PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of a multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialized diabetes centre in Denmark
AUTHORS	Safai, Narges; Carstensen, Bendix; Vestergaard, Henrik; Ridderstråle, Martin

VERSION 1 – REVIEW

REVIEWER	Dr Sandra Ofori University of Port Harcourt, Nigeria
REVIEW RETURNED	29-Oct-2017

GENERAL COMMENTS	Overall well written paper with a few grammatical errors. The results of the HbA1c and LDL-c in the abstract do not match what is in the results section. The discussion of change in BMI category and time trends in the discussion section seems out of place as these were not shown in the results section.

REVIEWER	Rimke Vos University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, the Netherlands
REVIEW RETURNED	27-Nov-2017

GENERAL COMMENTS	Title: Impact of a short term multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study I read the manuscript with interest. It describes the results of the performance of STENO-2 multifactorial treatment program in the real-life setting, based on routine care data of a tertiary diabetes center (the STENO Diabetes Center) and linked national register data. I think it is very valuable not only to present/ know results from RCTs but also how well the used intervention in the RCT performs in real-life. However, I have some questions and remarks about the manuscript in its current form.

	Abstract: - Which individuals were included only those with a dysregulated T2DM or also those newly diagnosed and/or starting new treatment. This is also not clear form the methods section. - Primary outcome includes change in pharmacological treatment, does this include all or only diabetes related? And the results about this outcome are not mentioned in the abstract. - It is not clear form the description of the outcomes that HbA1c, LDL-cholesterol and blood pressure absolute decrease as well as reaching target are evaluated. - Please also mention which statistical tests were used. - A brief description with a focus of the STENO-2 treatment program would be helpful. - I think it is important not only to mention the decrease in HbA1c, LDL-cholesterol and blood pressure, but also the baseline values. With higher values there is more room for improvement. - Please write the abbreviation NDR in full. Methods: - From the methods I understand that the short term treatment involves 8 months, in my opinion this is not really 'short-term', it is at lease a topic of debate. I would suggest not to mention it as a short term program but to mention the STENO-2 program (also in the title) en mention the duration of this program in the methods section. - I would like to suggest to restructure the subheadings in the methods section to get in more in line with the research questions (outcomes), as follows: 'design and setting' (first part and lines 8-10, page 6 of your study population), 'study population' (last part of your study population), STENO-2 program (this could also be described in a table), 'subject characteristics'(including the description of the anthropometric, clinical, biochemical measures and diabetes complications), 'pharmacological treatment', 'CVD-risk' (description of the two models used to calculate this), 'statistical analyses'. - Could you mention the range of the duration between baseline and evaluation of the included participants? - Is it possible to mention how the 16% of participants that were re-referred to the clinical performed at the end of the program the first time compared to the rest of the study population, did they perform less. This can give clinical relevant information about which kind of patients perform well with the STENO-2 program and which not (e.g. was it

	predominantly participants with dysregulated T2DM or those on new treatment?) - Which 12 predictors are included in the NDR risk engine? - Difference in gender is not mentioned in the aim of the study (or introduced in the introduction). - Are models adjusted for confounders (if not, why) and how was difference in repeated measures between participants handled? - Please describe in the statistical methods how change in pharmacological treatment was evaluated. Results: - It would be helpful if the results were presented in the same order as the outcomes (clinical, pharmacological treatment, CVD risk); - Is it possible to give some information about adherence to the program/ present during the meetings? - ABC control targets are described in the methods section, no need to repeat them in the results section. - In order to put the pharmacological treatment in perspective it would be helpful to know what Swedish guidelines recommend. Discussion - Please follow the same order as in the methods (outcomes)/ results as indicated above. - Lines 23-25 page 11, lines 3-5, page 12, and lines 10-11, page 14 are results. - Is the assumption from lines 6-9, page 12 checked in the data, or is his possible to look for? Table 1: - Is it possible to include the reason for referral; number of participants with dysregulated diabetes, those newly diagnosed and those on new treatment? - Was the program the same for all types of referral?

VERSION 1 – AUTHOR RESPONSE

Dear Editor,
First, we would like to thank the reviewers for taking their time to review our manuscript and giving such constructive feed-back. We have made an attempt to answer all questions and clarify issues where needed.

Editorial request:
Title changed to:

Impact of a multifactorial treatment program on clinical outcomes and cardiovascular risk estimates: a retrospective cohort study from a specialized diabetes centre in Denmark'
The manuscript has been proofread and the language has been changed from American English to British English.

Reviewer 1:
The results of the HbA1c and LDL-c in the abstract do not match what is in the results section.

Reply:
Thank you for noticing the differences in results on HbA1c and LDL cholesterol. They have now been changed to the correct numbers.

The discussion of change in BMI category and time trends in the discussion section seems out of place as these were not shown in the results section.

Reply:
The discussion on BMI changes is relevant when discussing increase in insulin treatment as many readers would ask how this increase might affect (increase) the weight and as in this case the weight did not change much. We think that this is an important aspect to discuss from many patients' point of view.

Reviewer 2:
Abstract:
- Which individuals were included only those with a dysregulated T2DM or also those newly diagnosed and/or starting new treatment. This is also not clear form the methods section.

Reply:
All patients referred to the type 2 clinic were in scope and included. Those excluded are mentioned in the methods section of the main document (page 6, lines 18-21). This was only applicable to those with a follow-up time of less than 30 days, as this would include those that never showed up or where visits were cancelled.

- Primary outcome includes change in pharmacological treatment, does this include all or only diabetes related? And the results about this outcome are not mentioned in the abstract.

Reply:
This is correct, we only investigated changes in the main treatment categories like antidiabetic, antihypertensive and lipid lowering treatment and in acetylsalicylic acid treatment. The reason not all results are mentioned is due to word limit. Therefore only main results are included in abstract.

- It is not clear form the description of the outcomes that HbA1c, LDL-cholesterol and blood pressure absolute decrease as well as reaching target are evaluated.
- Please also mention which statistical tests were used.

Reply:
We thank the reviewer for pointing this out. The outcome section has been revised with inclusion of all outcomes and statistical methods used.

- A brief description with a focus of the STENO-2 treatment program would be helpful.

Reply:

We hope that people understand the term ‘multifactorial treatment’ as treatment of hyperglycaemia, hypertension and dyslipidaemia, but have also included a brief description in the abstract (lines 8-9) and if there is a need to understand the term more precise, it is found in the Methods section of main text.

- I think it is important not only to mention the decrease in HbA1c, LDL-cholesterol and blood pressure, but also the baseline values. With higher values there is more room for improvement.

Reply:
This is absolutely correct, but because of word limitation we chose to only describe the difference from baseline to follow-up. The p-value though is from a liner mixed model adjusting for baseline values and with the subject as random effect. The mean baseline values can be found in table 1 and to not repeat ourselves we did not write from baseline value to follow-up value in the Results section, but chose to include the difference.

- Please write the abbreviation NDR in full.

Reply:
We have corrected this.

Methods:
- From the methods I understand that the short term treatment involves 8 months, in my opinion this is not really ‘short-term’, it is at lease a topic of debate. I would suggest not to mention it as a short term program but to mention the STENO-2 program (also in the title) en mention the duration of this program in the methods section.

Reply:
We thank the reviewer for this valuable suggestion. We agree that this term is both a matter of opinion and subject to local or national variation. Our intent was to point out the difference between a focused dedicated multifactorial program, and the routine follow-up of patients which of course also involves addressing multiple risk factors. We have chosen to delete the term “short term” in the title of the manuscript but keep it in the main text in its context. We do not believe that including the Steno-2 trial in the title would be appropriate.

- I would like to suggest to restructure the subheadings in the methods section to get in more in line with the research questions (outcomes), as follows: ‘design and setting’ (first part and lines 8-10, page 6 of your study population), ‘study population’ (last part of your study population), STENO-2 program (this could also be described in a table), ‘subject characteristics’(including the description of the anthropometric, clinical, biochemical measures and diabetes complications), ‘pharmacological 2 treatment’, ‘CVD-risk’ (description of the two models used to calculate this), ‘statistical analyses’.

Reply:
We acknowledge this valuable proposal. As proposed we have subdivided the Methods section further into ‘design and setting’, study population’, ‘measurements’ and ‘diabetes complications and pharmacological treatment’ as most of this data comes from registries and therefore same method, ‘CVD risk’ and ‘statistical methods’.

- Could you mention the range of the duration between baseline and evaluation of the included participants?

Reply:

Information on treatment duration with interquartile range has been included in the Results section, first paragraph; 'median treatment program duration was 8.4 months (IQR: 6.1, 11.3)'

- Is it possible to mention how the 16% of participants that were re-referred to the clinical performed at the end of the program the first time compared to the rest of the study population, did they perform less. This can give clinical relevant information about which kind of patients perform well with the STENO-2 program and which not (e.g. was it predominantly participants with dysregulated T2DM or those on new treatment?)

Reply:
We find this a very valid and interesting point. We did not find any difference between those that were re-referred and those that only had one treatment program. And the treatment programs were equally effective the second and third time, although of course based on much less data. But we did find that patients re-referred had a higher Hba1c (and were older) the second and third time they were referred. It seems that some patients need the close contact with the health care professionals more than others or maybe it is just the deterioration of the disease that makes it necessary to re-evaluate their treatment after a few years. However, as this was out of scope for the current investigation and the data volume is low, we fear that it would be too speculative to elaborate on and we have not discussed it in the manuscript.

- Which 12 predictors are included in the NDR risk engine?

Reply:
We thank the reviewer for pointing this out. This information has now been included in the Methods section. They are: sex, age, diabetes duration, TG, HDL cholesterol, HbA1c, systolic BP, BMI, smoking status, albuminuria, atrial fibrillation and previous CVD.

- Difference in gender is not mentioned in the aim of the study (or introduced in the introduction).

Reply:
We have now clarified this in the text (page 5 line 1). Although it was not part of the objectives to investigate differences in gender response to the treatment program, there are such clear and well known differences in CVD risk and risk factors between men and women that the analysis is called for.

- Are models adjusted for confounders (if not, why) and how was difference in repeated measures between participants handled?

Reply:
The mixed effect models were not adjusted for anything else than gender, as we only wanted to test for unadjusted changes and gender differences. To describe the changes from baseline to follow-up and account for the intra-individual variation we chose the linier mixed effect model. It has now been added to the statistical section that the subject was used as the random effect.

- Please describe in the statistical methods how change in pharmacological treatment was evaluated.

Reply:
The difference in treatment was evaluated with logistic regression adjusted for gender. This information has been included in the Methods section (page 9, line 18).

Results:

- It would be helpful if the results were presented in the same order as the outcomes (clinical, pharmacological treatment, CVD risk);

Reply:
The results are presented with clinical differences, changes in metabolic outcomes, changes in proportion reaching treatments targets, pharmacological changes and CVD risk estimates which are the same order as the objectives.

- Is it possible to give some information about adherence to the program/ present during the meetings?

Reply:
We agree with the reviewer that this would be valuable information. Unfortunately, we do not have the information on how many visits each person had, only when they were discharged from the clinic and could calculate the duration of attendance in the programme for each person.

- ABC control targets are described in the methods section, no need to repeat them in the results section.

Reply:
We have removed this information from the text.

- In order to put the pharmacological treatment in perspective it would be helpful to know what Swedish guidelines recommend.

Reply:
The Danish guidelines follow the general recommended guidelines from the EASD and ADA. In 2003 the treatments available and recommended were metformin, SU, acarbose, TZDs and insulin, prioritizing the treatment depending on problems with overweight or hypoglycaemia. In 2011 metformin was recommended as first-line treatment. Second-line treatments were SU, DPP-4 inhibitors, GLP-1 RA or insulin. We have included this information in the Methods section (page 6, lines 10-11).

Discussion
- Please follow the same order as in the methods (outcomes)/ results as indicated above.

Reply:
Only proportion reaching target and the CVD risk reduction has been discussed, with a few remarks on treatment, especially in relation to study limitations. And they have been discussed in that order, which is the same order as they are presented in the result section.

- Lines 23-25 page 11, lines 3-5, page 12, and lines 10-11, page 14 are results.

Reply:
Principally, this is correct. However, we believe that they are merely clarifying/deepen the mentioned parts of the discussion and not results that stand alone. The results from page 11 have been deleted, but the percentage that shifted from normal weight to overweight and vice versa we find important to explain with numbers instead of using the more unspecific term ‘some’. But if needed this can be changed.
The results mentioned on page 14 are shown in Table 2 and brought up in the discussion to compare with other study populations.

- Is the assumption from lines 6-9, page 12 checked in the data, or is this possible to look for?

Reply:
Unfortunately not, as we cannot adjust for the insulin dose or for the lifestyle changes.

Table 1:
- Is it possible to include the reason for referral; number of participants with dysregulated diabetes, those newly diagnosed and those on new treatment?

Reply:
It is possible to include percentage of newly diagnosed, which we now have done, and regarding percentage that were dysregulated, this can be viewed in Figure 2.

- Was the program the same for all types of referral?

Reply:
Yes, they were all offered the same basic visits, but depending on the need some would have more visits in between or phone consultations with nurse. The patients could also choose the individual consultations or group based consultations. We have not looked at who chose the different type of consultations and how the effect was from the different type of consultations. We have tried to elaborate on variations to the program with as few but effective words as possible in the Methods section (page 5 line 25 and page 6 lines 1-2).

VERSION 2 – REVIEW

REVIEWER	Rimke Vos Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	Most of my comments were addressed by the authors. There are only a few minor issues left: - I understand that due to word limits is not possible to include al results, I do however think it is important to mention primary outcomes. Since pharmacological treatment is only discussed briefly in the main paper as well, I would like to suggest to include it as secondary outcome instead of a primary outcome. - The authors explain in their rebuttal that they adjust their models for gender. This is however not mentioned as such in the paper. In the statistical analyses section adjustment of the models is not mentioned (difference in gender is tested by t-tests). I think this should be included.

REVIEWER	Sandra Ofori University of Port Harcourt Nigeria
REVIEW RETURNED	28-Dec-2017

GENERAL COMMENTS	I think all previous queries raised have been sufficiently addressed but there are minor spelling errors (e.g. abstract, line 13: linear). In the discussion on the CVD risk relative reduction that was more among males, it is also helpful to note that the greatest risk reduction is usually seen among individuals with greater relative risk

	and in this study, males had higher baseline risk compared to females.

VERSION 2 – AUTHOR RESPONSE

Dear Editor,
We would like to thank the reviewers for taking their time to review our manuscript again. We have made the changes requested.

Reviewer: 1

Spelling errors (e.g. abstract, line 13: linear)

-Thank you for noticing. It has now been corrected.

In the discussion on the CVD risk relative reduction that was more among males, it is also helpful to note that the greatest risk reduction is usually seen among individuals with greater relative risk and in this study, males had higher baseline risk compared to females.

-This is a good point and we have added it to the discussion (page 14, lines 22-23)

Reviewer: 2

There are only a few minor issues left:
I understand that due to word limits is not possible to include all results, I do however think it is important to mention primary outcomes. Since pharmacological treatment is only discussed briefly in the main paper as well, I would like to suggest to include it as secondary outcome instead of a primary outcome.

-The word limit has been an issue and we have chosen to exclude some results. We appreciate your suggestion and have now changed the primary and secondary outcomes in both the abstract and the main text (p. 5 line 2)

The authors explain in their rebuttal that they adjust their models for gender. This is however not mentioned as such in the paper. In the statistical analyses section adjustment of the models is not mentioned (difference in gender is tested by t-tests). I think this should be included.

-We did adjust for gender in all models, so this has now been added to our statistical methods section (p. 9 line 9 and 11. Thank you for reminding us. The t-test was used to test for gender difference at baseline or at follow-up.

Editorial Request:

We note that the study did not receive approval from a local ethics committee. Can you please explain why in the methods section of the manuscript?
-According to Danish law register studies like this do not need to get an approval from the ethics comittee. We have now added this in p. 8, lines 5-6

Was all data anonymised prior to analysis?

-yes, all data was anonymised prior to analysis and we have now stated it in p. 6, line 22

Can you please also state in the paper that permission to use data has been given by the Danish Data Protection Agency (ref. number: 2007-58-0015).

-We have now corrected our statement (p. 8, line 3)