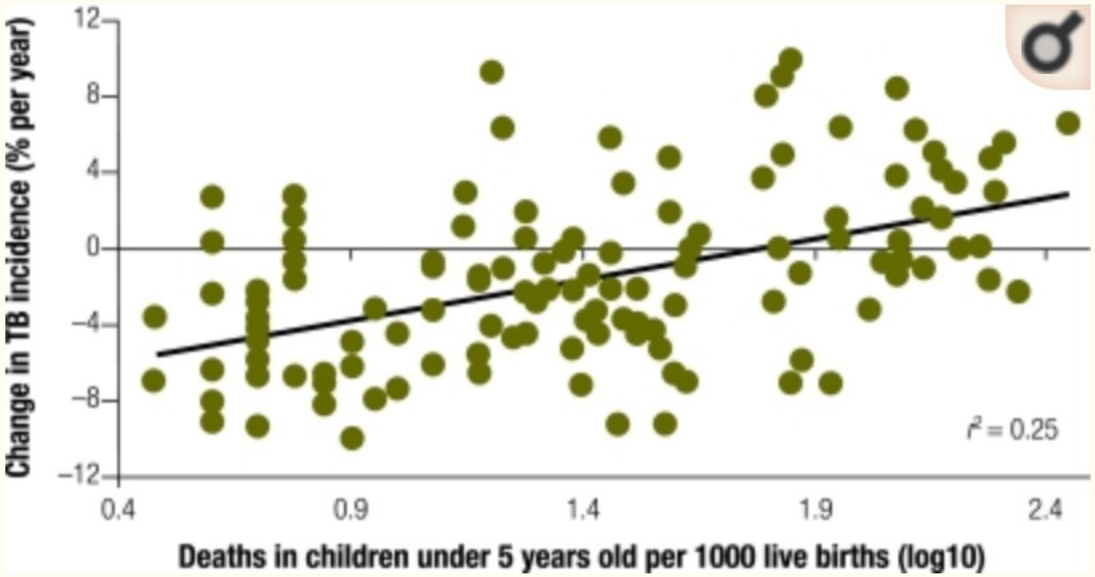
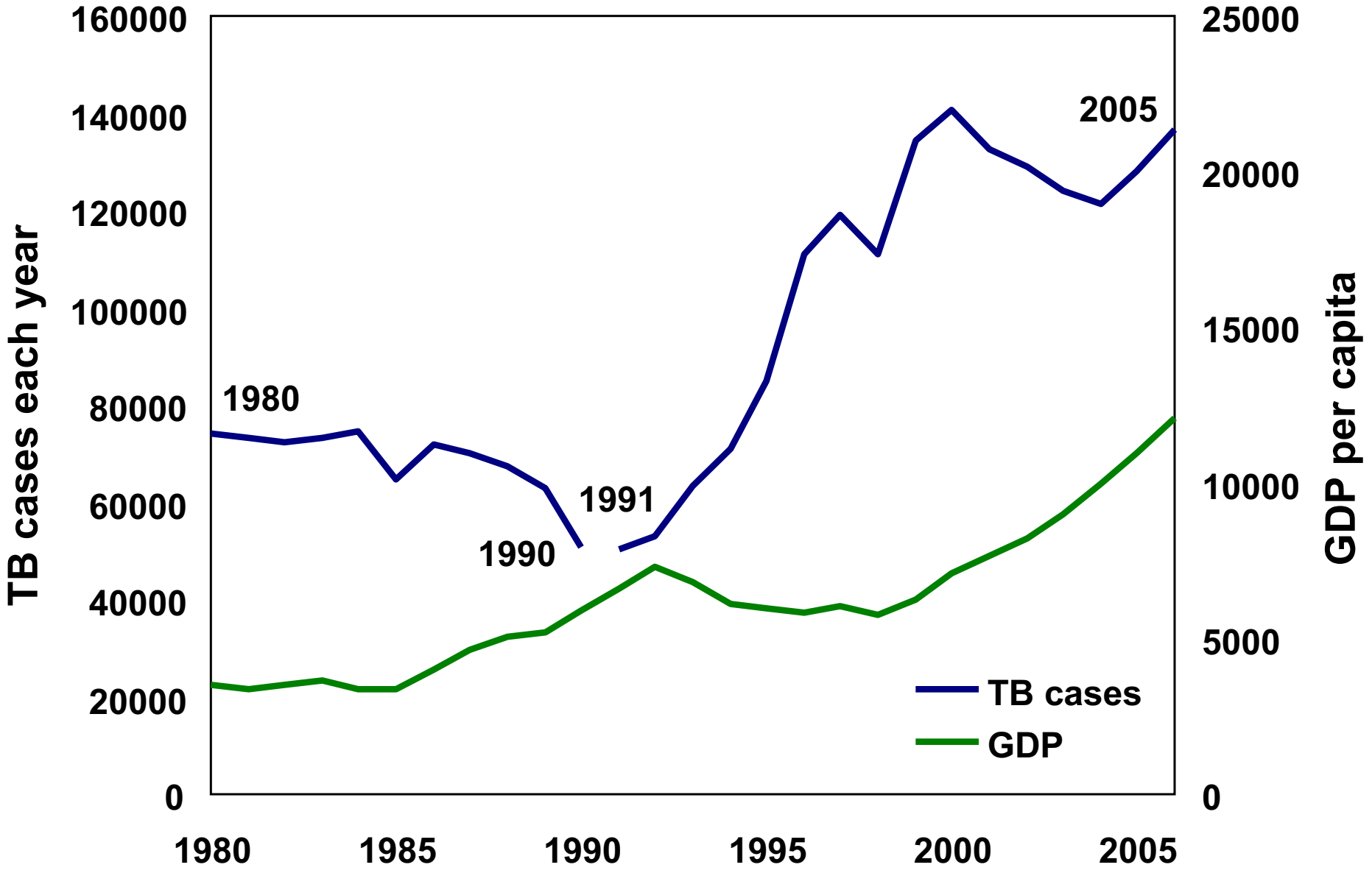


Fig. 4

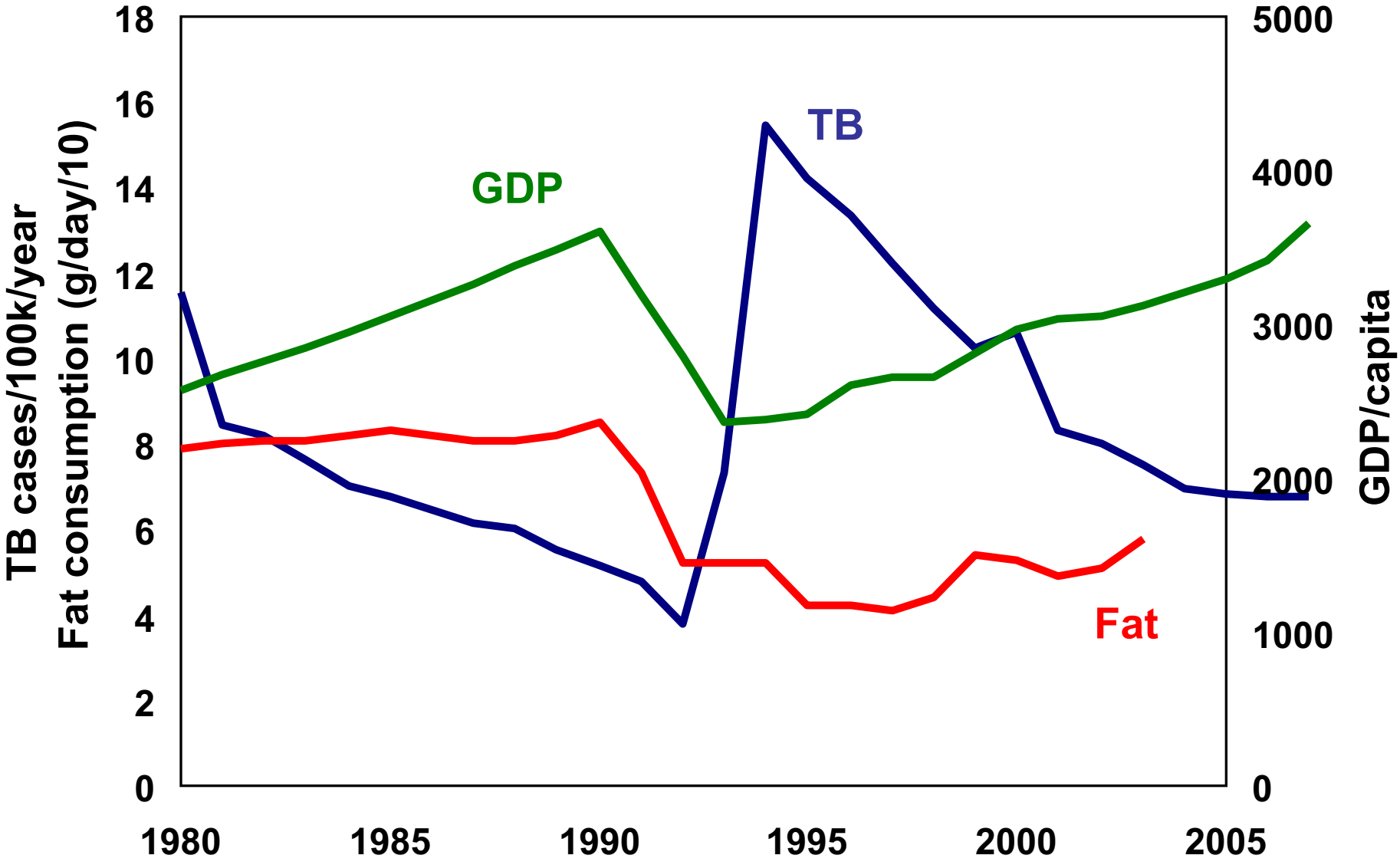
Child mortality: a statistically significant correlate of trends in TB incidence rate across six groups of countries over 1997–2006, as determined by univariate linear regression (fitted line)[a]

	OR (95% CI) individual factors	OR (95% CI) area factors	OR (95% CI) individual and area factors
Individual level			
Sex			
Male	2.20 (1.93–2.53)		2.21 (1.92–2.53)
Age group			
20–34 years	2.72 (2.07–3.59)		2.70 (2.06–3.55)
35–49 years	3.75 (2.90–4.85)		3.76 (2.91–4.86)
50–64 years	3.38 (2.73–4.20)		3.42 (2.74–4.25)
65 years	1.89 (1.46–2.45)		1.96 (1.52–2.54)
Illiterate	1.38 (1.15–1.66)		1.33 (1.11–1.61)
Not worked previous week	1.32 (1.13–1.53)		1.31 (1.13–1.52)
Possession of goods			
4–6	1.74 (1.36–2.23)		1.48 (1.16–1.90)
2–3	2.93 (2.24–3.84)		2.42 (1.86–3.15)
0–1	5.52 (3.57–7.64)		4.27 (2.88–6.34)
Area level			
Computers and literacy			
Intermediate		1.58 (1.25–2.00)	1.29 (1.00–1.67)
Low		2.12 (1.64–2.74)	1.59 (1.19–2.13)

Over the edge… Russia in the 1990s

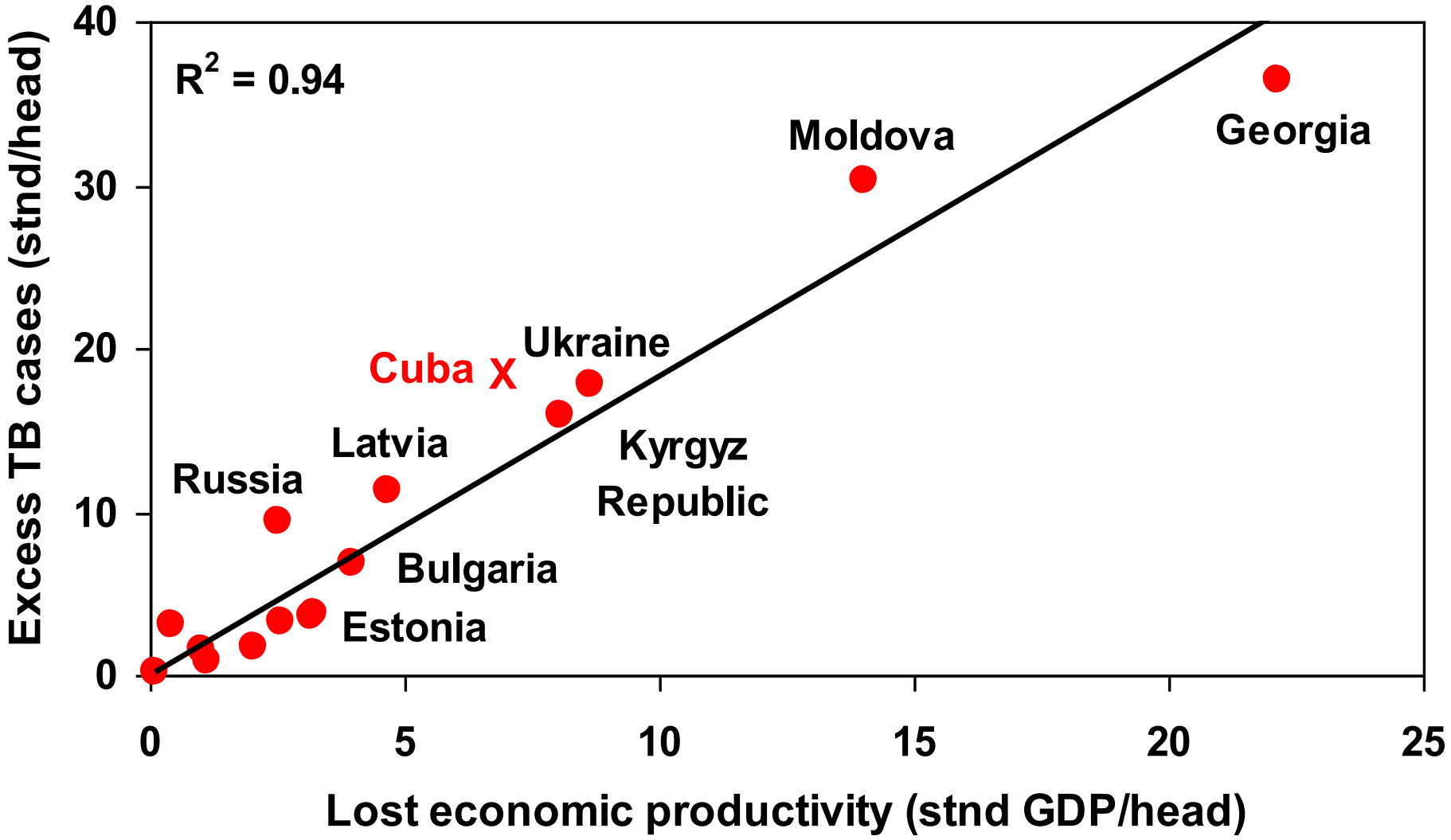


Cuba: upturn in TB linked to economic shock, partly mediated by nutritional crisis



TB and economic recession, 1990s

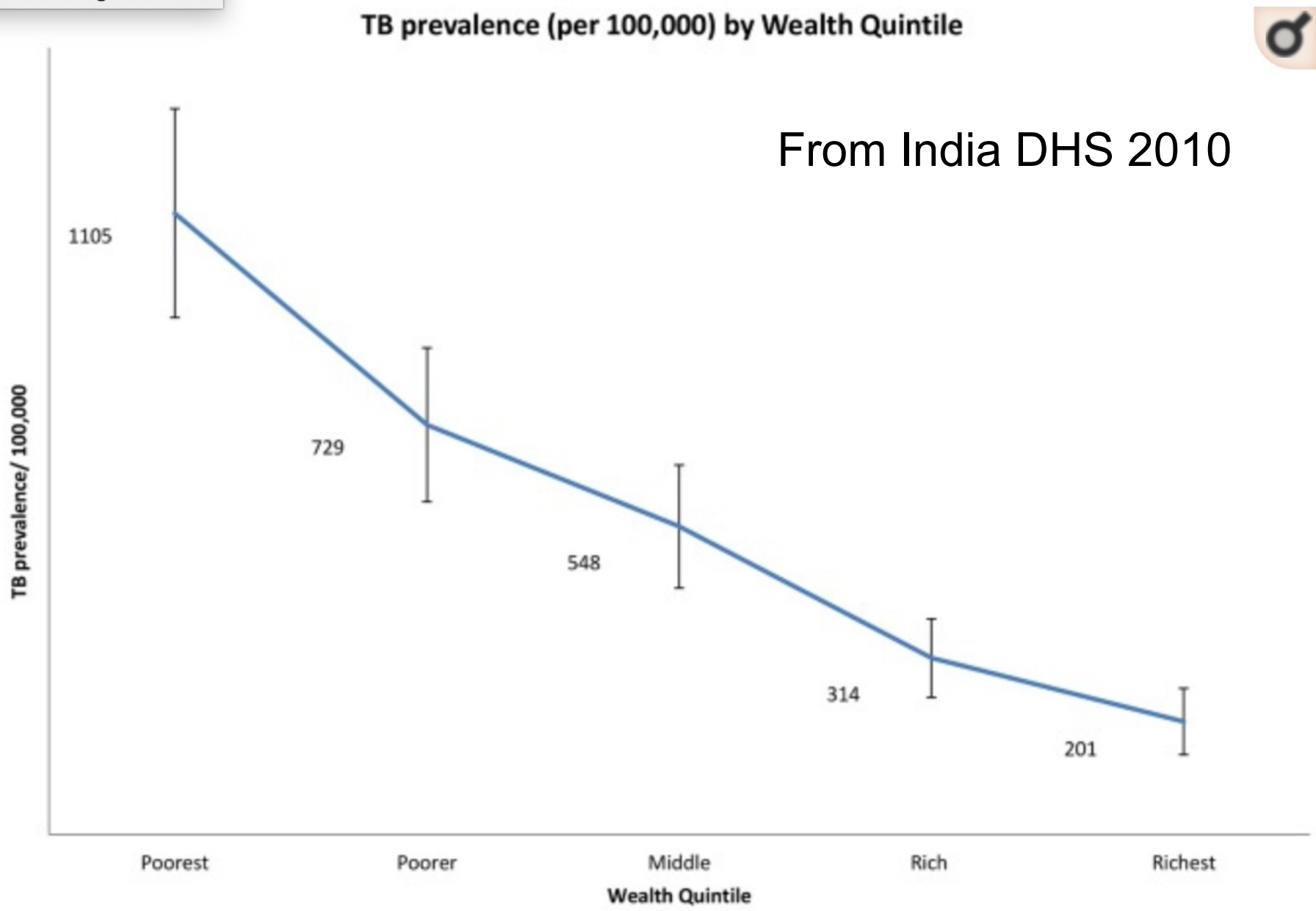
Excess morbidity driven by a process common to 15 Central & Eastern European countries

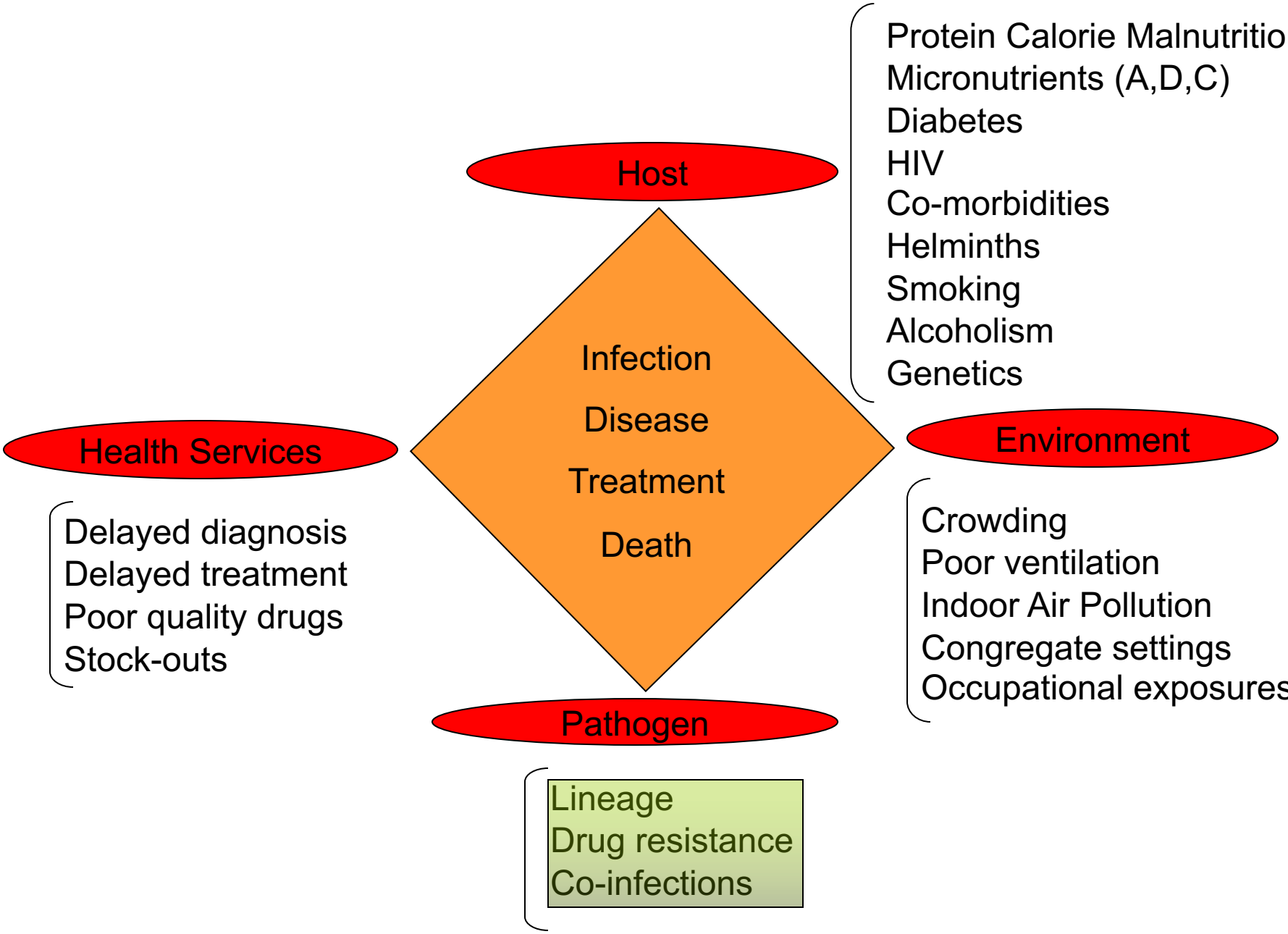


How does poverty cause TB?

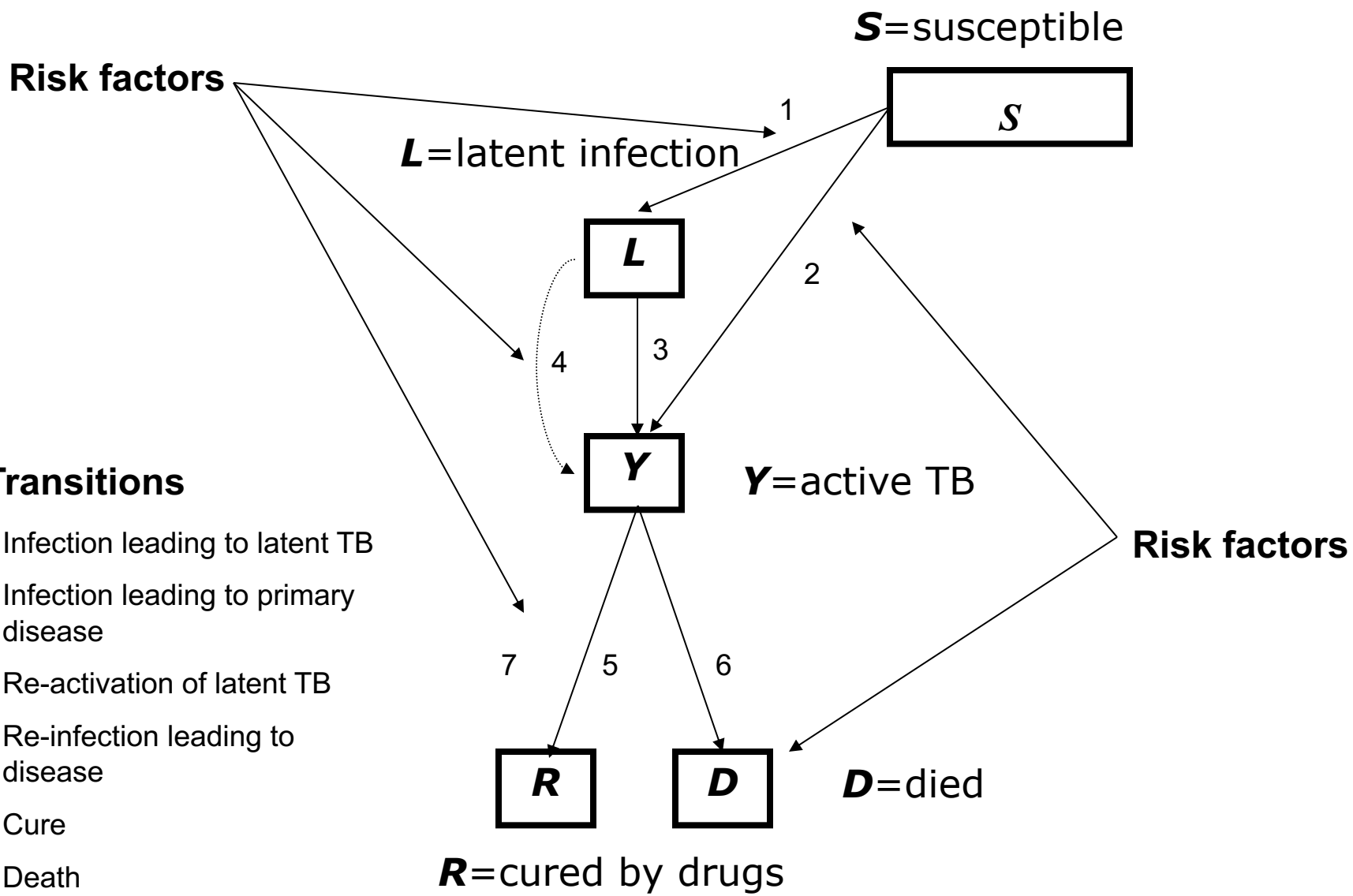
What can we do about it?

Click on image to zoom




Host
Protein Calorie Malnutrition
Micronutrients (A,D,C)
Diabetes
HIV
Co-morbidities
Helminths
Smoking
Alcoholism
Genetics
Health Services
Delayed diagnosis
Delayed treatment
Poor quality drugs
Stock-outs
Infection
Disease
Treatment
Death
Environment
Crowding
Poor ventilation
Indoor Air Pollution
Congregate settings
Occupational exposures
Pathogen
Lineage
Drug resistance
Co-infections

Pathogenesis model of TB progression



Transitions

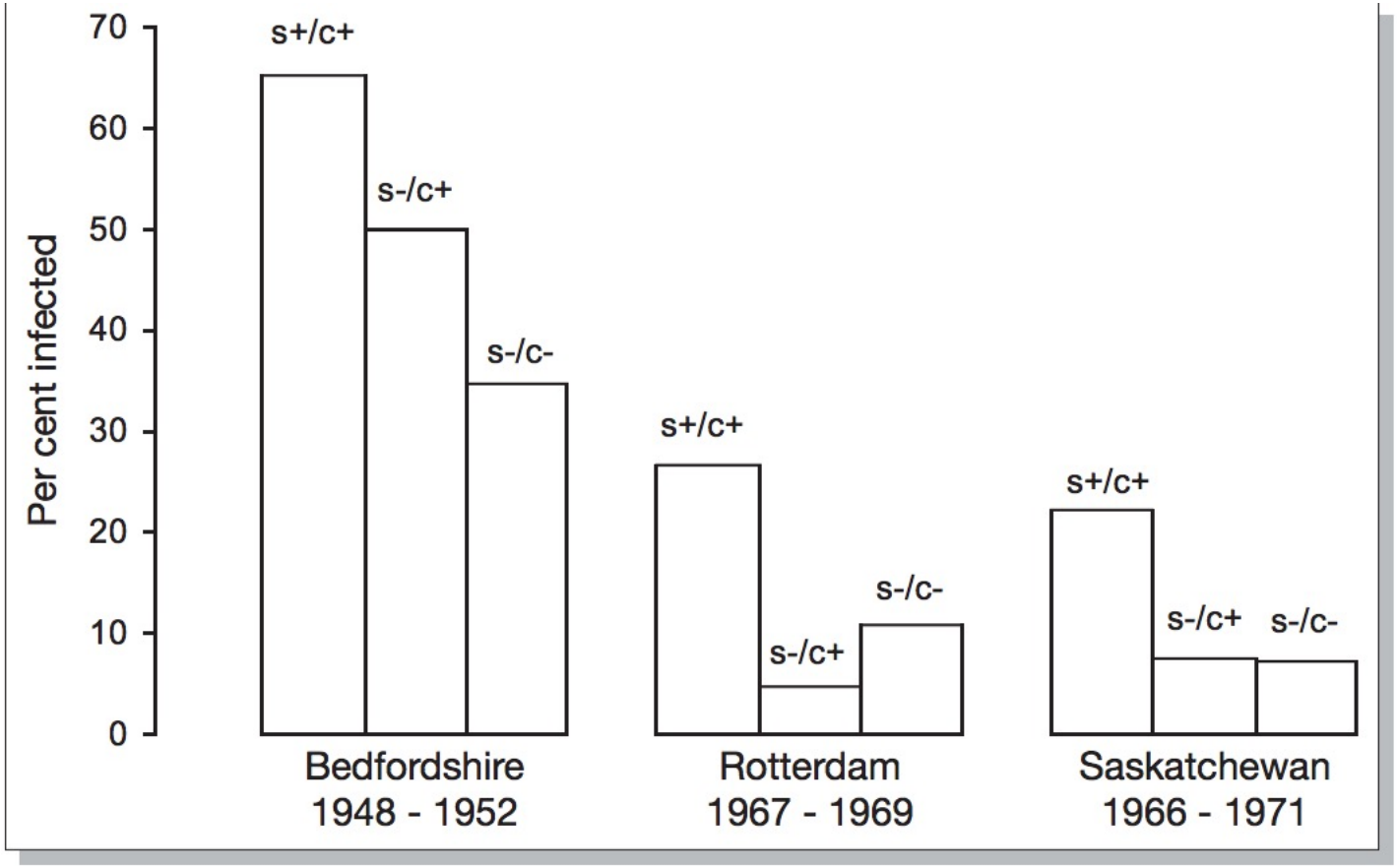
1. Infection leading to latent TB
2. Infection leading to primary disease
3. Re-activation of latent TB
4. Re-infection leading to disease
5. Cure
6. Death
7. Relapse

Individual risk factors for infection

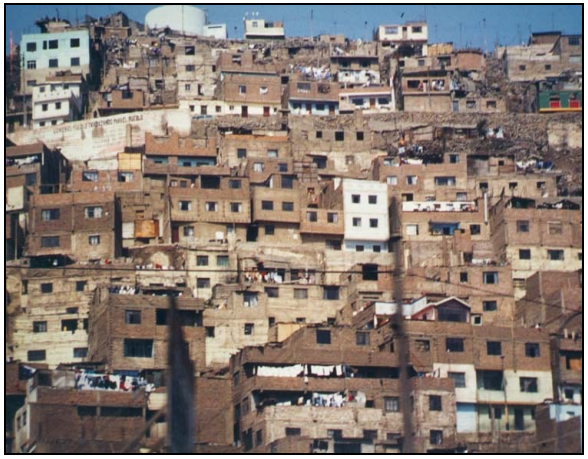
- Exposure to people and to people with TB
  - Urban versus rural OR 2 in Navy recruits
  - Intimate versus causal contact

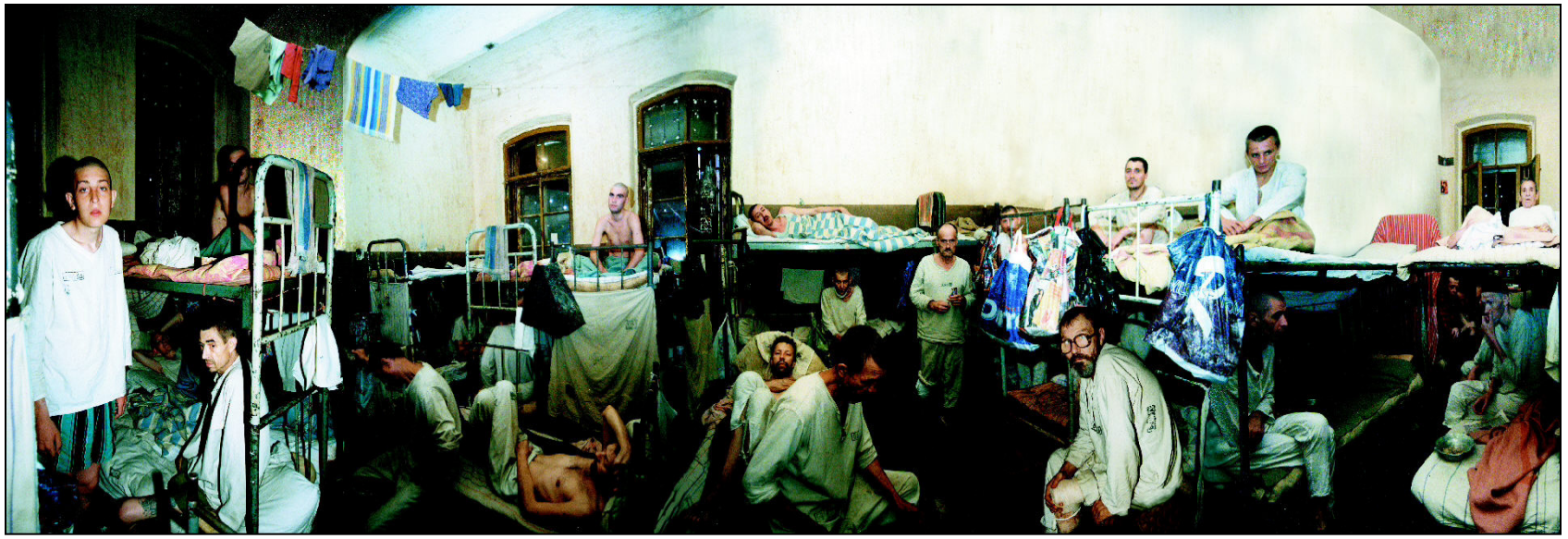
Age-adjusted % positive skin test reactors in children age 0-14 in British Columbia 1966-1971

	Race and closeness of TB contact			
Sputum status of source case	Indian Children		White children	
	Intimate (1012)	Casual(619)	Intimate (1873)	Casual (3031)
Positive smear	44.7	37.4	34.7	10.1
Positive culture	27.7	15.6	8.9	2.4
Negative culture	25.7	18.7	7.2	3.3


Per cent infected
70
60
50
40
30
20
10
0
s+/c+
s-/c+
s-/c-
s+/c+
s-/c+
s-/c-
s+/c+
s-/c+
s-/c-
Bedfordshire
1948 - 1952
Rotterdam
1967 - 1969
Saskatchewan
1966 - 1971

Environment





Attributes of index case

- Smear status
- Cavitary lesions
- Closeness of contact
- Treatment delay
- Smoking in index case (increases risk)
- HIV in index case (decreases risk)

- Lineage?
- Drug resistance?

Cough aerosols predict infection

Characteristic	Total (N = 369)	Tuberculosis Disease (n = 8)	No Tuberculosis Disease (n = 361)	Unadjusted OR (95% CI)	*P* Value	Adjusted OR With HIV (95% CI)	*P* Value	Adjusted OR Without HIV (95% CI)	*P* Value
Sputum volume, mL									
<5	129 (35)	1 (13)	128 (35)	Reference	. . .	. . .	. . .	. . .	. . .
≥5	240 (65)	7 (87)	233 (65)	3.9 (.48–31.4)	.20	. . .	. . .	. . .	. . .
Sputum appearance[f]									
Nonpurulent	151 (41)	2 (25)	149 (42)	Reference	. . .	. . .	. . .	. . .	. . .
Purulent	214 (59)	6 (75)	208 (58)	2.14 (.4–10.5)	.35	. . .	. . .	. . .	. . .
Sputum AFB smear grade									
1+[g]	60 (16)	0	60 (100)	. . .	.28[h]	. . .	. . .	. . .	. . .
2+	59 (16)	0	59 (100)	. . .	. . .	. . .	. . .	. . .	. . .
3+	250 (68)	8 (100)	242 (67)	. . .	. . .	. . .	. . .	. . .	. . .
Sputum MGIT, DTP									
Median (IQR)	6 (4–8)	3 (2–4)	6 (4–8)	0.67 (.48–.93)	.02	. . .	. . .	. . .	. . .
≥6	189 (52)	1 (13)	188 (53)	Reference	. . .	Reference	. . .	Reference	. . .
<6	172 (48)	7 (87)	165 (47)	7.9 (.98–64.7)	.05	8.2 (1.1–59.2)	.04	7.5 (1.1–52.6)	.04
Aerosol CFU count					. . .	. . .	. . .	. . .	. . .
Median (IQR)	0 (0–6)	16 (1–32)	0 (0–6)	1.01 (1.00–1.01)	.15	. . .	. . .	. . .	. . .
Mean (SD)	14.9 (47)	35.1 (55.6)	14.5 (46.8)	. . .	. . .	. . .	. . .	. . .	. . .
Range	0–378	0–163	0–378	. . .	. . .	. . .	. . .	. . .	. . .
<10	293 (79)	4 (50)	289 (80)	Reference	. . .	Reference	. . .	Reference	. . .
≥10	76 (21)	4 (50)	72 (20)	4.0 (.98–16.3)	.05	6.0 (1.4–25.2)	.01	4.3 (.98–18.8)	.05

Health services

Risk factors for Diagnostic delay	Positive association	Negative association
HIV	[10]	[11-13]
Coexistence of chronic cough and/or other lung diseases	[12, 14-16]	[7]
Negative sputum smear	[12, 19, 20]	[15]
Extrapulmonary TB	[7, 17, 18]	
Rural residence	[5, 11, 14, 16, 23, 25, 29-32]	
Low access to healthcare	[6, 8, 10, 14, 18, 23, 25, 27-30, 34, 42, 47, 48, 50]	
Initial visit to government low-level healthcare facility	[5, 6, 9-11, 23, 26, 32-34]	[35]
Initial visit to traditional or unqualified practitioner	[9, 10, 14, 26-29, 32, 36, 37]	
Initial visit to private practitioner	[9, 10, 14, 26-29, 32, 36, 37]	
Initial visit to tertiary-level services/hospital	[11]	[13, 23, 38, 39]
Old age	[5, 12, 14-16, 19, 23, 24, 26, 38, 40, 41]	[18, 35]
Poverty	[7, 20, 21, 27, 28, 34, 37, 40, 41, 47, 48, 54, 56]	[18]
Female sex	[8, 10, 11, 14-16, 20, 22, 31, 33, 39, 40]	[5, 21, 23, 25]
Alcoholism or substance abuse	[8, 21-25]	
History of immigration	[8, 15, 17, 22, 38, 39, 42]	
Low educational level and/or low awareness and knowledge about TB	[9, 15-17, 20, 21, 23, 24, 27, 28, 31-33, 38, 39]	[13]

Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health. 2008 Jan 14;8:15.

Impact of treatment delay on transmission

Table 4 Independent risk factors for tuberculin skin test (TST) positivity of household contacts identified by multivariate random intercept model among total contacts ($n = 1668$)

Variable	Adjusted odds ratio	95% CI	*P*-value
Total treatment delay of index case			
Non-TB index case (baseline group)	1		
TB index case with delay ≤30 d	0.61	0.20–1.87	0.38
TB index case with 30–60 d delay	1.86	1.20–2.89	0.007
TB index case with 60–90 d delay	2.37	1.56–4.11	<0.001
TB index case with delay >90 d	2.27	1.46–3.63	<0.001
Chest X-ray with cavitation of index case			
Negative	1		
Positive	1.64	1.25–2.21	<0.001
Age of contact (years)			
≤4	1		
4–14]	2.07	0.93–4.89	0.10
14–24	3.78	1.69–10.5	0.002
24–64	4.64	2.15–11.7	<0.001
>64	5.57	2.06–15.4	<0.001
Sleeping site relative to TB patient			
Different bedroom	1		
Same bedroom	2.29	1.67–2.94	<0.001

Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R. Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. Trans R Soc Trop Med Hyg. 2008;102:797-804.

Host factors associated with disease

- Malnutrition
- Co-morbidities
- HIV
- Helminths

Poverty

- Diabetes mellitus
- Smoking
- Alcoholism

Poor populations within wealthier countries

Table 1 Relative Risk, Prevalence and Population Attributable Risk of Selected Risk Factors for TB, in 22 High TB Burden Countries

Risk Factor (reference for relative risk and prevalence estimates, respectively)	Relative Risk for Active TB Disease (Range)[a]	Weighted Prevalence, Total Population, 22 TB High Burden Countries[b]	Population Attributable Fraction (Range)[c]
HIV infection[53,54]	8.3 (6.1–10.8)	1.1%	7.3% (5.2–9.6)
Malnutrition[46,55,d]	4.0 (2.0–6.0)	17.2%	34.1% (14.7–46.3)
Diabetes[51,56,e]	3.0 (1.5–7.8)	3.4%	6.3% (1.6–18.6)
Alcohol use $>$ 40g/day[50,f]	2.9 (1.9–4.6)	7.9%	13.1% (6.7–22.2)
Active smoking[48,57,g]	2.6 (1.6–4.3)	18.2%	22.7% (9.9–37.4)
Indoor pollution[47,49,h]	1.5 (1.2–3.2)	71.1%	26.2% (12.4–61.0)

Alcohol Use and TB Risk

Table 2: Pooled effect sizes for different sub-categories of studies.

Study category	No of studies	Hetero-geneity test Cochrane's Q p-value (I^2)	Pooled, fixed effect assumption (95% confidence interval)	Pooled, random effect assumption (95% confidence interval)
Level of exposure				
High exposure	11	< 0.01 (0.82)	2.90 (2.39–3.51)	3.50 (2.01–5.93)
Low exposure	4	0.46 (0.00)	1.08 (0.82–1.40)	1.08 (0.82–1.40)
High-exposure studies				
Controlled* for HIV status	7	0.03 (0.57)	2.93 (2.37–3.61)	3.26 (2.26–4.70)
Controlled* age, sex, SES, smoking	5	0.04 (0.61)	3.27 (2.38–4.50)	3.49 (2.06–5.90)
Controlled* HIV, age, sex, SES, smoking	4	0.07 (0.42)	3.92 (2.70–5.71)	4.08 (2.49–6.68)
Controlled* infection, age, sex, SES	4	0.23 (0.30)	4.11 (2.84–5.94)	4.21 (2.73–6.48)
Excluding three smallest studies	8	0.03 (0.59)	2.75 (2.19–3.46)	2.94 (1.89–4.59)
Excluding three smallest and Brown I and Kim	6	0.32 (0.15)	2.76 (2.34–3.81)	2.96 (2.28–3.85)
Pulmonary TB cases only**	2	0.49 (0.00)	3.67 (2.58–5.22)	3.67 (2.58–5.22)
All types of TB**	6	< 0.01 (0.83)	2.52 (1.98–3.19)	2.87 (1.47–5.58)

*Controlled for respective covariates, either by design (e.g. through inclusion/exclusion criteria) or in the analysis (stratification or multivariate analysis)
**Excluding three smallest studies

Research article

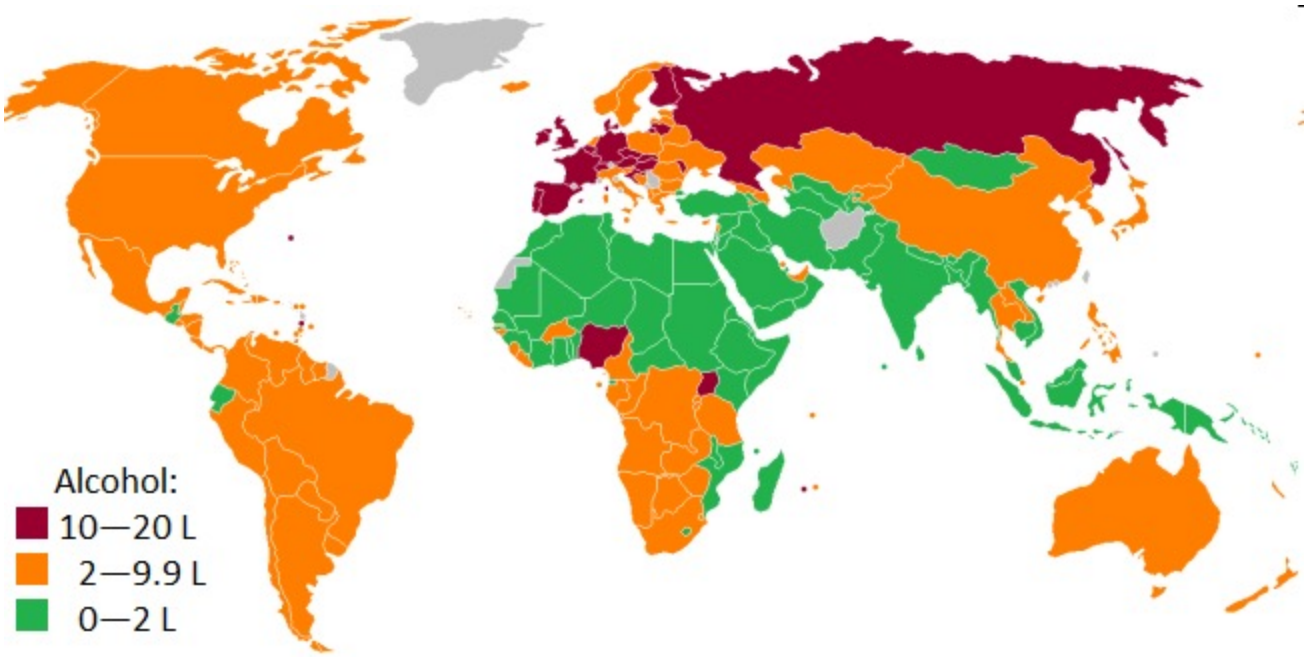
Open Access

Alcohol use as a risk factor for tuberculosis – a systematic review

Knut Lönnroth*, Brian G Williams, Stephanie Stadlin, Ernesto Jaramillo and Christopher Dye

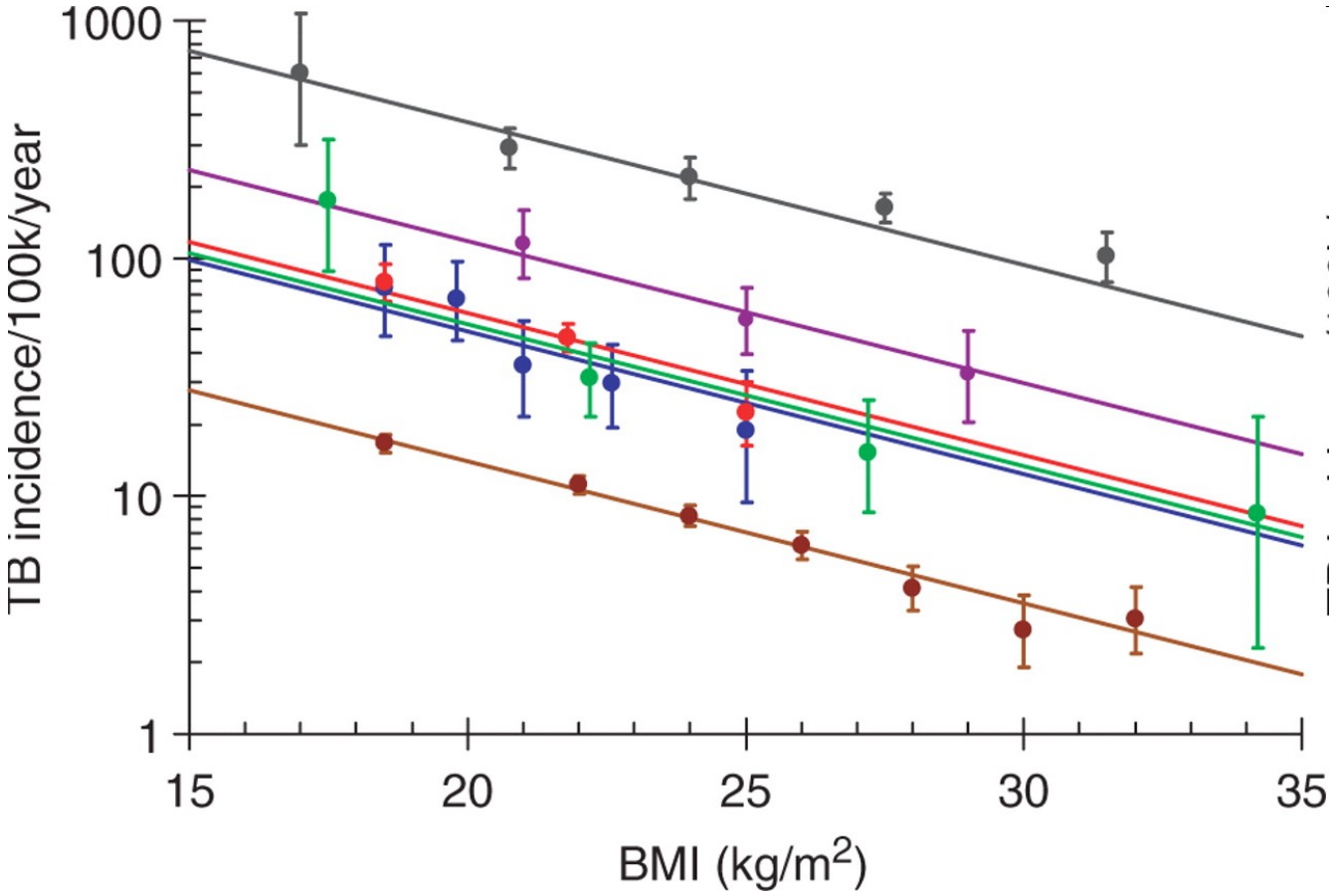
BMC Public Health 2008, 8:289

Host Factors:
Global distribution of alcohol use in men



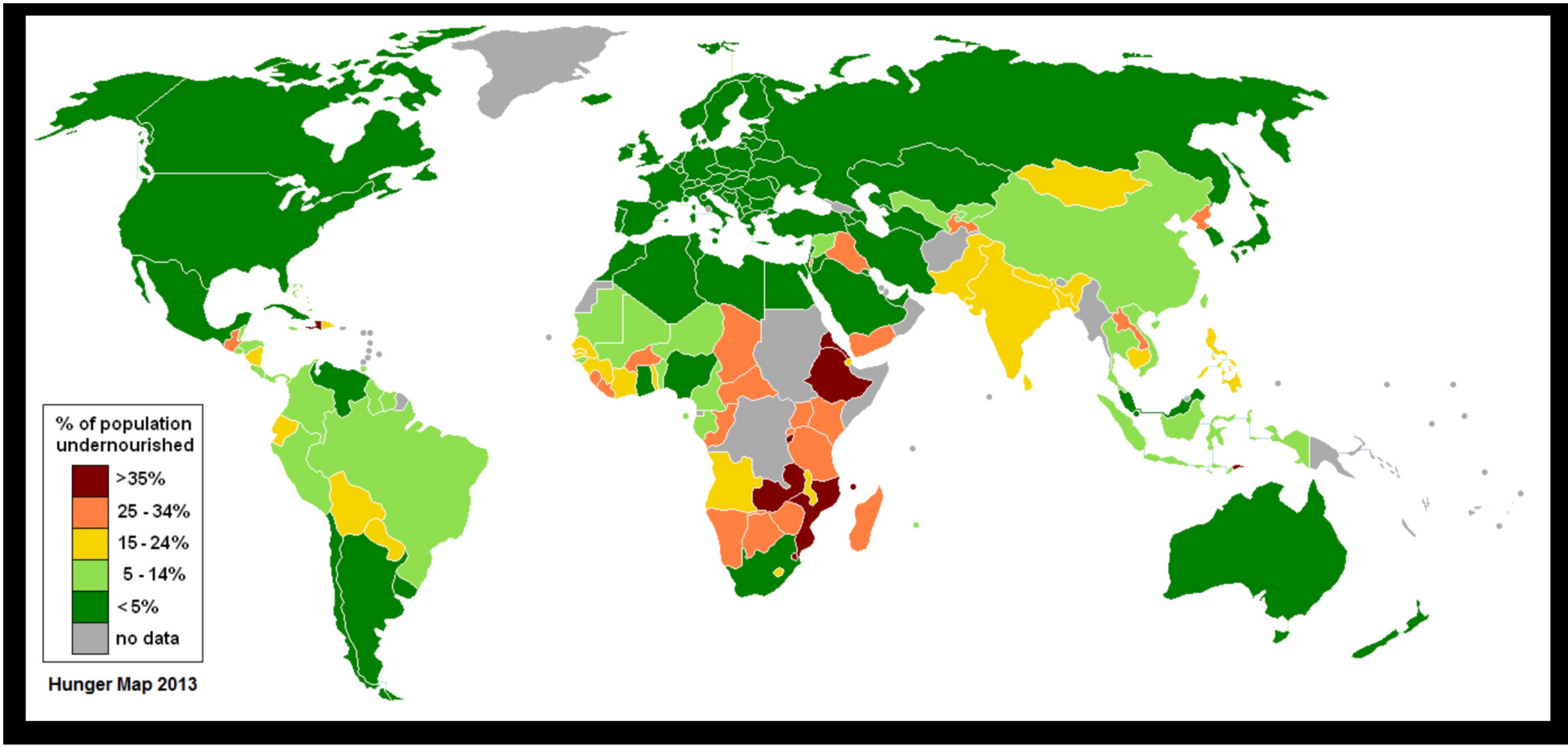
Host Factors: BMI

Dose–response relationship in the reviewed cohort studies on the association between BMI and TB incidence.

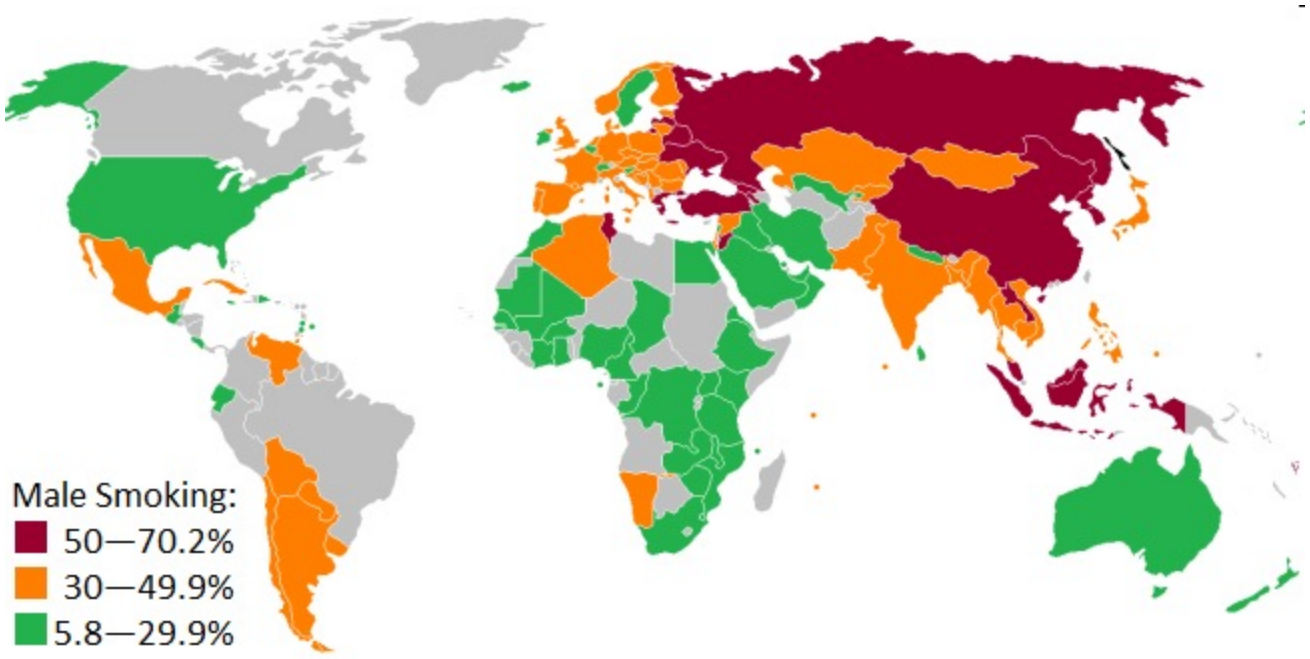


Lönnroth K, Williams BG, Cegielski P, Dye C. **A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol. 2009 Oct 9**. Ahead of print.

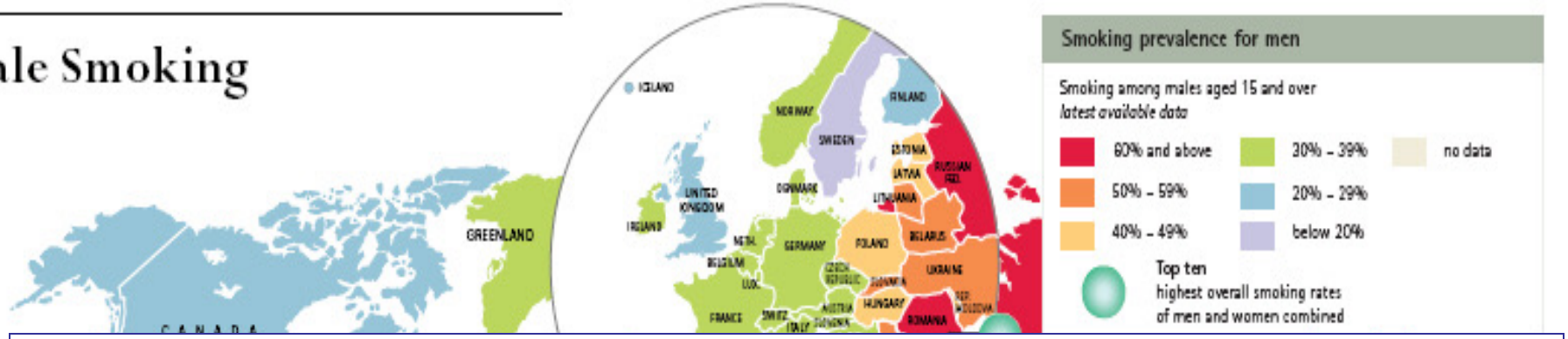
Undernutrition



Global Distribution Male Smoking



Male Smoking



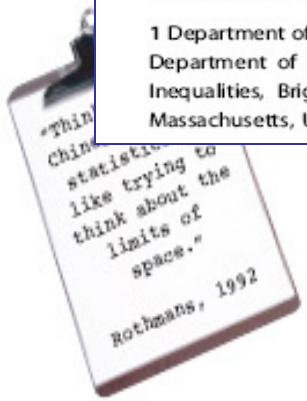
OPEN ACCESS Freely available online

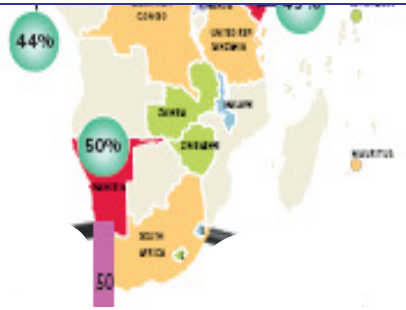
PLOS MEDICINE

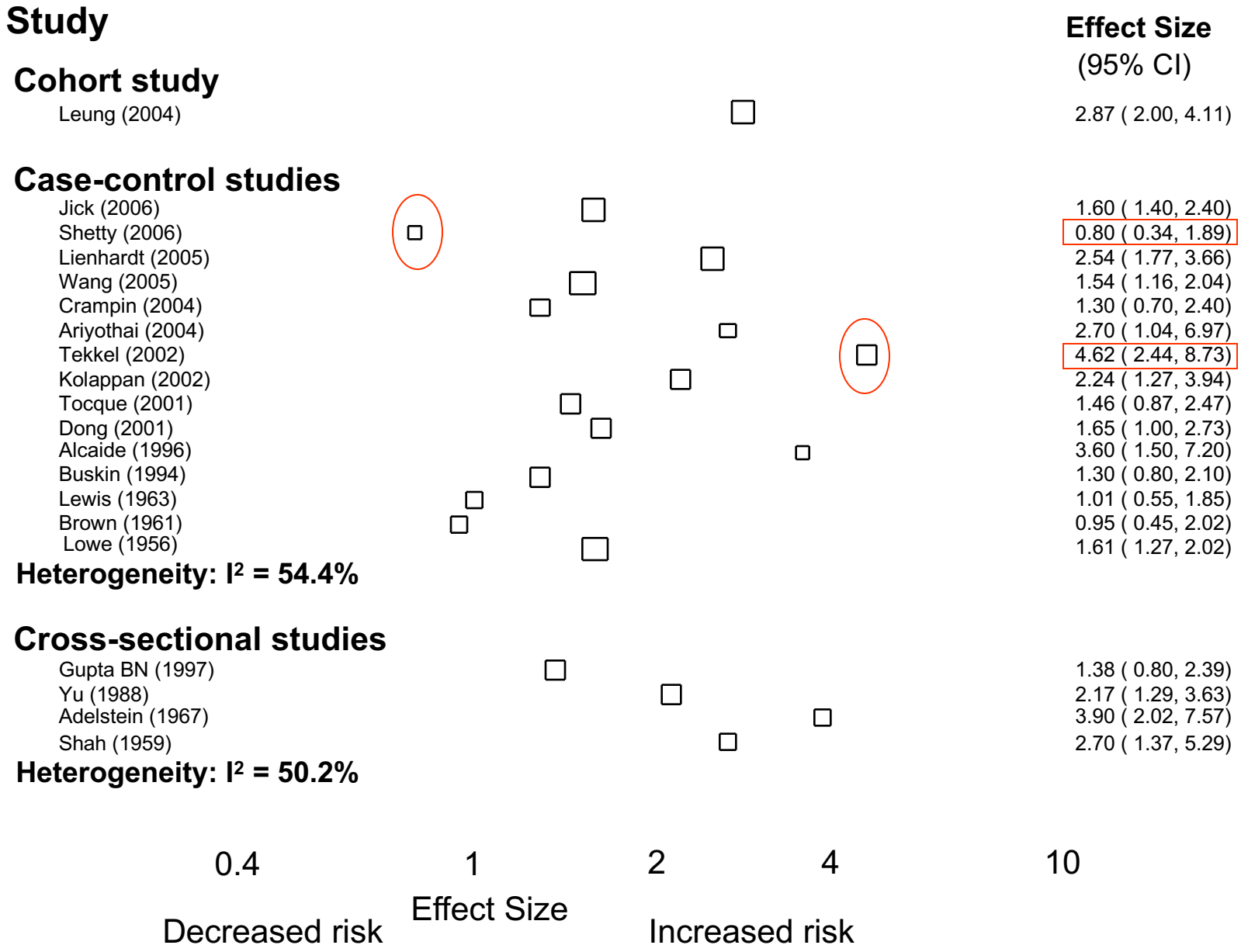
Tobacco Smoke, Indoor Air Pollution and Tuberculosis: A Systematic Review and Meta-Analysis

Hsien-Ho Lin[1], Majid Ezzati[2], Megan Murray[1,3,4*]

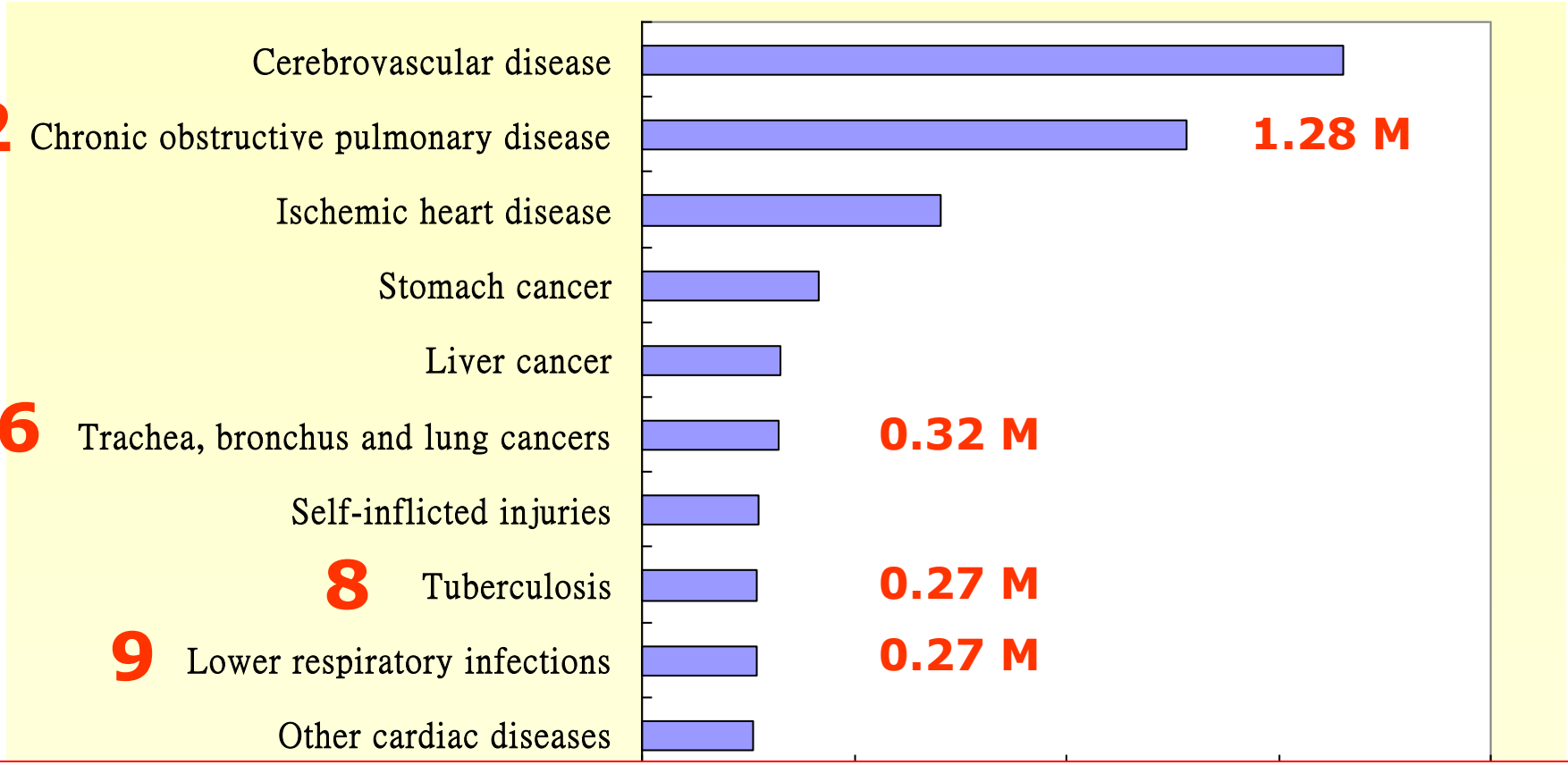
1 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, 2 Department of Population and International Health and Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, United States of America, 3 Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, Boston, Massachusetts, United States of America, 4 Infectious Disease Unit, Massachusetts General Hospital, Boston, Massachusetts, United States of America






Study
Effect Size
(95% CI)
Cohort study
Leung (2004)
2.87 (2.00, 4.11)
Case-control studies
Jick (2006)
1.60 (1.40, 2.40)
Shetty (2006)
0.80 (0.34, 1.89)
Lienhardt (2005)
2.54 (1.77, 3.66)
Wang (2005)
1.54 (1.16, 2.04)
Crampin (2004)
1.30 (0.70, 2.40)
Ariyothai (2004)
2.70 (1.04, 6.97)
Tekkel (2002)
4.62 (2.44, 8.73)
Kolappan (2002)
2.24 (1.27, 3.94)
Tocque (2001)
1.46 (0.87, 2.47)
Dong (2001)
1.65 (1.00, 2.73)
Alcaide (1996)
3.60 (1.50, 7.20)
Buskin (1994)
1.30 (0.80, 2.10)
Lewis (1963)
1.01 (0.55, 1.85)
Brown (1961)
0.95 (0.45, 2.02)
Lowe (1956)
1.61 (1.27, 2.02)
Heterogeneity: I² = 54.4%
Cross-sectional studies
Gupta BN (1997)
1.38 (0.80, 2.39)
Yu (1988)
2.17 (1.29, 3.63)
Adelstein (1967)
3.90 (2.02, 7.57)
Shah (1959)
2.70 (1.37, 5.29)
Heterogeneity: I² = 50.2%
0.4
1
2
4
10
Effect Size
Decreased risk
Increased risk

Leading causes of death in China - 2002

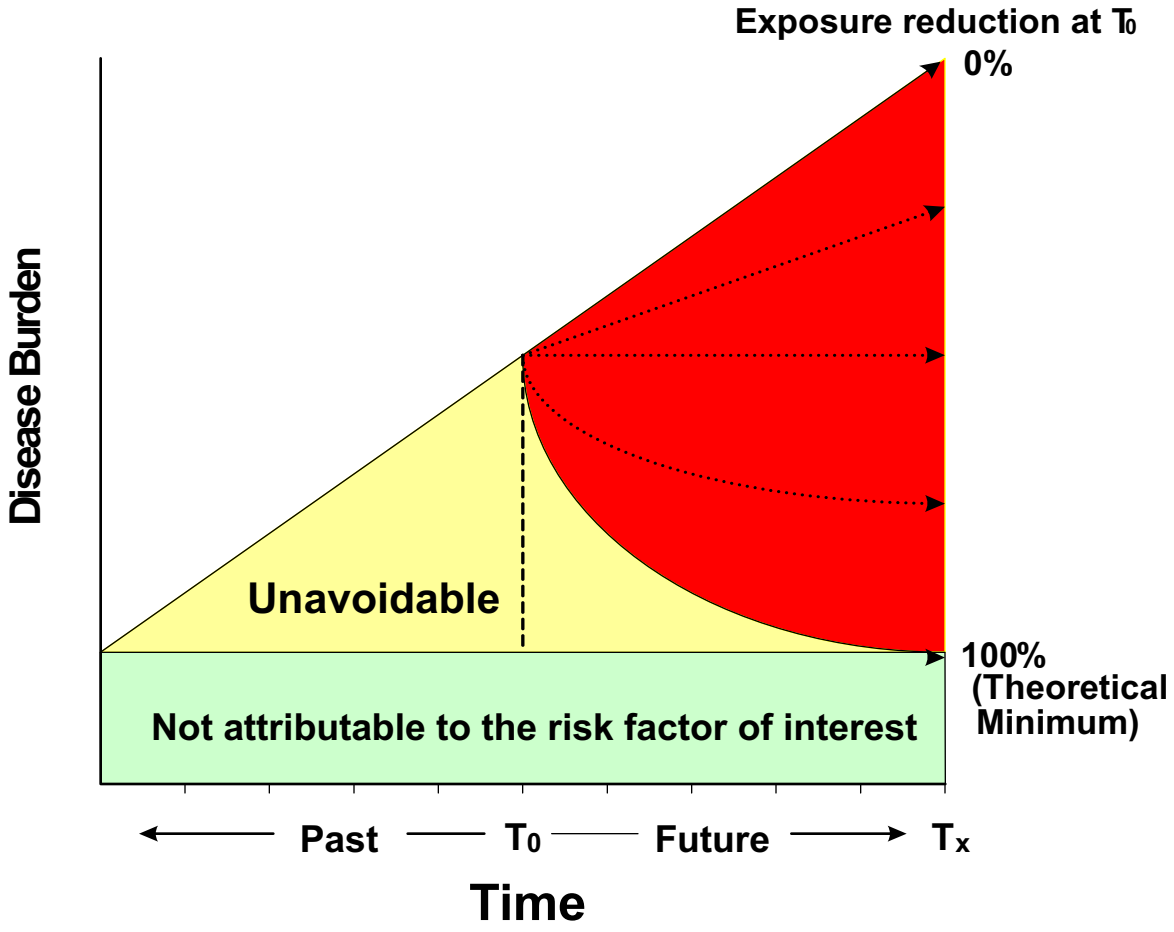


Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study

Hsien-Ho Lin, Megan Murray, Ted Cohen, Caroline Colijn, Majid Ezzati

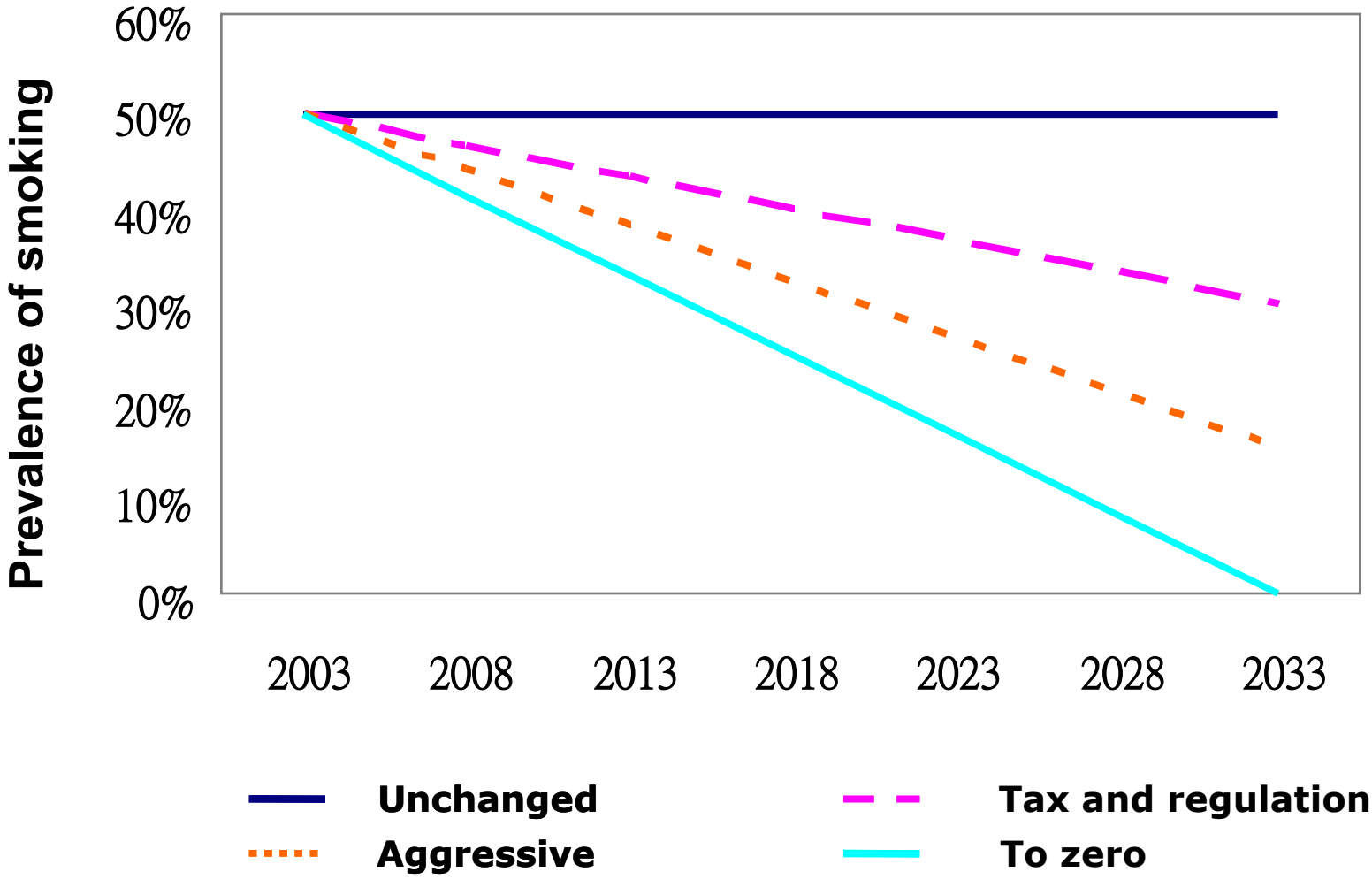
Lancet 2008; 372: 1473–83

Attributable and avoidable disease burden



Murray et al. 2003; Ezzati et al. 2004

Estimate and model smoking trends in China



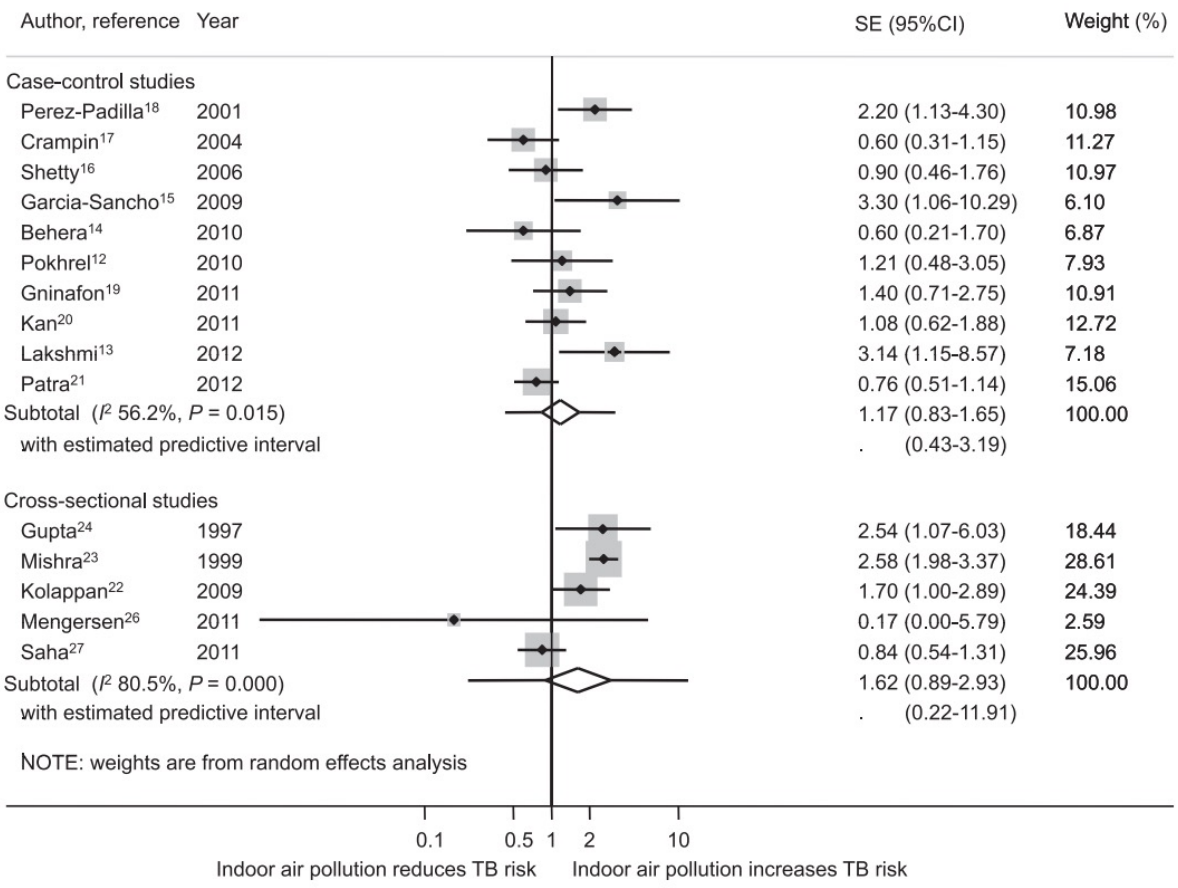
INT J TUBERC LUNG DIS 18(5):613–621

http://dx.doi.org/10.5588/ijtld.13.0765

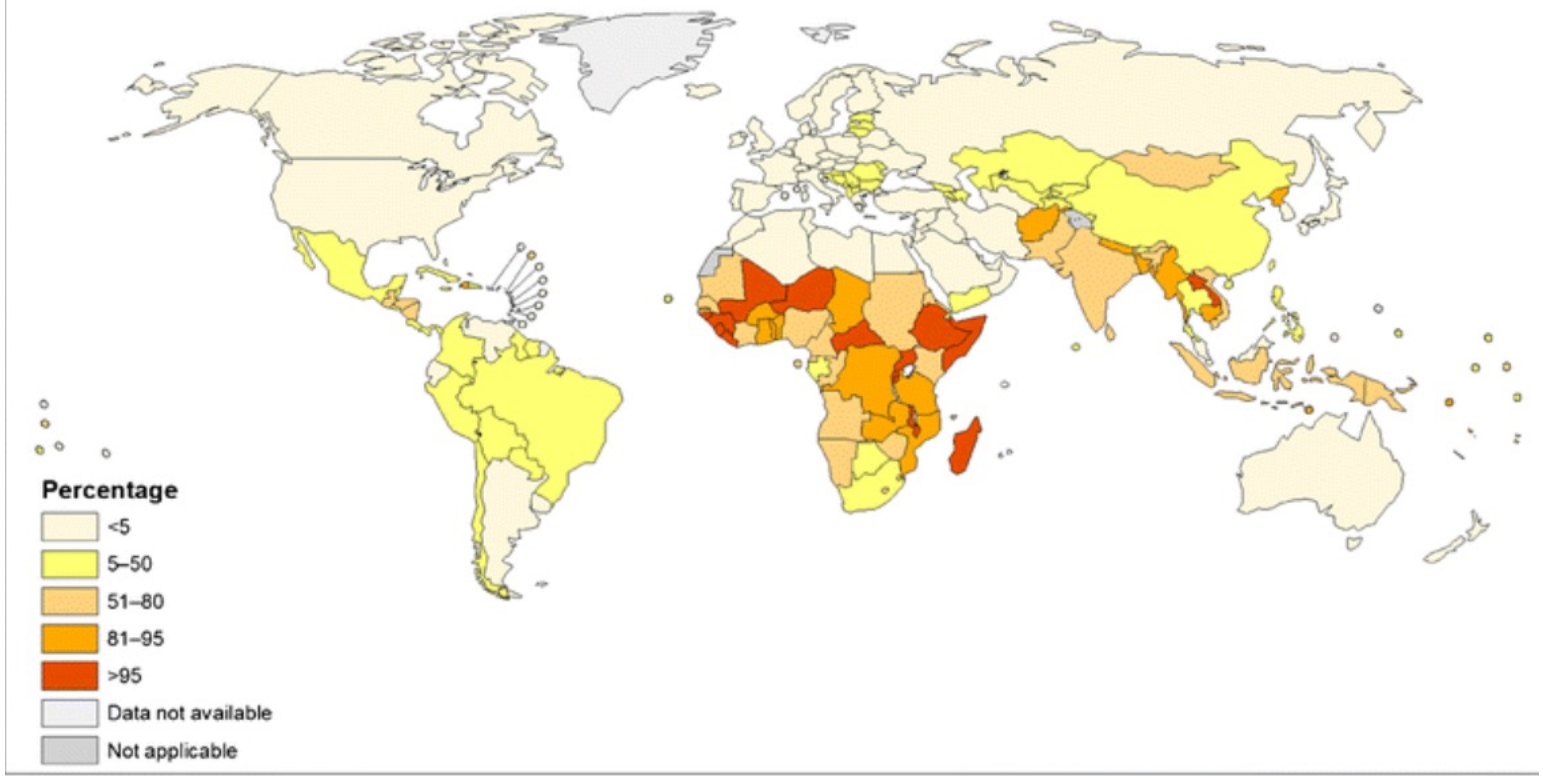
Indoor air pollution from solid fuel and tuberculosis: a systematic review and meta-analysis

H-H. Lin,* C-W. Suk,† H-L. Lo,‡ R-Y. Huang,‡ D. A. Enarson,§ C-Y. Chiang†§¶

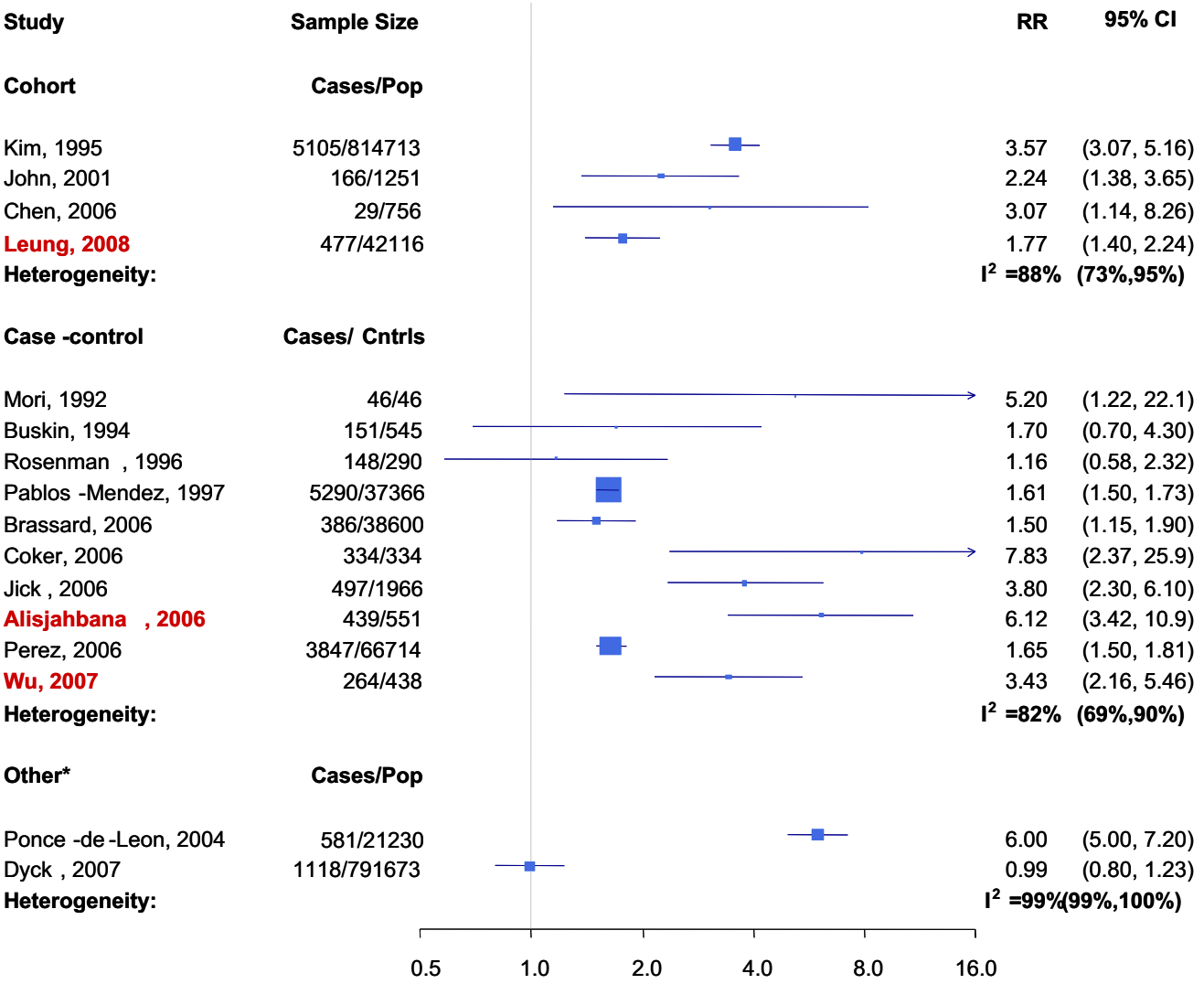
*Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, †Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, ‡Department of Community Health, Mennonite Christian Hospital, Hualien, Taiwan; §International Union Against Tuberculosis and Lung Disease, Paris, France; ¶Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan



Population using solid fuels (%), 2010
Total



Diabetes and TB risk



Severity of diabetes and risk of TB

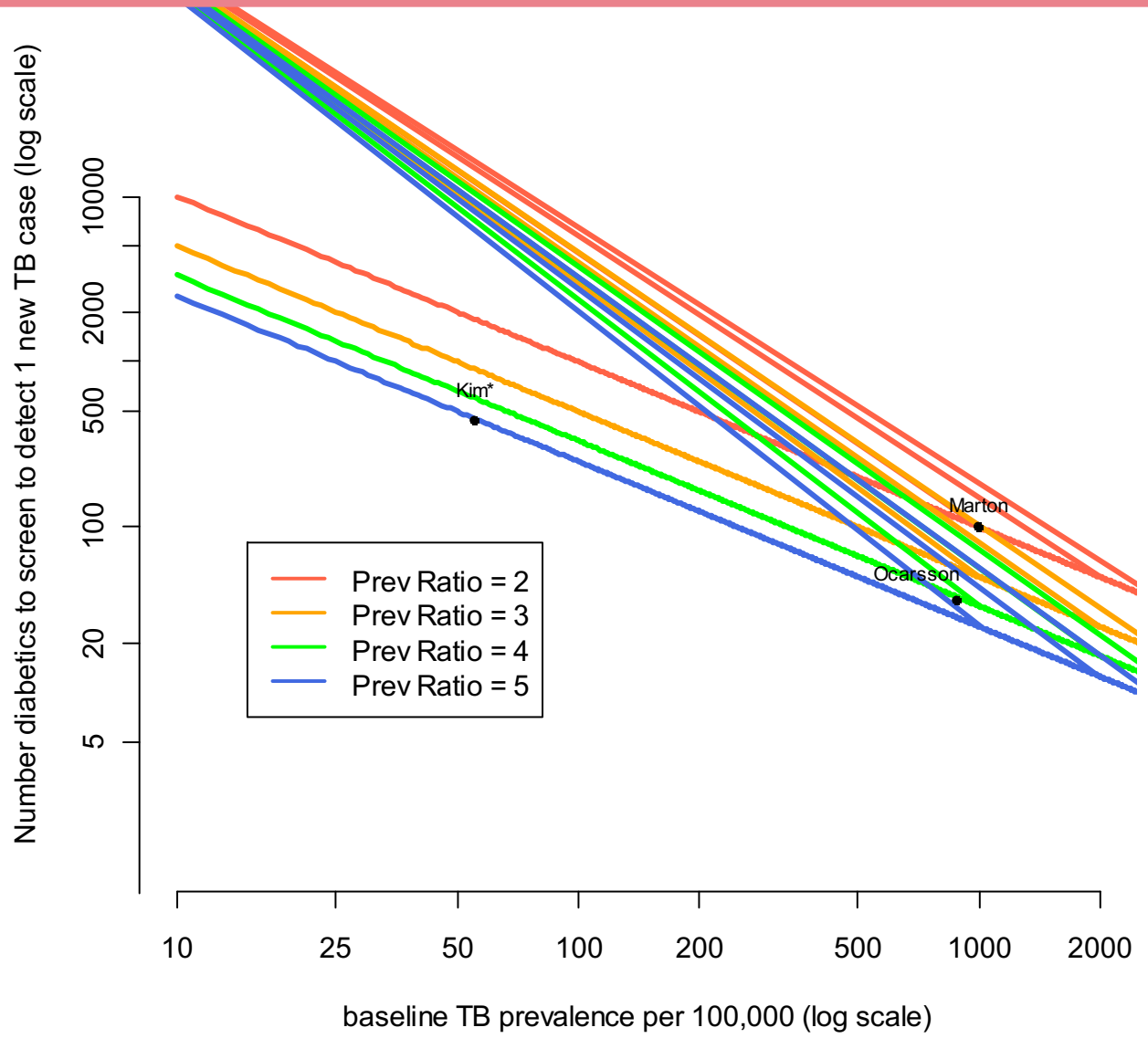
Study	Diabetes strata	Relative Risks	95% CI
Pablo-Mendez et al., 1997	No DM	1	--
	Type II DM, uncomplicated	1.08	(0.98-1.20)
	Type I DM, uncomplicated	1.47	(1.25, 1.73)
	Poorly controlled	2.75	(2.46, 3.06)
Leung et al., 2008		1	--
	DM, HbA1c<7%	0.81	(0.44, 1.48)
	DM, HbA1c>=7%	2.56	(1.95, 3.35)

Differential yield by severity of DM

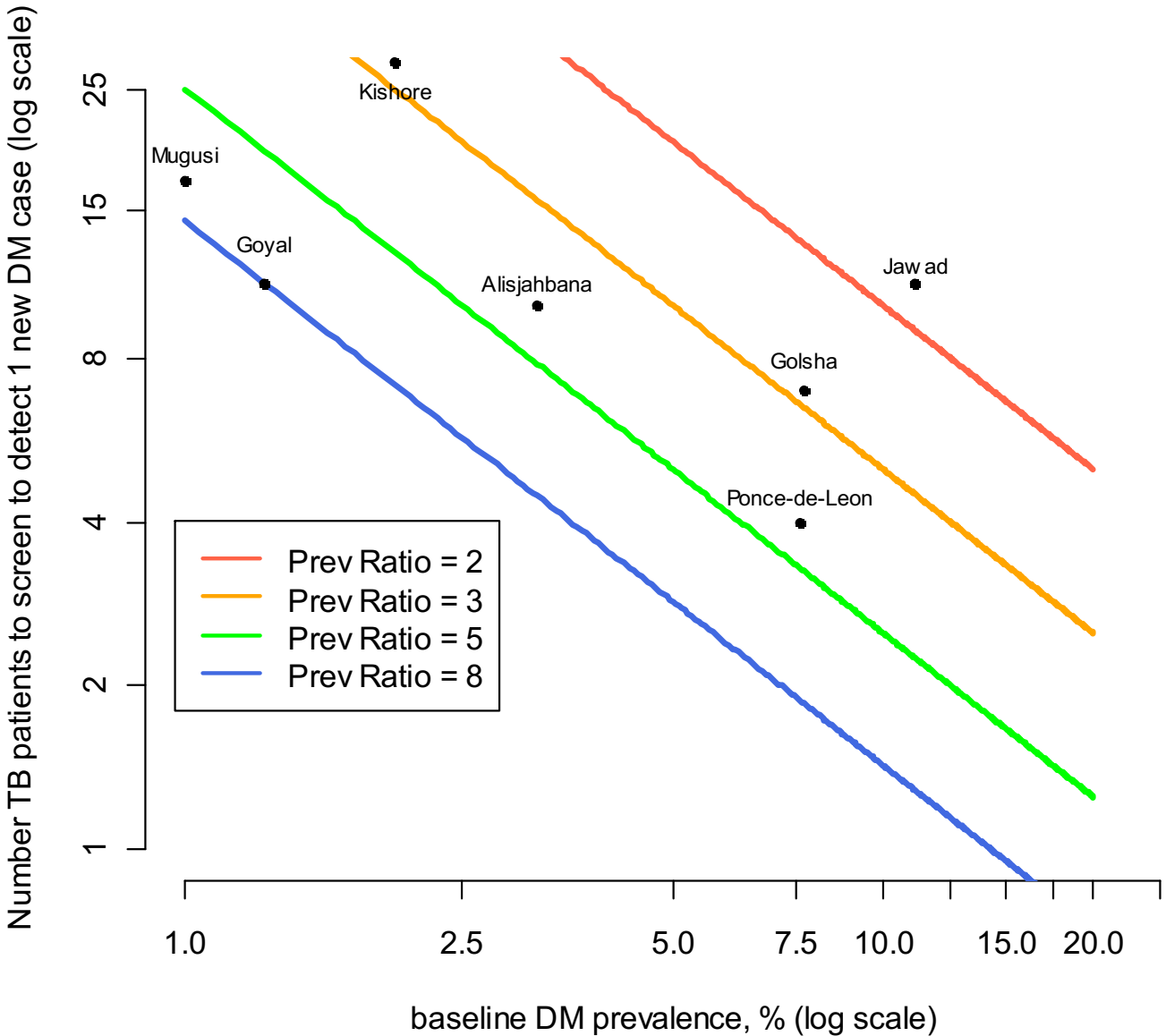
Relative detection of TB by severity of diabetes in studies that stratified by insulin dependence

Study	Diabetes Severity (Quantity of Insulin Required)			Prevalence or Incidence Ratio (compared to mild diabetes)		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Boucot et al., 1952	No insulin	1-39 u/day of insulin	**≥40 u/day of** insulin	1.0	1.3	3.9
Oscarsoon and Silwer , 1958	No insulin - 20u/day of insulin	20-39 u/day of insulin	**≥40 u/day of** insulin	1.0	4.2	20.9
Golli et al., 1975	No insulin	10-20 u/day of insulin	>20 u/day of insulin	1.0	0.6	2.8
Lester, 1984	No insulin	--	Insulin-dependent	1.0	--	7.2

Number of people with DM to screen to detect 1 additional TB case

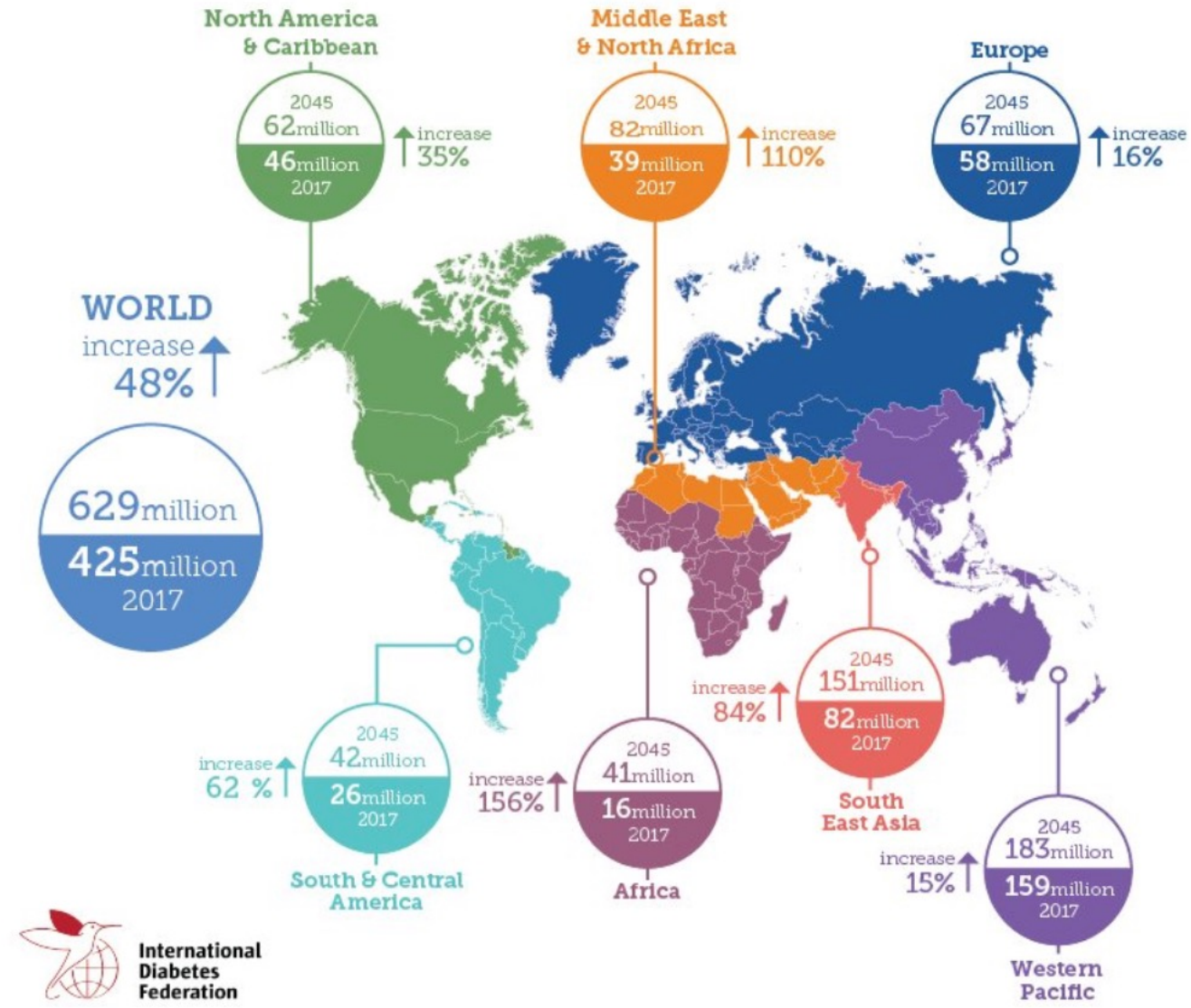


Number of people with TB to screen to detect 1 additional case of DM



Number of people with diabetes worldwide

in 2017 and 2045 (20-79 years)



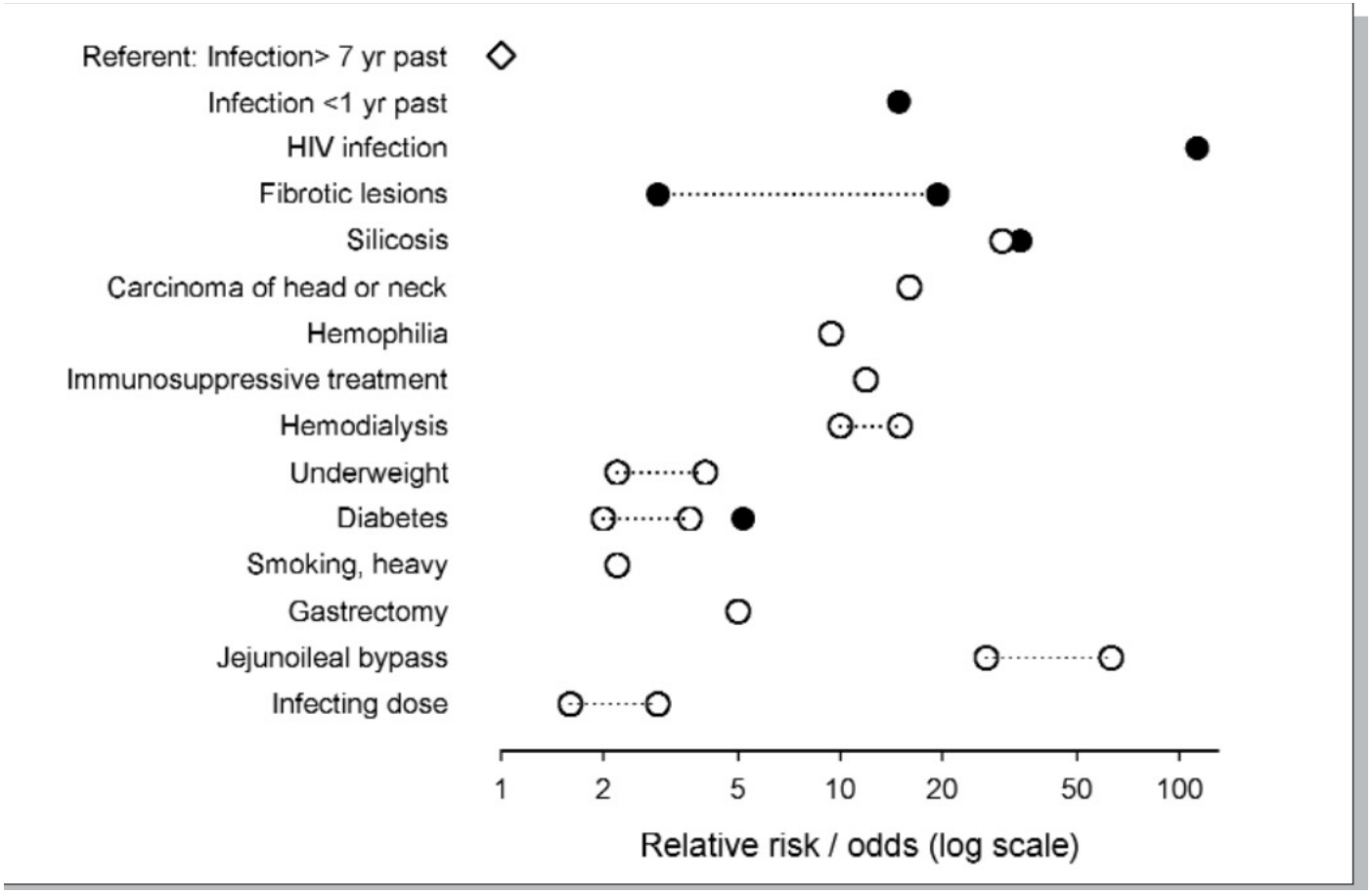
International Diabetes Federation

Others

- Malignancies
- Renal failure
- Gastrectomy and jejunoileal bypass

- Steroid use
- Infliximab
- RA?

Others

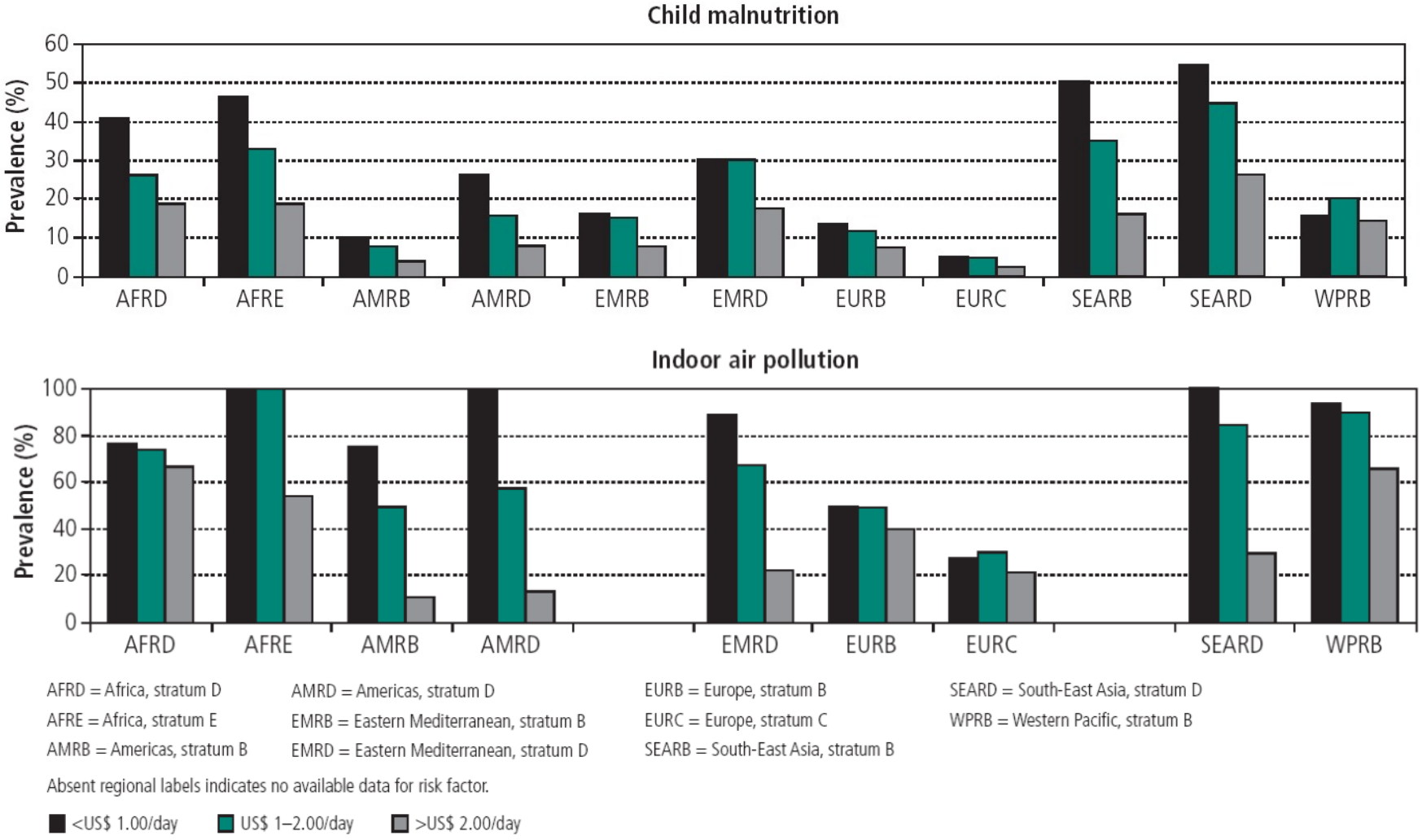

Referent: Infection> 7 yr past
Infection <1 yr past
HIV infection
Fibrotic lesions
Silicosis
Carcinoma of head or neck
Hemophilia
Immunosuppressive treatment
Hemodialysis
Underweight
Diabetes
Smoking, heavy
Gastrectomy
Jejunoileal bypass
Infecting dose
1
2
5
10
20
50
100
Relative risk / odds (log scale)

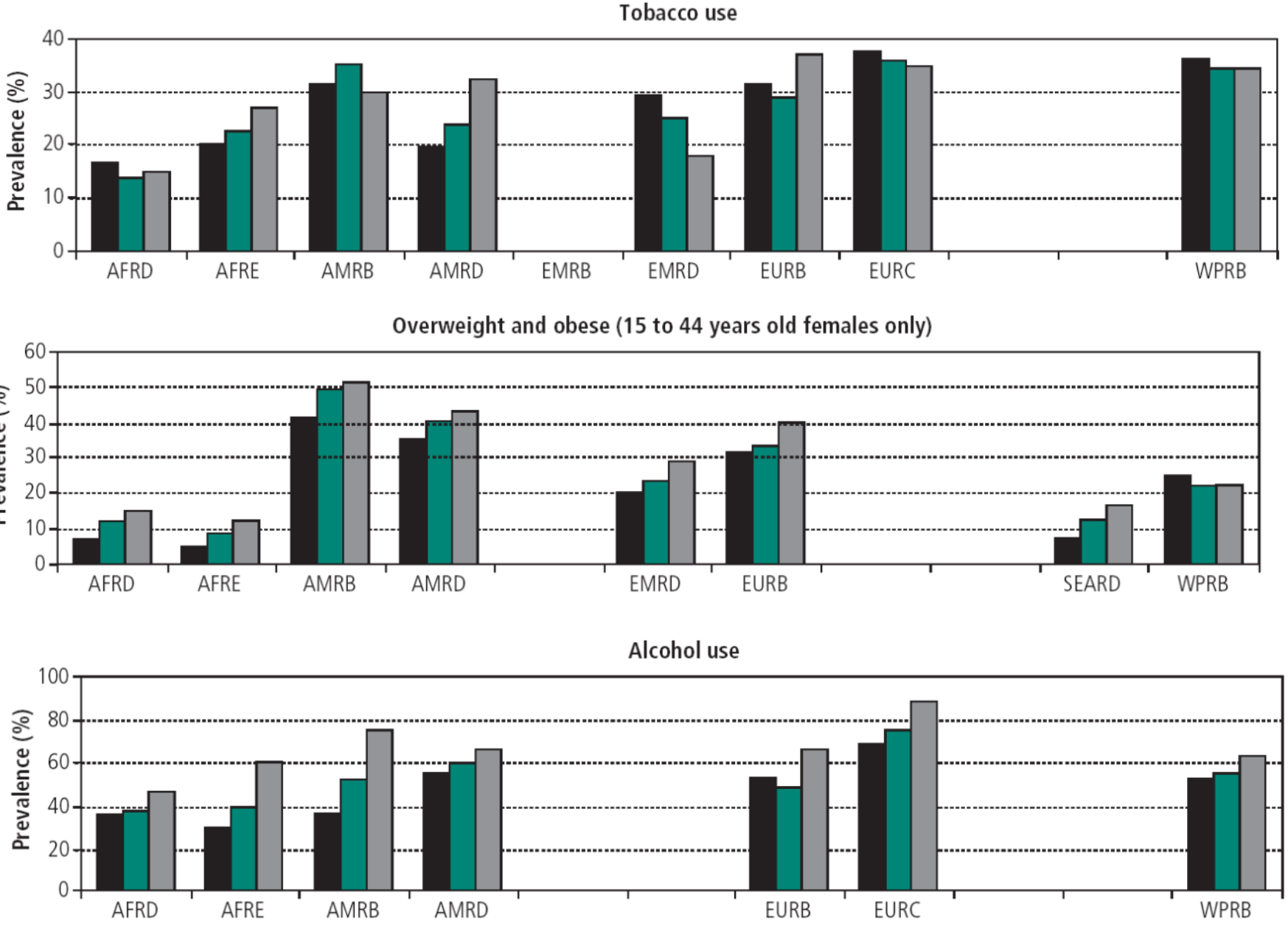
The global distribution of risk factors by poverty level

Tony Blakely,[1] Simon Hales,[2] Charlotte Kieft,[3] Nick Wilson,[4] & Alistair Woodward[5]

Bulletin of the World Health Organization | February 2005, 83 (2)

Fig. 3. **Prevalence of risk factors by level of absolute poverty**




Tobacco use
Prevalence (%)
40
30
20
10
0
AFRD
AFRE
AMRB
AMRD
EMRB
EMRD
EURB
EURC
WPRB
Overweight and obese (15 to 44 years old females only)
Prevalence (%)
60
50
40
30
20
10
0
AFRD
AFRE
AMRB
AMRD
EMRD
EURB
SEARD
WPRB
Alcohol use
Prevalence (%)
100
80
60
40
20
0
AFRD
AFRE
AMRB
AMRD
EURB
EURC
WPRB