Gender differences in the prospective associations of self-reported sleep quality with biomarkers of systemic inflammation and coagulation: findings from the Heart and Soul Study

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Abstract

Systemic inflammation is proposed as a putative mechanism underlying the link between poor sleep and cardiovascular disease. The aim of present study was to investigate the cross-sectional and prospective associations of self-reported sleep quality with biomarkers of inflammation and coagulation implicated in coronary heart disease (CHD) and to explore whether these associations differed between men and women. To this end, measures of sleep quality and markers of inflammation, including circulating levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (CRP), and fibrinogen assessed at baseline in 980 participants with established CHD and 626 at 5-year follow-up. In the sample as a whole, subjective sleep quality was unrelated to inflammatory markers in cross-sectional and prospective analyses. However, in gender stratified analyses, adjusting for age, ethnicity, education, body mass index, and regular snoring, poorer subjective sleep quality at baseline was prospectively associated with 5-year increases in IL-6 (b= 0.14, SE= 0.05, p= 0.003), CRP (b= 0.21, SE= 0.09, p= 0.02), and fibrinogen (b= 18.02, SE= 7.62, p= 0.02) in women but not men. These associations remained independent of lifestyle/ psychosocial factors, medical comorbidities, medication use, and cardiac function. Women who reported baseline sleep disturbances characterized by a tendency to wake up too early in the morning also showed significant 5-year increases in circulating IL-6 that withstood covariate adjustment. Further research is necessary to elucidate the pathways that underlie gender-specific associations between subjective sleep quality and markers of inflammation and coagulation as this may help clarify gender disparities in CHD.

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Contributors

Dr. Whooley designed the overall study and coordinated all data collection. Dr. Cohen assisted in coordinating data collection. Dr. Prather wrote the first draft of the manuscript and carried out all statistical analyses. Drs. Whooley, Cohen, Epel, and Neylan aided in editing the initial draft. All authors contributed to and approved the final manuscript.

Conflict of Interest

The authors have indicated no financial conflicts of interest with respect to this manuscript.

Keywords

sleep; inflammation; gender; coronary heart disease

INTRODUCTION

Growing evidence supports disturbed sleep as a behavioral risk factor for incidence and progression of a number of chronic medical conditions, including coronary heart disease (CHD) (Ayas et al., 2003a; Ayas et al., 2003b; Gangwisch et al., 2006; 2007; Gangwisch et al., 2010; Gottlieb et al., 2006; Hall et al., 2008; Mallon, Broman, & Hetta, 2002). These associations are not limited to objectively defined measures of sleep but also include an individual's subjective report of sleep quality. For instance, women with established coronary heart disease who reported poor sleep quality were 2.6 times more likely to experience a cardiac event than women reporting good sleep quality (Leineweber, Kecklund, Janszky, Akerstedt, & Orth-Gomer, 2003). The biological mechanisms that underlie associations between disrupted sleep and cardiovascular disease remain to be elucidated; however, recent research implicates sleeprelated changes in markers of inflammation as one plausible pathway (Miller & Cappuccio, 2007; Motivala, 2011; Mullington, Haack, Toth, Serrador, & Meier-Ewert, 2009; Simpson & Dinges, 2007).

Circulating levels of proinflammatory cytokines (e.g. interleukin (IL)-6), acute phase proteins (C-reactive protein), and pro-coagulation factors (e.g. fibrinogen) are strongly implicated in the pathophysiology of CHD and are elevated in CHD patients (Palmieri et al., 2003; Ridker, Hennekens, Buring, & Rifai, 2000; Ridker, Rifai, Stampfer, & Hennekens, 2000; Sarwar, Thompson, & Di Angelantonio, 2009; Stec et al., 2000). Elevated systemic levels of inflammation contribute to CHD by accelerating the development and progression of atherosclerotic plaques (Libby, 2002; Ross, 1999) and activating pro-coagulation pathways (Danesh, Collins, Appleby, & Peto, 1998; Kannel, Wolf, Castelli, & D'Agostino, 1987). Sleep has emerged as an important health behavior associated with inflammatory activity in humans (Miller, 2011). Indeed, epidemiologic and laboratory studies demonstrate that poor sleep, characterized by short sleep duration (e.g. <6 hours per night), poor continuity, and poor subjective sleep quality, is associated with elevations in markers of inflammation in most (Hong, Mills, Loredo, Adler, & Dimsdale, 2005; Matthews et al., 2010; Meier-Ewert et al., 2004; Miller et al., 2009; Okun, Coussons-Read, & Hall, 2009; Suarez, 2008; Vgontzas et al., 2004); but not all studies (Patel et al., 2009; Taheri et al., 2007).

Recent evidence suggests the association between disrupted sleep and markers of inflammation are stronger in women than men (Irwin, Carrillo, & Olmstead, 2010; Miller et al., 2009; Suarez, 2008). For instance, women reporting poor sleep quality and a greater frequency of disturbed sleep symptoms displayed elevated levels of IL-6 and CRP while no such association was observed in men (Suarez, 2008). Further, in a sub-analysis of the Whitehall II Study, shorter sleep duration was related to higher levels of circulating IL-6 and CRP in women but not men (Miller et al., 2009). While this evidence is limited to cross-sectional investigations, these findings are consistent with a prior report that found disturbed sleep to be a significant risk factor for cardiovascular disease in older women but not men (Newman et al., 2000).

The present study aims to extend prior cross-sectional literature in a sample of men and women with established coronary heart disease. To this end, we examined the associations of self-reported sleep quality with baseline, 5-year follow-up, and 5-year changes in circulating IL-6, CRP, and fibrinogen in a sample of men and women who participated in

the Heart and Soul Study. It was hypothesized that poorer subjective sleep quality would be associated with higher levels of these biomarkers in cross-sectional analyses as well as greater 5-year increases when assessed prospectively. Furthermore, we hypothesized, based on existing evidence, that associations of subjective sleep quality with biomarkers would be stronger in women as compared to men.

METHODS

Participants

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with established CHD. Methods have been described previously (Whooley et al., 2007). Briefly, participants were recruited from two separate Veterans Affairs Medical Centers (San Francisco and Palo Alto), one university medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had a history of the following: myocardial infarction (MI), angiographic evidence 50% stenosis in one of more coronary vessels, prior evidence of exercise induced ischemia by treadmill or nuclear testing, or coronary revascularization. Patients were ineligible for the study if they had acute coronary syndrome within the past 6 months, could not walk one block, or were planning to move out of the local area within 3 years.

Between September 2000 and December 2002, a total of 1024 participants enrolled and completed a daylong study protocol at the San Francisco Veterans Affairs Medical Center. Between September 2005 and December 2007, 667 participants (80% of the 829 survivors) completed a 5-year follow-up examination. Circulating levels of IL-6, CRP, and fibrinogen were available on 985 participants at baseline and 661 at the 5-year follow-up. The appropriate institutional review boards approved the Heart and Soul Study protocol, and all participants provided written, informed consent.

Sleep Measures

Subjective sleep quality was measured using a single item from the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire that assesses sleep quality and disturbances (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Participants were asked at baseline and 5 years later: "During the past month, how would you rate your overall sleep quality?" and indicated: "very good", "fairly good", "good", "fairly bad", "very bad", scored from 0 to 4, with higher scores indicating poorer sleep quality. This single-item measure is what comprises the sleep quality subscale for the full PSQI scale. As compared to the other PSQI subscales, the sleep quality subscale shows the highest correlation with the PSQI global sleep quality score (r's=0.76–0.83) across several different populations (Bush et al., 2012; Carpenter & Andrykowski, 1998). PSQI subjective sleep quality was treated as a continuous variable in all analyses. Secondary sleep variables were also administered, modified from the Cardiovascular Health Study, which were self-report items to assess difficulty initiating and maintaining sleep, including difficulty falling asleep, frequent awakenings, and waking too early (Newman, Enright, Manolio, Haponik, & Wahl, 1997). Specifically, participants were asked to answer "yes" or "no" to the following questions: "Do you usually have trouble falling asleep?", "Do you usually wake up several times at night?", and "Do you usually wake up far too early?" These secondary sleep measures were obtained at baseline only.

Biomarkers

Participants were asked to fast for 12 hours (except for medications, which they were able to take with water), not take aspirin for 1 week, and not to smoke for 5 hours before their study

appointment. Venous blood samples were obtained at baseline and 5 year follow-up. Plasma and serum samples were stored at −70°C for measurement of CRP, IL-6, and fibrinogen.

CRP was quantified using the Roche Integra high-sensitivity assay or the Beckman Extended Range assay at baseline and using the Roche Integra high-sensitivity assay at 5-year follow-up. Results from the two assays using baseline samples were highly correlated ($r = 0.99$ in 185 participants). IL-6 was determined using high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota). The inter-assay coefficient of variation is 6.5%–9.6%, and the intra-assay coefficient of variation is 6.9%–7.8%. The reportable range for IL-6 is 0.428–8.87 pg/ml.

Fibrinogen levels were determined by the Clauss assay. Dilutions of the plasma standard (of known concentrations) were clotted with a high concentration of thrombin, with the resultant clotting time being proportional to the fibrinogen concentration. The clotting time of the participant's plasma was used to read the fibrinogen concentration from the standard curve. The standard assay range is from 60 to 10,000 mg/dL and the interassay and intraassay coefficient of variation are both < 3%.

Other Participant Characteristics

Sociodemographic characteristics, including age, gender, ethnicity (Caucasian vs. non-Caucasian), and education (high school graduate vs. non-high school graduate) were determined by self-report questionnaire as were health behaviors including alcohol consumption, and smoking status. Similarly, participants completed a questionnaire on medical comorbidities, including history of hypertension, myocardial infarction, congestive heart failure, type 2 diabetes, and stroke. Because sleep disordered breathing is a strong predictor of CHD (Gottlieb et al., 2010; Shahar et al., 2001), body mass index (BMI) was calculated based on recorded heights and weights (weight in kilograms divided by the square of height in meters) and participants were asked "Have you ever snored?" and, if yes, "How often do you snore now?" (none, a little, some, much, or all of the time). History of regular snoring was defined as "much" or "all of the time".

Physical activity was determined with the multiple choice question, "which of the following statements best describes how physically active you have been during the past month, that is, done activities such as 15–20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" Participants who answered fairly, quite, very, or extremely active (vs. not at all or a little active) were considered physically active (Whooley et al., 2008).

Cardiac function was assessed with systolic blood pressure and left ventricular ejection fraction (LVEF) from a resting echocardiogram. Participants were instructed to bring all of their medication bottles to the study appointment, and trained research assistants recorded all current medications. History of medications included use of beta-blockers, ACE inhibitors, statins, antidepressants, benzodiazepines, and hormone replacement therapy/oral contraceptives. Finally, depressive symptoms over the past week were assessed using the Center for Epidemiologic Studies of Depression Scale (CES-D)(Radloff, 1977).

Data Analysis

The goal of this study was to examine the cross-sectional and prospective associations of PSQI subjective sleep quality with baseline, 5-year, and 5-year changes in levels of IL-6, CRP, and fibrinogen in men and women with stable CHD. Linear regression models were computed adjusting for sociodemographic characteristics (age, gender, ethnicity, education, body mass index), and regular snoring in the first step, followed by PSQI subjective sleep quality entered as a continuous variable in the second step of each model. If a regression model was statistically significant, additional covariates were added step-wise in groups as

follows: lifestyle/psychosocial variables (cigarette smoking status, physical activity, alcohol consumption, and depressive symptoms); history of medical comorbidities (hypertension, myocardial infarction, congestive heart failure, type 2 diabetes, and stroke); history of medication use (beta-blockers, statins, ACE inhibitors, hormone replacement therapy/oral contraceptive, antidepressant, and benzodiazepine use); and cardiac function (resting systolic blood pressure, and resting left ventricular ejection fraction), with PSQI subjective sleep quality entered as the final variable in the model. In instances where covariates were measured at baseline and 5-year time points, we included covariates consistent with the time frame of the dependent variable. Analyses predicting changes in levels of IL-6, CRP, and fibrinogen over the 5-year span of the study were computed by treating the 5-year biomarker as the dependent variable and statistically adjusting for baseline levels of the biomarker of interest.

To evaluate the moderating effects of gender, an interaction term (gender by PSQI subjective sleep quality) was computed and entered into the final step of the regression models. If the interaction term emerged as a significant predictor, gender-stratified regression analyses, adjusting sociodemographic characteristics, and regular snoring were carried out. If statistically significant, additional covariates were included in a stepwise manner as described above. To evaluate the role of sleep disturbances (difficulty initiating sleep, frequent awakening, and waking too early) on 5-year changes in IL-6, CRP, and fibrinogen, analyses were conducted on the sample as a whole and stratified by gender if supported by a significant interaction term. CRP and IL-6 values underwent a natural log transformation because they were not normally distributed. Fibrinogen values were normally distributed. Analyses were restricted to participants with complete data on PSQI subjective sleep quality and markers of inflammation at baseline (n=980) and 5-year follow-up (n=626).

RESULTS

Sample Characteristics

Sample characteristics for participants who had complete sleep quality and inflammation data at baseline (n=980) and at baseline and 5-year follow up (n=626) are provided in Table 1. Compared to the group of participants with baseline and follow-up data, those without follow-up data were older (t(978)= 2.86, p<0.005), regular snorers ($X^2(1)$=5.23, p<0.02), more depressed (t(977)=3.32, p<0.001), smokers ($X^2(1)$=10.54, p<0.005), less physically active ($X^2(1)$=6.68, p<0.01), had a history of congestive heart failure ($X^2(1)$=8.21, p<0.005), diabetes ($X^2(1)$=7.37, p<0.01), stroke ($X^2(1)$=4.46, p<0.04), were taking statins ($X^2(1)$=18.00, p<0.001) and antidepressants ($X^2(1)$=7.16, p<0.008), had a lower left ventricular ejection fraction (t(976)=2.75, p<0.007) and higher levels of inflammation (IL-6: t(978)=5.56, p<0.001; CRP: t(978)=4.70, p<0.001) and coagulation (fibrinogen: t(978)=3.60, p<0.001). Those without follow-up data were also more likely to report difficulties falling asleep ($X^2(1)$=12.91, p<0.001) and awaking too early ($X^2(1)$=4.35, p=0.04); however, these groups did not differ in levels of self-reported sleep quality (t(978)=0.95, p=0.34).

At baseline, participants reporting poorer PSQI subjective sleep quality were younger, more likely to be a regular snorer, to smoke, be inactive, have hypertension, take antidepressants, take benzodiazepines, and reported more depressive symptom (p's<0.05). At follow-up, poorer PSQI subjective sleep quality was associated with being younger, being inactive, having a higher BMI, being less likely to take ACE inhibitors, being more likely to take antidepressants and benzodiazepines, and reporting more depressive symptoms (p's<0.05). As expected, baseline and 5-year levels of IL-6, CRP, and fibrinogen were inter-correlated (r's= 0.26 to 0.59, p's< 0.001).

Sleep quality and markers of inflammation and coagulation

Table 2 displays the cross-sectional associations between baseline and 5-year PSQI subjective sleep quality with levels of IL-6, CRP, and fibrinogen. At baseline and follow-up, PSQI subjective sleep quality was unrelated to circulating levels of these biomarkers with the exception of baseline levels of fibrinogen. In this regard, poorer PSQI subjective sleep quality was associated with lower levels of fibrinogen, independent of sociodemographic factors and regular snoring; however, when the next block of covariates was included in the model (i.e., lifestyle/psychosocial factors), this relationship fell below statistical significance (b= –4.72, SE= 2.88, p= 0.10). Next, we tested the prospective associations between baseline PSQI subjective sleep quality and 5-year changes in levels of IL-6, CRP, and fibrinogen. Linear regression models revealed no statistically significant associations between PSQI subjective sleep quality and 5-year changes in these biomarkers.

Gender differences in associations of sleep quality with biomarkers

Baseline characteristics for participants stratified by gender are presented in Table 3. At baseline, women were younger, more ethnically diverse, and less educated compared to men. They also reported higher depressive symptoms, were more likely to be taking antidepressants, and less likely than men to have a history of taking beta-blockers, statins, and ACE/ARB inhibitors. Finally, compared to men, women had higher systolic blood pressure, resting left ventricular ejection fraction and circulating levels of CRP. There were no gender differences in baseline levels of IL-6, fibrinogen, or any on of the sleep measures. Furthermore, 5-year changes in circulating levels of IL-6, CRP, and fibrinogen were similar in men and women (p's ranged from 0.14–0.90).

Based on the prior literature, we investigated whether gender moderates associations of PSQI subjective sleep quality with levels of inflammation and coagulation in cross-sectional and prospective analyses. Here, adjusting for sociodemographic characteristics and regular snoring, a significant interaction term (gender by PSQI subjective sleep quality) emerged as an independent predictor of baseline IL-6 (interaction: b= –0.12, SE= 0.05, p= 0.02) and 5-year changes in all three biomarkers (interactions: IL-6: b= –0.18, SE= 0.06, p= 0.001; CRP: b= – 0.26, SE= 0.10, p= 0.01; fibrinogen: b= –19.07, SE= 7.37, p= 0.01).

Analyses stratified by gender were carried out for models supporting a significant gender by PSQI subjective sleep quality interaction. As displayed in Table 4, poorer PSQI subjective sleep quality at baseline was significantly associated with 5-year increases in IL-6, CRP, and fibrinogen in women but not men. These associations remained statistically significant after adjustment for sociodemographic characteristics, lifestyle/psychosocial variables, medical comorbidities, medication use, and cardiac function (Table 5). A significant gender by PSQI subjective sleep quality interaction was also observed in predicting baseline levels of IL-6. However, in gender-stratified analyses, associations between PSQI subjective sleep quality and circulating IL-6 were non-significant in men (b= –0.03, SE= 0.02, p= 0.15) and women (b= 0.08, SE= 0.05, p= 0.11).

Role of sleep disturbances

Because of the consistent gender-specific associations between PSQI subjective sleep quality and 5-year changes in IL-6, CRP, and fibrinogen, we investigated whether endorsement of sleep disturbances, including difficulty falling asleep, frequent awakenings, and waking up too early, were associated with 5-year changes in these biomarkers. Similar to prior analyses, there were no associations between type of sleep disturbance and 5-year changes in biomarker levels in the sample as a whole (data not shown); however, several significant gender by sleep disturbance interactions emerged. In this regard, gender moderated the association between endorsement of "trouble falling asleep" and 5-year

increases in IL-6 (interaction IL-6: b= −0.37, SE= 0.13, p= 0.003) as well as associations between an endorsed tendency to "wake up far too early" and 5-year increases in all three biomarkers (interaction IL-6: b= −0.33, SE= 0.12, p= 0.007; CRP: b= −0.48, SE= 0.23, p= 0.04; fibrinogen: b= −31.86, SE= 16.08, p= 0.05).

In gender-stratified analyses, there were no associations between sleep disturbance measures and 5-year changes in biomarkers in men (p's>0.05). In women, endorsement of "trouble falling asleep" was a significant predictor of 5-year increases in circulating IL-6, independent of age, ethnicity, education, BMI, and snoring (b= 0.24, SE= 0.11, p= 0.03). However, this did not remain statistically significant after adjustment for lifestyle/ psychosocial covariates (b= 0.20, SE= 0.12, p= 0.11). Women who endorsed at baseline a tendency to "wake up far too early" showed significant 5-year elevations in IL-6 (b= 0.31, SE= 0.11, p= 0.007) and fibrinogen (b= 32.35, SE= 15.52, p= 0.04), but not CRP (b= 0.31, SE= 0.19, p= 0.11). After adjusting for additional lifestyle/psychosocial covariates, medical comorbidities, medication use, and cardiac function, a tendency to "wake up far too early" remained a significant predictor of 5-year increases in IL-6 (b= 0.31, SE= 0.13, p= 0.01) but not fibrinogen (b= 30.98, SE= 17.13, p= 0.07). An endorsement of frequent awakenings (i.e., "wake up several times during the night") was unrelated to 5-year changes in any of the biomarkers and was not moderated by gender.

DISCUSSION

The present study examined cross-sectional and prospective associations of subjective sleep quality with biomarkers of inflammation and coagulation in a sample of men and women with established coronary heart disease. Contrary to our hypotheses, in this sample of outpatients we found no evidence that subjective sleep quality, as indexed by a single item of self-reported sleep quality from the Pittsburgh Sleep Quality Index (PSQI), was associated with cross-sectional or 5-year changes in levels of IL-6, CRP, and fibrinogen. However, in genderspecific analyses, women reporting poorer PSQI subjective sleep quality showed marked 5-year increases in all three biomarkers; no such association was seen in men. These associations withstood adjustment for a number of covariates, including sociodemographic and lifestyle/psychosocial characteristics, medical comorbidities, medication use, and cardiac function. In addition, women who endorsed sleep disturbances at baseline, particularly an endorsed tendency to "wake up far too early", predicted 5-year increases in IL-6 and to some extent fibrinogen, raising the possibility that specific aspects of sleep disruption may contribute to variation in biomarkers implicated in CHD progression. These results add to growing evidence that increased inflammation may contribute to the negative cardiovascular consequences often associated with poor sleep, including poor sleep quality.

The present findings contribute to a growing literature on gender differences in the link between sleep and inflammation. Indeed, Suarez (2008) demonstrated that higher PSQI sleep quality scores predicted higher levels of circulating IL-6 and CRP in a sample of premenopausal women, but not in men (Suarez, 2008). In the same study, higher levels of IL-6, CRP, and fibrinogen were observed in women who reported more frequent sleep disturbances, characterized primarily by difficulties falling asleep, as compared to men. The current study extends these findings by providing the first prospective evidence that poor subjective sleep quality is associated with inflammatory trajectories in women, which may help explain the stronger longitudinal links between sleep and incidence of hypertension and cardiovascular events observed in women as compared to men (Cappuccio et al., 2007; Newman et al., 2000).

The fact that sleep quality predicted 5-year changes in levels of biomarkers in women but was unrelated to these biomarkers at baseline and follow-up in cross-sectional analyses is difficult to reconcile, particularly given prior cross-sectional studies that support such gender differences (Miller et al., 2009; Suarez, 2008). One attribute that sets the current study apart from prior work, however, is that all participants had established CHD, which is a disease process marked by inflammatory activity. To the extent that CHD progressed in these participants from baseline to 5-year follow-up, it is possible that sleep quality would uniquely account for variation in rate of change in disease progression, as marked by elevations in markers inflammation and coagulation, but not when investigated cross-sectionally. Additional research utilizing other intermediate markers of CHD progression, such as intima-media thickness, is needed to test this possibility. If supported, this adds to the importance of assessing and treating sleep disturbance in vulnerable high-risk populations, including those with frank cardiovascular disease. Another explanation for why we observed longitudinal effects but not cross-sectional associations resides in the fact that while the presence of CHD is a stable attribute across this sample, it is otherwise heterogeneous. As such, sleep is only but one factor that can contribute to variability in inflammation. A constellation of other factors, including maladaptive dietary behaviors such as excess consumption of high sugar/high fat foods, and complex biological processes, including endothelial dysfunction and oxidative stress can contribute to heterogeneity in inflammatory activity. The strength of this longitudinal design, however, is the ability to isolate the effect of sleep on within-in subject changes in inflammation obviating the between-subject differences inherent in this population.

The physiologic mechanisms that underlie the gender differences observed in this study remain to be elucidated. In this regard, there is substantial evidence supporting the autonomic nervous system (ANS) in modulating inflammation (Nance & Sanders, 2007). For example, experimental increases in catecholamines upregulate NF-kB signaling pathways responsible for pro-inflammatory cytokine production (Bierhaus et al., 2003). Moreover, cross-sectional evidence shows heart rate variability, an index of the parasympathetic division of the ANS, is inversely associated with systemic levels of inflammation (Sloan et al., 2007). Sleep studies support increased sympathetic activation and parasympathetic withdrawal in those experiencing disrupted sleep, including insomniacs (Irwin, Clark, Kennedy, Christian Gillin, & Ziegler, 2003) and patients with chronic disease (Palesh et al., 2008). Furthermore, laboratory evidence suggests that women show greater monocyte expression of IL-6 during undisturbed sleep than men, a difference that is moderated by sex differences in tonic sympathovagal activity (O'Connor, Motivala, Valladares, Olmstead, & Irwin, 2007). Differences in levels of reproductive hormones may also aid in explaining these gender disparities. Plasma concentrations of estradiol are lower in postmenopausal women (<15 pg/ml) than pre-menopausal women (50–250 pg/ml) and men (50 pg/ml)(Walsh & Shiff, 2001). Estradiol acts to inhibit inflammatory gene expression and cellular production of pro-inflammatory cytokines (Deshpande, Khalili, Pergolizzi, Michael, & Chang, 1997; Ray, Ghosh, Zhang, & Ray, 1997). The women in this study were largely post-menopausal, and thus it is possible that lower circulating levels of reproductive hormones facilitated the increased levels of inflammatory activity associated with poor sleep. Of note, a small fraction of women reported use of hormone replacement therapy or oral contraceptives (OC) (n=4); however, adjusting for use in our analyses had little influence on the results.

The lack of an association between subjective sleep quality and inflammation in men raises the possibility that testosterone may represent another important biological pathway. Indeed, higher levels of testosterone have been associated with lower levels of systemic inflammation, including IL-6 and CRP (Jones & Saad, 2009; Kapoor, Clarke, Stanworth, Channer, & Jones, 2007) and experimental studies demonstrate that testosterone

replacement downregulates proinflammatory mediators in peripheral circulation (Malkin et al., 2004). Consequently, it is possible that testosterone, which is at higher levels in men, served to buffer the effects of poor subjective sleep quality on 5-year changes in inflammation. Future studies are needed to investigate the influence reproductive hormones, such as testosterone and estradiol, play in moderating the effects of sleep quality on systemic levels of inflammation and coagulation.

The strengths of this study include the large sample of patients with stable CHD, the prospective assessment of inflammation and coagulation, and the comprehensive measurement of potential confounding variables. However, several limitations must be considered in interpreting the results. First, the sample was restricted to older adults with CHD, limiting the generalizability of these results. In addition, sleep quality and sleep disturbance were assessed using single-item self-report measures. While there is evidence to suggest that a single-item measuring subjective sleep quality may be sufficient (Bush et al., 2012;Carpenter & Andrykowski, 1998), a more comprehensive characterization of sleep and sleep disturbance, including uses of objective sleep measures, such as actigraphy or in-home polysomnography, is needed in future studies. Another limitation is that this study was not explicitly designed to test gender differences. While our analyses supported several gender by sleep interactions, men comprised more than 80% of the sample. As such, future studies are needed using stratified samples to better clarify gender differences; that said, the findings in women may actually underestimate the true effect given the limited sample size. Finally, though we adjusted for history of regular snoring and BMI, obstructive sleep apnea (OSA), a well-known contributor to cardiovascular risk (Gottlieb et al., 2010; Shahar et al., 2001) and elevated inflammation (Shamsuzzaman et al., 2002), was not formally assessed in this study.

In conclusion, these findings provide the first prospective evidence for subjective sleep quality predicting 5-year increases in markers of inflammation and coagulation among women with established CHD. While this work requires replication, these results provide important evidence that inflammation may serve as a key biological pathway through which disturbed sleep contributes to CHD progression in women.

Acknowledgments

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Table 1

Sample characteristics at baseline and follow-up. Values displayed as means (standard deviation) or percentages.

	Baseline (n=980)[a]	Baseline (n=626)[b]	Follow-up (n=626)
Sociodemographic variables			
Age (years)	66.7 (11.0)	66.0 (10.2)	71.0 (10.1)
Sex (% male)	81.5%	82.1%	82.1%
Ethnicity (% Caucasian)	60.8%	60.5%	60.5%
Education (% with high graduate or higher)	87.2%	88.0%	88.0%
Body Mass Index (kg/m^2)	28.4 (5.4)	25.6 (5.2)	28.6 (5.5)
History of regular snoring (% yes)	18.6%	20.8%	20.8%
Comorbidities			
Hypertension	70.5%	68.7%	74.9%
Myocardial infarction	53.8%	52.7%	49.6%
Congestive heart failure	17.7%	15.1%	18.7%
Type 2 diabetes	26.4%	23.5%	29.0%
Stroke	14.1%	12.3%	15.5%
Medication History			
Beta blockers	57.3%	57.1%	57.1%
Statins	64.3%	69.3%	69.3%
ACE/ARBs (angiotensin)	51.3%	50.4%	50.4%
Antidepressants	18.5%	16.0%	16.0%
Benzodiazepines	8.1%	8.0%	8.0%
OC/HT (women)	0.4%	0.6%	0.6%
Cardiac function			
Systolic BP (mmHg)	133.0 (21.1)	132.6 (20.4)	136.5 (19.9)
Resting LVEF	0.62 (0.10)	0.62 (0.10)	0.62 (0.11)
Lifestyle/psychosocial variables			
Regular alcohol use	29.1%	30.3%	28.2%
Current smoking	19.9%	16.8%	14.8%
Physically active	33.1%	36.1%	36.1%
CES-D depression score	7.5 (5.5)	7.1 (5.5)	7.0 (5.1)
Sleep Measures			
PSQI subjective sleep quality (0–4; very good to very poor)	1.8 (1.1)	1.8 (1.1)	1.9 (1.2)
Difficulty falling asleep[c]	36.0%	31.8%	---
Frequent awakenings[c]	79.5%	78.7%	---
Waking too early[c]	44.9%	42.3%	---
Biomarkers			
Interleukin-6 (pg/mL), median (IQR)[d]	2.62 (1.62–4.20)	2.36 (1.48–3.65)	3.22 (2.17–5.46)
C-reactive protein (mg/L), median (IQR)[d]	2.27 (0.92–4.96)	1.96 (0.79–4.05)	1.41 (0.67–3.59)

	Baseline (n=980)[a]	Baseline (n=626)[b]	Follow-up (n=626)
Fibrinogen (mg/dL)	392.3 (90.4)	384.2 (83.7)	374.2 (85.9)

[a]
all available;

[b]
participants with baseline and follow-up data;

[c]
not measured a follow-up;

[d]
interquartile range (IQR)

Angiotensin converting enzyme/angiotensin II receptor blocker (ACE/ARB); Oral contraceptive/hormone replacement therapy (OR/HT); Blood pressure (BP); Left ventricular Ejection Fraction (LVEF); Center for Epidemiologic Studies of Depression Scale (CES-D); Pittsburgh Sleep Quality Index (PSQI)

Table 2

Cross-sectional results of linear regressions examining baseline and 5-year PSQI subjective sleep quality associations with baseline and 5-year levels of IL–6, CRP, and fibrinogen. Models adjusted for age, gender, ethnicity, education, BMI, and regular snoring.

	Baseline			5-Year			
	Beta	SE	B	p-value	Beta	SE	B	p-value
Circulating IL-6								
PSQI subjective sleep quality	−0.01	0.02	−0.02	0.54	0.00	0.02	0.01	0.88
Circulating CRP								
PSQI subjective sleep quality	−0.03	0.04	−0.02	0.50	0.01	0.04	0.01	0.84
Circulating fibrinogen								
PSQI subjective sleep quality	−6.70	2.59	−0.08	0.01	−0.33	2.90	−0.01	0.91

Table 3

Baseline characteristics stratified by gender. Values displayed as means (standard deviation) and percentages.

	Men (n=514)	Women (n=112)
Sociodemographic variables		
Age (years)	66.3 (10.1)	64.2 (10.1)[*]
Ethnicity (% Caucasian)	63.6%	46.4%[*]
Education (% with high graduate or higher)	89.5%	81.3%[*]
Body Mass Index (kg/m^2)	28.4 (4.9)	29.3 (6.1)
History of regular snoring (% yes)	20.0%	24.1%
Comorbidities		
Hypertension	68.3%	70.5%
Myocardial infarction	54.0%	46.8%
Congestive heart failure	15.6%	12.6%
Type 2 diabetes	23.0%	25.9%
Stroke	12.5%	11.6%
Medication History		
Beta blockers	59.3%	48.2%[*]
Statins	72.2%	55.4%[*]
ACE/ARBs (angiotensin)	52.3%	42.0%[*]
Antidepressants	13.8%	25.9%[*]
Benzodiazepines	7.6%	9.8%
OC/HT (women)	0.0%	3.6%[*]
Cardiac function		
Systolic BP (mmHg)	131.6 (20.3)	137.5 (20.5)[*]
Resting LVEF	0.62 (0.09)	0.65 (0.07)[*]
Lifestyle/psychosocial variables		
Regular alcohol use	33.7%	14.5%[*]
Current smoking	17.3%	14.3%
Physically active	37.4%	29.7%
CES-D depression score	6.8 (5.4)	8.4 (5.7)[*]
Sleep Measures		
PSQI subjective sleep quality	1.8 (1.1)	1.8 (1.1)
(0–4; very good to very poor)		
Difficulty falling asleep	30.9%	36.0%
Frequent awakenings	78.2%	81.3%
Waking too early	40.7%	49.5%
Biomarkers		
Interleukin-6 (pg/mL), median (IQR)[a]	2.43 (1.54–3.67)	2.04 (1.36–3.56)
C-reactive protein (mg/L), median (IQR)[a]	1.85 (0.68–3.92)	2.81 (1.15–6.37)[*]
Fibrinogen (mg/dL)	385.4 (84.7)	378.6 (78.6)

*
  p<0.05;

*a*presented as raw data and interquartile range (IQR), analyzed using natural log transformed values.

Angiotensin converting enzyme/angiotensin II receptor blocker (ACE/ARB); Oral contraceptive/hormone replacement therapy (OR/HT); Blood pressure (BP); Left ventricular Ejection Fraction (LVEF); Center for Epidemiologic Studies of Depression Scale (CES-D); Pittsburgh Sleep Quality Index (PSQI)

Table 4

Longitudinal results of regression analyses showing that poorer baseline PSQI subjective sleep quality predicts 5-year increases in IL-6, CRP, and fibrinogen in women but not men.

	5-year IL-6				5-year CRP				5-year fibrinogen			
	Beta	SE	B	p-value	Beta	SE	B	p-value	Beta	SE	B	p-value
Men (n=511)												
PSQI subjective sleep quality[a]	−0.04	0.02	−0.06	0.09	−0.08	0.04	−0.08	0.06	−0.47	3.03	−0.01	0.88
Women (n=112)												
PSQI subjective sleep quality[a]	0.14	0.05	0.22	0.003	0.21	0.09	0.18	0.02	18.02	7.62	0.21	0.02

[a] Model includes baseline biomarker, age, ethnicity, education, BMI, and regular snoring.

Table 5

Longitudinal results of regression analyses showing that poorer baseline PSQI subjective sleep quality predicts 5-year increases in IL-6, CRP, and fibrinogen among women, independent of study covariates.

	5-year IL-6				5-year CRP				5-year fibrinogen			
	Beta	SE	B	p-value	Beta	SE	B	p-value	Beta	SE	B	p-value
Model 1												
PSQI subjective sleep quality	0.14	0.05	0.22	0.003	0.21	0.09	0.18	0.02	18.02	7.62	0.21	0.02
Model 2[a]												
PSQI subjective sleep quality	0.13	0.05	0.20	0.02	0.22	0.10	0.18	0.03	18.78	8.07	0.22	0.02
Model 3[b]												
PSQI subjective sleep quality	0.13	0.06	0.21	0.02	0.28	0.10	0.24	0.009	20.70	8.92	0.24	0.02
Model 4[c]												
PSQI subjective sleep quality	0.15	0.06	0.23	0.01	0.31	0.11	0.26	0.005	20.92	9.17	0.24	0.03
Model 5[d]												
PSQI subjective sleep quality	0.15	0.06	0.23	0.01	0.32	0.11	0.27	0.004	20.71	9.33	0.24	0.03

Model 1= baseline biomarker, age, ethnicity, education, BMI, regular snoring;

[a] Model 1 + lifestyle/psychosocial characteristics;

[b] model 2 + medical comorbidities;

[c] model 3 + medications;

[d] model 4 + cardiac function.