Author's response to reviews

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

Authors:

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Version: 2 Date: 16 June 2006

Author's response to reviews: see over
Dear Nafisa:

Please find attached file containing 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 changed the text to clarify points suggested by the reviewer, and spent a great deal of time creating a sharper, more direct paper. We summarize the major modifications as the Attachment #1, and our responses to the two reviewers in the Attachment #2 and #3.

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.

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, substantially reorganize the text and sharpen its focus. His/her comments went beyond the call of duty, and, therefore, we felt 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,

[Signature]

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Attachment #1: Summary of the major modifications in the revised manuscript.

Manuscript number: 1950367689487375

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

First, as suggested by the reviewer, we modified our statistical methods. In order to meet the research question, we also retrieved our data. We first modified our analysis unit as only prescription with estrogen was selected to serve our outcome measurement in the statistical analysis. In addition, 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. In order to reduce the effect of repeated measurements, we estimated logistic regressions using random-effect model.

Second, as suggested by the reviewer, we have revised the statement of our result to make the interpretation of OR more clear. The content of discussion and conclusion has also been modified accordingly. The revised interpretation of OR made the results of this paper more informative to the readers.

Third, based on the reviewer’s concern, we modified the terms of hormone replacement therapy (HRT) based on the reviewer’s suggestion. The statement of hormone replacement therapy (HRT) in the manuscript had been replaced into menopausal hormone therapy (MHT).

Fourth, following the advice of the reviewer, we added a little more descriptive information on the variable resources we used to clarify the variables used in our statistical model.

Fifth, we have added explanations in paragraphs to clarify or elaborate our ideas, based on reviewer’s comments, elaborated in the following pages.

Sixth, we have made a lot of other changes to the text to make it more stylistically correct and direct, without, however, changing content.
Attachment #2: Responses to Reviewer A’s Comments

Reviewer A: COMMENTS FOR AUTHOR/S

Manuscript number: 1950367689487375

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

The authors analysed the influence of the publication of the results of the WHI on the decision to use HRT to treat menopausal women in Taiwan. This is an important question clearly defined, others groups have studied this issue in other countries.

We are glad the reviewer finds our research important, too.

Methods

1. To take into account the decision to use HRT, the authors selected 504 women for whom they had data for the analyses (i.e. women 45 years and older from a representative sample of Taiwan’s general population who consented to the linkage of their personal data and National Health Insurance (NHI) data). These 504 women had NIH records which indicated « they had sought treatment for menopause related problems » 6 months before and 6 months after the publication of the WHI. The dependant variable was the prescription of HRT during an outpatient visit for menopause. It is stated page 10 in the Results section that these 504 women had 2549 outpatient visits (in the one year period studied).

Page 9, in the section Statistical analysis, the authors write that they analyzed « the effect of the WHI on HRT, … on the likelihood that a woman would use HRT in the outpatient visit for menopause ». This sentence is not clear, and the occurrence of a prescription of HRT during an outpatient visit is not the same variable as HRT used by the woman.

We have re-written the sentence in the first paragraph (page 10) of Statistical Analysis based on the reviewer’s suggestions.

In our study, we would like to analyze the effect of the WHI report, women’s
characteristics such as age, educational level, marital status, employment status, personal monthly income, illness during the previous six months and osteoporosis on the likelihood that a woman would be prescribed menopausal hormone therapy (MHT) in the outpatient visit for menopause-related symptoms.

Our hormone utilization data was obtained from administrative data. Therefore, only the occurrence of a prescription of MHT during an outpatient visit could be retrieved. As a result, we modified our description “MHT used by the woman” into “hormone therapy being prescribed to these women” in the text.

2. The major problem is that we do not know if the analyses considered the number of outpatient visits or the number of women. On page 9, in the section Statistical analysis, it seems that the analyses considered outpatient visits, because the authors report « our reference group of outpatient visits consisted of those visits by unmarried and unemployed … ». We have re-written the first paragraph (page 10) of Statistical Analysis to make the major unit of analysis more clearly.

Our analysis unit in the logistic regression was 2,549 outpatient visits for menopause-related symptoms from the 504 selected women. Outpatient visits for menopause-related symptoms with prescription of MHT were the study group. While outpatient visits for menopause-related symptoms but without prescription of HT were served as the reference group. The results of logistic regression are displayed in table 3.

On the other hand, Table 1 and Table 2 provide the information for the characteristics of 3,439 females aged 45 years old or above extracted from the NHIS survey, and the characteristics of 504 women females further had NHI records indicating they had sought treatment for menopause-related problems during our study period.

3. The seven ICD9CM codes used to define menopausal conditions must be detailed.

The detailed ICD9-CM codes have been described in the first paragraph (page 8) of Measures.

4. HRT was defined by estrogen OR progestin. Usually HRT is defined by at least use of estrogen, but progestin alone cannot be considered as HRT.

We have modified the definition of hormone therapy based on the reviewer’s suggestions. Only prescription with estrogen was re-selected to describe our outcome measurement in the statistical analysis. Our outcome variable was created as a dummy variable to indicate whether or not MHT was prescribed in an outpatient
visit: 1, if estrogen was prescribed; zero, if not prescribed. The content of this article also modified accordingly in the first paragraph (page 8) of Measures.

5. The source of information for all variables should be mentioned, i.e. interview during the 2001 NHIS or outpatient records.

We added more detailed information for all variables in the second and third paragraph (page 8-10) of Measures based on the reviewer’s suggestions.

Variables related to outpatient visits for menopause including the categories of health care institution and physician specialty were mainly extracted from NHI outpatient records. Variables of patient demographics were obtained from the 2001 NHIS, which include age, marital status, employment status, and monthly income.

6. In the methods section there is a comparison between women who gave their consent to the linkage of their data and NHI data and women who did not, but the results of this comparison, and the differences observed between women is not discussed in the Discussion section, i.e. how these differences may have biased the results observed on prescription of HRT.

We have strengthened the text of discussion based on the suggestion of the reviewers.

In summary, our study is subject to potential bias for sample selection criteria. Only those who signed the inform consent for linking NHI claim data would be included in this study. Those who did not sign the inform consent were more likely to be older, lower educated, unmarried, unemployed, with lower personal income and better health status. Based on the prediction of our logistic regression, MHT was more likely to be prescribed in the outpatient visit for menopause-related problem by women who were unemployed and lower educated women. Thus, we would suspect that those women who were not included in this paper were those who were more likely to receive MHT prescription if they had outpatient visits for menopause-related problems than those who were included in this study. Besides, there was a significant effect in the interaction between WHI and patient education; after WHI report, women with undergraduate or graduate (higher education) were less likely to receive MHT; OR=0.30 (0.11-0.83) Thus, we would suspect that the effect of WHI on reducing prescription of MHT was over-estimated because lower-educated women were more likely to be excluded and who were less responsive to WHI report than higher-educated women.

7. The methods used to study the influence of WHI on the prescription of HRT need to be clarified. The two samples of women, before and after the publication of the WHI, are not independent: among the 504 women, 285 had NHI outpatient record for menopause during the 2 periods. It is not clear how this
was taken into account in the statistical analysis. The authors should specify how the methods they used—pooled analysis and random effect—dealt with this, and give references for these methods.

In this section, we kept the logistic regression of random effect because it is the right model for repeated measurement. We have re-analyzed the influence of WHI on the prescription of MHT. 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. In order to reduce the effect of repeated measurements, we estimated logistic regressions using random-effect model.

The description of the first paragraph (page 10) of Statistical analysis was also modified. Results of logistic regression are displayed in table 3.

8. What were the criteria used to include the variables in the logistic regression?

The variables included in the logistic regression were common in the literature of health services. They reflect the socio-demographic factors of patients, health status, and supplier characteristics.

9. The authors must indicate the statistical software they have used for the analyses.

Logistic regression model used in our study was done on SAS Version 8.0. The first paragraph (page 10) of Statistical analysis now provides the information on the statistical package we used in our study based on the reviewer’s suggestions.

10. Table 2 is difficult to understand and its usefulness is not clear. The term « cases » for the 504 women included in the analyses does not seem appropriate MP = ? menopausal? It is not easy to understand the meaning of the 2 groups: 402 before WHI, 360 after. In the text page 10, other numbers are reported (144 before, 102 after). Is it the number of outpatient visits?

We have modified table 2 to provide clearer information. The numbers reported in the first paragraph (page 11) of results was the 504 females who had NHI records indicating they had sought treatment for menopause related problems during the study period starting six months before and ending six months after the WHI was published. The numbers indicated individual patients.

11. Table 3: the overall sample size must be given for the logistic regression because of missing data, and also the size of each group for each variable: for instance, WHI report after, n= before, n= . And also to clarify the point concerning the
unit of analysis, outpatient visit or woman. For the line « Medical care », what is the meaning of the OR 3.27 ? (no OR is mentionned for the model b) How can the authors explain the differences between OR obtained with the 2 methods, because for medical care for instance, the ORs are quite different.

We have added the size of each group for each variable in table 3. We have re-analyzed the influence of WHI on the prescription of MHT. 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. In order to reduce the effect of repeated measurements, we estimated logistic regressions using random-effect model.

Results of logistic regression were displayed in table 3. Our analysis unit in the logistic regression was 2,549 outpatient visits for menopause-related symptoms from the 504 selected women. Information on the size of outpatient visits for each group for each variable was added into table 3 based on the reviewer’s suggestion.

In our re-analyzed logistic regression model, only random-effect model was used.

12. Results concerning interactions between for instance level of education and the period (before and after WHI) would be interesting. The results presented here show that on one side the period is related to the prescription of HRT, and that other factors, such as women’s characteristics, are also associated with HRT prescription. It would have been interesting to explore the association of the period and the prescription of HRT in different categories of level of education, or according to the physician’s specialty.

We have re-analyzed the influence of WHI on the prescription of MHT. 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. The paragraph (page 12-13) of Results also now helps provide descriptive information on this issue.

13. A general remark concerning this study is that the way the methods, the results and the tables are reported should be improved to correspond to the relevant standard of epidemiological analyses.

We have modified the methods, the results and the tables based on the reviewer’s suggestions.

Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.
Are the discussion and conclusions well balanced and adequately supported by the data?

1. The sentence « the decision whether to use HRT … was not purely dominated by the physicians » should be modified.

   We have modified the statement based on the reviewer’s suggestions. The statement had been modified into “the decision whether MHT for menopause-related symptoms was prescribed to selected women was not purely dominated by the physician.”

2. Concerning the limitations of the study, the authors report that they did not taken into account women who might stop seeking medical treatment for menopause, and so that they have underestimated women’s reaction to the WHI report. Does this mean that they hypothesized that women reported fewer complaints related to menopause after the publication of the WHI?

   Our data was drawn from two sources: the 2001 National Health Interview Survey (NHIS) and the NHI outpatient records of interviewees who consented to the linking of their personal information from the two sources. Therefore, only the occurrence of a prescription of MHT during an outpatient visit can be retrieved. Women searching for non-pharmacological treatment (ex. herbal products) instead of outpatient visits after the publication of WHI may not be shown in our study.

3. Another limitation of the study is that we do not know the proportion of the 144+258 women in the first period who were using HRT.

   We have modified the content of table 2 to provide the information on outpatient visits for menopause-related symptoms. Among 1,392 outpatient visits from 402 (144+258) women in the first period, 82.97% (1,157 outpatient visits) were prescribed MHT.

4. The interpretation of the results given in the conclusion should not mention « the different reactions from health providers and the patients », because these reactions can only be indirectly estimated through the data. The sentence « the decision whether to use HRT … was not purely dominated by the physicians » should be modified.

   We have modified the statement according to the reviewer’s suggestion.

Do the title and abstract accurately convey what has been found? Yes
Attachment #3: Responses to Reviewer A's Comments

Reviewer B: COMMENTS FOR AUTHOR/S

Manuscript number: 1950367689487375

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

General

1. The article is interesting in telling how hormone (HT) is used in Taiwan, and how WHI results in 2002 lowered HT prescribing. The article provided an interesting piece of information that Taiwan government openly promoted use of HT in 1999, although scientific evidence about HT preventive effects had not been proved.

We are grateful for the reviewer’s opinion. We hope our study could provide informative data on this issue.

2. The research question is whether WHI influenced in physicians' willingness to prescribe HT and women's willingness to use HT. The data make possible to study changes in physicians' prescribing practices but not necessary women's HT use. Women have bought the prescribed medication but it does not guarantee that they also take the prescribed medication.

We agreed with the reviewer’s comments. Our data was drawn from two sources: the 2001 National Health Interview Survey (NHIS) and the NHI outpatient records of interviewees who consented to the linking of their personal information from the two sources. Therefore, only the occurrence of a prescription of MHT during an outpatient visit can be retrieved. We also admit that patient compliance is always a common limitation in a study using secondary data analysis.

3. The chosen method is appropriate and well described with details. Statistical analysis is not very clear; description of reference group is confusingly described, it should be clarified in the text. Table 3 shows clearly the reference group.

We have re-analyzed the influence of WHI on the prescription of MHT. 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. In order to reduce the effect of repeated measurements, we estimated logistic regressions using random-effect model.

In terms of WHI effect, outpatient visits for menopause-related symptoms before the WHI report were the reference group. While outpatient visits for menopause-related symptoms after the WHI report served as the reference group. Other reference groups for each variable are listed as follows: the reference group of outpatient visits consisted of those visits by unmarried and unemployed 45 – 55 year-old women with undergraduate or graduate level educations, who had no personal monthly income, had no illness in the six-month period leading up to the survey and was not diagnosed as having osteoporosis. The reference group of outpatient visits also included the visits served not by an obstetrician or a gynecologist and at an academic medical center.

We kept the description of the reference group in terms of WHI effect in text only to avoid a misleading concept. Other reference groups for each variable are listed in the context of table 3.

The description of the first paragraph (page 10) of Statistical analysis was also modified. Results of logistic regression were displayed in table 3.

4. It remained unclear how women's illness was defined?

Two dummy health status variables were created. The first dummy health status variable represented whether the respondent experienced illnesses during the six-month period leading up to the interview was extracted from the 2001 NHIS. A value of 1 was assigned if illness had been experienced, and a value of 0 if not. Another dummy health status variable represented whether the patient had been diagnosed as having osteoporosis was extracted from the NHI outpatient record. A value of 1 was assigned if the patient had been diagnosed or treated for osteoporosis or osteoporosis-related condition (ICD9CM=733.00 Osteoporosis unspecified, 733.01 Senile osteoporosis, 733.02 Idiopathic osteoporosis, 733.03 Disuse osteoporosis, 733.09 other osteoporosis), and a value of 0 if not.

5. There is one major problem in reporting. The interpretation of OR is incorrect, OR shows difference but not its amount. Reporting needs revision.

Discussion and conclusion comes from the data but reporting need revision because of OR interpretation problem.

We have revised the statement of our result to make the interpretation of OR more clear. The content of discussion and conclusion have also modified accordingly.
6. The title is not very informative. The article describes rather physicians' description practices than women's decisions about HT. Problems in reporting results reflect also in the abstract.

We have modified the title into the “Changes of the Prescription of Hormone Therapy in Menopausal Women: An Observational Study in Taiwan”. The content of abstract have also modified accordingly.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. There is one major problem in reporting. The interpretation of OR is incorrect, OR shows difference but not its amount. Reporting needs revision. Discussion and conclusion comes from the data but reporting need revision because of OR interpretation problem.

We have revised the statement of our result to make the interpretation of OR more clear. The content of discussion and conclusion has also been modified accordingly.

2. The abstract need revision, as well, after the results have been revised.

We have revised the abstract due to the modification of our results.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Statistical analysis is not very clear; description of reference group is confusingly described, it should be clarified in the text. Table 3 shows clearly the reference group.

We have re-analyzed the influence of WHI on the prescription of MHT. 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. In order to reduce the effect of repeated measurements, we estimated logistic regressions using random-effect model.

Outpatient visits for menopause-related symptoms with prescription of HT were the study group. While outpatient visits for menopause-related symptoms but without prescription of HT were served as the reference group.
The description of the first paragraph (page 10) of Statistical analysis was also modified. Results of logistic regression are displayed in table 3.

2. It remained unclear how women's illness was defined?

Two dummy health status variables were created. The first dummy health status variable represented whether the respondent experienced illnesses during the six-month period leading up to the interview was extracted from the 2001 NHIS. A value of 1 was assigned if illness had been experienced, and a value of 0 if not. A value of 1 was assigned if the patient had been diagnosed or treated for osteoporosis or osteoporosis-related condition (ICD9CM=733.00 Osteoporosis unspecified, 733.01 Senile osteoporosis, 733.02 Idiopathic osteoporosis, 733.03 Disuse osteoporosis, 733.09 other osteoporosis), and a value of 0 if not.

3. In data sources (p. 6 down) I think the second source should be NHI (instead of NNHI)

We corrected the description in the text based on the reviewer’s suggestion. It should be NHI instead of NNHI.

4. In tables 1 and 2 in footnotes level of significance is given but they are not given in the tables.

We have modified table 1 and table 2 based on the reviewer’s suggestion.

Discretionary Revisions (which the author can choose to ignore)

1. I suggest that the authors consider the terminology in the manuscript. After WHI trial results hormone treatment (HT) seems to have become established instead of HRT when it concerns treatment around menopause. Alternative estrogen therapy (ET) estrogen-progestin therapy (EPT), menopausal hormone therapy (MHT) has been used. Instead, hormone replacement therapy (HRT) is currently used for treatment of hormone deficiency e.g. because of premature menopause.

We modified the terms of hormone replacement therapy (HRT) based on the reviewer’s suggestion. The statement of hormone replacement therapy (HRT) in the manuscript had been replaced into menopausal hormone therapy (MHT).

2. Few times the authors say “treatment for menopause”. This sounds peculiar; the indication usually is for menopause related symptoms, or for preventive purposes, but menopause itself do not need treatment.
We modified the terms of “treatment for menopause” based on the reviewer’s suggestion. The statement of “treatment for menopause” in the manuscript had been replaced into “treatment for menopause-related symptoms”. Our dependent variable was whether or not MHT treatment was prescribed during an outpatient visit for menopause-related symptoms for those selected women. Any outpatient visit during the study period was defined as a menopause-related visit if the patient was diagnosed as having menopausal-related symptoms. The detailed ICD9-CM codes were described in the first paragraph (page 8) of Measures.

3. The authors phrase "physicians used hormone therapy" in confusing while they are talking about HT prescribing. It is known that physicians, especially gynaecologists, themselves use HT more often than others.

We modified the terms of “physicians used hormone therapy” based on the reviewer’s suggestion. The statement of “physicians used hormone therapy” in the manuscript had been replaced into “physicians prescribed hormone therapy”.

4. Because majority of women were unemployed and without any personal income I wonder whether the authors could use family income to show women's socioeconomic situation?

We agree with the reviewer’s consideration. However, we chose to use personal income in this version for household income is related to household size. Nevertheless, we would agree to change if the reviewer insists the household income is better than personal income in this case.

5. Reference 9 is from the year 2002, there is also more recent publication, from the year 2005 and this could be used here.

We have added current literature in the background section based on the reviewer’s suggestions.