Comorbidities and Tuberculosis Outcomes

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Disclosures

- No relevant financial relationships

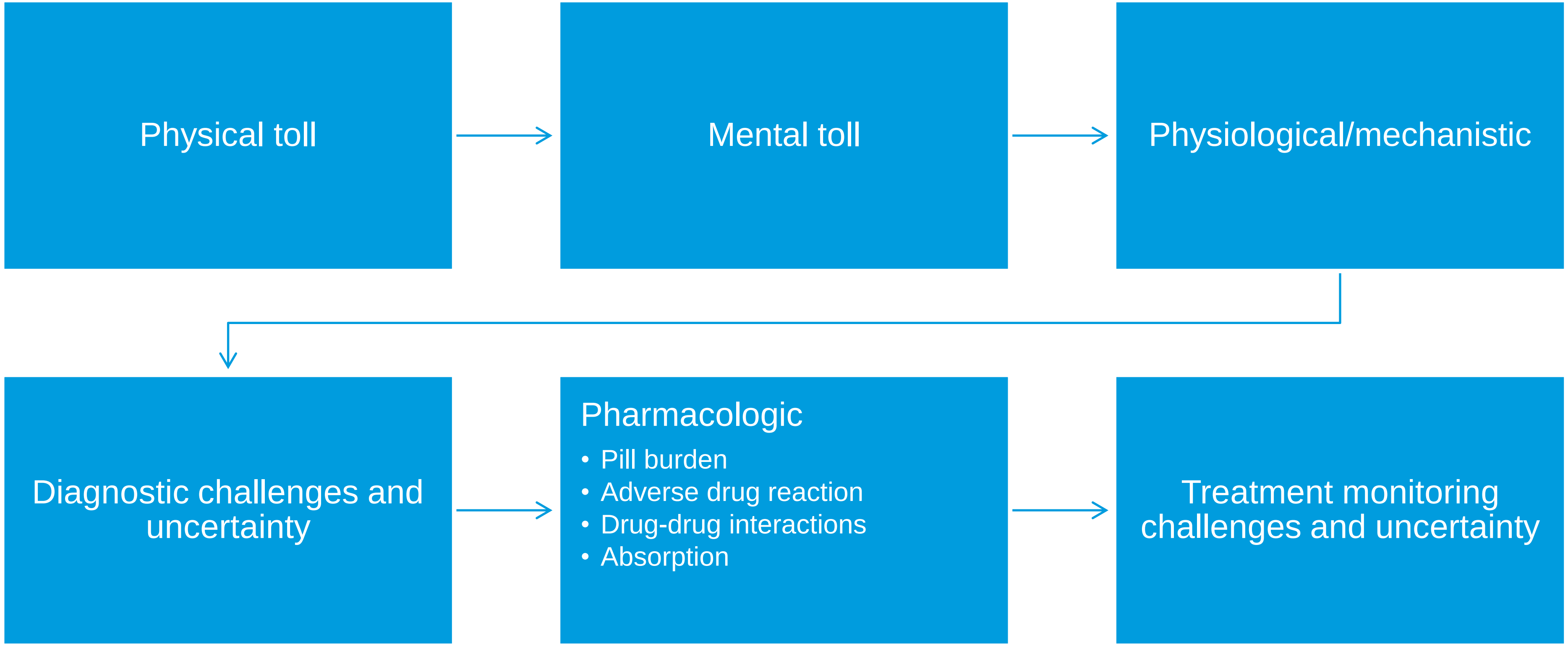
Learning Objectives

Describe	how HIV impacts TB outcomes
Describe	how diabetes impacts TB outcomes
Describe	how malnutrition impacts TB outcomes
Describe	how smoking impacts TB outcomes
Describe	how alcohol use impacts TB outcomes

Global estimates of tuberculosis episodes in 2022 attributable to selected risk factors

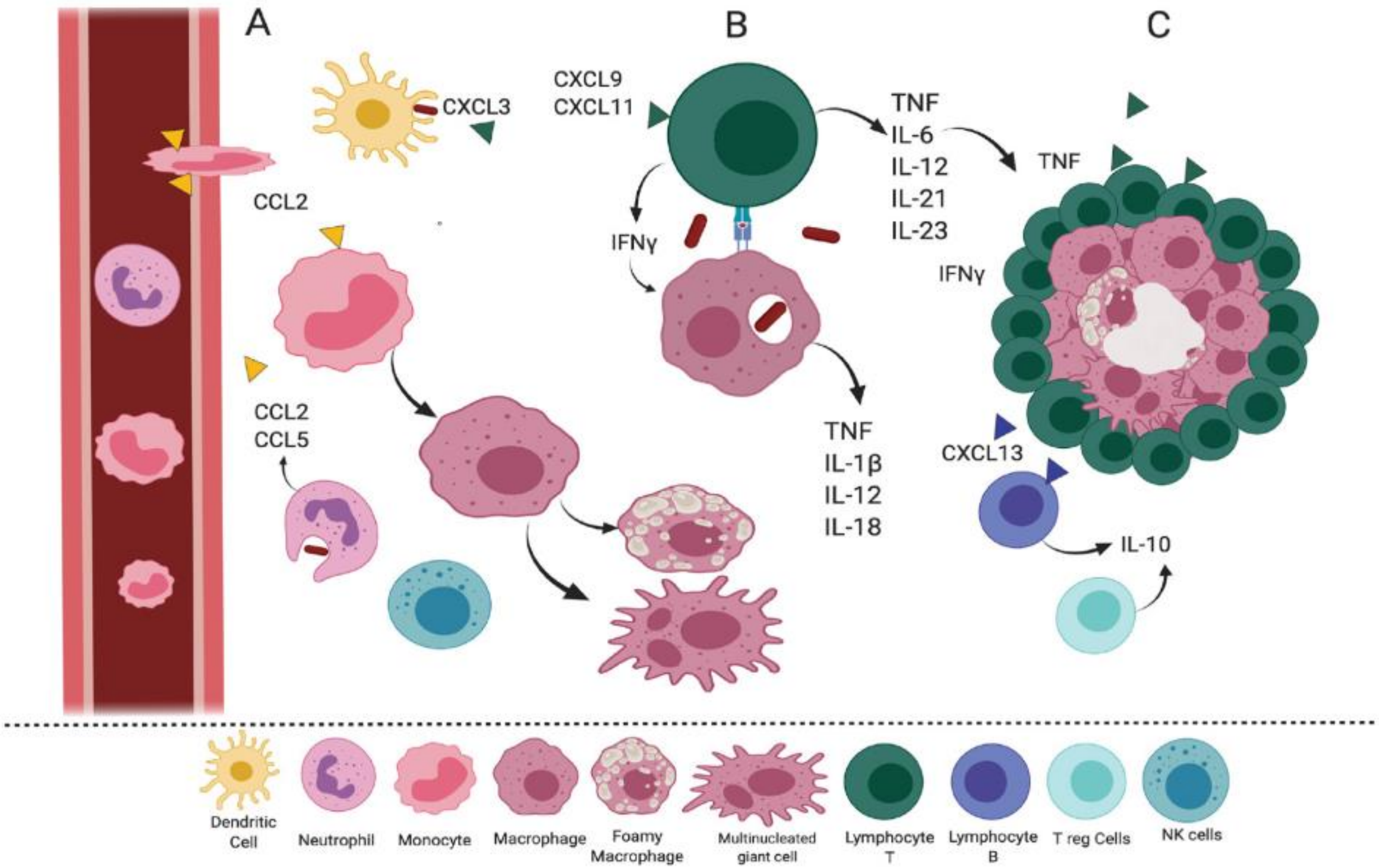
Risk factor	Risk ratio (uncertainty interval)		Number of people with the risk factor (millions)	Attributable TB episodes (millions, uncertainty interval)	
Alcohol use disorders	3.3	(2.1 to 5.2)	297	0.73	(0.52 to 0.99)
Diabetes	1.5	(1.3 to 1.8)	509	0.37	(0.27 to 0.48)
HIV infection	14	(12 to 16)	39	0.89	(0.73 to 1.1)
Smoking	1.6	(1.2 to 2.1)	998	0.70	(0.50 to 0.95)
Undernourishment	3.2	(3.1 to 3.3)	711	2.2	(2.0 to 2.4)

Impact of Comorbidities on TB Natural History and Outcomes



Impact of HIV on TB Outcomes

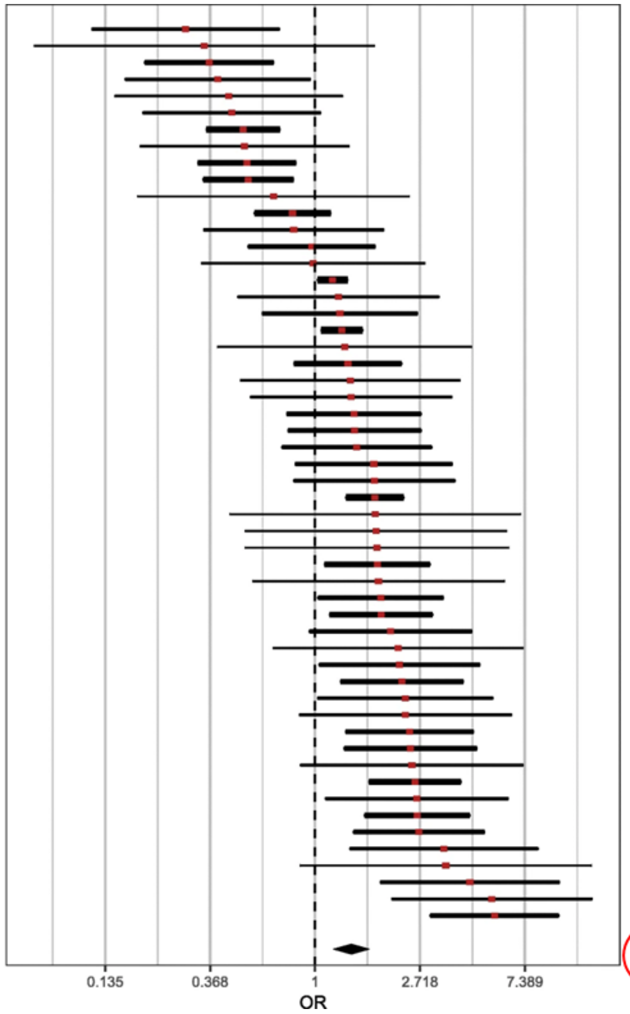
Granuloma formation during MTB infection



Téllez-Navarrete, Norma A et al. "Malnutrition and tuberculosis: the gap between basic research and clinical trials." Journal of infection in developing countries 15 3 (2021): 310-319 .

Sultana ZZ, Hoque FU, Beyene J, et al. HIV infection and multidrug resistant tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2021;21(1):51.

Authors, Year of publication	MDR TB+/HIV+	MDR TB+/HIV-	%W(random)	OR [95% CI]
Elmi et al., 2015	6/42	99/272	1.71	0.29 [0.12, 0.72]
Vadwai et al., 2011	3/6	181/244	0.94	0.35 [0.07, 1.77]
Hirpa et al., 2013	18/58	116/210	2.11	0.36 [0.20, 0.68]
Coelho et al., 2012	7/82	25/131	1.72	0.40 [0.16, 0.96]
Elduma et al., 2019	4/22	426/1268	1.46	0.44 [0.15, 1.31]
Sangare et al., 2011	7/91	35/225	1.77	0.45 [0.19, 1.06]
Zurcher et al., 2019	61/272	132/362	2.45	0.50 [0.35, 0.72]
Sangare et al., 2010	5/91	23/225	1.57	0.51 [0.19, 1.39]
Ricks et al. , 2012	55/196	53/124	2.31	0.52 [0.33, 0.84]
Assefa et al., 2017	31/142	184/533	2.36	0.53 [0.34, 0.82]
Shariff et al., 2015	3/20	27/130	1.22	0.67 [0.18, 2.47]
Chan et al., 2020	30/2562	547/37796	2.44	0.81 [0.56, 1.17]
Baya et al., 2019	14/24	120/190	1.75	0.82 [0.34, 1.94]
Desissa et al., 2018	22/67	51/152	2.12	0.97 [0.53, 1.78]
Sinha et al., 2017	6/15	89/220	1.49	0.98 [0.34, 2.85]
van Den Hof et al., 2013	288/721	18050/50138	2.63	1.18 [1.02, 1.37]
Metcalfe et al., 2014	18/88	7/41	1.62	1.25 [0.48, 3.28]
Lukoye et al., 2013	11/399	20/914	1.92	1.27 [0.60, 2.67]
Arroyo et al., 2020	106/16371	760/151355	2.6	1.29 [1.05, 1.58]
Tesseme et al., 2012	4/66	9/194	1.32	1.33 [0.39, 4.46]
Mulu et al., 2015	43/77	110/229	2.25	1.37 [0.81, 2.30]
Lee et al., 2016	5/18	128/593	1.51	1.40 [0.49, 3.99]
Satti et al., 2013	30/45	17/29	1.62	1.41 [0.54, 3.70]
Gunther et al., 2015	25/41	345/665	2.07	1.45 [0.76, 2.76]
van Halsema et al., 2012	106/1295	11/191	2.08	1.46 [0.77, 2.77]
Ulmasova et al., 2013	14/31	333/935	1.96	1.49 [0.72, 3.06]
Minion et al., 2013	9/508	29/2844	1.91	1.75 [0.82, 3.72]
Brito et al. , 2010	18/215	11/223	1.88	1.76 [0.81, 3.82]
Pavlenko et al., 2018	102/243	372/1282	2.53	1.77 [1.33, 2.35]
Salindri et al., 2016	3/10	49/252	1.14	1.78 [0.44, 7.11]
Chuchottaworn et al., 2015	7/11	138/279	1.27	1.79 [0.51, 6.25]
Fikre et al., 2019	7/11	95/193	1.26	1.81 [0.51, 6.37]
Alene et al., 2019	51/78	191/374	2.26	1.81 [1.09, 3.01]
Gobena et al., 2018	7/12	52/120	1.33	1.83 [0.55, 6.10]
Macedo et al. , 2012	16/427	34/1666	2.13	1.87 [1.02, 3.42]
Mor et al., 2014	19/190	188/3362	2.28	1.88 [1.14, 3.08]
Sethi et al., 2013	12/44	27/175	1.87	2.06 [0.94, 4.48]
Gaborit et al., 2018	6/12	38/122	1.34	2.21 [0.67, 7.30]
Gudo et al., 2011	15/334	12/583	1.89	2.24 [1.03, 4.84]
Kusumawati et al., 2018	17/73	81/692	2.15	2.29 [1.27, 4.13]
Okethwangu et al., 2019	16/46	14/76	1.79	2.36 [1.02, 5.47]
Ershova et al., 2015	7/18	36/170	1.55	2.37 [0.86, 6.55]
Workicho et al., 2017	45/71	45/109	2.11	2.46 [1.33, 4.55]
Padilla et al., 2012	102/451	12/114	2.08	2.48 [1.31, 4.70]
Abdella et al., 2015	10/23	11/47	1.49	2.52 [0.87, 7.31]
Tadasse, 2015	54/139	59/300	2.35	2.60 [1.66, 4.05]
Jitmuang et al., 2015	11/26	30/138	1.74	2.64 [1.10, 6.35]
Skrahina et al., 2013	49/72	557/1249	2.26	2.65 [1.59, 4.40]
Mulisa et al. , 2015	70/154	17/72	2.09	2.70 [1.44, 5.06]
Andrew et al. , 2010	200/278	9/21	1.7	3.42 [1.39, 8.43]
Hirama et al., 2020	3/10	43/392	1.14	3.48 [0.87, 13.95]
Post et al., 2014	47/98	8/46	1.76	4.38 [1.85, 10.34]
Hang et al., 2013	7/44	15/443	1.63	5.40 [2.07, 14.07]
Mesfin et al., 2018	71/128	18/98	2.11	5.54 [2.98, 10.28]
Summary: RE model (I^2 = 75.8%)				1.416 [1.19, 1.68]



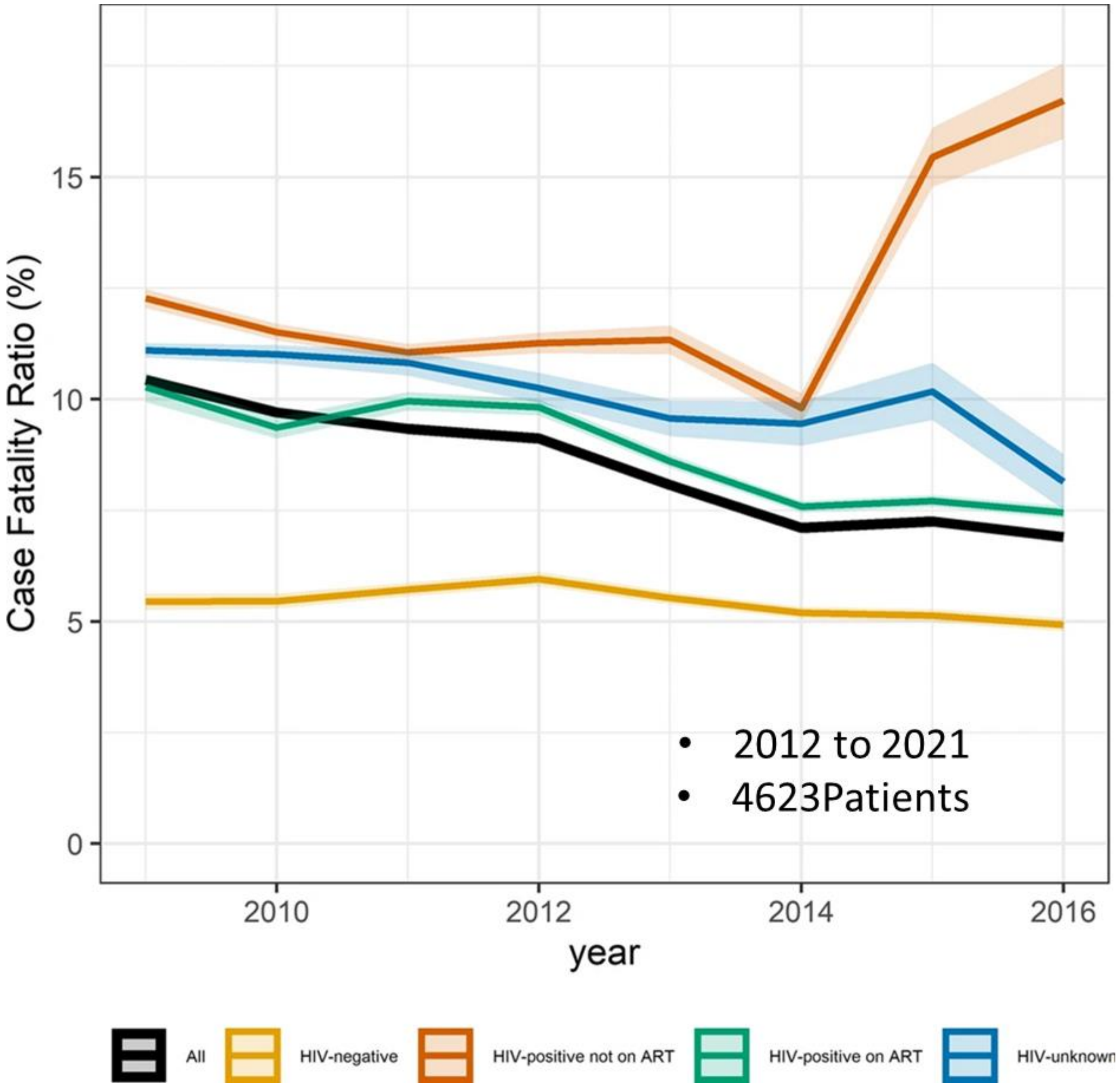
Trend in tuberculosis treatment success rates by HIV status

	Completed n(%)	Cured n(%)	Died n(%)	Failure n(%)	Lost to follow-up n(%)	*P*-value
HIV status						
Negative	1058(47.9)	390(17.7)	528(23.9)	31(1.4)	201(9.1)	
Positive	326(46.6)	49(7.0)	269(38.5)	5(0.7)	50(7.2)	<0.001

HIV negative status was associated with 22.0% higher proportion of successful treatment outcome compared with being HIV positive

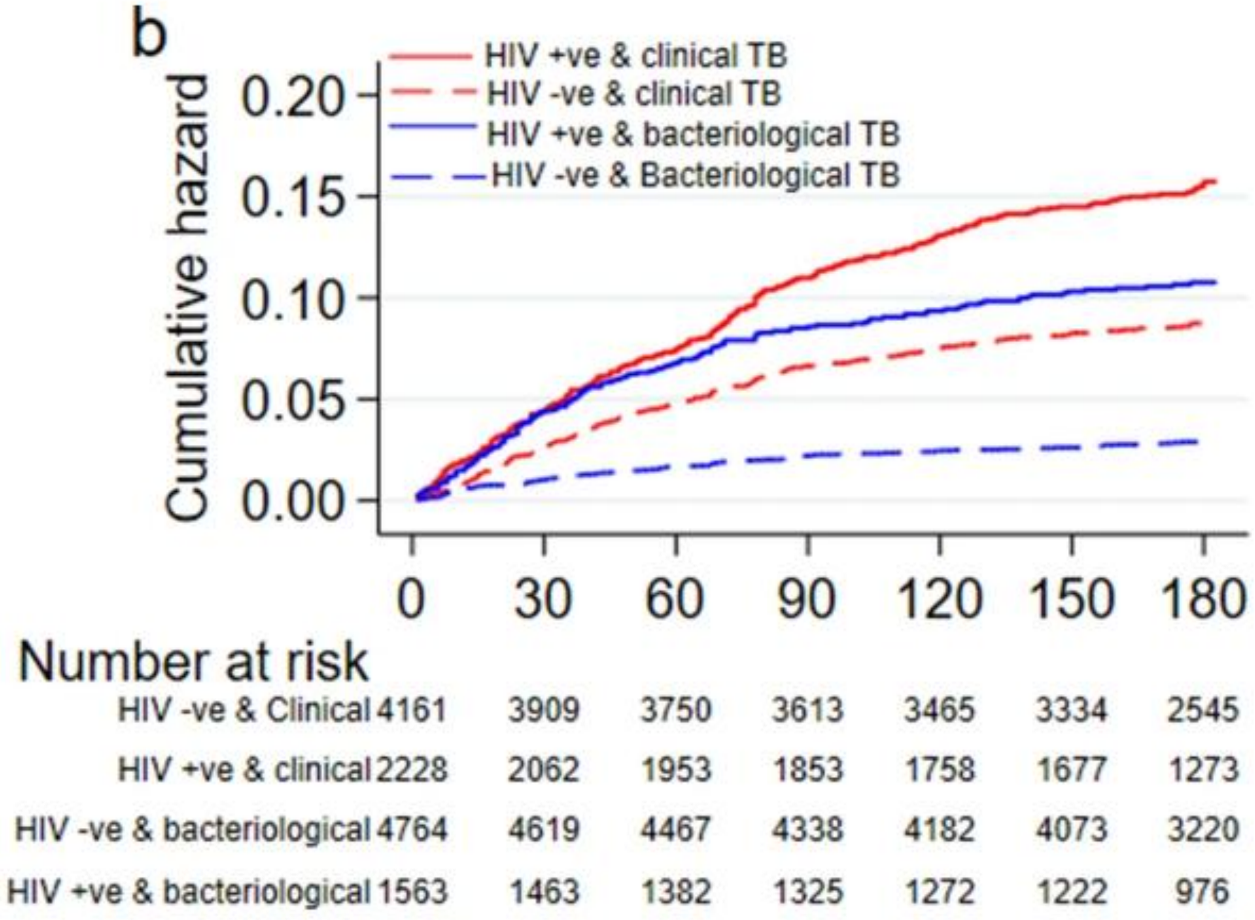
Puplampu P, Kyeremateng I, Asafu-Adjaye O, et al. Evaluation of treatment outcomes among adult patients diagnosed with tuberculosis in Ghana: A 10-year retrospective review. IJID Reg. 2023;10:9-14. Published 2023 Nov 10. doi:10.1016/j.ijregi.2023.11.004

Mortality during tuberculosis treatment in South Africa: an 8-year analysis



Sci Rep 11, 15894 (2021). https://doi.org/10.1038/s41598-021-95331-w

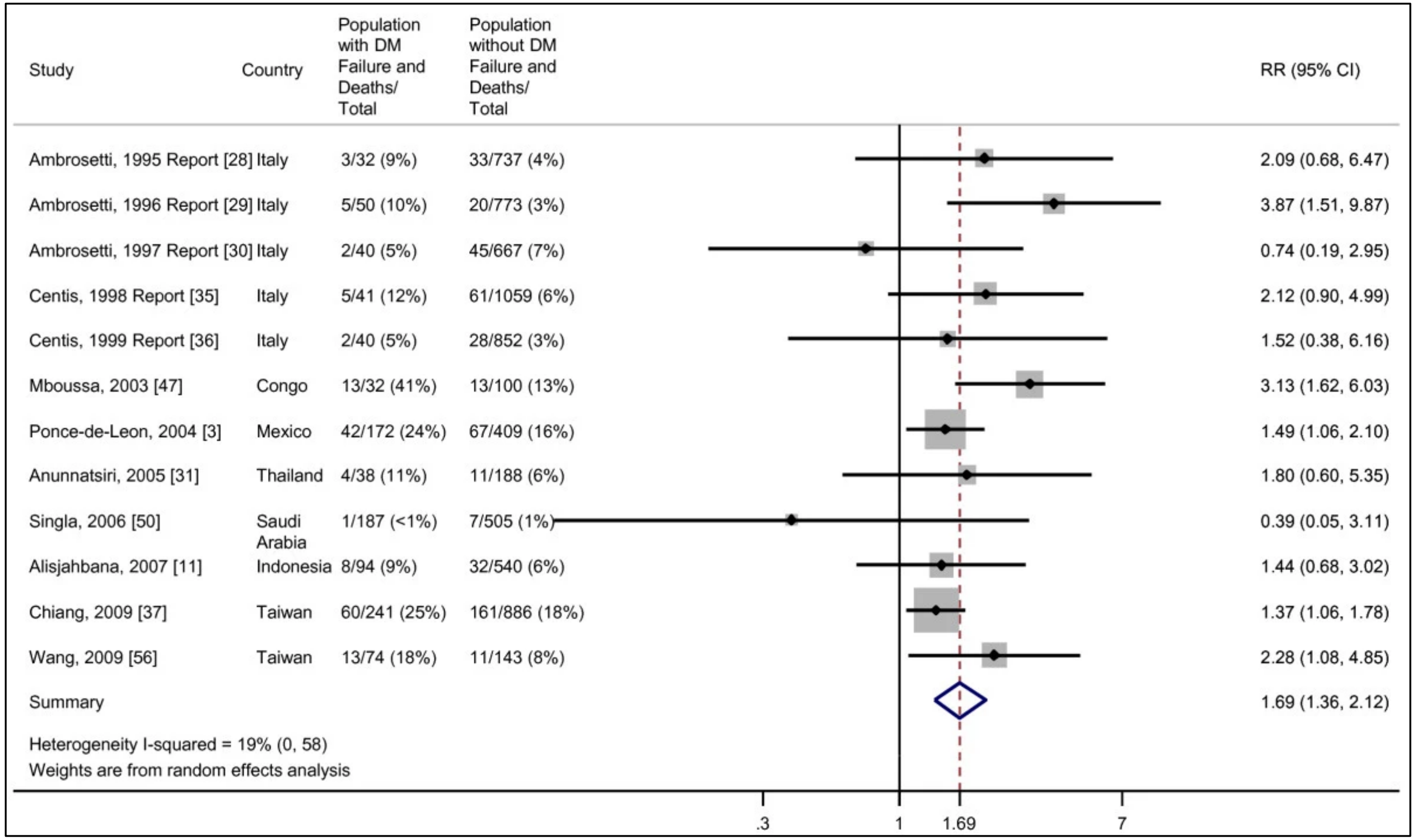
Cumulative hazard of deaths stratified by type of TB diagnosis with HIV status



Abdullahi, O., Moses, N., Sanga, D. et al. The effect of empirical and laboratory-confirmed tuberculosis on treatment outcomes. Sci Rep 11, 14854 (2021). https://doi.org/10.1038/s41598-021-94153-0

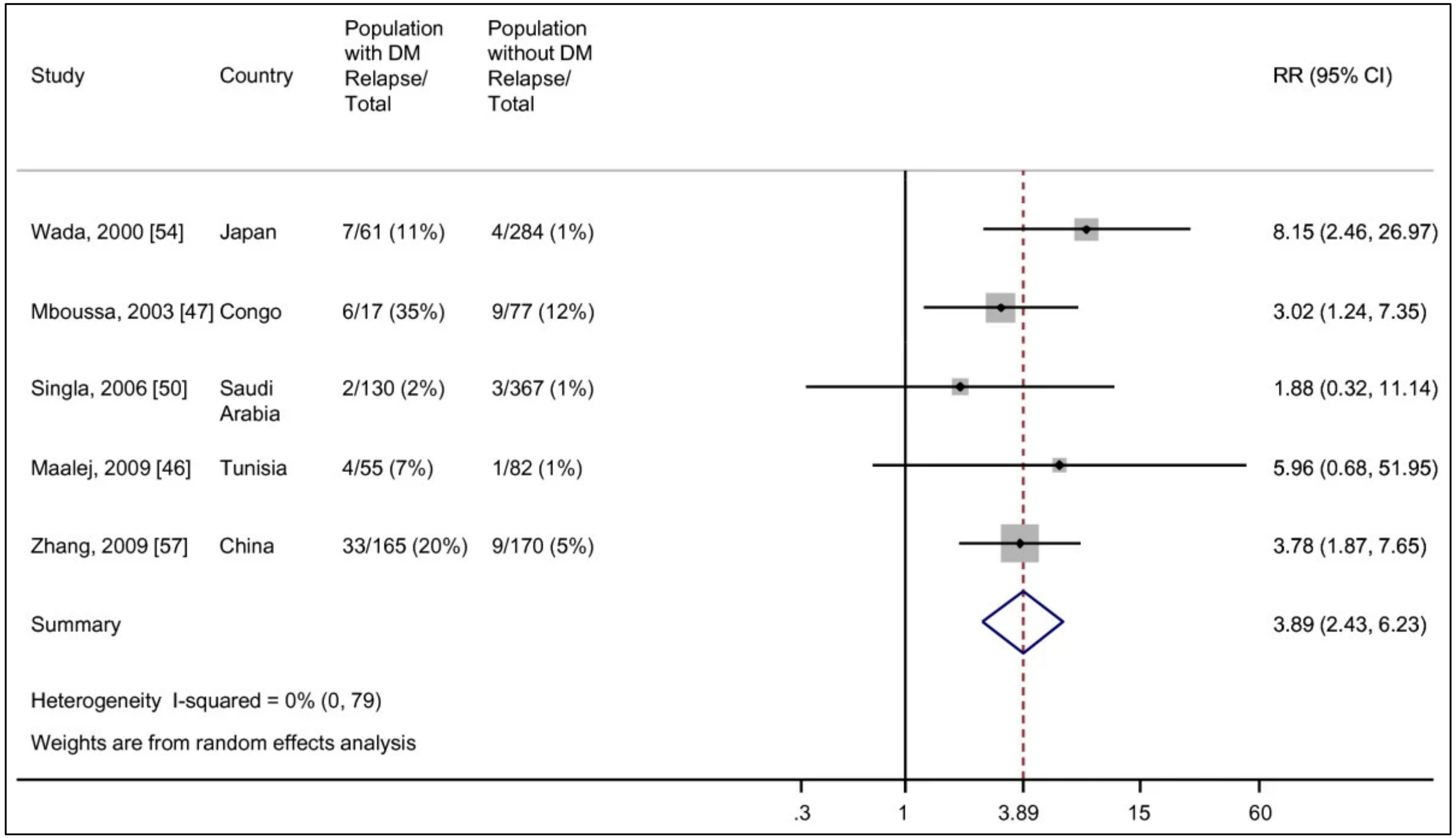
Impact of Diabetes on TB Outcomes

Risk of failure/death for TB patients with DM compared with TB patients without DM



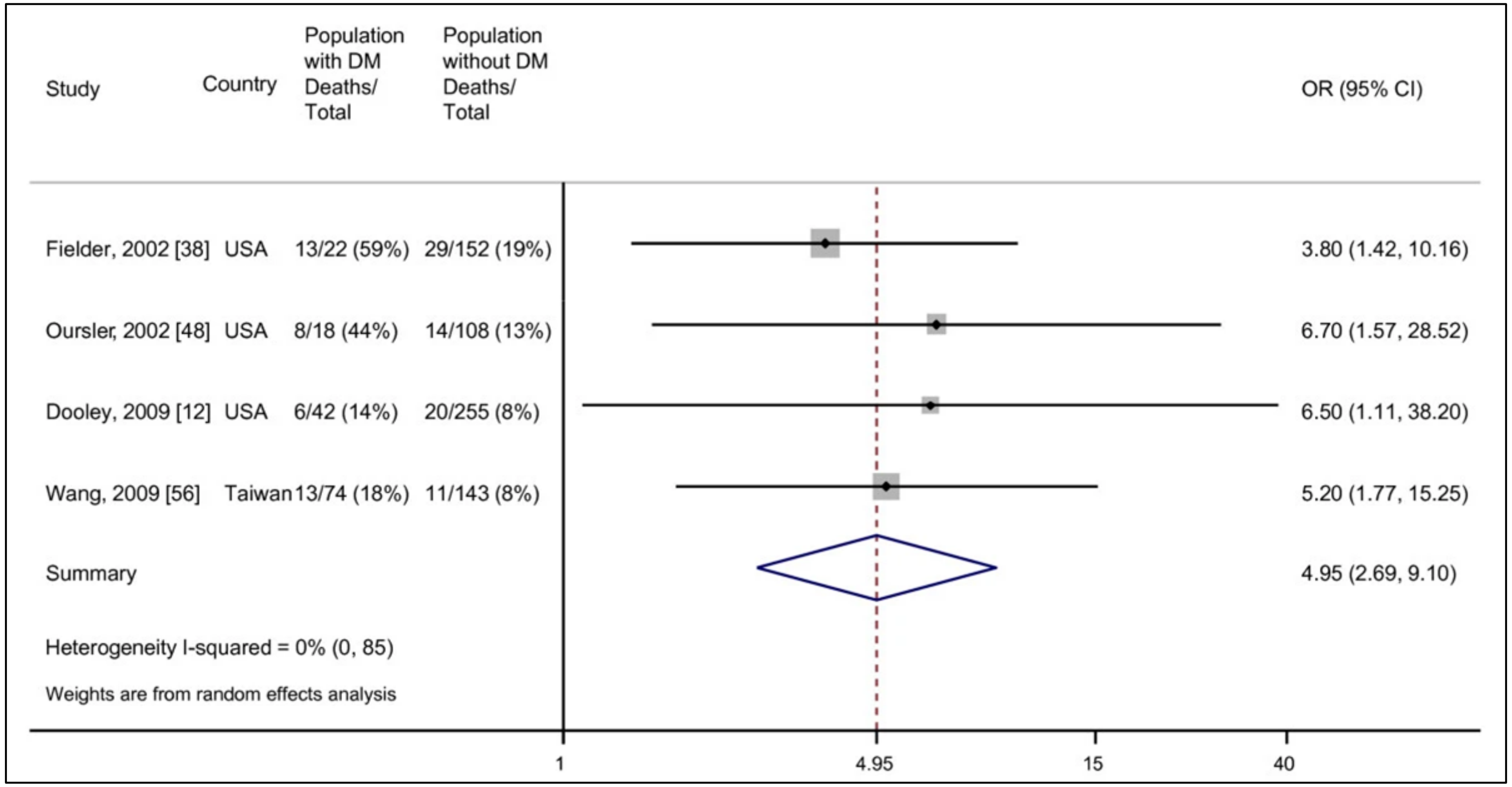
Baker, M.A., Harries, A.D., Jeon, C.Y. et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med 9, 81 (2011). https://doi.org/10.1186/1741-7015-9-81

Risk of TB relapse for TB patients with DM compared with TB patients without DM



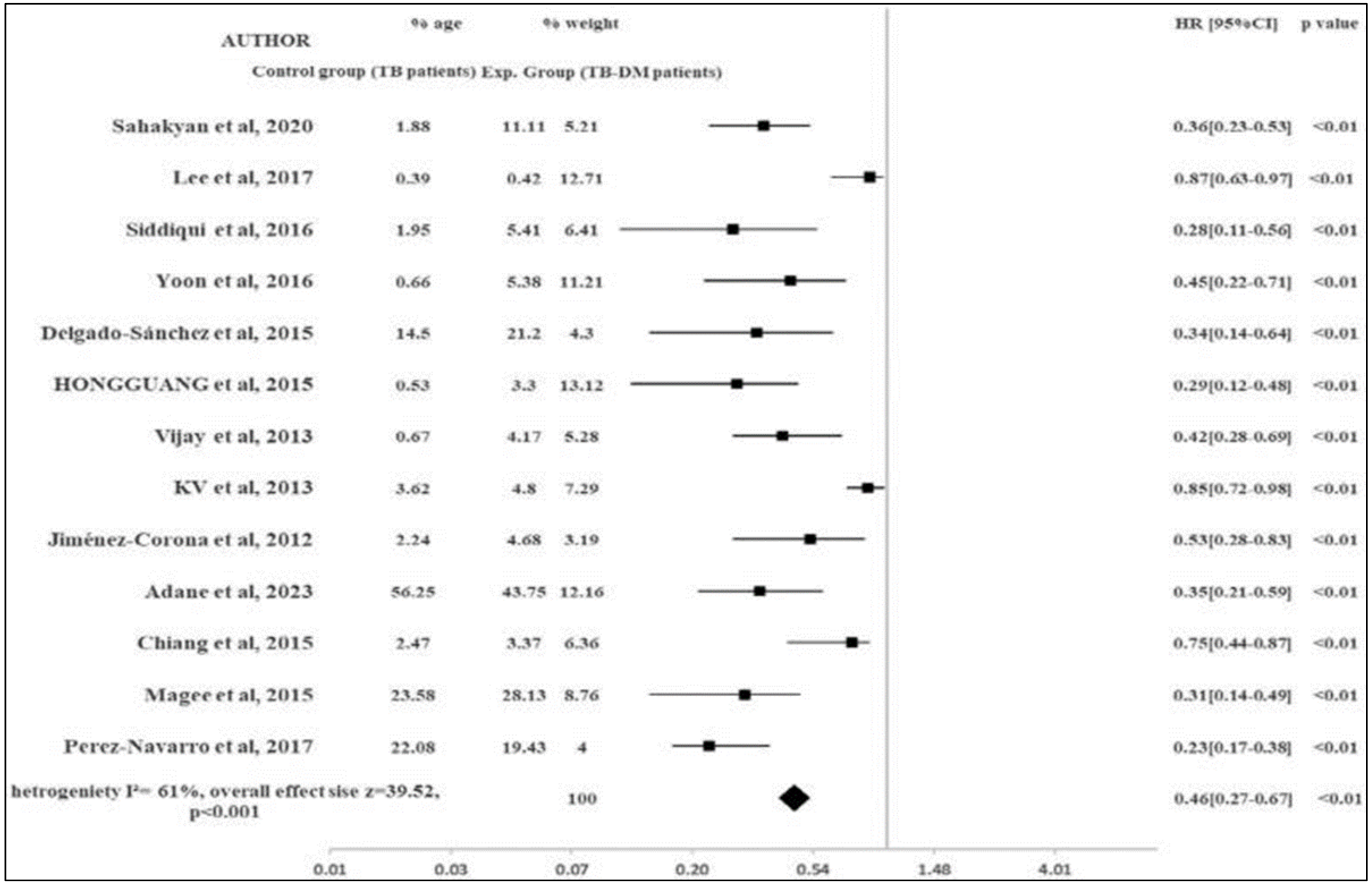
Baker, M.A., Harries, A.D., Jeon, C.Y. et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med 9, 81 (2011). https://doi.org/10.1186/1741-7015-9-81

Adjusted odds of death for TB patients with DM compared with TB patients without DM.



Baker, M.A., Harries, A.D., Jeon, C.Y. et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med 9, 81 (2011). https://doi.org/10.1186/1741-7015-9-81

Impact of DM on TB treatment failure rates



Rehman AU, Khattak M, Mushtaq U, et al. The impact of diabetes mellitus on the emergence of multi-drug-resistant tuberculosis and treatment failure in TB-diabetes comorbid patients: a systematic review and meta-analysis. Front Public Health. 2023;11:1244450.

Impact of Malnutrition on TB Outcomes

Malnutrition: Definition

Broadly defined by WHO as deficiencies or excesses in nutrient intake, an imbalance of essential nutrients or impaired nutrient utilization.

A spectrum of nutrition-related states from undernutrition to overweight and obesity.

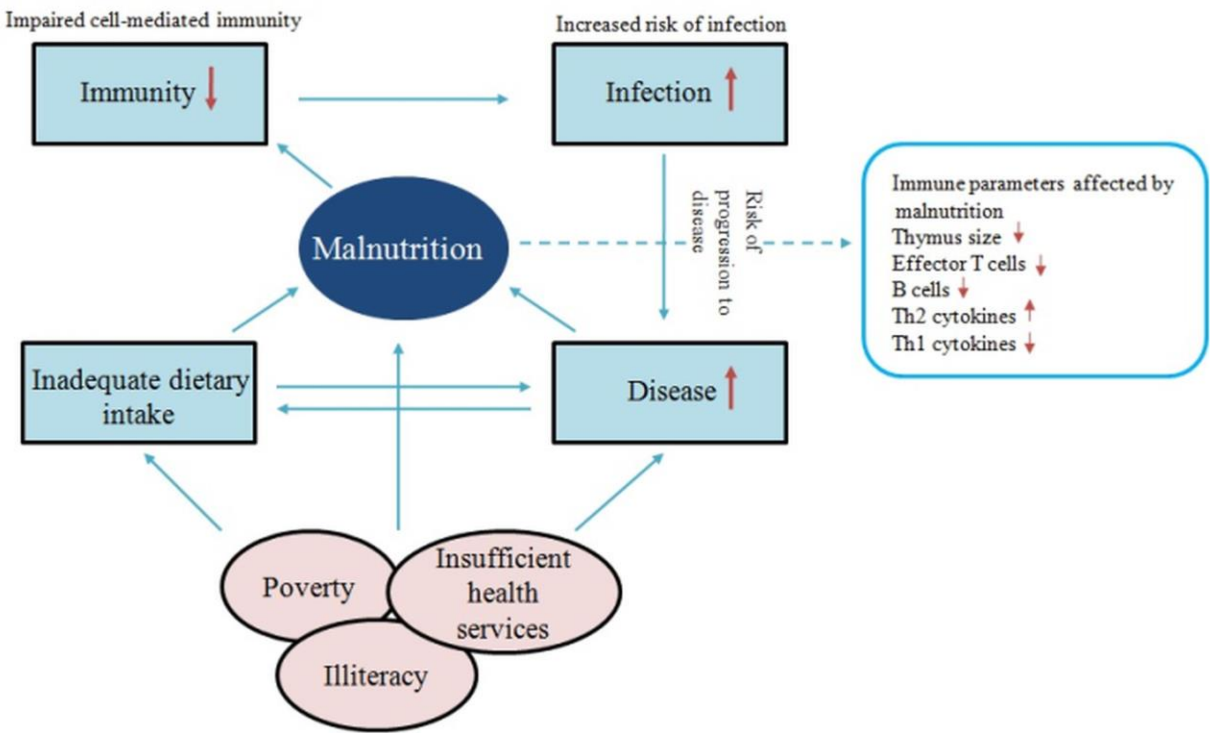
In practice, malnutrition is often used as a synonym for undernutrition in both academic literature and clinical discourse.

Malnutrition and Tuberculosis Key Facts

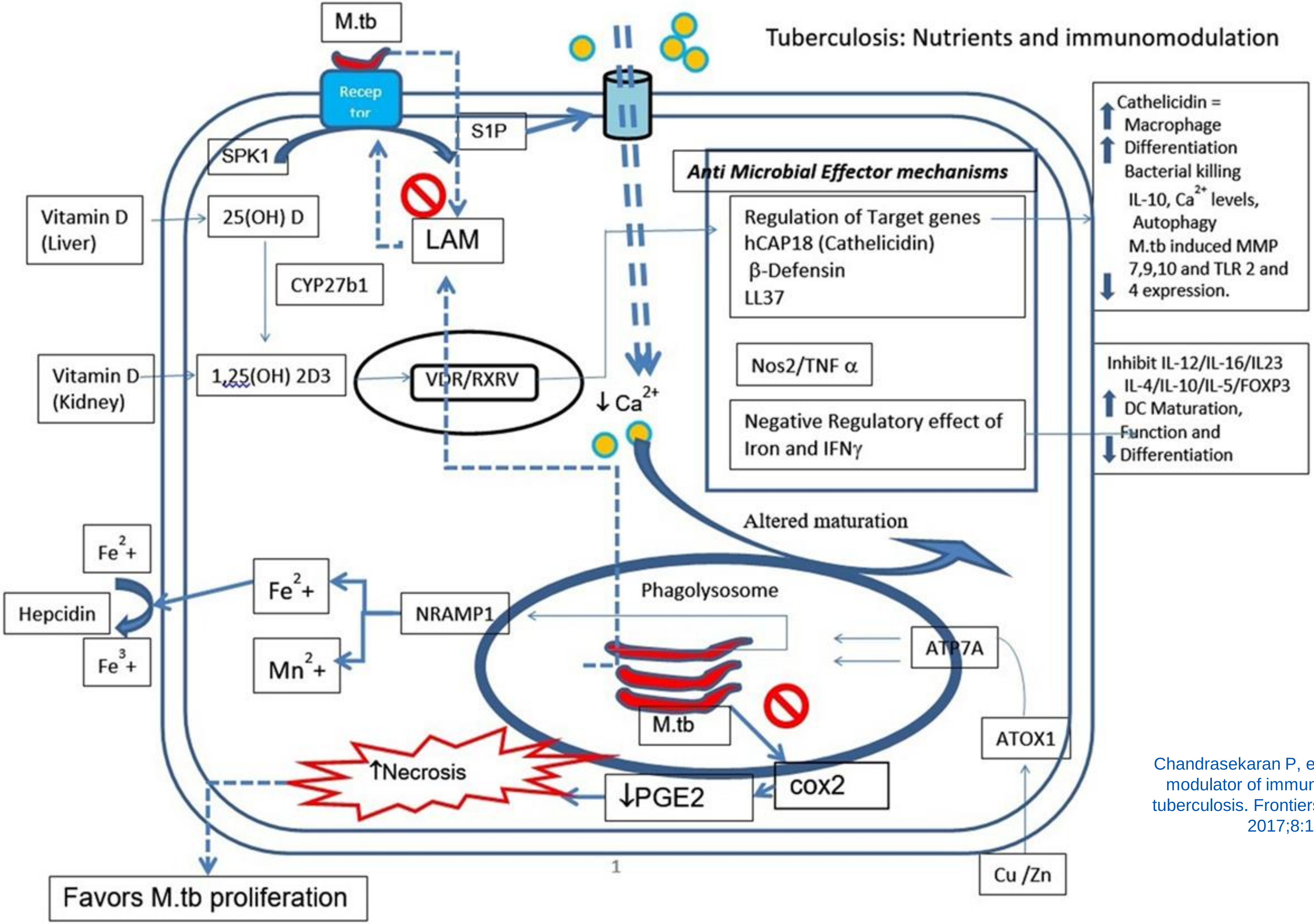
- Malnutrition is the leading attributable risk factor for tuberculosis (TB) infection.
- The risk of acquiring TB increases by 13.8% for each unit decrease in body mass index (BMI).
- Malnutrition is also a risk factor for conversion from latent TB to active disease.
- Malnourished TB patients experience poorer treatment outcomes.
- Malnourished patients are twice as likely to die from TB compared with non-malnourished patients.

Tuberculosis and malnutrition. World Health Organization 2024

Relationship between malnutrition, infection and immunity

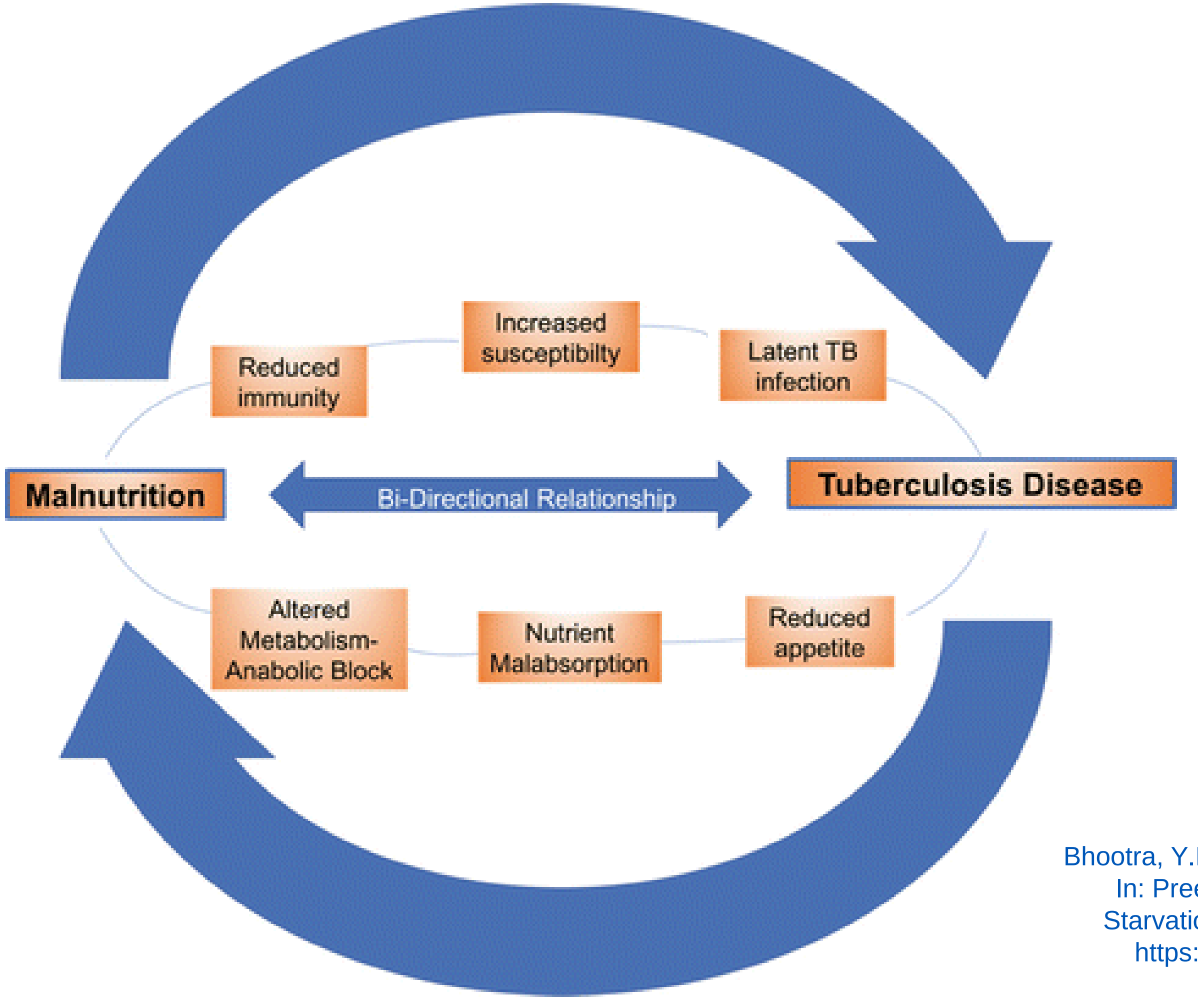


Tuberculosis: Nutrients and immunomodulation



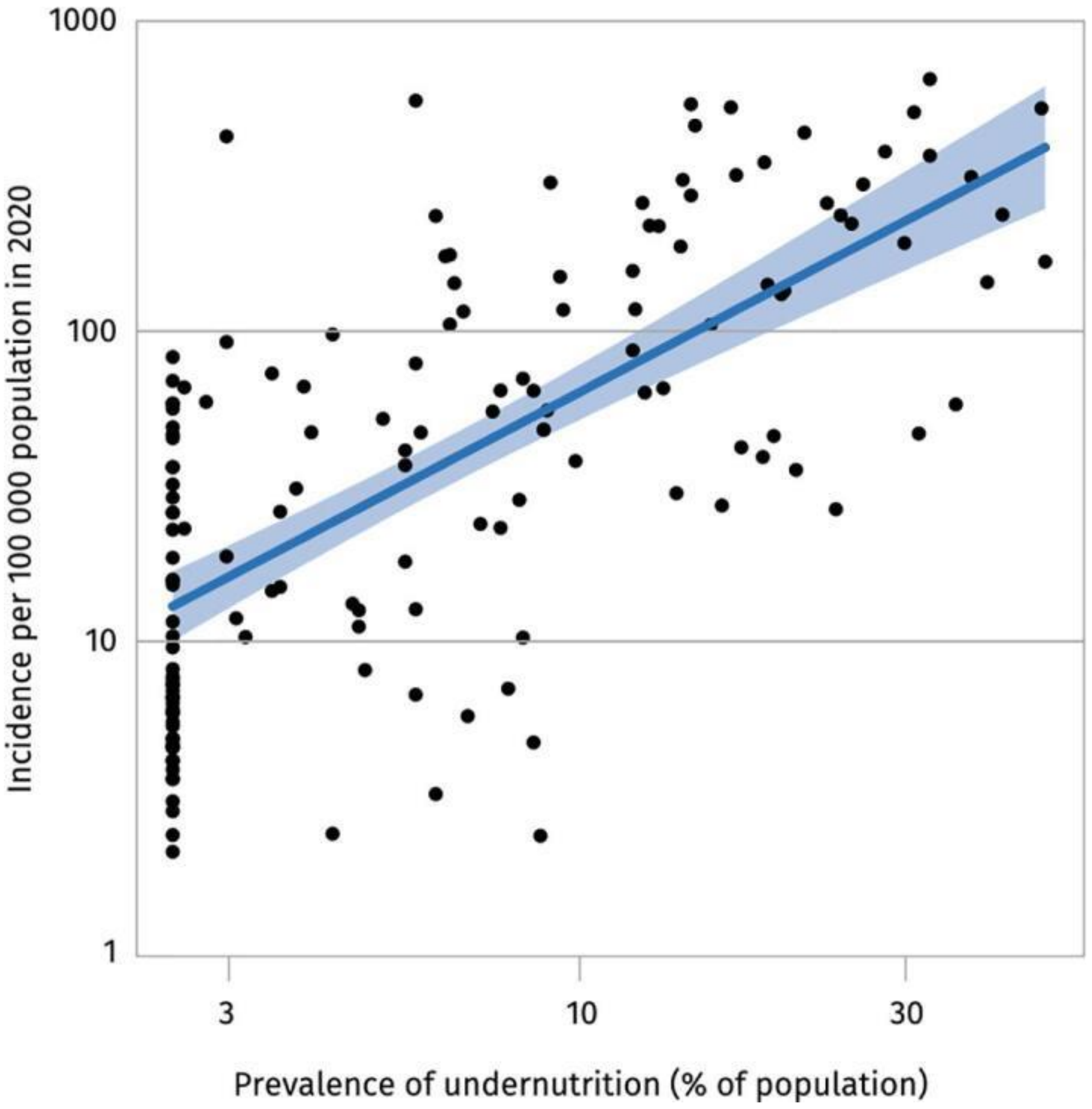
Chandrasekaran P, et al. Malnutrition: modulator of immune responses in tuberculosis. Frontiers in Immunology. 2017;8:1316.

Relationship between malnutrition, and Tuberculosis

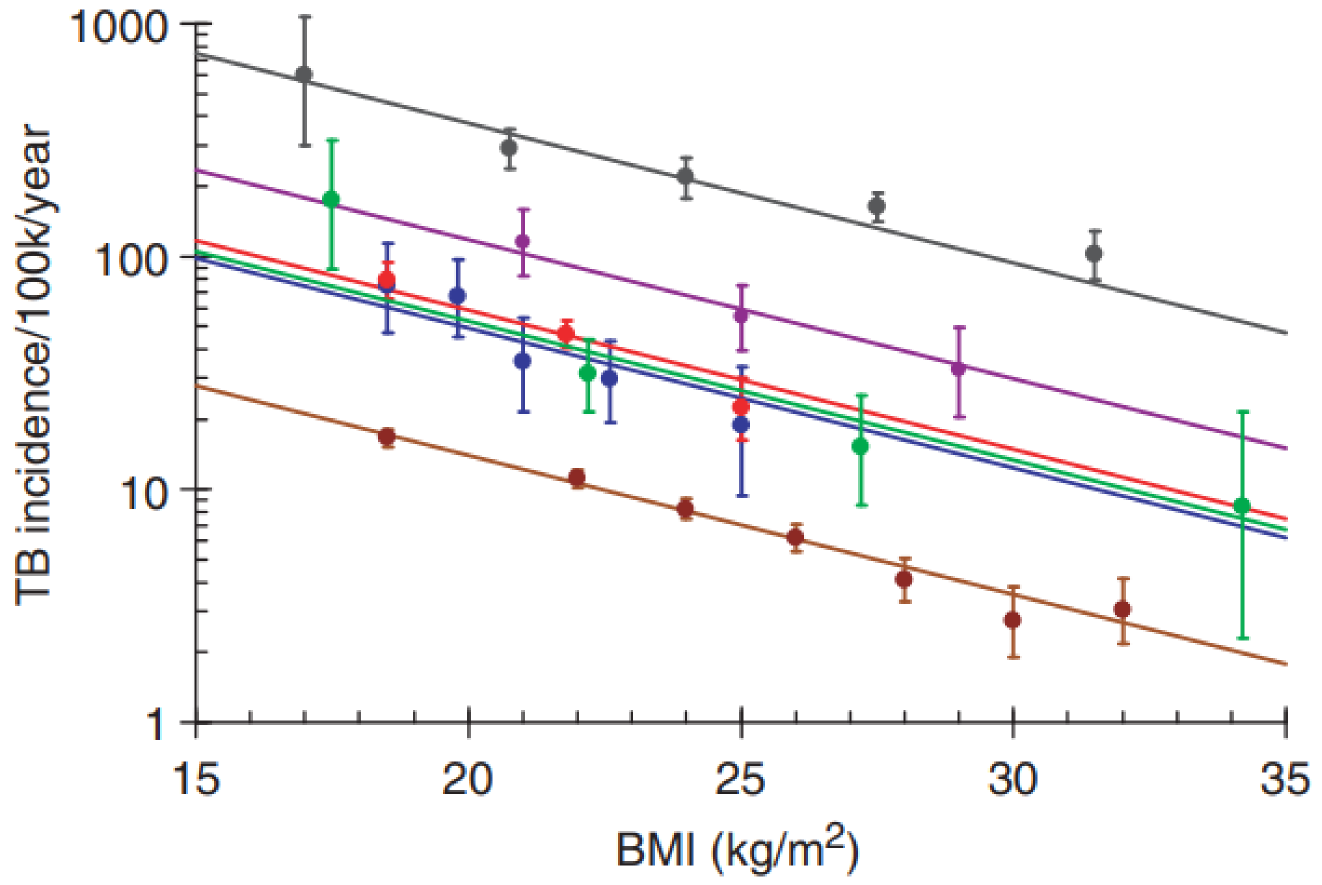


Bhootra, Y.M., Babu, S. (2018). Malnutrition in Tuberculosis. In: Preedy, V., Patel, V. (eds) Handbook of Famine, Starvation, and Nutrient Deprivation. Springer, Cham. https://doi.org/10.1007/978-3-319-40007-5_97-1

DANIELS M. Tuberculosis in Europe during and after the second world war. Br Med J. 1949;2(4636):1065-1072. doi:10.1136/bmj.2.4636.1065

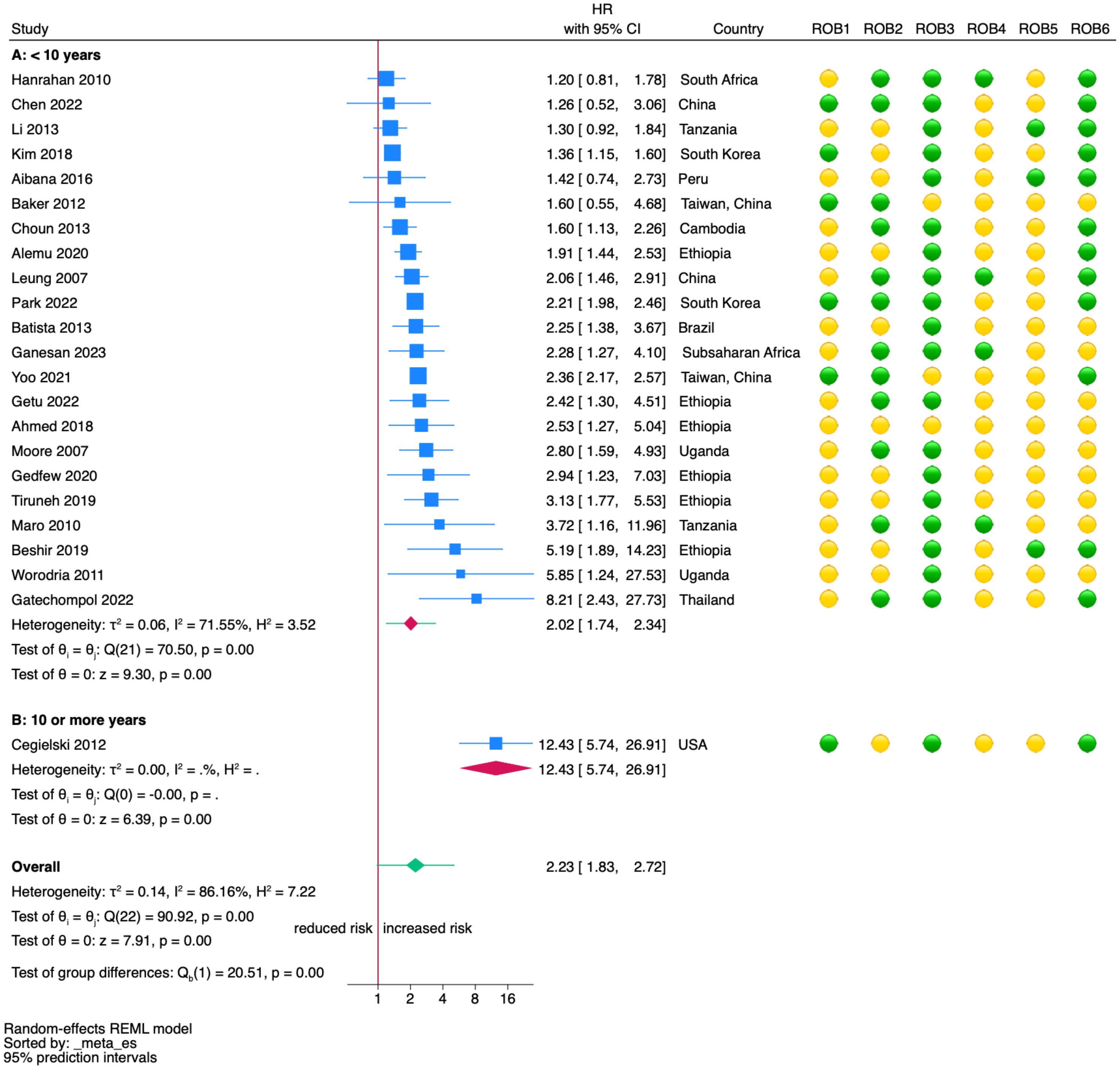


Global Tuberculosis Report 2021



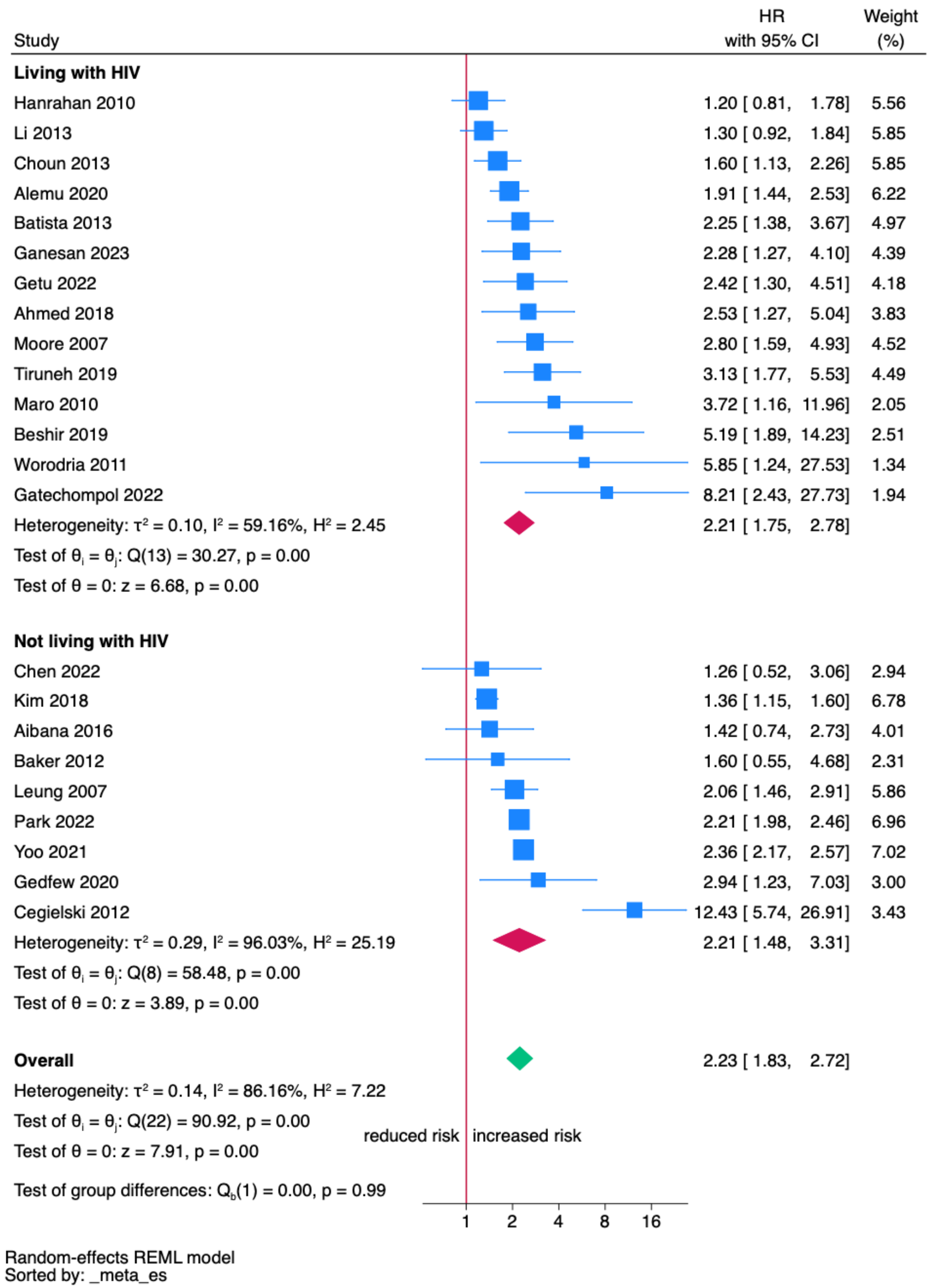
Lönnroth, Knut, et al. "A consistent log-linear relationship between tuberculosis incidence and body mass index." International journal of epidemiology 39.1 (2010): 149-155.

Hazard ratio of the risk of incident TB disease due to undernutrition.



Franco JVA, et al. Undernutrition as a risk factor for tuberculosis disease. Cochrane Database of Systematic Reviews 2024, Issue 6. Art. No.: CD015890. DOI: 10.1002/14651858.CD015890.pub2.

Subgroup analysis by HIV status for the risk of incident TB disease due to undernutrition.



Franco JVA, et al. Undernutrition as a risk factor for tuberculosis disease. Cochrane Database of Systematic Reviews 2024, Issue 6. Art. No.: CD015890. DOI: 10.1002/14651858.CD015890.pub2.

Nutritional Interventions and TB Outcomes

Increased calorie and protein intake can improve recovery from TB recovery

Nutritional support for TB patients was shown to increase treatment compliance.

Tuberculosis and malnutrition. World Health Organization 2024

Nutritional Assessment

- Taking a nutrition-oriented history and examination
- Anthropometric assessment such as BMI
- Dietary assessment
- Laboratory assessment, e.g. albumin, micronutrients (e.g., vitamin D, zinc)

Tuberculosis and malnutrition. World Health Organization 2024

Initial Assessment

Comprehensive Nutritional History

- Dietary intake,
- Weight history
- Potential barriers to adequate nutrition

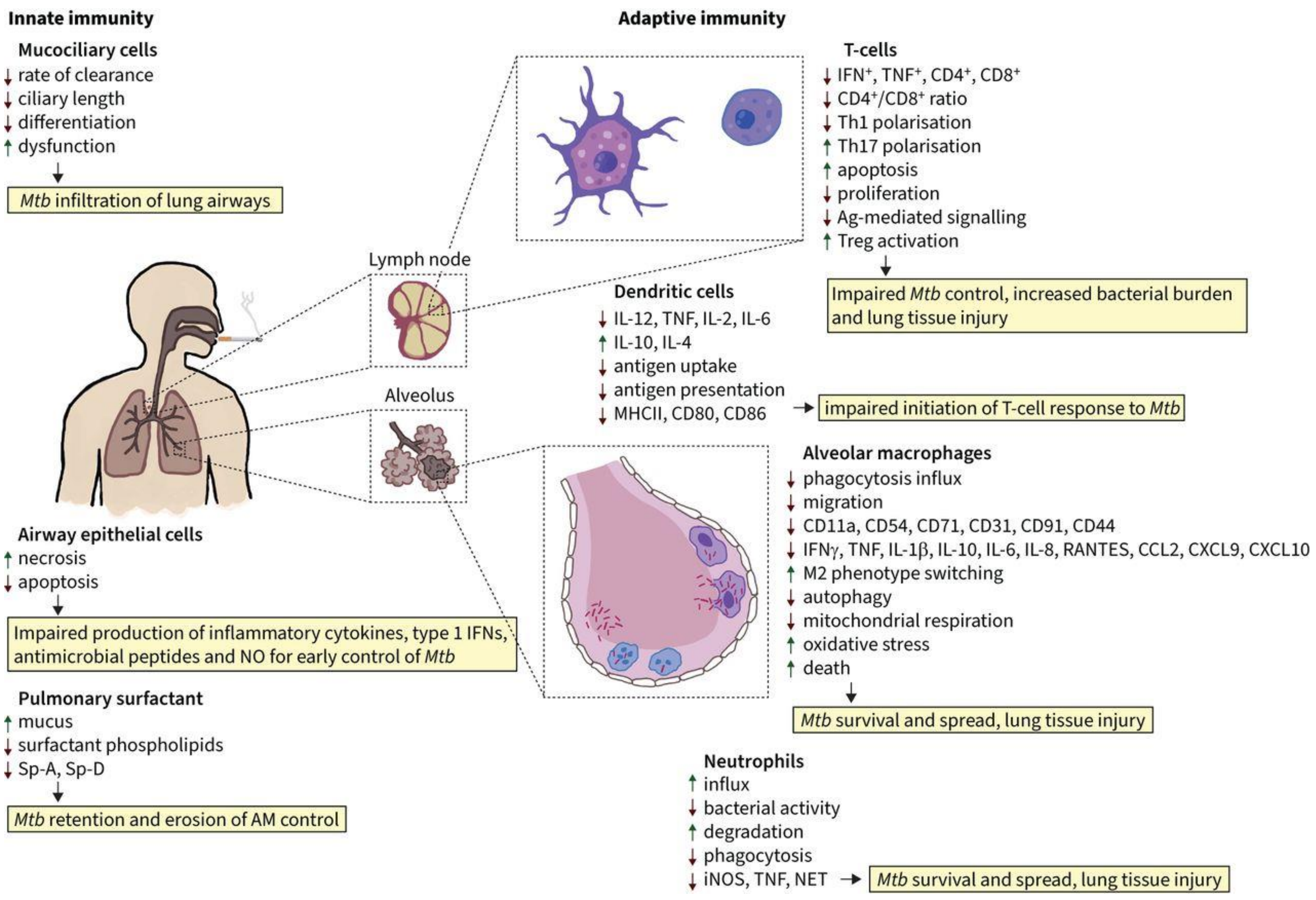
Physical Examination: Identify signs of malnutrition

- Muscle wasting
- Edema

Impact of Smoking on TB Outcomes

The impact of cigarette smoking on tuberculosis

- Increased risk of TB infection and active TB disease
- Delay in TB diagnosis
- Increased duration of culture positivity, higher bacillary loads, prolonged smear and culture positivity
- Increased progression of primary tuberculosis
- Increased severity of TB, more extensive pulmonary disease, more lung cavitation, greater need for hospitalization, and more prolonged hospitalization.
- TB treatment failure, recurrence of disease after successful treatment with anti-TB drugs, Treatment interruption, a negative effect on treatment completion, treatment default, treatment loss to follow-up
- Higher mortality
- Increased costs for the patient and the healthcare system.

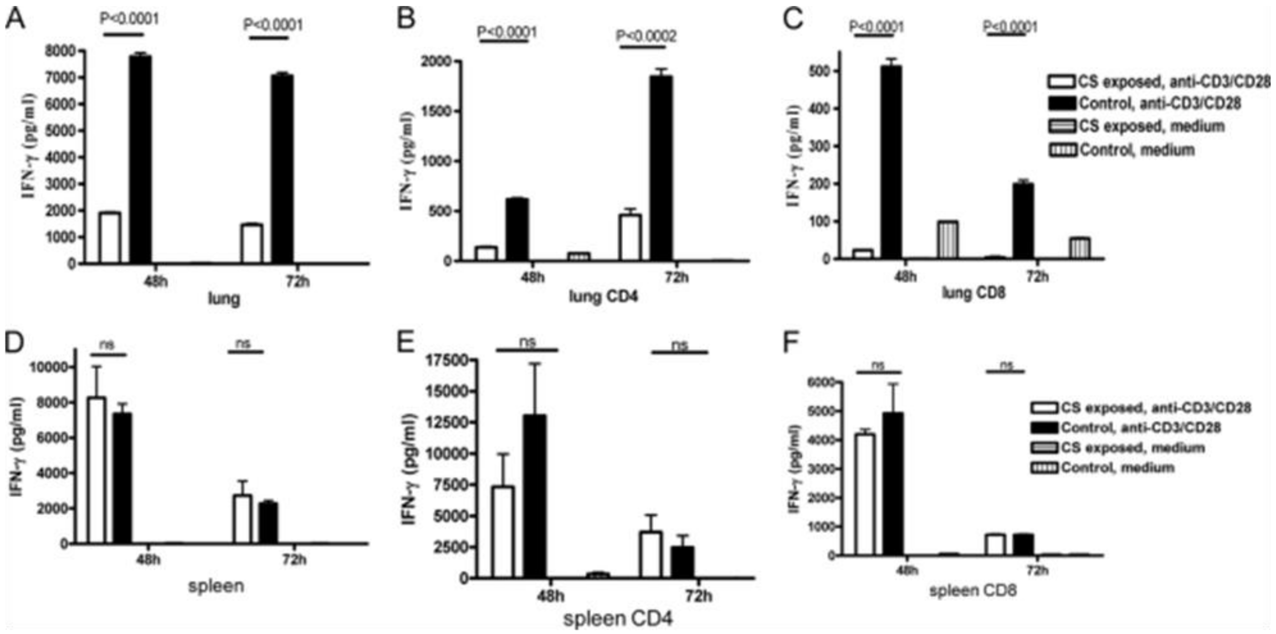


The effects of cigarette smoke exposure on innate and adaptive immunity that may influence the control of Mycobacterium tuberculosis infection.

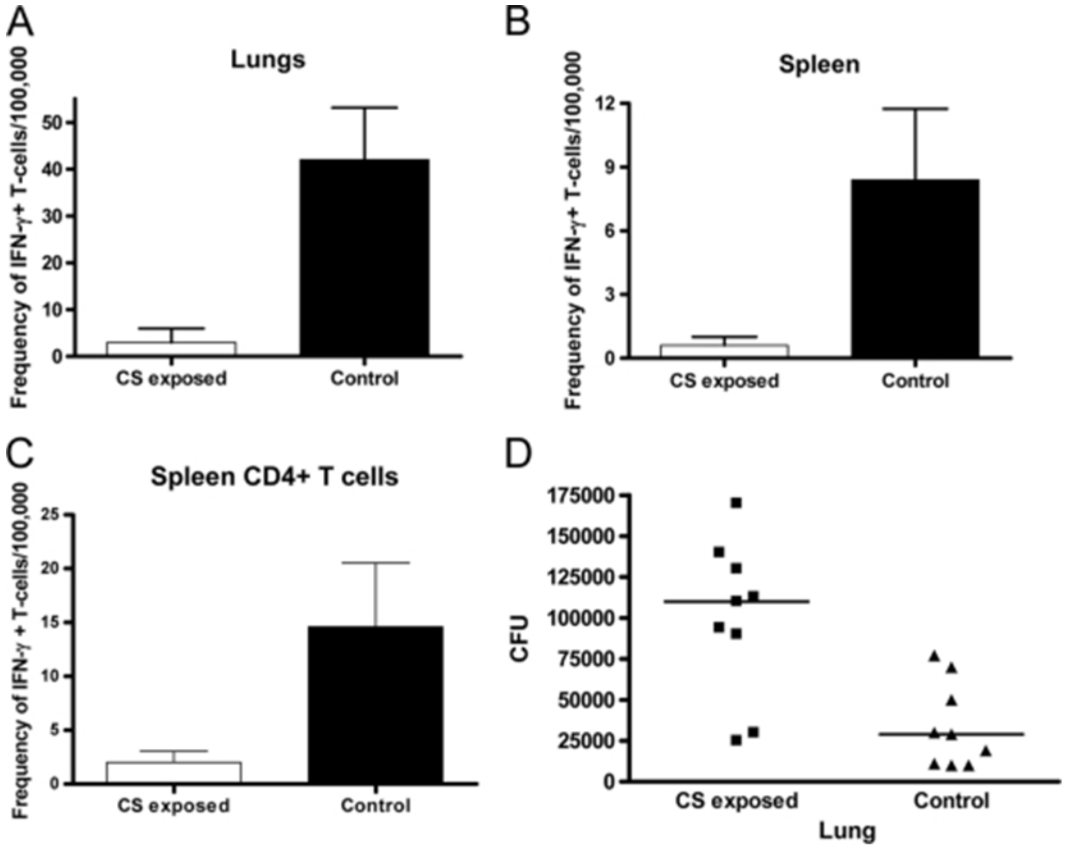
Mechanisms by which cigarette smoke and its nicotine constituent suppress alveolar macrophage anti-mycobacterial activity.

Impaired Alveolar Macrophage Function	Type of Study	Mechanism
Antimicrobial activity	Alveolar macrophages isolated from the lungs of smokers exposed to cigarette smoke extract in vitro	Attenuation of autophagolysosome formation due to failure of recruitment autophagy adaptors
Antimicrobial activity	Isolated lung macrophages from smokers exposed to *M. tuberculosis* in vitro	Failure of glycolytic reprogramming associated with decreased expression of genes encoding GLUT-1 as well as glycolysis-mediated activation of the NLRP3 inflammasome-IL-1β-maturation and release pathway
Phagocytosis	In vitro exposure of a macrophage cell line to cigarette smoke extract	Decreased expression of the PAMPs, TLR2 and MARCO
Phagocytosis	In vitro study using blood monocytes isolated from patients with long-term cigarette smoking-related active tuberculosis	Upregulated expression of the regulatory miRNA, mi-R-196b-5p, resulting in activation of suppressive STAT3
Antimicrobial activity	In vitro study involving smoke-exposed murine macrophages and macrophage cell lines depleted of nAChR or exposed to pure nicotine	Nicotine-mediated defective autophagosome formation due to inhibition of NFκB and activation of Tregs

Feldman C, et al. Cigarette Smoking as a Risk Factor for Tuberculosis in Adults: Epidemiology and Aspects of Disease Pathogenesis. Pathogens. 2024; 13(2):151.



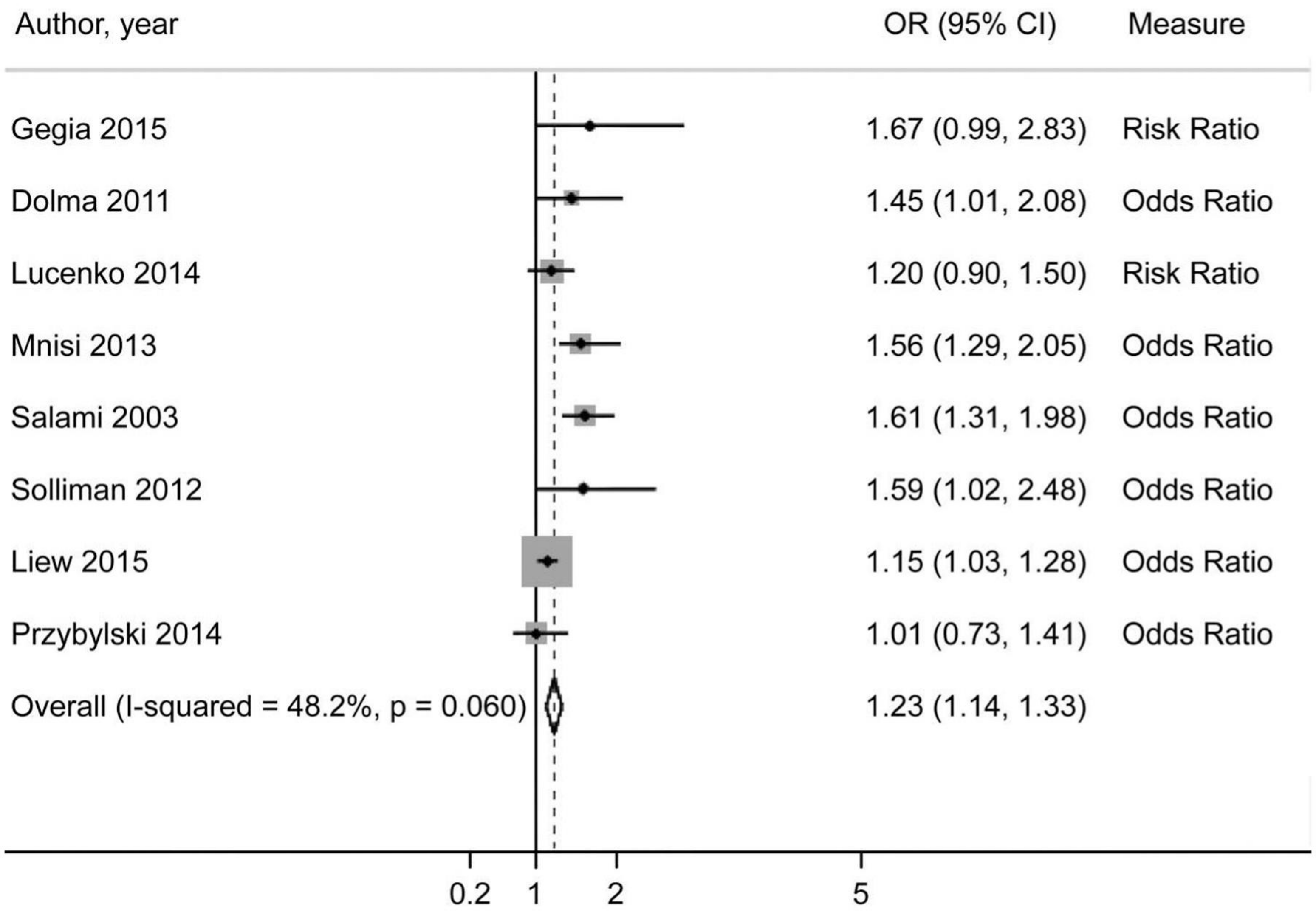
Effects of cigarette smoke exposure on IFN-γ production



Effects of cigarette smoke exposure on MTB bacterial burden and T cell response

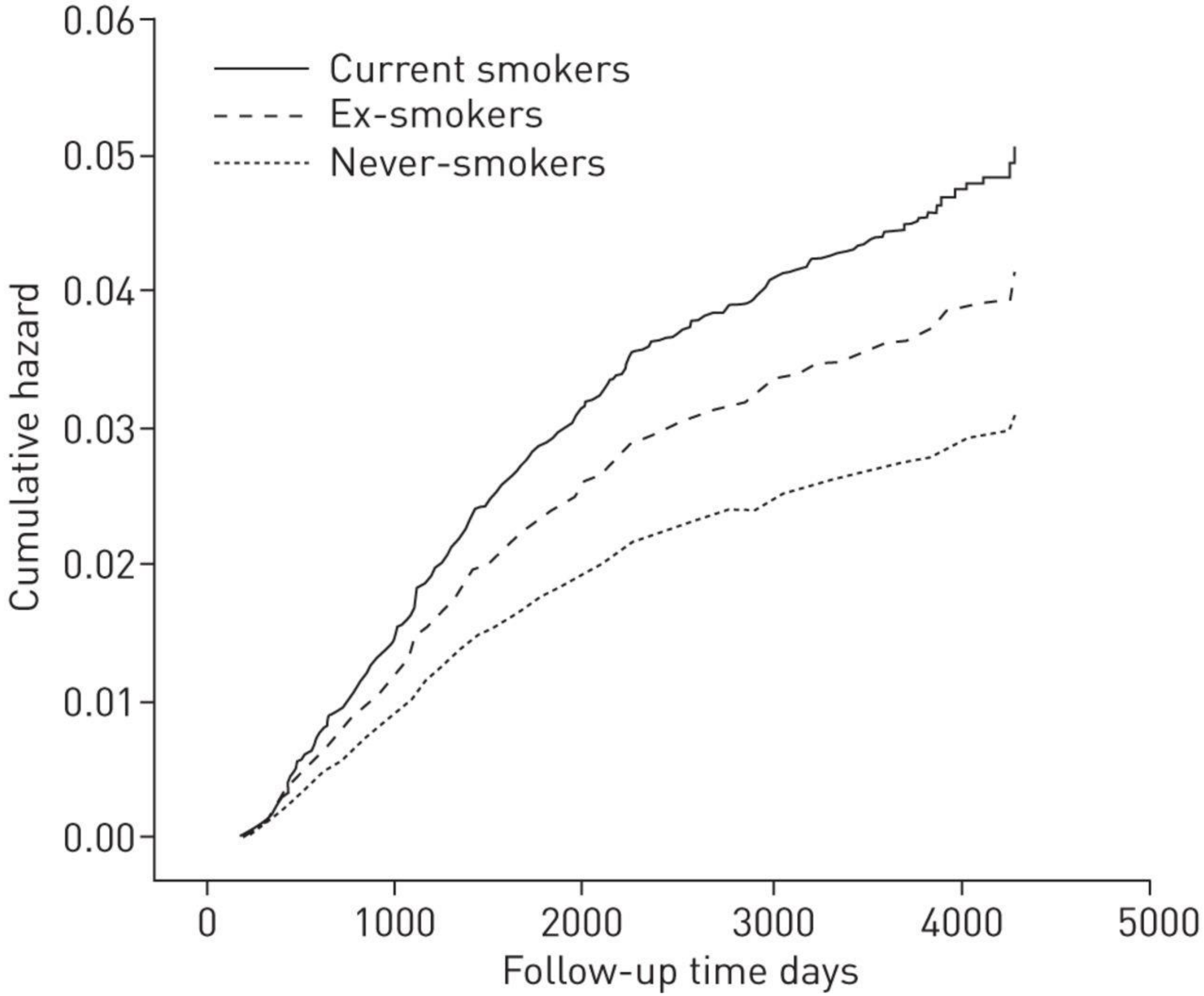
Feng Y, et al. Exposure to cigarette smoke inhibits the pulmonary T-cell response to influenza virus and Mycobacterium tuberculosis. Infect Immun. 2011;79(1):229-237. doi:10.1128/IAI.00709-10

Pooled effect estimate of current smokers and unfavorable treatment outcomes



Wang EY, et al. The impact of smoking on tuberculosis treatment outcomes: a meta-analysis. Int J Tuberc Lung Dis. 2020;24(2):170-175. doi:10.5588/ijtld.19.0002

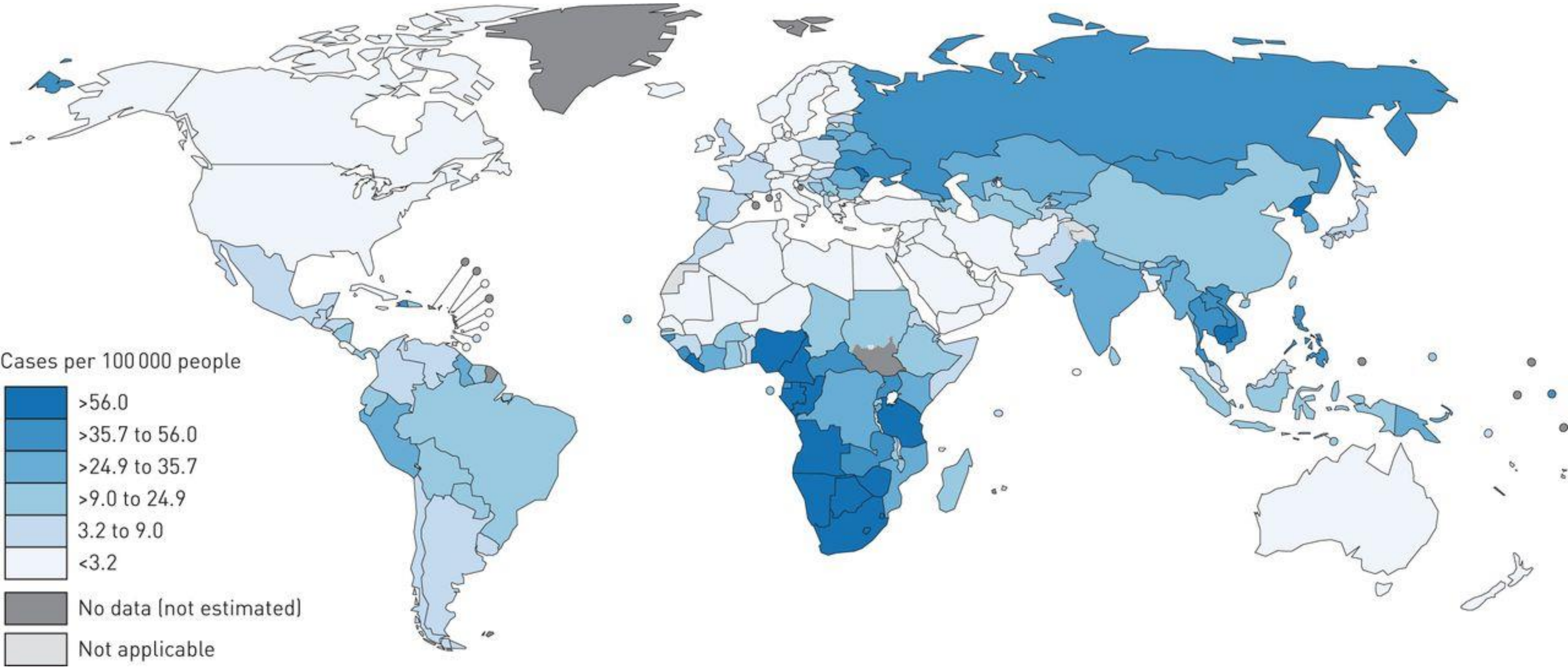
Cumulative hazards for tuberculosis relapse by smoking status



Leung CC, et al. European Respiratory Journal 2015 45(3): 738-745; DOI: https://doi.org/10.1183/09031936.00114214

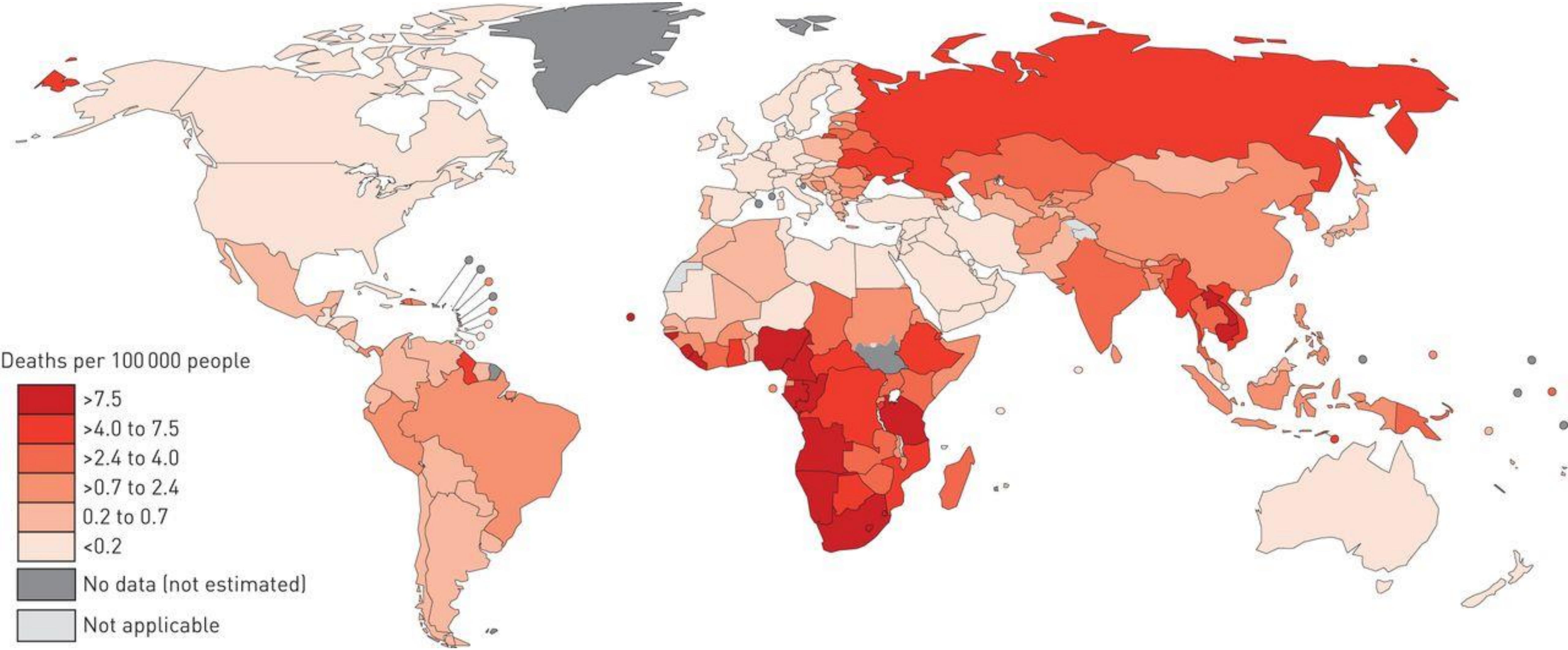
Impact of Alcohol Use on TB Outcomes

Estimated tuberculosis incidence rates per 100 000 people attributable to alcohol consumption by countries in 2014

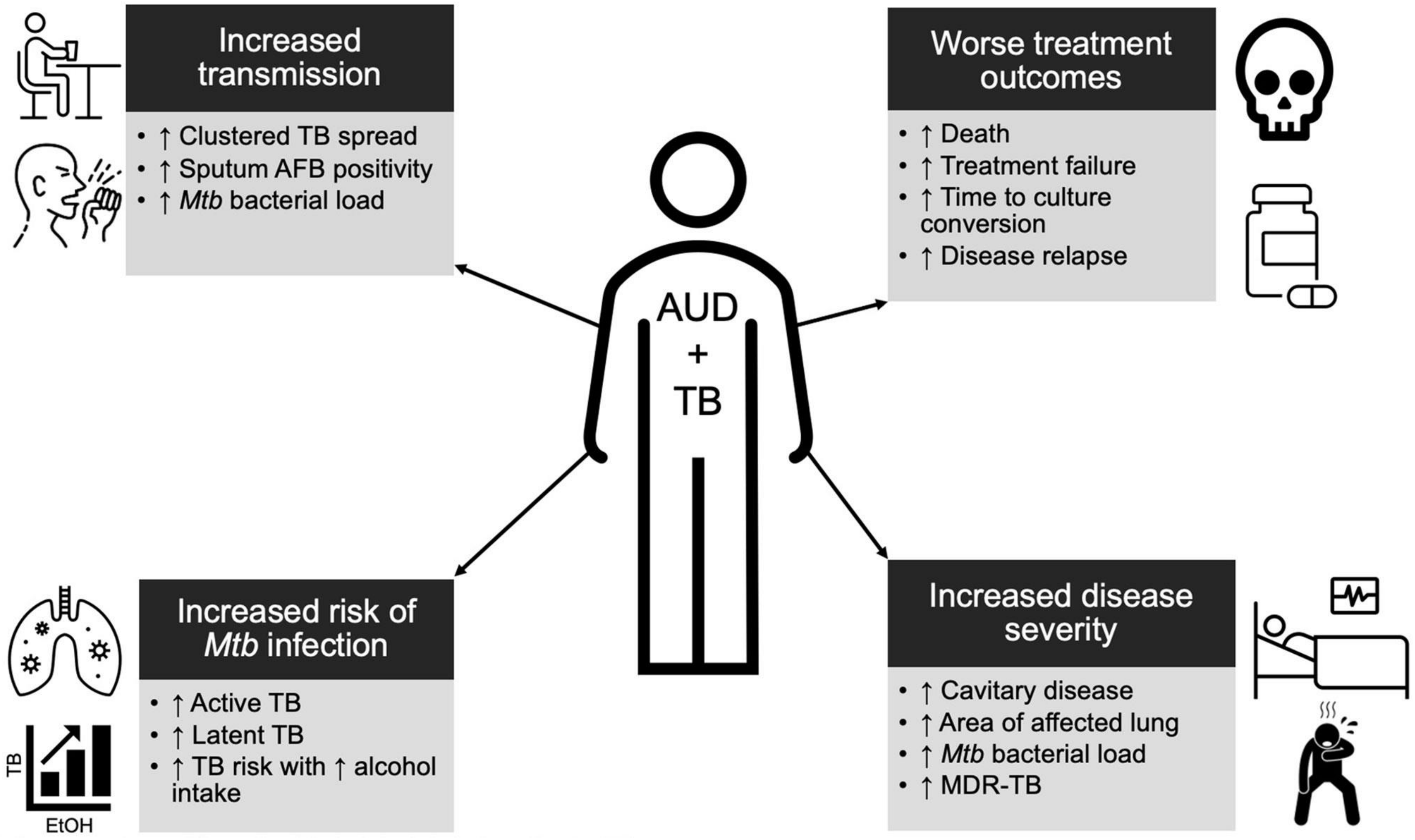


Imtiaz S, et al. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. European Respiratory Journal 2017 50(1): 1700216; DOI: https://doi.org/10.1183/13993003.00216-2017

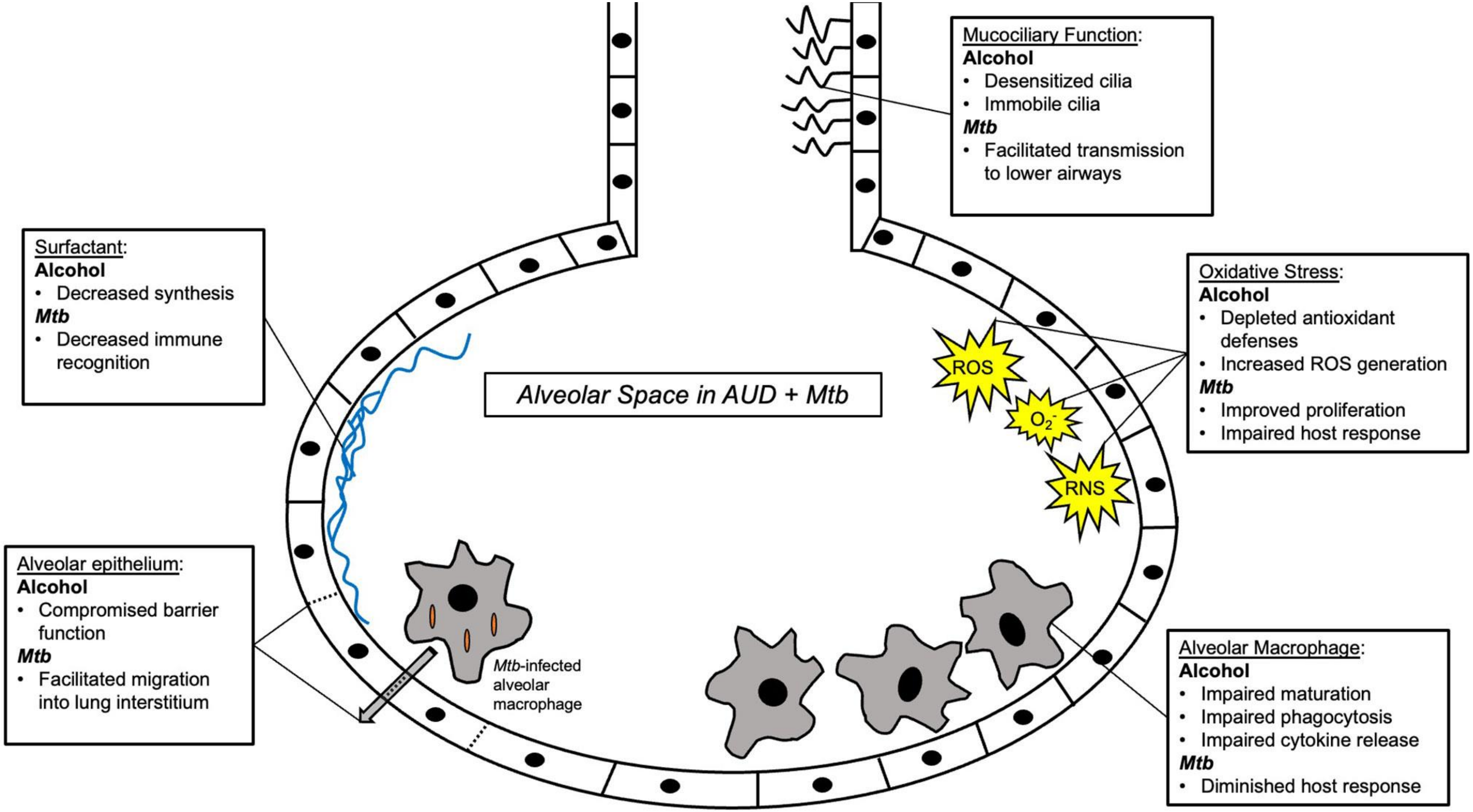
Estimated tuberculosis mortality rates per 100 000 people attributable to alcohol consumption by countries in 2014



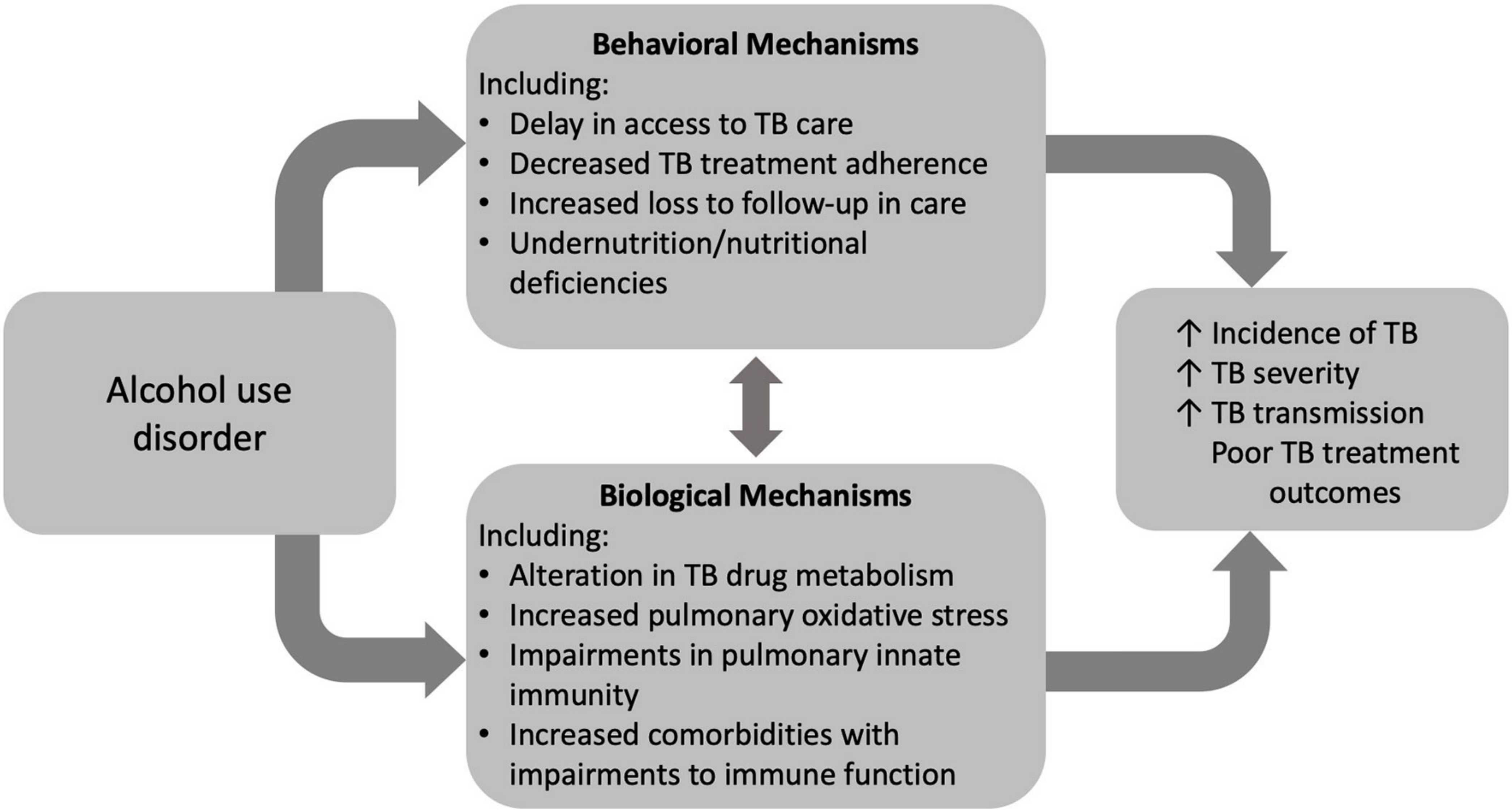
Imtiaz S, et al. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. European Respiratory Journal 2017 50(1): 1700216; DOI: https://doi.org/10.1183/13993003.00216-2017



Wigger GW, et al. The Impact of Alcohol Use Disorder on Tuberculosis: A Review of the Epidemiology and Potential Immunologic Mechanisms. Front Immunol. 2022;13:864817. doi:10.3389/fimmu.2022.864817



Wigger GW, et al. The Impact of Alcohol Use Disorder on Tuberculosis: A Review of the Epidemiology and Potential Immunologic Mechanisms. Front Immunol. 2022;13:864817. doi:10.3389/fimmu.2022.864817



Wigger GW, et al. The Impact of Alcohol Use Disorder on Tuberculosis: A Review of the Epidemiology and Potential Immunologic Mechanisms. Front Immunol. 2022;13:864817. doi:10.3389/fimmu.2022.864817

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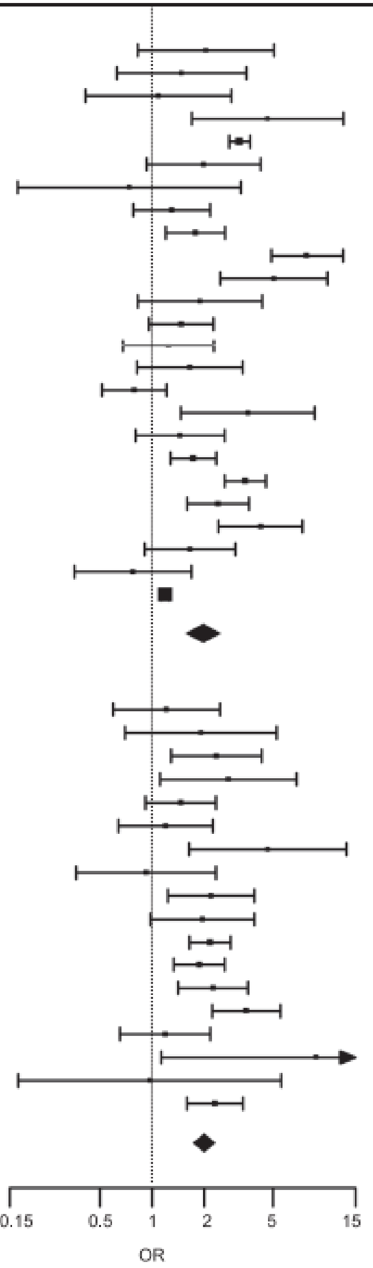
Author, year	Alcohol group Event	Alcohol group Total	Non-alcohol group Event	Non-alcohol group Total	OR [95% CI]
DS-TB					
Ambrosetti, 1999A	7	24	107	642	2.06 [0.83, 5.09]
Ambrosetti, 1999B	7	33	108	705	1.49 [0.63, 3.51]
Ambrosetti, 1999C	5	38	91	750	1.10 [0.42, 2.88]
Bhagat, 2010	17	42	7	55	4.66 [1.71, 12.73]
Bumburidi, 2006*	-	762	-	18203	3.20 [2.80, 3.70]
Centis, 2000	10	35	139	833	2.00 [0.94, 4.25]
Centis, 2002	2	19	104	764	0.75 [0.17, 3.28]
Chiang, 2012	36	88	74	214	1.31 [0.79, 2.18]
De Albuquerque, 2007*	-	-	-	-	1.79 [1.21, 2.66]
Diel, 2003	61	127	41	391	7.89 [4.91, 12.69]
Ismail, 2013	29	54	21	113	5.08 [2.49, 10.39]
Jain, 2016	10	52	21	189	1.90 [0.83, 4.35]
Kim, 2007	116	182	90	166	1.48 [0.97, 2.28]
Kittikraisak, 2009	45	386	16	168	1.25 [0.69, 2.29]
Lillebaek, 1999	14	48	45	227	1.67 [0.82, 3.36]
Lin, 2015	29	122	619	2200	0.80 [0.52, 1.22]
Magee, 2015	16	48	10	82	3.60 [1.47, 8.79]
Pimchan, 2012	21	55	101	340	1.46 [0.81, 2.64]
Przybylski, 2014*	-	534	-	1491	1.74 [1.29, 2.36]
Ramachandran, 2017	171	742	93	1170	3.47 [2.64, 4.55]
Santha, 2002	55	146	87	435	2.42 [1.61, 3.64]
Siemion-Szczesniak, 2012A	37	73	45	232	4.27 [2.43, 7.50]
Siemion-Szczesniak, 2012B	24	61	56	200	1.67 [0.92, 3.04]
Tabarsi, 2012	18	53	23	58	0.78 [0.36, 1.70]
Volkmann, 2014	2569	27145	12488	155897	1.20 [1.15, 1.26]
Random-effects model (P < 0.001; I^2 = 93%)					1.99 [1.57, 2.51]
MDR-TB					
Aibana, 2017	56	67	227	281	1.21 [0.59, 2.47]
Cox, 2007	10	20	23	67	1.91 [0.70, 5.26]
De Albuquerque, 2001	42	151	19	135	2.35 [1.29, 4.29]
Gadallah, 2016	11	21	59	207	2.76 [1.11, 6.84]
Gegia, 2012	51	94	128	286	1.46 [0.92, 2.34]
Gegia, 2015	20	104	29	175	1.20 [0.64, 2.25]
Jain, 2014	22	27	50	103	4.66 [1.64, 13.26]
Jeong, 2015	6	33	59	304	0.92 [0.36, 2.34]
Kendall, 2013	74	131	29	78	2.19 [1.23, 3.90]
Kuksa, 2014	36	64	27	68	1.95 [0.98, 3.90]
Kurbatova, 2012	207	489	121	478	2.17 [1.65, 2.85]
Leimane, 2010	122	479	62	402	1.87 [1.33, 2.63]
Magee, 2014	57	86	451	967	2.25 [1.41, 3.58]
Miller, 2012	126	253	34	154	3.50 [2.22, 5.51]
Oliveira, 2013	22	61	63	196	1.19 [0.65, 2.18]
Prajapati, 2017	19	20	60	88	8.87 [1.13, 69.59]
Scuffell, 2017	6	8	31	41	0.97 [0.17, 5.58]
Velasquez, 2016	66	122	481	1424	2.31 [1.59, 3.35]
Random-effects model (P < 0.001; I^2 = 32%)					2.00 [1.73, 2.32]

* Counts unavailable



Meta-analysis results for poor treatment outcomes

Treatment outcome	Studies *n*	Summary effect estimate	95% CI
Poor outcome A*	25	1.99	1.57–2.51
Poor outcome B†	12	2.55	1.77–3.66
Death	22	1.58	1.24–2.00
Treatment failure	13	3.12	1.83–5.33
LTFU	29	2.25	1.74–2.91

B) Meta-analysis results for poor treatment outcomes, studies on mu

Treatment outcome	Studies *n*	Summary effect estimate	95% CI
Poor outcome A*	18	2.00	1.73–2.32
Poor outcome B†	10	1.47	1.06–2.05
Death	6	1.38	1.04–1.83
Treatment failure	4	1.54	1.09–2.17
LTFU	15	1.87	1.56–2.24

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Tuberculosis and Comorbidities

- Several medical conditions are risk factors for TB and for poor TB treatment results.
- Identifying these conditions in people diagnosed with TB and providing the appropriate interventions will improve the outcomes of both these conditions and TB
- Many of these conditions are highly prevalent in the general population.
- Reducing the prevalence of these conditions can help prevent TB.

Thank you