SLEEP AND PAIN PERCEPTION

Polysomnographic Measurement of Sleep Duration and Bodily Pain Perception in the Sleep Heart Health Study

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Study Objectives: To determine whether total sleep time (TST) and specific sleep stage duration are associated with bodily pain perception and whether sex, age, or subjective sleepiness modifies this relationship.

Methods: Data from adults ages 39–90 y (n = 5,199) who took part in the Sleep Heart Health Study Exam 1 were analyzed. TST, rapid eye movement (REM) sleep time, and slow wave sleep (SWS) time were measured by unattended, in-home nocturnal polysomnography. Bodily pain perception was measured via the Short Form-36 questionnaire bodily pain component. We used logistic regression to examine associations between total and individual sleep stage durations and bodily pain perception controlling for age, sex, race, body mass index, apnea-hypopnea index, antidepressant use, and important cardiovascular conditions (smoking [pack-years], history of diabetes, and history of percutaneous coronary intervention and/or coronary artery bypass graft).

Results: In the fully adjusted model, REM sleep time and SWS time were not associated with "moderate to severe pain," whereas TST was: Each 1-h decrement in TST was associated with a 7% increased odds of "moderate to severe pain" (odds ratio 1.07, 95% confidence interval 1.002, 1.14). Due to modification of the association between SWS time and "moderate to severe pain" by sex (P for interaction = 0.01), we performed analyses stratified by sex: Each 1-h decrement in SWS time was associated with a 20% higher odds of "moderate to severe pain" among men (odds ratio 1.20, 95% confidence interval 1.03–1.42) whereas an association was not observed among women.

Conclusions: Shorter TST among all subjects and shorter SWS time in men was associated with "moderate to severe pain." REM sleep time was not associated with bodily pain perception in this cohort.

Keywords: epidemiology, pain, sleep architecture

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Significance

Recent literature suggests a bi-directional relationship between sleep quality/duration and pain perception, i.e., poor sleep likely increases pain and greater pain likely disrupts sleep. However, the sleep-pain relationship has been studied primarily in small cohorts or without accurate measures of sleep architecture or pain. To better characterize this association, we have analyzed sleep architecture (polysomnography) and pain measures (SF-36 bodily pain score) in a large community-based cohort from the Sleep Heart Health Study. We found that a reduction in total sleep duration was associated with increased pain and that gender modifies the relationship between pain and slow wave sleep. Future analyses with longitudinal datasets would likely help further clarify these findings and potentially enable testing of causal hypotheses.

INTRODUCTION

Sleep and pain are complex physiological processes. There is rich literature describing the association of sleep and pain. For example, sleep abnormalities and pain symptoms are the primary characteristics of fibromyalgia, a disease of chronic widespread musculoskeletal pain associated with fatigue and somatic complaints. Moldofsky et al.[1] theorized that pain and sleep abnormalities interact in a bidirectional, potentiating manner in fibromyalgia. Previous studies have attempted to define this relationship using varied methodology including cross-sectional studies, longitudinal and microlongitudinal studies, and experimental sleep deprivation (total, partial, stage selective) studies in both human and animal models. However, to our knowledge no study to date has evaluated the relationship of sleep and pain with both polysomnographic (PSG) measures of sleep and a well-established, reliable measure of overall bodily pain perception in a large, population-based sample.

Sleep and pain demonstrate a bidirectional relationship in that not only does pain affect sleep quality but sleep quality affects pain perception. In a large (n = 18,980) cross-sectional study of noninstitutionalized adults in Europe, Ohayon[2] demonstrated that among the subset of subjects who complained of a chronic painful physical condition (CPPC), 23.3% also complained of at least one symptom of insomnia whereas only 7.4% of those without CPPC complained of insomnia (odds ratio [OR] 3.7 [95% confidence interval (CI) 3.4–4.2]). Additionally, among those with insomnia, 40% reported CPPC whereas 15% of those without insomnia complained of CPPC. In children with migraine headaches, greater severity of headache has been correlated with complaints of greater sleep disturbance.[3] In adults, when measured temporally, next-day pain perception is frequently altered depending on sleep measures from the prior night,[4–7] whereas pain intensity does not necessarily predict next night sleep quality.[5] Adding another layer of complexity, pain perception differs among men and women; women generally have higher prevalence of most common forms of pain compared with men, report greater pain after invasive procedures, and demonstrate increased sensitivity to experimentally induced pain.[8] Therefore, sex may additionally modify the relationship of sleep and pain.

In order to further understand the relationship between sleep deprivation and next-day bodily pain measures, experimental studies with various sleep deprivation paradigms have been

performed in human subjects and animals. In general, total sleep deprivation resulted in decreased pain tolerance of applied mechanical pressure[9] and pain threshold to applied heat.[10] Partial, chronic nonstage-specific sleep deprivation (simulating clinical chronic sleep deprivation) resulted in increased pain sensitivity and mood deterioration.[11,12] These findings were confirmed in a single night of partial sleep deprivation.[12] There is also evidence that selective reduction of specific stages of sleep may influence pain. Deprivation of slow wave sleep (SWS; also referred to as stage N3), the stage considered most restorative, resulted in increased pain on both self-report and psychophysical measures.[1,9,13] Deprivation of rapid eye movement (REM) sleep, a sleep stage implicated in learning and memory consolidation and that varies in mood disorders, resulted in decreased pressure pain tolerance,[9] shorter finger withdrawal latency to a radiant heat stimulus,[14] and increased musculoskeletal pain.[15] In animal models, REM sleep deprivation was associated with increased pain sensitivity[16–21] and diminished pain attenuating effects of morphine[20] and amitriptyline.[21] In contrast, among sleepy individuals (multiple sleep latency testing mean sleep onset latency < 8 min, normal nocturnal sleep duration), extension of total sleep time (TST) resulted in a decrement in daytime pain sensitivity compared with their habitual sleep.[22]

Numerous limitations are present in studies describing the relationship between total and stage-specific sleep duration on bodily pain perception, including small sample size, inconsistent methods of sleep duration measurement, the absence of a validated global pain perception tool, and the lack of studies assessing the effects of sex on the relationship of sleep stage duration and pain perception. The Sleep Heart Health Study (SHHS)[23] was a large cohort study that collected objective polysomnographic data and the Short Form (SF)-36 bodily pain component, allowing the following aims to be addressed: to determine whether sleep architecture, as defined by the duration of specific sleep stages, can predict bodily pain perception measures; and to determine whether sex, age, or subjective sleepiness modifies the relationship between sleep stage duration and bodily pain perception measures.

METHODS

Study Design and Participants

Data from the SHHS were obtained from the National Sleep Research Resource (NSRR; www.sleepdata.org), a National Heart, Lung, and Blood Institute-funded data repository that provides open access to previously completed cohort studies for further academic inquiry.[24,25] Each participant in the SHHS provided written consent and the study protocol was approved by the institutional review board (IRB) of each participating site for the collection of sleep and questionnaire data. IRB approval and a waiver of informed consent was obtained for the current analysis from Columbia University Medical Center (New York, NY). As noted previously, the SHHS was a multicenter prospective cohort study (patients enrolled between 11/1995 to 1/1998) with a primary aim of examining associations between sleep-disordered breathing (SDB) and cardiovascular disease, cerebrovascular accidents, and all-cause mortality. Men and women age 40 y and older were recruited from several established cohorts: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), "New York cohorts," and the Strong Heart Study (SHS). The study design, rationale, and methods of the SHHS have been previously described.[23] In the current analysis, we included SHHS subjects who had baseline polysomnographic data and completed SF-36 questionnaires, and excluded data from the SHHS due to restrictions on data access for that cohort (5,244/5,804 [90.4%] of total cohort). Of the 5,244 SHHS participants who were eligible for this study, we excluded 45 participants with missing data (12 without antidepressant medication data and 34 without body mass index [BMI] data). The final sample analyzed included 5,199 participants.

Measures

The primary outcome was the raw SF-36 bodily pain score. The raw SF-36 bodily pain score is an ordinal measure ranging in value from 2 to 12, with a reliability of 0.82 and a relative precision of 0.75–0.95.[26] The score is calculated based on responses from two self-administered questions: 1. "How much bodily pain have you had during the past 4 w?" and 2. "During the past 2 w, how much did pain interfere with your normal work (including both work outside the home and housework)?" Question 1 is an ordinal value with six possible choices: none, very mild, mild, moderate, severe, and very severe. Question 2 is an ordinal value with five possible choices: not at all, slightly, moderately, quite a bit, and extremely. Lower scores indicate greater bodily pain perception. Due to significant skew in the SF-36 pain measure, specific thresholds to differentiate pain levels were used. Primary analysis was performed with two primary outcomes: 1. "Any pain" = the raw SF-36 bodily pain score dichotomized as any pain versus no pain (raw SF-36 score of < 12 versus equal to 12), and 2. "Moderate to severe pain" = the raw SF-36 bodily pain score dichotomized with cutoff points at sex-specific 25th percentile level consistent with prior studies (moderate to severe pain defined as the top 25th percent of raw SF-36 score).[27] Based on sex-specific thresholds at the 25th percentile, a score of $\leq$ 8.1 in men and $\leq$ 7.1 in women denotes moderate to severe bodily pain. We also performed sensitivity analyses with cutoff points at the 10th and 40th percentiles (cutoff point at raw SF-36 score at the sex-specific 10th and 40th percentiles).

The primary independent variables of interest were TST, REM sleep time, and SWS time obtained from the overnight polysomnography and scored using standard criteria.[25] Covariates included age, sex, BMI, race, apnea-hypopnea index (AHI), antidepressant use, and important cardiovascular comorbidities (smoking, history of diabetes, and history of percutaneous coronary intervention or coronary arterial bypass graft). Sensitivity analyses were additionally performed with alternate dichotomization of pain (as noted above) as well as substituting arousal index for AHI.

Statistical Analysis

We summarized continuous variables using means and standard deviations and summarized categorical variables as

frequencies and percentages. We used multivariable logistic regression to estimate associations between sleep duration (TST, REM sleep time, and SWS time) and SF-36 score. We sequentially added covariates in four separate models. For each independent variable of interest (TST, REM sleep time, and SWS time), model 1 included either TST, REM sleep time and TST, or SWS and TST. TST was included in all models when REM sleep time or SWS time were the primary independent variables of interest in order to isolate the association of REM and SWS on pain while controlling for TST. Model 2 added demographic variables (age, sex, BMI, and race). Model 3 included AHI and antidepressant use. The final model included measures of cardiovascular disease (smoking in pack-years, history of diabetes, and history of percutaneous coronary intervention or coronary arterial bypass graft). We examined effect modification by sex by including a multiplicative interaction product term (sleep time × gender). Because we detected an interaction between sex and SWS time, we reported models stratified by sex. Effect modification was also examined in age and subjective sleepiness (sleep time × age; sleep time × Epworth Sleepiness Scale). SAS version 9.4 (Cary, NC) was used for all statistical analyses.

RESULTS

Baseline characteristics of participants are presented in Table 1. A majority of participants were women (52%) and white (85%). The mean (± SD) AHI for the entire sample was 8.6 ± 12.1 events/h (median 4.2/h), with 54.9% having no evidence of obstructive sleep apnea (AHI less than 5 events/h) and 5.8% with severe obstructive sleep apnea (≥ 30 events/h). The mean (± SD) TST was 361 ± 64 min, mean REM sleep time was 72 ± 28 min, and mean SWS time was 65 ± 44 min. The mean (± SD) raw SF-36 score was 9.2 ± 2.3.

The raw SF-36 score (as a continuous variable) was lower (denoting more pain) in individuals with low TST compared with high TST (9.1 vs. 9.3; $P < 0.05$) when TST was dichotomized at the median (368 min); similar findings were not seen with REM sleep time or SWS time. Moderate to severe pain (25th percentile SF-36 score cutoff point) was more frequent among those with low TST compared with high (29% vs. 24%), low REM sleep time compared with high (28% vs. 25%), and low SWS time compared with high (28% vs. 25%), with sleep times dichotomized at the median. Women had a lower raw SF-36 bodily pain score (8.9 vs. 9.5; $P < 0.0001$) compared with men, denoting greater bodily pain perception (Table 2). Women had a higher absolute SWS duration (82 vs. 47 min; $P < 0.0001$) compared with men.

When analyzing the outcome of "any pain," in unadjusted models, shorter TST (OR 1.00 per 1 h decrease, 95% CI 0.95–1.07), shorter REM sleep time (OR 0.96 per 1 h decrease, 95% CI 0.80–1.14), and shorter SWS time (OR 1.00 per 1 h decrease, 95% CI 0.92–1.10; Table 3) were not associated with "any pain." After adjustment for demographic factors, shorter SWS time (OR 1.15 per 1-h decrease, 95% CI 1.05–1.27; Model 2 in Table 3) was associated with greater pain ("any pain"). In contrast, we did not detect any associations between shorter TST (OR 1.01 per 1- h decrease,

Table 1—Baseline characteristics of 5,199 participants in the Sleep Heart Health Study.

	Low SWS (n = 2,600)	High SWS (n = 2,599)
Age (y)	64.3 ± 11.3	62.3 ± 11.3
Sex		
Men	1,685 (65)	786 (30)
Women	915 (35)	1,813 (70)
Race		
White	2,153 (83)	2,243 (86)
Black	290 (11)	157 (6)
Other	157 (6)	199 (8)
BMI (kg/m^2)	28.3 ± 4.9	28.0 ± 5.3
AHI (events/h)	10.5 ± 13.9	6.7 ± 9.8
Antidepressant use (yes)	11 (0.4)	10 (0.4)
Total sleep time (min)	347.1 ± 66.4	374.4 ± 58.6
REM sleep time (min)	69.9 ± 27.8	74.5 ± 27.1
SWS time (min)	30.4 ± 19.3	100.5 ± 31.8
Raw SF-36 Bodily Pain Score	9.2 ± 2.3	9.2 ± 2.3
SF-36 Bodily Pain (mod-severe)	734 (28)	656 (25)

Continuous variables: mean ± standard deviation. Categorical variables: number (%). AHI, apnea-hypopnea index; BMI, body mass index; REM, rapid eye movement; SWS, slow wave sleep.

Table 2—Baseline characteristics, sex stratified.

	All (n = 5,199)	Men (2,471)	Women (n = 2,728)
Age (y)	63.3 ± 11.3	63.3 ± 11.1	63.3 ± 11.5
Sex			
Men	2,471 (48)		
Women	2,728 (52)		
Race			
White	4,396 (85)	2,120 (86)	2,276 (83)
Black	447 (9)	188 (8)	259 (9.5)
Other	356 (7)	163 (7)	193 (7)
BMI (kg/m^2)	28.1 ± 5.1	28.2 ± 4.3	28.0 ± 5.7
AHI (events/h)	8.6 ± 12.1	11.4 ± 14.0	6.0 ± 9.5
Anti-depressant use (yes)	21 (0.4)	7 (0.3)	14 (0.5)
REM sleep time (min)	72.2 ± 27.5	69.3 ± 26.6	74.8 ± 28.1
SWS time (min)	65.4 ± 43.8	47.3 ± 36.5	81.8 ± 43.4
Total sleep time (min)	360.8 ± 64.1	351.8 ± 61.1	368.9 ± 65.6
Raw SF-36 Bodily Pain Score	9.2 ± 2.3	9.5 ± 2.3	8.9 ± 2.4
SF-36 Bodily Pain (mod-severe)	1,390 (27)	632 (26)	758 (28)

Continuous variables: mean ± standard deviation. Categorical variables: number (%). AHI, apnea-hypopnea index; BMI, body mass index; REM, rapid eye movement; SWS, slow wave sleep.

Table 3—Multivariable logistic regression models of the associations of decreased sleep stage duration and pain.

	Outcome			
Exposure	**Model 1 (95% CI)**	**Model 2 (95% CI)**	**Model 3 (95% CI)**	**Model 4 (95% CI)**
Any pain				
Total sleep time	1.00 (0.95, 1.07)	1.01 (0.95, 1.07)	1.01 (0.95, 1.07)	1.02 (0.95, 1.08)
Rapid eye movement sleep time	0.96 (0.80, 1.14)	0.93 (0.78, 1.11)	0.92 (0.77, 1.10)	0.95 (0.79, 1.15)
Slow wave sleep time	1.00 (0.92, 1.10)	1.15 (1.05, 1.27)	1.15 (1.05, 1.27)	1.17 (1.06, 1.29)
Moderate to severe pain				
Total sleep time	1.11 (1.05, 1.17)	1.06 (0.99, 1.12)	1.06 (0.99, 1.12)	1.07 (1.002, 1.14)
Rapid eye movement sleep time	1.26 (1.06, 1.50)	1.14 (0.95, 1.36)	1.10 (0.92, 1.31)	1.16 (0.96, 1.40)
Slow wave sleep time	1.05 (0.96, 1.15)	1.10 (0.99, 1.21)	1.09 (0.99, 1.20)	1.06 (0.96, 1.17)
Men	1.32 (1.12, 1.54)	1.22 (1.04, 1.44)	1.20 (1.03, 1.42)	1.21 (1.02, 1.44)
Women	0.99 (0.88, 1.12)	1.02 (0.90, 1.16)	1.02 (0.90, 1.15)	1.02 (0.90, 1.15)

Model 1: unadjusted, rapid eye movement sleep time and slow wave sleep time adjusted for TST only. Model 2: Model 1 plus adjustment for body mass index, age, sex (where appropriate), race. Model 3: Model 2 plus adjustment for apnea-hypopnea index and antidepressant use. Model 4: Model 3 plus adjustment for smoking (pack-years), history of percutaneous coronary intervention or coronary artery bypass grafting, and history of diabetes. CI, confidence interval.

95% CI 0.95–1.07) or shorter REM sleep time (OR 0.93 per 1-h decrease, 95% CI 0.78–1.11) and pain. In Model 3, shorter SWS time again demonstrated an association with greater pain ("any pain") (OR 1.15 per 1 hour decrease, 95% CI 1.05–1.27; Model 3 in Table 3), whereas we did not detect any associations between shorter TST (OR 1.01 per 1-h decrease, 95% CI 0.95–1.07) or shorter REM sleep time (OR 0.92 per 1-h decrease, 95% CI 0.77–1.10) and "any pain." Finally, in the fully adjusted model including cardiovascular comorbidities, once again we observed an association between shorter SWS time and "any pain" (OR 1.17 per 1-h decrease, 95% CI 1.06–1.29; Model 4 in Table 3), and no association between shorter TST (OR 1.02 per 1-h decrease, 95% CI 0.95–1.08) or shorter REM sleep time (OR 0.95 per 1-h decrease, 95% CI 0.79–1.15) with "any pain." Sex did not modify the relationship of TST, REM sleep time, or SWS time and "any pain."

Due to the presence of a multiplicative interaction of SWS time and "moderate to severe pain" by sex (P for interaction = 0.01), we stratified SWS by sex in the "moderate to severe pain" analysis. In a fully adjusted model, for each 1-h decrement in SWS time among men, the odds of "moderate to severe pain" was 1.21 times higher (OR 1.21, 95% CI 1.02–1.44; Model 4 in Table 3). In women, no association between SWS time and "moderate to severe pain" was observed (OR 1.02, 95% CI 0.90–1.15). TST and REM sleep time were not stratified by sex due to the absence of multiplicative interaction. Among the entire cohort, TST was associated with "moderate to severe pain," with the odds of "moderate to severe pain" 1.07 times higher among those with shorter TST (OR 1.07, 95% CI 1.002–1.14). We did not identify any association of REM sleep time with "moderate to severe pain."

Sensitivity analyses with cutoff points at either the 10th percentile or 40th percentile of raw SF-36 bodily pain did not meaningfully alter the results, although when pain was dichotomized at the 10th percentile level, TST and SWS time in men were not independently associated with "moderate to severe pain" in the fully adjusted model, likely due to loss of power (Table S1 in the supplemental material). There was no multiplicative interaction between sleepiness (Epworth Sleepiness Scale score ≥ 10) or age (age ≥ 63 y [sample median]) and sleep times (P for interactions > 0.05) and therefore further stratified analyses were not pursued on these variables. Substituting arousal index for AHI also did not significantly change the findings (Table S2 supplemental material).

DISCUSSION

We have shown that electroencephalographically measured sleep stages were associated with generalized bodily pain perception as determined by the SF-36, a well-validated measure of generalized pain perception and functional impairment secondary to pain, in a large population-based sample of subjects. We found that shorter SWS time was associated with "any pain." In addition, shorter TST among the entire cohort and shorter SWS time in men only was associated with "moderate to severe pain." These associations were not explained by age, race, BMI, AHI, antidepressant use, smoking, history of percutaneous coronary intervention or coronary artery bypass graft surgery, or history of diabetes. In contrast, we did not detect any meaningful associations between REM sleep time and bodily pain. Sex did not modify the association of sleep duration and "any pain" while the interaction was present in the more clinically meaningful moderate to severe pain categorization.

Sleep and pain measures are related; however, the specific sleep stage and the specific type of pain measured has varied greatly in the literature.[28,29] Prior studies have looked at sleep and pain in samples with specific disease states, such as fibromyalgia,[1,15,30,31] burns,[5] chronic pain syndromes,[3,7,32] and sleep apnea.[27,33] Among studies that evaluated subjects without significant/previously treated sleep apnea (the focus of this study), only experimental sleep deprivation studies and a single longitudinal study[4] included polysomnographic data. In the study by Smith et al.,[4] 16 healthy women underwent thermal pain threshold testing. Results suggested that increased REM percentage and earlier REM onset latency were associated with increased pain. Interestingly, SWS percentage was negatively

associated with pain, although this finding did not reach statistical significance in a small sample. Among experimental sleep deprivation studies in humans, findings generally support increased pain and/or increased somatic complaints in SWS deprivation.[1,9,34,35] In REM sleep deprivation studies, findings were also consistent with increased pain/somatic complaints, although this was less consistent than the SWS deprivation studies.[9,14,15] Total and partial sleep deprivation also demonstrated generally increased pain measures,[9–14] with one notable exception in a study of 10 healthy adults subjected to total sleep deprivation who did not demonstrate any changes in pain measures.[36] A single study suggested that extending sleep time in sleepy subjects resulted in a reduction in pain sensitivity[22]; in our study, subjective sleepiness (as measured by an Epworth Sleepiness Scale score > 10) did not modify the relationship between sleep and pain and was therefore not further analyzed. Our study, which uses a common clinical pain measure, corroborates prior literature demonstrating that sleep time overall is associated with bodily pain perception; however, our findings add to this body of data, demonstrating that SWS time plays an important role in pain perception and that sex may modify the relationship between SWS time and pain perception.

Mechanistically, it is unclear why changes in sleep architecture are associated with pain and why disparities in specific sleep stage duration affect men and women differently. One proposed theory suggests that increased neurogenic inflammation (as measured by the flare response) in subjects with sleep deprivation results in increased excitability/sensitization of primary afferent nerves.[35] Another theory suggests that alterations in neurotransmitter systems (production of neurotransmitters or receptor affinity for neurotransmitters) may result from sleep deprivation and alter pain perception.[17,37] With regard to our finding that pain is associated with a specific reduction in SWS, several possible explanations are proposed. First, altered pain perception in association with reduced SWS may reflect changes in neuroendocrine function, inflammation, and autonomic nervous system activity that occur with acute or chronic SWS deprivation. In particular, SWS is associated with increased vagal tone and decreased sympathetic tone. Growth hormone release is closely tied to slow wave activity, and decreased SWS is associated with decreased growth hormone release, increased cortisol secretion, and insulin resistance.[38] Moreover, reductions in SWS are associated with incident hypertension[39] and atrial fibrillation,[40] visceral obesity,[41] and coronary artery calcium.[42] Second, it is well established that arousal as well as pain thresholds are elevated during SWS. Central pain and sleep neural pathways likely overlap and interact. Although the neurophysiological mechanisms relating pain and sleep are not well defined, functional magnetic resonance imaging studies have shown that habituation to pain stimuli involves thalamic structures,[43] which also respond to changes in sleep.[44] Whether changes in thalamic-cortical connectivity mediated by sleep influence the neural centers for pain perception and modulation requires further investigation. Third, SWS is the most restorative stage of sleep.[45] Therefore, increased pain with decreased SWS may reflect increased fatigue or sleepiness, with corresponding effects on mental or sensory processing. In our analysis, however, results were not altered after considering the influence of self-reported sleepiness. Additionally, the findings of overall greater pain perception in women along with greater absolute SWS duration as compared with men suggest that the relationship of SWS and pain is quite complex. A comprehensive review of the literature on sex differences in pain suggests the existence of variables that have differential contributions to pain in men and women.[8] The current results indicate that SWS may be one such variable having a qualitatively different relationship with pain between sexes: women, who report more bodily pain and have more SWS than men, may not experience an appreciable increase in pain with SWS decrement, whereas men may be more sensitive to SWS loss and respond with increased pain. Thus, one of many factors contributing to the pain experience, SWS appears to have a sex-specific relationship with pain in older adults without chronic pain conditions. Further research is needed to determine if specific interventions aimed at increasing SWS positively influence pain. In this regard, data in patients with fibromyalgia show that administration of sodium oxybate results in increased growth hormone levels, increased SWS, and decreased pain.[46] Whether these associations generalize to other patient populations, and whether this putative pharmacological effect on pain reflects mediation by change in SWS time also requires further study.

Several limitations of this study must be noted. The cross-sectional design limits inferences about the temporality of the association between sleep stage duration and pain perception, although if pain disrupted sleep stage duration, this would likely be seen for all sleep stages, which was not observed in this study. However, experimental studies are needed to determine if changes in SWS affect pain perception. The use of the SF-36 bodily pain measure, while perhaps more clinically meaningful than isolated noxious stimulus testing, is limited by the narrow range of information it conveys through its two questions (total of 11 possible levels) and modest reliability.[26] Participation by potentially healthier adults joining the original cohorts may have introduced selection bias; however, this would likely bias any finding toward the null and not negate our findings. Although we attempted to adjust for depression with the addition of the "antidepressant" covariate, this is unlikely to be a strong proxy for the presence of depression; however, as "antidepressant use" in our analysis denotes both clinically significant (medication requiring) depression and is in itself an important measure to adjust for given its effects on sleep architecture, we thought that this measure was adequate. Although we adjusted for several key covariates, including measures of sleep apnea and markers of cardiovascular morbidity, it is possible that there was residual confounding by chronic illness or physical activity. Regardless of these limitations, the large number of subjects, the sampling procedure, and the measurement of both electroencephalographically determined sleep architecture and an important measure of pain (SF-36 bodily pain score) strengthen the study compared with other available evidence.

The current findings have several potential implications: (1) as SWS time decreases with age (a normal physiological finding and more pronounced in men), bodily pain perception

may increase over the lifespan; (2) disorders that affect sleep may have a direct effect on bodily pain perception; and (3) timely diagnosis and treatment of sleep disorders may be a useful adjunct in patients with chronic pain conditions. Extending TST by treating concurrent sleep disorders and encouraging behavioral changes in individuals with insufficient sleep may reduce pain perception. Also, extending SWS time by interventions that improve sleep fragmentation, by exercise, by certain cognitive or behavioral tasks performed before sleep, and by certain pharmacologic interventions may be beneficial.

In summary, we have shown that in a large sample of US adults, TST and SWS time are independently associated with bodily pain perception and that the association of SWS and pain perception is modified by sex. Specifically, decreased TST duration and, in men, decreased SWS duration are associated with an increase in moderate to severe pain. Further delineation of the relationship between specific sleep stage duration and pain is needed, particularly with a more comprehensive evaluation of pain measures.

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