Author’s response to reviews

Title: A pragmatic lifestyle modification programme reduces the incidence of predictors of cardiometabolic disease and dysglycaemia in a young healthy urban South Asian population. A randomised controlled trial

Authors:
Mahen Wijesuriya (amrit@slt.lk)
Nikolaos Fountoulakis (nikolaos.fountoulakis@kcl.ac.uk)
Martin Gulliford (martin.gulliford@kcl.ac.uk)
Nicola Guess (nicola.guess@kcl.ac.uk)
Laksha Vasanthalarajah (dasl@sltnet.lk)
Sarath Banneheka (dasl@sltnet.lks)
Giancarlo Viberti (barbara.crowe@kcl.ac.uk)
Luigi Gnudi (luigi.gnudi@kcl.ac.uk)
Janaka Karalliedde (j.karalliedde@kcl.ac.uk)

Version: 1 Date: 26 May 2017

Author’s response to reviews:
Dear Editor,

BMC Medicine

Re;
BMED-D-17-00058
A pragmatic lifestyle modification programme reduces the incidence of predictors of cardiometabolic disease and dysglycaemia in a young healthy urban South Asian population. A randomised controlled trial

Thank you for giving us the opportunity to revise our manuscript. We wish to thank the reviewers for their helpful comments and advice which we have now incorporated in the revised manuscript.
As suggested we have included a detailed, point-by-point response to all the issues raised by the reviewers on separate pages and indicate where the changes have been made. Changes to the text of the manuscript have been highlighted in yellow in the revised manuscript.

We would like to thank the reviewers and the editor for all their comments which, we believe, have strengthened significantly this manuscript. We hope that you will now find the revised version of the manuscript suitable for publication.

Yours sincerely
Dr M Wijesuriya and Dr J Karalliedde

Reviewer #1 (Comments to the Author (Required):
We wish to thank the reviewer for his/her helpful comments and advice which have now been incorporated in the revised manuscript.
Please see below detailed, point-by-point response to all the issues raised and we indicate where the changes have been made. Changes to the text of the manuscript have been highlighted in yellow in the revised manuscript.

Reviewer #1: This is a well reported and well written paper describing an RCT of lifestyle advice through peer advisors to reduce cardiometabolic risk factors. It is an important piece of work.
1. Really 100% inactive? Do other papers saying the same?

Response
Participants aged between 5 to 40 years were first screened to identify the prevalence of four risk factors: namely first degree (parental) family history of T2DM, physical inactivity, raised body mass index and raised waist circumference. Physical inactivity was defined as less than 30 minutes continuous exercise for less than 3 days a week. In the screening phase results previously reported (Wijesuriya M et al Plos One 2015) the prevalence of physical inactivity was nearly 52% in those aged >20 years.
Participants with 2 or more risk factors identified in the screening phase were eligible to enter the RCT (the inclusion criterion for the trial was participants with two or more of the above risk factors).
Of the participants randomised, physical inactivity as defined was indeed 100%, as all participants eligible for randomisation had this risk factor.

We have now better clarified this in the methods section of the revised manuscript.

Page 5 lines 39 to 44, and Page 12 lines 31 to 34

2. Should be intention to treat - include participants even if they do not attend (as long as they have post data, but can also undertake data carried forward) and then a per protocol analysis for those attending the intervention –

Response

We reported the results of intention to treat analyses where participants had at least one post randomisation visit/attendance and their last observation was carried forward.

We did not include in this primary analysis participants who failed to attend for any visits post randomisation visit (as they did not receive either intervention).

We now report in the revised manuscript the results of analyses for primary endpoint from all participants randomised including those who failed to attend for any visit post randomisation. These results are consistent with primary analyses results and demonstrate a significant risk reduction with pragmatic life style intervention as compared to control intervention.

Page 11 line 5 to 12, Page 13 lines 53 to 59, and Page 14 line 1 to 3.

3. Fidelity of the intervention - did the peers deliver what was within the protocol?

Response

A standardized training manual was developed for the peer educators and their training supervised University of Ceylon staff, and 2 external experts on lifestyle modification from South India. Training refreshers sessions were done throughout the study. The training of peer educators in now more detailed in revised manuscript. With regard receipt of intervention this component of fidelity was evaluated by recording adherence to lifestyle goals and impact of intervention on motivating assessing behavior change and readiness change as detailed in results section and Supplement 1 Table 3.

We have now better detailed the aspects of intervention fidelity in the methods and discussion sections of the revised manuscript.

Page 7 lines 39 to 58, and Page 8 lines 1 to 5 and Supplement 1 Table 3
4. Although in the protocol paper, it would be helpful to have a summary included in this paper of the selection criteria to be a peer educator, the training involved, criteria for 'failing' the training, how many there were over the 3 years, their drop out and de novo training rate. what ongoing support did they have

Response
We now describe in more detail all of the above in the revised manuscript

Page 7 lines 29 to 58

5. Health economic analyses would be very useful—are these planned?

Response
These are planned and we have stated this in revised manuscript.

Page 18 line 2

6. There are some discussion points in the results e.g. "However the clinical impact/significance of these differences is likely to be modest." These should be removed

We have removed these sections/points from revised manuscript

Response

Page 14 lines 8 to 17

Reviewer #2:
We wish to thank the reviewer for his/her helpful comments and advice which have now been incorporated in the revised manuscript.

Please see below detailed, point-by-point response to all the issues raised and we indicate where the changes have been made. Changes to the text of the manuscript have been highlighted in yellow in the revised manuscript.

1. This paper compared a 3 monthly versus a 12 monthly lifestyle modification program on the incidence of new onset cardio-metabolic disease. Findings showed that more frequent lifestyle modification resulted in a reduced incidence of cardio-metabolic risk factors, specifically less glucose abnormalities in both young (6-18 years) and middle-aged (18-40 years) participants and lower BP in younger individuals. There was less evidence for what caused these effects however with no weight changes, a strong reliance on self-reported physical activity information over the past 7 days and no dietary changes reported. Absolute (adjusted) differences were modest and
not clinically significant between the groups. Results should be interpreted with caution considering low endpoint information in some cells (e.g. new onset T2DM in <18 years). There is uncertainty that the intervention accounted for the differences shown.

Response

We agree with the reviewers comments that further evidence would be helpful to explain the causes/mechanisms that could explain the beneficial effects observed with lifestyle modification. Diabetes prevention studies in Indian and Chinese participants with impaired glucose tolerance demonstrated significant reduction in T2DM but with modest effects on weight. The exact mechanisms explaining these results remain unclear. One hypothesis is that in Asian subjects the benefits may be related to increased physical activity however this remains to be confirmed. Exercise even in the absence of weight loss is known to improve insulin sensitivity which is a key determinant of the 2-hour glucose concentration following an oral glucose tolerance test. In our study we observed a significant increase in self-reported physical activity (detailed in Supplement 1 Table 3) as well as behavior change to increase physical activity in the intervention group as compared to the control group.

These results may in part explain some of the beneficial effects observed with the intervention. We acknowledge the limitations of our work, which was not designed to examine mechanism of effect, and the lack of data on the causal/mechanistic pathways that could explain our results in detail. We have revised the discussion section to include the above points and hope our work established the platform for further research in this area.

Page 16 lines 24 to 59, Page 17 lines 1 to 12.

Other considerations are:

1. Could the authors comment on the likelihood of early onset diabetes being type 1 and not type 2 given the young age of the cohort? There may be the potential that they are seeing the very early stages of the condition (type 1) develop and the suggestion of T2DM per se may be incorrect.

Response
Participants with a diabetes diagnosis had detailed medical and clinical review and no participant had any clinical or biochemical features indicative of type 1 diabetes. None of the participants diagnosed with diabetes required insulin treatment or had features of insulin deficiency. We have now stated this in the methods section.

Page 9 lines 27 to 39
2. The intervention involved quite specific dietary advice yet there were no data regarding change in diet over time. The sentence at the end of the Discussion (pg 16, line 53) should be modified to correct this overstatement.
Response
This sentence has been removed in the revised manuscript.

3. Was the IPAQ long or short form used? How was this administered for the younger children/teenagers given it is recommended for use in 15 to 69 year olds?
Response
The short version was used and this has been now reported in methods section.
In participants younger than 15 years of age we utilised this with parents or guardian to corroborate what was self-reported by younger participants.
We have revised the manuscript to include this detail.
Page 5 line 29 and 34 to 37
4. At what point in the assessment were participants asked about their readiness for behaviour change - before or after becoming aware of their results? The timing of this could have a significant impact on their response.
Response
Participants were asked about their readiness to change before assessing results. We have now clearly detailed this in the revised manuscript.
Page 8 line 12 to 14
5. Despite reference to the ADA criteria for diabetes diagnosis, the cut-offs used would be useful to be documented in the manuscript. Same for JNC7 definition of hypertension for <18 year olds.
Response
These cutoffs used are now included in the revised manuscript.
6. The Discussion is too long and efforts to shorten it should be made.
Response
We have shortened the discussion as advised.

7. Table 1 - include CIs and p-values.
Response
Mean 95% CI are now included in revised table 1. There were no statistically significant differences between the two trial arm groups at baseline and we have now more clearly stated this in the revised manuscript results section and revised table 1.
Page 12 line 24, Page 21 revised table 1

Minor suggestions:
8. Page 4, line 51. Add years of follow up + [range].
Response
These is now added
Page 4 line 53 to 54

Response
These is now added
Page 5 line 19

10. Page 8, line 46. Reference to a "fail-safe outcome" is confusing. What is meant by this?
Clarify.
Response
We have modified this statement and hope it is better clarified now,
Page 10 line 2

11. Page 8, line 54. Death (all cause?) seems to be an outcome (Table 2) but is not documented in the Methods. Consider mentioning it in Methods also.
Response
These is now mentioned and added to methods section.
Page 10 line 2 and page 22 revised Table 2

12. Page 11, line 15-20. Add smoking and alcohol consumption to Table 1.
These are now added to revised table 1
Response
Page 21 revised table 1 lines 30 to 32

13. Table 1, line 50. Total cholesterol for control lifestyle modification group needs correction.
Response
This has been corrected
Page 21 revised table 1 line 48

14. Supplementary Table 3. What is meant by "Increased PA (pre-action to action phase)"? Clarify.
Response
We have now better clarified this statement which is with regard readiness to change behavior.
Please see revised Supplement 1 Table 3

Reviewer #3:
We wish to thank the reviewer for his/her helpful comments and advice which have now been incorporated in the revised manuscript.
Please see below detailed, point-by-point response to all the issues raised and we indicate where the changes have been made. Changes to the text of the manuscript have been highlighted in the revised paper.

Thank you very much for having the chance to review the article. The article addresses an important topic - how intensive and less intensive lifestyle intervention can achieve a prevention of diabetes in practice. The authors have compared a control lifestyle intervention with an intensive lifestyle intervention in a large call in Sri Lanka. The results confer to a small conversion rate to diabetes in the intensive lifestyle intervention group. These results were
expected based on the known scientific studies but the achievement is that the authors have achieved this in general practice. There are two minor comments –

1. The authors should make an assumption or statement how the compliance has been to the lifestyle intervention. The results are good but the modulating effect to the success is the adherence or compliance to the lifestyle intervention. Do the authors have any information regarding participant adherence to the intervention?
Response
We report in Supplement 1 Table 3 the percentage of participants adhering to and achieving weight loss, physical activity goals, and behavior change for physical activity and stress reduction. As this is an important point raised by the reviewer we now include more detail on this aspect in the results and discussion sections of the revised manuscript.
Page 14 lines 22 to 39, Page 16 lines 44 to 58, Page 17 lines 1 to 12 and Supplement 1 Table 3

2. The authors should make a reference to the recent work of diabetes prevention and implementation into general practice [1, 2]. Finally, I am very supportive for this paper and recommend publication of the paper after my minor comments are addressed.
Response
We have now included a description of this work and have referenced these important/key publications on diabetes prevention and implementation in the discussion.
Page 18 lines 26 to 32 and new reference numbers 30 and 31

Editorial Requests
The TRN, date of registration and the words 'retrospectively registered' should be included as the last line of the manuscript abstract.
Response
We have now added wording this as requested
Page 3 line 9 to 11