

Sex differences in the association between obstructive sleep apnea and hypertension – what's next?

Irene Cano-Pumarega^{1,2}, Ferrán Barbé^{2,3}, Joaquín Durán-Cantolla^{2,4,5}

¹Respiratory Department, University Hospital of Getafe, Madrid, Spain; ²Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), ISCIII, Madrid, Spain; ³Respiratory Department, IRBLleida, Lleida, Spain; ⁴Research Department, OSI Araba University Hospital, Vitoria, Spain; ⁵Universidad del País Vasco, Vitoria, Spain

Correspondence to: Irene Cano-Pumarega, MD, PhD. Respiratory Department, Hospital Universitario de Getafe, Ctra. Toledo Km 12,500, 28905 Getafe, Madrid, Spain. Email: irene.cano@yahoo.com.

Provenance: This is an invited article commissioned by Section Editor Dr. Ning Ding (Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Response to: Fuchs FD, Fuchs SC, Martinez D. Obstructive sleep apnea—Hypertension link: almost there? *J Thorac Dis* 2017;9:3537-40. Freitas LS, Drager LF. Gender and cardiovascular impact of obstructive sleep apnea: work in progress! *J Thorac Dis* 2017;9:3579-82.

Submitted Nov 08, 2017. Accepted for publication Nov 14, 2017.

doi: 10.21037/jtd.2017.11.99

View this article at: <http://dx.doi.org/10.21037/jtd.2017.11.99>

We thank the editor for inviting both editorials on our recent publication in *Chest* and we also thank Freitas *et al.* and Fuchs *et al.* and appreciate their interest in our work (1). As the readership of *Journal of Thoracic Disease* is aware, most of the evidence on the cardiovascular impact of obstructive sleep apnea (OSA) comes from studies with a small proportion of women. However, over the last decade some studies have assessed the sex-related impact of OSA on cardiovascular outcomes, especially hypertension, with conflicting results (2-5). Along this line, we evaluated the relationship between OSA and incident hypertension in a previous analysis of the Vitoria Sleep Cohort and we did not find an independent association in men or in women (6). Subsequently, we performed a *post hoc* analysis to explore the relationship between OSA and incident stage 2 hypertension (blood pressure $\geq 160/100$ mmHg) and we found an association in men but not in women.

We decided to explore the association between OSA and the risk of developing moderate to severe hypertension (stage 2) and not stage 1 hypertension because, as we used office blood pressure measurements, it allowed us to reduce the number of false-positive results for hypertension, and also because of the potential benefit of treating OSA patients to prevent the cardiovascular consequences of moderate to severe hypertension. As

interestingly pointed out by Fuchs *et al.* (7), the findings of our study (OSA being a risk factor only for stage 2 hypertension and not for stage 1) as well as studies that have evaluated the positive OSA-resistant hypertension association, support the concept of a risk gradient. Future studies need to address this biological plausibility.

With regard to the sex differences found in the OSA-hypertension association, most studies (including ours) have been limited by sample size, which may reflect low statistical power rather than a lack of statistical significance. Supporting this, in our study the risk of incident hypertension for women with OSA was not so different from men, but in women it was not significant. However, we have to take into account that our population reflects the community-based nature of our study and, although the sample size was large and we included a similar proportion of men and women, patients with severe OSA were not well represented. This is especially relevant in the case of women, due to the lower prevalence of hypertension and OSA in premenopausal women compared to men (8) (67% of women included in our study were premenopausal). This leads us to highlight the essential role of female hormones in the OSA-hypertension relationship. In fact, when we analyzed the different clinical subgroups identified by the recursive

partitioning method, although the majority of women in our sample (81%) belonged to the lowest-risk subgroup for stage 2 hypertension incidence (young and non-obese), there was a subgroup of women (3.8%) (over the age of 56 years and with a neck circumference diameter >35.3 cm) who were all postmenopausal and had the highest stage 2 hypertension incidence of our sample (28.0%). This last subgroup may present similar characteristics to women with clinical suspicion of OSA usually seen in sleep-disorders clinics. All these data emphasize the importance of studying the role of the menopause in the OSA-hypertension association and raise the question of whether women require a longer exposure time than men for the expression of hypertension.

In summary, larger longitudinal studies with longer follow-up, especially in women, are needed in order to identify all the clinical variables, biomarkers and intermediary pathways that may play a role in the OSA-hypertension association and to determine if OSA management should differ according to sex and age. Moreover, further investigation should be undertaken into whether the OSA phenotype remains static throughout life or whether it changes with time and under different environmental conditions. Use of dense mapping of candidate genes would provide a better approach for identifying genotype-phenotype correlations for OSA and hypertension.

Acknowledgements

Funding: The authors were supported by Fondo de Investigaciones Sanitarias, Ministerio de Sanidad y Consumo (FIS 01/1577), Departamento de Sanidad del Gobierno Vasco (2001 1037) and Spanish Respiratory Foundation (FEPAR 2001).

Cite this article as: Cano-Pumarega I, Barbé F, Durán-Cantolla J. Sex differences in the association between obstructive sleep apnea and hypertension—what's next? *J Thorac Dis* 2017;9(12):E1156-E1157. doi: 10.21037/jtd.2017.11.99

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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