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Post Tuberculosis: from evidence to action

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October 2024

UBC a place of mind

BC Centre for Disease Control
An agency of the Provincial Health Services Authority

McGill

Acknowledgements

- Curry International TB Centre (Emily Mabry, Lisa Chen)
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- Patient partners and advocates
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JJ: conflict of interest statement

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- Salary grant from Health Research BC

Learning objectives

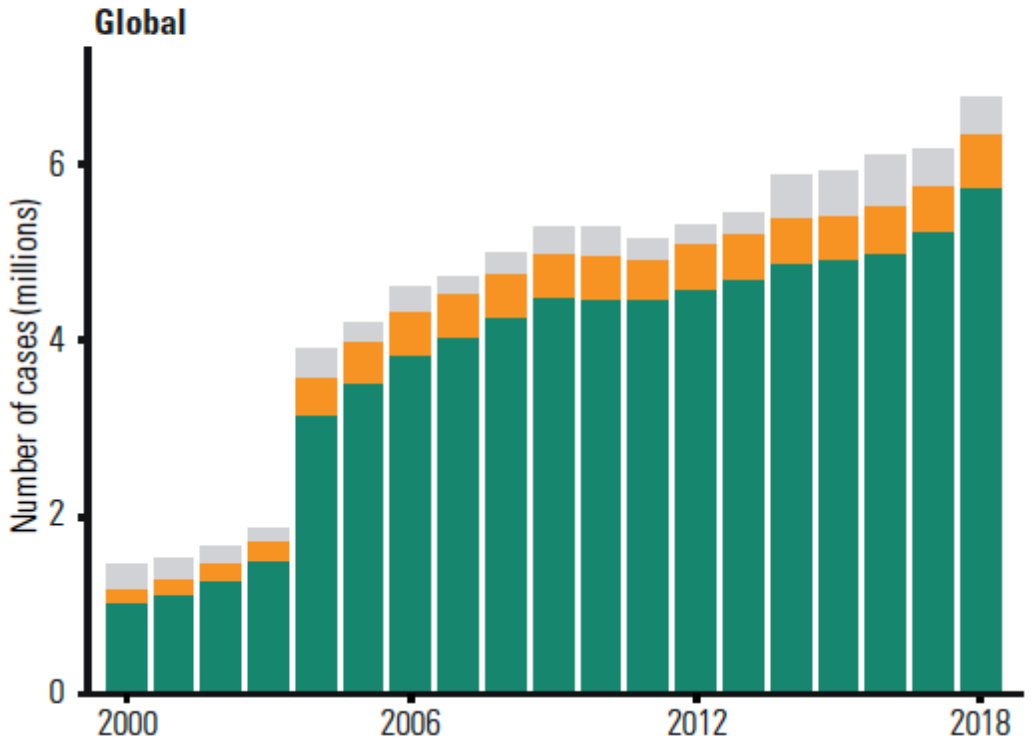
1. Describe the morbidity and mortality experienced by people with TB disease after treatment completion

2. Describe evidence to support interventions to mitigate post-TB morbidity and mortality

Global TB: reported outcomes

- Cured/treatment complete
- Death
- Failure
- Lost to follow-up
- Relapse

Treatment outcomes for new and relapse TB cases[a] (absolute numbers), globally and for WHO regions, 2000–2018



WHO Global TB report 2020

But what happens to people after they complete TB therapy?

Quantifying the global number of tuberculosis survivors: a modelling study

Peter J Dodd, Courtney M Yuen, Shamanthi M Jayasooriya, Marieke M van der Zalm, James A Seddon

Lancet Infect Dis 2021; 21: 984–92

Published Online February 25, 2021 https://doi.org/10.1016/S1473-3099(20)30919-1

Summary

Background People who survive tuberculosis face clinical and societal consequences after recovery, including increased risks of recurrent tuberculosis, premature death, reduced lung function, and ongoing stigma. To describe the size of this issue, we aimed to estimate the number of individuals who developed first-episode tuberculosis between 1980 and 2019, the number who survived to 2020, and the number who have been treated within the past 5 years or 2 years.

Over 155 million TB survivors living in 2020

Dodd et al. LancetID 2021

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Over 155 million TB survivors living in 2020

That's 1 in 50 people globally

Dodd et al. LancetID 2021

Post-TB mortality

TB survivors: three times the rate of death compared with age/sex matched groups

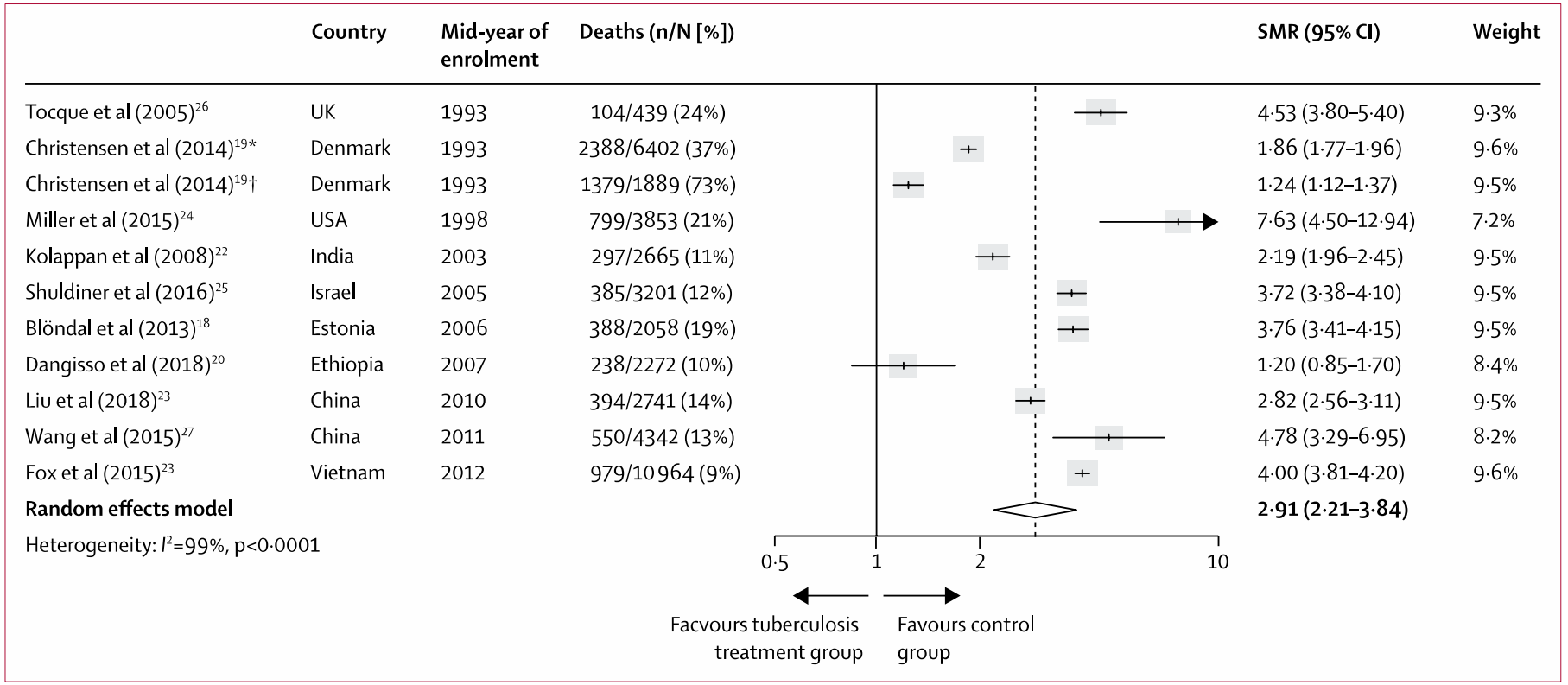


Figure 2: **SMR for all-cause mortality after tubeculosis treatment**
SMR=standardised mortality ratio. *Estimate for pulmonary tuberculosis. †Estimate for extrapulmonary tuberculosis.

Romanowski et al. Lancet ID 2019

Findings are consistent across different groups

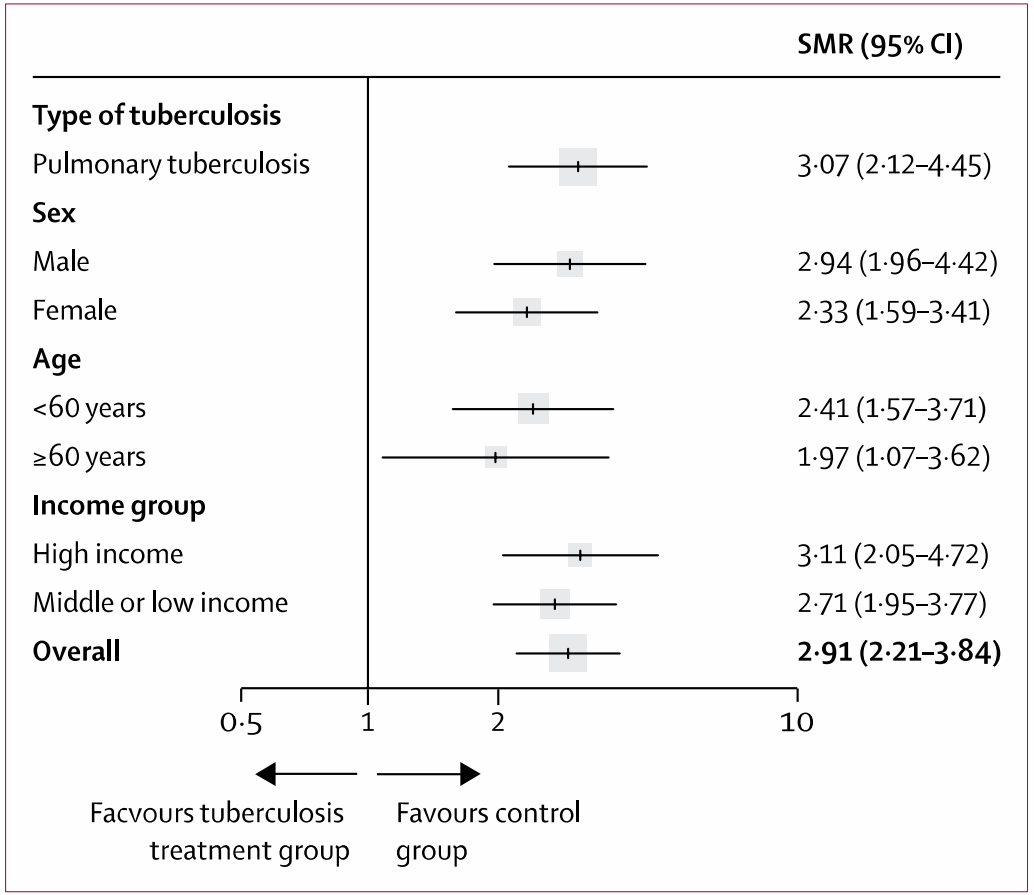
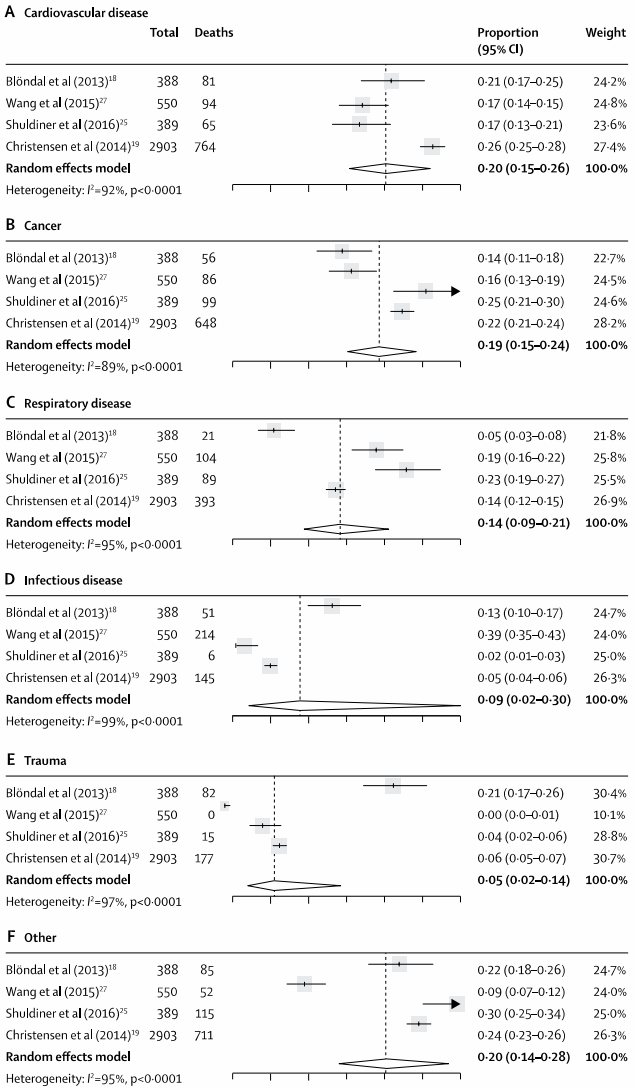


Figure 3: **SMR estimates for subgroup analysis**
SMR=standardised mortality ratio.

Romanowski et al. Lancet ID 2019

What do people die from after TB therapy?



Cardiovascular disease: 20%

Cancer: 19%

Respiratory disease: 14%

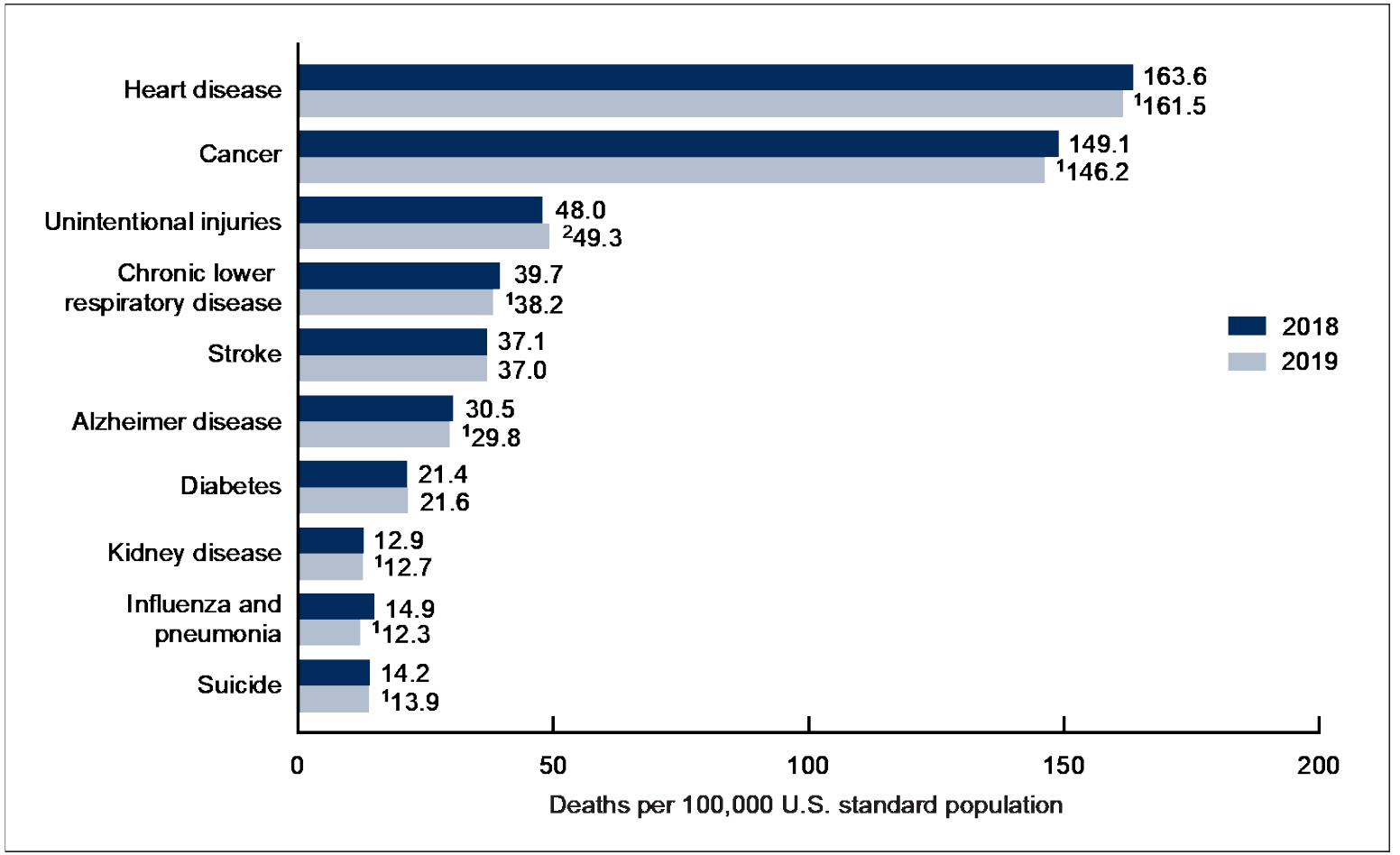
Infectious disease: 9%

Trauma: 5%

Other: 20%

Romanowski et al. Lancet ID 2019

Causes of death are similar to the general population



NCHS Data Brief No. 395, Dec. 2020

Data from British Columbia: the same

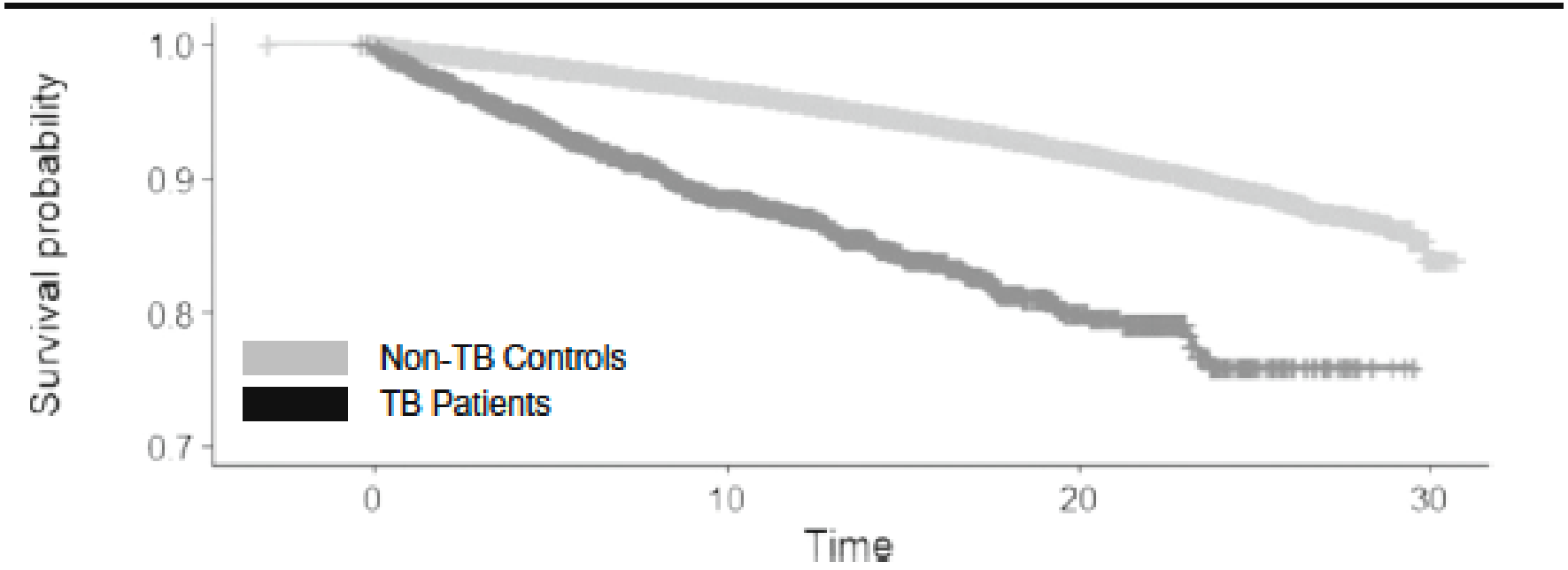
Primary cause of mortality	Crude HR (95% CI)	Age/sex-adjusted HR (95% CI)	Covariate-adjusted HR (95% CI)[a]
All non-TB diseases	4.01 (3.57–4.51)	1.95 (1.74–2.20)	1.69 (1.50–1.91)
Respiratory diseases	8.51 (6.31–11.50)	3.28 (2.43–4.43)	2.96 (2.18–4.00)
Cardiovascular diseases	4.26 (3.44–5.27)	1.78 (1.44–2.20)	1.63 (1.32–2.02)
Cancers	3.30 (2.65–4.10)	1.76 (1.41–2.19)	1.40 (1.13–1.75)
Injuries and poisonings	3.43 (2.33–5.06)	2.28 (1.55–3.36)	1.85 (1.25–2.72)

CI, confidence interval; *HR*, hazard ratio; *TB*, tuberculosis

[a] Covariate-adjusted analyses included the following baseline variables: age, sex, neighbourhood income quintile, educational qualification, index year, TB incidence in country of birth, and weighted Charlson comorbidity score calculated in the year prior to TB diagnosis or randomly selected reference date for non-TB controls

Basham et al. Can J Pub Health 2021

We have time to make a difference: mortality rate is high for years post-TB therapy



Number at-risk

Non-TB Controls	1,028,434	244,118	36,570	104
TB Patients	2,432	1,079	238	0
Follow-up year	0	10	20	30

Basham et al. Can J Pub Health 2021

Post-TB mortality

- People that experience TB have higher rates death compared with the general population
- People that experience TB appear to die of similar diseases as the general population, but at a much higher rate.
- **We have time to intervene**

Post tuberculosis lung disease

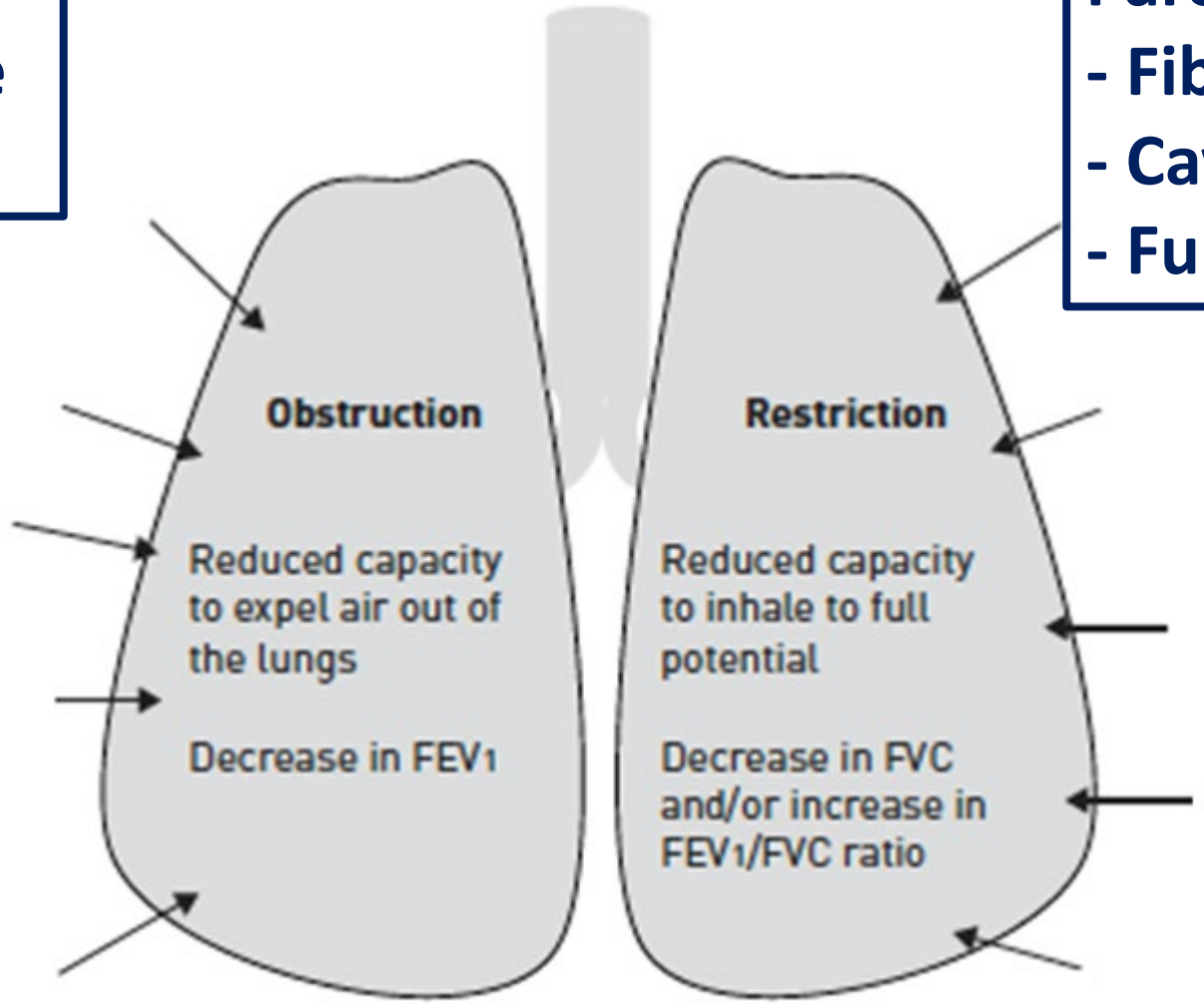
What is *post tuberculosis lung disease*?

Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous tuberculosis.

Allwood et al. IJTLD 202 24(8):820-828.

Airway disease
- **Obstructive disease**
- **Bronchiectasis**

Parenchymal disease
- **Fibrosis**
- **Cavitation**
- **Fungal disease**



Pulmonary vascular disease

Pleural disease

Shruthi Ravimohan *et al.* Eur Respir Rev 2018;27

High incidence of abnormal PFTs post-TB

Meta-analysis	Number of study populations	Proportion of participants (n/N)	Pooled estimate (95% CI)
All TB patients			
Abnormal	42	4082/9864	59.1% (48.8%–68.7%)
Obstruction	41	1882/9803	17.8% (13.4%–23.1%)
Restriction	35	1339/5822	21.3% (15.3%–28.9%)
Mixed pattern	30	861/5095	12.7% (8.2%–19.2%)
Controls			
Abnormal	4	794/21,804	5.4% (2.6%–10.8%)
Obstruction	4	794/21,804	5.4% (2.6%–10.8%)
Restriction/Mixed	0	–	–

59.1% of TB survivors had abnormal spirometry

Population	Outcome	Number of study populations	Proportion of participants (n/N)	Pooled estimate (95% CI)
All TB patients	MRC 1–2[b]	13	2439/3179	72.6% (64.4%–79.6%)
	MRC 3–5[b]	13	706/3179	24.7% (18.8%–31.7%)

25% MRC 3-5 dyspnea

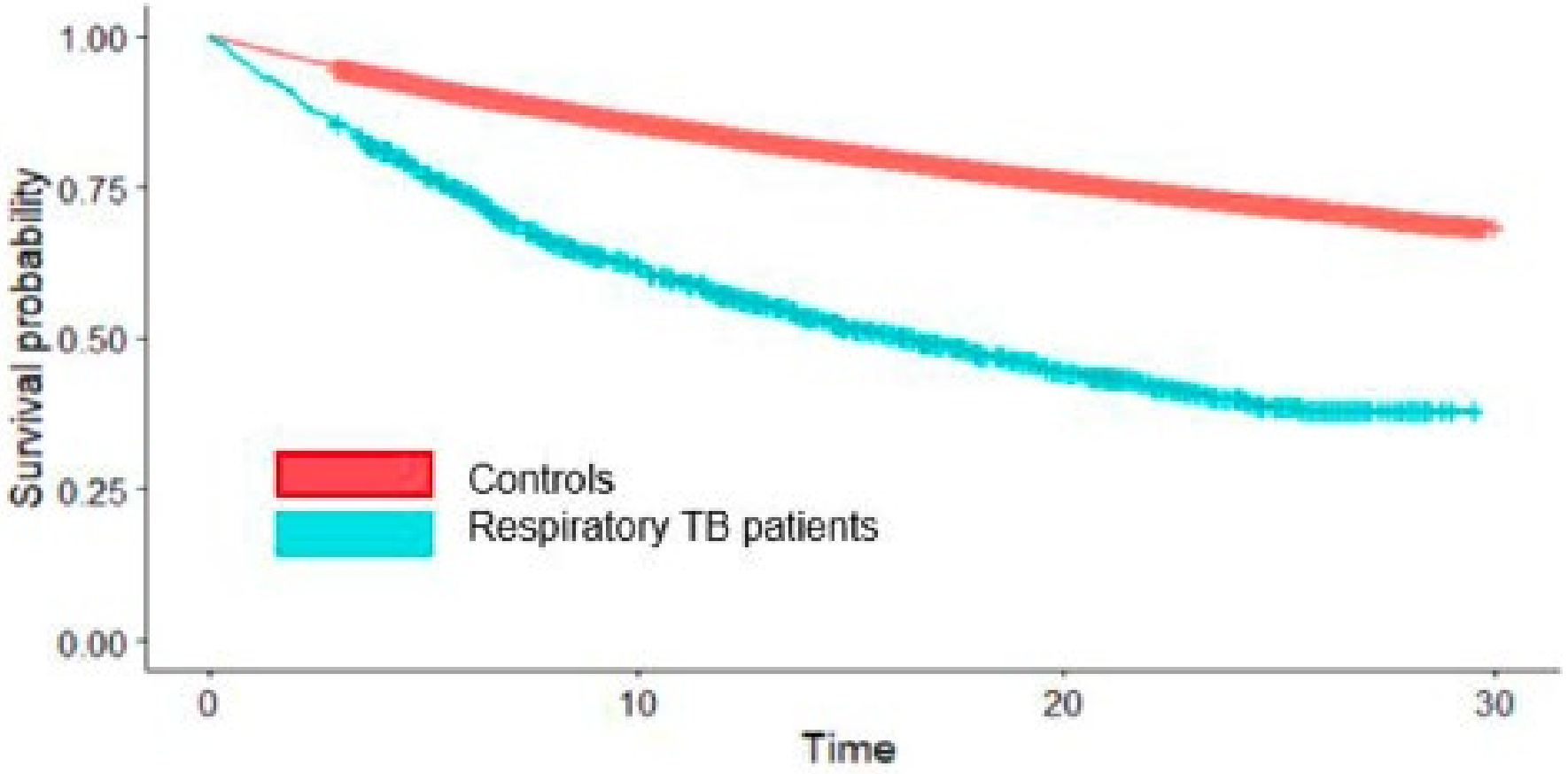
Taylor et al. EClinicalMedicine 2023; 59: 101979

High incidence of lung disease post-TB in never smokers & HIV negative

	Outcome	Abnormal	Obstruction	Restriction	Mixed Pattern
Never-smokers	Proportion of participants (n/N)	1507 / 2243	785 / 2243	335 / 1986	387 / 2243
	Pooled estimate (95% CI)	69.6% (60 - 77.8)	**30.5% (16.3 - 49.7)**	18.4% (10.7 - 29.7)	16.7% (12.6 - 21.7)
HIV negative	**Outcome**	**Abnormal**	**Obstruction**	**Restriction**	**Mixed Pattern**
	Proportion of participants (n/N)	739/985	396/985	123/728	220/826
	Pooled estimate (95% CI)	82.6% (65 - 93)	**30.1% (17.1 - 47.3)**	17.3% (14.0 – 51.4)	30.3% (1.7 – 91.7)

Taylor et al. EClinicalMedicine 2023; 59: 101979

This is true in high income regions: 43% with airway disease post-TB in BC



Basham et al. EclinicalMedicine 2021

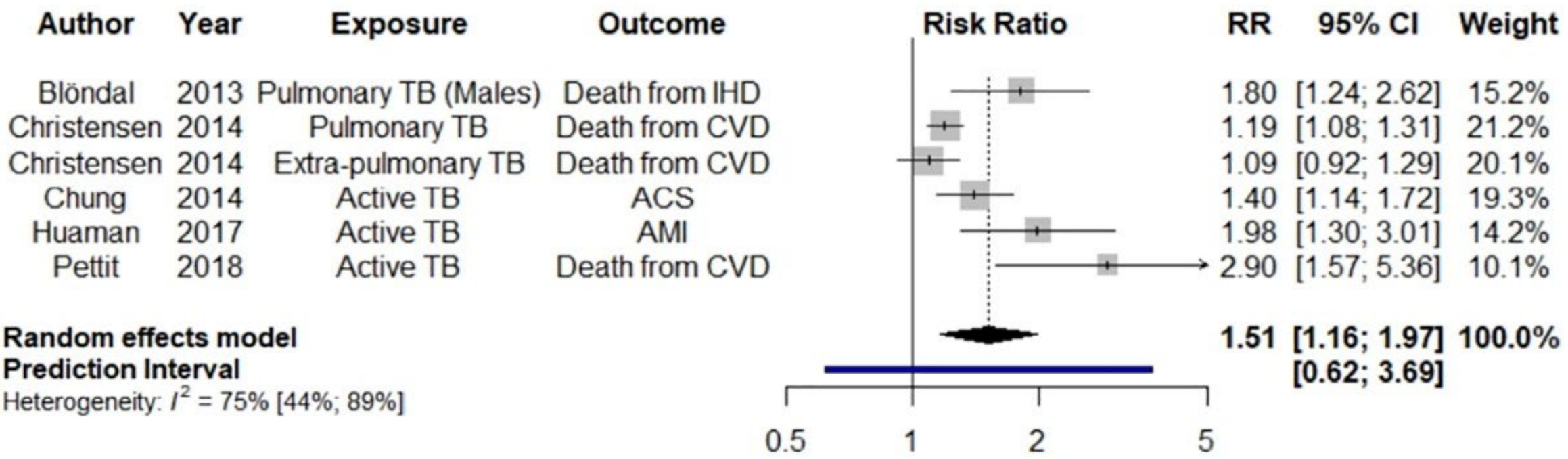
Is post-TB lung disease really a thing?

- High proportion of people with obstructive and/or restrictive disease after TB therapy
- Modelling suggests that post-TB respiratory disease may account for >50% of DALYs from TB each year
- From behaviours alone (i.e. smoking?)
- Due to low SES alone?

Menzies NA et al. Lancet Glob Health 2021

Cardiovascular disease

Increased risk of MACE in people with active TB



MACE: Acute myocardial infarction, unstable angina, cardiovascular mortality, nonfatal stroke

Basham et al. PLoS One 2020

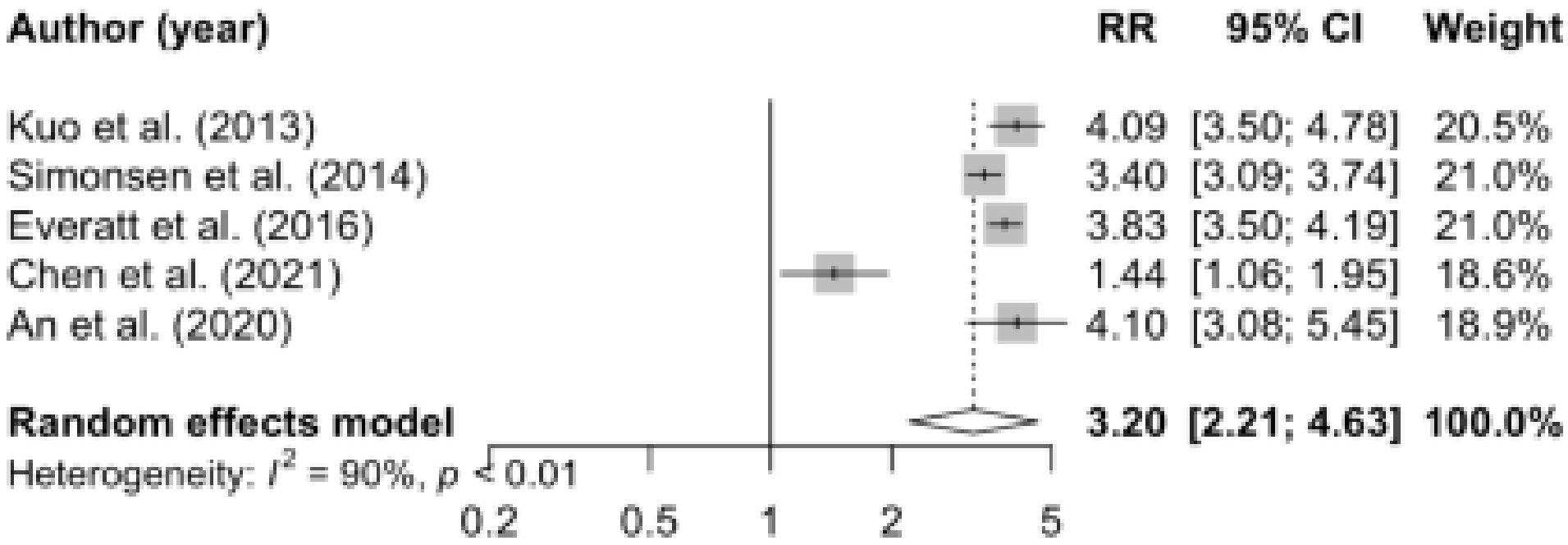
Cardiovascular disease (CVD)

- Is this from overrepresentation of CVD risk factors in people with TB: smoking, DM, socioeconomic status
- Pro-inflammatory cytokines promoting atherosclerosis?
- Does latent TB specifically play a role in coronary atherosclerosis?

Hossain *et al.* Epid and Infection (2023), 151, e68:1-8.
Huaman *et al.* Clin Inf Dis (2021); e3384-90 2021

Post-TB Cancer

Increase cancer risk in people post-TB treatment, particularly lung Ca



Luczynski et al. PLoS One 2022; 17(12):e0278661

Post-TB Cancer

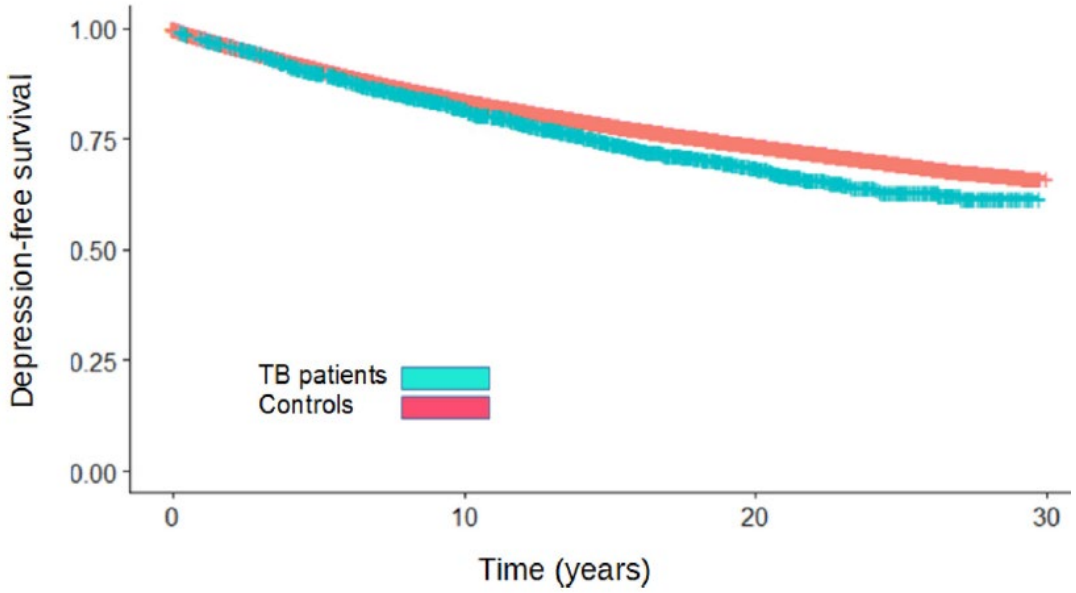
- Smoking and shared risk factors likely explains some risk
- Bidirectional association between TB and Lung Cancer?
- Occult cancer may also be a TB risk factor
- Chronic inflammation may also play a role

Luczynski et al. PLoS One 2022; 17(12):e0278661

Post-TB mental health

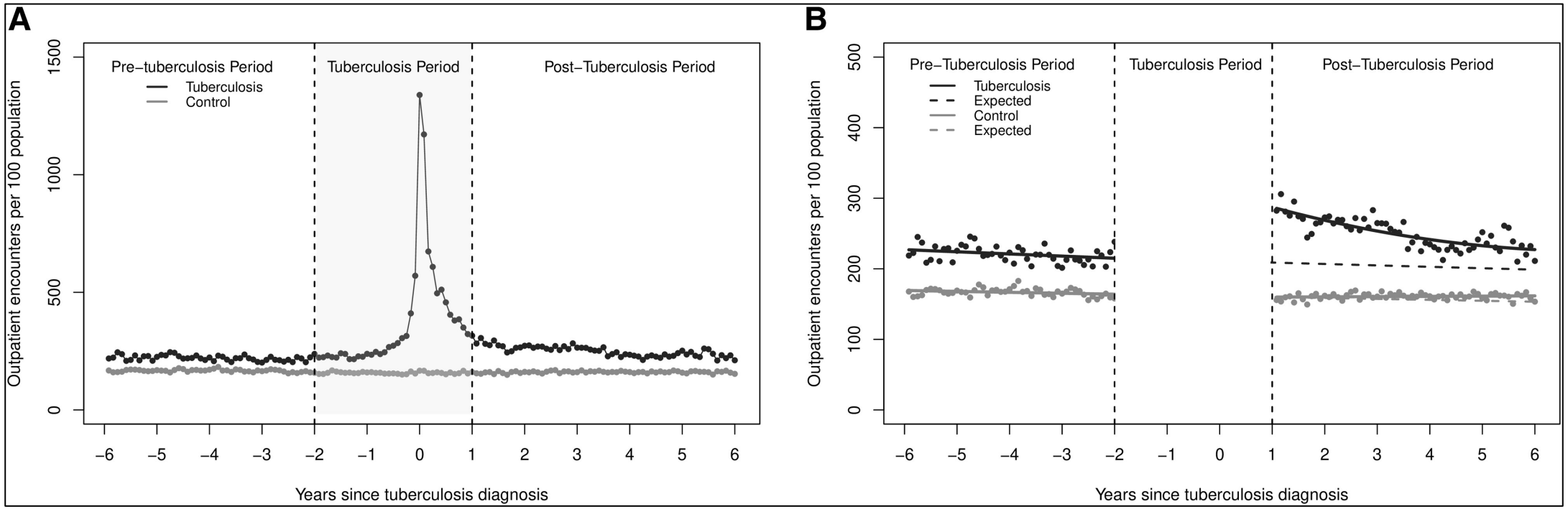
Post-TB mental health

- ~45% of people experience depression during TB therapy
- ~25% increase in the risk of depression in people in BC
- **Role of hospitalization? Isolation?**



Yen YF et al. J Clin Psych 2015
Duko et al. Ann Geri Psych 2020
Basham et al. Annals of Epidemiology 63(2017):7-14

Overall, compared with matched controls, people have higher healthcare use post-TB



Romanowski et al. Clin Inf Dis 2023

Summary of morbidity

- Higher rates of obstructive disease/COPD
- High rates of restrictive disease
- Higher rates of CVD
- Higher rates of cancer
- Higher rates of mood disorders and trauma
- Higher rates of healthcare utilization across the board

Socioeconomic Impacts

Not all people recover financially

Cohort study from Malawi:

- Paid work decreased from 72% to 63% 1-year post-TB
- 11% of people went “employed” to “self-employed”
- The proportion of people in poverty increased from 42% pre-TB to 58% one-year post TB

Meghji et al. Thorax 2020

Not all people recover financially

- Cohort study from Malawi:
- Paid work decreased from 72% to 63% 1 year post-TB
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Where is this data for North America?

Meghji et al. Thorax 2020

Common refrains

- “Association is not causation”
- “This highlights the importance of TB prevention”
- “The damage is done, what interventions will really help?”
- “This is a primary care issue”

Interventions for post-TB disease

A scoping review of interventions to address TB associated respiratory disability

Cassandra Mbanje,[a] Isla Kuhn,[b] Nozipho Musakwa,[a] Marzia Calvi,[c] Delia Boccia,[c,d] Jeremiah Chakaya Muhwa,[e] Lindiwe Mvusi,[f] Ernesto Jaramillo,[c] Denise Evans,[a,h] and Jamilah Meghji[g,h,]*

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[f]National Department of Health, Johannesburg, South Africa
[g]National Heart and Lung Institute, Imperial College London, London, UK

eClinicalMedicine 2024;73:102646

Interventions for pulmonary disease

- Inhaler therapy
- Host-directed therapies
- Pulmonary rehabilitation
- Smoking cessation
- Therapies for endobronchial disease

Inhaler therapy

INFINITY STUDY: RCT moderate to severe airflow limitation (n=136)

- Indacaterol versus placebo for 8 weeks, change in FEV1 at week 8
- Greater improvement in FEV1 after 8 weeks in the Indacaterol arm (140mL)
- This exceeds the minimal clinically important difference in FEV1
- 16% increase in the number of people with clinically significant improvement in dyspnea

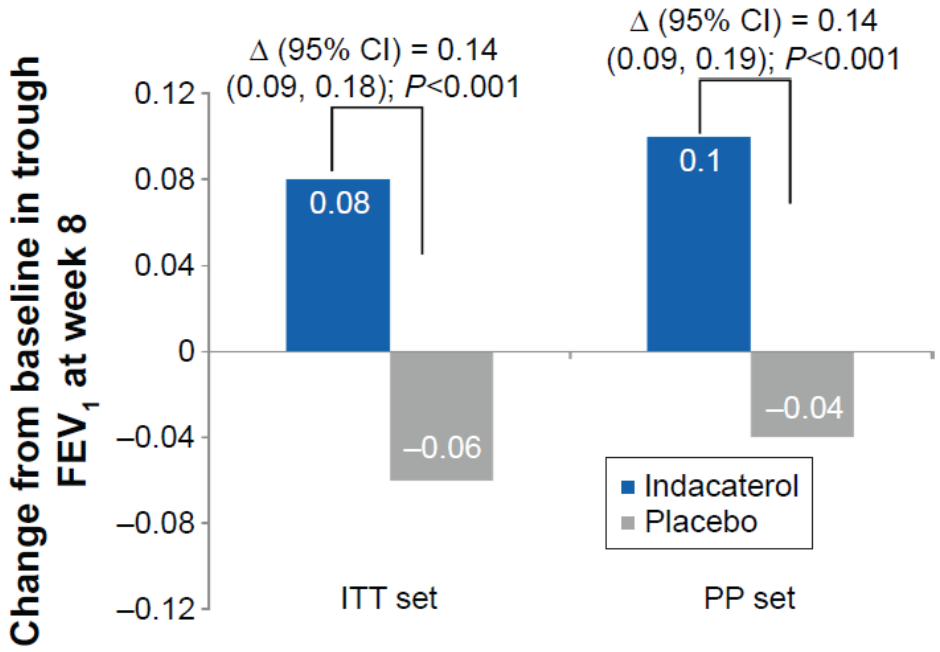


Figure 3 Change from baseline in trough FEV_1 at Week 8 (ITT set and PP set).
Notes: Data are presented as LS means. Δ, Treatment difference LS mean.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ITT, intent-to-treat; LS, least squares; PP, per protocol; SE, standard error.

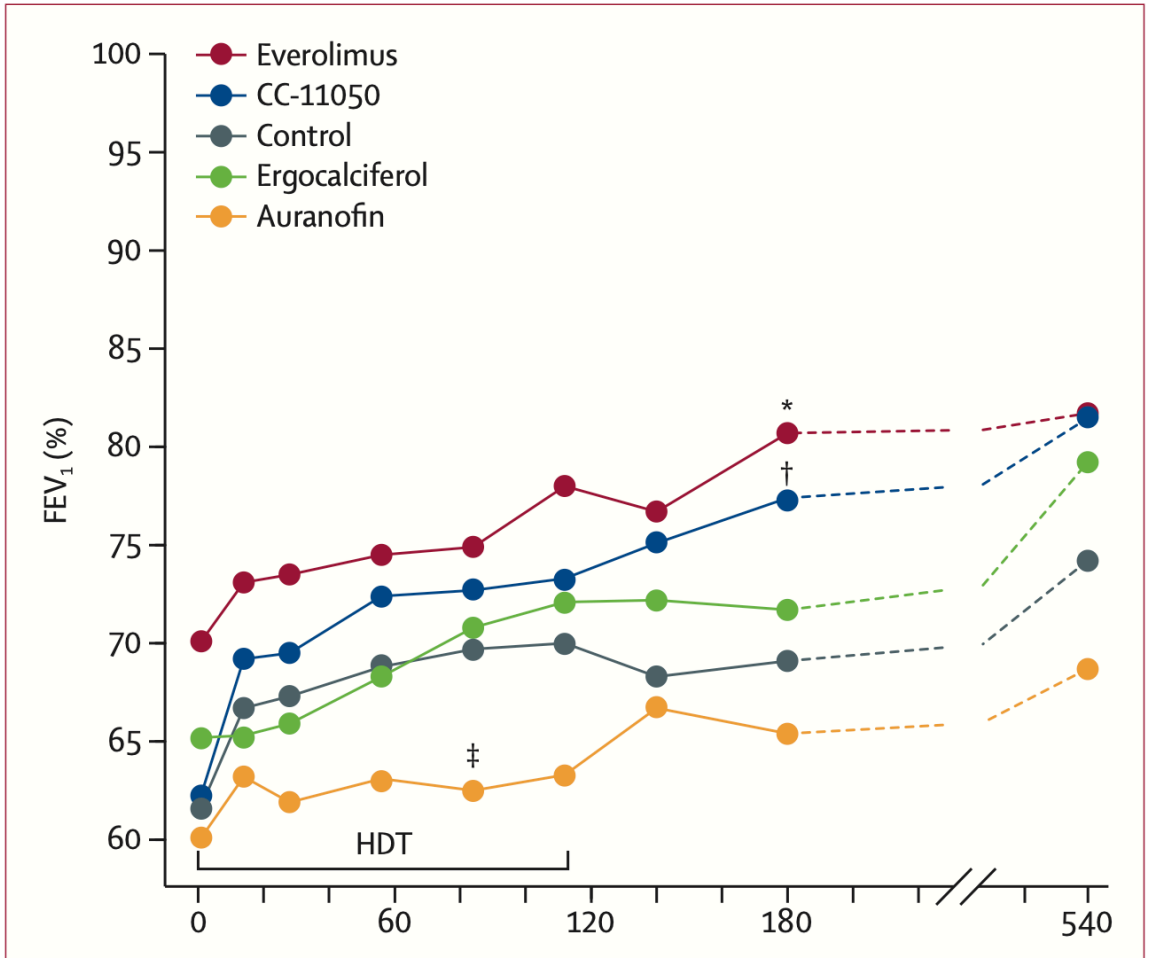
Kim et al. IJ-COPD 20187; 1589-96

Host directed therapy

- Multiple studies have failed to show effect
  - Vitamin D supplementation[1]
  - Studies on prednisone 1960s failed to show effect
  - More recent studies on prednisone[2]
    - Sub-analysis of the PredART trial (RCT using prednisone to prevent IRIS in PLHIV) was negative spiro/6MWD at week 28

1. Wejse et al. AJRCCM 2009; 179(9):843-850
2. Stek et al. ERJ 2020; 55(3):3.

Phase 2 RCT in people with moderate-severe pulmonary TB in South Africa



CC-11050: phosphodiesterase inhibitor

FEV_1% was significantly higher in the CC-11050 arm at 180d, but not at 540 days

Wallis et al. Lancet Resp Med 2021

Phase 2 RCT in people with moderate-severe pulmonary TB in Tanzania

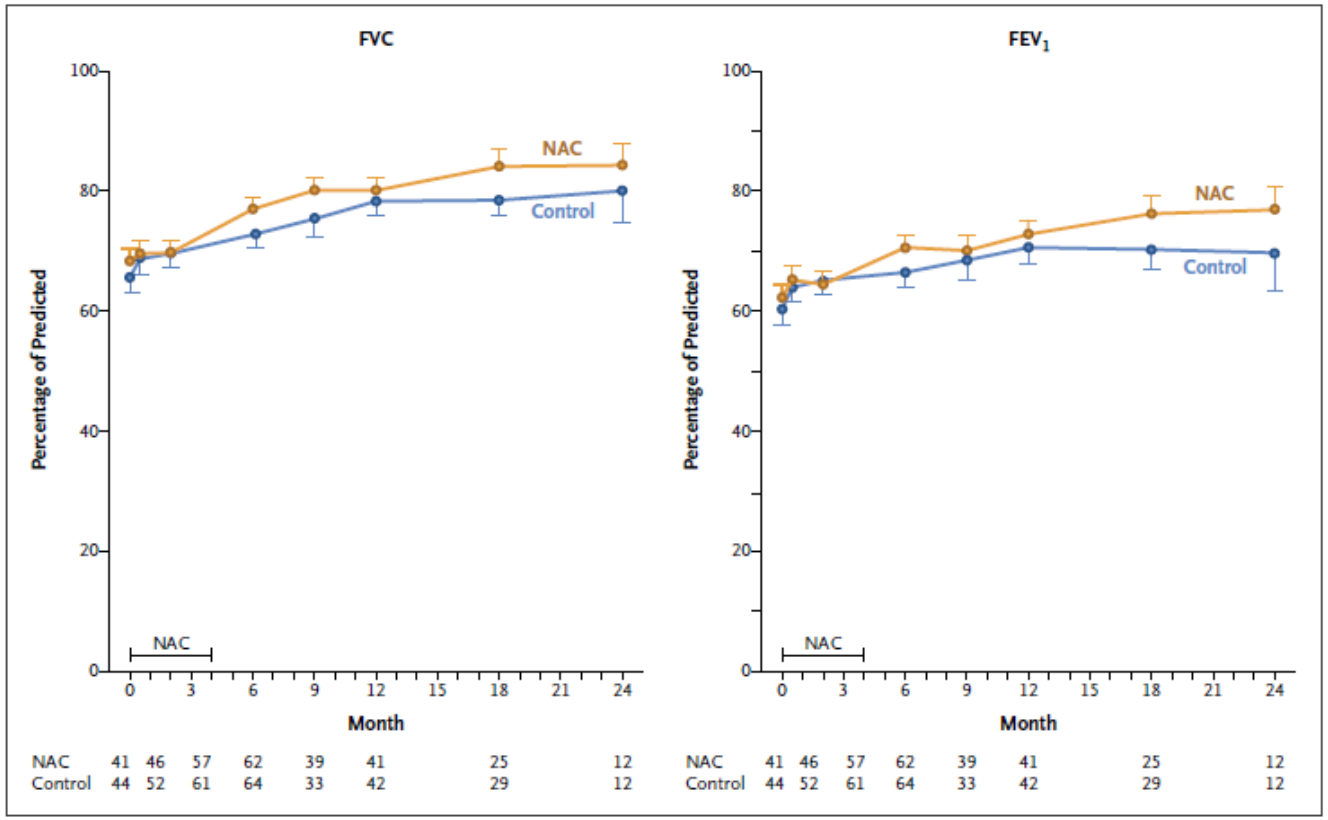


Figure 3. Mean Spirometry Values by Treatment Group in the Modified Intent-to-Treat Population.

- 1200mg oral N-acetylcysteine twice daily for first 112 days
- Primary outcome: sputum conversion, lung function was a secondary outcome
- FEV1 and FVC were significantly higher
- 2-4% increase in predicted values

Wallis et al. NEJM Evidence 2024; 3(9)

Pulmonary rehabilitation

- Generally pre-post cohort data to support these programs
- Associated with statistically significant improvement in spirometry, exercise testing and HRQoL measures from pre- to post-intervention

Jones et al. Int J Chron Obst Pulm Dis 2017
Jones et al. Int J Chron Obst Pulm Dis 2018
Wilson et al. J Clin Tuber Other Mycobact Dis 2017
Ando et al. Chest 2003

Endobronchial Tuberculosis

- Largely under-recognized in those without bronchoscopy
- Stenosis >1/3 of bronchus in 7% in a prospective cohort in Korea
- CXR is of limited value, physical exam can be helpful at times
- CT chest is more sensitive, but imperfect
- Bronchoscopy is the gold standard
- Consider bronchial stenosis in a person with respiratory symptoms, particularly a person with dyspnea >> spirometry/CT findings

Jung SS et al. Respirology (2015) 20, 488-495.

For now what can you do?

- Very limited data on inhalers, host-directed therapy, rehab
- Zero data on interventions for cancer, CVD, mood disorders
- What can we do?