Author's response to reviews

**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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**Version:** 3  **Date:** 13 August 2010

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

Thank you for the opportunity to revise and resubmit our manuscript ‘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’.

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 and underlined.

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

Yours sincerely,

Audrey H.H. Merry, MSc
Department of Epidemiology,
Maastricht University
The Netherlands
Reviewer: Yariv Gerber

Reviewer's report:
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

In this study, Merry et al. examine whether the association between selected life style factors and CHD risk differs by disease manifestation (MI vs. UAP) and by family CHD history. All in all the paper is relatively well written and the main study questions are legitimate. However, the paper is somewhat difficult to follow, as too much information is provided along the text and tables. This information should be presented in a more parsimonious manner. In addition, there are several points that need further clarification.

Specific Comments:

- What is the validity of self-reported smoking, physical activity and diet in this population? Did the author conducted any validation studies?

The study participants were retrieved from two large monitoring projects in the Netherlands: the Monitoring Project on Cardiovascular Risk Factors (PPHVZ) and the Monitoring Project on Chronic Disease Risk Factors (MORGEN). Several studies investigated the reproducibility and validity of the questionnaires used within these projects.

In the PPHVZ project, a short semi-quantitative food frequency questionnaire was used to measure the dietary habits of the participants. Bloemberg et al. [1] assessed the validity of this questionnaire in a subsample of 203 men and women aged 20-59 years by comparing the estimated amounts from the food frequency questionnaire with the amounts measured from a dietary history method developed by Burke [2]. For alcohol consumption, the difference between these two methods was larger than 10 percent [1].

In the MORGEN project, which is the Dutch component of the European Prospective Investigation into Cancer and Nutrition (EPIC), the reproducibility and relative validity of both the extensive and food frequency questionnaire were tested within the BALANS-study [3-5]. Compared with 12 monthly 24-hour recalls as reference method, the relative validity of the food frequency questionnaire seemed adequate for ranking participants according to their consumption of alcohol beverages (Spearman rank correlation coefficients 0.74 in men and 0.87 in women) [3]. In the study by Pols et al. [5], the short questionnaire to measure physical activity within the MORGEN project was compared with a 3-day activity diary. They found that the questionnaire was suitable for ranking participants according to their physical activity level.

To my knowledge, no validity studies have been performed on the self-reported smoking data within our study population. However, in a meta-analysis by Patrick et al. [6], high sensitivity and specificity estimates were found when self-reported smoking data were compared with biochemical measures, especially in the presence of some study characteristics such as observational design and reports by adults.

So, there may have been some misclassification of exposures. However, because the exposure measurements were performed before the occurrence of the disease, we expect this misclassification to be non-differential. As a result, the estimated risks in our study may have been attenuated.
To address this issue within the manuscript, we added the following sentences to the Discussion:

Page 16, line 15 “In this cohort study, family history and the life style factors were self-reported by the participants, which may have led to exposure misclassification. However, several studies have shown that self-reported data can be used quite accurately to define family history [49-51] and smoking status [53]. In addition, Pols et al. have shown that the questions on physical activity in the MORGEN study were suitable for ranking the participants according to their physical activity level [54]. Because the exposure measurements took place before the occurrence of the disease, the misclassification is probably non-differential [55]. Therefore, the use of self-reported data has probably not biased our results to a great extent.”


Please also see our answer on the fourth comment of reviewer 2 on page 11-13.

- *Is the estimated validity of UAP diagnosis similar to that of MI? Differences might affect the observed results.*

In our study, non-fatal cases with acute myocardial infarction and unstable angina pectoris were based on the clinical diagnosis made by experienced cardiologists, caring for the patient and registered in the Cardiology Information System (CIS). This clinical diagnosis was mostly based on the report to the general practitioner. The additional information in the CIS, for example ECG and echo findings and catheterisation results were used to investigate whether the patient’s characteristics and clinical signs were in agreement with the diagnosis. In case of doubt, the cardiologic information of the subject was discussed with an experienced cardiologist involved in this study (AG). If not enough information was available in the CIS, especially for early events (1980’s), the patient’s records were retrieved. After the completion of the registration from CIS, the cardiologist (AG) performed several quality controls to check the registered information in the CIS-based registry.

Among the AMI cases with a clinical diagnosis in the CIS, about 77% fulfilled the diagnostic criteria of the European Society of Cardiology and the American College of Cardiology [7]. The remaining 23% of the cases had incomplete data to test against these criteria. Although we acknowledge that the diagnosis of UAP is less well-defined than the diagnosis of AMI, 80.4% of the UAP cases underwent a coronary angiography. In only three cases, no coronary abnormalities (>50% stenosis in at least one coronary artery) were found, while in only two cases the results of the CAG were unknown. Nevertheless, these five cases all had typical chest pain and four of them had ECG abnormalities. Among the remaining 19.6% of the UAP cases without a registered CAG, only one case had neither typical chest pain nor ECG abnormalities. Furthermore, in only four cases (1% of the total number of UAP cases) no information on these symptoms was available.
Because the identification of AMI and UAP cases were performed in the same manner and because of the high prevalence of disease-specific signs and symptoms among the cases, we expect the validity of the UAP diagnosis to be similar to that of the AMI diagnosis.

- **Statistical analysis:** I am uncomfortable with the adjustment for PPHVZ/MORGEN cohort. Using a shared-frailty Cox model to account for possible intra-cohort correlation is recommended.

Because our study population is derived from two monitoring projects, we added the variable ‘study at baseline’ to the Cox proportional hazards models to adjust for possible differences between the two cohorts. In most Cox models, however, the effect of this variable was non-significant (p > 0.05). To investigate whether it makes any difference if we used a shared-frailty Cox model, we compared the risk ratios (RRs) from our models using study at baseline as covariate with shared-frailty Cox models for the endpoint total CHD, which consists of both AMI and UAP cases. We found no differences between the RRs from the two statistical methods (table 1). In addition, the likelihood-ratio test of $H_0$: $\theta = 0$ showed a non-significant frailty effect (p = 0.50).

Because no differences were found between the models with study at baseline as covariate and the shared frailty Cox models, we believe that our method is also accurate and can be maintained in the manuscript.

**Table 1 Multivariable Adjusted Rate Ratios according to two different analytic methods.**

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Cases / person-years</th>
<th>Model with baseline study as covariate</th>
<th>Shared-frailty Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Never</td>
<td>121 / 70,666</td>
<td>1 reference</td>
<td>1 reference</td>
</tr>
<tr>
<td>Ex</td>
<td>193 / 54,638</td>
<td>1.33, 1.05, 1.68</td>
<td>1.33, 1.05, 1.68</td>
</tr>
<tr>
<td>Current</td>
<td>435 / 84,269</td>
<td>2.38, 1.93, 2.94</td>
<td>2.38, 1.93, 2.94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Cases / person-years</th>
<th>Model with baseline study as covariate</th>
<th>Shared-frailty Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Never</td>
<td>115 / 26,819</td>
<td>1 reference</td>
<td>1 reference</td>
</tr>
<tr>
<td>Ex</td>
<td>21 / 2,676</td>
<td>1.01, 0.63, 1.61</td>
<td>1.01, 0.63, 1.61</td>
</tr>
<tr>
<td>Occasionally</td>
<td>140 / 48,218</td>
<td>0.91, 0.71, 1.17</td>
<td>0.91, 0.71, 1.17</td>
</tr>
<tr>
<td>Regular</td>
<td>473 / 131,859</td>
<td>0.67, 0.53, 0.83</td>
<td>0.67, 0.53, 0.83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-occupationally PA</th>
<th>Cases / person-years</th>
<th>Model with baseline study as covariate</th>
<th>Shared-frailty Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None to light</td>
<td>198 / 30,536</td>
<td>1 reference</td>
<td>1 reference</td>
</tr>
<tr>
<td>Moderate to heavy</td>
<td>309 / 57,503</td>
<td>0.93, 0.77, 1.12</td>
<td>0.94, 0.78, 1.13</td>
</tr>
</tbody>
</table>

|                       |                  |                                        |                          |
| **Women**             |                  |                                        |                          |
| None to light         | 73 / 45,070 | 1 reference | 1 reference |
| Moderate to heavy     | 116 / 59,466 | 1.48, 1.09, 2.01 | 1.49, 1.10, 2.02 |

<table>
<thead>
<tr>
<th>Number of parents affected</th>
<th>Cases / person-years</th>
<th>Model with baseline study as covariate</th>
<th>Shared-frailty Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>No parents affected</td>
<td>428 / 146,858</td>
<td>1 reference</td>
<td>1 reference</td>
</tr>
<tr>
<td>One parent affected</td>
<td>268 / 56,244</td>
<td>1.49, 1.28, 1.73</td>
<td>1.48, 1.27, 1.73</td>
</tr>
<tr>
<td>Both parents affected</td>
<td>51 / 5,977</td>
<td>2.12, 1.58, 2.85</td>
<td>2.11, 1.58, 2.83</td>
</tr>
</tbody>
</table>

CI, confidence interval; PA, physical activity; RR, rate ratio.
Rate ratios adjusted for age at baseline (years), sex, total alcohol consumption (glasses/day), diabetes mellitus (yes/no), level of education (primary school/junior vocational education, secondary vocational education or vocational college/university), and family history of premature myocardial infarction (yes/no).

- **Statistical analysis:** why was education the single SES measure accounted for? Other measures may be important as well. Using education only leaves uncertainties as to residual confounding.

Socioeconomic status (SES) can be measured by the educational level, occupation, and the income. In the baseline questionnaires, data were assessed about the occupation and highest educational level of the participants as indicators of their SES. No data were available about the income of the participants. In a previous study by Hoeymans et al. [8] within the study population of the Monitoring Project on Cardiovascular Risk Factors (PPHVZ), education was found to be a better predictor of health than occupation because of which they used education as the single SES measure. This suggests that the same may be true for CHD as outcome measure.

In addition, a disadvantage of occupation as SES measure is its validity in women. We assume that, especially in the earlier years of our study, only few women were employed (particularly in the older age categories) as traditionally in those years many women did the housekeeping. Therefore, using occupation as indicator for SES would result in a considerable amount of missing data. Furthermore, occupation may underestimate SES as women more often worked part-time and probably had fewer career opportunities within a company. Therefore, it was not possible for us to use other measures than education as indicators of SES. However, because education was found to be a better predictor of health than occupation [8], we expect the amount of residual confounding by other SES measures such as occupation to be small.

- **Cases are relatively young. This should be acknowledged and discussed.**

In this study, the cohort members were relatively young at baseline (20-59 years). Consequently, cases were diagnosed at a relatively young age (mean age at diagnosis: 56.5 years for the AMI cases and 58.4 years for the UAP cases). This may have affected our risk estimates. As the baseline risks of these coronary diseases increase with an increasing age, the difference in absolute risks between exposed and unexposed participants become relatively smaller, resulting in a lower RR. Therefore, the RRs in our study may be higher compared to other studies in which the study population and cases are relatively older.

To address this issue in the manuscript, we added the following sentences to the Discussion:

Page 17, line 3 “The participants included in this study were relatively young at baseline (20-59 years). Consequently, both the AMI and UAP cases were diagnosed at a relatively young age. This may have affected the RRs. As the risks of these coronary diseases increase with an increasing age, the difference in absolute risks between exposed and unexposed participants become relatively smaller, resulting in a lower RR. Therefore, the RRs in our study may be higher compared to other studies in which the study population and cases are relatively older.”

- **The manuscript lacks formal comparisons of the HR estimates (e.g., MI vs. UAP). I am currently uncertain whether all interpretations are correct (at least statistically).**
We performed additional analyses to evaluate differences in the risk estimates of AMI and UAP using the competing risks procedure in Stata. The results of these analyses show that a statistically significant difference between AMI and UAP was only present for the associations with smoking.

In the manuscript, we added the following sentences to the Materials and methods.

Page 11, line 1 “Tests for heterogeneity were performed to evaluate differences between the two coronary diseases (AMI versus UAP) using the competing risks procedure in Stata. However, the standard error for the difference of the log-RRs from this procedure assumes independence of both estimated RRs which would overestimate the standard error and thus overestimate the p-values for their difference. Therefore, these p-values and the associated confidence intervals were estimated based on a bootstrapping method. The log-RRs were obtained from the bootstrap samples using Stata’s competing risks procedure and recalculated for each bootstrap-replication. The confidence interval and p-value of the differences in RR between AMI and UAP were then calculated from the replicated statistics using the accelerated bias corrected method in Stata. Each bootstrap analysis was based on 1,000 replications.”

Furthermore, we added an extra column to the tables containing the p-value for the heterogeneity test between the endpoints AMI and UAP and added the following footnote to the legend of table 3 to 6: “Heterogeneity test for the difference in the RRs between AMI and UAP. The p values were similar for the models with and without adjustments for intermediates.” The second part of the footnote was not necessary for table 6.

- The results of physical activity are somewhat counterintuitive and suggest either selection or information bias.

We agree that our results of physical activity did not meet our expectations. However, we do not expect that this is due to either selection or information bias. In a prospective cohort study, selection bias can result from exposure-related loss to follow-up. In our study, only 12 participants (0.1%) were lost to follow-up, because of which selection bias is unlikely. In addition, selection bias may have occurred when migration of participants to municipalities outside the study region or to a foreign country is related to the exposure level. Although these participants were younger compared with participants who stayed living in the study region, no large differences were found in the number of smokers, regular alcohol consumption, and physical activity levels.

Furthermore, differential misclassification can be the cause of information bias in a prospective cohort study. However, because the exposure measurements took place before the occurrence of the disease the misclassification is probably non-differential. Another potential source of bias is reverse causation. When subjects have complaints such as chest pain, they may limit their amount of physical activity. However, this type of bias would strengthen a protective effect of physical activity, while we found physical activity to be a risk factor in some subgroups. Furthermore, the risk estimates did hardly change when we excluded the first year(s) of follow-up (data not shown). Therefore, reverse causation is also unlikely.

Although we have no clear explanation for our counterintuitive results of physical activity, possible reasons, mentioned in the manuscript on page 19, are residual confounding, the
limited contrast in the activity level between the comparison groups as subjects with a light activity level were included in the reference group, or chance.

- **I would suggest reducing the number of tables and amount of information and presenting the data in a more readily interpretable form.**

We acknowledge that the amount of data and the number of tables is quite large. However, because the second reviewer and the editor both had no problems with providing such detailed information, we decided to maintain the number of tables. Nevertheless, we followed the suggestion of the editor to include a brief summary of the main message in the footnote of table 3 to 7.

In the manuscript, we added the following footnotes to table 3 to 7:

Page 40, legend table 3: “Table summary: Smoking increased the risk of both AMI and UAP. Dose-response relationships were seen with the number of cigarettes smoked per day and the number of smoking years although this trend was less obvious for the latter. All RRrs were significantly higher for AMI than for UAP (p heterogeneity <0.03). Furthermore, the risks of AMI and UAP decreased the longer ago subjects quitted smoking.”

Page 43, legend table 4: “Table summary: Alcohol consumption was associated with a protective effect on the risk of both AMI and UAP, which was independent of the type of alcoholic beverage consumed. These associations seemed to be stronger for the risk of AMI than of UAP although not statistically significant (p heterogeneity >0.05).”

Page 45, legend table 5: “Table summary: Occupational physical activity seemed to be a risk factor for both AMI and UAP in men, while in women it was associated with lower risks of both coronary endpoints. However, these associations were only statistically significant in men for the risk of AMI after adjustment for possible intermediates. Non-occupational physical activity seemed to be protective in men, while it was found to be a risk factor in women, although these associations were only statistically significant for the risk of AMI in women. Associations seemed to be stronger with the risk of AMI than of UAP, although not statistically significant (p heterogeneity >0.05).”

Page 47, legend table 6: “Table summary: A positive family history is associated with increased risks of both AMI and UAP, especially when both parents are affected or when they are diagnosed at a younger age (premature MI). These associations seemed to be stronger for the risk of UAP than of AMI but the differences were not statistically significant (p heterogeneity >0.05).”

Page 49, legend table 7: “Table summary: None of the interactions between family history of premature MI and the life style factors smoking, alcohol consumption, and physical activity were statistically significant on a multiplicative scale for both AMI and UAP, except for occupational physical activity and the AMI risk in women (p interaction 0.03). Nevertheless, the highest risks of both coronary endpoints were found in subjects with both a positive family history and the most unfavorable level of the life style factors.”

- **Conclusions: given the observational nature of the data, it is impossible to deduce cause and effect relationships. Moreover, I am still not convinced that the associations indeed differ materially between MI and UAP. More sound data are required for such a strong conclusion.**
We agree that based on the results from one study, cause and effect relationships cannot be deduced. However, based on the results of previous studies, a cause and effect relationship is more likely. Furthermore, we have found clear dose-response relationships between smoking, alcohol consumption, and family history and the risks of both AMI and UAP, which strengthen the existence of such relationship. Nevertheless, more research is needed to elucidate these associations, especially for the risk of UAP. Therefore, we changed the formulations of our conclusions in the manuscript so that they are less definite.

Page 20, line 8 “In this prospective cohort study, smoking, alcohol consumption, and physical activity affected the risk of both AMI and UAP. However, the strength of these associations seemed to differ between these two coronary diseases in which they were mostly stronger for AMI, although the differences in risks were only statistically significant for smoking. Opposed to this, the association with family history of MI seemed to be stronger for UAP. Nevertheless, more research is needed to elucidate these associations, especially for the risk of UAP. Although no synergistic effects on a multiplicative scale were found between the life style factors and family history, the highest risks were found in subjects with both a positive family history and the most unfavorable level of the life style factors. Therefore, future studies should evaluate whether changes in the prevalences of these life style factors result in lower incidence rates of AMI and UAP and thus benefit the primary prevention of both coronary diseases, especially in subjects with a positive family history.”

Please also see our answer on the last major comment of reviewer 2.

To evaluate whether the strength of the associations with the life style factors differed between AMI and UAP, we performed heterogeneity tests and added the p-values to the tables in the manuscript (also see our answer on your comment on page 5/6).
Reviewer 2:

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 investigated 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 clinical presentation of patients with AMI or UAP depends on the degree of occlusion of the coronary artery [9, 10]. 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. Thrombotic and fibrinolytic processes may play a role in this difference in pathophysiology. Studies have shown that smoking is associated with an increased activity and adhesion of platelets, higher fibrinogen levels, and decreased fibrinolytic activity [11]. On the contrary, moderate alcohol consumption, which is a protective factor for the coronary endpoints, has been associated with reduced levels of fibrinogen and a thrombolytic profile [12, 13] favouring the occurrence of an incomplete or temporarily occlusion by a labile thrombus. Because of these haemostatic disturbances, the life style factors may be stronger related to the occurrence of AMI compared with that of UAP. Furthermore, only few studies have investigated the associations between the risk of (unstable) AP and smoking [14, 15], alcohol consumption [16-20], and physical activity [21-23]. To elucidate further the relationship between the life style factors and the risk of UAP and to see whether these associations indeed differed in strength between AMI and UAP, we investigated the effect of smoking, alcohol consumption, and physical activity on the risks of AMI and UAP as separate outcomes.

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

Page 5, line 12 “The clinical presentation with AMI 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 life style factors are associated with haemostatic disturbances affecting these processes [32-34], which suggests that the strength of the associations with etiological factors may be different for AMI and UAP.


Page 6, line 1 "To elucidate further the associations between life style factors and the risk of UAP and to see whether these associations indeed differ in strength between AMI and UAP, the objective of this study was to investigate the effects of smoking, alcohol consumption, and physical inactivity on the risks of AMI and UAP as separate endpoints."

- The definition of AMI used did not differentiate between STEMI and NSTEMI. According to the redefinition by the ESC/ACC in 2000 (49) 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.

Because STEMI and NSTEMI have been regarded as distinct pathophysiological entities by the ESC/ACC definition, it would be interesting to investigate the effects of the life style factors and family history on the risks of these outcomes separately. Unfortunately, we were not able to distinguish between STEMI and NSTEMI in our analyses because complete data on ECG abnormalities is not available at the moment.

Therefore, we added the following sentences to our Discussion:

Page 16, line 7 “According to the redefinition of AMI by the European Society of Cardiology and the American College of Cardiology [49], ST elevation myocardial infarctions (STEMI) and non-ST elevation myocardial infarctions can be considered as separate pathophysiological entities. This may suggest that the associations with the life style factors may differ between STEMI and non-STEMI. As no sufficient data on ECG abnormalities was available at the time of the statistical analyses to distinguish between STEMI and non-STEMI, separate analyses for these subtypes of AMI could not be performed within this study.”


- 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.

In a prospective cohort study, participants have to be at risk of the disease at the beginning of the study. Therefore, we excluded the 347 participants with CHD at baseline, which refers to the date they were included in the study.

In this study, we performed separate analyses for AMI and UAP. For each of these endpoints, incident cases were defined according to the first occurrence of that specific coronary disease, irrespective of the occurrence of the other coronary disease. As a result, an UAP case may have had an AMI during follow-up before the diagnosis of UAP, which is shown in table 2. So, these cases were free of CHD at baseline but developed both coronary events during follow-up. Furthermore, disease-specific calculations of the person time at risk were made with the diagnosis date of AMI as end of follow-up for the Cox models on AMI and the diagnosis date of UAP for the Cox models on UAP. As a result, the total amount of person time at risk differed between the analyses for AMI and UAP.

However, in time, we realized that ignoring other coronary events in the definition of incident cases is not appropriate as the risk of a ‘second’ coronary event, even if this is another subtype of CHD, may have changed due to interventions/medication for the first CHD event. Therefore, we have changed our definition of incident cases in the manuscript so that an incident AMI case is only taken into account if this is the person’s first CHD event during follow-up. The same goes for UAP; a subject is only defined as an incident UAP case if this event is the person’s first CHD event during follow-up.

As a result, follow-up ends at the time of the diagnosis of the person’s first CHD event, resulting in a similar total amount of person time at risk in the analyses for AMI and UAP.

In the manuscript, we made the following adaptations according to these new definitions:

Page 8, line 23 “Incident cases of AMI and UAP were identified in two ways, 1) by linkage to the Cardiologic Information System (CIS) of the University Hospital Maastricht (UHM), and 2) by linkage to the causes of death registry of Statistics Netherlands. Using the CIS, incident cases with AMI or UAP were based on the first recorded clinical diagnosis during follow-up.”

Page 9, line 18 “End of follow-up was determined by a clinical diagnosis of AMI, UAP, a coronary bypass artery grafting, or a percutaneous coronary intervention, migration out of the Maastricht region, emigration, death, or censoring at December 31st 2003, whichever occurred first. Person-time at risk was calculated from baseline until end of follow-up.”

Page 38, table 2: the information on the medical history in table 2 is now not applicable anymore and we have, therefore, removed this information from the table.

Page 39 to 49, table 3 to 7: the risk estimates of AMI and UAP in these tables have been adapted according to the changed definitions of AMI and UAP in the analyses.

In addition, we also changed the description of the results in the sections Abstract, Results, and Discussion if necessary.

- Assessment of data on alcohol consumption and physical activity: There is no 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.

In both monitoring projects (PPHVZ and MORGEN), from which our study participants were retrieved, these factors were measured by self-administered questionnaires. Several studies investigated the reproducibility and validity of these questionnaires.

In the study by Bloemberg et al. [1], the validity of the short semi-quantitative food frequency questionnaire used in the PPHVZ project was assessed by comparing the total amounts of energy and nutrients intake from this questionnaire with the amounts measured from a dietary history method developed by Burke [2]. They found that the differences between the two methods were not larger than 10 percent, except for alcohol consumption [1]. For this variable, the consumption measured by the food frequency questionnaire was lower compared with the consumption estimated by the dietary history method.

In the MORGEN project, which is the Dutch component of the European Prospective Investigation into Cancer and Nutrition (EPIC), the reproducibility and relative validity of both the extensive and food frequency questionnaire were tested within the BALANS-study [3-5]. In the study by Ocké et al. [3], the Spearman rank correlation coefficient as measure for the relative validity was calculated between the food frequency questionnaire and a 12 monthly 24-hour recalls as reference method. For alcoholic beverages, this relative validity was 0.74 in men and 0.87 in women. When the food frequency questionnaire was compared with a 24-hour recall (reproducibility), it was found that men significantly underreported their alcohol consumption, while women more adequately reported their amount of alcoholic beverages consumed.

Furthermore, the short questionnaire to measure physical activity within the MORGEN project was compared with a 3-day activity diary in the study by Pols et al. [5]. They found that the questionnaire was suitable for ranking participants according to their physical activity level.

Especially for alcohol consumption, there may have been some misclassification of exposure. Nevertheless, because ex-drinkers were included into the analyses as a separate category, we expect that the amount of bias by ‘sick quitters’ is small. Furthermore, because the exposure measurements were performed before the occurrence of the disease, we expect the misclassifications to be non-differential. As a result, the estimated risks in our study may have been attenuated.

We made the following changes in the Discussion section of the manuscript to address this issue:

Page 16, line 18 “In addition, Pols et al. have shown that the questions on physical activity in the MORGEN study were suitable for ranking the participants according to their physical activity level [54]. Because the exposure measurements took place before the occurrence of the disease, the misclassification is probably non-differential [55]. Therefore, the use of self-reported data has probably not biased our results to a great extent. However, two validation studies within subsamples of our study population found that the amount of alcohol consumption was underestimated by the food frequency questionnaire [56, 57]. This misclassification may have resulted in an underestimation of the effect of alcohol consumption in our study.”
Please also see our answer on the first comment of reviewer 1.

- 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 models for smoking and alcohol consumption were indeed not adjusted for physical activity. The main reason for this is that physical activity is not a confounder in the relationship between these factors and the risk of AMI and UAP as it did not change the risk estimates with more than 10% after adjustment (<2% change for both the models on smoking and alcohol consumption). Furthermore, to be a confounder a variable has to be associated with the risk of the disease outcome, while we have not found a clear association between physical activity and the risk of the coronary endpoints in our study population.

Therefore, we have decided not to include physical activity as a confounder in the models for smoking and alcohol consumption.

- 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.

We made the following adaptations in the conclusion of our study:

Page 20, line 17 “Therefore, future studies should evaluate whether changes in the prevalences of these life style factors result in lower incidences rate of AMI and UAP and thus benefit the primary prevention of both coronary diseases, especially in subjects with a positive family history.”

Minor Essential Revisions:

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

We changed the following sentence in the abstract, so that it includes the age range at baseline instead of the years of birth.
Page 3, line 9 **Methods:** The CAREMA study consists of 21,148 persons, aged 20-59 years at baseline and randomly sampled from the Maastricht region in 1987-1997.

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

We changed this sentence in the abstract of the manuscript as follows:

Page 3, line 17 “In men, an inverse association was found with physical activity during leisure time which seemed to be stronger for the risk of UAP than of AMI. On the contrary, physical activity during leisure time was associated with an increased risk of both AMI and UAP in women which seemed to be weaker for UAP than for AMI.

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

To clarify this sentence, we changed it as follows:

Page 6, line 6 “In addition, we investigated whether the associations between the life style factors and the risks of AMI and UAP differed for people with and without a family history of premature MI.”

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

Page 7, line 6 “Between 1987 and 1997, a new random sample of people aged 20-59 years was selected each year from the population registries of Maastricht and surrounding municipalities, i.e. Eijsden, Margraten, Meerssen, and Valkenburg aan de Geul. These samples were stratified according to sex and 5-year age groups to obtain equal numbers in each age category. From 1987 until 1997, 21,662 men and women were included in this study (response rate 43%).”

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

In the manuscript, we deleted “i.e.” in this sentence and replaced it with a colon:

Page 8, line 1 “For alcohol consumption, subjects were asked to report their drinking frequency: never, ex, occasional (<1 glass/week), or regular (≥1 glass/week).”

- **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?**

In our study, the causes of death were retrieved from the national causes of death registry of Statistics Netherlands. Statistics Netherlands contains information on all Dutch inhabitants who deceased. In the Netherlands, the physician who declares a person’s death is legally liable to send the death certificate including a certificate with the cause of death to the registrar of the municipality where the person deceased. In addition, the cause of death certificate is sent to Statistics Netherlands. The encoding of these ‘cause of death’ certificates by Statistics Netherlands occurs according to the guidelines of the World Health Organization.
using the International Classification of Diseases (ICD). In case of indistinct or incomplete data, the concerning physician is contacted for more clarity. To guarantee the quality of these data, quality controls and corrections are made by Statistics Netherlands for all of the primary causes of death and, to a lesser extent, for the secondary causes of death [24]. In this study, we included both the primary and secondary causes of death which increases the probability that all cases that died from the coronary heart disease were included.

Still, we acknowledge that the validity of causes of death might be a problem for cardiovascular diseases. However, some studies in the Netherlands showed that the validity of the registration and coding of causes of death by Statistics Netherlands is above average compared with several other European countries [25, 26]. Furthermore, only a small proportion (10%) of the cases in the CIS-based registry was retrieved only from the causes of death registry of Statistics Netherlands. Therefore, any misclassification of cases according to the cause of death will only minimally influence our risk estimates.

To clarify this issue in the manuscript, we added the following sentences to the Methods section:

Page 9, line 5 “From the causes of death registry of Statistics Netherlands, all incident cases were identified using the following International Classification of Diseases (ICD-) codes: ICD-9 410 and ICD-10 I21-I22 for AMI; ICD-9 413 and ICD-10 I20 for UAP. Statistics Netherlands receives the death certificate including a certificate with the cause of death for all Dutch inhabitants who deceased. This certificate is filled in by the physician who declares a person’s death. The encoding of these cause of death certificates by Statistics Netherlands occurs according to the guidelines of the World Health Organization using the International Classification of Diseases. In case of indistinct or incomplete data, the concerning physician is contacted for more clarity. To guarantee the quality of these data, quality controls and corrections are made by Statistics Netherlands for all of the primary causes of death and, to a lesser extent, for the secondary causes of death.”

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

Because no differences were seen in the median number of glasses/day consumed among regular drinkers between the cases and the total cohort, we deleted ‘large’ in this sentence:

Page 12, line 5 “Besides slightly higher percentages of never drinkers among the cases, no differences were found in the median amount of alcoholic beverages consumed.”

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

Because of the changed case definition in the statistical analyses (please see our answer on your comment on page 10), the interaction on a multiplicative scale between age at baseline and the smoking status for the risk of UAP was not statistically significant anymore (p interaction 0.053). For the risk of AMI, this interaction was also not statistically significant.

As already much information is given within the tables, we have chosen to only describe the results on possible effect modifiers within the text. However, because the above finding, we have decided to delete the following paragraph from the Results section:
Age at baseline was an effect modifier on a multiplicative scale in the association between smoking status and the UAP risk. In the age category 20-45 years, current smokers had a 3.0 times higher risk compared with never smokers, while this RR was 1.6 in the age category >45-60 years.

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.

In the manuscript, we changed this sentence as follows:

For AMI, the risk for current smokers without a family history was higher compared with ex-smokers with a family history, while the risk of UAP was higher for ex-smokers with a family history.

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).

Page 14, line 2 “For AMI, the risk for current smokers without a family history was higher compared with ex-smokers with a family history, while the risk of UAP was higher for ex-smokers with a family history.

Page 14, line 8 “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, although these risks were only statistically significant in men (table 7).”

Page 14, line 15 “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.

We added the following sentence to this paragraph to clarify the consequences of this interaction:

Page 14, line 15 “In women, however, there seemed to be a synergistic effect between non-occupational activity and family history for the risk of AMI with the highest risk for women with a positive family history and a moderate to heavy physical activity level, although this interaction was not statistically significant.”

References (reviewer 2):
2. G. Montalescot, J. Dallongeville, E. Van Belle, S. Rouanet, C. Baulac and A. Degrandtsart et al., STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry), Eur Heart J 28 (2007), pp. 1409–1417.
References


