Author's response to reviews

Title: Smoking, alcohol consumption, physical activity, and family history and the risks of acute myocardial infarction and unstable angina pectoris: a prospective cohort study

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Version: 4 Date: 25 October 2010

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

Thank you for the opportunity to re-revise and resubmit our manuscript ‘Smoking, alcohol consumption, physical activity, and family history and the risks of acute myocardial infarction and unstable angina pectoris: a prospective cohort study’ (adjusted title according to the comments of one of the reviewers).

You can find our detailed reply on the comments of the reviewers in the attachment. Furthermore, the changes made in the manuscript are in red font, using underlining for added words or strikethrough for deleted words.

We hope that you are satisfied with the revisions and that this manuscript will now be acceptable for publication in your journal.

Yours sincerely,

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Reviewer's report:

Title: Do smoking, alcohol consumption, physical activity, and family history have different effects on the risks of acute myocardial infarction and unstable angina pectoris? A prospective cohort study

Version: 3 Date: 11 September 2010
Reviewer: Yariv Gerber

Reviewer's report:
I have read the manuscript for several times now. Although the authors have clearly attempted to address most of the reviewers' concerns in their revised version, the manuscript still does not stand at the level deemed suitable for original contribution by this reviewer. The reasons are several, most importantly these findings are not novel and the manuscript is not coherent in presentation and lacks a well-developed hypothesis.

Major Compulsory Revisions:

* The manuscript is lengthy, many times redundant (for example, sample size is reported 3 times in Methods), not well organized and the writing is wordy and needs improvement.

In the manuscript, we deleted the following information from the methods to remove the redundant information about the sample size:

Page 7, line 16 “At baseline, all participants (n=21,662) filled in a self-administered questionnaire on demographics, medical history, family history of MI, and lifestyle factors such as smoking, alcohol consumption, and physical activity.

Page 8, line 16, “Of all participants the 21,662 persons that were included in this study, 21,148 subjects (97.6%) had given written informed consent to retrieve information from Municipal Population Registries and their general practitioner or specialist.”

Furthermore, we added headlines within the results and discussion sections, so that the manuscript may be better organized.

* The title of the paper does not match the findings. I am still not convinced that the associations differ between MI and UAP. Moreover, MI is obviously less prone to misclassification than UAP, possibly affecting the observed coefficients.

Because the title may imply that there are differences in the effects of the lifestyle factors and family history on the risk of AMI and UAP, while this difference was only present for smoking, we changed the title of our manuscript as follows:

“Do smoking, alcohol consumption, physical activity, and family history have different effects on the risks of acute myocardial infarction and unstable angina pectoris? A prospective cohort study”

* The Abstract's conclusion is ambiguous.

We changed the conclusion within the abstract as follows:
Page 4, line 3 “**Conclusions:** Changes in the prevalences of these lifestyle factors may benefit the primary prevention of both AMI and UAP. The strength of the associations with the lifestyle factors did not differ between AMI and UAP, except for smoking. Furthermore, the effects of the lifestyle factors on the risk of both coronary diseases were similar for subjects with and without a positive family history.”

* The number of references should be cut down by half. For example, why should one use 16 references to state that lifestyle factors have been linked to CHD risk?

The number of references is cut down to a total of 52 references.

* The manuscript should focus on a single, more developed hypothesis (currently there are just too many, eg, different CHD entities, various risk factors, family history, gender, etc).

This manuscript indeed describes more than one research question. However, it was a well-considered choice not to submit multiple manuscripts each on one specific hypothesis but to combine the results into one manuscript. The advantage of this, for the reader, is that it gives a comprehensive overview of the results of lifestyle factors within one cohort study. Apparently, this amount of information was not raised as an issue by the editor and second reviewer. Therefore, we decided to maintain the amount of information within this manuscript.

* The 43% study response rate should be discussed.

In our prospective cohort study, the response rate was 43% which is common for this kind of studies. Furthermore, as Rothman stated in his epidemiological handbook ‘Modern Epidemiology’: “selection of study groups that are representative of larger populations in the statistical sense will generally not enhance the ability to abstract universal statements from observations, but selection of study groups for characteristics that enable a study to distinguish effectively between competing scientific hypotheses will do so” [1]. So, one of the goals in the selection of the study population in cohort studies is to have a large variation in the exposure status of the cohort members instead of having a representative study population. Furthermore, the completeness of follow-up is more critical in prospective cohort studies. In our study, only twelve participants were lost to follow-up and also the cardiologic follow-up is expected to be nearly complete.

In the manuscript, we added the following sentences to the discussion:

Page 15, line 22 “The response rate of this prospective cohort study was 43%, which is not uncommon for this kind of studies. Furthermore, a large variation in the exposure status is more important to investigate etiological associations than having a representative study population. In prospective cohort studies, the completeness of follow-up is essential. In this study, during follow-up, only twelve participants (0.1%) were lost to follow-up.”

* P. 15 "The results in this prospective study are probably not influenced by selection or information bias"... This should be definitely removed.

We removed this sentence from the Discussion section on page 15.
* p. 16 "Furthermore, this misclassification would have attenuated the differences in effects between AMI and UAP". Again, I am disagree.

The potential misclassification of the outcome in our study is expected to be non-differential. In the handbook ‘Modern Epidemiology’ by Rothman and Greenland it is described that non-differential misclassification of the disease outcome will produce bias towards the null and may bias the risk difference downwardly [2]. Using the same reasoning, an interchange between the diagnoses of AMI and of UAP will decrease the differences in risk ratios of these two coronary diseases.

To clarify this in the manuscript, we changed the concerning paragraph as follows:

Page 16, line 9 “During follow-up, more sensitive screening tests became available for the diagnosis of AMI which may have led to misclassification of the outcome decreased the interchange between a diagnosis of AMI and of UAP. This misclassification interchange would have attenuated the differences in effects between AMI and UAP. However, as mentioned above, the way in which the AMI and UAP cases were identified is probably more accurate than using data from other registries such as hospital discharge registries [34]. Furthermore, no change in the ratio between the number of cases diagnosed with AMI and with UAP was seen before and after the introduction of the screening tests.

* Tables should be cut down in number and presented in a more effective and interpretable manner.

We acknowledge that the number of tables is large. However, we added brief summaries to the legend of every table to guide the reader through the data. As both the editor and the other reviewer have no problem with the amount of data presented in the tables, we decided to maintain the number of tables in our manuscript.
Reviewer's report:

**Title:** Do smoking, alcohol consumption, physical activity, and family history have different effects on the risks of acute myocardial infarction and unstable angina pectoris? A prospective cohort study

**Version:** 3  **Date:** 18 August 2010  **Reviewer:** Marcus Dörr

**Reviewer's report:**

My only specific comment refers to the first answer concerning the differences between AMI and UAP: The authors state that “The clinical presentation of patients with AMI or UAP depends on the degree of occlusion of the coronary artery. In case of an AMI, the coronary artery is completely and persistently occluded by a thrombus after plaque disruption. In case of UAP, however, the occlusion is caused by a labile thrombus that may not completely occlude the coronary artery or may lead to an early re-opening of the artery.” This statement is (partially) true for the comparison of UAP and STEMI. Differentiation between UAP and NSTEMI, however, is much more complicated. In many cases, underlying pathophysiology of UAP and NSTEMI may be quite similar and the only difference is elevation of myocardial enzymes (see ESC definition of MI and my second comment of the first review). Thus, the respective paragraph should be written more carefully. Over all, Merry et al. have addressed the important review questions and have modified the manuscript accordingly. I like very much the idea of adding brief summaries to the table legends. This makes it much easier to focus on the most important findings (Indeed the amount of data presented in this manuscript is extraordinary large, although I did not mention this point in my first review).

*We agree that the difference between STEMI and UAP may be more evident than between NSTEMI and UAP. Unfortunately, because complete data on ECG abnormalities is not available at the moment we were not able to distinguish between STEMI and NSTEMI. In the manuscript, we changed the paragraph in the introduction as follows:*  

Page 5, line 11. “The clinical presentation with UAP or AMI, especially ST elevation myocardial infarctions (STEMI), or UAP depends on the degree of occlusion of the coronary artery. Thrombotic and fibrinolytic processes may play a role in this difference in pathophysiology. Studies have shown that lifestyle factors are associated with haemostatic disturbances affecting these processes [22-24], which suggests that the strength of the associations with etiological factors may be different for UAP and AMI, in particular STEMI and UAP.”
References
