Author's response to reviews

Title: Changes of Hormone Replacement Therapy in Menopausal Women: An Observational Study in Taiwan

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Author’s response to reviews: see over
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RE: Changes of Hormone Replacement Therapy in Menopausal Women in Taiwan:  
An Observational Study

Dear Editor Puebla:

Please find attached file with the revised version of our manuscript entitled “Changes of Hormone Replacement Therapy in Menopausal Women in Taiwan: An Observational Study”

Thank you for providing us with this chance to revise the paper and we are very grateful for the reviewer’s helpful comments on reorganizing our paper. We appreciate the time and effort you spent helping us with our article. We have tried to revise our paper and answer questions brought up by the reviewers. We summarize the major modifications as follows:

First, as suggested by the reviewer, we have consulted epidemiologists and statisticians to confirm our methodology of the analyses. We kept three logistic regression models, including two interaction models, in our study as suggested by other reviewers. Interaction models were used to explore the association of the period (before and after the release of WHI report) and the prescription of HRT in different categories of level of education and the level of medical care institutions. In order to reduce the effect of repeated measurements, we estimated logistic regressions using random-effect model.
We also clarified our units of analyses as suggested by the reviewer.

Second, as suggested by the reviewer, we deleted the chi-square test in table 2 to avoid potential confusion.

Third, based on the reviewer’s concern, we clarified the information shown in table 3 and added footnote for table 3 to avoid potential confusion.

The revised manuscript is a much stronger paper as a result of the reviewer’s suggestions. We hope that the changes that we have made will satisfy the reviewers and the editors.
Reviewer A: COMMENTS FOR AUTHOR/S

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Title: Changes of Hormone Replacement Therapy in Menopausal Women in Taiwan: An Observational Study.

Author(s): Weng-Foung Huang, Yi-Wen Tsai, Fei-Yuan Hsiao, and Wen-Chun Liu

Question posed by the authors

All of the comments have been taken into account, but important questions remain concerning the methodology of the analyses.

At the beginning, we’d like to appreciate the reviewer’s suggestions. We have consulted epidemiologists and statisticians to confirm our methodology of the analyses. We hope the modifications that we have made will satisfy the reviewers and the editors.

1. As we already said, the two samples of women, 402 who had outpatient visits before and 360 women who had outpatient visits after the publication of the WHI, are not independent. So, to use a CHI 2 test is incorrect to compare these two groups.

   We have deleted the chi-square test in table 2 to avoid potential confusion.

2. The comparisons presented in table 2 should concern outpatient visits as unit of analyses, as it is the case for the second part of table 2. In the methodology of this work, a participant woman cannot be considered as unit of analysis.

   Firstly, we apologize for confusing the reviewer. We totally understand that using outpatient visits as unit of analysis in our study is an important concern. However, because of the potential repeated measurements of these outpatient visits (since the two samples of women were not independent as mentioned previously by the reviewer), we decided to keep the information regarding the women’s characteristics in table 2 to avoid potential over-estimation or under-estimation. However, we did use outpatient visits as unit of analysis in our logistic regression models as suggested by the reviewer.

3. The methods used to study the influence of WHI on the prescription of HRT still need to be clarified.
Firstly, we have modified our study objective (page 6) from “we examined whether WHI influenced the decision to use MHT to treat menopausal outpatients in Taiwan and to what extent the decision to use this treatment depended upon certain patient or health care provider” to “we examined the changes of prescription of MHT to treat menopausal outpatients in Taiwan before and after the publication of WHI report as well as to what extent certain patient or health care provider characteristics influenced the decision to use MHT” to avoid potential confusion.

Secondly, we have consulted epidemiologists and statisticians to evaluate methods used in our study. In this section, we kept the logistic regressions of random effect because it is the right model for repeated measurement. Three logistic regression models, including two interaction models, were used in our study. Interaction models were used to explore the association of the period (before and after the release of WHI report) and the prescription of HRT in different categories of level of education and the level of medical care institutions as suggested by other reviewers.

Results of logistic regression are displayed in table 3.

4. The criteria used to include the variables in the logistic regression are not mentionned (usually variables are selected after a first step of univariate analysis).

As suggested by other reviewers, we did not drop any variable in our logistic regression models even when they were not significant. We believed those non-significant variables might provide important information on this issue.

5. Table 3 is difficult to understand:

- The sample size of each group for each variable must be precised.

First, we apologize for confusing the reviewer. We have re-checked table 3 and provided the sample size of each group for each variable except for the interaction terms. Also, we have made sure that sample size of each group for each variable is precise.

- Percentages in the second column of table 3 seem to be the proportion of, for the first line, the number of outpatient visits after and before the publication of the WHI. Percentages giving information for the reader are the proportions of outpatient visit with a prescription of MHT in each category.

To clarify, percentages in the second column of table 3 were the proportion of the number of outpatient visits of each sub-group of patient or health-provider’s characteristics. For example, among the total 2,549 outpatient visits, there were 1,157 visits (45.4%) after the publication of WHI report while there were 1,392
visits (54.6%) after the publication of WHI report. And, among the total 2,549 outpatient visits, 627 (24.6%) were from metropolitan hospitals, 492 (19.3%) from local community hospitals, 955 (37.5%) from physician clinics, and 475 (18.6%) from academic medical centers. We have also added footnote for table 3 to avoid potential misunderstanding.

- It is difficult to understand the meaning of the ORs presented for the interactions.

To make this clearer, we made more explicit the results of logistic regression as follows to avoid any possible misunderstanding.

Three logistic regression models, including two interaction models, were used in our study. Interaction models were used to explore the association of the period (before and after the release of WHI report) and the prescription of HRT in different categories of level of women education and the level of medical care institutions as suggested by other reviewers.

A linear function of the coefficient was estimated and tested in these models with the interaction terms. Other covariates were also included in these models. However, in order to simplify interpretation, we showed the effect of publication of the WHI on the four types of hospital instead of the interaction terms. Also, we showed the effect of publication of the WHI on the five categories of level of women education instead of the interaction terms.

In our study, women with college level educations or higher were less likely to be prescribed MHT after the WHI report than they were before (Model 2; OR 0.30; 95% CI 0.11-0.83). Academic medical centers were less likely to prescribe MHT than other medical care institutions after the release of WHI report (Model 3; OR 0.15; 95% CI 0.34-0.63).

We have strengthened the second paragraph (page 10-11) of Statistical Analysis to make the statistical models used in our study more clearly. We have also added footnote for table 3 to avoid potential misunderstanding in this version.

- Confidence interval for ORs corresponding to medical institution seem very wide.

As suggested by the reviewer, we have consulted epidemiologists and statisticians to evaluate methods used in our study. Besides, we have re-run all our statistics to make sure all results in our study are precise. The wide confidence interval for ORs corresponding to medical institution should be due to data variation.
It is impossible to express how much we really appreciate the reviewer’s very thorough and thoughtful review of our paper. His/her opinions and valuable suggestions inspired us to think the whole paper over carefully, painfully cut out a lot of background research that helped us in the beginning but did not belong in the paper, re-evaluated our choice of statistical methods and re-ran our analysis, substantially reorganized the text and sharpen its focus. His/her comments went beyond the call of duty, and, therefore, we feel we owe him and you, the editor, our best response. I believe and hope that you will find this paper much better and quite suitable for publication.

Sincerely yours,

Weng-Foung Huang, Ph.D.
(on behalf of all authors)
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