

September 24, 2015

Dr. Ze-Mao Gong
Science Editor, Editorial Office

Dr. Lian-Sheng Ma
President and Company Editor-in-Chief

Thank you for your insightful review of our paper (ESPS Manuscript NO: 20906) entitled “Gender difference in Gastro-esophageal Reflux Disease”. As you suggested, we addressed all of the issues raised by the reviewers. We have incorporated the suggested revisions into the sentence.

Response to Reviewer 1:

Point 1. “However, most of these studies did not adjust for the life style modifications after menopause, including the diet, activity levels and other stress responses, which may be major confounding factors.”

We thank the reviewer for bringing this issue to our attention. We can't deny the possibility that the life style modification after menopause in women become a confounding factor and cause some effect to the results of epidemiologic studies we quoted in this article. Unfortunately there was no large-scale, epidemiologic study available that took this issue into account, nor articles demonstrating that life style modification in postmenopausal women prevented GERD. However we are very interested in this issue, so let us study about it in the future.

Point 2. “But given the profound evidence about the effect of leptin on obesity, the real significance of effect exerted by estrogen on the clinical outcome has to be carefully considered.”

The reviewer makes an excellent point and as suggested, we agree

the lack of evidence in the clinical outcome of estrogen in leptin level, although we have quoted the epidemiological study that demonstrated clinical outcome between leptin level and the prevalence of GERD in women. Therefore we modified the sentences in this article. Some studies revealed that in obese people, leptin level but not BMI was correlated to the prevalence of GERD and revealed that women's leptin level is higher than men's even though the prevalence of GERD is opposite. We speculated that estrogen level might cause the difference in the response to leptin in GERD patients, so we now engage some molecular biological studies in this point.

Point 3. "Is there any survival benefit if an elderly lady was identified to be a high risk patient in her 80s? And the potential role of hormone replacement therapy is still in question given the fact that men with heavy estrogen exposure did not reduce the risk of esophageal cancer."

We apologize for confusion on this issue. We did not recommend a hormone replacement therapy to prevent GERD. Moreover this therapy did not reduce the risk of esophageal adenocarcinoma in men as we quoted in this article. We would like to emphasize the importance to elucidate the molecular mechanism that could account for the gender difference in the GERD.

We thank the reviewers for their helpful suggestions. The incorporation of the modification of the sentence and suggested revisions has substantially strengthened our report. We hope that you now find it acceptable for publication. We look forward to hearing from you.

Sincerely,

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