Reviewer’s report

Title: Lack of association of two common polymorphisms on 9q21 with risk of coronary heart disease and myocardial infarction

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Reviewer: Qing Kenneth Wang

Reviewer’s report:

1. Is the question posed by the authors new and well defined?
Dehghan et al studied two SNPs, rs1075278 and rs1075274, on chromosome 9p21 for their association with CHD and MI in a very large prospective cohort of 7,983 individuals involved in the Rotterdam Study. The two SNPs associated with CHD and MI were identified by genome-wide SNP association studies. For a complex trait like CHD and MI, a positive finding should be validated by as many replication studies as possible. Thus, the question posed by the authors is appropriate and well-defined.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
The method used in the study is the strength of the manuscript. Many studies on 9p21 SNPs employed standard case-control association studies. Dehghan et al, on the other hand, employed a different approach, the prospective study. The 7,983 participants were started at baseline and followed up for 9.8 years. The Cox proportional hazards analysis was used to estimate the risk of 9p21 SNPs. The two 9p21 SNPs did not increase risk of CHD and MI. Although the results are negative, they offer a very interesting perspective on 9p21 CAD/MI SNPs and should be of considerable interest to the field.

3. Are the data sound and well controlled?
The sample size is large and the data are solid.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
The discussion is not complete. The authors should provide a comprehensive discussion of all publications related to the study topic. In particular, several recent positive replication studies were not discussed or cited.

population.


6. Do the title and abstract accurately convey what has been found?
Yes

7. Is the writing acceptable?
yes

Please make your review as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

â¢ Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. It is possible that the small odds ratios of 9p21 SNPs that can account for the lack of detectable risk of CHD and MI for these SNPs in a prospective study. The authors argue that the old age may be the main reason, but positive association was found in some populations with similar ages.

â¢ Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The authors made an error about the position of the SNPs. They are on 9p21, not on 9q21 as stated in the title and other places. This again emphasizes the importance that the authors should read relevant papers and ensure the accuracy of information form other papers.

2. Please add a column to show P values in Table 1.

â¢ Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. As discussed in #5, a comprehensive discussion or introduction should be
provided and recent publications by other groups should be discussed and cited.

2. Discussion, 4th and 5th paragraph: The authors should examine whether the lack of the family history of CHD and MI may be another factor for the negative result. In the recent J Hum Genetic publication, Shen et al. found that if the whole cohort was divided into those with family history and those without, the association was detected only in the sub-cohort with family history.

**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an article of outstanding merit and interest in its field

**What next?:** Accept for publication in BMC Medicine after minor essential revisions

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.