Author’s response to reviews

Title: Interactive web-based lifestyle intervention and metabolic syndrome: findings from the Red Ruby (a randomized controlled trial)

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Author’s response to reviews: see over
Dear Prof. Altman,

MS: 2120624690160849
Interactive web-based lifestyle intervention and metabolic syndrome: findings from the Red Ruby (a randomized controlled trial)

Thank you for your e-mail. We found the reviewers’ comments helpful and thus revised the manuscript accordingly. Please find the following point-by-point responses as requested:

Reviewer: Dr. Sandra Saperstein
Major Compulsory Revisions
1. This paper will require substantial revision for English usage. In most cases, the issues are minor, but there are grammatical errors throughout so a thorough review is recommended. In other cases, the wording will need to be edited for clarity, e.g. Sentences 2 and 3 in the Background in the Abstract. I am not sure what the authors are saying here.

Thank you. The manuscript was checked for English. However, we deleted both sentences.

2. Statistical analysis
   a. You state that you used mixed model analysis for within group differences and generalized linear mixed models for between group differences. However, according to the results, it looks like you used mixed model analysis for both within and between group differences on each metabolic syndrome component and generalized linear mixed model analysis for the analysis on changes in the sum of components. Please clarify the Statistical Analysis section.

Thank you for your valuable comments. We used separate Linear mixed models for the all analysis (Within and between group analysis), however we used the terms Mixed Model and Generalized Linear mixed model (the general class of this model) as an alternative. To be constant we have changed all terms to Linear Mixed model in the manuscript. Also, some changes were made on the statistical analysis section.

2. Discussion
   a. The discussion is not clearly written and needs to be substantially revised. Some points are irrelevant to the study and could be deleted (e.g. paragraph 2).

It was removed and the following sentences were added to the Discussion:
Similarly a study from Korea showed that an 8-week Internet-based cardiovascular risk reduction program resulted in significant changes in cardiovascular risk, waist circumference, diastolic blood pressure, and fasting plasma glucose among a sample of male worker with metabolic syndrome [27].
Although some studies were not able to detect any effect on cholesterol management [28], evidence from recent studies support our findings [29-31]. In another study, Bond et al. [32] reported that a 6-month web-based intervention in addition to usual simple care reduced cholesterol HDL-C, weight and HbA1C in patients with type 2 diabetes mellitus. In consistent with our study they reported that serum cholesterol and weight decreased in both intervention and control groups; however, the reduction were greater in the intervention group (P<0.05).

Web-based interactive programs may motivate participants to adhere better to clinical assessments and desired behaviors such as physical activity and healthy diet. Online health assessments provide valuable information and facilitate opportunistic interventions by including assessment of multiple risk factors that might provide a comprehensive picture for patients and thus might encourage them to change lifestyle risk factors [31, 33].

b. Other areas are not substantiated, e.g. paragraph 4, where you state that this study showed that regular updates of the study website or sending information by emails would be related to repeated and reliable visits to the website. However, no data was presented on number of log-ins to provide validity to the statement. You should include some of the rationale/previous research for the intervention design in the Introduction or as you discuss the website itself in the Methods section.

Thank you. This part was revised as suggested.

c. I think the most important points that you can make based on the evidence you present is that use of an interactive website utilizing frequently updated informational content with email notifications, interactive risk assessment tools, and tracking tools (plus whatever interaction there was about diet--See below comments about the Inbox) had a positive effect on metabolic syndrome components. This study showed that use of an interactive website utilizing frequently updated informational contents with email notifications, interactive risk assessment tools, and tracking tools may contribute to change in lifestyle and had positive effect on metabolic syndrome components. Assessing cardiovascular disease (CVD) risk through online easy-to-use risk assessment tool could facilitate better decision making about lifestyle recommendations. Risk factor assessment as the first step in primary prevention, guides treatment strategy because the intensity of preventive recommendations is tailored to the patient’s risk status [37,38].

d. In the last paragraph of the discussion, you bring up gender differences in participation. Why do you think more males were interested in this intervention? However, the last two sentences of this paragraph do not make sense with the gender discussion. This was revised and the last two sentences were removed.

Our findings were similar with a study by Cully et al. where they found that men were more interested for diet, weight, and physical activity in using the Internet [43]. This study highlights the importance of interactive web-based programs that probably prove effective in lifestyle change.

Minor Essential Revisions
1. I am not sure why the trial is called the ‘Red Ruby’ when the website is called the “My Healthy Heart Profile.’ Was this study part of a larger study called ‘Red Ruby.’ I was waiting for context around the study name. You could consider adding more contexts or change the title of the article.
The Red Ruby is the public name of our trial. We considered Heart as a Red Ruby that means to many the most magnificent for life.

2. In the description of the ‘My Healthy Heart Profile’
   a. You might consider calling the ‘Personal Homepage’ simply ‘Educational Materials.’ It sounds like the homepage is just educational materials. Were the educational materials tailored to the individual or did all users receive the same materials?
   The personal homepage changed to educational materials and following sentence was added to the suggested section.
   All users received the same educational materials.
   b. I am not sure why the Personal Information page is relevant at all to the intervention. I’m assuming it was there for the needs of the researchers to have this information, but it does not provide anything new or interactive for the user. If I am missing the point, this could be clarified.
   It was there for the needs of the researchers to have this information specially when some were changed such as telephone number, and e-mail addresses.
   c. Inbox – You state that the users received a tailored diet to their inbox. Was there ongoing discussion, or the potential for ongoing discussion, between the user and the dietician? Could the user only communicate with the dietician or could they communicate with anyone else through this part of the website? If the users and dietician could communicate, did they?
   Thank you for beneficial recommendation. The following sentences added.
   This part has the potential for ongoing discussion between users and the dietician. The users could only communicate with the dietician through this part of the website. Users could ask their answers at any time they wished and received their response within 24 hours.

3. Statistical analysis
   a. You state that you used mean, standard deviation, median, range, frequency and percentage. I don’t see the presentation of median or range in your tables, so that could be deleted.
   These were deleted.
   b. It might be nice to include a sentence in this section that states that change scores were calculated and how they were calculated. This would help the reader understand the change scores that are presented in Table 2.
   Thank you. The following sentence was added.
   The change scores were calculated by subtracting the score on the baseline measurements from the scores on the 3- and 6-month.

4. Figure 2: The Y-axis title was cut off.
   It was fixed.

Discretionary Revisions
1. I am curious about the effect of education and wonder about the education distribution of the final sample. Was there differential attrition between lower vs. higher education groups? Although education was not significant at baseline, it approached significance. I wonder if that changed by 3 or 6 months. If low education stayed in, maybe the website was filling an information void. If higher stayed in, maybe the reading level was too high for the participants with lower education. Anyway, this is just an area of curiosity and not a recommendation for additional analysis.
Thank you.
Attrition rate in the intervention and control groups at first follow-up were the same (20%). However, the control group had significantly higher attrition rate (33.7%) compared to the intervention group (20%) at 6 months follow up. The more information of the topic was reported previously in details [26].

Reviewer: DR. N A Alwan
P 1
11: ‘reduce metabolic syndrome’ is ambiguous. Do you mean incidence or management/treatment?
“To management” was added.
14: How was MS defined in the trial – I think this should go in the abstract.
Thank you, the following sentences were added to the abstract and method as suggested:
Metabolic syndrome was defined according to The National Cholesterol Education Program Adult Treatment Panel (ATP) III as the presence of three or more of the following conditions (except for waist circumference which was defined as ≥90 cm for both genders for Iranian population): triglycerides ≥150 mg/dL and/or HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, blood pressure ≥130/85 mmHg, fasting blood glucose ≥110 mg/dL fasting blood glucose.
17: ‘named’ not ‘namely’
Done.
19: how was glycemic status measured?
This was added to the method (P10, 21).
Fasting blood glucose (FBG) was measured by using the glucose oxidase method (intra- and inter assay coefficients of variation 2.1% and 2.6%, respectively).
P2
2: ‘levels’
Done.
3: I think this sentence starting with ‘Although …’ is redundant because you quantify the reductions in the following sentence.
Thank you. It was deleted.
P4
7: ‘Iranians’ and remove bracket – why is the cut-off different for Iranians? Please State
The following sentences were added as your suggestion.
The current definitions of central adiposity are based on data from western populations. However, a growing body of literature indicates that this cut-offs likely need to be lower among Asian populations and may not be appropriate among Western populations. Several epidemiologic studies in Iranian populations have shown that Iranian have waist circumference greater than 90 cm in both genders: men and women [5-7].
P6
8: How did the participants know their BP prior to recruitment? Were these based on previous visits to their doctor? Was the inclusion criterion a minimum of one reading of 130/85 mmHg or consistent high BP? Please clarify this point.
During call interview eligible participants who interested in pursuing the study, were asked to schedule for a free clinic visit and clinical measurements by a trained nursing staff at Tehran Heart Center.

P7
10: Did participants fulfill all the criteria for the diagnosis of MS? Were the measurements objectively verified before randomization? Were all outcome measures performed at baseline before deciding on whether to randomize or not? Thank you. This was revised at outcome measurements as following:

P11
Metabolic syndrome was defined according to The National Cholesterol Education Program Adult Treatment Panel (ATP) III as the presence of three or more of the following conditions (except for waist circumference which was defined as ≥90 cm for both genders for Iranian population): triglycerides≥150 mg/dL and/or HDL cholesterol<40 mg/dL for men and <50 mg/dL for women, blood pressure ≥130/85 mmHg, fasting blood glucose≥110 mg/dL.

1; did you use ‘intention to treat’ analysis?
Yes, we did. It was stated at p: 11, 7.
12: what does ‘living outside the study setting’ exactly mean?
This was added. (Not living in Tehran)
14: how were they screened for eligibility? From the information they provided on the form or by objective measurements?
This was stated at p:7, line 8 and revised accordingly.
The study website database was reviewed by a trained research assistance in order to recognize registrant aged 20 and over living in Tehran (the study setting). Afterward the initially enrolled participants were contacted by a telephone call for eligibility screening. During the call interview eligible participants who interested in participating in the study, were asked to schedule for a free clinic visit and clinical measurements by a trained nursing staff at Tehran Heart Center.

19: please expand on how the ‘171 met the criteria for inclusion’

P12
This was added.
Of the attending participants for clinical assessments only 171 met the criteria for inclusion and had metabolic syndrome… (figure 1).

17: how much weight?
It was stated at the p12:13.
P13
4: blood pressure not ‘pressures’
Done.
8: not clear what you mean by ‘overall number of syndromes’. Please clarify. Does this mean people fulfilling the criteria for diagnosis? If they don’t they shouldn’t have been included in the trial in the first place.
This was added in method (outcome measures) as suggested. Also for clarifying this part, the sentence was revised.
…metabolic syndromes (having at least 3 components)
Was there any risk of contamination? Was the webpage free to access to anybody? Could the controls have accessed and used it at all?

These sentences were added.

For the security and confidentiality, the users will receive personal username and password. We will recommend the participants to keep the password safe and avoid sharing it with anyone. They will not able to change the password. If any one forgets the password a new one will be sent to his/her e-mails address.

P19

17: correct citation needed

Done.


Table 1:
What is meant by ‘addiction’?

Drug addiction was replaced.

Table 2:
Fasting blood glucose, not ‘fast’

Done

Figure 1:
Only in this figure, it clarifies that people were excluded for not having at least 3 Component of MS. This needs to be expanded on in the methods section.

Thank you. This was added as your suggestion above. In inclusion criteria: blood pressure ≥ 130/85 and plus one more metabolic syndrome components.

Also added to outcome measures in defining metabolic syndrome:

Metabolic syndrome was defined according to The National Cholesterol Education Program Adult Treatment Panel (ATP) III as the presence of three or more of the following conditions (except for waist circumference which was defined as ≥90 cm for both genders for Iranian population): triglycerides≥150 mg/dL and/or HDL cholesterol<40 mg/dL for men and <50 mg/dL for women, blood pressure ≥130/85 mmHg, fasting blood glucose≥110 mg/dL.

Reply to editorial requests

1. Please ensure the Abstract is on a separate page. This should follow the title page.

Done

2. Please include the date of registration with the trial registration number at the end of the abstract.

Done.

This was a randomized controlled trial that conducted from Jun to August 2012 in Tehran, Iran.

In total, 1437 individuals registered on the study website.

3. Please include the full name of the approving ethical committee in the Methods section, along with the reference number provided with approval.

Done.
The ethics committee of Tehran University of Medical Sciences Vice Chancellor for Research approved the study (No. 90/130/1736).

4. Please include a list of abbreviations used and their meanings, after the Conclusions section.

A list of abbreviations was provided:

**Abbreviation**


5. Please mention each author individually in your Authors’ Contributions section. We suggest the following kind of format (please use initials to refer to each author’s contribution).

Done.

6. Please state clearly whether or not you have funding in the Acknowledgements section. If there is no funding, please state this.

This study was not funded by special institutes.

Done.

7. Please upload the figures as separate files via the online submission system. They should not be included within the main manuscript document.

Done.

8. For completed randomised controlled trials, Trials requires the submission of a populated CONSORT checklist and flow diagram. If appropriate, please provide the flow diagram and checklist as additional files.

Done.

I hope you find the corrections satisfactory.

Yours sincerely

Ali Montazeri