Author's response to reviews

Title: Hormone Replacement Therapy is associated with Gastro-Oesophageal Reflux Disease: a retrospective cohort study

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Author's response to reviews: see over
Dear Mr. Cardinez,

*Hormone Replacement Therapy is associated with Gastro-Oesophageal Reflux Disease: a retrospective cohort study*

Professor Hungin and I are grateful for the opportunity to revise and resubmit version 3 of the attached manuscript. We thank the editor for his helpful and constructive comments, and the reviewers for their acknowledgement of our previous responses. As requested, we attach a revised manuscript with all changes highlighted in yellow, and we include a point-by-point response to comments below. We would be happy to discuss any of these further if that would be helpful.

We confirm that the manuscript has not been published previously, and is not under consideration (in whole or in part) for publication elsewhere. The manuscript, including all changes, has been approved by all authors.

Thank you for your consideration.

Yours sincerely

Helen Close
Editor’s comments:

1) Please find the reviewers reports attached.

Please see below for a response.

2) Given the weakness of the study as acknowledged by the authors, I would suggest that they downplay the significant association between estrogen use and gastroesophageal reflux disease (odds ratio of 1.49). They could instead elude to a possible association between estrogen use and gastroesophageal reflux disease in the conclusions and add a comment that future well designed trials are needed to clarify this topic.

We acknowledge that the limitations of our study preclude definitive conclusions and we recognize the need for a prospectively designed study to carefully quantify the true strength of association (which is likely to be higher than our findings show). We have therefore altered the text in the following ways:

- The abstract conclusion has deleted the sentence “This may explain some of the prevalence of GORD and has clinical implications for the management of symptoms in HRT users”. The abstract now reads “This first large cohort study of the association between GORD and HRT found a statistically significant association between oestrogen-only hormone and GORD and PPI use. This should be further investigated using prospective follow-up to validate the strength of association and describe its clinical significance.”

- The discussion:
  - This was the first step in understanding the differences between forms of HRT and showed that oestrogen-only HRT presented a possible association with GORD.
  - This further supports the possible association between oestrogen-only HRT and GORD.
  - However, these data go some way to explain the risk of GORD and PPI use in this group and also provide a possible explanation for those now on HRT who may have GORD symptoms.

3) Since no changes in clinical practice can be recommended based on the results of this paper, I suggest that the authors not make any clinical recommendations in the conclusion section of the manuscript.

We recognise the need for further studies to develop clear clinical recommendations.

The discussion section therefore now reads:

- Our findings, if validated in a prospective study, may have important consequences for the management and resources used by patients with upper GI symptoms as these patients would normally constitute a higher use group for acid suppression therapy.

The following has been deleted from the discussion section: “Monitoring GORD symptoms prior to and after commencement of HRT may be appropriate in this group.”

The conclusion now reads: “There is a statistically significant independent association between oestrogen-only hormone and GORD and PPI use. This should be further investigated using prospective follow-up to examine the strength of association and describe its clinical significance.”

The following has been deleted from the conclusion: “Many women choose to stop using HRT in the first six months, possibly as a result of GORD; awareness about the potential risk of GORD may lead to more targeted prescribing of oestrogen-only HRT, and earlier identification and treatment of GORD symptoms. Awareness of the potential risk of GORD may also lead to higher levels of compliance.”
among women taking oestrogen-only HRT, and improved clinical management of GORD. This may lead to reduced demand on secondary care referrals for diagnosis and treatment of GORD in this group of patients.”

**First reviewer's report (1914502082668495):**

*Once again very well-written. I appreciate your responses to our initial critique. Just a couple of very minor revisions:*

1) "ppi-use" on page 7 should be properly capitalized as it is elsewhere in the paper.

The text on page 7 now reads: “PPI-use”.

2) What is the "MRC" mentioned on page 4?

The text on page 4 now reads: “Medical Research Council”.

**Second reviewer's report (4370421366819536):**

*No changes recommended.*