

Emerging co-morbidities of obstructive sleep apnea: cognition, kidney disease, and cancer

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Abstract: Obstructive sleep apnea (OSA) causes daytime fatigue and sleepiness, and has an established relationship with cardiovascular and metabolic disease. Recent years have seen the emergence of an evidence base linking OSA with an increased risk of degenerative neurological disease and associated cognitive impairment, an accelerated rate of decline in kidney function with an increased risk of clinically significant chronic kidney disease (CKD), and with a significantly higher rate of cancer incidence and death. This review evaluates the evidence base linking OSA with these seemingly unrelated co-morbidities, and explores potential mechanistic links underpinning their development in patients with OSA, including intermittent hypoxia (IH), sleep fragmentation, sympathetic excitation, and immune dysregulation.

Keywords: Cognitive impairment; chronic kidney disease (CKD); cancer; sleep apnea; continuous positive airway pressure (CPAP)

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Introduction

Obstructive sleep apnea (OSA) is a chronic, highly prevalent sleep disorder, with recent prevalence estimates of around 22% in men and 17% in women (1). Despite progress in raising public awareness of OSA, it remains underdiagnosed in the general population (2,3). Episodes of intermittent hypoxia (IH) and sleep fragmentation occur during nocturnal cycles of pharyngeal collapse, leading to a cascade of adaptive and maladaptive processes, such as systemic inflammation, endothelial dysfunction, and oxidative stress (3-5). Whilst the association of OSA with cardiovascular and metabolic co-morbidities is well recognised and described (6,7), its potential role in brain injury, leading to or aggravating existent neurological/psychiatric and neurodegenerative disorders, has only recently started receiving significant attention (5,8). Similarly, its potential role in the etiology of chronic kidney disease (CKD) and its association with

cancer are not well understood. These co-morbidities and the intricate interplay between OSA and their pathogenesis are the main focus of this review.

OSA and impaired cognition

A variety of cognitive deficits, such as difficulties with attention, memory, executive functioning, and quality of life have an established relationship with OSA, alongside a number of psychiatric disorders in susceptible patients (8). Some of these impairments have been associated with corresponding structural changes (9,10). Continuous positive airway pressure (CPAP)—still the mainstay of OSA treatment—has been shown to at least partially reverse some of the cognitive impairments and associated neuroanatomical changes (8,11-13).

In addition, difficulty in forming functional interpersonal relationships, irritability, decreased work and school

efficiency, and proneness to accidents, have all been documented in OSA patients (9,14,15). It has been proposed that OSA patients are two to thirteen times more likely to experience a driving-related traffic accident than the general population (16-19). Such accidents are more likely to occur in those with greater daytime sleepiness, but they are not necessarily related to sleepiness alone (16,20). In addition to cognitive and emotional deficits, the prevalence of OSA has been reported to be increased in several psychiatric disorders (21), with the strongest association seen with major depressive disorder (MDD), anxiety, and posttraumatic stress disorder (PTSD) (21-23).

The cognitive impairment seen in OSA tends to be more significant with increasing age (24-26), suggesting that older age groups are more susceptible to the effects of OSA on the brain (27), or that compensatory mechanisms that are perhaps present in younger people and help to recruit other areas of the brain to maintain performance, may no longer be as proficient (28). OSA is increasingly prevalent with age (29), although there tends to be less reported sleepiness in older patients. More recently, a link between Alzheimer's disease (AD) and OSA has been suggested by a number of studies (30-33), with some authors arguing that dysregulated immunological mechanisms in the brain in OSA patients may contribute to the evolution of AD (9,34,35).

The results of a recent meta-analysis suggest that subjects with AD have an approximately five-fold likelihood of having concomitant OSA when compared with healthy controls (33). The causal relationship between untreated OSA and neurodegenerative processes is, however, unclear (5,9). The results of genome-wide analyses have shown that several genes that increase the risk for sporadic AD, also encode factors that regulate glial clearance of misfolded proteins and neuroinflammation (33,34).

It has been suggested that treatment of OSA, particularly in the early stages of AD, when patients are still largely independent, may decelerate the progression of dementia (36,37). CPAP appears to be partially effective in improving episodic verbal learning, memory, cognitive flexibility and mental processing speed in patients with co-morbid AD and OSA (36). Similarly, a study that analysed patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort found a significant association of self-reported sleep-disordered breathing with an earlier age of onset of mild cognitive impairment (31); mild cognitive impairment was observed approximately one decade earlier in sleep apnea patients, even when accounting for possible confounding factors. However, in those patients who used CPAP, this

link appeared significantly attenuated, suggesting that use of CPAP may delay the progression of mild cognitive impairment (31).

Recent neuroimaging studies have suggested that sleep disruption and fragmentation provide a mechanism through which β -amyloid pathology contributes to hippocampus-dependent cognitive decline in the elderly (38,39). Inadequate sleep and significant sleep fragmentation present another important etiological aspect of OSA-induced brain injury and may contribute to the acceleration of 'normal aging' processes in patients with OSA (5).

Sleep fragmentation and deprivation

In previous studies that have deprived healthy individuals of sleep (40-42), sleep deprivation was associated with impairment in cortical and white matter regions, particularly those that likely underlie functions of attention and vigilance. It has been argued that sleep deprivation and fragmentation can independently lead to cognitive impairment, and in a similar pattern to what has been also associated with IH (43,44). Moreover, any significant sleep fragmentation likely disrupts restorative homeostatic synaptic processes in the brain and further interferes with memory consolidation and transformation, contingent on which sleep stages are affected (45,46). It also likely further precipitates neuroinflammatory processes and aggravates any predisposing immunological dysfunction (9,47). In a study assessing cognition in patients with untreated insomnia, narcolepsy and OSA versus controls, a shared impairment in alertness and selective attention, as well as decreased visual tracking, was identified (48). These findings were also associated with an increase in self-rated tiredness and daytime somnolence, and suggest a potential common pathological mechanism. Indeed, there is evidence that hypersomnolence itself (regardless of its cause) is an independent risk factor for cognitive impairment (49).

Residual cognitive impairment in patients who adhere well to their treatment with CPAP suggests a degree of irreversibility in some changes induced by OSA, and it likely points to importance of early recognition and induction of treatment (50,51). Equally, it is possible that CPAP as a treatment might not be a universal panacea for all stages of this chronic illness, and or that in certain susceptible patients CPAP treatment might need to be supplemented with other treatment modalities (e.g., antioxidants) in order to combat all aspects of neuroinflammation and oxidative stress injury induced by OSA (21).

IH

Hypoxia may affect the structure and function of the blood-brain barrier (52), leading to altered microvessel permeability and microregional oxidative processes, all of which could in the long term alter synaptic plasticity, and also contribute to cognitive impairment (3). Several mouse models have been used over the years to look at the effects of IH on the brain (53). Their results taken together suggest that IH leads to oxidative stress, inflammation, and regional and distant neuroanatomical and functional changes, depending on the severity, frequency and chronicity of the insult. IH-induced oxidative injury in the wake-promoting basal forebrain and brainstem in mice may lead to persistent hypersomnolence and associated cognitive impairment (54). Several studies comparing IH and sleep fragmentation in animal models have shown that similar brain regions are affected by both insults (24,43).

Apart from maladaptive processes, IH likely also starts cascade of adaptive homeostatic processes, such as ischaemic preconditioning, in all affected body systems, including the brain. Ischaemic pre-conditioning has been demonstrated in animal models in numerous body organs and systems (55,56). Moreover, it has been shown that ischemic insult in animals can lead to adult neurogenesis in neurogenic niches such as the dentate gyrus of the hippocampus and the olfactory bulb, and in some animals also in the striatum (57). Neurogliogenesis secondary to IH has also been postulated to occur in patients (58). In a recent study, hypertrophy of the hippocampi of patients with mild OSA was demonstrated, perhaps suggestive of such adaptive processes at work (59), whilst another study identified changes in creatine levels in the hippocampus in OSA patients, suggesting adjusted bioenergetics similar to those seen in ischaemic preconditioning (60).

Over the last several decades, numerous neuroimaging studies in patients with OSA have delineated a putative neurocircuitry fingerprint of sleep fragmentation and IH-induced brain injury (61). This wide circuitry suggests disconnection of the frontal regions [also see (21)], and the disruption of the (cerebello)-thalamocortical oscillator with involvement of the hippocampal formation.

Neuroanatomy of OSA

Historically, a number of voxel based morphometry (VBM) studies have investigated areas of the brain affected in patients with OSA with diverse regions being highlighted

as more or less impacted (62-66). An early study assessing changes in patients with OSA reported diffuse changes in the frontal, temporal and parietal cortices, as well as in the anterior cingulate gyrus, hippocampus, and cerebellum (67). Subsequently, a combined VBM and PET imaging study demonstrated hypotrophic changes in wider circuitry, as well as a decrease in cortical metabolism despite no clinically overt cognitive deficits being present (64). This has been argued to suggest early processes likely leading to later clinically measurable cognitive changes. Later studies demonstrated the correlation between neuroimaging changes and cognitive deficits, including those in executive functioning and verbal memory (65,68).

In a recent comprehensive meta-analysis of functional and structural neuroimaging studies (10), structural atrophy and functional disturbances in the right basolateral amygdala, the hippocampus and the right central insula were demonstrated (*Figures 1,2*). Behavioural analyses of these regions suggested associated dysfunction of emotional, sensory and cognitive processes (*Figure 3*), and further highlighted a diffuse network within the bilateral anterior insula, posterior-medial frontal cortex and thalamus (*Figure 4*).

The importance of the amygdala as one of structures affected by the chronic process of OSA has been previously also shown in children (69). In children with OSA, greater neural recruitment of regions involved in cognitive control, conflict monitoring, and attentional allocation is required in order to perform at the same level as children without OSA (69). Of further note is that the amygdala has a recognised role in the etiology of anxiety disorders, MDD, and PTSD, potentially contributing to the increased prevalence of these psychopathologies in patients with OSA (10). The activation of the amygdala during emotional arousal enhances memory, in part by modulating plasticity in the hippocampus. It is possible that aberrant functional connectivity of amygdala and hippocampus in patients with OSA may further impact already dysfunctional intrinsic network activity in MDD, and that this may underlie some of the psychological disturbances in patients with OSA (10). In a similar vein, an aberrant connectivity between the hippocampus and the cerebellum, which has been previously reported in OSA patients, may lead to alterations in a distributed memory system for associative learning (59). On the other hand, an atypical engagement of the insula within the salience network appears to be common feature of OSA as well as of several neuropsychiatric disorders, including AD and MDD (10).

Functional MRI has also been used to show that OSA patients display decreased levels of activation in the frontal

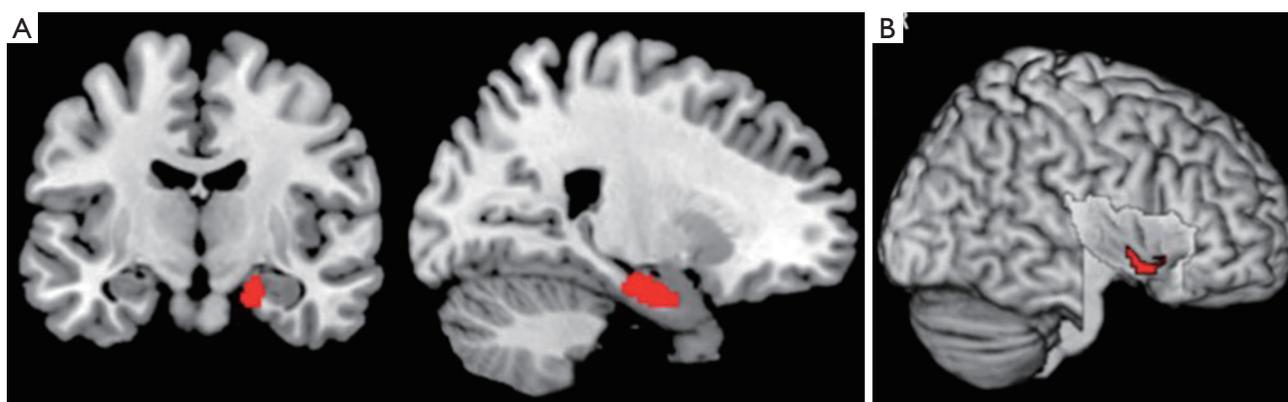


Figure 1 Convergence of structural and functional difference in obstructive sleep apnea compared with healthy controls (10). Location of the significant convergence of gray matter reduction and functional disturbance in the right basolateral nucleus of the human amygdala and the hippocampus ($P < 0.05$, cFWE corrected) (A) and in the right central insula ($P < 0.05$, cFWE corrected) (B) (10).

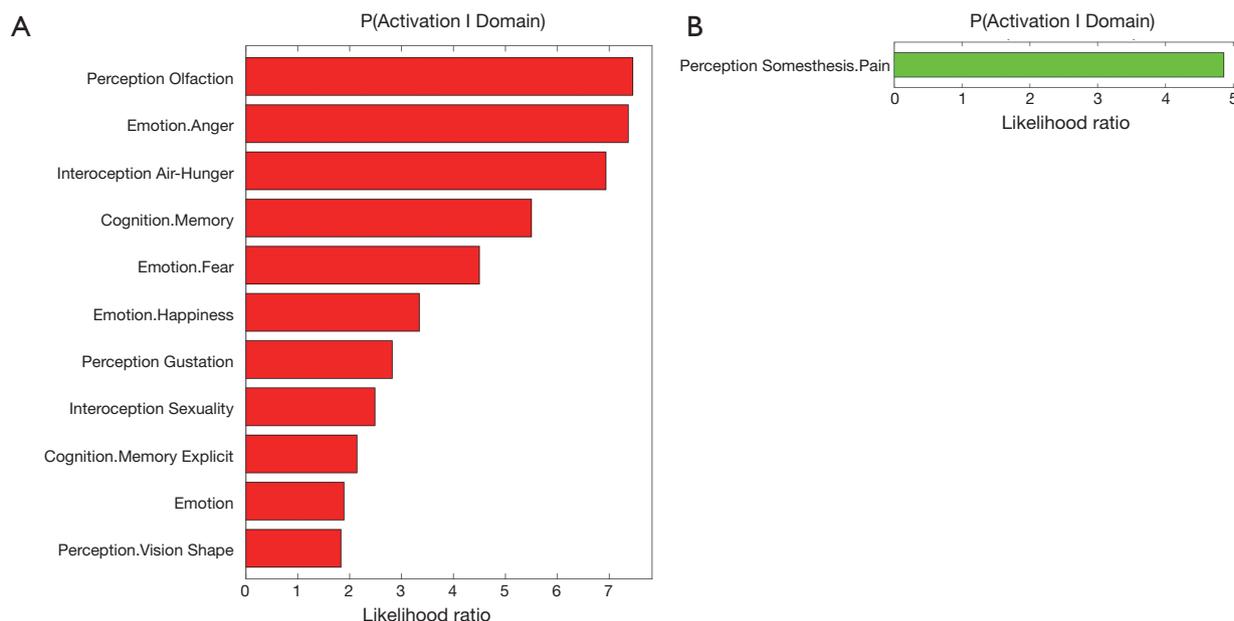


Figure 2 Behavioral characterization of the significant cluster in the right amygdala/hippocampus (A) and in the right central insula (B) which is shown affected in sleep apnea patients (10).

lobes (28,67), and an increased compensatory activation during memory and attention tasks in comparison to healthy controls (70,71). This increased activation was lost or ameliorated after CPAP treatment (71).

A beneficial effect of CPAP therapy in the treatment of cognitive deficits in subjects with OSA was suggested by results of a recent study by Canessa *et al.* (12). They showed that 3 months of CPAP treatment was associated with a significant increase in grey matter volume in the bilateral hippocampus and frontal structures, which

correlated with an improvement in executive function, memory and attention (12). Similarly, in a recent study that used randomised controlled design, one month of CPAP treatment resulted in a partial recovery of episodic and working-memory capacity (Figure 4) (13). The observed thalamocortical changes were associated with changes in bilateral hippocampi and cerebellar cortices (13). These data suggest that a relatively short period of CPAP treatment may allow rudimentary neuroplastic changes to occur within targeted brain structures of patients with moderate to severe

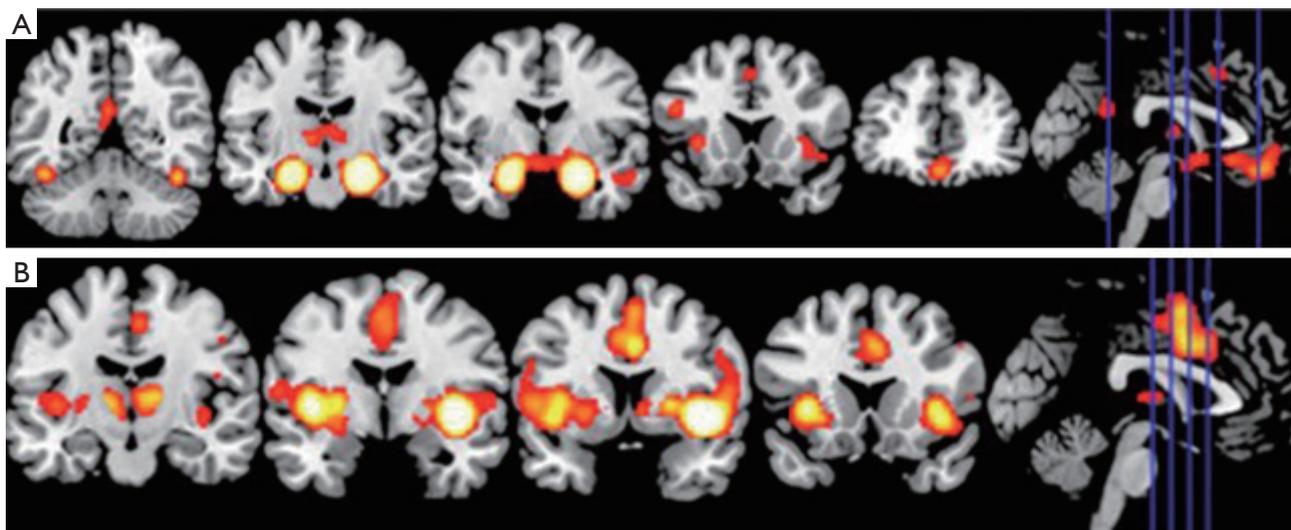


Figure 3 Task-based co-activation pattern of the right basolateral amygdala/hippocampus ($P < 0.05$, cFWE corrected) (A) and of the right central insula ($P < 0.05$, cFWE corrected) (B) in sleep apnea patients (10).

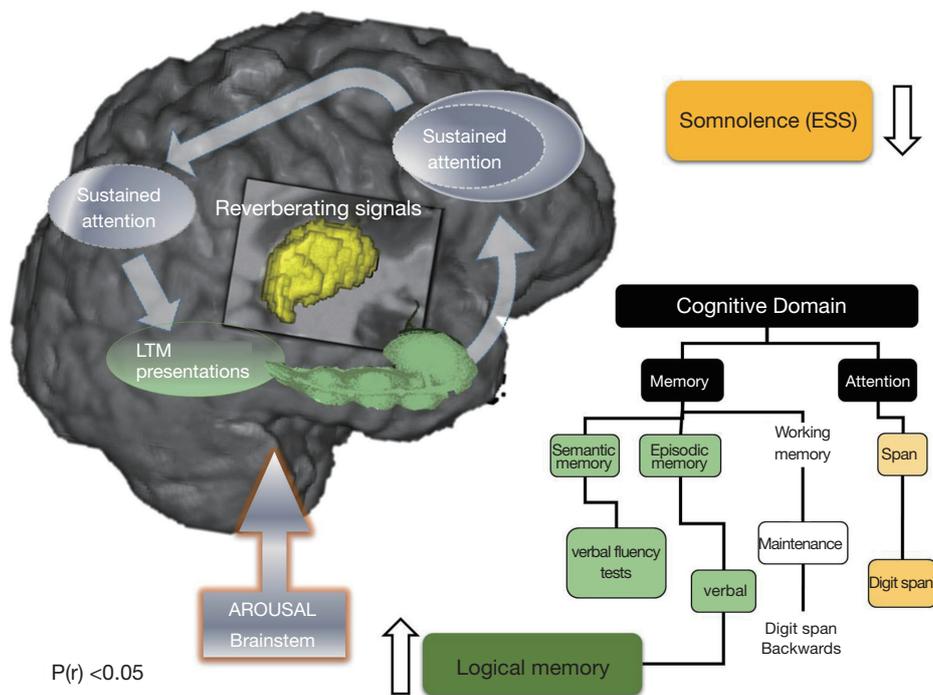


Figure 4 Schematic presentation of the neuroarchitecture behind working memory maintenance processes that might be implicated in improved daytime somnolence and verbal episodic memory by the CPAP treatment (13). Distributed nature of processes and representations involved to solve working-memory tasks is shown, with thalamus (central structure) acting as a functional interface between arousal and attentional regulation. The hippocampus (elongated green), is the structure most frequently reported affected by neuroimaging in OSA, here it is proposed to bind aspects of working and episodic memory. The list of cognitive tests used to investigate impact of CPAP treatment on associated cognitive domains is shown. CPAP treatment leads to improvement in verbal episodic memory (green box), which may be due to the interplay of the cascade of gradual changes in the semantic and verbal working memory. In addition, CPAP leads to the improvement of excessive daytime somnolence (yellow box), which in turn appears to be significantly, correlated to ensuing brainstem alterations (13). CPAP, continuous positive airway pressure; BSC, best supportive care; LTM, long term memory; ESS, Epworth Sleepiness Scale.

OSA, and that the structural changes observed provide a basic neurocognitive architectural scaffold for later reorganization that underscored some of the observed functional recovery in working and episodic memory (*Figure 4*). However, it has been also proposed that white matter changes observed in OSA patients may be refractory to treatment and may require longer treatment regimes (14), with a minimum of 12 months of CPAP treatment needed to reverse of some white matter changes recorded prior to commencement of therapy (11).

In conclusion, OSA-induced brain injury is an increasingly recognised entity and should be thought of as comprising a wide spectrum of related, if varied, neuropsychiatric presentations. Their variety and severity likely reflect idiosyncratic susceptibility of individual patients, as well as the interplay with the co-morbid impact of OSA on other body organs and systems, such as the cardiovascular system and the kidneys.

OSA and renal dysfunction

CKD is a highly prevalent disorder, associated with increased healthcare utilisation, hospitalisation and risk of death (72). Recognised contributory pathologies to its development include type 2 diabetes mellitus (T2DM) and hypertension, both common co-morbidities in patients with OSA. OSA appears to have a bi-directional relationship with CKD: the pathophysiological consequences of sleep disordered breathing have the potential to adversely affect kidney function, and lead to progression of established CKD (73), while altered fluid dynamics in advanced renal disease have an established detrimental effect on sleep breathing (74). Below we discuss the evidence in support of a role for OSA in the evolution of CKD, along with the impact of renal failure on OSA severity.

OSA as a risk factor for CKD

A potential relationship between OSA & CKD was first explored in 1988 (75) where 34 patients with OSA were reviewed and 6 found to have significant proteinuria on dipstick, 3 of which were seen to be in the nephrotic range. None of the healthy controls who were matched for age, sex and weight had proteinuria. Four OSA patients were followed for 4 years after starting CPAP therapy and a reduction in proteinuria was seen with treatment. However, it was some time before investigators began exploring this field in greater detail; more recent studies have suggested an

increased prevalence of CKD in OSA cohorts, and have also evaluated the potential underlying mechanisms.

A significantly higher prevalence of CKD among OSA patients was identified in over 9,000 Japanese subjects: CKD was present in 30.5% of subjects with an AHI >5 events/hour, compared with 9.1% of the general population (adjusted OR 4.5) (76). In a carefully selected cohort with severe OSA, but without key CKD risk factors such as hypertension and diabetes, prevalence of CKD was found to be around 18% (77). Data from a retrospective study of 161 non-obese Japanese patients with stage 3–4 CKD showed a relative fourfold rate of decline in eGFR in subjects with a 4% ODI ≥ 15 (78), while an adjusted OR of 2.89 for accelerated loss of renal function was observed among subjects with nocturnal hypoxemia (defined as spending $\geq 12\%$ of study time with an SpO₂ <90%) in another retrospective cohort study involving 858 subjects referred to a Canadian sleep unit (79). Perhaps the best population-level evidence in this fields comes from a longitudinal study of 4674 Taiwanese patients with sleep disordered breathing who were compared with 23,370 age- and sex-matched controls; following adjustment for relevant confounding diagnosis and demographic factors, subjects with sleep apnea had a 1.94-fold risk of developing CKD and a 2.2-fold increase in incidence of end stage renal disease (ESRD) over a 5-year period (80).

These are not uniform findings. A retrospective review evaluating kidney function in 634 Turkish patients with OSA and 62 healthy controls, compared estimated glomerular filtration rate (eGFR) in OSA patients with and without metabolic syndrome and LVH (81). Subjects with LVH and metabolic syndrome had a significantly lower eGFR when compared with OSA patients without these co-morbidities or with healthy controls. However, no significant differences were seen in eGFR in OSA patients without LVH or metabolic syndrome compared to controls, suggesting that indirect effects of OSA such as hypertension, precipitate renal changes and eventually dysfunction. Similarly, in a cross-sectional analysis of 8,112 participants in the multi-national ESADA study, diabetes and hypertension were independent predictors of mild-moderate renal impairment, while AHI and ODI were not (82).

Pathophysiology of CKD in OSA patients

Renal dysfunction in OSA patients may arise via traditional risk factors for CKD associated with OSA, or it may be the result of the characteristic pathophysiological consequences of sleep disordered breathing, such as increased sympathetic

output, oxidative stress, systemic inflammation, and nocturnal hypoxemia.

Conventional CKD risk factors and OSA

The relationship between OSA and cardio-metabolic disorders with established links to the evolution of CKD is the subject of an extensive and growing evidence base. OSA is an independent risk factor for the development of hypertension, and appears to have independent associations with the development of atherosclerosis and diabetes mellitus prevalence and control (83-85). The potential causative role of OSA in the development of these important comorbidities is the subject of recent dedicated reviews in the *Journal of Thoracic Disease* (7,86), and will not be discussed in detail here. Notably, OSA may hasten the development of diabetic nephropathy (DN), as evidenced by an increased prevalence of OSA in subjects with DN, and an increased rate of progression of CKD in OSA patients, in a cohort of 224 type 2 diabetes followed over 2.5 years (87).

Another potential confounding factor in studies assessing the relationship between kidney disease and OSA is the effect of obesity on renal function. Obesity is an established risk factor for the presence of CKD: a meta-analysis of 19 cohorts evaluating the relationship between increasing body mass and renal function identified a pooled relative risk of 1.83 (95% CI 1.57–2.13) for CKD among subjects with a BMI ≥ 30 kg/m² when compared with lean cohorts, following adjustment for relevant confounding factors (88). A case control study comparing renal biopsies in 95 morbidly obese patients undergoing bariatric surgery with 40 control subjects identified an independent relationship between BMI and likelihood of glomerular lesions (podocyte hypertrophy, increased mesangial cellularity or increased extracellular matrix) (89). Other investigators have found obesity to be associated with glomerular hypertrophy, basement membrane thickening, and overt proteinuria (90,91).

OSA as a causative factor in CKD

Pathways through which sleep disordered breathing may exert a direct impact on renal function include alterations in glomerular perfusion mediated by OSA-related changes in sympathetic tone, neurohumeral output, and endothelial function, alongside tubulointerstitial hypoxia due to repetitive nocturnal fluctuations in oxygen tension (73). Low grade systemic inflammation promotes endothelial dysfunction and subsequent atherosclerosis, and occurs in OSA patients as

a direct result of nocturnal IH (92). Similarly, IH promotes the generation of free oxygen radicals, with the consequent oxidative stress exerting a detrimental effect on the vascular endothelium (93), while apneic events also lead to increased sympathetic outflow, leading to profound alterations in vascular tone (94). In a study comparing healthy controls with newly diagnosed patients with moderate to severe OSA, but free of cardiovascular risk factors, the OSA patients showed evidence of endothelial dysfunction, impaired renal vasodilation and reduced endothelial nitric oxide synthase expression, despite a lack of overt signs of end organ disease. This suggests that OSA in itself is an independent risk factor for clinically occult renal endothelial damage which is not clinically detectable, which may then proceed to overt renal dysfunction (95).

An important potential mechanism mediating the development of CKD in OSA patients is activation of the renin-angiotensin system (RAS). Alongside increasing systemic blood pressure, disproportionate RAS activation leads to glomerular hyperperfusion and subsequent glomerulosclerosis. A number of studies have suggested that OSA may lead to systemic RAS activation, with data from rodent models suggesting that IH may play a key role (96). An elegant, sham controlled, cross-over study examined systemic BP changes in nine healthy subjects exposed variously to sham IH, IH with placebo, and IH with the type I angiotensin II receptor antagonist losartan. Exposure to IH, but not sham IH, lead to a significant increase in BP, an increase that was entirely abrogated by losartan, suggesting a key role for IH in causing alterations in RAS activation.

Recently, reduced renovascular sensitivity in response to a 60-minute angiotensin II infusion was observed in OSA patients with severe nocturnal hypoxemia when compared with milder OSA patients and non-apneic, obese controls (97). No changes were observed in BP or in circulating markers of RAS activation, suggesting a specific direct impact of IH on the kidney. The effects of IH on RAS activity may be mediated via changes in sympathetic tone, with renovascular denervation in a pig model of OSA preventing apnea-related changes in RAS activation (98).

Effect of CPAP on renal function

Were OSA contributing to the development of CKD, the use of nocturnal CPAP therapy might be expected to lead to measureable improvements in indices of renal RAS activation and renal function. There is evidence that

compliance with CPAP therapy in OSA patients with known renal disease can slow the progression of CKD—a retrospective study of 42 patients with OSA and stage 3–5 CKD found that decline in eGFR over 2 years was significantly more precipitous in subjects who were poorly compliant with CPAP therapy (99). A week of nocturnal CPAP reduced glomerular hyperfiltration in 24 men with moderately severe OSA (100), while two studies involving ultrasonographic evaluation of the renal circulation in OSA subjects, showed a significant improvement in intra-renal haemodynamics after initiation of CPAP (101,102). These changes may be attributable to alterations in RAS activity following commencement of CPAP therapy; Nicholl et al measured changes in renal plasma flow response to infused angiotensin II as an indirect measure of the intrarenal RAS before and after one month of CPAP therapy in 20 patients, finding that CPAP use was associated with reduced circulating aldosterone levels and reduced overall intra-renal RAS activity (103). Overall, a growing body of evidence suggests that OSA may directly and indirectly contribute to the decline of kidney function, and that CPAP therapy may at least partially ameliorate this decline, although further interventional studies examining the effect of CPAP on longitudinal outcomes are required.

CKD as a contributor to OSA severity

Sleep disordered breathing is common in CKD cohorts, and its prevalence increases as renal function deteriorates, with a study of 254 subjects representing the full spectrum of renal function finding that 41% of CKD patients and 57% of ESRD patients had significant sleep apnea, as defined by an RDI ≥ 15 , compared to 27% of those with an eGFR ≥ 60 mL/min/kg² (104). In OSA, a combination of anatomical features, changes in ventilatory control, and modifiable environmental factors such as obesity lead to an increased propensity for upper airways collapse during sleep (105). In advanced CKD & ESRD these mechanisms also apply, but there is increasing evidence that peripheral volume overload and rostral fluid shift - whereby fluid shifts from the legs and torso towards the head and neck while recumbent—may be important additional contributors (74).

Measurement of upper airway dimensions with acoustic pharyngometry shows that ESRD patients have reduced pharyngeal area when compared with subjects with normal renal function (106). Inducing a transient state of volume overload with the infusion of a high volume of isotonic saline solution during sleep in healthy men >40 years old

leads to a marked increase in AHI, occurring in parallel with an increase of neck circumference (107). In ESRD patients, the extent of rostral fluid shift, as measured by changes in leg fluid volume, correlates with OSA severity indices, a relationship which survives adjustment for confounding variables (108). Pulmonary congestion is common in dialysis patients, even when relatively asymptomatic, and may lead to altered chemosensitivity, loop gain and reduced ventilator stability, potentially further increasing the severity of sleep disordered breathing (109,110).

While ESRD may also contribute to sleep disordered breathing via uremic destabilisation of central respiratory control (109), data from studies of varying dialysis strategies suggest that alterations in extravascular fluid volume may be of more relevance to OSA severity. Conventional hemodialysis (HD) does not appear to significantly abrogate the degree of OSA present, but switching ESRD patients to a nocturnal HD strategy is associated with marked improvements in sleep breathing (111), while renal transplantation may lead to resolution of sleep apnea (112). That volume removal, rather than metabolic changes occurring post-HD, is the key factor here is suggested by a recent elegant study of changes in sleep breathing in 15 HD-dependent patients with moderate-severe OSA, who underwent PSG before and after aggressive fluid removal by ultra-filtration (UF) (113). Following UF, AHI was reduced by 36%, and a significant improvement in objective sleep quality was observed, with these improvements correlating with reductions in measures of peripheral volume overload.

It is certainly clear that renal dysfunction is associated with OSA, and that OSA is found in higher incidence in CKD patients. However, as with all research into patients with OSA, there are many potential confounding co-morbidities which are difficult to account for when determining underlying mechanisms. Further larger studies are needed to assess whether OSA and IH directly lead to CKD, and therefore whether more measures need to be taken to monitor and treat these patients earlier to prevent this end organ damage, and whether all patients with CKD and ESRD should be screened for OSA and treated as early as possible to prevent further decline.

OSA and cancer

A decade of research into the cardiovascular consequences of sleep disordered breathing has shown OSA to lead to chronic systemic inflammation, oxidative stress, and immune dysregulation. Alongside recurrent nocturnal

hypoxemia and local tissue hypoxia, these factors contribute to the development of an oncogenic milieu. A recognition of this has led to a recent spate of studies exploring how sleep apnea may influence cancer incidence and outcomes. Unusually, the evidence base in this field started with initial proof of concept studies in animal models of IH, before moving on to clinical studies confirming a potential causative role for OSA in carcinogenesis, but for the purposes of this brief review, longitudinal population studies shall be discussed first, before moving on to animal and mechanistic data.

Cancer incidence and outcomes in OSA populations

A number of community- and sleep laboratory-based population studies have found an association between severity of sleep disordered breathing and cancer incidence. In a multicentre sleep clinic cohort involving 4,910 patients followed for a median of 4.5 years, incidence of cancer was assessed across tertiles of nocturnal hypoxemia, as measured by the cumulative sleep time with oxygen saturations <90% (ct90) (114). Compared to subjects in the lowest tertile (ct90 <1.2%), those in the highest (ct90 >12%) had an adjusted HR of 2.33 for developing malignancy. This relationship was strongest in participants under the age of 65 yrs. A smaller study of 400 community based Australian subjects found that moderate-severe OSA (RDI >15) predicted a 2.5-fold risk of incident cancer over a 20-year follow-up (115). Data from an administrative claims database in Taiwan examined the relationship of OSA with organ-specific cancer risk. Among 23,055 OSA patients, the risk of central nervous system (CNS) malignancy was 1.5 times that of age- and gender-matched non-apneic controls over a 2-year period, with the greatest risk seen in subjects with both OSA and insomnia (HR 2.20) (116). A five year follow up of 846 women with OSA found a two-fold risk of breast cancer when compared to age-matched controls in a cohort derived from a subset of the same database (117).

Not all investigators have found a link between OSA and cancer risk, however. Over a mean follow-up of 13 years, no overall association between symptoms of sleep apnea and subsequent cancer risk was seen in 8,783 participants in the Copenhagen City Heart Study, although there was a relationship between subjective sleepiness and incident malignancy in younger subjects (118). While this study was limited by its lack of objective measurements of sleep disordered breathing, a large Canadian study of nearly

10,000 patients undergoing in-laboratory PSG similarly found that any association between OSA severity and cancer risk appeared to be attributable to conventional risk factors, such as age, smoking and obesity (119). Nonetheless, even within this latter cohort, sub-group analyses suggested a link between severity of nocturnal hypoxemia and smoking-related cancer incidence.

Fewer studies have evaluated the relationship between OSA and risk of cancer death. What data is available suggests that subjects with more severe sleep apnea are more likely to die of cancer than those with mild or no sleep disordered breathing. In a 22-year follow-up of 1,522 participants in the community-based Wisconsin Sleep Cohort Study, a dose-response relationship between OSA severity and cancer-specific mortality was observed, with severe OSA conferring a nearly five-fold risk of death from cancer (adjusted RR 4.8) (120). This relationship was particularly strong in those with the most severe degree of nocturnal hypoxemia, and in non-obese subjects. Participants in the Australian Busselton Health Study had a 3.4-fold risk of cancer death if they had moderate-severe OSA (115), while data from Spanish sleep laboratory patients followed for an average of 4.5 years demonstrated an increased risk of death with increasing degrees of nocturnal hypoxemia, particularly in patients <65 years of age (121). A summary of population and clinical studies of cancer incidence and death in OSA patients is presented in *Table 1*.

Cancer and OSA in animal models and clinical studies

Initial studies evaluating interactions between OSA and cancer were largely performed in animal models of IH. In a ground-breaking series of studies, Almendros *et al.* showed that IH had a clear detrimental effect in mice inoculated with melanoma cells. In animals where melanoma was induced by injection of malignant cells into the flank, exposure to 17 days of IH for 6 hours/day was associated with an increased rate of tumour growth, which occurred in parallel with increased circulating levels of vasoactive endothelial growth factor (VEGF) (122). Moreover, 30 days of IH lead to an increased number and volume of pulmonary metastases when compared to control mice (123). A similar study protocol using epithelial lung tumour cells also showed increased rates of cancer progression in IH-exposed animals (124), while other OSA-related factors,

Table 1 Population studies of associations between OSA and cancer incidence and death

| Authors (ref.) | Participants | Study design | Outcome measures | Findings |
|---|-----------------------|-------------------|---|--|
| Campos-Rodriguez <i>et al.</i> (114) | 4,910 subjects | Observational | Cancer incidence according to degree of nocturnal hypoxemia | Increased cancer incidence over 4.5 yrs with increasing hypoxemia |
| | Clinic based | – | Attended inpatient sleep studies | HR 2.2 for incident cancer if CT90 >12% |
| Christensen <i>et al.</i> (118) | 8,783 subjects | Observational | Cancer incidence according to presence of OSA symptoms | No overall relationship between OSA and cancer incidence over 13 yrs |
| | Community based | – | SDB symptoms identified by questionnaire | Increased alcohol related cancer incidence in sleepy subjects |
| Chen <i>et al.</i> (116) | 92,220 subjects | Historical cohort | CNS cancer incidence according to OSA diagnosis | Increased incidence of CNS cancer in OSA over 10 yrs (HR 1.54) |
| | Community based | – | Data abstracted from administrative claims database | Highest risk in OSA with insomnia (HR 2.20) |
| Chang <i>et al.</i> (117) | 5,076 female subjects | Historical cohort | Breast cancer incidence according to OSA diagnosis | Increased incidence of breast cancer in OSA over 5 years (HR 2.09) |
| | Community based | – | Data abstracted from administrative claims database | |
| Kendzerska <i>et al.</i> (119) | 9,629 subjects | Historical cohort | Cancer incidence from cancer registry according to OSA severity | No significant relationship between OSA and cancer incidence |
| | Clinic based | – | | Significant association between hypoxemia and smoking related cancer |
| Marshall <i>et al.</i> (115) | 400 subjects | Observational | Cancer incidence and mortality | Increased cancer incidence with moderate-severe OSA over 20 years (HR 2.5) |
| | Community based | – | Home cardio-respiratory polygraphy | Increased cancer related mortality with moderate-severe OSA (HR 3.4) |
| Nieto <i>et al.</i> (120) | 1,522 subjects | Observational | Cancer mortality | Increased cancer-specific mortality with severe OSA (HR 4.8) |
| | Community based | – | Attended inpatient PSG | Markedly increased cancer-specific mortality with nocturnal hypoxemia (HR 8.6) |

CT90, cumulative sleep time with SpO₂ <90%; HR, hazard ratio; OSA, obstructive sleep apnea; CNS, central nervous system; PSG, polysomnography.

such as sleep fragmentation, have similarly been shown to accelerate tumour growth in murine IH models (125).

There is at present a paucity of clinical studies examining the effect of OSA on cancer progression. In a multicentre observational studies of 82 patients diagnosed with cutaneous melanoma, OSA severity indices independently predicted tumour growth rate, along with other indicators of aggressiveness. These findings need to be confirmed in other clinic populations, and it is as yet unknown if CPAP therapy could have a modifying role in cancer outcomes.

Mechanisms of carcinogenesis in OSA

Systemic inflammation and oxidative stress

There is a longstanding recognition that any disorder associated with chronic local or systemic inflammation may be associated with an increased risk of cancer development, an effect potentially mediated or amplified by the generation of reactive oxygen and reactive nitrogen species, with associated DNA damage and impaired DNA repair (126). OSA and associated IH have been demonstrated to independently contribute to the development of low-grade

systemic inflammation (6), with increased expression of NF- κ B dependent cytokines in both clinical subjects (127) and *in vitro* models of disease (128). Similarly, a significant evidence base supports the notion that OSA is an oxidative stress disorder, with reactive oxygen and nitrogen species likely formed at least partially due to IH-mediated mitochondrial dysfunction (93). Nocturnal CPAP therapy may lead to an abrogation of both systemic inflammation and oxidative stress, suggesting that appropriate treatment may obviate any pro-carcinogenic effect of OSA.

Hypoxemia and tissue hypoxia

Local tissue hypoxia induces stability of hypoxia-inducible factor-1 α (HIF-1 α), which under normoxic conditions is degraded by a series proline hydroxylases (129). In general terms, this can be considered an adaptive process, with HIF acting as a master regulator of cellular responses to decreased oxygen supply or increased oxygen consumption, but it appears to play a key maladaptive role in tumour biology (130). HIF-1 dependent-genes promote cell proliferation and angiogenesis, and facilitate metabolic adaptation to the hypoxic environment, thereby promoting tumour survival and progression (130). While OSA leads to intermittent hypoxemia, it is unclear if this translates into intermittent or sustained hypoxia at a tissue level. Rodent data would suggest that severe chronic IH may lead to fluctuating oxygen levels in hepatic tissue, but sustained hypoxia in adipose tissue (131). Human data are lacking, but sustained tissue hypoxia leads to a robust increase in expression of HIF-dependent genes, perhaps promoting carcinogenesis. Moreover, hypoxia is a pro-inflammatory stimulus, with HIF and NF- κ B interacting to drive increased inflammatory cytokine expression (132,133).

Sleep fragmentation and increased sympathetic drive

Generally considered to be mediators of the adverse cardiovascular consequences of sleep disordered breathing, sleep fragmentation and increased sympathetic tone induced by apneic events may also contribute to cancer development. As mentioned above, animal models of sleep fragmentation lead to increased tumour progression; the potential immunological mechanisms behind this will be discussed below (125). Sleep disruption and restriction seen in shift workers are also associated with an increased risk of cancer incidence (134), but specific data examining the relationship

between sleep fragmentation *per se* and cancer are lacking (135). Increased adrenergic signalling may also promote cancer survival and growth, although there is again a paucity of evidence specific to OSA patients in this regard (135).

Alterations in immune function

A key effector cell in cancer biology is the macrophage, and robust evidence shows that an increase in tumour associated macrophages (TAMs), particularly those with an anti-inflammatory M2 phenotype, is associated with worse outcomes in a variety of cancers (136). TAMs appear to promote angiogenesis, and promote tumour invasion and metastatic capacity. In a murine model of IH, TAMs showed a shift in polarity to a pro-tumoural M2 phenotype, and TAMs explanted from IH-exposed mice enhanced proliferation and invasiveness of pulmonary epithelial cancer cells *in vitro* (124,137).

Data examining tumour-specific immune function in OSA patients also suggests that sleep disordered breathing may contribute to a reduction in innate anti-tumoural responses. Genome sequencing in circulating leucocytes harvested from treatment-naïve patient with severe OSA revealed an upregulation in pro-neoplastic gene sets (138), and a subsequent downregulation in expression of these genes following approximately one month of CPAP therapy.

Another important effector cell in host responses to tumour development is the invariant natural killer T cell (iNKT). These are potent immunomodulatory cells which play a key role in conducting both innate and adaptive immune responses, and which have been demonstrated to direct anti-tumour responses and to directly lyse tumour cells (139). A recent novel study found a marked reduction in circulating iNKT cells in patients with severe OSA, correlating directly with indices of OSA severity independently of the confounding effects of obesity (140). Furthermore, a year of CPAP therapy lead to a partial restoration in iNKT numbers, and a series of *in vitro* models showed that hypoxia lead to a reduction in their ability to lyse tumour cells.

Overall, circumstantial, epidemiological and animal-based data support a role for OSA in promoting carcinogenesis and cancer progression. However, further mechanistic studies are required to better understand the underlying molecular alterations that underpin this association, and large scale, well designed trials of CPAP therapy will be required to demonstrate that OSA constitutes a modifiable risk factor for cancer development.

Conclusions

The relationship between OSA and cardiovascular morbidity is well established, and it seems increasingly likely that sleep disordered breathing also promotes the development of metabolic disease. However, the pathophysiological effects of OSA appear to extend beyond the vasculature and endocrine function, with a growing evidence base suggesting that it is of significant relevance in neurocognitive functioning, the development of CKD, and cancer risk and outcomes. As emphasised above, all three of these areas represent emerging fields, and ongoing high quality studies are required to further our understanding of the processes concerned.

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Footnote

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