Author’s response to reviews

Title: The role of gender in a smoking cessation intervention: a cluster randomized clinical trial

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

Please find attached our manuscript entitled “The role of gender in a smoking cessation intervention: a cluster randomized clinical trial” which we would like to be reconsidered for publication in BMC Public Health.

The present work is a part of the ISTAPS study, a study that evaluates the effectiveness of a stepped smoking cessation intervention based on a trans-theoretical model of change, applied to an extensive group of Primary Care Centers (PCC) (Cabezas C et al. BMC Public Health 2009;9:48).

The results of this work will contribute to the improvement of an important issue in Public Health because it explores gender as a predictor of smoking cessation. We believe that our work could interest your readers were it to be published in your journal.

On behalf of the co-authors I affirm that neither the manuscript, nor any part of it, has been published or is currently under consideration for publication by any other journal. All authors have read and approved the current manuscript.

Below we have responded to the changes proposed by the reviewers, and we have included the new version of the article in the online application system.

We look forward to hearing your opinion on the suitability of our manuscript for inclusion in the journal.

Yours sincerely,

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**Reviewer’s report**

**Title:** The role of gender in a smoking cessation intervention: a cluster randomized clinical trial

**Referee: Iñaki Galán**

**Major compulsory revisions:**

The main limitation of the study comes from the analysis of the data. In my opinion, the design used is not the most appropriate to meet the objectives. To evaluate the role of gender as a predictor of smoking cessation, within the community trial, the authors include all participants in the study, the intervention group and control. By including the controls do not evaluate the intervention process of trial and the results shown reflect the likelihood of smoking cessation by gender. In my opinion the authors have two options to evaluate this objective: 1) Analyse the whole sample but including an interaction term between study group (intervention and control) and gender, 2) select only the intervention group.

We agree with the reviewer and we address the objective of the study including the interaction term. The interaction term was not found to be significant.

The alternative models were compared using the partial likelihood ratio test and Akaike’s information criterion (AIC) to see which model provided the best fit for the data. The model without interaction provided the best fit so we have kept the most parsimonious model, without the interaction.

We have added the following paragraph to the statistical analysis section to clarify this aspect:

“Homogeneity of the group effect over men and women was verified, and therefore this interaction was not included in the model”…..

“The alternative models were compared using the partial likelihood ratio test and Akaike’s information criterion (AIC) to determine which model provided the best fit for the data”.

Another confusing aspect should be clarified is the statistical analysis used. The authors point out un the Methods section (data analysis) that they have used a random-effects logistic regression. Actually it is a mixed effects (fixed and random) multilevel logistic regression analysis. The random effects corresponding to the primary care centers and the fixed effects to the predictor variables. However, this reviewer does not understand the purpose of using this analysis since the absence of significant predictors at the primary care level that could explain the observed variability between centers (contextual variables). The results as shown in Table 3 only describe a residual variability between centers (variance adjusted for the effect of individual variables). This reviewer, taking into account the type of cluster design and purpose of the study, would have preferred a logistic regression model which takes into account the sample design to estimate the standard errors, using the module of Stata Survey Data, which is the program that the authors have used.
Random-effects, multilevel or mixed-effect analyses are developed to correct for the dependency of the outcome within clusters (Goldstein H, Browne W, Rasbash J. Multilevel modelling of medical data. Stat Med 2002; 21(21):3291-3315). This study is a cluster randomized clinical trial in which the unit of randomization was the Basic Care Unit (BCU). The mixed model approach takes into account the correlation between observations taken on the same cluster that other classical models of analysis cannot explore.

Furthermore, we applied multilevel statistical procedures (Goldstein H, University of London, Institute of Education, Bedford Group for Lifecourse and Statistical Studies. Multilevel statistical models. 3rd ed. London: Arnold, 2003) (Raudenbush SW, Bryk AS. Hierarchical linear models: applications and data analysis methods. 2nd ed. Thousand Oaks; London: Sage, 2002) to investigate the effect of individual’s gender factor on the likelihood of quitting smoking, as well as to investigate to what extent the BCUs may account for any variation in the outcome. We modeled individual (level-1 units) as nested within BCUs (level-2 units).


1) Initially we examined whether there was significant variability among BCUs in the likelihood of smoking cessation fitting an unconditional model with no predictors at either level. If no significant variation is observed, it may be assumed that all BCUs have the same probability of smoking cessation and a logistic regression model would be required. In our study there was evidence of variation between BCUs in the odds of the outcome, as indicated by the random intercept (Variance = 0.337, Confidence Interval 95%: 0.159-0.714). Moreover, if we compare our logistic mixed-effects model to a logistic model, the likelihood ratio test was significant (P-value = 0.0002); then the logistic mixed-effects model provides a best fit for the data.

2) Second, as significant variation exists between BCUs, we built a conditional model adding level-1 individual fixed effects. This model estimated the effect of individual covariates in the outcome and assessed whether these effects were different by BCUs (i.e., we allowed for level-2 random effects). In our study, even after controlling for individual effects, BCUs still vary significantly in the probability of smoking cessation (variance = 0.222, 95% confidence interval = 0.075-0.657).

3) Third, level-2 predictors are added to the previous model to assess if the variation between BCUs can be accounted for by these contextual factors. In our study, no level-2 predictors variables have been collected, so variability in prevalence of smoking cessation between BCUs still exists and remains unexplained. For future studies, it would be desirable to collect additional features of the BCUs that could account for the differences among BCUs.

We've added the following paragraph to the statistical analysis section to clarify these aspects:
A logistic mixed-effects model was performed to assess gender as a predictor of continuous smoking abstinence, accounting for clustering at the level of the BCU (Eldridge SM, 2004). We used the binomial logit link with a Full Maximum likelihood method of estimation via the adaptive Gaussian quadrature with fifty integration points..

We modeled individual (level-1 units) as nested within BCUs (level-2 units). Initially we examined whether there was significant variability among BCUs in the likelihood of smoking cessation fitting an unconditional model with no predictors at either level. As significant variation existed between BCUs, we built a conditional model adding level-1 individual fixed effects. We did not consider contextual variables at the BCU level.

The method recommended by Raudenbaush & Bryck (2002) was followed to select a subset of covariates to include in the final regression model.

The alternative models were compared using the partial likelihood ratio test and Akaike’s information criterion (AIC) to determine which model provided the best fit for the data.

The logistic regression model is poorly specified. It is not define what variables are included in the model (the number of variable in Table 1 is much greater than that of Table 3). It is not include any mention to the selection steps of variables in the model. It is assumed that all variables of Table 3 are introduced simultaneously but is is unknown whether there is an initial selection process.

We agree with the reviewer and have added the following paragraph in the statistical analysis section to clarify this aspect:

We modeled individual (level-1 units) as nested within BCUs (level-2 units). Initially we examined whether there was significant variability among BCUs in the likelihood of smoking cessation fitting an unconditional model with no predictors at either level. As significant variation existed between BCUs, we built a conditional model adding level-1 individual fixed effects. We did not consider contextual variables at the BCU level.

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We agree with the reviewer and have added the following paragraph in the statistical analysis section to clarify this aspect:

The initial regression model was adjusted for gender, study group, age, social class, alcohol, physical exercise, age at smoking initiation, number of cigarettes consumed last month, Fagerström test scores, Richmond test scores, smoker partner, smoker friends, stage of change, number of previous smoking cessation attempts lasting at least 24 hours, reduction of number of cigarettes consumed over the last month, importance of quitting smoking, confidence in quitting smoking, readiness to quit smoking and tobacco-related disease. The authors checked for confounders and multi-collinearity among the independent variables. Homogeneity of the group effect over men and women was verified, and therefore this interaction was not included in the model.

The alternative models were compared using the partial likelihood ratio test and Akaike’s information criterion (AIC) to determine which model provided the best fit for the data.

Physical activity is not defined (e.g. leisure time, at work, whether or not includes household activities, etc.). This variable is classified in two categories that do not follow any recommendations known.

In the questionnaire, the question was as follows: “Do you take any physical exercise or sports, such as walking, running, swimming, etc., outside of your work activities (i.e. during your leisure time? If yes, how often? And for how long each time? This question is very similar to the question included in the Spanish National Health Survey of 2006. It does not allow the evaluator to determine whether subjects follow healthy exercise (or physical activity) recommendations; however, it does classify
subjects according to this aspect. In our case, subjects were classified into 2 categories, each containing approximately 50% of subjects: one category for subjects who exercised at least once weekly during their leisure time and one for those who did not. We have specified the meaning of this variable in the Methods section.

The information in Table 2 should be restructured. If the aim is to compare in a bivariate way gender differences at baseline and one year follow-up stratified by intervention group and control, should be restricted to individuals from whom information is available at one year. Thus, the information would be more comparable avoiding differential bias due to loss of follow-up.

Following the reviewer’s recommendations, we have repeated this analysis and included only smokers with available follow-up data at one year.

Minor essential revisions:

Abstract (Background): Change “The aim of our study was to analyze the role of gender in a specific intervention of conducted smoking cessation in Spain” for this one “The aim of our study was to evaluate the role of gender in the effectiveness of a specific intervention of smoking cessation conducted in Spain”.

This change has been made.

Abstract (Methods): Write Spain instead of SPAIN.

This change has been made.

Key words: Include “Clinical Trials”.

This keyword has been included.

Background: At the end of the first paragraph, the phrase “In the same year, 27.2% of woman and 19.4% of men reported an increase of tobacco consumption with respect to 2004” is out of context and lack of appropriate citation. It seems to indicate an increase in consumption compared to 2004 but at a fraction of the population. This information should be linked to the third paragraph, but rather to provide international data focus on the situation in Spain.

We agree with the reviewer. We have placed this sentence in the context of the third paragraph in the Background section.

Methods:
Data collection:
On page 7, lines 12-22, the paragraph about treatment could be excluded since it is not used in the analysis. Related to treatment rather than to exclude this variable (it is questionable the problem of overfitting) would have been interesting to assess whether there are gender differences in response to different treatments because, as the authors note in the case of nicotine replacement therapies, there seems to be less effective in women than in men. This information would be useful in assessing the therapeutic
strategy for primary health care. In any case it would be interesting to know the distribution of treatments by gender.

Pharmacological treatment is part of the intervention; however, some subjects in the control group also received pharmacological treatment. Thus, this variable cannot be included as a separate variable because it is assessed as a part of the intervention. However, we do not have specific data on the types of treatments that subjects received. We do know which percentage of males and females received some type of assistance to quit smoking (these percentages are included in the manuscript). We have kept the paragraph in the article with some changes.

The last paragraph of this section refers to variables measured only in women?

The depression, anxiety, etc. variables which are mentioned in the last paragraph were assessed in both genders. To avoid confusion and because these were not included in the analysis, this sentence has been removed from the article.

Data analysis:
There are a larger number of subjects lost to follow-up. Classified all of them as smokers it is questionable. For this reason, an analysis including these subjects could be performed to ensure that the results do not change (to quote these results in the text, no need to include tables).

Classifying subjects lost to follow-up as smokers is indeed questionable; nonetheless, we followed an intention-to-treat approach as it is a conservative bias as recommended by the CONSORT Statement (Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. BMJ. 2004; 328(7441):702-708).

We have included the following paragraph in the statistical analysis section:
“All subjects were included in the groups to which they were randomized and an intention-to-treat analysis was performed. Additionally, subjects lost to follow-up were considered unsuccessful in their attempt to quit smoking and therefore current smokers, which is the standard approach in smoking cessation intervention studies (Barnes S, Larsen M, Schroeder D, Hanson A, Decker P. Missing data assumptions and methods in a smoking cessation study. Addiction 2010; 105(3):431-7)”.

Results:
Lines 17-19, page 10, mentioned data not shown “It was observed that women had more smoking cravings confronted with difficult situations when such as depression, anger….. “This information, if relevant, should have been included in the overall analysis of the study. Otherwise adds more confusion.
As explained above, in order to avoid confusion and because these variables were not included in the model, we have removed this paragraph from the article, from both the Methods and the Results sections.
Page 11, lines 5-8 “… was adjusted for age, group…” should be included at the end of the phrase “at baseline”.

We have added “at baseline” at the end of the sentence.

Page 11, lines 10-21: the data are not shown in tables. If this information is relevant should be accompanied by the appropriate table.
As suggested by the reviewer, we have added a table summarizing the analysis of covariance and reworded the relevant paragraph in the article.

Discussion:
Page 12, lines 10-11: “was…but this effect due to the high of our study sample size”. This statement must be qualified as many of the differences are clinically significant and cannot be attributed to the sample size.

We believe that, partly, some differences observed in Table 1 may be due to the sample size; however, it is true that there is a gender pattern in socio-demographic and socio-economic aspects, as demonstrated by the Spanish National Health Survey conducted in 2006 (http://www.msc.es). This aspect has been clarified in the Discussion section.

Page 13, lines 4-6, quoted in the text the Bohadana and Pogun studies (references 24 and 27) but it lacks the authors of quotations 28 and 29.

References 28 and 29 were included as they supplemented the information for the studies by Bohadana and Pogun. We have kept both reference 28 and 29 in the text. However, we have reworded this sentence to improve clarity.

Tables:
Report to three decimals places for the p-values and p<0.001.

We have added one decimal.

Label the variables exactly the same in all tables.

We have corrected the differences found.

Follow the same order of variables in all tables.

We have re-ordered variables in all tables.

Table 3 should include the p-value in the estimation of the variance.

We have included the p-value provided by the Stata version 11 comparing our final model to the logistic regression model: Likelihood ratio test vs logistic regression p=0.0137.
Referee: Joan R Villalbí

Major compulsory revisions:

The contents of the intervention and the usual care received by the reference group need to be well explained. The intervention group seems to receive a structured and systematic intervention, while the comparison group supposedly receives “usual care”, which may consist (or not) in brief advice for smokers (specially if they have smoking-related conditions) but may also include pharmacological treatment to quit. This seems somewhat inconsistent, as these treatments are not usually covered by the NHS in Spain. The authors need to explain better what happens to smokers in the comparison group.

The intervention is fully explained in the protocol (BMC Public Health 2009;9:48) and is briefly summarized in the article. As the reviewer says, usual care consists of brief advice for smokers and may also include pharmacological treatment, although this treatment is not financed by the National Health Service. We have included this sentence in the Methods section.

The results must include proper presentation of quitting results. The authors state that the intervention was useful and then go on to gender comparisons. The major outcome is quitting, and it must be presented (ie in table 2) and discussed before attention is paid to comparisons by gender. If this major outcome is being published elsewhere, this reviewer would be concerned with the originality of the results.

The information on point prevalence and continued abstinence is explained in the text, even if not summarized in the form of a table. The authors’ intent was to focus on the effect of gender as seen at the one-year follow-up. The global effect of the intervention at 2 years has been assessed in another article which is currently being peer-reviewed.

In an international journal, the knowledge of some aspects of how publicly funded primary health care is organised in the NHS in Spain cannot be taken for granted. The authors need to change the UBA concept into a more general concept such as “family physician or nurse” all through the paper in the figure 1.

The Spanish National Health Service (NHS) provides universal cover and is financed, essentially, by general taxes. The system is divided into primary and secondary care. Primary care (PC) is organized as a network of primary health care teams (PHCT) that behave as geographical and administrative units where PC services are planned, managed and provided for a population ranging from 5,000 to 25,000 citizens. The PHCT staff includes: general practitioners (GPs), pediatricians, nurses, social workers, dentists and ancillary staff. Healthcare is free-of-charge and universal; however, certain special treatments, such as those used for quitting smoking, are not financed by the NHS. We have included the following sentence in the Methods section:

“The control group received usual care (standard care), including smoking cessation counseling offered in primary care to patients with diseases related to tobacco consumption. This is entirely free of charge, as the Spanish National Health Service (NHS) provides universal medical coverage and is financed essentially by general taxes.
The usual care could also include drug therapies, although these treatments were not covered by the National Health Service”.

The meaning of “BCU” is explained in the text. However, in Figure 1, we will replace it by “family physician and nurse”.

Other than that, there are some serious English language issues to be addressed (for instance “related disease” and not “associated pathology”).

We accepted the reviewer’s suggestion. The article will be proofread again.

Minor essential revisions:

Other minor issues to solve include the lack of a reference to the Prochaska model used all through the paper,

The reference to the Prochaska model is already included in the manuscript. Specifically, it is reference number 12.

The missing link to the report in reference 8.

We have included the link web in the reference.

Fagerström and Richmond test scores in tables should be reported similarly and as “scores”.

We accept the reviewer’s suggestion and have added the word ‘score’. In the tables, we have reported the mean and the standard deviation as the results.

Perhaps reference 11 could be changed or completed making reference to papers discussing this issue as it changed such as Med Clin (Barc) 2002; 118(3):81-5 and Med Clin (Barc) 2009;132(11):414-9.

We have followed the reviewer’s suggestion and added these two references.