Editorial

Gender and cardiovascular impact of obstructive sleep apnea: work in progress!

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In the last decades, obstructive sleep apnea (OSA) has gained substantial attention due to the high prevalence and multiple consequences not limited to sleep quality and quality of life (1). Particularly, the cardiovascular impact of OSA has been consistently suggested by multiple, basic (2), translational (2) and clinical studies (3-10). However, because OSA is at least twice more common in men than in women (11) much of this evidence comprised basically only men or a small proportion of women that prevented us to have substantial data stratified by sex. However, considering the current burden of OSA (12), the amount of women with significant OSA is by far relevant. Therefore, there is an obvious interest in exploring whether the cardiovascular impact of OSA is potentially true regardless of gender. This notion has been extensively explored in other cardiovascular research areas, and not surprisingly has been recently addressed in the sleep medicine field.

One of the examples of sex-related impact of OSA on cardiovascular diseases came out from the Victoria Sleep Cohort study (13), an adult cohort designed to assess the prevalence and natural history of OSA in residents of Vitoria-Gasteiz, Spain. In this study, Cano-Pumarega and colleagues explored the association of untreated OSA and incident stage 2 hypertension (blood pressure ≥160/100 mmHg) based on gender differences in 1,155 normotensive subjects (650 of them women, 56%) at baseline. The presence of moderate to severe OSA was higher in men than in women (18.6% *vs.* 8.6%). After a mean follow-up of 7.5 years, the authors found that 23% of the hypertensive patients developed stage 2 hypertension and they found a significant difference between men and women (13.7% *vs.* 3.2%, P<0.001). A respiratory disturbance index (RDI) ≥14/h (comprising moderate and severe OSA) was independently associated with incident stage 2 hypertension in men (OR 2.54, 95% CI: 1.09–5.95) but not in women. Interestingly, no significant association was observed in the baseline RDI between the subjects who developed stage 1 hypertension and the subjects who remained normotensive.

How to interpret these provocative and interesting prospective findings? Are women really protected from the cardiovascular effects of OSA, including clinical, relevant hypertension? Or the relative small sample of moderate to severe OSA women (n=48) may prevent us any definitive conclusion? Supporting the last, the OR for women with OSA to develop stage 2 hypertension was not so different from men (2.14, 95% CI: 0.40–11.36).

Putting the Victoria Sleep Cohort in context (*Table 1*), the next question is: how consistent are these results in comparison to recent evidence addressing surrogate markers, intermediary pathways and cardiovascular events in women with OSA? As described on *Table 1*, there are more questions than answers regarding this important research area. However, it is important to note that the majority of the evidence suggests that the presence of OSA in women

Table 1 Summary of the recent evidence addressing surrogate markers, intermediary pathways and cardiovascular events in women with obstructive sleep apnea (OSA)

Endpoint	First author, year	Main results	Comments
Blood pressure/ hypertension	Cano-Pumarega (13), 2017	1,155 normotensive subjects (650 of them women, 56%). Mean follow-up of 7.5 years. Moderate and severe OSA) was independently associated with incident stage 2 hypertension in men (OR 2.54, 95% CI: 1.09–5.95) but not in women	Cohort study
	Jenner (14), 2017	95 hypertensive patients (56% women). OSA was independently associated with non-dipping blood pressure in both gender	Cross-sectional data. Hypertensive patients with standardized anti-hypertensive treatment
	Pedrosa (15), 2014	277 perimenopause women without cardiovascular disease. Women with moderate to severe OSA had higher frequency of hypertension. Oxygen desaturation index during the night was independently associated with increased 24-h arterial blood pressure	Cross-sectional data from a cohort study in perimenopause women
Endothelial function	Faulx (16), 2004	193 participants (58% women). The apnea/hypopnea index was inversely associated with endothelial dysfunction exclusively in women	Cross-sectional data from the Cleveland Family Study
Arterial stiffness	Pedrosa (15), 2014	277 perimenopause women without cardiovascular disease. Women with moderate to severe OSA had higher arterial stiffness. Oxygen desaturation index during the night was independently associated with increased 24-h arterial blood pressure and arterial stiffness	Cross-sectional data from a cohort study in perimenopause women
	Jenner (14), 2017	95 hypertensive patients (56% women). OSA was independently associated with arterial stiffness in both gender	Cross-sectional data. Hypertensive patients with standardized anti-hypertensive treatment
Coronary calcium score	Medeiros (17), 2017	214 women. OSA is independently associated with coronary artery calcium (CAC)	Cross-sectional data from a cohort study in perimenopause women
	Weinreich (18), 2013	1,604 subjects (50.7% women). Apnoea-hypopnoea index (AHI) was associated with CAC in men aged <65 years and in women of any age. Doubling of the AHI was associated with a 19% increase of CAC in men aged 65 years and with a 17% increase in women of any age	Cross-sectional analysis of the Heinz Nixdorf Recall study. General population aged ≥50 years
Cardiac function	Roca (19), 2015	1,645 participants (54.3% women) without cardiovascular disease at baseline. Subjects were submitted of echocardiogram after 15.2 years of follow-up. Among surviving participants without incident cardiovascular (CV) event, OSA was independently associated with higher left ventricle mass index only among women	Participants from the atherosclerosis risk in the communities and the sleep heart health studies
	Javaheri (20), 2016	1,412 participants (53.6% women). Higher levels of AHI are independently associated with increased left ventricular mass in both men and women younger than 65 years	Cross-sectional analysis of data from the Multi-Ethnic Study of Atherosclerosis. Cardiac function evaluated by cardiac magnetic resonance imaging
Cardiovascular mortality	Campos-Rodriguez (21), 2012	1,116 women followed by a median of 72 months. OSA is associated with cardiovascular death in women and this risk can be reduced by adequate continuous positive airway pressure (CPAP) adherence	Observational data

were associated with significant impairment in arterial stiffness, coronary calcium, and higher cardiovascular risk (*Table 1*). Some of these studies pointed to the opposite direction: only women with OSA but not men are on risk! For instance, Faulx *et al.* found that the impact of OSA on endothelial function was only significant in women (16).

So, what is the take-home message so far: work in progress (22)! Particularly, future investigations addressing several endpoints with significant amount of women and men with similar OSA severity may help to clarify whether the apparently differences in women and men with OSA is justified by differences in frequency and severity of OSA. In addition, intervention studies addressing the effects of OSA treatment is highly desired. For instance, a recent randomized controlled trial investigation addressed the effects of CPAP or conservative treatment for 12 weeks on blood pressure levels and the glucose and lipid profile in 307 women with moderate-to-severe OSA. Compared with the control group, the CPAP group achieved a significantly greater decrease in diastolic blood pressure (–2.04 mmHg), and a non-significant greater decrease in systolic blood pressure (–1.54 mmHg) and mean blood pressure (–1.90 mmHg). CPAP therapy did not change any of the metabolic variables assessed (23). New studies with direct comparisons of men and women are warranted. Finally, despite the recent neutral results of OSA treatment in the second prevention scenario of coronary artery disease and stroke (24), there is still too much to respond in the primary prevention and in patients with established cardiovascular diseases.

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Footnote

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

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