Sleep characteristics that predict atrial fibrillation

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BACKGROUND The relationship between sleep disruption, independent of obstructive sleep apnea (OSA), and atrial fibrillation (AF) is unknown.

OBJECTIVE The purpose of this study was to determine whether poor sleep itself is a risk factor for AF.

METHODS We first performed an analysis of participants in the Health eHeart Study and validated those findings in the longitudinal Cardiovascular Health Study, including a subset of patients undergoing polysomnography. To determine whether the observed relationships readily translated to medical practice, we examined 2005–2009 data from the California Healthcare Cost and Utilization Project.

RESULTS Among 4553 Health eHeart participants, the 526 with AF exhibited more frequent nighttime awakening (odd ratio [OR] 1.47; 95% confidence interval [CI] 1.14–1.89; $P = .003$). In 5703 Cardiovascular Health Study participants followed for a median 11.6 years, frequent nighttime awakening predicted a 33% greater risk of AF (hazard ratio [HR] 1.33; 95% CI 1.17–1.51; $P < .001$). In patients with polysomnography (N = 1127), every standard deviation percentage decrease in rapid eye movement (REM) sleep was associated with a 18% higher risk of developing AF (HR 1.18; 95% CI 1.00–1.38; $P = .047$). Among 14,330,651 California residents followed for a median 3.9 years, an insomnia diagnosis predicted a 36% increased risk of new AF (HR 1.36; 95% CI 1.30–1.42; $P < .001$).

CONCLUSION Sleep disruption consistently predicted AF before and after adjustment for OSA and other potential confounders across several different populations. Sleep quality itself may be important in the pathogenesis of AF, potentially representing a novel target for prevention.

KEYWORDS Atrial fibrillation; Insomnia; Obstructive sleep apnea; Rapid eye movement (REM) sleep

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Introduction

There are several known risk factors for atrial fibrillation (AF),[1] but predicting its onset and identifying strategies for primary prevention remain difficult.[2] Obstructive sleep apnea (OSA) has been established as a risk factor for AF,[3] but the mechanism remains unclear. Although episodes of hypopnea and apnea may cause cardiopulmonary stress, induce inflammation, and contribute to cardiovascular disease, OSA also causes poor sleep.[4] Aspects of poor sleep, such as altered sleep duration, efficiency, and architecture, have been linked to other cardiovascular diseases.[5] Sleep disturbance in general is more common than OSA,[6] and because strategies to enhance sleep quality are different than those that focus on relieving airway obstruction,[7] it is important to investigate the relationship between sleep itself and AF.

One cross-sectional analysis demonstrated that those with prevalent AF had reduced sleep efficiency and reduced slow-wave sleep (also known as stage N3).[8] Furthermore, AF episodes follow a circadian variation,[9] and patients sometimes report that poor sleep can trigger an episode.[10] However, these studies were limited to patients who already had an AF diagnosis, so "effect–cause" remains a possibility—AF itself may impair sleep. Before considering methods to enhance sleep quality as a broadly relevant approach to prevent AF, the influence of sleep disturbance before disease onset must be determined. Therefore, we sought to determine whether poor sleep would predict an increased risk of developing AF independent of OSA.

Methods

We evaluated the sleep–AF relationship in 3 distinct datasets. First, we identified the characteristics of sleep that were associated with prevalent AF in the Health eHeart Study. Next, we used the Cardiovascular Health Study (CHS) to test whether the patterns of poor sleep identified in the Health eHeart Study would predict incident AF in a longitudinal cohort. We leveraged a subset of CHS with polysomnography (PSG) data to further validate our findings using objective measurements. Finally, to test for a sleep–AF association in clinical practice, we used the California Healthcare Cost and Utilization Project (HCUP) to assess a physician-coded diagnosis of insomnia as a predictor of incident AF. We adjusted for OSA using markers available in each dataset. Approval for the Health eHeart Study and permission to use de-identified data from CHS and HCUP was obtained from the University of California, San Francisco Institutional Review Board.

Health eHeart Study

To identify aspects of sleep associated with prevalent AF, we used the Health eHeart Study (www.health-eheartstudy.org), an Internet-based prospective cohort study that began enrolling interested adults age ≥18 years with an active e-mail address on March 8, 2013 (Supplementary Methods). Participants provided baseline demographic and medical information via online surveys during their initial "eVisit." Those who enrolled through February 21, 2016, and provided age, sex, AF status, and completed a sleep survey were included in this study.

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI).[11] Demographics and medical conditions, including prevalent AF and OSA, were determined by participant self-report. Self-reported AF in the Health eHeart Study has been previously validated by review of medical records of a subset (N = 42) of participants and was found to be 100% sensitive (exact 95% confidence interval [CI] 86–100) and 100% specific (exact 95% CI 80–100).[12]

The PSQI score, standard interpretation ("poor" sleep if score ≥5), component subscores, and individual questions were compared between participants with and without prevalent AF (Supplementary Methods). Sleep measures associated with prevalent AF with $P < .05$ for both the overall ordinal variable and test for trend were included together in a multivariable model.

Cardiovascular Health Study

CHS is a population-based prospective cohort study that has been described in detail elsewhere.[13] In brief, 5201 adults age ≥65 years were recruited in 1989–1990 from Medicare eligibility lists of 4 counties in the United States. An additional 687 African Americans were recruited during 1992–1993. Participants underwent a comprehensive baseline examination, including surveys, vital sign measurements, and an electrocardiogram (ECG). Participants were followed by alternating semiannual clinic visits and phone calls until 1999 and phone calls every 6 months thereafter. Participants with prevalent AF were excluded, and the remaining patients were censored at the time of incident AF or death, or were administratively censored at the end of follow-up.

Sleep quality was ascertained during the baseline examination by 5 yes-or-no questions. OSA status was determined by the affirmative answer to either of 2 questions regarding snoring and apneic episodes (Supplementary Methods). Objective measures of sleep quality and OSA were available in a subset of CHS participants co-enrolled in the Sleep Heart Health Study who underwent at-home PSG during 1995–1998.[14] For this subset, the apnea hypopnea index (AHI), a continuous measure of OSA severity, was used to adjust for OSA. In a sensitivity analysis, we adjusted for the dichotomous presence of OSA, defined as AHI ≥5, a standard clinical cutoff.[4]

Prevalent AF was identified from baseline ECG or self-report of a physician's diagnosis.[15] Incident AF was identified by ECGs at follow-up study visits or by hospital discharge diagnosis codes supplemented with Medicare inpatient claims data.[16] The analysis in the PSG subset excluded any AF detected before the PSG study. Other covariates were obtained by standardized questionnaire and from study personnel (Supplementary Methods).

California HCUP

The California HCUP is a set of medical records databases that has been described in detail previously.[17] In brief, all

Table 1 Baseline participant characteristics by study

Characteristic	HeH (N = 4553)	CHS (N = 5703)	HCUP (N = 14,330,651)
Follow-up (years)	Cross-sectional	11.6 (6.2–16.4)	3.9 (2.3–4.6)
Age (years)	51 ± 15	73 ± 6	49 ± 18
Female	2499 (55%)	3310 (58%)	8,159,023 (57%)
BMI (kg/m^2)	—	26.7 ± 4.7	—
Race/ethnicity			
White	3704 (81%)	4760 (83%)	7753,344 (54%)
Black	92 (2%)	907 (16%)	1,048,804 (7%)
Hispanic	249 (5%)	—	3,596,611 (25%)
Asian	305 (7%)	4 (0.07%)	1,931,892 (13%)
Other	203 (4%)	32 (0.6%)	—
Annual income category			
1 (lowest)	783 (21%)	1420 (27%)	3,152,668 (22%)
2	1017 (27%)	1872 (35%)	3,504,131 (24%)
3	773 (20%)	1353 (25%)	3,792,557 (26%)
4 (highest)	1209 (32%)	688 (13%)	3,881,295 (27%)
CAD	629 (14%)	1110 (19%)	1,085,791 (8%)
CHF	191 (4%)	232 (4%)	677,180 (5%)
Diabetes mellitus	298 (7%)	910 (16%)	1,834,375 (13%)
HTN	1584 (35%)	3338 (59%)	3,664,816 (26%)
OSA	546 (13%)	1455 (30%)	230,358 (2%)
Ever smoker	1599 (35%)	2708 (54%)	1,191,747 (8%)
Alcohol user	2484 (83%)	2826 (50%)	254,394 (3%)

Values are median (IQR), mean ± SD, or n (%).

BMI = body mass index; CAD = coronary heart disease; CHF = congestive heart failure; CHS = Cardiovascular Health Study; HeH = Health eHeart Study; HCUP = California Healthcare Cost and Utilization Project; HTN = hypertension; IQR = interquartile range; OSA = obstructive sleep apnea.

California residents age ≥21 years who received care in a California ambulatory surgery unit, emergency department, or inpatient hospital unit between January 1, 2005, and December 31, 2009, were identified using the HCUP databases (Supplementary Methods). Participants entered the cohort at their first encounter and were censored upon incident diagnosis of AF or at the time of inpatient death, or were administratively censored at the end of follow-up. Patients with prevalent AF (defined as carrying the diagnosis at the first recorded encounter) were excluded.

Demographics and medical diagnoses were accumulated at each encounter and carried forward over time. Up to 25 International Classification of Diseases, 9th Edition (ICD-9) codes were provided for each encounter. The specific codes used for insomnia, AF, and other covariates are described in Supplementary Table 1. Because postoperative AF after cardiothoracic surgery may have a different underlying mechanism, AF was not recorded if a patient had undergone cardiothoracic surgery during the same hospitalization or within the previous 30 days.

Statistical analysis

Normally distributed continuous variables are presented as mean ± SD, and others are presented as median (interquartile range [IQR]). For cross-sectional analyses in Health eHeart, logistic regression models were used to obtain crude and adjusted odds ratios (ORs) and 95% CIs. The likelihood ratio test was used to check for model misspecification, "dfbeta" influence statistics were used to assess for influential points, and the Hosmer–Lemeshow goodness-of-fit test was used to assess model fit. All logistic regression models were satisfactory. For longitudinal analyses in CHS and HCUP, Cox proportional hazards models were used to obtain crude and adjusted hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was checked using the Schoenfeld test and graphical assessment of scaled Schoenfeld residuals. All Cox models satisfied the proportional hazards assumption. Covariates in all adjusted analyses included baseline age, sex, race, hypertension (HTN), diabetes, coronary artery disease (CAD), congestive heart failure (CHF), smoking history, alcohol use, income, and available markers of OSA. Body mass index (BMI) was available in CHS only, and BMI was included as a covariate in all adjusted models using CHS data. All analyses were repeated after exclusion of all participants with OSA (according to available markers). No consistent interactions by sex were detected (Supplementary Table 2). There were no interactions by race (Supplementary Table 3).

Analyses for Health eHeart and CHS were performed using Stata 13 (StataCorp LP, College Station, TX), and those for HCUP were performed using SAS 9.4 (SAS Institute Inc, Cary, NC). A 2-tailed $P < .05$ was considered significant.

Results

Baseline characteristics of the participants in each study are given in Table 1. Participants in CHS tended to be older compared to those in Health eHeart and HCUP. Participants in Health eHeart and CHS were predominantly white, whereas HCUP had a substantial proportion of Hispanic patients. All analyses were repeated after exclusion of participants with OSA, and no meaningful differences were observed (Supplementary Figures 1–4).

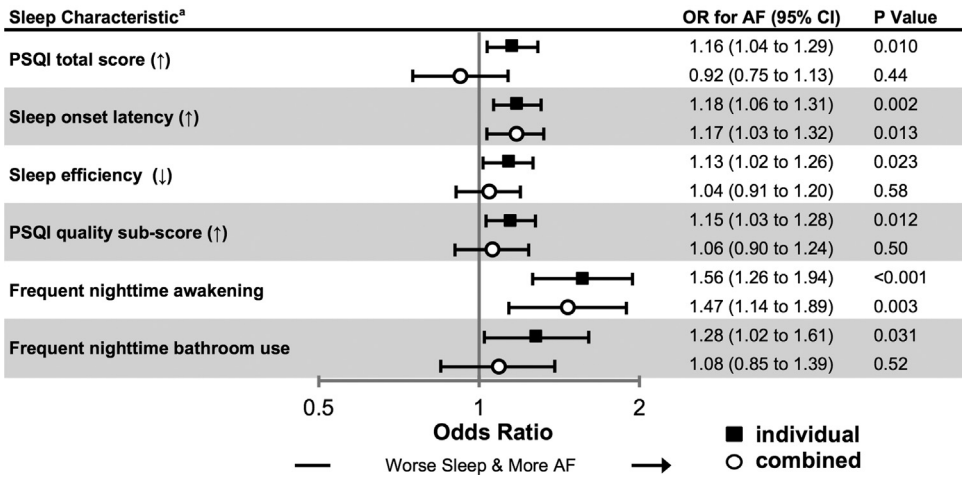

Figure 1 Associations between selected self-reported sleep characteristics and prevalent AF in the Health eHeart Study. Odds ratios (ORs) for AF from multivariable logistic regression models examining individual sleep characteristics *(black squares)* and all sleep characteristics *(white circles)*. Both types of analysis were adjusted for potential confounders: age, sex, race, hypertension, diabetes, obstructive sleep apnea, coronary artery disease, congestive heart failure, smoking history, alcohol use, and income. Bars denote 95% confidence intervals (CIs). [a]Continuous characteristics are scaled per SD increase (↑) or decrease (↓) in accordance with the direction of worse sleep. AF = atrial fibrillation; PSQI = Pittsburgh Sleep Quality Index.

Identification of sleep measures associated with prevalent AF in Health eHeart

Among 4553 Health eHeart participants, 526 (12%) had prevalent AF. In initial analyses of all components of the PSQI, 6 sleep measures remained statistically significantly associated with prevalent AF after adjustment (Supplementary Figure 5). After combining these sleep measures along with the other prespecified covariates into a single model, only longer (worse) sleep onset latency and frequent nighttime awakening remained statistically significantly associated with prevalent AF (Figure 1).

Associations between sleep measures and incident AF in CHS

Among 5703 participants in CHS, 1588 (28%) developed incident AF over a median of 11.6 years (IQR 6.2–16.4). As shown in Figure 2 and consistent with findings from Health eHeart, a report of nighttime awakening at baseline was associated with a statistically significant 33% increased risk of AF after adjusting for potential confounders and evidence of OSA. No other measure of sleep recorded at baseline in CHS revealed a statistically significant relationship with incident AF.

In the subset of 1127 CHS participants who underwent at-home PSG (characteristics given in Supplementary Table 4), 259 (23%) developed AF over median follow-up of 9.8 years (IQR 5.5–11.7). Less rapid eye movement (REM) sleep was associated with increased risk of AF after adjusting for confounders, including PSG-based measures of OSA (Figure 3). These results were not meaningfully different in a sensitivity analysis controlling for the dichotomous presence of OSA by AHI $\geq$5.

Assessment of sleep–AF relationship in the clinical setting in HCUP

Of the 14,330,651 patients in HCUP, 258,716 (1.8%) developed AF over median follow-up of 3.9 years (IQR 2.3–4.6). A diagnosis of insomnia was associated with an approximately 36% (HR 1.36; 95% CI 1.30–1.42; $P < .001$) increased risk of incident AF after adjusting for potential confounders, including OSA (Figure 4). By comparison, in the same model, a diagnosis of OSA was independently associated with an approximately 76% increased risk of AF (HR 1.76; 95% CI 1.72–1.80; $P < .001$) and smoking with a 32% increased risk of AF (HR 1.32; 95% CI 1.30–1.34; $P < .001$).

Discussion

Across 3 independent data sources, we found that sleep disruption was consistently associated with prevalent and incident AF. Examining sleep characteristics in a hypothesis-generating manner, we found that taking longer to fall asleep (greater sleep onset latency) and frequent nighttime awakening were independently associated with prevalent AF among a national Internet-based cohort (Health eHeart). Recognizing that effect–cause could not be excluded in such a cross-sectional analysis, we examined a longitudinal cohort study in which sleep assessments were performed on average many years before incident AF. In CHS, frequent nighttime awakening was associated with greater risk for incident AF, validating our findings from Health eHeart. Analyses of objective sleep quality measures from PSG pointed to decreased REM sleep as potentially important. Finally, in considering next steps and whether the sleep–AF association ascertained in formal studies might already be evident in clinical practice, we used HCUP, a large administrative dataset of healthcare encounters in California. Indeed, a diagnosis of insomnia predicted a subsequent diagnosis of AF. All of these positive findings persisted after adjustment for conventional AF risk factors and available measures of OSA. Taken together, these findings suggest that something inherent to sleep quality itself may be important in the pathogenesis of AF.

Our findings suggest that sleep quality is as important as previously described risk factors. In HCUP, the adjusted

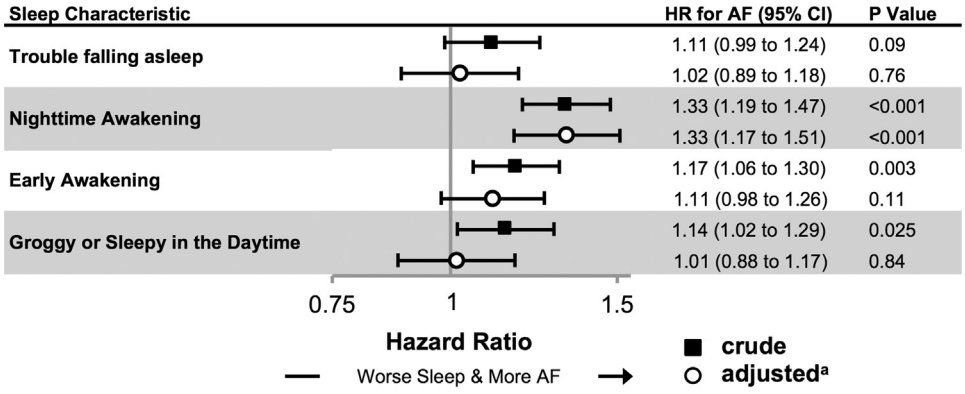

Figure 2 Associations between self-reported sleep measures and incident AF in the Cardiovascular Health Study (CHS). Crude *(black squares)* and adjusted *(white circles)* hazard ratios (HRs) from Cox proportional hazards models for incident AF. Bars denote 95% confidence intervals (CIs). [a]All adjusted models include age, sex, race, body mass index, hypertension, diabetes, obstructive sleep apnea, coronary artery disease, congestive heart failure, smoking history, alcohol use, and income. AF = atrial fibrillation.

HR for insomnia (1.36) was of a similar magnitude as the HRs for smoking (1.32) and OSA (1.76). This is consistent with the notion that sleep is an important but often underrecognized determinant of cardiovascular health.[18]

We found no evidence that sleep duration *per se* was a risk factor for AF. Indeed, the previous literature on this subject has been conflicting.[19] Instead, we consistently found sleep disruption to be an important risk factor. The underlying mechanisms remain unknown, but these findings may motivate novel ways to think about, and hence conduct future research into, factors that influence AF risk.

The influence of sleep on autonomic tone may explain the increased risk of AF. Enhanced vagal tone may be important in AF: stimulation of parasympathetic ganglia innervating the left atria results in AF,[20] and activities associated with more vagal tone can trigger AF episodes.[21] Sympathetic tone is high during REM sleep,[22] suggesting that those with less REM sleep may on average experience greater vagal tone. Kwon et al[8] reported a lower odds of AF among those with a longer duration of slow-wave sleep. Because the patients in that study already had a diagnosis of AF, it is possible the differences in sleep architecture were an effect (rather than a cause) of AF. Conversely, enhanced sympathetic tone may be the culprit, given evidence that postoperative AF can occur after greater sympathetic activity.[23] Transitions from sleep to wakefulness (normal waking and

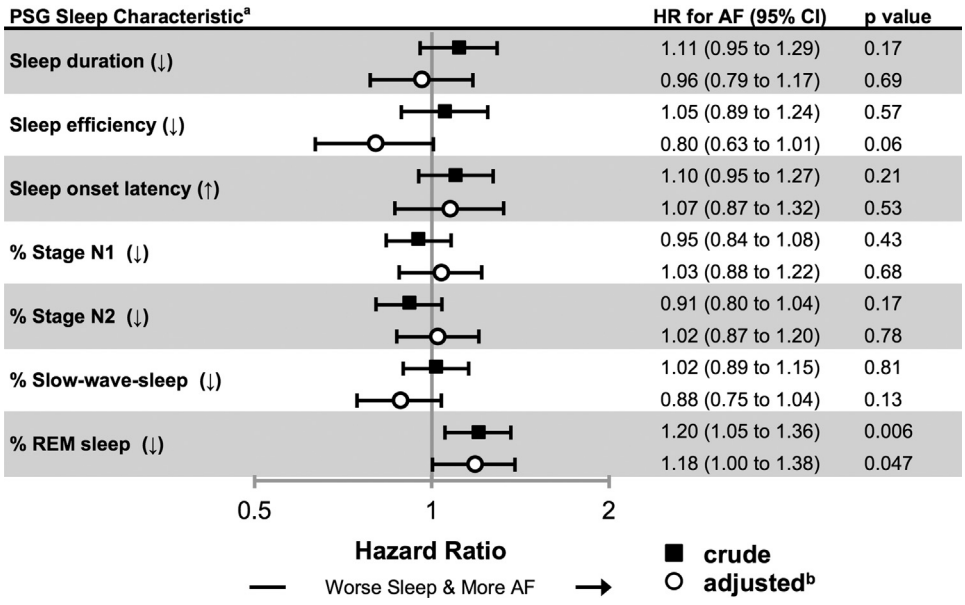

Figure 3 Associations between PSG sleep measures and incident AF in a subset (N = 1127) of the Cardiovascular Health Study (CHS). Crude *(black squares)* and adjusted *(white circles)* hazard ratios (HRs) for incident AF. Bars denote 95% confidence intervals (CIs). [a]Sleep onset latency is scaled per SD increase (↑); all other predictors are scaled per SD decrease (↓). [b]Covariates in the adjusted models include age, sex, race, body mass index, hypertension, diabetes, obstructive sleep apnea, coronary artery disease, congestive heart failure, smoking history, alcohol use, and income. AF = atrial fibrillation; PSG = polysomnography; REM = rapid eye movement.

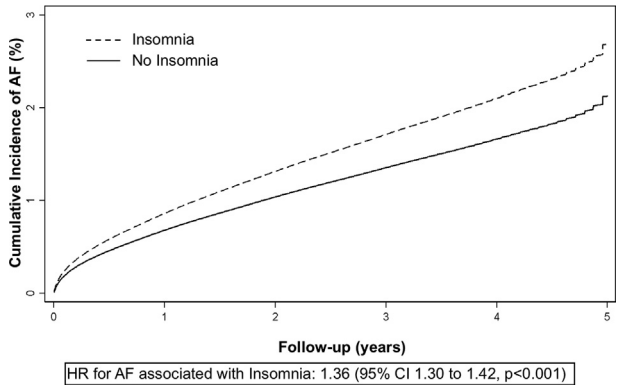

Figure 4 Cumulative incidence of AF by insomnia diagnosis in the California Healthcare Cost and Utilization Project (HCUP). Adjusted cumulative incidence of AF in patients with *(dashed line)* and without *(solid line)* a diagnosis of insomnia. Covariates include age, sex, race, hypertension, diabetes, obstructive sleep apnea, coronary artery disease, congestive heart failure, smoking history, alcohol use, and income. AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio.

sleep disruptions) are associated with increased sympathetic tone,[24] which may promote atrial changes via corresponding hemodynamic stress[10] or other pathways yet to be recognized. However, the relationships between sleep, AF, and autonomic tone are likely more complex than a simple increase or decrease of 1 branch of the autonomic nervous system.

Although consideration of mechanisms may inspire new research, one of the primary motivators for this study was to identify a common and modifiable risk factor for AF. Ultimately, the utility of the current findings would be realized if strategies to enhance sleep quality (eg, optimization of sleep hygiene,[7] avoidance of nighttime smartphone use,[25] and cognitive behavioral therapy)[26] demonstrably reduced the risk of AF, or the burden of AF episodes, in a randomized trial. If sleep quality itself is indeed a causal factor for AF, it may represent an important and common modifiable risk factor for AF. Our data from HCUP also suggest this problem may be easily recognizable and therefore ripe for meaningful interventions in clinical practice.

Study limitations

Our analyses bring several strengths: our multilayered assessment provided reproducible and robust results; each study used different populations; and as HCUP alone includes several million individuals, this is to our knowledge the largest study addressing sleep and AF. However, several limitations must be considered.

First, all 3 studies were observational, so we could not determine causality or exclude residual confounding. It remains possible that OSA was underdiagnosed. However, there is no association between survey-reported sleep disruption (as was used in the current study) and PSG-diagnosed OSA[27]; we adjusted for all available markers of OSA; and an analysis excluding all patients with sleep apnea revealed no meaningfully different results. Perhaps most compelling, our positive findings persisted after adjustment for the gold standard assessment of OSA in the PSG subset. Although we were able to adjust for alcohol use and smoking in all analyses, it remains possible that these were underreported, and that poor sleep was a bystander. Alcohol and nicotine are known risk factors for AF,[21,28] can cause sleep disruption,[7] and have variable effects on REM sleep.[29] However, impaired sleep could be a mechanism by which alcohol and smoking promote AF. Nocturia is another example of a factor that disrupts sleep, could impact REM sleep, and has been associated with increased cardiovascular morbidity.[30]

Misclassification of variables, particularly AF as an outcome, is commonly a challenge in clinical research. Although the Health eHeart dataset is limited by self-report, this method has previously been validated.[12] CHS relied on well-established methods to ascertain AF, including serial ECGs, hospital discharge records, and death certificates, and the cohort has previously served as the foundation of several seminal papers on predictors of AF.[16,31] HCUP relied on ICD-9 coding; notably, a previous study revealed administrative ICD-9 coding at a large health maintenance organization exhibited 95% sensitivity and 99% specificity for the diagnosis of AF compared to record review by trained abstractors.[32] In addition, research using these methods and particularly the HCUP database has proven to provide a powerful accepted tool for large population studies.[17] Although frequent awakening in the Health eHeart Study and CHS predicted AF, we were limited to a general diagnosis of insomnia as our primary predictor in HCUP. Although we believe that these findings provide compelling evidence of a relationship between poor sleep (in a general sense) and incident AF, we cannot exclude the possibility that the insomnia diagnoses captured some other element of sleep other than frequent nighttime awakening.

Lastly, as with many studies of AF, there is likely underascertainment of AF. However, for sleep measures and AF, it is likely that ascertainment of each was limited primarily by poor sensitivity rather than reduced specificity, which would decrease our power to detect associations rather than result in spurious false-positive results.

Conclusion

Sleep disruption independent of OSA seems to be an important risk factor for AF. This effect may be explained by a reduction in REM sleep. Given the high prevalence of sleep problems and the substantial negative impacts of AF, research examining interventions to improve sleep quality may prove valuable in preventing AF.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.05.008.

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