Risk of Tuberculosis From Exposure to Tobacco Smoke

A Systematic Review and Meta-analysis

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Background: There is no consensus whether tobacco smoking increases risk of tuberculosis (TB) infection, disease, or mortality. Whether this is so has substantial implications for tobacco and TB control policies.

Objective: To quantify the relationship between active tobacco smoking and TB infection, pulmonary disease, and mortality using meta-analytic methods.

Methods: Eight databases (PubMed, Current Contents, BIOSIS, EMBASE, Web of Science, Centers for Disease Control and Prevention Tobacco Information and Prevention Source [TIPS], Smoking and Health Database [Institute for Science and Health], and National Library of Medicine Gateway) and the Cochrane Tobacco Addiction Group Trials Register were searched for relevant articles published between 1953 and 2005.

Study Selection: Included were epidemiologic studies that provided a relative risk (RR) estimate for the association between TB (infection, pulmonary disease, or mortality) and active tobacco smoking stratified by (or adjusted for) at least age and sex and a corresponding 95% confidence interval (CI) (or data for calculation). Excluded were reports of extrapulmonary TB, studies conducted in populations prone to high levels of smoking or high rates of TB, and case-control studies in which controls were not representative of the population that generated the cases, as well as case series, case reports, abstracts, editorials, and literature reviews.

Data Extraction: Twenty-four studies were included in the meta-analysis. Extracted data included study design, population and diagnostic details, smoking type, and TB outcomes.

Data Synthesis: A random-effects model was used to pool data across studies. Separate analyses were performed for TB infection (6 studies), TB disease (13 studies), and TB mortality (5 studies). For TB infection, the summary RR estimate was 1.73 (95% CI, 1.46-2.04); for TB disease, estimates ranged from 2.33 (95% CI, 1.97-2.75) to 2.66 (95% CI, 2.15-3.28). This suggests an RR of 1.4 to 1.6 for development of disease in an infected population. The TB mortality RRs were mostly below the TB disease RRs, suggesting no additional mortality risk from smoking in those with active TB.

Conclusions: The meta-analysis produced evidence that smoking is a risk factor for TB infection and TB disease. However, it is not clear that smoking causes additional mortality risk in persons who already have active TB. Tuberculosis control policies should in the future incorporate tobacco control as a preventive intervention.

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TOBACCO SMOKING AND TUBERCULOSIS (TB) are 2 of the world's greatest public health problems, although TB is largely confined to developing countries. Tobacco-attributable deaths are projected to increase from 3 million in 1990 to 8.4 million in 2020. After human immunodeficiency virus and AIDS, TB is the leading infectious cause of death and disease worldwide, responsible for about 1.7 million deaths each year. One third of the world's population is infected with Mycobacterium tuberculosis, although the organism is contained by the immune system in most of these persons. Globally, an estimated 8.8 million individuals in 2003 developed active TB, and the incidence was increasing at 1% annually.

It has long been suggested that tobacco smoking may affect rates of TB morbidity and mortality. This could be a result of increasing the risk of infection with TB mycobacteria, increasing the rate of active TB disease, or increasing the TB mortality rate; plausible mechanisms exist. However, statistical relationships found in investigations may have been a result of confounding (eg, by alcohol use or by socioeconomic factors). Establishing whether smoking interacts with events leading to TB morbidity and mortality...
would provide useful information for prevention policies for TB and smoking. This study systematically reviews the published literature on the relationship between smoking and TB infection, disease, and mortality and presents meta-analyses of the relationships. From a clinician’s perspective, understanding the association between smoking and TB will facilitate educational and counseling interventions.

**METHODS**

**SEARCH**

Eight major databases (PubMed, Current Contents, BIOSIS, EMBASE, Web of Science, Centers for Disease Control and Prevention Tobacco Information and Prevention Source [TIPS], Smoking and Health Database [Institute for Science and Health], and National Library of Medicine Gateway) and the Cochrane Tobacco Addiction Group Trials Register were searched for published studies that included investigation of the relationship between smoking and TB infection, active pulmonary TB, or death due to TB. Variants of key words such as “tuberculosis,” “smoking,” and “tobacco smoke” were used. These yielded 3145 potentially relevant published articles between 1953 and 2005. Reference lists of articles identified were searched for additional relevant publications. We considered only articles in English, Chinese, Spanish, Portuguese, Italian, and German.

**CRITERIA FOR SELECTION**

Two independent reviewers (L.C. and F.L.) first screened titles and abstracts of publications using broad eligibility criteria, yielding 220 potentially eligible publications. These were reduced to 24 eligible publications by application of the following final study inclusion criteria: (1) use of an epidemiologic study design to conduct a primary or secondary data analysis, (2) inclusion of at least 1 comparison group without TB and a group of nonsmokers or never smokers, (3) provision of a relative risk (RR) estimate for the association between TB (infection, disease, or mortality) and active tobacco smoking (ie, not passive smoking exposure) stratified by (or adjusted for) at least age and sex and a corresponding 95% confidence interval (CI) (or sufficient data to calculate this), and (4) confirmation of TB status (infection, pulmonary disease, or death) in 1 of the following ways: (a) for TB infection, a tuberculin skin test, (b) for TB disease, bacteriologic confirmation (positive sputum smear or culture) or notification, and (c) for TB mortality, death certificates or verbal autopsies.

Publications were excluded if they (1) described case series or case reports or were abstracts, editorials, or literature reviews, (2) reported only extrapulmonary TB or did not distinguish pulmonary from extrapulmonary TB disease, (3) reported studies that were conducted in special populations prone to high levels of smoking or high rates of TB (eliminating studies on patients with lung cancer, stone crushers or miners, persons with silicosis, and subjects with human immunodeficiency virus or AIDS [although no otherwise eligible studies in the latter category were found]), or (4) reported case-control studies in which the control population was not representative of the population generating the cases. When appropriate, authors were contacted to supply details missing from their publications.

**DATA ANALYSIS**

All analyses were performed using commercially available meta-analysis add-on programs (STATA version 8.0; StatCorp LP, College Station, Tex). Forest plots were created for each outcome (TB infection, TB disease, and TB death), and summary effect estimates were calculated using the DerSimonian-Laird random-effects model, usually regarded as more appropriate for meta-analysis of observational studies. Heterogeneity across studies was assessed using the χ² test for homogeneity.

Subgroup analyses were used to explore sources of heterogeneity. Potential for publication bias was assessed using the Egger test and funnel plots.

**RESULTS**

**SELECTION OF ELIGIBLE PUBLICATIONS**

The selected articles are listed in Table 1. Except for 1 article in Chinese, all were in English. Six publications dealt with TB infection, 13 with TB disease, and 5 with TB mortality.

**META-ANALYSIS**

**TB Infection**

Figure 1 shows a forest plot for studies that examined TB infection. Four of 6 CIs excluded the null value. One study13 from among 6 eligible studies11-14,16 was not included in this meta-analysis (which includes 2 independent results from 1 study11), because the RR estimates presented were for different numbers of cigarettes smoked per day. The smoking measure (ex-smoker, current smoker, or ever smoker) is shown in parentheses following the first author name and publication year in Figure 1. The summary estimate of the RR was 1.58 (95% CI, 1.23-2.02). However, there is evidence of heterogeneity (P = .005), particularly because of the precise RR estimate obtained by the large study by Adib et al13 among prisoners in Lebanon. The Lebanon study used a minimum tuberculin skin test induration diameter of 8 mm for diagnosing TB infection, while all other investigations used 10 mm as the criterion. The smaller induration diameter may have led to misclassification of persons without TB infection as being infected. This, as well as the fact that the comparison group of nonsmokers likely to have included some ex-smokers, could account for the low RR estimate from this study. After excluding the Lebanon study, we obtained a summary RR estimate of 1.73 (95% CI, 1.46-2.04) with no evidence of heterogeneity (P = .71) among the remaining studies.

Figure 2 shows a funnel plot of the RR estimates for the studies11-14,16 against their standard errors. The P = .02 that was derived using the Egger test and the asymmetry of the distribution suggest potential for publication bias. When the Lebanon study13 was excluded, the Egger test provided no evidence of heterogeneity (P = .82). However, tests of publication bias are not necessarily sensitive for small numbers of studies.

**TB Disease**

A meta-analysis combining the TB disease RR estimates for men and women across all studies produced a summary RR estimate of 2.27 (95% CI, 1.90-2.71) with appreciable evidence of heterogeneity (P = .002). However, in many of the countries represented in the analysis, women
**Table 1. Studies Included in the Meta-analysis**

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>Location</th>
<th>Population</th>
<th>Year or Year Range</th>
<th>Diagnosis*</th>
<th>Sex</th>
<th>Age or Age Range, y</th>
<th>Other Confounders†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB infection</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>Migrant farm workers</td>
<td>1995</td>
<td>$\geq 10$ mm</td>
<td>M and F</td>
<td>$&gt;1$</td>
<td>Birthplace</td>
</tr>
<tr>
<td>Anderson et al.11, 1997</td>
<td>Case-control</td>
<td>United States</td>
<td>Prisoners</td>
<td>1992</td>
<td>$\geq 10$ mm</td>
<td>M and F</td>
<td>17-54</td>
<td>Living conditions, race/ethnicity</td>
</tr>
<tr>
<td>Addib et al.13, 1999</td>
<td>Cross-sectional</td>
<td>Lebanon</td>
<td>Prisoners</td>
<td>1995</td>
<td>$&gt;8$ mm</td>
<td>M and F</td>
<td>Mean ± SD, 32 ± 11</td>
<td>Residence area, occupation, duration of imprisonment</td>
</tr>
<tr>
<td>Plant et al.14, 2002</td>
<td>Cross-sectional</td>
<td>Vietnam</td>
<td>Prospective emigrants</td>
<td>1997-1999</td>
<td>$\geq 10$ mm</td>
<td>M and F</td>
<td>16-81, mean, 29</td>
<td>Education, duration of imprisonment, crowding of cell</td>
</tr>
<tr>
<td>Hussain et al.15, 2003</td>
<td>Case-control</td>
<td>Pakistan</td>
<td>Prisoners</td>
<td>2001</td>
<td>$\geq 10$ mm</td>
<td>M</td>
<td>18-60</td>
<td>Same-address clustering</td>
</tr>
<tr>
<td>den Boon et al.16, 2005</td>
<td>Cross-sectional</td>
<td>South Africa</td>
<td>Urban adults</td>
<td>2002</td>
<td>$\geq 10$ mm</td>
<td>M and F</td>
<td>$\geq 15$</td>
<td></td>
</tr>
<tr>
<td>TB disease</td>
<td>Case-control</td>
<td>England</td>
<td>Patients</td>
<td>1955</td>
<td>Notification</td>
<td>M</td>
<td>$\geq 20$</td>
<td></td>
</tr>
<tr>
<td>Yu et al.17, 1988</td>
<td>Cross-sectional</td>
<td>China</td>
<td>Sanitary workers</td>
<td>1985-1986</td>
<td>Smear or x-ray</td>
<td>M and F</td>
<td>Adults</td>
<td>Contact history, housing area, type of work</td>
</tr>
<tr>
<td>Gupta et al.18, 2001</td>
<td>Case-control</td>
<td>India</td>
<td>Chest clinic patients</td>
<td>1998-1999</td>
<td>Smear or x-ray</td>
<td>M and F</td>
<td>Mean, 37</td>
<td>Exposure to TB, SES</td>
</tr>
<tr>
<td>Perez-Padilla et al.19, 2001</td>
<td>Case-control</td>
<td>Mexico</td>
<td>Patients</td>
<td>1996-1997</td>
<td>Culture or smear</td>
<td>M and F</td>
<td>Mean, 36-42</td>
<td>Urban and rural residence, crowding, education, biomass smoke exposure, income District, SES, work, BCG vaccine, alcohol, environmental tobacco smoke exposure, kind of cigarettes</td>
</tr>
<tr>
<td>Tekioi et al.21, 2002</td>
<td>Case-control</td>
<td>Estonia</td>
<td>Population</td>
<td>1999-2000</td>
<td>Culture or smear</td>
<td>M and F</td>
<td>$\geq 15$</td>
<td>Place of birth, marital status, education</td>
</tr>
<tr>
<td>Kolappan and Gopii.22, 2002</td>
<td>Case-control</td>
<td>India</td>
<td>Population</td>
<td>1993-1996</td>
<td>Culture and smear</td>
<td>M</td>
<td>20-50</td>
<td></td>
</tr>
<tr>
<td>Leung et al.23, 2003</td>
<td>Case-control</td>
<td>Hong Kong</td>
<td>Population</td>
<td>1996</td>
<td>Culture, clinical, x-ray, or histologic findings</td>
<td>M and F</td>
<td>$&gt;15$</td>
<td></td>
</tr>
<tr>
<td>Leung et al.24, 2004</td>
<td>Cohort</td>
<td>Hong Kong</td>
<td>Older persons</td>
<td>2000-2002</td>
<td>Culture</td>
<td>M and F</td>
<td>$\geq 65$</td>
<td>Alcohol use, language, marital status, education, housing, work status, public financial assistance, expenditure, social participation, self-rated health status, hospital admission in the last 12 mo, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, heart disease, cerebrovascular disease</td>
</tr>
<tr>
<td>Ariyothai et al.25, 2004</td>
<td>Case-control</td>
<td>Thailand</td>
<td>Patients</td>
<td>2001</td>
<td>Smear and x-ray</td>
<td>M and F</td>
<td>$\geq 15$</td>
<td>Body mass index</td>
</tr>
<tr>
<td>Crampin et al.26, 2004</td>
<td>Case-control</td>
<td>Malawi</td>
<td>Population</td>
<td>1996-2001</td>
<td>Culture and smear</td>
<td>M and F</td>
<td>$\geq 15$</td>
<td>Area, HIV</td>
</tr>
<tr>
<td>Lienhardt et al.27, 2005</td>
<td>Case-control</td>
<td>West Africa</td>
<td>Population</td>
<td>1999-2001</td>
<td>Culture and smear</td>
<td>M and F</td>
<td>$\geq 15$</td>
<td>HIV, asthma, marital status, family history of TB, adults in household, house ownership</td>
</tr>
</tbody>
</table>

**TB death**

| Larm et al.29, 2001    | Case-control         | Hong Kong             | Population                | 1997-1999         | Death certificate | M and F | $>34$ | Education |

*For TB infection, the data indicate tuberculin skin test induration cut points.
†Considered in the analysis in addition to age and sex.

Abbreviations: HIV, human immunodeficiency virus; SES, socioeconomic status; TB, tuberculosis.

are less likely to be smokers than men.34 Therefore, we excluded the RR estimates for women only, leaving estimates for men only and for men and women combined. The resulting forest plot is shown in **Figure 3**. Thirteen of 16 CIs excluded the null. The summary RR estimate was 2.33 (95% CI, 1.97-
2.75) with less evidence of heterogeneity (P = .04).

Because cross-sectional studies can include selection bias, as would be caused by the death of persons with TB, we performed the meta-analysis without the single cross-sectional study.17 The summary RR estimate decreased slightly to 2.29 (95% CI, 1.93-2.71) (P = .04 for heterogeneity).

Data shown in Figure 3 suggest that, on average, the RRs may be lower for ex-smokers, which would be consistent with findings that many smoking-related RRs decline soon after smoking cessation.35 For current smokers alone (men only or men and women combined), the summary RR estimate was 2.66 (95% CI, 2.15-3.28) (P = .48 for heterogeneity), a little higher than when ex-smokers and ever smokers were included.

All the study results selected for this meta-analysis were adjusted for age and sex. Some investigations adjusted their results for additional potential confounders. After excluding results for women only, the summary RR estimate for the 5 results that were not adjusted for other potential confounding factors was 2.35 (95% CI, 1.95-2.84) (P = .80 for heterogeneity). The corresponding summary estimate for the 12 results that adjusted for other confounding factors (in addition to age and sex) was 2.33 (95% CI, 1.81-3.01), although there was more evidence of heterogeneity (P = .01).

**TB Mortality**

Figure 5 shows a forest plot of the RR estimates from the 5 eligible studies.29-33 There is a great deal of heterogeneity (P < .001), so the summary random-effects RR estimate of 2.15 (95% CI, 1.38-3.35) cannot be regarded as valid. Except for 2 investigations in India that used verbal autopsies to determine cause of death,31 all studies relied on official death certificates. When the studies using verbal autopsies were excluded from the analysis, the RR estimate was reduced to 1.60 (95% CI, 1.31-1.95) still with strong evidence of heterogeneity (P < .001).

When the 2 studies30 from China were considered separately,
the combined RR estimate was 1.26 (95% CI, 1.14-1.40) with no evidence of heterogeneity (P = .26). When the Indian studies\textsuperscript{31,33} were combined, the RR estimate was 3.81 (95% CI, 2.98-4.87); this was dominated by the results from the studies\textsuperscript{31} that used verbal autopsies, and much heterogeneity remained (P = .001).

No useful summary RR estimates were obtained from the mortality investigations. Therefore, no assessment of publication bias was carried out for these studies.

Dose-Response Relationships

Dose-response data were available for 4 studies\textsuperscript{12,14-16} of TB infection and for 3 studies\textsuperscript{30,19,27} of TB disease. One study\textsuperscript{12} included measures of smoking quantity and duration. The results are summarized in \textbf{Table 2}. Several smoking exposure metrics were used, making it impractical to combine results across studies. Six of 8 exposure-response analyses found a positive trend with increasing level or duration of smoking.

\textbf{COMMENT}

Well-known risk factors for TB infection or disease include crowding, poor nutrition, alcoholism, race/ethnicity, socioeconomic status, diabetes mellitus, and human immunodeficiency virus infection. Tobacco smoking is not widely considered a risk factor. A recent review\textsuperscript{38} of environmental risk factors for TB did not mention tobacco smoking. However, a subsequent review article\textsuperscript{37} identified smoking as a possible risk factor, although data were not combined across studies. Potentially, smoking is one of the most modifiable of exposures. In developing countries, where life expectancy is short, highlighting smoking as a risk factor for TB may have greater resonance than advertising its risks for cancer and cardiovascular disease.

Results of this meta-analysis suggest that smoking is associated with an RR of approximately 1.7 for TB infection and an RR of 2.3 to 2.7 for TB disease. The corresponding association with TB mortality is less clear because of heterogeneity in results across studies.

The RR estimates for TB infection, disease, and mortality are not independent. If smoking increases the risk of infection, this will increase the proportion of smokers who are infected and are at risk of TB disease. In turn, if smoking increases the risk of TB disease in those already infected, this will increase the proportion of smokers at risk of TB mortality. Therefore, the independent RR for TB disease can be estimated by dividing the study-derived RR for TB disease (2.3-2.7) by the RR for TB infection (1.7). This gives an estimated RR for development of TB disease in an infected population of 1.4 to 1.6. The most accurate estimate of this risk would come from a study of new TB disease occurrence in an infected population. To our knowledge, such a study has not been published.

The RR estimates for TB mortality were heterogeneous. However, for the investigations that based their cause-of-death assignments on death certificates, the summary RR was 1.60 (95% CI, 1.31-1.95). Because this is less than the estimated RR range for TB disease and smoking (2.3-2.7), it suggests that there is no additional contribution to TB mortality risk from smoking in a population with TB respiratory disease. However, 2 investigations that used verbal autopsies obtained RRs of 4.5 (95% CI, 4.0-5.0) and 4.2 (95% CI, 3.7-4.8) among urban and rural male Indian populations, respectively.\textsuperscript{31} These results suggest that the true mortality RR for smoking among patients with TB pulmonary disease is 1.6 to 2.0. This is not unreasonable because causes of death on death certificates are often unreliable, and verbal autopsies have been shown in some populations to give more com-
The traditional approach to global TB control has focused on the diag-

tigations of TB disease used hospital and clinic control subjects, although they excluded patients with smoking-related disease. Nevertheless, it is possible that there was still some tendency for the controls to more likely be smokers than their base populations. If so, the direction of the bias would be toward the null and could not account for our results.

Misclassification of smoking behavior is a potential problem. As reflected in the studies we considered, there are many ways to consider smoking, ranging from a simple classification of current or ever smoking status to more sophisticated measures of lifetime smoking by amount and duration. Overall, the misclassification is likely to be non-differential and would probably bias the RR estimates toward the null.

Except for mortality, outcome misclassification is less likely in our review than exposure misclassification because outcome was based on the results of objective tests. However, some misclassification may have occurred in the results for infection status, particularly if positive results of tuberculin skin tests were caused by nontuberculous bacteria or by prior BCG vaccine. False-negative results can occur with recent TB infections in which tuberculin skin tests may have been performed before tuberculin conversion. It is unlikely that these factors would have substantially affected our results, and not consistently across countries and studies. Any resulting bias would be toward the null. The greatest opportunity for outcome misclassification may have occurred with the use of death certificates to record cause of death. There is a high rate of inaccuracy in recording of causes of death and much variability in methods for identifying the principal cause of death from death certificates. Again, the bias is likely to be toward the null.

Most difficult to quantify is the possibility of unadjusted confounding in the analyses. For example, alcohol consumption may have confounded the RR estimates for smoking and TB, as alcohol is more likely to be consumed by smokers, and findings from studies suggest that alcohol use is a risk factor for TB disease. Other investigators have suggested more generally that socioeconomic factors may be responsible for confounding. The studies selected for this review had wide variation in the degree of possible confounding that was taken into account, although eligibility for this review required that age and sex were treated as confounders. The extent of further adjustment ranged from no additional confounders to extensive multivariate adjustment. Our comparison of results in which adjustment was only by age and sex with results that included additional adjustment factors produced similar summary RR estimates, suggesting that residual confounding is unlikely to account for the elevated risks found.

In conclusion, our results suggest that tobacco smoking interacts with M tuberculosis complex to the extent of promoting infection and disease. Data for TB mortality are too limited and heterogeneous for inferences to be confidently drawn.
nosis and treatment of smear-positive TB cases under the DOTS strategy recommended by the World Health Organization in an attempt to interrupt transmission.\textsuperscript{43} The DOTS program has achieved a modest decline in TB rates, but its success appears to have plateaued.\textsuperscript{46} It is apparent that treating active disease is insufficient for population-based TB control and that there is an urgent need to address prevention.\textsuperscript{46} Although the new Stop TB Strategy\textsuperscript{47} goes beyond the traditional paradigm by addressing issues in addition to DOTS expansion, it does not address population-based preventive interventions. Potentially modifiable risk factors that lead to TB infection and disease, such as tobacco smoking, should be targeted using appropriate interventions. Clinicians and health care workers can use the information to better educate their patients about risks of smoking, especially in countries where TB and smoking rates are high. Moreover, if cigarette smoking is a risk factor for TB, it adds credibility to the hypothesis that high smoke exposures from biomass cooking fires may also be a risk factor.\textsuperscript{20,26,50}

Finally, because smoking has not previously been considered a TB risk factor, acceptance that it is a risk factor will have implications for the assessment of global mortality from tobacco consumption. For illustrative purposes, we offer a simplified (but reasonable) estimate based on assumptions that the RR for TB disease associated with smoking is 2.5, that there is no additional mortality risk from smoking in those who already have TB disease, and that 30% of the at-risk population are smokers. Simple attributable proportion calculations suggest that 31% of TB cases and TB deaths are attributable to smoking. Because worldwide there are approximately 9 million new TB cases and 1.7 million TB deaths each year, this proportion equates to an annual global burden of 2.79 million new TB cases and 527,000 deaths. If smoking increases the mortality rate in those with TB, then the number of deaths would be even higher. Further studies comparing mortality rates in smoking and nonsmoking patients with TB disease could resolve this issue. Irrespective of this, it is clear that smoking prevention and cessation efforts should be a priority in any TB prevention program.

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Author Contributions: Dr Bates had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bates and Khalakdina contributed equally to this work. The authors were responsible for the content of the manuscript and the decision to submit it for publication. Study concept and design: Khalakdina, Pai, and Smith. Acquisition of data: Bates, Khalakdina, Chang, and Lessa. Analysis and interpretation of data: Bates, Khalakdina, Pai, and Smith. Drafting of the manuscript: Bates, Khalakdina, and Smith. Critical revision of the manuscript for important intellectual content: Bates, Khalakdina, Pai, Chang, Lessa, and Smith. Statistical analysis: Bates, Khalakdina, and Pai. Obtained funding: Khalakdina and Smith. Administrative, technical, and material support: Khalakdina, Lessa, and Smith. Study supervision: Khalakdina and Smith.

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