Author's response to reviews

Title: Genotype-Informed Calculation of Risk of Coronary Heart Disease Based on Genome-Wide Association Data Linked to the Electronic Medical Record

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Author's response to reviews: see over
Reviewer #3

1. The authors refer us to a reference related to how good the use of ICD 9 coding was (i.e. accuracy of phenotyping). Would recommend actually providing some information on how good this was. Given many readers will not have access to or will not bother looking it up, it would be useful to state if the phenotyping accuracy was good/average etc.

Most of the cardiovascular risk factors and comorbidities were captured from the EMR by ICD-9-CM codes with an accuracy of over 90%, comparing EMR with manual medical record review [1]. We have incorporated this statement in the revised manuscript (Page 3, paragraph 2).

2. I feel that either I do not get what the authors are stating or they are not getting what I am stating with reference to my point #6 of my review. Again, despite having a risk score of ~12 (i.e. “12 risk alleles”) one could have a lower risk. This to me suggests that the genetic risk score is weak and if the authors agree perhaps worth a mention in the limitations.

The entire premise of genetic risk scores for common diseases is based on the fact that such risk alleles have modest effects. We have quantified this in the results section by stating the 25th and 75th percentile of the odds ratio (0.77 and 1.26), corresponding to the presence of 11 and 14 risk alleles, respectively. In addition we made the following statement in the discussion section (Page 10, paragraph 2):

“The common variants identified in GWAS have modest effect sizes and explain only a small proportion of heritable risk.”

Reference: