Title: Apnea-hypopnea event duration predicts mortality in men and women in the Sleep Heart Health Study

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At a Glance Commentary:

- **Scientific Knowledge on the Subject.** Obstructive sleep apnea (OSA) is a disorder characterized by repetitive cycles of upper airway collapse during sleep and subsequent arousals from sleep. The most common OSA-defining metric, the apnea hypopnea index (AHI), has been shown to predict risk for mortality in some but not all studies, with differences in associations observed by age and gender. Emerging data indicate that there is considerable physiological variability across and between nights within patients with OSA that is not captured by the AHI. Studies using additional features of OSA may shed light on OSA-related morbidity and mortality in the population and provide insights into underlying pathophysiological differences that influence health outcomes.

- **What This Study Adds to the Field.** We characterized respiratory event duration, a heritable measure that reflects physiological features of OSA (arousal threshold) in a large prospective cohort. Adjusted analyses showed that short event duration predicts all-cause mortality over and beyond that predicted by the AHI. Moreover, associations between short event duration and mortality were observed in both men and women. This measure, readily available from routine polysomnography records, may help improve phenotyping of OSA-associated risk in the population, including helping to identify subgroups with low arousal threshold at risk for adverse outcomes.

Abstract

Rationale. Obstructive sleep apnea is a risk factor for mortality, but its diagnostic metric—the apnea-hypopnea index—is a poor risk predictor. This apnea-hypopnea index does not capture the range of physiological variability within and between patients, such as degree of hypoxemia and sleep fragmentation, that reflect differences in pathophysiological contributions of airway collapsibility, chemoreceptive negative feedback loop gain, and arousal threshold. Objective. To test whether respiratory event duration, a heritable sleep apnea trait reflective of arousal threshold, predicts all-cause mortality. Methods. Mortality risk as a function of event duration was estimated by Cox proportional hazards in the Sleep Heart Health Study, a prospective community-based cohort. Gender-specific hazard ratios were also calculated. Measurements and Main Results: Among 5712 participants, 1290 deaths occurred over 11 years of follow-up. After adjusting for demographic factors (mean age 63 years old; 52% female), apnea-hypopnea index (mean 13.8; standard deviation 15.0), smoking, and prevalent cardio-metabolic disease, individuals with the shortest duration events had a significant hazard ratio for all-cause mortality of 1.31 [95% confidence interval: 1.11-1.54]. This relationship was observed in both men and women and was strongest in those with moderate sleep apnea (hazard ratio = 1.59 [1.11-2.28]). Conclusions: Short respiratory event duration, a marker for low arousal threshold, predicts mortality in men and women. Individuals with shorter respiratory events may be predisposed to increased ventilatory instability and/or have augmented autonomic nervous system responses that increase the likelihood of adverse health outcomes, underscoring the importance of assessing physiological variation in obstructive sleep apnea.

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Key words: obstructive sleep apnea; sleep; epidemiology; mortality; prospective

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by repeated airway collapse during sleep. The occlusion of the airway causes a cascade of physiological responses including hypoxemia, hypercapnia, intrathoracic pressure swings due to inspiratory effort, activation of the sympathetic nervous system, and arousal from sleep (1). These acute consequences of each apnea are presumed to play a role in the long term comorbidities associated with OSA that include cardiovascular disease and mortality (1-4). Clinical practice characterizes OSA severity using the apnea hypopnea index (AHI), defined as the average number of respiratory events experienced per hour of sleep, calculated across the total sleep time. Although easy to calculate, this measure ignores other parameters of the apneas that may be informative, including associated hypoxemia and sleep fragmentation, as well as the duration of each event and the distribution of the events in each lying posture, within the night and within sleep stages (5-7).

Recent data suggest that OSA may be characterized by clusters of polysomnographic features that differ in their predictive associations with cerebro-and cardio-vascular outcomes (8), supporting the likelihood of significant physiological variability among patients with similar AHI levels. While this report included measurements of sleep fragmentation, it did not include direct measurements of arousal threshold or indirect measurements, such as duration of respiratory events. Event duration is readily calculated, but an inadequately studied trait which will partly determine the extent of hypoxemia, hypercapnia, and end inspiratory effort—all key physiological stressors. Event duration is a heritable phenotype (9) with shorter events reflecting greater arousability due to lower arousal threshold or increased sensitivity of the respiratory chemical control system (10-12). Therefore, short duration events may indicate a phenotype of

hypersensitivity and hyperarousability—expected to exhibit sympathoexcitation, sleep fragmentation and insomnia rather than sleepiness—that may respond to interventions that help consolidate sleep (13-17). The recent discovery of novel genetic loci that associate with event duration further supports the importance of this phenotype (18).

Given the heritability of event duration and its association with physiologically important traits, we analyzed data from the prospective Sleep Heart Health Study (SHHS) to test the hypothesis that respiratory event duration is associated with all-cause mortality. Given the inconsistencies of the literature in regards to the association between AHI and mortality and cardiovascular risk in women (2-4, 19, 20), we also explored gender-specific effects. Some preliminary results of these studies have been previously reported in an abstract (21).

Methods

Sample characteristics

The sample is a subset of 5804 subjects from the Sleep Heart Health Study (SHHS), publically available through the National Sleep Research Resource (https://sleepdata.org/). The SHHS is a community-based, prospective cohort study, designed to assess the cardiovascular consequences of sleep apnea (22). At baseline, participants completed questionnaires; had height, weight and blood pressure measured; and underwent overnight unattended polysomnography. Additional covariate data were provided by the parent cohorts. Cardiovascular outcomes and mortality data through 2010 were analyzed (mean follow-up of 11 years). The construction of the analytical sample is shown in **Fig. 1**. The SHHS protocol was approved by the Institutional Review Board of each participating center, and signed informed consent was provided by each

subject. The dataset has been pseudonymized by removing all PHI identifiers and assigning each participant a new randomly-generated code. The Institutional Review Board of Oregon Health & Science University determined that the current study of ~~de-identified~~pseudonymized data was not human subjects research (IRB ID 00017510). Complete methods are included in the Online Data Supplement and **Supplemental Tables E1** and **E2**.

Independent variables, covariates, and endpoints

The primary exposure variable was the mean duration of all apneas and hypopneas during any stage of sleep and in any body position (details in the Online Data Supplement). Respiratory events (>10 sec) were scored as apneas or hypopneas based on oronasal airflow from thermistry. ~~Only respiratory disturbances >10 sec qualified as events.~~ Obstructive apneas and hypopneas with and without desaturation criteria of 2, 3, or 4% were separately analyzed. Central apneas were not included in the analysis.

Other variables considered were age, gender, BMI, race, smoking status, and prevalent hypertension, diabetes, coronary heart disease, stroke, or heart failure. Variables derived from polysomnography included: total sleep time, duration of the nighttime spent awake after the initial sleep onset (WASO), AHI (respiratory events with ≥3% desaturation per hour of sleep), arousal index, and percent of sleep with oxygen saturation <90%.

The endpoint of all-cause mortality was defined as any confirmed death between the time of enrollment (1995-1998) and the end date of the study (2011). Mortality was ascertained from hospital records, obituaries, contact with next-of-kin, and the Social Security Administration, as described previously (2).

Statistical Analyses.

Associations between respiratory event duration and mortality were assessed with Cox proportional hazard models. ~~, with the proportional hazard assumption met according to~~ All models satisfied the proportional hazard assumption according to the ~~the~~ Grambsch and Therneau test ~~of Schoenfeld residuals~~ (23): all models had p>.12 for the global test. Individual plots of Schoenfeld residuals for each predictor against time-to-event showed no overt trends. Event duration was categorized into quartiles with quartile 1 (Q1: longest event durations) serving as a reference category for quartiles 2-4 (Q2-Q4, in order of decreasing event duration). Three models were constructed. The base model included event duration and covariates of age, gender, race, smoking status, and BMI. Model 2 included the variables in Model 1 plus AHI. Model 3 included the variables in Model 2 plus prevalent hypertension, diabetes, stroke, coronary heart disease, and heart failure. Several other variables were added to Model 3 in sensitivity analyses as described in the Results.

Adjusted survival plots were constructed from the Model 3 Cox regression coefficients. The reference survival curve represents the median risk based on the distribution of risk scores (coefficients × predictors) for the full population, and then incremented by the risk associated with each quartile of apnea duration. Plots were also constructed for the gender-stratified Cox models.

In cross-sectional analyses, the correlations among event duration and other continuous variables were assessed by Spearman's rho or X^2 likelihood ratio tests. Differences among quartiles were assessed by Wilcoxon/Kruskal-Wallis or 1-way ANOVA. All statistical tests were conducted in R (Rstudio 1.1.383 running R version 3.3.2) or JMP Pro 11.0.0 (SAS Institute, Cary NC).

Results

The sample of 5712 participants (**Table 1**) had a mean age of 63.3 years and mean BMI of 28 at baseline, and were followed for an average of 11.0 years (median 11.8, range 0.01-15.9). The sample was 52% female, 85% Caucasian, and 9% African American (because of small sample sizes, other racial groups were combined: 6% of the sample). The sample included people across the range of ~~AHI~~ OSA severity (12% severe, 20% moderate, 35% mild, 33% none). ~~67% with mild or more severe OSA)~~. Prevalent hypertension and diabetes were 43% and 8% respectively. During follow-up, 1290 deaths were recorded over 62,899 person-years. Adjudicated cardiovascular outcomes were available from the parent cohorts for 1166 deaths (other causes of death were not recorded). Within this set, 357 (30.6%) died of cardiovascular causes. This group included 233 deaths (20.0%) attributable to coronary heart disease and 35 deaths (3.0%) due to stroke. Two more people died from stroke but were not coded as dying from cardiovascular disease.

Relationship of event duration to demographics, prevalent health conditions, and sleep-disordered-breathing severity. Event duration varied from 11.2 to 57.6 seconds (mean 21.3, median 20.6), and varied significantly with several participant characteristics (**Table 2**). Participants with shorter event durations were more likely to be younger, female, African-American, and to be current smokers. Shorter event durations were also associated with higher BMI, lower AHI, and higher minimum blood oxygen saturation (trend test, all $p<0.001$; **Table 2** and **Supplemental Fig. E1**). The same pattern of significance was obtained when treating event duration as a continuous variable; event duration measured continuously ~~here duration~~ was also

significantly correlated with percent of sleep below 90% saturation (**Table 2**, Spearman's correlation). Absolute mortality rates declined from the longest event quartile to the shortest event quartile (trend test, z=4.3, p<0.001), but this association appeared to be confounded by age and gender (see below).

Adjusted associations between event duration and other measurements. Because anthropometric data varied with quartile, partial correlations between event duration and sleep measures were calculated after adjusting for age, gender, BMI, and AHI. Longer events were associated with a lower arousal index (partial correlation r=−0.12; p<0.001), lower minimum nocturnal saturation (r=−0.09; p<0.001), and slightly greater percentage of sleep time in REM (r=+0.04, p=0.0035). After adjusting for covariates, event duration was not significantly correlated with total sleep time, sleep efficiency, WASO, or percent time with saturation <90%.

Proportional Hazard Modeling for All-Cause Mortality. Associations of all-cause mortality with event duration quartile were assessed after adjusting for age, gender, BMI, race, and smoking status (Model 1). Individuals with the shortest duration events (Q4) experienced a 20% increased mortality rate compared to those with the longest duration events (Hazard Ratio, HR = 1.20, 95% confidence interval [1.02-1.40], p=0.024, **Table 3**). This relationship strengthened after adjusting for AHI (Model 2, 26% increased risk, p=0.0043; use of categorical severities yielded similar results). Adjusting for prevalent hypertension, diabetes, and cardiovascular disease also strengthened the results (Model 3, 31% increased risk, p=0.0013); the fully adjusted survival plot is shown in **Fig. 2**. Replacing event duration quartiles with continuously-measured duration did not alter the conclusion, showing that the results are not a function of quartile assignment. The hazard ratio per 10 sec decrease in event duration was 1.15 indicating that shorter events conferred additional risk (CI: 1.03-1.30, p=0.016). Finally, we

added arousal index because this is correlated to event duration and may be a similar physiological measure of arousal threshold. Including the arousal index in Model 3 slightly strengthened the association (34% increased risk, p<0.001).

~~Other sensitivity analyses found similar associations to the primary Model 3 results in models that treated event duration as a continuous variable, adjusted for clinically-defined OSA severity, or adjusted for CPAP treatment (Online Data Supplement).~~Sensitivity analyses. ~~O~~Other ~~S~~sensitivity analyses were conducted to test the potential role of ~~quartile binning,~~ OSA severity and~~, and~~ CPAP treatment in the fully adjusted Model 3. ~~Replacing event duration quartiles with the continuously measured duration variable did not alter the conclusion, showing that the results are not a function of quartile assignment: the hazard ratio per 10 sec decrease in event duration was 1.15 indicating that shorter events conferred additional risk (CI: 1.03-1.30, p=0.016).~~ Adjusting for OSA severity as defined by clinical categories of None/Mild/Moderate/Severe rather than continuous AHI also did not change the results (e.g., Q4 relative to Q1, HR = 1.28 [1.09-1.51], p=0.0030). ~~Finally, r~~Removing 120 subjects that either reported CPAP treatment or did not know at the interim SHHS2 follow-up likewise~~also~~ did not alter the results (Q4 relative to Q1, HR = 1.31 [1.11-1.54], p=0.0014).

Effect of event subtype. The magnitude of airflow limitation and the associated desaturation are factors used to classify apnea and hypopnea subtypes and characterize severity of each event. Therefore, we tested whether these factors would affect analyses. As expected, event duration was highly correlated across different event subtypes (**Fig. ~~2~~3**, all p<0.001). The duration of all events (apneas plus hypopneas) was more strongly correlated with hypopnea duration (ρ = 0.74-0.98) than with apnea duration (ρ = 0.51-0.72), reflecting the predominance of

hypopneas. The choice of event duration definition was further explored by separately considering obstructive apnea duration versus hypopnea duration in the Cox hazard models, each with and without a 3% desaturation criteria. Commonly used clinical definitions (all apneas without a desaturation threshold and hypopneas with ≥3% desaturation) are included in **Table 3**. Hazard ratios for the shortest events (Q4 versus Q1) were similar when assessing hypopneas only (all hypopneas: HR=1.27 [1.08-1.49], p=0.0035 and hypopneas with ≥3% desaturation: HR=1.30 [1.11-1.53], p=0.0012; see **Supplemental Table E3**). Hazard ratios (Q4 versus Q1) were slightly lower when events were restricted to obstructive apneas (all apneas: HR=1.21 [1.00-1.46], p=0.046). The sample size was smaller when only events with apneas with ≥3% desaturation were included, and this association was not significant though in the same direction (HR=1.17 [0.96-1.43], p=0.12).

NREM versus REM Events. Respiratory events in REM sleep tend to be longer than in NREM sleep, but separate analysis of events in NREM versus REM had a minimal effect on results (NREM only: Q4/Q1 HR = 1.28 [1.08-1.50], p=0.0036; REM only: Q4/Q1 HR = 1.30 [1.11 – 1.52], p=0.0014). Likewise, adjusting further for the percentage of events that were in REM vs. NREM did not account for the association of event duration with mortality (HR = 1.27 [1.08 – 1.50], p=0.0038). Finally, including the amount of time in slow wave sleep (N3/4) was added to Model 3; it was not significant (p=0.68), and did not affect the risk attributable to event duration.

Gender and mortality risk. Gender significantly predicted mortality in the fully adjusted model, but did not modify the effect of duration on mortality: a gender by event duration (continuous) interaction term was added but this was not significant (p = 0.88). Cox proportional hazard models were constructed for men and women alone to determine if hazard ratios were

similar in both groups. In the fully adjusted Model 3, women and men with the shortest event duration had a 32% and 26% increased hazard ratio for death, respectively, compared to their counterparts with the longest event duration (**Table 3** and **Supplemental Fig. E2**). This association was significant in women (p=0.019) and approached significance in men (p=0.050). For comparison, in alternative analyses, similar to a prior report (2), gender modified the mortality risk associated with AHI. Each additional 5 units of AHI increased the mortality risk in men (+3% risk, p=0.043) but not in women (+1% risk, p=0.48, **Table 3**, last column). Substituting categorical OSA severity for AHI or restratifying the quartiles within gender did not affect the conclusions (data not shown).

Interaction of event duration with AHI. Short event durations conferred mortality risk whether or not the model was adjusted for AHI. We next tested whether there was any interaction of AHI and event duration, and if the risk associations held across all severities of OSA. The fully adjusted proportional hazard model was re-run adjusting for continuous AHI, event duration, and their interaction. Short event duration remained a significant predictor (hazard ratio per 10 sec decrease in event duration was 1.20 [1.02 – 1.43], p=0.029). In this model, there was no significant association for either AHI (HR = 0.99 per 5 unit increase [0.92 – 1.07], p=0.86) or the interaction of event duration and AHI (p=0.45). After stratifying by clinical OSA severity categories, participants with the shortest events had a 15-59% increased risk for mortality depending on their clinical OSA severity, with highest hazard ratios in the group with an AHI of 15 to 30 (HR=1.59 [1.11-2.28], p=0.12; **Supplemental Table E4**).

Discussion

In this study, we identify the novel association between average respiratory event duration during sleep and all-cause mortality in a large community sample. Even after adjusting for risk conferred by OSA severity (AHI) and key confounders, shorter event duration predicted higher 11-year mortality rates. While the mechanisms that determine event durations are not fully understood, this measure is reflective of a low arousal threshold (24, 25), a phenotype that may associate with sleep fragmentation and elevated sympathetic tone. In contrast to the AHI, event duration predicted mortality in women, in whom OSA is often associated with insomnia symptoms and sleep fragmentation (26), but in whom long term outcomes related to elevated AHI levels are poorly understood. Risk associations also were strongest in those with intermediate levels of AHI (15 to 30), a group in whom there are also varying data regarding OSA and mortality associations. Our findings, which held for men as well as women, suggest that consideration of this polysomnographic metric may help phenotype individuals who differ in OSA pathogenesis and outcomes, and may particularly help identify individuals with intermediate high AHI levels at increased risk for death.

Identifying prognostic features is of high priority for risk stratification and for focusing interventions at specific physiological perturbations (1, 27). OSA, as defined by AHI levels, has been shown to be a risk factor for mortality in some but not all studies (2, 4, 20, 28-31). Some studies show increased OSA-related mortality in younger compared to older individuals (32, 33) and in men compared to women (2, 20). Differences may relate to our ignorance of the most important features of sleep disordered breathing that confer risk across the population. Other limitations of AHI-related prognosis relate to weaknesses of the AHI as a primary disease-defining metric, including its insensitivity to physiological disturbances of relevance to health outcomes (5-7, 34). This has led to efforts to identify better thresholds for risk based on cohort

outcomes (35, 36). It has also spurred efforts to test different aspects of the syndrome for risk (8). For example, relative to AHI, the extent of apnea related desaturation and overnight hypoxemia appear to be better predictors of stroke and mortality (2, 37, 38). OSA fragments sleep and increases the arousal index; in one cohort study, arousal index was associated with prevalent subclinical cardiovascular disease (39). Zinchuk et al. (8) also showed that individuals characterized by "arousal and poor sleep" tended to have higher rates of myocardial infarction, atrial fibrillation, and chronic lung disease. Nevertheless, these and most other published studies have not analyzed the duration of respiratory events. In this large prospective sample, we showed that event duration predicted mortality over and beyond AHI, and furthermore, suggested that the predictive information associated with event duration was strongest in individuals with moderate to severe OSA, a group in whom there has been inconsistency in relationships with clinical outcomes.

Event duration is of particular interest because it may be a genetically encoded feature of OSA (9) that varies across population groups (e.g., shorter in females and African Americans) (40). We also discovered a novel genetic locus (rs35424364) that is associated with event duration in Latino/Hispanic Americans (18). In the current study of individuals with generally mild to moderately high AHI levels, we found that event duration had only weak associations with many typically employed measures of sleep disturbance, including sleep time and efficiency, WASO, percent of sleep in REM, and percent of sleep with desaturation. This suggests that event duration contains unique information over and beyond other polysomnography measurements. These findings support the event duration as an independent, inherited trait that may be help explain individual differences in OSA related phenotypes.

Mechanistically, respiratory events will be terminated earlier (shorter duration) if, 1) an individual arouses from a lighter depth of sleep; 2) an individual arouses from the same stage of sleep but at a low level of chemical drive or respiratory effort (i.e. low arousal threshold); or 3) chemical drive builds up rapidly during an event (higher chemoreflex sensitivity to hypoxic hypercapnia or increased loop gain). All three mechanisms therefore reflect a state of increased "arousability" that could potentially promote mortality via greater sleep fragmentation, shorter sleep, and excess sympathetic tone. Indeed, we found that shorter events were associated with a greater arousal index (partial correlation: r=–0.12). Reduced sleepiness (consistent with greater arousability) is associated with increased sympathetic activity in heart failure (41). Hypersensitivity to chemical stimuli at the carotid bodies is also a mechanism of increased sympathoexcitation and attendant development of hypertension (42), and is a predictor of mortality in patients with heart failure (43).

Event duration varied significantly with several demographic and health-related factors. Individuals with shorter event duration were more likely to be younger, female, African American, and current smokers. The association of smoking with shorter events is especially interesting. Nicotine promotes alertness and lighter sleep, suggesting a lower arousal threshold. Smoking also disturbs EEG measures of sleep (44), and causes subjective complaints of disturbed sleep (45). Although nicotine can influence the release of central neurotransmitters associated with sleep-wake control (46), the mechanisms by which smoking may shorten apneas—for example, by reducing arousal threshold—requires further investigation.

In adjusted analyses, individuals with shorter events tended to have higher minimum SaO_2 (reflecting shorter periods of obstructive breathing or reduced metabolic rate). However, after adjusting for the AHI, event duration was not associated with sleep time spent at low levels

of oxygen saturation. ~~, but overall, did not have different degrees of hypoxemia~~. Hypoxic burden derives from the combination of number of events, their duration, and their desaturation. A larger product of event duration and desaturation has been associated with long term risk (5, 47). Our results—showing short rather than long events as predictors of risk—do not refute this. Rather, hypoxemia and event duration may represent different features of OSA-related stress, both of which may contribute to mortality through independent pathways. Our findings suggest a need to further identify the intermediate mechanisms that link event duration to long term outcomes.

Event duration predicted mortality in both men and women, while AHI was only associated with mortality in men, as has been reported before (2). OSA is more likely to be associated with insomnia in women than in men (26, 48), and it is possible that in women, OSA risk is less associated with the numbers of events during sleep and more associated with arousal-related responses to respiratory disturbances. Indeed, gender differences in OSA phenotypes are well-described, with women generally showing greater airflow limitation, increased work of breathing, and sleep fragmentation (26, 49), with recent studies also showing sex-specific genetic variants for OSA (50). The current results show that mortality risk in women can be predicted from features of their sleep disordered breathing, but the critical measure is not- likely the AHI.

Strengths and limitations of the study.

As a community based prospective cohort, the study sample was not influenced by clinic or treatment selection biases. The long follow-up time, adjudicated outcomes, and the rigorous collection of sleep data and other covariates allowed us to study the effects of event duration while also controlling for a number of confounders. Limitations include the single night of a sleep study which, though used for clinical decision making, may not fully characterize a

person's typical sleep. There is also no information about medications taken on the night of the sleep study. Some medications, especially psychoactive drugs, could alter arousability, though this community cohort is a general population sample that likely has ~~with~~ limited psychoactive medication use. Future studies of event duration should explore the potential role of medications on arousability and event duration. ~~A limitation is that our analysis does not indicate whether the short events are characteristic of a person's OSA or instead a secondary manifestation in sleep of some other underlying risk factor.~~ We also investigated a number of potential causes for heterogeneity through sensitivity analyses to ensure that the main conclusions were not affected by statistical modelling or definitions of events. First, we found the same conclusions when the clinical OSA severity grouping (none/mild/moderate/severe) was substituted for AHI. Second, results were consistent whether quartiles of event duration were based on the entire sample or were gender-specific. We also found generally consistent results when we only examined apneas and hypopneas, when we considered state-specific events, and when we included any event versus~~s~~ those associated with desaturations. We focused on all-cause mortality to maximize statistical power. Future research is needed to discern associations with cause-specific mortality. Finally, results were not altered by the inclusion of subjects that reported CPAP use at the interim follow up visit.

~~Though the hazard associated with short events may be due to a low arousal threshold,~~ ~~w~~We cannot determine ~~in this sample~~ whether the short events ~~are~~ reflect a direct causal mechanism for increased mortality, ~~-~~or rather are markers for underlying autonomic or other physiological phenotypes that associated with unfavorable outcomes. ~~characteristic of a person's OSA or instead a secondary manifestation in sleep of some other underlying risk factor. If the latter, then~~ Regardless, our data suggest that the occurrence of short event duration in individuals

with mild to moderately elevated AHI levels may help identify individuals at risk for adverse health. Current clinical trial data are ambiguous in regards to the role of OSA on mortality or cardiovascular incidence (SAVE Study, 51). Re-analysis of those data considering variation in event duration may provide insights into possible heterogeneity of response to CPAP related to this phenotype.

The sample had few participants with very long events: only 5% had events that averaged longer than 30 sec. Therefore, whether our results generalize to those with severe events is unclear~~not known~~. ~~Overall, the relationship of OSA severity (by AHI) to the event duration has not been well described. Here our results suggest only a modest relationship that may be explained in part by a positive correlation of both AHI and duration with age.~~ Further study, ~~particulary~~particularly in clinical populations, is warranted to understand the associations between very long event durations and hypoxemia to mortality. ~~determine whether the hazard ratios we found are maintained in those with very long durations (30-60 sec).~~

In summary, this study shows that a relatively easily derived parameter from overnight polysomnography, respiratory event duration, predicts all-cause mortality over and beyond that predicted by the AHI. Moreover, event duration predicted mortality in both men and women independent of many potential confounders. These data provide new information to inform emerging initiatives to identify sleep apnea subphenotypes reflective of individuals with different underlying mechanisms who may experience different outcomes and respond differently to treatments. Event duration may measure a component of a phenotype characterized by low arousal threshold. Further research is needed to address whether these individuals are at

increased risk for outcomes such as increased mortality due to elevated sympathetic tone or abnormalities in arousal-mediated stress responses.

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Figure Legends

1. Subject selection.

2. Differential survival from the fully adjusted Cox proportional hazard model 3. The reference survival curve represents the median risk over all predictors. Because the hazard ratio for Quartile 2 is 1.01, the curves for Quartiles 1 (reference) and 2 are almost superimposable.

~~2~~**3.** Respiratory event subtype correlation matrix. The matrix shows the relationship across different definitions of event type (apnea, hypopnea, and desaturation criteria). The combined apnea-hypopnea measure is more closely correlated with hypopnea duration than apnea duration. All correlations are significant but vary from 0.51-0.98 (blue to red). The highest correlations are between hypopnea duration and apnea-hypopnea duration for a given desaturation criteria (ρ = 0.96-0.98). Red lines are LOESS smoothed fits.

Tables

Table 1. Selected baseline characteristics

Sample characteristic	Subcategory	Mean (sd) [range] or %
N		5712
Age (yr)		63.3 (sd 11.1) [39-90]
BMI (kg/m^2)		28.1 (sd 5.1) [18-50]
Gender (%F)		52
AHI (events/h)*		13.8 (sd 15.0) [0-157]
Sleep Time (h)		360 (sd 64) [35-519]
Sleep Efficiency (%)		81.5 (sd 10) [11.3-98.5]
Sleep latency (min)		23.1 (sd 23) [0-218]
% time in REM		19.3 (sd 6.9) [0-43]
Wake After Sleep Onset (WASO) (min)		61.6 (sd 44) [0-368]
Arousal Index (h^{-1})		19.2 (sd 10.7) [0-110]
% sleep < 90% sat		3.5 (sd 10.3) [0-100]
AHI (events/h)		13.8 (sd 15.0) [0-157]
OSA severity	None (%)	33
	Mild (%)	35
	Moderate (%)	20
	Severe (%)	12
Race	Afr.Amer. (%)	9
	White (%)	85
	Other (%)	6
Smoking Status	Current (%)	10
	Former (%)	47
	Never (%)	43
Prevalent Disease	Hyperten. (%)	43
	Diabetes (%)	8
	CHD (%)	8
	Stroke (%)	3
	HF (%)	2
	†Any CVD (%)	11
Outcomes	Deaths	1290
	Follow-up time (person-years)	62899
	Mortality rate per 1000 person-years	20.5

*AHI defined by the respiratory disturbance index with a 3% desaturation threshold. †Any prevalent coronary heart disease, stroke, or heart failure.

Table 2. Sample characteristics by quartile of respiratory event duration (mean and SD, or %)

		Longest----------Quartiles----------Shortest				Statistical Tests		
		Q1	Q2	Q3	Q4	Quartile difference	Spearman ρ	Trend Test
Apnea duration	Range (sec)	(24.1-57.6]	(20.6-24.1]	(17.7-20.6]	[11.2,-17.7]			
	Mean (SD)	27.80 (3.72)	22.17 (0.98)	19.18 (0.81)	15.91 (1.25)			
N		1428	1428	1428	1428			
Age (yr)[A]		66 (11)	63 (11)	63 (11)	61 (11)	***	+0.17***	***
BMI (kg/m^2) [W]		27.4 (4.8)	28.1 (4.9)	28.5 (5.1)	28.5 (5.4)	***	−0.09***	***
Gender (%F) [X]		47	49	53	61	***		***
AHI (events/h) [W]		12.0 (14.7)	8.5 (12.2)	8.6 (11.9)	5.6 (9.6)	***	+0.19***	***
Min SaO2 (%) [W]		84.0 (8.4)	85.9 (6.1)	85.6 (6.2)	86.5 (5.4)	***	−0.11***	***
Sleep Time (h) [A]		6.0 (1.1)	6.0 (1.1)	6.0 (1.1)	6.0 (1.1)	n.s.	−0.03	#
Sleep Efficiency (%) [A]		81.2 (10.7)	81.5 (10.3)	81.5 (10.3)	81.9 (10.5)	n.s.	−0.02	n.s.
% time in REM [A]		19.1 (6.8)	19.6 (6.8)	19.5 (7.1)	19.1 (6.9)	*	−0.00	n.s.
WASO (min) [W]		65 (46)	63 (45)	60 (42)	58 (43)	***	+0.07#	***
Arousal Index (h^{-1}) [W]		19.4 (11.5)	18.7 (10.8)	19.3 (10.1)	19.3 (10.3)	#	−0.02	n.s.
% sleep < 90% sat [W]		4.3 (10.8)	2.9 (9.1)	3.4 (9.8)	3.4 (11.4)	**	+0.10***	#
Race [X]	Afr.Amer. (%)	6	9	10	10	**		
	White (%)	88	84	84	84			
	Other (%)	6	7	6	6			
Smoking Status [X]	Current (%)	6	8	9	16	***		
	Former (%)	45	44	45	39			
	Never (%)	49	49	45	45			
Prevalent Disease [X]	HTN (%)	50	42	43	39		***	***
	Diabetes (%)	8	8	8	8		n.s.	n.s.
	CHD (%)	15	11	11	9		***	***
	Stroke (%)	5	4	3	2		**	***
	HF (%)	6	3	3	2		***	***
	†Any CVD (%)	20	14	14	11		***	***
Outcomes	Deaths	385	301	315	286		***	***
	Follow-up time (person-years)	14,171	14,461	14,534	14,659			
	Mortality rate, /1000 person-years	27.2	20.8	21.7	19.5			***

Differences among quartiles were assessed by [A]1-way ANOVA, or [W]Wilcoxon/Kruskal-Wallis test when variances were unequal (Bartlett test). X^2 test was used to test for quartile differences in proportions. Bivariate correlation coefficients (Spearman's rho) against event duration were calculated for continuous measures. Trends across quartiles were assessed by the Cochran-Armitage trend test or by linear regression against quartile number. Significance indicated: # p<0.10, *p<0.05, **p<0.01, ***p<0.001. †Any prevalent CHD, Stroke, or HF. Gray indicates no analysis.

Table 3. Cox proportional hazard ratios [95% confidence interval]: association of event duration (quartile) with all-cause mortality.

		Longest----------Quartile---------- Shortest				
Dataset	Model	Q1	Q2	Q3	Q4	AHI (additional hazard / 5 units)
All subjects	1	Ref	0.94 [0.81-1.09]	1.12 [0.96-1.30]	**1.20 [1.02-1.40]***	**NA**
	2	Ref	0.96 [0.83-1.12]	**1.14 [0.98-1.33]#**	**1.26 [1.08-1.49]****	**1.03 [1.01 – 1.05]*****
	3	Ref	1.01 [0.86-1.17]	**1.18 [1.01-1.37]***	**1.31 [1.11-1.54]****	**1.02 [1.00 – 1.04]***
All apneas	3	Ref	0.98 [0.83 – 1.15]	0.96 [0.80 – 1.15]	**1.21 [1.00-1.46]***	**1.03 [1.01 – 1.05]***
Hypopneas, ≥3% desat	3	Ref	1.03 [0.88 – 1.19]	1.07 [0.92 – 1.25]	**1.30 [1.11-1.53]****	1.02 [1.00 – 1.04]#
NREM	3	Ref	1.04 [0.89 – 1.21]	1.11 [0.95 – 1.30]	**1.28 [1.08 – 1.50]****	**1.02 [1.00 – 1.04]***
REM	3	Ref	1.02 [0.87-1.20]	0.96 [0.82-1.13]	**1.30 [1.11 – 1.52]***	1.02 [1.00 – 1.04]#
Women	3	Ref	1.00 [0.79-1.26]	1.10 [0.87-1.39]	**1.32 [1.05-1.66]***	1.01 [0.98 – 1.05]
Men	3	Ref	1.01 [0.83 – 1.23]	1.23 [1.00-1.51]#	1.26 [1.00-1.59]#	**1.03 [1.00 – 1.05]***

Quartile 1 is the reference quartile. #p<0.1, *p<0.05, **p<0.01, compared to Q1.

Other covariates:
Model 1: Age, Gender, BMI, Race, Smoking Status (Gender not included in gender stratified models).
Model 2: Model 1 + AHI
Model 3: Model 2 + Prevalent hypertension, diabetes, CHD, stroke, heart failure.

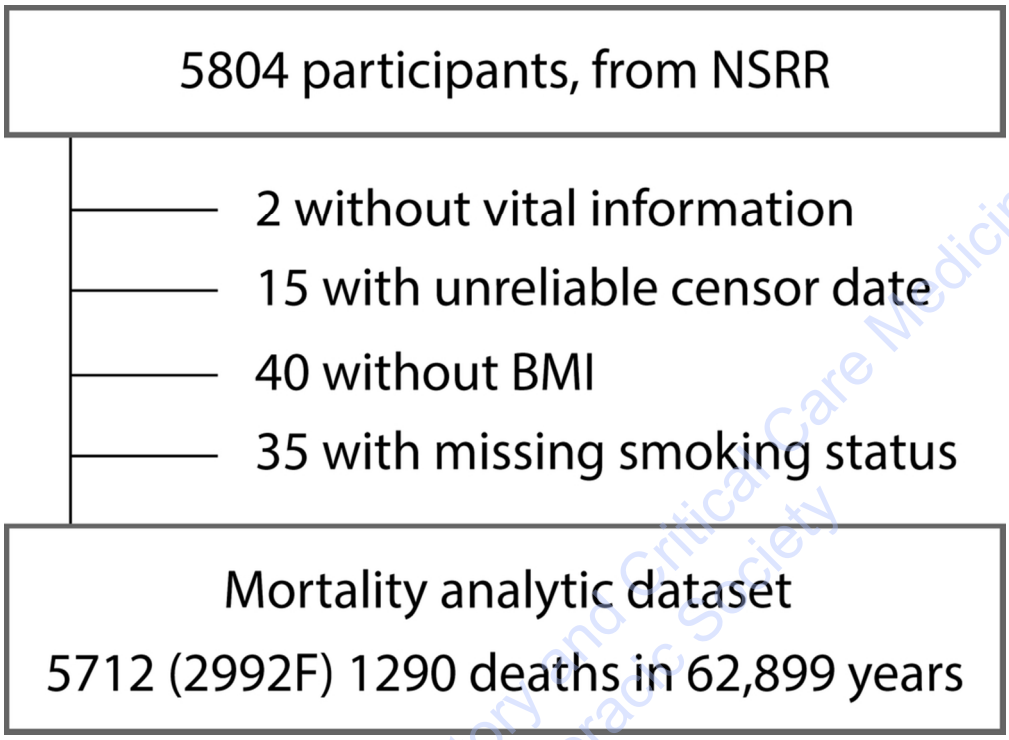

Figure 1. Subject selection

90x65mm (300 x 300 DPI)

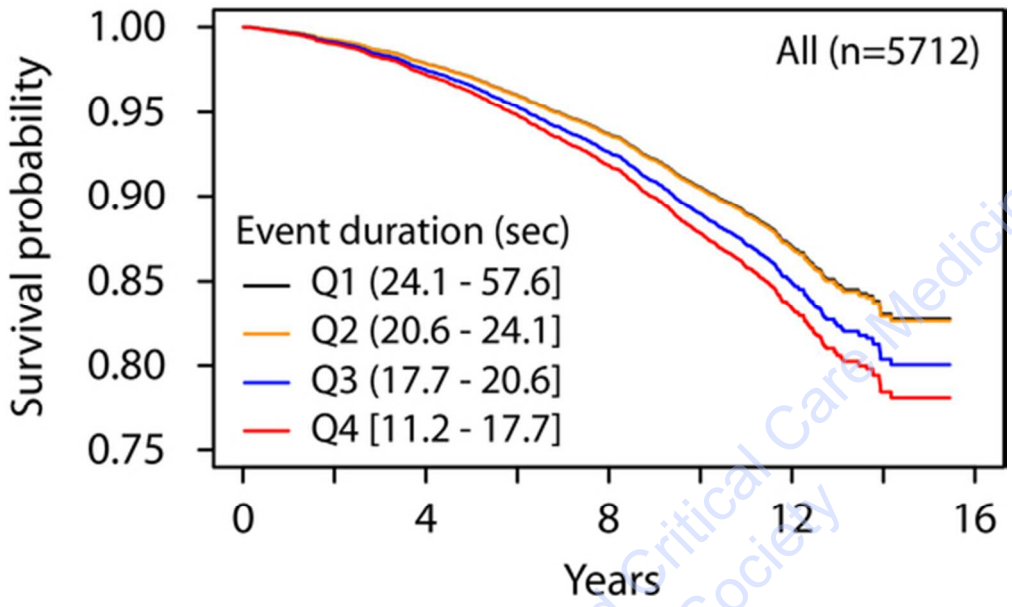

Figure 2. Differential survival from the fully adjusted Cox proportional hazard model 3. The reference survival curve represents the median risk over all predictors. Because the hazard ratio for Quartile 2 is 1.01, the curves for Quartiles 1 (Reference) and 2 are almost superimposable.

47x28mm (300 x 300 DPI)

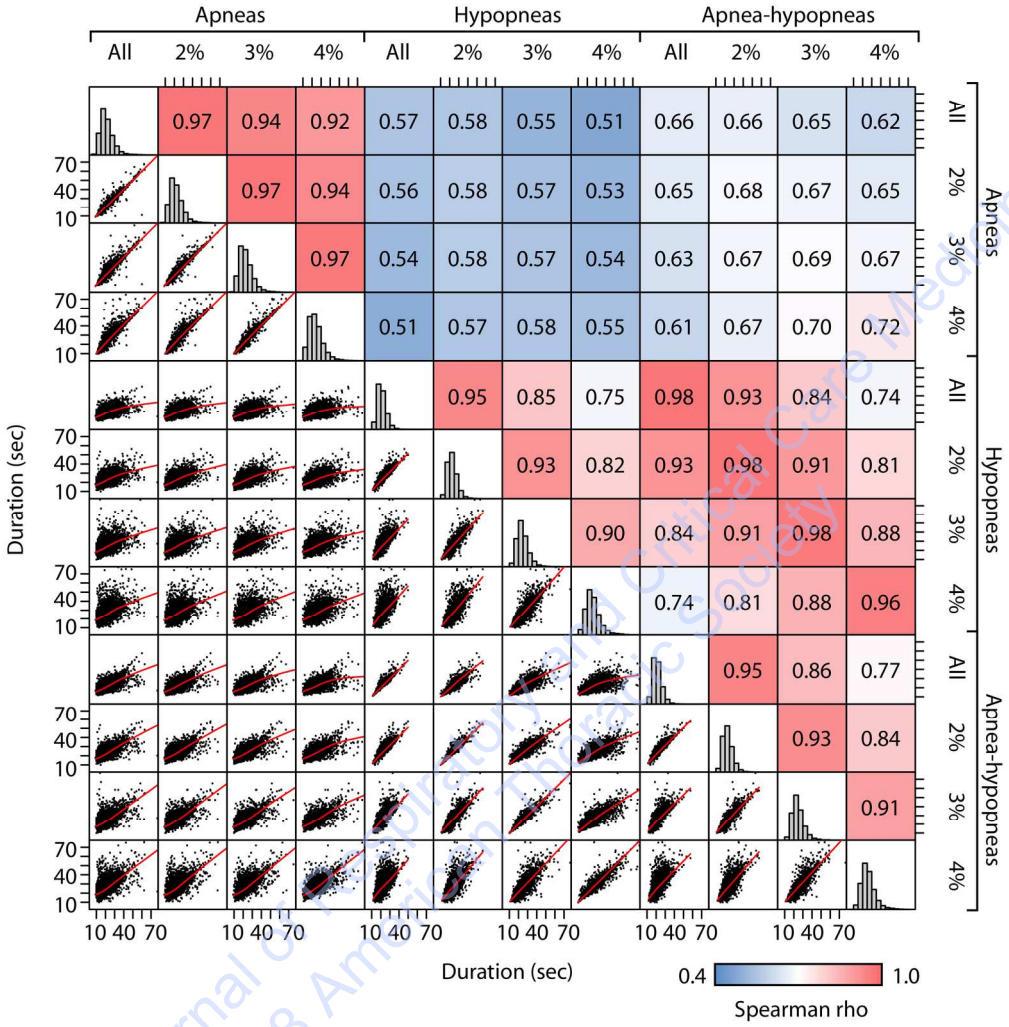

Figure 3. Respiratory event subtype correlation matrix. The matrix shows the relationship across different definitions of event type (apnea, hypopnea, and desaturation criteria). The combined apnea-hypopnea measure is more closely correlated with hypopnea duration than apnea duration. All correlations are significant but vary from 0.51-0.98 (blue to red). The highest correlations are between hypopnea duration and apnea-hypopnea duration for a given desaturation criteria (ρ = 0.96-0.98). Red lines are LOESS smoothed fits.

174x177mm (300 x 300 DPI)

ONLINE DATA SUPPLEMENT

Apnea-hypopnea duration predicts mortality in men and women in the Sleep Heart Health Study

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Online Methods

Sample characteristics

The sample is derived from the Sleep Heart Health Study (SHHS), a community-based, prospective cohort study designed to assess the cardiovascular consequences of sleep apnea. Briefly, 6441 men and women aged 40 years or older were recruited from among participants in seven ongoing cohort studies ("parent studies") as described previously (E1). Participants in the parent studies were ineligible to participate if they reported a history of OSA treatment with continuous positive airway pressure (CPAP) or nightly oxygen. At baseline (1995–1998), participants completed questionnaires; had height, weight and blood pressure measured; and underwent overnight unattended polysomnography. Additional covariate data were provided by the parent cohorts. Participants also had ongoing surveillance for cardiovascular events by parent cohorts. The current study analyzed follow-up data through 2010. The protocol was approved by the Institutional Review Board of each participating center, and signed informed consent was provided by each subject. The Institutional Review Board of Oregon Health & Science University determined that the current study of pseudonymized~~de-identified~~ data was not human subjects research.

The construction of the analytical sample is shown in **Fig. 1**. Of the 6441 participants enrolled in the SHHS, data for 5804 participants were available through the National Sleep Research Resource (https://sleepdata.org/), a publicly available research data set (data from the Strong Heart Study were excluded due to tribal data sharing restrictions). Excluding subjects with missing data in important covariates yielded a final analytic dataset of 5712 subjects with which to study all-cause mortality. Average follow-up time was 11 years, during which time 1290 deaths were recorded over 62,899 person-years.

Endpoints

All-cause mortality was defined as any confirmed death between the time of enrollment and the final censoring date. The censor dates for subjects were defined as the time of death or the last contact date, coded as days since the baseline sleep study.

Independent variables and covariates

The primary exposure variable was the mean duration of all apneas and hypopneas during any stage of sleep and in any body position. Respiratory events were measured from oronasal thermistors as specified in the SHHS Reading Center Manual of Operations (https://sleepdata.org/datasets/shhs/pages/mop/6-00-mop-toc.md). Apneas were defined by decreases in airflow to less than approximately 25% of the baseline breathing amplitude for > 10 sec. Hypopneas were defined by airflow decreases below 70% of baseline breathing for > 10 sec. These definitions were adopted because SHHS was scored beginning in 1994 before publication of the current definitions (90% reduction for apneas and 30% reduction for hypopneas). In the scoring, an attempt was made to harmonize with the approaches used by the Wisconsin Sleep

Cohort. Nonetheless, all definitions of flow reduction are at best semi-quantitative given that these are not calibrated signals. We found that operationalizing apnea identification to "less than 25% of baseline" in actuality identified events with virtually no to minimal flow (i.e., "90% reduction") as currently specified. The description we provided of hypopneas as 70% below baseline breathing equates to the current 30% reduction rule. Central apneas were not included in the analysis. Mean event duration in non-rapid eye movement (NREM) and REM sleep were also calculated.

Duration was scored for all events for individuals in the Sleep Heart Health Study, and the average duration is available in the National Sleep Research Resource, broken down for each person by event type (obstructive apnea, central apnea, or hypopnea), sleep stage (REM or NREM), and sleeping position (back position or other). These are available with and without desaturation criteria. The main exposure variable employed here was the average of obstructive apneas and hypopneas in all sleep stages and all body positions, weighted by the number of occurrences of each. For secondary analyses, the event duration was separately calculated for obstructive apneas alone, hypopneas alone, NREM sleep alone, and REM sleep alone. These were repeated for different desaturation classes (e.g., **Fig. ~~2~~3**). The variables used to calculate event duration are shown in **Supplemental Table E1**.

Other variables from the baseline examination considered were age, gender, BMI, race (African American/Caucasian American/Other), smoking status (current/former/never), prevalent hypertension (blood pressure > 140/90 mmHg or treatment with anti-hypertensive medication), prevalent diabetes (report of diagnosed diabetes or use of insulin or hypoglycemic agents), prevalent coronary heart disease (any previous MI or revascularization procedure), prevalent stroke, or prevalent heart failure. Variables extracted from polysomnography included: total

sleep time, wake after sleep onset (WASO), AHI (number of respiratory events, each with ≥3% desaturation per hour of sleep), arousal index, and percent of sleep with oxygen saturation <90%). At an interim follow-up, participants were asked whether they had been treated for sleep apnea by CPAP or oral appliance. Within the n=5712 analytical dataset, 115 reported treatment and 5 did not know. A sensitivity analysis was conducted by comparing models run with and without these 120 participants to determine if they would affect the results. Variables and their specific names as they appear in the NSRR database are shown in **Supplemental Tables E1 and E2)**.

Statistical Analyses

Associations between respiratory event duration and mortality were assessed with Cox proportional hazard models (E2). The proportional hazard assumption was tested by inspection of the Schoenfeld residuals and the Grambsch and Therneau test (E3). Event duration was categorized into quartiles with quartile 1 (Q1: longest event durations) serving as a reference category for quartiles 2-4 (in order of decreasing event duration). Three models were constructed. The base model included event duration and covariates of age, gender, race, smoking status, and BMI. Model 2 included the above plus AHI (considered alternatively as a continuous variable or according to clinical thresholds: ≥30, 15-30, 5-15, and <5 events per hour). Model 3 included all variables in Model 2 plus variables that may be in the intermediate pathways linking sleep disordered breathing to mortality, including prevalent hypertension, diabetes, stroke, coronary heart disease, and heart failure. Additional sensitivity analyses were conducted for event durations from NREM and REM sleep, calculated separately.

In cross-sectional analyses, the correlations among event duration and other continuous variables were assessed by Spearman's rho. Nominal outcome variables were assessed across quartiles with X^2 likelihood ratio tests; for dichotomous outcomes, trends across quartiles were assessed by the Cochran Armitage trend test. For continuous outcome variables, homogeneity of variance across quartiles was first tested with Bartlett's test. When variances were unequal, the Wilcoxon/Kruskal-Wallis test was used to test for differences among quartiles; otherwise 1-way ANOVA was used. The crude mortality rate trend across the quartiles was tested by linear regression by treating the quartile number as a continuous numeric variable. Significance was set at $\alpha = 0.05$. All statistical tests were conducted in R (Rstudio 1.1.383 running R version 3.3.2) or JMP Pro 11.0.0 (SAS Institute, Cary NC).

~~**Supplemental Results**~~

~~*Sensitivity analyses*. Sensitivity analyses were conducted to test the potential role of quartile binning, OSA severity, and CPAP treatment in the fully adjusted Model 3. Replacing event duration quartiles with the continuously measured duration variable did not alter the conclusion, showing that the results are not a function of quartile assignment: the hazard ratio per 10 sec decrease in event duration was 1.15 indicating that shorter events conferred additional risk (CI: 1.03-1.30, p=0.016). Adjusting for OSA severity as defined by clinical categories of None/Mild/Moderate/Severe rather than continuous AHI also did not change the results (e.g., Q4 relative to Q1, HR = 1.28 [1.09-1.51], p=0.0030). Finally, removing 120 subjects that either reported CPAP treatment or did not know at the interim SHHS2 follow-up also did not alter the results (Q4 relative to Q1, HR = 1.31 [1.11-1.54], p=0.0014).~~

Table E1

Variables for number and average duration of each type of respiratory event as coded in the National Sleep Research Resource (NSRR) database. # Desaturation criteria for each event (numbers indicate the oxygen saturation drop criteria (2-4%); no number at the end would indicate no desaturation criteria).

			NSRR ID	
Event type	**Sleep stage**	**Body position**	**Duration**	**Number**
Obstructive Apnea	NREM	Back	AvOANBP#	OANBP#
		Other	AvOANOP#	OANOP#
	REM	Back	AvOARBP#	OARBP#
		Other	AvOAROP#	OAROP#
Hypopnea	NREM	Back	AvHNBP#	HNRBP#
		Other	AvHNOP#	HNROP#
	REM	Back	AvHRBP#	HREMBP#
		Other	AvHROP#	HROP#

Table E2

Other variables employed in these analyses as coded and described in the National Sleep Research Resource (NSRR) database.

Data Category	Variable	NSRR ID
Demographics and sleep	Age at baseline	age_s1
	Gender	gender
	BMI at baseline	bmi_s1
	Race (Caucasian, African American, Other)	race
	Smoking status (Current, Former, Never)	smokstat_s1
	AHI	rdi3p
	Minimum nocturnal SaO2, minimum of:	
	Min. SaO2 in NREM sleep	MnSaO2NH
	Min. SaO2 in REM sleep	MnSaO2RH
	Arousal Index	ai_all
	Total sleep time	slp_time
	Sleep efficiency	Slp_eff
	Wake after sleep onset	WASO
	Percent of sleep time with O_2 saturation < 90%.	pctlt90
	Percent of sleep time in REM	TmREMP
	CPAP treatment since baseline	treatedsleepapnea
Prevalent Health Conditions	Hypertension	HTNDerv_s1
	Diabetes, defined by any of:	
	Patient report of diabetes	ParRptDiab
	Use of insulin	INSULN1
	Use of oral hypoglycemic agents	OHGA1
	Coronary heart disease (CHD), defined by any:	
	Myocardial infarctions	prev_mi
	Procedures related to heart attack	prev_mip
	Revascularization procedures	prev_revpro
	Congestive heart failure	prev_chf
Outcomes	Vital status at censor date	vital
	Time to last contact or death	censdate

Table E3

Fully adjusted Cox proportional hazard ratios [95% confidence interval] for mortality for different event definitions. Note that fewer participants have events with deeper desaturations: the smaller sample size reduced statistical power.

				Longest----------Quartile----------Shortest			
Event	Desaturation threshold	N	Deaths	Q1	Q2	Q3	Q4
apneas, hypopneas	NA	5712	1290	Ref	1.01 [0.86-1.17]	**1.18 [1.01-1.37]***	**1.31 [1.11-1.54]****
apneas, hypopneas	3%	5672	1285	Ref	1.01 [0.87 – 1.18]	1.03 [0.88 – 1.20]	**1.28 [1.09-1.51]****
hypopneas	NA	5712	1290	Ref	0.98 [0.84 – 1.14]	1.17 [1.00 – 1.36]	**1.27 [1.08-1.49]****
hypopneas	3%	5665	1282	Ref	1.03 [0.88 – 1.19]	1.07 [0.92 – 1.25]	**1.30 [1.11-1.53]****
apneas	NA	4562	1058	Ref	0.98 [0.83 – 1.15]	0.96 [0.80 – 1.15]	**1.21 [1.00-1.46]***
apneas	3%	4112	975	Ref	1.02 [0.86 – 1.20]	1.01 [0.84 – 1.22]	1.17 [0.96-1.43]

*p<0.05, **p<0.01 compared to reference Q1.
Other covariates
Model 1: Age, Gender, BMI, Race, Smoking Status, AHI, and prevalent hypertension, diabetes, CHD, stroke, heart failure.

Table E4

Fully adjusted Cox proportional hazard ratios [95% confidence interval] for mortality, stratified by OSA severity.

			Longest----------Quartile----------Shortest				
OSA Severity	N	Deaths	Q1 (longest)	Q2	Q3	Q4 (shortest)	AHI (additional hazard / 5 units)
AHI < 5	1880	320	Ref	0.86 [0.61 – 1.23]	1.20 [0.85 – 1.70]	1.29 [0.94-1.77]	1.18 [0.79 - 1.77]
5 ≤ AHI < 15	2008	468	Ref	1.09 [0.85 - 1.40]	1.19 [0.92 – 1.55]	1.15 [0.87 - 1.52]	1.01 [0.87 - 1.18]
15 ≤ AHI < 30	1153	300	Ref	1.07 [0.79 – 1.45]	1.15 [0.84 – 1.56]	**1.59 [1.11-2.28]***	**1.17 [1.02 - 1.33]***
30 ≤ AHI	671	202	Ref	0.85 [0.58 - 1.23]	1.12 [0.77 - 1.61]	1.32 [0.81 - 2.13]	1.03 [0.98 - 1.09]

*p<0.05 compared to reference Q1 or relative to a hazard ratio of 1.0.
Other covariates: Age, gender, BMI, race, smoking status, and prevalent hypertension, diabetes, coronary heart disease, stroke, and heart failure.

Online Data Supplement References

E1. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 1997; 20: 1077-1085.

E2. Therneau TM, Grambsch PM. Modeling survival data : extending the Cox model. New York: Springer; 2000.

E3. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals *Biometrika* 1994; 81: 515-526.

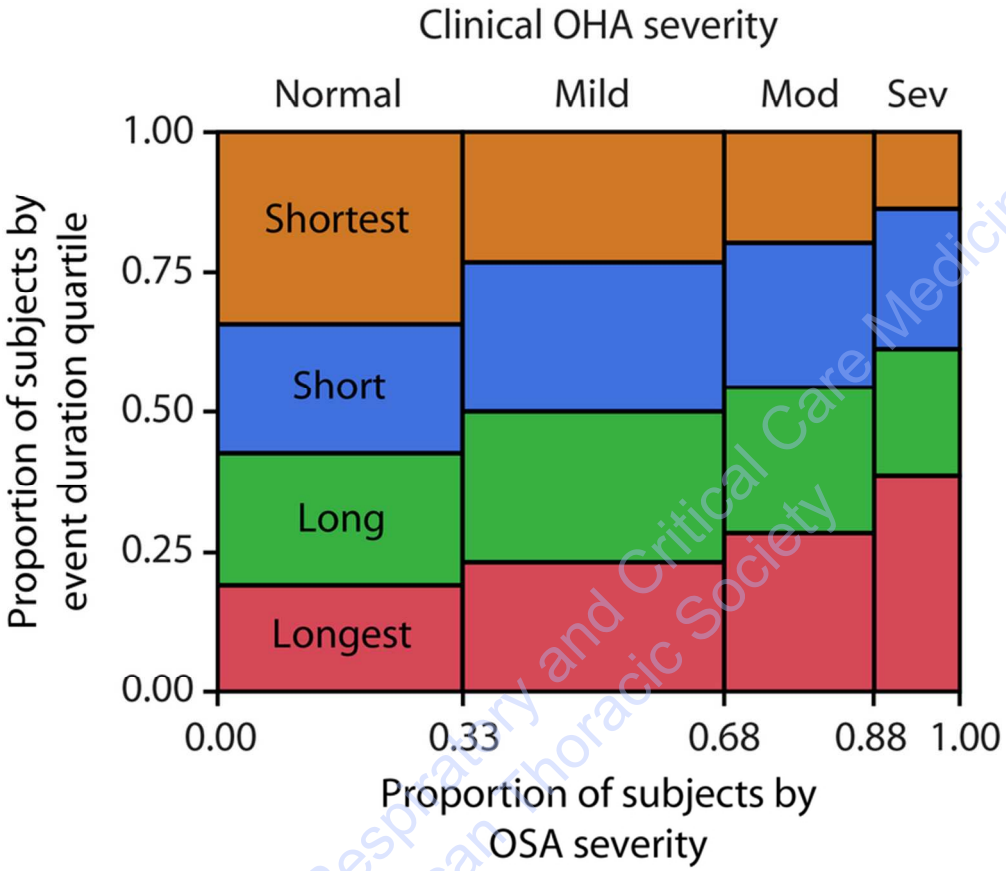

Figure E1. Mosaic plots showing the distribution of event duration quartiles against clinical OSA severity for all subjects. There were significant differences in the proportion of event duration quartiles (Longest, Long, Short, Shortest) among the different OSA severity levels (Likelihood ratio test: Mortality, X2 = 194, p<0.001).

73x63mm (300 x 300 DPI)

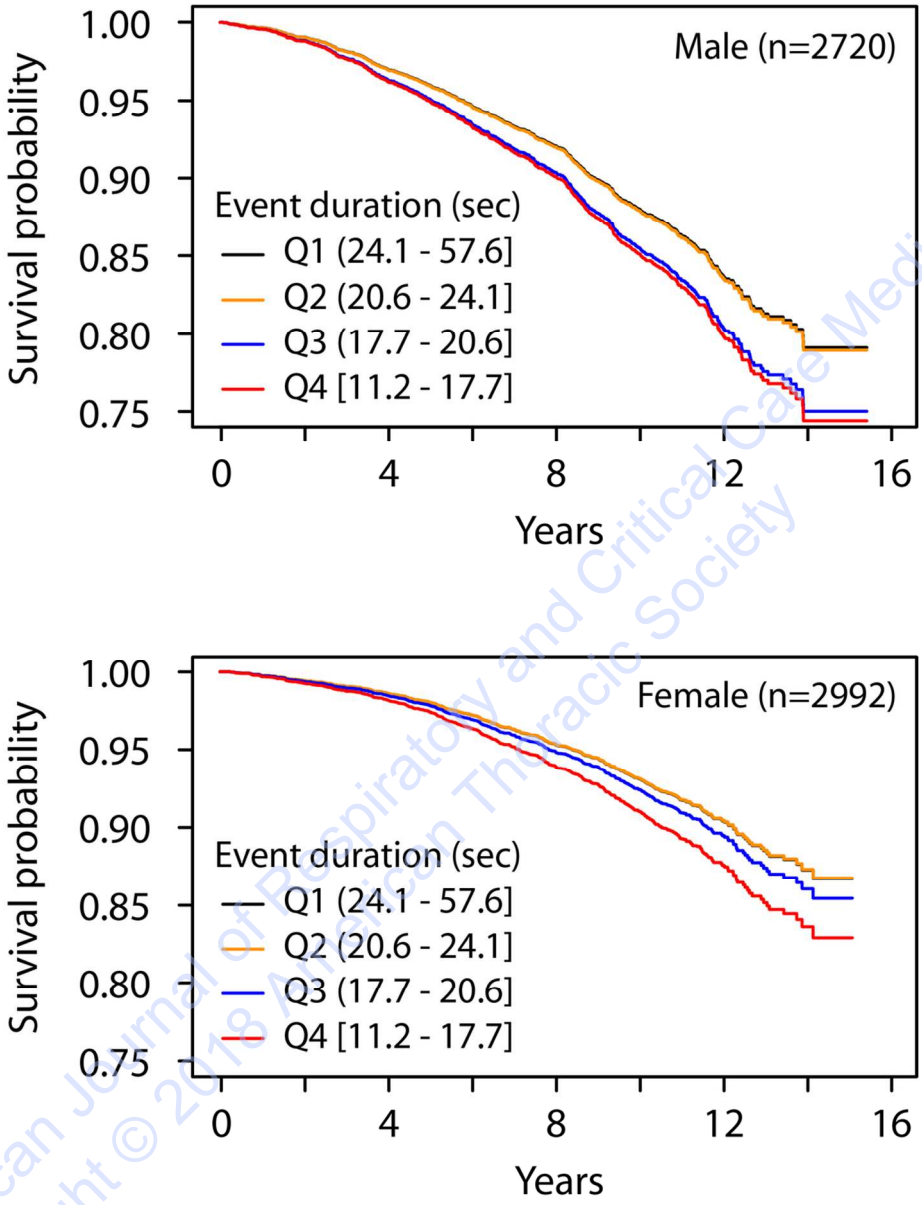

Figure E2. Survival plots for men and women based on the median risk profile from the Model 3 Cox regression analysis (Quartile 1, Q1, is the Reference). As the hazard ratio for Q2 is close to 1.0, the curve is almost superimposable on Q1.

102x134mm (300 x 300 DPI)

Title: Apnea-hypopnea event duration predicts mortality in men and women in the Sleep Heart Health Study

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Running Head (50 characters max): Apnea-hypopnea duration and health

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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

At a Glance Commentary:

- **Scientific Knowledge on the Subject.** Obstructive sleep apnea (OSA) is a disorder characterized by repetitive cycles of upper airway collapse during sleep and subsequent arousals from sleep. The most common OSA-defining metric, the apnea hypopnea index (AHI), has been shown to predict risk for mortality in some but not all studies, with differences in associations observed by age and gender. Emerging data indicate that there is considerable physiological variability across and between nights within patients with OSA that is not captured by the AHI. Studies using additional features of OSA may shed light on OSA-related morbidity and mortality in the population and provide insights into underlying pathophysiological differences that influence health outcomes.

- **What This Study Adds to the Field.** We characterized respiratory event duration, a heritable measure that reflects physiological features of OSA (arousal threshold) in a large prospective cohort. Adjusted analyses showed that short event duration predicts all-cause mortality over and beyond that predicted by the AHI. Moreover, associations between short event duration and mortality were observed in both men and women. This measure, readily available from routine polysomnography records, may help improve phenotyping of OSA-associated risk in the population, including helping to identify subgroups with low arousal threshold at risk for adverse outcomes.

Abstract

Rationale. Obstructive sleep apnea is a risk factor for mortality, but its diagnostic metric—the apnea-hypopnea index—is a poor risk predictor. This apnea-hypopnea index does not capture the range of physiological variability within and between patients, such as degree of hypoxemia and sleep fragmentation, that reflect differences in pathophysiological contributions of airway collapsibility, chemoreceptive negative feedback loop gain, and arousal threshold. Objective. To test whether respiratory event duration, a heritable sleep apnea trait reflective of arousal threshold, predicts all-cause mortality. Methods. Mortality risk as a function of event duration was estimated by Cox proportional hazards in the Sleep Heart Health Study, a prospective community-based cohort. Gender-specific hazard ratios were also calculated. Measurements and Main Results: Among 5712 participants, 1290 deaths occurred over 11 years of follow-up. After adjusting for demographic factors (mean age 63 years old; 52% female), apnea-hypopnea index (mean 13.8; standard deviation 15.0), smoking, and prevalent cardio-metabolic disease, individuals with the shortest duration events had a significant hazard ratio for all-cause mortality of 1.31 [95% confidence interval: 1.11-1.54]. This relationship was observed in both men and women and was strongest in those with moderate sleep apnea (hazard ratio = 1.59 [1.11-2.28]). Conclusions: Short respiratory event duration, a marker for low arousal threshold, predicts mortality in men and women. Individuals with shorter respiratory events may be predisposed to increased ventilatory instability and/or have augmented autonomic nervous system responses that increase the likelihood of adverse health outcomes, underscoring the importance of assessing physiological variation in obstructive sleep apnea.

Number of Words in Abstract (250 max): 249

Key words: obstructive sleep apnea; sleep; epidemiology; mortality; prospective

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by repeated airway collapse during sleep. The occlusion of the airway causes a cascade of physiological responses including hypoxemia, hypercapnia, intrathoracic pressure swings due to inspiratory effort, activation of the sympathetic nervous system, and arousal from sleep (1). These acute consequences of each apnea are presumed to play a role in the long term comorbidities associated with OSA that include cardiovascular disease and mortality (1-4). Clinical practice characterizes OSA severity using the apnea hypopnea index (AHI), defined as the average number of respiratory events experienced per hour of sleep, calculated across the total sleep time. Although easy to calculate, this measure ignores other parameters of the apneas that may be informative, including associated hypoxemia and sleep fragmentation, as well as the duration of each event and the distribution of the events in each lying posture, within the night and within sleep stages (5-7).

Recent data suggest that OSA may be characterized by clusters of polysomnographic features that differ in their predictive associations with cerebro-and cardio-vascular outcomes (8), supporting the likelihood of significant physiological variability among patients with similar AHI levels. While this report included measurements of sleep fragmentation, it did not include direct measurements of arousal threshold or indirect measurements, such as duration of respiratory events. Event duration is readily calculated, but an inadequately studied trait which will partly determine the extent of hypoxemia, hypercapnia, and end inspiratory effort—all key physiological stressors. Event duration is a heritable phenotype (9) with shorter events reflecting greater arousability due to lower arousal threshold or increased sensitivity of the respiratory chemical control system (10-12). Therefore, short duration events may indicate a phenotype of

hypersensitivity and hyperarousability—expected to exhibit sympathoexcitation, sleep fragmentation and insomnia rather than sleepiness—that may respond to interventions that help consolidate sleep (13-17). The recent discovery of novel genetic loci that associate with event duration further supports the importance of this phenotype (18).

Given the heritability of event duration and its association with physiologically important traits, we analyzed data from the prospective Sleep Heart Health Study (SHHS) to test the hypothesis that respiratory event duration is associated with all-cause mortality. Given the inconsistencies of the literature in regards to the association between AHI and mortality and cardiovascular risk in women (2-4, 19, 20), we also explored gender-specific effects. Some preliminary results of these studies have been previously reported in an abstract (21).

Methods

Sample characteristics

The sample is a subset of 5804 subjects from the Sleep Heart Health Study (SHHS), publically available through the National Sleep Research Resource (https://sleepdata.org/). The SHHS is a community-based, prospective cohort study, designed to assess the cardiovascular consequences of sleep apnea (22). At baseline, participants completed questionnaires; had height, weight and blood pressure measured; and underwent overnight unattended polysomnography. Additional covariate data were provided by the parent cohorts. Cardiovascular outcomes and mortality data through 2010 were analyzed (mean follow-up of 11 years). The construction of the analytical sample is shown in **Fig. 1**. The SHHS protocol was approved by the Institutional Review Board of each participating center, and signed informed consent was provided by each

subject. The dataset has been pseudonymized by removing all PHI identifiers and assigning each participant a new randomly-generated code. The Institutional Review Board of Oregon Health & Science University determined that the current study of pseudonymized data was not human subjects research (IRB ID 00017510). Complete methods are included in the Online Data Supplement and **Supplemental Tables E1** and **E2**.

Independent variables, covariates, and endpoints

The primary exposure variable was the mean duration of all apneas and hypopneas during any stage of sleep and in any body position (details in the Online Data Supplement). Respiratory events (>10 sec) were scored as apneas or hypopneas based on oronasal airflow from thermistry. Obstructive apneas and hypopneas with and without desaturation criteria of 2, 3, or 4% were separately analyzed. Central apneas were not included in the analysis.

Other variables considered were age, gender, BMI, race, smoking status, and prevalent hypertension, diabetes, coronary heart disease, stroke, or heart failure. Variables derived from polysomnography included: total sleep time, duration of the nighttime spent awake after the initial sleep onset (WASO), AHI (respiratory events with ≥3% desaturation per hour of sleep), arousal index, and percent of sleep with oxygen saturation <90%.

The endpoint of all-cause mortality was defined as any confirmed death between the time of enrollment (1995-1998) and the end date of the study (2011). Mortality was ascertained from hospital records, obituaries, contact with next-of-kin, and the Social Security Administration, as described previously (2).

Statistical Analyses.

Associations between respiratory event duration and mortality were assessed with Cox proportional hazard models. All models satisfied the proportional hazard assumption according to the Grambsch and Therneau test (23): all models had p>.12 for the global test. Individual plots of Schoenfeld residuals for each predictor against time-to-event showed no overt trends.Event duration was categorized into quartiles with quartile 1 (Q1: longest event durations) serving as a reference category for quartiles 2-4 (Q2-Q4, in order of decreasing event duration). Three models were constructed. The base model included event duration and covariates of age, gender, race, smoking status, and BMI. Model 2 included the variables in Model 1 plus AHI. Model 3 included the variables in Model 2 plus prevalent hypertension, diabetes, stroke, coronary heart disease, and heart failure. Several other variables were added to Model 3 in sensitivity analyses as described in the Results.

Adjusted survival plots were constructed from the Model 3 Cox regression coefficients. The reference survival curve represents the median risk based on the distribution of risk scores (coefficients × predictors) for the full population, and then incremented by the risk associated with each quartile of apnea duration. Plots were also constructed for the gender-stratified Cox models.

In cross-sectional analyses, the correlations among event duration and other continuous variables were assessed by Spearman's rho or X^2 likelihood ratio tests. Differences among quartiles were assessed by Wilcoxon/Kruskal-Wallis or 1-way ANOVA. All statistical tests were conducted in R (Rstudio 1.1.383 running R version 3.3.2) or JMP Pro 11.0.0 (SAS Institute, Cary NC).

Results

The sample of 5712 participants (**Table 1**) had a mean age of 63.3 years and mean BMI of 28 at baseline, and were followed for an average of 11.0 years (median 11.8, range 0.01-15.9). The sample was 52% female, 85% Caucasian, and 9% African American (because of small sample sizes, other racial groups were combined: 6% of the sample). The sample included people across the range of OSA severity (12% severe, 20% moderate, 35% mild, 33% none).. Prevalent hypertension and diabetes were 43% and 8% respectively. During follow-up, 1290 deaths were recorded over 62,899 person-years. Adjudicated cardiovascular outcomes were available from the parent cohorts for 1166 deaths (other causes of death were not recorded). Within this set, 357 (30.6%) died of cardiovascular causes. This group included 233 deaths (20.0%) attributable to coronary heart disease and 35 deaths (3.0%) due to stroke. Two more people died from stroke but were not coded as dying from cardiovascular disease.

Relationship of event duration to demographics, prevalent health conditions, and sleep-disordered-breathing severity. Event duration varied from 11.2 to 57.6 seconds (mean 21.3, median 20.6), and varied significantly with several participant characteristics (**Table 2**). Participants with shorter event durations were more likely to be younger, female, African-American, and to be current smokers. Shorter event durations were also associated with higher BMI, lower AHI, and higher minimum blood oxygen saturation (trend test, all $p<0.001$; **Table 2** and **Supplemental Fig. E1**). The same pattern of significance was obtained when treating event duration as a continuous variable; event duration measured continuously was also significantly correlated with percent of sleep below 90% saturation (**Table 2**, Spearman's correlation). Absolute mortality rates declined from the longest event quartile to the shortest event quartile

(trend test, z=4.3, p<0.001), but this association appeared to be confounded by age and gender (see below).

Adjusted associations between event duration and other measurements. Because anthropometric data varied with quartile, partial correlations between event duration and sleep measures were calculated after adjusting for age, gender, BMI, and AHI. Longer events were associated with a lower arousal index (partial correlation r=–0.12; p<0.001), lower minimum nocturnal saturation (r=–0.09; p<0.001), and slightly greater percentage of sleep time in REM (r=+0.04, p=0.0035). After adjusting for covariates, event duration was not significantly correlated with total sleep time, sleep efficiency, WASO, or percent time with saturation <90%.

Proportional Hazard Modeling for All-Cause Mortality. Associations of all-cause mortality with event duration quartile were assessed after adjusting for age, gender, BMI, race, and smoking status (Model 1). Individuals with the shortest duration events (Q4) experienced a 20% increased mortality rate compared to those with the longest duration events (Hazard Ratio, HR = 1.20, 95% confidence interval [1.02-1.40], p=0.024, **Table 3**). This relationship strengthened after adjusting for AHI (Model 2, 26% increased risk, p=0.0043; use of categorical severities yielded similar results). Adjusting for prevalent hypertension, diabetes, and cardiovascular disease also strengthened the results (Model 3, 31% increased risk, p=0.0013); the fully adjusted survival plot is shown in **Fig. 2**. Replacing event duration quartiles with continuously-measured duration did not alter the conclusion, showing that the results are not a function of quartile assignment. The hazard ratio per 10 sec decrease in event duration was 1.15 indicating that shorter events conferred additional risk (CI: 1.03-1.30, p=0.016). Finally, we added arousal index because this is correlated to event duration and may be a similar

physiological measure of arousal threshold. Including the arousal index in Model 3 slightly strengthened the association (34% increased risk, p<0.001).

Other sensitivity analyses were conducted to test the potential role of OSA severity and CPAP treatment in the fully adjusted Model 3. Adjusting for OSA severity as defined by clinical categories of None/Mild/Moderate/Severe rather than continuous AHI also did not change the results (e.g., Q4 relative to Q1, HR = 1.28 [1.09-1.51], p=0.0030). Removing 120 subjects that either reported CPAP treatment or did not know at the interim SHHS2 follow-up likewise did not alter the results (Q4 relative to Q1, HR = 1.31 [1.11-1.54], p=0.0014).

Effect of event subtype. The magnitude of airflow limitation and the associated desaturation are factors used to classify apnea and hypopnea subtypes and characterize severity of each event. Therefore, we tested whether these factors would affect analyses. As expected, event duration was highly correlated across different event subtypes (**Fig. 3**, all p<0.001). The duration of all events (apneas plus hypopneas) was more strongly correlated with hypopnea duration (ρ = 0.74-0.98) than with apnea duration (ρ = 0.51-0.72), reflecting the predominance of hypopneas. The choice of event duration definition was further explored by separately considering obstructive apnea duration versus hypopnea duration in the Cox hazard models, each with and without a 3% desaturation criteria. Commonly used clinical definitions (all apneas without a desaturation threshold and hypopneas with ≥3% desaturation) are included in **Table 3**. Hazard ratios for the shortest events (Q4 versus Q1) were similar when assessing hypopneas only (all hypopneas: HR=1.27 [1.08-1.49], p=0.0035 and hypopneas with ≥3% desaturation: HR=1.30 [1.11-1.53], p=0.0012; see **Supplemental Table E3**). Hazard ratios (Q4 versus Q1) were slightly lower when events were restricted to obstructive apneas (all apneas: HR=1.21 [1.00-1.46], p=0.046). The sample size was smaller when only events with apneas with ≥3% desaturation

were included, and this association was not significant though in the same direction (HR=1.17 [0.96-1.43], p=0.12).

NREM versus REM Events. Respiratory events in REM sleep tend to be longer than in NREM sleep, but separate analysis of events in NREM versus REM had a minimal effect on results (NREM only: Q4/Q1 HR = 1.28 [1.08-1.50], p=0.0036; REM only: Q4/Q1 HR = 1.30 [1.11 – 1.52], p=0.0014). Likewise, adjusting further for the percentage of events that were in REM vs. NREM did not account for the association of event duration with mortality (HR = 1.27 [1.08 – 1.50], p=0.0038). Finally, including the amount of time in slow wave sleep (N3/4) was added to Model 3; it was not significant (p=0.68), and did not affect the risk attributable to event duration.

Gender and mortality risk. Gender significantly predicted mortality in the fully adjusted model, but did not modify the effect of duration on mortality: a gender by event duration (continuous) interaction term was added but this was not significant (p = 0.88). Cox proportional hazard models were constructed for men and women alone to determine if hazard ratios were similar in both groups. In the fully adjusted Model 3, women and men with the shortest event duration had a 32% and 26% increased hazard ratio for death, respectively, compared to their counterparts with the longest event duration (**Table 3** and **Supplemental Fig. E2**). This association was significant in women (p=0.019) and approached significance in men (p=0.050). For comparison, in alternative analyses, similar to a prior report (2), gender modified the mortality risk associated with AHI. Each additional 5 units of AHI increased the mortality risk in men (+3% risk, p=0.043) but not in women (+1% risk, p=0.48, **Table 3**, last column). Substituting categorical OSA severity for AHI or restratifying the quartiles within gender did not affect the conclusions (data not shown).

Interaction of event duration with AHI. Short event durations conferred mortality risk whether or not the model was adjusted for AHI. We next tested whether there was any interaction of AHI and event duration, and if the risk associations held across all severities of OSA. The fully adjusted proportional hazard model was re-run adjusting for continuous AHI, event duration, and their interaction. Short event duration remained a significant predictor (hazard ratio per 10 sec decrease in event duration was 1.20 [1.02 – 1.43], p=0.029). In this model, there was no significant association for either AHI (HR = 0.99 per 5 unit increase [0.92 – 1.07], p=0.86) or the interaction of event duration and AHI (p=0.45). After stratifying by clinical OSA severity categories, participants with the shortest events had a 15-59% increased risk for mortality depending on their clinical OSA severity, with highest hazard ratios in the group with an AHI of 15 to 30 (HR=1.59 [1.11-2.28], p=0.12; **Supplemental Table E4**).

Discussion

In this study, we identify the novel association between average respiratory event duration during sleep and all-cause mortality in a large community sample. Even after adjusting for risk conferred by OSA severity (AHI) and key confounders, shorter event duration predicted higher 11-year mortality rates. While the mechanisms that determine event durations are not fully understood, this measure is reflective of a low arousal threshold (24, 25), a phenotype that may associate with sleep fragmentation and elevated sympathetic tone. In contrast to the AHI, event duration predicted mortality in women, in whom OSA is often associated with insomnia symptoms and sleep fragmentation (26), but in whom long term outcomes related to elevated AHI levels are poorly understood. Risk associations also were strongest in those with

intermediate levels of AHI (15 to 30), a group in whom there are also varying data regarding OSA and mortality associations. Our findings, which held for men as well as women, suggest that consideration of this polysomnographic metric may help phenotype individuals who differ in OSA pathogenesis and outcomes, and may particularly help identify individuals with intermediate high AHI levels at increased risk for death.

Identifying prognostic features is of high priority for risk stratification and for focusing interventions at specific physiological perturbations (1, 27). OSA, as defined by AHI levels, has been shown to be a risk factor for mortality in some but not all studies (2, 4, 20, 28-31). Some studies show increased OSA-related mortality in younger compared to older individuals (32, 33) and in men compared to women (2, 20). Differences may relate to our ignorance of the most important features of sleep disordered breathing that confer risk across the population. Other limitations of AHI-related prognosis relate to weaknesses of the AHI as a primary disease-defining metric, including its insensitivity to physiological disturbances of relevance to health outcomes (5-7, 34). This has led to efforts to identify better thresholds for risk based on cohort outcomes (35, 36). It has also spurred efforts to test different aspects of the syndrome for risk (8). For example, relative to AHI, the extent of apnea related desaturation and overnight hypoxemia appear to be better predictors of stroke and mortality (2, 37, 38). OSA fragments sleep and increases the arousal index; in one cohort study, arousal index was associated with prevalent subclinical cardiovascular disease (39). Zinchuk et al. (8) also showed that individuals characterized by "arousal and poor sleep" tended to have higher rates of myocardial infarction, atrial fibrillation, and chronic lung disease. Nevertheless, these and most other published studies have not analyzed the duration of respiratory events. In this large prospective sample, we showed that event duration predicted mortality over and beyond AHI, and furthermore, suggested that the

predictive information associated with event duration was strongest in individuals with moderate to severe OSA, a group in whom there has been inconsistency in relationships with clinical outcomes.

Event duration is of particular interest because it may be a genetically encoded feature of OSA (9) that varies across population groups (e.g., shorter in females and African Americans) (40). We also discovered a novel genetic locus (rs35424364) that is associated with event duration in Latino/Hispanic Americans (18). In the current study of individuals with generally mild to moderately high AHI levels, we found that event duration had only weak associations with many typically employed measures of sleep disturbance, including sleep time and efficiency, WASO, percent of sleep in REM, and percent of sleep with desaturation. This suggests that event duration contains unique information over and beyond other polysomnography measurements. These findings support the event duration as an independent, inherited trait that may be help explain individual differences in OSA related phenotypes.

Mechanistically, respiratory events will be terminated earlier (shorter duration) if, 1) an individual arouses from a lighter depth of sleep; 2) an individual arouses from the same stage of sleep but at a low level of chemical drive or respiratory effort (i.e. low arousal threshold); or 3) chemical drive builds up rapidly during an event (higher chemoreflex sensitivity to hypoxic hypercapnia or increased loop gain). All three mechanisms therefore reflect a state of increased "arousability" that could potentially promote mortality via greater sleep fragmentation, shorter sleep, and excess sympathetic tone. Indeed, we found that shorter events were associated with a greater arousal index (partial correlation: r=–0.12). Reduced sleepiness (consistent with greater arousability) is associated with increased sympathetic activity in heart failure (41). Hypersensitivity to chemical stimuli at the carotid bodies is also a mechanism of increased

sympathoexcitation and attendant development of hypertension (42), and is a predictor of mortality in patients with heart failure (43).

Event duration varied significantly with several demographic and health-related factors. Individuals with shorter event duration were more likely to be younger, female, African American, and current smokers. The association of smoking with shorter events is especially interesting. Nicotine promotes alertness and lighter sleep, suggesting a lower arousal threshold. Smoking also disturbs EEG measures of sleep (44), and causes subjective complaints of disturbed sleep (45). Although nicotine can influence the release of central neurotransmitters associated with sleep-wake control (46), the mechanisms by which smoking may shorten apneas—for example, by reducing arousal threshold—requires further investigation.

In adjusted analyses, individuals with shorter events tended to have higher minimum SaO_2 (reflecting shorter periods of obstructive breathing or reduced metabolic rate). However, after adjusting for the AHI, event duration was not associated with sleep time spent at low levels of oxygen saturation. . Hypoxic burden derives from the combination of number of events, their duration, and their desaturation. A larger product of event duration and desaturation has been associated with long term risk (5, 47). Our results—showing short rather than long events as predictors of risk—do not refute this. Rather, hypoxemia and event duration may represent different features of OSA-related stress, both of which may contribute to mortality through independent pathways. Our findings suggest a need to further identify the intermediate mechanisms that link event duration to long term outcomes.

Event duration predicted mortality in both men and women, while AHI was only associated with mortality in men, as has been reported before (2). OSA is more likely to be associated with insomnia in women than in men (26, 48), and it is possible that in women, OSA

risk is less associated with the numbers of events during sleep and more associated with arousal-related responses to respiratory disturbances. Indeed, gender differences in OSA phenotypes are well-described, with women generally showing greater airflow limitation, increased work of breathing, and sleep fragmentation (26, 49), with recent studies also showing sex-specific genetic variants for OSA (50). The current results show that mortality risk in women can be predicted from features of their sleep disordered breathing, but the critical measure is not likely the AHI.

Strengths and limitations of the study.

As a community based prospective cohort, the study sample was not influenced by clinic or treatment selection biases. The long follow-up time, adjudicated outcomes, and the rigorous collection of sleep data and other covariates allowed us to study the effects of event duration while also controlling for a number of confounders. Limitations include the single night of a sleep study which, though used for clinical decision making, may not fully characterize a person's typical sleep. There is also no information about medications taken on the night of the sleep study. Some medications, especially psychoactive drugs, could alter arousability, though this community cohort is a general population sample that likely has limited psychoactive medication use. Future studies of event duration should explore the potential role of medications on arousability and event duration. We also investigated a number of potential causes for heterogeneity through sensitivity analyses to ensure that the main conclusions were not affected by statistical modelling or definitions of events. First, we found the same conclusions when the clinical OSA severity grouping (none/mild/moderate/severe) was substituted for AHI. Second, results were consistent whether quartiles of event duration were based on the entire sample or were gender-specific. We also found generally consistent results when we only examined apneas

and hypopneas, when we considered state-specific events, and when we included any event versus those associated with desaturations. We focused on all-cause mortality to maximize statistical power. Future research is needed to discern associations with cause-specific mortality. Finally, results were not altered by the inclusion of subjects that reported CPAP use at the interim follow up visit.

We cannot determine whether the short events reflect a direct causal mechanism for increased mortality, or rather are markers for underlying autonomic or other physiological phenotypes that associated with unfavorable outcomes. Regardless, our data suggest that the occurrence of short event duration in individuals with mild to moderately elevated AHI levels may help identify individuals at risk for adverse health. Current clinical trial data are ambiguous in regards to the role of OSA on mortality or cardiovascular incidence (SAVE Study, 51). Re-analysis of those data considering variation in event duration may provide insights into possible heterogeneity of response to CPAP related to this phenotype.

The sample had few participants with very long events: only 5% had events that averaged longer than 30 sec. Therefore, whether our results generalize to those with severe events is unclear. Further study, particularly in clinical populations, is warranted to understand the associations between very long event durations and hypoxemia to mortality.

In summary, this study shows that a relatively easily derived parameter from overnight polysomnography, respiratory event duration, predicts all-cause mortality over and beyond that predicted by the AHI. Moreover, event duration predicted mortality in both men and women independent of many potential confounders. These data provide new information to inform emerging initiatives to identify sleep apnea subphenotypes reflective of individuals with different

underlying mechanisms who may experience different outcomes and respond differently to treatments. Event duration may measure a component of a phenotype characterized by low arousal threshold. Further research is needed to address whether these individuals are at increased risk for outcomes such as increased mortality due to elevated sympathetic tone or abnormalities in arousal-mediated stress responses.

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Figure Legends

1. Subject selection.

2. Differential survival from the fully adjusted Cox proportional hazard model 3. The reference survival curve represents the median risk over all predictors. Because the hazard ratio for Quartile 2 is 1.01, the curves for Quartiles 1 (reference) and 2 are almost superimposable.

3. Respiratory event subtype correlation matrix. The matrix shows the relationship across different definitions of event type (apnea, hypopnea, and desaturation criteria). The combined apnea-hypopnea measure is more closely correlated with hypopnea duration than apnea duration. All correlations are significant but vary from 0.51-0.98 (blue to red). The highest correlations are between hypopnea duration and apnea-hypopnea duration for a given desaturation criteria (ρ = 0.96-0.98). Red lines are LOESS smoothed fits.

Tables

Table 1. Selected baseline characteristics

Sample characteristic	Subcategory	Mean (sd) [range] or %
N		5712
Age (yr)		63.3 (sd 11.1) [39-90]
BMI (kg/m^2)		28.1 (sd 5.1) [18-50]
Gender (%F)		52
AHI (events/h)*		13.8 (sd 15.0) [0-157]
Sleep Time (h)		360 (sd 64) [35-519]
Sleep Efficiency (%)		81.5 (sd 10) [11.3-98.5]
Sleep latency (min)		23.1 (sd 23) [0-218]
% time in REM		19.3 (sd 6.9) [0-43]
Wake After Sleep Onset (WASO) (min)		61.6 (sd 44) [0-368]
Arousal Index (h^{-1})		19.2 (sd 10.7) [0-110]
% sleep < 90% sat		3.5 (sd 10.3) [0-100]
AHI (events/h)		13.8 (sd 15.0) [0-157]
OSA severity	None (%)	33
	Mild (%)	35
	Moderate (%)	20
	Severe (%)	12
Race	Afr.Amer. (%)	9
	White (%)	85
	Other (%)	6
Smoking Status	Current (%)	10
	Former (%)	47
	Never (%)	43
Prevalent Disease	Hyperten. (%)	43
	Diabetes (%)	8
	CHD (%)	8
	Stroke (%)	3
	HF (%)	2
	†Any CVD (%)	11
Outcomes	Deaths	1290
	Follow-up time (person-years)	62899
	Mortality rate per 1000 person-years	20.5

*AHI defined by the respiratory disturbance index with a 3% desaturation threshold. †Any prevalent coronary heart disease, stroke, or heart failure.

Table 2. Sample characteristics by quartile of respiratory event duration (mean and SD, or %)

		Longest----------Quartiles----------Shortest				Statistical Tests		
		Q1	Q2	Q3	Q4	Quartile difference	Spearman ρ	Trend Test
Apnea duration	Range (sec)	(24.1-57.6]	(20.6-24.1]	(17.7-20.6]	[11.2,17.7]			
	Mean (SD)	27.80 (3.72)	22.17 (0.98)	19.18 (0.81)	15.91 (1.25)			
N		1428	1428	1428	1428			
Age (yr)[A]		66 (11)	63 (11)	63 (11)	61 (11)	***	+0.17***	***
BMI (kg/m^2) [W]		27.4 (4.8)	28.1 (4.9)	28.5 (5.1)	28.5 (5.4)	***	−0.09***	***
Gender (%F) [X]		47	49	53	61	***		***
AHI (events/h) [W]		12.0 (14.7)	8.5 (12.2)	8.6 (11.9)	5.6 (9.6)	***	+0.19***	***
Min SaO2 (%) [W]		84.0 (8.4)	85.9 (6.1)	85.6 (6.2)	86.5 (5.4)	***	−0.11***	***
Sleep Time (h) [A]		6.0 (1.1)	6.0 (1.1)	6.0 (1.1)	6.0 (1.1)	n.s.	−0.03	#
Sleep Efficiency (%) [A]		81.2 (10.7)	81.5 (10.3)	81.5 (10.3)	81.9 (10.5)	n.s.	−0.02	n.s.
% time in REM [A]		19.1 (6.8)	19.6 (6.8)	19.5 (7.1)	19.1 (6.9)	*	−0.00	n.s.
WASO (min) [W]		65 (46)	63 (45)	60 (42)	58 (43)	***	+0.07#	***
Arousal Index (h^{-1}) [W]		19.4 (11.5)	18.7 (10.8)	19.3 (10.1)	19.3 (10.3)	#	−0.02	n.s.
% sleep < 90% sat [W]		4.3 (10.8)	2.9 (9.1)	3.4 (9.8)	3.4 (11.4)	**	+0.10***	#
Race [X]	Afr.Amer. (%)	6	9	10	10	**		
	White (%)	88	84	84	84			
	Other (%)	6	7	6	6			
Smoking Status [X]	Current (%)	6	8	9	16	***		
	Former (%)	45	44	45	39			
	Never (%)	49	49	45	45			
Prevalent Disease [X]	HTN (%)	50	42	43	39		***	***
	Diabetes (%)	8	8	8	8		n.s.	n.s.
	CHD (%)	15	11	11	9		***	***
	Stroke (%)	5	4	3	2		**	***
	HF (%)	6	3	3	2		***	***
	†Any CVD (%)	20	14	14	11		***	***
Outcomes	Deaths	385	301	315	286		***	***
	Follow-up time (person-years)	14,171	14,461	14,534	14,659			
	Mortality rate, /1000 person-years	27.2	20.8	21.7	19.5			***

Differences among quartiles were assessed by [A]1-way ANOVA, or [W]Wilcoxon/Kruskal-Wallis test when variances were unequal (Bartlett test). X^2 test was used to test for quartile differences in proportions. Bivariate correlation coefficients (Spearman's rho) against event duration were calculated for continuous measures. Trends across quartiles were assessed by the Cochran-Armitage trend test or by linear regression against quartile number. Significance indicated: # p<0.10, *p<0.05, **p<0.01, ***p<0.001. †Any prevalent CHD, Stroke, or HF. Gray indicates no analysis.

Table 3. Cox proportional hazard ratios [95% confidence interval]: association of event duration (quartile) with all-cause mortality.

		Longest----------Quartile---------- Shortest				
Dataset	Model	Q1	Q2	Q3	Q4	AHI (additional hazard / 5 units)
All subjects	1	Ref	0.94 [0.81-1.09]	1.12 [0.96-1.30]	**1.20 [1.02-1.40]***	**NA**
	2	Ref	0.96 [0.83-1.12]	**1.14 [0.98-1.33]#**	**1.26 [1.08-1.49]****	**1.03 [1.01 – 1.05]*****
	3	Ref	1.01 [0.86-1.17]	**1.18 [1.01-1.37]***	**1.31 [1.11-1.54]****	**1.02 [1.00 – 1.04]***
All apneas	3	Ref	0.98 [0.83 – 1.15]	0.96 [0.80 – 1.15]	**1.21 [1.00-1.46]***	**1.03 [1.01 – 1.05]***
Hypopneas, ≥3% desat	3	Ref	1.03 [0.88 – 1.19]	1.07 [0.92 – 1.25]	**1.30 [1.11-1.53]****	1.02 [1.00 – 1.04]#
NREM	3	Ref	1.04 [0.89 – 1.21]	1.11 [0.95 – 1.30]	**1.28 [1.08 – 1.50]****	**1.02 [1.00 – 1.04]***
REM	3	Ref	1.02 [0.87-1.20]	0.96 [0.82-1.13]	**1.30 [1.11 – 1.52]***	1.02 [1.00 – 1.04]#
Women	3	Ref	1.00 [0.79-1.26]	1.10 [0.87-1.39]	**1.32 [1.05-1.66]***	1.01 [0.98 – 1.05]
Men	3	Ref	1.01 [0.83 – 1.23]	1.23 [1.00-1.51]#	1.26 [1.00-1.59]#	**1.03 [1.00 – 1.05]***

Quartile 1 is the reference quartile. #p<0.1, *p<0.05, **p<0.01, compared to Q1.

Other covariates:
Model 1: Age, Gender, BMI, Race, Smoking Status (Gender not included in gender stratified models).
Model 2: Model 1 + AHI
Model 3: Model 2 + Prevalent hypertension, diabetes, CHD, stroke, heart failure.

ONLINE DATA SUPPLEMENT

Apnea-hypopnea duration predicts mortality in men and women in the Sleep Heart Health Study

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Online Methods

Sample characteristics

The sample is derived from the Sleep Heart Health Study (SHHS), a community-based, prospective cohort study designed to assess the cardiovascular consequences of sleep apnea. Briefly, 6441 men and women aged 40 years or older were recruited from among participants in seven ongoing cohort studies ("parent studies") as described previously (E1). Participants in the parent studies were ineligible to participate if they reported a history of OSA treatment with continuous positive airway pressure (CPAP) or nightly oxygen. At baseline (1995–1998), participants completed questionnaires; had height, weight and blood pressure measured; and underwent overnight unattended polysomnography. Additional covariate data were provided by the parent cohorts. Participants also had ongoing surveillance for cardiovascular events by parent cohorts. The current study analyzed follow-up data through 2010. The protocol was approved by the Institutional Review Board of each participating center, and signed informed consent was provided by each subject. The Institutional Review Board of Oregon Health & Science University determined that the current study of pseudonymized data was not human subjects research.

The construction of the analytical sample is shown in **Fig. 1**. Of the 6441 participants enrolled in the SHHS, data for 5804 participants were available through the National Sleep Research Resource (https://sleepdata.org/), a publicly available research data set (data from the Strong Heart Study were excluded due to tribal data sharing restrictions). Excluding subjects with missing data in important covariates yielded a final analytic dataset of 5712 subjects with which to study all-cause mortality. Average follow-up time was 11 years, during which time 1290 deaths were recorded over 62,899 person-years.

Endpoints

All-cause mortality was defined as any confirmed death between the time of enrollment and the final censoring date. The censor dates for subjects were defined as the time of death or the last contact date, coded as days since the baseline sleep study.

Independent variables and covariates

The primary exposure variable was the mean duration of all apneas and hypopneas during any stage of sleep and in any body position. Respiratory events were measured from oronasal thermistors as specified in the SHHS Reading Center Manual of Operations (https://sleepdata.org/datasets/shhs/pages/mop/6-00-mop-toc.md). Apneas were defined by decreases in airflow to less than approximately 25% of the baseline breathing amplitude for > 10 sec. Hypopneas were defined by airflow decreases below 70% of baseline breathing for > 10 sec. These definitions were adopted because SHHS was scored beginning in 1994 before publication of the current definitions (90% reduction for apneas and 30% reduction for hypopneas). In the scoring, an attempt was made to harmonize with the approaches used by the Wisconsin Sleep

Cohort. Nonetheless, all definitions of flow reduction are at best semi-quantitative given that these are not calibrated signals. We found that operationalizing apnea identification to "less than 25% of baseline" in actuality identified events with virtually no to minimal flow (i.e., "90% reduction") as currently specified. The description we provided of hypopneas as 70% below baseline breathing equates to the current 30% reduction rule. Central apneas were not included in the analysis. Mean event duration in non-rapid eye movement (NREM) and REM sleep were also calculated.

Duration was scored for all events for individuals in the Sleep Heart Health Study, and the average duration is available in the National Sleep Research Resource, broken down for each person by event type (obstructive apnea, central apnea, or hypopnea), sleep stage (REM or NREM), and sleeping position (back position or other). These are available with and without desaturation criteria. The main exposure variable employed here was the average of obstructive apneas and hypopneas in all sleep stages and all body positions, weighted by the number of occurrences of each. For secondary analyses, the event duration was separately calculated for obstructive apneas alone, hypopneas alone, NREM sleep alone, and REM sleep alone. These were repeated for different desaturation classes (e.g., **Fig. 3**). The variables used to calculate event duration are shown in **Supplemental Table E1**.

Other variables from the baseline examination considered were age, gender, BMI, race (African American/Caucasian American/Other), smoking status (current/former/never), prevalent hypertension (blood pressure > 140/90 mmHg or treatment with anti-hypertensive medication), prevalent diabetes (report of diagnosed diabetes or use of insulin or hypoglycemic agents), prevalent coronary heart disease (any previous MI or revascularization procedure), prevalent stroke, or prevalent heart failure. Variables extracted from polysomnography included: total

sleep time, wake after sleep onset (WASO), AHI (number of respiratory events, each with ≥3% desaturation per hour of sleep), arousal index, and percent of sleep with oxygen saturation <90%). At an interim follow-up, participants were asked whether they had been treated for sleep apnea by CPAP or oral appliance. Within the n=5712 analytical dataset, 115 reported treatment and 5 did not know. A sensitivity analysis was conducted by comparing models run with and without these 120 participants to determine if they would affect the results. Variables and their specific names as they appear in the NSRR database are shown in **Supplemental Tables E1 and E2)**.

Statistical Analyses

Associations between respiratory event duration and mortality were assessed with Cox proportional hazard models (E2). The proportional hazard assumption was tested by inspection of the Schoenfeld residuals and the Grambsch and Therneau test (E3). Event duration was categorized into quartiles with quartile 1 (Q1: longest event durations) serving as a reference category for quartiles 2-4 (in order of decreasing event duration). Three models were constructed. The base model included event duration and covariates of age, gender, race, smoking status, and BMI. Model 2 included the above plus AHI (considered alternatively as a continuous variable or according to clinical thresholds: ≥30, 15-30, 5-15, and <5 events per hour). Model 3 included all variables in Model 2 plus variables that may be in the intermediate pathways linking sleep disordered breathing to mortality, including prevalent hypertension, diabetes, stroke, coronary heart disease, and heart failure. Additional sensitivity analyses were conducted for event durations from NREM and REM sleep, calculated separately.

In cross-sectional analyses, the correlations among event duration and other continuous variables were assessed by Spearman's rho. Nominal outcome variables were assessed across quartiles with X^2 likelihood ratio tests; for dichotomous outcomes, trends across quartiles were assessed by the Cochran Armitage trend test. For continuous outcome variables, homogeneity of variance across quartiles was first tested with Bartlett's test. When variances were unequal, the Wilcoxon/Kruskal-Wallis test was used to test for differences among quartiles; otherwise 1-way ANOVA was used. The crude mortality rate trend across the quartiles was tested by linear regression by treating the quartile number as a continuous numeric variable. Significance was set at $\alpha = 0.05$. All statistical tests were conducted in R (Rstudio 1.1.383 running R version 3.3.2) or JMP Pro 11.0.0 (SAS Institute, Cary NC).

Table E1

Variables for number and average duration of each type of respiratory event as coded in the National Sleep Research Resource (NSRR) database. # Desaturation criteria for each event (numbers indicate the oxygen saturation drop criteria (2-4%); no number at the end would indicate no desaturation criteria).

			NSRR ID	
Event type	**Sleep stage**	**Body position**	**Duration**	**Number**
Obstructive Apnea	NREM	Back	AvOANBP#	OANBP#
		Other	AvOANOP#	OANOP#
	REM	Back	AvOARBP#	OARBP#
		Other	AvOAROP#	OAROP#
Hypopnea	NREM	Back	AvHNBP#	HNRBP#
		Other	AvHNOP#	HNROP#
	REM	Back	AvHRBP#	HREMBP#
		Other	AvHROP#	HROP#

Table E2

Other variables employed in these analyses as coded and described in the National Sleep Research Resource (NSRR) database.

Data Category	Variable	NSRR ID
Demographics and sleep	Age at baseline	age_s1
	Gender	gender
	BMI at baseline	bmi_s1
	Race (Caucasian, African American, Other)	race
	Smoking status (Current, Former, Never)	smokstat_s1
	AHI	rdi3p
	Minimum nocturnal SaO2, minimum of:	
	Min. SaO2 in NREM sleep	MnSaO2NH
	Min. SaO2 in REM sleep	MnSaO2RH
	Arousal Index	ai_all
	Total sleep time	slp_time
	Sleep efficiency	Slp_eff
	Wake after sleep onset	WASO
	Percent of sleep time with O_2 saturation < 90%.	pctlt90
	Percent of sleep time in REM	TmREMP
	CPAP treatment since baseline	treatedsleepapnea
Prevalent Health Conditions	Hypertension	HTNDerv_s1
	Diabetes, defined by any of:	
	Patient report of diabetes	ParRptDiab
	Use of insulin	INSULN1
	Use of oral hypoglycemic agents	OHGA1
	Coronary heart disease (CHD), defined by any:	
	Myocardial infarctions	prev_mi
	Procedures related to heart attack	prev_mip
	Revascularization procedures	prev_revpro
	Congestive heart failure	prev_chf
Outcomes	Vital status at censor date	vital
	Time to last contact or death	censdate

Table E3

Fully adjusted Cox proportional hazard ratios [95% confidence interval] for mortality for different event definitions. Note that fewer participants have events with deeper desaturations: the smaller sample size reduced statistical power.

				Longest----------Quartile----------Shortest			
Event	Desaturation threshold	N	Deaths	Q1	Q2	Q3	Q4
apneas, hypopneas	NA	5712	1290	Ref	1.01 [0.86-1.17]	**1.18 [1.01-1.37]***	**1.31 [1.11-1.54]****
apneas, hypopneas	3%	5672	1285	Ref	1.01 [0.87 – 1.18]	1.03 [0.88 – 1.20]	**1.28 [1.09-1.51]****
hypopneas	NA	5712	1290	Ref	0.98 [0.84 – 1.14]	1.17 [1.00 – 1.36]	**1.27 [1.08-1.49]****
hypopneas	3%	5665	1282	Ref	1.03 [0.88 – 1.19]	1.07 [0.92 – 1.25]	**1.30 [1.11-1.53]****
apneas	NA	4562	1058	Ref	0.98 [0.83 – 1.15]	0.96 [0.80 – 1.15]	**1.21 [1.00-1.46]***
apneas	3%	4112	975	Ref	1.02 [0.86 – 1.20]	1.01 [0.84 – 1.22]	1.17 [0.96-1.43]

*p<0.05, **p<0.01 compared to reference Q1.
Other covariates
Model 1: Age, Gender, BMI, Race, Smoking Status, AHI, and prevalent hypertension, diabetes, CHD, stroke, heart failure.

Table E4

Fully adjusted Cox proportional hazard ratios [95% confidence interval] for mortality, stratified by OSA severity.

			Longest----------Quartile----------Shortest				
OSA Severity	N	Deaths	Q1 (longest)	Q2	Q3	Q4 (shortest)	AHI (additional hazard / 5 units)
AHI < 5	1880	320	Ref	0.86 [0.61 – 1.23]	1.20 [0.85 – 1.70]	1.29 [0.94-1.77]	1.18 [0.79 - 1.77]
5 ≤ AHI < 15	2008	468	Ref	1.09 [0.85 - 1.40]	1.19 [0.92 – 1.55]	1.15 [0.87 - 1.52]	1.01 [0.87 - 1.18]
15 ≤ AHI < 30	1153	300	Ref	1.07 [0.79 – 1.45]	1.15 [0.84 – 1.56]	**1.59 [1.11-2.28]***	**1.17 [1.02 - 1.33]***
30 ≤ AHI	671	202	Ref	0.85 [0.58 - 1.23]	1.12 [0.77 - 1.61]	1.32 [0.81 - 2.13]	1.03 [0.98 - 1.09]

*p<0.05 compared to reference Q1 or relative to a hazard ratio of 1.0.
Other covariates: Age, gender, BMI, race, smoking status, and prevalent hypertension, diabetes, coronary heart disease, stroke, and heart failure.

Online Data Supplement References

E1. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 1997; 20: 1077-1085.

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E3. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals *Biometrika* 1994; 81: 515-526.