

# Sleep-disordered breathing in the elderly: is it distinct from that in the younger or middle-aged populations?

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## Introduction

Sleep-disordered breathing (SDB) is characterized by repetitive suspension or reduction of breathing, causing nocturnal intermittent hypoxia, which is followed by re-oxygenation. There is a growing evidence that SDB, particularly obstructive sleep apnea (OSA), is associated with cardiovascular (CV) risk factors, morbidity and mortality (1). Continuous positive airway pressure (CPAP) is the gold-standard for management of SDB, and its adequate use has a remarkable efficacy in the management of CV diseases (1). Currently, the data available regarding SDB is related to young or middle-aged patients and there is a lack of evidence in the elderly. Hence, there is a critical need for large scale population-based studies and clinical trials involving a broad range of elderly patients who represent the real-world patients in the aging society (2). The relationship between SDB and CV risk factors, morbidity, and mortality in the elderly still remains to be explored.

## The prevalence and characteristics of SDB in the elderly

The prevalence of SDB is high in elderly patients, while its prevalence in general population varies from 20% to 40%; that is a large variation and a more conservative estimate would suggest that the prevalence of SDB in elderly patients is at least double of that seen in the younger

population (3). According to a cross-sectional study involving 741 men aged >20 years [mean body mass index (BMI): 26.9], the prevalence of SDB [apnea hypopnea index (AHI) >10] increased with age (20–44 years: 3.2%; 45–64 years: 11.8%; 65–100 years: 23.9%), while the odds ratio of the prevalence of SDB in the oldest age group (65–100 years) compared with the middle age group was 2.3 (4). Furthermore, a separate analysis of 1,000 women (mean BMI: 29.6) from the same cohort revealed that the prevalence of SDB was highest among the oldest group of women (5). In a community-based longitudinal study, which followed 30 patients (mean entry age: 57.8 years) for 23.4 years, the rates of change in AHI were characterized by positive slopes along with aging; the mean rate of change was +0.43 events per hour per year (6). These findings suggest that aging is one of the significant predictors of SDB. In addition to the correlation between SDB and aging, there are several unique characteristics of elderly SDB. First, the effect of obesity on risk for SDB in elderly, was lower than that in other age groups (7). A review article which evaluated the interaction between SDB and obesity noted that this interaction in elderly subjects differed from that in younger adults. The risk of SDB between overweight (BMI: 25–29.9 kg/m<sup>2</sup>) and normal-weight (BMI: 20–24.9 kg/m<sup>2</sup>) groups in the elderly was not different (7). Secondly, self-reported breathing pause or snoring was less prevalent in the elderly than in middle-aged individuals with SDB (8). Therefore, it can be suggested that, SDB in

the elderly is quite common, but is under-recognized partly due to the absence of some well-known signs of SDB (e.g., obesity, breathing pause, and snoring).

### **Impact of SDB on cognitive function, CV morbidity and mortality in the elderly**

Despite its high prevalence, the distinct phenotype of SDB in elderly has led to the debate on its clinical implications on aspects such as cognitive function, CV morbidity and mortality in elderly patients. Several studies have suggested that SDB is associated with the occurrence of cognitive impairment. Among 298 older women (mean age: 82.3 years), those with SDB, had an increased risk of developing cognitive impairment, compared to those without SDB (9). A 5-year population-based cohort study involving nearly 8,000 subjects, also demonstrated that SDB patients had 1.70-times greater risk of developing dementia compared to age- and sex-matched non-SDB patients, and its statistical significance persisted in the 50–59 [adjusted hazard ratio (HR): 3.63; 95% CI, 1.67–7.88] years old and  $\geq 70$  (adjusted HR: 1.53; 95% CI, 1.01–2.33) years old groups (10). Because of the limited data on the relationship between SDB and CV morbidity or mortality in the elderly, the applicability of the results derived from the younger or middle-aged population is uncertain. According to the Sleep Heart Health Study (SHHS), a multi-center prospective cohort study, which followed 4,422 adults for a median of almost 9 years, the statistical association between increased risk of coronary artery disease (myocardial infarction, revascularization procedure, or coronary heart disease death) and untreated SDB appeared stronger in men aged  $\leq 70$  years than men  $> 70$  years (11). In contrast to the association with coronary artery disease, both the men older and younger than 70 years with severe untreated SDB, exhibited a trend toward higher incidence of heart failure than men of the same age who did not have SDB (11).

The data related to the impact of SDB on mortality in the elderly is limited and inconsistent. A retrospective cohort study revealed that elderly patients ( $\geq 65$  years) with severe SDB (respiratory disturbance index  $> 40$ ) had the same mortality as the age-, gender-, and ethnicity-matched general population cohorts (12). Another population-based probability sample of 426 elderly individuals (mean age: 72.5 years) reported that only age, CV disease and pulmonary disease, but not the degree of SDB, were independent predictors of death (13). A prospective cohort study from the SHHS, which followed 6,294 adults

for a median of almost 8 years, revealed that statistical association between all-cause mortality and untreated SDB noted in men younger than 70 years ( $n=2,169$ ), was not evident in men over 70 years ( $n=773$ ) and in women of any age ( $n=3,352$ ) (14). Conversely, another prospective cohort which followed 939 older patients ( $\geq 65$  years) being evaluated for suspected OSA for 69 months, revealed that the patients with untreated severe SDB (AHI  $\geq 30$ ) had an increased risk of all-cause and CV mortality (15). Although the reasons for these discrepancies remains unknown, it might be due to the difference in study population (population- or clinically-based) and CV risk profile. Nevertheless, most of the evidence related to elderly is from the subgroups of studies that include adults of all ages, which did not have enough events to either confirm or exclude the clinical significance of SDB in terms of CV morbidity and mortality in the elderly.

There also has been limited evidence for SDB treatment in elderly patients, with only few randomized control trials (RCTs) specifically related to the elderly. In the observational cohort study of elderly patients ( $\geq 65$  years) mentioned earlier, the risk of CV mortality reduced to a greater extent in the group with severe SDB which used CPAP compared to the group with severe SDB without CPAP therapy (15). Two recent RCTs have focused specifically on the elderly. One was an open-labelled randomized treatment with CPAP in 224 elderly patients with severe OSA ( $\geq 70$  years; mean entry age: 75.5 years) which demonstrated the effectiveness of CPAP in improving the quality of life, sleep apnea-related symptoms, symptoms of depression and anxiety, and certain neurocognitive aspects (16). The PREDICT study, was the other 12-month, multicenter, randomized trial involving 278 elderly patients with OSA syndrome ( $\geq 65$  years; mean entry age: 71.1 years), which revealed that CPAP reduced objective sleepiness and was cost-effective among older people. The incidence of new CV events did not differ between groups at 3 and 12 months (17).

### **Impact of SDB on CV risk factors in the elderly**

Few studies have simultaneously followed the parameters of CV risk factors and SDB in elderly subjects. We read with interest Dr. Monneret *et al.*'s article "*Serum lipid profile, sleep-disordered breathing and blood pressure in the elderly: a 10-year follow-up of the PROOF-SYNAPSE cohort*" published in November 2017 in the *Sleep Medicine* (18). This study was designed to follow the evolution of the serum lipid

**Table 1** Cohort studies on the relationship between SDB and hypertension in the elderly

Author [year] (Reference)	No.	Age (years)	Study design	Study subjects	Follow-up	Results
Monneret D <i>et al.</i> [2017] (18)	266	66	Cross-sectional analysis	General population	NA	SDB (ODI $\geq 15$ ) was associated with higher nocturnal diastolic blood pressure (OR: 1.1; 95% CI, 1.0–1.1)
		76	Cross-sectional analysis		NA	SDB (ODI $\geq 15$ ) was associated with higher diurnal systolic blood pressure (OR: 1.0; 95% CI, 1.0–1.1)
		66	Longitudinal analysis		9.6 years	Change in nocturnal diastolic blood pressure independently and positively associated with change in AHI (P=0.049)
Haas DC <i>et al.</i> [2005] (19)	3,643	70.2	Cross-sectional analysis	General population	NA	No association between AHI and systolic/diastolic hypertension
Guillot M <i>et al.</i> [2013] (20)	372	68.2	Longitudinal analysis	General population	3 years	Severe SDB (AHI $\geq 30$ ) was associated with new onset of hypertension (OR: 1.8; 95% CI, 1.1–2.8)

AHI, apnea-hypopnea index; CI, confidence interval; ODI, oxygen desaturation index; OR, odds ratio; SDB, sleep-disordered breathing; NA, not available.

profile and its relationships with SDB and blood pressure (BP) in healthy elderly individuals who were followed by general practitioners (18). The study conducted cross-sectional analyses at the two point; at the pre- and post-cohort of the trial for the same participants. Furthermore, the participants were followed for 10 years as a longitudinal cohort study for assessing the association between change of BP, serum lipid profile, and SDB severity. The study included 266 subjects with a mean age of 66 years and 44% women. The nocturnal oxygen desaturation index, a surrogate marker of SDB, was the main predictor of the likelihood of having hypertension at baseline and follow-up (*Table 1*). The nocturnal oxygen desaturation index increased (mean  $+2.3 \pm 6.7$  events/hour) between 66 and 76 years of age. However, these variations were not associated with serum lipid variations, with or without lipid-lowering treatments. While the BP decreased in the overall group mainly due to an increased use of antihypertensive drugs, systolic BP increased in the absence of antihypertensive treatments. The relationship between SDB and hypertension was supported by the positive correlation between changes in nocturnal diastolic BP and AHI during the observation period (*Table 1*) (18).

Despite the significant impact of SDB on the development of CV risk factors in younger or middle-

aged populations (1), the association between SDB and hypertension, the most common CV risk factors, is controversial in the elderly. *Table 1* summarize several incongruous evidences related to their correlation in the elderly. In the cross-sectional analysis of 6,120 participants from the SHHS, SDB was not associated with hypertension in subjects older than 60 years (19). On the contrary, the presence of severe OSA was associated with new onset hypertension after a period of 3 years in the normotensive elderly (PROOF-SYNAPSE cohort, mean age: 68.2 years) (20). A meta-analysis of 51 studies (4,888 patients) demonstrated that both CPAP and mandibular advancement devices were associated with reductions in BP (21); however, there were only 9 studies involving patients with a mean age  $\geq 60$  years (most of which had small sample size). Top three studies with the highest number of patients are listed in *Table 2*. Two randomized trials reported no significant difference in the changes in BP between CPAP therapy and non-CPAP therapy groups (17,23), whereas one RCT exhibited more effective BP reduction following CPAP therapy (22). In terms of the lipoprotein metabolism, the SHHS study demonstrated that the association between SDB and cholesterol level diminished in older individuals, while there was a trend of a modestly higher cholesterol in men  $<65$  years with severe SDB (24).

**Table 2** Randomized controlled trials exploring the effects of CPAP on blood pressure in the elderly

Author [year] (Reference)	No.	Age (years)	Study design	SDB definition	Study subjects	Follow-up	Results
Gottlieb DJ <i>et al.</i> [2014] (22)	281; 90 CPAP; 97 Control; 94 SO	63.2	RCT	50 $\geq$ AHI $\geq$ 15	CV diseases or multiple risk factors	12 weeks	Reduction in blood pressure; (-2.4 mmHg vs. control); (-2.8 mmHg vs. SO)
McMillan A <i>et al.</i> [2014] (17)	231; 114 CPAP; 117 Control	71.1	RCT	4% ODI >7.5 and ESS $\geq$ 9	Sleep clinic patients	12 months	No improvement in blood pressure
Muxfeldt ES <i>et al.</i> [2015] (23)	117; 57 CPAP; 60 Control	60.5	RCT	AHI $\geq$ 15	Resistant hypertension	6 months	No improvement in blood pressure

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; CV, cardiovascular; ESS, Epworth sleepiness score; ODI, oxygen desaturation index; RCT, randomized controlled trial; SDB, sleep-disordered breathing; SO, supplemental oxygen.

In the PREDICT study, significant improvement in total cholesterol levels was noted at 3 months in the CPAP group; but was not sustained at 12 months. There may be several unknown factors in the elderly which influence the interactions between serum lipid profile, SDB, and hypertension. Therefore, more and larger cohort studies are warranted clarify these interactions.

### Key points in the management of SDB in the elderly

The limited but emerging evidence regarding SDB in elderly has led researchers to consider whether SDB in elderly individuals is distinct from that in middle-aged people. The key points in the management of SDB in the elderly depending on the clinical endpoints such as patient-reported outcome, intermediate CV endpoints, and CV mortality can be summarized as follows. The main aim of SDB treatment in the elderly is to improve quality of life and well-being. Despite the lower prevalence of daytime sleepiness due to fragmented sleep, which is common in the elderly (3), medical providers still need to be careful about the presence of daytime sleepiness as a therapeutic target in the SDB management in elderly. The treatment of SDB with CPAP improves intermediate CV endpoints, such as blood pressure and cardiac ejection fraction in middle-aged population (1), but these effects were not established in the elderly population. In middle aged population with OSA, CPAP has been shown to reduce blood pressure levels (1), but not in OSA patients who were minimally

symptomatic (25), which is one of the characteristics of elderly SDB. Further studies to evaluate whether the impact of CPAP on hypertension in elderly with SDB could be modulated by the presence of SDB-related symptom are required. Current data from large-scale RCTs do not support the role of CPAP treatment in the reduction of CV mortality, even in younger or middle-aged populations (1). Collectively, it can be suggested that CPAP treatment has not proved its efficacy in terms of major clinical endpoints in the elderly, despite its efficacy in patient-reported outcomes.

In addition to clinical endpoints, issues related to aging should also be considered. For instance, shorter life expectancy could modify the economic benefits of CPAP in the elderly; therefore, the magnitude of treatment and economic benefits of CPAP shown in middle-aged populations cannot be extrapolated to older populations. Additionally, inadequate CPAP adherence, which is known to be more apparent in elderly individuals, might dilute the significant effect and hence, a strategy to improve adherence in elderly should also be considered. Furthermore, because of the anatomical and physiological predisposition for developing SDB with increasing age (3), elderly SDB patients could be heterogeneous. Therefore, careful identification of subgroups among the elderly who are most likely to respond to CPAP, might be the key to establish the efficacy of CPAP in this population.

In conclusion, despite high prevalence of SDB in elderly, as well as, its worsening during aging, there is uncertainty about the relationship between SDB and CV risk factors,

morbidity, and mortality. Further research is needed to clarify the impact of CPAP treatment on clinical outcomes including CV risk factors, morbidity, and mortality in elderly with SDB.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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