Reviewer’s report

Title: Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis

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Reviewer: Peter Byass

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Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis

This paper makes an innovative attempt to model global estimates for liver cirrhosis mortality, using the GBD platform as a basis for the data and modelling.

The major conceptual difficulty with the paper is the choice of liver cirrhosis as its specific focus. As pointed out on page 3, the case definition of liver cirrhosis is not entirely standardised or unanimously agreed. On top of this, there is clearly a huge global variation in terms of how deaths in general are registered, and specifically how individual causes of death are assigned. We know from much other work that across Africa and Asia most deaths are not certified by physicians, and so cause of death information, such as there is, relies heavily on sometimes questionable verbal autopsy (VA) findings. We also know from other work that some of the highest infectious hepatitis incidence rates and chronic infectious hepatitis carriage prevalence rates – which are risk factors for various kinds of liver disease - are found in Africa and Asia, where causes of death are generally least certain. These problems are discussed inconclusively in your penultimate paragraph, but remain as a serious methodological difficulty for this paper.

Major compulsory revisions

1. Against this background, my first specific recommendation is to expand Table2 into a useful entity. I want to see it split by GBD region, so that we can easily see how the various regions studied actually relied on various combinations of VR and/or VA data.

2. We then need some more serious discussion about the validity with which VA methods may or may not be able to separate liver cirrhosis, liver cancer and acute infectious hepatitis deaths. I looked briefly in the PHMRC VA dataset to see whether it might be able to address this question there – but without much success, because there although there are about 290 cases of cirrhosis, there are only 30 cases of liver cancer, and infectious hepatitis deaths are presumably subsumed under “other infectious diseases”. Thus it is hardly possible to determine from this whether there are distinct differences in VA history and symptomatology between different kinds of fatal liver disease. Do the authors have any better ideas on this problem?
3. I also looked at the numbers of liver-related deaths in GBD 2010. Globally in 2010 the GBD team estimated 307,700 deaths from infectious hepatitis, 752,100 from liver cancer (most of which were secondary to hepatitis B and C infections), and 1,030,800 from liver cirrhosis (also mostly secondary to hepatitis B and C infections). This overall panorama of liver disease needs to be seen explicitly in this paper. More fundamentally, I would rather see the paper re-written to include all these categories of liver disease, since at least there would be much more certainty around estimating the overall liver disease envelope, as a platform for more speculative conclusions about sub-classifications of liver disease (and possible mis-sub-classifications, particularly in areas relying on VA).

4. There are some statements in the paper which involve a degree of circularity in referring to other GBD work, for example in places where other GBD 2010 findings are cited in a way that suggests they back up the findings of this paper. Of course they do: they use very similar data and methods, done by the same team! These citations need rewording for clarity.

In conclusion, I am really not convinced that all the “liver cirrhosis” modelled in this paper is actually not a complex mis-classified mix of various liver diseases. A completely new paper looking at the overall spectrum of fatal liver disease would be far more informative and, at least at the overall level, much less subject to misclassification biases. This would also enable a more holistic view to be taken of risk factors such as hepatitis infections and alcohol consumption which act across various categories of liver disease.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.