Author’s response to reviews

Title: Effectiveness of a motivational intervention on overweight/obese patients in the Primary Healthcare: a cluster randomized trial

Authors:
Juan Jose Rodriguez-Cristobal (21002jrc@comb.cat)
Carlos Alonso-Villaverde (cvguta@hotmail.com)
Jose Mª Panisello (joima.panisello@gmail.com)
Pere Travé-Mercade (ptrave.cp.ics@gencat.net)
Francisca Rodríguez-Cortés (psicologia@canvis.net)
Josep R Marsal (joseprmarsal@yahoo.es)
Esther Peña (epena@csic-iccc.org)

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Author’s response to reviews:
Janet Hanley, PhD
BMC Family Practice

Dear Dr. J Hanley

We read with enthusiasm your letter giving us the option of resubmitting our manuscript entitled “Effectiveness of a motivational intervention on overweight/obese patients in the Primary Healthcare: a cluster randomized trial” to BMC Family Practice.

We have responded to the comments and queries of the reviewers. Responses are enclosed in separate pages for each reviewer and in the new version of the manuscript are shown in bold. We believe that the manuscript has been improved with the reviewers’ suggestions and hope that with these clarifications our manuscript will be now acceptable for publication in BMC Family Practice.
We confirm that this paper is not under consideration elsewhere, none of the paper's contents have been previously published, and all authors have read and approved the manuscript.

Looking forward to a prompt and favorable final review process,

We thank you in advance for your time and effort.

Kind regards,

Dr. Esther Peña
Corresponding Author
Cardiovascular Research Center; C/ Sant Antoni Mª Claret 167; 08025 Barcelona, Spain
Tel: 34 93 556 59 00; Fax: 34 93 556 55 59;
E-mail: epena@csic-iccc.org

REFEREE COMMENTS

Referee: 1 Reviewer #1: This is an interesting paper. The conclusions as the authors admit have to be tempered by the very high drop out rate. I do think they need to emphasise that limitation in the conclusions as it is likely that people who are unsuccessful in dieting are less likely to turn up for follow up than those who think they have been

As per reviewer suggestion a more accurate discussion about this are included in the new version of the manuscript (highlighted in bold).

Reviewer #2: Thank you for the opportunity to review this submission. This is an important and interesting topic and a well written paper. It focuses on whether a nurse led motivational intervention is more effective than a traditional intervention in promoting weight loss and its maintenance over a 24 month period. I have very few comments for consideration by the authors:

- The protocol has already been published. There is an overview of the methods included but some information is lacking on how randomisation took place etc. The reader is however, directed to the published protocol.
As per reviewer suggestion we have better clarified the randomisation protocol in the new version of the manuscript.

- The results, and figure 2, state that 1200 patients were initially included but 846 randomised. Please include an overview of reasons for the initial exclusions.

As per reviewer suggestion we have better clarified the exclusion criteria in the new version of the manuscript. Also in some cases invited participants choose not take part, or not give a sign consent form.

Exclusion Criteria:

- Patients with severe clinical pathology (bedridden, dementia, advanced neoplasia, etc.)
- Patients with secondary obesity (hypothyroidism, Cushing's disease, etc).
- Patients with severe sensorial disorders capable of interfering with the motivational intervention
- Patients with serious psychiatric disorders

- The results show that both groups lose weight with the motivational intervention group losing significantly more weight at both 12 and 24 months. The results also talk about the number of patient who lost 5% and 10% of their starting weight. However, it is not clear why these figures are important. I would be interested to read some clarity on the impact to health of a 5% or 10% weight loss and what we should be aiming for.

We appreciate the reviewer’s comment, and a more accurate discussion on the impact to health is included in the new version of the manuscript (highlighted in bold).

Reviewer #3:

Major comments:

1. The title of the manuscript should include "cluster randomised trial" in the title as per the CONSORT statement. Please refer to the CONSORT extension to cluster trials checklist: http://www.consort-statement.org/extensions?ContentWidgetId=554

According with the reviewer suggestion we have include “cluster randomised trial" in the title of the new version of the manuscript.
2. The description of the trial design could be improved. In particular, please clarify in the Methods section that the trial has a cluster randomised design and that the centres were randomised. How many clusters were randomised and what was the average size per cluster? What was the rationale for doing a cluster randomised trial?

We thank the reviewer for his/her pertinent observation. We have clarified the design and cluster randomization in the methods section of the new version of the manuscript (highlighted in bold).

3. Where exactly was the study conducted and how were the centres selected for inclusion in the study? What was the eligibility criteria for inclusion of clusters?

The study was conducted in Barcelona and L'Hospitalet de Llobregat (Spain). The coordinators have contacted the Basic Health Areas, to explain the protocol and confirm their participation.

After this period, it has been the distribution and randomization into the study groups: intervention/controls.

The inclusion and exclusion criteria were:

Inclusion criteria: Overweight (BMI>25) and obese (BMI>30) patients of both genders, registered in the medical history (MH) or recently diagnosed. Aged between 30 and 70 years. Agreement to participate in the study.
Exclusion criteria: Patients with severe clinical pathology (bedridden, dementia, advanced neoplasia, etc.). Patients with secondary obesity (hypothyroidism, Cushing's disease, etc). Patients with severe sensorial disorders capable of interfering with the motivational intervention (severe, uncorrected deafness, severe visual deficit, etc.). Patients with serious psychiatric disorders.

These criteria had been established to identify a trial population with overweight and obesity, and with sufficient statistical power with the proposed sample size. They were included sequentially, from the beginning of the study. To avoid possible bias in the selection of patients, and not overburden the nursing staff, patient recruitment and follow up were rolled out in stages during the first six months of the study to the first five patients who meet the study inclusion requirements and who present none of the exclusion criteria. This was carrying out superior quality control, using smaller sample size than would be possible if we randomized the patients.

4. Were patients recruited after the centres were randomized? Was any allocation concealment done at either the cluster or individual levels?

Patients were recruited always as the 5 first who meet the inclusion criteria after centers were randomized. Patients were never aware of the group in which they were allocated.

5. The primary outcome appears to have changed from the protocol paper. In the protocol paper (page 4) it suggests that the primary outcome is the proportion of patients showing a 5% reduction in weight loss, whereas this seems to have been changed to "change in continuous weight loss" in this results paper. Please explain the reasons for this change.

We apology for this mistake and we have amended this inaccuracy in the new version of the manuscript (highlighted in bold). The primary endpoint is to assess whether the efficacy of the healthcare professionals' usual practices, together with a motivational group intervention (delivered by a nurse trained by an expert psychologist), is more effective than an isolated traditional intervention on weight loss and its maintenance in overweight and obese patients. This will be calculated as the percentage of patients reducing their weight by 5% and maintenance over time.

6. It is not clear whether the 12 months weight loss outcome is primary or the 24 months outcome. The primary outcome is not clearly defined.
We apologize if we have not communicated properly our results. The primary endpoint is to assess that patients reducing their weight by 5% are able of maintenance those reduction over time (first 12 and after 24 months) in the motivational intervention group.

7. No sample size calculation is provided. If this is in the protocol paper then it should at least be referenced or reproduced in the current paper.

The number of subjects necessary to divide into two independent groups has been calculated. With the standard intervention, a weight reduction of 5% of weight is expected (P1). It was predicted that the experimental intervention would lead to 75% of the patients reducing their weight by 5%. It will be assumed an alpha risk of 0.05 (bilateral hypothesis) and a beta risk of 0.20 (a potential 80%). If the interventions will be assigned individually, in other words, per patient, the number of patients in each group would be 328 (756 in total). If we assume a percentage loss of 20% and apply a correction according to the formula \( Na = N [1/1-R] \) where \( N \) is the theoretical number of subjects, \( Na \) is the corrected number of subjects and \( R \) is the expected proportion of loss, a total of 946 patients would be necessary. Given that the assignment of the interventions will be done by BHA, we had to increase the sample size because of the design effect [28]; if 24 BHA (clusters) were to participate, 12 per type of information, it would be \( K = [m(1-CCI)]/[Z-(CCI \times m)] \) where \( K \) = number of subjects per cluster, \( m = 473 \) patients per intervention, \( Z = number of clusters per type of intervention = 12 \) and \( ICC = intra-class correlation coefficient. \) We assumed that the basic ICC for the percentage of obese patients who would reduce their weight by 5% was 0.005. The number of patients in each BHA (Cluster) would be 50. 50 subjects \( \times 12 \) BHA = 600 patients per arm or type of intervention. 600 subjects \( \times 2 \) interventions = a total of 1,200 patients.

We reference the sample size calculation in the new version of the paper.

8. Please give details about the randomisation method and type of randomisation. In the methods section there is a heading "Screening and randomization", but no details about the randomisation method are included beneath it. Please follow the CONSORT extension for cluster trials statement and describe who generated the randomization allocation sequence, who enrolled clusters etc.

Basic areas were randomly assigned to either control or intervention group as per a computer generated randomisation schedule. The coordinators have contacted the Basic Health Areas, to explain the protocol and confirm their participation. Patients were recruited always as the five first who meet the inclusion criteria after centers were randomized. Patients were never aware of the group in which they were allocated to minimize the effect of bias. We reference the randomization method in the new version of the paper.
9. Page 8 (statistical methods). "For categorical variables, mean and standard deviation were used..." It is not appropriate to calculate the mean and standard deviation of categorical data. We appreciate the reviewer’s comment. Accordingly, we have change “categorical variables” to “quantitative variables”.

10. Page 8: "multilevel statistical techniques". Please explain in more detail about the statistical analysis method. What variables were included in the models, and how was clustering taken into account?

   We adjusted different multilevel logistic/lineal models with the objective of avoid the possible effect introduced by the centers (the patients of the same center tends to be more similar than patients from other centers). The cluster was defined for each center. A random intercept was adjusted; in this model a unique random effect in the intercept is defined. Then, the estimated effects for the treatment are equal for all centers and it is considered the basal risk differ between them. In spite of we adjusted these kinds of models we decided to communicate the results using t-student and non-parametric test. The reason was:

   • We could confound the effect of the cluster with the real effect that we want to estimate. The centers were randomized in each treatment group: the variability explained by models is low.

   • Missing information could confound the reader.

11. For table 2, standard errors should be reported instead of standard deviations.

   Following the reviewer indications we have changed Table 2 and now we report standard errors.

12. If the \( p \)-value=0.05, then I interpret this result as being of borderline significance rather than statistically significant.

   We appreciate the reviewer’s comment. Accordingly, we have change \( p \)-value=0.05 and now is expressed as \( p<0.05 \).

13. Why were so many patients lost to follow-up between 12 and 24 months follow-up (figure 1), particularly in the control group? 34% were lost to follow-up between 12 and 24 months compared to only 10% in the intervention group. Overall, drop-out was as high as 53% in the
control group and 40% in the intervention group. Could the differential drop-out between trial arms have introduced bias into the analysis results at 24 months? What were the reasons for the differential drop-out? Was the drop-out similar across centres? Could the authors perform a missing data analysis to investigate possible predictors of the missing data? This should also be mentioned as an important limitation in the discussion section. Although "adherence was better in the intervention group" (page 13), this does NOT necessarily "confirm the long-term efficacy of the group motivational approach among patients" if the results are biased due to differential drop-out (e.g. if control patients with moderate or high weight loss were dropping out of the study).

Of course, the differences in the characteristics among the patients who concluded the study and the ones who had a dropout could introduce some bias. One of the known reason could be the fact that the patients without efficacy dropout in more frequency than the patients with a net effect. We studied the differences among them. The complainers were older, with more glucose and acid uric than not complainers. Other basal characteristics were the same. So, both profiles seem to be similar.

The drop out between centers was similar. We are so sorry but It is not possible perform a missing data analysis. This is a possibility for research that is not explored in our present study.

14. How was missing data dealt with in the primary analysis? The proportion of patients with missing primary outcome data is very high in this trial.

We didn’t deal the missing in any way. The analysis was performed with complete cases. In this particular study, with a high prevalence of missing in the primary outcome and with a high number of dropouts, we considered a non-assumable risk of introduce biases if we had had a missing imputation. On a hand, we cannot assume a multiple imputation in the context of a clinical trial and in other hand we want to communicate an intention-to-treat effect and we considered that a last observation carried forward was not the best option.

Minor comments:

15. Page 8: The statement "The hypothesis used to compare was the null hypothesis". doesn't make sense.

Amended.

16. Please report the intra-cluster correlation coefficient for the primary outcome.
17. It would be more informative if 95% confidence intervals were reported for at least the primary outcomes.

18. Page 9: "statically" should be "statistically".

19. Page 9: The statement "A significant reduction of the weight..." is vague. I think you mean "5% reduction in weight"?

20. It is not recommended to use significance tests to compare baseline differences in RCTs (see for example Knol MJ, Groenwold RHH, & Grobbee DE (2012). P-values in baseline tables of randomised controlled trials are inappropriate but still common in high impact journals. European journal of preventive cardiology, 19(2), 231-232).

We are more comfortable adding the significance tests to compare baseline differences so it is a study with a high rate of dropouts and missings.

21. Very small p-values should be reported as <0.0001 rather than 0.0000 in Table 3.

22. Page 11: Presumably "increased to 28.9%" should be "increased to 26.9%" as shown in Table 2?
23. First sentence of discussion: Significantly more patients achieved a reduction of 5% or more of the initial weight.

Amended.

24. Page 12, lines 5 - 29. Which study is this paragraph referring to?

Amended.

25. I could not see references for 29 to 31.

Amended.

26. Since the intervention was in addition to usual care, should "rather than the regular follow-up appointments" (page 13, line 14) be changed to "in addition to the regular follow-up appointments"?

Amended.

27. The Abstract states that "1,200 overweight/obese patients [were] randomly assigned", but I think you mean that 864 were randomly assigned. 1,200 were prescreened.

Amended.