Reviewer's report

Title: Alcohol as a risk factor for tuberculosis: a systematic review

Version: 1 Date: 17 March 2008

Reviewer: Annunziata Faustini

Reviewer's report:

COMMENTS TO THE AUTHORS

MAJOR COMMENTS

The authors carried out a systematic review to estimate the strength of the association between alcohol and tuberculosis (TB) and to determine if a causal nature of this association is adequately supported in the scientific literature.

After searching PubMed for papers dealing with alcohol or alcoholism and TB (n.2007), the authors selected 21 papers among those that analysed alcohol as a risk factor for TB. They found a three-fold risk increase of TB associated with high-level alcohol exposure (drinking more than 40g of alcohol per day or a diagnosis of alcoholism).

INTRODUCTION

The introduction provides sufficient information about both the TB risk among alcohol abusers and the possible biological mechanisms of alcohol on TB disease.

METHODS

1. The methodology of the Search Strategy was somewhat limited.
   - The authors only searched PubMed of all the available electronic databases.
   - They did not search the archives of any journal that specialises in TB, such as the International Journal of Tuberculosis and Lung Diseases, or journals that focus on alcohol such as Alcoholism, clinical and experimental research or the Journal of Alcohol Studies, or the WHO documents.
   - It is not clear how they used the systematic review on tobacco and TB: did the authors refer to the methods of this review or use the information about the covariates?
   - The authors have to define clearly the inclusion criteria as well as report the exclusion criteria with particular attention to the steps between the initial 2007 abstracts detected in PubMed and the final inclusion of 21 studies.
   - The possible limits used in the search are not reported; I refer specifically to the original language and the time interval.
   - The authors have to report the number of papers they excluded according to each criterion; summary tables of the papers excluded have to be prepared as additional documents available on demand.
- There is no mention of any quality score for the papers.

2. Apart from the methodological problems of the search strategy, which may be easily addressed by the authors, there are more important methodological problems that affect this revision.

2.1. The first basic problem deals with the authors’ choice of studying the risk factors for “TB disease” as a unique outcome. The term “TB disease” is used in the inclusion criteria for selecting papers, but actually it is clear that different manifestations of TB disease were included. Because this disease is a complex phenomenon, it is necessary to distinguish clearly the different characteristics or phases of TB and the corresponding risk factors to be studied in terms of causality.

This result may be obtained either by separately analysing different TB outcomes and alcohol exposure (as the review on tobacco and TB did), or analysing heterogeneity according to these characteristics. Three points have to be addressed:

a) infection and clinical onset of TB are associated with different causal factors. The authors themselves reported in the introduction the different ways alcoholics can be affected by the infection or the onset of clinical TB: social interaction patterns among alcoholics increase the probability of infection, while a break-down of the immune system due to alcohol abuse may contribute to the development of full-blown TB.

b) The occurrence, the clinic course and the factors that cause an initial TB differ from those that induce TB relapse.

c) Finally, factors associated with pulmonary TB differ from factors associated with extra-pulmonary TB.

2.2. Another basic problem deals with other criteria of causality any study of the association has to respect.

The authors were careful to study a dose-response relationship, and in fact they analysed high-exposure and low-exposure categories of alcohol consumption. However, the time relationship between exposure and outcome has not been accurately addressed. In some studies, such as those by Brown, Buskin, Dong, Riekstina, the timing of alcohol consumption was not reported while other studies like Lewis’s specify the amount of time elapsed between alcohol consumption and infection.

I suggest that the timing of alcohol exposure should be specified in any study, including in studies that define it at the same time of disease onset. A sensitivity analysis estimating the pooled effect after excluding these latter studies could contribute more to the discussion on the causal relationship.

Study assessment and analysis

I think that only 17 studies fulfilled the inclusion criteria, instead of the 21 reported by the authors. The reason is that the definition of exposure was defined
as the “individual level data on alcohol consumption, therefore the five studies “that did not report how exposure has been defined” should not be included at all.

I suggest that the authors report these 5 studies in a separate table as excluded studies, together with those excluded for having a small number of cases and high standard errors (SE).

This solution would help also to identify the excluded studies more easily that are not clearly presented. Of those five studies, the one by Schluger includes only 20 cases and classified alcohol consumption as “current, past or never”, which was presumably judged inadequate to attribute the high/low alcohol exposure in this study. On the other hand the same classification is reported in two other studies (Crampin and Lienhardt) that were apparently included in the analysis. The three studies with few cases and high SEs are possibly those authored by Mori, Spletter and Riekstina, but Schluger includes only twenty cases, and it is unclear why his study was included.

The authors reported that they had assessed heterogeneity with the Q statistic. However, the authors showed also the I2 in table 2; this is a good decision, but please report and explain this choice in the methods.

RESULTS

Please correct the reported number of studies included in the text to match the information in table 2 (see comments in the previous paragraph); I also suggest that the authors add to the text that the pooled effect reported for the high-exposure category was estimated from 11 studies and for the low-exposure category it was estimated from 6 studies.

I suggest dividing table 1 in two: one table to list the excluded studies and the other to list the 13 studies included (14 assuming the double reporting for Brown’s study). The authors have to clearly report the exclusion criteria in the former table.

Please highlight in figure 1 the excluded studies with different indicators of the exclusion criteria and report in figure 2 the first author’s name of the studies, at least in the notes.

Please check the results reported in table 2 on the third to last line (excluding the three smallest and Brown 1 and Kim): the pooled estimates are the same for fixed and random effect models. Now this is more likely for the group of pulmonary TB only, that includes two studies only and does not show heterogeneity than for the former group reported on the third to last line.

After the exclusion of the three smallest studies, heterogeneity decreased but was not completely explained. Among the possible explanations of heterogeneity due to the TB characteristics, the only one the authors analyzed was “pulmonary TB only” versus “all types of TB”.

First of all, I think the second group includes “all the other types of TB” excluding pulmonary cases since we know that there were a total of 8 studies (2 in the first
group and 6 in the second). The results show that there was no heterogeneity for pulmonary TB, while it was high for the other forms of TB. The authors underlined that the pooled estimates for the two categories did not differ statistically. I think the most important aspect of these results is that the heterogeneity of the other type of TB, apart from pulmonary TB, was very similar (both Q and I²) to that of the all high category exposures, suggesting that this group explained the whole heterogeneity observed at the beginning.

I suggest that the authors complete this analysis by showing the forest plot for the 11 high-exposure studies and for the two groups identified using the site of the TB lesions.

I suggest also that the authors carry out the same analysis by stratifying the studies into incident and relapse TB cases.

In the results, the authors report that the pooled estimate was not affected by heterogeneity after excluding two more papers with the highest and the lowest effect. Apart from the fact that the authors did not present this possible step in the methods, I think that the methodological choice to analyze heterogeneity is wrong and not useful to explain heterogeneity from an epidemiological point of view. This last step was only inspired by statistical criteria and was adopted to get a more precise pooled estimate, however it does not help to explain or present their hypothesis regarding heterogeneity.

DISCUSSION

1) The comments the authors made about controlling for confounding the association between alcohol and TB disease apply both to residual confounding and to the possible inverse causation between socio-economic status (SES) and alcoholism.

One possible approach to clarify these problems is to include only longitudinal studies since these are theoretically able to better measure the exposure and to detect the time relationship between outcome and cofactors.

I suggest that the authors discuss the differences between the cohort and the case-control studies (have they estimated a pooled effect according to the study design ?). Moreover, a sensitivity analysis could help by comparing the pooled estimates of the four studies that included SES among cofactors, when SES was included and excluded from cofactors.

2) The hypothesis made by the authors on page 9 of an increased risk of progressing from infection to TB disease is not supported adequately by the studies they analyzed. These studies included both incident and relapse TB, but since relapse indicates the recurrent form of TB due to a reactivation of internal infection, the factors that influence the reactivation differ from those of an infection and cannot be controlled for by using information on first infections.

I suggest that the authors analyze incident and recurrent TB separately; otherwise, they cannot discuss this point.

3) The direct toxic effect of alcohol on the immune system cannot be discussed
here because there are no studies that report related results. What is known from the literature is correctly reported in the introduction.

4) The previous comment is valid also for the topic of specific social mixing among alcoholics. None of the papers included in the revision deal with TB clusters or molecular-epidemiology.

5) The comparison between fixed and random effect models refer to the size of the studies, it does not refer to the setting of the studies. The random model may control the pooled estimate for the studies’ size but this choice is not always the best.

In this respect the authors have to explain which pooled measure they prefer. This point is not adequately explained in the paper. For example, in the results the authors mostly report the fixed pooled effect, but when they discuss infection status they refer to the pooled random effect.

6) No explanations at all were discussed for the heterogeneity.

7) I think the only conclusion the authors can reasonably present based on the results of the meta-analysis is the general estimate they found between alcohol consumption and TB disease.

MINOR COMMENTS

page 4. the low exposure category is defined as alcohol use below (not above) the cut-off point set at 40g (or 50 ml).

recurrent TB would have to be used instead of relapse because the latter term usually refers to the reactivation of a latent infection while recurrent TB also includes re-infections of Mycobacterium tuberculosis.

One of the studies reported in table 1 (Mori is the first author) was carried out in an Native Indian Reservation. Out of curiosity, we know that alcohol metabolism differs in this ethnic group. Do you consider if there is any impact in analysing alcohol as a risk factor for TB disease?

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.