# Online supplement

Sleep arousal burden is associated with long-term all-cause and cardiovascular mortality in 8,001 community-dwelling older men and women.

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## Study Populations

### MrOS sleep study

The MrOS cohort observational study enrolled 5995 community-dwelling men older than 65 years between March 2000 and April 2002 at six clinical centres in the United States to investigate the epidemiology of osteoporosis in older men and identify the risk factors for fracture and bone loss.1 Enrolled participants had to be able to walk without any assistance from another person and not have a bilateral hip replacement.2 The Outcomes of Sleep Disorders in Older Men (MrOS Sleep) substudy recruited 3135 participants from MrOS. All men provided written informed consent, and the Institutional Review Board approved the study at each site. All men completed the clinical visit and in-home overnight PSG between December 2003, and March 2005.3Of these participants, 2892 (92.2%) had adequate PSG datasets.

### SOF

The SOF observational cohort study enrolled 9704 community-dwelling Caucasian female participants aged *≤*65 years who lived in the US between September 1986 and October 1988.4 Later, 662 African-American women recruited between February 1997 and 1998 were added to the study. Participants were reassessed biannual follow-up visits. Four hundred sixty-one participants completed overnight in-home PSG between January 2002 and February 2004.3, 5 Of these women, 453 had adequate PSG.

### SHHS

The SHHS is a prospective multi-centre cohort study implemented by the National Heart Lung & Blood Institute to investigate OSA and other SDB as risk factors for the development of CV disease.6 Thus, SHHS participants were recruited from ongoing cohort studies of CV or respiratory disease with no treatment of SDB with continuous positive airway pressure (CPAP), no tracheostomy and no current home oxygen therapy.6 Among 11503 eligible individuals in parent cohort studies, 6841 (62%) participants completed the home overnight PSG sleep study between November 1995 and January 1998.6, 7 In this study, the PSG of 5791 participants were available for analysis (89.9%).

## Follow-up

MrOS sleep participants were followed up every four months to survey for new symptoms of CV or clinically relevant arrhythmia by postcards and/or phone with *>* 99% response rate. A board-certified cardiologist then verified all relevant medical records and supporting documents for centralised adjudication using a pre-specified protocol.8 The death certificate and hospital records from the time of death were collected for fatal events. If a fatal event did not occur at the hospital, a proxy interview with next of kin and the participant's most recent hospitalisation documents in the prior 12 months were collected. Only events confirmed by the adjudicator are included for analysis.3

Deaths of SOF participants were centrally adjudicated using a state-registered certificate of death which was submitted to the coordinating centre. The principal investigator at each of four clinical sites indicated the initial diagnosis for the cause of death. The final classification of cause-specific mortality was centrally adjudicated at the coordinating centre by a trained physician adjudicator, using the International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM).3

Deaths in the SHHS cohort from any cause were identified and confirmed using multiple concurrent approaches including follow-up interviews, written annual questionnaires or telephone contacts with study participants or next-of-kin, surveillance of local hospital records and community obituaries, and linkage with the Social Security Administration Death Master File.9

## In-home overnight polysomnography

Sleep recordings were performed using an unattended, portable in-home PSG over one night at the participant's residence using the Compumedics (Abbotsford, Australia) Safiro sleep monitoring system for MrOS Sleep, the Compumedics Siesta system for SOF3 and Compumedics P-series for SHHS.9 Trained staff members visited the participants to attach the sensors and electrodes and conduct overnight PSG. The setup included two central electroencephalograms (EEG), bilateral electrooculograms, bilateral chin electromyogram, a bipolar electrocardiogram, nasal-oral thermistor, nasal flow via pressure transducer and nasal cannula, abdominal and respiratory inductance plethysmography, finger pulse oximetry, bilateral leg movements by piezoelectric sensors and body position.3, 9, 10

## Sleep Scoring

Certified sleep technicians scored sleep events according to the standard criteria.11, 12 The apnoea-hypopnoea index (AHI) was calculated as the number of apnoea and hypopnea episodes per hour of sleep. Apnoea was defined as the complete or near-complete cessation of airflow for more than ten seconds, and hypopneas were scored if clear reductions in breathing amplitude (at least 30% below baseline breathing) occurred and lasted more than 10 seconds Only apnoea and hypopnea events that were associated with a 3% or greater desaturation were included in the AHI.10 The severity of sleep apnea/hypopnea syndrome can be determined through the AHI as mild those with 5≤AHI<15 events per hour, moderate (15≤AHI<30 h-1) and severe (AHI≥30 h-1). Sleep duration or total sleep time (TST) was obtained from REM and NREM sleep stages after PSG analysis. Sleep arousals were also scored according to the American sleep disorders association criteria12 and verified with AASM requirements for arousal scoring.13

Periodic limb movement (PLM) events were scored according to AASM criteria which includes individual movements with clear amplitude increase from baseline in legs movement and the duration between 0.5 and 5 seconds. To be considered periodic, at least 4 movements required to occur in succession no less than 5 seconds and no more than 90 seconds apart excluding PLM after respiratory events. The periodic limb movement index (PLMI) was the total number of PLM events per hour of sleep.8 PLM events were only scored in MrOS and SOF datasets.

Respiratory rate (RR) during sleep extracted from the thoracic respiratory inductance plethysmography belt signal of the PSG data. During pre-processing, signal offsets were removed and a low-pass forward and reverse Butterworth filter (1 Hz) was applied. Expiratory and inspiratory onsets were determined from the respiratory signal by identifying the peaks and valleys using the first-order derivative. The inspiratory onset of artifact-free breaths was used to compute a breath-by-breath measure of the respiratory interval which were then averaged within each subject.3

## Additional measures

In the MrOS and SOF cohorts, the participants' history of physician diagnosis of diabetes, hypertension (HT), coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), asthma, stroke and Parkinson were surveyed. The SOF questionnaires contained additional items on the history of depression. In contrast, MrOS questionnaires contained additional questions on the history of chronic obstructive pulmonary disease (COPD), atrial fibrillation or flutter (Afib), smoking habits and alcohol consumption. The SHHS questionnaire included items on the history of stroke, CHF, MI, diabetes, HT, Afib and smoking habits. The ethnicity of all participants in the three cohorts (MrOS, SOF and SHHS) was also included in the analysis.

## Survival analysis using the arousal index

Arousal index data of all cohorts were divided into AI quartiles. To compare participants in the fourth AI quartile against the participants in the lower three quartiles, we used cut-off values of 25 30 h-1 and 30 h-1 for women and men, respectively.

The AI was significantly higher in the MrOS cohort than in the SOF cohort (25.2±12.6 h-1 vs. 22.1±12.6 h-1, *p*<0.001). Within the SHHS cohort, the AI was also significantly higher in men than in women (25.2±13 h-1 vs. 19.9±10 h-1, p<0.001).

Kaplan-Meier curves of dichotomised AI data for all-cause mortality is shown in **Figure S4**. The competing risk of CV and non-CV mortality in four cohorts is depicted in **Figure S5**. In SOF cohort, the probability of CV mortality was significantly increased in women with AI>25 h-1 compared with women with an AI≤25 h-1 (about 10%). Similarly, CV mortality in SHHS-women with AI>25h-1 was nearly 4% greater. In the MrOS cohort, the CV mortality increased by about 5% in participants with AI>30 h-1 compared with men with AI<30 h-1. But no significant association between CV mortality and AI>30 h-1 was observed in SHHS-men.

All-cause mortality in SHHS-men with AI>30 h-1 was nearly 7% higher than men with AI<30. In SHHS-women, all-cause mortality for AI>25 h-1 was 11.5% greater. Log-rank tests showed no significant association between AI distribution and all-cause mortality in MrOS and SOF cohorts (MrOS: *p*=0.131; SOF: *p*=0.127).

In Cox proportional hazard analysis of the MrOS cohort, AI>30 h-1 was associated with CV mortality (univariate: HR=1.38 [1.09-1.76], *p*=0.009; multivariable: HR=1.29 [1.01-1.63], *p*=0.048), but not with all-cause mortality **(Table S1)**.

Similarly, AI>25 h-1 was significantly associated with CV mortality in SOF (univariate: HR=2.57 [1.30-5.11], *p*=0.001; multivariable: HR=2.68 [1.22-5.82], *p*=0.013), but not with all-cause mortality.

In women of the SHHS cohort, AI>25 h-1 was significantly associated with CV (univariate: HR=1.81 [1.27-2.58], *p*<0.001; multivariable: HR=1.53 [1.07-2.22], *p*=0.022) and all-cause mortality (univariate: HR=1.69 [1.39-2.05], *p*<0.001; multivariable: HR=1.47 [1.21-1.80], *p*<0.001). In men, AI>30 h-1 was only significantly associated with all-cause mortality in univiariate analysis (HR=1.24 [1.03-1.49], *p*=0.02).

In all datasets, ABI and AI values are highly correlated (**Figure S6**: ρ>0.9, p<0.001). The highest quartile of ABI (ABI>8.5% in men and ABI>6.5% in women) may reflect the highest quartile of AI (AI>30 h-1 in men and AI>25 h-1 in women).

To test whether combining AB and AI yields stronger associations with mortality, we dichotomised AB and AI values using the cohort medians to low/high AB and low/high AI, respectively, resulting in subgroups of participants with either low AB & low AI, high AB & high AI, low AB & high AI or high AB & low AI. We created KM plots for the resultant composite index. Neither all-cause mortality (Figure S7) nor CV mortality (Figure S8) was significantly different between the composite index subgroups. Owing to the strong the between AB and AI, the vast majority of participants with a high AB also have a high AI, and vice versa.

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**Figure S1**: Flow charts of participants included in the analysis of arousal burden index for **a**) the Osteoporotic Fractures in Men Study (MrOS), **b**) the Study of Osteoporotic Fractures (SOF) and **c**) the Sleep Heart Health Study (SHHS). PSG: polysomnography, BMI: body mass index, SDB: sleep-disordered breathing. CPAP: continuous positive airway pressure.

A close up of a map

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**Figure S2**: Association between arousal burden index (ABI) and total sleep time (TST) in **A**) the Osteoporotic Fractures in Men Study (MrOS), **B**) the Study of Osteoporotic Fractures (SOF), **C**) men in the Sleep Heart Health Study (SHHS) and **D**) women in SHHS. ρ – Spearman's correlation coefficient.

A close up of a map

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**Figure S3**: Association between arousal burden index (ABI) and apnoea-hypopnoea index (AHI) in **A**) the Osteoporotic Fractures in Men Study (MrOS), **B**) the Study of Osteoporotic Fractures (SOF), **C**) men in the Sleep Heart Health Study (SHHS) and **D**) women in SHHS. ρ – Spearman's correlation coefficient.

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**Figure S4**: Kaplan-Meier curves for arousal index (AI) and all-cause mortality in (**A**) the Osteoporotic Fractures in Men Study (MrOS) Sleep cohort, (**B**) men in Sleep Heart Health Study (SHHS), (**C**) the Study of Osteoporotic (SOF) cohort and (**D**) women in the SHHS cohort. AI values were dichotomised at 30 h-1 for men and 25 h-1 for women. P-values refer to log-rank test results.

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**Figure S5**: Cummulative incident function curves compare the competing risk of arousal index (AI) of cardiovascular (CV), non-cardiovascular and all-cause mortality in (A) men from the Osteoporotic Fractures in Men Study (MrOS) Sleep cohort, (B) men from the Sleep Heart Health Study, (C) in women from the Study of Osteoporotic (SOF) cohort and (D) women from the Sleep Heart Health Study. Hazard ratio (HR) and p-value were estimated through subdistributional Fine-Gray hazard model.



**Figure S6**: Association between arousal burden index (ABI) and arousal index (AI) in **A**) the Osteoporotic Fractures in Men Study (MrOS), **B**) the Study of Osteoporotic Fractures (SOF), **C**) men in the Sleep Heart Health Study (SHHS) and **D**) women in SHHS. ρ – Spearman's correlation coefficient.

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**Figure S7**: Kaplan-Meier curves of combined arousal burden (AB) and arousal index (AI) and all-cause mortality in (**A**) the Osteoporotic Fractures in Men Study (MrOS) Sleep cohort, (**B**) men in the Sleep Heart Health Study (SHHS), (**C**) the Study of Osteoporotic (SOF) cohort and (**D**) women in the SHHS cohort. AB and AI values were dichotomised based on cohort median values.

**Figure S8**: Kaplan-Meier curves of combined arousal burden (AB) and arousal index (AI) and cardiovascular mortality in (**A**) the Osteoporotic Fractures in Men Study (MrOS) Sleep cohort, (**B**) men in the Sleep Heart Health Study (SHHS), (**C**) the Study of Osteoporotic (SOF) cohort and (**D**) women in the SHHS cohort. AB and AI values were dichotomised based on cohort median values.

**Table S1**: Association of arousal index (AI) with cardiovascular and all-cause mortality. Hazard ratios (HR) for ABI (%) indicate the risk increment per 1% increase in ABI. For categorical risk analysis, ABI was dichotomised on the fourth quartile (men: ABI > 8.5; women: ABI > 6.5). Multivariable analysis was adjusted for total sleep duration, age, history of stroke, myocardial infarction/coronary artery disease, congestive heart failure, diabetes, hypertension, mean heart rate, mean respiratory rate, systolic and diastolic blood pressure, time of sleep spent below 90% oxygen saturation, categorised body mass index, apnea-hypopnea index and smoking habit, CI: confidence interval.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All-cause mortality** | | | | **Cardiovascular mortality** | | | | **Non-cardiovascular Mortality** | | | |
| **Univariate analysis** | | **Multivariable analysis** | | **Univariate analysis** | | **Multivariable analysis** | | **Univariate analysis** | | **Multivariable analysis** | |
| HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| **MrOS Sleep** | | | | | | | | | | | | |
| AI (h-1) | 1.01 (1.00–1.01) | **0.05** | 1.00 (0.99–1.01) | 0.312 | 1.01 (1.00–1.02) | **0.013** | 1.00 (0.99–1.01) | 0.092 | 1.00 (0.99–1.01) | 0.5 | 1.00 (0.99–1.01) | 0.944 |
| AI > 30 | 1.12 (0.96–1.31) | 0.126 | 1.07 (0.91–1.26) | 0.384 | 1.38 (1.09–1.76) | **0.009** | 1.29 (1.01–1.63) | **0.048** | 1.00 (0.82–1.20) | 0.9 | 0.97 (0.80–1.19) | 0.841 |
| **SOF** | | | | | | | | | | | | |
| AI ( h-1) | 1.03 (1.01 – 1.04) | **0.002** | 1.03 (1.00–1.05) | **0.002** | 1.04 (1.02 – 1.06) | **0.001** | 1.03 (1.01 – 1.06) | **0.001** | 1.01 (0.99–1.03) | 0.352 | 1.01 (0.99–1.04) | 0.287 |
| AI > 25 | 1.42 (0.90 – 2.24) | 0.1 | 1.45 (0.87–2.42) | 0.149 | 2.57 (1.30 – 5.11) | **0.001** | 2.68 (1.22 – 5.82) | **0.013** | 0.88 (0.46–1.67) | 0.688 | 0.89 (0.42–1.85) | 0.758 |
| **SHHS-men** | | | | | | | | | | | | |
| AB ( h-1) | 1.01 (1.00 – 1.02) | **0.01** | 1.00(0.99–1.02) | 0.192 | 1.00 (0.99 – 1.01) | 0.8 | 1.00 (0.98 – 1.01) | 0.247 | 1.01 (1.00–1.02) | **0.003** | 1.01(1.00–1.02) | **0.015** |
| AB > 30 | 1.24 (1.03 – 1.49) | **0.02** | 1.20 (0.97–1.48) | 0.094 | 1.01 (0.99 – 1.42) | 0.9 | 0.94 (0.63 – 1.41) | 0.764 | 1.36 (1.09–1.71) | **0.007** | 1.34 (1.04–1.72) | **0.024** |
| **SHHS-women** | | | | | | | | | | | | |
| AB ( h-1) | 1.02 (1.01 – 1.04) | **<0.001** | 1.02 (1.01–1.03) | ***<* 0.001** | 1.03 (1.02 – 1.04) | ***<* 0.001** | 1.03(1.01–1.04) | **<0.001** | 1.02 (1.01–1.03) | **<0.001** | 1.02 (1.01–1.03) | **0.001** |
| AB > 25 | 1.69 (1.39 – 2.05) | **<0.001** | 1.47 (1.21–1.80) | ***<* 0.001** | 1.81 (1.27 – 2.58) | ***<* 0.001** | 1.53 (1.07–2.22) | **0.022** | 1.64 (1.30–2.07) | **<0.001** | 1.44 (1.13–1.83) | **0.003** |