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SLEEP APNOEA IN THE ELDERLY: A GREAT CHALLENGE FOR THE FUTURE

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Abstract

Due in part to overall improvements in health, the population of elderly individuals is increasing rapidly. Similarly, obstructive sleep apnoea (OSA) is both gaining increased recognition and also increasing due to the worldwide obesity epidemic. The overlap of OSA and aging is large, but there is strong plausibility for causation in both directions: OSA is associated with pathological processes that may accelerate aging and aging related processes; aging may cause physical and neurological changes that predispose to obstructive (and central) apnoea. In addition, the common symptoms (e.g. excessive daytime somnolence, defects in memory and cognition), possible physiological consequences of OSA (e.g. accelerated cardiovascular and cerebrovascular atherosclerosis), and changes in metabolic and inflammatory markers overlap with the symptoms and associated conditions seen in aging. There is also the possibility of synergy in the effects of these symptoms and conditions on quality of life, as well as a need to separate treatable consequences of OSA from age-related complaints. Taken together, the above make it essential to review the interaction of OSA and aging, both proven and suspected. The present review examines some aspects of what is known and points to the need for further investigation of the relationships, given the large number of potentially affected subjects.

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1. Introduction:

International trends show a world population that is becoming older(1) but also healthier with a postponement of disabilities(2). A potentially important source of unrecognized morbidity in this group is obstructive sleep apnoea (OSA). OSA is associated with multiple health consequences, including neurological dysfunction (sleepiness and decreased cognitive function)(3), vascular disease (hypertension, cardiac and stroke)(4), metabolic dysfunction (type 2 diabetes)(5), depression(6), and cancer(7, 8). Many of these putative consequences of OSA overlap with changes seen in aging(9). This has motivated speculation on the bidirectional causal relationships that could exist between these overlapping conditions. Further complicating the science is that symptomatic OSA is clinically more prominent, although not less common, in middle age than in the elderly. It may also cause progressive damage over time that manifests only later, while OSA itself may change character and become less evident with aging(10).

OSA is very common in late life, especially in the mild-moderate range of severity, where its health consequences have not been conclusively demonstrated. However, if one accepts widely used criteria such as having an apnoea-hypopnoea index (AHI) defined by >5 events/hour, OSA is found in upwards of 20-60% of adults(11). In our own series, these criteria are met in at least 50% of the elderly population(12, 13). Using definitions of OSA including hypopnea's definition (AHI defined by arousals or 3% desaturation), it may affect up to 75% of individuals >65 years(14, 15). Sleepiness also seems less prominent among the elderly, suggesting the possibility of differential susceptibility and/or disorders, despite similar event indices(16). Moreover, there is conflicting information on the health consequences of OSA in the very old (>80 years) and the impact (or lack thereof) of treatment. In this manuscript, we review available information on the pathophysiology, epidemiology, diagnostic, and treatment aspects of OSA focusing on studies that included elderly individuals, and pointing out future challenges for this emerging field.

2. Pathophysiological aspects:

OSA is characterized by recurrent obstructions of the upper airway (UA) during sleep. While it was originally thought that the obstructions were entirely the result of abnormal anatomy interacting with the loss of muscle tone that occurs during sleep(17), it is now appreciated that there can be multiple other pathophysiological contributors to the phenomenon. In one approach first proposed by Wellman et al(18), these factors are divided into contributing components: i. collapsibility of the passive airway (*Pcrit* or closing pressure); ii. responsiveness of UA muscles to respiratory stimuli; iii. arousability; and, iv. 'loop gain' (i.e. response of the respiratory controller to a transient disturbance). As a result, there would be different endotypes of OSA, each characterized by combinations/predominance of the different factors. This approach has shown promise in describing

populations of OSA patients and predicting responses to therapy(19), but it remains to be confirmed as a tool to describe the pathophysiology(20). In a complimentary approach to describing the spectrum of OSA, clinical symptoms or consequences can also play a role in defining phenotypes(21). Over the past 30 years, definitions of the OSA syndrome have required a clinical consequence such as excessive daytime sleepiness (EDS), but this is not uniformly accepted(22). Clearly, inclusion of asymptomatic individuals, in contrast to requiring both an elevated index of obstructions and sleepiness or downstream organ dysfunction, will impact the epidemiology of OSA(23).

Aging effects on the individual elements implicated in the pathophysiology have been invoked to account for the clinical observations that: a. OSA is more common in the elderly(10); b. the risk factors for OSA (e.g. obesity) are different in the elderly phenotype(24-27); and, c. symptoms and natural history may be different than in the middle-age patient(28, 29). Aging has potential effects on all of these pathophysiological factors. The ability of pharyngeal dilator muscles to respond to chemical and mechanical stimuli during sleep declines with age due to: an increased deposition of para-pharyngeal fat(30); changes in muscle activity(31); changes in lung volume(32); changes in the UA dimensions(30); increased UA resistance and collapsibility(33); and sleep fragmentation(34). Table 1 shows some possible factors associated to greater airway collapsibility in elderly. From these age-related physiological changes, two studies, one performed by Eikermann et al in 21 healthy individuals (age 18-75 years)(33), the second by Edwards et al in 10 young (20-40 years) and old (>60 years) patients with OSA(32), suggest that UA anatomy/collapsibility plays a greater pathogenic role in late-life. This effect, however, would be mitigated by a reduced ventilatory demand and feedback control sensitivity that are typical in late-life(35, 36); in contrast to the OSA phenotype of younger adults, in which the airway is less collapsible, but where higher feedback control and ventilatory demand are dominant traits(32). Similarly, there is some evidence that the elderly become less sleepy as a result of sleep disruption(37-39), and it has been suggested that some consequences of OSA (e.g. EDS), are less prominent in the elderly(40). Finally, the association of OSA with mortality seems to be stronger in the young than in the elderly, but this remains to be conclusively established.

3. Prevalence and epidemiology projection:

By 2050, 20% of world population will be older than 60 (*2019 Revision of World Population Prospects*)(1). As demonstrated by several community-based studies, the prevalence of OSA in people older than 60 ranges from 27 to 80%(11) depending on the definition and on the population studied. In sleep clinic-based series, the prevalence can be even higher(41). Furthermore, as the prevalence of OSA continues to increase due to the obesity epidemic(42), this can be expected to eventually be reflected in the elderly population(10). A recent retrospective cross-sectional study performed in Spain (projected to become the world's oldest country in 2050)(1) using 51,229 medical records, demonstrated that almost 25% of current sleep-clinic studies were performed in individuals 65 and older, 71.5% of which showed an AHI ≥10 events/hour, with a mean AHI of 38.3±7.4events/hour (41). Table 2 below shows the prevalence of OSA observed in several seminal epidemiological studies that only included older individuals.

Snoring frequency increases with age up to 50 to 60 years of age and then decreases in both men and women(43, 44). In contrast, the prevalence of OSA increases throughout the life span, becoming in late middle age at least double than that seen in younger adults. There is a plateau in OSA frequency in people 60 and above(45, 46). The difference in prevalence observed between the different studies shown in Table 2 has been attributed to the different populations studied (e.g. community based vs. sleep clinic vs. nursing home), methodologies (e.g. limited channel vs. polysomnography), and hypopnoea definitions (e.g. 4% desaturation vs. 3% desaturation and arousal). There is a critical need for these data to be reconciled, and for large scale population-based studies to be performed with agreed criteria involving a broad range of elderly patients who represent real-world patients(47). However, it is important to highlight that clinically relevant nocturnal hypoxemia or AHI cutoffs (e.g. based on an AHI of 5 events/hour or greater) that can distinguish normal from abnormal sleep breathing are still not defined or agreed upon, especially in the elderly(12). Furthermore, even though the number of apnoeas/hypopnoeas increases with age(48), their impact on EDS, quality of life (QoL), cognition, depression, cardiovascular disease, or increased mortality is still a matter of much debate(47).

4. Why sleep apnoea in elderly is a special entity?

4.1. Clinical presentation and common symptoms.

OSA is largely under-recognized and under-diagnosed in older adults(49, 50). Those that are symptomatic or are referred to sleep clinics for OSA evaluation, however, seem to have a similar presentation to that of middle-age, except that elderly patients underreport snoring as a chief complaint, tend to be less obese, are less likely to be men, and are less objectively sleepy (see Table 3). Moreover, the incidence of EDS(37), metabolic syndrome(51), hypertension(52) and mortality associated with OSA decline with age(53). While this may reflect underreporting of OSA or its sequellae in this population, survivor or collider biases (e.g. stroke may preclude participation in epidemiological studies), it also suggests that older people with OSA may not suffer the same health consequences as their younger counterparts.

OSA could present distinctly in older populations owing to differences in the underlying risk factors for OSA (e.g. UA collapsibility and reduced ventilatory control); the characteristics of breathing disturbances (e.g. central vs. obstructive); to differences in physiological responses to UA occlusion (e.g. increased chemoresponsiveness, diminished inspiratory effort, or milder cardiovascular response to arousals); or to perceptions and expectations about symptoms such as EDS. Sympathetic tone is widely found to be increased during aging(54), while the sensitivity of α/β adrenergic receptors in the heart and blood vessels is reduced(55). Similarly, heart rate (HR) variability decreases with age(56) and HR changes in response to muscarinic receptor blocking agents are blunted(57). All of which would impair the ability to react to internal stimuli such as intermittent hypoxia or arousals with changes in autonomic function(54). Lastly, fatigue, nocturia, unintentional napping, and cognitive dysfunction may be ascribed to the aging process or to other disorders(58); while retirement or living alone may allow more opportunities to compensate for the consequences of sleep disruption(59).

4.2. Choosing the best diagnostic procedure

OSA is traditionally diagnosed in the laboratory with a full polysomnogram (PSG) that captures not only the respiratory phenomenon but also the electroencephalogram (EEG) and related sleep measures. Over the last several decades it has become clear that home testing, usually with more limited monitoring and particularly without the direct measures of sleep (i.e. EEG, electrooculogram and electromyogram) can capture moderate and severe OSA(60), and is more cost-effective with a lower per-patient cost(61). The trend to rely on limited testing has been accelerated by the current COVID-19 pandemic, as laboratory testing was felt to be associated with unjustified risks for both patients and technical staff(62). There remains, however, much debate about whether limited testing is sufficient to 'rule-out' OSA(63). Probably the clinical pre-test probability of suffering from OSA is especially important even in elderly. The position of the *American Academy of Sleep Medicine* (AASM) is that a negative home test in the presence of a strong clinical suspicion should still prompt a full laboratory PSG(63). This is, however, debated, and the recommendation is not followed uniformly in many settings and countries other than the USA(64). The strongest arguments for performing laboratory PSGs are when there is a substantial differential diagnosis other than OSA, when patients, especially the infirm or elderly, are not able to self-apply testing sensors in the home, when subjects have difficulty with sleep or obtaining a suitably long test, or when there is potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation(63). These situations are particularly common in the elderly: living alone, caregiving, dementia, history of stroke, limited mobility and dexterity, and coexisting conditions like heart failure that increase the likelihood of central sleep apnoea and other causes of sleep disruption not easily identified on typical home sleep tests(65).

A growing trend has been the use of non-EEG sensors that capture surrogates of recurrent arousals or the sympathetic surges that accompany obstructive apnoea. Thus, peripheral arterial tonometry (e.g. WatchPAT(66)) has been increasingly used to diagnose OSA without a laboratory study and show good results for moderate and severe disease. Other devices that capture surrogates of arousal (i.e. body movements, pulse changes, etc.) are being explored, including wrist based, mattress or even non-contact sensors, but these have had only limited validation to date, and suffer many of the limitations of actigraphy, which is not generally considered sufficient to diagnose OSA(67). It seems likely that the fully attended laboratory PSG will continue to have utility in most cases where the diagnosis is in question.

5. Sleep apnoea impact in elderly

5.1. Symptoms and Quality of life

OSA in symptomatic patients causes daytime and sleep-related symptoms, health consequences, and decreased quality of life (QoL)(68-71). The main daytime symptom of OSA is EDS. Its impact can be measured by both objective (e.g. Psychomotor Vigilance Test or Multiple Sleep Latency Test) and subjective methods (e.g. ESS or some QoL questionnaires)(72). QoL is commonly measured by subjective, non-specific (e.g. Short-term-36 Health Survey [SF-36](73, 74)), and specific (e.g. Functional Outcomes of Sleep Questionnaire [FOSQ], Quebec Sleep Questionnaire [QSQ], Sleep apnoea quality of life

index [SAQLI](70-74)) questionnaires. As with other aspects of OSA research, the vast majority of validation studies for QoL instruments have been performed in middle-aged individuals(75-77), and their findings may not extrapolate to the elderly. This is because the perception of sleep-related symptoms and QoL is subjective(78), and could be impacted by age in a similar manner to the gender related differences seen in sleep-related QoL across all age ranges(78). One of the most important limitations in the measurement of QoL in elderly with OSA is the presence of comorbidities such as sleep fragmentation, poly-pharmacy, cognitive impairment, different social environments, lifestyle factors (e.g. retirement), and decreased physical activity, all of which could act as confounders due to their impact on both QoL and EDS(12, 79). Moreover, there is no diagnostic tool of OSA specifically validated for the elderly nor are there established definitions of “clinically relevant” OSA(12, 79).

Several studies have analyzed whether the impact on symptoms and QoL in OSA patients is the same in advanced aged compared with middle age. Appleton et al., in a study of 837 men participants 40 years and older, observed that, overall, AHI was associated with an increase in EDS -measured with the Epworth Sleepiness Scale- (ESS) and a decrease in QoL, measured by SF-36. However, this association was not observed in patients that were older than 70(80). In a similar study that Martinez-Garcia et al performed in 212 OSA patients that were divided into those over and under 65 years, both the presence of OSA and ESS>11 were associated with an important deterioration of QoL compared with reference values adjusted by sex and age in the younger group(81). In contrast, in those patients over 65, the presence of OSA or ESS>11 had only a slight impact on QoL when compared with the reference values. Variables that were better predictors of poor QoL in this age group were advanced age, medical comorbidities, oxygen desaturation, and use of psychotropic medication(81).

5.2. Cardiovascular system and prognosis

Intermittent hypoxemia (IH) and sleep fragmentation can produce alterations related to a greater cardiovascular risk such as higher inflammation status, endothelial dysfunction, arterial stiffness or an increase in oxidative stress in elderly with OSA(82). However, some studies show that the impact of these cardiovascular consequences is less severe than the one seen in younger patients. Li et al(83) observed that OSA had less impact on cerebrovascular reactivity in elderly individuals, suggesting the existence of an age-related reduction in cerebrovascular susceptibility to OSA. Similarly, Castro-Grattoni et al(84) using a murine model for OSA, concluded that cardiovascular pathological remodeling induced by severe IH was moderated by the age at which the onset of that hypoxia occurred, suggesting that deleterious cardiovascular effects may be more pronounced in younger populations reflecting age-related change in cardiovascular structural integrity(84). This finding could explain the disparity found in OSA longitudinal studies on the incidence of cardiovascular events and their prognosis in late life. At the same time, it is worth mentioning that the vast majority of longitudinal studies, both on clinical and population-based samples, demonstrate that the presence of untreated severe OSA (AHI>30 events/hour) can increase cardiovascular morbidity and mortality in the elderly even in advanced ages Table 4)(85-90). However, it seems that this increase in the incidence of fatal and non-fatal cardiovascular events is more pronounced in the cerebral (mainly stroke), than in the coronary circulation (e.g. angina and

myocardial infarction) where there is no strong evidence of a greater risk(91-93). Figure 1 shows the increase in the incidence of all-cause and cardiovascular mortality due to the increased cerebrovascular and heart failure mortality but not due to ischemic heart disease mortality in elderly with severe non-treated OSA compared with mild-to moderate OSA or OSA treated with CPAP in a total of 969 elderly patients sent to a sleep units with suspected OSA(87).

To explain this phenomena, a few years ago the 'preconditioning hypoxia hypothesis' promulgated by Lavie et al gained notoriety, after they observed that the presence of OSA did not produce excess mortality in the elderly as opposed to younger individuals(94, 95). This was attributed to the fact that a low-grade, continuous IH produced coronary vascular collaterals through the activation of some key molecules such as hypoxia-inducible factor-1α and vascular endothelial growth factor (VEGF). The majority of studies on preconditioning hypoxia have been carried out in coronary circulation and the formation of this neovascularization has indeed been observed(96). However, in cerebral circulation the vascular regulation may be different. Thus, according to Wegener et al(97), cerebrovascular control seems to be governed more by neuro-hormonal factors than by neovascularization, which may at least partially explain the different action of IH in both types of circulations and thereby explain the different effects seen in clinical studies(97). On the other hand, some authors point out that with age the effect of IH on circulation may be affected(98). Along these lines, Dalmases et al(99) suggest that brain oxidative stress in aged rats is lower than in young rats in response to recurrent apnoeas mimicking OSA. This could be due to the different partial pressure of oxygen (PtO2) response observed between age groups and the increased antioxidant expression in aged rats(99). Table 4 shows the most significant characteristics and the most relevant results of the impact of OSA on the cardiovascular system in studies that exclusively included elderly patients.

5.3. Cognitive function:

OSA is believed to cause cognitive impairment by EDS or drowsiness from sleep fragmentation(100-102), neurological damage due to intermittent hypoxia(100, 103, 104), as well as from contributing effects of obesity, hypertension, diabetes, anxiety, or depression(100, 105), among others. For the most part, there is substantial evidence suggesting weak to strong associations between OSA and cognitive performance in middle age on measures of attention(106-109), memory(110-115), reaction time(115-117), processing speed(109), and executive function(106, 107, 109, 110, 113-115). Studies that restricted their populations to older adults (i.e., >60 years) generally show weaker, if any, links to impaired cognition(118-122). An important meta-analysis of several of these studies performed by Cross et al showed a small association between OSA severity and combined measures of cognition, processing speed and memory(123). However, this effect appeared to be driven by selection bias, with small case-control studies from sleep clinics observing the greatest associations, while larger cohort studies from community samples demonstrating no effects(123). An interpretation by the same authors is that the link between OSA severity and impaired cognition may be most pronounced in those seeking specialist assessments while absent in asymptomatic older adults or those with unrecognized symptoms. In this latter group, a recent study from Sforza et al in a randomly selected, population-based study

of 812 healthy older adults, found that sex and depression score -with a weak contribution of obesity-, but not AHI severity, were the only significant factors affecting the presence of EDS(124). This finding underlines the link between the perception of sleepiness and reduced mood and QoL in OSA patients, effectively showing mood disorders impacting cognition more than typical OSA-related symptoms in some cases. However, although a number of studies have been carried out on the link between OSA and depression(125), the results in the elderly have so far been inconclusive with most studies reporting no associations(38, 126).

Longitudinal studies from Blackwell et al in the Osteoporotic Fractures in Men (MrOS) (127), Martin et al in the PROgnostic indicator OF cardiovascular and cerebrovascular events (PROOF)(128), and Lutsey et al in the Atherosclerosis Risk in Communities (ARIC) (129) cohorts have also shown null(129) to modest associations with global measures of cognition(127) and attention(128), which in some cases were only evident in patients with severe OSA. In the ARIC cohort, some differences between subjects examined at follow-up and those excluded after the first cognitive and/or polygraphic studies were found (i.e. AHI of the lost to follow-up subjects was higher, and they differed in the rates of obesity and hypertension), which suggests potential selection biases in those studies that used non-random samples of healthy elderly with normal cognition. In contrast, studies examining the association between OSA and dementia outcomes (i.e. decline to mild cognitive impairment [MCI] and dementia or Alzheimer's disease [AD]) have been notoriously more consistent in their findings. Yaffe et al(130) in her seminal prospective study of OSA and cognition among women participating in the osteoporotic fractures (SOF) cohort, found that older adult women with OSA had an 85% higher risk of developing MCI/Dementia at follow-up. The expected high prevalence of Alzheimer disease (AD) in this age group (mean age 82 at inclusion) and absence of AD biomarker assessments do not preclude the possibility of reverse causation (i.e. preclinical or prodromal AD increasing the incidence of OSA). These findings however, have been replicated in subsequent studies among older male veterans(130, 131), severe OSA patients from the ARIC cohort(132), and several large national health insurance studies(133-135). We note here that several of these studies used medical records or administrative claims to make the diagnosis of OSA, which in most cases incorporates abnormal sleep breathing events alongside associated symptoms (e.g. EDS, stroke) or cardiovascular consequences that prompted these subjects to seek medical treatment. Thus, the link between OSA and cognitive decline to MCI or AD in these cases might also be driven by those seeking specialist assessments(136) and potentially absent in asymptomatic patients. For a systematic review of the above studies and findings see(136).

6. Effect of CPAP treatment of Sleep apnoea in elderly

6.1 Symptoms and Quality of life:

There is a clear evidence of CPAP efficacy in improving QoL in OSA patients particularly in those that are most symptomatic. However, the number of studies that focus on elderly adults is still small. Most studies report positive effects in both EDS (measured by EES) and QoL measured by different tools (SF-36, SAQLI, Fatigue Severity Scale [FSS], Patient-Health Questionnaire-9 [PHQ-9] and FOSQ)(137, 138). However, CPAP improvement is

less apparent in elderly than in younger OSA patients(80), probably because the clinical impact of OSA on QoL is less pronounced(81).

With regards to randomized controlled trials (RCTs), only four studies have analyzed the effect of CPAP on EDS or QoL (as a primary(139–141) or as a secondary outcome(142)) in elderly OSA patients. In the PREDICT trial(140), 278 elderly patients (>65 years) were randomly allocated in parallel groups to receive either CPAP or best supportive care. EDS reduction at 3 and 12 months was greater in those patients with higher CPAP usage and those with higher baseline EES. However, objective sleepiness (measured by the Osler test) was reduced at 3 months but not at 12 months. Similarly, two methodological-mirrored studies from Martinez-Garcia and Ponce et al(139, 141) (n=224 and 145, respectively) performed in elderly OSA patients (≥70 years) concluded that treatment with CPAP reduced EES by 3.4 and 2.6 points, respectively. These two studies also observed a significant reduction in snoring, witnessed apnoeas, choking, and nocturia. In contrast, Dalmases et al did not find differences in EES in their small RCT aimed to randomly comparing 33 patients(142).

Findings from the same four RCTs with regards to QoL change are more controversial. In the PREDICT trial from McMillan et al(140), no significant change in the SF36 at 3 and 12 months was found except for the energy/vitality domain, whereas a clear improvement was observed using the sleep-specific SAQLI at both 3 and 6 months. Similarly, the two Spanish RCTs from Martinez-Garcia and Ponce(139, 141), using the sleep-specific QSQ, observed a significant improvement in all 5 domains (hypersomnolence, diurnal symptoms, nocturnal symptoms, emotions and social interaction) in severe OSA patients, but only in the nocturnal symptoms and emotions in the moderate group. Improvements in QSQ's nocturnal symptoms and social interaction were also observed in the Dalmases et al trial(142). To conclude, a recent meta-analysis(143) of RCTs on CPAP efficacy for improvement in sleepiness and QoL (which included the four RCT previously discussed) concluded that CPAP treatment was associated with a decrease in 2.62 (95%CI, 1.93 to 3.30) points in EES and an improvement in all the QSQ domains although the quality of evidence was considered low using the GRADE system. Therefore, larger and longer follow-up studies are needed.

6.2. Cardiovascular system and prognosis:

The number of clinical studies that focus on the cardiovascular system among elderly OSA patients is also very small(85–90, 140, 141). Of these, only three are clinical trials(87, 140, 141), and none of them included a cardiovascular measure as the primary outcome. Table 4 shows the main characteristics and results of CPAP treatment on different risk factors and cardiovascular events, both in observational studies and clinical trials that included exclusively elderly adults. Regarding the clinical trials, neither of the two RCTs performed by Martinez-Garcia(87) and Ponce et al(141), in OSA patients 70 and older, observed changes in systolic (SBP) or diastolic blood pressure (DBP) levels after three months of CPAP treatment. In contrast, the study performed by McMillan et al(140), in OSA patients 65 and older, observed that CPAP achieved a significant reduction in total and low-density lypoproteins (LDL) cholesterol levels at 3 months of treatment (which were not maintained

at 12 months of follow-up), as well as in SBP of 3.7 mmHg at 12 months. However, these findings did not translate into a clinically relevant reduction in the incidence of cardiovascular events at the one year of follow-up (most of which were episodes of atrial fibrillation)(140).

Among the observational studies, the largest to date has been published by Martinez-Garcia et al(87) (Figure 1) in a multicenter cohort of 969 elderly individuals who attended a sleep clinic for suspected OSA. After dividing the subjects into 4 groups: those without OSA (AHI<15 events/hour), those with mild-moderate disease (AHI ≥15 and <30 events), severe disease (AHI ≥30 events) treated and non-treated effectively with CPAP; they observed that the group with good adherence to CPAP showed a decrease in the risk of total cardiovascular death, stroke and heart failure to values similar to that seen in the control group without OSA. However, no effect was observed on fatal coronary events. In an attempt to delve into the analysis on the differences found between the effect of CPAP on the incidence of cerebrovascular and coronary events, Catalan-Serra et al(85), in a secondary analysis using the same series of patients, divided the sample into those who had and had not suffered a previous coronary and cerebrovascular event, respectively. Both series were followed, dividing the patients into the 4 groups already described according to the severity of OSA and CPAP treatment. Again, the results were similar, and while CPAP seemed to protect against new non-fatal cerebrovascular events in the elderly, it had no effect on coronary events.

A meta-analysis published by Yan et al(144) (9), which included 7 studies, both observational and RCT, observed that those elderly patients with severe OSA undergoing CPAP treatment had a lower cardiovascular risk (HR, 0.49; 95%CI, 0.36 to 0.66), although they only included 4 studies in this analysis. On the other hand, these subjects also presented lower mortality HR, 2.22 (95%CI, 1.64 to 3.01), although only 3 studies were included in this analysis. In both analyzes, due to its size, the study by Martinez-Garcia et al with 969 included individuals had a great influence on the results(87).

6.3 Cognitive function

The number of RCTs studies that focus exclusively on cognition as a primary or secondary outcome among elderly OSA patients is also very small (Table 5). Nonetheless, a similar picture to that of observational studies on the relationship between OSA and cognition described in section 5.3 emerges: with single-center small-sample trials from Aloia and Dalmases et al (n=12 and n=33)(142, 145) showing the greatest improvements in attention, psychomotor speed, memory and executive function; in clear contrast to the larger, multicenter clinical cohorts from Ponce, Martinez-Garcia and McMillan et al (n=145, 224 and 278 respectively) where CPAP showed significant improvement only in attention/working memory(139) or null effects(140, 141).

The low adherence and short CPAP usage in the McMillan et al RCT(140), as well as the presence of comorbidities that affected cognition might have diluted the treatment effect in this trial. In addition, OSA participants were starting from a very high cognitive baseline indicating potential ceiling effects (i.e. cognitive scores were often within the age-adjusted normative range). Compliance, however, was good (>70%) with at least 4

h-day in both Ponce's and Martinez-Garcia et al trials(139, 141), showing levels of CPAP use similar or higher to those observed in middle-aged patient trials. It is noteworthy that Martinez-Garcia et al trial only included severe OSA patients, suggesting that cognitive impairment is more closely associated with severe OSA than with moderate OSA in late-life, and so a cognitive improvement with CPAP would be more likely only in the former. Of particular interest from the same trial are the findings that CPAP treatment was associated with marked improvements in anxiety and depression as measured by the Hospital Anxiety and Depression Scale (HADS). With regards to these changes in mood, the same meta-analysis(143) described on section 6.1, which pooled four of the RCT previously discussed, found that CPAP treatment was associated with a decrease of 0.94 points in the HADS-depression domain, with subgroup analyses showing better results in studies including populations ≥70 years old. Whether some of the observed improvements in cognition were mediated by improvements in mood in the elderly was not reported in any of the trials.

To conclude, a recent quasi-experimental study from Richards et al(146) with two comparison groups (pooled mean age of 70.1±7.9 years): 1) among prodromal AD patients: an MCI, OSA, and CPAP-adherent group (MCI + CPAP ≥4 h mean CPAP use per night for 1 year, n=29); and, 2) an MCI, OSA, CPAP-non-adherent group (MCI −CPAP <4 h mean CPAP use per night for 1 year, n=25), demonstrated significant improvements in psychomotor/cognitive processing speed using the Digits Symbol in the MCI + CPAP group *vs* the MCI −CPAP group after adjustment for age, race, and marital status(146).

6.4. CPAP adherence in the elderly

One of the key factors for a positive effect of CPAP on the cardiovascular prognosis is good adherence to the treatment, even in elderly patients(147–149). Although there is some debate regarding whether adherence to CPAP is different in young and elderly people, it is certain that the elderly can have characteristics that could be related to reduce adherence: living on their own, chronic pain, cognitive impairment, dental problems, etc(150, 151). A study undertaken exclusively on OSA patients aged over 65 demonstrated that the mean adherence to CPAP treatment fell below acceptable limits – i.e., less than 3 hours per day (2.9 ± 1.7 hours) –, particularly in patients aged 80 and older. In fact, only 23% of the patients used CPAP for at least 4 hours a day, on average, making it difficult to evaluate any positive effect of CPAP in the oldest old(152).

7. Central sleep apnoea in the elderly.

Thus far, most of the discussion has centered around OSA. The occurrence of events that transiently reduce breathing, but are not due to obstruction, i.e. central sleep apnoea (CSA), is a confound that affects very few of the younger patients coming to clinical attention in sleep clinics, with the exception of obvious neurological conditions such as genetic syndromes and disruptions of the neuro-respiratory apparatus(153–156). However, in the elderly, congestive heart failure is common, and upwards of 50% of patients with a reduced ejection fraction show the pattern of central apnoea called Hunter Cheyne Stokes (a waxing and waning respiration, with minimal obstruction and a somewhat longer period

than OSA)(157). CSA may overlap with OSA and can be difficult to extricate(158, 159). The importance of distinguishing the disorders is twofold. CSA has not been shown to have the same clinical associations as OSA, and may be an incidental manifestation of the cardiac dysfunction that is not implicated in the clearly observed increased mortality(160). In addition, CSA does not respond to the same therapy as OSA: Hunter Cheyne Stokes in heart failure has been resistant to positive airway pressure therapy, and even shown an increased mortality on some variations of PAP therapy (ASV)(161). The most effective therapy for Hunter Cheyne Stokes respiration has consistently been shown to be treatment of the cardiac dysfunction(162). The other major form of Hunter Cheyne Stokes and central apnoea is that associated with neurological dysfunction, such as strokes, which are clearly common in the elderly. While there are data supporting that untreated OSA leads to recurrent stroke(163, 164), the data for treating CSA associated with stroke is much less clear(165, 166). Finally, while few studies have exclusively addressed Hunter Cheyne Stokes or central apnoea in the elderly, these are the subjects with the greatest incidence of the underlying heart failure.

8. Other therapeutical options.

The most used therapy for OSA is the application of continuous positive airway pressure(167). This therapy, originally proposed by Colin Sullivan in 1981(168), is remarkably effective, as it appears to “splint” the upper airway and eliminates the obstructive events. However, there is increasing data showing that, even in ideal and symptomatic populations, it is used much less than would be anticipated from its efficacy; most clinical trials using CPAP average less than 4-5 hours of therapy, much less than the desirable 7-8 hours of good sleep recommended(169). However real-world studies using big data have shown better CPAP compliance(170). In the elderly, there is conflicting evidence, but CPAP usage may be higher than(137), or as poor as(140), in younger subjects with OSA in clinical populations(137). In contrast, usage may be much lower in epidemiological studies where asymptomatic elderly are being recruited for therapy, or to test an effect on dementia(171). Thus CPAP is rarely successfully implemented in clinical elderly populations with minimal symptoms where the rationale for therapy is only the associated (presumed) consequences of OSA discussed above (hypertension, memory loss, perceived risk of or early evidence of AD). While it makes sense to try other therapies for OSA, such as mandibular advancement devices, positional therapy and other modalities, most of these are less predictable in their efficacy than CPAP and only recently are being subjected to monitoring of use and long term studies in the elderly. Many clinicians balance the difficulty and discomfort of OSA therapy against the lack of proven benefit in asymptomatic populations (including the elderly), and chose to treat only willing patients and leave the others untreated for anything other than severe OSA. Clinical trial showing clear benefit on cardiovascular and neurological long-term outcomes and higher levels of acceptance of therapy will be needed to change this.

9. Conclusions and Future challenges

The epidemiology of OSA and its apparent consequences overlap heavily with the complaints of aging populations and common chronic conditions seen in the elderly. However, the number of elderly patients in sleep clinics referred due to OSA suspicion

is gradually rising, and it is predicted to continue rising in the next future. There is strong biological plausibility for causal associations between these common conditions, in both directions: OSA, perhaps though intermittent hypoxia or through sleep disturbance, could well cause accumulated neurological damage and/or accelerate AD pathology; conversely, the neurological deterioration that underlies aging and aging-related conditions like AD could easily affect the regulation of breathing and some of the mechanisms causing OSA. Alternatively, having OSA related consequences and symptoms could act on quality of life and exacerbate many of the most troublesome complaints of aging and its chronic conditions, independently of impacting their progression. However, at the present time there are insufficient data to prove causality of the associations between OSA and aging pathology; to do so would require a successful intervention for either condition as well as a long term follow-up. The implication is that when confronted with an elderly subject with OSA, one should treat severe symptomatic OSA as in all other groups. The implications for moderate, mild and asymptomatic disease are less clear. A rational approach is to offer therapeutic trials of CPAP and possibly mandibular advancement devices when disease is mild-moderate or minimally symptomatic, but not be too insistent on continuing therapy if the patient is not aware of improvements. The definitive approach will depend on yet-to-be performed clinical trials and improvements in obtaining long-term adherence to current or novel treatments. A better definition of the OSA phenotype in the elderly, with improved clinical criteria as well as novel treatment outcomes (e.g. novel AD blood biomarkers of neurodegeneration) are also important future directions. Table 6 shows some of most important future challenges that need to be urgently tackled in order to increase our understanding of OSA in these patients. Meanwhile, some important take home-messages can be stated on the management of OSA in the elderly (Table 7).

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Take Home Message:

Current evidence supporting obstructive sleep apnoea (OSA) in the elderly as a different clinical entity is still insufficient. In the meantime, older patients should be diagnosed and treated in the same manners as their younger counterparts with a particular focus on cognition and multi-morbidity.

Short sentence:

From clinical, prognostic and therapeutic points of view, obstructive sleep apnoea (OSA) in the elderly is both similar to, but also shows differences from, the syndrome in younger individuals and may contribute to unique disorders of the elderly. There are many gaps of knowledge of OSA in the elderly; the large number of aging people all over the world and the frequency of OSA make the overlap of these conditions an important area for future research

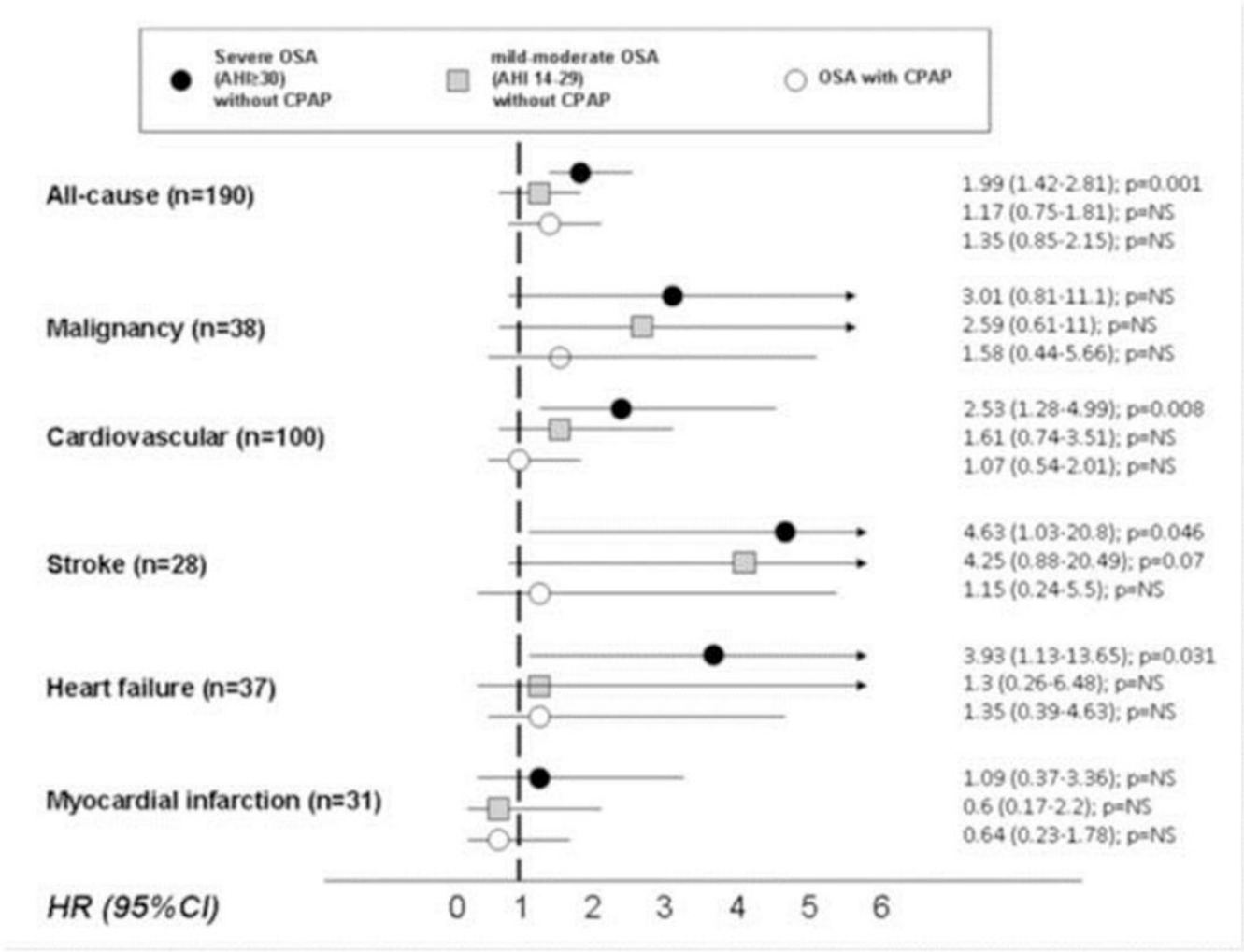

Figure 1.

Risk of cardiovascular mortality due to different causes in 939 elderly patients with severe OSA without CPAP (black circle), mild-moderate OSA without CPAP (grey square), and OSA with (good adherence to) CPAP (white circle). *Martínez-García MA, et al. American Journal of Respiratory and Critical Care Medicine 2012; 186(9): 909-16. With permission.* OSA: Obstructive sleep apnoea, CPAP: Continuous positive airway pressure; AHI: Apnoea-hypopnoea index; NS: non-significant; HR: Hazard ratio; CI: Confidence interval

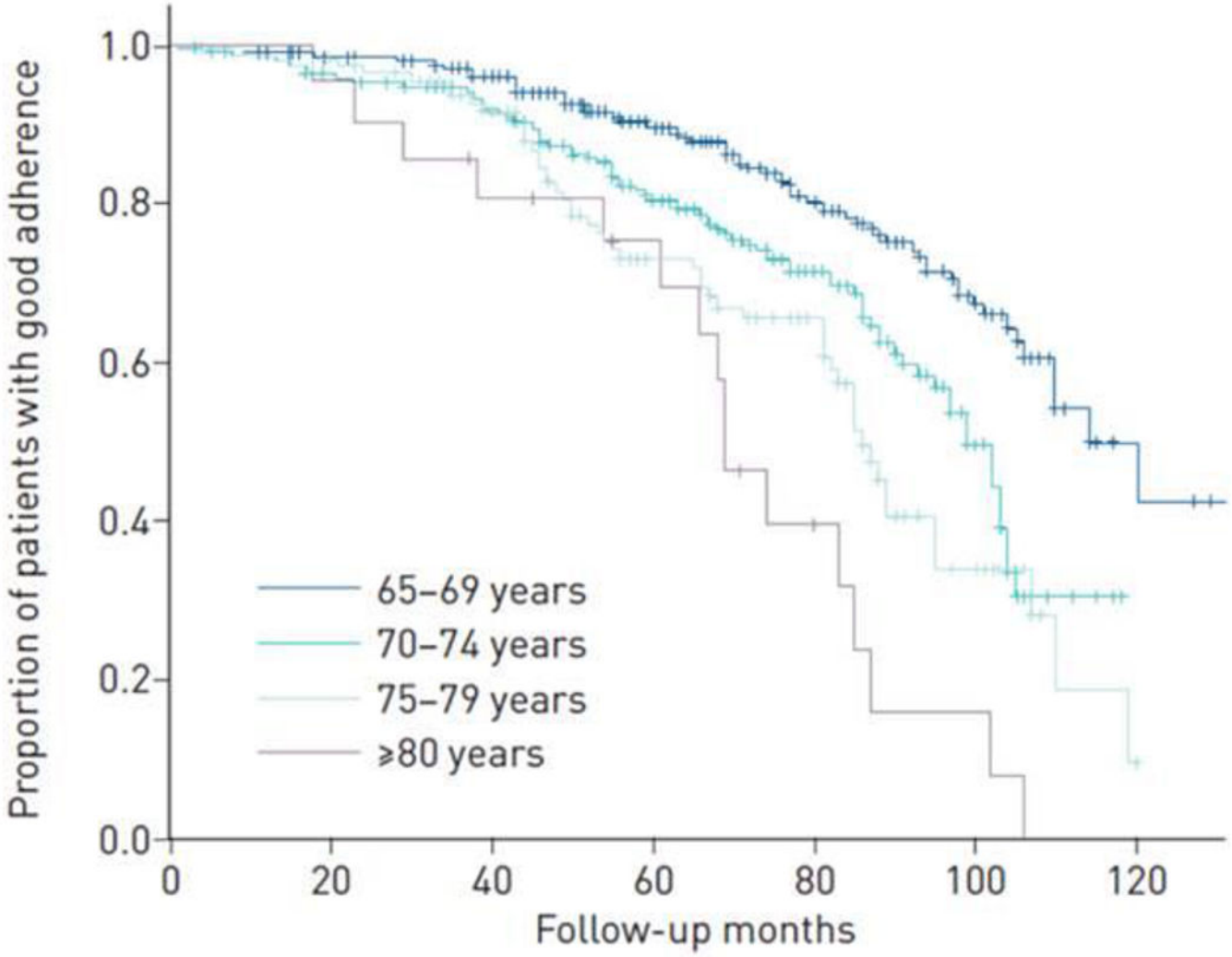

Figure 2.

Kaplan-Meier curve with the proportion of elderly patients with good adherence (at least 4 hours.day) depending on the age (between 65-69 yo, between 70-74 yo, between 75-79 yo, at least 80 yo). *Martinez-Garcia et al. ERJ Open Res. 2019 Mar 4;5(1). pii: 00178-2018, with permission*.

Table 1.

Pharyngeal collapsibility in elderly

Airway resistance during sleep(33, 172)	Increased
Deposition of parapharyngeal fat(173)	Increased or Decreased
Pharyngeal musculature activity(30)	Decreased
Lung elastic recoil (affects lung volume and tracheal traction)(32)	Decreased
Upper airway dimensions (fat deposition, structure changes, loss of teeth, etc.)(173)	Decreased
Sleep fragmentation(34)	Increased
Alterations of the pharynx muscular dilatory reflexes(174)	Increased
Respiratory instability during sleep (central events)(175)	Increased

Table 2.

Prevalence of obstructive sleep apnoea in studies exclusively of the elderly.

Author, year	n	Age, yrs	Females %	BMI Kg/m^2	Population	AHI≥5 %	AHI≥10/15 %
Ancoli-israel(176)	233	65-101	65	30.6 ± 6	Nursing home	70	--
Ancoli-Israel(177)	385	65-99	62.6	21.1 ± 4	Community	81	62
Bixler(48)	75	65-100	0	29.4	Community	31	24
Young(45)	3448	60-99	--	--	Community	54	20
Carskadon(178)	40	62-86	55	--	Community	36	--
McGinty(179)	26	61-81	0	--	Community		62
Hoch(180)	105	60-91	52	--	Community	26	13
Martinez-Garcia(41)	12,468	+65	--	--	Clinical series	71.5	--

BMI: Body mass index; AHI: Apnoea-hypopnoea index;

Table 3.

Characteristics of older adults with obstructive sleep apnoea (OSA)

Typical presentations (i.e. overweight male with loud snoring, nocturnal choking, nocturia, excessive daytime sleepiness, and cardiovascular consequences) do exist.
They are less likely to be men (particularly after menopause in women).
The association with obesity and neck circumference is present but less prominent, and snoring as a chief complaint is underreported.
There are decreased reports of excessive daytime sleepiness and fatigue.
Health consequences are rated differently for the same level of OSA (i.e. less debilitating), while cardiovascular consequences of OSA are less evident.
Atypical presentations like secondary enuresis and nocturia, cognitive impairment, ophthalmic conditions and repeated falls are common.

Table 4.

Main characteristics and results on the impact of OSA and the effects of CPAP on different risk factors and cardiovascular events, both in observational studies and clinical trials that only included elderly

Observational studies						
Study	**Methodology**	**Design**	**Mean age ± SD**	**Main outcome**	**Follow-up**	**Cardiovascular results**
Martinez-Garcia et al(87)	Multicenter Prospective (≥65 yo)	AHI<15 (n=155) AHI 15-29 (n=108) AHI≥30 without CPAP (n=173) OSA with CPAP (n=503)	70.8 ± 4.6	Cardiovascular death	Median 69 (IQR, 48-87 mo)	AHI≥30 without CPAP risk; OR 2.53 (95%CI, 1.28-4.99) respect to control group OSA with CPAP risk; OR 1.07 (95%CI, 0.54-2.01) respect to control group
Catalan-Serra et al(1)(85)	Multicenter Prospective (≥65 yo)	AHI <15 (n=141) AHI 15-29 (n=99) AHI>30 without CPAP (n=149) OSA with CPAP (n=470)	71.1 ± 4.9	Nonfatal stroke	Median 72 (IQR, 50-88.5) months	AHI≥30 without CPAP risk; OR 3.42 (95%CI, 1.37-8.52) respect to control group OSA with CPAP risk; OR 1.02 (95%CI, 0.41-2.56) respect to control group
Catalan-Serra et al(2)(85)	Multicenter Prospective (≥65 yo)	AHI <15 (n=138) AHI 15-29 (n=84) AHI≥30 without CPAP (n=146) OSA with CPAP (n=426)	70.9 ± 5.1	Non-fatal coronary disease	Median 71 (IQR, 51.1-89) months	AHI≥30 without CPAP risk; OR 2.05 (95%CI, 0.65-6.47) respect to control group OSA with CPAP risk; 1.07 (95%CI, 0.34-3.30) respect to control group (IAH<15)
Lopez-Padilla et al(86)	Single-center (≥80 yo)	CPAP (n=79) vs no CPAP (n=76)	81.5 ± 1.7	All-cause mortality (28% cardiovascular)	Median 53 (IQR 41-77 mo)	Decrease all-cause mortality adjusted by other CV risk factors, age, gender, and BMI. Treated OSA, HR 0.46 (95%CI, 0.27-0.78)
Ou et al(90)	Single-center (≥60 yo)	CPAP (n=36) vs no CPAP (n=88)	72.8 ± 6.2	Fatal and non-fatal death from CVE	Median 5 (2.5) (range 1-8 yrs)	Reduce mortality in moderate-severe OSA no treated Survival rate CPAP vs no CPAP; 5.6 vs 21.6%; p=0.035
Nishihata et al(89)	Single center (65-86 yo) Retrospective AH≥15 Prior hospitalization due to CVD	CPAP (n=64) vs no CPAP (n=66)	65-86 yo	All cause death or admission for relapse of CVE	Mean 32.9 ± 23.8 months	HR 5.13; 95%CI, 1.01-42 in moderate-to-severe OSA not treated with CPAP CPAP normalice the risk
Muñoz et al(88)	Single center 70-100 yrs old Population-based	394 non-institutionalized CPAP-free patients	70-100 yo	Incident of first-ever stroke	6 years	AHI≥30 vs control HR, 2.52; 95%CI:1.04-6.01
Randomized Clinical Trials						
McMillan et al(140)	Multicenter (≥65 yo)	140 CPAP vs 138 no CPAP	71.1 ± 3.7	ESS and cost-effectiveness	12 months	Reduced total and LDL colesterol at 3 months (p=0.048) in the CPAP group (not at 12 months) Improvement in SBP (−3.7; 0.2-7.2 mmHg; p=0.04) at 12 months No changes in incident CVE
Martinez-Garcia et al(139)	Multicenter (≥70 yo) Severe OSA	115 CPAP vs 109 no CPAP	75.5 ± 3.9	QoL (QSQ)	3 months	No changes in SBP and DBP levels
Ponce et al(141)	Multicenter (≥70 yo) Moderate OSA	73 CPAP vs 72 no CPAP	74.9 ± 4.6	ESS	3 months	No changes in SBP and DBP levels

AHI: Apnoea hypopnoea index; CPAP: Continuous positive airway pressure; QoL: Quality of Life; QSQ: Quebec Sleep Questionnaire; OSA: Obstructive sleep apnoea; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CE: cardiovascular events: LDL: Low-density lipoprotein; HR: Hazard ratio; CVD: Cardiovascular disease; ESS: Epworth Sleepiness Scale

Table 5

Neurocognitive impairment results in randomized clinical trial on the effect of CPAP in exclusively elderly series

Study (RCT)	n	Age	CPAP vs no-CPAP					
			Digit Span	Digit Symbol test	HADS depression	HADS anxiety	TMT-A	TMT-B
Aloia et al(145)	12	64.8 ± 4.7	-	5.74 (C95%, 1.69 - 9.79), p<0.001	-	-	-	1.8–48.0 (6.8 <0.05
Dalmases et al(142)	33	71.3 ± 5.5	0.79 (CI95%, −0.30, 1.88), N.S	5.74 (CI95%,1.69, 9.79), p<0.01	−0.42 (CI95%:−1.84, 0.99), N.S	−0.43 (CI95%:−1.0, −1.88), N.S	−2.68 (CI95%:−16, 10.6), N.S	−47.64 (CI95%: −81.8, −13.4), p<0.01
Mc Millan et al(140)	278	71.1	-	1.1 (CI95%,−0.6, 2.7) N.S.	−0.4 (CI95%: −1.0, 0.3); N.S	−0.2 (CI95%: −0.9, 0.5); N.S	-	6.2 (CI95% −3.4, 15.8); N.S
Martinez-Garcia et al(139)	224	75.5 ± 3.9	−0.08 (CI95%, −0.55, 0.4; N.S	−1.43 (CI95%, −2.84, −0.02); p<0.05.	1.98 (CI95%: 1.18-2.7), p<0.001	1.19 (CI95% 0.22-2.16); p=0.016	10 (−4–34) versus 0 (−16–11); p=0.029)	−9.4 (95% CI −24–5.3) N.S
Ponce et al(141)	145	74.9 ± 4.6	−0.2 (CI95%, −0.6, 0.9); NS	−0.9 (CI95%, −2.5, −4.3) N.S	0.2 (CI95%, −0.9, −0.5), N.S	0.8 (CI95%, 0.2–1.7), N.S	−5.6 (CI95%, −14.3–3), N.S	−9.4 (95% CI −24–5.3). p<0.05
Richards et al(146)	54	70.1 ± 8.3	-	1.68 (CI95%:0.73-2.62), p<0.05	-	-	-	-

HADS: Hospital Anxiety and Depression Scale; TMT: Trail making Test; CPAP: Continuous positive airway pressure, CI: Confidence interval; RCT: Randomized controlled trail.

Table 6.

Future challenges in obstructive sleep apnoea (OSA) in the elderly

To develop better polysomnographic parameter (beyond AHI) for evaluating OSA Validation of specific questionnaires (neurocognitive, diagnostic prediction, hypersomnia)
Validation of simplified diagnostic sleep test and development of new devices specifically for the elderly
Analysis of CPAP effectiveness (phenotypes of responders) in very old patients (more than 80 years old) and evaluation of the consequences of the withdrawal of CPAP in extreme old age
Educational programs aimed specifically at elderly people
To explore other therapeutic possibilities beyond CPAP
To analyze (especially by randomized controlled trials) the impact of OSA and the effect of CPAP on cardiovascular outcomes and mortality as well as Alheimer’s disease risk
Impact of comorbidities in the management of OSA in elderly

Table 7.

Some messages with clinical implications about obstructive sleep apnoea (OSA) and CPAP treatment in the elderly

OSA prevalence increases with age
Since it is not known what is the cut off in the apnoea-hypopnoea index and Epworth sleepiness scale that should be considered as pathological, it should be used as in younger individuals
A clinical history that includes findings specific to elderly people must be always undertaken
Sleepiness must not be considered a physiological situation in elderly. However it is not be assumed that it must be associated to OSA
The clinical picture of OSA in elderly is different than that seen in younger patients. Neurocognitive symptoms are especially prevalent
Full polysomnography is the gold standard in the diagnosis of OSA in elderly. However simplified tests can be used in patients without important comorbidities.
Randomized clinical trials demonstrated that CPAP is effective in symptomatic moderate to severe OSA patients
It is not known what happens in extreme old age (over 80 years) when the compliance to CPAP is very low, therefore a less aggressive approach may be appropriate when recommending treatment with CPAP