Reviewer’s report

Title: Association of cholesteryl ester transfer protein (CETP) gene polymorphism, high density lipoprotein cholesterol and risk of coronary artery disease: A meta-analysis using a Mendelian randomization approach

Version: 1 Date: 27 May 2014

Reviewer: Chao Xing

Reviewer’s report:

In this paper the authors aimed to investigate the causal relationship between HDL levels and risk of CAD by a Mendelian randomization approach using a CETP polymorphism as the instrumental variable.

The authors seem skilled in performing conventional meta-analysis—association between genotype and CAD in this paper. However, the Mendelian randomization meta-analysis part is not well calibrated.

Major compulsory Revisions:

1) Since the Mendelian randomization meta-analysis is the major selling point of the paper, as claimed in title, abstract, and introduction, I suggest redoing the Mendelian randomization meta-analysis and rewrite the relevant parts. In the current version, the majority is on the conventional meta-analysis of association between genotype and CAD, whereas the more important Mendelian randomization meta-analysis slight.

2) The issue of unbalanced proportions of different meta-analyses is related with the method the authors employed. In the current version, the Mendelian randomization meta-analysis is a naïve version that simply plugging in the estimates from association analysis of genotype-CAD and genotype-HDL. An integrated approach that takes into account of characteristics of each study (e.g. which studies provide both genotype-CAD and genotype-HDL association, and which studies provide only one of them) should be employed, as suggested by Minelli et al. (AJE 2004, 160:445-452), which was cited by the authors.

3) On the genotype-HDL association analysis, it’s unclear why only Caucasian studies were employed? An integrated analysis will possibly circumvent potential problems.

4) The conclusion is over-simplified if not arbitrary. The results of OR=0.79, 95% CI: 0.54-1.03, P=0.08 shouldn’t be simply concluded as no association. A well-calibrated Mendelian randomization meta-analysis may give more insights. Given the marginal significant results, a power analysis is worthwhile.

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