Author’s response to reviews

Title: The association of sleep disordered breathing with left ventricular remodeling in CAD patients: a cross-sectional study

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Author's response to reviewer 3

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Version: 2 Date: 15 May 2017
Dear Editors and Reviewers:

Thank you for your letter and for the reviewer’s comments concerning our manuscript entitled “The association of sleep disordered breathing with left ventricular remodeling in CAD patients: a cross-sectional study” (ID: BCAR-D-16-00535) by Audrius Alonderis et al.

We also thank the reviewer Phyllis K Stein for her constructive suggestions which are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. Thank you very much again.

In the following sections, you will find our responses (with line numbers in the revised article) to each of your points and suggestions. We are grateful for the time and energy you expended on our behalf. Now we are looking forward to your response and decision concerning our manuscript.

We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are highlighted in blue in the revised manuscript.

Yours sincerely

Audrius Alonderis

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Reviewer reports:

Phyllis K Stein (Reviewer 3): Abstract: This is a paper about association not causation. It is imperative that any suggestions of causation be removed. An example is the conclusion of the abstract where the phrase mild-to-moderate "increased" LV ... Even though in the second part of the conclusion you returned to "was associated with" this has to be the way all results are expressed. This is a cross-sectional study and there is no way to define causation or even the direction of causation.

Response: Thanks for your suggestions. We agree that in cross sectional study predictive models cannot provide direct causal explanations. However, by producing high-accuracy predictions
they shed light on new potential variables that are related to dependent variable (in our case – LVH) and on the types of relationships that can be further investigated in terms of causality.

At any rate, neither cross-sectional nor longitudinal survey research can definitively determine causal mechanisms. The direction of the arrow of causation (which might be pointing in opposite directions in different individuals) can be determined only by analysis in the cohort in the coming years and repeated polysomnography. Our results, if replicated in prospective, cohort data, should be of public health importance, especially in light of unfavorable secular trends in obesity, a major determinant of SDB.

We totally agree with your point of view, and thank you very much for your guidance, which have led us to found what remains to improve our manuscript. Under your guidance, we have used “association” or cross sectional predictor instead “prediction” and “predictor”

This is now clarified in Abstract: Mild to moderate sleep apnea was associated with increased LV wall thickness, LV mass, and with higher prevalence of concentric LV hypertrophy independently of coexisting obesity, hypertension, diabetes mellitus or advancing age.

Background: It is misleading to not include that fact that SA is prevalent among apparently healthy middle-aged and older adults as well, and cite some statistics about that prevalence.

Response: Thanks for your suggestions. We included in line 69:

The high prevalence and wide spectrum of severity of SA in adults have been well documented by several population-based cohort studies conducted in the United States, Europe, Australia, and Asia. Although measurement techniques and definitions have varied, most of these studies have shown that 1 in 5 adults has at least mild SA and 1 in 15 has moderate or severe SA [4].

You need to be clear about SA vs. SDB. The lack of clarity muddies the introduction. SDB includes OSA, obstructive hypopneas and central apneas. You are not being clear about what you are actually focusing on and the relationship of these to CV outcomes also needs to be focused on what YOU are studying.

Response: We totally agree with your point of view. SDB continuum ranges from simple snoring to obstructive sleep apnea (OSA). Upper airway resistance syndrome (UARS) occupies an intermediate position between these extremes. Note areas of overlap among the conditions. The apnea-hypopnea index (AHI) is the most commonly used characteristic of SA. Obstructive events (apneas) are not separated from partially obstructive events (hypopneas) in this index. Although SA syndrome includes both, a PSG abnormality and symptoms, its severity is often defined by AHI alone.

This is now clarified in Abstract/Background:
“Sleep apnea (SA) which is the most common form of SDB is associated with adverse health consequences, including an increased risk of death.”

Line 85. unclear what you mean by "targeted responses"
Response: This is now clarified:
Abnormalities in left ventricular (LV) geometry, including LV hypertrophy (LVH) is both a target organ response to chronic arterial hypertension and other cardiovascular ……..

Line 93 "sleep abnormalities” Again not focused and not defined in the context of your study
Response: This is now clarified:
Patients with SDB have a high prevalence of arterial hypertension and, more importantly, obesity, which represents the strongest predisposing factor for SDB [23-25].

Line 100 Again the word "consequence" implies causation and this is not acceptable.
Response: This is now clarified:
The present study was performed to determine the association of SDB with LV geometry

Line 103 "more concentric left ventricle" ??? What are you saying/?
Response: This is now clarified:
…………(2) a higher prevalence of concentric left ventricle than in patients without SA controlling for traditional recognized risk factors.

Methods:
Line 118 not consent needs to be changed to refusal to consent or something else that is grammatically correct
Response: This is now clarified:
………… having other severe diseases or has refused to participate in the program.
Several echocardiograms and PSGs were………

Anthropometric and clinical profile of the patients with CAD who not involved into the study did not differ significantly compared with the studied group.

Physiological variables collected …………

That is one of our limitations. Little is known about risk factors for CSA in persons without heart failure, and data on the prevalence and characteristics of CSA in other types of cardiovascular disease are sparse. But, in our next follow-up work, we will try to analyse central SA more detailed. This type of SA requires a deeper analysis in future.

We agree that conclusions based on research performed on men with CAD may not be valid for women and that more gender-related research is needed. The usual indication to diagnose and treat SA is subjective sleepiness. In our study, many CAD patients with SA do not experience daytime sleepiness. It should be noted that, although patients with SA had a higher mean value of the ESS than non-SA patients, the mean ESS score was within the normal range in both groups.
Excessive daytime sleepiness is suggested as the most important symptom of OSA, but only a fraction of subjects with AHI >5 report daytime sleepiness and one study did not find any relationship between daytime sleepiness and sleep apnea in women [Franklin2016].


Line 184: Echo.... blinded according to... should be "were blinded to the results of the PSG."
Response: This is now clarified:

Echocardiographic evaluation of the patients was blinded to the results of the PSG.

I am not an expert in echocardiography and therefore did not read the methods section for the echo in detail.

Statistics:

Line 224: "supposed clinical relevance" suggested??
Response: This is now clarified:

….., as well as the non-significant variables with suggested clinical relevance were included.

Model characteristics:

I recommend a statistical consult. Many of the independent risk factors are actually overlapping clinically.

Response: In our study main interest of logistic regression models is an association between LVH (dependent variable) and cross sectional predictors (risk factors, independent variables). This is especially true of the binary logistic model since it has no distributional assumption. We agree that model building can create many problems. Multivariable analysis is the real model building stage; however, we are likely to get erroneous results if we jump straight to multivariable analysis without carrying out the previous steps. We examined associations/correlation between explanatory variables and exclude one of a pair of highly correlated variables before conducting multivariable analysis. Alternatively, at least we can delete one of the pair during multivariable analysis if they pose problems. In last step we test associations of variables with the outcome after accounting for other variables and confounders.
Results:

Clinical Characteristics

The first paragraph should be in a Table. Table 1 compares non-SA and SA, but you could have a third column for all, if you want to describe the clinical characteristics of the study population. Do not write out this description in a paragraph. It is hard to read and hard to make sense of.

Response: Under your guidance, we have added in Table 1 a third column for all. We’ve have now changed the text accordingly. Thanks for your help.

Line 245: comparing to male  should be compared with male

Response: This is now clarified:

In females SA was less frequent comparing with male CAD patients

Although Table 2 compares patients with and without what is more correctly called OSAHS, the focus of the paper is on people with mild-to-moderate vs. no OSAHS. If you want the entire set of results could be put into a supplemental table, but basically, anything except the comparison of the two groups of interest is irrelevant and should not be in the main text.

Response: As stated above, we had analyzed SA (OSA, CSA with or without EDS, i.e. not only obstructive syndrome OSAHS) and we have taken a consistent ranking analysis from univariate analysis of differences in severity to multivariable adjusted association of LVH with cross sectional predictors.

In statistical analysis we had explained the analysis by SA severity: First, to identify demographic, polysomnographic and echocardiographic characteristics we compared non-SA versus SA patients to standard definition, i.e., non-SA (AHI<5) versus SA (AHI≥5). Subsequently, we compared patients according to SA severity as defined according to the apnea-hypopnea index (AHI) as mild (5-14.9), moderate (15-29.9), and severe (≥30 events/h). We reported only p value for trend in last column Table 4.

No matter what you keep, do not repeat the contents of the table except where you are highlighting an important finding.

Line 269---clinical characteristics by apnea severity... again, that is not what this paper is about and the contents of Table 2 do not need to repeated. Table 2 SHOULD be a comparison of no OSAHS and mild-to-moderate but even if you wanted to include everyone, the no OSAHS group would have to be in that table.
Response. The detailed methodology concerning the statistical analysis has been described in METHODS section.

In univariate analysis we not found differences between three groups according to SA severity. However multivariate regression analysis with confounders revealed that mild to moderate SA was associated with LVH. We used ANOVA minimizes the inflation of a Type 1 error due to multiple comparisons, reduces the number of tests required to identify a significant difference in means when comparing more than two groups, prevents further unnecessary analysis if the omnibus test (F-test) is not statistically significant, and is relatively robust to violations of assumptions in balanced study designs.

Notable also, the moderate and severe groups are relatively small and the initial presentation of the study as involving 772 CAD patients becomes misleading. I recommend a flow chart in the methods which shows how you went from the initial to the final cohorts.

Response: The detailed methodology concerning the study setting, data collection, inclusion and exclusion criteria have been described in Methods section. We wrote: “The study was a cross-sectional investigation of 1,027 consecutive stable CAD patients attending the Clinic of Cardiovascular Rehabilitation, from October 2007 until December 2014 for routine cardiac rehabilitation program.” The strengths of this study include relatively large sample size. First, by including a large sample of patients and numerous confounding covariates, our study has overcome many of methodological limitations and provides strong support for an independent cross-sectional association between SA and LV. Second, adjustments of echocardiographic parameters to BMI and hypertension have been successfully done.’

Table 3 needs a N for the non-SA group.

Response:

Variable non-SA
AHI<5
n=472

Line 283: A little disingenuous to say that "as expected .." this is almost by definition of the groups
Response: In fact the group is constructed according to AHI and……As expected, AHI and ODI were highest in patients with severe SA (p for trend<0.001), and these patients had both the lowest average SaO2 and highest maximal oxygen desaturation (p<0.001).

Discussion of Table 2. Even though, again, in the abstract, you describe the purpose of the study to be that association between SDB and LVH in stable CAD, the first aim was to fill in the gap of the possibility that asymptomatic SDB would be associated with LVH, this again reflects a lack of focus in this study. The proportion of people with severe OSA who had not been diagnosed was small and the more important finding is that, potentially, even people with recent ACS (which is a more specific way to characterize this population) with AHI<15 and no awareness of their SDB appear to have worse LV characteristics.

I will not continue to go over the results in detail except to say that you have to decide what this paper is really about and then focus on that. Clearly, my opinion is that the info about more severe SDB is not novel and the info about mild SDB is.

It is kind of frustrating to jump back and forth between comparing SA and non-SA and the other aspects of the analysis. I am not sure you have enough females to say anything when you look at AHI<15 vs AHI <5 but I am not going to try to figure that out. ???????????

Response: By including a large sample of patients and numerous confounding covariates, our study has overcome many of methodological limitations and provides strong support for an independent cross-sectional association with SA. Moreover, despite that CAD and SA share risk factors and that systemic conditions influenced by SA have a role as well in the pathogenesis of CAD, evidence is lacking to address OSA as a risk factor of CAD, as a prognostic factor of CAD. However, research in this field is growing rapidly, and data answering some of these questions may soon, be available.

Discussion:

Were these patients only "stable CAD" or were they all 2-week post ACS and stable. That would be different.

Response: Patients involved into the study were all 2 week post ACS and stable.

OSA may influence the onset of acute ischemic events, as ACS. A variable time gap existed between clinical assessment of patients and polysomnography, but it probably did not affect the association between severity of sleep-disordered breathing and diabetes, hypertension, metabolic syndrome, and depression, since these disorders are typically chronic conditions. There is some
evidence suggesting that the prevalence and the severity of SA are modified along the CAD evolution.

Line 390: not predicts.... is associated with

Response: This study extends this information with the novel finding that even mild level of SDB strongly is associated with LVH with increasing LV wall thickness …….

Line 394: The effect of SA on LVH risk is fully realized... again implies causation when that has not been show. This could be bi-directional and LVH risk is not meaningful here.

Response: We wrote “could suggest”:

These results could suggest that the effect of SA on LVH risk is fully realized at some SA.

Line 403: Our results discovered.... please correct Our results suggest. And AGAIN this is not causation, this is association and you imply, by using the word effect, that it is casual. It could be, but you cannot show that in this study.

Response: This is now clarified:

Of course we cannot make any causal claims here, but our results could suggest that even mild SA had additive effect…….

Line 415 to 420: Although this is an attempt to compare the prevalence of undiagnosed SDB (and here again you are muddying SA with OSAHS) in your population with those in the literature is totally muddy. You fouled 39%. Surely you can find a study that is well done to compare it to. It is meaningless to report a range of 26% to 60%. It adds no clarity whatsoever to this discussion.

Response: Thanks for your suggestions. Information regarding the prevalence of SA in CAD cohorts is unfortunately scarce. The data reported earlier show a wide range of prevalence rates for SA in CAD. In part, this is due to the use of different definitions of SDB and different cut-off values for AHI, which make comparing rates between studies difficult.

Line 422: correct the syntax.
Actually the whole paragraph needs to be clarified with correct English and a though to what you are trying to say. It might be possible to create a table but this is basically an undigested recitation of the results of prior studies without actually and coherently putting your study into context.

Response: Thanks for your suggestions. We have now tried to correct those mistakes in text:

“Mooe et al. reported that clinically significant sleep apnea (AHI >10) was documented in 37% of investigated 142 patients with stable angina pectoris and angiographically confirmed CAD [43]. In patients admitted with an acute coronary syndrome Peker et al. reported 30% prevalence of SA while Areias et al. claimed to be present SA in 43% of the study patients [12, 17, 41]. In CAD patients immediately after an acute myocardial infarction and after clinical stabilization of unstable angina pectoris Moruzzi et al. observed a significantly higher AHI compared to stable angina pectoris patients [12, 44].”

The next paragraph is no more helpful although I appreciate that you are trying to discuss your findings.

I give up on the discussion at this point. It is too long and again not focused. Maybe, for your own purposes, you can diagram the logic of it and it would help you. It is also completely irrelevant if you limit your study to the novel finding of the association of mild to moderate OSAHS with LV remodeling. Then you do not have to review the entire literature on various studies of SDB and of factors that influence LV remodeling. Perhaps this was a PHD thesis study, I don't know, but right now you have both a research result and a disorganized review of the literature.

Response: First of all we wanted to thank you again so much for this really helpful job. Thank you so much for your detailed analysis! We also look forward to hearing your suggestions for our further study. Thank you very much.