Reviewer's report

**Title:** Cardiovascular risk estimated after 13 years of follow-up in a low-incidence Mediterranean region with high-prevalence of cardiovascular risk factors

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**Reviewer:** Jesus Esteban-Hernandez

**Reviewer's report:**

Manuscript: “Cardiovascular risk estimated after 13 years of follow-up in a low-incidence Mediterranean region with high-prevalence of cardiovascular risk factors”

Huerta and colleagues have performed a longitudinal retrospective-prospective population-based cohort study. Authors aims to estimate Hazard Ratio, Relative Risk and Proportional Atributable Risk for classical cardiovascular risk factors in Murcia, a region located in the Mediterranean context, with high prevalence of classical factors, but with still low burden of CVD. They found higher incidence than previously reported in similar epidemiological context for AMI. Most Ischemic Heart disease cases were mainly attributable to smoking, hypertension and hypercholesterolemia. They also report data on incidence of stroke.

Introduction:

Authors clearly identify the lack of prospective information in this geographical context.

Minor Essential Revisions

1. Page 3. 2nd par. Both, REGICOR [1] and SCORE [2] have been calibrations of Framingham and SCORE risk functions respectively, but only REGICOR have been validated [3] yet.

Methods

Major compulsory revisions

2. Please clearly state study design at the beginning of the methods section. It seems that there was no an scheduled prospective follow up, but a retrospective-prospective search of information. This design, retrospective-prospective cohort, has its own sources of bias, that should be briefly commented in the discussion section.

3. Statistical analysis.

   a. Authors affirm “Kruskall-Wallis o # test were used to assess statistical differences”. Though people with enough statistical knowledge probably know that kruskall-wallis should be used instead of Analysis of Variance when requirements (homoscedasticity, gaussian distribution of residuals for each group to be compared, and similar sample size of the groups to be compared) are not
satisfied, readers should be given enough information about what for the method was used (homogeneity of proportions, means,...) and which variables were included in the comparison, although this was not the main statistical issue of the analysis.

b. There is no mention about population (World, European) used in age-standardized rates estimates mentioned in the 1st paragraph of the discussion section.

c. Hazard Ratio and Relative Risk are quite different things. In this sense there is no mention about how RR was obtained from HR, or if it was estimated as a ratio of cumulative incidences.

d. Authors write “Due to the limited number of ....sex was used as a stratum in Cox model instead of presenting disaggregated results for men or women”. But sex is not an stratum, but a variable with two strata. Therefore all estimates are adjusted by age, but results are not “stratified” by sex, since there are not results by age and sex. Please also update table legends were “stratified by age and sex” appear.

e. In the methods section, authors explain how heterogeneity by sex has been estimated (likelihood ratio). How did authors compare heterogeneity by sex between models for angina, stroke and myocardial infarction? Please explain.

f. On the other hand prevalences of CV risk factors were obtained from an study where subjects recruited were aged 20 or more [4]. So that age and sex distribution, and probably other covariates distributions as well, is different from that in the sample for estimating Relative Risk. How this could affect PAR estimation? Did the authors use some kind of adjustment of their estimates? If not, please discuss (in the discussion section) how this could have an effect on your conclusions.

Minor Essential Revisions

4. Study sample: “all participants voluntarily agreed to take part in the study” Please confirm that they agreed to participate not only in cross-sectional [5], but also to be contacted again for the follow-up.

5. Variable definition.

a. I am aware that at the time when cross-sectional study [5] was carried out, cut-off for considering high risk total cholesterol in primary prevention was 6.5 mmol/l (NCEP-ATPII). Anyway authors have lipids concentration at recruitment. Why did the authors use the 6.5 mmol/l cut-off for hypercholesterolemia definition instead of the currently accepted of 6.1 mmol/l since NCEP-ATPIII guidelines publication [6].

b. Since definition of hypertension is based on measurements at recruitment in 1992, please confirm that those subjects who were already diagnosed and treated at the time of recruitment, were considered to have hypertension regardless their blood pressure levels were bellow threshold (140/90) when recruited. Same for hypercholesterolemia and hypertriglyceridemia. Please also update table legends.
c. Variables Educational level, and physical activity are not defined. These two variables are probably well describe in the article with results of the cross-sectional study [5]. But since this article is in Spanish, it would be convenient to include a brief description of them in this section. This is especially important for physical activity, since in Table 1 of the results section it is not clear whether there is one (with several levels) or two (moderate and intense) with several categories.

6. Statistical analysis
d. Authors stated that “no significant violations of the proportionality assumption were detected”. This means that there is no significant changes in covariates during follow-up, and this is essential for using Cox model instead time-dependent Cox models, where we can introduce covariate changes with time. Since we are working with cardiovascular risk factors, it is quite possible and probable that prevalence of covariates change, and what is more important, that the magnitude of changes is probably different between covariates. Could you please explain how did you evaluate proportionality assumption, and what did you actually find?

e. Authors clearly explain how they have obtained PAR. Although is clear in ref n.5, please, include in the text that prevalence for traditional risk factors come from the same region, Murcia.

Results

Well explained, maybe too short. But this depends on the format of the article (brief?). Anyway most results are well presented in tables.

Major compulsory revisions

7. Age-standardized rates are mentioned at the beginning of the discussion section, but not in the results sections.

Minor Essential Revisions

Discussion

8. Main finding is clearly stated, but as I write above, there is no mention to these important estimates (age-standardized rates) at the results section.

9. To make it more readable, it would be convenient to reorder the paragraphs putting together those about cerebrovascular disease, and those about ischemic heart disease. For example, paragraph n. 4 “virtually no data…” should finished at “…precludes direct comparisons with the present study.,” and moved after “…CV risk assessed for diabetes might be underestimated and should be considered with caution.” Since this paragraph is about AMI.

Major compulsory revisions

Since PAR depends on the prevalence of the condition, using cut-off 6.5 mmol/l for hypercholesterolemia could have artificially reduced PAR for this risk factor. Please discuss briefly.
10. About the effect of selection bias on the RR estimates, I believe that over or underestimation it is not due to the fact that “fewer hypercholesterolemics and more ever-smoklers among participants lost to follow-up...”. We cannot predict under or over-estimation of RR since we cannot ascertain the incidence ratio among those who were not eventually recruited. It doesn’t matter whether hypercholesterolemia is more or less prevalent among those lost to follow-up. The important issue is to know whether the relationship (ratio) between incidence of the event (AMI, angina, stroke) within hypercholesterolemic group and incidence among non hypercholesterolemic group keeps the same among those who were not selected. Since we don’t have this information (outcome) we are unable to predict the effect of this selection bias.

11. Please also include a brief discussion about whether and how information bias, mainly due to retrospective-prospective nature of the study, could have distorted association.

Minor Essential Revisions

12. Given that high proportion of subjects with missing values (775/3089, 25%) plus those lost at follow-up (291/3089, 10%), it should be advisable to include more information about baseline differences between those subjects that were eventually included and those who were not, in order to evaluate potential selection bias.

13. Authors affirm: “Virtually no data exist in Spain on the prospective association between CVRF and incidence of ischemic or cerebrovascular events”. Unfortunately there is no mention to age-standardized rates for stroke, neither at the beginning of the discussion, nor in the results section. Please provide.

Tables and figures

Table 2.

14. Too large. Many RR and 95%CI occupy several lines.

References

15. Reference n 18 . Title should be in bold.

16. Reference n 19 “Edited by” is repeated.

Reference List


3. Marrugat J, Subirana I, Comin E, Cabezas C, Vila J, Elosua R et al.: Validity of


**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests