Original research

Effect of quitting smoking on health outcomes during treatment for tuberculosis: secondary analysis of the TB & Tobacco Trial

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ABSTRACT

Background Despite treatment, patients with tuberculosis (TB) who smoke have poorer outcomes compared with non-smokers. It is unknown, however, if quitting smoking during the 6 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 2472 patients with pulmonary TB 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 2273 (92%) trial participants. Overall, 25% (577/2273) of participants stopped smoking. Compared with 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 (−0.31 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 6 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 Patients with TB who stop smoking may have better outcomes than those who don’t. Health professionals should support patients in stopping smoking.

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 comorbid 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 comorbidities leads to a multifold 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 burden3; 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 twofold and threefold, respectively4; continued smoking by those with active TB disease worsens their clinical outcomes.5 Compared with non-smokers, patients with TB 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 deaths7 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 approaches8 and increasing policy support to help patients with TB quit smoking.9 However, no high-TB-burden country has so far integrated smoking cessation within their TB policies and programmes, and the vast majority of patients with TB 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. Moreover, many policy makers, programme managers and clinicians do not consider smoking cessation support as part of TB treatment. 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.

Given the very few published studies on the effects of stopping smoking on TB outcomes,2 we aimed to compare the health 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, multicentre individually randomised controlled trial (RCT) in two high-TB-burden countries, Bangladesh and Pakistan (ISRCTN43811467), known as the ‘TB & Tobacco Trial’. The trial investigated the effectiveness and safety of cytisine when added to brief behavioural support in achieving smoking abstinence in patients with TB; the results are published elsewhere.13 While cytisine was not found effective, the trial provided important opportunities to assess the impact of cessation in patients with TB.

**Composition of the study cohort**

We recruited adults newly diagnosed (within the last 4 weeks) with pulmonary TB, who smoked tobacco on a daily basis and who were interested in quitting. They were recruited from 32 hospitals; 17 subdistrict hospitals in four districts of Dhaka, Bangladesh, and 15 secondary care hospitals within Punjab and Khyber Pakhtunkhwa provinces in Pakistan. We excluded patients with TB complications and with conditions where cytisine was contraindicated. 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 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) versus non-quitters (unexposed)**

Quitters (exposed) were those participants who stopped smoking, that is, self-reported continuous abstinence verified biochemically at 6 and 12 months. Self-reported abstinence was defined as not smoking cigarettes, bids or water pipes on more than five occasions since the quit day (day-5 postrandomisation) nor switching to smokeless tobacco products after quitting smoking. Biochemical verification meant breath carbon monoxide reading of less than 10 ppm and a negative urine cotinine test (NicAlert/One Step) for smokeless tobacco users. These biochemical verifications occurred at month-6 and month-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.

**Health outcomes**

A number of health outcomes were assessed:

1. A validated TB score14 based on clinical signs and symptoms, that is, cough, chest pain, dyspnoea, anaemia, body mass index (BMI) <18 kg/m² and mid-upper arm circumference (MUAC) <220 mm. Each of the six indicators contributed one point except BMI and MUAC, which contributed an extra point, if <16 kg/m² and <200 mm, respectively, therefore a maximum score of eight (the higher the score, the worse the clinical condition). TB scores were assessed at baseline; weeks 5, 9 and 12; and months 6 and 12.

2. Sputum conversion (in those with sputum-positive TB) obtained at weeks 5 and 9 and at months 6 and 12.

3. 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 US grades.15

4. 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.

5. Quality of life measured by EQ-5D-5L16 at day 0 and months 6 and 12.

6. Relapse within 12 months, that is, those who were declared cured and/or completed their treatment after 6 months and had a recurrent episode of TB by 12 months.

7. Deaths from any cause during 12 months.

**Other variables**

Covariates of interest included age, sex, socioeconomic 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 health outcomes between quitters (self-reported continuous abstinence verified biochemically at 6 and 12 months) and non-quitters. Health 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 and a2) and mean EQ-5D-5L Index scores at 6 and 12 months (e1 and 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 either were cured or completed treatment at 6 and 12 months (d1 and d2) and 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 health outcomes: baseline TB score, age,
Table 1  Baseline characteristics by quit status at 12-month follow-up

| Biochemically verified quit status at 6 and 12 months | Quit, n=577 | Not quit, n=1696 |
|-------------------------------------------------------|-------------|-----------------|
| 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)     |

*Global Adult Tobacco Survey

socioeconomic status, smoking duration and frequency, TB treatment adherence and trial allocation (cytisine or placebo), were conducted. Each effect is presented as the relevant mean difference or OR as appropriate for quitters and non-quitters with 95% CIs 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 2472 patients with TB into the TB & Tobacco Trial, and our secondary analysis at 12 months used the data of 2273 (92%) patients with TB. These patients had a minimum follow-up of their health 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 four (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 1696 (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.

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 to 2.81, p=0.001) and 12 months (91% vs 80%, OR 2.54, 95% CI 1.86 to 3.48, p<0.001).

After 6 months of TB treatment, TB relapse rates were lower among quitters compared with non-quitter (6% vs 14%, OR 0.39, 95% CI 0.27 to 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-month TB treatment. However, after a year, the differences in TB scores between quitters and non-quitters became smaller and statistically insignificant (figure 1).

Among 1319 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 with non-quitters at 6 months (mean EQ-5D −0.08, p=0.001) at the end of their 6-month TB treatment. Differences in improvement rates between quitters and non-quitters became smaller and statistically insignificant between adjusted and unadjusted models.

DISCUSSION

This secondary analysis of the TB & Tobacco Trial aimed to test the hypothesis that smoking cessation improves health outcomes. We observed that patients with TB who quit smoking and remained abstinent showed significantly better health outcomes than non-quitters. Treatement success rate at completion of the 6-month regime was better in quitters compared with non-quitters. Similarly, TB relapse (post-treatment completion) rate was lower in those who quit smoking and remained abstinent. Clinical TB score at 6 months was also better in quitters compared with non-quitters, and this difference was statistically significant. Results were generally consistent between adjusted and unadjusted models.

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 strengthen the evidence and the case for quitting in patients with TB. Previous research has highlighted the negative impact of smoking on TB outcomes; 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. We observed improvements among quitters consistently across a range of laboratory and clinical outcomes, which strengthen the evidence and the case for quitting in patients with TB.

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TB. Long-term benefits of smoking cessation are well established including those with chronic respiratory conditions; our study provides new evidence of its short-term and medium-term benefits in patients with TB.

In relation to TB score, a benefit of quitting was observed at 6 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 6 months. In terms of those who were cured or completed treatment, a greater difference was observed between quitters and non-quitters at 12 months than at 6 months. An explanation could be that not all patients with TB 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 6 months, it is quite common for their TB records to be updated much later, that is, 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 health 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, while 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. Patients with TB 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), 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 men and women in South Asia). This could have implications for the generalisability and extrapolation of the findings to other settings, other types of patients with TB and 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 who were 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 patients with TB in recovering from TB. This study, together with previous research in this field, provides new evidence to support the importance of smoking cessation within TB care. In the 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. These two epidemics have been labelled as syndemics and thus framed as needing joint programmatic interventions. 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’s 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

Patients with TB 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 patients with TB to quit smoking by integrating effective smoking cessation support within routine TB care.

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Contributors KS originated the idea and drafted majority of the manuscript. AKe analysed the data and contributed in drafting the manuscript. All other authors contributed to the design and execution of the study and reviewed, revised and approved the manuscript.

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