TUBERCULOSIS SURVIVOR HEALTH

by

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Abstract

Background: Improvements in and expansion of tuberculosis (TB) diagnosis and treatment have yielded a growing population of TB survivors, with an estimated 155 million alive in 2020. While TB is preventable and curable, there is accumulating evidence of elevated chronic disease risk among survivors. Research objectives: (1) estimate the relative risk of non-TB mortality among TB survivors compared with controls, (2) systematically review the literature on cardiovascular disease (CVD) in TB and latent TB infection, (3) estimate the relative risk of airway disease among respiratory TB survivors compared with controls, and (4) estimate the relative risk of depression among TB survivors compared with controls, mediated by hospital length of stay (LOS).

Methods: A cohort of immigrants to British Columbia, Canada, 1985-2015, with linked health administrative and TB registry data was used for retrospective cohort studies of TB survivor health. Cox proportional hazards (PH) and time-varying models were used in statistical analyses. Causal mediation analysis of depression, mediated by hospital LOS, estimated depression risk. A prospectively registered systematic review and random-effects meta-analysis of TB and CVD was performed.

Results: In a time-varying Cox regression of non-TB mortality, an adjusted hazard ratio (aHR) of 1.69 (95% CI:1.50-1.91) was observed between TB exposed and non-TB exposed time. In the systematic review and meta-analysis, we found increased risk of major adverse cardiovascular events (MACE) among TB patients compared with non-TB controls (pooled RR = 1.51; 95% CI: 1.16-1.97). A higher risk of airway disease among respiratory TB survivors compared with non-TB controls was observed in our Cox PH regression (aHR=2.08; 95% CI: 1.91-2.28). In the causal mediation analysis of depression, TB survivors had aHR=1.24 (95% CI: 1.14-1.34) for depression by TB, decomposed into a natural direct effect of aHR=1.11 (95% CI: 1.02-1.21) and indirect effect of aHR=1.11 (95% CI: 1.10-1.12), indicating 50% (95% CI: 35-82%) mediation through hospital LOS.

Conclusion: TB survivors face higher mortality from non-TB causes, and higher risk of airway disease, CVD, and depression, compared with non-TB controls. Chronic disease screening and models of care development are needed to support TB survivors' health-related quality of life, during and after TB treatment.

Lay Summary

While tuberculosis (TB) is preventable and curable, it has health impacts beyond TB treatment, which have not been studied in Canada. Declining TB mortality has yielded a growing population of survivors. In 2020, approximately 155 million TB survivors were alive globally, illustrating the magnitude this issue. In British Columbia (BC), Canada, people immigrating to BC constitute ~80% of people diagnosed with TB. Among immigrants to BC, 1985-2015, this thesis studied non-TB mortality, airway disease, and depression, in TB survivors compared with controls. A literature review of cardiovascular disease (CVD) among people diagnosed with TB was also conducted. We found elevated risk of non-TB mortality, airway diseases, depression, and CVD, among TB survivors. We recommend chronic disease screening and management for TB survivors, during and after treatment, to improve TB survivor health. This thesis contributes to our understanding of TB survivor health, supporting policy and guideline development for person-centred TB care.

Preface

This thesis presents the results of a program of research that I designed, executed, and authored, in consultation with my thesis committee. The research projects conducted in this thesis were approved by the University of British Columbia's Clinical Research Ethics Board, under ethics certificate #H16-00265, and data access was approved through a Student Data Access Request under Data Access Request #Johnston-14-105 to Population Data BC. All inferences, opinions, and conclusions drawn in this thesis are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

My thesis committee members collaborated with me, as lead researcher and author, on the research chapters presented below. In consultation with my co-supervisors and thesis committee, I selected the research area based on my review of the literature and original thought about tuberculosis survivor health. I assembled the analytic data for each analysis, conducted statistical analyses, interpreted the results, and drafted the manuscripts for the following research chapters.

Chapter 1 has been published as:

- Basham CA, Karim ME, Cook VJ, Patrick DM, Johnston JC. Post-tuberculosis mortality risk among immigrants to British Columbia, Canada, 1985–2015: a time-dependent Cox regression analysis of linked immigration, public health, and vital statistics data. Can J Public Heal. 2021;112(1):132-141.

Chapter 2 has been published as:

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Chapter 3 has been published as:

- Basham CA, Karim ME, Cook VJ, Patrick DM, Johnston JC. Post-tuberculosis airway disease: a population-based cohort study of people immigrating to British Columbia, Canada, 1985–2015. EClinicalMedicine. 2021;33:100752.

Chapter 4 has been published as:

- Basham CA, Karim ME, Cook VJ, Patrick DM, Johnston JC. Tuberculosis-associated depression: a population-based cohort study of people immigrating to British Columbia, Canada, 1985–2015. *Annals of Epidemiology.* 2021; *63:*7-14.

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Dedication

To my parents,
who gave me the confidence to believe in myself.

To my father,
who taught me the value of questioning authority and being straightforward.

To my mother,
who taught me the value of caring for every single person, and that kindness is its own reward.

To Pam,
for believing in me and being a constant support and advisor in the good times and the bad.

To my friends,
who taught me to live and to laugh.

A. Introduction

Background and Rationale

Theme and Purpose

This thesis is about the health of people who survive tuberculosis (TB survivors). The purpose of this research was to develop evidence that may inform policy and guidelines development for improving the health of TB survivors.

Problem Statement

In 2019, 10.0 million people developed TB, with 1.2 million deaths estimated globally,[1] making TB one of the deadliest infectious diseases in the world. With improved TB diagnosis and treatment, and subsequent declines in mortality, there is a growing population of TB survivors. In 2020, an estimated 155 million TB survivors were alive, illustrating the magnitude of TB survivor health as a global public health issue.[2] While TB is considered preventable and curable, there is accumulating evidence of long-term health impacts on TB survivors. Evidence of elevated long-term respiratory disease, cardiovascular disease, depression, and all-cause mortality risk among TB survivors is being translated into a priority for global TB strategies at the time of writing.[3–6]

As a mycobacterial infection, latent TB activates the immune system in order to contain the infection, preventing it from becoming TB disease. In approximately 10% of people latently infected with *Mycobacterium tuberculosis*, TB disease occurs over the lifetime.[7] The latency period for TB infection to move from infection to TB disease may lie anywhere from a few weeks to a few decades. Moreover, our understanding of latent TB infection (LTBI) has evolved from believing it to be a small number of dormant bacilli encased in granulomas in a latent state waiting to activate into active TB disease, to

"spectrum of microbiological and pathological states",[7] involving multiple systems of the body and myriad immune responses to constant bacterial replication that does not generate symptoms.[7] TB disease with a prolonged latency period before activation may have different impacts on long-term TB survivor health than TB disease with shorter latency periods. Moreover, different forms of TB (pulmonary or extra-pulmonary, e.g.) likely have very different impacts on morbidity and mortality in TB survivors. The most obvious and established of such relationships being between pulmonary TB and chronic respiratory disease.[8–10]

Specific chronic health conditions associated with TB, and the mechanisms behind these associations, have been described in cardiovascular disease (CVD), respiratory disease, and depression. Huaman et al. summarized potential biological mechanisms operating between prolonged infection with mycobacterium tuberculosis and CVD, noting that chronic inflammation may promote arterial plaque generation, or potentially cause breaches in plaque.[11] TB may also contribute to autoimmune disease linked to CVD, or may direcly impact on a person's vasculature.[11] In post-TB airway disease, lung remodeling occurs through pulmonary cavitation, fibrosis, bronchiectasis, and small airway damage.[12] Due to the heterogeneity of pulmonary TB, these lung remodeling processes vary substantially between people diagnosed with TB. Meghji et al. reviewed 37 studies of post-TB lung impairment imaging (chest x-ray and computed tomography), noting wide ranges of each process, with cavitation and fibrosis being most common, and bronchiectasis less common.[13] Mental health may be impacted by latent or active TB, with relationships between chronic inflammation and immune system activation being tied to depression risk via changes in hypothalamic-pituitary-adrenal axis regulation.[14] Increases in pro-inflammatory cytokines by infection with *Mycobacterium tuberculosis* is hypothesized to influence production of phenylalanine and kynurenine, leading to depression.[14] Active TB creates physical symptoms that can reduce health-related quality of life, inducing a depressive episode in TB

patients or potentially chronic depression in TB survivors. Stigmatization of people diagnosed with TB can severely impact mental health and emotional well-being.[15–21] These are some of the causal mechanisms by which TB is hypothesized to contribute to chronic disease morbidity and mortality.

Beyond a potential causal role that TB may play in generating chronic disease morbidity and mortality risk, TB survivors may be at increased risk of these chronic diseases due to factors associated with TB, for which TB may be an important risk marker. However, the evidence regarding TB's role as a causal factor or risk marker is limited by a poor understanding of the various chronic diseases for which TB survivors may be at elevated risk. Regardless of causality, higher chronic disease risk among TB survivors may have important implications for health services beyond TB treatment completion, including prevention, diagnosis, and management of chronic disease during and after TB treatment.

Until recently, TB survivor health has been largely ignored in favour of TB prevention, diagnosis, and care, which have been historically underfunded. With an estimated 3 million people suffering from TB who go undiagnosed and untreated (the "missing millions"), comprising a third of estimated TB incidence globally,[22] it is difficult to justify investment in post-TB healthcare at the expense of expanding TB diagnosis and treatment. Adding an additional dimension of TB survivor health and care may not be feasible in many places in the world at present. Although, as strengthening health systems is a priority for global health, and care for many of the conditions TB survivors suffer would fall into strengthened health systems, the additional dimension of TB survivor health and aftercare is compatible with a vision of health systems strengthening.

Developed in 1995, the WHO DOTS Strategy is the oldest of three global TB strategies.[23] Along with the End TB Strategy and the Stop TB Partnership's Global Plan to End TB (formerly the Stop TB

Strategy), these documents constitute a framework for global TB policy.[24] Global TB policy and programming have been, naturally, focused on addressing TB prevention, diagnosis, and care, primarily through the use of DOTS (directly observed therapy-short course).[23] The End TB Strategy seeks to eliminate TB globally by 2035, and represents a paradigm shift, from TB control to TB elimination.[23] Supporting the goal of TB elimination, the Stop TB Partnership's "The Paradigm Shift 2016-2020: Global Plan to End TB" included thee targets (the 90-90-90 targets): 90% of people with TB are diagnosed and begin treatment with 90% of key populations also meeting this target, and 90% of people initiating treatment completing treatment.[25] This Global Plan is currently being updated and, in the wake of the mounting calls from survivors and expanding evidence of long-term health impairment, a "fourth 90" has been proposed as an addition to these targets.[4] This fourth 90 has been formulated as follows: "[e]nsuring that 90% of all people successfully completing treatment for TB can have a good health-related quality of life".[4] Thus TB survivor health is becoming a policy priority. However, large gaps in our understanding of the health of TB survivors necessitates clinical, population health, and social science research.

Setting: TB Survivorship in a low-TB-incidence country

The challenges facing TB survivors are generally quite different between low-TB-incidence, high-resource settings, and settings of medium to high-TB-incidence. High-TB-incidence settings often have fewer resources available for addressing TB itself, let alone post-TB aftercare for TB survivors. In most low-TB-incidence countries, TB primarily occurs among people immigrating from higher-TB-incidence settings, among people living in poverty, or among people with compromised immune systems that have exposure to TB.[26] The majority of persons diagnosed with TB annually in Canada, and over 80% of persons diagnosed with TB in BC, are born outside of Canada, and come almost

exclusively from countries with higher TB incidence rates than Canada.[27,28] Other than people immigrating to low-TB-incidence settings from higher TB incidence settings, the people who develop TB are often members of marginalized communities, such as Indigenous Peoples in Canada.[29]

In Canada, the Canadian Tuberculosis Standards guide the prevention, diagnosis, and care of TB.[30] In active TB treatment, these standards do not require microbiological confirmation of cure (e.g., negative culture at TB treatment end). In regards to follow-up post-TB treatment completion, the Canadian TB Standards state: "As a general rule, patients who have completed treatment and are judged to be cured do not need follow-up after treatment" (p. 118),[30] which is characteristic of the lack of long-term follow-up guidelines for TB survivors globally.[6] While, a "patient-centred treatment program" is recommended (p. 112), it is recommended with the express intention of improving TB treatment completion, and does not mention long-term TB survivor health.[30]

Overview of Thesis Research

Gaps in the literature

The long-term health outcomes of TB survivors, and their implications for health services, are only recently being investigated. A growing number of longitudinal studies of TB patients demonstrate increased risk of mortality, respiratory disease, cardiovascular disease, and depression, associated with TB, after TB treatment completion. However, this evidence is limited and originates primarily in countries with different TB epidemiology from Canada, as well as differences in populations, health systems, and social structures. Long-term health outcomes post-TB therapy have not been studied in Canadian populations prior to this thesis. Consequently, there was a need for cohort studies of TB survivor health.[9,11,16,31,32] As a low-TB-incidence setting, where the majority of TB occurs among people born outside of Canada, estimates of the risks of mortality, respiratory disease, and depression

among patients in BC, Canada, may be generalizable to settings with similar TB epidemiology, health systems, and social structures.

Research objectives

The following aims describe the literature and rationale for each of the research works undertaken as part of this thesis, and the research chapters written during this work. The four objectives of this thesis were to (1) Analyze post-tuberculosis mortality risk in a low-TB-incidence setting; (2) review the epidemiological literature on cardiovascular morbidity and mortality among TB patients; (3) analyze post-tuberculosis airway disease risk and assess potential unmeasured confounding by smoking; and (4) analyze TB-associated depression risk and the potential mediating role of hospital length of stay.

(1) Analyze post-tuberculosis mortality risk in a low-TB-incidence setting

A systematic review of long-term mortality among TB survivors demonstrated excess all-cause mortality among TB patients across settings, including types of TB, age groups, sexes, GDP per capita, and HIV prevalence (pooled SMR = 2.91; 95% CI: 2.21-3.84).[33] Within this review, it was noted that causes of death common in the general populations of each study figured prominently among TB survivors. Common causes of death among TB survivors included cardiovascular disease (pooled proportion = 0.20), cancer (pooled proportion = 0.19), respiratory disease (pooled proportion= 0.14), infectious disease (pooled proportion = 0.09), trauma (pooled proportion = 0.05), other (pooled proportion= 0.20), and unknown (pooled proportion= 0.03).[33] This review provided an important contribution to TB survivor health, but also highlights some of the limitations of existing studies. However, the heterogeneity study designs, data sources, and populations used in the reviewed studies

makes the pooled estimate of excess mortality risk difficulty to interpret in specific population or setting.

No studies of post-TB mortality have been conducted in Canada, overall or specific to major causes of death for which TB survivors may be at particular risk, such as respiratory diseases, cardiovascular diseases, cancers, or injuries and poisonings.[33] Therefore, the first objective of this research was to analyze post-TB mortality risk, overall and by cause, in British Columbia, Canada. The research question was: "Among people immigrating to British Columbia, from 1985-2015, did TB survivors have a higher risk of non-TB mortality than people not diagnosed with TB, overall and by cause of respiratory disease, cardiovascular disease, cancers, or injuries and poisonings?" It was hypothesized that TB survivors would have a higher risk of non-TB mortality than non-TB controls, after adjustment for measured confounders, overall and for each of the cause of death groups listed above.

(2) Review the epidemiological literature on cardiovascular disease among TB patients

A review by Huaman et al. (2015) noted an increased risk of cardiovascular disease (CVD) based on available case-control studies and one population-based retrospective cohort study describing a directional relationship between TB and CVD.[11] In terms of acute myocardial infarction (AMI), two studies led by Huaman found evidence of elevated risk of AMI for persons diagnosed with TB and latent TB infection (LTBI), respectively.[34,35] These results are consistent with other studies examining elevated CVD risk due to infections such as C*hlamydia pneumoniae*, human immunodeficiency virus (HIV), hepatitis B and C, cytomegalovirus (CMV), and Epstein Barr virus, which are hypothesized to affect CVD through chronic inflammation.[11,36] In another study examining the relationship between TB and cardiovascular disease, Sheu et al. found an increase in the risk of ischemic stroke (HR = 1.52;

95% CI: 1.21-1.91) after adjusting for known stroke risk factors, as well as income, urbanization, and region in a Taiwanese retrospective population-based cohort.[37] However, a second analysis of Taiwanese TB patients using similar data and methods, yet restricting to non-central nervous system TB, found no association between TB and ischemic stroke within 3 years of TB diagnosis.[38]

Other analyses of TB and CVD have been conducted, with mixed results for a variety of CVD outcome and TB exposure definitions, studied with differing designs, in a diversity of narrowly-defined or heterogeneous study populations. Several studies concluded that elevated CVD risk exists in TB patients; however, those findings had not been systematically reviewed prior to this thesis.[39,40] It is currently unclear what CVD outcomes warrant monitoring in TB survivors, or what CVD outcomes, or TB survivor groups, have been studied to date in the published literature. The association between TB and hypertension was systematically reviewed finding insufficient evidence to support a directional association.[32] However, those findings were interpreted with caution, due to lack of properly designed studies to evaluate post-TB hypertension risk.

If TB patients are at increased risk of long-term CVD outcomes, this would be important for prevention and management of CVD risk factors among TB patients. A broad synthesis of the literature on CVD outcomes, among both TB survivors and people diagnosed with LTBI, could inform future studies of TB-associated CVD and provide an understanding of the range of CVD outcomes that may affect people affected by TB.

The second objective of this program of research was to better understand the state of knowledge regarding CVD risk in TB patients through a systematic review of the epidemiological literature. Our review was guided by the following review question, registered in PROSPERO: “Do persons diagnosed

with latent TB infection (LTBI) or active TB (TB disease) have a greater risk of CVD or CVD-related mortality than persons without evidence of LTBI or TB disease?". A sub-question of this research questions was: "what types of CVD outcomes have been studied among TB survivors and people diagnosed with latent TB infection, in the published literature?" It was hypothesized that TB survivors and people diagnosed with LTBI, would each have a higher risk of CVD than non-TB controls and people without evidence of LTBI, after adjustment for measured confounders, based on the published literature and pooled effect estimates from that literature.

(3) Analyze post-tuberculosis airway disease risk in a low-TB-incidence setting and assess potential unmeasured confounding by smoking

The most well-described non-microbiologic sequelae of TB is chronic airway disease. Five systematic reviews of post-tuberculosis (post-TB) airway disease have been published with a consensus that there is an increased risk of respiratory impairment after TB treatment completion.[8–10,12,13] For example, the long-term impact of TB on airway disease was systematically reviewed by Byrne et al., who found a significant directional association of pulmonary TB on chronic airway disease (pooled odds ratio = 3.05).[9] However, these reviews identified limitations of the published literature, particularly the use of cross-sectional designs, small samples, and unmeasured confounding. While there are extensive studies of post-TB airway disease, Ravimohan et al. noted that most studies were unable to control for pre-existing airway disease, had small sample sizes, and relied heavily on self-reported TB histories.[12] A concern in published epidemiological studies of post-TB airway disease is the potential for unmeasured confounding, particularly by smoking, but also by biomass fuel use, or occupational exposures.[8,9] While addressed in several prospective cohort studies included in recent reviews, the evidence is still not considered definitive. A dearth of literature describing post-TB airway disease in

low-TB-incidence settings further limits the generalizability of review findings. To date, only a single cross-sectional study from Finland examined airway disease among people with past TB in a low-TB-incidence setting. This study was able to exclude people with pre-existing asthma, and found an adjusted odds ratio of 2.68 (95% CI: 2.00-3.61) for airway disease among people with a past history of TB compared to people without a history of TB.[41]

Three questions guided this research: (1) "To what extent are respiratory TB survivors at-risk of developing airway disease over an extended follow-up period in a low-TB-incidence setting?"; (2) "Is any increased risk of airway disease among respiratory TB survivors attributable to TB or is it possible that unmeasured confounding by smoking may be driving any observed association?"; and (3) "Does the hypothesized effect of respiratory TB on long-term airway disease risk vary by demographic, socioeconomic, or comorbidities?". We hypothesized a higher risk of airway disease among respiratory TB survivors. We hypothesized that smoking was unlikely to confound this relationship after adjustment for measured confounders. It was hypothesized that the effect of respiratory TB on airway disease risk would increase with increasing age at the time of immigration,[9] and with increasing TB incidence in country of birth,[9] based on the literature, and also with increasing comorbidity level, based on an original idea that less comorbidity would make TB a more potent impact on airways.

(4) Analyze TB-associated depression risk and the potential mediating role of hospital length of stay

Beyond its physical health impacts, awareness of the mental health burden associated with TB is a previously neglected area that is currently experiencing growth. The complexity of the relationships between TB and mental health, coupled with the high prevalence of depression (estimates ranging from 11.3-80.2%)[14,42] among TB patients, have stimulated interest in integrating TB and mental health

services.[14] A recent meta-analysis estimated a pooled prevalence of depression among TB patients of 45% (95% CI: 38–52%).[43] Depression among TB patients has been identified as a risk factor for poor TB treatment outcomes (pooled OR = 4.26; CI: 95%: 2.33-7.79).[44] Several studies have examined the relationship of TB to relatively common mental health disorders (depression and anxiety), finding a clear association between TB, mental health disorders, and treatment outcomes during and shortly after TB treatment.[14,16,45,46] Ambaw et al., analyzed a cohort of people diagnosed with TB in Ethiopia using a cohort design, finding that 8.7% of patients without depression at the time of TB diagnosis, developed depression within 6 months of initiative TB treatment.[47] However, the long-term effects of TB on mental health are not well understood.

A few studies of long-term depression risk have been conducted in medium and high-TB burden settings. Shen et al. (2014) identified a link between TB and depression risk post-TB treatment, after removing prevalent depression, pre-TB diagnosis (aHR=1.53; 95% CI: 1.36-1.72) among a Taiwanese cohort, with higher risk in males, those over 65 years of age, and with low income.[48] Another study conducted in Taiwan, examining depression among pulmonary TB patients, compared to matched controls, found a similarly elevated risk after adjustment for demographics, income, and select comorbidities (aHR=1.74; 95% CI: 1.35-2.25).[49] Yen et al., further noted a positive dose-response relationship between defined daily doses of ethambutol and risk of depression among pulmonary TB patients, highlighting the potential role of chemotherapy in depression risk post-TB diagnosis.[49] However, no studies of incident TB-associated depression have been conducted in a low-TB incidence setting. A lack of studies on mental health and TB among immigrants in Canada has been identified as a knowledge gap in Canada, out of step with international TB research.[16] The growing openness to integrating mental health supports in TB programming,[15] suggest that investigations of mental health

conditions, particularly depression, among persons affected by TB in low-TB-incidence settings, is warranted.

An important aspect of TB diagnosis and treatment, particularly (but not exclusively) when infectious pulmonary TB is diagnosed, is the role of hospitalization and its attendant isolation. TB survivors may spend prolonged periods in hospital in some cases, with mean and median of 17 and 11 days, respectively, among immigrants to Canada who are diagnosed with TB.[50] Intensive care unit (ICU) patients have been shown to suffer from post-traumatic stress disorder, depression, and anxiety, following discharge.[51] While most TB survivors are not placed in ICU, their stay in hospital may play a causal role in the development of any depression post-TB diagnosis. Narrative and qualitative research has uncovered the tremendous mental health impact of a TB diagnosis and the hospital experience on TB patients, although primarily in higher-TB-burden settings with fewer mental health resources.[52–54] The hypothesis that the length of stay in hospital may play a role in depression risk would have implications for depression prevention efforts for TB survivors, as those hospitalized for longer periods may be a key population for interventions, particularly while in-hospital. No quantitative studies of the potential mediating role of hospital LOS in depression risk have been conducted to date.

The research question for this objective was: “Are TB survivors at increased risk of short-, medium-, or long-term depression compared to non-TB controls, and if so, is the increased risk among TB survivors mediated by the length of stay in hospital?”. It was hypothesized that TB survivors have a higher risk of depression than non-TB controls, and that this risk of depression would be mediated substantially by hospital length of stay (percentage mediated >25%), based on isolation, disease severity, or contact

with healthcare leading to a higher probability of detecting depression among people in hospital for longer periods.

Dissertation summary

In the first research chapter, the findings are presented from a cohort study of post-TB mortality among people successfully completing treatment for TB in British Columbia, Canada, from 1985-2015. In that study, we used Cox time-varying regressions of person-time exposed to TB and unexposed to TB to analyze the risk of non-TB-caused mortality, overall, and by cause (respiratory disease, cardiovascular, cancer, injuries and poisoning). This study built on the knowledge from the systematic review of post-TB mortality by providing Canadian estimates of non-TB mortality risks among TB survivors. We used directed acyclic graphs (DAGs) to display the assumed relationships between variables in our study.[55,56] Time-varying Cox regression was used to overcome the pitfalls of immortal time bias.[57–59] In addition to the extended Kaplan-Meier curve appropriate for displaying events by exposed time and unexposed time in time-varying Cox regression analyses,[60] we used standard Kaplan-Meier curve with TB treatment completion date as the index for the TB survivors and random reference date for non-TB controls. To investigate sex-based differences in risk of post-TB mortality, we conducted sex-stratified analyses by males and by females.

In the second research chapter, a systematic literature review of cardiovascular disease (CVD) among people diagnosed with TB and LTBI was conducted. We employed a broad search strategy to include as many types of TB and CVD as possible. We used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[61] adapted to the observational studies included in our review and incorporating our protocol-anticipated concerns about confounding bias, to assess potential bias in the

reviewed studies. To quantitatively summarize the studies, we used random effect meta-analysis to pool the results of the studies according to per-protocol and post-hoc analysis plans. We calculated prediction intervals around the pooled relative risk estimates for CVD among TB survivors, which provides an interval that incorporates the heterogeneity of studies and is considered a best practice for reporting.[62]

In the third research chapter, a cohort study of linked healthcare administrative data was performed, examining post-TB airway disease. In this study, we estimated the risk of airway disease among TB survivors compared to non-TB controls during extended follow-up of a population-based cohort without baseline TB or airway disease (at-risk cohort). The exposure group was people diagnosed with respiratory TB, based on laboratory data, with successful TB treatment completion in BC. The control group was people not diagnosed with TB in BC. Follow-up time was initiated at 1-year post-immigration date for both exposure and control groups, ending at study end date (December 31, 2015), date of death from a non-airway disease cause, date left BC, or study outcome event date. A second study aim of this observational data analysis was to assess the potential for unmeasured confounding to bias our main analysis result through multiple sensitivity analysis methods. We used directed acyclic graphs (DAGs) to represent relationships between variables including potential unmeasured confounding by smoking.[55,56] As a theoretical sensitivity analysis, we employed E-values to assess the strength of association an unmeasured confounder, such as smoking, would require with both the exposure (TB) and the outcome (airway disease) to move our main analysis effect estimate for TB (the hazard ratio) to 1.0, or to move its 95% lower confidence limit to 1.0, rendering the effect estimate statistically non-significant.[63–65] We also used empirical sensitivity analyses, including high-dimensional propensity score (hdPS) and least absolute shrinkage and selection operator (LASSO) in a hybrid method for variable selection for hdPS.[66,67]

In the fourth research chapter, we conducted a study of time-to-depression in a large cohort without evidence of depression at baseline, comparing TB survivors with non-TB controls. The exposure group was people diagnosed with TB in BC. The control group was people not diagnosed with TB in BC. Follow-up time was initiated at 1-year post-immigration date for both exposure and control groups, ending at study end date (December 31, 2015), date of death from a non-depression cause, date left BC, or study outcome event date. We examined potential mediation of the effect of TB through the length of hospital stay, using causal mediation analysis.[68,69] Prior to analyzing the data, we illustrated the hypothesized relationships between TB and depression, mediated by hospital length of stay, using DAGs.[55,56] We used E-value as a sensitivity analysis for potential residual confounding in our main analysis of TB-associated depression risk.[63,64,70] We stratified the time-to-depression Cox regression analysis by follow-up time to assess potentially non-proportional hazards of depression by TB over follow-up time, similar to Shen et al.[48] We also tested for effect modification by sex to see if TB had a different effect on incident depression in males and females, also based on findings of Shen et al..[48] In the mediation analysis, we followed a weighting-based approach, which involved a proportional odds regression in analyzing the mediator variable (length of stay in hospital), generating mediation weights, and then a Cox proportional hazards regression for the outcome variable (time-to-depression) weighted by the mediation weights.[68,69]

In the Conclusion chapter, the research chapter findings are summarized and briefly compared with key findings in the published literature. Applications and limitations are discussed after, with some recommendations offered for future research.

B. Research Chapters

1 Post-tuberculosis mortality risk in British Columbia, Canada, 1985-2015: time-dependent Cox regressions of linked immigration, public health, and vital statistics data

1.1 SYNOPSIS

Objective: To compare non-tuberculosis (TB)-cause mortality risk overall and cause-specific mortality risks within the immigrant population of British Columbia (BC) with and without TB diagnosis through time-dependent Cox regressions.

Methods: All people immigrating to BC during 1985-2015 (N=1,030,873) were included with n=2,435 TB patients, and the remaining as non-TB controls. Outcomes were time-to-mortality for all non-TB causes, respiratory diseases, cardiovascular diseases, cancers, and injuries/poisonings, ascertained using ICD-coded vital statistics data. Cox regressions were used, with a time-varying exposure variable for TB diagnosis.

Results: The non-TB cause mortality hazard ratio (HR) was 4.01 (95%CI: 3.57-4.51) with covariate-adjusted HR of 1.69 (95%CI: 1.50-1.91). Cause-specific covariate-adjusted mortality risk was elevated for: respiratory diseases (aHR=2.96; 95%CI: 2.18-4.00), cardiovascular diseases (aHR=1.63; 95%CI: 1.32-2.02), cancers (aHR=1.40; 95%CI: 1.13-1.75), and injuries/poisonings (aHR=1.85; 95%CI: 1.25-2.72).

Conclusions: In any given year, if an immigrant to BC was diagnosed with TB, their risk of non-TB mortality was 69% higher than if they were not diagnosed with TB. Healthcare providers should consider multiple potential threats to the long-term health of TB patients during and after TB treatment. TB guidelines in high-income settings should address TB survivor health.

1.2 INTRODUCTION

In Canada, tuberculosis (TB) is primarily diagnosed among people who have immigrated from medium/high-TB-incidence countries.[71] In British Columbia (BC), a province of Canada, the percentage of incident TB occurring among people born outside of Canada (85%) is higher than that reported nationally (75%).[72,73] TB patients a have higher prevalence of alcohol and substance use,[74] mental health disorders,[16] diabetes,[75] HIV,[76] and exposure to poverty and related social determinants of health.[77–79] While TB itself is potentially fatal, leading to 1.7 million deaths annually worldwide,[80] it may also act as a marker for increased risk of mortality from causes other than TB after successful completion of TB treatment. These factors may include social determinants of health for which Canada TB programs have been criticized as neglecting among the Canadian immigrant population.[81] To date, no Canadian study of post-tuberculosis mortality risk exists.[33,82]

This study aimed to compare non-TB mortality risks between those diagnosed with TB compared to people not diagnosed with TB among persons immigrating to Canada and residing in BC using time-dependant Cox regressions. We studied the immigrant population of BC as this sub-population makes up the vast majority of people diagnosed with TB in BC.[28,82] Moreover, there are important differences in TB epidemiology and in mortality risk between persons born outside of Canada and Canadian-born populations.[82,83] We hypothesized higher mortality risk among immigrants diagnosed with TB compared to immigrants not diagnosed with TB.[33]

1.3 METHODS

1.3.1 Study Design, Population, Setting, and Analytic Sample

This study used a retrospective cohort study design. Our study population was all persons born outside of Canada and immigrating to Canada from January 1, 1985 to December 31, 2012, and residing in BC from January 1, 1985 to December 31, 2015 (Figure 1-A1). Data were derived from Population Data BC, a multiuniversity health data resource.[84] The Immigration, Refugee, and Citizenship Canada (IRCC) Permanent Residents database was used to include members of this population in our analytic sample.[71,85–87] Exclusion criteria included invalid dates for TB diagnosis or death (i.e., before January 1, 1985), diagnosis of TB and without documented TB treatment completion (e.g., death during treatment), and missing value for any covariate (<5% of cohort). Our primary outcome measure was post-TB treatment mortality from a non-TB cause. TB causes included ICD-9-CM codes 011-018 and ICD-10-CA codes A15-A19.

Mortality was ascertained from BC's Vital Statistic Agency's death certificates.[88] Data on tuberculosis diagnosis and treatment were obtained from the BC Centre for Disease Control (BCCDC) TB Registry.[71,89] Data on comorbidities were obtained through data from the hospital discharge abstracts database (DAD) and Medical Services Plan (MSP) Payment Information File for BC, and assembled using published algorithms.[90–93] Data on demographic, geographic, and socioeconomic factors were obtained from the IRCC Permanent Residents database, MSP Consolidation Files, and Canadian Census files.[71,87,94] This study was approved by the University of British Columbia's Clinical Research Ethics Board (H16-00265). Data linkage was conducted using scrambled unique identifiers.[95]

1.3.2 Variables

1.3.2.1 Outcome

The primary outcome of interest was time from index date to date of non-TB-caused death measured in person-years. Secondary outcomes were time from index date to date of cause-specific death measured in person-years. The Index date for this study was the date residency in BC was established, defined as (a) 90 days before MSP coverage start (*n* = 1,076,627; 99.45%) or (b) first healthcare contact in BC (*n* = 6,008; 0.55%), whichever came first. The censoring date was defined as the first of death, discontinuation of MSP coverage, or December 31, 2015. Primary causes of death were coded by the ICD-9-CM and ICD-10-CA recorded on death certificates. We grouped the primary causes of death into the following categories: all-non-TB-causes (ICD-9-CM: all codes other than 011x-018x; ICD-10-CA: all codes other than A15x-A19x), cardiovascular diseases (ICD-9-CM: 39x-41x; ICD-10-CA: Ix), respiratory diseases (ICD-9-CM: 46x-51x; ICD-10-CA: Jx), cancers (ICD-9-CM: 14x-23x; ICD-10-CA: Cx, D1x, D2x, D3x, D4x), and injuries/poisonings (ICD-9-CM: Ex; ICD-10-CA: Sx, Tx, Vx, Wx, Xx, Yx).

1.3.2.2 Exposure

The exposure of interest was diagnosis with TB during residency in BC. BCCDC TB Registry diagnosis, treatment, and laboratory files were used to develop a TB definition based on Canadian TB Standards.[30] Both clinically diagnosed and microbiologically confirmed cases were included in our TB definition.[71] Post-mortem TB diagnoses were removed from the TB exposure definition. We used a time-varying exposure variable for this analysis in which exposed time begins at TB diagnosis date and continued until a censor or event date was reached. Unexposed time from those diagnosed with TB

was time contributed from index date up to TB diagnosis date. We only considered the first diagnosis of TB; time thereafter was exposed time. The unit of time used in this analysis was 'year'.

1.3.2.3 Cohort Characteristics (Covariates)

Cohort members were described in terms of age, sex, TB incidence rate per 100,000 population in country of origin (<100, 100 to <200, 200 to <300, ≥300), neighbourhood income quintile, immigration class (economic, family, refugee, other), educational qualification (none/unknown, secondary or less, trade/diploma, or university degree), number of comorbidities in year prior to TB diagnosis or reference date (weighted Charlson Comorbidity Index: 17 conditions weighted from 1 to 6; continuous measure),[90,91,96] and year of index (0: 1985 to 30: 2015; continuous measure), which is the year BC residency began.

1.3.3 Statistical Analysis

We compared cohort characteristics between TB and non-TB groups by the use of standardized mean difference (SMD).[97] We compared categorical cohort characteristics between people experiencing the event (non-TB-mortality) and those censored using univariable Cox regressions of time-to-non-TB mortality. We plotted an extended Kaplan-Meier (KM) curve for non-TB mortality stratified by a time varying indicator of TB diagnosis, using the date of residency as index date, and date of diagnosis as beginning of TB exposed time, to visually display the time-varying effect of TB diagnosis on non-TB mortality risk over the study period.[60] We used time-dependent Cox regressions to compare time-to-death from date of residency between TB- exposed time (time from diagnosis with TB in BC until event or censoring date) with TB unexposed time (time from residency in BC up to TB diagnosis date

for those who developed TB, plus time from residency in BC to event or censoring date for those not diagnosed with TB) through hazard ratios (HRs) for risk of non-TB mortality.[98]

Unlike group-based Cox proportional hazards (PH) regression, which classifies people as exposed or unexposed for all person-time, and was used in a previous study of mortality among TB survivors in a low-incidence, high-income setting,[99] time-dependent Cox regression compares person-time under exposure versus person-time under no exposure. The resulting HR estimates for TB diagnosis are interpretable as the ratio of the hazard of mortality for a person with a TB diagnosis vs that for a person without a TB diagnosis (but who may be diagnosed later) at any given year.[100] This modelling technique is superior to group-based analyses as it allows individuals to have a common index date (immigration to BC) and to contribute both exposed and unexposed time to the analysis,[98] avoiding potential pitfalls due to immortal time bias.[57,58,101]

We conducted unadjusted time-dependent Cox regressions, then adjusted for age and sex, and then adjusted for covariates that were likely to confound the relationship between TB and mortality risk.[33] When constructing the covariate-adjusted model, we created a series of directed acyclic graphs (DAGs) through an iterative process.[55] After this DAG process, we assessed each covariate deemed valuable to our analysis based on association with the outcome through univariable Cox regressions at $\alpha = 0.50$ for consideration in the multivariable model (main analysis).[102] When the full model was fit to the data, we used backward selection based on Akaike's Information Criterion (AIC) to remove covariates, with decisions based on clinical and statistical considerations.[98]

1.3.4. Sensitivity and Sub-Group Analyses

A series of sensitivity analyses were performed. First, we included all persons diagnosed with TB, regardless of TB treatment outcome. Second, we required a minimum two-year observation window (alive and in BC) around the TB diagnosis or randomly-selected reference date (one year before and one year after). Third, we restricted the main analysis to ages 18 to 60 years and required treatment completion among those diagnosed with TB. Fourth, we required persons diagnosed with TB to have completed treatment and to have a minimum two-year observation window (alive and in BC) around the TB diagnosis or randomly-selected reference date (one year before and one year after). Fifth, we switched from the Charlson commorbidity index to the Elixhauser comorbidity index, which contains 30 comorbidities, and was used to control for comorbidities instead.[90,103]

For sub-group analysis, we analyzed data for males and females separately, requiring treatment completion among those diagnosed with TB, as sub-group analyses. We also conducted an effect modification analysis by immigration class. Finally, to examine the relationship between TB treatment completion and time-to-mortality from non-TB causes, we generated a group-based (standard) KM curve stratified by TB patients and non-TB controls using date of TB treatment completion and a randomly-selected reference date, respectively, as index dates. All analyses were conducted in Base SAS software v.9.4 and *R* v.3.4.4.

1.4 RESULTS

1.4.1 Analytic Sample

A total of 1,030,873 people immigrating to BC during 1985-2015 were included in our analytic sample (follow-up: 13.5 million person-years), with 2,435 people diagnosed with TB in BC with documented

treatment completion (Figure 1-A1). The remaining 1,028,438 people were not diagnosed with TB in BC. A total of 26,376 deaths occurred, with 285 deaths among TB patients and 24,887 deaths among non-TB controls. A total of 51,762 people (4.8%) were excluded from the analytic sample (Figure 1-A1).

1.4.2 Descriptive Analysis

The study sample was evenly distributed by sex (Table 1-A1). People diagnosed with TB were generally older, had higher levels of comorbidity, had lower socioeconomic status, were more frequently born in countries with the highest TB incidence, and tended to have earlier index dates than those without TB. Substantial differences between TB patients and non-TB controls were observed for most cohort characteristics. The most substantial differences were in mean Charlson Comorbidity Index score, TB incidence rate in the country of origin, with a smaller difference in mean index year, immigration class, and age at index. There were proportionately fewer TB diagnosed persons in the highest income and highest education categories than non-TB diagnosed controls.

All measured cohort characteristics had significant association with the outcome of non-TB death in univariable Cox regressions (Table 1-1). Age and Charlson comorbidity index were most strongly associated with non-TB mortality risk. A higher proportion of persons who died immigrated under family class (64.6%) than those who were censored (Table 1-1).

1.4.3 Survival Analysis

Unadjusted analyses indicated fourfold higher (HR = 4.01; 95% CI: 3.57-4.51) mortality risk for TB patients compared to non-TB controls (Table 1-2). Age/sex-adjustments attenuated the HR to twofold

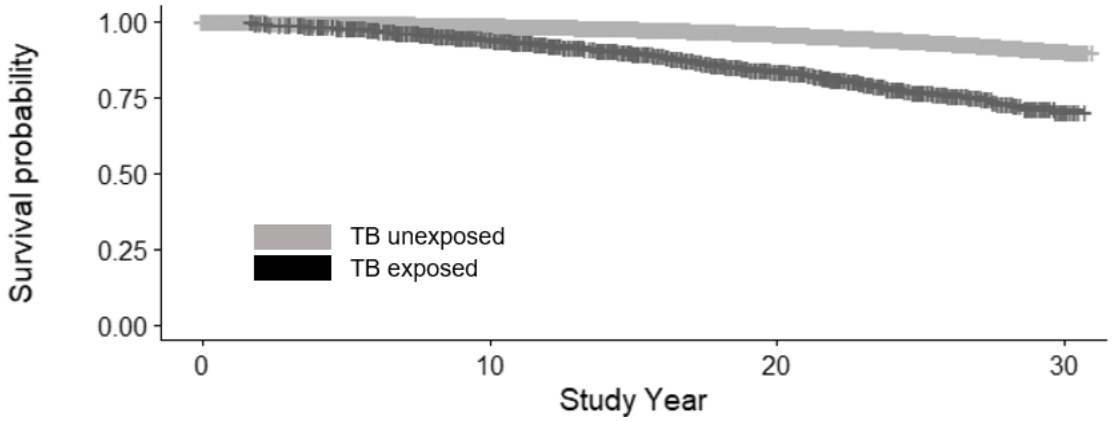
(aHR = 1.95; 95% CI: 1.74-2.20). Covariate adjustment further attenuated the HR (aHR = 1.69; 95% CI: 1.50-1.91), while remaining statistically significant. KM curves show an increasing difference in survival over the study period between TB exposed and TB unexposed time (Figure 1-1).

Table 1-1. Cohort characteristics among migrants to British Columbia, Canada, 1985-2015: comparison of people who died of non-TB causes (event) with those censored.

	Event *n* (%)	Censored *n* (%)	Crude HR[a]	*p*[a]
Total Cohort (N)	24887	1005986		
Tuberculosis Patients	285 (1.1)	2150 (0.2)	3.06	<0.01
Male	13389 (53.8)	487144 (48.4)	1.28	<0.01
Age at Index in years (mean (SD))	57.92 (17.51)	30.11 (16.14)	1.10	<0.01
Charlson Comorbidity Index (mean (SD))[b]	0.81 (1.67)	0.13 (0.50)	1.52	<0.01
Neighbourhood Income Quintile				<0.01
Highest 20%	3413 (13.7)	146827 (14.6)	1 (ref)	
Middle-High 20%	3624 (14.6)	144031 (14.3)	1.07	
Middle 20%	4534 (18.2)	183237 (18.2)	1.04	
Low-Middle 20%	6219 (25.0)	230383 (22.9)	1.09	
Lowest 20%	7097 (28.5)	301508 (30.0)	0.99	
Educational Qualification				<0.01
None/Unknown	3532 (14.2)	129308 (12.9)	1 (ref)	
Secondary or less	13756 (55.3)	427478 (42.5)	0.95	
Trade/diploma	4318 (17.4)	184562 (18.3)	0.74	
University degree	3281 (13.2)	264638 (26.3)	0.57	
Immigration Class				<0.01
Economic	4897 (19.7)	605414 (60.2)	1 (ref)	
Family	16072 (64.6)	295100 (29.3)	5.27	
Refugee	1499 (6.0)	79550 (7.9)	1.59	
Other	2419 (9.7)	25922 (2.6)	8.18	
TB Incidence in Country of Birth				<0.01
<100 per 100,000 population	8699 (35.0)	422089 (42.0)	1 (ref)	
100 to <200 per 100,000 population	8815 (35.4)	325569 (32.4)	0.99	
200 to <300 per 100,000 population	5322 (21.4)	141871 (14.1)	1.22	
300+ per 100,000 population	2051 (8.2)	116457 (11.6)	0.69	
Index Year (mean (SD))[c]	8.58 (5.88)	14.85 (7.12)	0.97	<0.01

Legend: HR = crude hazard ratio, p = p-value, SD = standard deviation, TB = tuberculosis.
Notes: [a] calculated from univariable Cox proportional hazards regressions for association between time-to-non-TB mortality and each cohort characteristic. [b] weighted Charlson comorbidity score calculated in the year prior to TB diagnosis or randomly-selected reference date for non-TB controls using both physician claims data and hospital discharge abstracts data (all diagnosis fields).[c] Index year is calculated as 0=1985 to 30=2015 (continuous) and represents the year residency in BC was established.

Figure 1-1. Extended Kaplan-Meier survival curve from date of residency in British Columbia (BC) to date of death from a non-tuberculosis (TB) cause among migrants to BC, Canada, 1985-2015.



TB unexposed	1,030860	601,666	229,490	7.089
TB exposed	523	1,317	977	44
Study year	0	10	20	30

Legend: TB = tuberculosis.

In any given year from date of immigration to BC, if an immigrant to BC was diagnosed with TB, their risk of non-TB mortality was 69% higher than it would be if they were not diagnosed with TB: 196% higher for respiratory mortality, 63% higher for cardiovascular mortality, 40% higher for cancer mortality, and 85% higher for injury or poisoning mortality (Table 1-2).

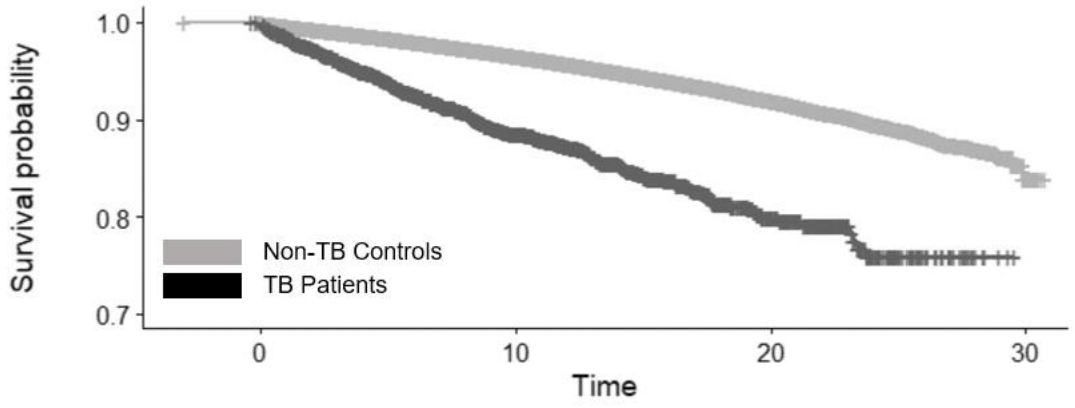
Table 1-2. Time-dependent Cox regression analyses of mortality risk among migrants to British Columbia, Canada, 1985-2015: tuberculosis (exposed) time compared to non-tuberculosis (unexposed) time.

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)

Legend: CI = confidence interval, HR = hazard ratio, TB = tuberculosis.
Notes: [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.

The analysis using KM plots with index time set to at treatment completion date (or randomly-selected reference date for non-TB controls) displays immediate divergence in the probability of death between TB patients and non-TB controls at the end of TB treatment, among those successfully completing treatment (Figure 1-2).

Figure 1-2. Kaplan-Meier survival curve calculated from date of TB treatment completion for TB patients and randomly selected reference date for non-TB controls: all non-TB causes of death among migrants to BC, Canada, 1985-2015.



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

Legend: TB = tuberculosis.
Notes: time means person-years from TB treatment completion date (TB patients) or randomly-selected reference date (non-TB controls) to event/censoring date.

1.4.3.1 Sensitivity and Sub-Group Analyses

Sex-specific sub-group analyses showed a higher overall HR for non-TB causes in males than females, as well as for each cause of death, particularly for injury/poisoning (Table 1-A2). Sensitivity analyses showed that the covariate-adjusted HR was higher when those not completing TB treatment were included in the analysis. This difference was reduced when we required TB patients and non-TB controls to be alive 1-year pre/post-diagnosis or reference date. In sensitivity analyses involving TB patients completing treatment the covariate-adjusted HR did not differ substantially from the main

analysis finding (Table 1-A3). We found evidence of modification of the effect of TB diagnosis by immigration class. Immigrants under the refugee class experienced less of an effect on mortality risk due to a TB diagnosis (aHR = 1.4) compared to economic (aHR = 2.4), family (aHR = 2.8), or other (aHR = 2.5) immigration classes.

1.5 DISCUSSION

1.5.1 Summary

This is the first Canadian study to examine long-term mortality risk among TB patients compared to non-TB controls. Moreover, this is the first study to examine mortality exclusively among migrants with and without TB. Across causes of death, we found a significantly increased risk of mortality among TB patients compared with people not diagnosed with TB. In addition, we noted a disproportionate number of respiratory deaths among TB patients with close to triple the respiratory mortality risk in any given year during follow-up. This discrepancy seems biologically plausible given that the majority of TB is respiratory, and may impact long-term pulmonary function.[9,104] Moreover, smoking is more prevalent among people affected by TB and may contribute to higher mortality from respiratory diseases.[105] Respiratory mortality is likely more directly attributable to pulmonary TB, while injury and poisoning mortality, which had the second-highest HR, is less clearly attributable to TB and may be mediated through the above-noted health determinants. Similarly, cancer mortality and cardiovascular mortality may be related to the prevalence of tobacco smoking among persons diagnosed with TB. However, we cannot rule out systemic inflammation as an additional driver of cardiovascular mortality in TB patients

This is the first study to demonstrate effect modification of TB diagnosis on mortality hazard by immigration class. We demonstrated that people immigrating under the refugee classification did not experience as large an effect of TB on mortality risk as those immigrating under economic, family, or other classes. This finding reinforces the possibility that it is factors for which TB is a marker, rather than TB itself, that is driving the "effect" of TB on mortality, rather than TB itself. As a corollary, the higher aHR for a diagnosis of TB within economic, family, and other immigrant classes may also be interpreted as a stronger marker of such factors for mortality risk, increasing the importance of post-TB treatment follow-up care among non-refugee immigrant classes.

Our findings signal that TB may function as either a marker or causal risk factor for various forms of morbidity and mortality.[106–108] Elevated prevalence of poverty, depression, alcohol, tobacco, and substance use among persons diagnosed with TB likely play roles in the relationship between TB and mortality risk.[14,74,77,105] Current TB care guidelines do not address long-term TB patient health, focusing entirely on successful TB treatment.[30,109] However, in HIV medicine, guidelines have embraced total patient health and involve complete patient histories, chronic disease screening, mental health supports, and other standards of care not generally applied in TB.[110] Evidence of unmet post-TB treatment health needs that may best be flagged during TB care, with linkage to other services before TB treatment completion, with intervention research and guideline development indicated.[6] As a low-barrier public health service, TB care reaches many populations that are generally under served, making TB programs a potential hub for service integration among this often vulnerable patient population.

Several cohort studies have examined excess death in persons diagnosed with TB.[106,107,111,112] A recent systematic review by Romanowski et al. found a pooled standardized mortality ratio for persons treated

for TB compared to the general population of 2.91 (95% CI: 2.21 – 3.84).[33] A review by Byrne et al. of respiratory disease in TB patients compared to non-TB controls showed a pooled OR of 3.01 (95% CI: 2.42-3.85). The studies included in the review by Romanowski et al. primarily used age and sex-specific rates to compute indirectly standardized mortality ratios or used age/sex-matched comparison groups. However, one study adjusted for covariates beyond age and sex,[99] while another employed sibling controls.[106] Because we confined our analysis to persons born outside Canada (migrants), adjusted for more confounders, and used a more extended follow-up period, we cannot directly compare our results with any of the studies reviewed by Romanowski et al. However, our conclusions are similar.

1.5.2 Strengths and Limitations

This study has important strengths, including use of a long follow-up period (almost 3 decades), virtually complete capture of the entire immigrant population of BC, including a large number of controls; a modern statistical modeling strategy, employing DAGs, extended Cox regressions to overcome potential immortal time bias; population-based, legislated, data sources for outcome, exposure, and covariate ascertainment; and multiple sensitivity and sub-group analyses.

As with any observational study, we can only demonstrate that TB is correlated with increased mortality risk and cannot make a causal interpretation. Moreover, observational administrative data is limited to variables collected in the provision of healthcare and other services. The relationship observed between TB and mortality risk is likely due, at least in part, to unmeasured risk factors for mortality. In this study, smoking was a key unmeasured potential source of confounding in the relationship between TB and time-to-mortality that we were unable to adjust for in this analysis.

However, we did control for the Charlson comorbidity score, several conditions of which are strongly related to smoking, such as COPD. Our measure of neighbourhood income quintile may be subject to misclassification bias due to the use of an area-level measure for individuals, although results were robust to inclusion/exclusion of the income quintile variable. Generalization of the results of this study should be limited to immigrants within Canada but may have external validity in other high-income settings.

1.5.3 Future Research

With an increasing number of people who have completed TB treatment worldwide, there is a growing concern about the long-term health outcomes of TB patients.[9,11,113] Prospective longitudinal research could provide a vital data source for future studies of long-term health outcomes, and would enable measurement of variables not recorded in administrative data, such as health behaviours. Such prospective research may help elucidate relationships between TB and long-term morbidity and mortality that would, in turn, provide evidence for public health interventions to improve long-term health outcomes for TB patients. Establishing longitudinal cohorts of TB patients would also provide opportunities to conduct qualitative and mixed methods research to develop interventions for improving TB survivor health.

1.5.4 Conclusion

Among immigrants to BC, a diagnosis of TB increases long-term risk of mortality from causes other than TB. This increased risk appears immediately post-TB treatment completion. Immigrants diagnosed with TB are also at increased risk of mortality from causes with limited biological relationship to TB, raising new questions about TB's potential role as a marker for risk, in addition to

being a potential causal risk factor. Prolonged follow-up post-TB treatment, and chronic disease prevention and management integrated with TB care, may provide avenues for improving post-TB survival and quality of life. The true cost-effectiveness of TB prevention activities is likely underestimated by not considering long-term morbidity and mortality among people surviving TB. We hope that our findings serve as a call to action for TB programs and care providers in high-income settings to address all potential threats to TB patients' health.

2 Cardiovascular morbidity and mortality among persons diagnosed with tuberculosis: a systematic review and meta-analysis

2.1 SYNOPSIS

Introduction: The emerging epidemiological evidence of increased cardiovascular disease (CVD) risk among persons diagnosed with tuberculosis (TB) has not been systematically reviewed to date. Our aim was to review the existing epidemiological evidence for elevated risk of CVD morbidity and mortality among persons diagnosed with TB compared to controls.

Methods: EMBASE, MEDLINE, and Cochrane databases were searched (inception to January 2020) for terms related to "tuberculosis" and "cardiovascular diseases". Inclusion criteria: trial, cohort, or case-control study design; patient population included persons diagnosed with TB infection or disease; relative risk (RR) estimate and confidence interval reported for CVD morbidity or mortality compared to suitable controls. Exclusion criteria: no TB or CVD outcome definition; duplicate study; non-English abstract; non-human participants. Two reviewers screened studies, applied ROBINS-I tool to assess risk of bias, and extracted data independently. Random effects meta-analysis estimated a pooled RR of CVD morbidity and mortality for persons diagnosed with TB compared to controls.

Results: 6,042 articles were identified, 244 full texts were reviewed, and 16 were included, meta-analyzing subsets of 8 studies' RR estimates. We estimated a pooled RR of 1.51 (95% CI: 1.16-1.97) for major adverse cardiac events among those diagnosed with TB compared to non-TB controls (p=0.0024). A 'serious' pooled risk of bias was found across studies with between-study heterogeneity (I2 = 75.3%).

Conclusions: TB appears to be a marker for increased CVD risk; however, the literature is limited and is accompanied by serious risk of confounding bias and evidence of publication bias. Further retrospective and prospective studies are needed. Pending this evidence, best practice may be to consider persons diagnosed with TB at higher risk of CVD as a precautionary measure.

2.2 INTRODUCTION

Tuberculosis (TB) is the world's leading cause of death from an infectious disease with the highest incidence in low- and middle-income countries.[113] In 2018, 10 million persons were estimated to develop active TB with approximately 1.2 million deaths attributable to active TB among persons without known human immunodeficiency virus (HIV).[80] The absolute number of deaths attributable to active TB has declined 27% (from 1.8 million) between 2000 and 2018, with an estimated 42% drop in the TB mortality rate.[80] With declining mortality and increasing survival beyond treatment, there is a growing need to consider the long-term health of persons surviving TB treatment.[9,39,41,108,114] If the *End TB Strategy's* target of a 95% reduction in mortality from TB by 2035 is met,[115] the importance of considering the long-term health of persons surviving TB treatment will rise dramatically.

Cardiovascular disease (CVD) is a leading cause of death worldwide with epidemic increases in rates among low- and middle-income countries.[116] Links between infectious diseases and CVD have been drawn in recent years.[36] A recent review of literature on pneumonia and myocardial infarction showed significantly increased short- and long-term risk of myocardial infarction in those with pneumonia compared to those without.[117]

Given the chronic nature of TB, these links raise questions about the contribution of TB to CVD and its role as a potential risk factor (or marker) for CVD beyond traditional risk factors such as smoking, diet, and physical activity.[11,36] A recent narrative review described several plausible biological mechanisms for TB in CVD processes, including both active and latent TB,[11] while a series of analyses from Taiwan investigated a range of CVD outcomes associated with TB, such as ischaemic stroke and acute coronary syndrome.[37,118] Acute myocardial infarction risk has also been linked to active and latent TB

and other infectious diseases.[34,117,119,120] A systematic review of TB and hypertension did not find a significant association.[32]

As survival among persons diagnosed with TB improves, post-TB health is becoming a priority for TB researchers, programs, and care providers.[108] While HIV programs have adopted guidelines for noncommunicable disease screening and care,[121–123] similar guidance for patients diagnosed with TB is lacking. We therefore systematically reviewed the published literature on TB and CVD as a logical step towards evidence-based guidance.

Our objective was to critically appraise the epidemiological evidence for an association between TB and CVD. We sought to evaluate our hypothesis of elevated CVD among persons diagnosed with active or latent TB compared to the general population or suitable controls through a pooled relative risk (RR) estimate. In this study, CVD included death from, or diagnosis of, unstable angina, atherosclerosis, ischemic heart disease, coronary heart disease, myocardial infarction, ischemic stroke, hemorrhagic stroke, heart failure, cerebrovascular event, or peripheral arterial disease.

2.3 METHODS

This systematic review and meta-analysis was designed and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, as well as the Meta-Analysis of Observational Studies in Epidemiology checklist.[124–126] The study was prospectively registered.[127] We worked with a university librarian specializing in health research to develop our search strategy.

2.3.1 Data sources and searches

Both MeSH and text words were employed in the search strategy. MeSH search terms included "cardiovascular diseases" and "tuberculosis", including all subheadings for each, and various terms for trial, cohort, or case-control study designs (S1-S3 Tables). We also searched for specific cardiovascular diseases and variants of "tuberculosis" as text words based on our protocol.[127] The databases EMBASE®/Ovid®, MEDLINE®/PubMed® were searched for studies published between 1946 and January 17, 2020 (Table 2-A1, Table 2-A2). The Cochrane Database of Systematic Reviews and CENTRAL Registry of Clinical Trials were searched using similar terms from inception to January 10, 2020 and December 2019, respectively (Table 2-A3). The *International Journal of Tuberculosis and Lung Disease* was manually reviewed from June 1, 2013 to December 1, 2019 for relevant studies. Reference lists of included studies were manually searched for additional studies.

2.3.2 Study selection

We included published studies that: used trial, cohort or case-control study design; had a clinical or microbiological definition of TB; reported outcomes from a patient population that included persons diagnosed with TB; and reported a risk estimate of one or more types of CVD morbidity or mortality in persons diagnosed with TB compared to suitable control subjects with an estimate of precision. A study was excluded if it: did not provide a definition of TB for the population studied; did not provide a definition of the outcome(s) used in the study; was a duplicate study; did not have an abstract published in English; or did not involve human participants.

After duplicate articles were removed, two independent reviewers (CAB and SJS) screened titles and abstracts for relevance. The same two independent reviewers then reviewed the full text of all

remaining studies, applying inclusion and exclusion criteria independently, with any disagreements resolved by a third reviewer (JCJ).

2.3.3 Data extraction and quality assessment

Data required to describe the studies and conduct a meta-analysis were extracted and coded by two independent reviewers (CAB and SJS) using a common template. The extractions were reconciled through discussion and a third reviewer (JCJ) when necessary. From each study, we extracted first author's surname, country or setting of study, year published, study objective, source of the study sample, time period for enrollment, type of RR measure reported, RR estimate and 95% confidence interval, number of persons diagnosed with TB, type of TB among the exposure group, follow-up time, the CVD morbidity and mortality outcome, whether pre-existing CVD was removed from analytic sample (or otherwise analyzed incident CVD), the proportion of study population with HIV, and adjustment variables for the RR estimate used in the meta-analysis.

Two reviewers (CAB and SJS) independently assessed included studies for risk of bias (RoB) within studies using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, adapted to the observational studies included in our review and incorporating our protocol-anticipated concerns regarding confounding.[61,127] After RoB assessment was complete, reviewers arrived at an overall RoB judgment for each study by consensus. To provide a review-level RoB assessment, we calculated the mode of the overall RoB judgments across studies.

2.3.4 Data synthesis and analysis

A subset of reviewed studies with sufficient data appropriate to answer the review question and from non-overlapping populations were considered for quantitative synthesis. To synthesize the summary

measures across studies, we implemented an inverse-variance weighted meta-analytic approach to estimate a pooled RR and 95% confidence interval using the empirical Bayes estimator from a random effects model.[128–130] Between-study heterogeneity was quantified by the I^2 statistic and meaningfully presented in prediction intervals.[62] Forest plots were created displaying meta-analytic results.

We conducted both a per-protocol meta-analysis as well as a *post hoc* meta-analysis. The per-protocol meta-analysis adhered to the prospectively registered data analysis plan, and all sensitivity analyses flowed from this meta-analysis. A *post hoc* meta-analysis was conducted to provide a more interpretable pooled RR, restricted to active tuberculosis and major adverse cardiovascular events (MACE) including: cardiovascular mortality, acute myocardial infarction, unstable angina, and nonfatal stroke. However, because of the programmatic and clinical value of treating TB as a binary division of latent and active TB, we considered the *post hoc* meta-analysis as our main meta-analysis and base our final interpretations on this meta-analysis.

To assess the robustness of the findings from our per-protocol meta-analysis, we conducted three sensitivity analyses: first, we removed estimates from studies that required a medical condition other than TB for inclusion (i.e., HIV infection,[76,131] and non-chest surgery);[132] second, we excluded estimates that were not adjusted for risk factors beyond age and sex; and third, we removed one estimate that was of extra-pulmonary TB.. Two sub-group analyses were conducted, one analyzing only CVD mortality, and one analyzing only CVD events (acute myocardial infarction, ischaemic stroke, or cerebrovascular event). Publication bias was assessed through construction of Galbraith (radial) and funnel plots.[128,133] We used linear regression (Egger's) test and rank correlation test for

asymmetry with $\alpha = 0.05$ to judge significance of publication bias. All data analyses were conducted in *R* version 3.4.4.

2.4 RESULTS

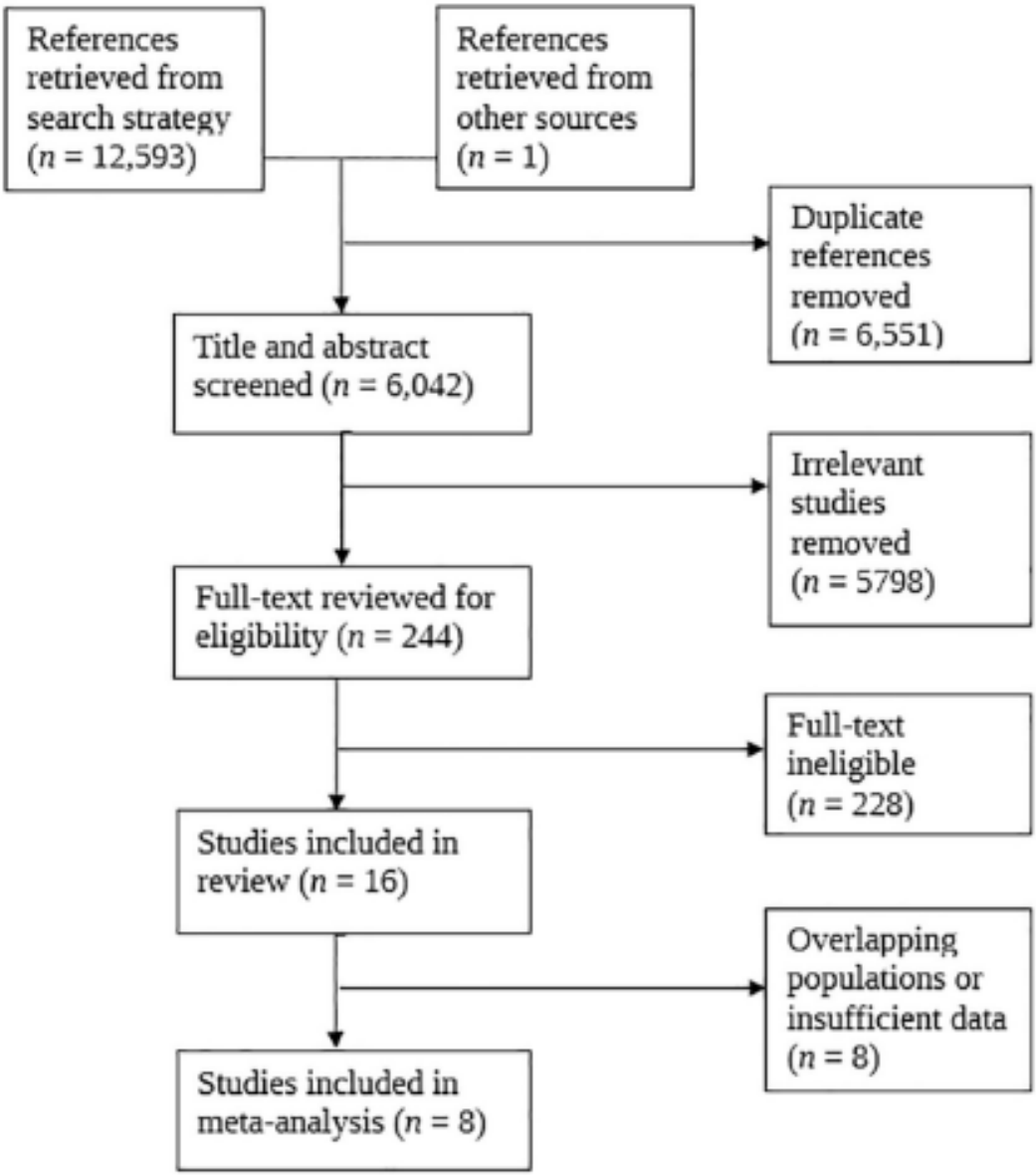
We identified 6,042 unique studies through our search strategy, including one identified through personal library search by CAB.[38] After removing irrelevant studies, we assessed the full text of 244 studies for eligibility, excluding 228 studies, keeping 16 studies, and meta-analyzing a subset of estimates extracted from these studies (Figure 2-1). We included one abstract found in our search as it provided data from a large number of people diagnosed with TB (n = 69,023), was presented at a reputable conference (CHEST), and was not otherwise published.[120] We also included one other study in our review that did not meet all inclusion criteria (did not define CVD)[112] because it involved a population (Russia) not otherwise represented in the review, and merited review in our opinion. However, neither was included in the meta-analyses.

2.4.1 Characteristics of included studies

Table 2-1 presents the characteristics of included studies. Fourteen studies examined active TB and CVD morbidity and mortality while two studies investigated latent TB and CVD. The included studies were from a variety of countries, sourcing their analytic samples from TB registries, hospitals, and the general population. Publication dates spanned 2006 to 2018. Eleven countries and one multi-centre cohort are represented in our review, with five studies based on Taiwan's National Health Insurance Dataset. Four studies sourced individuals from hospitals, seven from the general population, and four from TB registries, while one study did not identify its data source and another sourced data from

multiple centres. Follow-up time varied considerably across studies, ranging from 1 to 32 years, but averaged approximately five years (Table 2-1).

Figure 2-1. PRISMA flow diagram for articles related to cardiovascular morbidity and mortality among people diagnosed with tuberculosis.



Notes: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 2-1. Characteristics of included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality

First Author	Year	Country	Source of TB Data	Enrolment Period	People Diagnosed with TB	Design	Study Objective (page no.)	Follow-up in years: mean / median (max)	ROBINS-I Overall ROB
Bakari	2013	Tanzania	Hospital	2009-2010	34	Case-control	Identify factors (e.g., TB) associated with heart failure in people living with HIV with cardiac complaint (p. 1)	N/A	Serious
Blöndal	2013	Estonia	TB Register	2002-2009	2449	Cohort	Overall and cause-specific mortality among people with TB and MDR-TB compared to the general population (p. 961)	Mean = 5.3 (9 years)*	Serious
Christensen	2014	Denmark	TB Register	1977-2008	8291	Cohort	Long-term mortality in TB survivors compared with the general population (p. 406)	Mean = 9.6 (32 years)**	Serious
Chung	2014	Taiwan	Administrative Data	1997-2010	10168	Cohort	Assess risk of ACS in people with TB compared to controls (p. 80)	Not stated (13 years)	Serious
Giral	2007	France	Hospital	Not Stated	147	Case-control	Analysis of past TB in relation to carotid and femoral atherosclerosis (p. 151)	Mean = 25; SD = 11 between TB diagnosis and sonography	Serious
Hasanain	2018	Egypt	Hospital	2016-2017	54	Case-control	Assess LTBI prevalence among those with/without CAS and evaluate LTBI as predictor of CAS	N/A	Serious
Huaman	2017	United States	Administrative Data	2008-2010	2026	Cohort	Assess whether TB increased the risk of AMI after adjusting for CVD risk factors (p. 1364)	Not stated (1 year)	Moderate
Huaman	2018	Peru	Hospital	2015-2017	120	Case-control	Assess association between LTBI and AMI (p. 887)	N/A	Serious
Ke	2015	Taiwan	Administrative Data	2008-2010	6911	Cohort	Analyze CVD and other adverse outcomes after non-chest surgeries in people with pulmonary TB compared to people without TB (p. 2)	Not stated (2 years)	Moderate

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Table 2-1. Characteristics of included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality (continued)

First Author	Year	Country	Source of TB Data	Enrolment Period	People Diagnosed with TB	Design	Study Objective (page no.)	Follow-up in years: mean / median (max)	ROBINS-I Overall ROB
Mathew	2006	Russia	TB Register	2002-2003	1916	Cohort	Risk factors for death during TB treatment (p. 857)	Median = 241 days (censored at death or TB treatment completion)	Serious
Oh	2017	South Korea	Not Stated	2010-2014	69023	Cohort	Assess incidence of cardiovascular events during TB treatment and if pyrazinamide adds to this risk (p. A199)	Not stated (4 years)	NI
Pettit	2017	International	ART-CC Data Coordinating Centre	1996-2014	2174	Cohort	Assess the effect of TB (and other ADEs) on non-AIDS mortality risk (p. 2)	Median = 5.18 (IQR: 2.28 – 9.42 years)	Serious
Sheu	2010	Taiwan	Administrative Data	2000-2003	2283	Cohort	Assess ischemic stroke risk among people with TB during a 3-year period after diagnosis compared control patients (p. 244)	Not stated (3 years)	Serious
Shuldiner	2016	Israel	TB Register	2000-2010	3201	Cohort	Assess long-term mortality among TB survivors in Israel, compared to the general population (p. 43)	Median = 5.9 (11 years)	Critical
Wang	2017	Taiwan	Administrative Data	2000-2010	14350	Cohort	Assess PAD risk in people with TB compared to controls (p. 1671).	Mean = 5.82 (11 years)*	Moderate
Wu	2014	Taiwan	Administrative Data	2001	5804	Cohort	Assess ischemic stroke after contracting TB (p. 2)	Not stated (3 years)	Serious

Legend: ACS = acute coronary syndrome, ADE = AIDS defining event, AIDS = autoimmune deficiency syndrome, AMI = acute myocardial infarction, ART = antiretroviral therapy, ART-CC = Antiretroviral Therapy Cohort Collaboration, CAS = coronary artery stenosis, HIV = human immunodeficiency virus, MDR-TB = multi-drug resistant tuberculosis, NADE = non-AIDS defining event, NI = no information, PAD = peripheral arterial disease, ROBINS-I = Risk of Bias In Non-Randomized Studies of Interventions, ROB = risk of bias, TB = tuberculosis.
Notes: *average of means for each group, **average of medians for each group,

Table 2-2 presents all risk estimates extracted from the included studies. Study outcomes included CVD morbidity and mortality, which were primarily defined from ICD coding. One study defined CVD using the third universal definition of myocardial infarction,[119] while another defined CVD from multiple, variously coded, centres' datasets, using the CoDe Project protocol for coding causes of death

in HIV.[76,134] People with prevalent (pre-existing) CVD prior to or at time of TB diagnosis were excluded from most studies, with the aim of measuring incident CVD post-TB diagnosis, rather than co-existing TB and CVD. Studies analyzing CVD deaths did not remove people with pre-existing CVD. For the exposure variable, TB, ICD coding was also the most common method of ascertaining exposed persons. However, one study of latent TB infection (LTBI) and acute myocardial infarction (AMI) assessed LTBI using QuantiFERON-TB Gold,[119] Bakari et al. used a history of TB in medical records,[131] while Oh et al. and Pettit et al. did not provide TB definitions.[76,120] Another LTBI study with coronary artery stenosis (CAS) as the outcome, measured via percutaneous coronary angiography, used both tuberculin skin test (TST>10mm) and QuantiFERON-TB Gold positive as their exposure assessment.[135] People with HIV were variously: included in study populations (two studies included only people living with HIV in their analytic samples),[76,131] excluded from study populations,[34,119,135] or included as a proportion of the study population. The models and types of risk estimates varied considerably between studies but all were appropriate to answer our review question. Adjustments were made for age and sex in all studies considered for meta-analysis through either standardization or regression. Additional confounding factors were included in other risk estimates from included studies' regression analyses.

Table 2-2. Relative risk data extracted from included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality

First Author	TB Group (definition)	Prevalent CVD Excluded	HIV Population (percent)	CVD Outcome (definition)	Adjustment Variables	Type	Est[a]	95% CI	
Bakari	All active TB (history of TB)	No	Yes (only HIV included)	Heart failure (echocardiography)	Age, sex, primary education or less, haemoglobin level, CD4 count	OR	3.01	1.32	11.56
Blöndal	Pulmonary-Males (ICD10: A15-A16)	No	Mix (6.1% HIV)	Death from IHD (ICD-10: I20-I25)	Age and sex standardized	SMR	1.80	1.21	2.57
	Pulmonary-Females (ICD10: A15-A16)	No	Mix (3.4% HIV)	Death from IHD (ICD-10: I20-I25)	Age and sex standardized	SMR	3.94	1.28	9.20
	Pulmonary-Males (ICD10: A15-A16)	No	Mix (6.1% HIV)	Death from CBVD (ICD-10: I60-I69)	Age and sex standardized	SMR	2.08	1.04	3.71
	Pulmonary-Females (ICD10: A15-A16)	No	Mix (3.4% HIV)	Death from CBVD (ICD-10: I60-I69)	Age and sex standardized	SMR	3.50	0.72	10.23
Christensen	Pulmonary (ICD8: 011-013; ICD10: A15-A17)	No	Mix (1.7% among TB patients)	Death from CVD (ICD-8: 390–458.99; ICD-10: I00–I99)	Age and sex adjusted	MRR	1.19	1.08	1.31
	Extra-pulmonary (ICD8: 014-019; ICD10: A18-A20)	No	Mix (1.2% among TB patients)	Death from CVD (ICD-8: 390–458.99; ICD-10: I00–I99)	Age and sex adjusted	MRR	1.09	0.92	1.28
Chung	All active TB (ICD9: 011-018)	Yes (excluded anyone with ACS history)	Not stated (presume included)	ACS (ICD9: 410 and 411.1)	Age, sex, hypertension, diabetes, hyperlipidemia, cerebrovascular accident, COPD	HR	1.40	1.14	1.72
Hasanain	LTBI (TST>10mm and QuantiFERON-TB Gold positive on both tests)	No (studied first diagnosis of CAS but did not exclude people with other forms of prevalent CVD)	No (people with HIV excluded)	CAS (percutaneous coronary angiography)	Tobacco smoking, obesity, diabetes, dyslipidemia, metabolic syndrome.	OR	2.50	1.20	17.30

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Table 2-2. Relative risk data extracted from included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality

First Author	TB Group (definition)	Prevalent CVD Excluded	HIV Population (percent)	CVD Outcome (definition)	Adjustment Variables	Type	Est[a]	95% CI	
Huaman (2017)	All active TB (ICD9: 010.0-018.9)	Yes (excluded anyone with AMI claim in prior year or same month of TB claim)	No (people with HIV excluded)	AMI (ICD9: 410.0-410.9)	Age, sex, race, diabetes mellitus, hypertension, hyperlipidemia, obesity, tobacco use, CKD, major autoimmune disease	HR	1.98	1.30	3.00
	Pulmonary (not stated)	Yes (excluded anyone with AMI claim in prior year or same month of TB claim)	No (people with HIV excluded)	AMI (ICD9: 410.0-410.9)	Age, sex, race, diabetes mellitus, hypertension, hyperlipidemia, obesity, tobacco use, CKD, major autoimmune disease	HR	2.43	1.50	4.10
Huaman (2018)	LTBI (QuantiFERON-TB Gold)	Yes (only first AMI was studied)	No (people with HIV excluded)	AMI (third universal definition of myocardial infarction)	Age, sex, history of hypertension, history of diabetes mellitus, current tobacco use, history of dyslipidemia, family history of CAD, obesity	OR	1.90	1.05	3.45
Ke	Pulmonary (ICD9: 011)	No	Mix (1.1% HIV of matched cohort)	Stroke (ICD9: 430-438)	Age, sex, low income, urbanization, types of anesthesia, types of surgery, coexisting diseases (anemia, atrial fibrillation, CHF, COPD, diabetes, HIV, IHD, liver cirrhosis, mental disorder, Parkinson's, PVD, renal dialysis), organ transplantation, steroid use, emergency operation	OR	1.02	0.85	1.21

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Table 2-2. Relative risk data extracted from included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality

First Author	TB Group (definition)	Prevalent CVD Excluded	HIV Population (percent)	CVD Outcome (definition)	Adjustment Variables	Type	Est[a]	95% CI	
	Pulmonary (ICD9: 011)	No	Mix (1.1% HIV of matched cohort)	AMI (ICD9: 410)	Age, sex, low income, urbanization, types of anesthesia, types of surgery, coexisting diseases (anemia, atrial fibrillation, CHF, COPD, diabetes, HIV, IHD, liver cirrhosis, mental disorder, Parkinson's, PVD, renal dialysis), organ transplantation, steroid use, emergency operation	OR	0.89	0.57	1.38
Mathew	All active TB (Tomsk Oblast TB Services)	No	Mix (0.4% HIV)	Vascular disease death (death certificate primary cause of death)	Age and sex standardized	SMR	1.75	1.45	2.09
Oh	All active TB (treated with standard regimen)	Not stated	Not stated	CBVE or AMI (not stated)	Age and sex standardized	SIR	2.89	2.58	3.23
Pettit	All active TB (US-CDC definition of confirmed case)	No	Yes (only HIV included)	Death from CVD (CoDe: 08, 09, 12, 24)	CD4+ count, baseline HIV-1 RNA, sex, HIV transmission risk group, age, year of ART initiation, baseline ART regimen, ADE at or prior to the time of enrollment and ART-CC cohort	HR	2.90	1.57	5.36
Sheu	Non-CNS and non-meningitis TB (ICD9: 010-012, 014-018)	Yes (excluded anyone with stroke prior to index)	Mix (<0.1% HIV)	Ischemic stroke (ICD9: 433-438)	Age, sex, hypertension, diabetes, malignancy, coronary heart disease, hyperlipidemia, monthly income, geographical region, urbanization level, number of CT/MRI scans during follow-up period	HR	1.52	1.21	1.91

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Table 2-2. Relative risk data extracted from included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality

First Author	TB Group (definition)	Prevalent CVD Excluded	HIV Population (percent)	CVD Outcome (definition)	Adjustment Variables	Type	Est[a]	95% CI	
	Non-CNS and non-meningitis TB (ICD9: 010-012, 014-018)	Yes (excluded anyone with stroke prior to index)	Mix (<0.1% HIV)	Hemorrhagic stroke (not stated)	Age, sex, hypertension, diabetes, malignancy, coronary heart disease, hyperlipidemia, monthly income, geographical region, urbanization level, number of CT/MRI scans during follow-up period	HR	0.94	0.50	1.79
	Non-CNS and non-meningitis TB (ICD9: 010-012, 014-018)	Yes (excluded anyone with stroke prior to index)	Mix (<0.1% HIV)	Coronary Heart Disease (not stated)	Age, sex, hypertension, diabetes, malignancy, coronary heart disease, hyperlipidemia, monthly income, geographical region, urbanization level, number of CT/MRI scans during follow-up period	HR	1.21	1.08	1.36
Wang	All active TB (ICD9: 010-018)	Yes (excluded anyone with PAD prior to index)	Mix (<1% HIV)	PAD (ICD9: 440.0, 440.2–440.3, 440.8–440.9, 443, 444.0, 444.22, 444.8 and 447.8–447.9)	Age, sex, diabetes mellitus, hypertension, hyperlipidemia, CVD, stroke, COPD, asthma, CKD, HIV, HCV, urbanization level, insured premium	HR	3.93	3.03	4.95
	Pulmonary (ICD9: 011)	Yes (excluded anyone with PAD prior to index)	Mix (<1% HIV)	PAD (ICD9: 440.0, 440.2–440.3, 440.8–440.9, 443, 444.0, 444.22, 444.8 and 447.8–447.9)	Age, sex, diabetes mellitus, hypertension, hyperlipidemia, CVD, stroke, COPD, asthma, CKD, HIV, HCV, urbanization level, insured premium	HR	3.90	2.94	4.86

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Table 2-2. Relative risk data extracted from included studies for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality

First Author	TB Group (definition)	Prevalent CVD Excluded	HIV Population (percent)	CVD Outcome (definition)	Adjustment Variables	Type	Est[a]	95% CI	
	Extra-Pulmonary (ICD9: 010, 012-017)	Yes (excluded anyone with PAD prior to index)	Mix (<1% HIV)	PAD (ICD9: 440.0, 440.2–440.3, 440.8–440.9, 443, 444.0, 444.22, 444.8 and 447.8–447.9)	Age, sex, diabetes mellitus, hypertension, hyperlipidemia, CVD, stroke, COPD, asthma, CKD, HIV, HCV, urbanization level, insured premium	HR	2.11	1.31	3.56
	Miliary (ICD9: 018)	Yes (excluded anyone with PAD prior to index)	Mix (<1% HIV)	PAD (ICD9: 440.0, 440.2–440.3, 440.8–440.9, 443, 444.0, 444.22, 444.8 and 447.8–447.9)	Age, sex, diabetes mellitus, hypertension, hyperlipidemia, CVD, stroke, COPD, asthma, CKD, HIV, HCV, urbanization level, insured premium	HR	2.56	0.68	10.49
Wu	Non-CNS and non-meningitis TB (ICD9: 010-012, 014-018)	Yes (excluded anyone with stroke prior to index)	Not stated	Ischemic stroke (ICD9: 433-437)	Age, sex, hypertension, diabetes, atrial fibrillation, chronic rheumatic heart disease, coronary heart disease, other heart disease, hyperlipidemia, monthly income, urbanization level, and geographic region,	HR	0.92	0.73	1.14

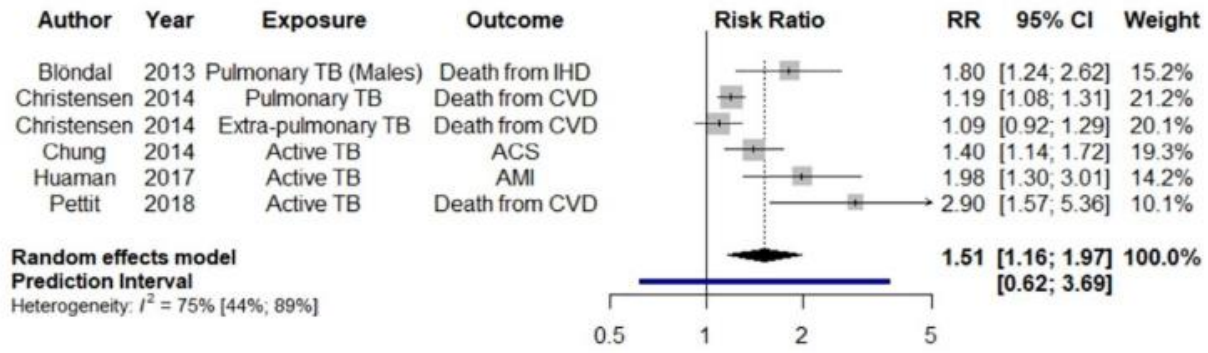
Legend: ACS = acute coronary syndrome, ADE = AIDS defining event, AMI = acute myocardial infarction, ART = anti-retroviral treatment, ART-CC = Antiretroviral Therapy Cohort Collaboration, CAD = coronary artery disease, CAS = coronary artery stenosis, CBVD = cerebrovascular disease, CBVE = cerebrovascular event, CHF = congestive heart failure, CI = confidence interval, CKD = chronic kidney disease, CNS = central nervous system, CoDe = Coding of Death in HIV Project, COPD = chronic obstructive pulmonary disorder, CVD = cardiovascular disease, CT = computed tomography, Est. = estimate, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HR = hazard ratio, IHD = ischemic heart disease, LTBI = latent tuberculosis infection, MRI = magnetic resonance imaging, MRR = mortality rate ratio, NI = no information, OR = odds ratio, PAD = peripheral arterial disease, PVD = peripheral vascular disease, TB = tuberculosis, SIR = standardized incidence ratio, SMR = standardized mortality ratio.
Notes: [a]All estimates (Est.) are adjusted for (or standardized by) variables listed in "Adjustment Variables" column.

2.4.2 Data synthesis and analysis

A subset of included studies (*n* =8) were meta-analyzed.[34,76,106,107,119,131,135,136] Because of overlapping populations from studies in Taiwan, we included only the study with the largest sample,[136] removing others.[37,38,132,137] Blöndal et al. reported two relevant outcomes, death from ischaemic heart disease and death from cerebrovascular event, with sex-specific estimates for each;[107] therefore, we included one outcome, ischemic heart disease death, including both sex-specific estimates, in our per-protocol meta-analysis. Wang et al. and Huaman et al. (2017) reported TB type-specific estimates but we opted to use the overall TB estimates as they were more stable and in line with our protocol.[35,136] We excluded from all meta-analyses two studies (Giral et al., and Shuldiner et al.) that presented only frequency tables for CVD outcomes.[111,138] We excluded Mathew et al. from the meta-analyses as the authors did not present a definition of CVD and their study contained only 4 deaths from CVD among TB patients;[112] excluded Oh et al. as they did not provide definitions for TB or CVD,[120] and excluded the estimate for females from Blondal et al., as its confidence interval was asymmetrical.[107]

Figure 2-2 presents our *post hoc* meta-analysis results for MACE among persons diagnosed with active TB (pooled RR = 1.51; 95% CI 1.16-1.97, p=0.0024), with I^2 = 75.3%, and prediction interval of 0.62 to 3.69. For the *post hoc* meta-analysis, we removed the studies of latent TB.[119,135] We then pooled studies reporting MACE.[131,136] For this analysis, in place of Wang et al. (outcome: peripheral arterial disease),[136] we substituted the second largest study from Taiwan, which analyzed AMI and unstable angina as the combined endpoint of acute coronary syndrome.[139] We consider this meta-analysis the main analysis as it is more interpretable due to more harmonized definitions of TB and CVD.

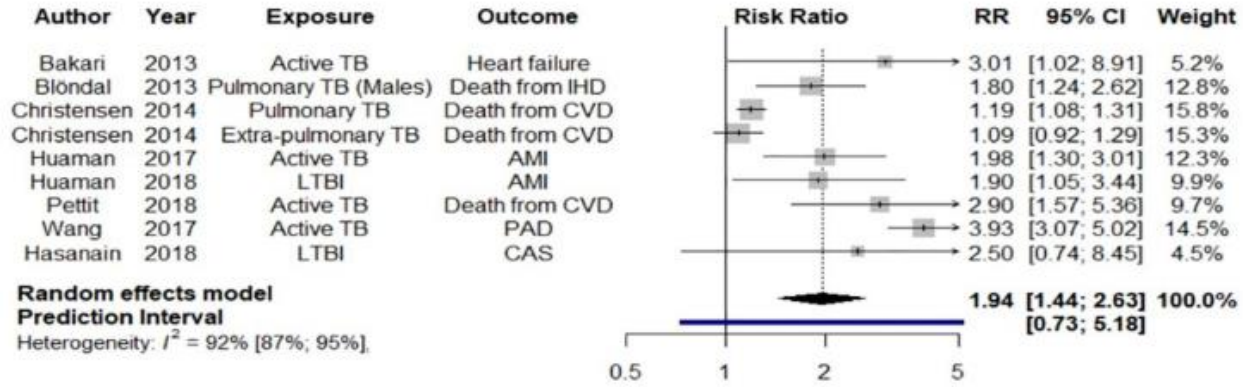
Figure 2-2. Forest plot of *post hoc* random effects meta-analysis results for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality



Legend: ACS = acute coronary syndrome, AMI = acute myocardial infarction, CBVE = cerebrovascular event, CI = confidence interval, CVD = cardiovascular disease, IHD = ischemic heart disease, RR = risk ratio, TB = tuberculosis. Black diamond = pooled RR and 95% confidence interval; blue bar = 95% prediction interval.

Figure 2-3 presents our per-protocol meta-analysis results of CVD morbidity and mortality risk among persons diagnosed with TB. The pooled RR of CVD morbidity and mortality among persons diagnosed with TB was 1.94 (95% CI 1.44-2.67, p<0.0001). Significant heterogeneity was found between estimates (I^2 = 92%), and this heterogeneity is reflected in the prediction interval of 0.73 to 5.18.

Figure 2-3. Forest plot of per-protocol meta-analysis for systematic literature review of tuberculosis and risk of cardiovascular disease and related mortality



Legend: AMI = acute myocardial infarction, CAS = coronary artery stenosis, CBVE = cerebrovascular event, CI = confidence interval, CVD = cardiovascular disease, IHD = ischemic heart disease, PAD = peripheral arterial disease, RR = risk ratio, TB = tuberculosis. Black diamond = pooled RR and 95% confidence interval; blue bar = 95% prediction interval.

2.4.3 Risk of bias within and across studies

One study had insufficient information to judge RoB, while the remaining were judged at 'critical' (n = 1), 'serious' (n = 11), 'moderate' (n= 3), or 'no information' (n = 1) for RoB using the ROBINS-I tool (Table 2-1). The mode of the RoB of individual studies in the confounding domain was 'serious', which determined the overall RoB of most studies as 'serious', based on the ROBINS-I guidance.[61] We estimated the pooled RoB across studies to be 'serious'. Radial and funnel plots for the per-protocol analysis indicated potential publication bias (Figure 2-4 and Figure 2-5), yet insufficient evidence to reject the null hypothesis of symmetry (linear regression test: $p = 0.1095$; rank correlation test: $p = 0.5316$).

Figure 2-4. Publication bias assessment: radial plot for per-protocol meta-analysis of tuberculosis and risk of cardiovascular disease and related mortality

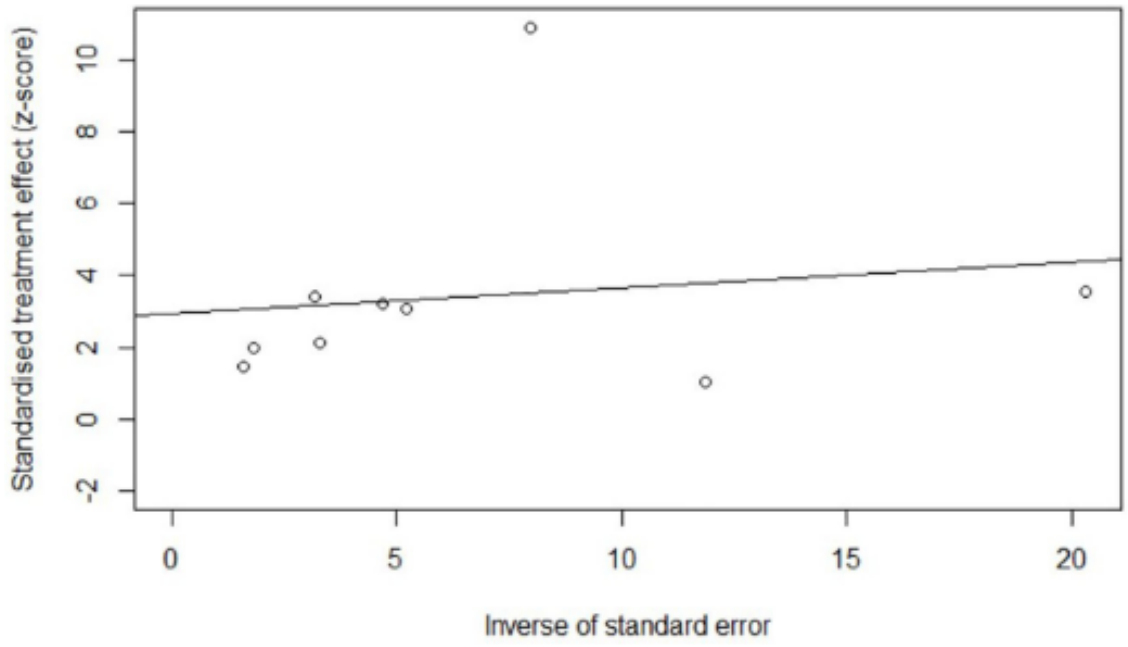
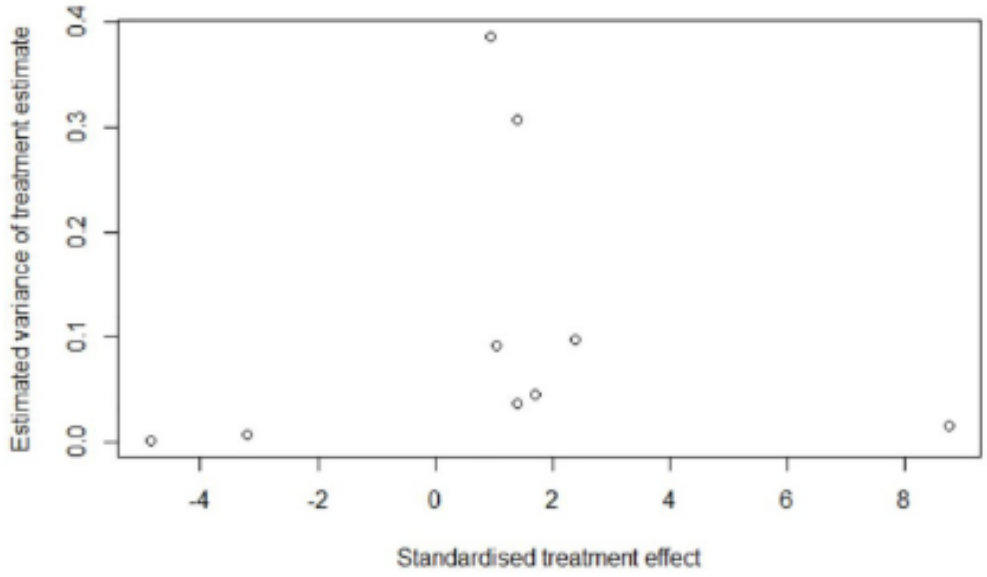


Figure 2-5. Publication bias assessment: funnel plot for per-protocol meta-analysis of tuberculosis and risk of cardiovascular disease and related mortality



However, when the post hoc meta-analysis was subjected to these tests, we observed asymmetry (Fig 6 and Fig 7) with sufficient evidence to conclude that the hypothesis of no publication bias could be rejected (linear regression test: $p = 0.0186$; rank correlation test: $p = 0.0146$)

Figure 2-6. Publication bias assessment: radial plot for *post hoc* meta-analysis of tuberculosis and risk of cardiovascular disease and related mortality

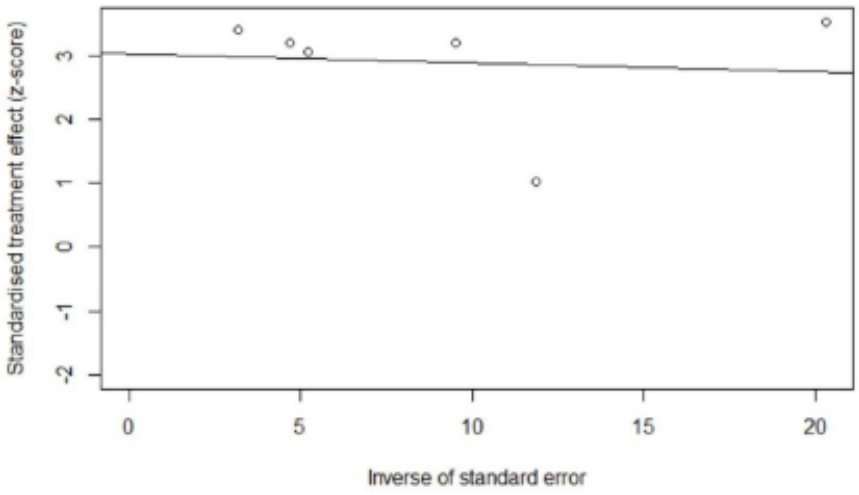
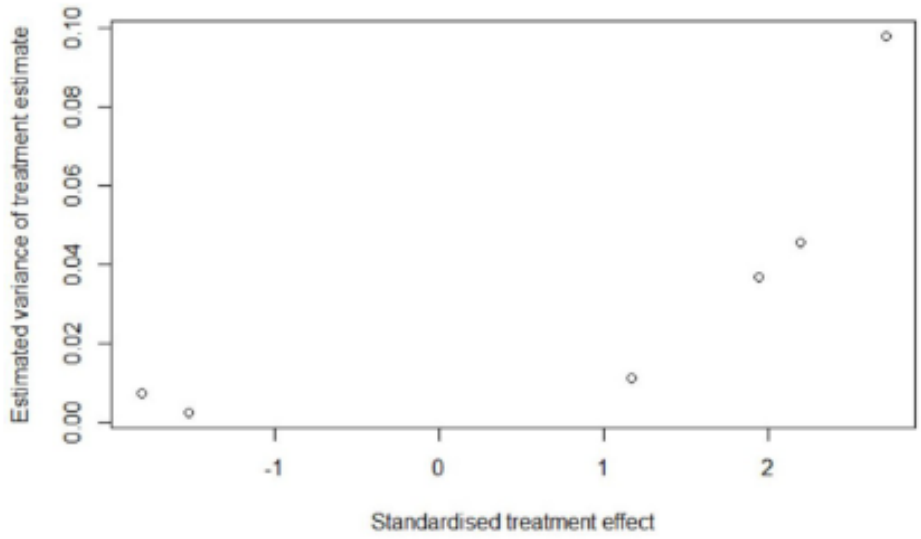


Figure 2-7. Publication bias assessment: funnel plot for *post hoc* meta-analysis of tuberculosis and risk of cardiovascular disease and related mortality



2.4.4 Sensitivity and subgroup analyses

The finding of elevated CVD morbidity and mortality from both the per-protocol and post hoc meta-analyses were robust to inclusion/exclusion of: estimates from studies enrolling populations requiring a medical condition beyond TB (people living with HIV,[76,131] hospitalized persons,[119] and non-chest surgery patients);[132] estimates that were not adjusted for risk factors beyond age and sex;[34,76,119,131,136] and the estimate from a study of extrapulmonary TB and CVD mortality[106] (Table 2-3). Sub-group analyses showed lower pooled RRs from the per-protocol meta-analysis, for both CVD mortality,[76,106,107,112] and CVD events,[34,38,119] yet were consistent with the *post hoc* meta-analysis pooled RR, although the CVD events sub-group analysis was not statistically significant (p = 0.1557). Prediction intervals for all meta-analyses showed wide heterogeneity in potential RRs for patients with TB and future studies of TB and risk of CVD morbidity and mortality.

Table 2-3. Sensitivity and sub-group random effects meta-analyses of tuberculosis and risk of cardiovascular disease and related mortality

Sensitivity / Sub-Group Meta-Analysis	Pooled RR	95% CI	95% PI	p-value
Removed studies requiring a medical condition other than TB for inclusion from per-protocol meta-analysis	1.77	1.12–2.78	0.31–10.17	0.0140
Removed non-RF-adjusted estimates from per-protocol meta-analysis	2.78	2.12-3.63	1.46-5.29	<0.0001
Removed extra-pulmonary TB estimate from per-protocol meta-analysis.	2.22	1.66-2.95	0.93-5.24	<0.001
Sub-group: cardiovascular death only	1.70	1.09-2.67	.034-8.66	0.0205
Sub-group: cardiovascular events only	1.44	0.87-2.40	0.0036-584.38	0.1557

Legend: CI = confidence interval, PI = prediction interval, RF = risk factor, RR = risk ratio, TB = tuberculosis.

2.5 DISCUSSION

To our knowledge, this is the first systematic review to examine the relationship between TB and risk of CVD morbidity and mortality. Our findings indicate that persons diagnosed with TB are at elevated risk of CVD morbidity and mortality compared to persons not diagnosed with TB. Sensitivity and sub-group analyses had consistent conclusions. The significant and positive association observed between TB and CVD risk may be causal or proximal in nature due to the limitations of the studies included, as noted below. A pooled 51% increased for MACE among people diagnosed with TB compared to non-TB controls was found (95% CI: 16-97%). Because only two reviewed study examined LTBI and CVD,[35,135] our findings are not generalizable beyond active TB.

Our finding of increased CVD risk among people diagnosed with TB is consistent with the literature. A related review of the relationship between acute infections and AMI showed pooled RRs for CVD events in persons diagnosed with pneumonia compared to those without pneumonia ranged from 3.2 to 6.3 during the first four weeks from infection onset, with long-term (1 to 4 years post-infection onset) RRs ranging from 1.5 to 2.5.[117] A systematic review of TB and all-cause mortality found a similarly

elevated mortality rate among those diagnosed with TB (pooled standardized mortality ratio = 2.91; 95% CI 2.21-3.84), for which the authors attributed 20% (95% CI 15-26) to CVD.[33] These findings are consistent with our meta-analytic conclusion of increased risk, but our pooled effect size was considerably lower than that for post-TB mortality.

2.5.1 Strengths and limitations

From an epidemiological point of view, there are important strengths yet critical limitations to our review. The search strategy was limited to English language studies. The pooled RR estimate included a wide range of CVD outcomes from diverse source populations, including a mix of pulmonary and extra-pulmonary forms of TB, examined through a variety of designs and statistical models producing a variety of effect estimates. While this review contains many types of CVD morbidity and mortality, we view this as a strength: guarding against underestimation of TB's role as a marker for CVD risk. Most reviewed studies adjusted for multiple potential confounders.

Within included studies, lack of control for smoking was a key source of potential bias and thus affected our review-level pooled RoB estimate. However, three studies adjusted for current tobacco use all of which found increased CVD risk among those diagnosed with TB.[34,119,135] The adjustment for chronic obstructive pulmonary disease in two studies provided an indirect form of adjustment for confounding by smoking.[136,139] The effects of other infectious diseases (e.g., HIV) and socioeconomic status were also potential sources of bias that were not adjusted for in all analyses. Income and socioeconomic status generally are related to CVD risk. Adjustment for income was made in three of the reviewed studies.[37,38,136] Two of the studies, Sheu et al. and Wang et al.,[37,136] found a significant association between TB and CVD, and one of the studies, Wu et al., had a null finding.[38] Bakari et al.

adjusted for education in their analysis of heart failure among patients with a history of TB compared to no TB history, and found a significant association between TB and CVD.[131]

These limitations preclude unbiased causal inference about the association between TB and CVD. However, they were considered in the ROBINS-I assessments and our conclusion about the significant positive association between TB and incident CVD can be tempered by the 'Serious' RoB assigned to our pooled RR estimate. Moreover, concern about lack of adjustment for these factors, or residual confounding, is less important when viewing our pooled RR as evidence of TB being a marker for CVD risk. However, critical knowledge gaps and study design challenges remain for future studies seeking to make causal inferences about TB and CVD risk, especially given that study data will largely remain observational in nature.[4,140]

2.5.2 Biological and clinical considerations

The mounting evidence for increased noncommunicable disease risk among TB patients has prompted numerous hypotheses and studies of potential mechanisms for the multi-directional relationships between TB and noncommunicable diseases.[4,140] There are a number of potential biological mechanisms relating TB to CVD, although none are definitive. It is possible that there are common biological mechanisms between TB and pneumonia in generating excess CVD risk.[11,36,117] In their narrative review, Huaman et al. summarized hypothesized biological mechanisms of CVD in people infected by TB as follows: direct effects on the myocardium or coronary arteries; pro-inflammatory cytokine expression; immune activation via macrophages and monocytes or $CD4^+$, TH1 and TH7 cells; and auto-immune mediation through mycobacterial heat-shock protein 65 antibodies.[11] These mechanisms are consistent with literature on CVD in infectious diseases such as pneumonia, hepatitis

C, and HIV.[36,119,135,138] These mechanisms are proposed to contribute to atherosclerotic plaque development over the long term, and to short-term increases in risk of cardiovascular events such as AMI.[11,36,117,139] In contrast, Giral et al. found no evidence of increased atherosclerosis among patients with a history of TB compared with those without a history of TB, although with a limited sample.[138]

Review-level conclusions about the epidemiological association between LTBI and CVD cannot be reached from the two included studies. However, TB exists on a continuum between LTBI and active TB, with an unknown latency period that could last a few months to a few decades.[7] LTBI involves continual production and clearance of *M. Tuberculosis* within the host and involves multiple potential sites in the body, with various host-organism immune interactions. These mechanisms are acting throughout the latent period, which may lead to long-term cardiovascular damage that manifests in adverse cardiovascular outcomes after active TB disease develops, similar, to some degree, as the hypothesized role of LTBI in development of diabetes mellitus.[140]

Although the evidence for CVD risk among persons diagnosed with TB is seriously limited from a causal inference perspective, we believe it is appropriate to adopt a precautionary approach to this evidence. A precautionary approach to CVD in TB care means that programs and practitioners consider the risks of not acting to prevent CVD morbidity and mortality until more complete evidence of increased risk is produced, versus the potential practical benefits for TB patients of implementing CVD prevention strategies based on provisional evidence, reasonable suspicion of risk, and often irreversible harm.[141] A first step may be to ensure existing CVD is diagnosed and known CVD risk factors prevalent among persons diagnosed with TB (for example, exposure to tobacco smoke,[105] alcohol consumption,[74] and diabetes)[75] are identified and managed.

CVD risk assessment among persons diagnosed with TB should follow current guidelines and evidence regarding screening asymptomatic adults.[142] There is likely limited risk to TB patients in screening for CVD and modifiable CVD risk factors, although randomized trial risk-benefit data for systematic CVD screening among TB patients is currently unavailable. In HIV medicine, CVD screening among people living with HIV has been incorporated into treatment guidelines.[121,122] A scientific statement was recently issued by the American Heart Association reviewing the mounting evidence for the risk of CVD, as well as prevention and management strategies, for people living with HIV.[143] In this statement, the REPRIEVE trial for vascular event prevention among people living with HIV is mentioned for its potential to provide the first RCT evidence of statins' efficacy in CVD prevention among people living with HIV.[144]

In TB medicine, statins have potential for improving TB treatment outcomes,[145] and are being considered as host-directed therapy in two trials where they are used as adjuvants to TB chemotherapy.[146–148] While not designed to assess the efficacy of statins for CVD prevention in TB patients, dose-safety data from these trials may inform future trials for TB patients with such a goal, similar, perhaps, to the REPRIEVE trial for HIV patients.[144] In the absence of RCT evidence of statin efficacy for CVD prevention in TB, a subgroup analysis of people with a history of TB within the REPRIEVE trial might provide estimates of statins' effectiveness for reducing CVD risk in people living with HIV with a history of TB. Retrospective pharmacoepidemiological studies of people diagnosed with TB who have received statin therapy may also provide observational evidence regarding statins' potential for reducing CVD risk in TB.

2.5.3 Conclusions

This paper reviewed the epidemiological evidence for increased risk of incident CVD among TB patients. Our meta-analysis suggests that a diagnosis of TB is a marker for elevated risk of CVD. This finding has implications for TB research and care: physicians treating patients with a diagnosis of active TB may consider these patients at elevated risk of CVD; hypothesized mechanisms leading to increased risk of CVD among persons diagnosed with TB could be examined prospectively; TB programs and care providers may also consider offering cardiovascular health assessment to persons diagnosed with active TB, guided by current CVD screening guidelines. While further research is needed that addresses the limitations of existing studies, by considering these implications, TB programs and care providers may be able to improve cardiovascular outcomes for people affected by TB.

3 Post-tuberculosis airway disease: a population-based cohort study of people immigrating to British Columbia, Canada, 1985-2015

3.1 SYNOPSIS

Background: Current epidemiological evidence of post-TB airway disease is largely cross-sectional and derived from high-TB-incidence settings. We present the first cohort study of post-TB airway disease in a low-TB-incidence setting. Aims: (1) analyze the risk of airway disease by respiratory TB, (2) assess potential unmeasured confounding between TB and airway disease, and (3) investigate TB effect measure modification.

Methods: A population-based cohort study using healthcare claims data for immigrants to British Columbia (BC), Canada, 1985-2015. Airway disease included chronic airway disease, asthma, bronchitis, or emphysema. Respiratory TB was defined from TB registry data. Adjusted Cox proportional hazards (PH) regressions were used analyzed time-to-airway disease by respiratory TB. Sensitivity analyses included varying definitions of TB and airway disease. Potential unmeasured confounding by smoking was evaluated by E-value and hybrid least absolute shrinkage and selection operator (LASSO)-high-dimensional propensity score (hdPS).

Results: In our cohort (N=1 005 328; n_{TB}=1141) there were 116 840 incident cases of airway disease during our 30-year study period (10.43 per 1,000 person-years of follow-up), with cumulative incidence of 42.5% among respiratory TB patients compared with 11.6% among non-TB controls. The covariate-adjusted hazard ratio (aHR) for airway disease by respiratory TB was 2.08 (95% CI: 1.91-2.28) with E-value=3.58. The LASSO-hdPS analysis produced aHR=2.26 (95% CI: 2.07-2.47).

Conclusions: A twofold higher risk of airway disease was observed among immigrants diagnosed with respiratory TB, compared with controls, in a low-TB-incidence setting. Unmeasured confounding is unlikely to explain this relationship. Models of post-TB care are needed.

3.2 INTRODUCTION

With an estimated 155 million TB survivors globally in 2020,[2] post-tuberculosis (post-TB) health has come to the forefront of international TB discourse and has become a research priority.[4,5,108,110] The elevated risk of post-TB respiratory disease has been demonstrated in TB survivors, but the evidence is currently limited in terms of study designs, small sample sizes, lack of studies from low-TB-incidence settings, and potential confounding bias in published studies.[8,9,12,13]

Despite limitations in the epidemiologic literature, it is apparent that post-TB airway disease is an important problem.[3,8,9,12,33,41,104,149,150] While resource constraints in high-TB-incidence settings limit the practicality of systematically assessing airway disease in TB survivors, high resource nations in North America and Western Europe have also not addressed this issue, even with simple investigations such as spirometry or exercise testing.[6,151] In fact, few epidemiological studies to date have examined post-TB airway disease risk in low-TB-incidence settings, and none have used cohort designs.[9,12] These studies have been unable to control for pre-existing airway disease.[12] Other studies, from higher TB incidence settings, have also primarily used cross-sectional designs.[9,12] Limited study of post-TB airway disease in low-TB-incidence settings raises questions about the generalizability of systematic review findings, including the relative and absolute risk of airway disease attributable to respiratory TB, in low-TB-incidence settings.

To the best of our knowledge, this paper presents the first cohort study of post-TB airway disease risk in a low-TB-incidence setting.[8,9,12] Our primary aim was to assess the risk of airway disease in TB survivors compared with non-TB controls in British Columbia (BC), Canada . Our secondary aim was to reduce the impact of unmeasured confounding such as smoking, for which information is frequently absent from health administrative datasets, and is considered a critical potential confounder.[9] Our third

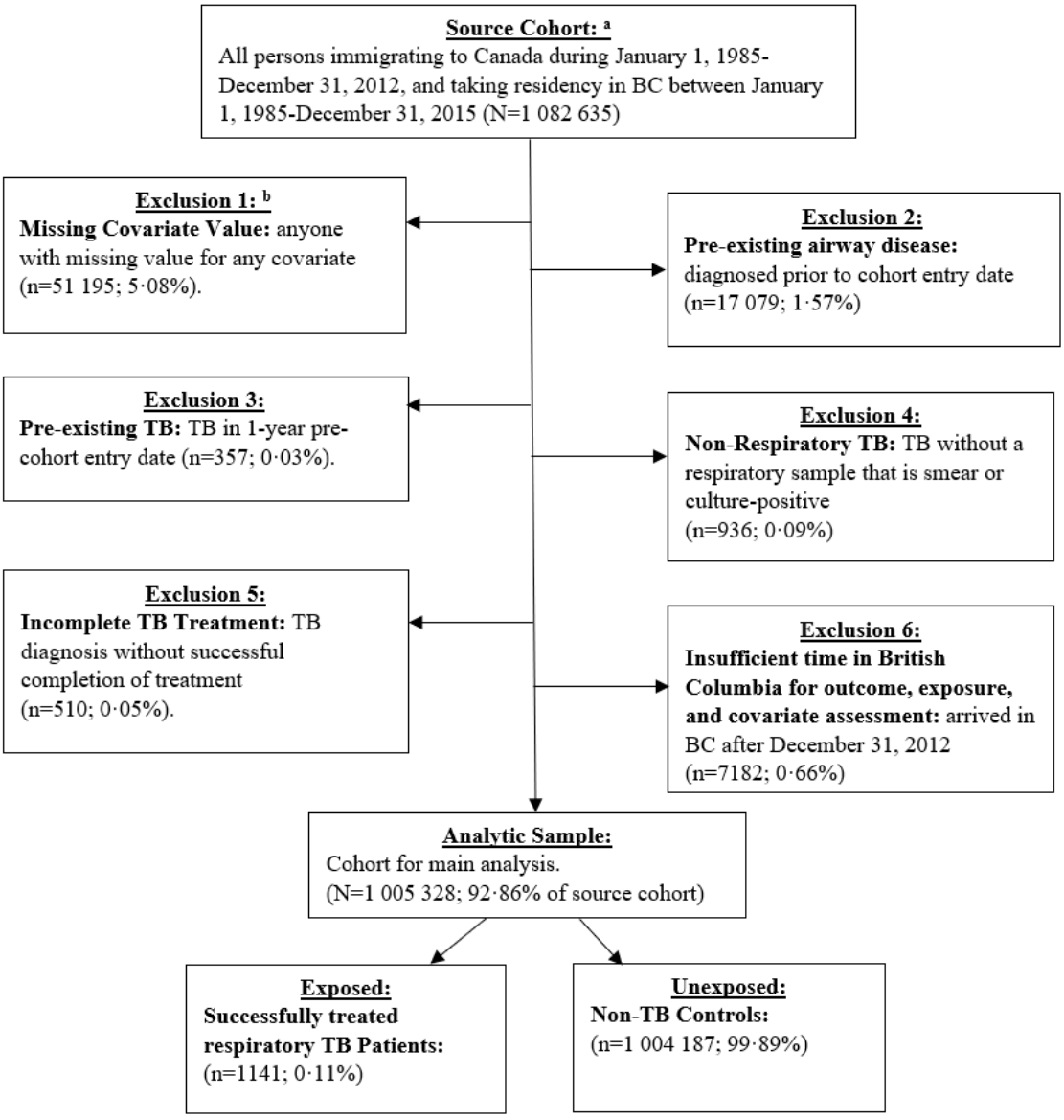
aim was to assess modification of respiratory TB's measure of effect on airway disease. We hypothesized a higher risk of airway disease among TB patients. In terms of effect measure modification, we hypothesized higher relative risk for airway disease by TB in younger age groups,[9] females,[152] people born in countries with higher TB incidence,[9] people who were not classified as 'at personal health risk' by our proxy variable,[153] people without baseline Charlson comorbidities,[9] and people in higher socioeconomic classes (due to expected lower exposure to airway disease risk factors).

3.3 METHODS

3.3.1 Study design and participants

We conducted a retrospective cohort study based on linked immigration, public health surveillance, and health administrative data to estimate incident airway disease and death, post-TB treatment completion. Population-wide health administrative data were sourced from the Province of BC, Canada, and the Government of Canada, with access provided through Population Data BC (Appendix C).[154] CAB and MEK accessed the data for this study's statistical analyses during March 2020-January 2021. The source cohort included all persons immigrating to Canada and taking residency in BC during January 1st, 1985-December, 31st, 2015. The cohort entry date (CED) was set to 365 days after the date of residency in BC, which was defined as 90 days prior to provincial health insurance coverage date, or date of first healthcare contact (Appendix C).[85,155] The 365 days prior to CED was used as a covariate assessment window, and time after CED was used for exposure and outcome assessment.[155] We excluded from the analytic sample people with: missing covariate values, airway disease prior to CED, respiratory TB prior to CED, non-respiratory TB, not classified as "completed-successfully" in TB registry, or residence in BC after December 31, 2012 (Figure 3-1). Altogether, these exclusion criteria removed 7.14% of participants (n=77 307) from the source cohort.

Figure 3-1. Flow chart: analytic sample for post-tuberculosis airway disease among people immigrating to British Columbia, Canada, 1985-2015.



Legend: BC = British Columbia, BCCDC = British Columbia Centre for Disease Control, IRCC = Immigration, Refugees, and Citizenship Canada, TB = tuberculosis. Notes: a Ascertained from IRCC permanent resident database. Residency in BC defined by acquisition of provincial health insurance (MSP) registration minus 90 days, or first healthcare contact, whichever occurred first. b Covariates for which people with a missing value were excluded were age, sex, income quintile, country of birth, immigration class, educational qualification, Charlson comorbidity index, or index year. Most people excluded in exclusion 3 were due to missing values for income quintile.

Ethics approval was provided by the University of British Columbia (H16-00265). Patient consent is not required when data collected during the administration of healthcare are anonymised and used for research. We obtained approval from each data steward prior to accessing the data, and for the manuscript.

3.3.2 Outcome: airway disease

The primary outcome for our study, time-to-airway disease, was described using total respiratory morbidity (TRM), which is an indicator variable developed by the Manitoba Centre for Health Policy for use with health administrative data in order to overcome coding variability between providers, patients of differing ages, and over time.[156] First published in 1993,[157] TRM has been used in various publications, spanning almost three decades, as a measure of airway disease incidence and prevalence in administrative data.[156] TRM was defined by the following diagnostic codes (ICD-9-CM: 466, 490-493, and 496; ICD-10-CA: J20-J21, J40-J45): asthma, bronchitis, bronchiolitis, emphysema, and chronic airway obstruction .[156] In our cohort, airway disease was ascertained from BC's hospital discharge abstracts, outpatient physician claims, and vital statistics death certificates. To meet our definition of airway disease, we required a single hospital visit (any diagnosis field), three or more physician visits within a 1-year period, or a death certificate with one of the codes above as the primary cause. The first date of hospital admission, physician service, or death with airway disease, was considered the event date for survival analysis. Participants were censored if they did not meet the airway disease definition prior to: death from another cause, loss of provincial health insurance coverage (proxy for residence in BC), or December 31, 2015 (end of study period). Time-to-airway disease, the outcome variable for our survival analyses, was calculated in person-years from the cohort entry date to censoring/event date.

3.3.3 Exposure: respiratory tuberculosis

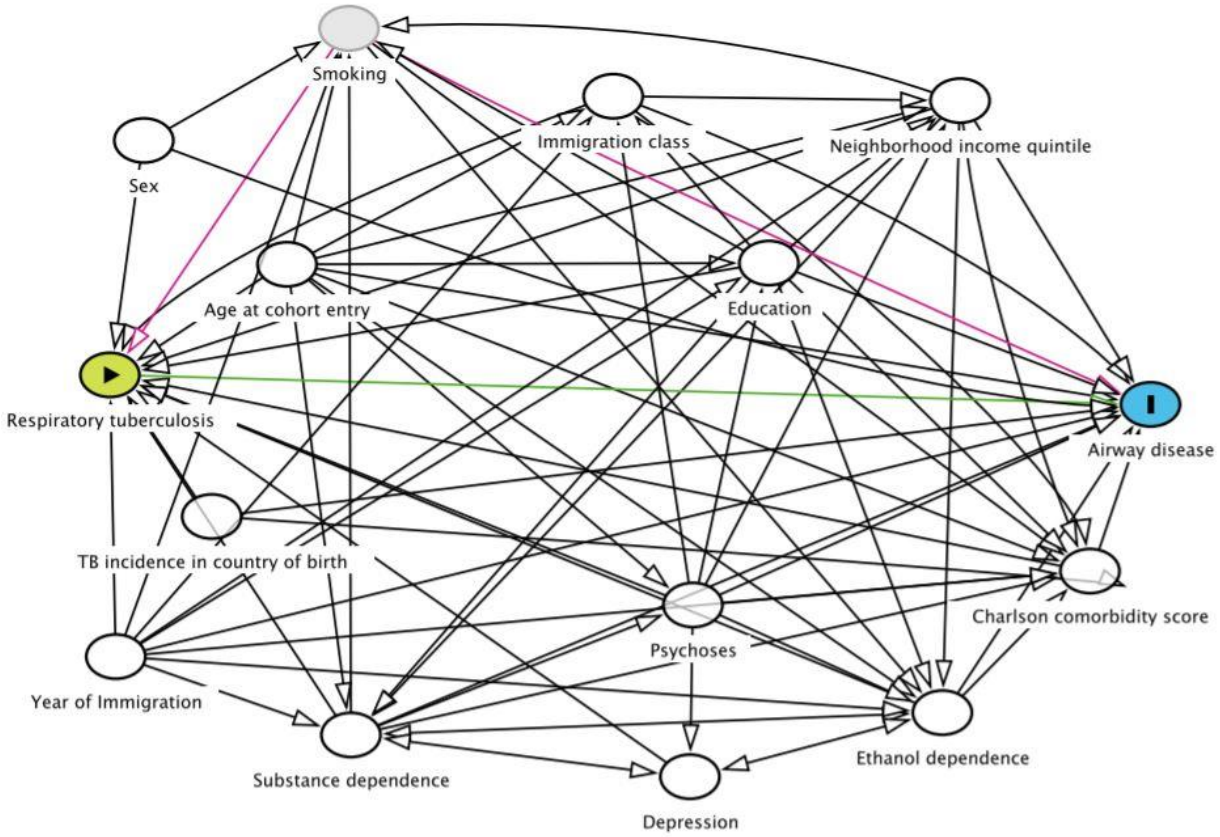
Our exposure variable was microbiologically confirmed respiratory TB, which was defined using BC Centre for Disease Control (BCCDC) TB registry data. In this definition, people with confirmed TB with a respiratory sample (sputum = 71.4%, bronchial washings = 10.3%, pleural fluids = 4.8%, other = 13.5%) from a respiratory system site (lung = 84.5%, bronchi = 9.9%, pleura = 3.3%, other = 2.3%) that tested positive for TB on acid-fast bacilli (AFB) smear (52.3%) or culture (47.7%) were considered exposed persons (n = 1141). People diagnosed with non-respiratory TB were excluded. People without successful completion of TB treatment were also excluded from the analytic sample in order to provide a more conservative effect estimate of respiratory TB on the risk of airway disease.[99,150,158] Successful treatment completion was defined using the treatment outcome description (value: "complete-successful") registered in the BCCDC TB registry's treatment dataset, which is maintained by TB surveillance staff, in collaboration with TB clinic staff, according to Canadian TB Standards.[30]

3.3.4 Covariates

Our directed acyclic graph (DAG) identifies assumed interrelationships among baseline covariates, respiratory TB, and airway disease (Figure 3-2). Baseline covariates were defined in a 1-year covariate assessment window prior to CED (Figure 3-A1). Age at CED, sex, income quintile of neighbourhood at CED,[9,159] educational qualification (less than secondary, secondary, college or trades school, university) at CED,[9,12,159] weighted Charlson comorbidity score (continuous) prior to CED,[90] TB incidence in birth country (<100, 100-200, and 300+ cases per 100,000 annually) at CED,[9] and year of residency in BC (to account for declining TB prevalence and rising airway disease prevalence over the study period).[73,160] Ethanol dependence (ETOH), drug abuse, depression, and psychoses are associated with

both TB and airway disease,[42,161] and were adjusted for in the analysis ascertained from physician claims or hospital visits and Elixhauser comorbidity index definitions.[90]

Figure 3-2. Directed acyclic graph (DAG) for post-tuberculosis airway disease among people immigrating to British Columbia, Canada, 1985-2015.



Legend: TB = tuberculosis. **Notes:** Developed using Daggity online tool. Respiratory tuberculosis is defined from surveillance data. Airway disease includes COPD, asthma, chronic bronchitis, bronchiolitis, and emphysema.

3.3.5 Statistical Analysis

We first calculated airway disease incidence rates among exposed (TB) and unexposed (non-TB controls) to understand the absolute risk of airway disease during follow-up. We then plotted a Kaplan-Meier curve to assess airway disease-free survival between respiratory TB patients and controls, as

well as the cumulative incidence of airway disease in each group, during follow-up. Data management was conducted in SAS 9.4 while statistical analyses were conducted in R v. 3.6.1.

Aim 1: analyzing post-tuberculosis airway disease risk

Cox proportional hazards (PH) regression was used for our analyses of time-to-airway disease, with the adjusted hazard ratio (aHR) as our measure of association. First, we conducted univariable Cox PH regressions of time-to-airway disease on each covariate. Second, we conducted an age and sex-adjusted analysis of time-to-airway disease by TB status. Third, we included, as main effects, all variables identified in the DAG as potential confounders in a multivariable Cox PH regression of time-to-airway disease (main analysis). Sensitivity analyses included: (i) we specified a reduced Cox PH model that excluded ETOH, substance dependence, psychoses, and depression variables, which had relatively low numbers; (ii) replacing the weighted Charlson comorbidity score with the van Walraven-weighted Elixhauser comorbidity score,[162] to check for consistency in the effect estimate; (iii) adding bronchiectasis and fibrosis codes (ICD9=494, 515, and ICD10=J47, J84) to the airway disease definition used in the main analysis; and (iv) removing TB patients with pleural samples (n=55) from the exposure group. Additional sensitivity analyses changed the definition of TB used in the study: we first analyzed all forms of TB; second, we analyzed people with with non-respiratory TB; last, we analyzed pleural TB vs non-pleural respiratory TB.

Aim 2: assessing potential unmeasured confounding

We conducted several sensitivity analyses to address the potential for unmeasured confounding. For example, smoking is a well-known risk factor common to TB and airway disease,[9,105] but this variable is not generally available in health administrative databases, including ours. To examine the theoretical

ability for an unmeasured confounder to explain away our effect estimate, we calculated E-values,[63,70] based on the prevalence of the outcome in our study population and our main analysis results. An E-value tell us what the minimum adjusted association an unmeasured confounder would have to have with both the exposure variable and the outcome variable to nullify the effect estimate of interest.[63] To assess the robustness of the primary analysis' effect estimates, we took the following approaches: (i) a propensity scores (PS) approach that included the covariates used in the primary analysis in a logistic regression PS model and then adjusted for deciles of the PS in a Cox PH regression outcome model; (ii) we incorporated empirical covariates (i.e., proxy variables from added data dimensions) identified through the hdPS algorithm (Appendix C), in addition to the covariates used in the primary analysis, as additional covariate adjustment;[66] (iii) we used a hybrid of the hdPS algorithm and the least absolute shrinkage and selection operator(LASSO), to eliminate highly collinear proxy variables from the hdPS model above while keeping the primary analysis covariates (Appendix C);[67] (iv) we used a subset of the analytic sample that were listed in the BCCDC TB Registry's "Person Table" that had a tobacco use variable (yes/no) available; and (v) we created a "personal health risk" proxy variable for smoking behaviour from the tobacco use variable in the BCCDC TB Registry, which was available for <5% of the cohort, and supplemented it with administrative data available for the entire cohort. This personal health risk proxy variable was included as an additional adjustment variable added to the main analysis. Administrative codes in physician claims and hospital abstracts were used to ascertain 'personal health risk', including codes related to: respiratory symptoms, cardiac symptoms, harmful exposures, personal health histories, substance dependence, nutrition and weight issues, and pregnancy complications. In addition to TB Registry tobacco use data, physician claims data, and hospital abstracts data, pharmacy dispensations data for bupropion, varenicline, or nicotine replacement therapies were added to the algorithm for ascertaining baseline personal health risk (Appendix C).

Aim 3: investigating effect measure modification

We created a series of separate adjusted Cox PH regression models to assess modification of the effect of respiratory TB on airway disease by: age group (age <40 vs 40+ years),[9] sex, TB incidence in country of birth (<200 vs 200+ cases annually per 100,000 population),[9] neighbourhood income quintile, personal health risk, education level, immigration class, baseline weighted Charlson comorbidity score (0, 1, 2+), and depression. In these analyses, we used Cox PH regressions with a variable for respiratory TB, in addition to the main analysis covariates, a covariate for the hypothesized effect modifier, and an interaction term for respiratory TB by the hypothesized effect modifier. Each effect modification term was analyzed separately.

3.4 RESULTS

3.4.1 Cohort characteristics

There were 1 005 328 people in our analytic sample (Figure 3-1) contributing 11 202 533 person-years of follow-up. The percentage of respiratory TB patients in our cohort was 0.11% (n=1141). The median follow-up time for respiratory TB patients was 11.83 years (inter-quartile range (IQR) = 6.25-18.91), and 9.75 years (IQR = 5.08-16.75) for non-TB-diagnosed controls. During follow-up, 42.5% (n=485) of respiratory TB patients developed airway disease after successful treatment completion, compared to 11.6% (n=116 355) of non-TB controls (p<0.00001, Table 3-A3). In participants developing airway disease (median follow-up = 6.60 years, IQR = 3.03-11.78), compared to those censored (median follow-up = 10.25 years, IQR = 5.49-17.41), we identified a higher proportion of: TB patients, females, older aged, lower neighbourhood income, lower education, non-economic immigration classifications, earlier date of immigration to BC, higher mean Charlson comorbidity score, ETOH, substance dependence, psychoses, depression, and people classified as ‘at personal health risk’ by our proxy

variable (Table 3-1). Univariable analyses indicated that all presumed confounders were associated with the outcome.

Table 3-1. Cohort characteristics stratified by outcome (airway disease or censored) among people immigrating to British Columbia, Canada, 1985-2015

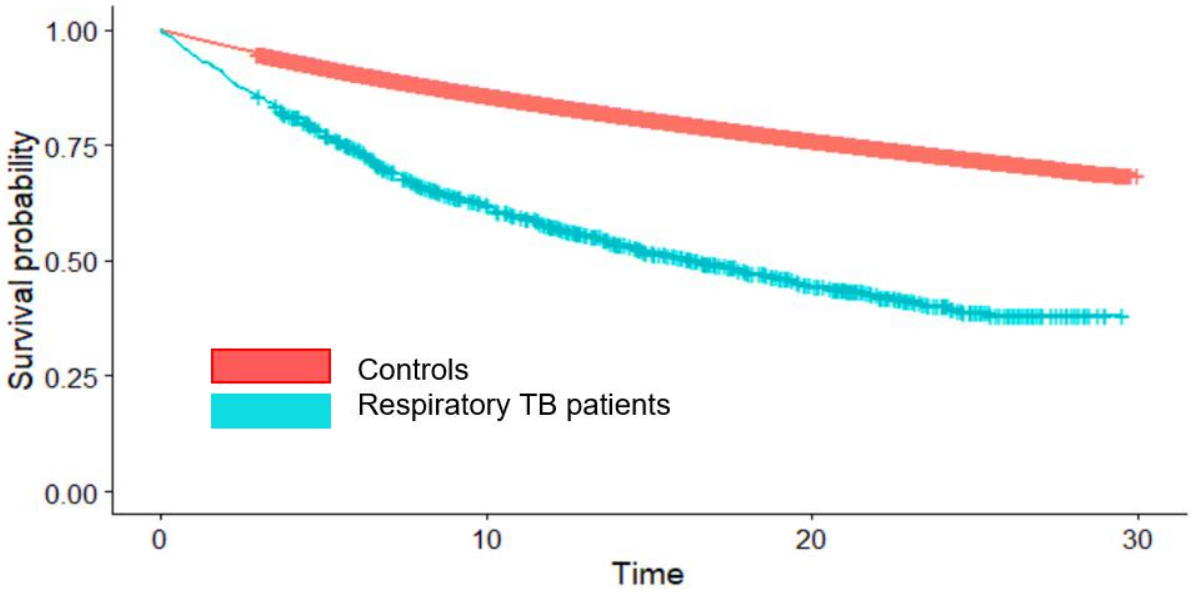
Characteristic	Censored N (%)	Airway disease N (%)	Crude HR	95% CI
Total	888 488	116 840	-	-
Respiratory tuberculosis	656 (0.07)	485 (0.42)	3.24*	2.96-3.54
Follow-up time (mean (SD))	11.56 (7.36)	7.97 (6.02)	-	-
Sex	-	-	-	-
Female	455 737 (51.29)	62 248 (53.28)	Ref	Ref
Male	432 751 (48.71)	54 592 (46.72)	0.95*	0.94-0.96
Age, years (mean (SD))	32.41 (16.33)	35.04 (18.81)	1.01*	1.01-1.01
Neighbourhood income quintile	-	-	-	-
Highest 20%	133 301 (15.00)	13 468 (11.53)	Ref	Ref
Middle-High 20%	128 939 (14.51)	15 001 (12.84)	1.14*	1.12-1.17
Middle 20%	161 746 (18.20)	21 343 (18.27)	1.28*	1.25-1.31
Low-Middle 20%	201 033 (22.63)	29 692 (25.41)	1.40*	1.37-1.43
Lowest 20%	263 469 (29.65)	37 336 (31.95)	1.37*	1.35-1.40
Education level	-	-	-	-
None/Unknown	109 282 (12.30)	18 657 (15.97)	Ref	Ref
Secondary or less	374 619 (42.16)	57 554 (49.26)	0.76*	0.74-0.77
Trade/diploma	164 367 (18.50)	20 595 (17.63)	0.65*	0.64-0.66
University degree	240 220 (27.04)	20 034 (17.15)	0.54*	0.53-0.55
Immigration class	-	-	-	-
Economic	544 098 (61.24)	50 362 (43.10)	Ref	Ref
Family	253 158 (28.49)	50 522 (43.24)	1.86*	1.84-1.88
Refugee	23 900 (2.69)	3957 (3.39)	1.52*	1.49-1.55
Other	67 332 (7.58)	11 999 (10.27)	1.49*	1.44-1.54
TB incidence rate in country of origin at time of immigration	-	-	-	-
<100 per 100 000 pop.	381 530 (42.94)	36 967 (31.64)	Ref	Ref
100 to <200 per 100 000 pop.	292 116 (32.88)	35 552 (30.43)	1.02*	1.00-1.03
200 to <300 per 100 000 pop.	112 878 (12.70)	30 077 (25.74)	2.01*	1.98-2.04
300+ per 100 000 pop.	101 964 (11.48)	14 244 (12.19)	1.23*	1.20-1.25
Year of immigration (mean (SD))	15.16 (7.01)	10.21 (6.16)	0.96*	0.96-0.96
Charlson comorbidity score (mean (SD))	0.05 (0.33)	0.09 (0.37)	1.38*	1.37-1.39
Ethanol dependence	-	-	-	-
No	888 331 (99.98)	116 442 (99.70)	Ref	Ref
Yes	157 (0.018)	398 (0.30)	2.02*	1.83-2.23
Substance dependence	-	-	-	-
No	888 359	116 440 (99.70)	Ref	Ref
Yes	129 (0.015)	400 (0.30)	1.75*	1.59-1.93
Psychosis	-	-	-	-
No	888 314 (99.98)	116 366 (99.60)	Ref	Ref
Yes	174 (0.02)	474 (0.40)	1.53*	1.40-1.68
Depression	-	-	-	-
No	883 806 (99.47)	107 651 (92.10)	Ref	Ref
Yes	4682 (0.53)	9189 (7.90)	1.78*	1.75-1.82
Personal health risk proxy variable	-	-	-	-
No	826 181 (92.99)	101 531 (86.90)	Ref	Ref
Yes	62 307 (7.01)	15 309 (13.10)	1.83*	1.80-1.86

Legend: CI = confidence interval; ETOH = ethanol dependence; HR = hazard ratio; Ref = reference category for HR; asterisk (*) indicates result was significant at α=0.05. **Notes:** The censored group includes all people who did not experience the event (airway disease) prior to or at the time of death, leaving BC, or December 31, 2015. Univariable Cox proportional hazards regression was used for hazard ratios for airway disease by each covariate.

3.4.2 Statistical analysis results

The Kaplan-Meier curve showed a large the difference in airway disease-free survival between people with and without respiratory TB (Figure 3-3). In terms of absolute risk, we found that airway disease was diagnosed in 116 840 people during follow-up, yielding an incidence rate of 10.29 per 1,000 person-years, which differed between respiratory TB patients and non-TB controls (33.73 vs 10.04, respectively). In terms of relative risk, our main analysis found a covariate-adjusted hazard ratio of 2.08 (95% CI: 1.91-2.28) times the risk of airway disease among people diagnosed and completing treatment for airway disease compared with non-TB controls (Table 3-2). A sensitivity analysis that removed ETOH, drug dependence, psychoses, and depression variables had a similar result to the main analysis (aHR=2.11, 95% CI: 1.93-2.30). Replacing the Charlson comorbidity score with the van Walraven-weighted Elixhauser score changed the aHR to 2.06 (95% CI: 1.89-2.26). When bronchiectasis and fibrosis codes were added to the outcome definition, the adjusted HR increased to 2.18 (95% CI: 2.00-2.18). When TB patients with pleural samples (n=55) were removed from the exposure group, the updated effect of TB was aHR=2.10 (95% CI: 1.92-2.30). People with any type of TB had a 75% increased risk of airway disease, while people with non-respiratory TB experienced a 36% increased risk of airway disease (Table 3-2). Among people with respiratory TB, there was no significant difference between those with pleural vs non-pleural TB (aHR=0.87; 95% CI: 0.57-1.32; Table 3-2).

Figure 3-3. Kaplan-Meier plot for airway disease-free time (years) among people immigrating to British Columbia, Canada 1985-2015: tuberculosis patients vs non-tuberculosis controls



Time (years)	0	10	20	30
Number at-risk	-	-	-	-
Respiratory TB	1141	644	244	*
Controls	1 004 187	487 329	147 470	*
Number events (censored)	-	-	-	-
Respiratory TB	0 (0)	333 (164)	132 (268)	20 (264)
Controls	0 (38)	78 734 (438 105)	32 279 (307 577)	5342 (142 112)

Legend: Black = Respiratory TB; Grey = non-TB controls.
Notes: Asterisk (*) indicates suppressed due to cell count <6, or cross-suppressed as next lowest value.

In our assessment of potential unmeasured confounding by smoking, we calculated an E-value of 3.58 for the main analysis' aHR, and an E-value of 3.23 for the 95% confidence limit closest to the null. A standard PS analysis estimated an aHR of 2.29 (95% CI: 2.10-2.51) for airway disease by respiratory TB, while PS analyses utilizing additional data dimensions for proxy adjustment of unmeasured confounding via hdPS empirical covariates yielded aHR's ranging from 2.26 to 2.28 (Table 3-2). A subgroup analysis of the cohort with non-missing values for tobacco use (n=31 063; 3.1% of analytic sample) estimated an aHR=1.53 (95% CI: 1.37-1.71). A sensitivity analysis that added an investigator-

defined proxy variable for "personal health risk" showed slight attenuation of the main analysis result (aHR=2.03, 95% CI: 1.85-2.22).

Table 3-2. Cox proportional hazards regression analyses: time-to-airway disease among people immigrating to British Columbia, Canada, 1985-2015

Statistical Analysis [a]	N	Adjusted HR	95% CI
Aim 1: analyzing post-TB airway disease risk			
Covariate-adjusted (main analysis: respiratory TB vs controls)	1 005 328	2.08	1.91-2.28
Sensitivity analyses			
Covariate-adjusted (removed ETOH, substance dependence, psychoses, and depression) [c]	1 005 328	2.11	1.93-2.30
Covariate-adjusted (van Walraven-weighted Elixhauser comorbidity score) [d]	1 005 328	2.06	1.89-2.26
Covariate-adjusted (bronchiectasis and fibrosis added to the airway disease definition)	1 005 283	2.18	2.00-2.38
Covariate-adjusted (removed respiratory TB patients with pleural samples; n=55)	1 005 273	2.10	1.92-2.30
Different TB definitions			
Covariate-adjusted (all forms of TB vs controls)	1 006 271	1.75	1.63-1.88
Covariate-adjusted (non-respiratory TB vs controls) [b]	1 004 733	1.36	1.20-1.53
Age/sex-adjusted (pleural TB vs non-pleural TB)	1141	0.87	0.57-1.32
Aim 2: assessing potential unmeasured confounding			
PS methods			
PS decile-adjusted (main covariates)	1 005 328	2.27	2.08-2.49
hdPS decile-adjusted (main covariates + empirical covariates)	1 005 328	2.28	2.09-2.50
LASSO-hdPS decile-adjusted (main covariates + LASSO-refined empirical covariates)	1 005 328	2.26	2.07-2.47
Adjustment for smoking behaviour proxy variables			
Covariate-adjusted subdata analysis (main covariates + tobacco use variable) [f]	31 063	1.53	1.37-1.71
Covariate-adjusted (main covariates + personal health risk proxy variable)	1 005 328	2.03	1.85-2.22

Legend: BC = British Columbia; BCCDC = British Columbia Centre for Disease Control; CI = confidence interval; ETOH = ethanol dependence; hdPS = high-dimensional propensity score; HR = hazard ratio; LASSO = least absolute shrinkage and selection operator; N = analytic sample size; PS = propensity score; TB = tuberculosis.

Notes: [a] Covariate-adjusted models included as adjustment variables: age at index, sex, income quintile at index, educational qualification upon immigration, immigration class, TB incidence in country of birth, weighted Charlson comorbidity score, year of arrival in BC, ETOH, substance dependence, psychoses, and depression. [b] Non-respiratory TB included everyone who was a confirmed case of TB but did not have a smear or culture positive respiratory sample in the laboratory dataset of the BCCDC TB Registry. [c] due to lower than expected numbers, we removed these three variables from the set of adjustment variables. [d] We replaced the Charlson comorbidity score with the van Walraven-weighted Elixhauser comorbidity score and removed ETOH, substance dependence, psychoses, and depression variables as individual binary covariates because they are included in the van Walraven Elixhauser comorbidity score. [e] The e-value is a theoretical measure of the strength of association for an unmeasured confounder (e.g., smoking) to have, adjusted for the main analysis covariates, with both the exposure (respiratory TB) and the outcome (airway disease) to nullify the main analysis adjusted HR. [f] This analysis used a lower number of cohort members because it includes only people who were in the BCCDC TB Registry's Person dataset, which is a client list used by Provincial TB Services to track people who are tested or treated for active and latent TB within BC.

There was no discernible pattern of effect measure modification by age group, sex, education level, income quintile, immigration class, or by our personal health risk variable (Table 3-A4). We observed a higher aHR for airway disease by respiratory TB among people born in lower-TB-incidence countries with aHR=2.57 for people from countries with <200 TB cases annually per 100,000 population, compared with aHR=1.79 for people born in countries with 200+ TB cases annually per 100,000 population (Table 3-A4). Effect measure modification was also observed in the relationship between TB and airway by comorbidity level, with aHR=2.25 among people with no Charlson comorbidities at baseline, compared with people with 1 or 2+ Charlson comorbidities at baseline (aHR=1.04 and aHR=1.52, respectively).

3.5 DISCUSSION

In our cohort, 42.5% of people diagnosed with respiratory TB developed airway disease compared to 11.6% of non-TB controls (rates were, respectively: 33.73 and 10.04, per 1000 person-years). After covariate adjustment, we found a 108% increased risk of airway disease in people diagnosed with respiratory TB than non-TB controls. This finding was robust to multiple sensitivity analyses, except for the analysis looking at non-respiratory TB. In aim 2, we attempted to assess the impact of potential unmeasured confounding through multiple sensitivity analyses, which supported the main analysis conclusion. In aim 3, we found evidence of effect measure modification of the effect of TB on airway disease risk by level of comorbidity and by TB incidence rate in country of birth.

Our finding of increased risk of airway disease, post-TB treatment completion, was consistent with existing systematic reviews, which concluded that people diagnosed with TB are at increased risk of various forms of respiratory disease.[8,9,12,13] The most recent published meta-analysis, by Byrne et al.,[9] found a pooled odds ratio of 3.05 (95% CI: 2.42-3.85) for chronic respiratory disease among people

previously treated for TB compared to people without a history of TB. However, in that meta-analysis, only one study was a cohort study, which reported an adjusted HR of 2.05 (95% CI: 1.77-2.39),[163] which our main and PS analyses hover around, and which was closer to ours than other estimates.[9,12]

Two studies of post-TB airway disease risk from high-resource low-TB-incidence settings were published at the time of writing, both observing increased risk of respiratory disease by active TB diagnosis: one from United States (case-control study) with aOR=5.37 (95% CI: 2.98-9.68) for pulmonary impairment by active TB vs latent TB patients,[150] and another from Finland (cross-sectional study) with aOR=2.68 (95% CI: 2.00-3.61) for COPD by past TB vs no TB.[41] Both studies made efforts to control for potential confounders in their cross-sectional analyses. Pasinapodya et al. acknowledged the lack of ability to control for pre-existing lung impairment,[150] while Mattila et al. were able to exclude people with asthma prior to study enrollment,[41] leading their result closer to our main analysis result.[41] The limitations of these cross-sectional studies may imply an overestimation of post-TB airway disease risk compared with our study, although differences in populations, study designs, and measures of association limit comparability. Numerous other studies from higher TB-incidence settings have consistent findings with ours.[153,163–166]

In terms of effect modification, our findings do not align with those of Byrne et al., who noted increasing study log-odds ratios for post-TB airway disease by increasing national TB incidence rate for the country in which the study was conducted.[9] Byrne et al. also suggested effect modification by age group, with younger age groups (<40 years) being at higher risk of COPD by TB history.[9] However, our analysis did not find significant effect measure modification by age. Importantly, difference in study design (cohort study vs meta-analysis) may explain the incongruent findings between our study and Byrne et al.[9] The finding that people from lower-TB-incidence countries had

higher aHR than people from higher-TB-incidence countries may indicate lower exposure to risk factors for airway disease among people from lower-TB-incidence countries. A lower level of exposure to airway disease risk factors may, in turn, have made TB a potentially greater impact in this group. This speculation is supported by a finding of lower mean Charlson comorbidity score and lower proportion at personal health risk at baseline in people from countries with TB incidence <200 per 100,000 annually. A similar phenomenon may explain why people with no baseline comorbidities experienced a greater effect of respiratory TB on airway disease risk. These effect modification findings, and our speculation about their meaning, warrant further investigation.

Ravimohan et al. recently reviewed the topic of post-TB airway disease and noted the lack of precise understanding of the pathophysiological mechanisms in generating post TB airway disease.[12] Ravimohan et al. recommended population-based epidemiological studies that examine the prevalence of various types of airway deficits stratified by key risk groups (e.g., HIV, diabetes) and suggest immunopathogenesis and genome-wide association studies for correlates of lung damage and hyper-inflammation. In clinical research, studies of diagnostics during and after TB treatment, and investigations of adjunctive host-directed therapies and common COPD medications, are recommended. Our study did not seek to differentiate between subtypes of airway disease, nor to explore mechanisms by which airway disease develops. However, we observed a higher proportion of emphysema, chronic airway obstruction, and chronic bronchitis among people diagnosed with respiratory TB than controls, which may be expanded upon in future studies. When bronchiectasis and fibrosis were added to our definition of airway disease, we observed an increase in the aHR from 2.08 to 2.18, suggesting additional disease burden when more forms of respiratory disease are considered.

Our study overcomes the temporality limitation of previous cross-sectional studies.[9] We used a large (>1M) population-based longitudinal cohort containing data for all people immigrating to BC over 30 years.[85] We adjusted for multiple known confounders and removed pre-existing TB and airway disease. Additionally, these population-based data enabled near-complete capture of physician visits, hospital encounters, and deaths related to the outcome within the province of British Columbia. We used legislated, population-based TB surveillance and laboratory data to ascertain exposure status and timing, which improves upon previous studies.[9,12] An advantage of our definition of airway disease (compared with individual ICD codes) is that, by including a family of codes, our definition overcomes potential misclassification in longitudinal healthcare claims data due to code shifts over time, and is also robust to variations in coding practices between providers.[156]

Our study is limited to the population of people immigrating to BC (a low-TB-incidence setting with high-income and universal public healthcare), and our results should not be generalized to domestic TB patients within similar settings, nor to higher TB-burden settings. As a study of healthcare claims data, these results are based on treatment data, and do not include symptomatic yet untreated airway disease. Like all observational studies, causality cannot be inferred from these data. We cannot rule out time-dependent confounding as the covariates used in our study were measured at baseline, which means changes over time in, for example, education or comorbidities, would not be registered.

Smoking was a known unmeasured confounder in our study. Based on our E-value calculation, an aHR≥3.58 for such an unmeasured confounder, adjusted for the covariates included in the main analysis, could explain away our main analysis result, but a weaker confounder could not. Moreover, an unmeasured confounder would need an adjusted association ≥3.23, on risk ratio scale, with both the exposure and the outcome, to render our main analysis result non-significant at $\alpha=0.05$. We do not

expect that such a strong independent confounder (specifically, smoking) was omitted from our analyses, based on an adjusted OR of 1.80 for "ever smoking" in a US case-control study of post-TB lung impairment.[150] However, E-values, are theoretical and not based on real data, they make the assumption of a symmetrical relationship of the unmeasured confounder with both exposure and outcome (generally unrealistic), and are subject to any biases already incorporated in the effect estimate (selection bias, reporting bias, etc).[167]

Our exclusion of people with pre-existing airway disease from the cohort would have also removed a reasonable proportion of smokers at baseline (11.5% of excluded persons were classified as at "personal health risk" by our proxy variable, whereas, in the analytic sample, only 7.7% were classified as such). Adjustment for empirical covariates derived from the hdPS algorithm deployed on hospital and physician claims data in sensitivity analyses, attempted to address unmeasured or residual confounding, yet showed a slight increase in the effect estimate for airway disease by respiratory TB status, compared with the standard PS model. PS approaches are not preferred in settings where exposure prevalence is rare (<1% in our case),[168] which is why regression was used in our main analysis, and may explain the difference between our main analysis aHR and aHRs from the PS analyses. Our subgroup analysis of participants in the TB registry, adjusted for tobacco use variable available for <5% of participants, as well as and an analysis using a "personal health risk" proxy variable defined from administrative data available for the entire cohort, both found elevated risk of airway disease among people with TB, reinforcing our main analysis. Irrespective of these analyses, smoking remains a known confounder that was unmeasurable in our study.

This study demonstrates that post-TB airway disease is a problem for TB survivors in low-TB-incidence, high-resource settings. There is a paucity of guidance on diagnosis and treatment of post-TB

airway disease in high-resource regions,[3,6] despite the widespread availability of pulmonary specialists, pulmonary function testing, and potential therapies such as pulmonary rehabilitation and pharmacologic measures. While unmeasured confounding by smoking is unlikely to explain our finding of increased airway disease risk among respiratory TB patients, TB programs should routinely collect and record information about smoking behaviour and consider diagnosis with TB a teachable moment to promote smoking cessation. Achieving a fourth 90, "[e]nsuring that 90% of all people successfully completing treatment for TB can have a good health-related quality of life",[4] requires addressing post-TB airway disease.[151] Moreover, post-TB airway disease has a substantial health economic impact in terms of DALY estimates,[169] in which acute-illness and mortality-based methods for assessing TB's impact accounted for only a quarter of estimated DALYs when chronic lung impairment was incorporated in DALY calculation in a low-TB-incidence setting.[114] Given our findings, along with data showing similar associations from other high resource settings,[41,150,170] we strongly urge investment in the diagnosis of post-TB airway disease, and research on potential evidence-based interventions,[158] as well as a health economic re-evaluation of latent TB screening and treatment, in low-TB-incidence settings.

4 Tuberculosis-associated depression: a population-based cohort study of people immigrating to British Columbia, Canada, 1985-2015

4.1 SYNOPSIS

Introduction: There is growing evidence that TB negatively impacts mental health due to stigma, isolation, and physical health issues caused or exacerbated by TB. The effects of TB on mental health may last months after TB treatment completion. However, no studies have been conducted to assess the risk of post-TB depression in low-TB-incidence settings. A study of tuberculosis (TB)-associated depression was conducted to estimate the risk. We also aimed to estimate the extent to which any increased risk of depression among TB patients may be mediated by the length of hospital length stay (LOS).

Methods: Retrospective cohort study of linked healthcare claims and public health surveillance data. Our primary outcome, time-to-depression, was analyzed using Cox proportional hazards (PH) regressions. Causal mediation analysis was used to estimate the natural direct and indirect effect of TB mediated by hospital LOS.

Results: Among 755,836 participants (52.2% female, median age=35 years, median follow-up=8.75 years), 2295 were diagnosed with TB (exposure), and 128,963 were diagnosed with depression (outcome). We observed a covariate-adjusted hazard ratio (aHR) of 1.24 (95% CI, 1.14-1.34) for depression by TB. The total effect of TB on depression was decomposed into a natural direct effect of TB of aHR=1.11 (95% CI, 1.02-1.21) and an indirect effect through hospital LOS of aHR=1.11 (95% CI, 1.10-1.12), indicating that TB's total effect was mediated by 50% (95% CI, 35-82%) through hospital LOS.

Conclusions: TB patients had a 24% higher risk of developing depression. TB's effect was mediated substantially by hospital LOS, requiring further study. Depression screening among TB patients is warranted.

4.2 INTRODUCTION

Recent clinical and epidemiological evidence demonstrates a higher prevalence of depression among tuberculosis (TB) patients than in the general population.[16,43,171] A cross-sectional study of 48 countries found depression prevalence among those with TB to be approximately 24%, compared to 7% among those without TB, translating to an adjusted odds ratio (aOR) of 3.68 (95% CI, 3.01–4.51).[172] A systematic review estimated a pooled prevalence of depression among TB patients of 45.2%.[43] Depression among TB patients has been associated with fourfold higher odds of negative TB treatment outcomes,[44] indicating the importance of addressing depression within this population. A lesser characterized phenomenon is the extent to which TB may increase the risk of incident depression.

TB has a physical impact on health that reduces quality of life among TB patients, at least during treatment and potentially lasting beyond treatment completion.[31,48,173–177] TB has social impacts on TB patients' ability to work and attend social or family gatherings, particularly during the intensive treatment phase.[16,21] Social stigmatization of TB patients may further isolate TB patients from family and friends.[15,48] Internalized stigma is also experienced by TB patients processing their diagnoses.[16] In addition to stigmatization, a TB diagnosis can also lead to prolonged hospitalization, which may itself increase the risk of depression, as has been observed among intensive care unit (ICU) survivors.[51] During 2001-2014, among people immigrating to Canada (comprising two-thirds of TB patients), the median length of stay (LOS) for hospitalized TB patients was 11 days.[50] Hospital LOS may, therefore, be one of the mediators of the hypothesized effect of TB on depression risk.

Through these mechanisms, TB's effect on mental health may be sufficient to instigate a depressive episode requiring medical treatment.[48] However, only two published studies (both set in Taiwan using the same health administrative data) have analyzed the extent to which TB patients are at increased risk

of depression, with one study reporting a 53% higher risk of depression among all TB patients compared to non-TB controls (95% CI: 36-72%),[48] and the other reporting a 74% increased risk of depression among pulmonary TB patients (95% CI: 35-125%),[49] in multivariable analyses. No studies of TB-associated depression have been conducted in low-TB-incidence jurisdictions, and no study of the potential mediating role of hospital LOS in TB-associated depression in any setting.

Furthermore, depression prevalence is higher among females globally, including among TB patients. However, effect modification by sex in the risk of TB-associated depression was observed in previous studies, with higher aHRs for depression by TB among males than females in stratified analyses.[48,49] Although this potential effect modification by sex was only statistically significant in Shen et al. with aHR_{males}=1.71 (95% CI, 1.53-2.05) and $aHR_{females}$=1.21 (95% CI, 1.00-1.47) compared with Yen et al.'s aHR_{males}=1.79 (95% CI, 1.30-2.46) and $aHR_{females}$=1.65 (95% CI, 1.06-2.56), indicating potential differences in the mechanics of TB-associated depression, warranting further study.[48,49]

In 2015, immigrants comprised 71% of TB patients in Canada.[178] Among the 29% of TB occurring in Canadian-born persons, 17% occurred among Indigenous and 11% among non-Indigenous.[178] Epidemiological differences between TB patients born inside and outside Canada, with respect to socioeconomic status, history of trauma, mental health, and substance dependence might obfuscate population-level interpretations if they were combined in one analysis.[30] In the Canadian province of British Columbia (BC), 85% of TB patients are born outside Canada,[72] further supporting an immigrant population-specific analysis.

In this study, we investigated the association between TB diagnosis and risk of depression among immigrants to a low-TB-incidence, high-income setting. Aim 1 was to estimate the relative risk of

depression among TB patients compared with non-TB controls. Within aim 1, we also investigated modification of TB's effect by sex and by follow-up time, based on the literature. In aim 2 we sought to understand the potential mediating role of hospital LOS in TB's hypothesized effect on depression risk as natural direct and indirect effect estimates.

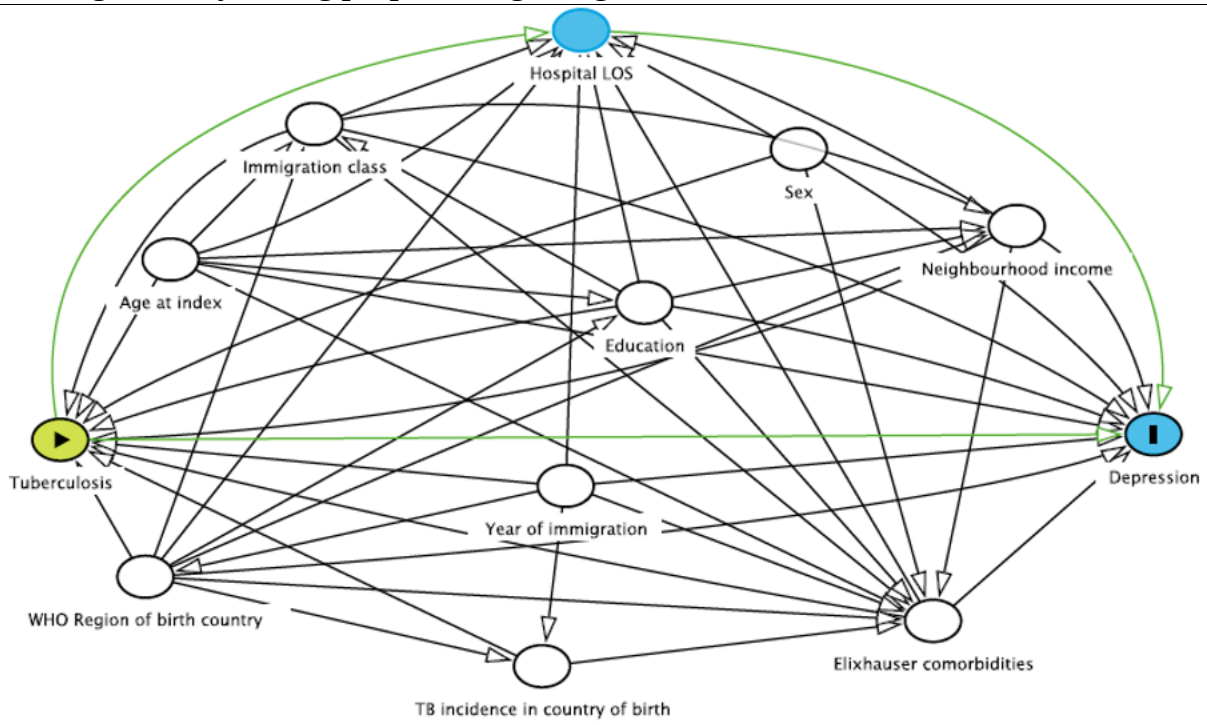
METHODS

Study Population, Design, and Data Sources

The study population includes all people immigrating to BC, Canada, and diagnosed with TB compared to those not diagnosed with TB. A retrospective cohort study design was employed to assess the relationship between TB and depression, as well as the mediating role of hospital LOS (Figure 4-1).

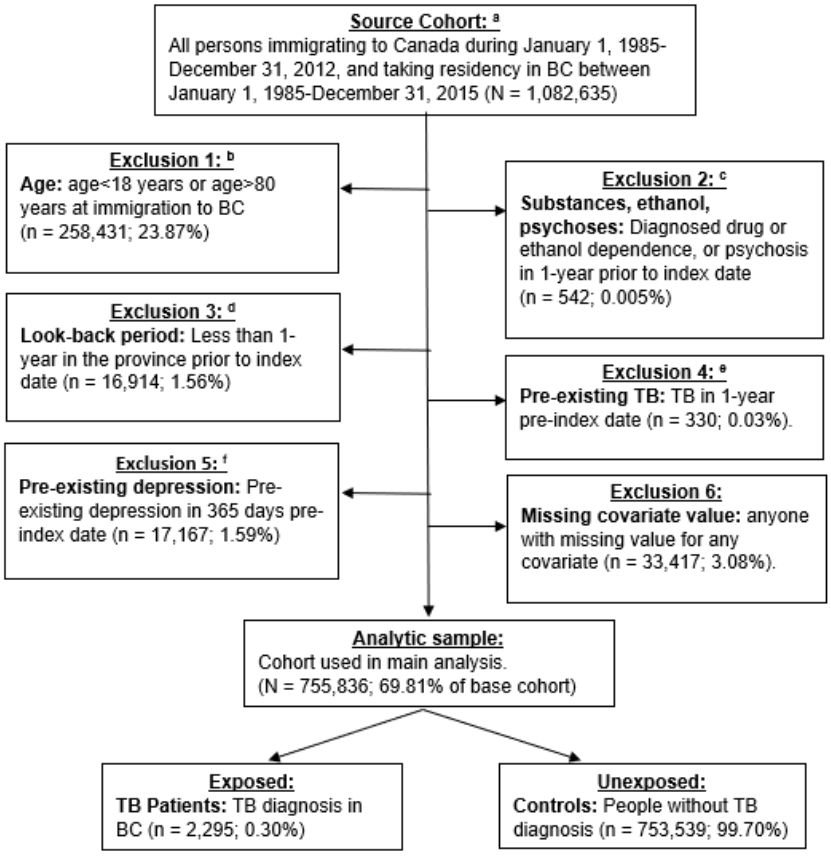
Our study start date was January 1, 1985 and study end date was December 31, 2015. We included people immigrating to BC from outside Canada and used linked health administrative data for follow-up (Figure 4-2). The index date (baseline) was defined as 365-days after immigration to BC (Figure 4-A1). Exclusion criteria were: age less than 18 or greater than 80 years at index date; substance, ethanol, or psychoses diagnoses in BC; less than 1-year of observation prior to index date; pre-existing TB in year prior to index date; pre-existing depression in year prior to index date; or missing covariate values (Figure 4-2). Data management for this analysis was generated using SAS software (Version 9.4 of the SAS System for Windows Copyright © 2013 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).[179] Statistical analyses were performed in R v3.6.1.[180] Ethical approval of the study was provided by the University of British Columbia Clinical Research Ethics Board (Clinical Research Ethics Board Certificate #H16-00265).

Figure 4-1. Directed acyclic graph for depression risk by tuberculosis diagnosis mediated through hospital length of stay among people immigrating to British Columbia, Canada, 1985-2015



Abbreviations: LOS = length of stay, OR = odds ratio, TB = tuberculosis.
Notes: The adjusted effect of TB on the mediator (hospital LOS) was OR=10.8 in a proportional odds regression. The following Elixhauser comorbidities, ascertained in the year prior to index date, were used in the statistical analysis: congestive heart failure, valvular disease, hypertension with complications, other neurological disorders, chronic pulmonary disease, diabetes without complications, hypothyroidism, renal failure, peptic ulcer disease excluding bleeding, HIV/AIDS, solid tumour without metastasis, rheumatoid arthritis/collagen, coagulopathy, fluid and electrolyte disorders, and deficiency anemia. Ethanol and substance use variables were unmeasured potential confounders. However, for simplicity and better visualization of measured confounders and the mediator, we have not included these unmeasured variables in the DAG.

Figure 4-2. Flow chart of analytic sample for retrospective cohort study of depression risk by tuberculosis diagnosis among people immigrating to British Columbia, Canada, 1985-2015



Abbreviations: BC = British Columbia, BCCDC = British Columbia Centre for Disease Control, IRCC = Immigration, Refugees, and Citizenship Canada, MSP = Medical Services Plan of BC, TB = tuberculosis, WHO = World Health Organization

Notes: [a] Ascertained from IRCC permanent resident database. Residency in BC defined by acquisition of provincial health insurance (MSP registration) and 365 days after this was used as the CED. [b] Excluded due to limited diagnosis of depression in people age<18 years or age>80 years. [c] Excluded due to potential for potential misclassification as depressed based on ICD-9/ICD-10 codes. [d] Excluded due to inability to ascertain baseline TB, depression, and covariates. [e] Excluded to ensure a cohort of people without TB at baseline. [f] Excluded to measure incident depression during follow-up.

4.3.2 Outcomes

Depression was defined based on a validated definition, which used ICD-9-CM and ICD-10-CA codes in hospital abstracts and physician claims from the universal health insurance system of BC.[181] In this definition, one hospital visit, or two or more physician visits within one year, were considered depression (Table 4-A2).[181] The depression definition validated by Doktorchik et al. was developed

using a chart review of 64 family physician clinics in Canada, 2001-2004, examining for the presence of major depressive episode or antidepressant use.[181] In our definition, we added a BC-specific MSP code, "50B" (depression/anxiety), that was not included by Doktorchik et al. in their algorithms, which we believe would have improved sensitivity of this depression definition in BC. These algorithms included slightly different ICD-9 codes (296.2, 296.3, 296.5, 300.4, 309x, 311) than that of Shen et al. (296.2x, 296.3x, 300.4x and 311x),[48] or Yen et al. (296.2x–296.3x, 300.4x, and 311x).[49] For our statistical analyses, the outcome variable was time-to-depression diagnosis or censoring date (leaving BC, death, or study end date). Time-to-depression was measured in person-years from the index date until the first date of depression diagnosis, death, termination of BC residence, or study end date.

4.3.3 Exposure

The exposure for this study was diagnosis with active TB according to Canadian TB Standards.[30] TB included both clinically and microbiologically diagnosed TB. This active TB definition followed the Canadian Tuberculosis Reporting System (CTBRS) guidelines,[30] with culture-based laboratory-confirmed case definitions and clinical-radiological requirements for clinical definition. The culture-based CTBRS laboratory definitions are more specific for TB compared with WHO guidelines.[182] All forms of TB were included in our definition,[71] consistent with a previous study of TB-associated depression.[48] We grouped people into two exposure categories, TB patients and non-TB controls for our analysis.

4.3.4 Mediator

Our mediator variable, hospital LOS, was calculated from hospital discharge abstracts generated by a universal health insurance system. The mediator index date was a randomly selected date between the

index date and censoring date for non-TB controls, and was the TB diagnosis date for TB patients.[183] We counted days between first admission date and last discharge date for all hospital discharge abstracts with admission dates between the mediator index date and 120 days after the mediator index date. We then categorized the sum of days in hospital into: 0, 1, 2-3, 4-5, and 6+ days as an ordinal mediator variable.

4.3.5 Covariates

Covariates were selected through literature review, subject knowledge, and development of a directed acyclic graph (DAG) (Figure 4-1). A 1-year covariate assessment window before index date was used to define baseline covariates (Figure 4-A1). Socio-demographic covariates included age at index date, sex, neighbourhood income quintile, education level at immigration, immigration classification (an indicator of socioeconomic status), TB incidence rate in country of origin, and World Health Organization (WHO) Region. For medical conditions that may confound the TB-depression relationship, we included Elixhauser comorbidity index conditions, defined using ICD-9 and ICD-10 coding in hospital abstracts and physician claims during a 1-year period prior to index date.[90,103] Due to the large number of Elixhauser comorbidities (31 conditions), we selected Elixhauser comorbidities that may empirically confound the relationship between TB and depression (Appendix D).

4.3.6 Statistical Analysis

In aim 1, to assess crude depression-free-survival time between TB patients and controls, we plotted a Kaplan-Meier curve. To compare the risk of depression between TB patients and non-TB controls we used Cox proportional hazards (PH) regressions of time-to-depression. We first fit crude and age/sex-adjusted Cox PH regression models to the data. Our covariate-adjusted main analysis included the TB

indicator variable and potential confounders, identified in our DAG, in a multivariable Cox PH regression (Figure 4-1). We assessed the validity of the PH assumption in our final model through a Schoenfeld residual test and plot. To assess the potential for residual confounding to nullify our main analysis finding, we calculated E-values for the aHR and its lower 95% confidence limit (LCL), assuming >15% cumulative incidence of depression during 30-year follow-up.[63,70] Six additional sensitivity analyses were conducted to test the robustness of our main analysis finding to changes in modelling strategy, depression definition, washout and covariate assessment periods, and comorbidity adjustment (Appendix D). We investigated effect measure modification by sex and by follow-up time using interaction terms between TB by sex and TB by follow-up time (0-2, 2-5, 5-10, and 10+ years), in two additional Cox PH regressions.

In aim 2, we conducted a mediation analysis to decompose the total effect of TB, based on the counterfactual framework, using a weighting approach.[68,69,184] Lange et al. proposed a unified approach to causal mediation analysis,[68] which enabled our study's analysis to decompose the total effect of TB on depression into a natural direct effect (NDE) of TB and a natural indirect effect (NIE) of TB through hospital LOS (an ordinal multi-category mediator variable), on depression risk, after adjusting for all measured confounders in our DAG (Figure 4-1), and expressed as aHRs (Appendix D). As a sensitivity analysis, we also developed a simpler alternative mediator variable indicating whether the study participant was hospitalized for at least 1 day (binary) to check the robustness of our mediator's definition used in the analysis of aim 2.

4.4 RESULTS

4.4.1 Analytic Sample

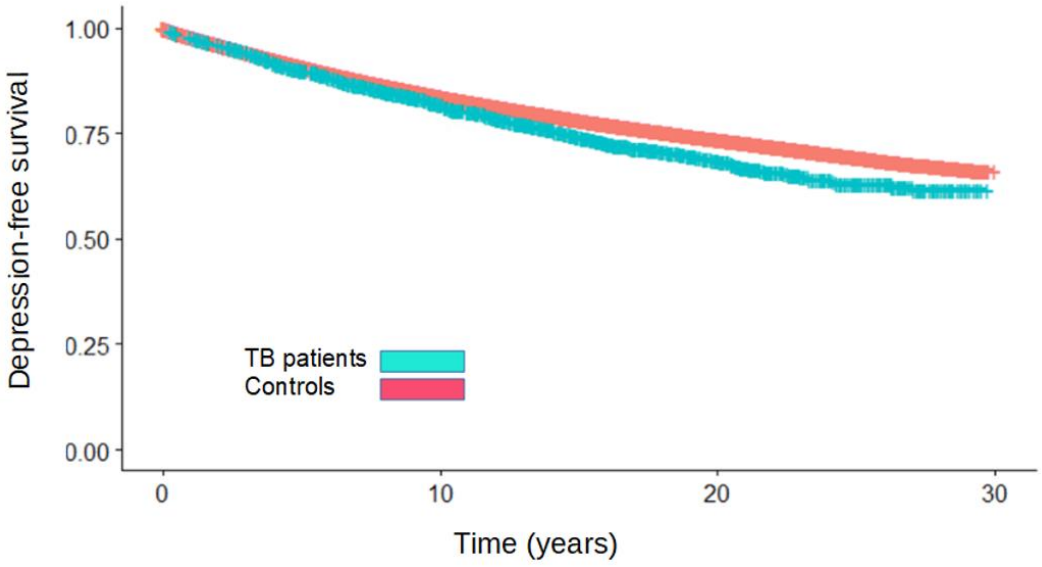
Figure 4-2 presents the number of cohort members included and excluded at each step in developing the analytic sample. A final analytic sample of 755,834 people immigrating to BC during 1985-2015 were included, with 2,295 diagnosed with TB and 753,539 controls, contributing, a total of 32,305 (median=14.0 [IQR,7.6 -20.5]) and 7,817,398 (median=8.7 [(IQR, 4.3-15.7]) person-years of follow-up, respectively. Cumulatively, incident depression occurred in 128,963 people (17% of the analytic sample), yielding a depression incidence rate of 19.16 per 1,000 person-years for TB patients and 16.42 per 1,000 person-years for non-TB controls (crude incidence rate ratio = 1.17).

4.4.2 Aim 1: effect of TB on the risk of depression

A Kaplan-Meier curve showed lower depression-free survival for TB patients than non-TB controls (log-rank test $p<0.0001$) (Figure 4-3). Our covariate-adjusted main analysis found an aHR=1.24 for risk of depression among TB patients compared to non-TB controls, averaged over the 30-year study period (Table 4-1). An E-value of 1.59 was calculated from our main analysis point estimate, and E-value of 1.42 for our lower 95% confidence limit. Our main analysis finding was robust to a switch in modeling strategy to propensity scores analysis, changing the definition of depression, increasing the washout and covariate assessment periods to two years, substituting comorbidity adjustment variables, and analyzing a binary outcome measure for depression with modified Poisson regression (Table 4-1).[185] In the presence of a large dataset with extended follow-up, the Schoenfeld test for TB diagnosis (exposure) variable had p-value=0.001, suggesting evidence of violation of the PH assumption. However, visually, in the Schoenfeld residual plot, there was no serious deviation in the residuals over time (Figure 4-A2). Effect modification by sex was observed, with males experiencing an aHR=1.53

(95% CI, 1.36-1.72) for depression by TB, compared with females, who experienced an aHR=1.07 (95% CI, 0.96-1.19) for depression by TB. We observed the following modification of TB's effect by follow-up time (aHR=1.82 in 0-2 years [95% CI, 1.68-1.97], 1.51 in 2-5 years [95% CI, 1.25-1.82], aHR=1.33 [95% CI, 1.12-1.58] in 5-10 years, and 1.30 [95% CI, 1.11-1.51] in 10+ years, respectively) (Table 4-1).

Figure 4-3. Kaplan-Meier curve for depression-free survival time by tuberculosis among people immigrating to British Columbia, Canada, 1985-2015



Group	Status	Follow-up time (years)			
		0	10	20	30
TB patients	At-risk	2,295	1,495	615	0[b]
	Events	0	390	192	40[b]
	Censored	0	410	688	580[b]
Controls	At-risk	753,539	329,735	100,950[a]	0[b]
	Events	0	96,388	27,780	4,180[b]
	Censored	30	327,400[b]	200,970[b]	96,790[b]

Notes: Values suppressed due to privacy law as follows: a Rounded to nearest 50 people as a complementary suppression method to prevent unmasking of a suppressed value. b Rounded to the nearest 10 as a complementary suppression method to prevent unmasking of cell values≤5.

Table 4-1. Cox proportional hazards regressions of time-to-depression among people immigrating to British Columbia, Canada, 1985-2015: TB patients vs non-TB controls

Analysis	N	Adjusted HR (TB vs Controls) [a]	Lower 95% CL	Upper 95% CL
Primary Analysis				
Crude	755834	1.21	1.12	1.31
Age/sex-adjusted	755834	1.26	1.17	1.37
Covariate-adjusted (main analysis)	755834	1.24	1.14	1.34
Sensitivity analyses [b]				
(1) PS decile-adjusted	755834	1.22	1.13	1.32
(2) Removed diagnosis code "50B" from the depression definition	761954	1.29	1.16	1.43
(3) Increased washout and covariate assessment periods to 2-years pre-index date	724065	1.26	1.16	1.37
(4) Charlson comorbidity score instead of Elixhauser comorbidities	755834	1.23	1.13	1.33
(5) Study-specific Elixhauser score instead of Elixhauser comorbidities	755834	1.24	1.14	1.34
(6) modified Poisson regression of depression (binary mediator variable offset by log follow-up time)	755834	1.34	1.24	1.45
Effect modification analyses				
(i) Follow-up time				
0-2 years	82351	1.84	1.70	2.00
2-5 years	140396	1.52	1.27	1.84
5-10 years	201874	1.34	1.13	1.59
10+ years	331213	1.31	1.12	1.52
(ii) Sex				
Male	361136	1.54	1.37	1.74
Female	394698	1.07	0.97	1.19

Abbreviations: BC = British Columbia, CL = confidence limit, PH = proportional hazards, PS = propensity score, MSP = Medical Services Plan of BC, TB = tuberculosis.
Notes: [a] Covariates included: age, sex, neighbourhood income quintile, TB incidence in country of birth, immigration class, educational qualification, WHO Region of birth country, year residence established in BC, and the following Elixhauser comorbidities: congestive heart failure, valvular disease, hypertension with complications, other neurological disorders, chronic pulmonary disease, diabetes without complications, hypothyroidism, renal failure, peptic ulcer disease excluding bleeding, HIV/AIDS, solid tumour without metastasis, rheumatoid arthritis/collagen, coagulopathy, fluid and electrolyte disorders, and deficiency anemia. [b]sensitivity analyses are explained in Appendix D.

4.4.3 Aim 2: mediation analysis of TB's effect on depression risk by hospital length of stay

The ordinal mediator variable for hospital LOS days was distributed as follows: 0 days = 734,268 (97.14%); 1 day= 10654 (1.41%); 2-3 days = 4988 (0.66%); 4-5 days 3007 (0.40%); ≥6 days = 2917 (0.38%). Among hospitalized cohort members, the mean hospital LOS was 28.5 (median=13) days for TB patients (IQR=2 to 39 days) and 3.78 (median=1) days for non-TB controls (IQR=1 to 4 days). The

total effect of TB on risk of depression (aHR=1.24; 95% CI, 1.13-1.35) was decomposed into a direct TB effect of aHR=1.11 (95% CI, 1.02-1.21) and an indirect TB effect mediated through hospital LOS of aHR=1.11 (95% CI, 1.10-1.12) (Table 4-2). Therefore, 50% of TB's effect on depression risk was mediated by hospital LOS (95% CI, 35-82%). In the sensitivity analysis that used a binary mediator variable for hospitalization (no = 734,268 [97.14%]; yes = 21,566 [2.86%]), the total effect of TB on depression risk was similar to the main analysis (aHR=1.23; 95% CI, 1.20-1.27), with direct TB effect (aHR=1.12; 95% CI, 1.10-1.16) and indirect TB effect mediated through hospitalization (aHR=1.09; 95 % CI, 1.09-1.10), with percent mediated (43%) through hospitalization (95% CI, 37-48%) (Table 4-2).

Table 4-2. Mediation analysis of the effect of tuberculosis on depression risk via hospital LOS among people immigrating to British Columbia, Canada, 1985-2015

Effects of TB on Depression Risk	Estimate [a]	95% CI [b]
Hospital Days (ordinal mediator) [c]		
Total effect of TB	1.23	1.13 – 1.35
Direct effect of TB	1.11	1.02 – 1.21
Indirect effect of TB through hospital LOS	1.11	1.10 – 1.12
Percent mediated by hospital LOS	50%	35 – 82%
Hospitalization (binary mediator) [d]		
Total effect of TB	1.22	1.12 – 1.31
Direct effect of TB	1.12	1.02 – 1.19
Indirect effect of TB through hospital LOS	1.09	1.08 – 1.11
Percent mediated by hospital LOS	43%	32 – 71%

Abbreviations: CI = confidence interval, LOS = length of stay, PH = proportional hazards, TB = tuberculosis.
Notes: a Hazard ratio point estimates estimated from weighted Cox PH regression of depression-free survival time by TB diagnosis, adjusted for age, sex, neighbourhood income quintile, TB incidence in country of birth, immigration class, educational qualification, WHO Region of birth country, year residence established in BC, and the following Elixhauser comorbidities: congestive heart failure, valvular disease, hypertension with complications, other neurological disorders, chronic pulmonary disease, diabetes without complications, hypothyroidism, renal failure, peptic ulcer disease excluding bleeding, HIV/AIDS, solid tumour without metastasis, rheumatoid arthritis/collagen, coagulopathy, fluid and electrolyte disorders, and deficiency anemia.
b 95% CI drawn from the 2.5th percentile and 97.5th percentile of the aHR from 200 bootstrap resamples.
c Minimum mediation weight = 0.10 (95% CI: 0.09-0.11), maximum mediation weight = 10.14 (95% CI: 8.96-11.14).
d Minimum mediation weight = 0.12 (95% CI: 0.11-0.13), maximum mediation weight = 8.31 (95% CI: 7.65-9.09).

4.5 DISCUSSION

4.5.1 Summary

In a large retrospective cohort of people immigrating to BC over a 30-year period, we observed a 24% higher risk of depression among TB patients compared with non-TB controls (95% CI: 12-31%), averaged across follow-up from index date. This result appeared to be robust to multiple sensitivity analyses. Males experienced a more potent effect of TB on depression risk (aHR=1.54; 95% CI, 1.37-1.74) than females (aHR=1.07; 95% CI, 0.97-1.19) in our effect modification analysis. There was also a stronger TB effect in shorter follow-up times (aHR=1.84 in 0-2 years post-index date, declining to aHR=1.31 in 10+ years post-index date). In our causal mediation analysis, we decomposed TB's effect on depression risk into natural direct (aHR=1.11) and an indirect (aHR=1.11) effects of TB, observing substantial mediation of the total effect of TB through hospital LOS (50%).

4.5.2 Comparison with literature

Our study contributes to a growing literature on post-TB health as well as mental health among TB patients and survivors. This is the first report of TB's effect on depression risk in a low-TB-incidence setting. Two previous studies of TB-associated depression risk from Taiwan found an aHR=1.53 (95% CI, 1.36 – 1.72),[48] and aHR=1.74 (95% CI, 1.35-2.25),[49] for depression risk among TB patients versus non-TB controls, respectively. Both studies estimated higher relative risk of depression by TB than our estimates but were consistent with our conclusion of increased risk. Those studies were conducted in Taiwan, an intermediate TB burden setting (43.9 per 100,000 in 2016),[186] Moreover, TB patients in Taiwan are from a largely homogenous domestic population,[187] which differs from ours in the following ways: first, Canada is a low-TB-incidence setting, with a TB incidence rate nearly 10 times lower than that of Taiwan (4.8 per 100,00 in 2016); second, over 70% of Canadian TB patients are

people who have immigrated to Canada,[73] and our study was conducted entirely within the immigrant population of BC; third, mental health and depression may be perceived, diagnosed, and treated differently in Canada and Taiwan.[48] Our study also used a much longer follow-up period, and excluded people immigrating at ages <18 years or >80 years at the time of immigration. Last, we analyzed time-to-depression starting from 1-year post-immigration, among TB diagnosed vs. non-TB controls, rather than only post-TB diagnosis, as was done in previous studies. Those differences likely contributed to the lower effect estimates for depression by TB in our study.

Our finding of a larger effect of TB on depression risk among males compared to females (53% vs 7%) is similar to that of Shen et al.,[48] who found 77% higher risk by TB among males compared with 21% higher depression risk by TB among females. In the literature, a higher prevalence of depression among females is known, with a similarly higher prevalence of depression among female than male TB patients.[43] However, our study and those of Shen et al.,[48] and Yen et al., both of which removed people with prevalent depression, created different study populations (people without pre-existing depression), indicate that TB's effect on increasing depression may be sex-specific. We also observed effect modification by follow-up time, confirming a previous study that found higher TB effect estimates in earlier time periods (aHR=2.53 in 0-6 months, and aHR=1.50 in 6 months to 3 years).[48] Together these findings suggest that the effect of TB on depression risk decreases over time: manifesting a dose-response relationship.

4.5.3 Implications of the mediation analysis

Our study is also the first study to investigate the mediating role of hospital LOS in TB's impact on the risk of depression. We hypothesized that "isolation-induced" depression, due to the lengthy

hospitalization frequently experienced by TB patients in Canada,[50] may be one of the plausible causal pathways in TB's effect on depression risk. Our analysis showed that the proportion of our cohort hospitalized was low, however, among those hospitalized for at least one day, the average LOS for TB patients (median=13) was much higher than for non-TB controls (median=1). The mediating role of hospital LOS in our statistical analysis might be interpreted in four important ways. First, that hospital LOS following TB contributes substantially to the risk of incident depression, as has been shown among ICU survivors,[51,188] making the causal pathway between TB and depression highly plausible. Second, any period of hospitalization may facilitate detection of depressive symptoms that might otherwise go undetected, particularly because this study used hospital data in measuring depression, which may indicate that mediation by hospital LOS indicates detection bias among TB patients.[189] Third, hospitalized TB patients likely have more severe illness or infectious TB,[190] which could increase levels of physical health impact of TB and/or stigma, which may reduce to a greater extent TB patients' health-related quality of life during and after TB treatment completion, making mediation by hospital LOS an indicator of TB disease severity. A fourth interpretation is that people who are hospitalized for TB may have less social support than TB patients treated on an outpatient basis, which could exacerbate the effects of TB diagnosis on mental health, making hospital LOS an indicator of low social support among TB patients.

Because the nature of the mediating role of hospital LOS in the development of TB-associated depression is unclear, the first implication of these findings is that the intersections of TB, hospitalization, and depression require further study, including primary, prospective data collection on mental health. Screening for prevalent depression at the time of TB diagnosis should also be conducted to separate incident from prevalent depression, as incident depression is more likely due to TB and may be mediated by hospital LOS. If hospital LOS is a causal pathway between TB and depression risk,

rather than an indicator of detection bias, then efforts to shorten stays in hospital due to TB may be helpful, including community housing and services to support outpatient TB care. During a stay in hospital, efforts to ensure patient mental health is supported should be taken. After discharge from hospital, links to mental health support for TB patients may improve both TB treatment outcomes and reduce depression risk or burden.

4.5.4 Limitations

Our findings may be generalized to immigrant-receiving low-TB-incidence settings with high-income and low to no barriers to healthcare access, and interpretations should be limited to these settings. Our definition of depression was based upon physician and hospital visits, limiting our analysis to diagnosed depression. We identified potential violation of the PH assumption by the Schoenfeld residual test in our models, although visually there was no serious violation in the Schoenfeld residual plot. In our experience, it is not uncommon to have a significant test result in data with long follow-up and very large sample size (N = 755,834 in our case). In response to the violation, we also presented an effect-modification model with time, where the association is being modified over time. This effect-modification model represents the aHR's change over follow-up time for depression by TB (a decreasing pattern over time between 1.31 to 1.84, see Table 4-1, all aHRs being significant). We also presented results from a covariate-adjusted modified Poisson regression, which produced a similar conclusion (aRR=1.34; 95% CI 1.24-1.45) to the main analysis using Cox PH regression (aHR=1.24; 95% CI 1.14–1.34).

In our study, traumatic life experiences, untreated or undiagnosed mental disorder, or combinations of these unmeasured variables may potentially confound our study of TB-associated depression risk.

Although we excluded people with baseline ethanol or substance use disorder diagnoses by a physician (rare), we did not have access to quality data on ethanol or illicit substance use available to us and were thus unable to adjust for them as potential confounders. We list these variables in the notes of the DAG for this study as unmeasured potential confounders (Figure 4-1). E-values provide us with theoretical support to claim that an unmeasured confounder (or series of confounders) would require an exposure (TB)-confounder association of aHR≥1.58 and confounder-outcome (depression) association of aHR≥1.58, at minimum, to move the main analysis aHR to 1.0. An aHR≥1.42 in both those relationships could render the main analysis point estimate non-significant at $\alpha=0.05$.[63] These E-values suggest that our analysis may be susceptible to relatively modest residual confounding. However, we adjusted for many potentially confounding factors in all our analyses. Better collection of ethanol and substance use data among TB patients in TB surveillance datasets, such as the BC TB Registry used in our study, may facilitate understanding of theses factors' relationship with TB and depression.

4.5.5 Conclusion

We observed an average 24% increased risk of depression among TB patients compared with non-TB controls in a low-TB-incidence setting, during a 30-year follow-up period. Substantial mediation of the effect of TB was observed by hospitalization post-TB diagnosis. TB patients may benefit from depression screening for both a higher baseline prevalence of depression, as well as the potential for TB, and hospitalization for TB, to contribute to depression risk.[15] TB program directors have expressed high receptivity to integration of mental health in TB care.[15] Policy-makers might invest in depression screening and mental health support for current and former TB patients in low-TB-incidence settings, particularly among patients experiencing extended hospitalization. Healthcare

professionals may be warranted in screening for depression among current and former TB patients based on all of the available evidence.

C. Conclusion

SUMMARY

The focus of this doctoral research was TB survivor health, which included (1) an analysis of cause-specific mortality rates among people successfully completing TB treatment, (2) a review of the epidemiological literature on cardiovascular disease among TB survivors, (3) analyses of post-TB airway disease, with an assessment of potential confounding by smoking, and (4) a causal mediation analysis of depression incidence among TB survivors, with hypothesized mediation by the length of hospital stay.

(1) Post-TB mortality

We hypothesized a higher risk of mortality among TB survivors compared with non-TB controls, after adjusting for potentially confounding factors. We rejected the null hypothesis that there was no significant difference in the risk of mortality between TB patients and non-TB controls. Based on these findings, TB survivors in low-TB-incidence settings are at substantially increased risk of major causes of death, particularly from respiratory causes. We also observed a more potent effect of TB in males than in females across causes of death in our sex-stratified analyses. Our findings are consistent with a systematic review of all-cause mortality among TB survivors found a pooled SMR of 2.91 (95% CI: 2.21-3.84) across studies.[33] That review included five studies from high-income countries (USA, UK, Israel, Denmark, and Estonia), which yielded a pooled SMR of 3.11 (95% CI: 2.05-4.72), when meta-analyzed as a subgroup. This relative risk estimate was substantially higher than our covariate-adjusted aHR of 1.69 (95% CI: 1.50-1.91). This may be due to a larger number of covariates adjusted for in our study than were adjusted for in the studies included in the high-income subgroup meta-analysis.[33]

In terms of sex-based differences, a higher relative risk of mortality in TB survivors compared to non-TB controls among males than females was observed among pulmonary TB survivors in Denmark, where males had a mortality rate ratio (MRR) of 2.04 (95% CI: 1.92-2.17) compared with females MRR of 1.61 (95% CI: 1.48-1.75).[106] This finding was similar to our sex-stratified analyses of mortality, which showed aHR=1.88 for males and aHR=1.43 for females. In contrast, a US study found a lower aHR for TB survivors compared with LTBI controls among males (aHR=6.66; 95% CI: 1.81-11.51) compared with females (aHR=9.29; 95% CI: 2.84-15.75).[99] However, the different comparison groups (people diagnosed with LTBI) may have influenced those results.[99]

(2) Cardiovascular disease among TB patients

Our systematic review of CVD and TB revealed heterogeneous literature on CVD among TB survivors and people with LTBI. Multiple study populations, outcomes, and TB types were analyzed through a variety of study designs and analysis models (Table 2-2). We concluded there was a significantly increased risk of major adverse cardiovascular events (MACE) following TB treatment compared with non-TB controls. Our meta-analysis finding for MACE among TB survivors was consistent with a systematic review of coronary heart disease among TB survivors that found a pooled risk ratio of 1.76 (95% CI: 1.05-2.95).[191] There was overlap in the studies included in our review and that of Wongtrakul et al., but different inclusion criteria led to a different number of studies reviewed. Differences in types of CVD and TB included in the studies reviewed prevents direct comparison of these two studies' findings. However, common biological mechanisms are discussed, such as chronic inflammation due to TB infection and disease, and potential autoimmunity due to TB, as well as the potential for TB to act as a marker for poorer general health or low SES.[191]

(3) Post-TB airway disease

In terms of post-TB airway disease, we demonstrated a twofold increased risk of airway disease by respiratory TB compared to controls. Cumulatively, 42% of respiratory TB patients in our cohort, who did not have airway disease prior to cohort entry, developed airway disease during follow-up, compared with 11% of non-TB controls. Multiple sensitivity analyses suggest that unmeasured confounding by smoking is unlikely to completely account for the increased risk of airway disease by respiratory TB. We concluded that TB is a driver of airway disease in low-TB-incidence settings, and that unmeasured confounding by smoking is unlikely to explain this relationship or render it statistically non-significant. Previous systematic reviews have identified an elevated risk of airway disease among TB survivors.[3,9,12]

The most recent systematic review and meta-analysis of pulmonary TB and COPD found a pooled OR of 2.59 (95% CI: 2.12-3.15).[10] An earlier systematic review and meta-analysis found a pooled OR of 3.05 (95% CI: 2.42-3.85) for COPD or bronchiectasis by all forms of TB.[9] These reviews are consistent with our finding of aHR=2.08 for post-TB airway disease. The difference in measures of association (odds ratios vs. hazard ratios) may explain the difference in estimates between our study and the meta-analytic results of the two systematic reviews.[9,10] Our use of a cohort design that removed cohort members with pre-existing airway disease, which several of the meta-analyzed studies were unable to do, may also have influenced the difference in estimates. In terms of unmeasured confounding by smoking, a subgroup meta-analyses among never smokers found a pooled OR=2.41 (95% CI: 1.74–3.32), supporting our finding that unmeasured confounding by smoking was unlikely to explain the higher risk of airway disease among respiratory TB patients.

(4) TB-associated depression

In the analysis of TB-associated depression, this research found a 24% higher risk of depression by TB, which. The mediation analysis indicated that half of TB's effect on depression risk was mediated by the length of stay in hospital. Effect modification by sex was observed, with males having a higher risk of depression than females, which was statistically significantly different from the null in males only. This effect modification by sex may be a consequence of a higher baseline prevalence of depression in females,[43] and the removal of people with baseline depression from the analytic sample, done to enable an examination of incident depression.

Our finding of increased depression risk associated with TB was consistent with two studies conducted in Taiwan.[48,49] Those studies found substantially higher aHRs for depression by TB than our finding of aHR=1.24. Shen et al. studied all forms of TB, while Yen et al. studied pulmonary TB, finding aHRs of 1.53 (95% CI: 1.36-1.72) and 1.74 (95% CI: 1.65-2.25), respectively. The difference may have been related to the much longer follow-up period in our study than either Shen et al. or Yen et al., although this is not possible to confirm. Other factors, such as cultural differences, may also have influenced the disparity in our aHR estimates.

In terms of effect modification by sex, our finding of higher relative risk of depression by TB among males (aHR=1.54; 95% CI: 1.37-1.74) than females (aHR=1.07; 95% CI: 0.97-1.19) was similar to a finding by Shen et al., who observed for males an aHR=1.77 (95% CI: 1.53-2.05) and for females an aHR=1.21 (95% CI: 1.00-1.47).[48] Although, Yen et al., who studied pulmonary TB, found no statistically significant effect modification by sex in the relationship between TB and depression, with males' aHR=1.79 (95% CI: 1.30-2.46) and females' aHR=1.65 (95% CI: 1.06-2.56), the aHR estimate

was still higher in males than females.[49] The mediation analysis was novel, and the finding of substantial mediation in depression risk by hospital LOS may indicate a previously unexplored causal mechanism for TB-associated depression.

Strengths and Limitations

The use of cohort designs for the analyses of longitudinal administrative health data allowed the measurement of the timing of exposures and outcomes, enabling adjustments for pre-existing conditions as baseline confounders. For example, we could remove people who had the outcome prior to the index date (prevalent cases) in order to study incident cases of airway disease (Chapter 4), and of depression (Chapter 5). The administrative data used is population-based and derived from a universal healthcare system, leaving a low risk of selection bias. Various methods were used to address unmeasured confounding, including E-values and hdPS, and we assessed the robustness of our main analysis models to various assumptions through multiple sensitivity analyses.

This research was limited to observational designs. This means there is potential for unmeasured confounding to bias our results. Notably, tobacco, alcohol, and illicit substance consumption data are unavailable, for the most part, in health administrative data. Another important limitation of this research pertains to the generalizability of findings beyond people immigrating to Canada. Results of these analyses should not be generalized to Indigenous Peoples in Canada or to non-Indigenous Canadians, due to their exclusion from the data used to create the analytic sample for this study. However, generalizability to immigrants to other high-income, low-TB-incidence settings may be valid. In healthcare administrative data it is only possible to measure conditions among people who presented to either a hospital or physician for diagnosis and treatment. This may mean that more severe forms of the conditions studied are ascertained with these data, which should be taken into

account as a potential limitation when interpreting our findings, particularly for depression (i.e., we did not study symptomatic but undiagnosed conditions).

In Chapter 1, a potential misclassification of TB exposed time as unexposed may have occurred as TB disease may be present for some time prior to diagnosis. To address this, a sensitivity analysis was conducted wherein 90 days was subtracted from the follow-up start date for TB exposed time. This resulted in slight drop in the aHR for non-TB causes of morality by TB exposed versus TB unexposed time (aHR=1.67 (CI: 1.49-1.88), which is quite similar to main analysis aHR of 1.69, indicating low risk of exposure misclassification biasing our main analysis aHR.

In Chapters 3 and 4, a potential limitation of our statistical analysis using Cox PH regressions was that competing risk of mortality was ignored, which may have been higher in the TB diagnosed (exposure) groups. To address this potential source of bias, we implemented two Fine-Gray models for competing risk regression, considering non-airway disease death, and non-depression deaths, as competing risks in these analyses. Potential issues with balance of covariates in Chapters 3 and 4 were addressed through the use of PS-matched analyses. The results of these additional sensitivity analyses are presented in Appendix E and briefly described here. There was minimal change from the main analyses presented in Chapters 3 and 4 when competing risks regressions were used. The aHR for TB in the Fine-Gray model for airway disease was 2.11, compared with 2.08 in the main analysis for Chapter 3 (Table E1-2), while the aHR for TB in the Fine-Gray model for time-to-depression was 1.22, compared with 1.24 in the main analysis for Chapter 4 (Table E2-2). In the PS-matched sample for the airway disease analysis, we found a lower aHR (1.83) than our main analysis (aHR=2.08) (Table E1-2). This finding might suggest some residual confounding in our main analysis due to imbalance in measured confounders. However, there is controversy around use of PS methods in rare exposures,[168,192] and our

PS-decile adjusted analyses of post-TB airway disease showed much higher aHRs for TB (ranging from 2.26-2.28; Table 3-2). For these reasons, standard Cox PH regressions were used for main analyses in both studies. Competing risk regressions in PS-matched samples showed similar results to the Cox PH regressions in the PS-matched samples for both analyses.

Unmeasured confounding is a major threat to observational studies. In all observational studies used to estimate effects of exposures on outcomes, such as TB and mortality risk, there should be a complete accounting of unmeasured confounders in DAGs. In our DAGs for Chapters 1, 3, and 4, we omitted some potential unmeasured confounders, such as body mass index (BMI), as our understanding of confounding in these relationships is limited, and we did not want to overemphasize variables that are not known confounders. Additionally, residual confounding from the measured covariates may have biased our results, although the extent of such potential bias is unknown.

Implications and Applications

This research has implications for TB survivors in low-TB-incidence nations, as it provides evidence of chronic health risk, which warrant attention from both healthcare professionals and policy makers. Policy makers and TB care providers in Canada and similar low-TB-incidence settings should consider TB survivors as being at higher risk of mortality, CVD, airway disease, and depression. Risk stratification and screening tools for airway disease and CVD might be employed during TB treatment, and continuing at 6-month intervals beyond TB treatment completion, as per recent advice.[193] In terms of CVD prevention, diagnosis, and management, basic CVD screening strategies, may help identify TB survivors at greatest risk.[142] Routine pulmonary function testing in TB patients near the end of TB treatment could be an important step towards post-TB respiratory care planning.[194] In BC, the level of pulmonary function testing among respiratory TB patients is less than 15% (lifetime) and only 2.9%

within 90 days of treatment completion,[151] indicating substantial room for increased testing. The finding of increased depression risk among TB survivors indicates a need for mental health support during TB treatment, in both inpatient and outpatient settings, to prevent TB and its treatment from contributing to either short- or long-term depression. Depression screening for TB survivors appears to be warranted, given the risk of new incident depression, post-TB diagnosis, combined with review-level evidence of prevalent depression among TB survivors at the time of diagnosis.[43] However, the effectiveness of screening tools among TB survivors is unknown in terms of prevention and management of chronic sequelae.

To advance these potential interventions, a "Partnership for Post-TB Health" has been proposed as a knowledge exchange and models of care development network. A "Partnership for Post-TB Health" that would bring together health professionals and researchers from several fields where survivorship has become a priority for research and care. For example, oncology,[195,196] HIV/AIDS,[143,197] and critical care medicine,[51] have each seen developments in research and care of survivors. These fields, and the survivorship specialists working in them, may have important lessons that could be shared in terms of research methodologies, models of care, and strategies for advocating for policy and programming aimed to improve survivor health. A Partnership for Post-TB Health may be a mechanism to create synergies across these fields.

Future Research

Future TB survivorship research should include mixed-methods research with TB survivors to help understand their priorities for post-TB care, and then employing qualitative and quantitative methods to address these outcomes from multiple analytical perspectives. Schoeman and Sifumba pointedly note that:

> "Although quantitative analyses help to highlight the vast numbers of tuberculosis survivors to health systems and governments that might have forgotten them, these analyses risk minimising the individual stories that underlie each statistic. It is essential for tuberculosis policy and programmatic planning to include the perspectives of people affected by tuberculosis."[193]

The inclusion of TB survivors should be a starting point for future research aimed at improving TB survivor health. Prospective cohort studies of TB survivors and comparable non-TB controls should be initiated across Canada and other low-TB-incidence settings to ascertain factors related to mortality and morbidity and inform interventions research to reduce mortality and morbidity among TB survivors, post-TB treatment completion. TB survivors could be partners in developing such a cohort through a knowledge exchange and models of care development network. Intervention studies are needed to investigate the effectiveness of various screening tools, for CVD, airway disease, and depression in improving TB survivor health outcomes. Both TB and LTBI were associated with various CVD outcomes, opening many potential avenues for further research in this area. Effect modification by sex in both mortality and depression risk, with males having higher relative risk than females, may indicate important mechanistic differences, warranting further investigation. The relationships between sex, TB, and depression, require further consideration, along with the mediating role of hospital LOS. Further research that assesses unmeasured confounding in studies of post-TB health outcomes is also needed, including construction of large "complete" DAGs with input from international experts.

In the process of conducting this research, questions about survivorship research in other areas began to develop. For example, cancer survivorship has been established,[195,196] while HIV/AIDS, and critical illness are expanding into this field.[51,197] There is also currently a growing interest in the long-term health outcomes of COVID-19 survivors.[198] However, a unified theory of survivorship epidemiology,

along with customized and transferable methods for survivorship research, is lacking. Emerging from this thesis is the idea for developing a "survivorship epidemiology", specifically in TB, but also beyond TB, to draw from other fields where survivorship has become more important with increasing survival rates. Unifying the lessons from these fields into a "survivorship epidemiology", which looks at diseases like TB, cancer, HIV/AIDs, and their diagnostic and treatment processes, as exposures of interest, may be an important avenue for future research.

Significance

This thesis has added to the body of knowledge on TB survivor health through a systematic literature review, original quantitative research studies, and commentary pieces that have advanced understandings of TB survivor health and epidemiological research into TB survivor health. The research chapters have filled several gaps in the published literature, including lack of cohort studies of mortality among TB survivors in Canada, post-TB airway disease in low-TB-incidence setting, or TB-associated depression in a low-TB-incidence setting. In the cohort studies, new applications of advanced epidemiological methods, including time-varying exposure, DAGs, hdPS, and causal mediation, were demonstrated in the field of TB survivor health, contributing to the epidemiological literature on TB survivorship. This thesis contributes to the growing body of work emphasizing a more holistic and person-centred approach to TB survivor health and should inform the development of new recommendations in the Canadian Tuberculosis Standards that address TB survivor health. At an international level, a recommendation has been made for the Stop TB Partnership to add a 'fourth 90' (where 90% of TB survivors "can have a good health-related quality of life"), to its Global Plan to End TB,[4] which the findings of this research support. Ultimately, however, "a good health-related quality of life" must be defined by TB survivors. Similarly, the significance of this research must also be judged by TB survivors.

Conclusion

This thesis examined TB survivor health in terms of post-TB mortality, cardiovascular disease, airway disease, and depression in four research chapters. Cohort studies were used in three chapters, and a systematic literature review was used for in one. In these research chapters, we identified higher risk in TB patients than non-TB controls in each health outcome domain. Our results were potentially susceptible to unmeasured confounding, although multiple sensitivity analyses were employed to reduce this potential risk of bias. The findings support the development of recommendations for TB survivor care in Canada and similar jurisdictions. Future research is warranted to evaluate potential interventions designed to improve TB survivor health, including screening for depression, cardiovascular disease, and airway disease, during and after TB treatment completion. As the population of TB survivors grows globally, there is an urgent need to implement high-level policies and targets for TB survivor health.

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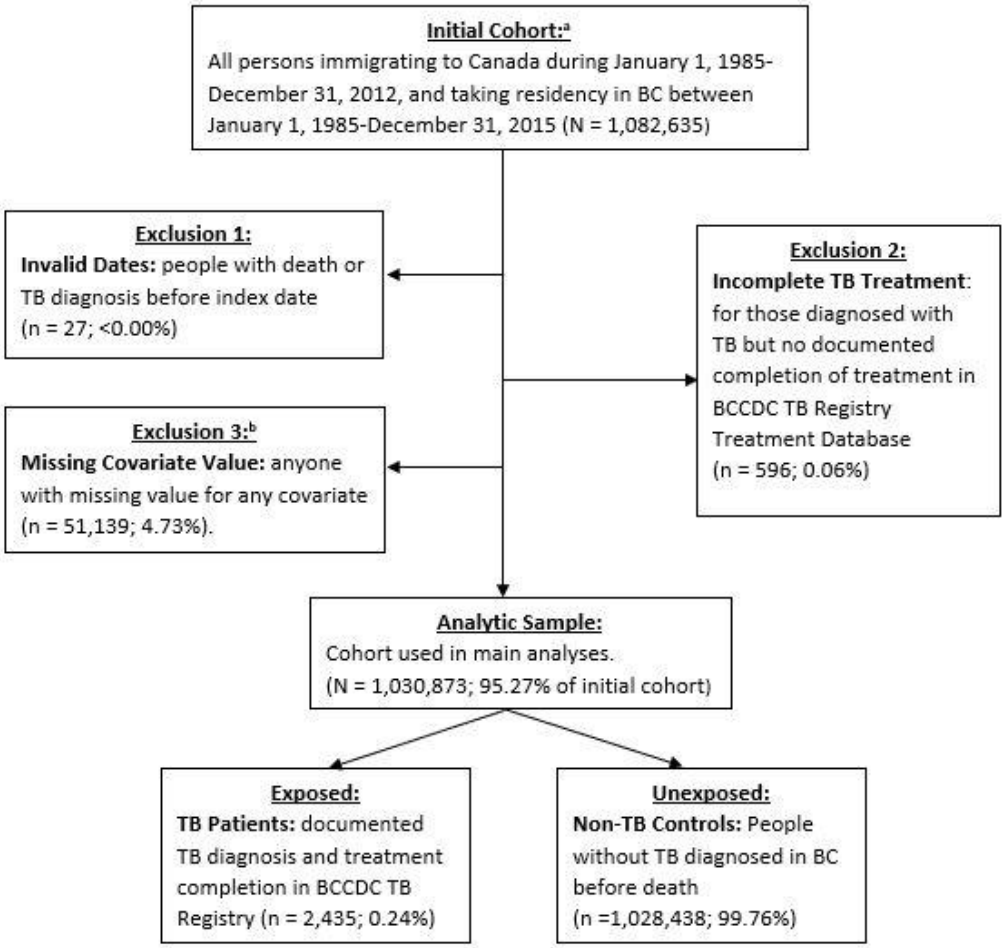
Appendices

Appendix A

Sub-Appendix A.1: Appendix Figures

Figure 1-A1. Cohort and analytic sample flow chart of tuberculosis (TB) patients and non-TB controls among migrants to British Columbia, Canada, 1985-2015.



Legend: BC = British Columbia, BCCDC = British Columbia Centre for Disease Control, IRCC = Immigration, Refugees, and Citizenship Canada, TB = tuberculosis.
Notes: [a] Ascertained from IRCC permanent resident database. Residency in BC defined by acquisition of provincial health insurance (MSP) registration. [b] Covariates for which people with a missing value were excluded were age, sex, income quintile, country of birth, immigration class, educational qualification, Charlson comorbidity index, or index year. Most people excluded in Exclusion 3 were due to missing value for income quintile (n = 51,084; 4.72%).

Sub-Appendix A.2: Appendix Tables

Table 1-A1. Cohort characteristics among migrants to British Columbia, Canada, 1985-2015: tuberculosis patients compared to non-tuberculosis controls.

	TB Patients n (%)	Non-TB Controls n (%)	SMD	p
Total Cohort (N)	2435	1028438		
Non-TB Deaths	285 (11.7)	24602 (2.4)	0.37	<0.01
Male	1195 (49.1)	499338 (48.6)	0.01	0.62
Age at Index in years (mean (SD))	38.66 (18.32)	30.76 (16.72)	0.45	<0.01
Charlson Comorbidity Index (mean (SD))[a]	0.91 (1.72)	0.14 (0.56)	0.60	<0.01
Neighbourhood Income Quintile			0.24	<0.01
Highest 20%	208 (8.5)	150032 (14.6)		
Middle-High 20%	265 (10.9)	147390 (14.3)		
Middle 20%	441 (18.1)	187330 (18.2)		
Low-Middle 20%	627 (25.7)	235975 (22.9)		
Lowest 20%	894 (36.7)	307711 (29.9)		
Educational Qualification			0.27	<0.01
None/Unknown	269 (11.0)	132571 (12.9)		
Secondary or less	1340 (55.0)	439894 (42.8)		
Trade/diploma	401 (16.5)	188479 (18.3)		
University degree	425 (17.5)	267494 (26.0)		
Immigration Class			0.49	<0.01
Economic	862 (35.4)	609449 (59.3)		
Family	1152 (47.3)	310020 (30.1)		
Refugee	316 (13.0)	80733 (7.9)		
Other	105 (4.3)	28236 (2.7)		
TB Incidence in Country of Birth			0.86	
<100 per 100,000 population	238 (9.8)	430550 (41.9)		
100 to <200 per 100,000 population	824 (33.8)	333560 (32.4)		
200 to <300 per 100,000 population	768 (31.5)	146425 (14.2)		
300+ per 100,000 population	605 (24.8)	117903 (11.5)		
Index Year (mean (SD))[b]	10.74 (6.41)	14.71 (7.15)	0.58	<0.01

Legend: p = p-value from Chi-square test, SD = standard deviation, SMD = standardized mean difference, TB = tuberculosis.

Notes: [a] weighted Charlson comorbidity score calculated in the year prior to TB diagnosis or randomly-selected reference date for non-TB controls using both physician claims data and hospital discharge abstracts data (all diagnosis fields). [b] Index year is calculated as 0=1985 to 30=2015 (continuous) and represents the year residency in BC was established.

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Table 1-A2. Sex sub-group time-dependent Cox regression analyses of time-to-mortality among migrants to British Columbia, Canada, 1985-2015: tuberculosis (exposed) time compared to non-tuberculosis (unexposed) time.

Cause of Death	Females Covariate-Adjusted HR (95% CI)[a]	Males Covariate-Adjusted HR (95% CI)[a]
All non-TB causes	1.43 (1.18 – 1.75)	1.88 (1.62 – 2.17)
Respiratory Diseases	2.50 (1.43 – 4.38)	2.97 (2.07 – 4.27)
Cardiovascular Diseases	1.45 (1.02 – 2.07)	1.78 (1.36 – 2.34)
Cancers and Malignant Neoplasms	1.27 (0.89 – 1.07)	1.46 (1.10 – 1.93)
Injuries and Poisonings	1.31 (0.62 – 2.76)	2.28 (1.44 – 3.59)

Legend: BC = British Columbia, CI = confidence interval, HR = hazard ratio, TB = tuberculosis.
Notes: [a] covariate-adjusted analyses included the following baseline variables age, 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.
Interpretations: Higher HR for injuries and poisonings among males than females makes sense given that males are more likely to die of injury/poisoning than women generally. Higher respiratory mortality has similar interpretation.

Table 1-A3. Sensitivity time-dependent Cox regression analyses of time-to-mortality from non-TB causes among migrants to British Columbia, Canada, 1985-2015: tuberculosis (exposed) time compared to non-tuberculosis (unexposed) time.

Sensitivity / Sub-Group Analysis	Age/Sex-Adjusted HR (95% CI)	Covariate-Adjusted HR (95% CI)[a]
TB diagnosis but not necessarily treatment completion	2.34 (2.11 – 2.58)	2.05 (1.85 – 2.26)[b]
Minimum two year observation period (alive and in BC for one year pre-/post-diagnosis/reference date)	2.13 (1.89 – 2.40)	1.80 (1.60 – 2.03)[c]
TB Treatment Complete		
Ages 18 to 60 years at time of immigration to BC	2.36 (1.96 – 2.84)	1.59 (1.32 – 1.92)[d]
Minimum two year observation period (alive and in BC for one year pre-/post-diagnosis/reference date)	2.20 (1.94 – 2.49)	1.85 (1.64 – 2.10)[e]
Elixhauser comorbidity index instead of Charlson comorbidity index	1.95 (1.74 – 2.20)	1.81 (1.61 – 2.03)[f]

Legend: BC = British Columbia, CI = confidence interval, HR = hazard ratio, TB = tuberculosis.

Notes: [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 (and Elixhauser) comorbidity score calculated in the year prior to TB diagnosis or randomly-selected reference date for non-TB controls. [b] people diagnosed but not completing treatment had a higher HR than those completing treatment because death was the leading reason for non-complete treatment. [c] It is unclear why this HR is higher than that of the main analysis. [d] This HR is slightly lower than the main analysis, likely because TB patients were on average older, and restricting the age range improved confounding control between TB and mortality risk. [e] This HR is similar to the previous sensitivity analysis that required a 2-year observation window. [f] somewhat higher than main analysis covariate-adjusted HR.

Appendix B

Table 2-A1. EMBASE database search for systematic review of tuberculosis and the risk of cardiovascular disease and related mortality

Number	Search	Records
1	exp tuberculosis/	184989
2	(tuberculosis or mycobacterium tuberculosis or TB or mycobacterial infection or TBC or MDR-TB or LTBI).tw.	200178
3	1 or 2	249919
4	exp cardiovascular disease/ or cardiovascular dis*.tw.	3978199
5	(coronary or myocard* or ischem* or ischaem* or stroke or cerebrovasc* or cerebral vascular or peripheral arter* or angina).tw.	1497943
6	4 or 5	4257165
7	3 and 6	22485
8	randomized controlled trial/	587336
9	clinical study/ or exp case control study/ or exp clinical trial/ or exp longitudinal study/ or exp prospective study/ or exp retrospective study/	3051255
10	(random* or cohort or case control or RCT).tw.	2414305
11	8 or 9 or 10	4424075
12	7 and 11	5433
13	12 not ((exp animal/ or nonhuman/) not exp human/)	5396
14	vasc*.ti,ab.	902815
15	4 or 5 or 14	4664088
16	3 and 15	23891
17	11 and 16	5645
18	peripheral vascular disease/ or exp vascular disease/	2377903
19	1 and 3	184989
20	3 and 18	12151
21	6 or 14 or 18	4664088
22	3 and 21	23891
23	11 and 22	5645
24	13 and 23	5396

Notes: EMBASE 1974 to 2020 January 10 (search date January 19, 2020).

Table 2-A2. MEDLINE database search for systematic review of tuberculosis and the risk of cardiovascular disease and related mortality

Number	Search	Records
1	exp tuberculosis/	192086
2	(tuberculosis or mycobacterium tuberculosis or TB or mycobacterial infection or TBC or MDR-TB or LTBI).tw.	204779
3	1 or 2	263653
4	exp cardiovascular disease/ or cardiovascular dis*.tw.	2404799
5	(coronary or myocard* or ischem* or ischaem* or stroke or cerebrovasc* or cerebral vascular or peripheral arter* or angina).tw.	1064046
6	4 or 5	2733612
7	3 and 6	8827
8	randomized controlled trial/	498940
9	clinical study/ or exp case control study/ or exp clinical trial/ or exp longitudinal study/ or exp prospective study/ or exp retrospective study/	2328426
10	(random* or cohort or case control or RCT).tw.	1659803
11	8 or 9 or 10	3270287
12	7 and 11	1055
13	12 not ((exp animal/ or nonhuman/) not exp human/)	1042
14	vasc*.ti,ab.	658166
15	4 or 5 or 14	3123047
16	3 and 15	10050
17	11 and 16	1259
18	peripheral vascular disease/ or exp vascular disease/	1634216
19	6 or 14 or 18	3123047
20	3 and 19	10050
21	11 and 20	1259
22	13 and 21	1042

Notes: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to January 17 (search date: January 19, 2020).

Table 2-A3. Cochrane database search for systematic review of tuberculosis and the risk of cardiovascular disease and related mortality

Number	Search	Records
1	exp tuberculosis/	2084
2	(tuberculosis or mycobacterium tuberculosis or TB or mycobacterial infection or TBC or MDR-TB or LTBI).tw.	7070
3	1 or 2	7373
4	exp cardiovascular disease/ or cardiovascular dis*.tw.	112422
5	(coronary or myocard* or ischem* or ischaem* or stroke or cerebrovasc* or cerebral vascular or peripheral arter* or angina).tw	130775
6	4 or 5	196945
7	3 and 6	261
8	randomized controlled trial/	131
9	clinical study/ or exp case control study/ or exp clinical trial/ or exp longitudinal study/ or exp prospective study/ or exp retrospective study/	144776
10	(random* or cohort or case control or RCT).tw.	933551
11	8 or 9 or 10	967954
12	7 and 11	196
13	12 not ((exp animal/ or nonhuman/) not exp human/)	116
14	vasc*.ti,ab.	38912
15	4 or 5 or 14	218064
16	3 and 15	309
17	11 and 16	227
18	peripheral vascular disease/ or exp vascular disease/	73474
19	1 and 3	2084
20	3 and 18	32
21	6 or 14 or 18	218064
22	3 and 21	309
23	11 and 22	227

Notes: EBM Reviews - Cochrane Central Register of Controlled Trials May 2018, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 10, 2020 (search date: January 19, 2020).

Appendix C

Sub-Appendix C.1: Additional Methods Text

Health administrative data sources

Individually linked, population-wide, health administrative data for people immigrating to British Columbia (BC), Canada, 1985-2015 were sourced from the Province of BC, and the Government of Canada, with access provided through Population Data BC.[87–89,93,154,199,200] These data have been described elsewhere.[71,85,154]

Assessment of unmeasured confounding using added data dimensions

We attempted to apply the modified disjunctive cause criterion in our study by including empirical proxy covariates for potential unmeasured confounders,[201] in addition to covariates selected using substantive knowledge of associations with the exposure and the outcome. Our study attempted to control for confounding using multiple methods because the performance of various methods in reducing potential bias in the association of interest in our study (respiratory TB and airway disease) is unclear. Below we describe the two methods employing added data dimensions for proxy adjustment of unmeasured or poorly measured confounders.

High-dimensional propensity score method

The high-dimensional propensity score (hdPS) algorithm identified proxy variables, known as empirical covariates, from added data dimensions (physician claims data and hospital abstracts data in this study). For determining the most relevant proxy or empirical covariates helpful to reduced the bias

due to unmeasured or poorly measured confounding, this algorithm examines the prevalence and potential for reducing bias (association with the exposure and the outcome, separately) using a modification of the Bross formula.[66] The seven steps in the hdPS algorithm are as follows: (1) include added data dimensions from which the proxy or empirical variables will be ascertained, (2) identify candidate empirical covariates using the n most prevalent codes (e.g., ICD-9-CM) within the added data dimensions (default is n=200), (3) determine frequency of code occurrence for these empirical covariates via three dummy variables for each code within each cohort member as either once, sporadically, or frequently (cov_{once}=1 when occurs once; $cov_{sporadic}$=1 if occurs more than the median number of times across cohort members; $cov_{frequent}$=1 when occurs for that person more than the 75th percentile across cohort members), (4) rank empirical covariates in terms of potential for causing/reducing bias via the Bross formula for binary covariates (wherein the relative risk of the binary covariate is used in conjunction with that covariate's prevalence in the unexposed and exposed groups), and then sort them in descending order (5) choose a prespecified number of empirical covariates (k=400 in this study) based on their Bross formula bias assessment rank, (6) include any investigator-specified covariates (e.g., age, sex, education, etc.) with the selected empirical proxy variables (i.e., these selected variables are known as hdPS variables) identified in step 5 in an exposure variable (respiratory TB in our study) prediction model (e.g., logistic regression) to estimate the hdPS, (7) use the resulting hdPS in an exposure-outcome model, such as by grouping cohort members into hdPS deciles and including the hdPS decile variable, along with the exposure variable (respiratory TB in our study), in a regression model (Cox proportional hazards regression in our study of time-to-airway disease/censoring) we then estimated the effect of respiratory TB.

VanderWeele describes the pros and cons of the hdPS in comparison with forward and backward (p-value based) methods used commonly in epidemiological effect studies.[201] One advantage of the hdPS

over p-value-based methods is its assessment of each variables potential for reducing biasing by measuring association with both exposure and outcome, whereas p-value (or information criteria)-based methods only check association with the outcome.[201] A disadvantage of the hdPS is the inability to ensure a minimum adjustment set guaranteed to control for bias if the initial adjustment set is known to suffice to control for confounding, because the hdPS algorithm models each individual covariate individually.[201] Additionally, the hdPS alone may result in overfitting in the final PS model. A second approach to the hdPS was taken that added a regularization technique to select the final list of proxy variables for inclusions in the hdPS estimation model.

LASSO-hdPS method

As the hdPS-generated proxy or empirical covariates for addressing unmeasured confounders are assessed individually, some or many of them may be highly collinear, creating unstable PS estimates (e.g., lack of overlap in the PS between exposure and control groups). We, therefore, used a hybrid of hdPS and least absolute shrinkage and selection operator (LASSO), whereby (a) we obtain the final set of empirical covariates or hdPS variables, and (b) these hdPS variables are then entered into a LASSO logistic regression for a binary version of the outcome (airway disease: censored or event).[67,202] In this hybrid LASSO-hdPS method, we sought to reduce the number of proxy covariates generated by the hdPS algorithm to avoid potential overfitting in the PS model, which can lead to poor overlap in the PS between the exposed (respiratory TB) and unexposed (non-TB control) groups. The LASSO method works by shrinking the value of standardized covariate coefficients for the proxy variables to zero when, after applying the penalty term lambda, the variable is non-significantly associated with the outcome variable (airway disease) after controlling for the other covariates, including the investigator-specified covariates, as well as the exposure variable (respiratory TB). The final set of LASSO-refined hdPS variables are selected from a LASSO logistic regression model using a lambda value that

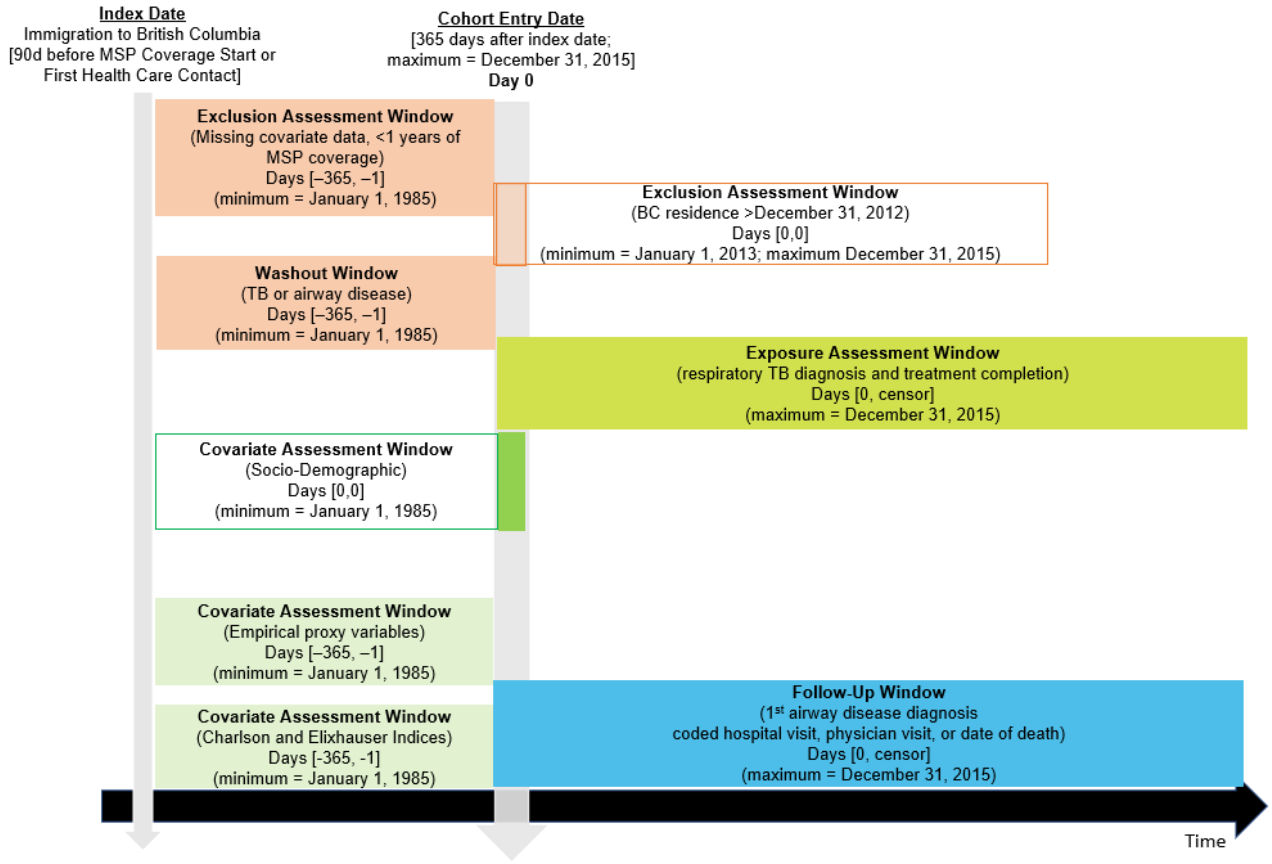
minimized the mean squared error (MSE), with optimal lambda value identified through a grid search across the 5-folds of the data.[67,202] The resulting LASSO-selected proxy variables were then included with the investigator-specified covariates (e.g., age, sex, etc.) in a standard logistic regression to predict the exposure (respiratory TB) and generate a LASSO-hdPS (step 6 in the hdPS algorithm). These propensity scores are then used to create PS deciles that are adjusted for in the outcome Cox PH regression for time-to-airway disease by respiratory TB (step 7 in the hdPS algorithm).

Sub-Appendix C.2: Post-TB airway disease among respiratory TB patients

To compare airway disease among people diagnosed with respiratory TB, we created an outcome-stratified table of the covariates, with tests for differences between airway disease and censored groups by Chi-square tests for categorical variables and t-tests for continuous variables (Table 3-A5).

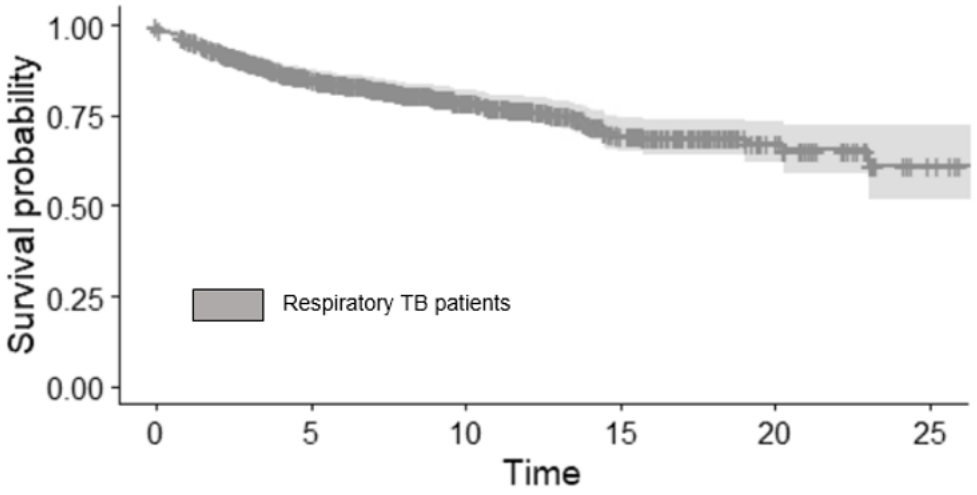
Sub-Appendix C.3: Appendix Figures

Figure 3-A1: Design of retrospective cohort study of post-tuberculosis airway disease among immigrants to British Columbia, Canada, 1985-2015.



Acronyms: MSP, Medical Services Plan of British Columbia.
Notes: The MSP is a population-wide provincial health insurance registry that provides a reliable population-based denominator for the province of British Columbia.

Figure 3-A2. Kaplan-Meier plot of airway disease-free survival time (years) from TB diagnosis date among immigrants to British Columbia, Canada, 1985-2015 who were diagnosed with TB



Follow-up	0 years	5 years	10 years	15 years	20 years	25 years
Number at-risk	1141	526	282	119	39	6
Number events (censored)	≤5 (313)	112 (187)	30 (214)	23	≤5 (77)	≤5 (31)

Notes: ≤5 = suppressed for privacy reasons.

Sub-Appendix C.3: Appendix Tables

Table 3-A1. International Classification of Diseases (ICD) and billing claims codes for physician visits and hospital encounters used to generate a proxy variable for personal health risk

Variable component	BC MSP Fee Item	ICD-9	ICD-10
Respiratory or chest symptoms		786	R069, R064, R0601, R0681, R063, R0602, R0682, R062, R0600, R0609, R063, R0683, R0689, R061, R05, R042, R049, R0481, R0489, R093, R079, R072, R071, R0781, R0782, R0789, R222, R0989, R066, R0689
Cardiovascular symptoms		785	R000, R002, R011, R012, I96, R579, R570, R6521, R571, R578, R599, R0989,
Non-dependent abuse of drugs		305	F17200, F1010, F1210, F1290, F10610, F10310, F1110, F10610, F1410, F1510, F1910, F1810, F10610
Nutrition, metabolism, and development		783	R630, R635, R634, R636, R633, R6250, R6251, R620, R6252, R631, R632, R627, R638, R635,
Other personal history presenting hazards to health		V15	Z91010, Z91011, Z91012, Z91013, Z91018, Z91038, Z91040, Z91041, Z91048, Z9889, Z98870, Z98871, Z9889, Z923, Z91410, Z91411, Z91412, Z9149, Z8781, Z87820, Z87821, Z87828, Z9189, Z920, Z9283, Z9119, Z87891, Z283, Z77090, Z578, Z77011, Z9281, Z9181, Z779, Z9289, Z9189,
Toxic effect of other substances chiefly nonmedicinal as to source		989	T63, T55, T64, T65, T57
Other conditions or status of the mother complicating pregnancy, childbirth, or the puerperium		649	O99, 026, 075
Personal health risk assessment physician consultation	G14066		

Legend: BC = British Columbia, Fee Item = MSP billing code, MSP = Medical Services Plan of British Columbia.
Notes: The first date of a physician visit, hospital encounter, or prescription dispensation was used to determine whether the proxy variable definition was met within the covariate assessment period, 1 to 365 days prior to cohort entry date.

Table 3-A2: First diagnosis for people developing airway disease during follow-up among immigrants to British Columbia, Canada, 1985-2015: stratified by exposure group (respiratory TB vs controls)

Type of airway disease	Controls [*n* (%)]	Respiratory TB [*n* (%)]
Acute bronchitis	57 043 (49.0)	217 (44.7)
Asthma	31 237 (26.8)	95 (19.6)
Bronchitis	19 961 (17.2)	87 (17.9)
Chronic airway obstruction	4491 (3.9)	47 (9.7)
Chronic bronchitis	2656 (2.3)	25 (5.2)
Emphysema	952 (0.8)	14 (2.9)
Acute bronchiolitis	15 (0.0009)	0 (0.0)
Total	116 355 (100)	485 (100)

Legend: ICD = International Classification of Diseases.
Notes: airway disease was defined using ICD-9-CM ICD-10-CA codes. A person required one hospital visit, or three of more physician visits within one year, with one or more of the above conditions to be considered to have airway disease.

Table 3-A3. Cohort characteristics stratified by respiratory tuberculosis status among people immigrating to British Columbia, Canada, 1985-2015

Characteristic	Controls N (%)	Respiratory TB N (%)	SMD
N	1 004 187	1141	-
Airway disease	116 355 (11.6)	485 (42.5)	0.742
Follow-up time-at-risk (mean (SD))	11.1 (7.3)	12.6 (7.6)	0.199
Sex = Male	486 680 (48.5)	663 (58.1)	0.194
Age, years (mean (SD))	32.7 (16.6)	43.6 (19.1)	0.607
Neighbourhood income quintile	-	-	0.214
Highest 20%	146 670 (14.6)	99 (8.7)	-
Middle-High 20%	143 795 (14.3)	145 (12.7)	-
Middle 20%	182 888 (18.2)	201 (17.6)	-
Low-Middle 20%	230 440 (22.9)	285 (25.0)	-
Lowest 20%	300 394 (29.9)	411 (36.0)	-
Education level	-	-	0.312
None/Unknown	127 787 (12.7)	152 (13.3)	-
Secondary or less	431 531 (43.0)	642 (56.3)	-
Trade/diploma	184 793 (18.4)	169 (14.8)	-
University degree	260 076 (25.9)	178 (15.6)	-
Immigration class	-	-	0.540
Economic	594 081 (59.2)	379 (33.2)	-
Family	303 110 (30.2)	570 (50.0)	-
Refugee	27 799 (2.8)	58 (5.1)	-
Other	79 197 (7.9)	134 (11.7)	-
TB incidence rate in country of origin at time of immigration	-	-	0.806
<100 per 100 000 pop.	418 376 (41.7)	121 (10.6)	-
100 to <200 per 100 000 pop.	327 249 (32.6)	419 (36.7)	-
200 to <300 per 100 000 pop.	142 613 (14.2)	342 (30.0)	-
300+ per 100 000 pop.	115 949 (11.5)	259 (22.7)	-
Year of immigration (mean (SD))	14.6 (7.1)	10.5 (6.2)	0.613
Charlson comorbidity score (mean (SD))	0.05 (0.3)	0.13 (0.6)	0.167
Ethanol dependence	1488 (0.1)	≤5	0.065
Substance dependence	1732 (0.2)	≤5	0.048
Psychosis	2319 (0.2)	11 (1.0)	0.095
Depression	42 286 (4.2)	67 (5.9)	0.076
Personal health risk proxy variable	77 416 (7.7)	200 (17.5)	0.299

Legend: Asterisk (*) indicates suppressed value due to cell size ≤5, including cross-suppression of nearest value, due to privacy legislation in British Columbia; SD = standard deviation; TB = tuberculosis.

Table 3-A4. Effect measure modification of airway disease risk by respiratory tuberculosis, modified by key covariates among people immigrating to British Columbia, Canada, 1985-2015

Effect modifier	N	Adjusted HR (TB vs controls)	95% CI
Age group			
<40 years	702 821	2.05	1.76 – 2.38
40+ years	302 507	2.48	2.22 – 2.77
Sex		-	
Male	487 343	2.13	1.89 – 2.33
Female	517 985	2.03	1.78 – 2.33
Immigration class		-	
Economic	594 460	2.49	2.08 – 2.98
Family	303 680	1.95	1.74 – 2.20
Refugee	27 857	1.88	1.42 – 2.47
Other	79 331	2.49	1.73 – 3.59
Education level		-	
University degree	260 254	2.57	1.98 – 3.34
Trade/diploma	184 962	2.33	1.81 – 3.00
Secondary or less	432 173	2.17	1.93 – 2.45
None/unknown	127 939	1.61	1.31 – 1.97
Neighbourhood income quintile			
Highest 20%	146 769	1.99	1.42 – 2.80
Middle-High 20%	143 940	2.86	2.24 – 3.67
Middle 20%	183 089	2.34	1.91 – 2.87
Low-Middle 20%	230 725	2.09	1.76 – 2.43
Lowest 20%	300 805	1.80	1.54 – 2.09
TB incidence in country of birth			
<200 per 100 000	746 165	2.57	2.24 – 2.94
200+ per 100 000	259 163	1.79	1.59 – 2.01
Charlson comorbidity score			
0	963 174	2.25	2.05 – 2.47
1	35 943	1.04	0.72 – 1.50
2+	6211	1.52	0.82 – 2.84
Depression			
No	962 975	1.63	1.60 – 1.67
Yes	42 353	1.12	0.80 – 1.57
Personal health risk proxy variable			
No	927 712	2.15	1.95 – 2.37
Yes	77 616	1.63	1.33 – 2.00

Legend: BC = British Columbia; CI = confidence interval; ETOH = ethanol dependence; HR = hazard ratio; N = analytic sample size; SD = standard deviation; TB = tuberculosis.

Notes: Cox proportional hazards regression was used with the following covariates included to adjust for potential confounding in the relationship between respiratory TB and airway disease: age at index, sex, income quintile at index, educational qualification upon immigration, immigration class, TB incidence in country of birth, weighted Charlson comorbidity score, year of immigration, ETOH, substance dependence, psychoses, and depression.

Table 3-A5. Cohort characteristics of people diagnosed with respiratory tuberculosis, stratified by airway disease or censoring (outcome) status among people immigrating to British Columbia, Canada, 1985-2015

Characteristic	Censored N (%)	Airway disease N (%)	p-value [a]
Respiratory TB patients	656	485	
Follow-up time (mean (SD))	16.08 (6.93)	7.96 (5.89)	<0.001
Sex= Male	389 (59.3)	274 (56.5)	0.374
Age, years (mean (SD))	38.07 (17.84)	48.67 (19.05)	<0.001
Neighbourhood income quintile			0.138
Highest 20%	66 (10.1)	33 (6.8)	
Middle-High 20%	82 (12.5)	63 (13.0)	
Middle 20%	108 (16.5)	93 (19.2)	
Low-Middle 20%	154 (23.5)	131 (27.0)	
Lowest 20%	246 (37.5)	165 (34.0)	
Education level			<0.001
None/Unknown	57 (8.7)	95 (19.6)	
Secondary or less	368 (56.1)	274 (56.5)	
Trade/diploma	109 (16.6)	60 (12.4)	
University degree	122 (18.6)	56 (11.5)	
Immigration class			<0.001
Economic	259 (39.5)	120 (24.7)	
Family	285 (43.4)	285 (58.8)	
Other	29 (4.4)	29 (6.0)	
Refugee	83 (12.7)	51 (10.5)	
TB incidence rate in country of origin at time of immigration			<0.001
<100 per 100 000 pop.	88 (13.4)	33 (6.8)	
100 to <200 per 100 000 pop.	140 (21.3)	202 (41.6)	
200 to <300 per 100 000 pop.	240 (36.6)	179 (36.9)	
300+ per 100 000 pop.	188 (28.7)	71 (14.6)	
Year of immigration (mean (SD))	11.81 (6.45)	8.72 (5.40)	<0.001
Charlson comorbidity score (mean (SD))	0.12 (0.57)	0.13 (0.57)	0.761
Personal health risk proxy variable	109 (16.6)	91 (18.8)	0.387

Legend: BC = British Columbia; CI = confidence interval; HR = hazard ratio; N = analytic sample size; SD = standard deviation; TB = tuberculosis.

Notes: [a] p-values are derived from Chi-square tests for goodness-of-fit for categorical variables, and t-test for equality of means for continuous variables.

Appendix D

Sub-Appendix D.1: Additional Methods Text

Data description and analytic sample creation

The source cohort was created through identification of people immigrating to BC during the period of January 1, 1985-December 31, 2012, based on Immigration, Refugees, and Citizenship Canada (IRCC) permanent residents database.[85,87] Administrative healthcare data, from the period January 1, 1985-December 31, 2015, including the Canadian Institutes of Health Information's hospital discharge abstracts database (DAD),[93] the BC Medical Services Plan (MSP) fee-for-service physician claims,[92] and community pharmacy dispensations data (PharmaNet),[200] which are stored at Population Data BC,[154] were linked by the authors using unique anonymized personal health numbers.[95] We included permanent residents among immigrants to BC and defined the index date as 365 days after immigration to BC (index date) (Figure 4-A1).[155] TB data were sourced from the BC Centre for Disease Control (BCCDC).[89]

Elixhauser comorbidities selected for comorbidity adjustment

To select Elixhauser comorbidities that may confound the relationship between TB and depression, we used a multivariable logistic regression of TB on all the Elixhauser comorbidities, removing those with $p>0.50$. We then ran a second multivariable logistic regression of incident depression on the remaining Elixhauser comorbidities from the first logistic regression, again eliminating those with $p>0.50$. The remaining set of comorbidities was included in our main analysis as potential confounders. This method ensured the selected comorbidities were associated with both the exposure and the outcome.[201]

Mediation analysis

In our mediated outcome analysis, we adjusted for all measured confounders in a weighted Cox regression of time-to-depression, using a duplicated dataset with two counterfactual values for the mediator variable (hospital LOS) where, in one dataset, TB is set to its original value (either TB or non-TB-control), and in the duplicate data TB is set to the opposite (counterfactual) value whereby TB patients are considered controls, and controls are considered TB patients.[68] The mediation weights were calculated as P(M | A*, C)/ P(M | A, C), where P(.) was generated from an ordered logistic regression, M = mediator (hospital LOS), A = original exposure value (TB patient or control), A* = counterfactual TB value (opposite of original exposure value), and C = baseline confounder set shown in the DAG (Figure 4-1).[69] Adjusted hazard ratios obtained from a weighted Cox PH regression of time-to-depression on A and A*, as well as the measured confounders in the DAG, are used as estimates of the direct effect of TB and indirect effect of TB through hospital LOS, on the risk of depression, assuming that informative censoring and non-proportional hazards are not present data.10,11 Multiplying the two adjusted hazard ratios for A and A* together yields the total effect of TB on risk of depression. We used 200 bootstrap re-samples of the dataset to obtain 95% confidence intervals for the NDE, NIE, the total effect of TB, the proportion mediated, and the minimum and maximum mediation weights.[68,69]

Sensitivity analyses for aim 1

First, to check the robustness of our model specification, we conducted a propensity scores analysis an alternative modeling strategy, including our main analysis covariates in generating the PS for tuberculosis (exposure), creating deciles of the propensity score as an adjustment variable for a subsequent outcome logistic regression with a TB indicator variable. Second, we dropped the MSP-

specific code (50B), for depression/anxiety physician billing claims in BC, from our depression case ascertainment algorithm, as this was not included in the validated depression definition of Doktorchik et al, on which our outcome definition is based. Third, to address potential lack of detection of pre-existing conditions, we doubled our washout and covariate assessment periods from 365 days to 730 days pre-CED. Fourth, as the Charlson is more widely used for comorbidity adjustment in studies involving administrative data, we replaced the individual Elixhauser comorbidities with the weighted Charlson comorbidity score.[90,96] Fifth, because the Elixhauser and Charlson comorbidity indices were developed for comorbidity adjustment in studies of mortality rather than for adjusting for confounding in analyses of depression risk, and were developed in very different populations than ours,[90,103,203] we developed a study-specific weighting scheme for the Elixhauser comorbidities (development described below). We used this study-specific Elixhauser score in the fifth sensitivity analysis instead of the individual Elixhauser comorbidities selected for the main analysis. Sixth, as a sensitivity analysis for potential violation of the proportional hazards assumption, we used robust Poisson regression, with depression or censored as a binary outcome measure, with TB as the exposure, and adjusting for the main analysis covariates, offset by the natural logarithm of follow-up time. Poisson regression requires other simplifying assumptions but does not depend on the proportional hazards assumption.

Developing a weighted Elixhauser score for comorbidity adjustment in depression risk analysis

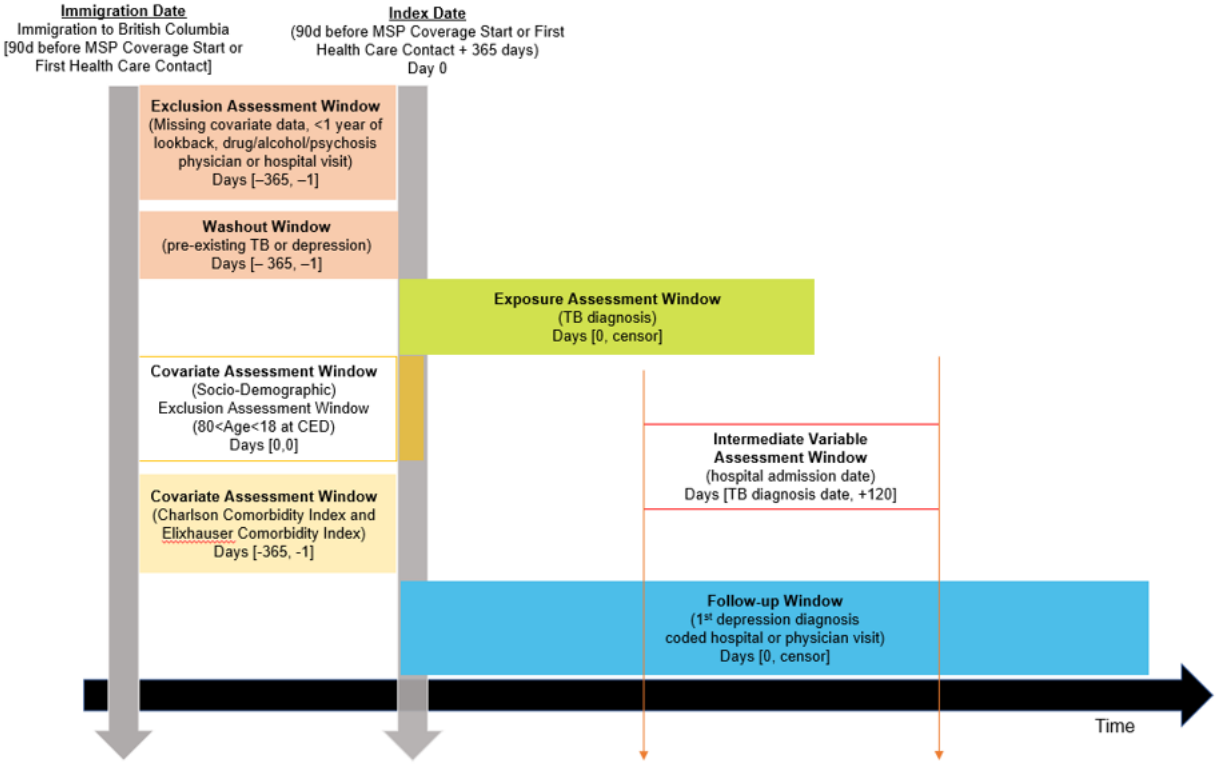
To develop a weighted Elixhauser score for comorbidity adjustment that was appropriate to our outcome of depression in our sample of people immigrating to British Columbia,[203] we used a Cox proportional hazards (PH) regression model of time-to-depression (the outcome variable for our study). In the Cox PH regression model, time-to-depression was regressed on age, sex, and the individual Elixhauser comorbidities, excluding depression, psychoses, ethanol dependence, and substance

dependence, which were used as the outcome, and exclusion criteria, respectively. The coefficients for each comorbidity were multiplied by the indicator variable value, and then summed, for each study participant, to create an Elixhauser depression risk score for adjustment of confounding by baseline comorbidities. We then used the resulting weighted Elixhauser score as a comorbidity adjustment variable in place of the individual Elixhauser comorbidities used in the main analysis.

To assess the association between the new Elixhauser score and depression risk, we used a crude Cox PH regression. The new Elixhauser score had a hazard ratio (HR) of 2.70 (95% CI, 2.55-2.87) for time-to-depression. To assess the association between the new Elixhauser score and tuberculosis (TB), we used a crude logistic regression. The new Elixhauser score had an odds ratio (OR) of 5.39 (95% CI, 3.60-7.84) for TB. In the sensitivity analysis that replaced the individual Elixhauser comorbidities with this score, we found HR=1.96 (95% CI, 1.84-2.08). All of these indicate strong association with depression risk, as expected, as well as TB, which are two important criteria for confounding.

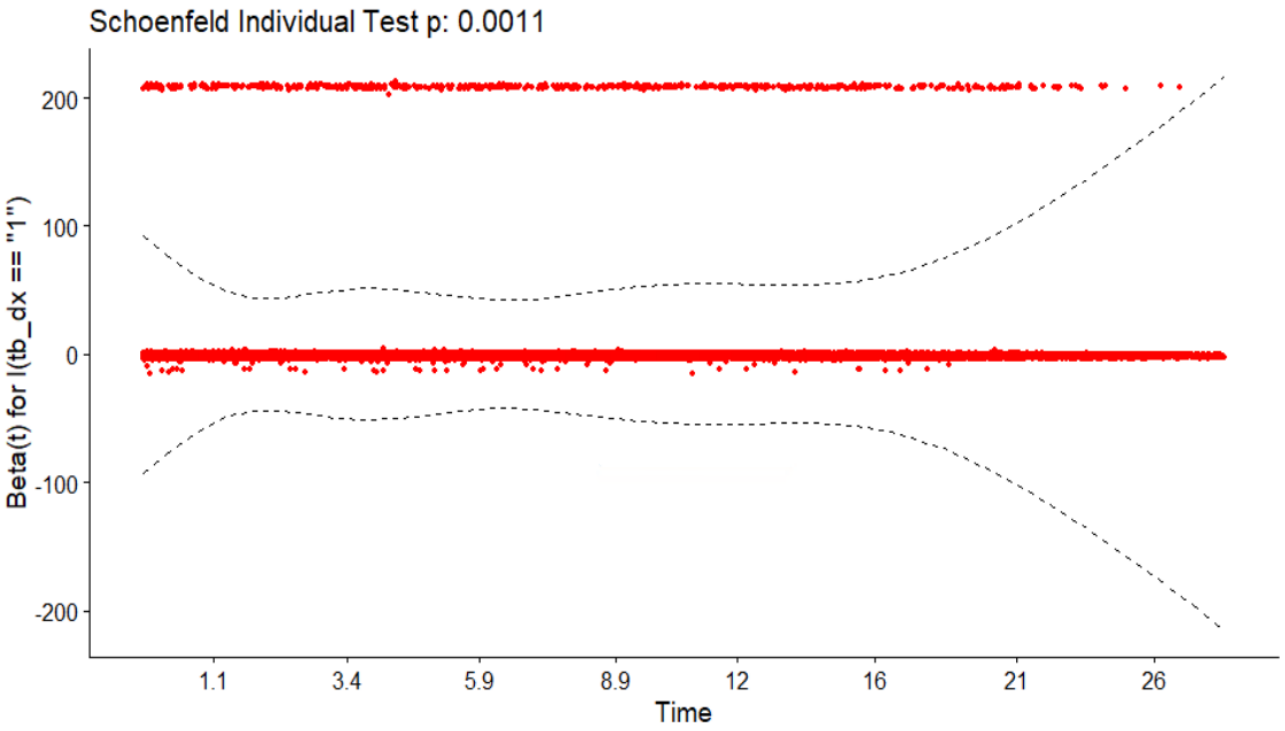
Sub-Appendix D.2: Appendix Figures

Figure 4-A1. Study design for retrospective cohort study of depression risk by tuberculosis among people immigrating to British Columbia, Canada, 1985-2015



Abbreviations: BC = British Columbia, BCCDC = British Columbia Centre for Disease Control, IRCC = Immigration, Refugees, and Citizenship Canada, LOS = length of stay (separation date minus admission date), MSP = Medical Services Plan of BC, TB = tuberculosis. **Notes:** Censoring date defined as first of depression, death, leaving BC, or December 31, 2015.

Figure 4-A2. Schoenfeld residual plot for depression by tuberculosis over time



Sub-Appendix D.3: Appendix Tables

Table 4-A1. Characteristics of people who immigrated at ages 18-80 years to British Columbia, Canada, 1985-2015, stratified by follow-up status.

Characteristic	Censored [a]	Depression [a]	Crude HR [b]	LCL	UCL
Cohort size	626871	128963			
Tuberculosis diagnosis	1676 (0.3)	619 (0.5)	1.21	1.12	1.31
Follow-up, y (mean (SD))	11.12 (7.4)	6.83 (5.7)			
Sex = Male	316581 (50.5)	44555 (34.5)	0.55	0.54	0.56
Age at immigration, y (mean (SD))	37.33 (12.9)	35.79 (12.8)	0.99	0.99	0.99
Neighbourhood income quintile					
Highest 20%	89401 (14.3)	16549 (12.8)	Ref	Ref	Ref
Middle-High 20%	89898 (14.3)	17302 (13.4)	1.04	1.01	1.06
Middle 20%	114306 (18.2)	23603 (18.3)	1.09	1.07	1.12
Low-Middle 20%	145224 (23.2)	31320 (24.3)	1.11	1.09	1.13
Lowest 20%	188042 (30.0)	40189 (31.2)	1.12	1.1	1.15
Education level					
None/Unknown	30384 (4.8)	6790 (5.3)	Ref	Ref	Ref
Secondary or less	225938 (36.0)	55280 (42.9)	0.84	0.82	0.86
Trade/diploma	148553 (23.7)	32106 (24.9)	0.79	0.76	0.81
University degree	221996 (35.4)	34787 (27.0)	0.70	0.68	0.72
Immigration class (%)					
Economic	359717 (57.4)	53056 (41.1)	Ref	Ref	Ref
Family	205436 (32.8)	57515 (44.6)	1.62	1.60	1.64
Other	20255 (3.2)	4110 (3.2)	1.13	1.09	1.17
Refugee	41463 (6.6)	14282 (11.1)	1.83	1.80	1.87
TB incidence rate in country of birth					
<100 per 100,000 population	257260 (41.0)	52594 (40.8)	Ref	Ref	Ref
100 to <200 per 100,000 population	210617 (33.6)	32007 (24.8)	0.62	0.61	0.63
200 to <300 per 100,000 population	84455 (13.5)	32245 (25.0)	1.35	1.33	1.37
300+ per 100,000 population	74539 (11.9)	12117 (9.4)	0.67	0.65	0.68
WHO Region of birth					
Africa	16284 (2.6)	4234 (3.3)	Ref	Ref	Ref
Americas	38036 (6.1)	12259 (9.5)	1.20	1.16	1.24
Eastern Mediterranean	42660 (6.8)	12579 (9.8)	1.24	1.20	1.28
Europe	78068 (12.5)	22219 (17.2)	1.01	0.98	1.04
South-East Asia	90435 (14.4)	29934 (23.2)	1.19	1.15	1.23
Western Pacific	361388 (57.6)	47738 (37.0)	0.49	0.47	0.50
Year of immigration (mean (SD)) [b]	15.5 (7.1)	11.4 (6.7)	0.98	0.98	0.98
Elixhauser comorbidities					
Congestive heart failure	383 (0.1)	96 (0.1)	1.04	0.85	1.27
Valvular disease	248 (0.0)	102 (0.1)	1.50	1.23	1.82
Hypertension with complications	232 (0.0)	66 (0.1)	1.09	0.86	1.39
Other neurological disorders [c]	518 (0.1)	219 (0.2)	1.67	1.46	1.90
Chronic pulmonary disease	3728 (0.6)	1488 (1.2)	1.47	1.40	1.55
Diabetes without complications	5655 (0.9)	1404 (1.1)	1.07	1.01	1.12
Hypothyroidism	2277 (0.4)	833 (0.6)	1.56	1.46	1.67
Renal failure	248 (0.0)	57 (0.0)	1.07	0.82	1.39
Peptic ulcer disease excluding bleeding	1237 (0.2)	446 (0.3)	1.29	1.17	1.41
HIV/AIDS	48 (0.0)	16 (0.0)	1.78	1.09	2.90
Solid tumour without metastasis	707 (0.1)	213 (0.2)	1.21	1.06	1.38
Rheumatoid arthritis/collagen	4693 (0.7)	1884 (1.5)	1.46	1.39	1.52
Coagulopathy	166 (0.0)	53 (0.0)	1.35	1.03	1.77
Fluid and electrolyte disorders	93 (0.0)	36 (0.0)	1.61	1.16	2.23
Deficiency anemia	1962 (0.3)	944 (0.7)	1.92	1.80	2.05

Abbreviations: HR = hazard ratio for depression, LCL = lower 95% confidence limit, SD = standard deviation, TB = tuberculosis, UCL = upper confidence 95% limit, WHO = World Health Organization, y = years. **Notes**: a Values are n (%) unless otherwise noted. b Year of immigration is defined as: 0=1985, 30=2015 (continuous). c "Other neurological disorders" are defined by Elixhauser as non-paralytic nervous system disorders.

Table 4-A2. First recorded depression diagnosis in the outcome variable, defined among who immigrated at ages 18-80 years to British Columbia, Canada, 1985-2015.

Diagnosis label	Administrative Data Code [a]	Frequency (N)	Percent (%)
Anxiety/depression	MSP code 50B	67,658	52.45
Depressive disorder	ICD-9-CM: 311	46,803	36.28
Adjustment reaction	ICD-9-CM: 309	10,011	7.76
Affective psychoses	ICD-9-CM: 296	4,146	3.21
Depressive episode	ICD-10-CA: F32, F33	387	0.30

Abbreviations: ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CA = International Classification of Diseases, 10th Revision, Canadian Adaptation; MSP = Medical Services Plan of British Columbia. **Notes**: a ICD-9-CM and ICD-10-CA codes were used to ascertain depression based on physician visit claims data and hospital discharge abstracts data from January 1, 1985-December 31, 2015.

Sub-Appendix D.4: code for Figure 4-1, directed acyclic graph (DAG), from Daggity.net

```
dag {
"Age at index" [adjusted,pos="0.310,0.111"]
"Elixhauser comorbidities" [adjusted,pos="0.580,0.423"]
"Hospital LOS" [pos="0.455,-0.087"]
"Immigration class" [adjusted,pos="0.361,-0.006"]
"Neighbourhood income" [adjusted,pos="0.609,0.082"]
"TB incidence in country of birth" [adjusted,pos="0.441,0.463"]
"WHO Region of birth country" [adjusted,pos="0.301,0.385"]
"Year of immigration" [adjusted,pos="0.450,0.307"]
Depression [outcome,pos="0.658,0.262"]
Education [adjusted,pos="0.478,0.148"]
Sex [adjusted,pos="0.532,0.015"]
Tuberculosis [exposure,pos="0.271,0.267"]
"Age at index" -> "Elixhauser comorbidities"
"Age at index" -> "Hospital LOS" [pos="0.383,0.064"]
"Age at index" -> "Immigration class"
"Age at index" -> "Neighbourhood income"
"Age at index" -> Depression
"Age at index" -> Education
"Age at index" -> Tuberculosis
"Elixhauser comorbidities" -> "Hospital LOS"
"Elixhauser comorbidities" -> Depression
"Elixhauser comorbidities" -> Tuberculosis [pos="0.427,0.363"]
"Hospital LOS" -> Depression [pos="0.685,-0.061"]
"Immigration class" -> "Elixhauser comorbidities"
"Immigration class" -> "Hospital LOS"
"Immigration class" -> "Neighbourhood income" [pos="0.490,-0.066"]
"Immigration class" -> Depression [pos="0.575,0.110"]
"Immigration class" -> Tuberculosis [pos="0.291,0.046"]
"Neighbourhood income" -> "Elixhauser comorbidities"
"Neighbourhood income" -> "Hospital LOS" [pos="0.519,-0.049"]
"Neighbourhood income" -> Depression [pos="0.649,0.141"]
"Neighbourhood income" -> Tuberculosis [pos="0.472,0.258"]
"TB incidence in country of birth" -> "Elixhauser comorbidities"
"TB incidence in country of birth" -> Tuberculosis
"WHO Region of birth country" -> "Elixhauser comorbidities"
"WHO Region of birth country" -> "Hospital LOS"
"WHO Region of birth country" -> "Immigration class"
"WHO Region of birth country" -> "Neighbourhood income" [pos="0.487,0.188"]
"WHO Region of birth country" -> "TB incidence in country of birth"
"WHO Region of birth country" -> Depression [pos="0.598,0.336"]
"WHO Region of birth country" -> Education
"WHO Region of birth country" -> Tuberculosis
"Year of immigration" -> "Elixhauser comorbidities"
"Year of immigration" -> "Hospital LOS"
"Year of immigration" -> "TB incidence in country of birth"
"Year of immigration" -> "WHO Region of birth country"
"Year of immigration" -> Depression
"Year of immigration" -> Tuberculosis
Education -> "Elixhauser comorbidities"
Education -> "Hospital LOS"
Education -> "Immigration class"
Education -> "Neighbourhood income"
Education -> Depression [pos="0.581,0.188"]
Education -> Tuberculosis [pos="0.350,0.195"]
Sex -> "Elixhauser comorbidities"
Sex -> "Hospital LOS"
Sex -> Depression [pos="0.631,0.159"]
Sex -> Tuberculosis [pos="0.310,0.183"]
Tuberculosis -> "Hospital LOS" [pos="0.250,-0.051"]
Tuberculosis -> Depression}
```

Appendix E

Sub-Appendix E1: sensitivity analyses of time-to-airway disease by respiratory TB diagnosis and treatment completion among people immigrating to British Columbia, Canada, 1985-2015.

Table E1-1. Frequency of censor variable values for Fine-Gray competing risk regression analysis of time-to-airway disease by respiratory TB diagnosis diagnosis and treatment completion with competing risk of non-airway disease death among people immigrating to British Columbia, Canada, 1985-2015.

	Full cohort		PS-matched	
Censor variable value	***N***	**%**	***N***	**%**
0: left BC, end of study	872325	86.77	1393	60.10
1: airway disease (event)	116835	11.62	751	32.94
2: mortality from non-airway disease cause (competing risk)	16168	1.61	136	5.96

Abbreviations: BC = British Columbia, N = sample size, PS = propensity score, TB = tuberculosis.

Table E1-2. Sensitivity analyses of time-to-airway disease by respiratory TB diagnosis and treatment completion among people immigrating to British Columbia, Canada, 1985-2015: Fine-Gray model, PS-matched Fine-Gray model, and PS-matched Cox PH regression

Analysis description	N	HR	95% CI
Fine-Gray competing risk regression in the full analytic sample[a]	1005328	2.11	1.92-2.32
Fine-Gray competing risk regression in 1:1 PS-matched sample[a,b]	2280	1.86	1.60-2.16
Cox PH regression in 1:1 PS-matched sample[b,c]	2280	1.83	1.58-2.13

Abbreviations: CI = confidence interval, HR = hazard ratio, N = sample size, PH = propotional hazards, PS = propensity score, TB = tuberculosis.

Notes:

[a] Competing risk for airway disease diagnosis or death was defined as non-airway disease death on or before censoring (leaving BC, study end December 31, 2015) or event (airway disease diagnosis or death) date.

[b] To create the PS-matched sample, a PS for respiratory TB diagnosis and treatment completion was calculated for each cohort member using predictors: age, sex, income quintile of neighbourhood, educational qualification, weighted Charlson comorbidity score (continuous), TB incidence in birth country, year of residency in BC, ethanol dependence, substance dependence, depression, and psychoses. Matching was 1:1 using greedy nearest neighbour matching without replacement and caliper=0.2 SD. In PS-matched sample, all covariates were balaneced (all SMD≤0.1).

[c] In the Cox PH regression, the Schoenfeld residual test for non-proportional hazards was non-significant (p=0.82).

Sub-Appendix E2: sensitivity analyses for time-to-depression by TB diagnosis among people immigrating to British Columbia, Canada, 1985-2015.

Table E2-1. Frequency of censor variable values for Fine-Gray competing risk regression analysis of time-to-depression by TB diagnosis with non-depression death as a competing risk among people immigrating to British Columbia, Canada, 1985-2015

	Full cohort		PS-matched	
Censor variable value	**N**	**%**	**N**	**%**
0: left BC, end of study	611747	80.94	3142	68.48
1: depression (event)	128962	17.06	1097	23.91
2: mortality from non-depression cause (competing risk)	15125	2.00	349	7.61

Abbreviations: BC = British Columbia, N = sample size, PS = propensity score, TB = tuberculosis.

Table E2-2. Sensitivity analyses of time-to-depression by TB diagnosis with non-depression death as a competing risk among people immigrating to British Columbia, Canada, 1985-2015: Fine-Gray model, PS-matched Fine-Gray model, and PS-matched Cox PH regression

Analysis description	N	HR	95% CI
Fine-Gray competing risk regression in the full analytic sample[a]	755834	1.22	1.12-1.32
Fine-Gray competing risk regression in 1:1 PS-matched sample[a,b]	4588	1.23	1.09-1.38
Cox PH regression in 1:1 PS-matched sample[b,c]	4588	1.25	1.11-1.41

Abbreviations: CI = confidence interval, HR = hazard ratio, N = sample size, PH = proportional hazards, PS = propensity score, TB = tuberculosis.

Notes:

[a] Competing risk for depression diagnosis or death was defined as non-depression death on or before censoring (leaving province, study end December 31, 2015) or event (depression diagnosis or death) date.

[b] To create the PS-matched sample, a PS for TB diagnosis was calculated for each cohort member using predictors: age, sex, neighbourhood income quintile, TB incidence in country of birth, World Health Organization region of birth, year of immigration, educational qualification at immigration, immigration class, and individual Elixhauser comorbidities backwards selected using $p>0.50$ to remove variables in two steps employing consecutive multivariable logistic regressions: (1) regressing TB diagnosis (exposure variable) on all 31 Elixhauser comorbidities, and (2) regressing incident depression (binary outcome variable) on the Elixhauser comorbidities that were retained in the first step. Elixhauser comorbidities retained after both steps were: congestive heart failure, valvular disease, hypertension with complications, other neurological disorders, chronic pulmonary disease, diabetes without complications, hypothyroidism, renal failure, peptic ulcer disease excluding bleeding, HIV/AIDS, solid tumour without metastasis, rheumatoid arthritis/collagen, coagulopathy, fluid and electrolyte disorders, and deficiency anemia). Matching was 1:1 using greedy nearest neighbour matching without replacement and caliper=0.2 SD. In PS-matched sample, all covariates were balanced (all SMD≤0.1).

[c] In the Cox PH regression, the Schoenfeld residual test for non-proportional hazards was non-significant ($p=0.53$).