Eur Respir Rev 2007; 16: 106, 203–210
DOI: 10.1183/09059180.00010610

Mortality in sleep apnoea syndrome: a review of the evidence

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ABSTRACT: Sleep apnoea syndrome is associated with cardiovascular morbidity, but it is less clear if it is also associated with increased mortality.

Studies investigating mortality in sleep apnoea have 1) compared mortality rates of patients with different levels of severity of the syndrome relying on sleep laboratory populations, 2) compared treated and untreated patients, 3) examined the effect of co-existing cardiovascular diseases on survival and 4) investigated the effect of sleep-disordered breathing on mortality in the elderly.

In spite of methodological limitations, the accumulated data generally support an increased risk of mortality in patients with severe sleep apnoea in comparison with mild or no sleep apnoea, and indicate that efficient treatment decreases mortality. Surprisingly, several studies have shown that the highest risk of mortality in sleep apnoea occurs in patients younger than 50 yrs of age, that risk tends to decline with age and that the occurrence of disordered breathing in sleep in the elderly does not affect mortality. It is as yet unclear if this finding represents a selection bias, differences in apnoea severity or in compliance with treatment between young and old patients, or an adaptation to the syndrome with age.

There is conflicting evidence as to whether the occurrence of sleep apnoea in patients with existing cardiovascular diseases increases the risk of mortality beyond that associated with the cardiovascular diseases themselves.

KEYWORDS: All-cause mortality, cardiovascular mortality, continuous positive airway pressure, sleep apnoea

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STATEMENT OF INTEREST
The present article was presented as part of the international symposim ''Respiratory somnology: a clinical update'', sponsored by GlaxoSmithKline, Belgium.
P. Lavie is a founder and board member of Itamar Medical Ltd, SLP Ltd, Sleep Health Centers US and Sleep Disorders Center Israel. He owns shares and options in these companies.

The association of obstructive sleep apnoea with cardiovascular morbidity has been extensively investigated in recent years. There is convincing evidence based on cross-sectional, prospective and interventional studies [1] that sleep apnoea is causally related to hypertension. Sleep apnoea has also been reported to be associated with the occurrence of ischaemic heart disease [2], strokes [3] and chronic heart failure [4], although most of these associations have been inferred from cross-sectional studies. It has been shown that intermittent hypoxia initiates a cascade of events involving oxidative stress and inflammatory processes leading to atherogenesis, which provides at least one pathway through which sleep apnoea affects the cardiovascular system [5]. Others have suggested the participation of sympathetic activation and swings in intrathoracic pressure in this process [1]. In view of these studies, it can be expected that sleep apnoea patients will be at an increased risk of mortality, particularly from cardiovascular causes. Studies on mortality in sleep apnoea relying on sleep laboratory clinical populations were reported as early as 1988 [6]. Although in comparison with controls without sleep apnoea, patients are generally reported to have higher rates of mortality, the results are far from being uniform or consistent. The present article reviews the available data on mortality in sleep apnoea patients, and demonstrates that, in contrast with what could be expected based on the wealth of the literature on increased cardiovascular risk in these patients, excess mortality in sleep apnoea appears to be age dependent.

SLEEP LABORATORY POPULATIONS

The first paper investigating mortality in patients with sleep apnoea syndrome was published by HE *et al.* in 1988 [6]. In this widely cited paper, the authors reported the mortality data of 385 patients diagnosed with sleep apnoea between 1978 and 1986, of which 246 were untreated and 22 died. Patients with and apnoea index (AI) >20 events·h^{-1} had significantly higher mortality than those with an AI <20 events·h^{-1}, but there was a significant interaction effect between

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

apnoea severity and age on mortality, such that the difference in mortality as a function of AI was significant only in patients younger than 50 yrs. Thus, HE *et al.* [6] concluded that: ''Patients with AI exceeding 20 have a higher mortality than patients with an AI of less than 20. This effect is apparent when examining the population of individuals below the age of 50 years when other diseases normally do not increase mortality. On the other hand, on examining the population above the age of 50, the result is not as clear cut.'' It should be noted that only a handful of >750 papers citing the article by HE *et al.* [6] mortality study have mentioned the age dependency of mortality. LAVIE *et al.* [7] investigated all cause mortality rates in a group of 1,620 sleep apnoea patients consecutively diagnosed by polysomnography (PSG) during 1976–1988; 57 out of the 1,620 had died by 1990. Comparison of sleep apnoea mortality rates with those of the general population in Israel revealed significantly excessive mortality only for patients aged 30–50 yrs. Surprisingly, patients >70 yrs of age showed lower mortality than their counterparts in the general population (fig. 1). Comorbidities, particularly lung diseases, in addition to body mass index (BMI) and age, but not apnoea severity, were significant predictors of mortality. No information on treatment was available for the investigated population.

Mortality rates in a population of treated patients were investigated by VEALE *et al.* [8]. They investigated mortality of sleep apnoea patients treated with nasal continuous positive airway pressure (nCPAP), using the database of Á Domicile de L'Insuffisance Respiratoire Chronique (ANTADIR), the French National Association for Respiratory Home Care, that included all registered nCPAP users in France. Mortality rates were calculated on patients diagnosed with sleep apnoea alone and equipped with nCPAP during a 9-yr period (1985–1993) and were compared with the general population in France, adjusted for age and sex. In the second part of the study, a case-control design was used to investigate predictors of mortality of the nCPAP-treated patients. Out of 5,669 patients equipped with nCPAP during the study period, 276 (4.9%) died, 3,906 still used nCPAP, and 1,487 were lost to follow-up. Comparison of the mortality rates of the treated patients with the rates in the general population did not reveal any significant differences, except for a greater survival in patients >70 yrs of age. Analysis of the data of a subgroup of 112 patients who died due to cardiovascular reasons showed significant excess mortality in comparison with the general population. The case-control part of the study, based on 124 matched pairs, revealed that the percentage of time spent <90% arterial oxygen saturation, compliance with nCPAP treatment and a past medical history of cardiac dysrhythmia, ischaemic, respiratory and neuropsychiatric events, were all prognostic factors of mortality. A similar study performed on a much smaller population was reported by CHAOUAT [9], who followed 296 patients treated with nCPAP for 11 yrs and 6 months, and reported that smoking, age and lung function were predictors of mortality. Once patients with chronic obstructive pulmonary disease (COPD) were excluded from the analysis, the rate of mortality of the treated sleep apnoea patients was the same as in the general population.

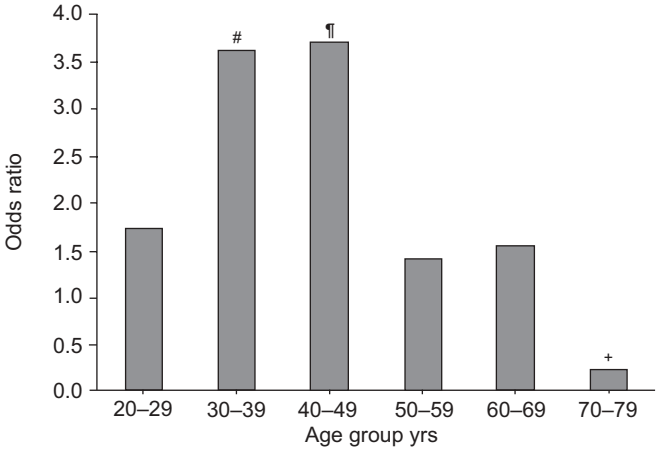

FIGURE 1. Odds ratios for mortality in males with sleep apnoea at different ages. #: $p<0.002$; ¶: $p<0.0002$; +: $p<0.0007$.

MARTI *et al.* [10] evaluated the viability status of all patients residing in Catalonia, Spain, and diagnosed by PSG with sleep apnoea during a 10-yr period (1982–1992). Mortality of sleep apnoea-related causes (cardiovascular, respiratory, or accidents and mortality of ''all causes'') were compared between treated and untreated patients, and with data of the general population of Catalonia. The population studied consisted of 404 patients out of 808 diagnosed with sleep apnoea, of whom 98 were not treated while the remainder were treated with nCPAP (n=124), diet (n=134) or surgery (n=88). A total of 49 patients had died by the end of the follow-up period. Cox regression analysis revealed that treatment reduced all-cause mortality as well as sleep apnoea-related mortality, while a history of COPD and obesity increased mortality. Sex, apnoea severity and a history of hypertension did not have an effect on mortality. In comparison with the general population, mortality was significantly higher in untreated patients, particularly in patients <50 yrs of age. In contrast, in treated patients, mortality was similar to the general population.

A single study, reported in a preliminary form, showed sex-related differences in mortality of sleep apnoea patients [11]. In a 5-yr follow-up study of 354 patients investigated at the University of Wisconsin sleep disorders clinic, females with apnoea/hypopnoea index (AHI) >5 events·h^{-1} showed a significantly higher proportion of deaths than males, a difference that was not seen in patients with an AHI <5 events·h^{-1}. Moreover, only females with sleep apnoea showed significantly greater mortality than the general population in Wisconsin.

More recently, MARIN *et al.* [12] followed a cohort of males examined for obstructive sleep apnoea during 1992–1994 and recorded the incidence of fatal (death from myocardial infarction or stroke) and nonfatal cardiovascular events (occurrence of myocardial infarction, stroke or acute coronary insufficiency that needed coronary arterial bypass, percutaneous transluminal coronary angiography, or both). The incidence of fatal and nonfatal cardiovascular events was investigated in five groups: healthy males, simple snorers, mild-to-moderate and severe untreated sleep apnoea patients, and severe patients treated with nCPAP. The authors included a control group (healthy males) of age- and BMI- matched males who did not have excessive daytime sleepiness, did not

snore, and had an AHI <5 events·h^{-1}. After adjustment for possible confounding factors, untreated patients with severe sleep apnoea showed a significantly higher incidence of both fatal and nonfatal events than all other groups. There was no difference in the rates of mortality between any of the other groups and normal controls (fig. 2). Unpublished results of the study by MARIN *et al.* [12] revealed that in untreated severe patients, there were more deaths in patients <30 yrs of age than in patients aged 30–50 and 50–70 yrs (fig. 3; personal communication, J.M. Marin, Hospital Universitario Miguel Servet, Isabel la Catolica, Zaragoza, Spain). As can be seen in fig. 3, this result differed from the pattern of monotonous increase in the number of deaths with increasing age observed in all other groups.

YAGGI *et al.* [13] compared the rate of all-cause mortality and the occurrence of strokes in patients with a diagnosis of sleep apnoea (n=697), with a group of patients referred for PSG because of suspected sleep apnoea and found to have AHI <5 events·h^{-1} (n=325). Only patients >50 yrs of age without prior history of stroke, myocardial infarction or tracheostomy, were included. After a mean follow-up period of 3.4 yrs, 50 patients had died and 22 had had strokes in the obstructive sleep apnoea syndrome group, which was significantly more than the 14 deaths and two strokes in the comparison group. The association between sleep apnoea and the combined rate of deaths and strokes remained significant after adjustment for all confounding variables, although the association with death as a single outcome measure was not statistically significant (fig. 4). A trend analysis revealed a stepwise increase in the risk of stroke or death as a function of increased severity of sleep apnoea. It is interesting to note that the significant association of stroke and death with sleep apnoea was obtained despite the administrations of various treatments to the studied population.

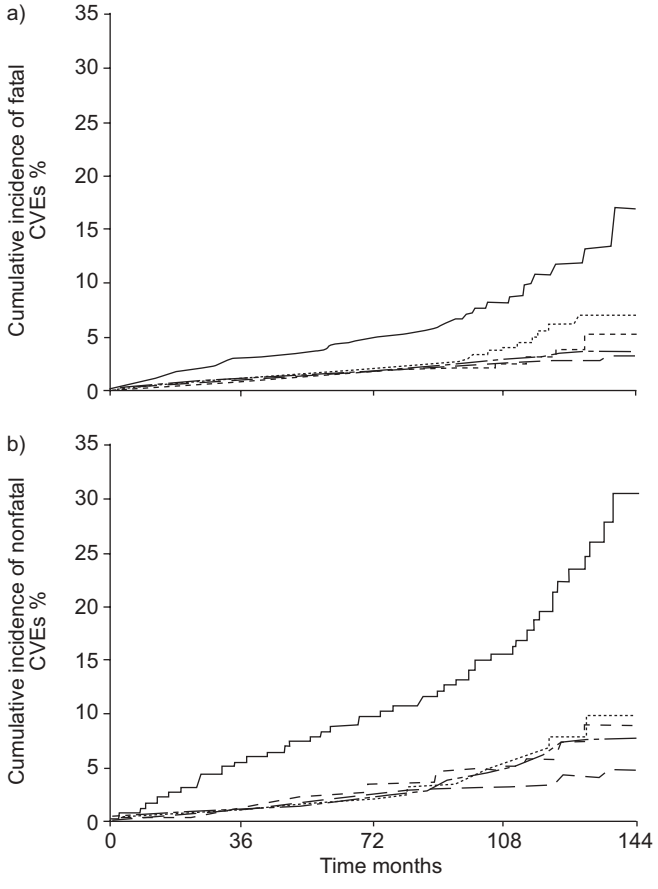

FIGURE 2. Cumulative percentage incidences of individuals with new a) fatal and b) nonfatal cardiovascular events (CVEs) in each of the five groups studied. ———: severe obstructive sleep apnoea syndrome (OSAS); ·····: mild OSAS; -------: OSAS with continuous positive airway pressure; —— – ——: snorers; — — —: controls. Reproduced from [12] with permission from the publisher.

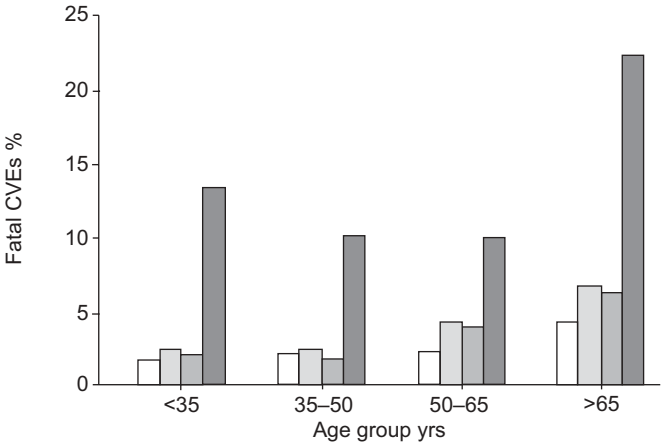

FIGURE 3. Percentage of patients with fatal cardiovascular events (CVEs) in the five groups investigated by age group (personal communication, J.M. Marin, Hospital Universitario Miguel Servet, Isabel la Catolica, Zaragoza, Spain). □: snoring; ■: mild-to moderate obstructive sleep apnoea syndrome (OSAS); ■: treated with continuous positive airway pressure; ■: severe OSAS.

Two large-scale studies on all-cause mortality of males with sleep apnoea were reported by LAVIE *et al.* [14, 15]. In the first study [14], mortality rates of 14,589 males, all examined by PSG because of suspected sleep apnoea, of whom 372 died after a median follow-up of 4.6 yrs, were compared between patients with increasing severities of sleep apnoea and those with an AHI <10 events·h^{-1}. Age-specific mortality rates of sleep apnoea patients were also compared with the general population in Israel. LAVIE *et al.* [14] reported that the hazard of mortality significantly increased with the severity of sleep apnoea, and that the highest mortality rate (11.47 out of 1,000 patient-yrs) was found in obese patients (BMI ⩾31.0 kg·m^{-2}) with severe sleep apnoea (AHI >40 events·h^{-1}). Although patients with moderate-to-severe sleep apnoea (AHI >30 events·h^{-1}) had significantly higher mortality rates than the general population, comparison of the age-specific rates revealed that relative mortality decreased with age. Moreover, in a subgroup of males all having very severe sleep apnoea (AHI >50 events·h^{-1}, median AHI 73 events·h^{-1}), the relative mortality rate for ages 20–29 yrs was 9.8, while it was ~1.0 for ages 50–79 yrs (fig. 5). In their subsequent study, LAVIE *et al.* [15] utilised a case-control design to determine the predictors of mortality in a large group of males diagnosed with sleep apnoea syndrome, drawn from the same parent population investigated in their first study. The study population

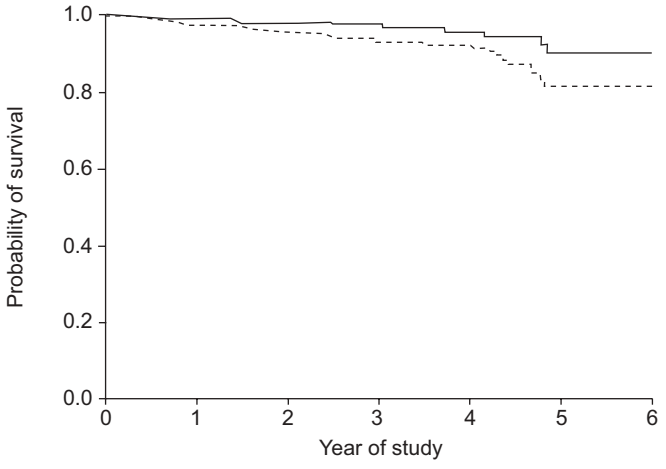

FIGURE 4. Kaplan–Meier estimates of the probability of overall survival among patients with the obstructive sleep apnoea syndrome (-----) and controls (———). p=0.02. Reproduced from [13] with permission from the publisher.

consisted of 331 males with sleep apnoea who had died during the study period, of whom 277 could be matched by age, site and time of PSG testing with live controls. Multivariate analysis showed that the risk of mortality was significantly associated with the existence of COPD, chronic heart failure, diabetes mellitus and obesity at the time of sleep apnoea diagnosis. In contrast, upper airway problems were associated with survival. Although sleep apnoea severity was not identified as a mortality risk factor, it significantly interacted with obesity and COPD to affect mortality.

POPULATION STUDIES

So far, there have been no studies investigating the association between sleep apnoea and mortality in the general population. A single population study demonstrated an association between excessive daytime sleepiness that is a typical symptom in sleep apnoea and an increased risk of mortality in the elderly, particularly elderly females [16]. However, excessive sleepiness is common in the elderly and may be caused by multiple reasons, not necessarily sleep apnoea. LINDBERG *et al.* [17] investigated the association between mortality and the two most typical symptoms of sleep apnoea, snoring and excessive sleepiness. For 10 yrs, the authors followed a sample of 3,100 males from Uppsala, Sweden; 213 of these males died, 88 for cardiovascular reasons. Compared with males without snoring or excessive daytime sleepiness, the combination of both complaints was associated with a significant increase in mortality. However, mortality decreased with increasing age, and no effect on mortality was found in males >50 yrs of age (fig. 6).

EFFECT OF TREATMENTS

Studies on the effects of treatment in sleep apnoea patients can also provide evidence on the possible association between sleep apnoea and mortality. PARTINEN *et al.* [18] conducted a 5-yr follow-up study on 198 sleep apnoea patients who were recommended either tracheostomy (n=71) or weight loss (n=127). There were 14 deaths, eight of which were considered ''vascular'', all of them from the weight-reduction group. There were no significant differences in demographic data or occurrence of comorbidities between live and dead patients in the weight-reduction group and between the tracheostomy and weight-reduction group, except that the age at entry, which was slightly higher in the weight-reduction group. DOHERTY *et al.* [19] performed a long-term follow-up study comparing cardiovascular morbidity and mortality of 168 patients who complied with nCPAP treatment with 55 patients who quit therapy. During the follow-up period, there was a significant excess of cardiovascular deaths (14.8 *versus* 1.9%) and a nonsignificant increase in cardiovascular morbidity in the untreated group. Both ischaemic heart disease and diabetes were significant predictors of mortality. A similar study was conducted by CAMPOS-RODRIGUEZ *et al.* [20], who investigated mortality rates in 871 nonselected sleep apnoea patients who had been prescribed with nCPAP treatment and were followed for a mean of 48.5 months. A group of 46 of the 871 patients had died by the end of the study period. Mortality was related to the degree of compliance with treatment with noncomplying patients showing the highest mortality. Arterial hypertension, age and lung function were also identified as predicting mortality. MILLERON *et al.* [21] followed up 54 sleep apnoea patients, most of them with coronary artery disease, of whom 25 patients were treated with either nCPAP or upper airway surgery, and 29 declined treatment. The treated and untreated groups were comparable with respect to apnoea severity, and demographic and clinical data. After a mean follow-up period of 86.5 months, there was a significant difference between the groups in the rate of cardiovascular events that comprised cardiovascular death, acute coronary syndrome or a need for coronary revascularisation.

MORTALITY IN PATIENTS WITH PRE-EXISTING CARDIOVASCULAR MORBIDITY

Respiratory sleep-disordered breathing (SDB) is a prevalent finding among patients with cardiovascular diseases, such as stroke, ischaemic heart disease and congestive heart failure (CHF). In view of the well-documented effects of sleep apnoea on changes in blood pressure, hypoxaemia and sympathetic

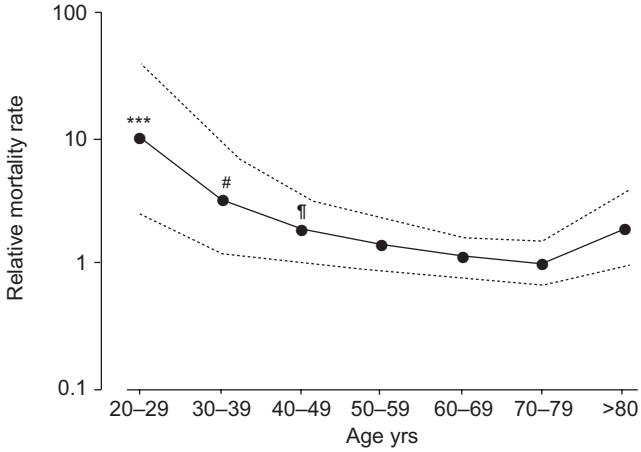

FIGURE 5. Relative rates (——) and 95% confidence intervals (-----) of all cause mortality in males with severe sleep apnoea (apnoea/hypopnoea index >50 events·h^{-1}, median 75 events·h^{-1}) referenced to the corresponding rates in the general population. #: p<0.002; ¶: p<0.03. *** p<0.001. Reproduced from [14].

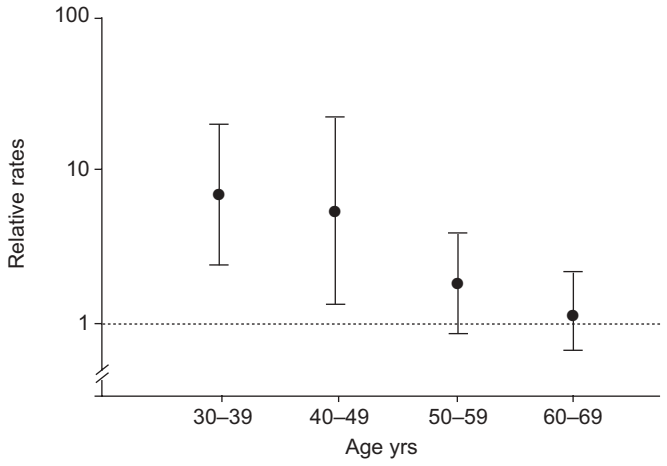

FIGURE 6. Relative rates and 95% confidence intervals of mortality during a 10-yr period in males with snoring and excessive daytime sleepiness compared with males with no snoring or excessive sleepiness. A logarithmic scale was used. Reproduced from [17] with permission from the publisher.

activation, it is reasonable to assume that SDB may exacerbate mortality risk in cardiovascular patients.

ISCHAEMIC HEART DISEASE

PEKER *et al.* [22] conducted a 5-yr follow-up of 62 consecutive patients with coronary artery disease requiring intensive care whose sleep was evaluated within 4–21 months after hospitalisation. The existence of SDB, defined as a respiratory disturbance index of at least 10 events·h^{-1}, was found to be an independent significant predictor of cardiovascular mortality that occurred in 37.5% of the patients with SDB in comparison with only 9.3% mortality in patients without SDB. Similarly, MOOE *et al.* [23] conducted a 5-yr follow-up on patients referred for coronary angiography because of disabling angina pectoris. SDB was independently and significantly associated with a composite end-point of death, cardiovascular events and myocardial infarction. HAGENAH *et al.* [24], however, failed to confirm these observations. They conducted a 10-yr follow-up on 50 patients with cardiovascular disease, all >70 yrs of age, of whom half had an AHI >10 events·h^{-1}. Their results show no significant increased risk with SDB, as four patients died in the sleep apnoea group and eight died in the nonapnoea group. Likewise, there were no significant differences in the rate of incident cardiovascular events, such as myocardial infarction or stroke. However, no demographic data was provided for either group, and the authors noted in the discussion section that there was a tendency for a more severe cardiovascular disease in the nonapnoeic group. MARIN *et al.* [25] compared the immediate outcomes of patients with acute myocardial infarction with and without co-existing sleep apnoea. Even though patients with sleep apnoea had a greater incidence of some types of cardiac arrhythmias, there was no difference in the clinical course or in mortality rate between the two groups.

STROKE

Increased rates of SDB in stroke patients have been widely reported [3] and several studies have investigated whether these rates predict mortality. PARRA *et al.* [26] investigated the impact of SDB on mortality of 161 patients all having their first-ever stroke or transient ischaemic attack. After a mean follow-up period of 23 months, 22 patients had died, mostly because of vascular disease. Multivariate analysis revealed that age, apnoea severity and existing ischaemic heart disease were significant predictors of mortality, in addition to involvement of the middle cerebral artery. Interestingly, after follow-up it appeared that the baseline AI was slightly higher in the patients still alive in comparison with the patients who died, while the patients who presented at baseline with a much higher rate of Cheyne–Stokes respiration (CSR) died during follow-up. Although significant, the hazard ratio associated with apnoea severity was very low: 1.05. A similar study was reported by TURKINGTON *et al.* [27], who investigated if upper airway obstructions occurring within the first 24 h after a stroke were associated with a 6-month mortality. Based on a sample of 120 patients, they reported that death, as well as the degree of dependency after stroke, were independently associated with the severity of apnoeas, and in particular with longer apnoeas. Conflicting results, however, were reported by IRANZO *et al.* [28], who failed to demonstrate any association between the occurrence of sleep apnoea during the first night after hemispheric ischaemic stroke and functional outcome at 6 months.

CHF

SDB in the form of obstructive sleep apnoea, central sleep apnoea, or CSR affect as many as 11–42% of patients with CHF [4]. Although clinical data suggest that sleep apnoea plays a role in ventricular impairment, it is unclear if this is independent of hypertension, ischaemic heart disease and obesity. Several studies assessed the impact of SDB on mortality and cardiac transplantation in CHF patients. ROEBUCK *et al.* [29] followed up a group of 78 patients with severe CHF who were assessed for heart transplantation, for a median period of 52 months. Survival was analysed based on the existence of mostly central (n=33), obstructive (n=22) or no SDB (n=23). There were no significant differences in the percentages of death, transplantations or in the combined death and transplantations rate between the three groups. Moreover, comparison of the nonsurvivors with survivors indicated no significant difference in any of the relevant sleep apnoea variables. These results remained when analysis was repeated after combining the two groups of patients with SDB. ANCOLI-ISRAEL *et al.* [30] investigated the influence of central and obstructive sleep apnoeas on the mortality of 353 elderly patients, of whom 32% had CHF. Subjects were followed for a mean of 5.7 yrs. Subjects with CHF who also had central sleep apnoea had significantly shorter survival times than those with CHF without sleep apnoea, or those with sleep apnoea without CHF. The mortality of those with sleep apnoea alone, either central or obstructive, was no different than subjects without sleep apnoea and heart disease. A large-scale study investigating the effects of nCPAP treatment on survival of patients with central sleep apnoea and heart failure showed that even though CPAP attenuated central sleep apnoea and improved nocturnal oxygenation, it did not affect survival [31]. More recently, WANG *et al.* [32] reported that in a group of 113 heart failure patients with mild or no obstructive sleep apnoea, or moderate-to-severe sleep apnoea, followed for a mean of 2.9 yrs, hazards of mortality were significantly higher in

patients with moderate-to-severe sleep apnoea. Treatment with CPAP tended to decrease mortality but the effect fell short of statistical significance.

SDB AND MORTALITY IN THE AGED

SDB is particularly prevalent in the elderly population; one in two elderly people >60 yrs of age have at least 15 respiratory events·h^{-1} of sleep [33]. Thus, the question as to whether SDB constitutes a risk of mortality in the elderly has an important clinical significance. ANCOLI-ISRAEL *et al.* [34] studied older nursing home populations and found that the respiratory disturbance index was a significant independent risk factor for mortality in institutionalised females. These results were not confirmed, however, in a later study by the same group, in which a sample of 426 community-dwelling elderly people were followed for a mean of 9.5 yrs [35], only age and a history of cardiovascular disease were significant predictors of mortality. Using PSG, BLIWISE *et al.* [36] investigated 198 aged individuals, 69 males and 129 females, recruited from the community. Although sleep apnoea, defined as at least 10 respiratory events·h^{-1} of sleep, was related marginally to mortality in an odds ratio, the results of the Cox proportional hazards model did not reveal a significant effect of sleep apnoea on mortality. MANT *et al.* [37] followed up 163 retirement village residents for 4 yrs and failed to find any association between SDB and mortality. Of the subjects with respiratory disturbance index (RDI) >15 at entry, 27% died, in comparison with 22% of the subjects with RDI <15. Moreover, no matter which cut-off point was chosen for apnoea severity, there was no significant association between apnoeas and mortality. Similar results were reported by PHILLIPS *et al.* [38], who followed a group of 95 normal elderly subjects for 5 yrs.

WHAT DOES THE EVIDENCE SHOW?

The results of the mortality studies in sleep apnoea patients should be interpreted with great caution in view of several methodological limitations. Most of the studies investigated sleep laboratory populations that did not represent the general population, or the population of patients with sleep apnoea syndrome, which could introduce selection bias into the results. Moreover, the definition of sleep apnoea varies from study to study. In some, sleep apnoea was defined as the combination of a PSG finding of either 5 or 10 respiratory events·h^{-1} of sleep and typical complaints; while in others, diagnosis was based on the number of respiratory events as determined by either PSG or ambulatory monitoring, regardless of subjective complaints. In studies examining the effects of treatment on mortality, ethical considerations did not allow randomisation of treatment or use of placebo treatments. It also should be mentioned that sleep apnoea may be linked with mortality in a rather complex and indirect way. While findings demonstrating the increased rate of nocturnal deaths in sleep apnoea patients may suggest a direct effect of the nocturnal events on mortality [39], sleep apnoea can also be the trigger of a cascade of events starting with a slow-progressing atherogenic process and endothelial dysfunction leading to overt cardiovascular disease and eventually to cardiovascular death. Thus, the lack of a statistically significant relationship between apnoea severity *per se* and mortality may not necessarily mean a lack of association.

Keeping these reservations in mind, what does the evidence show so far? First, there is a general agreement that patients with severe sleep apnoea having an AHI $\geqslant$30 events·h^{-1} have higher mortality rates than patients with no or mild forms of sleep apnoea. Furthermore, effective treatment of these patients, particularly with nCPAP, is associated with reduced mortality. Compliance, however, appears to be an important factor, but more information is needed to determine the minimum number of hours of nCPAP use per night needed to reduce mortality risk. There is also a general agreement among studies that lung disease is a significant predictor of mortality in sleep apnoea. It is not clear at this time, however, if co-existence of sleep apnoea and other diseases, such as stroke or ischaemic heart disease, is associated with a higher risk of mortality than the risk associated with stroke or heart disease without sleep apnoea. Certainly more research is needed to answer this question.

A large number of studies demonstrated a surprising age-related decline in the risk of mortality in sleep apnoea patients. This finding is unexpected as patients with severely disordered breathing in sleep have additional risk factors, such as obesity and cardiovascular diseases, which can be expected to greatly exacerbate their risk of mortality [40] by acting synergistically with the apnoeas. Furthermore, most studies did not show any effect of sleep apnoea on mortality in the elderly. It is possible that the age-related decline in relative mortality reflects methodological weaknesses of the studies, such as referral bias of performing diagnostic sleep recordings in younger sleep patients who were at a greater risk of death than the older patients, or the occurrence of more severe sleep apnoea in younger patients. It is also possible that there are differences in compliance with treatment between older than younger patients. It cannot be excluded, however, that the age decline in relative mortality reflects successful adaptation to the nightly apnoeic events by an as yet unknown mechanism [41]. Further studies are needed to verify this exciting possibility. Whatever the explanation for this observation, it implies that diagnosis and treatment of sleep should be carried out at the youngest age possible. Likewise, further studies are indeed in order to determine the clinical significance of the occurrence of apnoeas in the elderly.

In conclusion, mortality studies of sleep apnoea syndrome have generally shown that severe sleep apnoea constitutes an important mortality risk that can be reduced by proper treatment. Moreover, in view of the higher mortality risks in younger patients, diagnosis and treatment of the syndrome should be carried out at the earliest age possible.

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