Effect of quitting smoking on health outcomes during treatment for tuberculosis

Do smokers with tuberculosis who quit smoking during treatment have better health outcomes than those who don't? A secondary analysis of the TB & Tobacco Trial

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ABSTRACT

Background

Despite treatment, TB patients who smoke have poorer outcomes compared to non-smokers. It is unknown, however, if quitting smoking during the six-months of TB treatment improves TB outcomes.

Methods

The TB & Tobacco Trial was a double-blind, placebo-controlled randomised trial of cytisine for smoking cessation in 2,472 pulmonary TB patients in Bangladesh and Pakistan. In a secondary analysis, we investigated the hypothesis that smoking cessation improves health outcomes in patients during the TB treatment course. The outcomes included an eight-point TB clinical score, sputum conversion rates, chest X-ray grades, quality of life (EQ-5D-5L), TB cure *plus* treatment completion rates, and relapse rates. These were compared between those who stopped smoking, and those who did not, using regression analysis.

Results

We analysed the data of 2,273 (92%) trial participants. Overall, 25% (577/2,273) of participants stopped smoking. Compared to non-quitters, those who quit had better TB cure *plus* treatment completion rates (91% vs. 80%, p<0.001) and lower TB relapse rates (6% vs. 14%, p<0.001). Among quitters, a higher sputum conversion rate at week 9 (91% vs. 87%, p=0.036), lower mean TB clinical scores (-0.20 points, 95%CI -0.31 to -0.08, p=0.001) and slightly better quality of life (mean EQ-5D-5L 0.86 vs. 0.85, p=0.015) at six months were also observed. These differences, except quality of life, remained statistically significant after adjusting for baseline values, trial arm and TB treatment adherence rates.

Conclusion

TB patients who stop smoking may have better outcomes than those who don't. Health professionals should support patients in stopping smoking.

Key words

Tuberculosis, TB, Tobacco, Smoking cessation, quitting, relapse

Key Messages

What is the key question?

Do clinical outcomes of TB patients improve by stopping smoking during their six-months of TB treatment?

What is the bottom line?

TB patients who stop smoking are likely to have better clinical outcomes than those who don't.

Why read on?

This is the first study to assess the effect of stopping smoking during TB treatment on a range of clinical outcomes including TB relapse. The study used validated TB outcome measures and a biochemical measure to verify quit status.

INTRODUCTION

Tuberculosis (TB) affected over 10 million people in 2018 and approximately 1.5 million died as a result.[1] While investment in TB control has resulted in a decline in incidence and improvements in TB outcomes over the last two decades, the TB pandemic continues to be fuelled by presence of co-morbid conditions and risk factors.[2] These include HIV, diabetes, malnutrition, alcohol use, tobacco use and indoor air pollution.[3] The adverse interaction between TB and the above triggers and co-morbidities, leads to a multi-fold increase in the risk of acquiring TB infection as well as worsening TB outcomes. Among these risk factors, smoking alone is responsible for 16% of the total TB disease-burden;[3] this population attributable fraction is even higher in countries with high tobacco use. Smoking increases the chances of acquiring TB infection and TB disease by two- and three-folds, respectively;[4] continued smoking by those with active TB disease worsens their clinical outcomes.[5] Compared to non-smokers, TB patients who smoke are more likely to have severe forms of clinical presentation, poor bacteriological and clinical responses to treatment(s), and high rates of treatment failure.[6] It is estimated that 17% of total TB treatment failure can be attributed to smoking. Moreover, smoking doubles the risk of TB-related deaths[4] and, in survivors, TB recurrence.[7]

The strong association between smoking and TB has led to increasing recognition of the need for evidence-based smoking cessation approaches[8] and increasing policy support to help TB patients quit smoking.[9] However, no TB high-burden country has so far integrated smoking cessation within their TB policies and programmes; and the vast majority of TB patients are neither routinely asked about their smoking status nor advised to quit.[10] A number of contextual and system barriers to integrate smoking cessation within TB programmes have been identified.[11] Moreover, many policy makers, programme managers and clinicians do not consider smoking cessation support as part of TB treatment.[11] This situation is unlikely to change unless the body of evidence not only indicates that those who smoke have worse TB outcomes than non-smokers, but also demonstrates that those patients who quit smoking have better TB outcomes than those who continue to smoke. Such evidence is necessary to motivate TB programmes to include tobacco cessation as an integral component of the series and systems within routine TB programmes. Such evidence would also convince health professionals that offering cessation support is vital to enhancing quit rates and improving TB outcomes. Given the very few published studies on the effects of stopping smoking on TB outcomes,[2] we aimed to compare the outcomes of those who quit smoking during the course of their TB treatment and subsequently sustained this abstinence with those who did not.

METHODS

We conducted a secondary analysis on data from participants recruited into a large two-arm, parallel, double-blind, placebo-controlled, multi-centre individually randomised controlled trial in two high-TB burden countries, Bangladesh and Pakistan (ISRCTN43811467) known as the 'TB & Tobacco Trial'.[12] The trial investigated the effectiveness and safety of cytisine when added to brief behavioural support in achieving smoking abstinence in TB patients; the results published elsewhere.[13] While cytisine was not found effective, the trial provided important opportunities to assess the impact of cessation in TB patients.

Composition of the study cohort

We recruited adults newly diagnosed (within the last four weeks) with pulmonary TB, who smoked tobacco on a daily basis and who were interested in quitting. They were recruited from 32 hospitals;

17 sub-district hospitals in four districts of Dhaka, Bangladesh and 15 secondary care hospitals within Punjab and Khyberpakhtunkhwa provinces in Pakistan. We excluded patients with TB complications and with conditions where cytisine was contraindicated.[12] After collecting baseline data and centrally randomising participants to receive either cytisine or placebo, we followed them up for a period of 12 months, with scheduled data collection at weeks 5, 9 and 12 and months 6 and 12. Except for the month-12 visit, these follow-ups corresponded with routine hospital visits to receive TB care (see protocol for further details).[12]

Quitters (exposed) vs. non-quitters (unexposed)

Quitters (*exposed*) were those participants who stopped smoking, i.e., self-reported continuous abstinence verified biochemically at six- and 12-months. Self-reported abstinence was defined as not smoking cigarettes, bidis, or water-pipes on more than five occasions since the quit day (day-5 post-randomisation) nor switching to smokeless tobacco products after quitting smoking. Biochemical verification meant breath carbon monoxide (CO) reading of less than 10 ppm and a negative urine cotinine test (NicAlert/One Step) for smokeless tobacco users. These biochemical verifications occurred at months 6 and 12 follow-ups, and therefore quitters were categorised as those being continuously abstinent and verified biochemically at 6 and 12 months.

Non-quitters (*unexposed*) were participants reporting either not remaining continuously abstinent during the respective periods or claiming abstinence, but their self-reports were not verified biochemically at 6 or 12 months. Participants with missing data for any reason were assumed to have a non-quit status.

TB outcomes

A number of TB outcomes were assessed: (a) a validated TB score[14] based on clinical signs and symptoms i.e. cough, chest pain, dyspnoea, anaemia, body mass index (BMI) <18 kg/m^2, mid-upper arm circumference (MUAC) < 220 mm. Each of the six indicators contributed 1 point except BMI and MUAC, which contributed an extra point, if <16 kg/m^2 and <200 mm, respectively; therefore a maximum score of 8 (the higher the score the worse was the clinical condition). TB scores were assessed at baseline, weeks 5, 9 and 12 and at months 6 and 12; (b) Sputum conversion (in those with sputum positive TB) obtained at weeks 5 and 9 and at months 6 and 12; (c) Chest X-ray results obtained at day 0, week 9 and months 6 and 12 and graded by a senior radiologist as 0 (normal), 1 (mild), 2 (moderate) and 3 (far advanced TB) according to the National Tuberculosis Association of the USA Grades;[15] (d) TB outcomes, recorded from routine TB registers at month 6 and assessed at month 12 follow-up- including proportion of those who were cured and/or completed treatment; (e) Quality of life measured by EQ-5D-5L[16] at day 0, months 6 and 12; (f) Relapse within 12 months i.e. those who were declared cured and/or completed their treatment after 6 months and had a recurrent episode of TB by 12 months; and (g) Deaths from any cause during 12 months.

Other variables

Covariates of interest included age, sex, socio-economic status (high or low), smoking duration (in years) and cigarettes/day as well as adherence to TB medication. Medication adherence was recorded from routinely collected data (TB cards) at baseline, week 9 and month 6 (daily record of medication taken, not taken or not recorded).[12]

Statistical analysis

We compared TB outcomes between quitters (self-reported continuous abstinence verified biochemically at 6 and 12 months) and non-quitters. TB outcomes were expressed as continuous or binary outcomes and were analysed as follows. We used linear regression for continuous outcomes: average TB scores at 6 and 12 months (a1, a2) and mean EQ-5D-5L index scores at 6 and 12 months (e1, e2); and we used logistic regression for binary outcomes: proportion of participants with smear positive TB who converted to smear negative by week 9 (b), proportion of participants with moderate or advanced grade on chest X-rays at baseline who changed to mild or normal categories by week 9 (c) proportion of patients who were either cured or completed treatment at 6 and 12 months (d1, d2) , as well as proportion of treatment completers at 6 months who relapsed by 12 months (f). As follow-up of patients was restricted to 12 months, no deaths could have occurred for anyone with verified quit status at 12 months, therefore death was not included as an outcome in the analysis.

For each comparison, a simple base model (adjusting for baseline TB score only as an indicator of initial TB severity) and an adjusted model, adjusting for characteristics that were expected to be associated with TB outcomes: baseline TB score, age, socioeconomic status, smoking duration and frequency, TB treatment adherence as well as trial allocation (cytisine or placebo) were conducted. Each effect is presented as the relevant mean difference or odds ratio as appropriate for quitters and non-quitters with 95% confidence intervals and associated p-value. Given that the sample included >90% men, sex was not included as a covariate, as there was a lack of variability in its distribution. All analyses were based on complete cases.

Ethical permissions

The study was granted ethical permission by the University of York's Research Governance committee as well as the respective national bioethics committees in Bangladesh and Pakistan.

RESULTS

We recruited 2,472 TB patients into the TB & Tobacco Trial and our secondary analysis at 12 months used the data of 2,273 (92%) TB patients. These patients had a minimum follow-up of their TB outcomes represented by an available TB score at 6 months. Of the excluded data, 68 (3%) had died, 127 (5%) were permanently lost to follow-up or had missing TB score data and 4 (0.2%) were retrospectively identified as ineligible. Based on their self-reports and biochemical verifications, there were 577 (25%) quitters (self-reported continuous abstinence verified biochemically at 6 and 12 months) and 1,696 (75%) non-quitters. A comparison between the baseline characteristics of the two groups is presented in Table 1. In general, quitters tended to be marginally younger and more affluent than non-quitters. TB severity based on TB score was similar between the two groups.

Table 1: Baseline Characteristics by Quit Status at 12 months follow-up

Biochemically verified quit status at 6 and 12 months		
	Quit, N=577	Not Quit, N=1,696
Age		
N	577	1696
Mean (SD)	41.52 (14.91)	42.42 (13.97)
Median (IQR)	40 (28, 53)	42 (30, 52)
Wealth Index Quartiles (based on GATS)		
Q1 least affluent, n(%)	146 (25%)	435 (26%)

Q2, n(%)	188 (33%)	569 (34%)
Q3, n(%)	87 (15%)	280 (17%)
Q4 most affluent, n(%)	156 (27%)	412 (24%)
TB Score		
N	577	1696
Mean (SD)	3.34 (1.62)	3.36 (1.58)
Median (IQR)	3 (2, 4)	3 (2, 4)
Smoking Frequency (times per day)		
N	576	1696
Mean (SD)	9.31 (7.89)	12.57 (8.86)
Median (IQR)	7 (5, 10)	10 (6, 20)
Strength of Urges to Smoke (0-5 max)		
N	577	1695
Mean (SD)	2.50 (1.06)	2.86 (1.10)
Median (IQR)	2 (2, 3)	3 (2, 3)
Mood and Physical Symptoms Scale (Severity 0-28 max)		
N	574	1686
Mean (SD)	12.99 (3.72)	12.89 (3.43)
Median (IQR)	13 (10, 16)	13 (10, 15)

Results of the regression analyses for quitters and non-quitters are shown in Table 2. For many outcomes (TB scores at 6 months, sputum conversion, quality of life, TB outcome and TB relapse), quitters demonstrated modest and statistically significant improvements over non-quitters. Results were generally consistent between adjusted and unadjusted models.

TB cure and treatment completion rates were higher for quitters than non-quitters, and this difference was statistically significant between quitters and non-quitters at both 6 (94% vs. 89%, OR 1.92; 95%CI 1.31-2.81, p=0.001) and 12 months (91% vs. 80%; OR 2.54; 95%CI 1.86-3.48, p<0.001).

After six months of TB treatment, TB relapse rates were lower among quitters compared to non-quitter (6% vs. 14%, OR 0.39; 95%CI 0.27-0.57, p<0.001).

Quitters were associated with better TB scores than non-quitters (mean difference of -0.20 points, 95%CI -0.31 to -0.08, p=0.001) at the end of their 6-months TB treatment. However, after a year the differences in TB scores between quitters and non-quitters became smaller and statistically insignificant (Figure 1).

Among 1,319 patients with a TB positive sputum smear at baseline, a greater number of quitters converted to negative status by week 9 than non-quitters (91% vs. 87%, p=0.036).

X-ray grades at 9 weeks were available for 417 patients who had moderate-to-severe graded x-rays at baseline. Differences in improvement rates between quitters and non-quitters were not statistically significant. X-ray data had not been collected for many participants, especially at later time points; therefore no further analysis was conducted.

Minor difference in quality of life was observed among quitters as compared to non-quitters at six months (mean EQ-5D 0.86 vs. 0.85, p=0.015), but not at 12 months; this improvement became non-significant in the adjusted analysis.

Table 2: TB outcomes in quitters vs. non quitters

TB Outcomes	Quit		No Quit		Base Model*			Adjusted Model**		
	N	Mean (SD)	N	Mean (SD)	Mean Diff	95% CI	p	Mean Diff	95% CI	p
TB Score at 6 months	577	1.12 (1.42)	1696	1.32 (1.46)	-0.20	-0.31 to -0.08	0.001	-0.16	-0.28 to -0.04	**0.007**
TB Score at 12 months	577	0.90 (1.36)	1615	0.99 (1.30)	-0.087	-0.20 to 0.03	0.136	-0.05	-0.17 to 0.06	**0.357**
EQ-5D-5L Index at 6 months	575	0.86 (0.07)	1693	0.85 (0.08)	0.0087	0.0017 to 0.0158	0.015	0.0057	-0.0013 to 0.1268	**0.112**
EQ-5D-5L Index at 12 months	574	0.86 (0.09)	1618	0.85 (0.12)	0.0079	-0.0025 to 0.0184	0.137	0.0065	-0.0039 to 0.0169	**0.224**
	N/Total	%	N/Total	%	OR	95% CI	p	OR	95% CI	p
TB Outcome (cured / completed) at 6 months	536/570	94%	1489/1670	89%	1.92	1.31 to 2.81	0.001	1.92	1.30 to 2.83	**0.001**
TB Outcome (cured / completed) at 12 months	525/576	91%	1296/1615	80%	2.54	1.86 to 3.48	<0.001	2.64	1.92 to 3.65	**<0.001**

Relapse between 6 and 12 months	33/535	6%	208/1450	14%	0.39	0.27 to 0.57	<0.001	0.38	0.26 to 0.57	**<0.001**
Sputum Conversion by week 9	314/345	91%	845/974	87%	1.56	1.03 to 2.35	0.036	1.62	1.06 to 2.47	**0.025**
X-ray Improvement by week 9	30/103	29%	100/314	32%	0.85	0.52 to 1.39	0.519	0.82	0.49 to 1.36	**0.435**

* Regression models adjusted for baseline TB score only

** Regression models adjusted for baseline TB score, age, socioeconomic status, smoking duration and frequency, proportion of TB medication compliant days as well as trial allocation (Cytisine or Placebo)

DISCUSSION

This secondary analysis of the TB & Tobacco Trial aimed to test the hypothesis that smoking cessation improves TB outcomes. We observed that TB patients who quit smoking and remained abstinent showed significantly better TB outcomes than non-quitters. Treatment success rate at completion of the six months regime was better in quitters compared to non-quitters. Similarly, TB relapse (post-treatment completion) rate was lower in those who quit smoking and remained abstinent. Clinical TB score at six months was also better in quitters than non-quitters. A higher proportion of quitters with TB positive sputum converted to negative at nine weeks (a TB treatment milestone) compared to non-quitters.

Previous research has highlighted the negative impact of smoking on TB;[4–6] this study provides additional evidence that, while smoking tobacco worsens TB outcomes, quitting smoking may improve these outcomes. Further to this, our findings support previous research, which has observed an improvement in TB outcomes as the consequence of smoking cessation.[17] We add to this by highlighting specific clinical measurements, which show improvements in TB outcomes following smoking cessation. We observed improvements among quitters consistently across a range of laboratory and clinical outcomes, which strengthens the evidence and the case for quitting in TB patients. Long-term benefits of smoking cessation are well established including those with chronic respiratory conditions; our study provides new evidence of its short- and medium-term benefits in TB patients.

In relation to TB score, a benefit of quitting was observed at six months, however no benefit was observed at 12 months, post quit. One potential reason for this is that the TB clinical scores improve linearly from the onset of anti-TB treatment to its completion; after this time point in those who have recovered, TB scores then remain more or less the same (Figure 1). Therefore, any difference between the two groups would become even harder to demonstrate at 12 months than at six months. In terms of those cured or completed treatment, a greater difference was observed between quitters and non-quitters at 12 months than at six months. An explanation could be that not all TB patients finish their course of treatment at the standard 6-month treatment endpoint. Instead, based on clinician's judgement, many would have continued to receive medication for another few weeks. Even for those patients where treatment is completed at six months, it is quite common for their TB records to be updated much later i.e. after month 6; this practice was observed at some sites.

This is the first study to show the effects of quitting smoking during TB treatment on a wide range of TB outcomes. In doing this, robust methods were employed, which included; the use of validated TB outcome measures and a biochemical objective measure of tobacco smoking to verify quit status. The study also accounted for key confounding variables in the analysis, such as age, socioeconomic status, baseline TB score, smoking duration and frequency and compliance to TB medication. Further to this, patients were followed up for 12 months, whilst other studies in this area have typically only followed-up patients for 6 months. This allowed us to establish the effects of longer-term quitting on TB disease outcomes such as relapse and recurrence; these outcomes are rarely evaluated but are important considerations for TB treatment programmes.

There are limitations, which should be considered when interpreting the findings. This is a secondary analysis based on a non-randomised comparison, which bears the risk of residual confounding. TB patients were recruited into a large RCT and therefore, the selection criteria applied were restricted to those with pulmonary drug sensitive TB. The study recruited adult patients who were daily tobacco

smokers. Given the gender distribution of smoking in Bangladesh and Pakistan (smoking is predominantly a male behaviour),[18] we were able to recruit only a handful of women in the study. Given the nature of the comparison, there was an imbalance in the sample sizes of the groups being compared (25% quitters vs 75% non-quitters). We also excluded those using smokeless tobacco only, which further reduced our chances to recruit women (smokeless tobacco is equally popular among males and females in South Asia).[19] This could have implications for the generalisability and extrapolation of the findings to other settings, other types of TB patients and to those with different patterns of tobacco use. Our study included only those smokers who were motivated to quit and therefore our findings may have limited generalisability among all smokers with TB. Some of our outcomes (number of patients cured/completed treatment) relied on data collected routinely and recorded in TB registers; therefore some of these data may be subject to misclassification bias. However, if any misclassification took place, it would have been non-differential and therefore might not have influenced the direction of our results. In addition to this, as this study was conducted in South Asia, findings should be interpreted within this context.

We have demonstrated new evidence to promote smoking cessation integrated in routine TB services in Bangladesh and Pakistan. Previous studies have established that smoking significantly increases the risks of acquiring TB and decreases the rate of successfully recovering from it. This study adds to this evidence base by providing the effects of quitting smoking during TB treatment, and demonstrates the benefits for TB patients in recovering from TB. This study, together with previous research in this field[4,8] provides new evidence to support the importance of smoking cessation within TB care. In future, this evidence will be further strengthened by a large RCT of an effective smoking cessation intervention with TB success (cure *plus* treatment completion) as the primary outcome.

The WHO/Union Monograph on TB and Tobacco emphasises the need for more systemic policy application and standardisation for tobacco cessation advice in TB programmes.[20] These two epidemics have been labelled as syndemics and thus framed as needing joint programmatic interventions.[21]. Implementation research is also needed to understand the changes needed within health systems to sustain effective smoking cessation interventions in routine TB care. We also recommend TB programmes to include smoking status and quit outcomes within its recording and reporting systems. Such data will not only help in monitoring programme' performance on an important risk factor, but also provide opportunities to assess the impact of smoking cessation on TB outcomes, including TB deaths in a variety of settings.

CONCLUSIONS

TB patients who quit smoking tobacco at the time of diagnosis and remained abstinent during and after their course of TB treatment fared clinically better than those who continued to smoke. A lower TB relapse rate among those who quit smoking means reduced retreatment case burden for TB programmes. In addition to offering standard TB treatment, health professionals should also assist TB patients to quit smoking by integrating effective smoking cessation support within routine TB care.

COMPETING INTERESTS

DK reports an unrestricted grant from Pfizer in 2009 for an investigator-initiated trial on the effectiveness of practice nurse counselling and varenicline for smoking cessation in primary care. KS

reports an unrestricted research grant from Pfizer to study the effects of varenicline on waterpipe smoking cessation.

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Figure 1: TB Score over time (95% CI) for quitters and non quitters