Author's response to reviews

Title: Serum Thyroid-Stimulating Hormone Levels are not Associated with Exercise Capacity and Lung Function Parameters in two Population-Based Studies

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Author's response to reviews: see over
Dear Prof. Bakolis, dear Reviewers,

we highly appreciate the invitation to resubmit our manuscript after taking into account the comments from the reviewers. We would like to thank the reviewers for their helpful comments.

We have addressed the issues raised by the reviewers. In general, we share their opinions and revised the manuscript accordingly. Enclosed you will find our detailed responses to the reviewers’ suggestions and the revised version of the manuscript. Changes to the manuscript are coloured in red.

We hope that with these modifications to our manuscript, our study is now suitable for publication in BMC Pulmonary Medicine.

Sincerely,

Dr. Till Ittermann
Reviewer 2

The authors have duly taken on board many of the comments I raised in my initial review of this manuscript. My feedback is noted below addressing each of the original comments

MAJOR

1. Initial comment: The researchers have not described any of the demographic characteristics of the patients with high/low TSH.

Comment based on revised manuscript: The changes made to the text (Results section) were minor and not consistent. For example, the authors state that "in the pooled population measurements of spirometry and CPET were lower in individuals with low TSH compared to individuals with serum TSH in the reference range while these measurements did not differ substantially between individuals with low TSH and individuals with TSH in the reference range".

Please be specific and consistent.

There was a typo in the second part of the sentence. High instead of low TSH was meant. As recommended by the reviewer we enhanced the description of Table 1 in the results section (page 7, lines 1-5).

2. Initial comment: The authors rightfully identify in the Discussion that their analyses are based on a population based sample with few subjects with clinically relevant hyperthyroidism.

Comment based on revised manuscript: While the authors did not perform the sample size calculation requested, it is clear that they have considered the issue. I would suggest, however, that they include in the manuscript some statistics on the number of individuals in their study that they consider to have clinically relevant hyper/hypothyroidism.
Unfortunately we have no data on triiodothyronine and thyroxine in SHIP-1 and SHIP-
Trend to distinct subclinical and overt forms of thyroid dysfunction – this issue is
pointed out in the limitation section (page 10, lines 12-14). However, in SHIP-0, the
baseline of SHIP-1, these thyroid hormones were measured. Results from SHIP-0
indicate that the prevalence of overt thyroid dysfunctions might be low in our study
population. In SHIP-0 there were only 28 individuals (0.7%) with overt
hyperthyroidism and 36 individuals (0.9%) with overt hypothyroidism.
We provide these numbers now in the discussion (page 9, lines 8-12).

MINOR

1. Original comment: Please indicate whether the lack of consistency in how
the blood samples were taken might have influenced the interpretation of TSH
levels.

Comment on revised manuscript: The authors addressed this issue in their
letter to the editor. It would be helpful, however, for the exact results presented
in this letter to be included in the manuscript as well.
We followed the recommendation and provide now the exact results in the methods
section (page 5, lines 20-21).

2. Original comment: The participation rate of CPET and spirometry is low. It
would be helpful to have some details of how participants differed from non-
participants.

Comment on the revised manuscript: The authors did a good job of addressing
this issue through the use of inverse probability weighting. It would be helpful,
however, if the direction of the bias (initially) were described in the text. For example, was the BMI higher or lower in non-participants? This should also be discussed in the Discussion section.

As recommended by the Reviewer we now provide more detailed information on the differences between participants and non-participants on page 6 lines 16-17 and in addition cite a manuscript, in which the differences between participants and non-participants are illustrated for the SHIP-1 population. We furthermore included two sentences in the discussion section on this issue (page 10, lines 16-18).

7. Original comment: In the discussion the authors state that their data "provides evidence that serum TSH levels are not associated with spirometry and exercise capacity." It would be prudent to rephrase this as not having found evidence of an association.

Comment on the revised manuscript: This was addressed satisfactorily although the conclusion (page 10, lines 11-12) could be re-worded to "Our results suggest that there is no evidence of an association between thyroid dysfunction and lung function and CPET in the general population."

We reworded this sentence as recommended by the Reviewer.

ADDITIONAL MINOR COMMENTS:

1. The authors state that "FEV1, FVC and FEV1/FVC values did not differ significantly across TSH quintiles (table 30)" (page 7, lines 8-9). This statement does not accurately reflect the analysis that was performed. The analysis compared quintile of TSH with the median quintile.

As recommended by the reviewer we reworded this sentence.
2. The authors conducted a sensitivity analysis excluding individuals taking thyroid medication (page 7, last 2 lines). It would be helpful to have had such results in an online appendix.

As recommended by the Reviewer we have now prepared a supplementary table, in which we have repeated the analyses displayed in Table 2 for individuals without thyroid medication intake.

3. In the first sentence of the discussion the authors state that "In two independent large population-based studies from Northeast-Germany.." (page 8, lines 2-3). The authors would be better to state "In data pooled from two independent large population-based studies from Northeast-Germany..". As recommended by the reviewer we reworded this sentence.

4. Throughout the discussion the authors suggest that no significant associations were found, yet later state that those results that were statistically significant were likely due to chance (page 9, lines 21-23). It would be sensible to acknowledge such significant findings earlier then describe that such associations may be due to chance.

We agree with the Reviewer and have now shifted the paragraph discussing the significant findings up into the first paragraph of the discussion.