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Effect of smoking on drug-resistant tuberculosis treatment outcomes and potential mechanistic pathways: a multicountry cohort study

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ABSTRACT

Background People who smoke are at increased risk of unfavourable tuberculosis treatment outcomes compared with those who do not, but the pathways that explain this disparity are unclear.

Objective To estimate the difference in a successful end-of-treatment outcome by smoking status among people with multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) and to examine if this difference changes if people who smoked had the same retention in treatment as those who did not smoke.

Design and methods Using data from the prospective endTB Observational Study, we estimated the difference in treatment success by cigarette smoking status, adjusting for baseline confounders including demographics, social history and comorbidities. To examine how this difference changed if everyone was retained in treatment, we censored participants who were lost to follow-up and applied inverse probability of censoring weights to simulate this scenario.

Results Among 1786 participants in 12 countries, 539 (30.2%) reported smoking at least one cigarette daily. People who smoked were more frequently found in post-Soviet countries and had a complex social history (eg, incarceration and substance use) and infectious comorbidities (eg, hepatitis C). At the end of treatment, 73.5% of people who smoked and 80.3% of people who did not smoke had treatment success (risk difference in percentage points: −6.8, 95% CI −11.1 to −2.6). After adjusting for baseline confounders, the risk difference was similar (−5.2 percentage points), but the 95% CI was less precise (−14.1 to 3.2). When simulating a scenario in which everyone was retained in treatment, the risk difference was attenuated (−1.9 percentage points; 95% CI −11.1 to 4.7).

Conclusion People who smoked had a lower frequency of MDR/RR-TB treatment success than those who did not smoke. Eliminating loss to follow-up reduced this difference by smoking status, suggesting that pathways related to retention in treatment were a major driver of this disparity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most observational research supports that cigarette smoking negatively impacts tuberculosis treatment outcomes, but it is unclear why.

WHAT THIS STUDY ADDS

⇒ People who smoked had a lower frequency of multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) treatment success than those who did not smoke. Eliminating loss to follow-up attenuated this difference.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Implementing interventions that address causes of loss to follow-up, in addition to smoking cessation services, could improve MDR/RR-TB treatment outcomes among people who smoke.

INTRODUCTION

Tuberculosis (TB) and tobacco smoking are both major contributors to morbidity and mortality.[1 2] Their intersection is also substantial, with a higher prevalence of tobacco smoking in high TB burden countries and among populations that are disproportionately affected by TB, such as men, people living with HIV, incarcerated people and mine workers.[1 2] The dual burden of TB and smoking is not coincidental. Epidemiological evidence consistently shows that tobacco smoke increases the risk of TB infection and disease.[3 4] Tobacco smoking has also been associated with more severe TB disease presentation, including greater sputum mycobacterial load, more cavitary lesions and higher probability of disease requiring

hospitalisation[5–7]; and worse TB treatment outcomes, specifically increased risk of delayed smear and culture conversion, an unsuccessful end-of-treatment outcome and recurrence.[8–11]

The negative effect of smoking on TB treatment outcomes could be explained by the direct biological effects of tobacco smoke. Tobacco smoke causes profound structural and functional damage to the respiratory tract[12] and impairs the pulmonary immune response to TB infection.[13] These changes favour the pathogen's survival, persistence and proliferation, and could compromise TB treatment effectiveness. Another pathway to unfavourable treatment outcomes is greater adherence challenges among people who smoke, culminating in early discontinuation from treatment, that is, loss to follow-up after treatment initiation.[14] This pathway is complex and likely related to multiple factors at different levels among people who smoke, rather than caused by smoking itself. Factors involved in this pathway might include competing economic responsibilities, suboptimal social support, negative experiences accessing care, and clinical evolution and adverse events on TB treatment.[15–19] The observed association between smoking and TB treatment outcomes may also be spurious, as smoking is frequently accompanied by other factors known to affect TB treatment outcomes, such as alcohol and other substance use.[20–22]

Multidrug- or rifampicin-resistant TB (MDR/RR-TB) is more difficult to treat than drug-susceptible TB,[1] and individuals often endure an extended duration of complicated drug regimens with multiple toxicities.[23] Impacts may be experienced by the individual as well as by their family and others around them.[24–26] Therefore, identifying areas for intervention that effectively increase treatment success is of high clinical and public health importance. Most of the evidence for the negative effect of smoking on TB treatment outcomes comes from studies enrolling people with drug-susceptible TB.[8 10 11] A meta-analysis of observational studies focused on MDR/RR-TB reported that TB treatment outcomes were similar by smoking status; however, most of the studies defined smoking as ever smoking rather than current smoking at the time of treatment initiation and heterogeneity among the studies was very high.[27] These observational studies among people with drug-susceptible TB or MDR/RR-TB have largely examined the association between smoking and treatment outcomes without an explicit focus on causality and have not applied methods to clarify the contribution of underlying mechanistic pathways.

Using epidemiological methods rooted in causal inference, we estimate the effect of smoking on MDR/RR-TB end-of-treatment outcomes. To understand how differential loss to follow-up may contribute to worse treatment outcomes among people who smoke, we estimated the difference in treatment success that would be expected if everyone were retained in treatment.

METHODS

Setting and participants

We used data from the endTB Observational Study (ClinicalTrials.gov Identifier: NCT03259269), a prospective cohort of people with MDR/RR-TB who were treated with longer regimens containing bedaquiline and/or delamanid.[28 29] Participants were enrolled from April 2015 through September 2018 in 17 countries. The study sites selected for the cohort reflect the heterogeneity of high-burden MDR/RR-TB settings globally. Participants received treatment regimens with drug selection informed by national TB programme guidelines and the endTB clinical guide.[29] The study captured routine clinical data under programme conditions, with standardised data collection that was managed centrally. After enrolment, study visits typically occurred at 2 weeks and then monthly thereafter throughout treatment. Details on study procedures are available elsewhere.[28] If individuals were treated multiple times during the study, we included only the first treatment regimen for these analyses. For these analyses, we excluded participants who: were treated in the Democratic People's Republic of Korea; had confirmed rifampicin-susceptible TB; had only extrapulmonary TB; enrolled in the endTB Observational Study more than 1 month after MDR/RR-TB treatment initiation; were under 15 years of age; were treated at a site with no participants who reported smoking; were treated at a site that did not collect adherence data or had inconsistent reporting[30]; had an unknown cigarette smoking status; or transferred out or had an unknown end-of-treatment outcome. Rationale for each exclusion criterion is provided in online supplemental table 1. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this secondary data analysis.

Variables

Exposure and outcome

Our exposure of interest was smoking status, which was assessed at the enrolment visit based on a yes/no response when participants were asked if they smoked at least one cigarette daily. End-of-treatment outcomes were assigned by the treating clinician based on WHO outcome definitions.[31] Successful treatment comprised an outcome of cured or completed. Unsuccessful treatment comprised an outcome of death, treatment failure or lost to follow-up. Lost to follow-up was defined as a treatment interruption for ≥2 consecutive months.

Other variables

Demographics (country, sex, age) and social history variables (currently married or living with partner, employed, homeless in past year, ever incarcerated, refugee/displaced person/migrant status, alcohol use and drug use) were self-reported at enrolment. We categorised countries as a post-Soviet country or other country, in

Table 1 Characteristics at cohort enrolment among participants included in the analysis, overall and by cigarette smoking status

Characteristic at cohort enrolment	n	Overall, n=1786	Smokes cigarettes: Yes, n=539	Smokes cigarettes: No, n=1247
		n (%)	n (%)	n (%)
Demographics				
Country	1786			
Post-Soviet country (Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan)		1056 (59.1)	500 (92.8)	556 (44.6)
Other countries (Ethiopia, Indonesia, Myanmar, Pakistan, Peru, South Africa, Vietnam)		730 (40.9)	39 (7.2)	691 (55.4)
Male sex	1786	1136 (63.6)	480 (89.1)	656 (52.6)
Age in years, median (IQR; range)	1786	35 (27–46; 15–83)	41 (34–50; 17–70)	32 (25–43; 15–83)
Social history				
Married or living with partner	1780	919 (51.6)	259 (48.4)	660 (53.0)
Employed	1777	270 (15.2)	77 (14.4)	193 (15.5)
Homeless in past year	1727	69 (4.0)	24 (4.8)	45 (3.7)
Ever incarcerated	1485	273 (18.4)	185 (35.4)	88 (9.2)
Refugee, displaced person or migrant	1757	57 (3.2)	33 (6.4)	24 (1.9)
Drinks alcohol	1762	216 (12.3)	177 (33.5)	39 (3.2)
Used non-prescribed illicit drugs and/or intravenous drugs in past year	1718	93 (5.4)	63 (12.9)	30 (2.4)
Comorbidities				
HIV	1785	118 (6.6)	45 (8.4)	73 (5.9)
Hepatitis B virus infection	1782	73 (4.1)	27 (5.0)	46 (3.7)
Hepatitis C virus infection	1782	246 (13.8)	155 (28.8)	91 (7.3)
Diabetes	1785	243 (13.6)	60 (11.2)	183 (14.7)
Underweight (body mass index <18.5 kg/m^2)	1777	647 (36.4)	159 (29.7)	488 (39.3)
TB disease characteristics				
Concurrent extrapulmonary disease	1786	30 (1.7)	13 (2.4)	17 (1.4)
Bilateral lung involvement	1710	1137 (66.5)	377 (71.4)	760 (64.3)
Fibrosis	1646	1105 (67.1)	345 (67.9)	760 (66.8)
Cavitary disease	1676	1140 (68.0)	349 (67.1)	791 (68.4)
Positive sputum smear	1683	946 (56.2)	314 (61.8)	632 (53.8)
Sputum smear grade (among positive)	946			
Scanty		70 (7.4)	28 (8.9)	42 (6.7)
1+		420 (44.4)	155 (49.4)	265 (41.9)
2+		228 (24.1)	57 (18.2)	171 (27.1)
3+		228 (24.1)	74 (23.6)	154 (24.4)
Extensive disease (ie, cavitary disease and smear grade 3+)	1582	172 (10.9)	53 (10.8)	119 (10.9)
Positive sputum culture	1656	1049 (63.4)	350 (70.9)	699 (60.2)
Known prior TB treatment with second-line drugs	1471	1282 (87.2)	405 (89.8)	877 (86.0)
Fluoroquinolone resistance	1701	1122 (66.0)	358 (68.9)	764 (64.7)
Initial TB treatment regimen characteristics				
Number of likely effective drugs in regimen,* median (IQR; range)	1786	4 (4–5; 0–8)	4 (4–5; 0–7)	4 (4–5; 0–8)

Continued

Table 1 Continued

Characteristic at cohort enrolment	n	Overall, n=1786	Smokes cigarettes: Yes, n=539	Smokes cigarettes: No, n=1247
		n (%)	n (%)	n (%)
Number of WHO Group A drugs (moxifloxacin or levofloxacin; bedaquiline; linezolid), median (IQR; range)	1786	2 (2–3; 0–3)	2 (2–3; 0–3)	2 (2–3; 0–3)
Number of WHO Group B drugs (clofazimine; cycloserine or terizidone), median (IQR; range)	1786	1 (1–2; 0–2)	1 (1–2; 0–2)	1 (1–2; 0–2)

*A drug was considered likely effective if all reported resistance testing to that drug confirmed susceptibility, or, in the absence of drug susceptibility testing, the individual had not previously received the drug for 1 month or longer.
TB, tuberculosis.

recognition of the higher proportion of participants who smoked in the former.

Comorbidities at enrolment included HIV; hepatitis B virus infection, based on a positive surface antigen; hepatitis C virus infection, based on a positive antibody, PCR or viral load; diabetes, based on self-reported diagnosis, random plasma glucose >200 mg/dL (11.1 mmol/L) or haemoglobin A1C ≥6.5%; and underweight, defined as a body mass index <18.5 kg/m^2 using measured height and weight.

TB disease and treatment characteristics at enrolment included the presence of extrapulmonary TB; presence of bilateral disease, fibrosis and cavitary disease based on chest X-ray; sputum smear positive and grade; sputum culture positivity; known prior treatment with second-line TB drugs; drug susceptibility results categorised as to whether fluoroquinolone resistance was present or not; and baseline TB regimen composition, including the number of likely effective drugs.

Variables assessed during follow-up included indicators of TB disease severity (ie, sputum smear positivity, sputum culture positivity and presence of cavitary disease) and TB treatment adherence. Adherence, typically assessed monthly, was computed as the number of days all medications were taken as prescribed divided by the number of days those medications were prescribed.[30] This proportion was dichotomised as <80% and ≥80% for each time period it was measured. These variables were treated as time-varying, reflecting changes throughout follow-up.

Statistical analyses

We estimated the difference in the frequency of treatment success by smoking status in an unadjusted model and a model adjusted for baseline confounders using marginal standardisation to compute risk differences and ratios. The bias-corrected and accelerated bootstrap with 1000 resamples was used to obtain 95% CIs. We used the missing indicator method to account for missing data on baseline confounders. Most missing data were for the past incarceration variable (301/1786 (16.9%) missing; table 1), with two sites having >90% missing responses. Because unmeasured, site-level factors likely contributed, we did not expect that other methods of addressing missing data, specifically multiple imputation, would be advantageous. We used directed acyclic graphs (figure 1A–D) to specify the underlying causal structure between smoking and MDR/RR-TB treatment outcome and identified potential baseline demographic, social and clinical confounders a priori. In primary analyses, we assumed that baseline indicators of TB disease severity were a result of smoking and, therefore, part of the pathway through which smoking could impact TB treatment outcomes (figure 1B).[5–7] However, it may be that these characteristics coincide with, but are unrelated to smoking. We therefore conducted a sensitivity analysis that additionally adjusted for these characteristics.

To understand if differential loss to follow-up drove the difference in treatment success by smoking status, we censored participants who were lost to follow-up and used time-varying stabilised inverse probability of censoring weights to simulate a scenario in which no one was lost to follow-up (ie, everyone was retained in treatment; figure 1D). Computation of weights included fitting a pooled logistic regression model to predict whether participants remained uncensored, conditional on smoking status; baseline demographics, social history and comorbidities; baseline indicators of TB disease severity; and time-varying indicators of TB severity and TB medication adherence (online supplemental table 3). This weighting is important because people who are lost to follow-up and those who remain in care may be different in ways that also determine the end-of-treatment outcome. We carried observations forward for time-varying variables and used the missing indicator method to account for any remaining missing data. As with the other analyses, we used marginal standardisation to estimate risk differences and ratios and bootstrapping for 95% CIs.

We used SAS V.9.4 (SAS Institute, Cary, North Carolina) and R V.4.4.2 (R Core Team, 2023) for analyses.

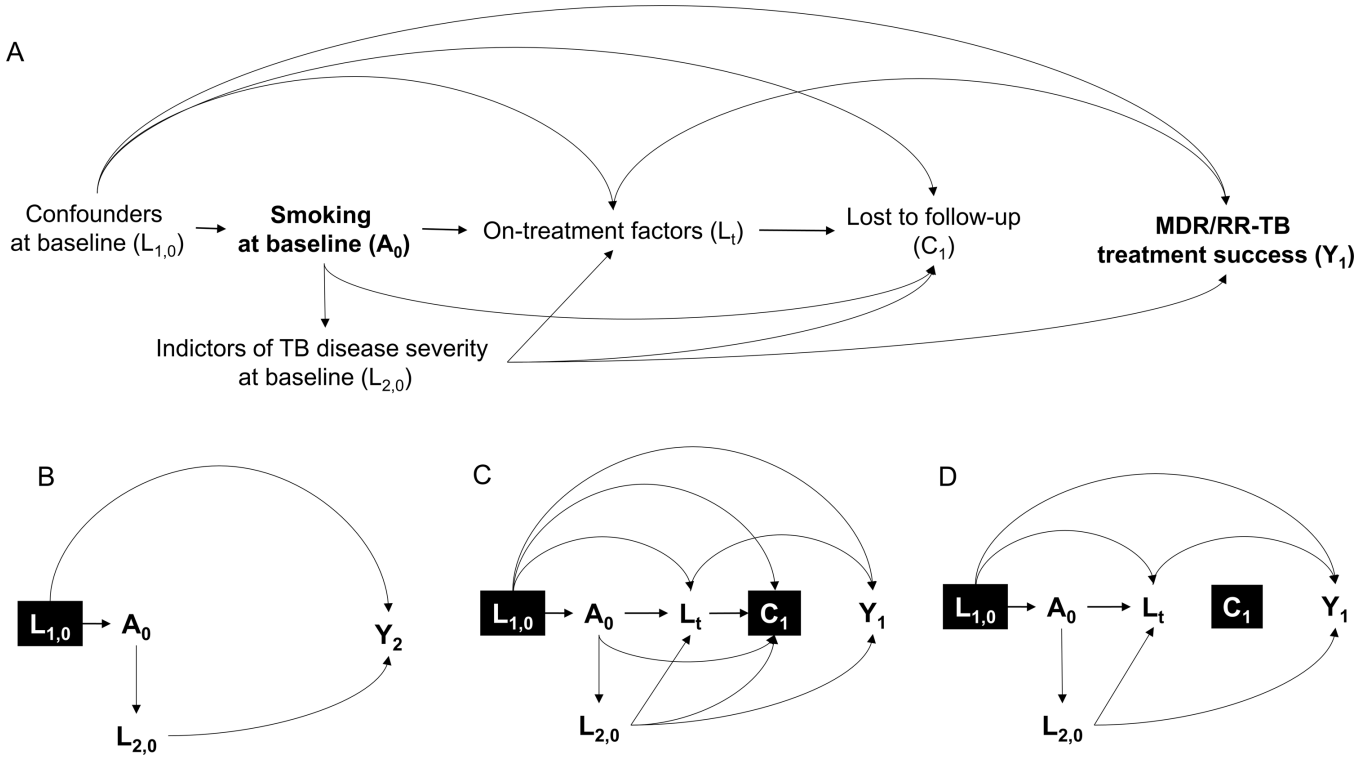

Figure 1 Directed acyclic graphs illustrating the relationship between cigarette smoking and MDR/RR-TB end-of-treatment outcome. $L_{1,0}$: baseline confounders: demographics (country, sex, age), social history (ever incarcerated, refugee/displaced person/migrant, alcohol use, drug use) and comorbidities (HIV, hepatitis C, diabetes, underweight); $L_{2,0}$: baseline indicators of TB disease severity (sputum smear and culture positivity, and cavitary disease); A_0: cigarette smoking status at enrolment; L_t: on-treatment factors on the causal path from A_0 to Y: time-varying indicators of TB disease severity (sputum smear and culture positivity, cavitary disease) and TB treatment adherence; C_1: lost to follow-up; Y_1: successful (cured or completed) or unsuccessful (treatment failure or death) MDR/RR-TB treatment outcome; Y_2: successful (cured or completed) or unsuccessful (treatment failure, death or lost to follow-up) MDR/RR-TB treatment outcome. (A) The directed acyclic graph shows the hypothesised causal relationship between cigarette smoking status at enrolment (A_0) and a successful or unsuccessful MDR/RR-TB treatment outcome (Y_1). Each arrow represents a one-way direct causal effect of one variable on another. (B) The directed acyclic graph shows the causal relationship between A_0 and Y_2, adjusting for baseline confounders. Participants who were lost to follow-up were classified as not having a successful MDR/RR-TB treatment outcome. For this model, we condition on $L_{1,0}$ (indicated by the black box), but not $L_{2,0}$ which is expected to be on the causal path between A_0 and Y_2 as a mediator. As a sensitivity analysis, we explored adjusting for $L_{2,0}$, treating it as a potential confounder (ie, arrow changes direction between $L_{2,0}$ and A_0). (C) The directed acyclic graph shows the causal relationship between A_0 and Y_1, but we additionally censor participants who were lost to follow-up (C_1). The black box for C_1 indicates that we are conditioning on it by limiting our analysis to participants who were not lost to follow-up. We also show additional time-varying variables (L_t) expected to be affected by smoking and associated with loss to follow-up and the MDR/RR-TB treatment outcome. By censoring participants who were lost to follow-up, this model is unrealistic and potentially biased because it assumes that loss to follow-up was not a possible outcome during MDR/RR-TB treatment. (D) The directed acyclic graph depicts the causal relationship between A_0 and Y_1, applying stabilised inverse probability of censoring weights to uncensored individuals (ie, those who were not lost to follow-up) that were conditional on A_0, $L_{1,0}$, $L_{2,0}$ and L_t. Applying these weights and additionally adjusting for $L_{1,0}$ in the final model effectively removes all of the arrows pointing to C_1. In other words, we re-weight uncensored individuals to also account for censored individuals, creating a population where everyone is retained in treatment. MDR/RR-TB, multidrug- or rifampicin-resistant tuberculosis; TB, tuberculosis.

RESULTS

Description of selection of the analytic study population and participant characteristics

Of 2788 endTB Observational Study participants enrolled in 17 countries, 1002 were excluded (figure 2), resulting in a final analytic study population of 1786 participants in 12 countries: Armenia (93 (5.2%)), Belarus (101 (5.7%)), Ethiopia (34 (1.9%)), Georgia (208 (11.7%)), Indonesia (61 (3.4%)), Kazakhstan (641 (35.9%)), Kyrgyzstan (13 (0.7%)), Myanmar (42 (2.4%)), Pakistan (262 (14.7%)), Peru (260 (14.6%)), South Africa (39 (2.2%)) and Vietnam (32 (1.8%)). A comparison of included and excluded participants is provided in online supplemental table 2; most characteristics were similar.

Of the 1786 included participants, 539 (30.2%) reported smoking cigarettes daily. There were some notable differences in demographics, social history, comorbidities and TB disease characteristics at enrolment by smoking status (table 1). Compared with those who did not smoke, participants who smoked resided

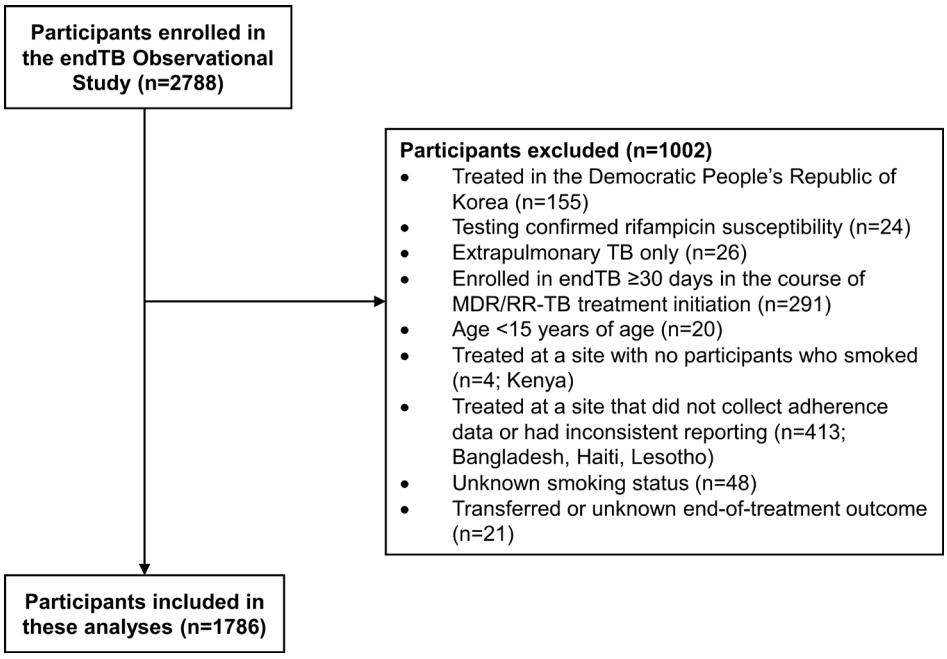

Figure 2 Flowchart of participants enrolled in the endTB Observational Study and their inclusion in these analyses. MDR/RR-TB, multidrug- or rifampicin-resistant tuberculosis.

more commonly in post-Soviet countries (92.8% vs 44.6%) and were more frequently male (89.1% vs 52.6%), older (median age 41 years vs 32 years), ever incarcerated (35.4% vs 9.2%), and identified as a refugee, displaced person or migrant (6.4% vs 1.9%). They also more commonly drank alcohol (33.5% vs 3.2%) and used drugs (12.9% vs 2.4%). Regarding comorbidities, participants who smoked more often had HIV (8.4% vs 5.9%), hepatitis B (5.0% vs 3.7%) and hepatitis C (28.8% vs 7.3%) and less often had diabetes (11.2% vs 14.7%) and were underweight (29.7% vs 39.3%) compared with those who did not smoke. Participants who smoked more often had bilateral disease (71.4% vs 64.3%), a positive sputum smear (61.8% vs 53.8%), and a positive sputum culture (70.9% vs 60.2%) compared with those who did not smoke. The number of likely effective drugs in the baseline TB treatment regimen was similar by smoking status (median of 4 for both smoking categories).

Frequencies of end-of-treatment MDR/RR-TB treatment outcomes

Overall, 1397 (78.2%) had a successful treatment outcome of cured or completed (table 2). Regarding unsuccessful outcomes, 137 (7.7%) died, 97 (5.4%) had treatment failure and 155 (8.7%) were lost to follow-up. The median (IQR) time from cohort enrolment to death was 5.6 (2.4, 11.5) months, and to lost to follow-up was 8.7 (5.7, 13.4) months. With regard to unsuccessful outcomes by smoking status, the frequency of death among participants who smoked was 5.0% versus 8.8% in those who did not. Compared with participants who did not smoke, the frequency of treatment failure (8.5% vs 4.1%) and lost to follow-up (13.0% vs 6.8%) was higher for participants who smoked.

Effect of smoking on MDR/RR-TB treatment success and eliminating loss to follow-up

In the unadjusted model (table 3), the frequency of treatment success was 6.8 percentage points lower among participants who smoked (73.5%) versus those who did not (80.3%; 95% CI for risk difference: –11.1 to –2.6) with a risk ratio of 0.92 (95% CI 0.86 to 0.97). When adjusting for baseline confounders related to demographics, social history and comorbidities, the risk difference was –5.2 percentage points (95% CI –14.1 to 3.2) and the risk ratio was 0.93 (95% CI 0.82 to 1.04). In the sensitivity analysis that also adjusted for baseline indicators of TB disease severity, the risk difference was –4.4 percentage points (95% CI –12.7 to 3.2) and the risk ratio was 0.94 (95% CI 0.84 to 1.04).

When eliminating loss to follow-up, the frequency of treatment success was 84.0% among participants who smoked compared with 85.9% in those who did not (risk difference –1.9 percentage points, 95% CI –11.1 to 4.7; risk ratio: 0.98, 95% CI 0.87 to 1.05).

DISCUSSION

Cigarette smoking was common at the start of MDR/RR-TB treatment, particularly in post-Soviet countries, and was frequently accompanied by a complex social history, including past incarceration and substance use, and infectious comorbidities, especially hepatitis C. We found that people who smoked had a lower frequency of MDR/RR-TB treatment success than those who did not

Table 2 Frequencies of clinician-assigned multidrug- or rifampicin-resistant tuberculosis end-of-treatment outcomes, overall and by cigarette smoking status

		Smokes cigarettes	
	Overall, n=1786	Yes, n=539	No, n=1247
Outcomes	n (%)	n (%)	n (%)
Successful treatment	**1397 (78.2)**	**396 (73.5)**	**1001 (80.3)**
Cured	1299 (72.7)	368 (68.3)	931 (74.7)
Completed	98 (5.5)	28 (5.2)	70 (5.6)
Unsuccessful treatment	**389 (21.8)**	**143 (26.5)**	**246 (19.7)**
Death (and causes)	137 (7.7)	27 (5.0)	110 (8.8)
TB-related*	64 (3.6)	12 (2.2)	52 (4.2)
Non-TB-related	47 (2.6)	11 (2.0)	36 (2.9)
Unknown	26 (1.5)	4 (0.7)	22 (1.8)
Treatment failure (and reasons)†	97 (5.4)	46 (8.5)	51 (4.1)
Lack of sputum culture conversion	32 (1.8)	19 (3.5)	13 (1.0)
Bacteriological reversion	44 (2.5)	15 (2.8)	29 (2.3)
Adverse drug reaction	10 (0.6)	8 (1.5)	2 (0.2)
Other/unknown	15 (0.8)	7 (1.3)	8 (0.6)
Lost to follow-up (and reasons)†	155 (8.7)	70 (13.0)	85 (6.8)
Participant refusal	71 (4.0)	27 (5.0)	44 (3.5)
Left region/country	32 (1.8)	21 (3.9)	11 (0.9)
Family, financial or other social problems	35 (2.0)	12 (2.2)	23 (1.8)
Substance abuse	12 (0.7)	5 (0.6)	7 (0.6)
Other/unknown	36 (2.0)	14 (2.6)	22 (1.8)

*TB was known to be an immediate or contributing cause of death, or death was related to surgery/treatment of TB.
†Participants may have more than one clinician-assigned reason for treatment failure (with the exception of simultaneous lack of sputum culture conversion and bacteriological reversion) or loss to follow-up.
TB, tuberculosis.

smoke. Simulating elimination of loss to follow-up (ie, ensuring everyone completed treatment) attenuated the difference in treatment success by smoking status. This finding suggests that smoking may negatively impact MDR/RR-TB treatment outcomes through complex adherence-related pathways leading to loss to follow-up. However, since some differences by smoking status remained, other pathways, like the direct biological pathways leading to treatment failure, are relevant.

In the model adjusted for baseline confounders, the risk difference of treatment success by smoking status was −5.2 percentage points, which is clinically meaningful and similar to that observed in other studies. For example, in a large prospective cohort from Hong Kong with 16 345 people who had drug-susceptible TB, the risk difference in treatment success by smoking status (current vs never) was about −3.3 percentage points.[7] When we adjusted for confounders, the CI was less precise than for the unadjusted estimate and included the null value of 1. However, since we estimated causal effects, we focus our interpretation on magnitude and precision rather than solely statistical significance (ie, p<0.05).[32 33] Despite less precision, the adjusted risk difference was similar in magnitude to the unadjusted risk difference and thus, baseline confounding did not appear to be a major driver of the observed association. Selection of confounders requires a clear understanding of temporality relative to the exposure, which may not always be known. For example, more advanced TB disease may result from smoking through direct biological effects, but may also coincide with smoking if people who smoke have delays in diagnosis (eg, if they are less likely to identify TB symptoms as indicative of illness). In our sensitivity analysis, adjusting for sputum smear and culture positivity and the presence of cavitary disease slightly attenuated the risk difference but did not lead to a different conclusion. Because many social factors and medical conditions can influence how TB presents, we recommend conducting sensitivity analyses to assess how assumptions about whether a variable is a confounder or part of the causal pathway may affect the results.

To understand the extent to which adverse outcomes among people who smoked were explained by treatment lapses versus the biological effects of smoking, we

Table 3 Effect of smoking status on a successful multidrug- or rifampicin-resistant tuberculosis end-of-treatment outcome and impact of intervening on loss to follow-up

Outcome and analysis*	Risk, percentage		Risk difference, percentage points (95% CI)	Risk ratio (95% CI)
	Participants who smoked	Participants who did not smoke		
Successful treatment (with loss to follow-up classified as unsuccessful treatment)				
Unadjusted	73.5	80.3	−6.8 (−11.1 to −2.6)	0.92 (0.86 to 0.97)
Adjusted for baseline confounders†	73.8	79.0	−5.2 (−14.1 to 3.2)	0.93 (0.82 to 1.04)
Adjusted for baseline confounders† and baseline indicators of TB disease severity‡ (sensitivity analysis)	74.5	78.9	−4.4 (−12.7 to 3.2)	0.94 (0.84 to 1.04)
Successful treatment (with everyone retained in treatment)				
IP weighted and adjusted for baseline confounders†	84.0	85.9	−1.9 (−11.1 to 4.7)	0.98 (0.87 to 1.05)

*Generalised linear models with logit links were used to estimate risks separately by smoking status and risk differences and ratios were computed by standardising mean predicted risks of the outcome. The bias-corrected and accelerated bootstrap with 1000 resamples was used to obtain 95% CIs for the risk differences and ratios. The missing indicator method used to handle missing data on baseline confounders except for HIV status (n=1 (0.1%)), hepatitis C (n=4 (0.2%)) and diabetes (n=1 (0.1%)) for which we assumed the condition to be absent because very few missing observations precluded use of missing indicators and these were low prevalence conditions.
†Demographics (country, sex, age), social history (ever incarcerated, refugee/displaced person/migrant, drinks alcohol, drug use) and comorbidities (HIV, hepatitis C, diabetes, underweight).
‡Sputum and culture positivity, and presence of cavitary disease.
IP, inverse probability; TB, tuberculosis.

estimated the effect of smoking in the absence of loss to follow-up. In practical terms, this analysis was analogous to implementing an intervention that equalised retention in treatment by smoking status. We found that the risk difference in treatment success by smoking status decreased from −5.2 to −1.9 percentage points, supporting that complex adherence-related pathways leading to loss to follow-up were a driver of worse treatment outcomes among people who smoked. Although this finding may seem intuitive, eliminating loss to follow-up would not be expected to reduce the disparity among people who smoked if, for example, poor clinical evolution contributed to early treatment discontinuation. If this were true, eliminating loss to follow-up could result in retention of individuals at increased risk of treatment failure. Our analytic approach accounted for this potential scenario by including time-varying factors associated with loss to follow-up and unfavourable treatment outcomes (ie, measures of TB disease severity and TB medication adherence) in our inverse probability of censoring weights. The attenuated risk difference when eliminating loss to follow-up suggests that interventions that facilitate retention in treatment, particularly among people who smoke, could reduce the observed difference in TB treatment outcomes by smoking status. The reasons why people disengage from MDR/RR-TB treatment are complex,[18 34 35] but evidence supports interventions providing psychosocial support throughout TB treatment, such as through counselling sessions and home visits by healthcare workers, as one possible way.[36] Adding conditional cash transfers to psychosocial support interventions may also address economic factors that contribute to loss to follow-up.[37] Although such interventions might be broadly beneficial for people undergoing TB treatment, further research is needed to understand how reasons for loss to follow-up might differ for specific groups (eg, people who smoke) to optimise and better target interventions.

The remaining difference in TB treatment outcomes after eliminating loss to follow-up could plausibly be attributed to random variability, but most likely to a direct biological effect of smoking on TB treatment failure. Evidence from drug-susceptible TB supports that smoking cessation after a TB diagnosis and continuing not to smoke during treatment may increase treatment success and lower recurrence compared with those who continue to smoke.[38 39] Recognising the intersections in TB and lung health, the WHO recommends an integrated approach to care,[40] for example, implementing guideline recommendations on tobacco cessation[41] into the delivery of MDR/RR-TB treatment. Multiple studies in various high-burden countries have demonstrated the feasibility of integrating smoking cessation into TB treatment and care programmes.[42–44] Implementation research would be beneficial to optimise integration of services and should consider the multiple issues that face people with TB, not limited to complex social and economic contexts and comorbidities related to both physical and mental health.

Aside from leveraging a large, high-quality observational cohort of people with MDR/RR-TB with extensive data collection, the major strength of this analysis lies in its methodology. Specifically, we applied a causal inference framework when designing the analysis,

including the use of directed acyclic graphs to transparently guide analysis decisions and weighting to appropriately account for baseline and on-treatment factors that predicted loss to follow-up. Such methodology is novel in the field of TB and tobacco, and its application in this analysis contributes to existing knowledge. Our findings should also be interpreted in the context of limitations. The definition of smoking status is subject to potential misclassification. For example, some participants who smoked might have chosen to report that they did not smoke, and since smoking was only assessed at enrolment, we do not know if individuals quit smoking during treatment. We would expect that each of these sources of potential misclassification would diminish differences in TB treatment outcomes by smoking status, biasing toward the null. Despite analysing a large cohort, we had limited precision in some analyses. However, since we aimed to estimate causal effects, our interpretation focused on the magnitude and precision of these effects instead, as recommended by causal inference experts and the American Statistical Association.[32 33] To increase confidence in our findings, we would recommend replication in other cohorts. Most people who smoked were in post-Soviet countries, so although we leveraged a multicountry cohort, generalisability may still be limited. Despite our best efforts to identify and control for potential confounders, residual and unmeasured confounding (eg, due to mental health morbidity) might have resulted in bias.

In conclusion, people who smoked had a lower frequency of MDR/RR-TB treatment success than those who did not smoke. Eliminating loss to follow-up substantially reduced, but did not eliminate, the difference in treatment outcomes experienced by people who smoked. This finding suggests that complex pathways related to retention in treatment were the driver of this disparity, although other pathways, such as those related to the direct biological effects of smoking, may also contribute. Implementing interventions to address causes of loss to follow-up, for example, counselling and home visits, and financial support, and integrating smoking cessation services could improve MDR/RR-TB treatment outcomes among people who smoke.

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