

**Dear Editors and Reviewers:**

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "**Systematic Review of Yougui Pills Combined with Levothyroxine Sodium in the Treatment of Hypothyroidism**" (NO: 72773, Meta-Analysis). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

**Reviewer's comments:****Reviewer #1:**

Keywords: are the same as the title. You can use different types of words to increase the visibility of your paper in the research. The authors mentioned "incidence of hypothyroidism is rising year by year due to the increase of iodine content in the diet". Is it right?. Please, clarify it within the text. This sentence "And excessive doses are likely to induce hyperthyroidism or abnormal bone metabolism" begins with "and". it is better to be inside the sentence. No need to write Chinese terms within a paper written in English like: ". The Chinese search terms included "右归丸" (Yougui pills), "甲状腺功能减退", "甲低", "甲状腺功能低下", "甲状腺机能低下", "甲状腺机能减退", "甲减" (hypothyroidism), and the Chinese search strategy was ("右归丸") AND ("甲低" OR "甲状腺功能减退" OR "甲状腺机能低下" OR "甲状腺机能减退" OR "甲减" OR "甲状腺功能低下"). " The first paragraph in Discussion "Studies have shown that the combination of Yougui pills and western medicine can produce a synergistic effect, reduce the dosage and duration of hormone taking, and reduce or eliminate the adverse reactions caused by hormone taking. However, the value of Yougui pills combined with levothyroxine sodium for hypothyroidism is not clear at present. A total of 9 randomized controlled studies were included in this study, involving 936 research subjects, with 326 in the Yougui pills group and 323 in the levothyroxine sodium group. The main findings of this study are as follows: (1)" is a repetition of same meaning mentioned before. Nothing appears about the Yougui effect on young ages suffering from hypothyroidism. You may clarify it.

**Responds:** Thank you for your valuable comment, we have changed the keyword and title to be consistent, page 4. We want to express that excessive iodine intake may lead to hypothyroidism, Sang also concluded in the literature, see DOI: 10.3945/ AJCN.111.028001. PubMed's retrieval strategy is shown in table1. After carefully reading the reviewer's comments, we decided to delete the discussion section repeatedly. After careful reading of relevant literature, we found that the effect of Yougui effect on young ages suffering from hypothyroidism was not consistent with our conclusions, so we deleted

this finding.

**Reviewer#2:**

This is a clearly and well-presented systematic review/meta-analysis that employed methods standardly employed by the Cochrane Collaboration. Therefore (although in my personal opinion Cochrane meta-analyses are not always "optimal") - I have no methodological comments. There is only one minor comment about a point that needs to be addressed in the Discussion section: all included RCTs were open-label with no-treatment control - patients received levothyroxine + T preparation vs. levothyroxine alone. By this virtue, all patients and investigators were aware of the assigned treatments. It has been shown repeatedly that in such "no-treatment-control" trials effect estimates are typically quite larger than in double-blind (placebo-controlled) trials. Although it may seem that hormone levels are objective outcomes, it is beyond doubt that awareness of treatment/no treatment may influence the levels of thyroid hormones and TSH. Also, non-blinded conditions could have (beyond doubt) affect the spontaneous subject reporting of own condition (symptoms, side-effects) or their detection by the investigators. Therefore, although the results are rather consistent and do indicate a benefit of adding T treatment to levothyroxine, there should be comment to state that, while data are strongly suggestive, it is likely that the extent of benefit is overestimated. The exact extent of the effect of T (that is separated from the effect of "awareness about the received treatment") could be only estimated in an adequately powered placebo-controlled double-blind trial.

**Responds:** We are very grateful for the reviewer's comments. For the valuable comments of reviewers, we added the limitations section in the discussion section: All included RCTs were open-label, with no treatment control, in which patients were treated with levothyroxine + T preparation alone. Therefore, all patients and investigators are aware of the prescribed treatment, and knowledge of the treatment also affects thyroid hormone and TSH levels. In such "no treatment controlled" trials, effect estimates are usually much larger than in double-blind (placebo-controlled) trials.

**Reviewer#3:**

the paper is good and well written

**Responds:** We are very grateful to the reviewers for such high comments on our article.

**EDITOR'S COMMENT**

**(1) Science editor:**

The author's manuscript reports that Yougui Pill Combined with levothyroxine sodium may be better than levothyroxine sodium alone in the

treatment of hypothyroidism. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario. Nevertheless, there are a number points that may deserve some revisions. 1.The aim in the abstract is wrong. The author only explores the advantages of combination therapy and does not explain the benefits of single drug use. 2.Did Yougui Pill enter the medication guide? 3. It is better to organize the retrieval strategy into tables and put them into supplementary documents.

**Responds:** 1. We have changed the abstract to 'To explore the clinical efficacy and safety of Yougui pills combined with levothyroxine sodium in the treatment of hypothyroidism.'. 2. Yougui Pill doesn't make it into the guidelines for treating hypothyroidism. 3. We merge the retrieval strategy into Table1.

**(2) Company editor-in-chief:**

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

**Responds:** All the figure are original. We have provided relevant documents

according to the requirements of the editor.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.