CONVERGING EPIDEMICS: TUBERCULOSIS AND DIABETES

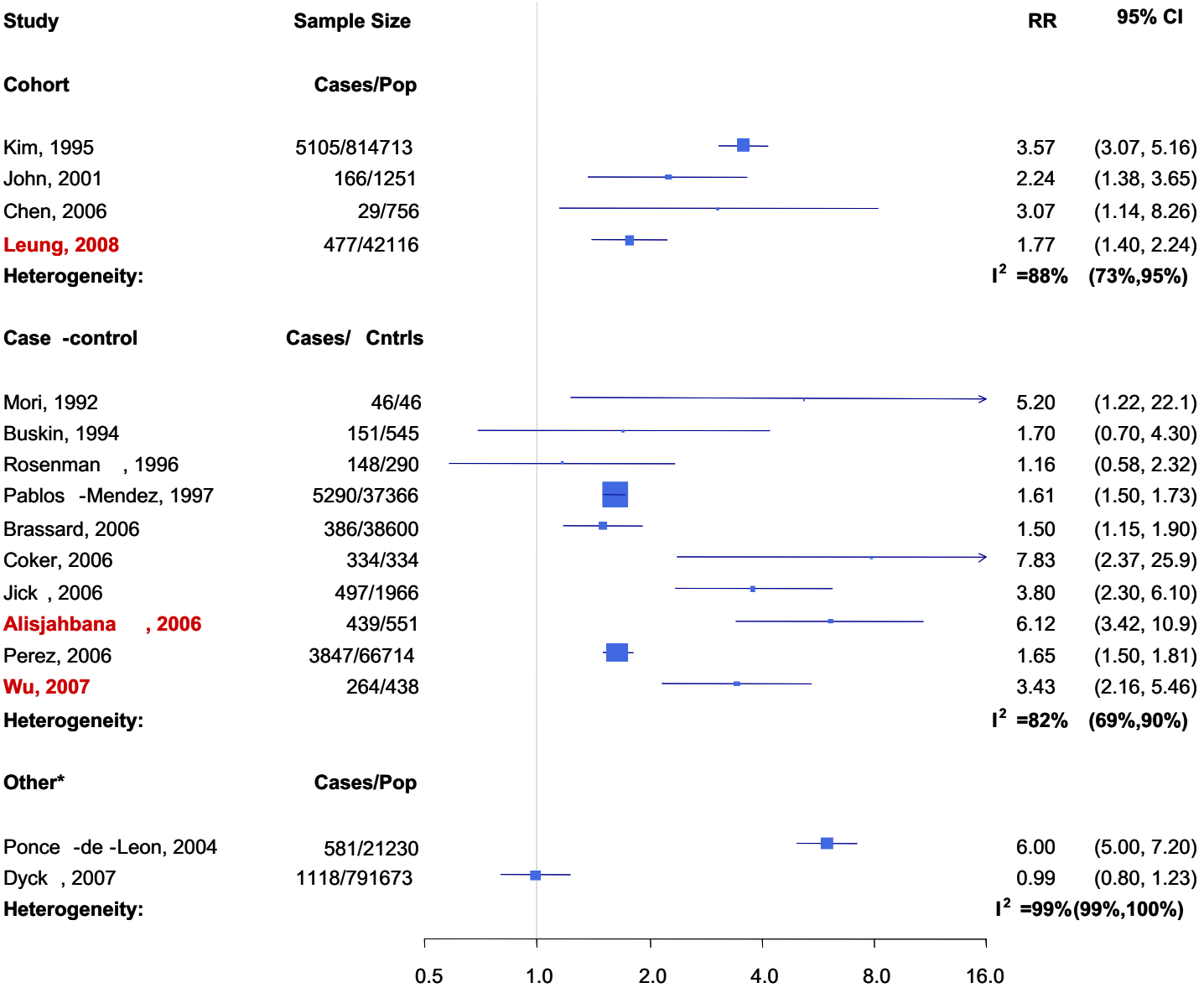
Overview

- Clinical Impact of DM on TB
- Immunological impact of DM on TB
- Burden of TB and DM globally
- What to do
  - Screening
  - Prevention
  - TB treatment
  - DM treatment

DM accounts for a substantial portion of global TB.

Diabetes and risk of TB disease

Christie Jeon



Jeon CY, Murray MB (2008) Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies. PLoS Med 5(7): e152. doi:10.1371/journal.pmed.0050152

Severity of diabetes and risk of TB

Study	Diabetes strata	Relative Risks	95% CI
Pablo-Mendez 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 2008	No DM	1	--
	DM, HbA1c<7%	0.81	(0.44, 1.48)
	DM, HbA1c>=7%	2.80	(1.95, 3.35)

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.

Meghan Baker

Baseline data

17,715 persons > 12 yo

SES

Other co-variates

DM diagnosis

ICD-9 code OR

prescription for anti-DM drugs

# of DM complications OR

DCSI (ICD-9)

TB diagnosis

ICD-9 code AND

>2 anti-TB drugs for >28 days

AND

No misdiagnosis

Univariate and Multivariate Associations Among Diabetes Mellitus, Other Covariates, and Tuberculosis Disease

Variable	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
DM		
Treated DM	4.37 (2.35–8.12)[a]	2.60 (1.34–5.03)[a]
All DM	3.60 (1.99–6.48)[a]	2.09 (1.10–3.95)[a]
Male sex	1.62 (.95–2.76)	1.19 (.61–2.32)
Age (per 1-year increase)	1.05 (1.04–1.07)[a]	1.05 (1.03–1.08)[a]
Living in a crowded home	1.64 (.78–3.46)	1.31 (.59–2.88)
Low income	2.11 (1.22–3.66)[a]	0.94 (.51–1.73)
Receiving government subsidy	3.23 (1.91–5.44)[a]	1.38 (.76–2.49)
Employed	0.52 (.31–.90)[a]	0.98 (.51–1.90)
Residence in an indigenous community	4.93 (2.77–8.78)[a]	3.15 (1.62–6.12)[a]

Hsien-ho Lin

Multivariate Associations for Tuberculosis Disease, by Complications of Diabetes Mellitus

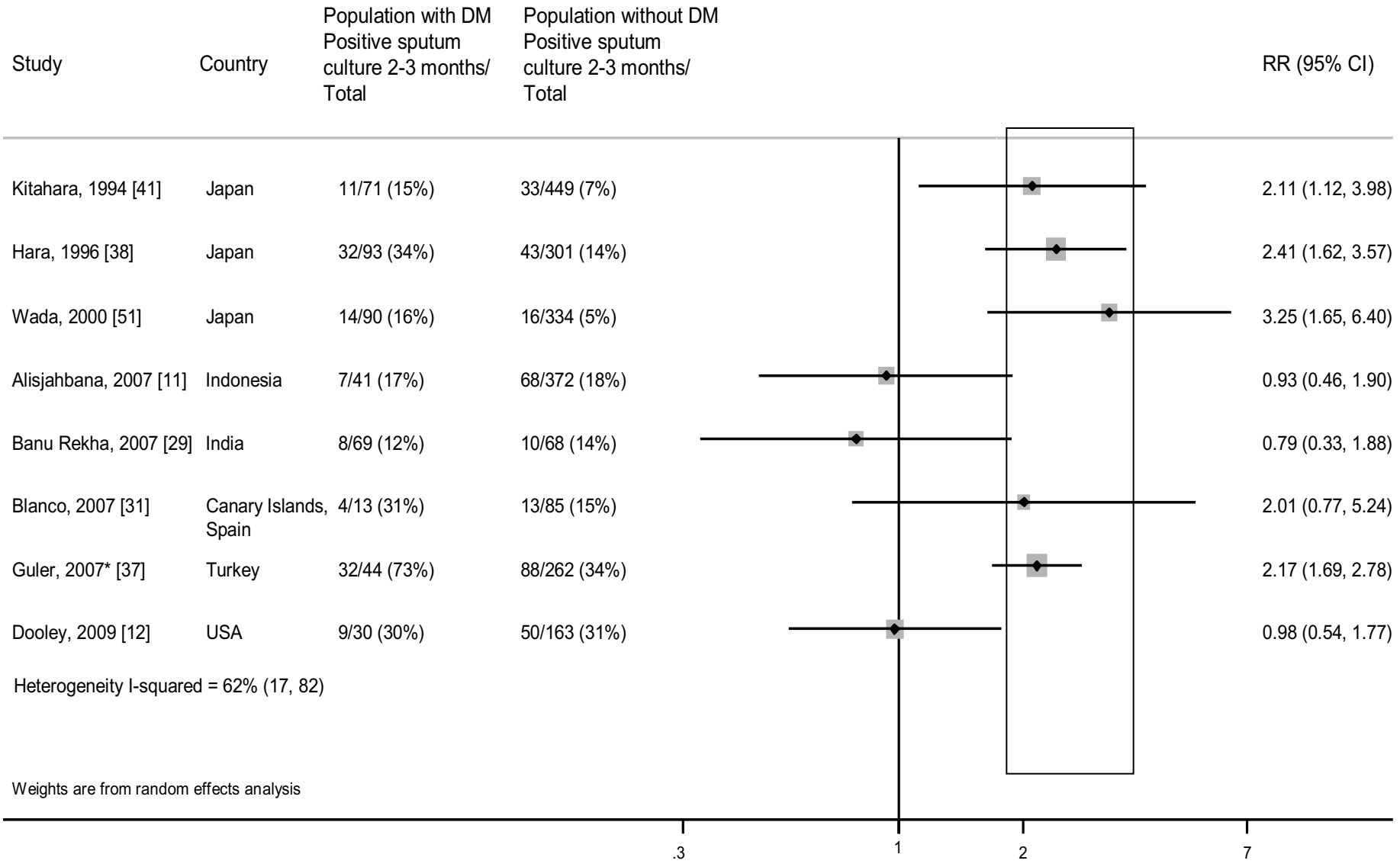
Variable	Tuberculosis Cases	Total Population	Adjusted Hazard Ratio (95% CI)	*P*
Complications of DM				.0016
No DM	44	16 557	1.00	
Treated DM and ≤1 complication	4	609	1.73 (.61–4.89)	
Treated DM and ≥2 complications	9	549	3.45 (1.59–7.50)	
Diabetes Complications Severity Index				
No DM	44	16 557	1.00	.0002
Treated DM and severity score ≤3	6	881	1.72 (.72–4.13)	
Treated DM and severity score ≥4	7	277	5.05 (2.11–12.04)	

Baker MA, Lin HH, Chang HY, Murray MB. The risk of tuberculosis disease among persons with diabetes mellitus: a prospective cohort study. Clin Infect Dis. 2012 Mar;54(6):818-25. Epub 2012 Jan 11.

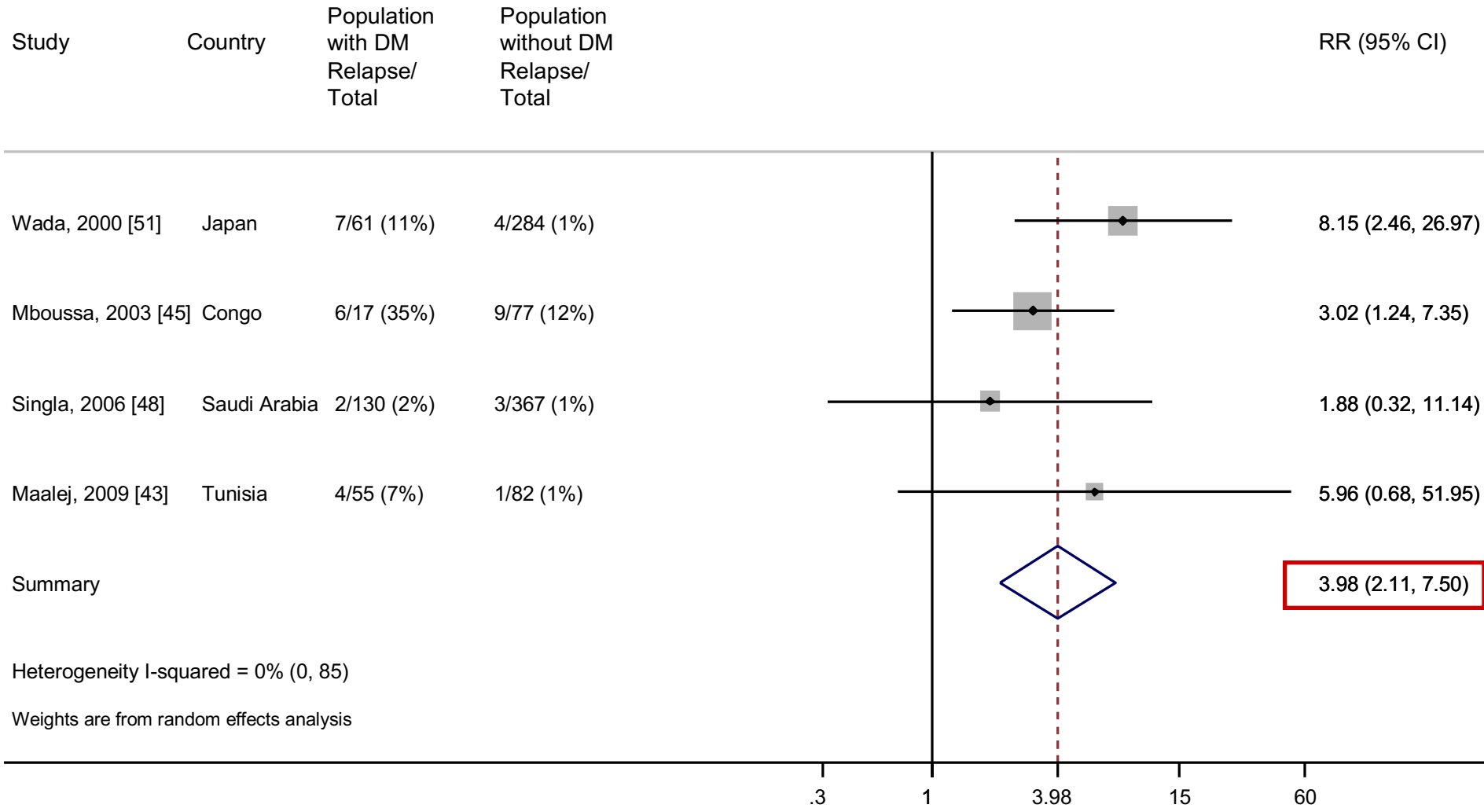
TB Outcomes among People with DM

- Early culture conversion
  - Proportion of treated patients who experience culture conversion at 2-3 months
- Relapse
  - Bacteriologically positive TB disease that occurred after a patient was considered to have completed treatment or to have been cured.
- Death
  - Death for any reason during course of treatment

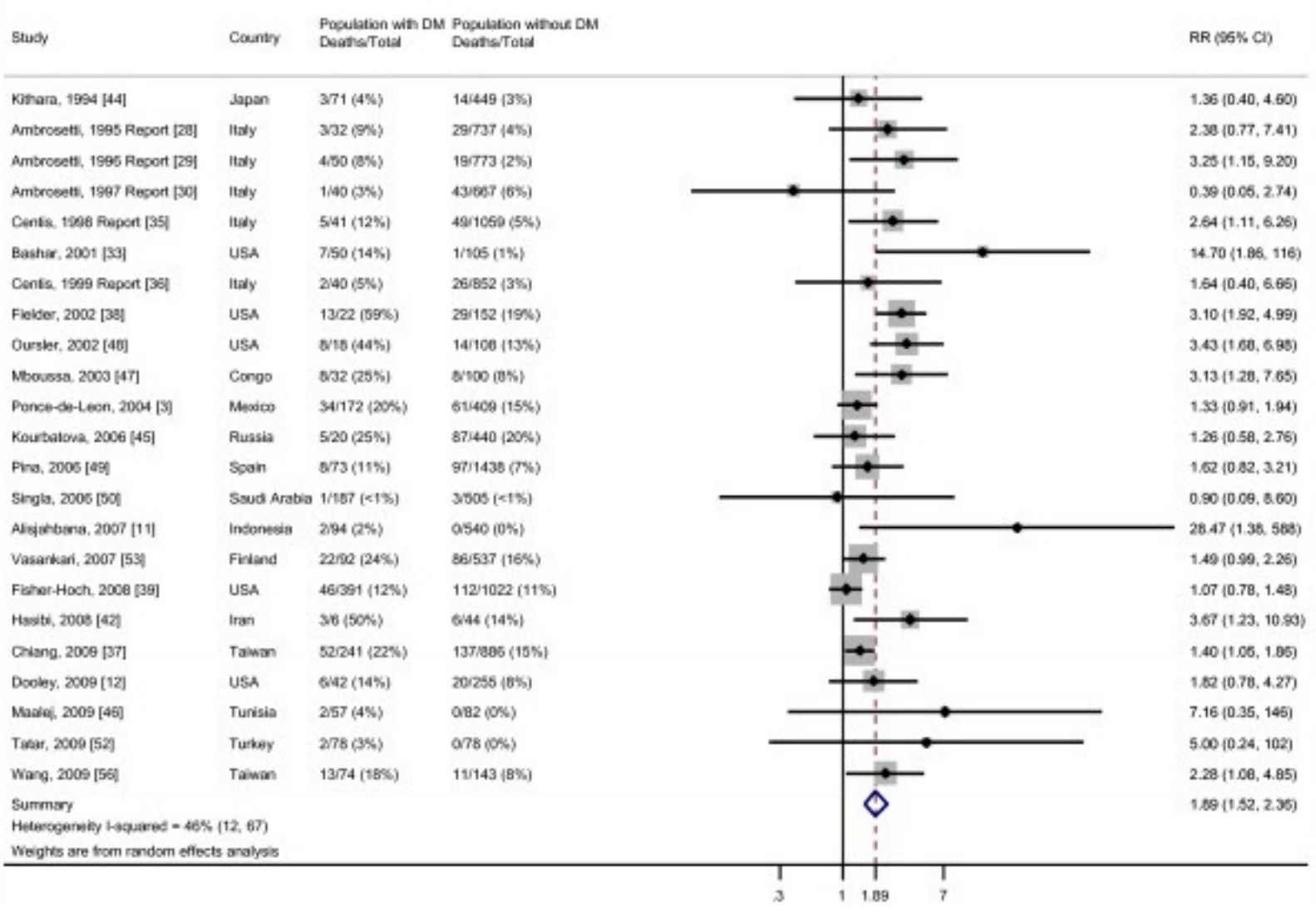
Culture conversion at 2-3 months

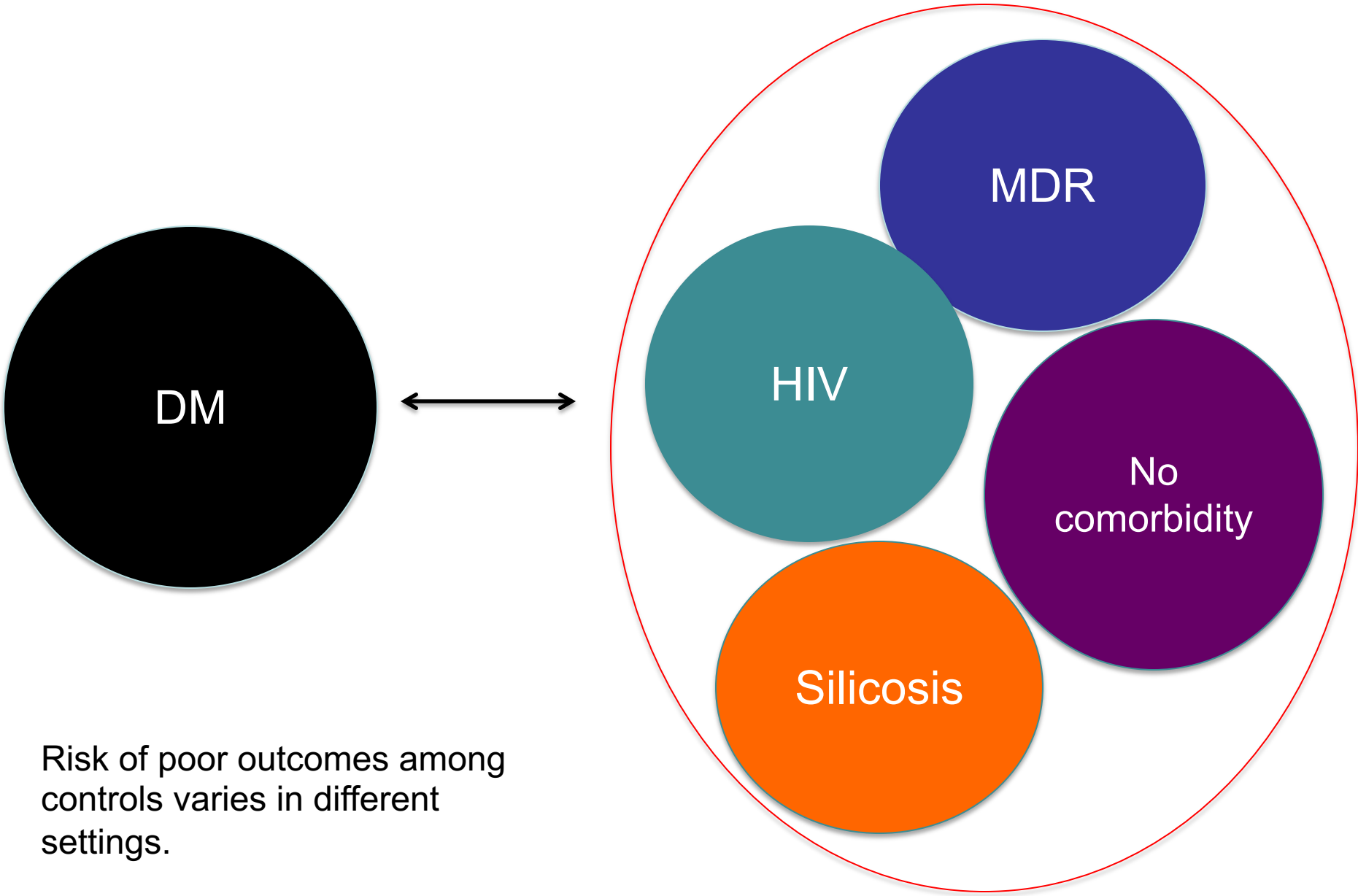


Relapse


Study
Country
Population with DM Relapse/ Total
Population without DM Relapse/ Total
RR (95% CI)
Wada, 2000 [51]
Japan
7/61 (11%)
4/284 (1%)
8.15 (2.46, 26.97)
Mboussa, 2003 [45]
Congo
6/17 (35%)
9/77 (12%)
3.02 (1.24, 7.35)
Singla, 2006 [48]
Saudi Arabia
2/130 (2%)
3/367 (1%)
1.88 (0.32, 11.14)
Maalej, 2009 [43]
Tunisia
4/55 (7%)
1/82 (1%)
5.96 (0.68, 51.95)
Summary
3.98 (2.11, 7.50)
Heterogeneity I-squared = 0% (0, 85)
Weights are from random effects analysis
.3
1
3.98
15
60

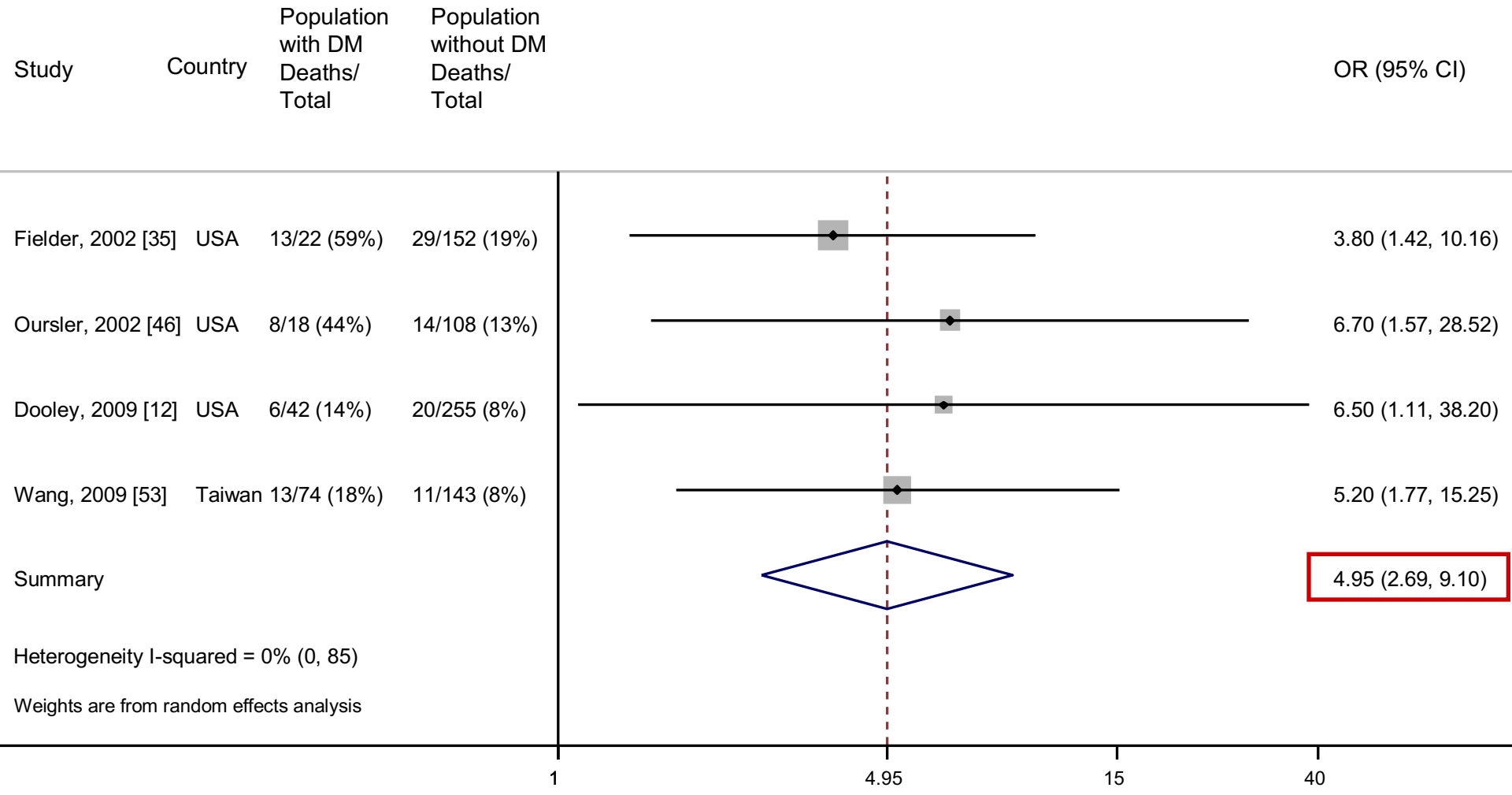
Death (No stratification)



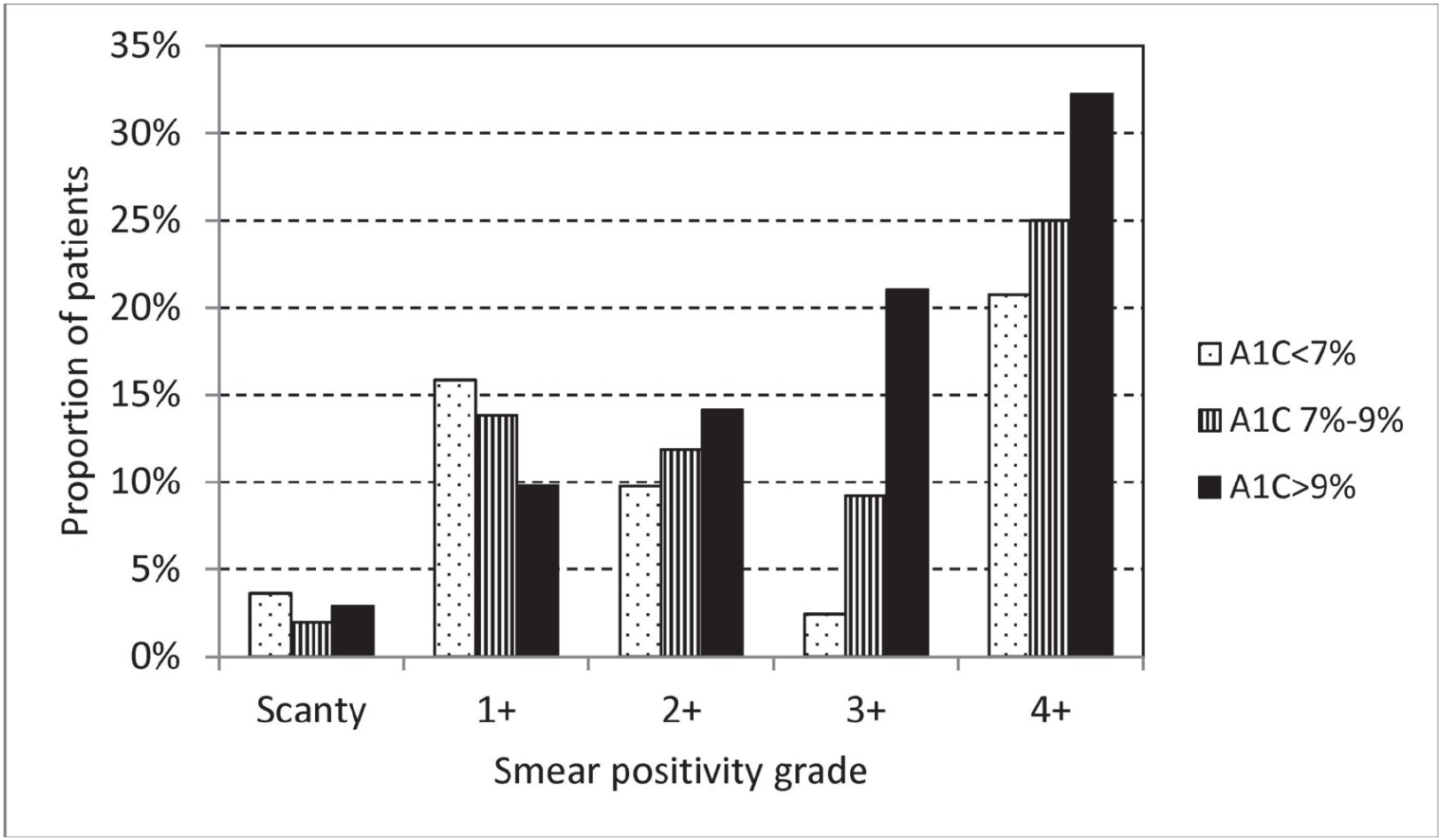


Risk of poor outcomes among controls varies in different settings.

Death stratifying on age and other risk factors



The Influence of Diabetes, Glycemic Control, and Diabetes-Related Comorbidities on Pulmonary Tuberculosis



Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, Lee TI, Yu MC. The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PLoS One. 2015 Mar 30;10(3):e0121698.

Research: Complications

Impact of underlying diabetes and presence of lung cavities on treatment outcomes in patients with pulmonary tuberculosis

A. Nakamura[1], E. Hagiwara[2], J. Hamai[1], M. Taguri[3] and Y. Terauchi[1]

. Diabet Med. 2014 Jun;31(6):707-13.

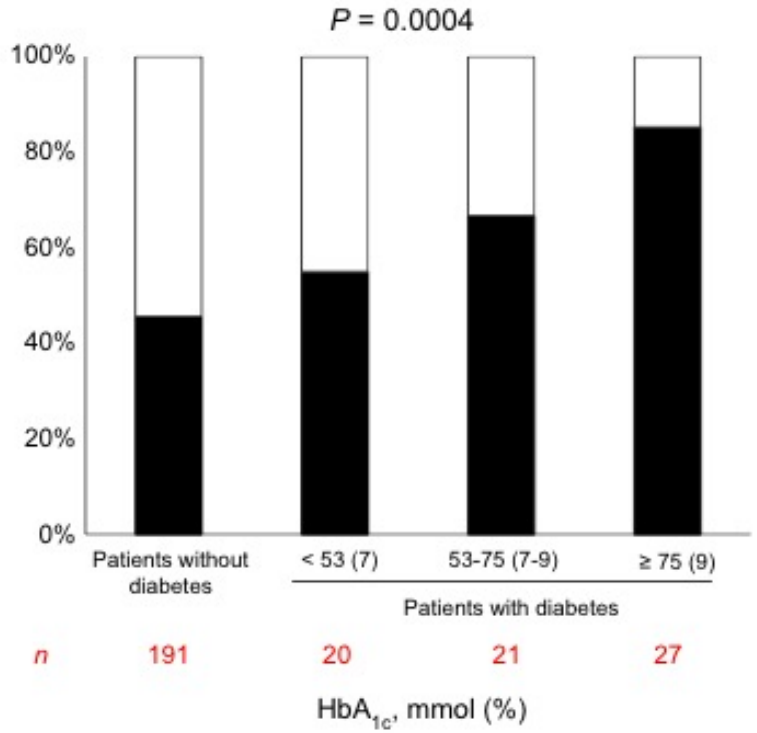
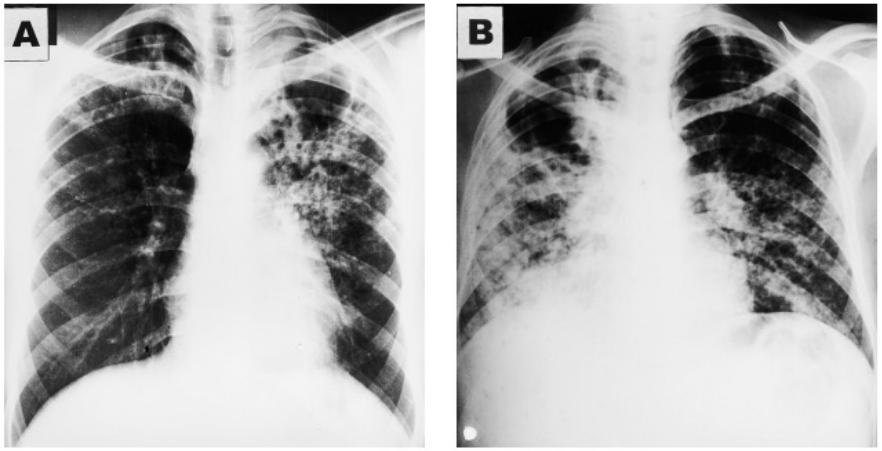


FIGURE 1 Percentage of patients with (black bars) and without (white bars) cavitary pulmonary tuberculosis in relation to the HbA_{1c} levels.

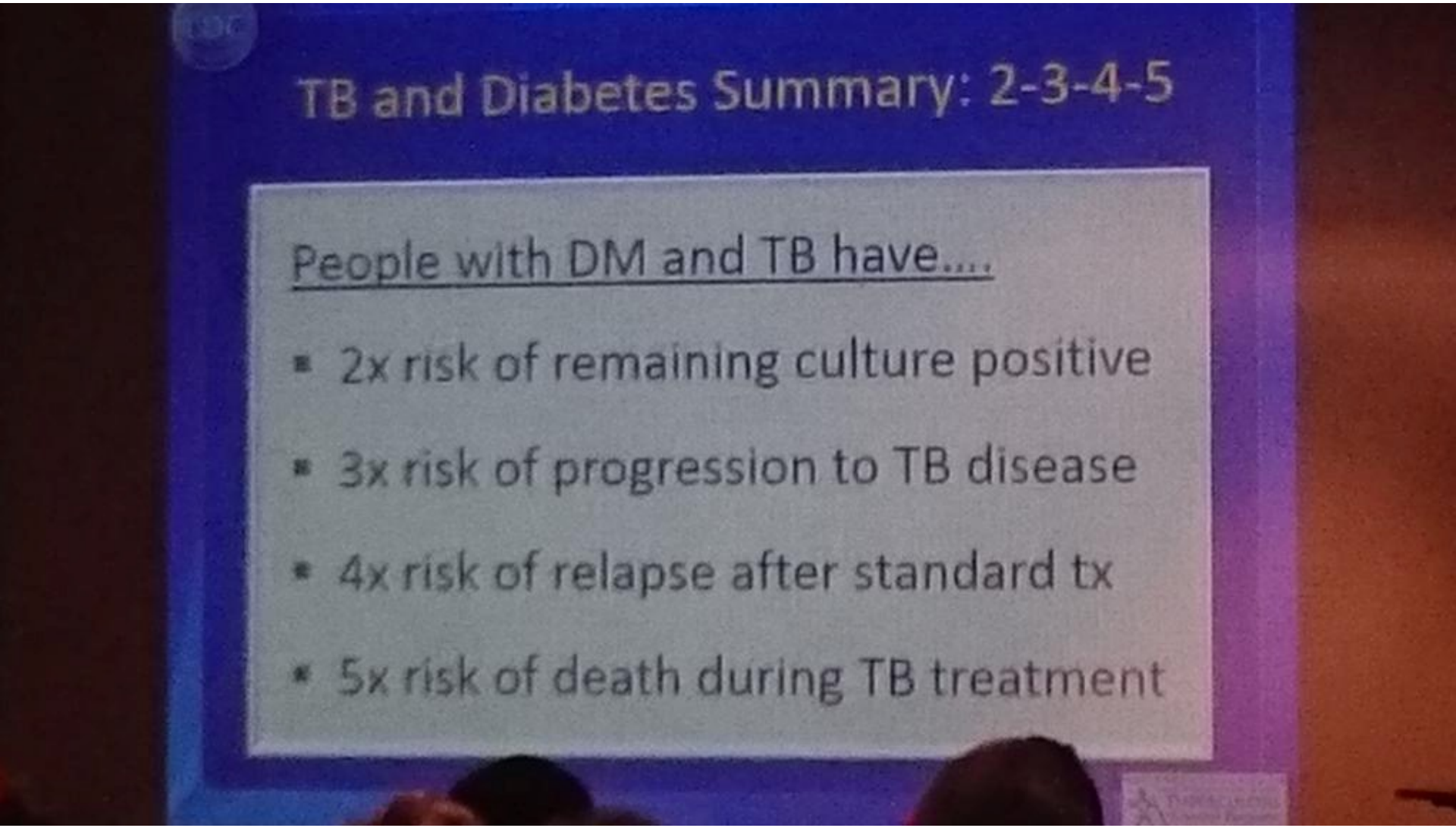
Atypical radiological images of pulmonary tuberculosis in 192 diabetic patients: a comparative study

C. Pérez-Guzmán,*† A. Torres-Cruz,* H. Villarreal-Velarde,‡ M. A. Salazar-Lezama,* M. H. Vargas*§

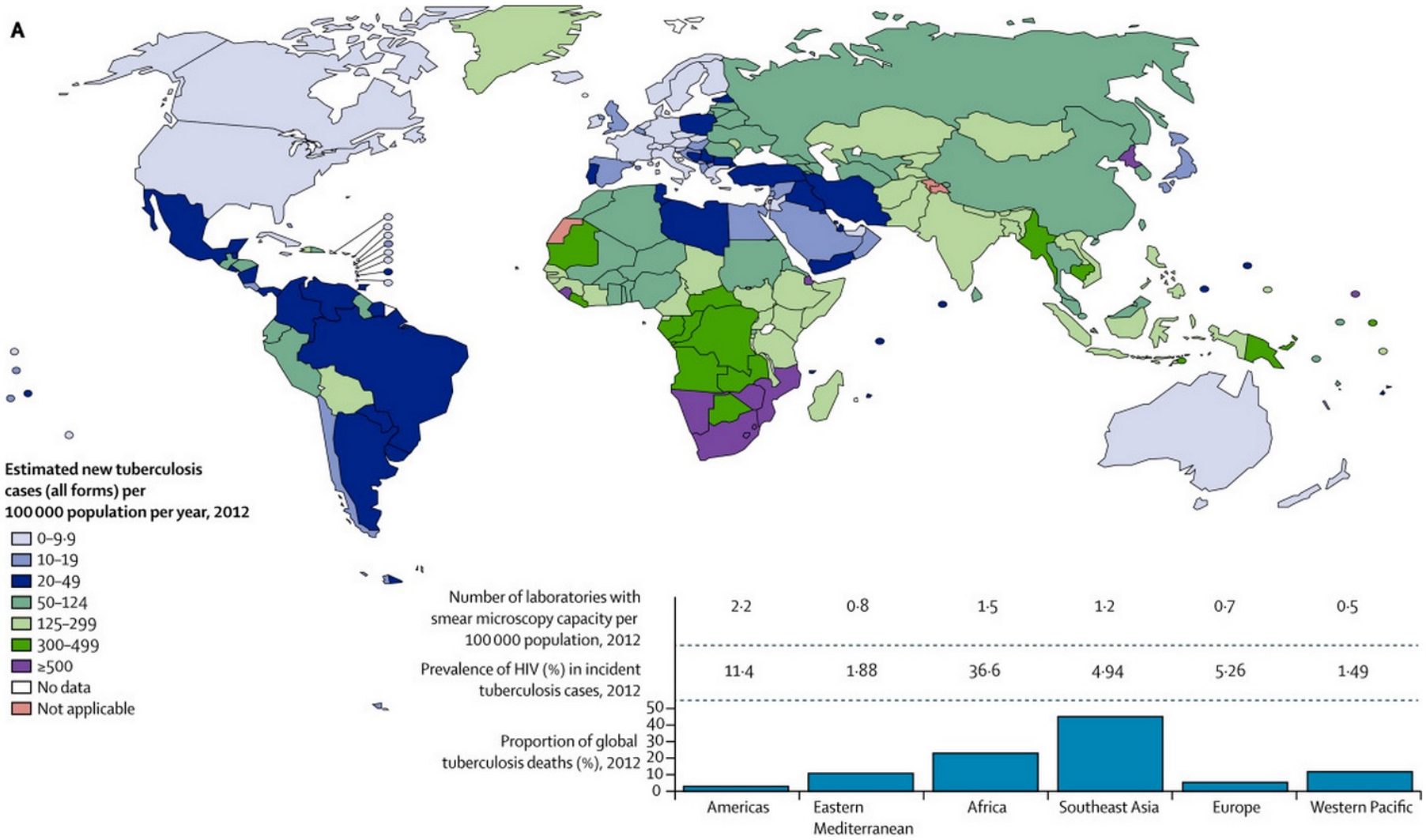
Int J Tuberc Lung Dis. 2001 May;5(5):455-61.



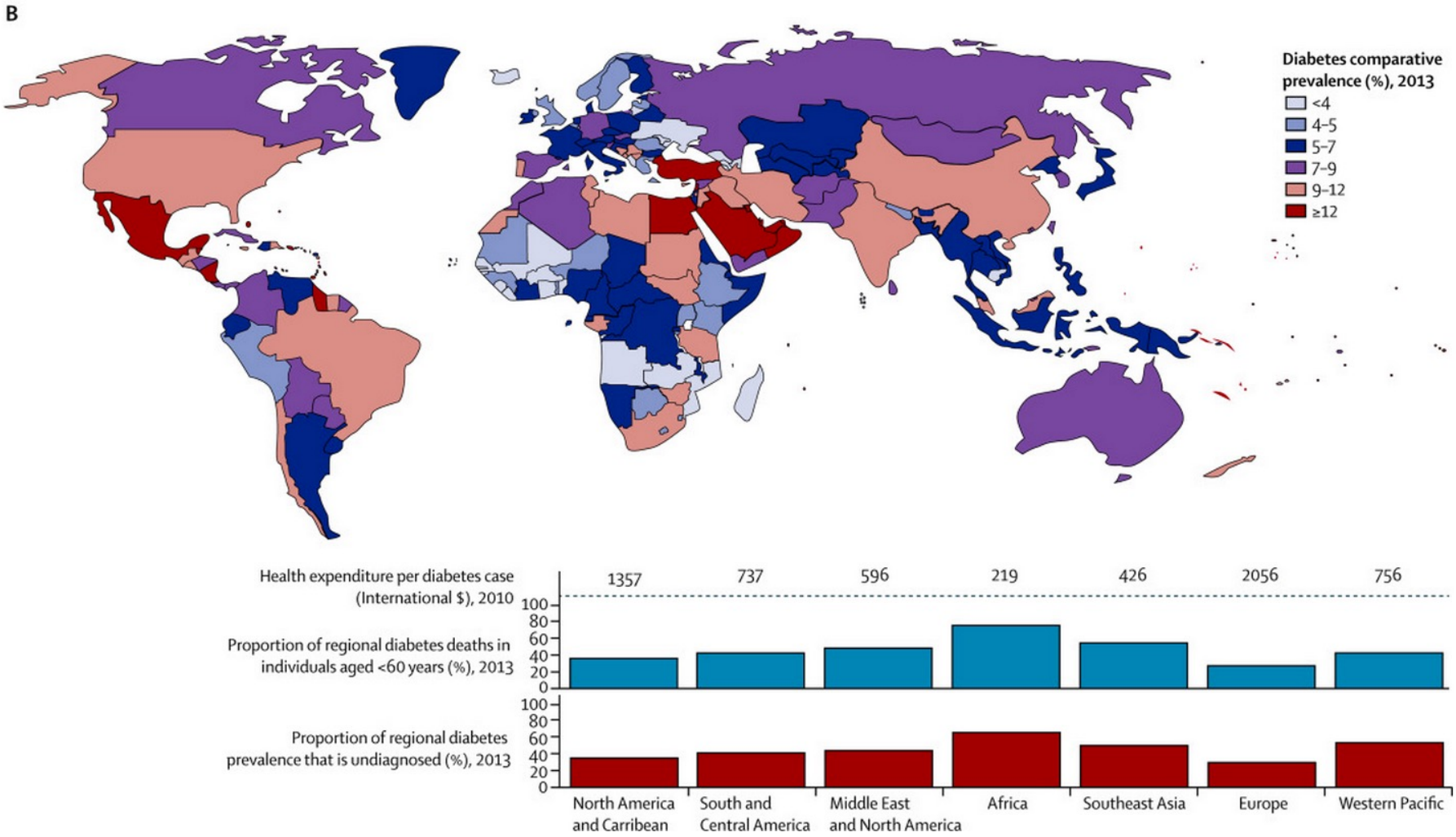
More TBDM patients developed cavitations (82% vs. 59%) more often in the lower lung fields (29% vs. 3%). More multiple cavities were seen in TBDM patients (25% vs. 2%).

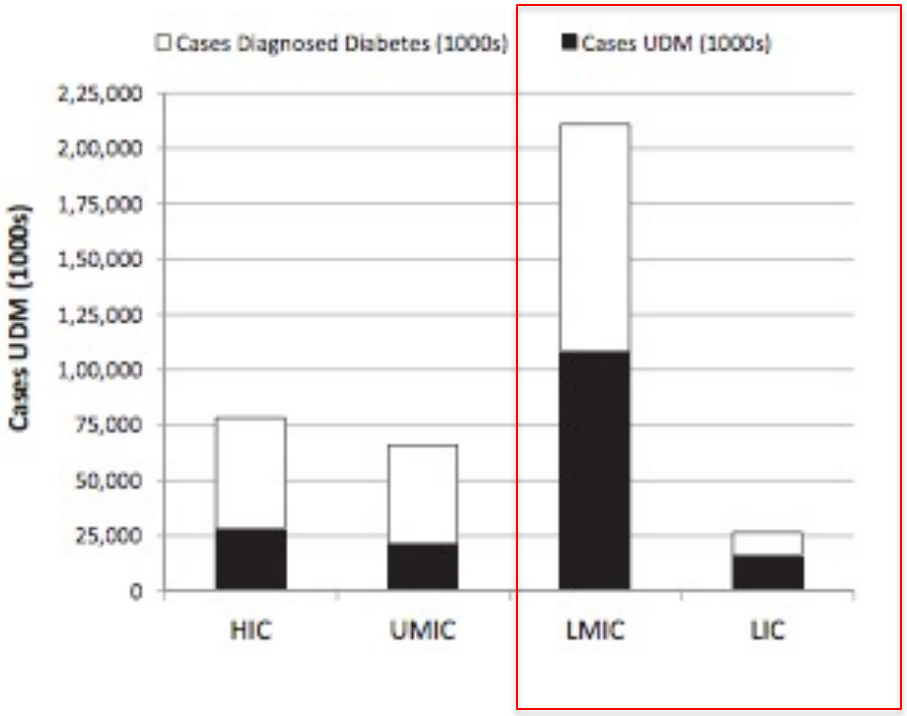

TB and Diabetes Summary: 2-3-4-5
People with DM and TB have....
2x risk of remaining culture positive
3x risk of progression to TB disease
4x risk of relapse after standard tx
5x risk of death during TB treatment

Global Burden of Tuberculosis



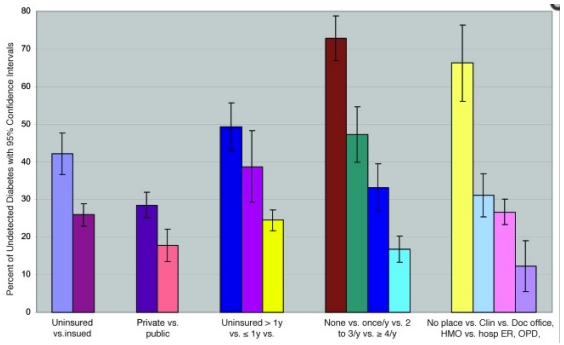
Global Burden of Diabetes



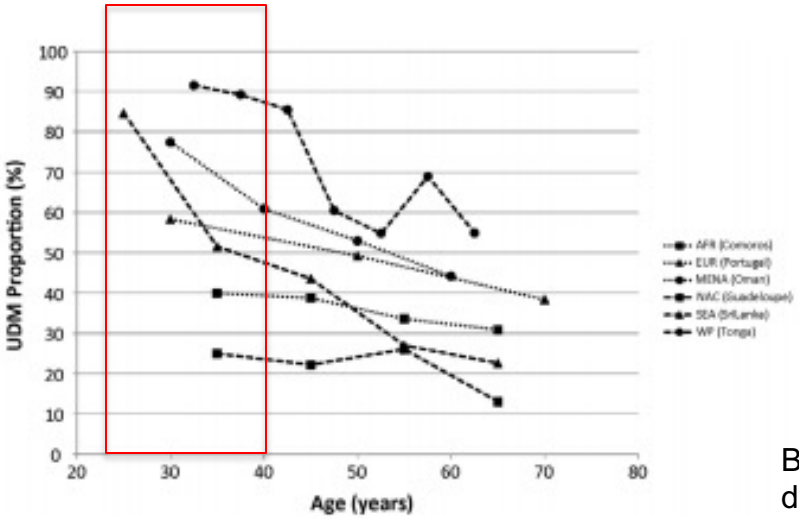


Globally, 45.8% DM is undetected.

83.8% UDMs in LMICs and LICs.



Zhang X,. The missed patient with diabetes: how access to health care affects the detection of diabetes. Diabetes Care. 2008 Sep;31(9):1748-53



UDM more frequent at younger ages.

Beagley J et al. Global estimates of undiagnosed diabetes in adults. Diabetes Res Clin Pract. 2014 Feb;103(2):150-60.

But
PAF = 22.6 if DM prevalence is 9.5.

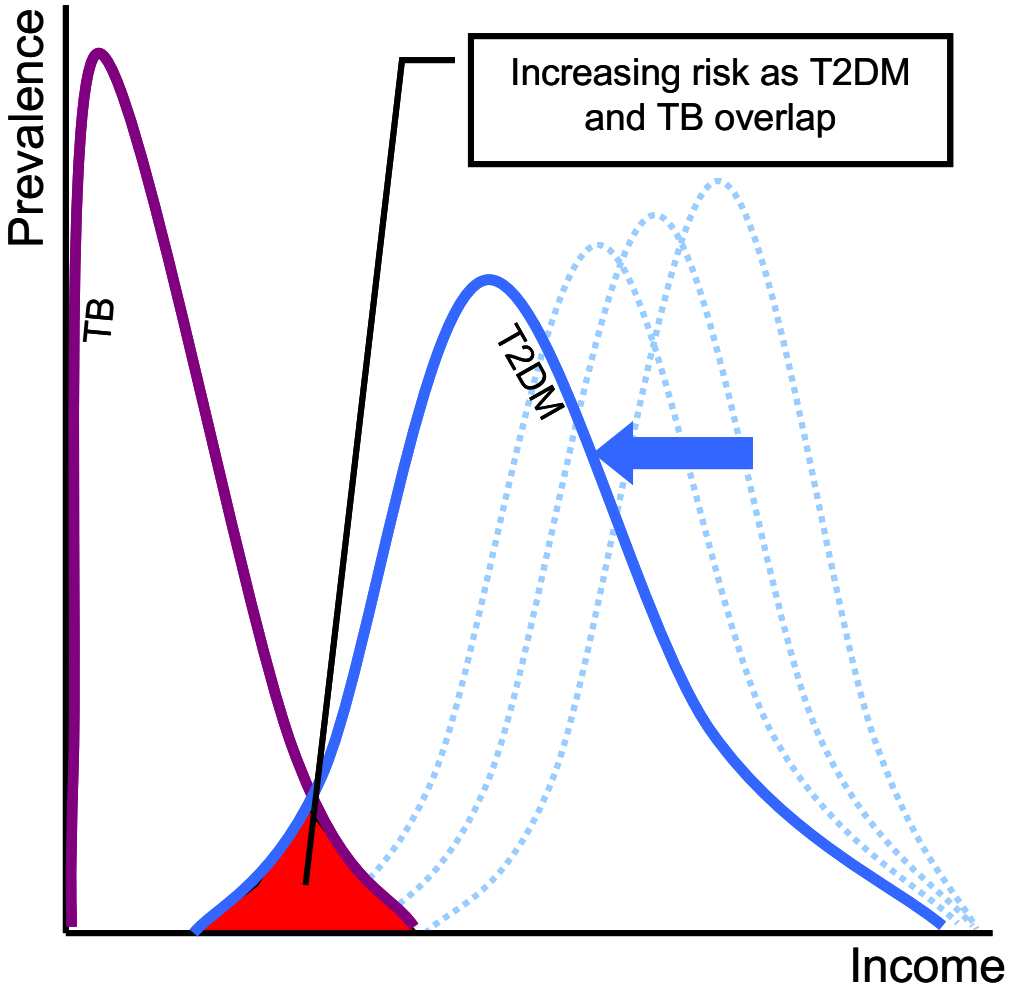
WHO THE STOP TB DEPARTMENT

Population attributable fraction - risk factors for progression to disease

$$PAF = \frac{P \times (RR - 1)}{P \times (RR - 1) + 1}$$

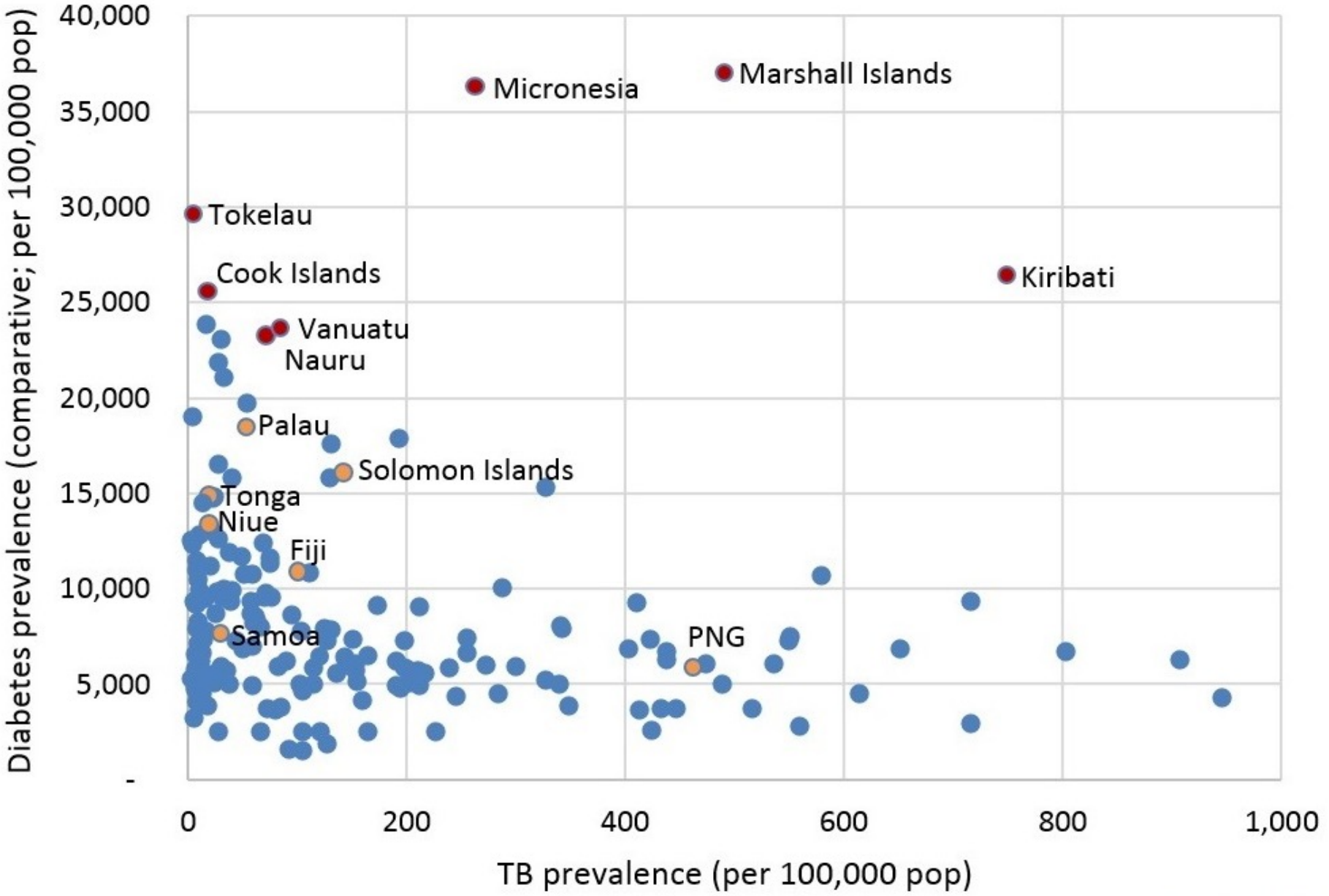
	Relative risk for active TB disease	Weighted prevalence (adults 22 HBCs)	Population Attributable Fraction (adults)
HIV infection	20.6/26.7*	0.8%	**16%**
Malnutrition	3.2**	16.7%	**27%**
Diabetes	3.1	5.4%	**10%**
Alcohol use (>40g / d)	2.9	8.1%	**13%**
Active smoking	2.0	26%	**21%**
Indoor Air Pollution	1.4	71.2%	**22%**

Hypothesized Relationship between Individual-level T2DM/TB Interactions and Increased Population Health Risk.



Jeremy Goldhaber-Fiebert

Jeremy D Goldhaber-Fiebert, Christie Y Jeon, Ted Cohen, and Megan B Murray
Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants
Int. J. Epidemiol. (2011) 40 (2): 417-428



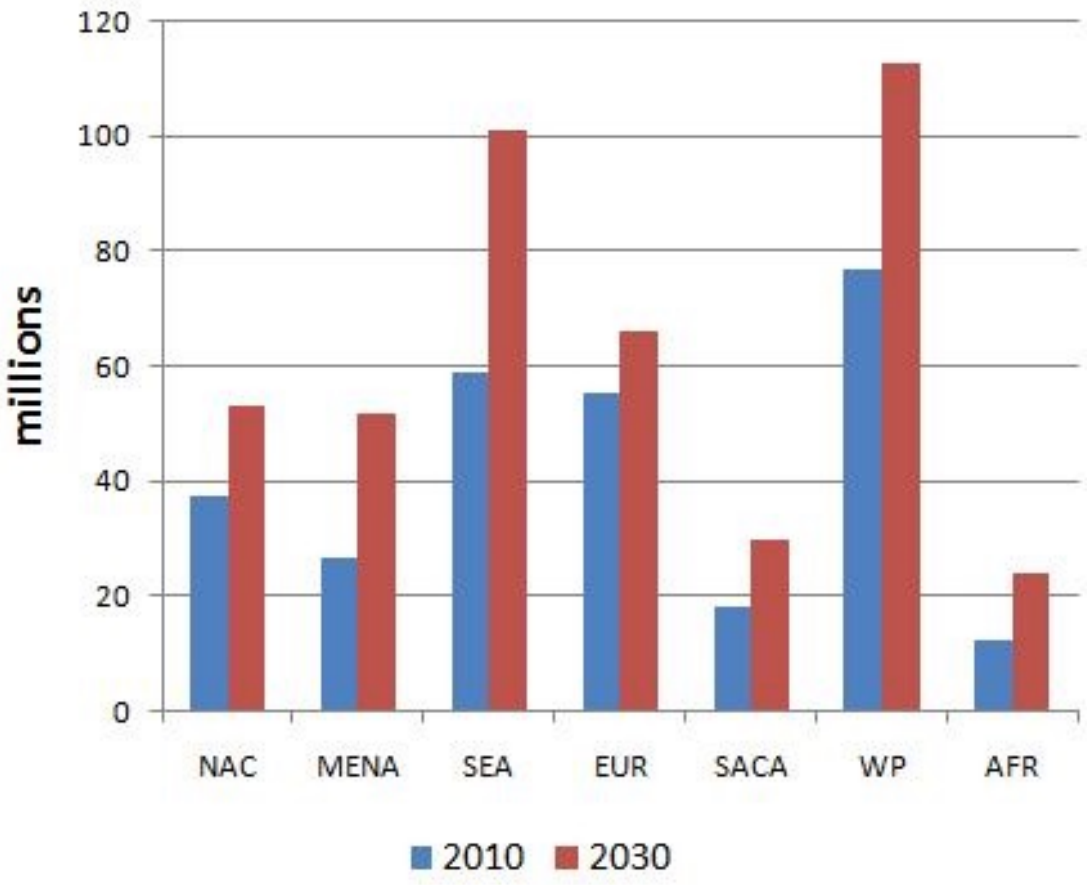
1 2

TB and diabetes prevalence for 195 countries

WORLD at a glance

Diabetes in the world (20-79 years)	2014	2035
Adult population (billions)	4.6	5.9
Diabetes cases (millions)	386.7	591.9
Global diabetes prevalence (%)	8.3	10.1
Comparative prevalence (%)	8.2	8.8
Undiagnosed cases (millions)	179.2	-
Total diabetes-related deaths (millions)	4.9	-
Deaths under the age of 60 (%)	48.2	-
Total health expenditure (USD billions)	612.2	627.3

Prevalence of Diabetes Mellitus (Age 20-79) by Region, 2010 & 2030



Original Investigation

Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012

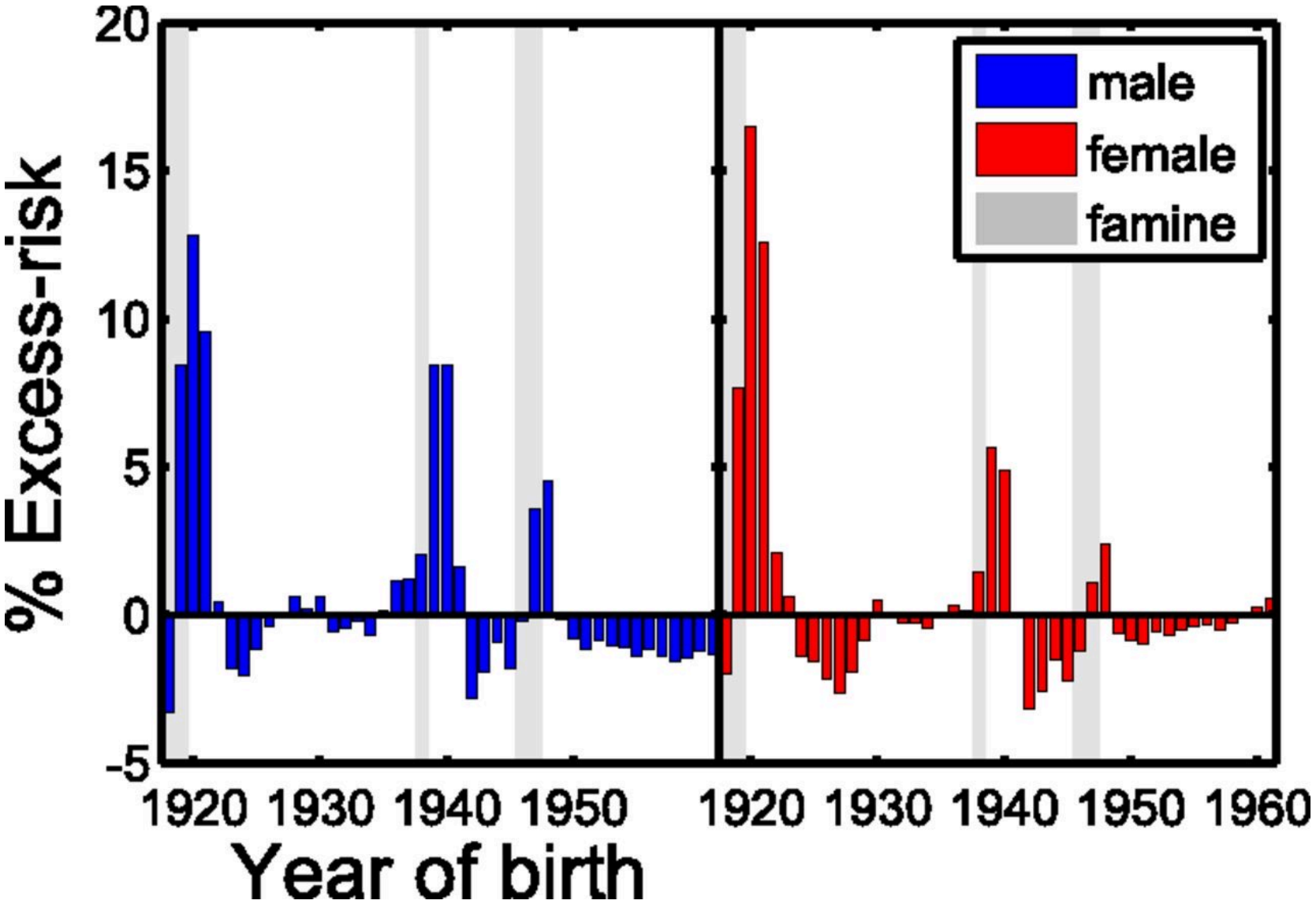
Andy Menke, PhD; Sarah Casagrande, PhD; Linda Geiss, MA; Catherine C. Cowie, PhD

Table 3. Age-Standardized Weighted Total Diabetes Prevalence per 100 Adults Aged 20 Years or Older in the US General Population Using Hemoglobin A_{1c} Level or Fasting Plasma Glucose Level to Define Diabetes, 1988-2012

	Total Diabetes Prevalence, % (95% CI)[a]								
	1988-1994 (n = 8478)	1999-2000 (n = 2168)	2001-2002 (n = 2479)	2003-2004 (n = 2299)	2005-2006 (n = 2191)	2007-2008 (n = 2901)	2009-2010 (n = 3118)	2011-2012 (n = 2781)	P for Trend[b]
No. with diabetes[c]	2136	606	669	676	635	991	955	910	
Overall prevalence	9.8 (8.9-10.6)	9.8 (8.5-11.0)	10.8 (9.5-12.0)	11.7 (10.3-13.0)	10.8 (9.5-12.2)	12.5 (10.9-14.2)	12.1 (10.3-13.9)	12.4 (10.8-14.2)	<.001
Age group, y									
20-44	2.7 (2.1-3.4)	2.9 (1.4-4.4)	3.8 (2.6-5.0)	3.5 (2.4-4.6)	4.2 (3.2-5.2)	3.7 (2.7-4.6)	3.3 (2.6-4.1)	4.5 (3.5-5.8)	.01
45-64	13.3 (11.9-14.8)	13.1 (10.8-15.4)	12.6 (9.9-15.2)	14.6 (12.3-16.8)	12.9 (10.1-15.7)	15.5 (12.0-19.0)	15.8 (12.0-19.6)	16.2 (13.4-19.6)	.02
≥65	20.5 (18.3-22.6)	20.6 (16.7-24.5)	25.1 (22.3-27.8)	26.7 (21.6-31.8)	23.7 (19.6-27.8)	29.3 (26.2-32.4)	27.0 (23.4-30.5)	24.7 (21.6-28.1)	<.001
Sex									
Male	10.3 (9.4-11.3)	10.5 (8.9-12.0)	12.3 (10.6-14.1)	12.8 (11.2-14.5)	11.2 (9.2-13.1)	13.7 (11.9-15.5)	14.4 (11.3-17.4)	13.6 (12.0-15.3)	<.001
Female	9.3 (8.2-10.4)	9.1 (7.7-10.6)	9.4 (8.0-10.7)	10.7 (9.4-11.9)	10.5 (8.7-12.3)	11.6 (9.7-13.5)	10.1 (8.9-11.2)	11.4 (9.6-13.6)	.005
Race/ethnicity[d]									
Non-Hispanic									
White	8.6 (7.7-9.5)	8.3 (7.1-9.5)	8.9 (7.7-10.1)	10.2 (8.7-11.7)	8.9 (7.4-10.4)	10.6 (8.3-12.9)	10.0 (7.8-12.2)	9.5 (8.0-11.2)	.04
Black	16.3 (14.6-18.0)	17.1 (13.5-20.8)	16.9 (13.9-20.0)	16.0 (13.5-18.4)	18.8 (15.8-21.8)	22.6 (19.3-26.0)	18.6 (16.6-20.6)	20.6 (16.9-24.8)	.003
Mexican American	17.5 (15.6-19.3)	13.2 (11.1-15.3)	16.1 (13.9-18.4)	16.6 (13.8-19.3)	18.5 (15.9-21.2)	18.1 (16.3-20.0)	20.8 (17.5-24.2)	20.5 (16.3-25.4)	<.001
Education level									
<High school	14.1 (12.7-15.5)	15.1 (12.2-17.9)	16.2 (14.4-18.1)	17.0 (15.2-18.7)	16.6 (13.0-20.2)	17.8 (15.1-20.5)	17.0 (14.6-19.3)	18.6 (14.7-22.5)	<.001
High school graduate	9.6 (8.2-10.9)	10.5 (8.6-12.4)	10.4 (8.1-12.7)	10.5 (8.7-12.3)	12.1 (9.4-14.8)	14.0 (10.6-17.4)	11.8 (8.2-15.4)	15.0 (12.0-17.9)	<.001
>High school	6.8 (5.8-7.8)	6.1 (4.6-7.6)	8.6 (7.0-10.3)	10.4 (8.5-12.3)	8.7 (7.0-10.4)	9.7 (8.0-11.4)	10.5 (8.4-12.7)	9.7 (7.9-11.5)	<.001
Poverty income ratio tertile									
Lowest	13.0 (11.7-14.4)	13.2 (11.1-15.4)	14.7 (12.0-17.3)	14.6 (12.3-16.9)	15.3 (12.5-18.1)	18.0 (15.6-20.4)	14.7 (12.1-17.3)	17.8 (15.1-20.5)	<.001
Middle	9.1 (8.0-10.3)	10.6 (7.9-13.4)	10.6 (9.4-11.8)	11.1 (9.0-13.3)	10.8 (7.3-14.2)	10.8 (8.9-12.7)	12.3 (9.8-14.9)	11.5 (9.1-13.8)	.01
Highest	7.5 (6.2-8.8)	5.1 (3.6-6.6)	7.1 (5.4-8.8)	9.2 (7.2-11.2)	6.8 (5.6-8.1)	9.9 (7.3-12.6)	9.0 (6.5-11.5)	8.0 (5.3-10.7)	.06

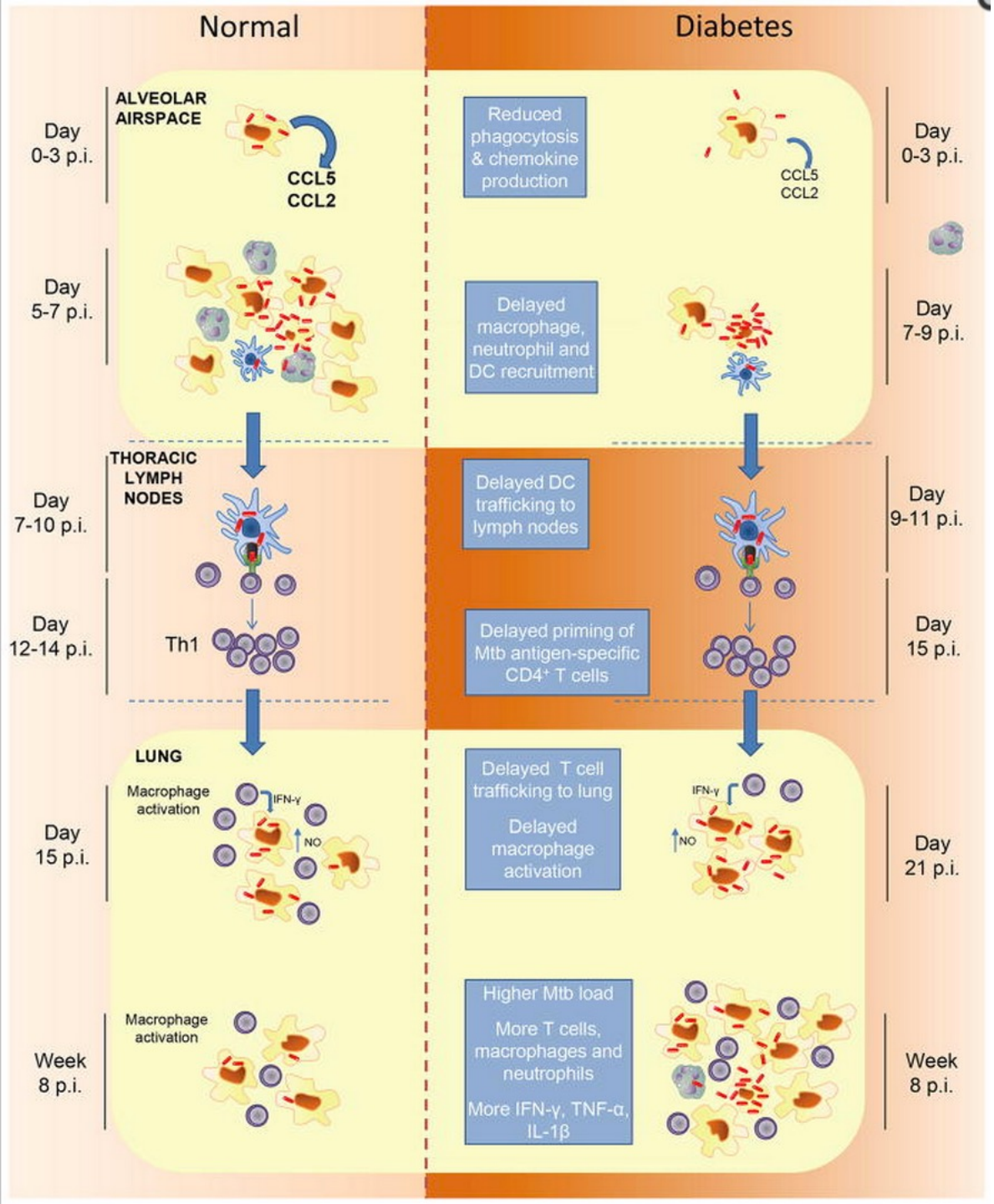
Jama, Sept 2015; 314:10

Excess risk of diabetes patients divided into genders between 1917 and 1961 for the Austrian data.



Stefan Thurner et al. PNAS 2013;110:4703-4707

Why?



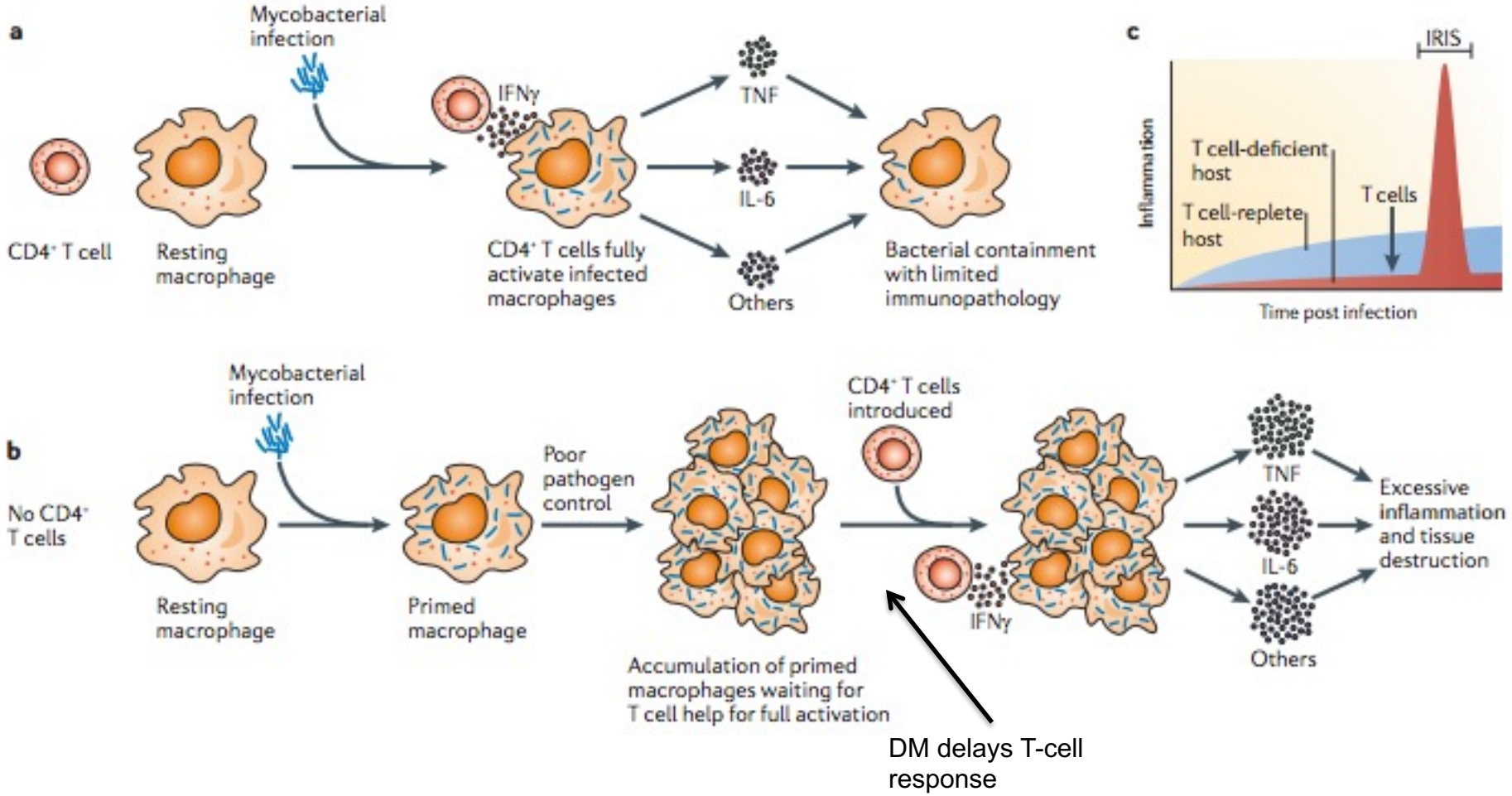
A proposed model for TB susceptibility in DM.

A defective innate response to inhaled Mtb by diabetic hosts results in a critical delay in priming adaptive immunity.

Martinez N, Kornfeld H. Diabetes and immunity to tuberculosis. Eur J Immunol. 2014 Mar;44(3):617-26.

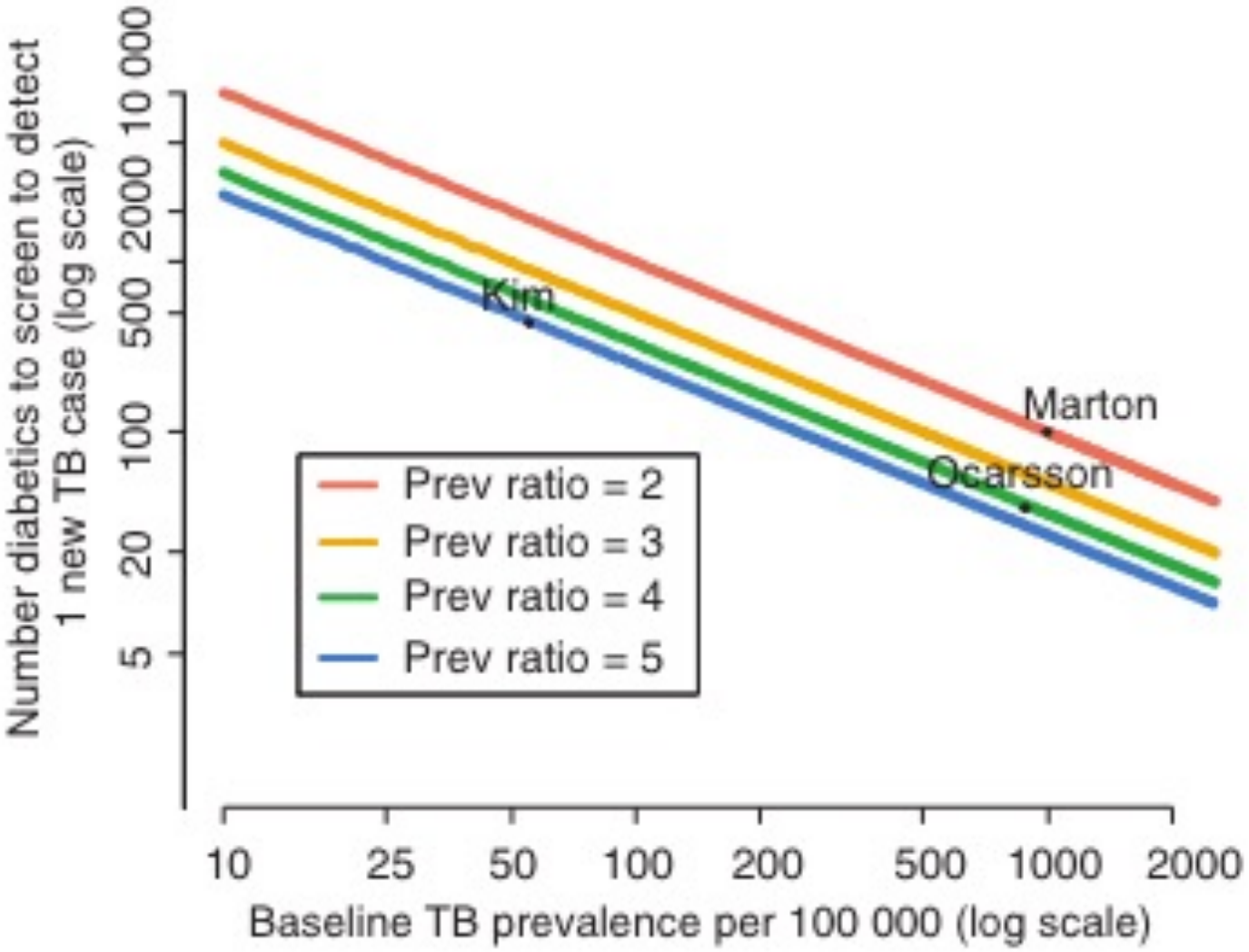
Immune reconstitution inflammatory syndrome: the trouble with immunity when you had none

Daniel L. Barber, Bruno B. Andrade, Irini Sereti and Alan Sher



What to do?

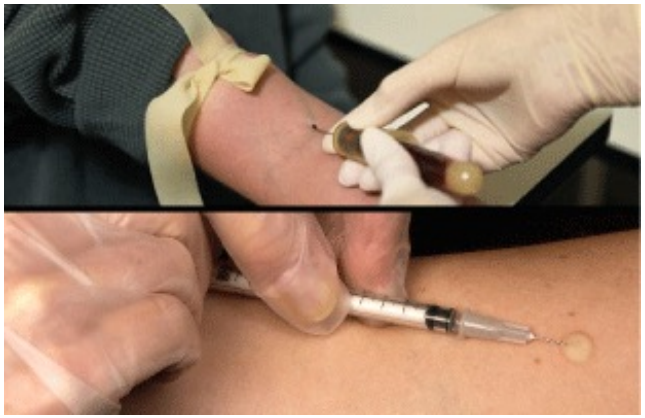
Screening People with DM for Active TB



Jeon C et al. Bi-directional screening for tuberculosis and diabetes:a systematic review. Trop Med Int Health. 2010 Nov;15(11):1300-14

Screening for latent TB

- What test?



Walsh MC et al. Int J Tuberc Lung Dis. 2011 Feb;15(2):179-84

Table 2 Characteristics of TB patients associated with QFT-G results

	QFT-G positive (n = 119) n (row %)*	QFT-G negative (n = 50) n (row %)*	P value	OR_{adj} (95% CI)	Variable(s) adjusted for in final model
Diabetes and body mass index					
Diabetes			0.01		Age, BMI
Yes	59 (80.8)	14 (19.2)		2.4 (1.1–5.0)	
No	60 (62.5)	36 (37.5)		1	
HbA_{1c} ≥6.5%			0.007		Age, BMI
Yes	47 (83.9)	9 (16.1)		2.7 (1.2–6.2)†	
No	72 (63.7)	41 (36.3)		1	
Hyperglycemia			0.003		BMI, COE
Yes	41 (87.2)	6 (12.8)		3.7 (1.4–9.7)	
No	78 (63.9)	44 (36.1)		1	
Body mass index			0.049		
Underweight	19 (57.6)	14 (42.4)		0.5 (0.2–1.1)	
Normal weight	65 (69.1)	29 (30.9)		1	None
Overweight or obese	35 (83.3)	7 (16.7)		2.6 (1.0–6.2)	

The sensitivity of interferon-gamma release assays is not compromised in tuberculosis patients with diabetes

But…

Midori Kato-Maeda

Reduced sensitivity of the QuantiFERON® test in diabetic patients with smear-negative tuberculosis

Table 6 Risk factors for a false-negative QFT assay in 150 patients with sputum smear-negative pulmonary tuberculosis

	Negative QFT ($n = 49$) *n/N* (%)	Positive QFT ($n = 101$) *n/N* (%)	Unadjusted		Adjusted	
			OR (95%CI)	*P* value	OR (95%CI)	*P* value
Male sex	32/49 (65.3)	68/101 (67.3)	0.91 (0.44–1.88)	0.81		
Age, years, mean ± SD	49.3 ± 22.6	47.3 ± 19.0	1.01 (0.99–1.02)	0.57		
Age >65 years	13/49 (26.5)	18/101 (17.8)	1.67 (0.74–3.76)	0.22	1.48 (0.59–3.74)	0.40
History of smoking	17/48 (35.4)	38/100 (38.0)	0.89 (0.44–1.83)	0.76		
US born	14/49 (28.6)	12/101 (11.9)	2.97 (1.25–7.04)	0.01		
HIV-positive*	5/49 (10.2)	3/101 (3.0)	3.89 (0.88–17.1)	0.07	3.97 (0.84–18.7)	0.08
Chronic renal disease	0/48 (0)	1/100 (1.0)	0.68 (0.03–17.1)	1.00	Could not calculate	
Hepatic disease	1/48 (2.1)	3/100 (3.0)	0.69 (0.07–6.79)	0.75		
Diabetes mellitus	11/48 (22.9)	10/100 (10.0)	2.68 (1.05–6.84)	0.04	2.85 (1.02–7.97)	0.045
Other immunosuppressive condition†	4/48 (8.3)	3/99 (3.0)	2.91 (0.62–13.6)	0.17	1.93 (0.37–10.2)	0.44

Choi JC et al. Int J Tuberc Lung Dis. 2015 May;19(5):582-8.

Neither study assesses these tests for latent TB. Or how test positive latent TB should be managed.

Efficacy of Treatment for latent TB among Diabetics

- AV Lesnichii, LZ Karpina, Experience with the chemoprophylaxis of pulmonary tuberculosis in diabetes mellitus patients, Probl Tuberk, 47 (1969), pp. 1–3 (in Russian).
- R Pfaffenberg, H Jahler, Isoniazid & recurrence of tuberculosis in diabetics, Z Tuberk, 111 (1958), pp. 167–173 (in German).

Current US Practice

RISK FACTOR	YES	NO
Recent close or prolonged contact with someone with infectious TB disease		
Foreign-born person from or recent traveler to high-prevalence area		
Chest radiographs with fibrotic changes suggesting inactive or past TB		
HIV infection		
Organ transplant recipient		
Immunosuppression secondary to use of prednisone (equivalent of ≥15 mg/day for ≥1 month) or other immunosuppressive medication such as TNF-α antagonists		
Injection drug user		
Resident or employee of high-risk congregate setting (e.g., prison, long term care facility, hospital, homeless shelter)		
Medical conditions associated with risk of progressing to TB disease if infected (e.g., diabetes mellitus, silicosis, cancer of head or neck, Hodgkin's disease, leukemia, and end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndrome, low body weight [10% or more below ideal for given population])		
Signs and symptoms of TB disease		

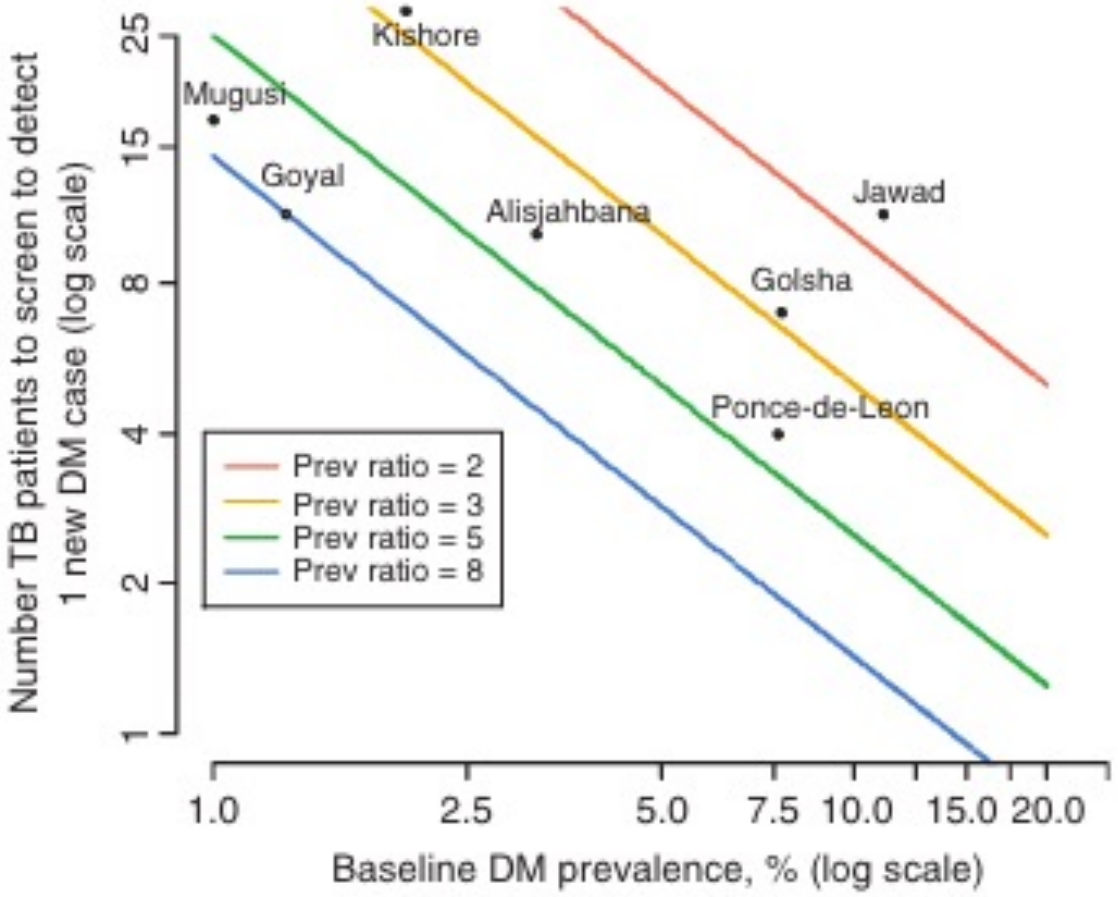
Adapted from a form developed by Minnesota Department of Health TB Prevention and Control Program

Current WHO Guidelines

The following are the key recommendations of the guidelines:

- Systematic testing and treatment of LTBI should be performed in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. Either interferon-gamma release assays (IGRA) or Mantoux tuberculin skin test (TST) should be used to test for LTBI. *(Strong recommendation, low to very low quality of evidence)*
- Systematic testing and treatment of LTBI should be considered for prisoners, health-care workers, immigrants from high TB burden countries, homeless persons and illicit drug users. Either IGRA or TST should be used to test for LTBI. *(Conditional recommendation, low to very low quality of evidence)*
- Systematic testing for LTBI is not recommended in people with diabetes, people with harmful alcohol use, tobacco smokers, and underweight people provided they are not already included in the above recommendations. *(Conditional recommendation, very low quality of evidence)*

Screening TB patients for DM



Number of patients with active TB to screen to detect one additional case of DM.

Some hyperglycemia will resolve during the course of TB treatment.

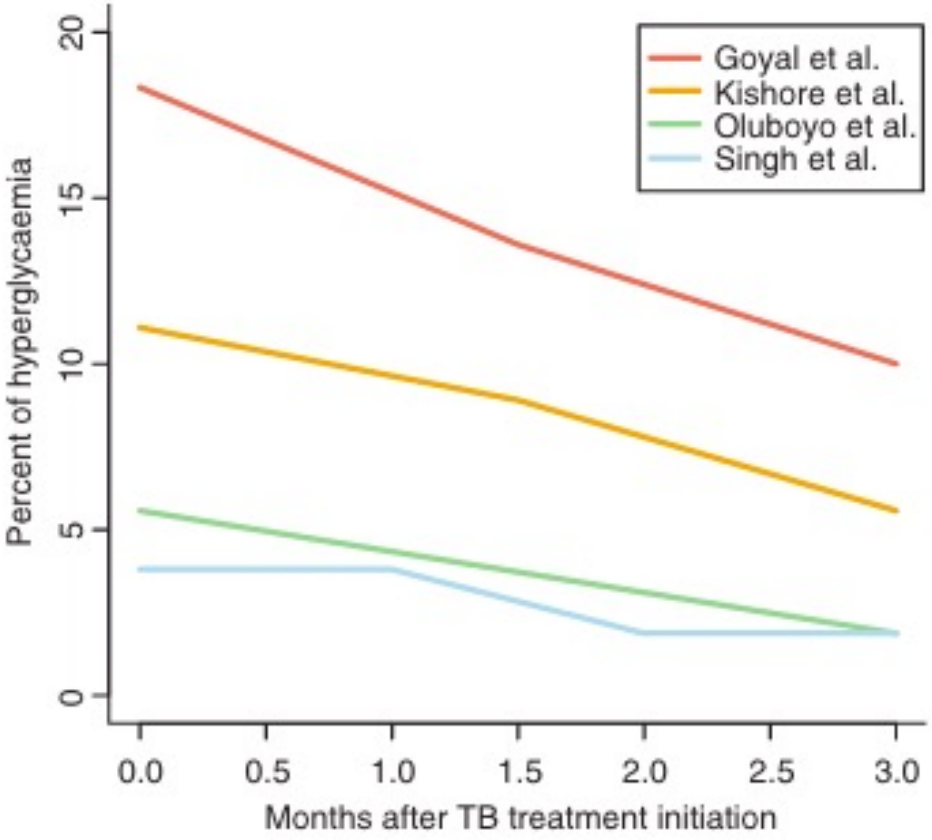
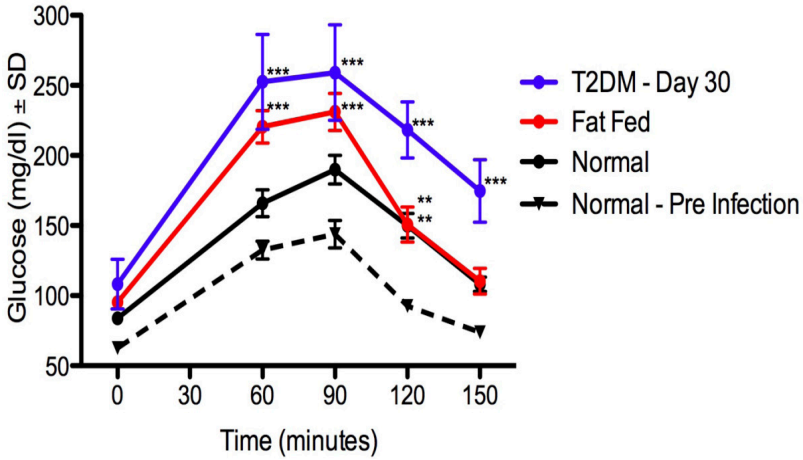
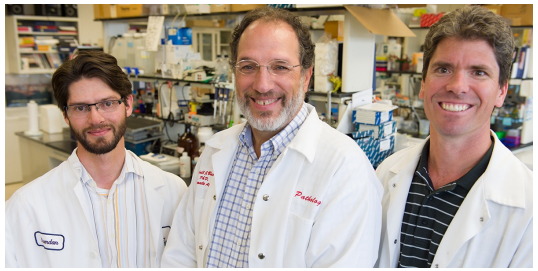


Figure 3 Decreasing trend in hyperglycaemia in patients with tuberculosis undergoing tuberculosis treatment.

Jeon et al, Bidirectional Screening, 2010

Hyperglycemia after TB infection reproduced in a guinea pig model.





Randy Basaraba and Brendan Podell

How to screen for DM in TB patients?

Evaluation of performance of A1c and FPG tests for screening newly diagnosed diabetes defined by an OGTT among tuberculosis patients—A study from India☆

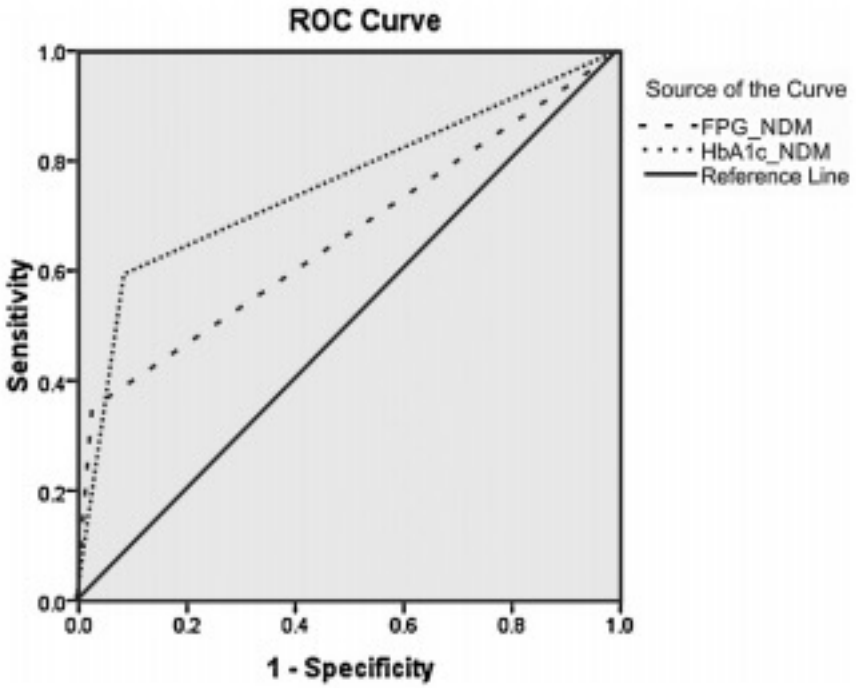


Fig. 2 – ROC curve for newly diagnosed diabetes (NDD), (· · · ·) HbA1c) (- - - -) FPG.

Hemoglobin A1c performed better than fasting blood sugar versus OGTT for diagnosis of DM among patients with TB.

Whom should we screen?

Increased risk of tuberculosis among foreign-born persons with diabetes in California, 2010–2012

Table 3 Estimates of the number needed to screen and treat (NNS) for TB infection to prevent one case of active TB in the subsequent 5 years among groups by demographic and diabetes status in California

Target population of TB screening and treatment	NNS	TB Infection prevalence[a]	Rate of progression to active TB[a]

Table 3 Estimates of the number needed to screen and treat (NNS) for TB infection to prevent one case of active TB in the subsequent 5 years among groups by demographic and diabetes status in California

Target population of TB screening and treatment	NNS base case	TB Infection prevalence[a]		Rate of progression to active TB[a]	
		High	Low	High	Low
All adults	7,930	6,667	10,000	3,846	14,286
All foreign-born adults	1,526	1,136	2,128	763	2,941
All adults with diabetes	2,740	2,222	3,448	1,370	5,556
U.S.-born adults with diabetes	9,551	7,143	12,500	4,762	20,000
Foreign-born adults with diabetes	596	442	826	298	1,163
Foreign-born adults with diabetes by location of birth					
Latin America	741	526	877	370	1,493
Southeast Asia/Pacific Islands	296	206	361	148	585
East Asia	372	260	452	186	730
South Asia	335	234	408	168	662
Europe	2,221	1,493	3,448	1,111	4,545
Africa/Middle East	384	270	562	192	769

Demlow *et al. BMC Public Health* (2015) 15:263
DOI 10.1186/s12889-015-1600-1

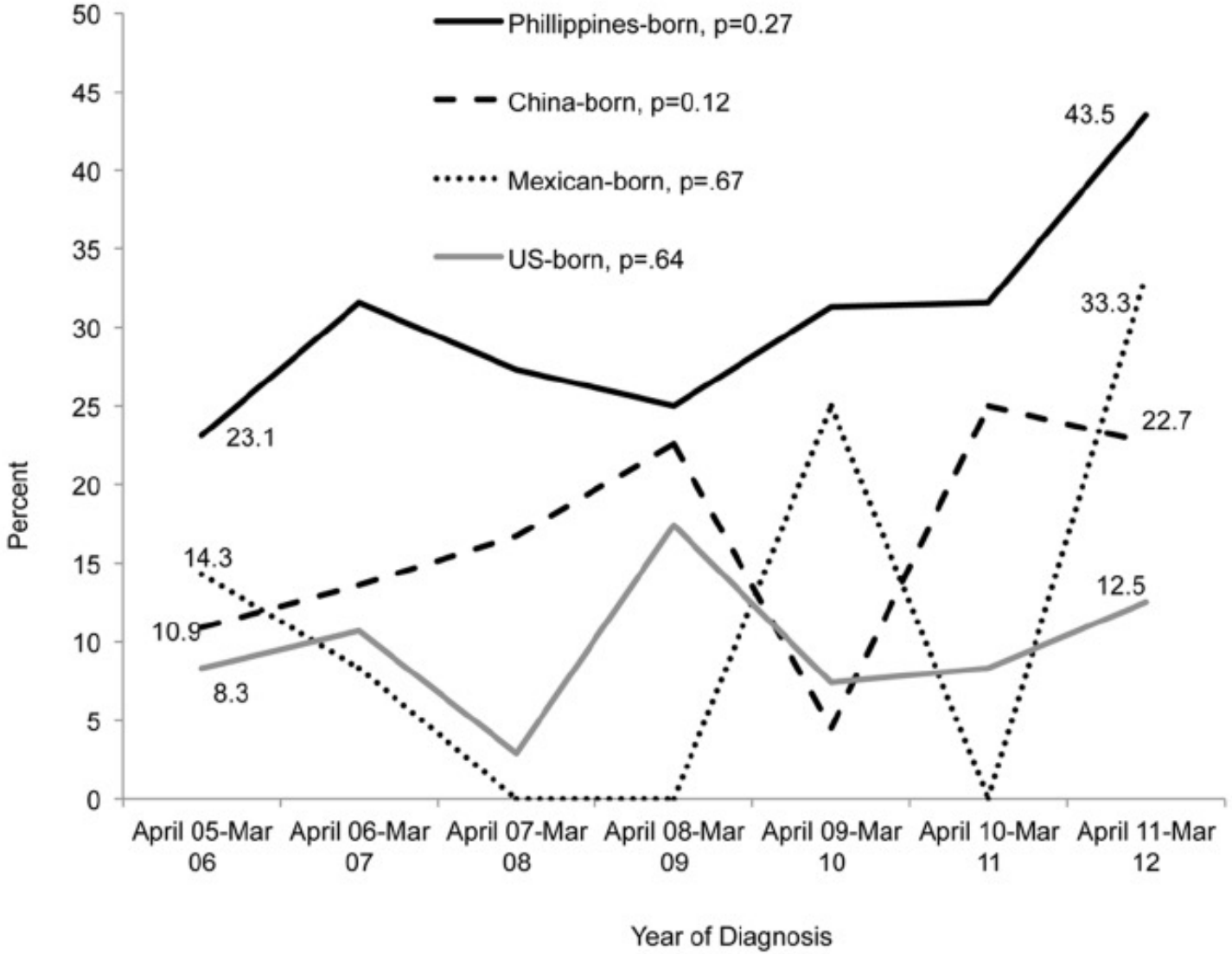


Figure 2. Prevalence of DM among TB patients in the US and foreign-born populations: April 2005-March 2012. The temporal trend of DM prevalence was assessed using Cochran-Armitage test for trends.

Should we treat TB in DM differently than in non-DM?

Optimal Duration of Anti-TB Treatment in Patients With Diabetes

Nine or Six Months?

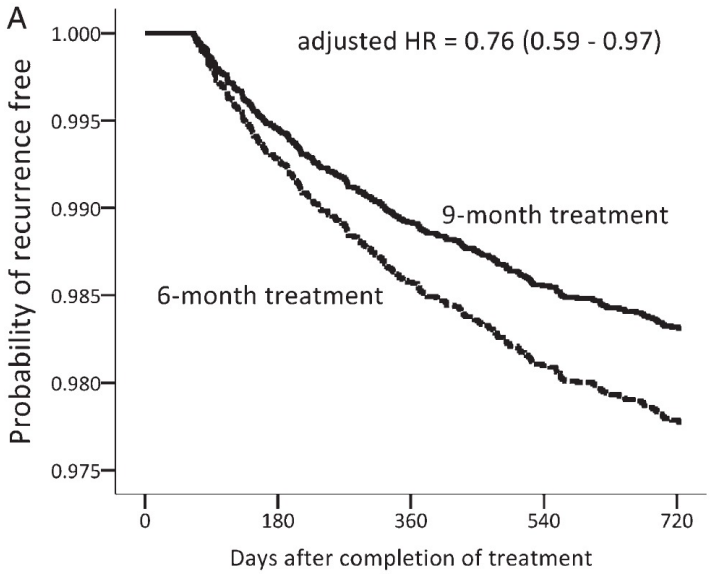


TABLE 2] Independent Risk Factors for TB Recurrence Within 2 y After Completion of Anti-TB Among the 12,688 Patients With Diabetes, by Cox Proportional Hazards Regression Analysis

Risk Factor	*P* Value	Adjusted HR	95% CI	
			Lower	Upper
Age, per-y increment	<.001	0.97	0.96	0.98
Sex, male vs female	.022	1.40	1.05	1.87
Later TB diagnostic y, per-y increment	<.001	0.81	0.77	0.86
Malignancy, yes vs no	.039	1.64	1.03	2.63
Culture positivity after 2-mo anti-TB treatment, yes vs no	<.001	1.96	1.36	2.83
80% Consistency with standard anti-TB treatment, yes vs no	.010	0.72	0.56	0.93
Duration of anti-TB treatment, 9 mo vs 6 mo	.030	0.76	0.59	0.97

HR = hazard ratio.

Wang JY, Lee MC, Shu CC, Lee CH, Lee LN, Chao KM, Chang FY. Optimal duration of anti-TB treatment in patients with diabetes: nine or six months? Chest. 2015, Feb;147(2):520-8.

Drug levels?

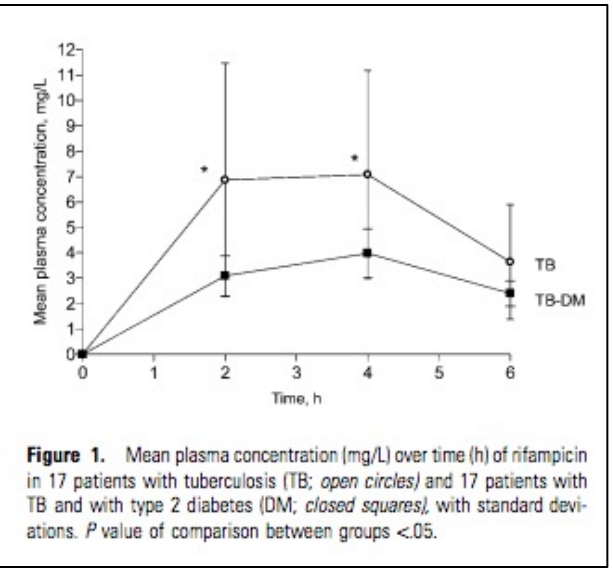


Figure 1. Mean plasma concentration (mg/L) over time (h) of rifampicin in 17 patients with tuberculosis (TB; *open circles)* and 17 patients with TB and with type 2 diabetes (DM; *closed squares),* with standard deviations. *P* value of comparison between groups <.05.

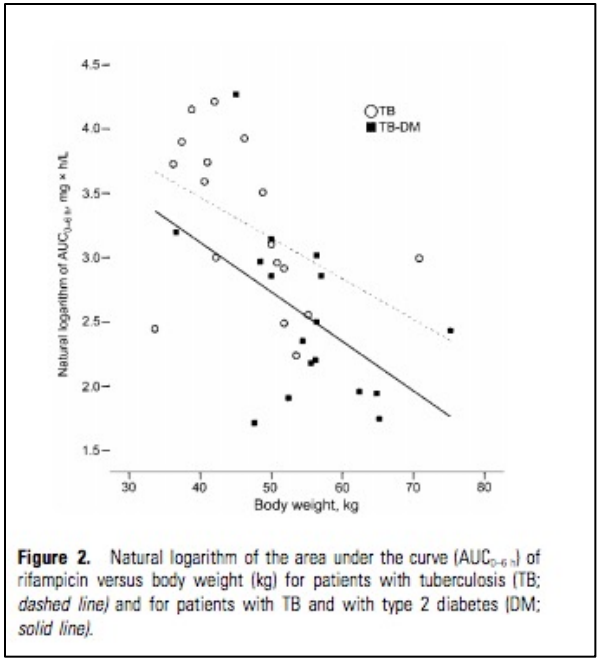


Figure 2. Natural logarithm of the area under the curve ($AUC_{0-6\ h}$) of rifampicin versus body weight (kg) for patients with tuberculosis (TB; *dashed line)* and for patients with TB and with type 2 diabetes (DM; *solid line).*

Continuation phase

Exposure to rifampicin was 53% lower in Indonesian patients with TB and DM, compared with patients with TB only.

Nijland H et al. Clin Infect Dis, 43 (2006), pp. 848–854

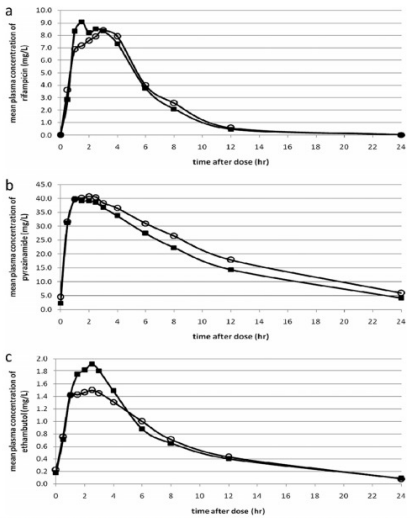


FIG. 2. Mean steady-state plasma concentration-time profiles of antituberculosis drugs. Mean steady-state plasma concentration-time profiles of rifampin (n = 17) (a), pyrazinamide (n = 18) (b), and ethambutol (n = 17) (c) in TB patients with (■) and without (○) DM are shown.

Intensification phase

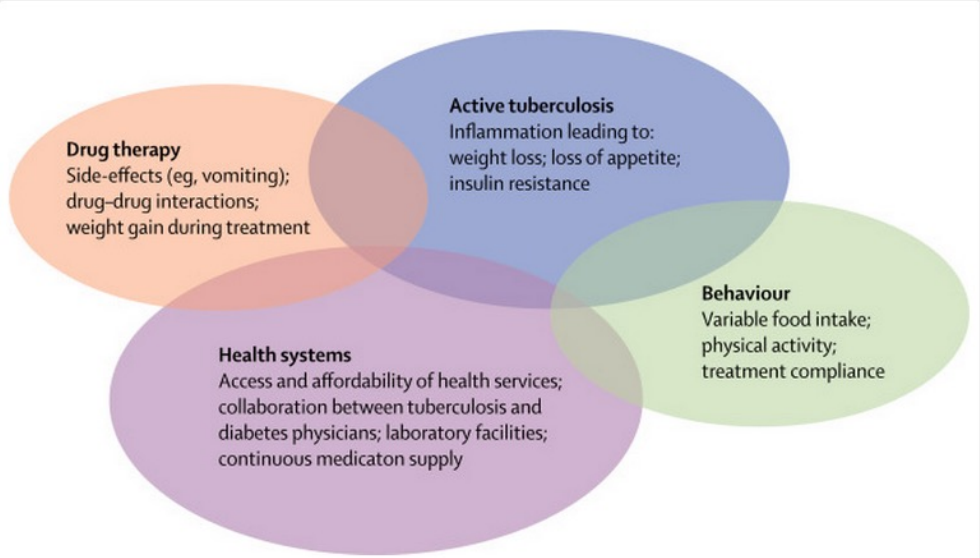
No difference in Rifampicin, PZA or Ethambutol levels in DM.

Ruslami R. et al. Antimicrob Agents Chemother, 54 (2010), pp. 1068–1074

Reinout van Crevel and Rovina Ruslami in Indonesia

How to treat DM in TB?

- Optimal hypoglycemic drugs
  - Drug-drug interactions
  - Interactions with TB immune responses
- Frequency of monitoring
  - Expected weight gain with clinical improvement
  - Expected resolution of TB-specific hyperglycemia
- Glycemic targets
  - Tight versus loose control



Is There an Effect of Glucose Lowering Treatment on Incidence and Prognosis of Tuberculosis? A Systematic Review

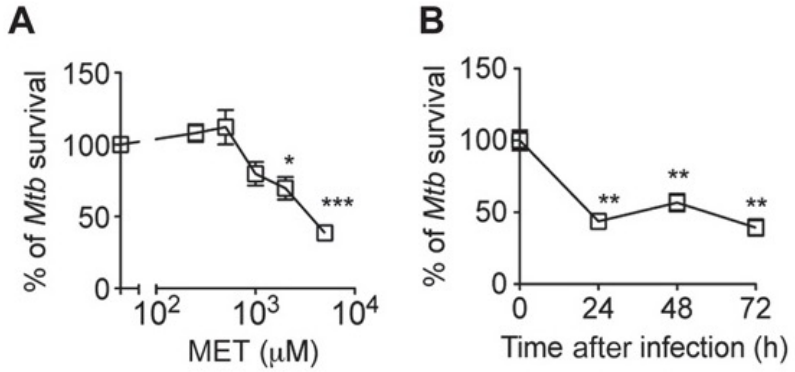
Marit Eika Jørgensen · Daniel Faurholt-Jepsen

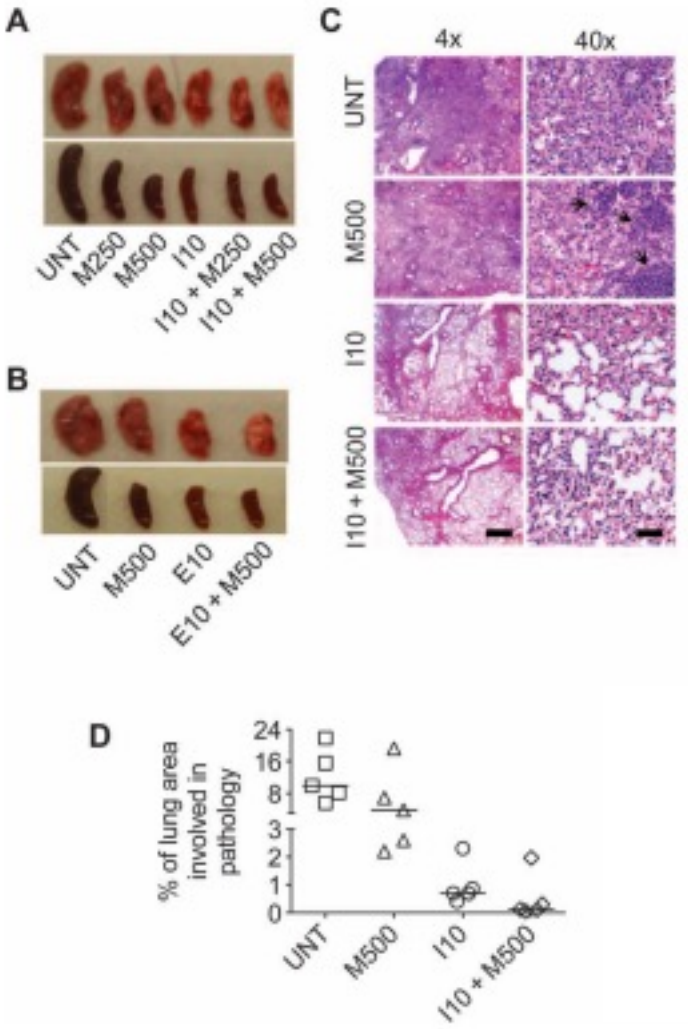
Jørgensen ME, Faurholt-Jepsen D.
CurrDiab Rep. 2014 Jul;14(7):505.

- If hyperglycemia reflects disease severity, lowering it may not improve outcome.
- Studies in ICU patients have shown that tight control can be detrimental.
- Some hypoglycemic agents may affect immune responses to TB in ways other than by lowering sugars.

Drugs

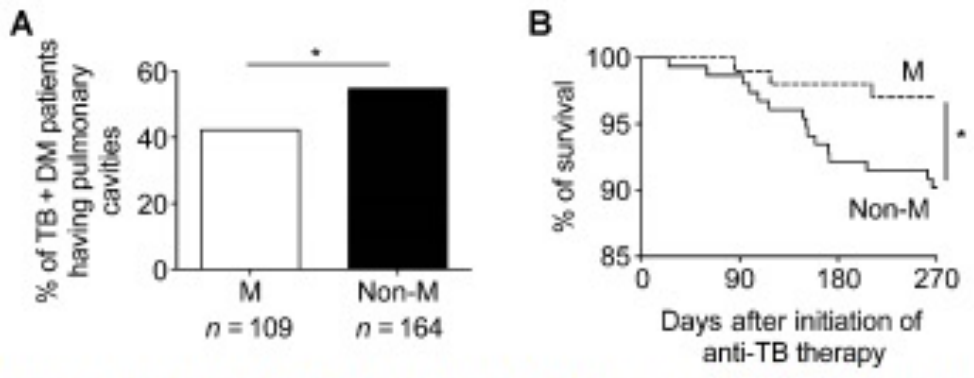
- Metformin



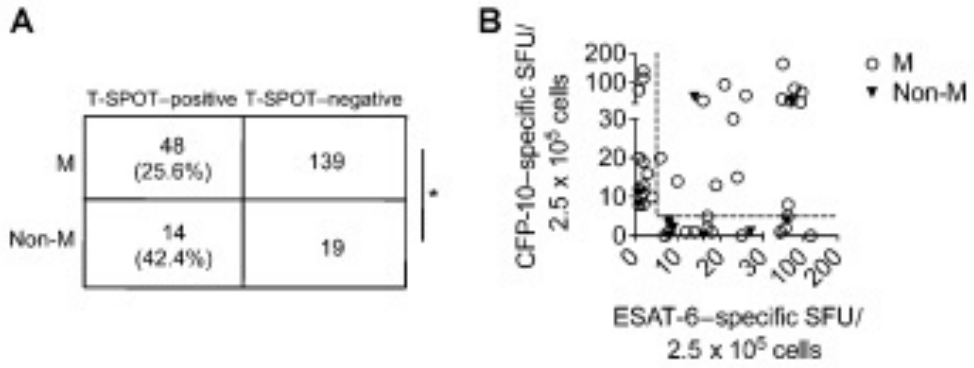


Mtb survival, pathology and extent of lung involvement in mice reduced by metformin.

In humans:



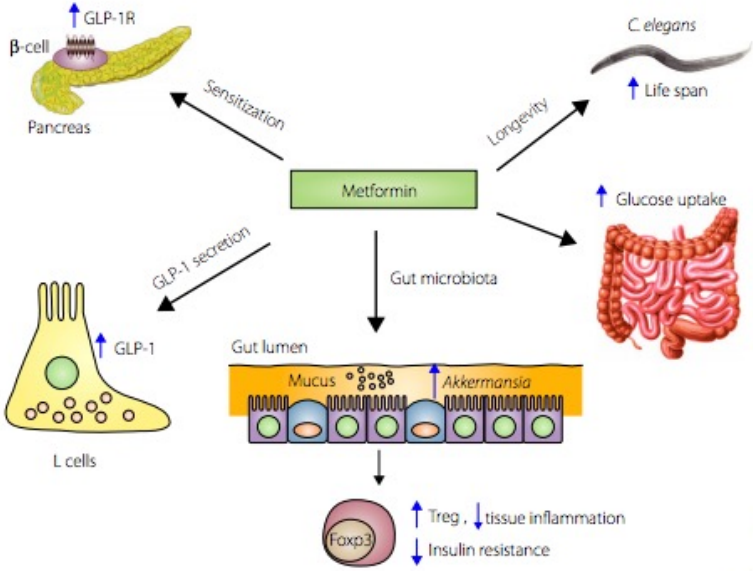
Effect of Met in TB patients with DM as comorbidity.

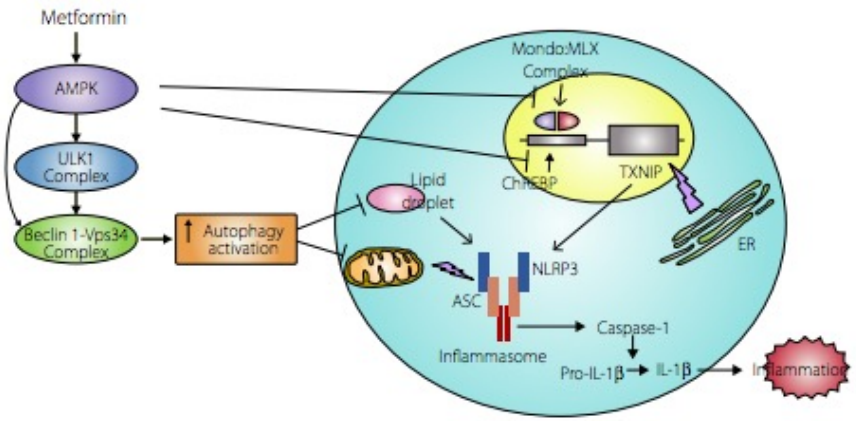


Reduced incidence of LTBI in MET-treated DM patients.

New mechanisms of metformin action: Focusing on mitochondria and the gut

Kyu Yeon Hur, Myung-Shik Lee*

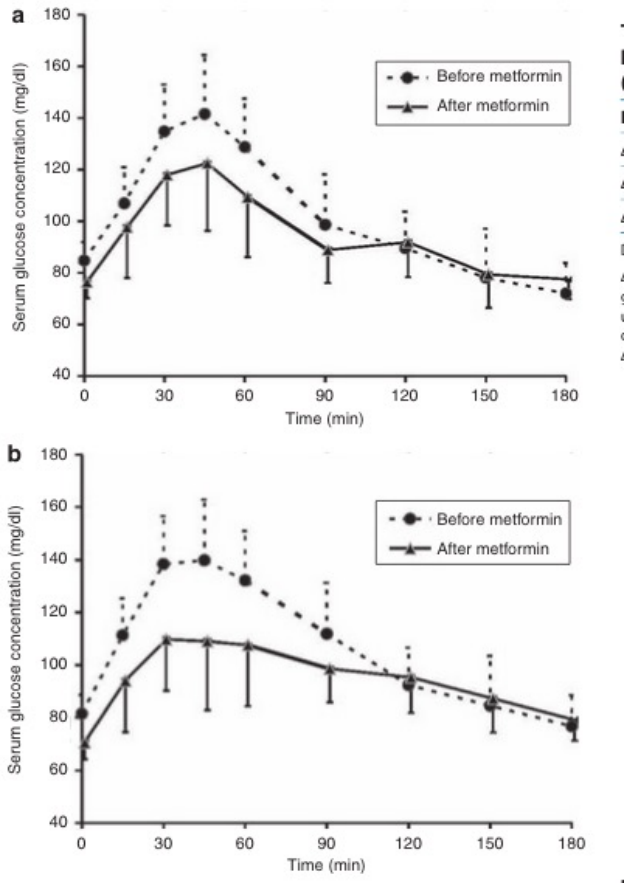




Rifampin Enhances the Glucose-Lowering Effect of Metformin and Increases OCT1 mRNA Levels in Healthy Participants

SK Cho[1,2], JS Yoon[3], MG Lee[1], DH Lee[1,2], LA Lim[1,2], K Park[1], MS Park[4] and J-Y Chung[1]

Clin Pharmacol Ther. 2011 Mar;89(3):416-21.



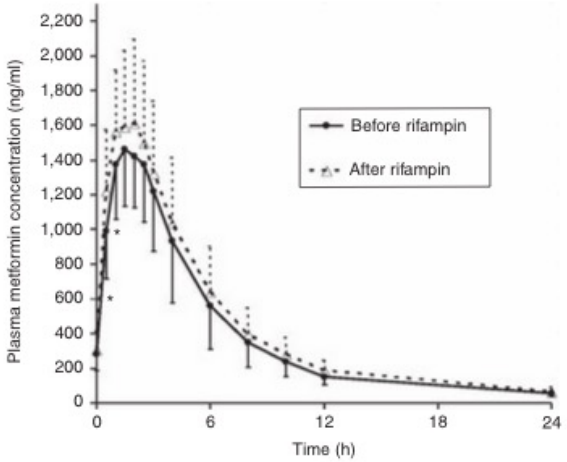
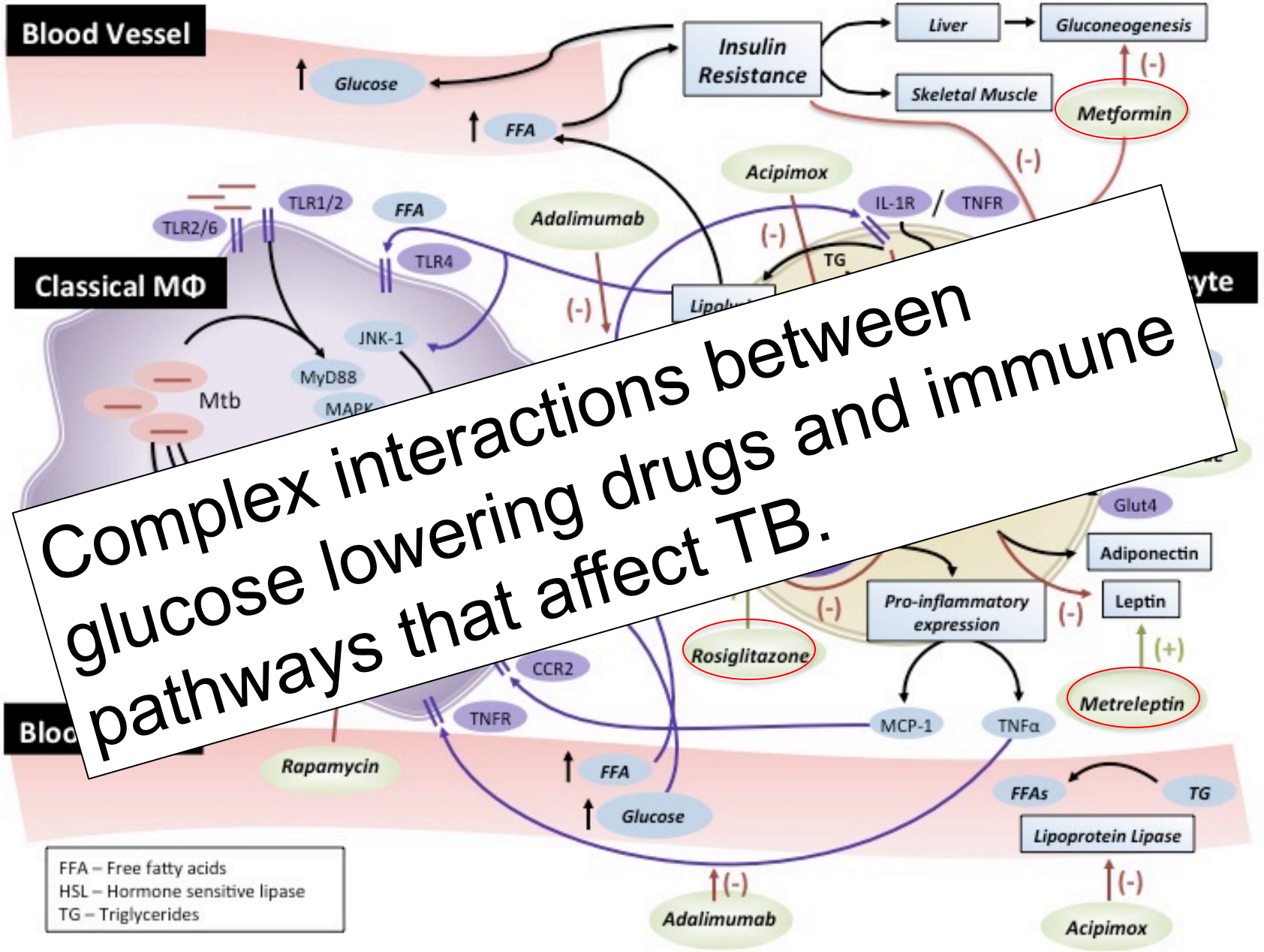


Table 1 The glucose-lowering effect parameters of metformin before and after rifampin treatment in healthy participants ($n = 16$)

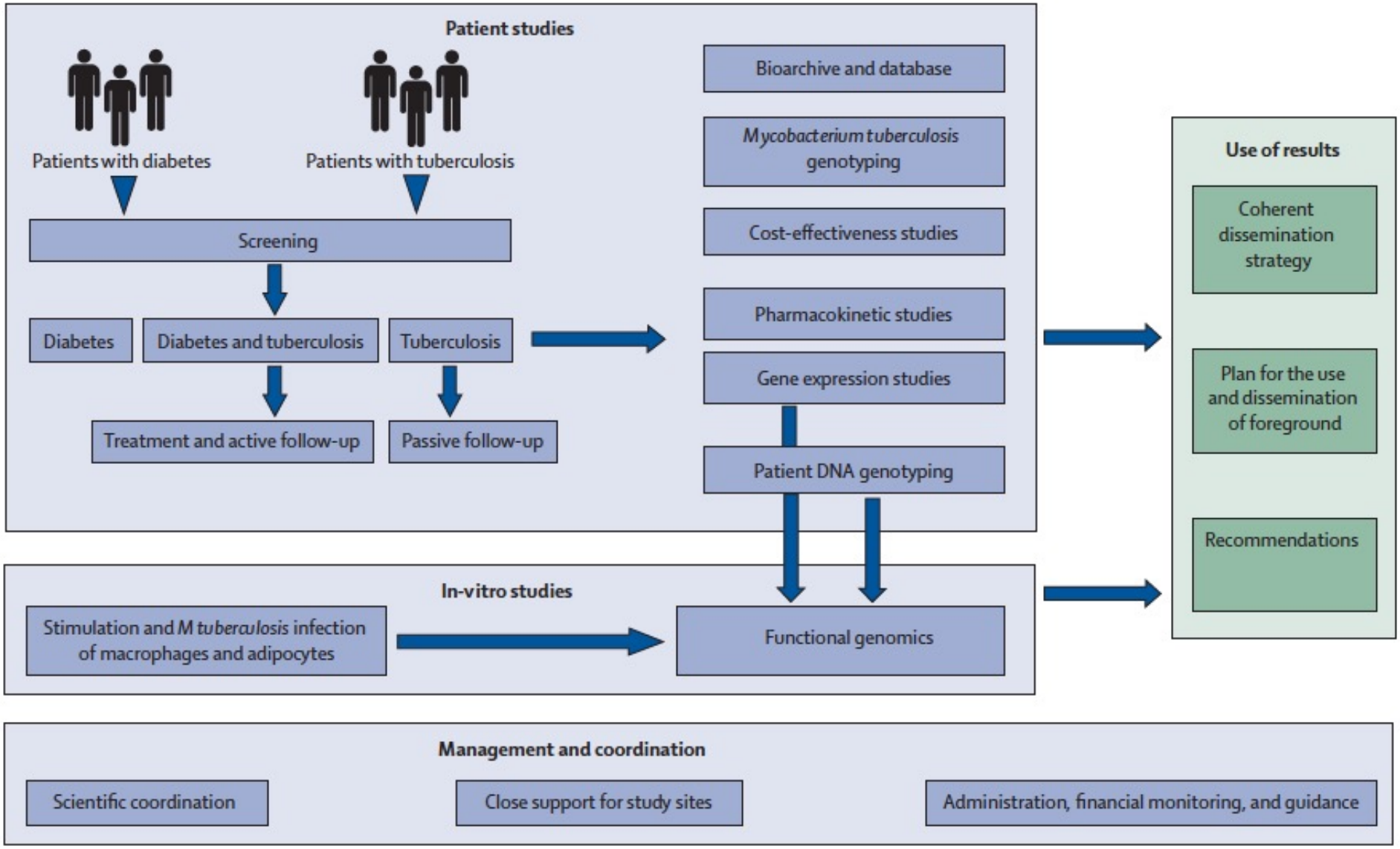
Parameter	Before rifampin	After rifampin	*P*
ΔG_{max} (mg/dl)	31 ± 14	44 ± 14	0.024
ΔAUC_{gluc60} (mg/dl·min)	914 ± 510	1,412 ± 555	0.020
ΔAUC_{gluc} (mg/dl·min)	1,679 ± 1,155	2,378 ± 1,316	0.121

Data were evaluated by Wilcoxon signed-rank test and are expressed as mean ± SD.



Complex interactions between glucose lowering drugs and immune pathways that affect TB.

TANDEM STUDY
International Consortium funded by the European Union



Richard Brostrom, CDC

In the meantime……

Pacific Standards for Management of Tuberculosis and Diabetes

TB-DM Stds V 2.3 11-21-13

Screening for DM in persons with TB

Standard 1 Every person with tuberculosis (TB) over the age of 18 should be screened for diabetes mellitus (DM)

- 1.1 The diagnosis of DM may be made using one of the following criteria:
  - Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l)
  - Random plasma glucose ≥ 200 mg/dl (11.1 mmol/l)
  - Hemoglobin A_1C ≥ 6.5 % (48 mmol/mol)
- 1.2 Abnormal glucose values should be verified in patients who have no symptoms of DM.
- 1.3 Rifampin can elevate blood glucose in TB patients. Glucose testing may be repeated after 2-4 weeks of TB treatment, or if symptoms of hyperglycemia develop during TB treatment.

Screening for TB in persons with DM

Standard 2 Every person with DM should be screened for TB disease and TB infection

- 2.1 Persons with TB symptoms or TB disease should be referred to the local TB Program for TB management.
- 2.2 A test for TB infection should be done at the time of DM diagnosis.
- 2.3 Screening should be repeated as often as the local TB epidemiology may warrant.

Standard 3 Persons with DM and TB infection should be encouraged to take preventive therapy

- 3.1 Persons with DM are at increased risk of peripheral neuropathy. If INH is used for prevention, give B6 to prevent neuropathy (10 – 25 mg/day).
- 3.2 Monitor for adherence and side effects of preventive treatment.

Treating TB in persons with DM

Standard 4 Clinicians may need to adjust TB treatment in persons with DM

- 4.1 Make sure that TB medications are properly dosed.
  Check creatinine for diabetic nephropathy, and if present, adjust the frequency of PZA and EMB according to ATS-CDC guidelines.*
  Administer B6 to prevent INH-induced neuropathy (10 – 25 mg/day).
- 4.2 Observe closely for TB treatment failure in persons with DM.
  Be aware of poor absorption of some TB meds in DM.
  Manage the many interactions between TB and DM meds.
  Some programs follow INH or RIF levels in persons with DM.
- 4.3 "Assure the Cure"
  Consider extending treatment to 9 months for persons with DM, especially persons with cavitary disease or delayed sputum clearance.*
  Upon completion of therapy, obtain sputum for AFB smear and culture.
  Evaluate at one year after treatment for evidence of relapse.

*Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society, MMWR 2003;52

Managing DM in persons with TB

Standard 5 Use TB clinic visits to help persons manage their DM

- 5.1 There should be a glucometer in every TB clinic for monitoring glucose.
- 5.2 TB patients with DM should have their glucose checked at least weekly for the first 4 weeks, and less frequently thereafter if diabetes is controlled. Monthly glucose testing during treatment is recommended.
- 5.3 All clinic staff should reinforce lifestyle changes at TB clinic visits.
- 5.4 If available, refer persons with DM to the Diabetes Clinic for diabetes care. Ensure DM clinician is aware of TB diagnosis and TB medications.

Standard 6 Use DOT visits to help persons manage their DM

- 6.1 DOT workers should encourage lifestyle changes at every encounter.
  DOT workers should use structured and culturally-appropriate diabetes educational materials.*
  Dietary changes and physical activity are the most important in this effort.
- 6.2 Consider delivering DM meds with TB meds via DOT for persons with poorly-controlled DM who have non-adherence to diabetic medications.

* ARC TB and DM Flipchart: http://www.thearc.org.au/TBandDiabetes.aspx
* NDEP, US Dept of Health and Human Services: http://www.yourdiabetesinfo.org/

PITCA

Pacific Chronic Disease Coalition

Acknowledgements

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