Author's response to reviews

Title: Serum IL8 is not associated with cardiovascular events but with all-cause mortality

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Author's response to reviews:

Editor-in-Chief

BMC Cardiovascular Disorders

Dear Editor,

Enclosed please find a revised version of our manuscript (BCAR-D-18-00667) entitled “Serum IL8 is not associated with cardiovascular events but with all-cause mortality” we would like to submit for publication on BMC Cardiovascular Disorders.

In the revised version we have addressed all the comments raised by the two Reviewers. In particular, survival curves have been added to summarize the analysis results for all the outcomes presented in our manuscript.

The changes made throughout the manuscript are highlighted in yellow.

We hope that our work is now suitable for publication in BMC Cardiovascular Disorders.
Answers to Reviewer 1.

The Authors would like to thank the Reviewer for his/her positive review of our work and for his/her comments and suggestions that have certainly improved the quality of our work.

1. “Table 1 needs some improvements i.e. please depict percentages (quartile based) for categorical variables and provide statistics (e.g. chi-square or ANOVA) concerning associations between IL8 quartiles and variables depicted.”

According to the suggestion of both Reviewers, Table I has been completely re-written. In particular we have added the quartile boundaries for IL8, specified the dispersion measures used in the table, added the percentage of individuals with a specific risk factor within each IL8 quartile. In addition, we identified some mistakes in the reported values in the table. This has been corrected and we apologize for this inconvenience.

Since the Strobe guidelines [1] discourage the use of statistical analyses in the descriptive tables, we have added a short paragraph in the Results describing in details the main differences observed across the IL8 quartiles for the different risk factors (Results section page 10, paragraph 1, line 2).

2. “Kaplan-Meier curves should be presented for all outcomes analysed”

According to Reviewer’s suggestion, Kaplan-Meier curves have been reported for all the outcomes analyzed. Kaplan-Meier curves related to risk estimates reported in Table 2 have been added as Supplemental Figures II-IV; Kaplan-Meier curves related to risk estimates reported in Table 3 have been added as Supplemental Figures V-VII.
This is now clearly stated in the text. Results page 14, paragraph 1, line 7 and page 16, last paragraph, line 1.

3. “Power calculation should be provided in order to get estimates of effect sizes that may be detected in the studied population.”

The cohort of 60 years old from Stockholm was designed in 1996 to identify novel predictors (risk factors and biomarkers) of cardiovascular risk. Study participants have been followed up for 16 years now with 100% follow up and we have identified several biomarkers associated with the risk of CVE [2]. In addition our data are derived from a large cardiovascular cohort, as compared to the previous studies addressing the association of IL8 with the risk of CVE [3, 4] and with the risk of all cause mortality [5]. However we agree with the Reviewer that our study could be underpowered for the analysis of cancer related mortality.

To comply with the Reviewer comment, we have added a paragraph in the Discussion in the limitation section where we address this point: page 21, paragraph 1, line 7.

4. “Please provide values of IL8 level thresholds for quartiles in table 1”.

IL8 level thresholds for each quartile have been added to Table 1.

Answers to Reviewer 2.

The Authors would like to thank the Reviewer for his/her positive review of our work and for his/her comments and suggestions that have certainly improved the quality of our work.

1. “Intra-assay variability of IL8 was a quite large (5.8%) whereas the intra-assay variability was much smaller. How can you explain this? “

The inter-assay variability was calculated on pooled serum samples replicated in different plates (n=15) while the intra-assay variability was calculated from individual duplicate samples. No samples were excluded in the calculation of the intra assay variability.

Even though the intra assay variability is slightly higher than the inter assay variability, both coefficients are well below the limits suggested by the manufacturer of the assay used where
mean intra-assay coefficient of variation should not exceed 15% and mean inter-assay 18%. This is clearly reported in the Material and Methods, IL8 measurements section, page 8, second line.

2. “In Table 1 (results section) the data were presented to a limited extend. I would like to see more details, eg. besides numbers, percentage distribution of quantitative data in IL8 quartiles and statistical details of the comparative analyses. The Authors only very shortly summarized that "participants who were current smokers, had the largest daily alcohol consumption, had a history of diabetes and had a central obesity were more likely to have high IL8 levels". Are statistical significance were observed? “

According to the suggestion of both Reviewers, Table I has been completely re-written. In particular we have added the quartile boundaries for IL8, specified the dispersion measures used in the table, added the percentage of individuals with a specific risk factor within each IL8 quartile. In addition, we identified some mistakes in the reported values in the table. This has been corrected and we apologize for this inconvenience.

Since the Strobe guidelines [1] discourage the use of statistical analyses in the descriptive tables, we have added a short paragraph in the Results describing in details the main differences observed across the IL8 quartiles for the different risk factors (Results section page 10, paragraph 1, line 2).

3 “What measure of the SBP/DBP, cholesterol (total?), alcohol, LDL and glucose dispersion are given in brackets (range, IQR)? “

Data represent median and interquartile range. This has been added to the footnote to Table 1.

4 “I would exclude presentation of SBP/DBP data from the part devoted to the presentation of anthropometric data (Table 1).”

The Reviewer is absolutely right. SBP and DBP have been moved upwards in Table I and are not classified as anthropometric measures.
The presented analyses included the traditional cardiovascular risk factors. Did the authors try to establish the potential confounding effect of other non-classical risk factors related to atherogenesis?

The Reviewer raises an important point, since residual confounding is an important aspect of risk prediction in complex diseases such as cardiovascular disease and cancer.

Residual confounding is one of the potential limitation of our study, please see Discussion, page 21, 1st paragraph, line 6

6. “Did you try to analyze the IL8 as a continuous variable trying to establish the cut-off values linked with higher risk of all-cause mortality, as well CV and cancer in older people?”

We thank you the Reviewer for this comment. We have analyzed IL8 as a continuous and categorical variable, no specific cut off was identified. Of note, IL8 has been measured and reported using different methodologies and biological samples (serum, plasma) across studies, hampering the establishment of cut-offs values. We now report both analyses in the text.

Materials and Methods, Statistical Analysis, page 9, 2nd paragraph, line 1.

Results, Page 14, lines 2-4 and page 16, 2nd paragraph lines 1-3.

References


