ORIGINAL RESEARCH

The Association between All-Cause Mortality and Obstructive Sleep Apnea in Adults: A U-Shaped Curve

Mehrnaz Azarian[1,3*], Amin Ramezani[1,3*], Amir Sharafkhaneh[2,3], Arash Maghsoudi[1,3], Meir Kryger[5], Robert J. Thomas[6], M. Brandon Westover[7,8], and Javad Razjouyan[1,3,4]

[1]Center for Innovations in Quality, Effectiveness, and Safety and [2]Pulmonary, Critical Care, and Sleep Medicine Section, Medical Care Line, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [3]Department of Medicine, Baylor College of Medicine, Houston, Texas; [4]Big Data Scientist Training Enhancement Program (BD-STEP), Veterans Affairs Office of Research and Development, Washington, District of Columbia; [5]Pulmonary, Critical Care, and Sleep Medicine, Yale School of Medicine, Yale University, New Haven, Connecticut; [6]Division of Pulmonary, Critical Care, and Sleep Medicine and [7]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and [8]Division of Sleep Medicine, Harvard Medical School, Boston, Massachusetts

ORCID IDs: 0009-0000-1555-678X (M.A.); 0009-0002-7952-3009 (A.R.); 0000-0002-7893-2946 (A.S.); 0000-0002-1883-0753 (A.M.); 0009-0007-3799-8280 (M.K.); 0000-0002-5575-3953 (R.J.T.); 0000-0003-4803-312X (M.B.W.); 0000-0003-1157-159X (J.R.).

Abstract

Rationale: The relationship between sleep apnea (SA) and mortality remains a topic of debate.

Objectives: We explored the relationship between the severity of SA and mortality and the effect of age on this association.

Methods: Using a veterans' database, we extracted an apnea–hypopnea index (AHI) from physician interpretations of sleep studies by developing a natural language processing pipeline (with 944 manually annotated notes), which achieved more than 85% accuracy. We categorized the participants into no SA (n-SA; AHI, <5), mild to moderate SA (m-SA; $5 \leqslant \text{AHI} < 30$), and severe SA (s-SA; AHI, $\geqslant 30$). We propensity-matched the m-SA and s-SA categories with n-SA on the basis of age, sex, race, ethnicity, body mass index, and 38 components of the Elixhauser Comorbidity Index. Using logistic regression, we estimated the odds ratio (OR) for all-cause mortality using m-SA as a reference. Also, we stratified the findings on the basis of age: young, $\leqslant 40$; middle aged, >40 and <65; and older, $\geqslant 65$ adults.

Results: We extracted the AHI on 179,121 propensity-matched participants (mean age = 45.85 [SD = 14.1]; BMI = 30.15 $\pm$ 5.37 kg/m^2; male, 79.09%; White, 64.5%). All-cause mortality rates among three AHI categories showed a U-shaped curve (11.55%, 7.07%, and 8.15% for n-SA, m-SA, and s-SA, respectively), regardless of age group. Compared with m-SA, the odds of all-cause mortality in n-SA (OR, 1.72; 95% confidence interval = 1.65–1.79) and s-SA (OR, 1.17; 95% confidence interval = 1.12–1.22) were higher. Stratifying by age yielded consistent findings.

Conclusions: All-cause mortality showed a U-shaped association with the AHI. Further investigations to understand the underlying mechanisms of this phenomenon are warranted.

Keywords: sleep apnea; Apnea–Hypopnea index; mortality; natural language processing; intermittent hypoxia

(Received in original form July 20, 2024; accepted in final form December 11, 2024)

*Co–first authors.

Supported by National Heart, Lung, and Blood Institute K25 funding (1K25HL152006-01 to J.R.); the Airborne Hazards and Burn Pits Center of Excellence (award FY2024-002 to J.R.); and the Center for Innovations in Quality, Effectiveness, and Safety (CIN 13-413), Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas. The opinions expressed are those of the authors and not necessarily those of the Department of Veterans Affairs, the U.S. government, or Baylor College of Medicine. The authors do not report any off-label or investigational use related to the topic of this study.

Author Contributions: All authors were responsible for the conception and design of the study, provided methodological and statistical analysis guidance, and contributed to data interpretation. J.R., A.R., A.M., M.A., and A.S. contributed to data acquisition and analysis. M.A., A.R., A.S., A.M., and J.R. drafted the manuscript. All authors (M.A., A.R., A.S., A.M., M.K., R.J.T., M.B.W., and J.R.) reviewed and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for the integrity and accuracy of the work.

Correspondence and requests for reprints should be addressed to Amir Sharafkhaneh, M.D., Ph.D., Department of Medicine, Baylor College of Medicine, 2002 Holcombe Blvd, Houston, TX 77030. E-mail: amirs@bcm.edu.

This article has a data supplement, which is accessible at the Supplements tab.

Ann Am Thorac Soc Vol 22, No 4, pp 581–590, Apr 2025

DOI: 10.1513/AnnalsATS.202407-755OC
Internet address: www.atsjournals.org

Sleep apnea (SA) involves reduced or stopped airflow that is due to airway blockage during sleep, leading to disrupted breathing, intermittent hypoxia (IH), and fragmented sleep (1). In a minority of cases, SA is due to central respiratory events (2). SA is a major public health issue that is linked to increased risk of various adverse health outcomes (3) and all-cause mortality (4, 5). The severity of SA is measured by an apnea–hypopnea index (AHI), which counts the episodes of apneas and hypopneas during sleep (6, 7).

The connection between SA severity and mortality is debated. Some studies find a positive link between higher AHI and mortality (8–12), whereas others suggest that moderate SA and IH may protect against death (13, 14). Although IH may contribute to the development of SA-related comorbidities (15), recent research suggests that IH may also provide protective advantages during and after acute vital organ injuries (16, 17). This phenomenon, known as ischemic or hypoxic preconditioning, occurs when chronic IH is administered below the threshold of damage, resulting in increased tolerance to severe ischemia exposure (18). The impact of SA on mortality varies by gender (10) and age, with higher mortality rates observed in those under 50 (5, 19).

To extract the AHI from clinical notes, we used natural language processing (NLP) (20–22). We further developed the NLP pipeline by using a transformer-based language model to identify the AHI in the text and determine the correct value from any sleep notes. In this study, we explored the relationship among different categories of SA severity (measured by the AHI) and odds of all-cause mortality, particularly considering the role of age, hypothesizing a nonlinear relation between AHI category and mortality.

Methods

The research project received approval from the Baylor College of Medicine Institutional Review Board (Protocol H-35366) and the Research and Development Committee at the Michael E. DeBakey Veterans Affairs (VA) Medical Center.

Research Design and Participant Data Collection

This retrospective cohort study utilized electronic medical records from the Veterans Health Administration (VHA) to investigate sleep-related conditions. We used the entire national VA database. The database included all the diagnosis and procedures from inpatient and outpatient encounters within the VHA healthcare system, in addition to the encounters that the VHA paid for them. The initial cohort comprised veterans who had been referred to the VHA between October 1, 1999, and September 30, 2022, with sleep-related International Classification of Diseases (ICD) codes (ninth edition or 10th edition; ICD-9 or ICD-10, respectively) and Current Procedural Terminology (CPT) codes related to sleep services (0203T, 0204T, 95782, 95783, 95800, 95801, 95806, 95808, 95810, 95811, 95819, 95821, 95822, 95827, 95828, 99508, G0398, G0399, and G0400). The cohort was refined to include individuals with specific CPT codes, and reports that contained key search terms in their titles (e.g., "home sleep testing (HST)," "polysomnography (PSG)," "SLEEP," "Polysomnography (POLY)," and "Home Sleep Apnea Testing (HSAT)") were selected. Further refinement involved the presence of specific search terms in the text's main body (e.g., "AHI," "Apnea," "Hypopnea"). For patients with multiple visits, data from the first visit that documented the AHI in freeform text were considered as referring to the index date. We further limited the study population to individuals without positive airway pressure (PAP) treatment before the index date, as identified with CPT codes for PAP treatment that were provided by the National Sleep Program executive director's office to identify the documentation of PAP usage (94660, E0452, E0470, E0471, E0472, E0601, G8845, and G8852). For a depiction of the strobe diagram, *see* Figure E1 in the data supplement.

Study Variables

Outcome variables. The primary outcome was all-cause mortality. All-cause mortality data were obtained from the Corporate Data Warehouse VHA Vital Status table, with combined information from Medicare, VA, Social Security, and VA Compensation and Pension Benefits to determine date of death, demonstrating a sensitivity of 98.3% and a specificity of 99.8% relative to the National Death Index (23, 24). Mortality data were recorded up to August 23, 2023. To assess the role of time in this association, we also reported the rate of all-cause mortality at an interval of 15 years after the index date.

Exposure variable. The exposure variable utilized in the study was the AHI. No sleep apnea (n-SA) was defined as an AHI of <5, mild to moderate sleep apnea (m-SA) was defined as $5 \leqslant \text{AHI} < 30$, and severe sleep apnea (s-SA) was defined as an AHI of $\geqslant 30$ (25). We excluded any participant with no SA receiving a PAP prescription 1 year after the index date.

Other variables. We collected patient demographics, including age (stratified into $\leqslant 40$, 40–65, and $\geqslant 65$ yr), body mass index (BMI; categorized as obese with a BMI of $\geqslant 30$ kg/m^2), sex, race (categorized as White, Black, and other), ethnicity (Hispanic), Charlson Comorbidity Index (CCI), and Elixhauser Comorbidity Index (Elix-CI). For ethnicity, we considered those with documentation of ethnicity as one. The rest—null, unknown, or unanswered—were considered as zero. Using ICD-9 and ICD-10 codes for different comorbidities (*see* Table E1), we calculated the CCI, in addition to specific rates of each associated condition. The data on comorbid conditions were collected from inpatient or outpatient encounters within a year before the index date (26). Using PAP-related CPT codes, we calculated the proportion of patients with PAP prescriptions within 1 year after the index date. The follow-up time was extracted on the basis of the duration between the index date of each participant until the time of death or the end of the study period (September 2022).

NLP Method and Validation for AHI

In this study, we developed a specialized NLP pipeline tailored to extract AHI data from unstructured physician notes on the basis of PSG and HST interpretations of study participants. Initially, text preprocessing techniques such as stemming, lemmatization, and tokenization were applied. They utilized a pre-trained large language model (specifically, deepset-roberta-base-squad2 from the Hugging Face Hub) to generate concise summaries. The pipeline identified relevant segments by targeting search terms such as "AHI," "Apnea–Hypopnea Index," and "Sleep Apnea." Using formulated queries, the model extracted corresponding AHI values from the reports.

Validation involved testing the model on 40% of the cohort split equally between validation and test sets. To ensure diversity, we selected 10% of the records randomly from each center, preserving statistical distribution across different centers. This validation process confirmed the model's effectiveness across a varied population. RoBERTa was selected for its improvements

over BERT, offering enhanced word representations through a larger training dataset and dynamic masking. Custom NLP tasks were implemented using their own code (available on GitHub at https://github.com/aminramezani345/AHI_extraction_HST_PSG).

The study validated its NLP pipeline using 944 annotated notes categorized into three groups on the basis of AHI levels: n-SA (AHI $<$ 5), m-SA (5 $\leqslant$ AHI $<$ 30), and s-SA (30 $\leqslant$ AHI $\leqslant$ 80). Performance metrics such as recall (sensitivity), specificity (selectivity), positive predictive value (precision), negative predictive value, F1 score, and accuracy were calculated for each group (*see* Tables E1 and E2). Results showed an overall accuracy exceeding 87% for the NLP algorithm in extracting AHI information from unstructured notes. Discriminant performance between groups, showing the proportion of number of correct decisions to wrong decisions, was consistently high, surpassing 86% between groups (Table E2) and over 90% within each individual group (Table E3).

Statistical Analysis

We performed propensity score matching to balance covariates and to control for confounding factors (27, 28). The participants in the m-SA and s-SA categories were propensity-matched separately with the n-SA category on the basis of the following traits: age, sex, race, ethnicity, BMI, and 38 components of the Elixhauser Comorbidity Index. It is noteworthy that, because we assumed that the participants had VHA connectivity of care, we did not use the insurance status and service connection as additional variables for propensity score matching. The final sample of each category was randomly drawn from eligible propensity-matched participants using a ratio of 1-to-1 for a total of 59,707 in each category. We utilized R software (RStudio Team; http://www.rstudio.com/).

We used the chi-square test for categorical variables and the Student *t* test for continuous variables. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) reported for patients with s-SA and n-SA were referenced to those with m-SA. We performed subgroup analysis on the basis of age, and statistical significance was set at $P < 0.05$. To illustrate the relationship between SA groups and survival rate, we used Kaplan–Meier curves for the entire follow-up period and within 15 years. Additionally, we developed proportional hazard regression models to calculate relative hazard ratios for all-cause mortality. These analyses aimed to provide a comprehensive understanding of the impact of SA on mortality.

Results

The analysis cohort included 179,121 participants. Table 1 shows demographic characteristics for the entire cohort and among various SA categories. The cohort was predominantly male (79.09%), and the majority of participants were White (64.55) followed by Black (24.95%) and other races (10.5%). The mean age and mean BMI were 45.85 $\pm$ 14.1 and 30.15 $\pm$ 5.37 kg/m^2, respectively. The mean CCI for the entire cohort was 0.68 $\pm$ 1.32, with 14.68% of participants having a CCI of $\geqslant$2. The CCI values were similar among different SA categories because of propensity matching. The overall weighted average rates of mortality in the entire cohort, n-SA, m-SA, and s-SA, were 8.92%, 11.55%, 7.07%, and 8.15%, respectively. Limiting the follow-up period to 15 years showed rates of 8.48% for the entire cohort, and 10.87%, 6.78%, and 7.78% for the n-SA, m-SA, and s-SA, respectively. The mean follow-up times of the entire cohort, n-SA, m-SA, and s-SA, were 5.36 (SD = 4.45), 6.35 (SD = 4.63), 4.96 (SD = 4) and 4.77 (SD = 4.54), respectively. A table reporting the data before propensity matching is attached (*see* Table E4).

Table 2 illustrates the comprehensive stratification of baseline and clinical characteristics across different age groups and SA categories. Demographic characteristics did not differ among the groups because of propensity matching. Proportion of participants with a CCI of $\geqslant$2 increased with age. Medical comorbid conditions (cardiovascular, metabolic, neurologic, renal, and pulmonary) increased,

Table 1. Baseline characteristics of the sleep study cohort by AHI category

Characteristic	All Participants (*N* = 179,121)	n-SA, AHI < 5 (*n* = 59,707)	m-SA, 5 ⩽ AHI < 30 (*n* = 59,707)	s-SA, AHI ⩾ 30 (*n* = 59,707)
Male sex, *n* (%)	141,673 (79.09)	46,768 (78.33)	47,100 (78.89)	47,805 (80.07)
Ethnicity, Hispanic, *n* (%)	14,690 (8.2)	5,088 (8.52)	4,969 (8.32)	4,633 (7.76)
Race, *n* (%)				
White	115,625 (64.55)	37,919 (63.51)	38,274 (64.1)	39,432 (66.04)
Black	44,691 (24.95)	16,018 (26.83)	15,287 (25.6)	13,386 (22.42)
Other	18,805 (10.5)	5,770 (9.66)	6,146 (10.29)	6,889 (11.54)
Age, yr, mean (SD)	45.85 (14.1)	45.77 (14.5)	45.63 (14.3)	46.14 (13.48)
Young, ⩽40, *n* (%)	76,190 (42.54)	25,522 (42.75)	25,752 (43.13)	24,916 (41.73)
Middle aged, 40 < age < 65, *n* (%)	81,799 (45.67)	26,901 (45.06)	26,827 (44.93)	28,071 (47.01)
Older, ⩾65, *n* (%)	21,132 (11.8)	7,284 (12.2)	7,128 (11.94)	6,720 (11.25)
BMI, mean (SD)	30.15 (5.37)	30.14 (5.41)	30.21 (5.23)	30.11 (5.46)
BMI ⩾ 30 kg/m^2, *n* (%)	84,891 (47.39)	27,721 (46.43)	28,919 (48.43)	28,251 (47.32)
CCI, mean (SD)	0.68 (1.32)	0.68 (1.34)	0.68 (1.33)	0.67 (1.3)
CCI ⩾ 2, *n* (%)	26,291 (14.68)	8,981 (15.04)	8,717 (14.6)	8,593 (14.39)
Follow up time, mean (SD)	5.36 (4.45)	6.35 (4.63)	4.96 (4)	4.77 (4.54)
Overall all-cause mortality, *n* (%)	15,985 (8.92)	6,896 (11.55)	4,224 (7.07)	4,865 (8.15)
All-cause mortality in 15 yr, *n* (%)	15,184 (8.48)	6,490 (10.87)	4,050 (6.78)	4,644 (7.78)
Average AHI, mean (SD)	20.83 (21.8)	2.07 (1.37)	12.95 (6.66)	47.47 (16.01)

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CCI = Charlson Comorbidity Index; m-SA = mild to moderate sleep apnea; n-SA = no sleep apnea; s-SA = severe sleep apnea.

Table 2. Mortality rate and other clinical characteristics stratified by age groups and AHI categories

Clinical Characteristic and Mortality Rate	AHI Category by Age Group									
	Young			Middle-Aged			Older			
	n-SA	m-SA	s-SA	n-SA	m-SA	s-SA	n-SA	m-SA	s-SA
n	25,522	25,752	24,916	26,901	26,827	28,071	7,284	7,128	6,720
AHI, mean (SD)	1.97 (1.34)	12.22 (6.53)	43.77 (15.25)	2.13 (1.38)	13.32 (6.66)	49.53 (15.59)	2.22 (1.39)	14.21 (6.84)	52.54 (17.48)
BMI ⩾ 30 kg/m^2, mean (SD)	11,744 (46.02)	12,607 (48.96)	11,513 (46.21)	12,955 (48.16)	13,401 (49.95)	13,871 (49.41)	3,022 (41.49)	2,911 (40.84)	2,867 (42.66)
CCI ⩾ 2, *n* (%)	692 (2.71)	814 (3.16)	811 (3.25)	4,927 (18.32)	4,588 (17.1)	4,800 (17.1)	3,362 (46.16)	3,315 (46.51)	2,982 (44.38)
Insomnia, *n* (%)	6,925 (27.13)	6,190 (24.04)	6,346 (25.47)	6,162 (22.91)	5,666 (21.12)	5,556 (19.79)	1,275 (17.5)	1,227 (17.21)	1,093 (16.26)
Cardiovascular, *n* (%)	4,143 (16.23)	4,049 (15.72)	4,204 (16.87)	15,423 (57.33)	13,943 (51.97)	13,941 (49.66)	6,276 (86.16)	5,863 (82.25)	5,455 (81.18)
Metabolic, *n* (%)	5,788 (22.68)	7,103 (27.58)	7,048 (28.29)	16,577 (61.62)	17,030 (63.48)	17,438 (62.12)	6,131 (84.17)	6,101 (85.59)	5,624 (83.69)
Neurologic, *n* (%)	4,302 (16.86)	4,453 (17.29)	4,143 (16.63)	6,282 (23.35)	6,004 (22.38)	5,748 (20.48)	2,171 (29.81)	1,951 (27.37)	1,826 (27.17)
Psychiatry, *n* (%)	19,087 (74.79)	19,523 (75.81)	18,849 (75.65)	17,499 (65.05)	17,752 (66.17)	18,724 (66.7)	3,403 (46.72)	3,774 (52.95)	3,440 (51.19)
Renal, *n* (%)	1,019 (3.99)	1,210 (4.7)	1,309 (5.25)	3,728 (13.86)	3,805 (14.18)	3,673 (13.08)	2,221 (30.49)	2,240 (31.43)	1,987 (29.57)
Pulmonary, *n* (%)	2,963 (11.61)	3,662 (14.22)	3,678 (14.76)	7,407 (27.53)	7,216 (26.9)	7,863 (28.01)	3,370 (46.27)	3,036 (42.59)	2,706 (40.27)
PAP, *n* (%)	0 (0)	11,374 (44.17)	10,622 (42.63)	0 (0)	14,070 (52.45)	15,421 (54.94)	0 (0)	3,803 (53.35)	4,074 (60.62)
Overall all-cause mortality, *n* (%)	380 (1.49)	333 (1.29)	409 (1.64)	3,589 (13.34)	2,097 (7.82)	2,703 (9.63)	2,927 (40.18)	1,794 (25.17)	1,753 (26.09)
All-cause mortality in 15 yr, *n* (%)	366 (1.43)	328 (1.27)	392 (1.57)	3,303 (12.28)	1,969 (7.34)	2,538 (9.04)	2,821 (38.73)	1,753 (24.59)	1,714 (25.51)

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CCI = Charlson Comorbidity Index; m-SA = mild to moderate sleep apnea; n-SA = no sleep apnea; PAP = positive airway pressure; s-SA = severe sleep apnea.

whereas insomnia and psychiatry conditions declined with age. The proportion of those with PAP prescription increased with advancing age among both m-SA and s-SA categories.

Among all age groups, m-SA was associated with the lowest rate of all-cause mortality. In the young adult group, the rate of mortality was the lowest in the m-SA category, followed by the n-SA and s-SA categories (1.49%, 1.29%, and 1.64% for n-SA, m-SA, and s-SA, respectively; $P < 0.001$), whereas in the middle-aged group, n-SA (13.34%) had a prominently higher rate of all-cause mortality than that of s-SA (9.63%) which both were significantly higher than that of m-SA (7.82%) ($P < 0.001$). Similarly, in the older group, n-SA had the highest rate of all-cause mortality (40.18%), followed by s-SA (26.09%) and m-SA (25.17%) ($P < 0.001$). Limiting the time interval to 15 years showed a similar pattern among all age groups. The rate of mortality in 15 years among young adults in the m-SA category is 1.27%, followed by 1.43% in n-SA and 1.57% in s-SA. The rate for the middle-aged group was 7.34% in m-SA, followed by 9.04% in s-SA and 12.28% in n-SA. Also, among older adults, the rates were 24.59%, 25.51%, and 38.73% for m-SA, s-SA, and n-SA, respectively. Figure 1 compares all-cause mortality rates among the three SA categories for all participants and across the age groups and shows that the lowest rate of all-cause mortality is in the m-SA category, compared with rates in the two other categories, regardless of age. All-cause mortality in s-SA surpassed that in the n-SA category in the young adult group. However, in both middle-aged and older adults, this rate was considerably higher in the n-SA category. A similar table reporting the data before propensity matching is shown elsewhere (*see* Table E5).

Figure 2, which shows a comparison of the ORs and 95% CIs for the three SA categories, demonstrates a U-shaped association among categories of SA severity and the risk of all-cause mortality for all the age groups. A more detailed description of U-shaped behavior can be extracted from Table 3, showing that among all age groups, individuals with n-SA exhibited a noticeable elevation in the risk of all-cause mortality (OR, 1.72; 95% CI, 1.65–1.79) compared with the m-SA reference group. Similarly, the s-SA group manifested a modest increase in the odds of all-cause mortality, with an OR of

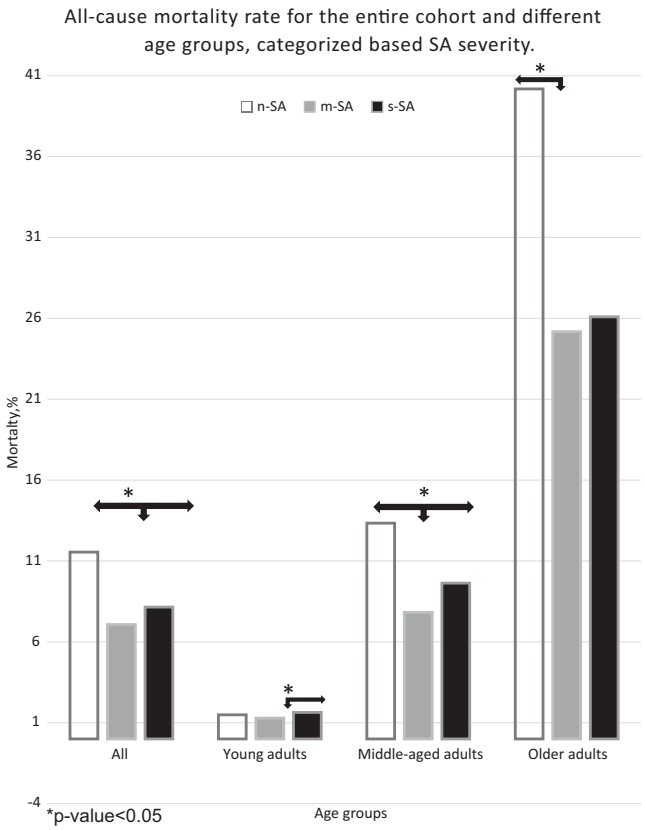

Figure 1. All-cause mortality rates for the entire cohort and different age groups, categorized on the basis of SA severity. *$p < 0.05$. m-SA = mild to moderate SA; n-SA = no SA; SA = sleep apnea; s-SA = severe SA.

1.17 (95% CI, 1.12–1.22), compared with the m-SA group. Within the cohort of young adults, those with s-SA had a 28% higher risk of all-cause mortality, compared with those with m-SA (OR, 1.28; 95% CI, 1.1–1.47), whereas those in the n-SA category did not have a significant difference in the risk of all-cause mortality compared with those in the m-SA category (OR, 1.15; 95% CI, 0.99–1.34). Among participants in the middle-aged group, n-SA was associated with an 82% elevated risk of all-cause mortality compared with the m-SA category (OR, 1.82; 95% CI, 1.72–1.92); and for the s-SA category, this rate was 25% (OR, 1.25; 95% CI, 1.18–1.33). Similarly, older adults exhibited double elevated risk of all-cause mortality for n-SA (OR, 2.00; 95% CI, 1.86–2.14) and no significant increase for s-SA (OR, 1.05; 95% CI, 0.97–1.13) in comparison with m-SA.

Figure 3 presents the Kaplan–Meier survival curves of the entire follow-up time, revealing distinctive survival patterns across varying SA severity categories for the three age groups. In the young adult group (Figure 3A), m-SA (reference) had the highest survival, followed by n-SA (hazard ratio [HR], 1.15; 95% CI, 0.99–1.33), and then s-SA with the lowest survival (HR, 1.27; 95% CI, 1.1–1.47). In contrast, among participants older than 40, although the highest survival again was found with m-SA (reference), this ranking was followed by s-SA (HR, 1.24; 95% CI, 1.18–1.32) and n-SA (HR, 1.75; 95% CI, 1.66–1.84) in the middle-aged group (Figure 3B), and there was a more prominent difference between s-SA and n-SA in the older group (for s-SA: HR, 1.04; 95% CI, 0.97–1.11; for n-SA: HR, 1.70; 95% CI, 1.61–1.81) (Figure 3C). The HRs for the entire cohort and different age groups showed a similar pattern to that shown in Figure 3; this pattern is summarized in Table 3. The OR and HR results of the data before being propensity-matched are reported elsewhere (*see* Tables E6 and E7). Table E6 reports the unadjusted and adjusted ORs on the basis of age, sex, race, ethnicity, BMI, and CCI. Table E7 reports the unadjusted and adjusted ORs on the basis of the mentioned variables. In addition, the Kaplan–Meier survival curves within the 15-year follow-up time are demonstrated (*see* Figure E2).

Discussion

In a retrospective study using AHI to measure SA in a large cohort of propensity-matched veterans, we found a U-shaped association between SA severity and all-cause mortality across different age groups. m-SA ($5 \leqslant$ AHI < 30) showed the lowest mortality rates compared with n-SA (AHI < 5) or s-SA (AHI $\geqslant 30$). This U-shaped pattern persisted across all age groups and became more pronounced with increasing age, with those without SA exhibiting the highest mortality rates.

Our findings provide real-world healthcare confirmation of prior investigations showing the survival advantage of SA (29–34). However, to our knowledge, this study is the first one demonstrating the U-shaped appearance among all ages. Although some studies have found that m-SA is associated with better survival among the elderly population (29), and some others have found that m-SA is associated with increased incidence of cardiovascular disease and all-cause mortality, with the exception of those with participants older than 60 (35, 36), none have comprehensively investigated the role of age on the association between different levels of AHI and all-cause mortality in a propensity-matched population of participants referred to sleep clinics. The nationwide study by Mohananey and colleagues found that patients hospitalized with myocardial infarction and recognized obstructive sleep apnea (OSA) had lower in-hospital mortality rates compared with those without OSA (30). Furthermore, two prior studies by our team revealed that SA is associated with lower in-hospital mortality in patients who were admitted for acute myocardial infarction, independent of demographic and comorbidity factors. In the first study, the adjusted OR of inpatient mortality reported 46% lower mortality in patients with SA compared with those without (13), and a 52% lower in-hospital mortality among obese patients with SA and a 46% reduction in nonobese patients with SA compared with that in the group of patients with neither obesity nor apnea, suggesting that SA contributes to the improved survival of obese patients with acute myocardial infarction (14).

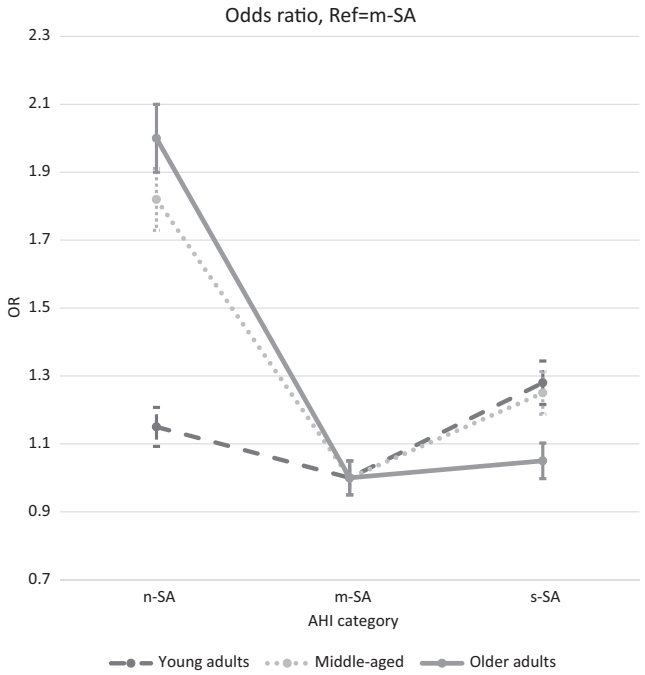

Figure 2. OR of all-cause mortality on the basis of sleep apnea (SA) severity for different age groups. Ref=m-SA. n-SA = no SA; OR = odds ratio; Ref=m-SA = reference was mild to moderate sleep apnea; s-SA = severe SA.

Moreover, another study by Masa and colleagues on patients with obesity hypoventilation syndrome showed that SA severity was associated with a lower risk of cardiovascular morbidity (37), which, by itself, is attributed to higher mortality observed in these patients (38).

Several potential mechanisms, such as ischemic preconditioning and compensatory physiologic adaptation, including vascular collateralization, may explain the observed survival advantage in patients with SA. These patients experience varying levels of hypoxia for years before receiving a diagnosis and undergoing treatment. This chronic intermittent hypoxic exposure may potentially lead to hypoxic preconditioning, enhancing the ability of organs to handle ischemia and reducing ischemia-reperfusion injuries (39–41). This effect resembles remote ischemic preconditioning, where brief cycles of ischemia and reperfusion in one tissue can protect distant organs from future ischemic damage (42).

The protective effects of SA on mortality may not apply universally across all bodily functions, including metabolic, inflammatory, and cognitive aspects. Sleep studies were prompted by clinical symptoms, suggesting that individuals were not entirely shielded from harm. Although cardiac benefits might reduce mortality, other mechanisms could mitigate the overall impact of SA-related distress, such as varying degrees of sleepiness and insomnia symptoms for any given AHI.

Lavie and colleagues (43) have reported that lower rates of mortality in patients with OSA who were older than 50 compared to the corresponding mortality rates in the general population. This survival advantage in older adults with m-SA, along with potential cardioprotective effects of chronic IH, suggests that SA may trigger adaptive pathways in the elderly (29). Additionally, another study by our team among patients in the same cohort explored the mortality risk between those with s-SA and those without SA and found that those older than 40 with s-SA had a significantly lower risk of mortality compared with those with n-SA. This phenomenon suggests that older adults with s-SA may be protected against adverse outcomes (44).

Furthermore, aligned with data from other studies, our data demonstrated higher adoption and utilization of PAP treatment among older adults. This may positively impact clinical outcomes in this group (45, 46). Further studies in our database are required to identify differential effects of PAP utilization on the U-shaped association of SA severity and all-cause mortality. The second possible explanation for this finding could be the beneficial healthcare utilization, as the older population has more encounters with the healthcare system for other comorbidities like SA, and some incidental conditions would be diagnosed in early stages (47). Furthermore, the highest rate of all-cause mortality among those with n-SA might be related to other deadly comorbidities other than SA, which increased the risk of death. Also, the differential effect of SA on all-cause mortality in different age groups may stem from their vulnerability to survivor bias.

The study utilized a large cohort of veterans from VHA sleep clinics, with rigorous propensity matching across various

Table 3. ORs and HRs (and 95% CIs) for all-cause mortality associated with SA

Entire Cohort	OR (95% CI)	HR (95% CI)
n-SA, AHI < 5	1.72 (1.65–1.79)	1.66 (1.6–1.73)
m-SA, 5 ⩽ AHI < 30	REF	REF
s-SA, AHI ⩾ 30	1.17 (1.12–1.22)	1.16 (1.11–1.21)
Age, yr, ⩽40		
n-SA, AHI < 5	1.15 (0.99–1.34)	1.15 (0.99–1.33)
m-SA, 5 ⩽ AHI < 30	REF	REF
s-SA, AHI ⩾ 30	1.28 (1.1–1.47)	1.27 (1.1–1.47)
Age, yr, 40 < age < 65		
n-SA, AHI < 5	1.82 (1.72–1.92)	1.75 (1.66–1.84)
m-SA, 5 ⩽ AHI < 30	REF	REF
s-SA, AHI ⩾ 30	1.25 (1.18–1.33)	1.24 (1.18–1.32)
Age, yr, ⩾65		
n-SA, AHI < 5	2 (1.86–2.14)	1.7 (1.61–1.81)
m-SA, 5 ⩽ AHI < 30	REF	REF
s-SA, AHI ⩾ 30	1.05 (0.97–1.13)	1.04 (0.97–1.11)

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; HR = hazard ratio; m-SA = mild to moderate SA; n-SA = no SA; OR = odds ratio; REF = reference; SA = sleep apnea; s-SA = severe SA.

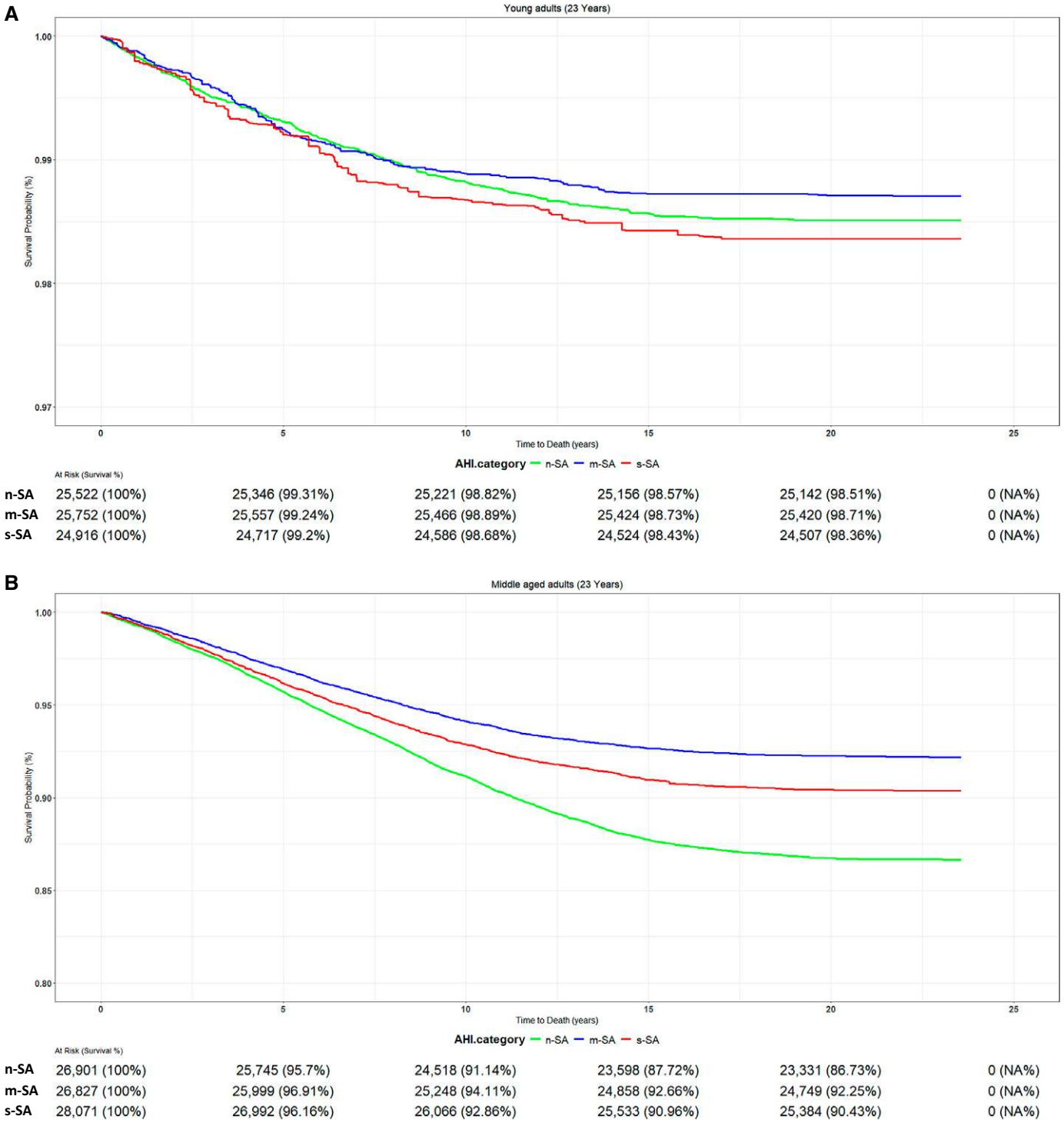

Figure 3. Kaplan–Meier survival curves of the entire follow up time across different age groups and AHI categories. (*A*) Young adults, (*B*) Middle-aged adults, and (*C*) Older adults. AHI = Apnea–Hypopnea Index; m-SA = mild to moderate sleep apnea; n-SA = no sleep apnea; s-SA = severe sleep apnea.

demographic and clinical factors. It stands out for its comprehensive size and extended follow-up duration compared with prior studies. Unlike community-based approaches, this study exclusively focuses on VHA participants, ensuring diversity across age, BMI, CCI, ethnicity, and race, with distributions approximating normality. Spanning from 2000 to 2022, the study covers nationwide VA centers and incorporates artificial intelligence–driven NLP for robust data extraction from physician notes. Notably, it stratifies age groups and AHI categories to provide detailed insights.

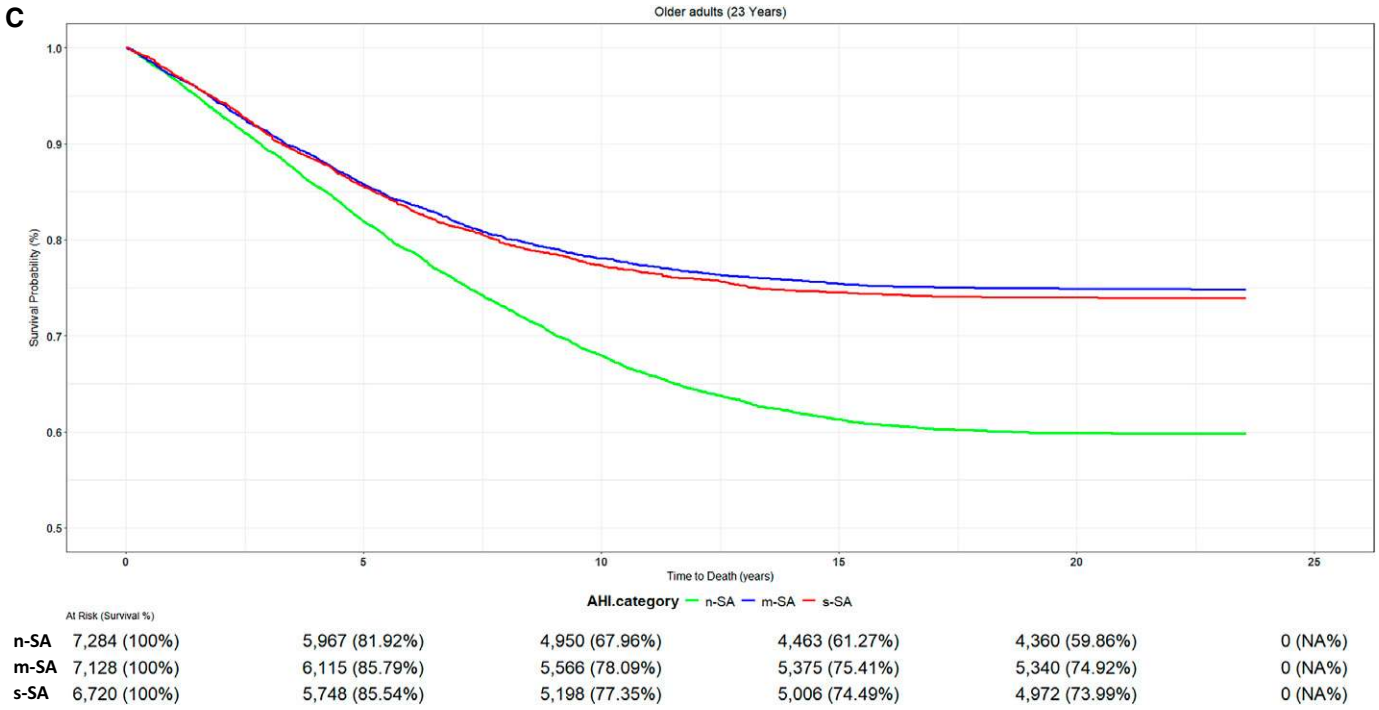

Figure 3. Continued.

Our study has several limitations. First, we relied solely on the AHI for diagnosing SA, lacking data on hypoxia severity and specific AHI types (e.g., AHI with a ⩾4% fall in oxyhemoglobin saturation, or AHI with a ⩾3% fall in oxyhemoglobin saturation or an event-related arousal), which may result in the misclassification of SA to different severity groups (48). Access to raw data and definitions of hypopneas used in sleep studies was also unavailable. Furthermore, the impact of potential night-to-night variabilities of SA on the findings should not be overlooked (49, 50). Additionally, insufficient PAP treatment data, including usage and adherence, could impact mortality outcomes. The n-SA category may not represent a true control group, as all patients had sleep-related issues. However, we did not have the information regarding the symptomology of various SA categories such as excessive daytime sleepiness and snoring. It is worth noting that sleep complaints—especially in older individuals, for whom specific information may be lacking—serve as a biomarker for poor outcomes, regardless of the presence of SA. Human error in annotating documents and a small number of annotated notes compromised the reliability of our NLP tasks, with an 85% accuracy limitation for the AHI. The study was predominantly male (approximately 80%), reflecting VHA demographics, which could bias results. We lacked data on causes of death and excluded veterans with sleep studies outside the VHA, potentially affecting cohort representativeness (insurance and socioeconomic status). We recognize the need for additional information, such as the distinction between OSA and central sleep apnea (CSA) and the consideration of study type (PSG vs. HST) and geographic location in our analysis. Previous investigations within our cohort have addressed some of these issues; for example, we studied OSA and CSA separately to compare mortality patterns, finding a trivial number of CSA cases (2). Another study that compared SA with mortality found no difference between PSG and HST results (44). Future research should explore gender-specific factors, assess how SA treatment variables such as PAP dosage and adherence affect SA severity and overall mortality, and investigate the utility of consumable disbursement as a treatment adherence indicator compared with PAP machine usage alone.

Conclusion

Our real-life clinical data revealed a U-shaped relationship between SA and all-cause mortality. Patients with mild to moderate SA exhibit the lowest mortality rates across all ages. Exploring the underlying pathophysiological mechanisms is essential. Future studies should identify an optimal AHI cutoff associated with reduced mortality, offering significant clinical insights. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors acknowledge the team of premedical and medical students who helped them with annotating several freeform text notes in the natural language processing development phase (Sanam Sharafkhaneh, Pooneh Rahimi, Trung Nguyen, and Sharonya Shetty).

References

1 Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. *JAMA* 2020;323:1389–1400.
2 Agrawal R, Sharafkhaneh A, Gottlieb DJ, Nowakowski S, Razjouyan J. Mortality patterns associated with central sleep apnea among veterans: a large, retrospective, longitudinal report. *Ann Am Thorac Soc* 2023;20: 450–455.
3 Mehrdad M, Azarian M, Sharafkhaneh A, Alavi A, Leili EK, Rad AH, *et al.* The association between OSA and glycemic control in diabetes. *Int J Prev Med* 2023;14:26.
4 Wang X, Ouyang Y, Wang Z, Zhao G, Liu L, Bi Y. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol* 2013;169: 207–214.
5 He J, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest* 1988;94:9–14.
6 Lim DC, Mazzotti DR, Sutherland K, Mindel JW, Kim J, Cistulli PA, *et al.*; SAGIC Investigators. Reinventing polysomnography in the age of precision medicine. *Sleep Med Rev* 2020;52:101313.
7 Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, Mcardle N, *et al.* Metrics of sleep apnea severity: beyond the apnea-hypopnea index. *Sleep* 2021;44:zsab030.
8 Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, *et al.* Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin Sleep Cohort. *Sleep* 2008;31:1071–1078.
9 Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, *et al.* Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6:e1000132.
10 Xie C, Zhu R, Tian Y, Wang K. Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. *BMJ Open* 2017;7:e013983.
11 Chung J, Goodman M, Huang T, Wallace ML, Lutsey PL, Chen JT, *et al.* Multi-dimensional sleep and mortality: the multi-ethnic study of atherosclerosis. *Sleep* 2023;46:zsad048.
12 Heilbrunn ES, Ssentongo P, Chinchilli VM, Oh J, Ssentongo AE. Sudden death in individuals with obstructive sleep apnoea: a systematic review and meta-analysis. *BMJ Open Respir Res* 2021;8:e000656.
13 Agrawal R, Sharafkhaneh A, Nambi V, BaHammam A, Razjouyan J. Obstructive sleep apnea modulates clinical outcomes post-acute myocardial infarction: a large longitudinal veterans' dataset report. *Respir Med* 2023;211:107214.
14 Sharafkhaneh A, Agrawal R, Nambi V, BaHammam A, Razjouyan J. Obesity paradox or hypoxia preconditioning: how obstructive sleep apnea modifies the obesity-MI relationship. *Sleep Med* 2023;110: 132–136.
15 Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. *Chest* 2015;147:266–274.
16 Almendros I, Wang Y, Gozal D. The polymorphic and contradictory aspects of intermittent hypoxia. *Am J Physiol Lung Cell Mol Physiol* 2014;307:L129–L140.
17 Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 2009;373:82–93.
18 Lavie L, Lavie P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. *Med Hypotheses* 2006;66:1069–1073.
19 Rich J, Raviv A, Raviv N, Brietzke SE. All-cause mortality and obstructive sleep apnea severity revisited. *Otolaryngol Head Neck Surg* 2012;147: 583–587.
20 Nadkarni PM, Ohno-Machado L, Chapman WW. Natural language processing: an introduction. *J Am Med Inform Assoc* 2011;18:544–551.
21 Gehrmann S, Dernoncourt F, Li Y, Carlson ET, Wu JT, Welt J, et al. Comparing rule-based and deep learning models for patient phenotyping [preprint]. arXiv; 2017: arXiv:1703.08705 [accessed 2024 Jan 20]. Available from: https://arxiv.org/abs/1703.08705.
22 Rahman M, Nowakowski S, Agrawal R, Naik A, Sharafkhaneh A, Razjouyan J, editors. Validation of a natural language processing algorithm for the extraction of the sleep parameters from the polysomnography reports. *Healthcare* 2022;10:1837.
23 Ramanathan D. VIReC factbook: Corporate Data Warehouse (CDW) vital signs 1.1 domain. Hines, IL. 2018. Available from: https://www.vendorportal.ecms.va.gov.
24 Sohn M-W, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr* 2006;4:2.
25 Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine task force. *Sleep* 1999;22:667–689.
26 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619.
27 Lee Y, Leite WL, Leroux AJ. Propensity score matching with cross-classified data structures: a comparison of methods. *J Exp Educ* 2024; 92:359–376.
28 Wong EC, Dulai PS, Marshall JK, Jairath V, Reinisch W, Narula N. Matching-adjusted indirect comparisons vs propensity score matching with individual patient-level data to estimate treatment efficacy. *Inflamm Bowel Dis* 2024;30:311–313.
29 Lavie P, Lavie L. Unexpected survival advantage in elderly people with moderate sleep apnoea. *J Sleep Res* 2009;18:397–403.
30 Mohananey D, Villablanca PA, Gupta T, Agrawal S, Faulx M, Menon V, *et al.* Recognized obstructive sleep apnea is associated with improved in-hospital outcomes after ST elevation myocardial infarction. *J Am Heart Assoc* 2017;6:e006133.
31 Naranjo M, Willes L, Prillaman BA, Quan SF, Sharma S. Undiagnosed OSA may significantly affect outcomes in adults admitted for COPD in an inner-city hospital. *Chest* 2020;158:1198–1207.
32 Lyons PG, Zadravecz FJ, Edelson DP, Mokhlesi B, Churpek MM. Obstructive sleep apnea and adverse outcomes in surgical and nonsurgical patients on the wards. *J Hosp Med* 2015;10: 592–598.
33 May AM. Sleep-disordered breathing and inpatient outcomes in nonsurgical patients: analysis of the Nationwide Inpatient Cohort. *Ann Am Thorac Soc* 2023;20:1784–1790.
34 Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after bariatric surgery: analysis of the nationwide inpatient sample. *Obes Surg* 2013; 23:1842–1851.
35 Vgontzas AN, Karagkouni E, He F, Li Y, Karataraki M, Fernandez-Mendoza J, *et al.* Mild-to-moderate obstructive sleep apnea and mortality risk in a general population sample: the modifying effect of age and cardiovascular/cerebrovascular comorbidity. *J Sleep Res* 2024;33:e13944.
36 Vgontzas AN, He F, Fernandez-Mendoza J, Karagkouni E, Pejovic S, Karataraki M, *et al.* Age-related differences in the association of mild-to-moderate sleep apnea with incident cardiovascular and cerebrovascular diseases. *Sleep Med* 2024;113:306–312.
37 Masa JF, Corral J, Romero A, Caballero C, Terán-Santos J, Alonso-Álvarez ML, *et al.*; Spanish Sleep Network. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. *Chest* 2016;150:68–79.
38 Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, *et al.* Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004; 116:1–7.
39 Jarrard CP, Nagel MJ, Stray-Gundersen S, Tanaka H, Lalande S. Hypoxic preconditioning attenuates ischemia-reperfusion injury in young healthy adults. *J Appl Physiol (1985)* 2021;130:846–852.
40 Ozeke O, Ozer C, Gungor M, Celenk MK, Dincer H, Ilicin G. Chronic intermittent hypoxia caused by obstructive sleep apnea may play an important role in explaining the morbidity-mortality paradox of obesity. *Med Hypotheses* 2011;76:61–63.
41 Sharp FR, Ran R, Lu A, Tang Y, Strauss KI, Glass T, *et al.* Hypoxic preconditioning protects against ischemic brain injury. *NeuroRx* 2004;1: 26–35.
42 Donato M, Bin EP, D'Annunzio V, Gelpi RJ. Myocardial remote ischemic preconditioning: from cell biology to clinical application. *Mol Cell Biochem* 2021;476:3857–3867.

43 Lavie P, Lavie L, Herer P. All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. *Eur Respir J* 2005;25: 514–520.
44 Ramezani A, Azarian M, Sharafkhaneh A, Maghsoudi A, Jones MB, Penzel T, *et al.* Age modifies the association between severe sleep apnea and all-cause mortality. *Sleep Med* 2024;121:18–24.
45 Broström A, Ulander M, Nilsen P, Lin C-Y, Pakpour AH. Development and psychometric evaluation of the Motivation to Use CPAP Scale (MUC-S) using factorial structure and Rasch analysis among patients with obstructive sleep apnea before CPAP treatment is initiated. *Sleep Breath* 2021;25:627–637.
46 May AM, Gharibeh T, Wang L, Hurley A, Walia H, Strohl KP, *et al.* CPAP adherence predictors in a randomized trial of moderate-to-severe OSA enriched with women and minorities. *Chest* 2018;154:567–578.
47 Terret C, Castel-Kremer E, Albrand G, Droz JP. Effects of comorbidity on screening and early diagnosis of cancer in elderly people. *Lancet Oncol* 2009;10:80–87.
48 Mansukhani MP, Kolla BP, Wang Z, Morgenthaler TI. Effect of varying definitions of hypopnea on the diagnosis and clinical outcomes of sleep-disordered breathing: a systematic review and meta-analysis. *J Clin Sleep Med* 2019;15:687–696.
49 Lechat B, Naik G, Reynolds A, Aishah A, Scott H, Loffler KA, *et al.* Multinight prevalence, variability, and diagnostic misclassification of obstructive sleep apnea. *Am J Respir Crit Care Med* 2022;205: 563–569.
50 Punjabi NM, Patil S, Crainiceanu C, Aurora RN. Variability and misclassification of sleep apnea severity based on multi-night testing. *Chest* 2020;158:365–373.