

Post-TB Morbidity and Mortality: Extrapulmonary Complications

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a place of mind



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



Conflict of interest statement

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- I have a salary grant from the Michael Smith Foundation
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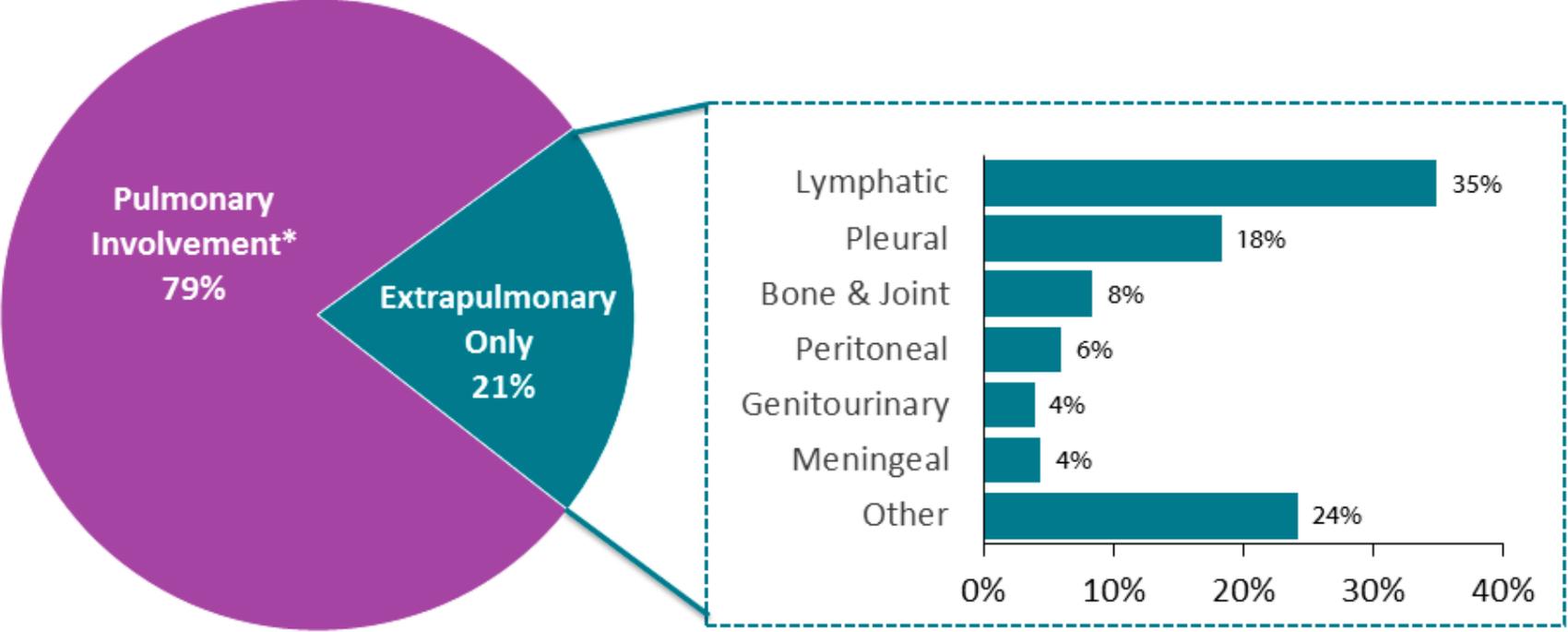


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Potentially extensive list of extra-pulmonary complications

U.S. TB Cases by Site of Disease, 2019



*Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary. Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

Note: Percentages are rounded.

**What complications are common
in people treated for TB?**

Outline

1. Post-TB mortality
2. Cardiovascular disease
3. Cancer
4. Mental health disorders
5. Financial impacts

1. Post-TB mortality

People with TB have three times the mortality of age- and sex- matched populations

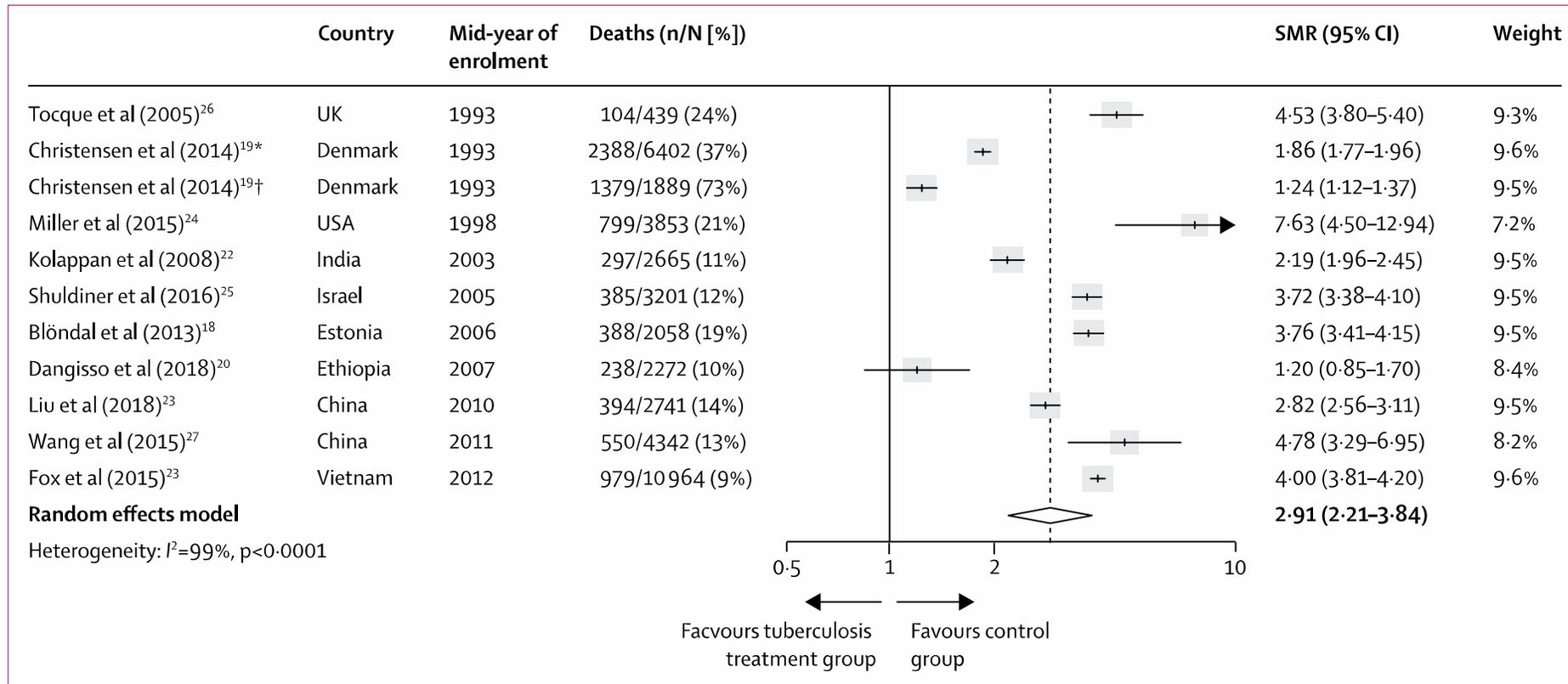


Figure 2: SMR for all-cause mortality after tuberculosis treatment

SMR=standardised mortality ratio. *Estimate for pulmonary tuberculosis. †Estimate for extrapulmonary tuberculosis.

Findings were consistent across subgroups

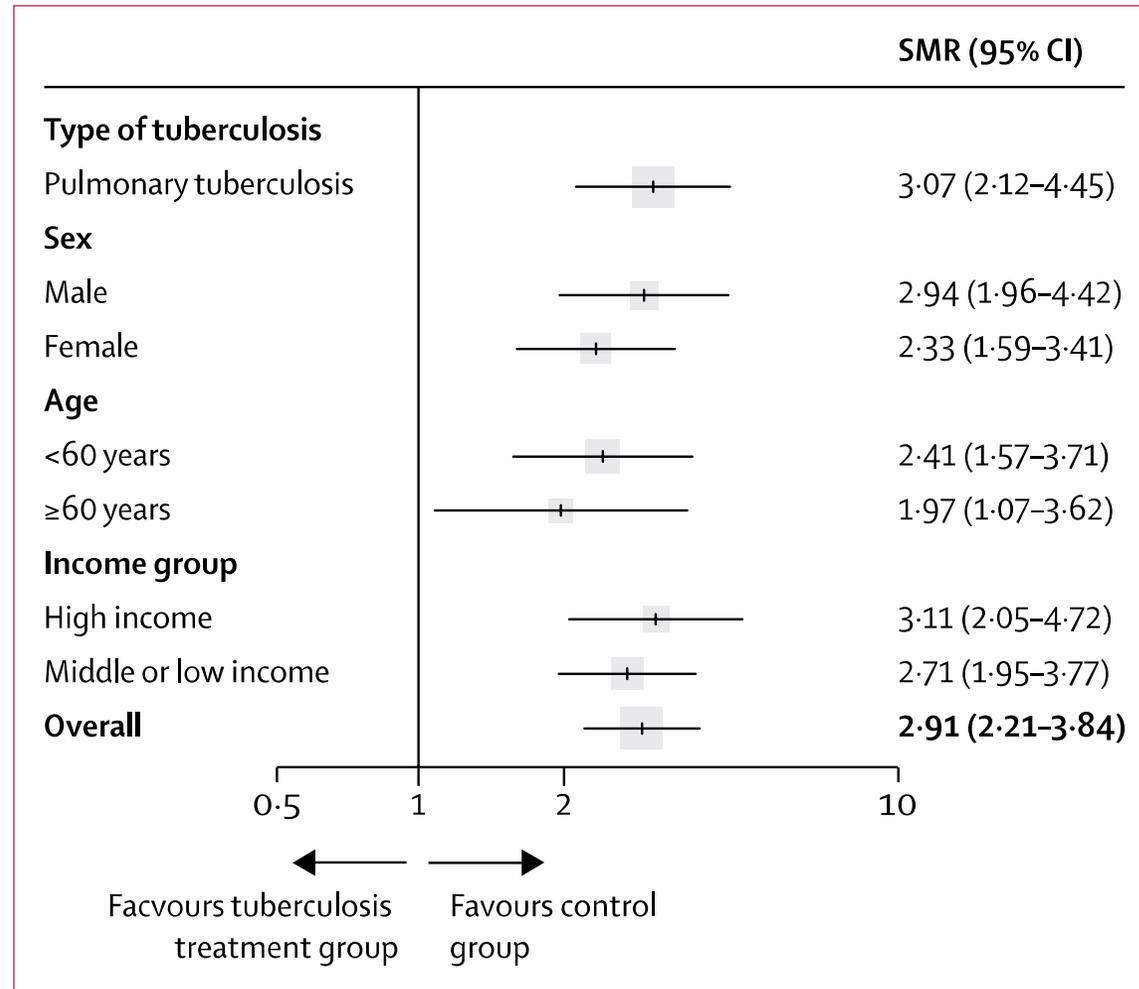
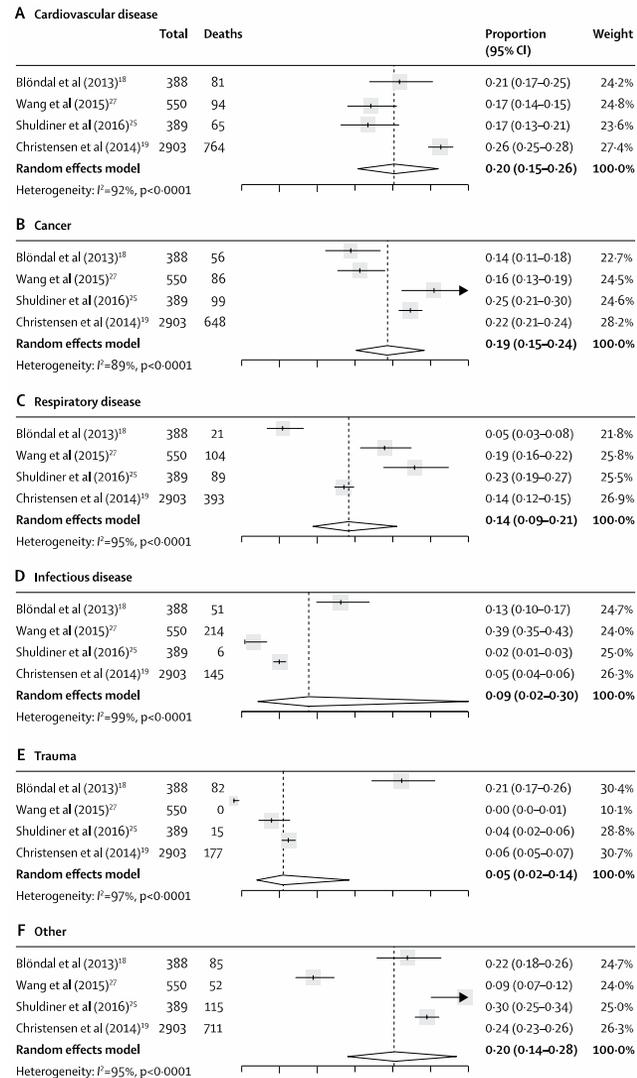


Figure 3: SMR estimates for subgroup analysis
SMR=standardised mortality ratio.

What are the causes of death post-TB?



Cardiovascular disease: 20%

Cancer: 19%

Respiratory disease: 14%

Infectious disease: 9%

Trauma: 5%

Other: 20%

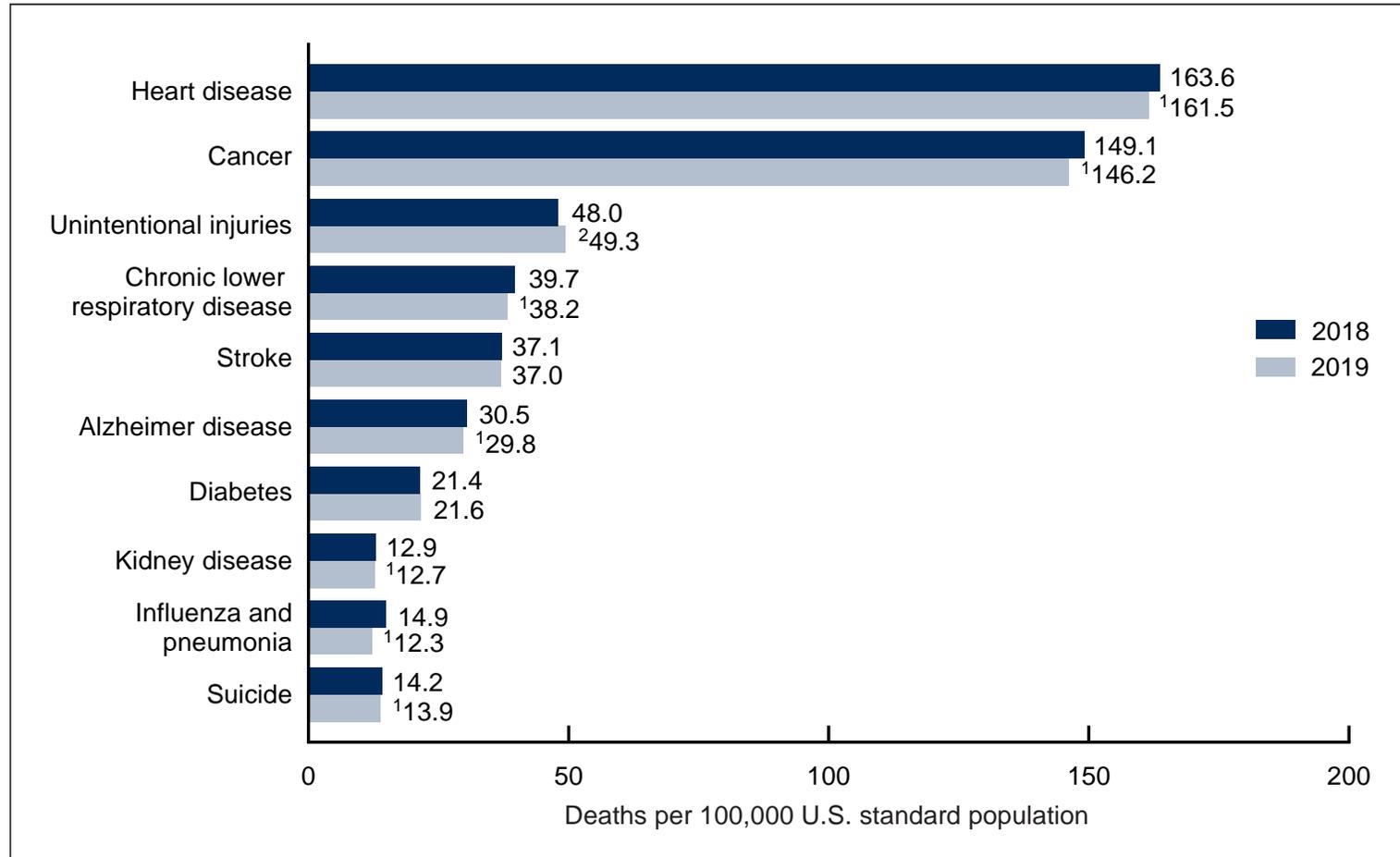
Is this similar in North America?

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)

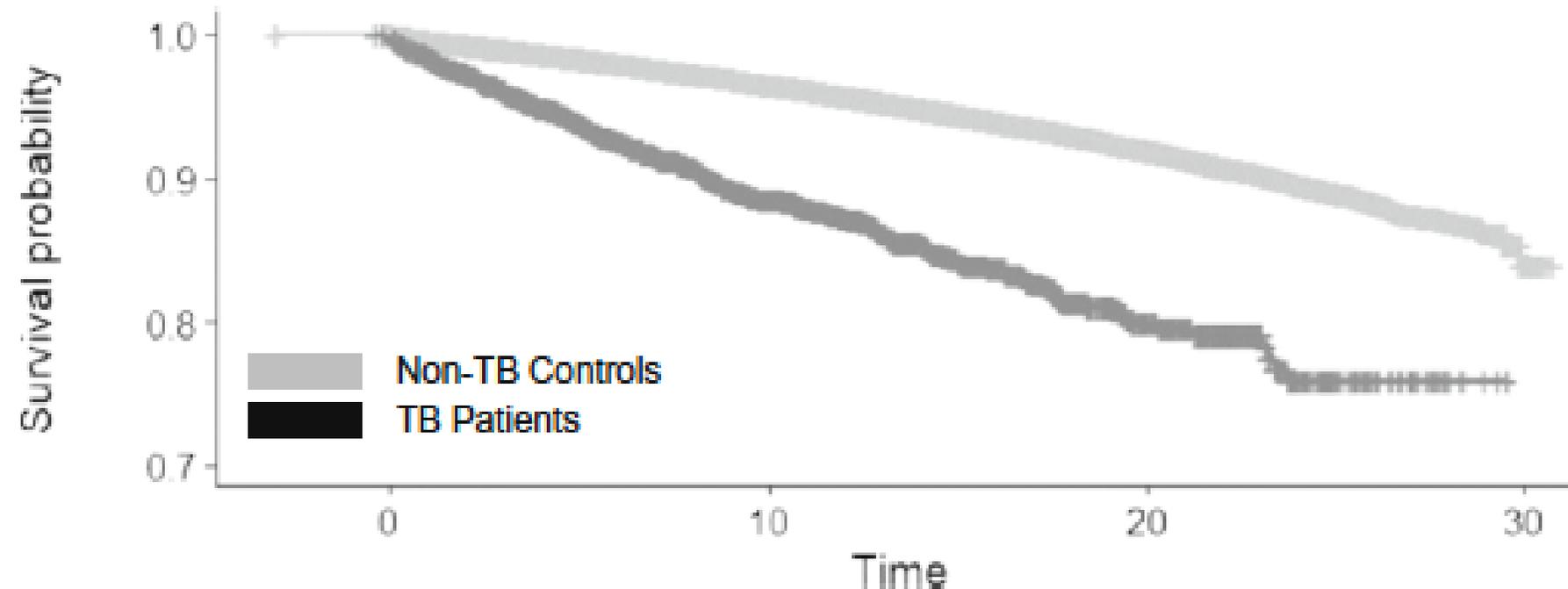
CI, confidence interval; *HR*, hazard ratio; *TB*, tuberculosis

^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

Leading causes of death are similar in the general population



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



Number at-risk

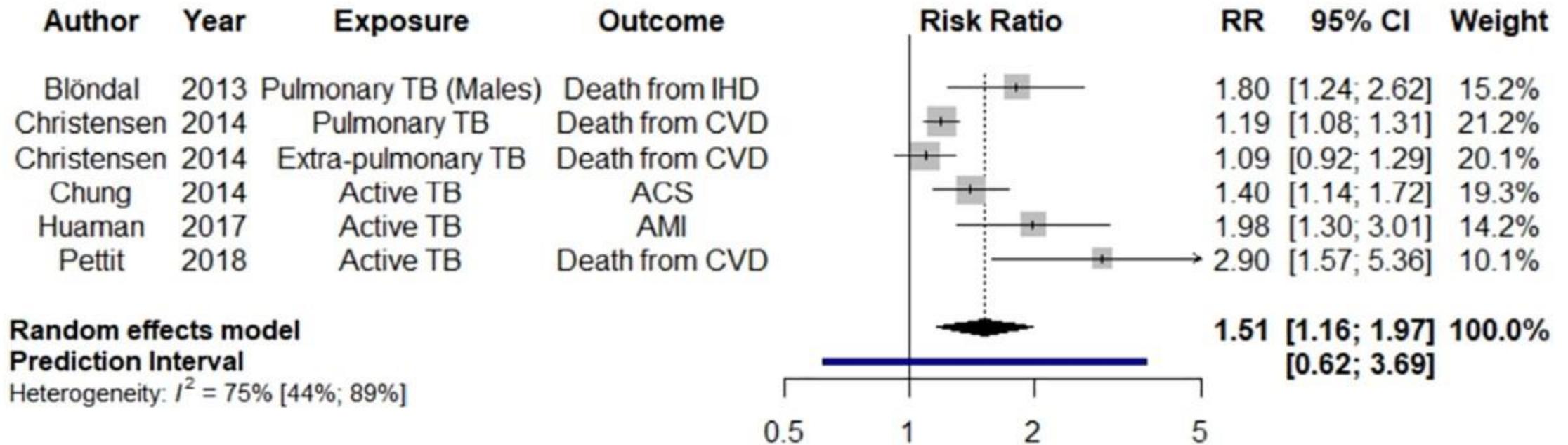
Non-TB Controls	1,028,434	244,118	36,570	104
TB Patients	2,432	1,079	238	0
Follow-up year	0	10	20	30

2. Cardiovascular disease

Cardiovascular disease (CVD)

- Appears to be an association between TB and CVD
- Specifically, an association between TB and major adverse cardiac events (MACE):
 - Acute myocardial infarction
 - Unstable angina
 - Cardiovascular mortality
 - Nonfatal stroke

Increased risk of MACE in people with active TB compared with matched controls



Cardiovascular disease (CVD)

- Is this from over-representation of CVD risk factors in people with TB?
 - e.g. smoking, diabetes, age, socioeconomic status
- Pro-inflammatory cytokines promoting atherosclerosis?
- Does latent TB specifically play a role in coronary atherosclerosis?

Increased risk of CVD in people with latent TB after adjustment including ASCVD risk score

<u>Variable</u>	<u>Adjusted OR (95%CI)</u>	<u>P-value</u>
ASCVD score	1.1 (1.05 - 1.16)	<0.001
Latent TB	4.96 (1.05 – 23.44)	0.043
HIV infection	1.24 (0.4 – 7.37)	0.814
Site (Peru vs. Uganda)	0.83 (0.4 – 1.72)	0.625

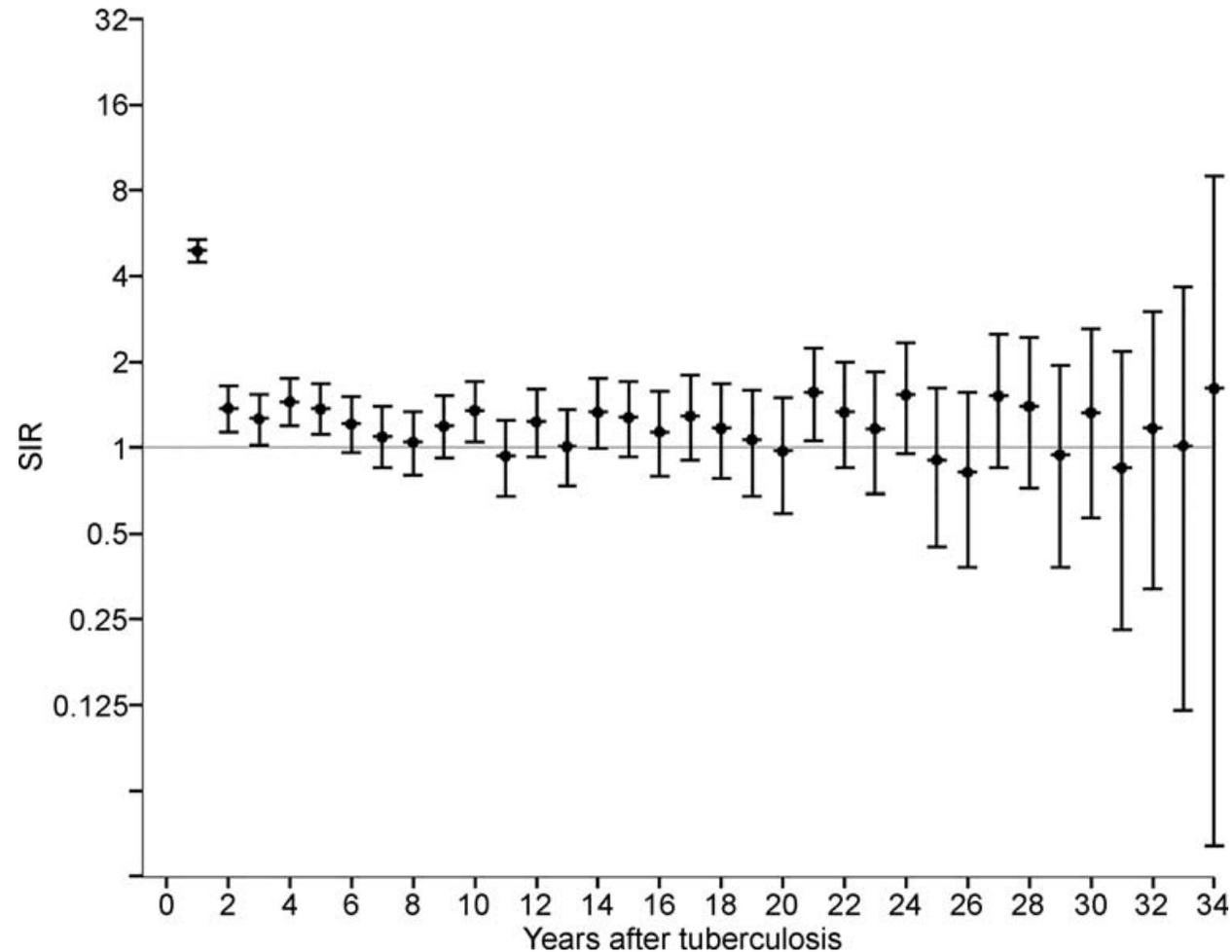
- 29% of LTBI and 24% of non-LTBI participants had a plaque
- 9% of LTBI and 3% of non-LTBI participants had obstructive CAD

3. Post-TB Cancer

Post-TB Cancer

- Some malignancies are established TB risk factors
- Lung, head and neck, and hematologic cancers all appear to have the strongest association with TB risk
- But cancer risk also appears elevated post-TB therapy

Increase cancer risk in people post-TB treatment in Denmark



Lung cancer risk appears to be a driver of long term cancer risk (i.e. >5 years)

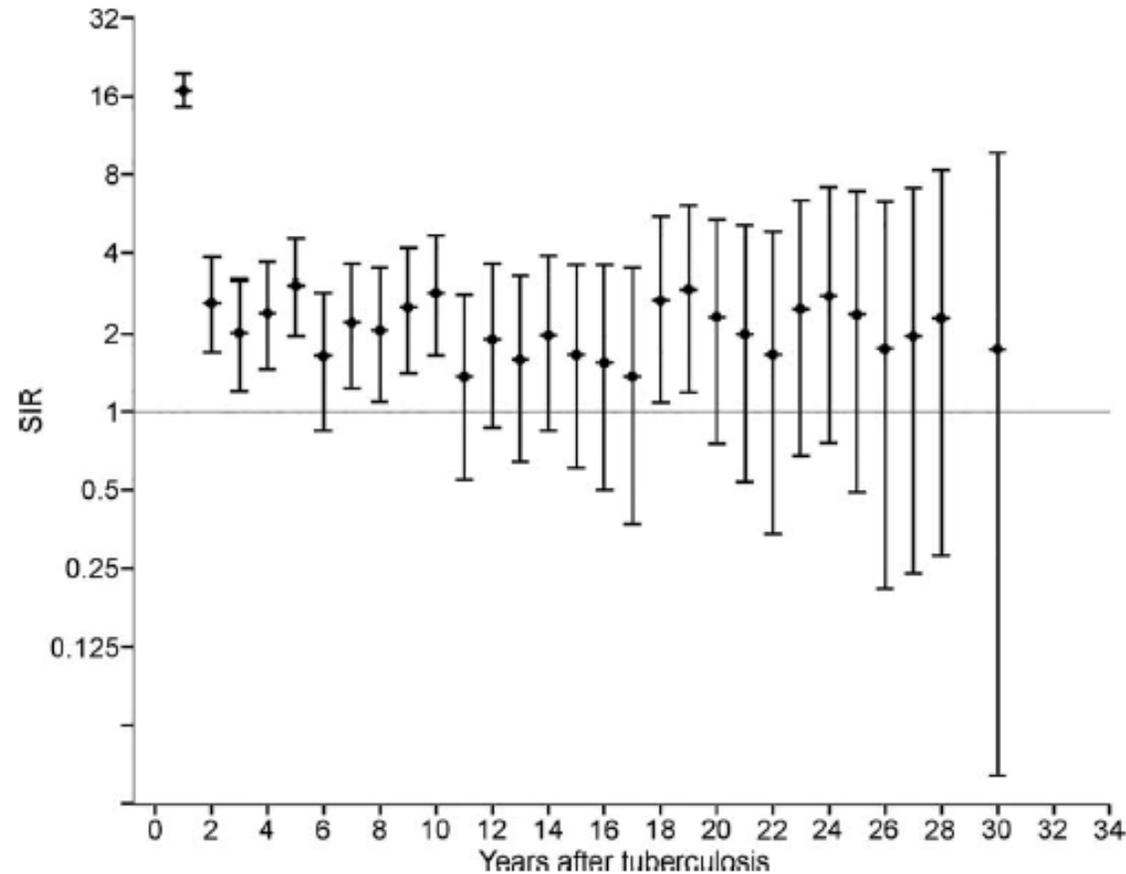


Figure 2 SIRs for lung cancer calculated for each year after diagnosis. SIR = standardised incidence ratio.

Post-TB Cancer

- Shared risk factors, specifically smoking, likely explains some risk
- Occult cancer may also be a TB risk factor
- Chronic inflammation may also play a role
- Further research is needed to understand the relationship between TB and cancer subtypes and the populations at highest risk for future malignancies

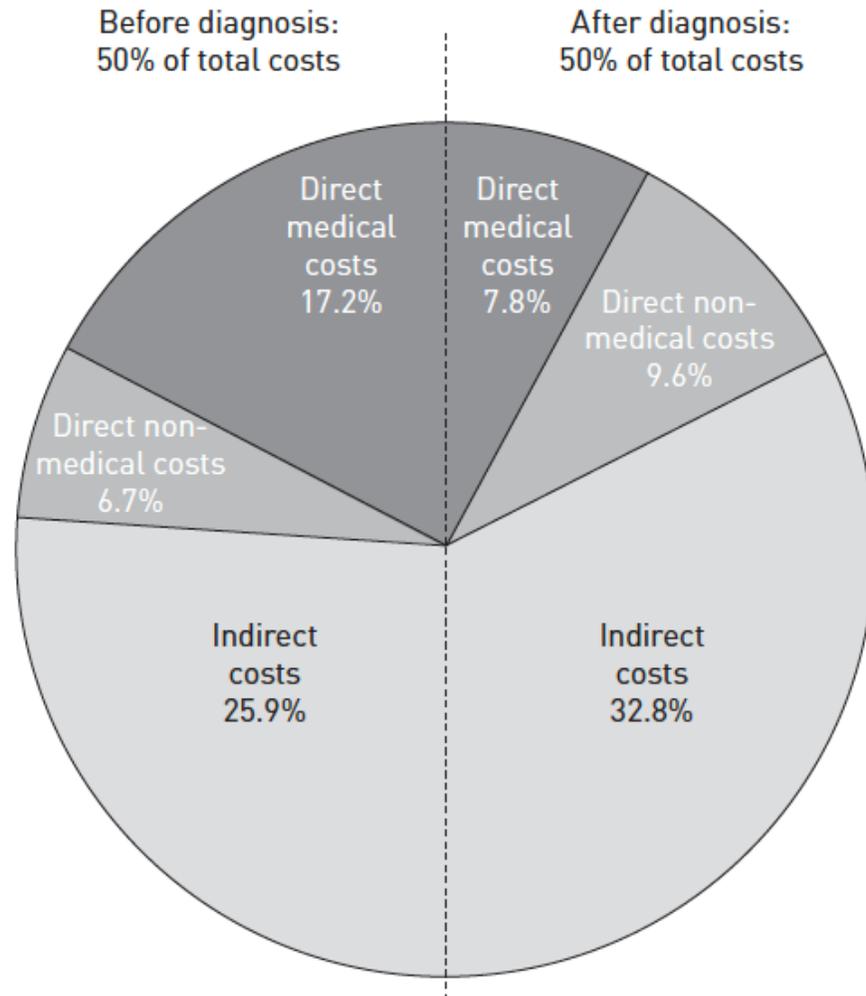
4. Post-TB mental health

Post-TB mental health

- There is limited data examining mental health and substance use post-TB
- We know depression prevalence is high amongst TB patients with a pooled prevalence of 45.2% in people with TB
- Evidence is emerging that examines post-TB depression and potential drivers of depression: we should see some of this evidence in our final abstract so stay tuned!

5. Socioeconomic Impacts

Cost before and during TB treatment in low & middle income countries



Cost was equivalent to 39% (4-148%) of household income.

Half of costs occurred before therapy and half of cost during therapy.

Data on post-TB therapy not reported

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- Income decreased overall and did not recover to pre-TB levels
- The proportion of people living in poverty increased from 41.6% pre-TB to 57.7% one year post TB

Summary: post-TB complications may not appear extraordinary, but they are

- People die of similar non-communicable diseases as the general population, but at a much higher rate.
- People develop cardiovascular disease at a higher rate
- People are likely diagnosed with cancer at a higher rate
- People suffer from mood disorders and trauma post-TB
- People suffer financial losses and may not recover

Post TB disease: a common refrain

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

Post TB disease: a response

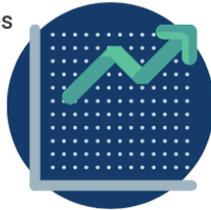
- We can risk stratify for CVD, cancer, mood disorders
- We can enroll in smoking cessation programs
- We can enroll in drug and alcohol misuse programs
- We can limit the financial impacts of TB disease

THE IMPORTANCE OF LINKING TUBERCULOSIS SURVIVORS TO PRIMARY CARE



1 We have a growing population of TB survivors

The World Health Organization estimates **58 million people survived TB** between 2000 and 2018, due to improvements in TB treatment and detection.



! TB survivors may be living with chronic conditions associated with, caused by, or made worse by TB.

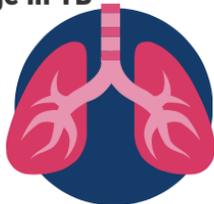
2 TB survivors are at an increased risk for premature mortality



Despite completing treatment, TB survivors, in both high and low income countries, experience **three times higher mortality** than their local populations.

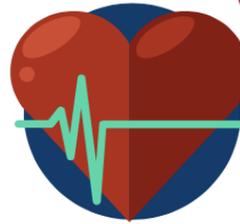
3 Estimates of residual lung damage in TB survivors range from 18 to 80%

Pulmonary TB can cause **irreversible lung damage**, which can lead to loss of lung function, long-term respiratory symptoms, and chronic respiratory disease.



💡 Emerging evidence suggests that pulmonary rehabilitation programs may be beneficial for post-TB lung disorders.

4 TB may play a role in the development of cardiovascular disease



TB appears to be a marker for increased cardiovascular disease risk. This risk may be related to **smoking** or **systemic inflammation** caused by TB, but the research is limited.



We need to evaluate TB survivors for the presence of comorbidities and provide support for modifiable risk factors, such as cessation programs for smoking.

5 TB can have long-term harmful effects on mental health

Mental health after completion of TB treatment is poorly documented, but up to 70% of people on TB treatment experience changes in their mental health due to **stigma**, **isolation**, and **inadequate social support**.



A simple assessment tool, such as the Patient Health Questionnaire-9[®] could be used to assess mental health in TB survivors. Those with depression or severe anxiety should be referred.

6 We need to better advocate for the health and wellbeing of TB survivors



We need to **support TB survivors** through their treatment by recognizing the long term effects of TB. An excellent first step is to ensure that people completing treatment are **linked to primary care**.



Scan the QR code for the references used to create this infographic.



Thank you

Contact information: James.Johnston@bccdc.ca

Post-TB infographic: <https://sites.google.com/view/link-tb-survivors-to-care/home> (credit to Kamila Romanowski)



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