Author’s response to reviews

Title: Lifestyle and Clinical factors associated with elevated C-reactive protein among newly diagnosed Type 2 diabetes mellitus patients: A cross-sectional study from the nationwide DD2 cohort

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The Editorial Board
BMC Endocrine Disorders

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Re: MS: 1594547442123729 - Lifestyle and Clinical factors associated with elevated C-reactive protein among newly diagnosed Type 2 diabetes mellitus patients: A cross-sectional study from the nationwide DD2 cohort

Thank you for the constructive and thoughtful comments regarding the manuscript. Below are our point-by-point responses to the concerns:

Comments:
From the Editors
- We have provided a heading for the conclusion section
- We have asked a native English speaking colleague to edit the paper.
- We have ensured that the manuscript conforms to the journal style

Referee 1:
Minor essential corrections:
1. It would be interesting to have information on the influence of diabetic vascular disease (not only coronary artery disease, but also diabetic neuropathy) on CRP. Please comment and/or add this in the limitations of the study.

Other complications, such as diabetic neuropathy at diagnosis would also be of interest. Unfortunately, we were not able to assess this, and have added it in as a note in the discussion.

233-236: It would also be of interest to examine the relationship of diabetic microvascular complications, such as diabetic neuropathy, with CRP elevation, but reliable information on microvascular complications was unfortunately not available in our present data.

2. Please clarify in the title, abstract and manuscript that this is all about high sensitivity-CRP.

While the method used (Tina-quant C-reactive Protein Gen.3, Roche Diagnostics), is a sensitive method and has the possibility of measuring CRP within the limits of 0.3 - 350 mg/l, this method is not deemed a hs-CRP method.

Referee 2
No comments to address

Referee 3
Major issues
• Please define “recently diagnosed”.

We agree that “recently diagnosed” is a rather vague definition, and thank you for the opportunity to clarify this. We have been looking at this more thoroughly by examining time of antidiabetic prescription. This has been clarified in the methods section.

Line 68-69: At entry into the study 66% used antidiabetic treatment [10], among the patients included in this current study 71% started within one year prior to study start or after.

• History of comorbidities has been obtained through discharge records from hospitals. This, however, does not exclude that certain serious medical conditions, not related to a hospital admission, might co-exist. This should be reported as a limitation.

We agree that it is a limitation that we only have reports of comorbidities from hospital in- and outpatient treatment in Denmark. The Danish National Registry of Patients will catch all records of all acute, non-psychiatric hospitalizations and hospital specialist out-patient clinic and emergency room visits, that is, virtually all acute and specialized medical care in Denmark. Thus, primarily chronic diseases, taking long time to develop and not requiring specialized care in the early phases would not be captured. We have added this as a limitation.
CRP levels might have been influenced by a recent event related to diagnosis of diabetes. For instance, diabetes might have been diagnosed during hospitalization for an infection, a common cause of CRP elevation. The authors addressed this issue by performing a sensitivity analysis in which individuals with a CRP>10mg/dl were excluded. However, I recommend to perform an additional sensitivity analysis, excluding persons with recent hospitalization. Alternatively, you might examine if the results are affected by adjusting for the patient enrollment site (primary care or hospital). In case the data are available, I also suggest to include recent hospitalization into your multivariable model.

Thank you for this pertinent suggestion. To address this issue, we have examined hospitalizations for all causes 14 days prior to enrolment in the DD2. There were 111 of the 1037 patients with an in-or outpatient visit 14 days prior to entry into the DD2 study. We conducted a sensitivity analysis, excluding these patients. This has been added in the methods and results section:

Lines 127-128: … the second restricting to individuals not hospitalized 14 days prior to entry into the study.

And

Lines 179-180: … and the analyses restricting on no previous hospitalization the past 14-days showed consistent results with the full analysis.

I understand that blood pressure, smoking, BMI and plasma lipids were derived from previous recordings. Hence, this part of the analysis contains information from different time-points. Since the time period between time-points can vary substantially and lead to erroneous results, I recommend to disregard this part of the analysis (the sub-cohort of 525 patients).

We agree with the reviewer. It is a certain concern that the recording of data in the DDDA is at another time point. We have therefore disregarded this part in the revised manuscript, as suggested.

Although in the text the authors describe that “alcohol intake” was measured and taken into account, in Table 1 (multivariable regression model), only “alcohol abuse” is reported. Actually, only 18 individuals were classified as alcohol abusers. Alcohol intake should be incorporated in the analysis, only if a more precise measure of it is available (eg. low, moderate, high).

In the revised manuscript, we have altered our wording from “alcohol abuse” to the more correct “high alcohol intake”. We used – and only have - information whether alcohol intake is less or more than 14/21 units/ week, which is the official Danish Health and Medicines Authority’s recommended maximum intake of alcohol. We still believe in the importance of including this variable – although rather few were exposed.

Please discuss in more detail your finding regarding the association between statin treatment and CRP only in women.
We have added some extra discussion with respect to the finding regarding the association between statin treatment and CRP in women only. Lines 205-207: The explanation remains unclear as recent meta-analyses and rapports that statins works similarly between the genders [20]. The present results suggest that at least an anti-inflammatory effect of statins can be expected in women.

• In table 2, please report standardized beta coefficients as well.
The standardized betas are now reported in table 2 as well.

• Please rephrase your conclusion. The first sentence is rather vague. Please focus on your specific findings.
We deleted the first sentence, and have rephrased the conclusion:
Lines 256-260: T2DM patients with elevated CRP are likely to benefit from targeted gender-specific lifestyle interventions [26,28], for females including weight loss and potentially statin treatment, while for males, physical activity seems particularly important.

Minor comments
Some improvements in spelling and syntax are necessary (e.g., lines 38-39: “elevated CRP was elevated among patients…”, or line 104: “who also were also included…”
Response: We have proof-read the entire article changing spelling and syntax where applicable.

Please specify whether hs-CRP was measured.
Response: No, hs-CRP was not measured, and this is specified. Please see comment to referee 1.

Lines 145-146: “…overall and stratified by gender.” To my understanding a gender-stratified analysis only is reported.
Response: Overall has been deleted

We hope that we have sufficiently addressed all identified issues, and we look forward to and hope for a positive reply. Please, do not hesitate to contact us if there are any further questions.

On behalf of all authors,
Yours,
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