Reviewer’s report

Title: Using Hashimoto thyroiditis as gold standard to determine the upper limit value of thyroid stimulating hormone in a Chinese cohort

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Reviewer: James V Hennessey

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I read with interest the manuscript entitled "Using Hashimoto thyroiditis as gold standard to determine the upper limit value of thyroid stimulating hormone in a Chinese cohort. In this interesting cross sectional study the authors have attempted to redefine the functional upper limit of the TSH range using sophisticated statistical methods. The authors conclude that currently utilized values of 4.5 mIU/mL should be decreased to 2.6 or 2.9 in order to capture more patients with Hashimoto's thyroiditis. As no interventions were undertaken to assess potential clinical response to LT4 treatment of individuals identified as hypothyroid, the clinical impact of redefining the TSH down to this level other than adding millions (billions?) of patients to the ranks of the hypothyroid is unknown.

Specific Comments: Numbering the pages is helpful.

Background: lines 47-56. I understand wat the authors are expressing here but the concept is a little different. Glucose is directly involved in the generation of advanced glycation products and therefore the fasting blood sugar and more directly the post prandial blood sugar correlates nicely with this relationship. TSH does not cause hypothyroidism, TSH is a tissue reflection of inadequate thyroid hormone action in the hypothalamus and pituitary so a physiologic response to hypothyroidism rather than the etiology. All that being said, both are clinically used to make these diagnoses.

Results: lines 49-53 These subjects are on average very young. Several studies (Surks and Hollowel) have clearly indicated that the age of the patient is critical to interpreting the results of TSH testing. The authors should break out the mean and 2.5th as well as 97.5th percentiles in a table with age in decades being the dividing factor.

Prevalence of HT by deciles……..Lines 42-49and 53-59 These sentences are very unclear, not sure what the authors are communicating.
ROC curve for the value of TSH…… Lines 7-10 Does this mean that 2.6 is used to designate the upper limit of non-Hashimoto's subjects? This gets confusing. How many subjects with TSH (measured just once correct? What would happen if TSH were measured 2 or 3 times and averaged or the range was used?) < 2.6 would be found to have Hashimoto's by antibodies or US?

Discussion: page 2 Line2-3 But this is a Danish population with iodine issues, look at Surks and Hollowel). The Spencer paper has always been difficult to interpret.

Lines 46-54 Again this is a very young population, not sure we are ready to change the worlds practice based on this group.

Page 3 Lines 24-30 This sentence is unclear. Lines 34-44 This is a big limitation.

Conclusion: Line 56-58 Would suggest that the authors insert the word "Young" between the words for and Chinese.

Table 1 Creatinine tend to go up in hypothyroidism. The significance of this finding is very unclear to me. Why would uric acis go down in supposedly hypothyroid individuals.

Table 2 The usual statistical approach has been to determine the 95% CI so the upper cut off has been pegged at the 97.5% and the lower cutoff has been placed at the 2.5%. Looking at the numbers here, it would appear that the authors population is very similar to the subjects reported by Surks and Hollowell). This should be reassuring that there is internal validity and comparability with other studies. Would the authors consider comparing the 97.5% TSH values in the non-Hashimoto's subjects with the outcomes of the other approaches? I guess I finally have understood what the authors are trying to point out here, that alternative methods of determining the upper expected TSH in a relatively young population is more likely to uncover underlying Hashimoto's thyroiditis. So looking at this from the perspective of false positives and negative may be helpful for clinical understanding. For example, if the TSH > 2.6 we are likely to find that X% will have Hashimoto's thyroiditis, which may or may not benefit from intervention (LT4 only intervention I would consider) but of course there is no data on LT4 outcomes. OR if TSH < 2.6 we can be reassured that only Y% of Hashimoto's (that would otherwise eventually benefit from LT4 therapy) will be missed. The authors should consider putting these findings into a clinical contest for the sake of the readers understanding.

Missing table Would the authors include a table with the mean and 97.5% of TSH by decade in the HT and non-HT groups?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I recommend additional statistical review

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