Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

CPAP Treatment for Obstructive Sleep Apnea

Evidence Summary

Continuous positive airway pressure (CPAP) treatment shows efficacy for complications related to obstructive sleep apnea (OSA) including cognition, Alzheimer's disease, cardiovascular disease, metabolic disease, and mortality, though its effectiveness is related to length of use, severity of disease, and adherence.

Neuroprotective Benefit: Treating sleep apnea with CPAP may improve cognition in healthy and AD patients, improve AD biomarkers, and improve cognition in AD, but results may depend on CPAP adherence, length of use, and severity of OSA.

Aging and related health concerns: CPAP use may improve certain aspects of CVD and metabolic disease, but outcomes may depend on length of treatment, adherence, and severity of OSA.

Safety: CPAP use is associated with side effects, that, although they are minor, often lead to discontinuation.

Availability: Available online or through a doctor's office	**Dose**: >4 hours per night on average	**Molecular Formula:** N/A **Molecular weight:** N/A
Half-life: N/A	**BBB**: N/A	
Clinical trials: ~20 for cognition in healthy adults (>1500 patients), two for AD biomarkers (85 individuals), four for cognition in AD (~120 patients), >10 for mortality (>7,000 patients), >20 for CVD outcomes (>7,000 patients), >10 for metabolism	**Observational studies**: One for risk of AD with CPAP use (~20,000 individuals), ~13 observational studies for AD biomarkers in OSA patients (~1,000 patients), one for cognition in AD (~2,700 individuals), >20 for mortality (>500,000 individuals with OSA), >20 for CVD outcomes (>500,000 individuals with OSA), ~20 for metabolism (~6,000 patients for risk with OSA)	

What is it?

Obstructive sleep apnea (OSA) is the partial or total closure of the upper airway during sleep due to the loss of muscle tone in the throat muscles. This can cause transient hypoxic events and disruption of sleep architecture. OSA is classified by the apnea-hypopnea index (AHI) which is the number of apnea and hypopnea episodes per hour. Apneas are defined as a decrease in respiratory airflow greater than 90% for more than 10 seconds (i.e., complete air blockage) while hypopneas are a decrease of inspiratory airflow of greater than 30% for more than 10 seconds (i.e., partial air blockage). Both can cause a drop in oxygen saturation in the blood or cause arousal from sleep (Andrade et al, 2017). Generally, mild sleep apnea is defined as an apnea hypopnea index (AHI) of 5-14 (an average of 5-14 apnea or hypopnea events per hour), moderate sleep apnea is an AHI of 15-30, while severe sleep apnea is an AHI >30. It is estimated that almost 80-90% of OSA patients remain undiagnosed (Kuo et al, 2021; Young et al, 1997), but potential signs may be snoring or excessive daytime sleepiness.

OSA increases with age, and may impact 30-80% of elderly individuals, depending on how it is defined and the population in which it is diagnosed (Sharma et al, 2017). It is estimated that 35-40% of the variance in sleep apnea cases may be due to genetic factors (mainly due to changes in craniofacial structure, body fat distribution, and neural control of the upper airway muscles) (Casale et al, 2009).

OSA can also be caused by other factors such as old age, being male, obesity, smoking, and alcohol consumption. Some cases of sleep apnea can be treated with lifestyle interventions such as diet, exercise, improved sleep hygiene, and smoking and alcohol cessation. A meta-analysis of 13 RCTs and 22 open-label studies suggested that lifestyle interventions can improve AHI, oxygen saturation, and excessive daytime sleepiness. However, the specific type of intervention that is most effective is still unknown and may depend on the risk factors present in certain individuals (Carneiro-Barrera et al, 2018).

OSA can also be treated with continuous positive airway pressure (CPAP) and a mandibular advancement device (MAD – a dental device). A network meta-analysis of 80 RCTs comparing CPAP, MAD, aerobic exercise, and dietary weight loss suggested that CPAP was most effective at decreasing AHI (by 25.27 events/hour), improving the oxygen desaturation index (ODI), and improving the O_2 nadir (minimum oxygen saturation). Exercise was most effective at improving sleep efficiency and scores on the Epworth Sleepiness Scale. Of the different interventions, CPAP was most effective for AHI, (Iftikhar et al, 2016).

The most common treatment for OSA is CPAP. There are two types of CPAP devices, nasal CPAP (the "gold standard") and oronasal CPAP. The nasal CPAP device pushes air through the nasal cavity keeping the tongue muscles from collapsing. Although oronasal CPAP is commonly used in the clinic, there is concern it may not be as effective as nasal CPAP since air is going through both the nasal cavity and the mouth. A meta-analysis of five randomized and eight nonrandomized trials suggested that nasal CPAP was more effective than oronasal CPAP. Oronasal CPAP required higher air pressure, did not reduce AHI as much as nasal CPAP, and was associated with less adherences (48 fewer minutes used per night) (Andrade et al, 2017).

Unlike drug studies, placebo-controlled studies are more difficult for CPAP. Studies may use sham CPAP (where, for instance, air leaks out of the machine so that it does not provide continuous pressure), oral placebos, lifestyle interventions, or no treatment.

There are several studies that have examined potential therapeutics for OSA. However, according to a Cochrane meta-analysis, most of the studies are small and the results inconclusive (Mason et al, 2013).

Finally, surgical options are also available for OSA. However, this should be a last line treatment for patients with severe OSA who cannot tolerate CPAP. Surgical options depend on the specific anatomical characteristics in the individual that are causing OSA (American Sleep Apnea Association).

Neuroprotective benefit: Treating sleep apnea with CPAP may improve cognition in healthy and AD patients, improve AD biomarkers, and improve cognition in AD, but results may depend on CPAP adherence, length of use, and severity of OSA.

Types of evidence:

- A meta-review for cognitive deficits in healthy individuals
- Three meta-analyses on CPAP use in cognitively healthy individuals
- One meta-analysis on OSA and the risk of cognitive decline
- One meta-analysis on prevalence of OSA in AD patients
- Two meta-analyses on ApoE4 and risk of OSA
- One review of 10 cross-sectional studies on OSA and risk of AD biomarkers
- One RCT on CPAP use in cognitively healthy individuals
- Four RCTs of CPAP use and cognition in MCI/AD patients
- One RCT on CSAP use in subjective cognitive impairment patients on AD biomarkers
- One open-label study on CPAP use and AD biomarkers
- Two observational studies on OSA and the risk of future MCI/Alzheimer's
- Three longitudinal studies on OSA and the risk of AD biomarkers
- One cross-sectional study on CPAP use and AD biomarkers
- One observational study on CPAP use vs. non-use in OSA patients and risk of Alzheimer's
- One observational study on CPAP use and cognition in AD patients
- Three observational studies on ApoE4 carriers with OSA and risk of cognitive impairment vs. non-carriers
- One review on potential mechanism of actions

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Studies on cognition in cognitively healthy individuals

Cognitive deficits associated with OSA: **Increases risk of cognitive impairment in certain cognitive domains**

In a meta-review examining the cognitive effects of OSA in non-AD patients, Bucks et al (2012) reported that OSA was commonly associated with deficits in attention, vigilance, long-term visual and verbal memory, visuospatial/constructional abilities, and executive function. However, OSA did not affect language ability and psychomotor function. The effects of OSA on working memory, short-term memory, or global cognition were still unclear.

CPAP use in cognitively healthy patients with OSA: **Possible benefit for certain cognitive domains**
A meta-analysis of 13 RCTs that included 1,744 middle-aged obese patients diagnosed with mild to severe OSA measured outcomes in seven cognitive domains (attention, vigilance, processing speed, working memory, memory, verbal fluency, and visuoconstructive skills) and compared CPAP use to controls. The length of treatment in the studies was 1-24 weeks. The only significant effect was an improvement in vigilance, though many of the other outcomes numerically favored CPAP use (Pan et al, 2015). Another meta-analysis using partially overlapping studies and measuring outcomes on the same cognitive domains reported a small significant effect on attention after CPAP use (Kylstra et al, 2013). Similar results were reported in a more recent meta-analysis using partially overlapping studies looking at the use of CPAP in middle-aged adults with OSA. Effects on perceived daytime sleepiness numerically favored CPAP but were not significant . An analysis of attention, executive function, and memory found that CPAP only improved attention and was only observed in patients with severe OSA (Wang et al, 2020). A small RCT in 31 patients with OSA reported that three-month treatment with CPAP improved declarative memory compared to no treatment (Djonlagic et al, 2020).

Overall, data from RCTs in middle-aged individuals without overt cognitive impairment suggests that the use of CPAP may have subtle effects on certain cognitive domains, though the effect on most domains are not significant. There are several explanations for these results. First, cognitive benefits from the use of CPAP may depend on compliance. In Wang et al (2020), the average compliance was 3.8 hours per night (generally >4 is considered good). In addition, cognitive benefits from the use of CPAP may depend on longer treatment periods. Although the length of the studies from these meta-analyses were 1-24 weeks, most of the included studies were no more than six weeks.

OSA and Alzheimer's Risk Studies

Meta-analysis for risk of cognitive decline or Alzheimer's disease (AD) with OSA: **Increased risk of cognitive decline or AD w/OSA**
A meta-analysis of cross-sectional and prospective cohort studies reported that sleep problems are associated with the risk of cognitive decline or AD. A sub-study of this meta-analysis reported that OSA was associated with a more than two-fold risk of cognitive decline or AD (Bubu et al, 2017).

Longitudinal studies on OSA and risk of AD: **Increased risk of MCI or AD in patients with OSA**
Two hundred and ninety-eight cognitively normal (CN) women (avg. age 82.3) underwent a polysomnography to measure the presence of sleep-disordered breathing (SDB). After a mean follow up of 4.7 years, the presence of SDB at baseline was associated with an increased risk of MCI (**OR 1.85; 95%CI 1.11-3.08**) and combined MCI or dementia (**OR 2.04; 95%CI 1.10-3.78**) after controlling for

demographics and comorbid conditions. Hypoxic episodes correlated with an increased risk for MCI and dementia while sleep fragmentation and total sleep time did not (Yaffe et al, 2011).

In another study from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, patients with SDB developed MCI and AD at a younger age. There was also a trend for the development of MCI at an older age in SBD patients using CPAP versus non-treated SBD patients. The lack of significance could be due to the low number of patients in this sub-study (n=28) (Osorio et al, 2015).

CPAP use and the risk of AD in OSA patients: **Potential benefit for CPAP use in OSA and risk of AD**
Data from 3,978 OSA patients and 15,912 non-OSA patients were collected from 1997-2012 from the National Health Insurance Database of Taiwan. Those with a diagnosis of OSA were more likely to be diagnosed with AD (**HR: 2.12; 95%CI 1.27-3.56**). CPAP-treated OSA patients were at a decreased risk for AD compared to non-treated patients, and CPAP-treated OSA patients were no longer at an increased risk of AD. Two weaknesses of the study are its retrospective observational nature and the potential inaccuracies of insurance data (Tsai et al, 2020).

AD Biomarker Studies
Longitudinal studies of AD biomarkers in OSA patients: **Possible worsening of AD biomarkers with OSA**
A group of 208 CN individuals between the ages of 55 and 90 were followed for two years. OSA was present in 53% of the individuals at baseline. Baseline OSA severity was associated with a reduction in CSF levels of Aβ42 (CSF Aβ42 goes down with increased brain amyloid burden) but not an increase in amyloid PET levels (possibly because of the low numbers in the PET sub-study). There were also no differences in CSF p-tau or total tau (Sharma et al, 2017).

In another study from the ADNI database which included 514 CN, 798 MCI, and 325 AD individuals followed for an average of 2.52 years, CN and MCI individuals with a self-reported a diagnosis of OSA (experienced an accelerated increase in amyloid PET, a decrease in CSF levels of Aβ42, and an increase in CSF tau and p-tau. There were no differences in AD biomarkers for AD patients with OSA compared to non-OSA AD patients. One limitation of this study was the use of self-reported OSA (so cases of OSA might have been missed), and, in fact, the prevalence of OSA in this cohort is lower than what would be expected (Bubu et al, 2019).

Lutsey et al (2016) studied 312 patients from the Atherosclerosis Risk in Communities Study (ARIC). Sleep parameters were measured in middle-age adults and brain MRI scans conducted about 15 years later. They reported no association between OSA and abnormal brain scans (including infarcts, white

matter hyperintensities, and brain atrophy) at follow-up. Two limitations of the study include the fact that there were no MRI scans at baseline and there could be selection bias (about 1/3 of the participants were lost due to death or attrition).

Cross-sectional studies on AD biomarkers and OSA patients: **Possible association of AD biomarkers with OSA**
In a study of young, active-duty military males without a history of TBI, individuals diagnosed with moderate-to-severe OSA had higher levels of plasma tau and IL-6 than those with mild OSA or healthy controls (Motamedi et al, 2018).

Several other cross-sectional studies have reported an association between OSA in middle-aged and older adults and AD biomarkers, such as CSF and PET amyloid (Bubu et al, 2020).

Intervention studies for AD biomarkers: **Potential benefit for APAP use in OSA and AD biomarkers**
In an open label pilot study, 35 patients diagnosed with OSA (avg. age 60) were treated with APAP (autotitrated PAP) for one-to-four months. Treatment had no effect on total sleep time but did increase the amount of time in slow wave sleep (SWS – important for memory consolidation). Although treatment did not improve CSF levels of Aβ40, Aβ42 or tau, there was a correlation between improvements in SWS and AD biomarkers (Ju et al, 2019).

In 50 patients with subjective cognitive impairment, Liguori et al (2017) compared individuals with OSA, CPAP-treated OSA, and without OSA. Individuals with OSA had worse levels for AD biomarkers (Aβ42 and t-tau/Aβ42, but not t-tau or p-tau) and impaired cognition compared to non-OSA controls. Cognition and AD biomarkers in CPAP-treated OSA individuals were not significantly different from non-OSA controls.

Human research to suggest benefits to patients with dementia:
OSA prevalence in AD patients: **OSA more prevalent in AD**
A meta-analysis of five studies with 236 AD or age-matched control patients who were not using CPAP showed that having OSA was associated with an increased risk of AD (**OR: 5.05; 95CI 2.42-10.56**) (Emamian et al, 2016).

CPAP use and cognition in MCI/AD patients with OSA: **Possible benefit for CPAP use over longer time periods**

Seventeen CPAP naïve aMCI patients with OSA were treated over one year. They were divided into two groups, CPAP adherent (>4 hours per night) and CPAP nonadherent (<4 hours per night). At the end of the treatment period, those who were CPAP adherent scored better on a cognitive processing speed test (Digit Symbol Coding Test, p=0.01, effect size 1.40), but there were no differences on other cognitive tests (a memory test, a global cognitive test – MoCA, and a test on everyday function). There were also no differences on AD cognitive tests (CDR, ADCS-CGIC – although numerically they favored the adherent group). Two limitations of the study are the small sample size and the comparison of adherent vs. nonadherent rather than a placebo (Wang et al, 2020). Another study reported similar results in 54 patients with aMCI showing that CPAP adherence over one year improved cognitive processing speed while there were no significant effects on other measures (e.g., memory, global cognition, attention, daytime sleepiness, everyday function) (Richards et al, 2019).

Fifty-two patients with mild to moderate AD and OSA were randomized to CPAP or placebo CPAP (holes were drilled into the machine to cause an air leak) for three weeks followed by a three-week open label extension where the placebo group was assigned to normal CPAP. There were no differences between groups with adherence (both the regular CPAP group and the group with leaky CPAP machines) or their knowledge to which group they were assigned to. The study found no differences in a composite neuropsychological test between the two groups after the three-week period. However, each group improved from baseline after a three-week treatment period (Ancoli-Israel et al, 2008). A follow up 13 months later from participants in this study comparing five patients who continued on CPAP vs. individuals who had stopped CPAP treatment after the study suggested numerically cognitive benefits with the continued use of CPAP treatment. However, due to the small numbers, most of the cognitive measures where not significant (a measure of intelligence – Wechsler Adult Intelligence Scale – trended toward significance) (Cooke et al, 2009).

Another observational study compared 23 mild-to-moderate Alzheimer's patients diagnosed with sleep apnea who either had good compliance using CPAP over the last three months to those who either refused CPAP treatment or had poor compliance. At a median follow up time of 3.3 years, patients in the CPAP group declined less on the MMSE than those in the non-CPAP/poor adherence group (Troussiere et al, 2014).

Mechanisms of action for neuroprotection identified from laboratory and clinical research

There are several possible mechanisms for how OSA may impact the progression of Alzheimer's disease. OSA is associated with hypertension, cardiovascular disease, depression, and diabetes, risk factors for Alzheimer's disease, as well as chronic inflammation and oxidative stress. In addition, sleep fragmentation may disrupt the memory consolidation process and intermittent hypoxic episodes may promote amyloid accumulation (Bubu et al, 2019).

APOE4 Interactions:

Two meta-analyses of 8 and 14 studies suggested that ApoE4 is not associated with an increased risk of OSA (Thakre et al, 2009; Lu et al, 2016). However, ApoE4 patients with OSA may be at a greater risk of cognitive impairment than non-ApoE4 patients. In a cross-sectional study of 755 participants (avg. age 54), those with moderate-to-severe OSA and ApoE4 performed worse on two cognitive tests (one for executive function and one for memory) than non-ApoE4 patients with moderate-to-severe OSA. However, there were no differences on two other executive function tests or a psychomotor function test (Nikodemova et al, 2013). Another study in 36 patients (avg. age 70) reported that there was a correlation between more severe OSA and worse memory performance in ApoE4 carriers but not in ApoE4 non-carriers (O'Hara et al, 2005). Finally, another study of 48 patients (avg. age 58) reported that ApoE4 carriers with moderate-to-severe OSA had impaired performance on spatial working memory compared to non-carriers but there were no differences on other memory tests (Cosentino et al, 2008). Overall, while it does not appear that ApoE4 increases the risk of OSA, some studies suggest that ApoE4 carriers with more severe OSA may have impairments on certain aspects of cognition, but the studies are small and the data is mixed.

Aging and related health concerns: CPAP use may improve certain aspects of CVD and metabolic disease, but outcomes may depend on length of treatment, adherence, and severity of OSA.

Types of evidence:

- Five meta-analyses on the use of CPAP in OSA patients and risk of death
- Four meta-analyses on OSA and risk of cardiovascular disease
- Three meta-analyses on CPAP use in OSA patients and CVD outcomes (e.g., MACE, MI, etc.)
- Two meta-analyses on the use of CPAP in OSA hypertensive patients
- Two meta-analyses on the use of CPAP and arterial stiffness and one on atherosclerosis
- One meta-analysis on the use of CPAP and arterial fibrillation
- One meta-analysis on the use of anti-hypertensives and severity of OSA

- Four meta-analyses on the use of CPAP and CVD biomarkers (e.g., lipids, inflammatory markers)
- Three meta-analyses on OSA and the risk of metabolic diseases
- Three meta-analyses on the use of CPAP in type two diabetics
- Two meta-analyses on the use of CPAP and metabolic parameters in non-diabetics
- One meta-analysis on OSA and the risk of cancer

Lifespan

OSA, CPAP use and risk of mortality – observational studies: **Increased risk of mortality and cardiovascular mortality in patients with OSA; potential benefit for CPAP use**

A meta-analysis of seventeen observational studies (n=681,072 individuals) reported that mild and moderate OSA were not associated with all-cause or cardiovascular mortality. However, severe OSA was associated with an increased risk of all-cause (**HR: 2.13; 95%CI 1.68-2.68**) and cardiovascular mortality (**HR: 2.73; 95%CI 1.94-3.85**). However, CPAP use in OSA subjects was associated with a reduced risk of all-cause mortality compared to non-users (**HR: 0.66; 95%CI 0.59-0.73**) and only a slightly increased risk for all-cause mortality than in individuals without OSA (**HR: 1.35; 95%CI 1.21-1.50**) (Fu et al, 2016). Another meta-analysis of six studies (n=11,932 patients) reported that OSA patients using CPAP did not have an increased risk of cardiovascular mortality compared to non-OSA patients (Ge et al, 2013).

OSA, CPAP use and risk of mortality – RCTs: **No benefit for mortality with the use of CPAP in OSA**

A meta-analysis of nine RCTs (n=3,314 patients) for secondary prevention of cardiovascular disease in OSA patients reported that CPAP use did not improve all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke compared to non-use. Some of the reasons that could explain the lack of significant results include the duration of the trials (1-60 months) or lack of adherence to CPAP treatment (Paulitsch and Zhang, 2018). Another meta-analysis of 10 RCTs (n=7,266 patients) all greater than 12 weeks in length for either primary or secondary prevention of cardiovascular disease (CVD) in patients with OSA or central sleep apnea (CSA) reported that positive airway pressure (PAP – nine studies) or adaptive servo-ventilation (ASV – one study) had no effect on major adverse cardiovascular events (MACE), cardiovascular death, all-cause mortality, acute coronary syndrome, stroke, or heart failure. There was also no association with apnea severity, follow-up duration, or adherence (Yu et al, 2017).

On the other hand, a meta-analysis of nine studies (four observational and 5 RCTs) that looked at cardiovascular outcomes (follow-up period between one and >88 months) reported that CPAP use was associated with a significant reduction in CVD mortality (**HR = 0.34; 95%CI 0.17-0.68**), an increase in left

ventricular ejection fraction, but no reduction in all-cause mortality (**HR = 0.92; 95%CI 0.73-1.15**). There was no significant reduction in the number of CVD events (Aslan et al, 2018).

Cardiovascular disease

OSA and risk of cardiovascular disease: **Increased risk for hypertension and cIMT in OSA patients**

A meta-analysis of six studies suggested that a diagnosis of OSA was associated with an increased risk of hypertension (**OR: 2.84; 95%CI 1.170-3.980**) (Hou et al, 2018). In a meta-analysis of 40 studies, prevalence of OSA in patients following surgical intervention due to acute coronary syndrome (ACS) was estimated at 70% for mild OSA and 22% for severe OSA (Grande et al, 2020). In a meta-analysis of nine studies (n=893), OSA (or the severity of OSA) was not associated with arterial stiffness (Joyeux-Faure et al, 2018). Another meta-analysis of eighteen studies (n=1,896 patients) reported that OSA was associated with increased carotid intima-media thickness (cIMT). In addition, severity of OSA increase the severity of cIMT (Zhou et al, 2016).

CPAP use and cardiovascular disease, hard outcomes: **Potential benefit with good adherence**

A meta-analysis of four RCTs (n=3,780 OSA patients) reported that CPAP use was not associated with a reduced risk of a major cardiovascular event (MACE) compared to non-use except in a sub-group of those with good adherence to CPAP (>4 hours of use per night) (**RR: 0.70; 95%CI 0.52-0.94**) (Abuzaid et al, 2017). Another meta-analysis of seven RCTs (n=4,268 OSA patients, follow-up between 3 and 60 months) reported that CPAP use was not associated with a reduced risk of MACE, stroke, myocardial infarction (MI), atrial fibrillation, or heart failure. However, a subgroup analysis of patients with good adherence to CPAP (>4 hours of use per night, partially overlapping studies from previous meta-analysis) reported a reduced risk of MACE (**RR = 0.43; 95%CI 0.23-0.80**) with no significant impact for MI or stroke (Khan et al, 2018).

Use of CPAP in hypertensive patients with OSA: **Potential benefit**

In a meta-analysis of seven studies with ~1,100 patients with OSA and hypertension, CPAP treatment slightly reduced 24-hour, nocturnal, and clinic systolic and diastolic blood pressure but did not influence daytime SBP. In a subgroup of studies that reported CVD outcomes, with a mean follow up of 28 months (n~850 patients), the use of CPAP also reduced the risk of CVD events (e.g., mortality, myocardial infarction, heart failure, and stroke) (**OR: 0.59; 95%CI 0.36-0.98**) (Sun et al, 2017). Another meta-analysis of five RCTs in patients with treatment-resistant hypertension and moderate-to-severe OSA reported that the use of CPAP reduced 24-hour SBP by ~5 mmHg (Liu et al, 2016). Finally, meta-analysis of 11 studies suggested that anti-hypertensive treatment reduced the severity of OSA in patients with hypertension and sleep apnea (Khurshid et al, 2016).

The use of CPAP on arterial stiffness and hypertension: **Potential benefit**
A meta-analysis of three studies (n=186 patients, two observational studies and one RCT) suggested that the use of CPAP was associated with a decrease in arterial stiffness in hypertensive patients with OSA (measured with pulse wave velocity) (Lin et al, 2016).

However, another meta-analysis of RCTs in patients with OSA (but not necessarily hypertension) reported that CPAP use improved the augmentation index (an indirect measure of arterial stiffness) but not carotid femoral pulse wave velocity (a direct measure of arterial stiffness) (Ning et al, 2019).

CPAP use on atherosclerosis plaques: **Potential benefit in patients with severe OSA and for longer treatment periods**
In a meta-analysis of seven studies (two RCTs, five observational cohorts, n=167) with newly diagnosed OSA, the use of CPAP was not associated with a reduction in carotid intima-media thickness (cIMT). However, a subgroup analysis showed that cIMT decreased in patients with more severe OSA (AHI>50) and with a therapeutic duration >6 months (Chen et al, 2017).

The use of CPAP on atrial fibrillation: **Potential benefit**
A meta-analysis of eight studies (one RCT and seven cohort studies; n=1,247) of OSA patients with at least one type of arrhythmia reported that the use of CPAP was associated with a reduced risk for recurrence of atrial fibrillation (**RR = 0.56; 95%CI 0.47-0.68**). Similar to other meta-analyses that include cohort studies, benefits with the use of CPAP may require longer periods of time than most RCTs and need to include more patients. The benefits of CPAP use were more pronounced in younger, obese, and male individuals (Qureshi et al, 2015).

CPAP and cardiovascular biomarkers: **Potential benefit**
In a meta-analysis of 15 RCTs (n=1,090 patients) in patients with OSA, the use of CPAP reduced serum levels of hsCRP and improved vascular flow-mediated dilation. It had no effect on IL-6 or TNFα levels (Ning et al, 2019). In a meta-analysis of six trials (~700 patients) the use of CPAP in OSA patients reduced levels of triglycerides and *reduced* HDL-c. However, it had no effect on LDL-c levels (Lin et al 2014). A meta-analysis of prospective cohort studies and RCTs reported that the use of CPAP improved endothelial function in patients with OSA (measured by flow-mediated dilation) (Cammaroto et al, 2019).

Finally, meta-analysis of up to 24 studies (for CRP, 24 studies; IL-6, 16 studies; IL-8, 3 studies; TNFα, 12 studies) reported that the use of CPAP was associated with improvements in all inflammatory

biomarkers. Subgroup analysis suggested that the results were generally better for longer therapy duration (>3 months) and better adherence (>4 hours/night) (Xie et al, 2013).

Metabolic Syndrome

Association between OSA and metabolic syndrome: **Increased risk**

In a meta-analysis of 15 cross-sectional studies (n=4,161 individuals) and 5 case-control studies (n=1,660 individuals), OSA was associated with an increased risk of metabolic syndrome (mild OSA: **OR = 2.39; 95%CI 1.65-3.46**, moderate-severe OSA: **OR = 3.45; 95%CI 2.33-5.12**) (Xu et al, 2015). In a meta-analysis of six prospective cohort studies (n=5,953 participants, follow-up periods of 2.7-16 years), the diagnosis of moderate-to-severe OSA was associated with a greater risk of diabetes (**RR = 1.63; 95%CI 1.09-2.45**) (note: no information on CPAP use). Mild OSA was not associated with a greater risk of diabetes (Wang et al, 2012). In another meta-analysis of five case-control studies (n=670 subjects) in patients without cardiovascular disease or diabetes, newly diagnosed OSA was associated with greater levels of advanced glycation end products (AGEs) in the serum (Wu et al, 2018).

CPAP use and type 2 diabetes: **Potential benefit in observational studies, mixed results in RCTs**

A meta-analysis of six RCTs in patients with type 2 diabetes and OSA (n=581 patients, CPAP treatment period 12-24 weeks) reported no differences in metabolic outcomes (HbA1c, fasting glucose) between treated patients and controls, regardless of CPAP adherence (Labarca et al, 2018; Zhu et al, 2017). Another meta-analysis of 23 studies (19 prospective cohort studies, 4 RCTs) suggested that CPAP use in diabetics improved HOMA-IR scores overall, but a subgroup analysis suggested no benefits in the RCTs. This suggests that the lack of benefit in RCTs may be due to the short duration and smaller patient populations in these studies. There were no differences in fasting blood glucose and fasting insulin (though a subgroup analysis showed there were improvements in fasting insulin in the RCTs) (Chen et al, 2017).

Another study in nine RCTs in non-diabetic patients (n=443, treatment period 2-24 weeks) reported that the use of CPAP in OSA patients improved HOMA-IR but had no effect on fasting glucose levels (Abud et al, 2019; Iftikhar et al, 2013).

OSA and cancer risk: **Potential harm**

In a meta-analysis of five studies, diagnosis of OSA was associated with incident cancer. However, when adjusted for traditional risk factors (e.g., age, smoking, BMI, etc.) the results were only slightly significant (**RR = 1.40; 95%CI 1.01-1.95**) (Shantha et al, 2015).

Safety: CPAP use is associated with side effects, that, although they are minor, often lead to discontinuation.

Types of evidence:

- One meta-analysis for CPAP
- Information from the American Sleep Association

CPAP

Many studies do not report side effects from the use of CPAP. However, a Cochrane meta-analysis reported that potential adverse effects include excess pressure on the face, mask leakage, dry upper airways, stuffy nose, and inconvenience. It also reported that the use of CPAP was associated with fewer adverse events than in individuals treated with mandibular advancement devices (Giles et al, 2006).

The American Sleep Association also reports that CPAP may be associated with swallowing air, discomfort, claustrophobia, nosebleeds, skin irritation, infections (if the CPAP machine and mask are not properly cleaned), headaches (if the pressure is too high or you have sinus blockage), lung discomfort (if the air is too cold), dizziness, and shortness of breath. Most of these side effects are mild and may be mitigated by the proper use of the CPAP machine. However, they could result in lack of adherence.

Drug interactions:

None reported for CPAP use

Sources and dosing:

CPAP machines are available online or through a visit with a sleep specialist. There are many different brand names and types of CPAP devices. The devices that go directly into the nostrils, rather than mouth/nose masks appear to be more effective. In addition, some CPAP devices come equipped with a humidifier to prevent nosebleeds. The best CPAP device will be largely based on personal preference. Greater than 4 hours per night on average is considered good adherence.

Research underway:

There are more than 400 trials ongoing using CPAP for OSA (link). One six-month study with 304 patients with cognitive impairment and OSA is ongoing (NCT04335994).

Search terms:

CPAP + cognition (meta-analysis), diabetes (meta-analysis), cardiovascular (meta-analysis), mortality (meta-analysis)

sleep apnea + Alzheimer, cardiovascular (meta-analysis), metabolic syndrome (meta-analysis), diabetes (meta-analysis), obesity (meta-analysis), ApoE4, cancer (meta-analysis)

Websites visited:

- Clinicaltrials.gov
- Pubmed
- Drugs.com