Reviewer's report

Title: Association between bilirubin and cardiovascular disease risk factors: Using Mendelian randomization to assess causal inference

Version: 3 Date: 18 January 2012

Reviewer: Frank Dudbridge

Reviewer's report:

Although the authors responded to all the reviewer’s comments, several comments marked as "major compulsory revisions" did not result in changes to the paper. Therefore, the following points should be referred back to the authors:

1. Referee 1 #1 “F statistic of one degree of freedom is equivalent” - not an accurate response; an F statistic has a pair of df, and while there is equivalence between F and its p-value given sample size and number of instruments, the actual value of F has a useful interpretation as a measure of instrumental strength. Therefore, this simple revision should be made.

2. Referee 1 #3, I found this response to be generic, and it did not address the main point which is that the brachial artery MR association is discussed at length, yet there was no observational association. This is the reverse of the usual situation in which MR negates a significant observational association. One could imagine a whole range of phenotypes without observational associations which could be "mined" by MR - the fact that this association survived multiple testing correction is only a result of the limited number of phenotypes measured. At least, the authors ought to recognise (in the text) that the MR association occurs in the absence of an observational association, which must imply less posterior belief than if there had been an observational association.

3. Referee 3 #1 "We report uncorrected p-values and the reader is thus able to make the corrections felt appropriate" - this position is defensible, but ought to be written out in the text, not just in the author response.

Level of interest: An article whose findings are important to those with closely related research interests

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