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

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**Reviewer:** Marcus Dörr

**Reviewer's report:**

Merry et al. analyzed longitudinal data of more than 19,000 participants of the CAREMA study (16.9 years of follow-up). The study aim was to investigate whether the associations of smoking, alcohol consumption, and physical activity with UAP differed from those with AMI and whether these effects differed between subjects with and without a family history of myocardial infarction. The authors demonstrated that these risk factors indeed affected the risk of both AMI and UAP while the strength of the observed associations was mostly stronger for AMI. In contrast, the association with family history of MI was stronger for UAP.

This is a careful and well designed study. The statistical methods used are appropriate. The manuscript is well written and easy to follow. Nevertheless, there are some important points to answer:

- **Major Comments**

  - The research question should be explained more precisely. It is not obvious, why it is important to distinguish between AMI and UAP, particularly since the conclusions are the same for both diseases: (primary) prevention and modification of lifestyle-related risk factors.
  
  - The definition of AMI used did not differentiate between STEMI and NSTEMI. According to the redefinition by the ESC/ACC in 2000 ( ) STEMI and NSTEMI can be considered as two distinct pathophysiological entities, representing STEMI a transmural event and NSTEMI a sub-endocardial one. However, it has been demonstrated that patients with STEMI and NSTEMI have similar in-hospital and long-term prognoses as well as similar independent correlates of outcome, despite different management strategies (i.e. ). I wonder whether it would be possible to distinguish between these two entities of AMI? It seems likely that STEMI and NSTEMI differ with respect to the associated risk profiles. If differentiation between STEMI and NSTEMI is not doable it should be discussed whether separate analyses could have affect led to different results.

  - In the method section it is stated that “Participants with CHD at baseline (n=347) … were excluded from the analyses”. In contrast, table 2 shows that 69 UAP cases had a previous AMI (during follow-up?). Moreover, “End of follow-up was determined by a clinical diagnosis of the disease, …”. These statements are confusing and appear self-contradictory.
- Assessment of data on alcohol consumption and physical activity: There is nor information given which (standardized!) questionnaires were used. Which efforts have been made to reduce potential misclassifications, i.e. with respect to “sick quitters” for alcohol consumption? The higher number of “never-drinkers” among the cases might be a subtle hint for such bias. Any limitations related to this issue should be reported and discussed.

- If I have understood correctly, multivariable adjustments for smoking and alcohol consumption did not include physical activity but the models for physical activity were adjusted for both smoking and alcohol consumption. All adjustments should be done consistent across the different phenotypes and models.

- The conclusions of the study should be made a little more carefully. I agree that in face of the presented data (and that of previous studies) one can assumed that patients would benefit from more extensive prevention with respect to smoking, alcohol consumption and physical activity. However, the present study did not investigate whether these parameters improve risk prediction independent from the variable used in current risk scores neither this was an intervention trial which provides evidence for the hypothesis of an improved outcome.

• Minor Essential Revisions

- Abstract, methods: I would suggest to report the age range of study subjects instead of the years of birth.

- Abstract, results: „In men, the association with...“. This sentence should be worded more precisely (positiv/negative association?, compared to...?).

- Introduction, last sentence: Please check wording („risk factor“ instead of „risk“?).

- Methods: The authors should report more details on the recruitment methods/strategies of their study population.

- Page 7, first sentence: „i.e.“ can be deleted.

- Page 8: Death registries were used for case identification using the ICD coding. Was this assessment made by a single person and (how) were these cases validated? This process should be reported more in detail. My particular concern is that misclassification of UAP cases should have been present. How was this excluded?

- Page 10, first paragraph: What does “no large difference” mean? Please check the wording.

- Page 10, last paragraph: Was there a similar effect modification seen for AMI? A more detailed presentation of these data should be considered.

- Page 12, line 8: “..., while the opposite is true for UAP”: What does “opposite” mean in this context. Please clarify and change this paragraph accordingly.

- Page 12, second paragraph: It is stated “For occupational physical activity, the highest risks of AMI and UAP were found in subjects with a positive family history and a moderate to heavy activity level (table 7).” This true only in men (large CI in women; ns).
In women, however, there seemed to be a synergistic effect between non-occupational activity and family history for the risk of AMI, ... Please clarify that this interaction leads to an increased risk of AMI.

References:

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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