Author's response to reviews

Title: The contribution of a 9p21.3 variant, a KIF6 variant, and C-reactive protein to predicting risk of myocardial infarction in a prospective study

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Author's response to reviews: see over
Dear Doctor,

We are submitting our revision to the manuscript entitled “The contribution of a 9p21.3 variant, a KIF6 variant, and C-reactive protein to predicting risk of myocardial infarction in a prospective study” for your consideration.

This manuscript investigates whether the addition of genetic information (the 9p21.3 or KIF6 variants) or a well-established non-genetic risk factor (C-reactive protein) can improve risk prediction by the Framingham Risk Score in the Cardiovascular Health Study. We evaluated improvement in risk prediction by change in the area under the receiver operator characteristics curve and by net reclassification improvement. We found that while none of these risk markers individually or in combination improved risk prediction among women, a combination of KIF6 719Arg carrier status and CRP levels modestly improved risk prediction among white men.

We have modified the manuscript to address the comments in the Reviewers’ Reports. We have provided a point-by-point response to each of these comments and indicated how we modified the manuscript to address the reviewers’ comments.

We hope that you find this revised manuscript suitable for publication in BMC Cardiovascular Disorders.

Sincerely,

Dov Shiffman, PhD
Reviewer: Seamus Harrison
Reviewer’s report:
The reference to Northwick Park Heart Study II is incorrect; 9p21 did not improve the AROC significantly.

We agree with Dr. Harrison that Talmud et al. reported that in the Northwick Park Heart Study II adding 9p21 genotype information did not improve the area under the ROC curve. Talmud et al. did report improvement in reclassification. We have now corrected the text in the Background and Discussion section to reflect this fact as follows:

Background section now reads:

“The results of these studies have been mixed, one study found that adding 9p21.3 to a traditional risk factor-based model improved the area under the receiver operator characteristic curve (AUC) as well as patient reclassification [8], a second study found improvement in reclassification, but not in AUC [9], while a third study found that 9p21.3 did not improve either AUC or patient reclassification [10].”

Discussion section now reads:

“However, in ARIC [8] the addition of 9p21.3 to the FRS resulted in a modest but statistically significant improvement in risk prediction as measured by AUC or reclassification, and in the Northwick Park Heart Study II [9] adding 9p21.3 improved reclassification but not AUC.”

Reviewer: Benjamin D Horne
Reviewer’s report:
Shiffman and colleagues evaluated three predictors of CHD risk in the Cardiovascular Health Study.

Major compulsory revisions:
1. The improvement in the FRS with addition of KIF6, CRP, and 9p21 is minimal in the best cases of the results presented here. Given that the FRS did not predict risk as well as it does in other populations (AUC is less than 0.60 for men, just above 0.60 for women), it is not clear whether these markers improve on the FRS or they improve risk prediction in a population to which FRS does not apply well.

We are grateful to Dr. Horne for his insightful comment. We have now modified the limitation paragraph of Discussion section to reflect this limitation as follows:

“This study has several limitations. The AUC of the FRS model for white men (0.581) and white women (0.619) in this study of older individuals is lower than the AUC that has been reported for middle age populations (e.g., 0.75 and 0.83
among white men and among white women in ARIC [2]), thus the markers we studied may only improve risk prediction in populations in which the ability of the FRS to predict CHD is modest.”

2. The study presents the results for many models for multiple biomarkers, combinations of the biomarkers, and multiple populations including for males and females. Some level of correction for multiple comparisons is in order. It is interesting to note that even correction for just 3 comparisons (p=0.05/3 as the corrected threshold for significance) makes most of the results with p<0.05 become non-significant (i.e., p>0.01667). It appears that a more cautious interpretation of the results is that these biomarkers are not predictors of CHD outcomes in an older population.

We have modified the Discussion section of the abstract, and the conclusion paragraph of the discussion to indicate that after multiple-testing correction, none of the results would be statistically significant, as follows:

Abstract now reads:

“Conclusions: While none of these risk markers individually or in combination improved risk prediction among women, a combination of KIF6 719Arg carrier status and CRP levels modestly improved risk prediction among white men; although this improvement is not significant after multiple-testing correction. These observations should be investigated in other prospective studies.”

Discussion now reads:

“In conclusion, in the white male population of CHS, the addition of KIF6 719Arg in combination with 9p21.3, CRP, or both modestly improved risk prediction. This improvement was not significant after multiple-testing correction and was not observed in the combined male and female population.”

Minor essential revisions:
1. The application of KIF6, 9p21, and hsCRP to an older population is also a limitation that should be addressed in the limitations section.

We have modified the limitation paragraph of the Discussion to indicate the older age of the study population as follows:

“Lastly, the effect of these single and multiple marker additions on risk prediction was investigated in a population of individuals aged 65 or older at baseline and our observations may not be generalizable to younger populations.”

Discretionary revisions:
1. Were the characteristics of those participants who declined to have their DNA used in studies by private companies and were thus excluded from this study systematically different than the characteristics of those who were included?
We agree with Dr. Horne that this is an interesting question, and the CHS Coordinating Center could propose this analysis as a CHS ancillary study. However, we feel that investigating this question is beyond the scope of this manuscript because our goal is not to show that our results are generalizable to the entire specific CHS cohort but simply to investigate these markers in an elderly cohort, while adjusting for baseline characteristics.

2. The date of censoring was June 30, 2006. Given that more than 4.5 years have now passed, it may improve the risk differentiation to obtain current follow-up outcomes data so that the study has many more cardiovascular events to evaluate.

June 30th 2006 was the latest censoring date available when funding for these analyses was available. While it would be interesting to extend this analysis to the next censoring date, such a proposal would need to be submitted to a future funding cycle.