Author’s response to reviews

Title: Nepal Pioneer Worksite Intervention Study to Lower Cardio-metabolic Risk Factors: Design and Protocol

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Author’s response to reviews:

It is with enthusiasm that I resubmit a revised version of the manuscript titled "Nepal Pioneer Worksite Intervention Study – Design and Protocol". Thank you for giving us the opportunity to revise and resubmit this manuscript. I appreciate the time and effort provided by each reviewer. I have incorporated the suggested changes into the manuscript to the best of my ability. The manuscript has certainly benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication.

Append to this letter is our response to the comments raised by the reviewers. As you will notice, we agreed with all the comments raised by the reviewers. Accordingly, we have uploaded the revised manuscript.

Editor Comments:
1) Please change the headings in the abstract to ensure that they match what is outlined in our Submission Guidelines (https://bmccardiovascdisord.biomedcentral.com/submission-guidelines/preparing-your-manuscript/study-protocol#preparing+your+manuscript). In addition, please integrate the section “Data analysis plan” into “Methods”.

Headings have been changed.

2) In the main text, please change “Introduction” to “Background” and “Methods and Design” to “Methods”.

We have changed in the main text.

3) Please include the date of registration of the trial along with the registration number.

We have included the date of registration of the trial.

4) Please describe the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

The funding agency had no role in design of the study and collection, analysis, and interpretation of data and in writing the manuscript. We have added this in the funding section.

5) Please represent authors' names using their full initials, not their full name, in the Authors’ Contributions section. If there are any duplicated initials, please differentiate them to make it clear that the initials refer to separate authors.

We have represented authors’ names using their full initials.

6) Please include figure titles/legends should be placed at the end of the main manuscript, after the References.

We have added the figure titles/legends at the end of the main manuscript.

7) Please add a section "Additional files" (after the References/Figure legends) where you list the following information for each additional/supplementary file in the file inventory:

- File name (e.g. Additional file 1)

- Title of data

- Description of data

We have added the list of additional files.

In addition, please ensure that the table has no shading.
We have ensured that the table has no shading

BMC Cardiovascular Disorders operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Thank you for the information. This is helpful.

Reviewer reports:

Michael Wirth (Reviewer 1): Review for BCAR-D-18-00582

Overall: This protocol described the implementation of a worksite intervention to reduce cardio-metabolic risk factors in Nepal. A diet-based program is going to be designed for use in the cafeteria. After that, participants will be randomly assigned to a cafeteria-only intervention or an individual-based program using the DPP. This is an interesting topic that warrants further study. However, there were some limitation/questions, that I listed below with the design. There also were points that needed further clarification. These also are listed below.

Abstract:

1. In your first sentence, what about increasing physical activity as well?

We agree that worksites facilitate increased physical activity as well. We have added it in the first sentence.

2. I see you have the different arms listed in the second phase in the data analysis plan section of the Abstract. They need to be listed or at least made clearer under the Methods/Design section.

We have specified the information in the methods section as follows: In the second step, we will conduct a 6-month, open-masked, two-arm randomized trial by allocating half of the participants to an individual behavioral intervention for the prevention of cardio-metabolic risk.

3. Can you list ideas for what the individual behavioral interventions may include in parentheses or just list the DPP?

We added the DPP in the abstract

Introduction:
4. I think it is important to highlight the number of people who work in places where worksite programs could be offered. In other words, how many people work in office buildings in Nepal. My colleagues and I have done some work in Asia and we know there are places where small percentages of the population actually work in places where a worksite program could be conducted. How much of the population could you really get to with a worksite program in Nepal if this was expanded on a large scale?

There is limited data on the workforce in Nepal. However, we have added the information that was available in the introduction section as follows: If proven effective, the cafeteria, behavioral or both interventions can be scaled up in the worksites in Nepal. According of to the Labor Force Survey 2008, the labor force comprises of 12 million people with a participation rate of 83.4%. An estimated 3 million adults work in formal employment including legislators, professionals, technicians, clerks, service workers, market agriculture, craft and trade, machine operators and armed forces. Hence, the worksite based health promotion programs have potential to impact on the population health at large in Nepal.

5. What are the major gaps that your protocol addresses that needs to be filled compared to what has been done previously? You provided me evidence that this work has been effective before, so why do this study? I am assuming part of that argument is that there is limited work in areas in low and middle income countries.

Thank you for the comment. We agree with the reviewer. We have added this information in the background section as follows: However, much of these evidences come from high income countries and there is limited studies from low income setting.

6. You mention cafeteria-based intervention, can you put in parentheses very broadly what this means? Are you referring to providing healthy foods, doing cooking demonstrations, creating a reward system for selecting health foods…etc)?

We have added the parenthesis cafeteria-based intervention (adding healthy foods and reducing or removing unhealthy foods)

Methods and Materials:

7. What is the difference between the cafeteria intervention in stage 1 and the cafeteria-intervention in stage 2?

There is on difference. The stage 2 intervention is the continuation from the stage 1. We have clarified in the methods as follows:

We will conduct an unmasked two-arm randomized trial by allocating half of the participants to continue the cafeteria intervention in addition to a behavioral (CB) intervention for the prevention of cardio-metabolic risk, while the other half of participants will receive the cafeteria-only (CO) intervention.
8. I think the study design section needs a little more detail that incorporates the various time points and what is happening at each one.

We highlighted the time in table 1 and study flow chart (figure 1). We also added a narrative in the methods section as follows: At baseline, we will measure demographics, anthropometry, blood pressure, lifestyle, blood sugar and lipid profile. After six months of control period (without any intervention), we will measure the anthropometry, lifestyle, blood sugar and lipid profile. We will implement the cafeteria intervention for six months and re-measure the anthropometry, lifestyle, blood sugar and lipid profile at 12 months. Then, we will randomize half of the participants to continue the cafeteria intervention in addition to a behavioral intervention for the prevention of cardio-metabolic risk, while the other half of participants will receive the cafeteria-only intervention. We measure the anthropometry, lifestyle, blood sugar and lipid profile at 18 months.

9. When describing the hospital setting, are there any gyms or facilities on site that can be used to help facilitate the physical activity components? Are there showers and locker rooms accessible by the employees?

There are no gyms or other facilitates to help physical activity at the worksite. We added the information in the study setting.

10. Are there any other employee wellness programs available that may contaminate your protocol?

There are no other wellness programs available that may contaminate the protocol. We have added the information in the study setting.

11. What about shift workers? In looking at your eligibility, I don't see any mention of this. Shift workers are going to have a hard time participating in worksite interventions, especially if the cafeteria is not running at full capacity. They also may not be able to easily conduct the individual behavioral component if selected for that study arm. Also, their biological measures are going to be strongly influenced by their shifts, especially their metabolic markers. If they are not excluded, there needs to be strong justification and explanation of how these issues will be overcome.

There are workers who work in shifts and they are not excluded from the study. We agree that their biological measures will be influenced by their shifts and their participation in the individual behavior component will be compromised. We offer the behavior classes three times a day, which could address this issue to some extent.

12. Why is your inclusion of HbA1c set to 5.7-6.4%, but your blood sugar is ≥ 100? So, they can have diabetes based on blood sugar criteria, but not HbA1c%?

Our objective was to exclude those who take medication so that our intervention is not contaminated by medication use and other counseling services provided by the hospital. The hospital uses HbA1c as a confirmatory test for diagnosis of diabetes. Hence, if a person has
HbA1c lower than 6.5%, the person would not be prescribed diabetes medication irrespective of their fasting blood sugar level.

13. If you are screening everyone anyway on HbA1C and glucose, why exclude those taking T2DM medications? Many people take such medications, but are still poorly controlled and could easily meet your other inclusion criteria.

Those employees who are taking T2DM medication receive free drugs and lifestyle counselling in the hospital’s diabetes clinic. This might contaminate our intervention. So, we decided to exclude them. We have added this information in our methods section.

14. I think the repeat baseline term in the Table is confusing, what is that?

The first six months of the study is control period such that the employees do not get any intervention other than screening. So, we mentioned it as repeat baseline. However, we have changed it to the first follow-up and revised other follow-ups accordingly.

15. For the blood pressure, what happens if for some reason the first reading is really high, let's say 160 over 100, but the next two are around 110 over 70. The first reading is clearly an outlier and would drive their average value up beyond what is normal for that person. Do you have plans to modify how blood pressure is averaged in these situations?

We do not have plans to modify the blood pressure in these situations. We think that this random variation will occur at all the measurement points leading to non-differential measurement error, hence the bias would be towards the null. Correcting for the outliers using judgement might bias the study results.

16. Is any software going to be used for the 24-hour dietary recall or are you manually going to have dieticians compare recalls to the food composition table?

We are not using any software as there were no software available at the time when we planned the study. A nutritionist will compare the recalls to the food composition table.

17. Also, what days are eligible for recalls? The standard practice is to do 2 weekdays and 1 weekend day. So, if only doing 2 days, are you going to include weekends?

Due to practical limitations, we are collecting the recalls in the days that are feasible to the participants. We have added this as a limitation of our study in discussion section as follows: We will collect the 24-hour dietary recall on the days that are feasible to the participants. So, these may not be well representation of both week days and weekends. However, we will use the same strategy at all points of data collection. Therefore, the error will be non-differential to the cafeteria or behavioral intervention.

18. I am assuming the blood draws will occur in the morning, correct? Again, if you are including shift workers, this issues needs to be dealt with: are you collecting bloods (even if it is in the morning for all people) before or after a work shift?
We are collecting the blood samples in the morning after a minimum of 8 hours of fasting for all people irrespective of their work shift. However, our approach of blood collection at all time points are same. The under or over-estimation will occur at all time points.

19. What was the basis for the decreases in values of the outcomes? Were those cut-points for successful decreases based on past literature?

The decrease in values are based on the past literature and judgement of the study team that these decreases are clinically relevant in Nepalese context.

20. With the t-test and regression analyses you mentioned, several assumptions need to be met. Although most of your outcomes are normally distributed which usually means the model residuals will be normally distributed, that doesn't guarantee that the assumptions will be upheld for those analyses. Do you have plans to move to other analyses such as the Wilcoxon rank sums test or quantile regression if necessary?

We do not plan to use other tests. Our sample size calculation is powered enough for the t-test. However, in case of non-normal distribution, the effect size is same. The t-test and regression analysis gives more conservative estimates of standard error compared to Wilcoxon rank sums test or quantile regression.

21. What statistical software will you be using?

We will use STATA-15. We have added the information in the data analysis section.

22. For the behavioral classes outside of the worksite, what type of facility or setting will that be in?

All the classes will be conducted within the worksite. We have already specified this in our protocol in the methods section as follows: All of the sessions will be conducted at the worksite during the workday.

23. How will you make adjustments for any contamination? I am referring to the last sentence in the minimization of contamination section.

We will add a variable as contamination (yes/no) in the final model during our secondary analysis. However, our primary analysis will be intent-to-treat. We elaborated it in the minimization of contamination section as follows: If the contamination is found to be significant, we will make adjustments by adding the contamination as a variable in the final model while estimating the effect in secondary analysis.

Discussion:

24. Can you provide any further details on how this could be scaled up? Also, what happens if you find the individual-level intervention doesn't work compared to the environmental
or vice-versa? Would you still scale everything up at that point or focus on what the components that worked?

We take the success of this program as a primary step towards scaling up. However, we acknowledge that the study needs to be tested in variety of workplace settings that are likely to represent different context; and the scale up approach would not be straight forward. We have added this in the discussion section as follows: The study needs to be tested in variety of workplace settings that are likely to represent different contexts that will be encountered at full scale. The study will provide the effectiveness of each level of intervention separately, which will be a vital information on what to focus in these settings in future. Advocacy, dialogue and planning with multiple stakeholders including the government and other partners would be necessary for scaling up the effective interventions at worksites to prevent cardio-metabolic risk. This study will provide the groundwork for it.

Daniel Ter Goon (Reviewer 2): I commend the authors for an excellent, scientifically robust and clear research protocol. The study will add to the understanding of environmental and behavioural attributes of employers in a workplace. If the study demonstrates a significant effect, a scaled up approach could produce an important reduction in CVD burden through environmental and individual level prevention programs. The lessons learned may also be replicated in similar worksites in Nepal and translated to similar settings globally.

We thank the reviewer for acknowledging our effort.