Author's response to reviews

Title: Effect of lifestyle intervention for diabetics and prediabetics in real-world primary care: propensity score analysis.

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Author's response to reviews: see over
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Dear Editor,

We would like to thank you for the opportunity to respond to your comments and the comments of the reviewers. We responded to the concerns point-by-point. We hope you will accept our manuscript for publication in your journal.

Title: Effect of lifestyle intervention for (pre)diabetics in real-world primary care: propensity score analysis.
Joris J Linmans, Mark G Spigt, Linda Deneer, Annelies EM Lucas, Marlies de Bakker, Luc G Gidding, Rik Linssen and J André Knottnerus

Point-by-point response to the concerns of the reviewers

Editor's Comments
• The question to be answered is interesting and important but requires clarification. An important issue raised by one of the reviewers relates to the justification in extrapolating the findings from this study to the national programme in a wider sphere. Part of the uncertainty regarding the validity of extrapolation hinges on the observation that 186 recruited to the programme from the 10 centres seems rather small - how many who were referred were excluded due to lack of measurement data? Also, I agree with the reviewer who has the view that results are either statistically significant or not - particularly in respect of primary outcomes and in the abstract where definitive statement should be made - if there is inadequate power to reach a conclusion this should be stated. The comments made by all reviewers require to be answered prior to reaching a decision about publication.

Response:
Thank you for pointing out these concerns. We would like to respond to your comments:
- In our opinion our study was surely not underpowered. It is true that we did not include all patients that followed this nationwide program, but that is usually the case in research and the reason to perform statistics. By presenting the means and standard deviations in the tables, the readers can calculate the statistical power for each outcome measure and by presenting the 95CI the precision of our effect estimates can be judged. With more statistical power the small effects on fasting glucose and HbA1c could become statistically significant, but considering the 95CI we do not expect clinically worthwhile effects, especially because the effects on the other outcome measures were also very close to zero and in some cases even in a negative direction.
To clarify the point of power and extrapolation we added a paragraph to the Discussion section (page 15).

- It is possible that patients who were referred to the exercise consultant did not show up for an actual appointment. It is not possible to retrieve this exact number from the data, but presumably in the Netherlands not many people ignore a referral from the GP. The outcome data was routinely collected for all diabetics and prediabetics, regardless of their participation in the lifestyle programme. In individual cases (not related to treatment exposure) it is possible that no data was available for certain outcome measures. This number can be found in tables 2 and 3 where we present the exact numbers included in each analysis. To clarify that the measurement of data was routinely collected regardless of participation in the lifestyle programme, we added a line in the Methods section/outcome measures (page 8).

- We agree that results are either statistically significant or not. Therefore we changed this in both the Abstract and the Results (page 2 & 11).

- Please clarify the ethical approval of your study. Research reported in the manuscript should be performed with the approval of an appropriate ethics committee. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

  **Response:**
  This study was part of a larger study using anonymous medical data that was approved by the Medical Ethical Committee of the Maastricht University Medical Centre. To avoid confusing we changed the text regarding this issue in the Methods section/participants (page 8).

**First Reviewer:** Paulina Vermunt

**Reviewer’s report:**

1. In the baseline matching covariates: is a difference in educational level accounted for in socio-economic status?

  **Response:**
  Yes, educational level is accounted for in socio-economic status. As reported in the Methods section, socio-economic status was calculated based on postal codes (Ref 23). The Dutch Ministry of Health, Welfare and Sports calculated the SES using four variables:
  - average income
  - percentage of household with a low income
  - percentage of inhabitants without a paid job
  - percentage of households with an average low educational level
2. To my opinion, there’s no such thing as ‘nearly significant’. Results are either significant or not. A better expression would for example be that a trend was observed, which was however not significant.

*Response:*
We agree and we changed this in both the Abstract and the Results (page 2 & 11).

3. I agree with the authors that implementation of lifestyle interventions in real life settings is challenging and can therefore not be expected to have the same effectiveness as in experimental settings (see for example the review of Rosal, 2008 and the article from Simmons, 2010). However, the authors describe the translation of lifestyle interventions for (prevention of) type 2 diabetes in real life settings as ‘problematic’, which is to my opinion not supported by the literature mentioned (1 to 2.5 kilos weight loss compared to weight gain in the general population is not problematic). In line with this comment: the background- section is written in a very negative manner, which does not tempt to continue reading.

*Response:*
We agree that the word ‘problematic’ may not be fully appropriate and therefore we changed it into ‘promising, yet challenging’ (page 2 & 4). We agree that lifestyle programmes can achieve the weight reduction as stated by the reviewer. However, the results of the review and meta-analysis by Cardona-Morrell et al. (Ref 11), stated that despite this weight reduction, lifestyle interventions in routine clinical settings are of limited clinical benefit and translation of trials into routine practice has less effect on diabetes risk reduction. The results did not show positive effects on diabetes prevention. Simmons et al (Diabetes research and Clinical Practice, 2010) also stated that investments in the development and evaluation of population level interventions remain inadequate. In addition, cost-effectiveness and primary prevention has not been universally demonstrated. Other articles stated that lifestyle programmes may not be sustainable if not reimbursed (Ref 10) and that results are lower compared to trial settings (Ref 8-12). Besides, many translation studies are small or without a control group. In addition, diabetes is rising globally (Goodarz et al. the Lancet, July 2, 2011) and it is estimated that it will continue to rise (Wild et al. Diabetes Care, May, 2004). Because of these points, we stated that translation in primary care settings is still challenging.

We agree with the reviewer that our back-ground section is rather negatively written. However, in our view, the fact that there is such a big challenge in translating evidence from trials to the real-world, justifies our study, which is also pointed out by the editor and the other reviewers as one of the strong points of our study.

4. In the methods-section: Motivation to lifestyle change is one of the inclusion criteria mentioned. However, the authors do not mention how this motivation is measured.
Response:
This part of the Methods section describes the general outline of the BeweegKuur. The inclusion criteria for our study are mentioned under ‘Participants’. The BeweegKuur had no formal criteria to assess motivation, probably because applying such a measurement in routine care would not be feasible.

5. In the methods-section: the authors do not describe what ‘usual care’ consists of.
Response:
We added information in the Methods section/study design about using a diabetes management programme (page 6).

6. In the methods-section: the authors mention that four out of ten centres were selected for inclusion of participants: on what criteria were these four selected and could this lead to bias?
Response:
We added extra information in the Methods section/participants (page 7). The SGE was approached by the NISB as described in reference 18. The centres that participated were selected based on the possibility and willingness to participate. If this would have lead to confounding bias one would expect bias towards a (falsely) positive result. However, since our study shows that the BeweegKuur was not effective our analysis does not seem to be biased.

7. Are prediabetes part of the regular diabetes management program? And if not, how / when were outcome measures of this group registered?
Response:
To clarify this, we added information in the Methods section/outcome measures (page 8). The registered patients with prediabetes receive quarterly check-ups similar as in the diabetes management programme and therefore outcome measures are registered similar as for patients with diabetes.

8. The authors do not show how they arrived at their sample-size calculation and whether the lack of significant results can be due to a lack of statistical power.
Response:
Please see our response to the first comment of the editor.

9. In the methods section: the authors describe very well how they performed the propensity score matching. However, to my opinion further detail is required on the secondary analyses, in which intervention effectiveness (with corresponding p-values) is assessed.
Response:
We added extra information about using the t-test for calculating differences between the two group means in the Methods section/statistical analyses (page 10).
10. In table 1: the authors should reflect on the major differences between groups for example age and marital status (which are both known to influence behavioural change).

Response:
We added extra information in Results section (page 11). The differences as described in table 1 were exactly the reason why we used propensity score matching to control for the confounding effect of these group differences.

11. In table 1: for the frequencies: both N and % are mentioned, which does however not correspond with the legend. Furthermore, mentioning only % would to my opinion would lead to a more clear presentation of the results.

Response:
We changed table 1 according to the comments of the reviewer (page 21).

12. In the results-section: only some of the information from the tables are described in the results section. The authors could at least for example list which outcome variables were analyzed to make the results-section more consistent.

Response:
In the Results section we added a line which describes all outcome variables (page 11).

13. The authors do not reflect on the differences between prediabetics and diabetics, while motivation (and effectiveness?) of prediabetics may for example be lower than that of diabetics.

Response:
We wanted to evaluate the lifestyle programme as it was developed at the time by the Dutch Institute for Sports and Physical Activity and this programme was developed for diabetics as well as for prediabetics. Hence, we chose to investigate the effectiveness of the programme in general as it was developed, so for diabetics as well as for prediabetics. Considering the relatively small amount of prediabetics additional subgroup analysis was not possible.

14. The authors do not reflect on the differences between their study and other studies in primary care, which found much larger results on for example body weight (for example: intensity of the intervention, baseline risk profile).

Response:
We agree that other studies found other results, on for example body weight, than we did. However, as responded to comment 3, the conclusion remains that translation is challenging and that effectiveness is less in routine daily care than in trial settings.
We added a reflection as suggested by the reviewer (page 13) considering the review of Cardona-Morrell et al. (Ref. 11) that concluded that lifestyle
interventions in routine clinical settings are of limited clinical benefit and 
translation of trials into routine practice has less effect on diabetes risk 
reduction. The conclusion of this study is consistent with our conclusion, 
despite differences in exact numbers.

15. Participants were included in the study if they were referred by a 
professional (and had at least one lifestyle consultation). The authors 
should reflect on the percentage of patients that was referred to the 
program and how this (subjective?) referral method could lead to bias in 
the results. 
Response: 
Please see our response to the first comment of the editor. 
In our opinion there is less chance of bias in our study compared with 
common controlled research setting, since the referrals occurred as they 
would occur in the real world. Therefore, our results probably give a better 
estimate of the treatment effect compared to a research setting with a 
selection procedure that is not comparable to the real-world situation.

16. In the discussion-section: the authors do not discuss that their measure of 
exercise behavior is the opinion of the lifestyle coach and is therefore very 
subjective. 
Response: 
We agree that the subjective measurement of exercise behaviour is not 
optimal. Of course it would have been better to measure exercise by a 
blinded assessor. However, as described in the Discussion section, if the 
judgement of the lifestyle coaches would have been biased one would expect 
positive results of the intervention. This makes us confident that the 
judgement of the lifestyle coaches was not biased.

17. In table 2 / 3: decreases in for example fasting glucose within the 
treatment group were relatively large: were decreases of this magnitude 
also not significant within groups? (I assume ‘we found no relevant 
changes in both the intervention group and the control group’ means no 
significant differences within groups were found?’). Could this be due to a 
lack of statistical power? 
Response: 
In our opinion within group analyses of treatment effects are not relevant 
when there is the possibility to compare the results with a control group. Many 
aspects, not related to the intervention, such as co-interventions, natural 
course of the disease, placebo effects, etc can add up to a favourable effect 
in a group of patients.

Second Reviewer: Nefyn Williams 
Reviewer’s report: 
18. Method, statistical analysis, paragraph 1, line 7. ‘We only used those 
patients for analysis who had at least one measurement of the particular
outcome measure...’ So please report in the results the number of patients who had to be excluded because outcomes were not reported.

Response:
The number of patients for analyses is described in tables 2 and 3.

19. Results, paragraph 2 and Tables. The physical activity outcome is categorical but is reported and analysed as if it is a continuous outcome. It would be better to report the numbers in each category, or the numbers that exercise at least for half an hour 5 or more days per week. The t test is not appropriate for this outcome.

Response:
We agree with the reviewer that strictly speaking physical activity is not a continuous variable. However, exercise level was measured on an ordinal level, meaning that a higher score represents more physical activity. We could present the data for physical activity as Odds Ratios for the different categories, but this would make the tables more difficult to understand and it would not change the results, considering the absolute lack of effect on this outcome.

20. The title is confusing, change to ‘diabetics and prediabetics’ or ‘patients with diabetes and impaired glucose tolerance’

Response:
We changed the title conform the recommendations made (page 1).

21. Report study type in abstract and under study design in methods section

Response:
We reported the study type in the Abstract (page 2) and in the Methods section (page 6).

22. Text under ‘study design’ sub-heading is actually describing the ‘setting’

Response:
We agree, please see the amendments in the manuscript (page 6).

23. Background 3, last sentence. Please state aim of study more clearly. ‘The aim of the study was...’

Response:
We agree, please see the amendments in the manuscript (page 5).

24. Methods, lifestyle programme, paragraph 2, lines 6 & 7. Please state how physical activity and motivation to change lifestyle was assessed.

Response:
Please see our response to comments 4 and 16.

25. Method, statistical analysis, paragraph 2, last 2 sentences. ‘This quasi-experimental...during intervention’ These two sentences overstate the value of controlling the matching, please delete them.
Response:
We agree and deleted the sentences (page 10).

26. Abstract, results section line 1. ‘There was no significant difference in any outcome measure between either group.’
Response:
We agree, please see the amendments in the manuscript (page 2).

27. Background paragraph 2, line 1. ‘Paradigm shift’ is a bit strong, what about ‘change in emphasis’
Response:
We agree, please see the amendments in the manuscript (page 4).

28. Background paragraph 3, line 9. ‘Therefore, information about their real-world...’
Response:
We agree, please see the amendments in the manuscript (page 4).

29. Methods, lifestyle programme, paragraph 2, lines 8 & 9. ‘Patients could not participate if they had three or more diabetic complications, or polypharmacy (defined how?) or hypertension above...’
Response:
We agree and added the definition of polypharmacy (page 7).

30. Methods, participants, paragraph 2, line 2. ‘registered with SGE on...’
Response:
We agree, please see the amendments in the manuscript (page 8).

31. Methods, participants, paragraph 2, line 4. ‘Subsequently, we examined all...’
Response:
We agree, please see the amendments in the manuscript (page 8).

32. Methods, participants, paragraph 2, line 5. ‘for analysis’
Response:
We agree, please see the amendments in the manuscript (page 8).

33. Methods, outcome measures, paragraph 1, line 10. ‘Fasting glucose was measured in capillary blood...triglyceride in venous blood.’
Response:
We agree, please see the amendments in the manuscript (page 9).

34. Results, paragraph 2, lines 6 & 7. ‘Similar results were found for fasting glucose...between either group.’
Response:
We agree, please see the amendments in the manuscript (page 11).
35. Results, paragraph 2, line 9. ‘between either group.’
   Response:
   We agree, please see the amendments in the manuscript (page 11).

36. Results, paragraph 2, line 10. ‘compared with the control group.’
   Response:
   We agree, please see the amendments in the manuscript (page 11).

37. Discussion. Personally I prefer sub-headings with: summary of results, strengths and weaknesses, comparison with other studies, implications for practice, policy and future research
   Response:
   We agree, please see the amendments in the manuscript (page 13 & 14).

38. Discussion, paragraph 2, line 4. 'similar trend to the results...
   Response:
   We agree, please see the amendments in the manuscript (page 13).

39. Discussion, paragraph 3, line 3 & 4. ‘Different aspects...in a trial setting’ is not clear, please clarify.
   Response:
   The following sentences in the manuscript make clear what we mean with this statement and therefore, we do not see what the reviewer finds unclear in this respect.

**Third Reviewer: Magnolia Cardona-Morrell**

**Reviewer’s report:**

40. The research question is not specified clearly in the abstract or the study design section of the manuscript. It is implied but should be explicit.
   Response:
   We agree, please see the amendments in the manuscript (please see also comment 23).

41. The study type should be called by its name in the abstract and methods: a retrospective cohort with a control group matched by propensity score.
   Response:
   We agree, please see the amendments in the manuscript (please see also comment 21).

42. Summarise reasons why 2,362 people who ended up in the control group were not eligible for referral. Was it the ‘motivation’ factor or the co-morbidity factor? or was it social or geographic reasons?
   Response:
In the Methods section/participants, we described that four out of ten centres participated in the intervention. To enhance power, we selected all (pre)diabetics from all 10 centres who were, theoretically eligible for participating in the intervention. For further information we would like to refer to our response to comment 15.

43. In Figure 1, specify N= for prediabetics and T2D in both the intervention and control group nodes of the flow-chart. This distinction is important.

Response:
We are aware that we did not make this distinction in figure 1, but we did in table 1. Furthermore, we wanted to evaluate the lifestyle programme as designed, so for diabetics as well as for prediabetics. For further information we would like to refer to our response to comment 13.

44. The authors mention that exercise levels were monitored during the quarterly checkups. Yet on page 13 of the discussion they argue that they had no data on treatment adherence after the first consultation. Analysis of level of exposure may give important clues to the success factors for interventions in real life (we know they are determinants in intensive, highly controlled settings where the RCTs were conducted). Was there similar information on people NOT referred to the program? Perhaps authors could attempt to analyse these data or alternatively explain the reasons for omission in the limitations of the study, beyond assuming that “effect was inherent to the intervention”.

Response:
The measurement of exercise levels (and all other data) was part of the regular check-ups that all (pre)diabetics registered with SGE receive. Therefore, the measurements of exercise levels were not related to the lifestyle programme and can not be used to assess the adherence to the lifestyle programme. On the other hand, since these measurements were not related to the intervention, this ensures that there is no information bias between intervention and control group.

For further information, please see our response to the second comment of the editor.

45. It is unclear if the number of matched control was the same for each person in the intervention group. Also unclear is whether matching on all those variables was done for each individual or whether some individuals were matched on some variables and other individuals on others. This may explain why the matching was not completely balanced (table 1). Given this differentials in age, presence of COPD or CVD, ad marital status, the analysis needs to be either linear regression (for continuous outcomes) adjusting for the above variables among others or conditional regression analysis (for dichotomous outcomes).

Response:
It is difficult to explain exactly how propensity score matching works when there is limited space in an article. We feel that we already used quite some space to illustrate what we have done. We also referred to the relevant literature on this topic. Propensity score matching is increasingly being used and many papers, both empirical and statistical, exist nowadays that use or illustrate this method.

Based on the reviewers comment, we added information in the Methods section/statistical analyses to clarify that all covariates were used to calculate the propensity score of all individuals (page 9). Furthermore, we explained the number of matched patients in tables 2 and 3 (page 22 & 23). The number of matched control cases is the same for each person in the intervention group. The Kernel matching procedures applies a weight, based on the distance in propensity score of the subject in the control group versus the matched intervention subject, for all subjects.

Table 1 shows the baseline covariates before matching. To clarify this, we changed the title of table 1 (page 21).

46. The column ‘Adjusted effect intervention (95%CI)” in Tables 2 and 3 doesn’t seem to be showing Relative Risks or Odds Ratios. The estimate of the effect could also have been a difference or a ratio between intervention/control. It is unclear what the estimate is and why the p value is treated as “adjusted” if there was an imbalance on age, CVD, COPD and marital status at baseline.

Response:
The presented effects are the adjusted differences in mean values between the two groups. We added information in table 2 and 3 to clarify that the results are the differences after matching (page 22 & 23). The fact that there were differences between the intervention and control group at baseline, was exactly the reason why we controlled for this imbalance in our analysis by using propensity score matching. Therefore, there is no imbalance on age, cvd, copd etc. after matching. Please also see our response to comment 10.

47. It appears that the estimates shown in the “intervention” and “control” columns are the mean BMI, FPG, BP, etc.

Response:
We agree and changed the explanations in tables 2 and 3 (page 22 & 22).

48. I may have misunderstood the above from the ‘statistical Analyses’ section. But in general, the reader would benefit from a more comprehensive explanation of the statistical methods on page 9, and self-explanatory notes under tables 2 and 3.

Response:
Please see our response to comment 45.

49. While the BeweegKuur is a national intervention, the evaluation 186 participants from 10 practices is hardly a representative nation-wide
sample of all the regions in the Netherlands. Make the over-statement (second sentence in the discussion) reflect that you evaluated a regional or sub-sample or pilot rather than imply you conducted a nationwide evaluation of translation in PHC.

Response:
Please see our response to the first comment of the editor.

50. If possible, in order to improve the power of the study, expand the sample analysed by including data from more than 10 PHC centres using the same inclusion criteria and MPS analysis. Results may be very different. Alternatively, I would strongly suggest the authors revise analysis for the diabetics only (i.e. excluding pre-diabetics). Their sample of pre-diabetics is too small for meaningful interpretation and the predictors of success for pre-diabetics may be different from the predictor of success for people with a diagnosis. Combining both groups may have diluted the true effect of the intervention.

Response:
It is not possible to extend the dataset to more health care centres, since we can only be certain of the quality of medical-registration in the Eindhoven region/SGE. We do not agree that it is necessary to increase the power of this study as we discussed in our response to the first comment of the editor. For further information about analyzing prediabetics as well as diabetics, please see our response to comments 7 and 13.

51. Discuss the possibility that lack of effect was due to impact evaluation conducted too early (first few participants enrolled at 1 Jan 2008, lifestyle counsellors were inexperienced with the first few participants, access to services was not sorted out, etc) and sample size may have been insufficiently powered.

Response:
Please see our response to the first comment of the editor about the power/sample size.
We agree that an incomplete overview of services could have led to less effect of the programme. However, we wanted to evaluate to intervention as developed and implemented at the time. On of our conclusions is therefore that improvement of the programme as evaluated is needed. After adaptations are made, a new evaluation is needed again.
Besides, according to the protocol of the BeweegKuur (Ref 18), patients are guided during one year by the diabetes practice nurse and, if necessary, by the physiotherapist. Together with the professionals, patients searched for suitable services within this year. We evaluated the effects in this year. After this year, patients are not guided anymore and should independently continue the lifestyle improvement.
In addition, diabetes care in The Netherlands is highly structured according to a nationwide GP-guideline, so there should be no large differences in diabetes care. The diabetes management programme was already running
for a couple of years at the time and therefore we can assume that health care professionals were not inexperienced. Besides, all health care professionals involved in the BeweegKuur were trained in motivational interviewing (Ref 18).

52. Emphasise the extensive matching on propensity scores efforts because this is one of the strengths of the study, but clarify the intervention/control matching ratio.

Response:
We changed the Methods section/Statistical analyses as described at comments 45, 46, 47.
For further explanation about the sample sizes/ratio, please see our response to the first comment of the editor.

53. Also clarify if the use of participants with outcome information 1 year before and after the intervention is the reason for the different N= in tables 2&3 for each adjusted model.

Response:
We agree and changed the legend of table 3 (page 23).

54. Perhaps suggest in the title that this is a preliminary evaluation or a pilot evaluation (larger sample could come later and show better results)

Response:
Our evaluation is the first evaluation of this program and other evaluations may follow. However, as discussed before (response to the editor), we do not think that our study is underpowered and we doubt whether other evaluations will show different results, provided that the research methods reflect the real-world situation as precisely as we did.

55. Perhaps under the limitations, consider addressing the fact that the BeweegKuur underwent formative and process evaluation but data were not prospectively collected for an impact evaluation as it was designed as a pragmatic program to be run in routine PHC.

Response:
We evaluated the lifestyle programme according to the goals as designed by the Dutch Institute for Sports and Physical Activity.

56. It was interesting that despite not observing changes in BMI or exercise level between intervention and control groups, but there were differences in FPG and HbA1c. Any possible explanation for this? Adherence to dietary recommendations? The DPP in China and India showed that diabetes prevention is possible without weight loss.

Response:
We agree that there is data available about the prevention without weight loss. We did reflect our data with the existing literature in the Discussion
section. However, our primary aim was to investigate the effectiveness of the intervention and not to study the possible causes for the lack of effectiveness.

57. In the conclusions section authors mention that process evaluation ‘might reveal the barriers and facilitators...’ As I understand it, BeweegKuur already conducted process evaluation and this information is available [your Helmink reference 2010]. Perhaps include some of the old recommendations from the 2008 process evaluation & recommend that these be explored further.

Response:
The article of Helmink from 2010 (Ref 18) describes the developmental process and the contents of the intervention. We wanted to evaluate the goals of the programme as developed and implemented and made recommendations based on our results in the Discussion section. An article from Helmink et al. in the Journal of Evaluation in Clinical Practice (2011) described motivation factors of heath care providers but not the effectiveness on the primary goals of the BeweegKuur and therefore we didn’t reflect on this article.

Also on behalf of the other authors,
Yours sincerely,

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