Author’s response to reviews

Title: Socio-demographic determinants and effect of structured personal diabetes care: a 19-year follow-up of the randomized controlled study Diabetes Care in General Practice (DCGP)

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Author’s response to reviews:

Dear Stavros Liatis

BMC Endocrine Disorders

ATT: BEND-D-17-00167

Dear Editor-in-chief and Reviewers

We thank the editor-in-chief, associate editor, and reviewers for the valuable and constructive comments to which we have responded point-by-point below addressing each of the reviewers' suggestions, and highlighted these in the text (manuscript) an gave page and line numbering of the revisions.

We also attributed the manuscript with recent studies and current recommendations on the topic.
We also found minor typos in manuscript and tables but this did not change the results of the article.

We edited the reference style according to the BMC Endocrine Disorders.

REVIEWER COMMENTS

Reviewer reports:

Hung-Yuan Li (Reviewer 1): The manuscript by Andreas Heltberg et al. studied the interaction effect of socio-demographic factors on the effect of structured personal diabetes care using data from a randomized trial DCGP. They found that the effect of intervention was modified by the residence. Patients in urban areas showed better response of any diabetes-related endpoints to intervention, compared with patients in rural areas. However, they did not found any interaction effect of these socio-demographic factors over intervention in terms of cardiovascular risk factors, behaviour, attitudes and process-of-care.

Overall, the manuscript discussed an interesting question, and the analyses were done in a good way. However, many of the interpretation on their data is not based on the results of statistical tests, and the main positive finding cannot be supported by the other negative findings (see point 1). Besides, the study was done since 1988, which is a long time ago and many things change, including socio-demographic characteristics. Therefore, the findings may not be applied nowadays.

Response: We thank the reviewer for this feedback and have made relevant changes in the manuscript.

We acknowledge the point that the study started off in 1988. Hence, on one hand the findings may have less applicability in present day, but on the other the study has the opportunity to offer data on long-term endpoints in a 19-year follow-up of the cohort - total mortality and any-diabetes-related endpoint - as these normally very rarely are available. This study could therefore prove valuable also for present day health care initiatives and further research on the topic, as the intervention tested is much like the present day diabetes care intervention used in primary care offering valuable data on a complex intervention that currently is in use.

Many things have changed since the start of the study in 1988. One of the most important being the gradual introduction of a structured diabetes care in Danish primary care which in effect equalized the intervention and control group about halfway though the 19-year follow-up. The objective of the present study was to see whether the structured care intervention was taken up better – gave more outspoken differences between intervention and control on the long term outcomes – in particular socio-economic groups. Hence, the socio-economic position of the study participants in the intervention period is of importance. Furthermore, the data collection
starting in 1988 may be viewed as the latest date to start to assess a structured care intervention in primary care in Denmark since, as mentioned, at present all general practices have a structured diabetes care implemented. The results of the present analyses will give us the most timely assessment possible; they will tell us whether structured diabetes care may have been detrimental for certain socio-economic groups. While the make-up of the Danish population may change, and possibly its association with the course of the diabetes, the effect of the structured care intervention may be more robust.

The reviewer mentions that the difference in uptake of the intervention was not seen in e.g. risk factors and life style variables. In the main trial, however, we saw a relative risk reduction of approx. 20% for intervention vs. control group in both MI and the aggregate outcome, any diabetes-related outcome, without seeing any differences e.g. antidiabetic treatment. It is of course impossible to judge which elements of a complex intervention that actually worked, but the effects are often subtle and not necessarily mirrored in intermediate outcomes.

Therefore we included a broaden description of the intervention in the material and methods section (page 7 l. 117-120): “Goal-setting for blood glucose, blood pressure, lipids and weight was individualized,[24] and…” and how this intervention is resembling the present day diabetes care intervention used in primary care national and internationally (including NICE) (page 7, l 120-121): “resembling present day recommendations for diabetes care [25, 26]”.

And the abstract (page 3 line 35-36): “resembling present day recommendations.”

And included percentage of overall results of the intervention in the discussion section (page 11, l 208) “…overall patients receiving structured personal care experienced a 20% lower risk…”

We also revised the strengths and limitations section included in the discussion section (page 13, line 259-269): “This study contributes to the knowledge on how SES and urbanization influence the uptake and effect of diabetes interventions and may offer some advantages in comparison to prior studies. It is a strength of the present study that it reports hard endpoints after 19 years of follow up, but on the other hand a limitation that the results are from an early cohort.”

Furthermore, the results are likely to be generalizable to the wider population of patients with T2DM because the study was population-based, with no upper age limit, but also because the study was conducted in general practice where most T2DM patients are treated. Also, the elements of the intervention, including the negotiation of treatment goals between patient and doctor, resemble standard treatment procedures in current day general practice diabetes care and recommendations [34]. Finally, the study had a relative high number of GPs participating and the patient attrition rate was low.” And revised the references (p.14 l 285).
Specific points:

1. The main positive finding was that the effect of intervention on any diabetes-related endpoint was modified by residence area. However, residence area did not show significant interaction effect on cardiovascular risk factors, such as BMI, systolic blood pressure, HbA1c, total cholesterol and micro- or proteinuria, nor patient attitudes, motivation, behaviour, diabetes-related consultations/year (Table 3). The authors should discuss how to reconcile these findings.

Response: We revised the manuscript, were we discuss these findings in conjunction and added additional references on the topic (page 12-13 243-256):

“Our results indicate that patients living in rural areas may have less benefit of the intervention compared to urban patients. An explanation for this finding could be because the uptake of the intervention was lower among rural doctors and/or because the compliance with the intervention among rural patients was low. We could not see any systematic differences in the 6 year follow up, on cardiovascular risk factors or behaviour between urban and rural patients that could reconcile these finding (Table 3). However, our data suggest that rural patients are less often treated with cholesterol-lowering drugs as a result of the intervention, but few patients were actually treated with this medication in the middle of the 1990s. Other studies have reported that cholesterol-lowering agents are less often prescribed in deprived areas [32]. A previous Scandinavian study reported no difference in mortality between urban and rural patients [8], like our study, while other studies suggested that people residing in more rural areas more often have undiagnosed diabetes [33, 34]. This implies that rural patients may be diagnosed at a later stage of the disease [10, 14], possibly with a higher risk of complications and maybe less susceptible to treatment interventions than patients living in urban areas, this have to be investigated further.”

And later included (page13-14, l 274-278): “We although found a minor difference in randomization regarding residence that means one should be cautious when interpreting these results. The fact that we could not describe any substantial difference between rural and urban patients at the 6 years clinical follow up – means that the described potential difference in effect has to be investigated further.”

We also revised the discussion; please see beneath (section 9).

We firstly revised the conclusion section addressing these limitations (page 14-15, l 299-301): “Patients living in rural areas, however, seemed to have gained less from the intervention compared to patients living in urban areas this finding has to be investigated further.”

Accordingly we revised the abstract (page 4, l 53-55): “Residence modified the uptake of the intervention with patients living in urban areas having more to gain of the intervention than rural patients, further investigations is warranted.”
2. Following point 1, the authors described in Discussion (page 12) that the effect of residence area by be explained by the lower uptake of the intervention and the lower compliance with the intervention. The authors should provide data to support their points if the data are available.

Response: we acknowledged and in addition to the above described revision of the strength and limitation, the conclusion and abstract conclusion we revised our discussion taking this into account: (page 12-13, l 243-256): “Our results indicate that patients living in rural areas may have less benefit of the intervention compared to urban patients. An explanation for this finding could be because the uptake of the intervention was lower among rural doctors and/or because the compliance with the intervention among rural patients was low. We could not see any systematic differences in the 6 year follow up, on cardiovascular risk factors or behaviour between urban and rural patients that could reconcile these finding (Table 3). However, our data suggest that rural patients are less often treated with cholesterol-lowering drugs as a result of the intervention, but few patients were actually treated with this medication in the middle of the 1990s. Other studies have reported that cholesterol-lowering agents are less often prescribed in deprived areas [32]. A previous Scandinavian study reported no difference in mortality between urban and rural patients [8], like our study, other studies have suggested that people residing in more rural areas more often have undiagnosed diabetes [33, 34]. This implies that rural patients may be diagnosed at a later stage of the disease [10, 14], possibly with a higher risk of complications and maybe less susceptible to treatment interventions than patients living in urban areas, this have to be investigated further.


Response: We defined diabetes-related outcomes in the methods section as suggested and gave reference to this rather exhaustive definition in Additional file 1 (page 8, l 152-155): “The outcomes used in the registry-based follow up were all-cause mortality and any diabetes-related endpoint (e.g. stroke, myocardial infarction and renal failure full list see (Additional file 1)), previously defined [18] and also used in the UK Prospective Diabetes Study[29].”

4. Results: page 10, line 2. Overall patients living alone or …… (Figure 2). However, living alone or now was not analysed in Figure 2. Please explain or revise.

Response: We revised the results section accordingly (page 10, l 183-186): “Overall, a low level of education was associated with higher all-cause mortality (Figure 2) and any diabetes-related
endpoint (Figure 3) showing significant difference between the 4 groups in respectively all cause-mortality and any diabetes related endpoint (log-rank test, p<0.0001).”

5. Please do statistical tests to compare survival or diabetes-related outcomes in the 4 groups in Figure 2 & Figure 3.

Response: We performed a log rank test. This test, can be viewed as a proof-of-concept, assessing whether there is any difference between the four groups defined by SES and the intervention, i.e. whether there is power in this study at all to find differences in intervention effect between SES groups – our primary interest. We inserted in the statistics section a paragraph (page 9, l 177-179): “We performed a log rank test for all-cause mortality and any diabetes-related endpoint comparing the four groups defined by educational background and the intervention.

“and in the results section (page 10, line 185-186): “…showing significant difference between the 4 groups in respectively all cause-mortality and any diabetes related endpoint (log-rank test, p<0.0001).”

6. Please provide definition of basic and higher education in legends of Figure 2 & footnote of Table 2.

Response: We edited the legends of Figure 2, footnote of Table 2, Figure 3 accordingly and also revised the description of education level in the methods section (page 7, l 129-130) “… highest attained education level (basic school education only or higher education level).”

7. Figure 2, the colour for some lines are different from the colour in caption.

Response: We could not see this difference. There was no colour in caption.

8. Table 2: the footnote is confusing, esp. for e & f. Besides, when reporting HR, please describe which group was the reference group (HR=1).

Response: We revised the footnote for better the understanding and likewise revised the Header for table 2, describing which group was the reference group: “…versus routine care (=reference group)”. 
Discussion: page 11, line 1-3. The authors described that the effect showed a statically non-significant tendency to be more pronounced among patients with …… However, based on the results in Table 2. The p values for these interaction terms were not significant or even borderline significant (0.05-0.10). So the interpretation is not correct.

Response: We acknowledge the comment and revised the discussion accordingly (page 11, 1 209-213): “This effect was greater among patients living in urban areas compared to rural patients, otherwise, there was no evidence of effect modification of education, employment and civil status on the intervention for the endpoints. Overall, the effect of the intervention on behavioural, biochemical and process-of-care measures was not seen different between the subgroups of the four aspects of socio-demography.”

Jorgen Lauridsen (Reviewer 2): The study is professionally performed, and the presentation is sufficiently narrow. Furthermore, there is a substantial innovative contribution that calls for publication.

I have only one major request, and that is related to the choice of Poisson regression.

It is commonly accepted that the Poisson regression is subject to a dispersion problem, given that the variance is restricted to be equal to the mean, and it is common practice to use Negative Binomial (Negbin) regression instead.

I recommend the authors to follow this practice. Indeed, it is easy to implement the Negbin in SAS - just Google the words "negbin in SAS", and you will be taken directly to the few statements used.

Response: We thank the reviewer for this constructive comment, and we agree with the reviewer on using the NegBin regression instead. We therefor revised Table 3 and Supplementary Tables 1 through 4 using the NeGbin regression for the count variables (the variables XXX and YYY). This did not change the overall results of these analyses. We also changed the methods section accordingly (page 9, 1 171-172): “For behavioural, clinical, biochemical and process-of-care variables at the 6-year examination we used multivariable generalized linear regression models (ordinary linear regression for continuous variables, logistic regression for binary variables and negative binomial regression for count variables) ....”

Furthermore, I would like to call the authors' attention to two recent (2017) studies by Sortsø et al., where socioeconomic inequality in morbidity and healthcare utilisation among Danish
diabetes patients are analysed along the lines of van Doorslaer et al. It would be natural to include these among the references.

Response: We thank the reviewer for drawing our attention to these interesting and very recent papers and we have included them in the introduction and in the revised discussion section; (page 5, l 66 and 76 and page 12, l 224, 231 and 237).

We also included additional recently published study (page 14, l 285): reference A. Heltberg et al 2017, primary care diabetes

I wish you good luck with the revision, and I look forward to see the final result.

References:


Camilla Sortsø, Jørgen Lauridsen, Martha Emneus, Anders Green and Peter Bjødstrup Jensen: Social inequality in Diabetes Patients' Morbidity Patterns from Diagnosis to Death - A Danish Register based Investigation. Scandinavian Journal of Public Health (OnlineFirst).