Author’s response to reviews

Title: The effect of hormone replacement therapy on all cause and cardiovascular mortality in women with chronic kidney disease: protocol for a systematic review and meta-analysis

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Dear Dr. Moher
Editor in Chief, Systematic Reviews

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**Title:** The effect of hormone therapy on all cause and cardiovascular mortality in women with chronic kidney disease: protocol for a systematic review and meta-analysis

Thank you for allowing us the opportunity to resubmit our manuscript, based on the thorough review and thoughtful comments provided by the Editor and Reviewer. We feel that we have been able to satisfactorily address all of the comments raised, which has further enhanced the quality of the manuscript. We have provided an itemized summary of the changes made to the paper below with the reviewer’s comments provided in bold, followed by our responses. Corresponding changes are included in **bold** in the revised manuscript.

1. **In the general medical literature the term “hormone replacement therapy” (HRT) has been replaced by “hormone therapy” (HT) as the older term infers that hormone therapy is replacing the function of a defective organ. Hormone therapy (HT) is now the preferred term for this intervention.** (Discretionary Revision)

   We would like to thank the reviewer for bringing our attention to this important distinction. We have changed the term “hormone replacement therapy” in the manuscript to “hormone therapy”.

2. **Page 4: ESKD (End-Stage Kidney Disease) needs to be written in full time first time.** (Minor Essential Revision)

   We apologize for the oversight, this error has been corrected (page: 4 lines: 19-21)

3. **Page 4; Para 3; line 4: “In contrast to healthy women [27], women with ESKD have similar mortality rates compared to men [28-30]”.**

   Does this refer to CV or overall mortality, and are these age matched controls? Could the authors please clarify? (Minor Essential Revision)

   This sentence has been amended for clarity as follows (page: 4 lines: 19-21)

   “In contrast to healthy women (1), women with ESKD have similar overall mortality rates compared to age-matched men(2-4)”.

4. **Page 4; Para 3; line 6: “compared older women”. Addition of with needed.** (Minor Essential Revision)
We apologize for the oversight. This sentence has been modified as follows (page: 5 lines: 22-25)

“In contrast to the general population, women with ESKD have the same cardiovascular mortality as do age-matched men, and it hypothesized that this increased risk may be due to the lower lifetime exposure to estradiol as a result of onset of kidney disease earlier in life.(3)”

5. Page 5; Para 1; line 9: “In amenorrheic women with CKD, estrogen therapy has favorable effects on atherosclerosis risk parameters”. It would be useful for clarity to state which parameters. (Minor Essential Revision)

We have amended the sentence to specify the atherosclerotic risk parameters. Please see page: 5 lines: 25-26)

“In amenorrheic women with CKD, estrogen therapy has favorable effects on lipid profiles by decreasing LDL levels and increasing HDL levels (5)”

6. Page 5; Para 2; line 1: “Although a recent meta-analysis of postmenopausal hormone therapy in healthy postmenopausal women found no evidence of cardioprotection”. It should be noted that 8 out of 13 of the trials included in this review were in secondary prevention, and therefore participants had established CV disease having undergone a previous CV event (revascularization procedure, MI or TIA, angina or thrombo-embolic event, PE or DVT) and were therefore high risk CV populations. (Minor Essential Revision)

We would like to thank the reviewer for bringing up this important point. We have amended the manuscript to clarify that most of the trials included in the meta-analysis were aimed for secondary prevention in postmenopausal women. (Page: 5 lines: 27-33)

“Although a recent meta-analysis of postmenopausal hormone therapy in healthy postmenopausal women found no evidence of cardioprotection, the results varied among the included studies due to the different hormone regimens, timing of hormone therapy initiation and the type of estradiol and progestin used(6, 7). Additionally it is important to note that 8 of the 13 trials included in the meta-analysis were examining the effect of hormone therapy as secondary, rather than primary, prevention in a high CV risk population(6)”

7. Page 5; Para 2; line 10: “and to determine whether age at administration of hormone treatment modifies outcomes”. Surely it is the underlying level of atherosclerosis potentially mediated by severity or length of CKD that is that likely to impact upon CV mortality/morbidity, rather than age? I assume the authors are using age as a proxy for underlying atherosclerosis, but am unclear as to how they envisage this relationship to be having stated in the background that “women with ESKD <45 years of age have a higher risk of cardiovascular mortality compared older women with ESKD”. However, it is well
established that older women with later onset ESKD will also have a higher base line risk of CV events, due to age related atherosclerotic processes, and therefore using age as a proxy for baseline CV risk appears to be overly simplistic. Could the authors please clarify the supposed relationship between age and outcome, and how this is mediated. (Minor Essential Revision).

We would like to thank the reviewer for the important point and highlighting the need for clarification. We agree with the reviewer that underlying atherosclerosis is an important risk factor for cardiovascular morbidity and mortality; as such we will be conducting subgroup and sensitivity analysis in order to account for atherosclerotic risk factors such as lipid profile and CAD when possible. In addition to that, we are interested in examining the role of age in the effect of hormone therapy in this population due to the evidence showing benefits and harms depending on the timing of initiation of hormone therapy (8). Women who start hormone therapy in the perimenopausal period have been found to have lower cardiovascular mortality and morbidity compared to women who start hormone therapy later during menopause. Please see page: 5 lines: 35-41 for the amended version.

“Given the paucity of work on the therapeutic role of hormone therapy in the CKD population, we propose to complete a systematic review to determine the effect of hormone therapy on all cause mortality, cardiovascular mortality and cardiovascular morbidity in women with CKD. Additionally, given that the timing of the administration of hormone therapy (perimenopausal vs postmenopausal) influences risk, we aim to determine whether age, a surrogate for menopausal status, at administration of hormone treatment modifies outcomes in the CKD population(8).”

8. PECOD Questions used for the review:-

Population: Women with Chronic Kidney Disease (as defined by eGFR or presence of kidney damage) Could the authors clarify whether studies of participants with other co-morbidities will be eligible for inclusion? If so, do they intend to conduct sub-group analysis with participants stratified according to baseline level of CKD or presence/absence of other co-morbidities?

The reviewer raises an important point. We will be including studies of participants with other comorbidities in order to summarize results from a broad and generalizable patient population. In addition, we will be conducting stratified analysis for both CKD stage and the presence of co-morbidities. Please see page 11 and lines 166-170 for the revised version.

“If there is significant statistical heterogeneity, univariate meta-regression analysis will be done to assess the effects of the following variables on risk estimates: mean age, diabetes, cardiac history, comorbidities, mean estimated glomerular filtration rate, CKD stage, and route of administration of hormone therapy.”
Exposure: Hormone Therapy (HRT) (all types of HRT including estradiol alone or estradiol and progesterone) The route of administration needs clarification. Does this include only oral HT or HT delivered via patches, tablets, creams, troches, intrauterine device (IUD), vaginal rings, gels or injections as well? There are significant differences between oral and transdermal estrogens in terms of hormonal bioavailability and metabolism, with implications for clinical efficacy, potential side effects, and risk profile. If the authors intend to include all routes of administration of HT in the review, how do they intend to quantify the differences between administration routes in their analysis? Could this please be clarified?

We agree with the reviewer about the importance of taking into consideration of the route of administration of hormone therapy. We will be including studies examining the effect of all routes of administration of hormone therapy. However, recognizing that the route of administration has been found to play an important role in CV risk we will be conducting an analysis stratified by route of administration in order to determine if there are any differences in cardiovascular risk in this patient population. These changes have been made in the manuscript on page 11 lines 166-170.

“If there is significant statistical heterogeneity, univariate meta-regression analysis will be done to assess the effects of the following variables on risk estimates: mean age, diabetes, cardiac history, comorbidities, mean estimated glomerular filtration rate, CKD stage, and route of administration of hormone therapy”

Comparator: Placebo or No HRT: No comments

Outcome: All cause and cardiovascular mortality.

The stated outcomes of interest are inconsistent within the protocol. In some places it is stated that all cause and cardiovascular mortality will be assessed, and is some cardiovascular morbidity is stated in addition. If CV morbidity of interest, it needs to be stated how this is defined.

We apologize for this oversight and thank the reviewer for the comment. We have changed the manuscript to include cardiovascular morbidity as an outcome of interest. Cardiovascular morbidity as defined by the authors of all included studies will be accepted for the purposes of this review. We will provide the definitions of cardiovascular morbidity while describing the study characteristics. This clarification is reflected in page 6 lines 48-51.

“To determine the effect of hormone therapy on all cause mortality, cardiovascular mortality and cardiovascular morbidity (as defined by individual studies) in women with CKD, we developed a systematic review and meta-analysis protocol using the Cochrane guidelines for systematic review and meta-analysis (9).”
Design: RCTs and cohort studies. This is not consistent both between different parts of the protocol and the methods used to construct the electronic search. The abstract and the PECOS bullet points in the text state RCTs, cohort studies and case-control studies will be eligible for inclusion. Table 1 indicates that only RCTs and cohort studies will be included. Case control studies are not of a suitable design to address the review question and therefore should be removed from the inclusion criteria. (All above Major Compulsory Revisions)

We have corrected the PECOD question to include RCTs, cohort studies and case-control studies. Although we recognize that case-control studies are not usually used to determine risk of outcome, we included the case control design in our PECOD question in order to increase the sensitivity of our search, as recommended by the Cochrane handbook of systematic review(9).

9. Electronic search The search strategy in Table 2 is comprehensive and appears complete. Line 60 however is redundant given the patient population. (Minor Essential Revision).

We would like to thank the reviewer for highlighting this point. The filter for limiting to studies on humans is a part of a search filter recommended by the Cochrane handbook for systematic reviews. As such, we have included it in our search strategy (9).

10. The Medline search is from 1950 to 2014; have the authors considered the impact of changes in diagnosis and definition of CKD within this time period. Much of the older literature may be redundant in relation to the present patient populations. It may therefore be more economical to consider searching from only 1980 onwards to be consistent with the EMBASE search. (Discretionary Revision)

We agree with the reviewer regarding the impact of the historical development for the understanding of CKD on publications. However, in order to maximize sensitivity and identify all relevant articles we have chosen not to limit our search to a particular time period.

11. It is unclear why two separate searches need to be conducted. The first search will yield studies of women with CKD who are treated with or without HT. The second will yield studies of HT (in any patient population) which report CV outcomes. These have then been limited to RCTs. Given the stated inclusion criteria, search 2 appears to be redundant. For efficiency search 1 should be combined with the outcomes stated in search 2 (without limits to RCTs) in order identify the relevant literature. (Minor Essential Revision)

We would like to thank the reviewer for bringing up the need for clarification. While the first search identify studies that examined the effect of hormone therapy in CKD patients, the second search strategy aims to identify larger randomized trials whose main population of interest was
not patients with CKD but that have conducted subgroup analysis on patients who have CKD. The manuscript has been changed to reflect this rationale (page 8 lines: 86-88).

“The second search will include the exposure, outcome and design terms of the PECOD question (Table 3). The purpose of this search is to identify randomized controlled trials that included subjects with CKD and conducted subgroup analysis for these subjects.”

12. How will the authors handle the management of the electronic searches and in what software? This needs to be explicitly stated. (Minor Essential Revision)

The data will be organized and managed in Endnote X7 and Excel 2007. Please see page 10-11 lines 145-147 and page 12 lines 172-173 for the clarifications:

“The data will be organized and managed in Endnote (version X7, Thomson Reuters, New York, NY) and Excel (version 2007, Microsoft Corporation, Redmond, WA)”

“All analysis will be performed using STATA (version 12, StataCorp LP, College Station, TX)”

13. Identification of Articles for Eligibility Initial screening Could the authors clarify the meaning of a ‘calibration’ exercise, as it is unclear what this means within this context. (Discretionary Revision)

The calibration exercise is to ensure that the two reviewers were using similar guidelines for the inclusion and exclusion of abstracts and in order to identify any systematic discrepancies early in the process of classification of abstracts. Page 9, lines 108-110

“After a calibration exercise in order to identify any systematic discrepancies in classification of abstracts between the two reviewers, screening will be conducted by two independent reviewers to determine articles eligible for the systematic review.”

14. Identification of Articles for Eligibility Initial screening the authors need to refer to the initial PECOD criteria for both the initial electronic title and abstract screening and full-text screening. The inclusion criteria for both stages need to be consistent in order for the review to be reproducible. (Minor Essential Revision)

We apologize for the error and thank the reviewer for bringing up this important point. We have corrected the manuscript to reflect this change. Please see page 9 lines 112-113.

“An abstract from the search will be considered for a full text review if it meets the PECOD question criteria”

15. Data synthesis and analysis more details needs to be provided in the section. Is the HR or RR for all cause mortality, CV mortality and morbidity of primary interest, and if both are reported what methods to do authors intend to use to combine both HR’s and RR’s?
How will the level of magnitude of heterogeneity between trials be assessed? Are the authors intending to undertake sub-group analyses to assess the impact of clinical heterogeneity? If so these need to be stated a priori. References for publication bias need to be added. (Discretionary Revisions)

We thank the reviewer for highlighting the need for clarification. The RR for all cause mortality, CV mortality and morbidity is of primary interest. If only one of the two is reported we will abstract the number of events (if possible) and calculate the RR. If the above is not possible we will present both RR and HR estimates separately.

The level of magnitude of heterogeneity will be assessed using the Cochrane Q statistic and $I^2$ statistic. If there is significant statistical heterogeneity, univariate meta-regression analysis will be done to assess the effects of the following variables on risk estimates: mean age, diabetes, cardiac history, comorbidities, mean estimated glomerular filtration rate, CKD stage, and route of administration of hormone therapy.

Please see page 11 lines 158-163 and page 11-12 lines 166-171:

“The primary outcome of the risk ratio of all cause mortality, cardiovascular mortality and cardiovascular morbidity with hormone therapy compared to placebo or no hormone replacement therapy will be reported from a potential meta-analysis of the RCTs and observational studies. If only the hazard ratio is presented, the number of events in each group will be abstracted from the study (if possible) and a risk ratio will be presented. If the above is not possible we will present both risk ratio and hazard ratio estimates separately.”

“Furthermore statistical heterogeneity will be assessed using the Cochrane Q statistic and $I^2$ statistic. If there is significant statistical heterogeneity, univariate meta-regression analysis will be performed to assess the effects of the following variables on risk estimates: mean age, diabetes, cardiac history, comorbidities, mean estimated glomerular filtration rate, CKD stage, and route of administration of hormone therapy.”

References