Author’s response to reviews

Title: Obstructive sleep apnea and multimorbidity

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Author's response to reviews: see over
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The BioMed Central Editorial Team

Dear Editor,

On behalf of my colleagues and myself, I would like to thank you and the reviewers for the comments made to our manuscript, “MS: 1841744401698949 - Obstructive sleep apnea and multimorbidity” submitted to BMC Pulmonary Medicine. We found the comments constructive and we were able to address them all. Below, you will find a detailed and specific response to each reviewer comment.

Should you have any questions, please do not hesitate to contact me as corresponding author for this paper. We look forward to hearing from you.

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Author’s response to Referee 1: Ariel Tarasiuk

Introduction

COMMENT:
First paragraph Introduction – The investigators should discuss the findings of a study by Reuveni et al. (Sleep 2004;27(8):1518-25) demonstrating that primary care physicians cannot identify a common disorder associated with cardiovascular and neurobehavioral disease. They concluded that education programs need to be developed to increase the level of suspicion of obstructive sleep apnea syndrome among practicing primary care physicians.

RESPONSE:
Thank you for the reference. We added a sentence in the background section on page 4, as well as the appropriate reference.

COMMENT:
The text of the first paragraph can be extensively shortened: For example: a) “L6-9 in paragraph 1 of the Introduction – “…There are three…” , “… respiratory arrest…” – can be deleted from the text.

RESPONSE:
It has been deleted.

COMMENT:
b) L11–14 can be deleted – “… use an alternate 3% … which records sleep cycles and quantifies apnea and snoring …”.

RESPONSE:
The introduction has been rewritten to reflect this suggestion.

COMMENT:
P5 1st line – this sentence should be revised; the investigators should acknowledge that clinicians (especially primary care physicians) and decision-makers are following the results of the Sleep Heart Health Study that provides data on OSA patients starting from forty years of age. However, Reuveni et al. (Eur Respir J 2008;31:273-9) explored morbidity and health care utilization among young adult males with OSA over the five-year period preceding diagnosis. Compared to middle-aged males with OSA in whom increased expenditure was related to CVD and BMI, in younger (<40 years) patients utilization was not related to any specific disease.
RESPONSE:
We are not quite sure that we understand the reviewer’s comment. The reference we used was Young et al., 2004. Other studies use 40 and over as criteria and conclude that at this age the risk of having a new disease is more important. Young used 40 and more as a risk factor for SAOS. Young, T., Skatrud, J., & Peppard, P. E. (2004). Risk factors for obstructive sleep apnea in adults. JAMA: The Journal of the American Medical Association, 291(16), 2013-2016. doi:10.1001/jama.291.16.2013. We do acknowledge the relevance of making reference to Reuveni’s work, which we did in the previous paragraph and have adjusted the text accordingly.

Methodology
COMMENT:
1) 1st paragraph – it is not clear how cluster sampling was done, e.g., random.
RESPONSE:
The sentence now reads: “We selected 50 consecutive patients from each category to ensure proportional representation (25% each) of the four OSA categories.”

COMMENT:
2) How many patients underwent PSG in 2008? How did you calculate your sample size?
RESPONSE:
Each year, the sleep lab sees approximately 400 patients; we sent the questionnaire to 200 patients. Due to the exploratory nature of the study, we based our sample size estimation on the availability of the data and feasibility more than a power calculation. We aimed for a sample size of 120 (30 per OSA group) to ensure a good representation of each category of the independent variable. We oversampled by 30% for potential non response. We adjusted the methods section to reflect the sample size estimation. We also clarified the description to reflect this comment made by both reviewers. (paragraph 4 of the methods section, pages 6-7)

COMMENT:
3) What was the rationale to ensure proportional representation (25% each) of the four OSA categories? Was it performed according to the distribution of OSA severity in 2008?
RESPONSE:
The proportional representation of each four OSA categories was not performed according to the distribution of OSA in the population. We decided to sample 50 in each group to ensure a good spread of the independent variable. That was what we meant by: “to ensure proportional representation (25% each) of the four OSA categories” in the Methods section (1st paragraph, page 5).
COMMENT:
4) The investigators should carefully describe their PSG referral population in their area. In your area how are patients referred to PSG (e.g., ENT, pulmonary, sleep medicine), do your subjects have typical symptoms for OSA?

RESPONSE:
We cannot provide this information which is unknown to us.

COMMENT:
5) You must calculate statistical power to convince readers that you have the minimal sample size required.

RESPONSE:
See previous response regarding the sample size. We believe that the statistically significant results are a demonstration of the sufficient statistical power. However according to the G-Power 3.1.4 statistical analysis program, assuming a moderate effect size, of 0.15, an alpha of 0.05 and a power of 0.95, a sample of 120 would be enough for up to five predictors in a logistic regression model. In this respect, the sample size for this study was adequate. However we do not think that this information should be presented *a posteriori*.

Discussion

COMMENT:
In the discussion section the investigators should acknowledge several important studies from Manitoba, Canada, that explored what obstructive sleep apnea patients are being treated for years prior to diagnosis (Chest 2002;121:164-72; Thorax 2002;57:417-22). Their results and others from the same group provided important clues to the thought that multimorbidity exists in OSA. Other studies from Israel using the health care utilization approach have also provided important clues to this thought, in relation to gender, age, and OSA severity.

RESPONSE:
We thank the reviewer and have added a sentence and the appropriate reference to reflect this comment.
Author’s response to Referee 2: Kazuo Chin

Major comments:

COMMENT:
1. In addition to the lack of hypothesis, the objectives of this study did not quite fit the Introduction. The first sentence of the last paragraph of the Introduction states, "Evidence of an association between OSA and multimorbidity…thereby affecting the quality of life and health of patients.". However, the health status of patients was not evaluated in this study.

RESPONSE:
The introduction has been cut and is now more focused and better aligned with the objectives. Specifically, we removed the part of the sentence related to quality of life that was indeed out of scope for this paper. We thought that wording our hypothesis of an association between the OSA and multimorbidity would be redundant with the objective that is directly related to exploring this association. Therefore we did not add a sentence stating the main hypothesis. We hope that the rewriting of the introduction addresses the comment made by the reviewer.

COMMENT:
2. Regarding Table 2, the authors said that there was a correlation between the severity of OSA and the proportion of patients with comorbidities. The statistical method and the results of these analyses should be given.

RESPONSE:
We are grateful to the reviewer for this comment. We agree that the text was misleading the reader. We removed the mention of a correlation. Table 2 is simply descriptive and no statistical test was performed. We cannot draw any conclusion from this description but we wanted the reader to have an idea of the distribution of the various chronic diseases across the level of severity of OSA. Numbers are too low for drawing conclusions. The text has been modified to reflect that. We did not add a limitation for this inconclusive description as it was beyond the scope of the paper.

COMMENT:
3. Why did the authors use bivariate analyses (absent and mild vs. moderate and severe) in Table 3? Using the absolute value of AHI as continuous variables or ANOVA with each OSA severity seem to be appropriate.

RESPONSE:
The assumptions for using ANOVA were not respected. Therefore, we limited our analyses to non-parametric tests (Spearman correlation).
Minor comments:

COMMENT:
1. The authors should explain DBMA in detail, because most of readers do not know DBMA well.

RESPONSE:
The description of the DBMA has been expanded.

COMMENT:
2. Page 8, lines 16 to 17. Did the authors estimate 'sufficient' sample size? In addition, I would like you to show how you estimated the sample size in this study.

RESPONSE:
Due to the exploratory nature of the study, we based our sample size estimation on the availability of the data and feasibility more than power calculation. We aimed for a sample size of 120 (30 per OSA group) to ensure a good representation of each category of the independent variable. We oversampled for a potential non response of 30%. We adjusted the methods to reflect the sample size estimation. We clarified the description of our sampling.

COMMENT:
3. The response rate to the questionnaire in this study is low.

RESPONSE:
Our study generated a response rate of 64%; this rate is higher than the rate reported (50%) when a mail questionnaire is used. Dillman, D. A. (1978). *Mail and telephone surveys: The total design method*. New York ; Toronto: Wiley. Nonetheless, we adjusted the text in the section on limitations to better reflect the limitation due to the response rate.