BRN Reviews REVIEW

The Case of Sleep Apnoea and Cardiovascular Events

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ABSTRACT

For 30 years evidence has pointed to sleep apnoea being a cause of cardiovascular (CV) disease and major CV events. However, five recent large randomised controlled trials (RCTs) of positive airways pressure treatment of sleep apnoea in high CV risk populations have reported neutral results, and in one case, harm. I review the various strands of evidence in an attempt to reconcile these conflicting results arguing that: 1) Cohort and clinical case control studies have likely overestimated the CV risk associated with sleep apnoea; 2) Rodent models have similarly overstated the risk of CV injury from sleep apnoea by focussing on the effects of extremely severe intermittent hypoxia; and 3) Significant heterogeneity in susceptibility to vascular injury may exist between patients. These factors, coupled with low adherence to positive airway pressure mask treatment, may help explain the neutral results of recent RCTs. Suggestions for future research are provided. **(BRN Rev. 2020;6(1):5-21)**

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Key words: Cardiovascular events. Controversy. Sleep apnoea.

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Received in original form: 15-01-2020
Accepted in final form: 23-01-2020
DOI: 10.23866/BRNRev:2020-0001

INTRODUCTION

It is over 30 years since the first clinical studies appeared suggesting that obstructive sleep apnoea (OSA) might increase cardiovascular (CV) mortality[1,2]. The unique pattern of episodic hypoxia accompanying apnoea and hypopnoea events coupled with autonomic instability and brief surges in blood pressure made it biologically plausible that this relatively recently discovered respiratory disorder could result in vascular injury. A sustained research effort has occurred since these reports in 1988 in an attempt to substantiate causal links between both obstructive and central sleep apnoea (OSA, CSA) and CV disease. This has included longitudinal community and clinic-based cohort studies; experimental animal models and in vitro cell culture studies replicating a key feature of OSA and CSA, intermittent hypoxia; and short-term case-control and randomised trials investigating the impact of sleep apnoea and its treatment on intermediate markers of CV risk (e.g. hypertension, glycaemic control, dyslipidaemia). By approximately 2005 the collective results of these various investigations had provided a strong *prima facie* case for OSA and CSA being on the causal pathway to major CV events such as stroke, myocardial infarction and heart failure[3,4]. Moreover, evidence had accumulated implicating three major pathogenic pathways: oxidative stress and systemic inflammation caused by intermittent hypoxia; direct mechanical stress on the heart and major blood vessels during obstructive breathing; and OSA-related hypertension[3]. However, consensus was building that definitive evidence of a causal link between OSA and CSA and CV disease would require larger-scale randomised controlled trials (RCTs) with longer follow-up to show that treatment of sleep apnoea reduced the incidence of major fatal and non-fatal CV events[3,5]. Without this evidence, clinical practice was unlikely to change toward sleep apnoea screening for primary or secondary CV disease prevention. To address this evidence gap, several groups began to plan larger multicentre RCTs of positive airway pressure treatment focussing on hard CV endpoints. Investigators have published the results of five of these studies; two other studies are recruiting (ClinicalTrials.gov: NCT01128816 and NCT03812653). To the surprise of many, four of these large RCTs have been neutral – showing neither CV protection nor harm from continuous positive airway pressure (CPAP) treatment – while another in patients with heart failure and CSA found an increase in sudden cardiac death following assisted servo-ventilator (ASV) positive pressure treatment. The discordance between recent RCT findings (Fig. 1) and the results of the prior epidemiological and mechanistic studies came as a surprise to many, which is leading to a re-evaluation of the evidence and mechanisms linking sleep apnoea and CV disease.

In this article, I summarise the main findings arising from these various lines of investigation. I focus on some potential methodological weaknesses in the research, which on the one hand may have exaggerated the strength of association between sleep apnoea and CV disease and the role of several putative pathways to vascular injury, and on the other, may have contributed to the failure of RCT studies to show CV protection from sleep apnoea treatment. I will point to several studies, which suggest that sleep apnoea, and its treatment, may affect CV risk in a heterogeneous, non-linear and organ-specific fashion, such

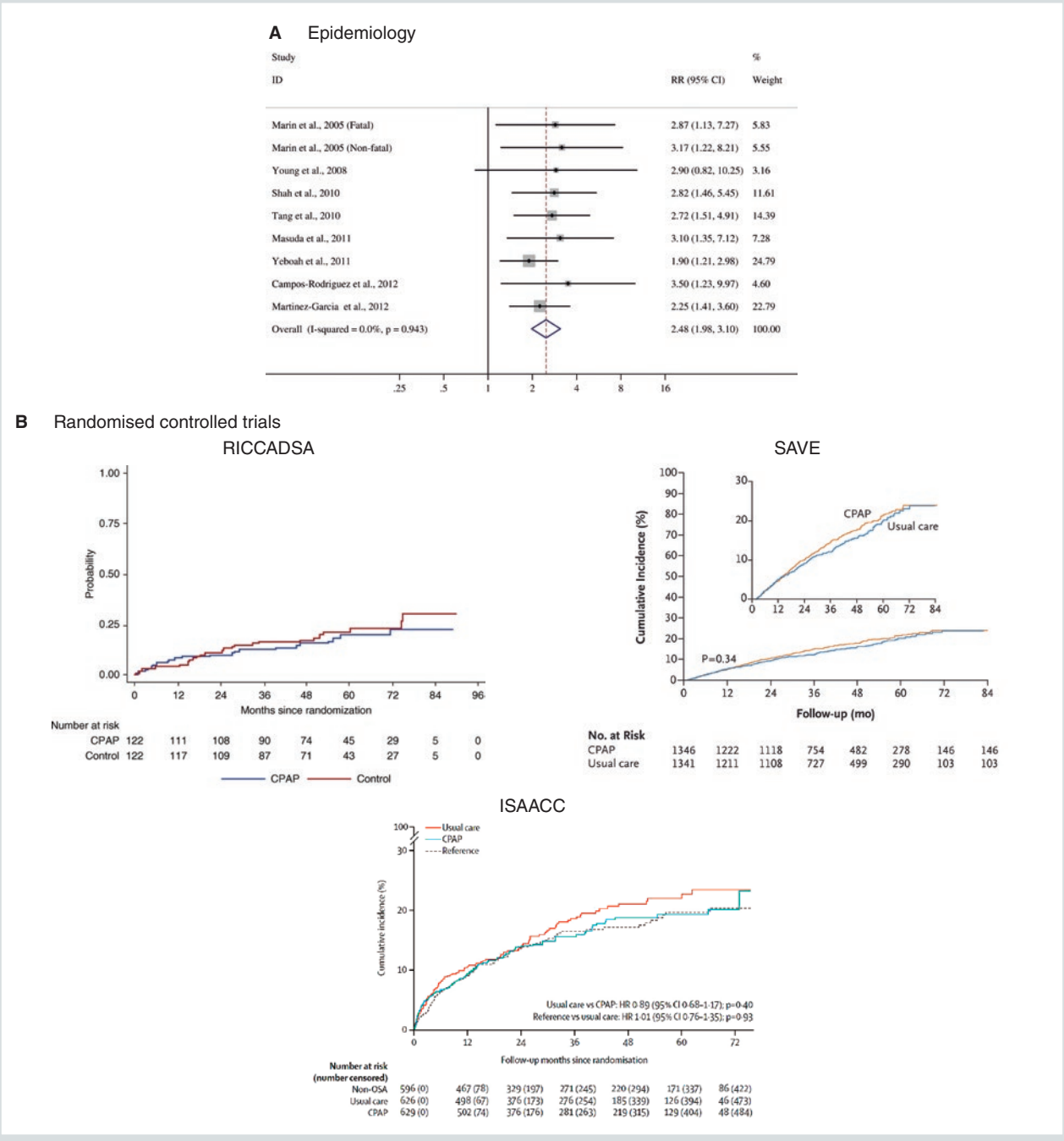


Figure 1. Obstructive sleep apnoea (OSA) and cardiovascular (CV) events – A conundrum. There is discordance between the results of longitudinal cohort studies **(A)** *(reproduced with permission from Dong Y et al.[13] © 2013 Elsevier Ireland Ltd. All rights reserved)* that show an increased risk of fatal and non-fatal cardiovascular events in moderate-severe OSA and the neutral results of recent randomised controlled trials **(B)** *(RICCADSA trial's figure is reprinted from Peker Y et al.[61] with permission of the American Thoracic Society, © 2020 American Thoracic Society; SAVE's image is reprinted with permission from McEvoy RD et al.[60]; ISAAC trial's figure is reprinted with permission from Sánchez-de-la-Torre M et al.[62], © 2019 Elsevier Ltd. All rights reserved)* of CPAP treatment of OSA in high CV risk populations.
CI: confidence interval; CPAP: continuous positive airway pressure; ISAACC trial: Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome. Effect of intervention with CPAP[62]. RICCADSA trial: Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA[61]; RR: relative risk; SAVE trial: Sleep Apnea cardioVascular Endpoints trial[60].

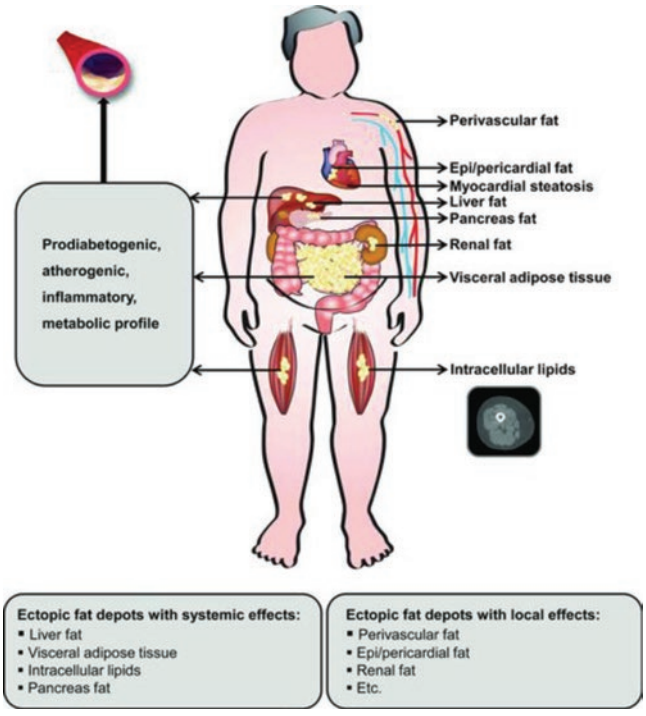
that certain distinct OSA patient endotypes or clinical phenotypes are more vulnerable to CV injury than others while in other patients OSA may actually be cardio-protective. I conclude by providing a clinician's perspective on the current evidence regarding sleep apnoea, its treatment and CV events (i.e. how should our patients be advised?) and offer some suggestions for future research.

COHORT STUDIES

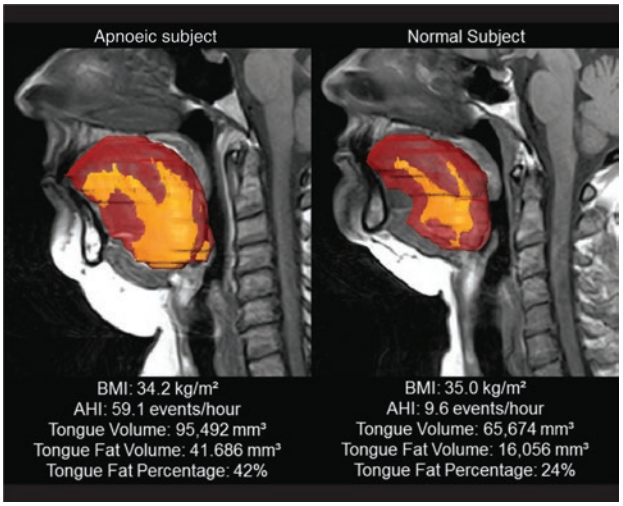
Longitudinal community and sleep clinic cohort studies support an independent relationship between OSA and new CV events[6] including stroke[7], myocardial infarction and heart failure[8] and CV mortality and the onset of CV risk factors such as hypertension[9,10], diabetes[11] and atrial fibrillation (AF)[12]. Meta-analyses suggest that OSA is more strongly associated with cerebrovascular than coronary artery events[13,14], and CV risk is greater in men than women. While the data in patients with co-existing CV disease and OSA are limited, they suggest that the risk is similar for recurrent stroke, myocardial infarction and all-cause mortality[15]. Whilst there is uncertainty regarding the dose response relationship between apnoea-hypopnoea index (AHI) and these various CV outcomes, meta-regression of available studies suggest that it is semi-logarithmic[14,16]. Cardiovascular risk increases exponentially with rising AHI, but increased risk is observed mainly in patients with severe OSA (i.e. AHI > 30 events/hour)[17].

While cohort studies point to an independent association between OSA and CV events, observational studies do not establish causality and are subject to bias from residual confounding, including from co-morbid conditions such as obesity, diabetes, and smoking, and from frequently unaccounted CV risk factors such as low socioeconomic status, low heath literacy, poor diet, and sedentary lifestyle. In considering OSA, the most problematic of these confounders is obesity, a known cause of OSA **and** a well-known risk factor for hypertension, diabetes, dyslipidaemia and CV disease (Fig. 2). Visceral (intra-abdominal) and ectopic (hepatic, intramuscular, pancreatic, epicardial and perivascular) fat, rather than subcutaneous fat, are the major drivers of obesity-related cardiovascular and metabolic disease[18,19]. Whilst body mass index (BMI) is a clinically convenient way to adjust for obesity, research shows that much more precise measurements using magnetic resonance imaging (MRI) or computerised axial tomography are required to measure visceral and ectopic fat deposits accurately[18,19]. The same applies to the use of waist circumference to estimate abdominal visceral adiposity[20]. No sleep apnoea cohort study has specifically measured or adjusted for visceral and ectopic fat, adjusting instead by BMI and, very occasionally, waist circumference[17]. This limitation is extremely important when interpreting OSA cohort data since MRI and CT-measured intra-abominal fat[21] and ectopic fat in the tongue[22,23] are also the major drivers of OSA (AHI). Furthermore, tongue fat is strongly associated with visceral abdominal fat[22,24] and with increased risk of metabolic syndrome[24]. Abdominal fat increases the risk and severity of OSA by increasing intra-abdominal pressure[25] and decreasing lung volume[26] and longitudinal traction on the upper airway[27]; genioglossus fat does this by increasing tongue volume[22,23]. Thus, failure to adjust for visceral and ectopic fat in sleep apnoea cohort studies may have caused the cardiovascular and metabolic risk

A Ectopic and abdominal visceral fat - strong drivers of CV disease



B Tongue ectopic fat – strong driver of OSA



Tongue fat in OSA patients was increased compared with BMI-matched controls ($p = 0.01$). Tongue fat ∝ abdominal visceral fat (rho 0.44; $p < 0.0001$).

FIGURE 2. Residual confounding from visceral and ectopic fat in sleep apnoea cohort studies. A: Ectopic and abdominal visceral fat – strong drivers of CV disease (*reproduced with permission from Després J-P[18], © 2012 American Heart Association, Inc.).* **B:** Tongue ectopic fat – strong driver of OSA *(reproduced with permission from Kim AM et al.[22], © 2014 Associated Professional Sleep Societies, LLC.).* Failure to measure and adjust for visceral and ectopic fat may have led to significant residual confounding in cohort studies causing the association between obstructive sleep apnoea (OSA) and risk of cardiovascular (CV) disease and events to be overestimated. Abdominal visceral fat and intramuscular ectopic fat deposits are pro-inflammatory, diabetogenic and atherogenic (A)[18]. Intramuscular fat deposits in the tongue cause the tongue to enlarge, encroach on the upper airway lumen and increase the risk of OSA (B)[22,23].
AHI: apnoea-hypopnea index; BMI: body mass index.

attributed to OSA to be overestimated including in studies of incident diabetes[28], hypertension[9] and metabolic syndrome[29]. Visceral fat is the main source of circulating biomarkers of inflammation. Failure to adjust for visceral and ectopic fat in case-control studies may help explain why OSA seems to be related to systemic inflammation in a dose-dependent manner yet investigators have found it difficult to reduce the levels of inflammatory bio-makers in OSA patients with CPAP treatment[30].

Central sleep apnoea commonly co-occurs with OSA and, except in patients with heart failure or AF, is rarely the dominant type of sleep apnoea. Whilst the primary cause of CSA and OSA in heart failure patients is different (i.e. respiratory control instability versus upper airway narrowing), the physiological sequelae are similar (i.e. intermittent hypoxia, autonomic nervous system instability, blood pressure surges and sleep fragmentation) with the exception that CSA patients do not experience the large intrathoracic pressure swings that are characteristic of OSA. There is uncertainty regarding the relative importance of CSA versus OSA in the development of heart failure and their impacts on morbidity and mortality in heart failure populations. The Sleep Heart Health Study (SHHS) found OSA to be an independent risk factor for incident heart failure[8]. In contrast, a recent community cohort study of older men reported that Cheyne-Stokes breathing and CSA, but not OSA, were predictive of incident heart failure[31]. In a clinical cohort study of patients with heart failure, moderate-to-severe OSA was associated with a two-fold increase in all-cause mortality compared with mild or no sleep apnoea[32]. Three other studies in heart failure patients who had predominant CSA reported conflicting results: two studies, one in patients admitted to hospital with acute heart failure and another in patients with stable heart failure, showed a similar two-fold increase in mortality[33,34], while a third study found no effect of CSA on transplant free survival[35]. To add another layer of complexity, there are strong physiological reasons to believe that heart failure can cause CSA and Cheyne-Stokes breathing (i.e. be a marker of deteriorating ventricular function rather than cause of heart failure) and furthermore that these forms of disordered breathing could even be adaptive or protective[36,37].

The findings of one cohort study stand out from all others (Fig. 3). In 2009, Lavie and Lavie[38] reported the mortality rates in approximately 660 patients, average age 70, who had attended their sleep centre in Haifa, Israel, for investigation of possible sleep apnoea. After an average follow up of five years they found patients with moderate sleep apnoea (respiratory disturbance index 20-40 events/hour) had increased survival compared with an age, sex and ethnicity matched cohort from the Israeli general population (standardised mortality rate 0.42 (95% confidence interval [CI]: 0.26–0.67; $P < 0.0002$)). People with no/mild apnoea (respiratory disturbance index < 20) also tended to have lower mortality and those with severe sleep apnoea (respiratory disturbance index < 40) had the same mortality as matched population cohorts. The survival advantage observed in patients with moderate sleep apnoea occurred despite patients having higher rates of CV and metabolic comorbidities than expected for people of similar age in the general population. The authors speculated that "the survival advantage of elderly people with moderate sleep apnoea and the lack of excess

mortality in severe patients reflect apnoea-related activation of cardio-protective adaptive pathways" and suggested ischaemic preconditioning was the most likely explanation.

Animal and human intermittent hypoxia experiments

Researchers have conducted extensive research in experimental animals to identify potential pathophysiological, cellular and molecular mechanisms responsible for vascular and metabolic injury in sleep apnoea. Early attempts to find naturally occurring animal models of obstructive or central sleep apnoea proved largely unsuccessful - the models proved to have only mild sleep disordered breathing and were unsuitable for high throughput experiments. Most work in this area has therefore been in freely behaving rodents housed in sealed cages cyclically exposed to an influx of nitrogen gas for ~30 seconds in an attempt to mimic the intermittent hypoxia experienced by patients with sleep apnoea. Typically, exposure to intermittent hypoxia has lasted for several hours each day and continued for a few days to 10-12 weeks. The great majority of experiments have occurred in animals exposed to severe hypoxia (fractional inspired oxygen concentration of 5-6%). The experimental findings are too numerous to describe in detail here and have been described comprehensively elsewhere[39] but have included evidence of intermittent hypoxia-induced hypertension, vascular and cardiac remodelling and arrhythmias and atherosclerosis each underpinned by evidence of oxidative stress and upregulation of several pro-inflammatory molecular pathways (e.g. transcription factor nuclear factor-kappa β).

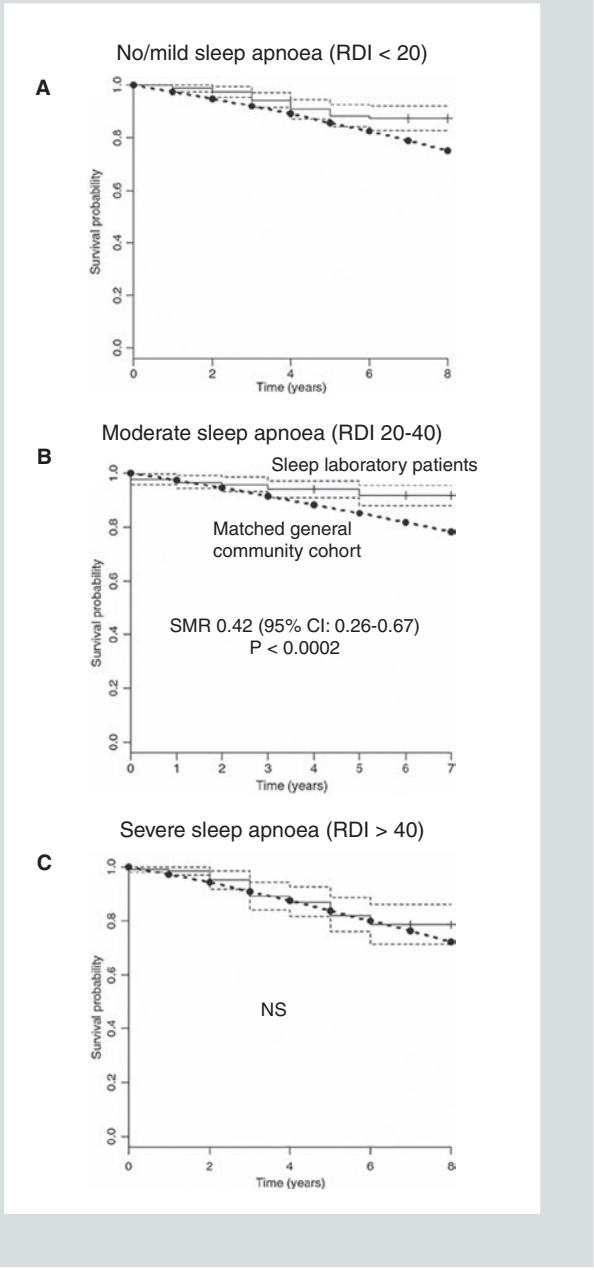


FIGURE 3. Survival advantage for sleep apnoea patients with moderate severity sleep apnoea. The Kaplan–Meier estimates of survival probability for the sleep laboratory groups: **A**: no/mild (respiratory disturbance index [RDI] < 20); **B**: moderate (RDI 20-40); **C**: severe sleep apnoea (RDI > 40) (solid line) with its associated 95% confidence interval (dashed lines), and the expected survival curve based on the general population data plotted as the dotted line and filled circles. General population cohort matched for age, sex and ethnicity *(reproduced with permission from Lavie P, Lavie L[38], © 2009 European Sleep Research Society).*
CI: confidence interval; RDI: respiratory disturbance index (events/hr of sleep); SMR: standardised mortality ratio.

In contrast to the results of intermittent hypoxia in mice and rats, nocturnal exposure to intermittent hypoxia in healthy humans for 10 and 14 days did not increase markers of systemic inflammation[40,41].

Investigators working in this area acknowledge that as a model of human OSA the rodent model of intermittent hypoxia has a number of shortcomings[42]. Apart from potential species differences, the most important limitation is that almost all the experimental work has exposed animals to very severe intermittent hypoxia producing a nadir arterial haemoglobin oxygen saturation value with each event of 50-60%. It is rare to see intermittent hypoxia of this severity and persistence clinically and thus it simulates the hypoxic burden at one extreme end of human OSA. In this context it is relevant to note that end organ protection rather than injury occurs when rodents are exposed to moderate versus very severe intermittent hypoxia[43,44]. Another concern is the very abrupt introduction of intermittent hypoxia regimens in rodent models. This contrasts with the gradual development over many months to years of clinical OSA due to ageing and weight gain, which may allow more opportunity for adaptive responses.

Continuous positive airway pressure treatment of obstructive sleep apnoea and intermediate markers of cardiovascular risk

Continuous positive airway pressure is the gold standard treatment of OSA - with the mask in place and a suitable pressure applied to splint the airway open obstructive events are virtually abolished along with their associated pathophysiological disturbances viz. hypoxaemia, autonomic nervous system instability, mechanical loading of the heart and great vessels and sleep fragmentation. In light of the associations found in observational studies between OSA and CV disease and some CV risk markers[6,14], short-term randomised controlled studies of CPAP have been conducted to assess the effects of OSA treatment on key parameters of cardiovascular risk such as blood pressure, glycaemic control and lipids and on markers of oxidative stress, systemic inflammation and endothelial function. Short-term studies in normotensive and hypertensive OSA patients report a similar modest reduction in blood pressure (2-4 mmHg) with CPAP treatment[45], which may attenuate with longer term follow up[46]. However, there is no evidence yet that CPAP treatment prevents the onset of hypertension[47] or reduces dependence on medication amongst OSA patients who are hypertensive. Short term (1-12 week) CPAP treatment reduces insulin resistance[48] but CPAP trials lasting up to 6 months have shown no improvement in overall glycaemic control in type 2 diabetes[45]. However, recent proof-of-concept, 1-2 week supervised laboratory studies that ensured complete overnight CPAP use showed improved response to the oral glucose load and insulin sensitivity in OSA patients with pre-diabetes[49], and improvements in 24-hour glucose without altering insulin levels in patients with type 2 diabetes[50]. Whilst in one study post-prandial triglyceride levels were reduced by CPAP[51], a recent RCT suggests that the lipid profile of OSA patients is not changed by CPAP treatment[52]. Impaired endothelial dysfunction improves after one to three months of

CPAP treatment in patients with moderate or severe OSA[53].

It has been hypothesised that cyclical oxygen desaturation in OSA and CSA is analogous to ischaemia reperfusion injury and leads to oxidative stress, an excessive production of reactive oxygen species and inflammatory molecules, which lead in turn to endothelial injury and ultimately atherosclerosis and cerebro- and cardiovascular disease[54,55]. Whilst there have been several uncontrolled before-after CPAP treatment studies in small numbers of patients with severe OSA showing a reduction in oxidative stress makers there have been no RCTs[54,55]. Two weeks of CPAP withdrawal (sham CPAP, n = 29) versus continued active CPAP (n = 30) in patients with severe OSA who were previously habituated and compliant with CPAP showed a decrease rather than increase in oxidative stress on return of OSA and an up-regulation of superoxide dismutase, an antioxidant enzyme associated with hypoxic preconditioning[56]. Observational and case control studies have suggested OSA is associated with an increase in pro-inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6; however, RCTs have not been able to demonstrate a reduction in systemic markers of inflammation with CPAP treatment[52].

A meta-analysis of short-term RCTs of positive airways pressure treatment of CSA in patients with systolic heart failure confirm a small but nonetheless clinically relevant improvement in left ventricular ejection fraction[57]. The evidence linking OSA with AF is also moderately strong[58]: the proposed pathogenic mechanisms include atrial stretch/remodelling as well as intermittent hypoxia and increased sympathetic activity; and observational studies show a reduction in AF recurrence after electrical cardioversion and atrial ablation surgery. There is also a temporal relationship between the night-to-night severity of OSA and episodes of paroxysmal AF[59].

Positive airways pressure treatment of sleep apnoea - hard cardiovascular endpoint trials

Obstructive sleep apnoea. The intention-to-treat results of three recent RCTs specifically designed to ascertain the effects of CPAP treatment of OSA on hard CV endpoints were neutral[60-62]. Each study enrolled patients OSA with co-occurring CV disease – ischaemic heart disease in two studies, and either stroke or ischaemic heart disease in the other – and had a composite CV event primary endpoint.

Central sleep apnoea. An earlier RCT of CPAP treatment of CSA in a heart failure population was also neutral with respect to the primary endpoint, transplantation-free survival, although this study was stopped early due to futility[63]. A more recent RCT in a similar population but using a more advanced positive airways pressure treatment device (i.e. ASV), which more effectively controls CSA, found excess CV and all-cause mortality in ASV treated patients[64].

In 2017, we conducted a meta-analysis[65] from information available to us at the time from these RCTs and information from other RCTs that systematically reported on hard cardiovascular endpoints (stroke and acute coronary artery syndromes) even though the studies had another

primary endpoint. We concluded that the use of positive airway pressure treatment, compared with no treatment or sham, was not associated with reduced risks of CV death or major adverse events for patients with sleep apnoea.

Can the discordant results of observational, mechanistic and hard cardiovascular endpoint randomized clinical trials be reconciled?

The neutral RCT findings and, in one instance, evidence of a harmful effect of positive airway pressure sleep apnoea treatment on major CV events are clearly at odds with the findings from earlier observational and experimental studies. There are two broad explanations to consider. First is that due to inadequate sample size or low adherence to positive airway pressure treatment the RCTs were underpowered to test the hypothesis that sleep apnoea causes CV events. The second, that the observational human and animal experimental data may have overestimated the risk associated with sleep apnoea and its treatment.

There has been debate about whether serious methodological weaknesses may have rendered the results of recent RCTs uninformative or misleading[66-69]. While some have criticised certain aspects of the studies' designs, the studies have in the main been very carefully planned and painstakingly performed. The main concern has been incomplete adherence to treatment, which varied between 2.8 and 3.7 hours per night in the five reported studies[60-64]. Adherence to treatment protocols in trials is common, underreported, and certainly not unique to sleep apnoea studies[70]. Low treatment adherence weakens the capacity to show both benefits and harms; however, when possible, power and sample size calculations in the sleep apnoea RCTs took into account published data on the strength of association between sleep apnoea and CV risk, primary endpoint event rates in similar populations and the likelihood of partial reduction of sleep apnoea due to incomplete device adherence. Despite reduced treatment adherence and lack of improvement in cardiovascular outcomes neurobehavioral improvements were evident in several of the studies[60,62,71]. This, combined with the absence of even a trend toward reduced CV events in the intention to treat analyses, and the non-significant meta-regression on major adverse cardiovascular events according to adherence[65], suggests that inadequate adherence to therapy was not the sole reason for the neutral results.

Another possible explanation for the neutral RCT results is that the relationship between OSA and CV risk may not be as strong as previously reported in meta regression analyses of prospective cohort studies (i.e. ~30% increase in CV risk for 10-unit increase in AHI[14-16]). As argued above, observational studies may have overestimated the risk of CV disease because of residual confounding, particularly the failure to adjust adequately for obesity. In addition, within the broad population of people with sleep apnoea (defined according to AHI) there may exist considerable heterogeneity of CV risk. Certain sleep apnoea *endotypes* (e.g. defined by specific physiological responses to intermittent upper airway obstructions and central breathing pauses), or clinical *phenotypes* (defined according to patient demographics, anthropometrics, symptoms and co-morbidities) may have a

greater or lower CV risk. Indeed, sleep apnoea may actually be protective against CV events in some patients[38]. If this is true, enrolment of patients in randomised trials simply on the basis of the frequency of sleep apnoea and hypopnoea events (AHI) may make it very difficult to show a treatment benefit.

These considerations have stimulated investigators to try to identify high CV risk endotypes and phenotypes from within existing OSA – CV cohorts (e.g. Sleep Heart Health Study [SHHS], Osteoporotic Fractures in Men Study [MrOS], Study of Osteoporotic Fractures [SOF], Determining Risk of Vascular Events by Apnoea Monitoring [DREAM] study and Sleep Apnoea cardio Vascular Endpoints [SAVE] study). While this is a promising avenue for discovery, thus far results are difficult to connect in any coherent fashion. Two groups[72,73], using algorithms to assess the patterns and cumulative extent of oxygen desaturation in polysomnography pulse oximetry recordings have shown that the overall cumulative night-time burden of hypoxia is more strongly predictive of CV events and CV mortality than is AHI or the frequency of desaturation events. Results from the DREAM clinical cohort study that identified seven distinct polysomnographic phenotypes also support the importance of hypoxic burden rather than AHI in predicting CV outcomes[74]. Others have reported that average respiratory rate during sleep is predictive of CV mortality[75] while in another study short duration obstructive events were linked to all-cause mortality[76]. A latent class analysis of SHHS participants with OSA (AHI > 15) identified four distinct OSA phenotypes[77]: excessively sleepy (17%, mean Epworth Sleepiness Scale [ESS] 13), moderately sleepy (39%, mean ESS 10.6), disturbed sleep (12%, mean ESS 7) and minimally symptomatic (33%, mean ESS 4.5). Fully adjusted Cox proportional hazards regression models found a substantial increased risk of incident coronary heart disease events and heart failure in the excessively sleepy phenotype compared to each of the other subtypes. In the SAVE study cohort (i.e. patients with moderate and severe OSA – ODI > 12 - and co-occurring CV disease) latent class analysis identified four distinct OSA clinical phenotypes and showed that patients with concurrent diabetes and cerebrovascular disease had a very high rate of subsequent stroke (hazard ratio [HR] 6·8, 95% CI 3·8-12·4)[78].

Hypoxic burden seems to be emerging as a much stronger predictor of CV risk than AHI, while for OSA patients who have had previous CV events traditional risk factors such as diabetes remain the strongest predictors of future CV morbidity and death. However, the statistical methods used to define patient clusters and physiological phenotypes have varied from study to study. Each of these studies needs to be replicated in other study populations before firm conclusions can be reached.

The recent neutral RCT results could also be explained, at least in part, by the inclusion of a mixture of sleep apnoea patients in the studies, some with predominantly adaptive/protective CV responses to intermittent hypoxia and others with high oxidative stress and inflammatory responses causing injury. Evidence has been accumulating that OSA may protect against CV disease in some patient subgroups. Lavie and Lavie[38] found in a cohort of older sleep clinic patients that those with moderately severe OSA had increased survival compared to an age and sex-matched

general population cohort (Fig. 2) and consider this was most likely due to hypoxic or ischaemic pre-conditioning[55]. Ischaemic preconditioning was first described in a landmark study in dogs in which short occlusions of a coronary artery dramatically decreased the size of myocardial infarction when the same artery was subsequently ligated[79]. Extensive experimental work has since shown similar results in brain, kidney and other organs and by using hypoxia instead of arterial occlusions[80], including experimental intermittent hypoxia to mimic sleep apnoea[39,55]. There are now several clinical reports of OSA protecting patients from cardiovascular events: review of the hospital records of over one million patients who had undergone major surgery revealed decreased post-operative mortality in those with a diagnosis of OSA[81]; more coronary artery collateral vessels compensating for coronary artery occlusion were found in patients with OSA than in patients without OSA[82,83]; lower blood troponin levels[48,84,85] and higher numbers of circulating endothelial progenitor cells[86] were present after acute myocardial infarction in patients with OSA versus those without, suggesting less cardiac damage and enhanced repair as a result of having OSA; and finally, a recent cross-sectional study of patients with obesity hypoventilation syndrome found that a higher frequency of apnoea-hypopnoea events and greater sleep hypoxaemia was associated with less CV disease[87]. It is possible that these various examples of apparent OSA-related CV protection are due to hypoxic preconditioning and occur in patients who have a lower hypoxic burden. Rodent experiments comparing moderate versus severe intermittent hypoxia have shown dichotomous effects - protection against ischaemia and infarction in brain and heart after preconditioning by moderate intermittent hypoxia but marked vascular injury following preconditioning with severe intermittent hypoxia[43,44]. The observation of more CV events in CPAP-treated versus usual care patients in the CANPAP study during the first 2 years of follow up[63]; a similar finding for patients with intermediate severity OSA (oxygen desaturation index indices between 20 and 30) in the SAVE study[60]; and increased CV mortality in ASV treated patients in Treatment of sleep-disordered breathing with predominant central sleep apnea by adaptive servo ventilation in patients with heart failure (SERVE-HF)[64] are each consist with the idea that sleep apnoea may have been actively CV protective in these populations.

Finally, a recent systematic review and meta-analysis of "per protocol" results extracted from recent RCTs has reported a differential end-organ OSA treatment effect[88]. Trial participants allocated to CPAP who were able to use the device for four hours or more each night had fewer cerebrovascular events but showed no change in cardiac events compared with participants allocated to usual care. As acknowledged by the authors, the results need to be treated with caution since the comparisons are no longer made between randomised groups and results may be biased because of healthy user effects. Nonetheless, the differential treatment effect on brain and heart is interesting and fits with observational data suggesting greater OSA-related stroke versus cardiac risk[14]. Such a finding could be explained by different OSA-related drivers of end organ vascular damage e.g. greater exposure of cerebral arteries than coronary arteries to nighttime apnoea-related blood pressure surges,

Table 1. Sleep apnoea and cardiovascular (CV) events: knowledge gaps, future research directions

Weaknesses in current evidence and knowledge gaps	Possible remedies and new research directions
Residual confounding has likely caused the CV risk associated with OSA to be overestimated e.g. from unmeasured visceral and ectopic adiposity, sedentary lifestyle, lower socioeconomic status, poor health literacy.	New cohort studies are needed that: a) Measure and adjust for a broader range of confounding CV risk factors. b) Measure pathophysiological characteristics of sleep apnoea in greater detail e.g. pattern and extent of hypoxia, acute apnoea-related BP changes, cumulative nocturnal sympathetic nervous system activation, sleep disruption, snoring energy. c) Take into account night-to-night variability in sleep apnea severity and long-term changes in exposure. d) Measure blood bio-molecular markers of vascular injury, repair and protection. e) Use non-invasive functional vascular measurements and imaging techniques to measure atherosclerosis – cIMT, and plaque formation, progression and activity -as it relates to sleep apnoea.
The key pathophysiological features of sleep apnoea which are driving CV risk are still not well understood. E.g. Are they the overall burden of hypoxia, cardiac and mechanical stress from snoring and obstructed breathing, mean BP changes, or the acute apnoea-related surges in BP?	
Poor understanding of the adaptive responses to sleep apnoea i.e. how and when sleep apnoea leads to CV protection versus injury.	
Present evidence from animal models is largely confined to rodent models that were exposed to very severe intermittent hypoxia.	Animal models should be used to explore the CV effects across a much broader range of intermittent hypoxia, focussing on protective as well as injury provoking pathways, and their differential expression within various end-organs of interest (e.g. brain heart, kidneys).
Clinical trials have been hampered by low adherence to positive airway pressure mask treatment and were underpowered to detect reductions in the incidence of CV events if the CV risk is smaller, and more heterogeneous, than estimated from previous cohort studies.	Efforts should continue to find ways to improve adherence to CPAP/ASV. Until such time as more information becomes available to enrol patients based on a better understanding of their OSA-related CV risk, enrolment of severe OSA patients, with a focus on stroke prevention may yield results. Consideration needs to be given to the possibility that OSA treatment could increase CV risk in certain patient subgroups.

ASV: adaptive servo ventilation; BP: blood pressure; cIMT; carotid intima-media thickness; CV: cardiovascular; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea.

or snoring-related trauma specific to carotid arteries[89,90].

SUMMARY AND CONCLUSIONS (Table 1)

The case of sleep apnoea and CV events is one of confusion and uncertainty at the moment. There is a disjunction between prospective cohort study results, which have shown an association between OSA, CV risk factors (e.g. hypertension and type 2 diabetes) and CV mortality and morbidity, and randomised studies of sleep apnoea treatment (CPAP/ASV) which have shown very little impact on known CV risk factors, and no reduction in the incidence of major CV events and death. Several possible reasons for this discrepancy in findings can be advanced: 1. The CV risk attributed to OSA may have been overestimated in cohort studies because of residual confounding (known and unknown), visceral obesity being a particular case in point; 2. The results of cohort studies suggest that OSA confers a greater risk for stroke than coronary events, and that the relationship between AHI and CV risk is curvilinear with very little risk in people until AHI exceeds 30 or 40 events per hour; 3. OSA- and CSA-related CV risk may also be quite heterogeneous within and between populations and relate more to overall hypoxic burden than to AHI; and to the balance between protective and damaging influences of intermittent hypoxia; and, 4. If points 1-3 are correct, the overall CV risk of

patients enrolled in recent RCTs, particularly trials using composite CV endpoints, may have been considerably less than was assumed when designing these trials. Combined with low levels of positive pressure device adherence, the RCTs may have been underpowered to show a CV benefit from sleep apnoea treatment.

So, where to go from here? What are the likely most fruitful directions and goals for future research in this area? And given our current state of knowledge, how should we advise our sleep apnoea patients on their risks of experiencing a future CV event and of benefitting from sleep apnoea treatment?

My priority list for future research regarding the link between sleep apnoea and CV events is as follows. More research is needed to:

1. **Identify the key physiological characteristics of sleep apnoea driving CV risk**. For example, is it severe intermittent hypoxia and oxidative stress as suspected for so long; or, given the apparent predilection for stroke, is it the effect of repeated arousal-related blood pressure surges at night, or direct snoring-related injury to the carotid arteries?
2. **Define how susceptibility to CV injury varies between individual patients and patient groups** and identify specific demographic, clinical, physiological and molecular markers of sleep apnoea-related CV risk. Post hoc analyses of data from previous OSA-CV cohort studies will likely help in this regard, e.g. novel methods for assessing overnight sympathetic nervous system activity, quantitative electroencephalograph (EEG) methods to better describe sleep disturbance and cluster analyses of clinical characteristics. Combining cohorts to create mega databases may open up the possibility for machine learning and replication studies. However, key pieces of information are likely to be missing from these older studies, so it will be necessary to
3. **Design new, multi-ethnic, multinational, prospective cohort studies.** It will be important to correct for visceral/ectopic fat using MRI scans or similar, and in addition to currently available techniques for quantifying the nocturnal physiological disturbance accompanying sleep apnoea, consider new measures to assess acute blood pressure fluctuations and snoring energy and,
4. **Measure the protective as well as injurious molecular signatures of sleep apnoea/intermittent hypoxia.** Animal experiments will likely provide important new information that can be incorporated into human studies. A systematic assessment is needed of the transcription molecular responses to intermittent hypoxia across a much wider range of exposures than has been employed previously.
5. **Conduct new "smart" clinical trials in sleep apnoea** enrolling patients selected on the basis of a high likelihood of adverse CV events, using the new information and tests gleaned from 1-4 above. Ways to enhance adherence to CPAP/ASV should ideally be found before conducting such trials but it may be unrealistic to substantially improve adherence to mask treatments in high CV risk populations who, in the main, are minimally symptomatic. Treatments that ameliorate rather than abolish obstruction and hypoxia yet are applied for longer each night – e.g. surgery, mandibular advancement devices or oxygen for OSA; oxygen

for CSA - may be sufficient if they reduce the exposure to hypoxia below a theoretical injury threshold. Notwithstanding the obvious challenges likely to be encountered with recruitment and CPAP adherence, the present observational evidence linking OSA to stroke and atrial fibrillation is sufficiently strong to justify RCTs on these outcomes. A trial in stroke patients is currently in progress (NCT03812653).

In the meantime, I believe clinicians need to advise their patients that sleep apnoea treatments improve symptoms, mood and quality of life. However, based on current evidence there is uncertainty whether OSA/CSA is a cause of serious CV events and insufficient evidence at present to recommend treatment solely or primarily for CV disease prevention. Sleep physicians should be diligent in advising their OSA patients on lifestyle factors relevant to CV risk, particularly weight control, and ensure that other well-established CV risk factors (diabetes, dyslipidaemia, and hypertension) are identified and optimally managed. CPAP should be encouraged as adjunctive treatment for resistant hypertension, and ASV avoided in patients with systolic heart failure.

ACKNOWLEDGEMENTS

Dr. McEvoy was the recipient of an Australian NHMRC Practitioner Fellowship.

DISCLOSURES

Dr. McEvoy reports grants from National Health and Medical Research Council, Australia, during the conduct of the study; and grants from Philips Respironics outside the submitted work.

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