



# Effects of sleep apnoea therapy on blood pressure and metabolism: a CPAP sex gap?

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**CPAP therapy reduces blood pressure but has no impact on metabolic profile in women with sleep apnoea** <http://ow.ly/AAKj30cQb6X>

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Obstructive sleep apnoea (OSA) is a highly prevalent disease characterised by recurrent episodes of complete or partial upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation. Most recent estimates of OSA prevalence suggest that 13% of men and 6% of women have clinically significant OSA [1, 2]. There is evidence from population-based and clinic-based cohort studies that moderate-to-severe OSA is independently associated with an increased incidence of cardiovascular events [3, 4]. Besides OSA-related variables, comorbid conditions including hypertension and metabolic dysfunction play an important role in the development of cardiovascular diseases in OSA patients [4]. In the clinical setting, it has been estimated that at least half of patients with OSA fulfil the criteria for the metabolic syndrome [5]. Furthermore, the prevalence of metabolic syndrome increases with OSA severity [5, 6]. An independent dose–response relationship has been demonstrated between OSA severity and the features of metabolic syndrome, including visceral adiposity [7], hypertension [8], metabolic dyslipidaemia [6] and impaired glucose metabolism [9, 10]. Considering cardiovascular prevention as a therapeutic objective in OSA patients, it is crucial to determine whether OSA therapy can lead to clinically relevant improvements in blood pressure, and glucose and lipid metabolism.

Most previous randomised controlled trials (RCTs) evaluating the impact of continuous positive airway pressure (CPAP) therapy on health outcomes were performed in unselected, predominantly male OSA patients. It is increasingly recognised that there is a between-sex difference in the clinical manifestations of OSA, with women more frequently experiencing symptoms of depression and anxiety, and less frequently complaining of excessive daytime sleepiness [11–13]. Sex differences have also been observed in cardiovascular outcomes, with more severe endothelial dysfunction [14], and higher risks of coronary heart disease and stroke in women [15]. Epidemiological data have shown that OSA in females is related to obesity, hypertension and diabetes but not to daytime sleepiness [11]. Altogether, these findings highlight the need for adequately powered RCTs examining sex differences in CPAP treatment response with particular focus on blood pressure and metabolic profile.

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In this issue of the *European Respiratory Journal*, CAMPOS-RODRIGUEZ *et al.* [16] address this important concern in a multicentre, open-label RCT examining the effect of CPAP on blood pressure, glucose and lipid profile in 307 women diagnosed with moderate-to-severe OSA. Among included patients, 31% satisfied the hypertension criteria at baseline and 55% were on antihypertensive medication. The study has a number of important strengths including a large sample size, a multicentre design, the use of fixed pressure CPAP (which has been found to be more effective than auto-CPAP in reducing 24 h diastolic BP [17]) and a relatively high rate of CPAP compliance with 75% of participants using the device for at least 4 h per night. The main limitation of the study is the use of office rather than 24-h ambulatory blood pressure monitoring, which is considered the reference standard for the diagnosis of hypertension, particularly in OSA patients in whom hypertension is predominantly nocturnal [8].

The first finding of this study was that 12 weeks of CPAP therapy was associated with a modest but significant reduction in diastolic blood pressure ( $-2.04$  mmHg, 95% CI  $-4.02$ – $-0.05$  mmHg) compared to controls [16]. This finding is highly consistent with most RCTs and meta-analyses reporting drops of 2–2.5 mmHg and 1.5–2 mmHg in systolic and diastolic blood pressure, respectively, in unselected OSA populations [18]. In line with previous reports [19], several characteristics at baseline were associated with a greater blood pressure reduction on CPAP including severe OSA, and higher baseline blood pressure and excessive daytime sleepiness. Improving blood pressure control in hypertensive patients is a major concern as lowering blood pressure reduces cardiovascular risk in a dose-dependent manner [20]. In the SAVE (Sleep Apnea CardioVascular Endpoints) trial, CPAP therapy averaging 3.3 h per night had no significant impact on blood pressure, and did not prevent cardiovascular events in patients with moderate-to-severe OSA and established cardiovascular disease [21]. Although the minimum threshold of CPAP adherence needed to obtain a clinically significant blood pressure reduction is unknown, improving CPAP compliance may contribute to improving blood pressure control, especially by avoiding residual rapid eye movement-related sleep disordered breathing at the end of the night [22]. The superiority of fixed pressure CPAP over auto-CPAP in reducing 24-h blood pressure might also be of particular interest in OSA patients with poorly controlled or resistant hypertension [17]. Considering the multifactorial pathophysiology of OSA-associated hypertension, the combination of CPAP therapy, antihypertensive drugs and weight-loss interventions appears to be the most promising strategy to improve blood pressure control in OSA patients [18]. Although antihypertensive drugs such as valsartan have been found to be markedly more effective than CPAP on OSA-associated hypertension [23], the combination of blood pressure-lowering drugs and CPAP has additive effects on blood pressure [23, 24]. As randomised trials have shown the beneficial effects of weight loss on blood pressure [25], weight-loss intervention may also be a major component of the strategies used to improve blood pressure control in obese patients with OSA. In a recent randomised trial including 146 patients with obesity and moderate-to-severe OSA, adherence to a regimen of weight loss and CPAP resulted in incremental reductions in blood pressure compared with either intervention alone [26].

The second finding of this study is that CPAP therapy for 3 months had no impact on metabolic profile in women with moderate-to-severe OSA [16]. As acknowledged by the authors, most women had baseline glucose and lipid values within the normal range, which may have been associated with a floor effect of the intervention. However, the present finding is in accordance with most recent RCTs and meta-analyses. A systematic review of RCTs concluded that in unselected OSA patients, it is unrealistic to expect a clinically relevant improvement in metabolic and inflammatory markers with CPAP therapy [27]. In a recent RCT, CPAP therapy alone had remarkably limited effects on metabolic dysfunction in obese patients with OSA whereas weight loss provided an incremental reduction in insulin resistance and serum triglyceride levels when combined with CPAP [26]. Whether CPAP therapy has the power to improve glucose metabolism is still debated. In OSA patients with pre-diabetes or overt type 2 diabetes, laboratory-based RCTs found that short-term CPAP therapy with high levels of compliance may improve glucose control [28, 29]. However, these findings were not confirmed by a large multicentre RCT, which showed that 6 months of CPAP therapy had no effect on glycated haemoglobin in diabetic patients with moderate-to-severe OSA [30].

The study by CAMPOS-RODRIGUEZ *et al.* [16] provides no strong argument in support of between-sex differences in the effect of CPAP on blood pressure and metabolism. In line with previous data in unselected OSA populations, the present findings highlight the need for a multidisciplinary approach to manage OSA patients with cardiometabolic comorbidities [27]. Further studies are required to evaluate the effects of CPAP therapy on cardiometabolic health in the context of weight-loss interventions for OSA patients with metabolic disorders. Personalised medicine is an emerging concept taking into account the marked heterogeneity of OSA in terms of structural and physiological risk factors, clinical phenotypes, molecular signatures, health outcomes, and treatment response [12, 31, 32]. A recent report demonstrated that blood pressure response to CPAP in OSA patients with resistant hypertension can be predicted by a cluster of three specific plasma microribonucleic acids [33]. Further studies are needed to identify metabolic phenotypes that are more likely to be responsive to CPAP therapy.

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