Author’s response to reviews

Title: Subclinical Hypothyroidism Would Not Lead To Female Sexual Dysfunction in Chinese Women

Authors:

Han Luo (byrant_luohan@live.cn)
Hongliu Yang (saturday_me@msn.cn)
Wanjun Zhao (524675158@qq.com)
Qianqian Han (1173825864@qq.com)
Li Zeng (32471488@qq.com)
Huairong Tang (HuairongTang@163.com)
Jingqiang Zhu (zjq-wkys@163.com)

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Editor Comments:

1. Please add a “Conclusions” section after the “Discussion” section. This should state clearly the main conclusions of the research article and give a clear explanation of their importance and relevance.

2. Please note that all manuscripts must contain all the following sections under the heading ‘Declarations’. The Declarations should follow the Conclusions section, and be before the References.

Abbreviations

Ethics approval and consent to participate

Consent for publication

Availability of data and material
Competing interests

Funding

Authors' contributions

Acknowledgements

Please see here for details on the information to be included in these sections:
https://bmcwomenshealth.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article

If the information required is already provided in the main manuscript, please also copy the relevant statements to the Declarations.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Response: I have corrected it accordingly.

Reviewer reports:

Murat Bozlu (Reviewer 1): I think that this is an interesting paper.

Although the authors did not mention the pregnancy status, more recent paper "Küçükdurmaz F et al. Prevalence and correlates of female sexual dysfunction among Turkish pregnant women. Turk J Urol. 2016 Sep;42(3):178-83. doi: 10.5152/tud.2016.49207" may be discussed in the discussion section.

Response: Thank for your excellent suggestion. I have commented in the discussion.

Daniela Pasquali (Reviewer 2): Comments to Author

1. 1119 participants were recruited to evaluate the relationship between subclinical hypothyroidism (ScHt) and sexual dysfunction in Chinese women. Risk factors of FSD
were identified. CVFSFI>23.45 was the value to identify sexual dysfunction. The authors did not find significant differences between women with ScHt and controls. This is an original report but I have some concerns about the study design that could affect the results.

2. ScHt participants and 951 controls. In this case control study there are important numerical differences between ScHT (n168) and controls (n 951). I have some doubt about possible bias linked to this discrepancy.

Response: Thank for your excellent question. It is true, potential bias is inevitable. In cross sectional study, some researchers would like to choose age- and sex- matched study, but others still prefer to pool the data in FSD analysis[1-3], because match also bring bias, it is hard to tell which one is more accurate. Therefore, we did not adapt match analysis. Besides, most of results in our study are consistent with previous reports, like age, income. And Lee et al demonstrated that ScHt is not a risk factor for FSD in Korean middle-aged women [4]. We furtherly confirm this result in all domain of FSD. So we are confident in our analysis result.

3. In this hospital based research was the control population affected by diseases that can affect the research results other than subclinical hypothyroidism?

Response: I am sorry to make you confused. Actually, absolutely most of participants are healthy people, and the most common cases affecting result is hormone therapy or hormone replacement. Thank for your suggestion, I revised the exclusion part to make it more specific, excluding systemic lupus erythematosus, chronic kidney disease, thyroxine replacement et al.

4. In table 1 TSH and AbTPO values in ScHt group were 5.4(4.7, 6.5) mU/L and 9.0(5.2, 41.5) respectively. Surprisingly, this data demonstrated that ScHt was not related to Hashimoto's thyroiditis, the most common thyroidal cause of SCHt in adults. How can the authors explain this very uncommon data?

Response: I fully understand your consideration. In the manuscript, due to non-normal distribution, TPOab is presented as median (interquartile range). Hashimoto thyroiditis is currently established by a combination of presence of serum antibodies against thyroid antigens (mainly to thyroperoxidase and thyroglobulin), and (or) appearance on thyroid sonogram. Reference of thyroid hormone in the study: TSH 0.27-4.2 mU/L; TgAb: <115 IU/mL; TPOAb:<34 IU/mL. In this study (table 1), the incidence of Hashimoto Thyroiditis in Subclinical hypothyroidism (ScHT) group is 14.28%, which is higher than control group (5.25%) significantly. Besides, we should also consider the reference of Tgab and ultrasonography, other than TPOab[5]. And another specific condition is the location of the study where conducted.
Sichuan province locates at western inside mountainous land of China, and element iodine is relative deficient [6]. As we know, iodine deficiency also contributes to TSH elevation, yet without positive TPOab. What is more, it is known, 10-15% of Hashimoto thyroiditis is negative in TPOab[7]. Consider all of three factors above, we consider the result is reasonable.

5. The diagnosis of ScHt requires the repetition of TSH value at least one more time to confirm this condition. Do the authors confirm the TSH data? If not, I have some concern considering the ScHt group really affected by thyroid disease. The results do not support the conclusions.

Response: I am sorry to make you confused. Let me specify the check-up process in our intuition for you. All the participants are membership (more than 10,000 membership in our institution), and they will undergo annual check-up. If any test out of reference, or abnormal sign, the health promotion center would reserve the same test and respective physician accordingly for them. So the TSH data presented in our study has been double confirmed. Besides, absolutely most of participants are healthy population, so it may be not affected by other severe disease, other than the most common case-thyroiditis.

6. In the discussion section the authors affirm: To our limited knowledge, it is the first study to explore the relationship between thyroid hormone and female sexual dysfunction (FSD).

This sentence is incorrect, several reports have studied the relationship between thyroid function and FSD (i.e. Clin Endocrinol (Oxf). 2016 Jun;84(6):925-31. doi: 10.1111/cen.12956. Epub 2015 Oct 19.Sexual function and depressive symptoms in young women with thyroid autoimmunity and subclinical hypothyroidism.Krysiak R1, Drosdzol-Cop A2, Skrzypulec-Plinta V2, Okopien B1) and the authors also reported in the references some of the literature data (Pasquali D et al ) and some of them are discussed (Atis G et al)

Response: Thank for your excellent suggestion. Actually, I mean it is the first study in China, and I have revised in manuscript. As you know, because of conservative cultural background, the literature in Chinses female sexual dysfunction is still limited, only 5 articles reported it. And no study investigated the relation between thyroid function and female sexual dysfunction before.

Minor points
- English form should be evaluated.
- References sometimes are not appropriate.
Response: Thank for your review, I have evaluated thoroughly and revised it accordingly.

Roisin Worsley (Reviewer 3): Thank you for asking me to review this interesting manuscript. I think this study would be useful for clinicians and is worthy of publication. However, the methods need more detail. I think most of the points I raise will be fairly easy to address.

Abstract: Very minor point: in the abstract the cut-off for CVFSFI is stated as >23.45 rather than < 23.45

Response: I am sorry for the mistake, I have corrected it.

Intro: The definition of FSD could be more precise/accurate- suggest reference to McCabe et al, Definitions of Sexual Dysfunctions in Women and Men: A Consensus Statement From the Fourth International Consultation on Sexual Medicine 2015 February 2016 Volume 13, Issue 2, Pages 135-143

Response: Thank for your excellent suggestion. I have revised it accordingly.

Methods: it is stated that women were recruited from a health promotion that provided 'routine checkups for all included women'. Please elaborate - does this mean all women in the local area attend every year - if so are they sent reminder? what proportion attend? Or are women attending because they have a medical problem or they self refer for preventive care? what is meant by 'routine checkup' ie blood pressure check? pap smear? How many women attended the centre over the recruitment period? Who recruited the women and asked if they wanted to do the study and had been sexually active?

Response: Let me specify the check-up process in our intuition for you. All the participants are membership (more than 10,000 membership in our institution), and they will undergo annual routine check-up. As you see, absolutely most of participants are healthy population. Actually, it includes blood test for CBC, lipid profile, basic metabolic panel and tumor marker etc. and chest X-ray, ultrasonography and Pap smear and so on. And usually, around 350 persons have reservation every business day (including Saturday). Female participants would be approached in waiting room of gynecological inspection by gynecological nurse. And if they approved, the volunteers besides the nurse would lead them into a separate room next it after inspection.
How did you determine who to approach - or did you approach all women of a certain age?
Response: As I said above, we will approach every female participant in the waiting room.

What does it mean 'completed the CVFSFI in high quality' ie do you mean completed all questions?
Response: Thank for your excellent question. Other than completion, we set a rule by ourselves. If participant finishes it within 30 seconds or very short time, we would exclude it from final analysis. As you know, it is nearly impossible to read, understand and answer for 29 questions in 30 seconds.

Were questionnaires deidentified? could women have been concerned that the person receiving the questionnaire would know whose response it was - this might be a problem if they had concern that their primary health care provider at the centre might see their responses.
Response: Yes, we fully understand your concern about de-identification of protected healthy information. So we remove any identifier on the questionnaire. After participant completed, the volunteer would collect the questionnaire, and one staff in health promotion center (Li Zeng) would record participants’ tracking number in order to extract check-up reports for us. What’s more important, we will explain the whole process of de-identification for participants before they fill the questionnaire and make sure they will not worry about this issue.

As women were completing the questionnaire in a separate room on site with a physician or volunteer nearby to answer questions, how was it dealt with if women changed their mind about completing the survey? what if they wanted to complete it at home?
Response: In accordance with principle of voluntary compliance, when they changed mind, we would respect their decision and excluded it. And if they cannot complete in the room, we also excluded it.

Thyroid status: please clarify what levels for TSH T3 and T4 you used for defining subclinical hypothyroidism, and overt hypo/hyperthyroidism. what platform was used for analysis of thyroid hormones and can you give a brief description of the assays performance eg CV values
Response: ScHt is defined as elevated TSH concentration with normal fT4. Overt hypothyroidism means elevated TSH and deceased fT4; overt hyperthyroidism means decreased
TSH and elevated fT4. Reference of thyroid hormone: TSH 0.27-4.2 mU/L; fT3 3.6-7.5 pmol/L; fT4 12-22 pmol/L. Electrochemiluminescence immunoassay (Roche, USA) was used for analysis of thyroid hormone. CV value ranges between 1.5%-3%.

How did you determine menopausal status - it is mentioned in results but not methods
Response: I am sorry to make you confused. Menopausal status was extracted from the final report of check-up, which was judged by gynecological physician (Dr. He) when gynecological inspection. I have revised it in method part, and acknowledge Dr. He specifically in acknowledgement.

Statistics: can you pls clarify regarding the logistic regression - did you make separate models for FSD and each of the FSFI domains?
Response: I am not very sure what you mean, yet I think table 3 may be what you want.

Results: the rate of SCH seems high at 15% given the young age of participants - is this usual for the area? Is the area known for iodine deficiency? pls comment
Response: Thank for your excellent question. It is true, Sichuan province locates at western inside mountainous land of China, and element iodine is relative deficient, so government forces to sell iodized salt for 16 years[6]. And I have commented it in discussion part.

I think it inaccurate to say that those with a low score were ‘diganosed with FSD’ as you rightly say the FSFI is a screening tool - consider other terminology such as ‘at risk for FSD’
Response: Thank for your excellent suggestion. I have correct it accordingly.

Table 1 - pls provide percentages in each column. What does it mean parity is 1 for both groups
Response: I have added percentage in table 1. The variable was presented as median (interquartile range) and compared by U-test, because ‘parity’ dose not distribute normally.
Table 3: From the table it's not clear what the reference groups are eg for 'medium depression' is that compared to no depression or everyone else? where you've referred to HT - do you just mean TPO positive or do you mean SCH and TPO+

Response: Psychological status was evaluated by second version of Beck Depression Inventory (BDI-II), a 21-item self-reported inventory. Participants scoring 0-13 were classified into No depression status; 14-19 Light depression status; 20-28 Medium depression status; 29-63 Severe depression status. In the manuscript, Hashimoto thyroiditis is currently established by a combination of presence of serum antibodies against thyroid antigens (mainly to thyroperoxidase and thyroglobulin), and (or) appearance on thyroid sonogram. Reference of thyroid hormone in the study: TSH 0.27-4.2 mU/L; TgAb: <115 IU/mL; TPOAb:<34 IU/mL.


