

## EDITORIAL

# Sleep disorders and hypertension risk

*Journal of Human Hypertension* (2017) 31, 371–372; doi:10.1038/jhh.2017.2

A large number of observational studies link sleep disorders, particularly obstructive sleep apnoea (OSA) and insomnia, to risk of cardiovascular (CV) disease, including hypertension, ischaemic heart disease, stroke and sudden death.<sup>1–7</sup> For example, Shah *et al.*<sup>6</sup> conducted a longitudinal analysis of over 1400 patients who had been diagnosed with at least mild OSA (apnoea-hypopnoea index (AHI)  $\geq 5$  events  $h^{-1}$ ). During a mean duration of follow-up of 2.9 years and after adjustment for traditional risk factors, having been diagnosed with OSA was associated with a doubling of risk for combined CV complications, including myocardial infarction, coronary artery revascularization or death from CV disease. Utilizing The Sleep Heart Health Study cohort, investigators determined the risk of stroke in 5422 study participants during a median follow-up of 8.7 years.<sup>5</sup> Overall, there was a strong positive association between incident stroke and severity of OSA in men. Men with the most severe OSA (AHI  $> 19$  events  $h^{-1}$ ) had an adjusted hazard ratio for risk of stroke of 2.86, while men with mild-moderate OSA (AHI 5–25 events  $h^{-1}$ ) manifested an estimated 6% increase in risk of stroke for each one-unit increase in the AHI. In women, risk of stroke was not increased with mild-moderate OSA, but was higher in association with having severe OSA ( $> 25$  events  $h^{-1}$ ).

Increased risk of prevalent and incident hypertension attributable to OSA is likewise supported by a large number of observational studies. In a cross-sectional analysis of participants in the Sleep Heart Health Study, Neito *et al.*<sup>8</sup> reported, after adjustment for demographic variables, that severe OSA was associated with a more than twofold increase in risk of having hypertension compared with participants without OSA, while mild or moderate OSA was associated with a 60–70% increased risk. Likewise, observational studies indicate a positive relation between increasing severity of OSA and risk of incident hypertension. Analysing participants in the Wisconsin Sleep Cohort Study who were normotensive at the time of their sleep study, investigators reported that after a minimum of 4 years of follow-up, having mild OSA was associated with a more than twofold increased risk of developing hypertension, and having moderate-severe OSA was associated with an almost threefold increase in incident hypertension.<sup>9</sup>

Although less studied compared with OSA, insomnia likewise has been linked to risk of hypertension and CV disease. For example, Fernandez-Mendoza conducted a longitudinal analysis of participants in a cohort study who had self-reported chronic insomnia and who had confirmed short sleep duration ( $< 6$  h) during polysomnographic evaluation.<sup>1</sup> After a follow-up of 7.5 years and having controlled for OSA, the highest risk for incident hypertension was in chronic insomniacs with observed short sleep duration. Other observational studies also demonstrated that chronic insomnia is associated with increased risk of heart disease. Laugsand *et al.*<sup>2</sup> related self-reported symptoms of insomnia and non-restorative sleep to risk of incident acute myocardial infarction (MI) in a large, population-based study. The investigators found, after adjustment, that persons with nightly or near nightly difficulties initiating or maintaining sleep or who reported a least one night of non-restorative sleep per week had a significantly increased risk (45% and 27%, respectively) of having

an acute MI during the follow-up period compared with participants without those sleep complaints.

In the current edition of the *Journal of Human Hypertension*, Lin *et al.*<sup>10</sup> add importantly to the body literature relating the presence of sleep disorders to risk of CV disease, in this case, specifically, risk of incident hypertension. The study is impressive in having utilised the National Health Insurance Database that includes all 23.7 million individuals living in Taiwan. Of these individuals, one million were randomly selected by the investigators for their retrospective analysis. During a 1-year time period, all individuals without a history of hypertension and who had been newly diagnosed with a sleep-related disorder based on ICD-9 codes were identified. The affected individuals were then divided into four groups based on diagnostic disease categories (insomnia, sleep disturbance, sleep apnoea and other) and followed until the onset of hypertension or up to 5 years.

The authors report that the risk of incident hypertension is significantly increased in individuals diagnosed with a sleep disturbance versus participants without a sleep-related disorder.<sup>10</sup> Overall, risk of developing hypertension was increased in the former by about 60% during the almost five-year follow-up period. The higher risk was true for all age groups and both genders. There was, however, a surprising difference in risk in relation to having insomnia versus sleep apnoea. Compared with individuals without insomnia, individuals with insomnia had a 21% higher risk of developing hypertension, which was statistically significant. In contrast, individuals diagnosed with sleep apnoea syndrome compared with individuals without sleep apnoea likewise demonstrated an increase in risk of hypertension, but in contrast to having insomnia, the increase in risk was not statistically significant.

The study of Lin *et al.* is important in confirming the increased risk of hypertension attributable to sleep disorders in a large Asian cohort and is strengthened by its relatively lengthy follow-up. The divergent risk observed with insomnia versus sleep apnoea is perplexing. A positive relation between CV risk, including hypertension, and sleep-related disorders is likely more firmly established for OSA compared with insomnia, so for Lin *et al.* to report the opposite is intriguing, but unexplained by the current study design. One can speculate that perhaps the lack of a significant relation with sleep apnoea and incident hypertension in the current analysis is related to how sleep apnoea or even hypertension is diagnosed and/or coded in Taiwan versus other countries; differences in severity of OSA compared with other study cohorts; or use of continuous positive airway pressure (CPAP) for treatment of OSA, which was not accounted for in the current results. Clearly, more intensive assessments, including prospective intervention studies, are needed to provide insight into this important observation.

Publication of the Lin *et al.* study is timely because of another recently published study. In a recent edition of *The New England Journal of Medicine*, McEvoy *et al.*<sup>11</sup> report the results of randomized comparison of CPAP versus usual care (which did not include use of CPAP except for a few exceptions) in subjects with moderate-severe OSA. During study follow-up, in the CPAP group, the mean duration of adherence to CPAP was 3.3 h per night. After a mean follow-up of 3.7 years, there was no difference in the number of combined CV events, including CV death, MI, stroke, unstable angina, heart failure or transient ischaemic attack. This overall lack of benefit of CPAP to prevent CV in this mostly

middle-aged cohort events is consistent with other randomized assessments of CPAP that have generally demonstrated no or, at best, modest benefit in terms of reducing CV event rates.<sup>12–14</sup> CPAP, when assessed in rigorous, randomized trials, has likewise been demonstrated to provide only limited antihypertensive benefit. In some cases, antihypertensive benefit is absent, or limited to modest reduction in nocturnal blood pressure levels.<sup>12,15–17</sup> So, it has been frustrating that while observational studies, including the current study by Lin *et al.*, are largely consistent in showing that OSA contributes importantly to increased risk of developing hypertension and other CV complications, treatment of OSA with CPAP provides limited, if any, benefit in reversing that risk. The observed low benefit of CPAP is no doubt related to the generally poor adherence with CPAP, even in a clinical trial setting, as *post hoc* analyses generally indicate increased CV risk reduction with CPAP, including antihypertensive benefit, in relation to the degree of adherence with CPAP.<sup>12,14,16,17</sup> Accordingly, while observational studies clearly implicate sleep disorders as important mediators of CV risk, the limited benefit of treating those disorders, as suggested by recent interventional trials, highlights our need to better understand the mechanisms of CV disease progression associated with sleep disturbances in order to better prevent and/or reverse that associated risk.

#### CONFLICT OF INTEREST

The author declares no conflict of interest.

#### ACKNOWLEDGEMENTS

Research support was provided by NIH R01 HL113004.

DA Calhoun

*Vascular Biology and Hypertension Program, University of Alabama at Birmingham, Birmingham, AL, USA*  
E-mail: dcalhoun@uab.edu

#### REFERENCES

- Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Vela-Bueno A, Basta M *et al.* Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension* 2012; **60**(4): 929–935.
- Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation* 2011; **124**(19): 2073–2081.
- Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ *et al.* Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* 2012; **307**(20): 2169–2176.
- Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; **365** (9464): 1046–1053.
- Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE *et al.* Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 2010; **182**(2): 269–277.
- Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath* 2010; **14**(2): 131–136.
- Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ *et al.* Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008; **31**(8): 1071–1078.
- Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S *et al.* Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000; **283**(14): 1829–1836.
- Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; **342**(19): 1378–1384.
- Lin C-L, Liu T-C, Lin F-H, Chung C-H, Chien W-C. Association between sleep disorders and hypertension in Taiwan: a nationwide population-based retrospective study. *J Hum Hypertens* 2017; **31**: 220–224.
- McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X *et al.* CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016; **375**(10): 919–931.
- Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, Martinez-Alonso M, Carmona C, Barcelo A *et al.* Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012; **307**(20): 2161–2168.
- Parra O, Sanchez-Armengol A, Bonnin M, Arboix A, Campos-Rodriguez F, Perez-Ronchel J *et al.* Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J* 2011; **37**(5): 1128–1136.
- Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the riccadsa randomized controlled trial. *Am J Respir Crit Care Med* 2016; **194**(5): 613–620.
- Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 2007; **50**(2): 417–423.
- Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerd S, Poppe K, Dupont A *et al.* The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. *Arch Intern Med* 2007; **167**(8): 757–764.
- Martinez-Garcia MA, Capote F, Campos-Rodriguez F, Lloberes P, Diaz de Atauri MJ, Somoza M *et al.* Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA* 2013; **310**(22): 2407–2415.