Reviewer's report

Title: Alcohol use, alcohol use disorders and incidence and disease course of tuberculosis (TB) - is there a causal connection? A systematic review.

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Reviewer: Annunziata Faustini

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Alcohol use, alcohol use disorders and incidence and disease course of tuberculosis (TB) – is there a causal connection? A systematic review.

BMC_Central II revision

I made many initial comments in the first revision of this manuscript about the methods used to select studies for a systematic review intended to study the causal relationship between alcohol use disorders and TB incidence. While I have noted the many improvements the authors have made to their draft, I have still a few reservations about the methods used for the systematic review (the causal relationship between alcohol and TB is still the topic of the paper, as the title shows).

In their answer to the reviewers, the authors reaffirm they referred to a previous review for the causal criteria. This previous paper by Lönnroth et al., which discussed a causal relationship between alcohol and TB, was careful to select only studies such as cohorts and case-controls, that allow determining if the factors studied increase the probability of developing TB. In contrast, in this manuscript the authors included studies designed to estimate the prevalence of AUD among TB patients, where TB illness may have anticipated alcohol use at great length. These prevalence studies in which the temporal relationship between the exposure and the outcome is not clearly defined, do not permit a discussion of causality. Moreover, the exclusion criteria generically refer to “not having sufficient data” (page 4 and figure 1); nothing is said about the quality of these data.

In contrast, the studies included in the review by Lönnroth et al. were assessed with respect to: (1) the outcome definition, (2) the method to detect the outcome, (3) the exposure definition. The term “outcome” by definition indicates a temporal relationship between a risk factor and the consequent disease; on the other hand, the authors discussed the possible misclassification due to the case-controls studies that are likely to be biased about temporal relationship exposure/outcome.

The authors of this manuscript were not asked to expatiate on causal criteria but to use methods for the systematic review that allow them to discuss a causal relationship between alcohol and TB. To avoid further discussion, I suggest that the authors conduct an operational exercise: they should title the 3rd column in the tables 1 and 2 as “study design and study population” instead of the actual
“sample/cohort” that may misrepresent the study design; the population is already described but the explicit definition of the study design allows a better evaluation about the adequacy of the selected studies.

Two other observations on this point are:

- It is not clear why the authors refer often to the methods used in the previous study by Lönnroth et al., for specific points like the formal test of consistency (page 9), because the reviews differ in the specific topic and inclusion criteria (only 9 studies are included in both the reviews). Moreover the authors here did not apply many methodological steps they cited in their text. Thanks to the repeated references to the previous review, I think it could be interesting if the authors explain what this manuscript adds to the topic of causal connection between alcohol use and TB, since this manuscript is not a simple continuance of the previous study.

- The authors discuss the causal relationship on the basis of meta-analysis of the literature. The revision of causal association is a completely separate contribution and no specific methods are given regarding the parameters of this search. It is still not clear how the systematic review of TB prevalence studies may contribute to the causal relationship.

**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 have no competing interests