CROSSTALK

CrossTalk proposal: Metabolic syndrome causes sleep apnoea

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Obstructive sleep apnoea (OSA) is a prevalent sleep disorder characterized by upper airway obstruction during sleep, resulting in intermittent breathing pauses despite effort, reduced blood oxygen saturation, hypoxia and arousals. With prevalence in the general population estimated at 17–24% of men and 5–9% of women (Young et al. 1993; Bixler et al. 1998, 2001), OSA has been linked to the key components of the metabolic syndrome: central obesity, insulin resistance (Vgontzas et al. 2000; Coughlin et al. 2004), elevated triglycerides, reduced HDL cholesterol (Coughlin et al. 2004), and elevated blood pressure (Bixler et al. 2000; Coughlin et al. 2004).

While many have proposed that inflammation resulting from intermittent hypoxia is the culprit behind the development of metabolic aberrations in those with OSA, obesity and the metabolic syndrome in fact appear to precede the development of the disorder. Rather, considerable evidence suggests that OSA is a manifestation of the metabolic syndrome, including the impact of visceral adiposity on upper airway pathophysiology, mediated by inflammation (Fig. 1A).

The role of obesity in the development of OSA

Physicians in the nineteenth century originally lumped OSA symptoms into the term ‘Pickwickian syndrome’, inspired by the maladies of Charles Dickens’s character ‘Joe the Fat Boy’ in The Pickwick Papers. Early research seeking to characterize the natural course of OSA cited obesity and snoring as the ‘first phase[s] of developing the syndrome’ (Lugaresi, 1975). More recent prospective findings in the Wisconsin Sleep Cohort indicate that the increased prevalence of OSA has mirrored the surge in obesity over the last two decades (Young et al. 2009). Importantly, a longitudinal study in the same cohort reported that a 10% weight gain predicts a 32% increase in apnoea–hypopnoea index (AHI) and 6-fold odds of developing moderate-to-severe OSA, while a 10% weight loss predicts a 26% decrease in AHI (Peppard et al. 2000). Indeed, a recent study highlighted how rates of sleep-disordered breathing (SDB) have increased between 14% and 55%, depending on the subpopulation studied, in conjunction with the ongoing obesity epidemic (Peppard et al. 2013).

Visceral (abdominal) fat, compared to subcutaneous fat, is a metabolically active organ; immune dysregulation by resident visceral fat macrophages has been linked to impaired glucose intake and other cardio-metabolic morbidities. Notably, compared to age- and BMI-matched controls, visceral fat area in obese (Vgontzas et al. 2000) and even non-obese (Kritikou et al. 2013) men as measured by CT scan is elevated in those with OSA. Furthermore, a recent longitudinal general population study examining incident SDB in adolescents reported that childhood waist circumference was a significant predictor of adolescent SDB, while visceral fat area (measured cross-sectionally) was the strongest predictor of all variables examined (Bixler et al. 2016).

While genetic factors play a role in upper airway (UA) narrowing among individuals with OSA, neck fat accumulation, which is associated with central obesity and the metabolic syndrome, is also a major contributor (Kim et al. 2014). Specifically, the pattern of fat accumulation around the oropharynx results in altered UA geometry, with a switch from maximum dimensions in the lateral plane to maximum dimensions in the anteroposterior plane, compromising the efficiency of genioglossus muscle contraction (Deegan & McNicholas, 1995). Visceral obesity also lowers the functional residual capacity of the lungs, which further contributes to reduced UA dimensions, possibly by reflex mechanisms.

The metabolic syndrome affects upper airway pathophysiology

The pathophysiology of OSA is fundamentally based on mechanisms whereby collapsing forces within the UA exceed the ability of dilating muscles to maintain airway patency leading to complete or partial UA occlusion (Deegan & McNicholas, 1995). There is extensive evidence that manifestations of the...
metabolic syndrome not only contribute to UA narrowing, but also diminished UA muscle contraction and respiratory control abnormalities that promote respiratory instability and diminished respiratory drive (Eckert et al. 2013).

The maintenance of UA patency is critically dependent on dilating muscle contraction, which is especially important in a narrowed airway. The metabolic syndrome is associated with sarcopenia and generalized skeletal muscle dysfunction (Atlantis et al. 2009), which is likely to promote the development of OSA by UA skeletal muscle dysfunction. Mechanisms involved likely include lipid accumulation in muscles (Gueugneau et al. 2015) and increased inflammatory gene expression in muscle tissue (Poelkens et al. 2013).

While local UA factors are most important in the pathophysiology of OSA, there is strong evidence that respiratory control factors also contribute (Deegan & McNicholas, 1995). Factors that diminish respiratory drive or alter loop gain predispose one to OSA (Eckert et al. 2013), and some of these factors are present in the metabolic syndrome. Besides the direct effects of obesity on UA anatomy, central adiposity is associated with blunting of UA neuromuscular responses, and the adipose tissue-derived hormone leptin may play an important role. Rodents deficient in leptin demonstrate evidence of respiratory depression and also increased pharyngeal collapsibility, which is reversed following leptin replacement (Pho et al. 2016).

In obese humans, high concentrations of serum leptin are associated with reduced respiratory drive and impaired hypercapnic responses, suggesting resistance to the effects of leptin on respiratory function (Campo et al. 2007). However, intermittent hypoxia in OSA seems to stimulate leptin secretion, and leptin levels normalize with continuous positive airway pressure (CPAP) therapy (Piper et al. 1994), suggesting that hypoventilation, in turn, might cause hyperleptinaemia and leptin resistance. A recent study suggests that this response may represent a compensatory neural mechanism in response to UA obstruction, potentially minimizing airway collapse (Shapiro et al. 2014). Further studies are required to determine the influence of leptin on the respiratory control and UA collapsibility in OSA.

Sleep apnoea peaks in middle age, similar to the prevalence of metabolic syndrome

In the Penn State Adult Cohort, a general population sample of 1741 adults assessed in the 1990s, the prevalence of OSA peaks around age 55 years for men and 65 years for women (Bixler et al. 1998, 2001). Interestingly, this quadratic relationship mirrors the prevalence of the metabolic syndrome in U.S. adults according to the Third National Health and Nutrition Examination Survey (NHANES) data collected in the same time frame (1988–1994; Ford et al. 2002) (Fig. 1B). Particularly in women, OSA is more frequent following hormonal changes such as menopause, which may explain the delay in peak prevalence compared to men (Bixler et al. 2001). OSA is also 30 times more common in premenopausal women with polycystic ovarian syndrome (PCOS) – an endocrine disorder characterized by insulin resistance and hyperandrogenism – compared to controls (Vgontzas et al. 2001), suggesting a causative role in the development of apnoea.

Just as the prevalence of metabolic syndrome declines with older age, the cardiometabolic effects associated with OSA also diminish with ageing. A cross-sectional study of the Penn State Adult Cohort reported that although AHI was independently associated with blood pressure, the relationship was strongest in the youngest, suggesting that OSA is not an independent risk factor for hypertension in the elderly (Bixler et al. 2000). Similarly, a prospective investigation of the Sleep Heart Health Study found that the risks of coronary heart disease and heart failure were not significantly increased for older men or women, even at the level of ‘severe’ OSA (AHI ≥ 30) (Gottlieb et al. 2010). Mortality was also not increased in an

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Figure 1. Heuristic model of the association between metabolic syndrome and sleep apnoea

A, model illustrating the development of obstructive sleep apnoea (OSA). Mediated by inflammation, accumulating visceral obesity may eventually lead to metabolic syndrome, which is associated with reduced upper airway (UA) patency, depression of ventilation, and reduced residual lung capacity that manifests as OSA. B, the prevalence of clinically defined OSA in men and women (top) and metabolic syndrome in U.S. men (bottom; NHANES 1988–1994).
elderly cohort (≥65 years), even in those with a respiratory disturbance index (RDI) >40 (Lavie & Lavie, 2009). Together, these findings suggest that the declining cardio-metabolic morbidities in older age occur independently from—and are not a result of—OSA defined by AHI alone, and that OSA in old age is not as strongly associated with the metabolic syndrome as in younger age.

**Inflammation may mediate the association between metabolic syndrome and OSA**

A number of studies have reported elevated systemic inflammation with OSA (Vgontzas et al. 1997), which is independent of obesity in both adults (Vgontzas et al. 2000) and children (Tsoussoglou et al. 2010). A study which administered etanercept to obese apnoeic men for 3 weeks found that the tumour necrosis factor α (TNFα) antagonist significantly reduces AHI (Vgontzas et al. 2004), suggesting a mediating role of inflammation in the development of OSA. A recent study demonstrated that apnoeic men and women with hypertension have elevated C-reactive protein (CRP) levels compared to those without hypertension (Gaines et al. 2015); though cross-sectional, these findings provide evidence for a potential mediating role of inflammation in the association between metabolic aberrations and OSA.

In sum, there is considerable evidence suggesting that the metabolic syndrome causes OSA, including the well-characterized role of obesity in the development of OSA, the effect of metabolic syndrome on upper airway pathophysiology, the parallel prevalence of metabolic syndrome and OSA across the lifetime, and emerging evidence that inflammation mediates this relationship.

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**References**


**Additional information**

**Conflict of interest**

All authors report no biomedical financial interests or potential conflicts of interest.

**Author contributions**

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.