Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis

Kamila Romanowski, Brett Baumann, C Andrew Basham, Faiz Ahmad Khan, Greg J Fox, James C Johnston

Summary

Background Accurate estimates of long-term mortality following tuberculosis treatment are scarce. This systematic review and meta-analysis aimed to estimate the post-treatment mortality among tuberculosis survivors, and examine differences in mortality risk by demographic and clinical characteristics.

Methods We systematically searched Embase, MEDLINE, and the Cochrane Database of Systematic Reviews for cohort studies published in English between Jan 1, 1997, and May 31, 2018. We included research papers that used a cohort study design, included bacteriological or clinical confirmation of tuberculosis disease for all participants, and reported, or provided enough data to calculate, mortality estimates for people with tuberculosis and a valid control group representative of the general population. We excluded studies that reported duplicate data, had a study population of fewer than 50 people overall, had a follow-up period shorter than 12 months after treatment completion, or had a loss to follow-up of more than 30%. From eligible studies, we extracted standardised mortality ratios (SMRs), or calculated them when the data were sufficient, by dividing the sum of the observed deaths by the sum of the expected deaths. For studies that did not report SMR as their mortality estimate, either mortality hazard ratios or mortality rate ratios were extracted and pooled with SMRs. Random-effects meta-analysis was used to obtain pooled SMRs. Between-study heterogeneity was estimated with I^2. This study was prospectively registered in PROSPERO (CRD42018092592).

Findings Of the 7283 unique studies identified, data from ten studies, reporting on 40 781 individuals and 6922 deaths, were included. The pooled SMR for all-cause mortality among people with tuberculosis, compared with the control group, was 2·91 (95% CI 2·21–3·84; I^2=99%, $p_{heterogeneity}$<0·0001). When restricted to people with confirmed treatment completion or cure, the pooled SMR was 3·76 (95% CI 3·04–4·66; I^2=95%). Effect estimates were similar when stratified by tuberculosis type, sex, age, and country income category. Causes of mortality were extracted for 4226 deaths that occurred post-treatment, with most deaths attributable to cardiovascular disease (20% [95% CI 15–26]; I^2=92%).

Interpretation People treated for tuberculosis have significantly increased mortality following treatment compared with the general population or matched controls. These findings support the need for further research to understand and address the biomedical and social factors that affect the long-term prognosis of this population.

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See Comment page 1045

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Introduction

Tuberculosis is a substantial cause of mortality globally. For the past 5 years, tuberculosis has been the leading cause of death from a single infectious disease agent worldwide, ranking higher than HIV.[1] WHO estimates that, in 2017, more than 10 million people were affected by tuberculosis, resulting in an estimated 1·6 million deaths.[1] These WHO mortality data estimate the number of people with tuberculosis who die before starting or during tuberculosis treatment irrespective of cause of death. However, the routine reporting upon which WHO estimates are based does not capture mortality in the post-treatment period.[2] Consequently, accurate programmatic estimates of mortality following tuberculosis treatment are unavailable.

Several lines of evidence suggest that people treated for tuberculosis have persistent health impairment after treatment. Studies have noted an association between previous tuberculosis treatment and chronic lung disease, coronary artery disease, chronic infections, and persistent neurological deficits.[3–6] Comorbidities that result in an increased risk of premature mortality, including HIV infection, diabetes, chronic kidney disease, cancer, and rheumatological diseases, are more common among people treated for tuberculosis than the general population.[7] Socio-economic disadvantage is also associated with an increased risk of tuberculosis, as well as other lifestyle factors associated with premature mortality, such as alcohol use, smoking, and drug-use disorders.[8,9] The association between these risk factors and post-tuberculosis mortality is complex, since many of the tuberculosis risk factors also predispose individuals to premature mortality.

Considering the focus upon mortality as a part of the WHO End TB Strategy,[10] we did a systematic review to explore long-term mortality in people treated for tuberculosis and its potential causes.

Research in context

Evidence before this study

Tuberculosis is the leading cause of death from a single infectious agent worldwide. WHO estimates that, in 2017, 1·6 million deaths were due to tuberculosis. These tuberculosis-associated mortality estimates reflect the number of people with tuberculosis who die before starting, or during, tuberculosis treatment. Accumulating research, however, suggests that the mortality post-tuberculosis treatment is high, but these data have not yet been comprehensively assessed.

We searched three electronic databases (Embase, MEDLINE, and the Cochrane Database of Systematic Reviews) with the search terms "tuberculosis AND (mortality OR long-term outcome OR standardized mortality)", for cohort studies, published in English, from Jan 1, 1997, to May 31, 2018.

Ten studies were identified that reported a mortality estimate for both treated tuberculosis patients and a control group from the general population or other suitable controls from the same setting. All studies were published after 2013, with cohorts commencing treatment during the period from 1977 to 2015, and consisted of data from nine countries over five WHO regions. Mortality ratios for these studies ranged from 1·20 to 7·63.

Added value of this study

To our knowledge, this study is the first systematic review and meta-analysis to examine mortality in people after tuberculosis treatment. We found that, overall, the pooled standardised mortality ratio for people treated for tuberculosis was close to three-times higher than that of the general population or matched controls. These findings remained consistent when the data was stratified by tuberculosis type, country income category, patient demographic factors, and co-infection of HIV.

Implications of all the available evidence

People treated for tuberculosis, as a group, are at high risk of premature death after treatment. These individuals frequently have negative health effects after treatment, in addition to lower socioeconomic status and more comorbidities than the general population. Further research investigating the pathways linking both medical and social factors to long-term mortality among this population is needed. Improved characterisation of the factors contributing to the excess mortality in people treated for tuberculosis could bolster the case for more comprehensive socioeconomic and medical interventions, which promise to have a substantial effect on the long-term prognosis and survival of this population.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we systematically searched Embase, MEDLINE, and the Cochrane Database of Systematic Reviews published from Jan 1, 1997, to May 31, 2018, using a broad search strategy developed in consultation with a medical informationist. Studies were restricted to clinical cohort studies written in English. Keywords included "tuberculosis AND (mortality OR long-term outcome OR standardized mortality)". Details of the search strategy are presented in the appendix (p 1). The dates we chose for the search strategy reflect modern tuberculosis treatment practices and limit the effect of untreated or suboptimally treated HIV infection before the widespread introduction of highly active antiretroviral therapy. Potentially relevant articles were accessed for full-text review. Citations from eligible articles were also searched to identify other relevant studies.

See Online for appendix

Studies were included if they met all of the following criteria: were original research papers that used a cohort study design; included bacteriological or clinical confirmation of tuberculosis disease for all participants; reported confirmed all-cause mortality as the outcome; reported, or provided enough data to calculate, a mortality estimate for both people treated for tuberculosis and a control group from the general population or other suitable controls from the same setting; and were written in English. Studies were excluded if they did not report, or did not provide enough data to calculate, a mortality estimate; reported duplicate data; had a study population of fewer than 50 people overall; had a follow-up period shorter than 12 months after treatment completion; or had a loss to follow-up of more than 30%.

Two authors (KR and BB) did the literature search and extracted the data. Uncertainties regarding the inclusion or exclusion of articles and data extraction were settled by a third reviewer (JCJ). Authors of screened articles were contacted to provide additional information when necessary. When multiple articles from the same data sources reported on the same endpoint, we included the article with the most complete reporting of outcomes. In studies that presented results stratified by treatment outcome, we selected results for those who had been classified as treatment complete or cure.

The search strategy and items for data extraction were predefined and agreed upon by all authors. Variables that were extracted from each study were name of first author, name of study, year of publication, country of study, data sources, baseline study years, duration of follow-up, study endpoints, sample size, number of deaths, level of adjustment or standardisation, measure of association and associated 95% CIs, and causes of death.

Quality assessment

Quality assessment of individual studies was done using the Newcastle-Ottawa scale. This scale, specific for cohort studies, uses a star rating system to score three aspects of the study: selection of study groups (0–4 stars), comparability or quality of adjustment for confounding factors (0–2 stars), and ascertainment of the outcome of interest

(0–3 stars), for a maximum of nine stars representing the highest methodological quality. Stars were assigned if the cohort was truly representative of exposed individuals in the population and if the control population was drawn from the same community as the exposed population. One star was given if studies adjusted or standardised for at least age and sex; an additional star was given for any additional factors that were controlled for. Additional stars were given if the studies used independent blind assessment or secure record linkage to assess outcome. Follow-up was judged adequate if less than 10% of patients were lost to follow-up.

Outcomes

The primary endpoint of this study was pooled all-cause mortality after tuberculosis treatment completion compared with pooled mortality in matched control groups. The secondary endpoint was the pooled proportion of specific causes of death in people after tuberculosis treatment as defined in the original published studies.

Statistical analysis

From eligible studies, we extracted standardised mortality ratios (SMRs), or calculated SMRs when data were sufficient, by dividing the sum of the observed deaths by the sum of the expected deaths. For studies that did not report SMR as their mortality estimate, either mortality hazard ratios (MHRs) or mortality rate ratios (MRRs) were extracted and pooled with SMRs. If studies did not provide 95% CIs in the original published study, we calculated them according to the formula described by Rothman and Greenland.[11] For articles that reported separate mortality estimates by tuberculosis site (ie, mortality estimates for pulmonary and extrapulmonary tuberculosis), we included both estimates in our analysis since mortality was examined in two non-overlapping populations.

Once extracted, all mortality estimates were log-transformed, and the 95% CIs were used to calculate corresponding standard errors. Data were then pooled using random-effects meta-analysis with inverse variance weighting since SMRs are known to vary widely among sites because of differences in populations and disease incidence.[11] The pooled log-SMRs were then back-transformed for interpretation as SMRs.

Our primary analysis included all eligible studies. Since some included studies also reported in-treatment mortality, we did a secondary analysis that included studies that reported mortality after treatment completion separately. Further subgroup analyses were done to examine crucial variables that might effect mortality and to assess sources of heterogeneity. Subgroup analyses included stratification by tuberculosis type, country income category, patient demographic factors, prevalence of HIV co-infection in study sites, and prevalence of multidrug-resistant tuberculosis in study sites. To assess the effect of country income category, we stratified

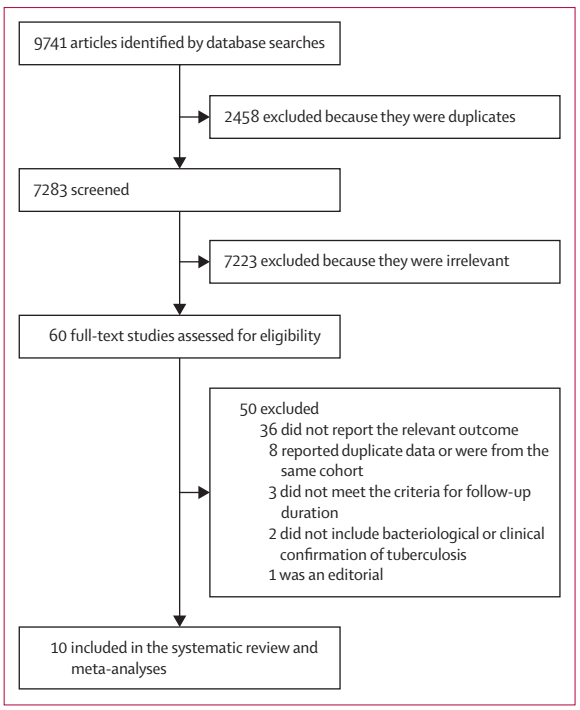

Figure 1: **Study selection**

outcomes according to the gross national income (GNI) per capita of the study sites and used World Bank standard classifications for GNI per capita at the mid-year of study enrolment.[12] Co-infection with HIV was estimated using WHO annual country-specific estimates at the midpoint of study enrolment.[13] Country-specific estimates for the proportion of individuals with multidrug-resistant tuberculosis among newly diagnosed patients with pulmonary tuberculosis were obtained from the 2017 WHO tuberculosis country profiles.[14] We did not do any formal statistical analysis on these subanalyses in line with recommended practice.[15] We also did additional post-hoc analyses, which included stratifying effect estimates by year of cohort entry, restricting analyses to only studies that reported an SMR, and removing studies containing non-symmetrical CIs.

Between-study heterogeneity was estimated with I^2, and classified as low-level (I^2<25%), moderate-level (I^2=25–49%), substantial-level (I^2=50–74%), or high-level (I^2>75%).[16] In case of high heterogeneity, subset analyses were repeated multiple times, with the removal of one or more studies to investigate the source of high heterogeneity.

Causes of death data were extracted when available and classified according to the following categories: respiratory (pneumonia, chronic respiratory disease), cardiovascular (endocarditis, myocardial infarction, circulatory system disease, cardiovascular disease, cerebrovascular disease), cancer (neoplasm, tumour, and carcinoma), infectious disease (tuberculosis, HIV), traumatic (accident, homicide, injury, violence), other disorders not

	Country	Number of participants	Number of deaths	Source of sample	Assessment of mortality	Study enrolment period	Follow-up duration	Tuberculosis type	Treatment complete confirmed	Comparison group	Outcome measure	Level of adjustment or standardisation	Proportion of HIV co-infection*
Blöndal et al (2013)[18]	Estonia	2058	388	Medical or administrative records	Medical or administrative records	2002–09	Men, 7950 person-years, 5·5 years†; women, 3420 person-years, 6·0 years†	Pulmonary tuberculosis	Yes	General population of the country	Standardised mortality ratio	Age and sex standardised mortality estimates	8·6%
Christensen et al (2014)[19]	Denmark	8291	2903	Tuberculosis register	Medical or administrative records	1977–2008	Pulmonary tuberculosis, 64 212 person-years, 8·1 years‡; extra-pulmonary tuberculosis, 20 339 person-years, 9·3 years‡	Pulmonary and extrapulmonary tuberculosis	No	Age and sex matched population from the general population	Mortality rate ratio	Mortality estimate adjusted for age and sex	1·8%
Dangisso et al (2018)[20]	Ethiopia	238	238	Tuberculosis register	Interviews, home visits	2002–12	8780·7 person-years	Pulmonary tuberculosis	No	General population of the city	Standardised mortality ratio	Age, sex, and geographical zone standardised mortality estimates	12·0%
Fox et al (2018)[21]	Vietnam	10964	979	Nested within randomised trial	Interviews, home visits	2010–13	27 922 person-years, 2·9 years‡	Pulmonary tuberculosis	Yes	Age and sex matched household contact population	Standardised mortality ratio	Age and sex standardised mortality estimates	7·0%
Kolappan et al (2008)[22]	India	2665	297	Tuberculosis register	Interviews, home visits	2002–03	3·3 years†	Pulmonary and extrapulmonary tuberculosis	Yes	General population of the country	Standardised mortality ratio	Age and sex standardised mortality estimates	7·0%
Liu et al (2018)[23]	China	2741	394	Tuberculosis register	Interviews, home visits; death certificates	2004–15	17 167·5 person-years	Pulmonary tuberculosis	No	General population of the city	Standardised mortality ratio	Age and sex standardised mortality estimates	1·2%
Miller et al (2015)[24]	USA	3853	799	Tuberculosis register	Medical or administrative records	1993–2002	119 772 person-years, 11 years†	Pulmonary and extrapulmonary tuberculosis	Yes	Age and sex matched latent tuberculosis infection population	Mortality hazard ratio	Mortality estimate adjusted for age, sex, race, HIV status, and nativity	16·0%
Shuldiner et al (2016)[25]	Israel	3201	385	Tuberculosis register	Death register or death certificates	2000–10	18 246 person-years, 5·9 years‡	Pulmonary and extrapulmonary tuberculosis	Yes	General population of the country	Standardised mortality ratio	Age and sex standardised mortality estimates	4·6%
Tocque et al (2005)[26]	UK	439	104	Tuberculosis notification record	Death certificates, medical or administrative records	1989–96	1–9 years (total overall follow-up time)	Pulmonary and extrapulmonary tuberculosis	No	General population of the city	Standardised mortality ratio	Age and sex standardised mortality estimates	4·3%
Wang et al (2015)[27]	China	4342	550	Tuberculosis register	Interviews, home visits	2007–14	21 850 person-years, 5·0 years†	Pulmonary and extrapulmonary tuberculosis	Yes	General population of the country	Standardised mortality ratio	Age and sex standardised mortality estimates	1·2%

*Co-prevalence of HIV estimates based on WHO country data at mid-year of study enrollment. †Mean duration of follow-up. ‡Median duration of follow-up.

Table 1: **Summary of included studies**

	Selection				Comparability	Outcome			Total quality score
	Representativeness of exposed cohort (maximum 1 star)	Selection of non-exposed cohort (maximum 1 star)	Ascertainment of exposure (maximum 1 star)	Showing that outcome of interest was not present at the start of the study (maximum 1 star)	Comparability of the cohorts based on design or analysis (maximum 2 stars)	Assessment of outcome (maximum 1 star)	Follow-up long enough for outcomes to occur (maximum 1 star)	Adequacy of follow-up of the cohort (maximum 1 star)	
Blöndal et al (2013)[18]	1	0	1	1	1	1	1	1	7
Christensen et al (2014)[19]	1	1	1	1	1	1	1	1	8
Dangisso et al (2018)[20]	1	0	1	1	2	0	1	1	7
Fox et al (2018)[21]	1	1	1	1	2	0	1	1	8
Kolappan et al (2008)[22]	1	0	1	1	1	0	1	1	6
Liu et al (2018)[23]	1	1	1	1	1	0	1	1	7
Miller et al (2015)[24]	1	0	1	1	2	1	1	1	8
Shuldiner et al (2016)[25]	1	0	1	1	1	1	1	1	7
Tocque et al (2005)[26]	1	1	1	1	1	1	1	1	7
Wang et al (2015)[27]	1	0	1	1	1	1	0	1	6

Table 2: **Quality assessment of included studies**

already classified (eg, digestive disorders, liver disease, kidney disease), and unknown cause of death. A pooled proportion for causes of death was calculated for each category using a random effects model.

All statistical analyses were done with R (version 3.4.3). This study was prospectively registered in the PROSPERO (number CRD42018092592).[17]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 7283 unique articles identified in our search, 60 qualified for full-text review, of which ten were included in the meta-analysis (figure 1). The ten included studies reported all-cause mortality in people treated for tuberculosis from nine countries over five WHO regions (table 1). All studies were published after 2013, with the cohorts commencing treatment during the period from 1977 to 2015. Five studies were retrospective cohorts established by linking tuberculosis registries or administrative data.[18,19,24–26] One study prospectively followed up all individuals enrolled in a randomised trial.[21] Eight studies reported an SMR compared with the general population or other suitable controls as an outcome,[18,20–23,25–27] whereas one study[24] reported an MHR based on a 2:1 age-matched and sex-matched latent tuberculosis infection comparison population. One study[19] reported an MRR based on a 3:1 age-matched and sex-matched population selected from the general population. Six studies calculated excess mortality among people with confirmed treatment completion,[18,21,22,24,26,27] whereas the remainder reported the cumulative all-cause mortality among all patients who initiated treatment.

The quality of the included studies ranged from moderate to high in all three categories assessed (table 2). The majority of studies used nationally linked tuberculosis registries or administrative data to create their study cohort and relied on death certificates or administrative data to confirm mortality.

Among 40 781 people with tuberculosis included in the analysis, 6922 deaths were reported due to any cause. In the ten studies included for analysis, the pooled SMR for all-cause mortality was 2·91 (95% CI 2·21–3·84, I^2=99%; figure 2). When analysis was restricted to patients in whom treatment completion was confirmed, the pooled SMR for all-cause mortality was 3·76 (3·04–4·6, I^2=95%; appendix p 2).

Pooled estimates of SMR were relatively consistent across all subgroup analyses, with 95% CIs overlapping between all pooled effect estimates (figure 3). No association between SMR and increasing proportion of HIV co-infection or multidrug-resistant tuberculosis was observed (appendix p 9). Forest plots for all subgroup analyses are presented in the appendix (pp 3–9).

Despite multiple subset analyses, a high level of heterogeneity remained. Furthermore, heterogeneity remained high in post-hoc analyses that stratified the effect estimates by the year of cohort entry (before 2005 *vs* after 2005), and in analyses restricted to only studies that reported an SMR (appendix pp 7–8).

We also did an additional post-hoc analysis removing two studies[21,23] that contained non-symmetrical CIs, that when back-transformed did not match extracted CIs. The pooled SMR of this analysis was 2·56 (95% CI 1·90–3·45).

Comprehensive data on cause of mortality were reported in four studies, from Estonia, Israel, China, and

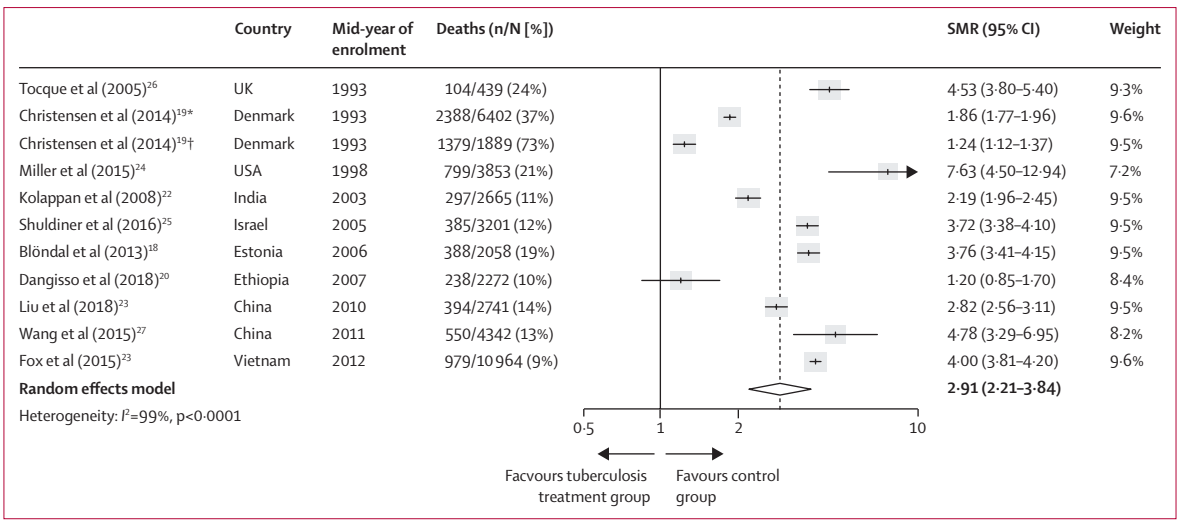

Figure 2: **SMR for all-cause mortality after tuberculosis treatment**
SMR=standardised mortality ratio. *Estimate for pulmonary tuberculosis. †Estimate for extrapulmonary tuberculosis.

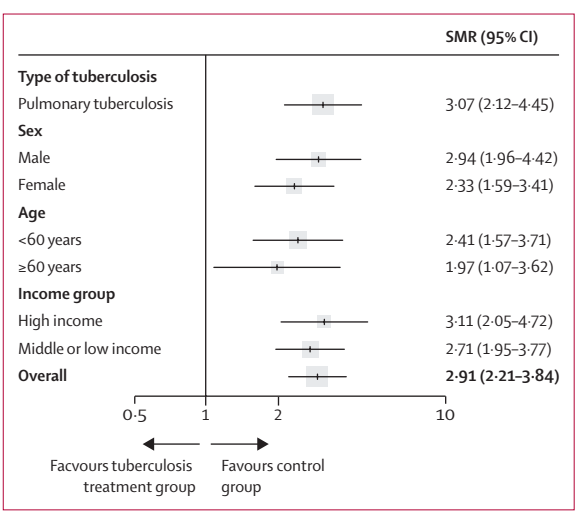

Figure 3: **SMR estimates for subgroup analysis**
SMR=standardised mortality ratio.

Denmark.[18,19,25,27] In total, causes of mortality were available for 4226 post-treatment deaths. Cardiovascular disease was the leading cause of pooled post-treatment mortality, followed by mortality due to cancer, and infectious diseases, defined as mortality related to tuberculosis or HIV (figure 4). Further details on how causes of mortality were assessed for each study can be found in the appendix (p 10).

Given that only a few studies reported tuberculosis-related mortality, we also did a post-hoc analysis examining if the cause of mortality was related to tuberculosis. Tuberculosis-related mortality was extracted from six studies for 4537 individuals.[18,19,21,23,26,27] The proportion of tuberculosis-related mortality ranged from 5% in Denmark to 54% in Vietnam (appendix p 11).

Discussion

This systematic review and meta-analysis found that people treated for tuberculosis have significantly increased mortality following treatment compared with the general population or matched controls. Overall, the pooled SMR for people treated for tuberculosis was almost three-times higher than that for the control population. Moreover, approximately 20% of post-treatment deaths were attributed to either cardiovascular disease or cancer.

Morbidity after tuberculosis treatment is well described in the published literature and might be one of the drivers of excess mortality in this population. People treated for tuberculosis frequently have pulmonary sequelae after successful treatment completion.[28,29] Pasipanodya and colleagues[28] found that, in the USA, more than half of people with microbiologically cured tuberculosis had some form of lung impairment after treatment, with approximately 10% having less than half of their expected forced vital capacity.[28] The association between tuberculosis and cardiovascular disease has also been noted in numerous publications. Chung and colleagues[5] reported in 2014 that incidence of acute coronary syndrome increased by 40% in people with a history of tuberculosis treatment after adjusting for age, sex, and comorbidities, which is concordant with findings reported by Huaman and colleagues,[6,30] suggesting that tuberculosis might have a role in the pathogenesis of cardiovascular disease. Tuberculosis is also associated with increased cancer risk.[31] Using population data from Taiwan, Yu and colleagues[32] found that the incidence of lung cancer was approximately 11-times higher in individuals with tuberculosis than in population controls. From our included studies, Christensen and colleagues[19] found that individuals with pulmonary tuberculosis in Denmark had a slightly increased risk of death from cardiovascular disease than the general population (MRR 1·19 [95% CI 1·08–1·31]),

whereas their risk of mortality due to any malignant neoplasms or respiratory disease was substantially higher (1·56 [1·14–1·73] and 2·98 [2·59–3·43], respectively). These findings are similar to findings from Estonia, where Blöndal and colleagues[18] found that men treated for tuberculosis had an SMR of 2·04 (1·58–2·60) for mortality due to cardiovascular disease and 2·26 (1·63–3·04) due to all neoplasms.

Interpreting the association between tuberculosis and mortality is complicated by the presence of confounding factors that might cause both tuberculosis and premature death. People treated for tuberculosis seem to have a higher prevalence of socioeconomic disadvantage than the general population. The bidirectional relationship between tuberculosis and socioeconomic disadvantage[33]—ie, lower socioeconomic status might be related to poor health conditions, or these poor health conditions might induce socioeconomic disadvantage by reducing opportunities to work—might have contributed to the increased mortality observed in our findings. Previous studies have also identified that populations with tuberculosis have high rates of independent risk factors for mortality, such as smoking, alcohol use, and medical comorbidities (eg, HIV).[8] Researchers have found consistent evidence showing that smoking tobacco is associated with an increased risk of tuberculosis and this unmeasured confounding factor might partly explain the observed excess mortality calculated in our study.[34] The excess mortality might also be in part related to biomass smoke exposure, which has been linked to chronic obstructive pulmonary disease, cardiovascular disease, and cancer.[35] Although we did not observe an association between SMR and increasing proportion of HIV co-infection, increased mortality after tuberculosis treatment might also have been, in part, due to a high prevalence of HIV in the study population. Most studies included in our analysis were unable to account for much of the confounding mentioned; however, two studies attempted to control for potential family-related factors by selecting household members as the control population or examining the long-term mortality of siblings of individuals with tuberculosis.[19,21] In both, the mortality estimate remained elevated, arguing against substantial confounding by unmeasured socioeconomic or genetic factors.

Our findings indicate that the pooled SMR was higher in the subgroup of people with confirmed treatment completion than the overall SMR for all people treated for tuberculosis. We speculate that mortality was higher in the post-treatment group because many people are less likely to engage with health-care services after treatment completion than during treatment, which in turn might result in later detection of recurrent tuberculosis or non-communicable disease. Improved characterisation of the medical and socioeconomic factors contributing to the excess mortality measured in this population could bolster the case for more comprehensive socioeconomic and

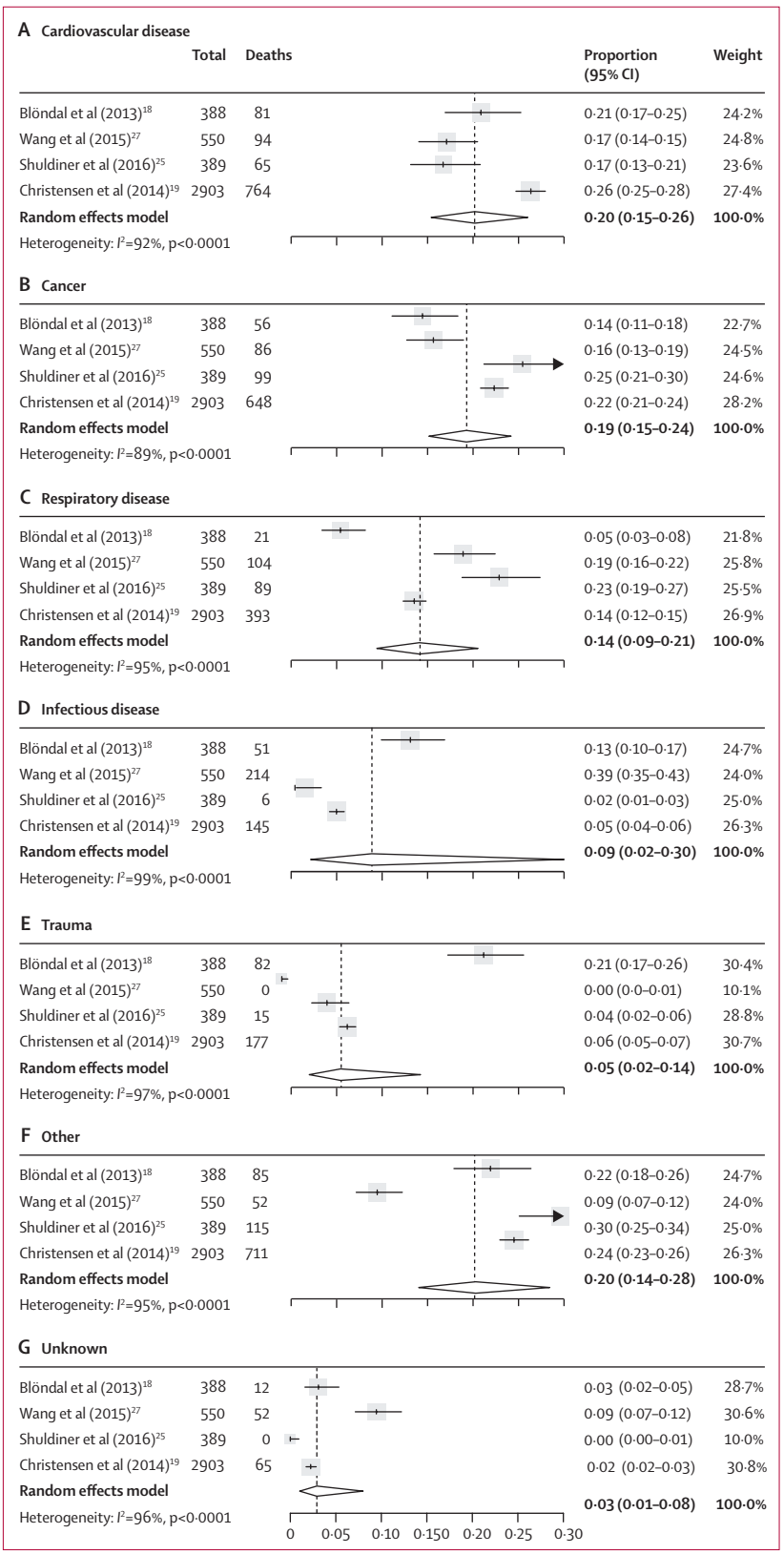

Figure 4: **Estimates for causes of mortality after tuberculosis treatment**

medical interventions that could be instituted. Incorporating medical and social interventions as part of tuberculosis treatment is not a new concept and might in fact be a key component of reducing global tuberculosis incidence and mortality.[36,37] Often, these interventions encompass the need for poverty alleviation, improved access to comprehensive health care, and primary and secondary prevention of comorbidities,[7–9] pointing towards the need for investment into high-quality health systems and universal health coverage.[38]

The limitations of this study are in part related to the use of published data. Our analysis was based on estimates derived from cohort studies that were unable to untangle the drivers of mortality. The included studies used a wide range of control or reference populations to calculate mortality estimates, and we did not have access to individual patient data so we were unable to account for clinical parameters or behavioural factors that might have affected mortality. Despite doing a range of analyses, we were also unable to explain most heterogeneity between studies for the primary outcome, and thus our results should be interpreted with caution. Given that there were no inconsistencies in the direction of effect of the extracted mortality estimates, we determined that pooling through a random effects model was appropriate. We explored heterogeneity using predefined subgroup analyses, as detailed in the Cochrane Handbook.[15] In our study, the between-study heterogeneity could represent true variation in excess mortality in the study populations but could also result from differences in the methods, such as case selection methods, diagnostic criteria, and study quality. We were also unable to adjust for the proportion of multidrug-resistant tuberculosis or HIV co-infection within the study population and rather had to use estimates based on WHO data; unfortunately, too few studies reported data on both these populations. Finally, our meta-analysis only included four studies from the 20 countries with highest tuberculosis burden (according to WHO) and we were only able to extract comprehensive data on cause of mortality from predominately high-income countries with relatively low tuberculosis burden. When examining our post-hoc analysis of mortality cause, we noted that in countries with high tuberculosis incidence, the proportion of tuberculosis-related deaths was substantially higher than in low tuberculosis incidence countries, suggesting that in these settings a higher proportion of post-treatment deaths might be attributable to tuberculosis relapse or reinfection.

Currently, there is little focus on the long-term implication of tuberculosis in global tuberculosis elimination strategies. However, there are a substantial number of individuals globally who have survived tuberculosis and these people frequently have negative health effects after treatment, in addition to lower socioeconomic status and more comorbidities.[4,5,7,8,30] Our study presents evidence showing that people affected by tuberculosis, overall, have a higher mortality than that in the general population or matched controls. Additionally, there is little known about the specific causes of death among individuals treated for tuberculosis and the role of palliative care. Further research investigating the pathways linking both medical and social factors to long-term mortality among individuals treated for tuberculosis is needed to broaden the scope of our efforts against tuberculosis elimination. Identifying and intervening for preventable causes of death promises to have substantial effects on the long-term prognosis and survival of this population.

Contributors

JCJ, GJF, and KR initiated the project and were responsible for the design of the protocol. KR and BB did the literature review, collected the data, and assessed the quality of the studies. KR analysed the data. KR, BB, CAB, FAK, GJF, and JCJ interpreted the data. KR wrote the initial draft of the manuscript. JCJ, FAK, GJF, CAB, and BB were responsible for critical revisions of the manuscript and provided important intellectual content. All authors approved the final version submitted for publication.

Declaration of interests

We declare no competing interests.

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