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Jeremy Rich, Ayelette Raviv, Nataly Raviv and Scott E. Brietzke
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What is This?
All-Cause Mortality and Obstructive Sleep Apnea Severity Revisited

Jeremy Rich, MD1, Ayelette Raviv2, Nataly Raviv3, and Scott E. Brietzke, MD, MPH1

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. Obstructive sleep apnea syndrome (OSAS) is a pervasive problem that affects millions worldwide. It is strongly linked to hypertension, coronary artery disease, and stroke. However, its association with mortality is not clearly quantified. A large database of patients who underwent sleep testing was explored for associations with all-cause mortality.

Study Design. Database study.

Setting. Community-based use of a portable sleep study device.

Subjects and Methods. More than 77,000 patients who underwent a validated, portable sleep study were matched to the Social Security Death File to establish mortality. Measures of OSAS severity and other confounding factors were correlated to all-cause mortality using survival analysis with multivariate Cox proportional hazards regression.

Results. As expected, increasing age (adjusted hazard ratio [HR], 1.080; 95% confidence interval [CI], 1.074-1.086; P < .0001), body mass index (HR, 1.042; 95% CI, 1.033-1.051; P < .0001), and male sex (HR, 1.378; 95% CI, 1.190-1.595; P < .001) were associated with increased all-cause mortality. Epworth sleepiness score was also associated with mortality (HR, 1.015; 95% CI, 1.005-1.025; P = .002). Apnea-hypopnea index (AHI) was not associated with mortality after adjustment for age (HR, 1.001; 95% CI, 0.998-1.004; P = .416). However, within 10-year age subgroups, desaturation index (ages 41-50 years; adjusted HR, 1.217; 95% CI, 1.014-1.461; P = .035), apnea index (ages 21-30 years; HR, 1.632; 95% CI, 1.053-2.532; P = .028), and AHI (ages 31-40 years; HR, 1.222; 95% CI, 1.010-1.478; P = .039) were significantly associated with all-cause mortality in younger patients. In patients older than 50 years, age, sex, and body mass index were dominantly associated with mortality.

Conclusion. Increasing OSAS severity, measured by a validated home sleep test and quantified by AHI, the apnea index, and the desaturation index, is independently associated with modestly increased all-cause mortality in patients younger than 50 years after adjustment for major confounding factors.

Keywords

sleep apnea, mortality, database study, epidemiology

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Obstructive sleep apnea syndrome (OSAS) is a common condition affecting up to 9% of women and 24% of men in the United States.1 Multiple risk factors have been associated with OSAS, including male sex, age, and particularly obesity,2 which has noticeably increased in the general population over the past 4 decades.3 Significant research has been conducted looking at the associated comorbidities of OSAS such as hypertension, coronary artery disease, stroke, and respiratory failure.4-6 The primary mechanism of injury is thought to be due to repetitive hypoxic episodes during apneic events followed by reoxygenation, leading to inflammatory changes and atherosclerosis.4 Although significant research has been done to elucidate the comorbidities and mechanisms of OSAS, additional studies have also identified OSAS as an independent risk factor for all-cause mortality7-9; these studies focused primarily on the apnea-hypopnea index (AHI) as their sole measure of sleep apnea severity. The goal of this study was to thoroughly evaluate a large ambulatory sleep test patient database and objectively evaluate the association between OSAS severity and all-cause mortality.

1Department of Otolaryngology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA
2Syracuse University, Syracuse, New York, USA
3Case Western University, Cleveland, Ohio, USA

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Corresponding Author:
Scott E. Brietzke, MD, MPH, Department of Otolaryngology, Walter Reed National Military Medical Center, 8901 Wisconsin Ave, Bethesda, MD 20889, USA
Email: SEBrietzke@msn.com
Methods

This study was approved by the Walter Reed Army Medical Center Institutional Review Board. All data were provided by SNAP Diagnostics, Inc (Wheeling, Illinois) unconditionally without any restrictions as to the analysis performed or the study conclusions.

As previously noted from a prior study, home sleep test data were obtained from the SNAP Diagnostics database. The SNAP test is a portable home sleep study used to screen for sleep apnea and has been validated vs traditional polysomnograms. The SNAP test is a 3-channel home sleep test that uses an oronasal cannula that measures sound (pressure) to screen breathing for apnea and hypopnea events and also includes a pulse oximeter as well as an optional respiratory effort belt. For the interested reader, instructional videos and further descriptive information are available on the product website (www.snapdiagnostics.com). Home sleep tests by SNAP Diagnostics, Inc are used nationwide and represent a diverse patient population.

The following variables were evaluated from the data set: AHI, apnea index (AI), hypopnea index (HI), and desaturation index (DI; defined as number of events less than 93% per hour). The database also includes patients’ height, weight, body mass index (BMI), neck girth, sex, Epworth Sleepiness Scale, age, and the date of the test. For patients who underwent multiple studies, only the most recent test was used. The overall quality of the database was excellent, with less than 1% of database entries having missing key data for the analysis. Most of the missing data were pulse oximeter data, which were not of primary importance in this analysis. Given that the overall number of subjects with missing key data (age, sex, AHI, snoring indices) was small, the decision was made to simply exclude these subjects with missing key data. An analysis of the demographic and SNAP test data of the missing data subjects and included subjects revealed no difference in mean age, BMI, AHI, or sex.

The data obtained from the SNAP database were cross-matched with the Social Security Death Master File. This is a public-access database available online with purchase and is maintained by the US Department of Commerce-National Technical Information Service (http://www.ntis.gov/products/ssa-dmf.aspx). It provides the date of death and was used to establish all-cause mortality. The cause of death is not included in the database. The date of access of the Death File Master file was February 2010. Therefore, the available follow-up time for possible mortality is variable for each patient and included the time from his or her most recent SNAP test to either the end of the study time (February 2010) or his or her matched death.

Statistical analysis was performed using Stata 8.2 (StataCorp, College Station, Texas). As the data set represents survival data, Cox proportional hazards regression was used as the primary method of analysis. Initially, univariate analysis was performed. Subsequent stepwise (forward and backward) multivariate Cox proportional hazard regression was then used to model all-cause mortality with multiple covariates. Continuous variables were stratified into equal quartiles and/or quintiles. Effect modification among covariates was extensively explored, particularly among age, BMI, and AHI, but this did not appear to significantly affect the results. P values less than .05 were considered statistically significant.

Results

The SNAP database contained 75,305 patients with complete data sets. These were matched to the Social Security Death Master File. The death-matched cohort included 1645 patients, with 73,660 patients in the non-death-matched cohort. The mean and median follow-up time for all patients was 6.86 years and 7.42 years (range, 1 month to 11 years), respectively. Table 1 demonstrates the characteristics of the 2 cohorts. As expected, the death-matched group was older and had a higher BMI, a greater predominance of male subjects, and more severe OSAS measurements. Also, as may be expected, the death-matched group had a shorter mean follow-up time (due to their death), but the difference (0.19 years) was not considered clinically significant.

| Table 1. Characteristics of the Death- and Non-Death-Matched Groups |
|--------------------------|-------------------|-------------------|-------------------|
| Variable                 | Death-Matched Group (n = 1645) | Non-Death-Matched Group (n = 73,660) | P Value |
| Mean follow-up time, y   | 6.67              | 6.86              | <.0001            |
| Mean age, y              | 55.4              | 46.1              | <.0001            |
| Body mass index          | 32.7              | 31.0              | <.0001            |
| Male sex, %              | 73.9              | 70.3              | <.0001            |
| Neck girth, in           | 16.7              | 16.3              | <.0001            |
| Epworth score (0-24)     | 6.9               | 6.5               | .05               |
| Apnea-hypopnea index     | 26.6              | 22.0              | <.0001            |
| Apnea index              | 11.9              | 9.0               | <.0001            |
| Hypopnea index           | 14.7              | 13.1              | <.0001            |
| Desaturation index, events less than 93%/h | 17.6 | 13.1 | <.0001 |

P values generated using the 2-tailed Student t test.
Univariate Cox Proportional Hazards Regression Analysis

On univariate analysis, several variables were associated with an increased risk of all-cause mortality. As expected, the most strongly associated variables with all-cause mortality were male sex (hazard ratio [HR], 1.188; 95% confidence interval [CI], 1.064-1.328; \(P = .001\)), age (HR, 1.079; 95% CI, 1.074-1.084; \(<.001\)), and BMI (HR, 1.033; 95% CI, 1.026-1.040; \(<.001\)) (see Table 2). Several individual OSAS severity measurements were also significantly associated with all-cause mortality to include the AHI, AI, HI, and DI. However, suspicion for confounding by age, sex, BMI, and/or other covariates was high, leading to a multivariate analysis.

Stepwise Multivariate Cox Proportional Hazards Regression Analysis

Stepwise multivariate Cox proportional hazards regression, using both forward and backward model development, was used to more fully assess the relationship between the measured variables and all-cause mortality. Age, sex, BMI, neck girth, Epworth Sleepiness Scale (ESS), AHI, HI, AI, and DI were evaluated as possible covariates. The AHI, BMI, and age were divided into 5 equal quintiles. As shown in Table 3, the base model of all-cause mortality included AHI only. Subsequently, several important covariates were added into the model in a stepwise fashion. With the addition of the age quintile (HR, 1.765; 95% CI, 1.674-1.861) into the model, the AHI becomes a nonsignificant covariate (HR, 0.995; 95% CI, 0.950-1.041). This suggests a possible confounding relationship between sleep apnea severity, age, and all-cause mortality.

To further elucidate the effects of age in the all-cause mortality model, age was divided into 10-year strata and the models were recalculated. Obstructive sleep apnea syndrome was also stratified into mild, moderate, and severe groups based on AHI (mild AHI, 5-15; moderate, 16-30; severe, >30) to be more consistent with the clinical staging system currently in use. The AI and DI were also divided into 4 equal quartiles. In the youngest age group (ages 21-30 years), the dominant covariate was AI (HR, 1.632; 95% CI, 1.053-2.532) (see Table 4). In the subsequent age group (ages 31-40 years), the dominant covariates were both AI and DI (HR, 1.407; 95% CI, 1.181-1.717 and HR, 1.478; 95% CI, 1.062-2.043, respectively) followed closely by OSAS severity (HR, 1.380; 95% CI, 1.053-1.808). In the 41- to 50-year age group, the dominant covariate was AI (HR, 1.632; 95% CI, 1.053-2.532) (see Table 4). In the subsequent age group (ages 31-40 years), the dominant covariates were both AI and DI (HR, 1.407; 95% CI, 1.181-1.717 and HR, 1.478; 95% CI, 1.062-2.043, respectively) followed closely by OSAS severity (HR, 1.380; 95% CI, 1.053-1.808). In the 41- to 50-year age group, DI and AI are the dominant covariates (HR, 1.217; 95% CI, 1.014-1.461 and HR, 1.140; 95% CI, 1.001-1.298, respectively). However, with advancing age, beginning in the 41- to 50-year age group, BMI (HRs 1.022, 1.057, and 1.047) and male sex (HRs 0.959, 1.419, and 1.408) begin to become the dominant covariates. This analysis suggests that in the lower age groups, sleep apnea severity is associated with a modest increase in all-cause mortality, but this association is likely masked in

### Table 2. Univariate Cox Proportional Hazard Regression Analysis of All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.188</td>
<td>1.064-1.328</td>
<td>.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.079</td>
<td>1.074-1.084</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.033</td>
<td>1.026-1.040</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neck girth, in</td>
<td>1.018</td>
<td>1.011-1.025</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Desaturation index, events/h(^a)</td>
<td>1.011</td>
<td>1.008-1.014</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apnea index, events/h</td>
<td>1.010</td>
<td>1.007-1.012</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypopnea index, events/h</td>
<td>1.010</td>
<td>1.007-1.014</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Epworth score (0-24)</td>
<td>1.009</td>
<td>1.000-1.019</td>
<td>.05</td>
</tr>
<tr>
<td>Apnea hypopnea index, events/h</td>
<td>1.008</td>
<td>1.006-1.010</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^a\)Desaturation index defined as pulse oximeter values below 94% per hour.

### Table 3. Stepwise, Multivariate Cox Proportional Hazard Regression Models of All-Cause Mortality

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI quintile</td>
<td>1.126 (1.088-1.165)</td>
<td>1.119 (1.080-1.158)</td>
<td>1.091 (1.051-1.134)</td>
<td>1.093 (1.044-1.143)</td>
<td>0.995 (0.950-1.041)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.117 (1.000-1.249)</td>
<td>1.194 (1.057-1.348)</td>
<td>1.194 (1.033-1.380)</td>
<td>1.351 (1.169-1.561)</td>
<td></td>
</tr>
<tr>
<td>BMI quintile</td>
<td>1.155 (1.112-1.200)</td>
<td>1.153 (1.102-1.207)</td>
<td>1.193 (1.139-1.249)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epworth score</td>
<td>1.004 (0.995-1.014)</td>
<td>1.012 (1.003-1.022)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age quintile</td>
<td>1.765 (1.674-1.861)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values presented as hazard ratio (95% confidence interval). Note how with the addition of age into the model, the AHI becomes a nonsignificant covariate. Abbreviations: AHI, apnea-hypopnea index (events/h); BMI, body mass index.
older age groups by the increasingly predominant association between sex and BMI with all-cause mortality likely by way of cardiovascular disease.

Discussion

Our findings show as expected that with advancing age, sex- and BMI-related etiologies of all-cause mortality begin to dominate. This is most likely due to systemic cardiovascular, cerebrovascular, or pulmonary diseases, which are the common etiologies of death in an older demographic. These conditions are also closely intertwined with OSAS, making it difficult if not impossible to separate the effects of each in the data set.

However, in the younger age group (ages 21-40 years), it was observed that a measurable all-cause mortality risk was associated with various increasing measures of obstructive sleep apnea severity. The reason for this may be that younger patients in general tend to have fewer confounding health issues, and it may be easier to identify the relatively weaker association of OSAS severity to all-cause mortality. In the same vein, this is likely the reason that AI and DI were associated with a measurable increase in all-cause mortality as they are more robust, definitive measure of physiologic OSAS severity as compared with HI and AHI. Similar findings were suggested in prior studies. He et al evaluated mortality and obstructive sleep apnea, using solely the apnea index as their measure of OSAS severity. They found that an apnea index >20 was associated with an increased mortality in patients younger than 50 years but not clearly associated with an increased mortality in patients older than 50 years. Similar to our findings, this observation is likely related to confounding variables with advancing age. In other large prospective studies, such as the Wisconsin Sleep Cohort,7 Busselton Health Study,8 and the Sleep Heart Health Study,9 the authors clearly identified OSAS as an independent risk factor for all-cause mortality. However, these studies looked primarily at AHI alone as a measure of sleep apnea severity. In addition, the Sleep Heart Health cohort stratified ages either older or younger than 70 years, and the Busselton cohorts had a minimum age of 40, with no stratification for younger patients. This observation of increased mortality in younger patients may be associated with a number of factors. The leading cause of death in the population between ages 1 and 44 years is unintentional injuries.14 One common untreated consequence of OSAS is increased daytime somnolence. Perhaps the interplay of OSAS and hypersonomnolence manifests itself in the younger patient population as an increased risk of accidental death. For example, the effect of OSAS on increased risk of motor vehicle accidents has been clearly demonstrated in the general population.15,16 The Epworth Sleepiness Score, as a measure of subjective sleepiness, was explored to assess for this relationship, but no significant age-, sex-, and BMI-adjusted relationship could be found between the ESS and all-cause mortality.

The study does have limitations. Primarily, as a database study, our data cannot show a causal relationship between sleep apnea severity and mortality but rather is an epidemiologic hypothesis-generating study. It can only be suggested that there is an association between all-cause mortality and OSAS. As also noted in a prior study using the same data set, the quality of the results is of course dependent on the quality of the databases. The SNAP Diagnostics database is an internally maintained database and is believed to be very accurate. Both databases are subject to random distribution of error that should have been accounted for within the analysis using standard statistical methods. Also, although the SNAP test has been validated compared with traditional polysomnograms, there is a possibility of sampling bias as patients with more severe sleep apnea may be referred to formal sleep labs vs home testing. Another important limitation of the study is that the data could be adjusted only for the variables that were available within the databases (AHI, AI, DI, BMI, age, male sex, neck girth, ESS). There may very well be other important confounding variables that could not be taken into consideration due to unavailability. In addition, neither database accounted for any possible

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### Table 4. Age- and Sex-Adjusted Hazard Ratios for Various Covariates Stratified Over 10-Year Age Groups

<table>
<thead>
<tr>
<th>Age Range, y</th>
<th>OSAS Severity, HR (95% CI)</th>
<th>Apnea Index, HR (95% CI)</th>
<th>Desaturation Index, HR (95% CI)</th>
<th>BMI, HR adjusted (95% CI)</th>
<th>Male Sex, HR adjusted (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30 (n = 4367)</td>
<td>0.75 (1.063-1.922)</td>
<td>1.632 (1.053-2.532)</td>
<td>1.195 (0.576-2.480)</td>
<td>1.040 (0.991-1.092)</td>
<td>1.626 (0.657-4.014)</td>
</tr>
<tr>
<td>31-40 (n = 15,965)</td>
<td>0.85 (1.001-1.298)</td>
<td>1.140 (1.118-1.771)</td>
<td>1.478 (1.069-2.043)</td>
<td>1.047 (1.019-1.075)</td>
<td>1.973 (1.188-3.278)</td>
</tr>
<tr>
<td>41-50 (n = 25,195)</td>
<td>1.23 (1.094-1.339)</td>
<td>1.140 (1.001-1.298)</td>
<td>1.217 (1.014-1.461)</td>
<td>1.022 (1.004-1.041)</td>
<td>0.959 (0.740-1.241)</td>
</tr>
<tr>
<td>51-60 (n = 20,306)</td>
<td>2.54 (0.828-1.066)</td>
<td>0.972 (0.877-1.076)</td>
<td>0.946 (0.815-1.098)</td>
<td>1.057 (1.043-1.071)</td>
<td>1.419 (1.149-1.752)</td>
</tr>
<tr>
<td>61-70 (n = 7816)</td>
<td>6.01 (0.922-1.194)</td>
<td>1.066 (0.954-1.191)</td>
<td>0.962 (0.812-1.141)</td>
<td>1.047 (1.031-1.063)</td>
<td>1.408 (1.123-1.764)</td>
</tr>
</tbody>
</table>

Notice how in the younger subjects, the apnea-hypopnea index (AHI) and similar measures are significantly associated with all-cause mortality, but as age advances, body mass index (BMI) and male sex begin to dominate. Bold values indicate statistically significant hazard ratios. Abbreviations: CI, confidence interval; HR, hazard ratio; OSAS, obstructive sleep apnea syndrome.

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*aBMI and sex-adjusted HR for increasing OSAS severity: mild (AHI = 5-15), moderate (16-30), and severe (>30).

*bBMI and sex-adjusted HR for the apnea index (events/h) divided into 4 equal quartiles.

*cBMI and sex-adjusted HR for pulse oximetry desaturation index (events below 94% per hour) divided into 4 equal quartiles.
medical or surgical treatment for obstructive sleep apnea, which could necessarily have affected the mortality rate.

**Conclusion**

In conclusion, after adjusting for strong confounding variables such as age, sex, and BMI, there is a modest association between sleep apnea severity measurements and all-cause mortality. This relationship is more evident in younger patients due to less confounding by age and BMI. Further prospective investigation is required to more precisely explore the association between sleep apnea severity and mortality.

**Disclaimer**

The views herein are the private views of the authors and do not reflect the views of the Department of the Army or the Department of Defense.

**Author Contributions**

Jeremy Rich, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; Ayelette Raviv, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, final approval of the version to be published, contributed to data collection and to analysis but did not have final decision regarding data analysis and interpretation; Nataly Raviv, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, final approval of the version to be published, contributed to data collection and to analysis but did not have final decision regarding data analysis and interpretation; Scott E. Brietzke, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published, supervision, and final decisions on data analysis and interpretation.

**Disclosures**

**Competing interests:** Ayelette Raviv, familial relationship to president and CEO of SNAP Diagnostics; stock valued at $500; independent contractor and representative of the company in New York since April 2010. Nataly Raviv, familial relationship to president and CEO of SNAP Diagnostics; stock valued at less than $500 in shares.

**Sponsorships:** Snap Diagnostics provided unrestricted access to its proprietary database of SNAP study results. The sponsor had no influence over the data analysis or interpretation.

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**References**