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

Authors:

Till Ittermann (till.ittermann@uni-greifswald.de)
Sven Gläser (sven.glaeser@uni-greifswald.de)
Ralf Ewert (ewert@uni-greifswald.de)
Stephan Felix (felix@uni-greifswald.de)
Henry Völzke (voelzke@uni-greifswald.de)
Marcus Dörr (mdoerr@uni-greifswald.de)

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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
Response to editorial comments:

1. The abbreviation of SHIP-TREND should be explained in the abstract.

The name SHIP-Trend was chosen, because one of the aims of this study was to investigate prevalence trends of diseases in the general population of Northeast Germany in comparison to SHIP-0, which was conducted 10 years earlier. Thus, Trend is no abbreviation. To make this clearer, we have now substituted TREND by Trend throughout the whole manuscript.

2. Did the missing individuals have different population characteristics than the ones included in this analysis?

To check this we have conducted a logistic regression model with participation at CPET examination as outcome (1 if yes; 0 if no) and several population characteristics as independent variables. This model demonstrated an inverse association between serum TSH levels and participation at CPET examination. Furthermore, age, body mass index, beta blocker use, physical activity, current smoking, and education were associated with participation. To account for these differences between participants and non-participants we applied inverse probability weights in all regression analyses.

We now state on page 6 that significant differences regarding population characteristics exist between participants and non-participants.
Reviewer 1:

The authors propose to investigate the association between TSH levels and lung function in the general population, based on evidence from patients with cardio-pulmonary disease showing that low levels of TSH might be related to a poorer lung function. The methods are very well described. An advantage of this study is the fact the authors used two populations with the same methodology, which enhances the sample size of the study.

Major compulsory revisions

A major difficulty in the paper is the justification for carrying out such an analysis in the general population. It is clear why there is evidence of TSH being related to poor lung function outcomes in individuals with cardiovascular diseases, but the rationale for expecting hypothyroidism to be related to lower lung function in the general population needs a better justification.

The Discussion section needs more work to understand the justification of the study and compare it to the existing literature. The authors dedicate a long paragraph to compare their findings with those of a very small clinical study at the beginning, which does not contribute much. Several of the studies cited in the Background/introduction section could be included here and an analysis of the differences could be laid out. There are several other studies though in small samples of individuals, which would help the discussion. Some studies on COPD and TSH explain the role of poor lung function and the interaction with thyroid function (El-Yazed et al Egyptian J Chest Dis Tub 2013, Terzano et al Lung 2014). There is another study by Valjevac C et al (Acta Inform Med 2011) which would also help explain the rationale for poor lung function and thyroid function, and a very good review by Schlenker (Respir Physiol
Neurobiol 2012) which explains several possible mechanisms by which hypothyroidism is related to lung function.

We thank the reviewer for these comments which helped to substantially improve the manuscript. We have adapted the background section and the second paragraph of the discussion section according to the comments of the reviewer. Indeed, the motivation for the association between thyroid dysfunction and lung function was not given in the background section, since we were more focussing on the association between thyroid dysfunction and cardiopulmonary exercise testing (CPET). We have now included putative mechanisms explaining associations of thyroid dysfunction with lung function in the background section. Furthermore, we have extended the discussion on the putative association between thyroid dysfunction and lung function by including more patient studies.

To clarify that we discuss parameters from two distinct measurement techniques of pulmonary function namely lung function (FEV-1, FVC, and FEV-1/FVC) and CPET (peakVO₂, VO₂@AT, Vₑ vs. VCO₂ slope, O₂HR, maximum power, and exercise duration) separately we have now included subheadings in the discussion section.

**Discretionary revisions**

The authors address the possible issue of multiple comparisons in their analyses. Although there were no findings of statistical significance, the authors could include some form of adjustment for multiple comparison.

We thank the reviewer for this comment. At the Bonferroni corrected α-level of 0.0007 none of the statistical tests in our analysis revealed statistical significance. We now include this information in the discussion on page 9.
Reviewer 2

The authors have submitted an interesting study of the potential impact of thyroid dysfunction on cardiorespiratory health and exercise capacity. Compared to other studies in this field they have used a large data sample from the general population. By studying such a population they can make inferences to the wider population. Crucially, however, they have few patients who would be classified as having hypo/hyperthyroidism and as such direct comparisons with published studies of select populations become difficult.

The research question is interesting and well defined. The data are sound and well controlled. I propose the following revisions:

MAJOR

1. The researchers have not described any of the demographic characteristics of patients with high/low TSH. This would be helpful to put subsequent results into context. While the regression models adjusted for many characteristics, details of the resulting regression coefficients are not presented.

   We followed the suggestion and now report the demographic characteristics for the pooled study population stratified by serum TSH levels in Table 1. Beside the characteristics which were already part of the original version of Table 1 we now added information on education, systolic, and diastolic blood pressure in the new version of Table 1. Furthermore, we added one sentence in the results section describing this table (page 6)

The regression models were designed to investigate the association between serum TSH levels and parameters of spirometry and CPET. Thus, only the \( \beta \) coefficients for the association of serum TSH levels with parameters of spirometry and CPET are interpretable. The other covariables in the model were used to minimize the bias due
to confounding. For example, to investigate the association between BMI and parameters of spirometry and CPET one might use a different set of confounders than the one we used in our analyses. Thus, the β coefficients of the covariables are not interpretable and might give rise to false interpretations. Thus, we omitted presentation of β coefficients for covariables in Tables 2 and 3.

2. The authors rightfully identify in the Discussion that their analyses are based on a population based sample with few subjects with clinically relevant hyperthyroidism. Have the authors performed a sample size calculation to determine how many patients would be required to identify meaningful changes in spirometry when classifying TSH by <=0.3, 0.3-3 and >3? The authors make reference to low power in the Discussion, but do not provide figures.

According to the reported differences in CPET measurements by thyroid dysfunction in previous patient studies we would have sufficient power to investigate the association between serum TSH levels and measurements of CPET. However, since previous association magnitudes solely rely on patient studies it is questionable whether these magnitudes can be used as a basis for a power calculation in a population-based study, because it can be assumed that study populations are different: In contrast to most of the previous studies on the association between thyroid dysfunction and CPET the majority of individuals with TSH outside the reference range in our study have probably no clinically relevant forms of thyroid dysfunction. We discuss this issue on page 8 (lines 19 – 23) and on page 9 (lines 9 - 11).

MINOR

1. Please indicate whether the lack of consistency in how the blood samples
were taken (non-fasting in SHIP and fasting in SHIP-TREND-0) might have influenced the interpretation of TSH levels.

In SHIP-Trend blood samples were taken fasting in 75% of the study population, which we now state precisely in the methods (page 5; lines 17 – 18). In SHIP-Trend-0 median serum TSH levels are comparable between fasting and non-fasting individuals (1.15 mIU/L vs 1.10 mIU/L). We included this information in the manuscript (page 5; line 20).

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

To test for differences between participants and non-participants we have conducted a logistic regression model with participation at CPET examination as outcome (1 if yes; 0 if no) and several population characteristics as independent variables. Serum TSH levels, age, body mass index, beta blocker use, physical activity, current smoking, and education were significantly associated with participation. To account for these differences between participants and non-participants we applied inverse probability weights in all regression analyses. We now state on page 6 (lines 13 – 15) that significant differences regarding population characteristics exist between participants and non-participants.

3. The authors used median regression for their analyses. While certainly an acceptable method of analysis it would be helpful if the authors provided some insight into their reasoning for this choice.

We first looked at linear regression models to associate TSH with CPET measurements. For some of the outcomes, however, residuals were not normally distributed. Thus, we had two options. The first one was to conduct a Box-Cox-transformation on the respective outcomes. The problem with this option is that regression results based on transformed outcomes are hard to interpret regarding its
dose-response relationship. Thus, we decided to choose the second option and applied the median regression. This method is robust against non-normality of the error term, so that the outcome variable has not to be transformed and the dose-response relationship can be directly seen in the regression coefficients. Another advantage of median regression over linear regression is the robustness against outliers in the outcome variable, because the median is more robust against outliers than the mean. As recommended by the reviewer we now explain our reasoning in the statistical analysis section (page 6; lines 12 – 13)

4. Table 1 provides details of the age distribution of participants in both studies. By presenting only the median and 25th/75th percentiles – and not explicitly stating the study eligibility criteria in the methods – the reader does not have a full sense of the age distribution. Please quote the minimum and maximum as well as interquartile statistics.

As requested by the reviewer we now include information on the age ranges in SHIP-1 and SHIP-Trend-0 on page 4 (line 21 and line 25).

5. It would be helpful to report what proportion of the cohort were currently taking treatments for hypo/hyperthyroidism and incorporate this into the analysis.

We included information on thyroid medication in Table 1 and performed a sensitivity analysis in which individuals on thyroid medication were excluded. Results from this sensitivity analysis did not differ substantially from those of the main analysis. We now include this information in the results (page 7 lines 22 – 23).

6. The presentation of results in table 2 is unclear. It would be helpful to more obviously separate out the different models for the different measures of TSH.

As recommended by the reviewer we have improved the presentation of Table 2. Therefore, we have added a title row, in which the models are specified. This should
make clear that three regression models were calculated for each outcome; the first one for TSH over the full range, the second model for TSH categorized into three groups using the cut-offs 0.3 mIU/L and 3.0 mIU/L, and the third model for TSH in the reference range under exclusion of individuals with low or high TSH. To optically separate these three models in Table 2 we additionally added two vertical lines.

7. 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.

As recommended by the reviewer we reworded this sentence. (page 9; line 26 – page 10; line 2)

DISCRETIONARY

1. The authors define all of the abbreviations used in the manuscript in the methods section. It would, however, be helpful if these are used consistently through the paper and tables. For example, in the text they make reference to VO2@AT while this is written out long-hand in the tables. Such terms should be consistently reported.

As recommended by the reviewer we now use the abbreviations also in the Tables.