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Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: Evidence for gender disparity

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Abstract

Self-reported ratings of sleep quality and symptoms of poor sleep have been linked to increased risk of coronary heart disease (CHD), Type 2 diabetes, and hypertension with recent evidence suggesting stronger associations in women. At this time, the mechanisms of action that underlie these gender-specific associations are incompletely defined. The current study examined whether gender moderates the relation of subjective sleep and sleep-related symptoms to indices of inflammation, coagulation, insulin resistance (IR), and psychosocial distress, factors associated with increased risk of cardiovascular and metabolic disorders. Subjects were 210 healthy men and women without a history of sleep disorders. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and frequency of sleep symptoms. In multivariate-adjusted models, overall poor sleep quality, more frequent problems falling asleep (> 2 night/week), and longer periods to fall asleep (> 30 min) were associated with greater psychosocial distress, higher fasting insulin, fibrinogen and inflammatory biomarkers, but only for women. The data suggest that subjective ratings of poor sleep, greater frequency of sleep-related symptoms, and longer period of time to fall asleep are associated with a mosaic of biobehavioral mechanisms in women and that these gender-specific associations have direct implications to recent observations suggesting gender differences in the association between symptoms of poor sleep and cardiovascular disease.

Keywords

sleep disturbance; inflammation; coagulation; adiposity; psychosocial distress; gender differences

1. Introduction

Recent evidence from large epidemiological studies has suggested that poor sleep and sleep-related problems are more strongly associated with poor health outcomes in women than in men. For example, in one study, subjective symptoms of disturbed sleep were associated with a greater risk of cardiovascular disease (CVD) in older women than in men and these associations persisted even after adjustments for potential confounders (Newman, et al., 2000). Similar findings were observed by researchers from the Whitehall II community

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study who showed that short sleep duration was associated with both prevalence and incidence of hypertension with these associations found to be significant only for women (Cappuccio, et al., 2007). These novel, but important, gender differences suggest that disturbances in sleep quantity and quality may be differentially associated with putative mechanisms implicated in the onset and progression of cardiovascular and metabolic diseases in men and women. To date, no study has examined mechanisms of actions that could explain the observed gender-specific differences in the relation of sleep to disease outcomes.

Researchers have postulated a number of pathways whereby poor sleep quantity and quality can contribute to poor cardiovascular and metabolic health. One set of hypotheses posit that poor sleep quality is associated with physiological perturbations such as inflammation, coagulation and insulin resistance (IR), mechanisms that alone or in conjunction are implicated in both coronary heart disease (CHD) and Type 2 diabetes (e.g., Dandona, et al., 2003; Libby & Ridker, 2006). A second set of hypotheses suggests that the increased risk of CHD and Type 2 diabetes associated with poor sleep reflects greater psychosocial distress as indexed by elevations in hostility, anger and depression (Ford & Cooper-Patrick, 2001; Neckelmann, et al., 2007; Pilcher, et al., 1997), and lower levels of perceived social support (Akerstedt, et al., 2002; Brummett, et al., 2006). The indicators of psychosocial distress, alone or in combination, have been shown to be associated with increased risk of cardiovascular and metabolic disorders (Boyle, et al., 2007; Krantz & McCeney, 2002). Thus, evidence linking sleep quality and quantity to putative mechanisms provides a framework for understanding how sleep incurs a heightened risk for poor health.

In testing the above described hypotheses, most studies have employed clinical samples of individuals with a diagnosis of clinical sleep disorders. For example, there is a large body of evidence linking obstructive sleep apnea to increases in IR and biomarkers of inflammation. (Parati, et al., 2007; Vgontzas, et al., 2005) Considerably fewer studies, however, have employed non-clinical samples that are composed of individuals whose reported sleep disturbances do not reach clinical criteria. Although few in number, results have indicated that elevations in biomarkers of inflammation (Friedman, et al., 2005; McDade, et al., 2006) and coagulation (von Kanel, et al., 2006) as well as IR and psychosocial distress (Brummett, et al., 2006) are associated with individual differences in sleep quality and quantity.

Due to small sample size and/or the exclusion of women, statistical evaluation of the proposed hypothesis that gender moderates the relation of sleep to putative mechanisms has not been conducted. One recently published study, however, did suggest that gender is a characteristic that could modify the relation of poor sleep to inflammatory biomarkers, but due to small number of men and women in the sample, the investigators indicated that they were not able to test this association (Hong, et al., 2005). In light of the evidence from epidemiological studies for gender-specific association in sleep and healthy outcomes, and the fact that individual differences in sleep quality and quantity have been associated with putative mechanisms of cardiovascular and metabolic disease, the current observational study examined whether gender significantly moderates the relation of symptoms of disturbed sleep to markers of psychosocial distress and pathophysiological mechanisms in a large sample of men and women (Trenell, et al., 2007). Guided by previous observations, selection of biological and psychosocial markers was based on prior evidence indicating that elevations in levels of inflammatory (C-reactive protein (CRP) and interleukin (IL)-6) (Pradhan, et al., 2001; Ridker & Morrow, 2003), coagulation (fibrinogen) (Fibrinogen Studies, 2007; Temelkova-Kurktschiev, et al., 2002) and metabolic (fasting insulin, glucose and insulin resistance) (Arad, et al., 2001; Yanase, et al., 2004) biomarkers, as well as indicators of psychosocial distress (hostility, anger, depression and social support) (Krantz & McCeney, 2002; Rozanski, et al., 1999; Rozanski, et al., 2005), are associated with an

increased risk of cardiovascular and metabolic disorders. It was hypothesized that self-reported poor sleep quality and severity of sleep-related symptoms would be more strongly associated with elevated levels of inflammatory (CRP and IL-6), coagulation (fibrinogen), metabolic (fasting insulin, glucose and insulin resistance) biomarkers and indicators of psychosocial distress (hostility, anger, depression and social support) in women than in men.

2. Materials and Methods

2.1 Participants

The study sample consisted of 210 healthy, nonsmoking men ($n = 115$) and women ($n = 95$) recruited from the surrounding community using community flyers and advertisements placed in local newspapers as well as online announcements on the Duke Clinical Trials website. Interested individuals were asked to contact the laboratory where they were initially screened for inclusion criteria. Individuals were included if they were non-smokers and in good health, defined as having no history of chronic medical illness, no acute medical conditions or injuries, and no current or recent (< 1 month) use of medications, whether over-the-counter or prescribed. Individuals taking low-dose aspirin on a regular basis were excluded. Premenopausal women were excluded if they reported use of oral contraceptives within the previous 6 months and postmenopausal women were excluded if the reported use of hormone replacement therapy within the previous 6 months. Women suspected of being perimenopausal (i.e., irregular menstrual cycle during the previous 6 months) were excluded. Men were excluded if they were currently or had been treated with androgen replacement therapy 6 months prior to participation. The Institutional Review Board (IRB) of Duke University Health System (DUHS) approved this study and appropriate informed consent was obtained from participants prior to their participation.

Procedures—Subjects reported to the laboratory between 8:00 and 9:00 AM after fasting for approximately 12 hours. Premenopausal women were scheduled during the follicular phase (days 5–10) of the menses to minimize the effects of menstrual hormone fluctuation. Blood samples were collected in chilled EDTA tubes, spun and stored at -80°C until assays were conducted. Blood related measures included CRP, IL-6, fibrinogen, fasting insulin and glucose. Adiposity was measured by calculating body mass index (BMI) from height and weight.

After blood draw, subjects completed the Pittsburgh Sleep Quality Index (PSQI) (Buysse, et al., 1989). The PSQI is a well established and validated paper-and-pencil questionnaire that assesses over-all sleep quality and sleep related symptoms over the previous 1-month period. The 19-items yield 7-component scores that reflect the frequency of sleep problems in the areas of: subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleep medication and daytime dysfunction. The sum of the 7-components yields one global score that ranges from 0 to 21 with poor sleep quality associated with higher scores. A PSQI global score of 5 and above has a diagnostic sensitivity of 89.6 and specificity of 86.5 in differentiating “poor sleepers” from “good sleepers” (e.g., PSQI global score < 5) subjects (Buysse, et al., 1989). Subjects also provided the average number of minutes it takes to fall asleep and the average number of hours slept.

In addition to the PSQI, subjects completed the Beck Depression Inventory (BDI) (Beck, et al., 1988), to assess severity of depressive symptoms, the Buss-Perry Aggression Inventory (BPAI) (Buss & Perry, 1992) used to assess anger, the Cook-Medley Hostility (CMHO) Inventory (Cook & Medley, 1954) used to assess hostility, and the Interpersonal Social Evaluation List (ISEL) (Cohen, et al., 1985) used to assess perceived level of social support.

Blood Assays—Plasma glucose was measured using a hexokinase-coupled reaction and plasma insulin was measured using a solid phase radioimmunoassay procedure. IR was determined using the Homeostatic Model assessment (HOMA) method as described by Matthews et al (Matthews, et al., 1985). The HOMA-IR index was calculated as the product of fasting glucose (G_0) (mmol/liter) and fasting insulin (I_0) (μ U/liter) values divided by the constant 22.5: $HOMA = (G_0 \times I_0)/22.5$.

CRP was measured in duplicate with an ultrasensitive, enzyme-linked, immunometric latex-enhanced assay (Diagnostic Product Corporation, Los Angeles, CA) using purified protein and polyclonal anti-CRP antibodies (Macy, et al., 1997). This system has a lower detection level of < 0.10 mg/L with coefficients of variation ranging from 6.6% to 9.9%. IL-6 was assessed using an enzyme-linked immunosorbent assay (ELISA) kit (Peirce-Endogen, Rockford, IL). Samples were assayed in duplicate and IL-6 concentrations were derived from a standard curve. The detectable limit of plasma IL-6 was < 1 pg/ml and the intra- and inter-assay coefficients of variation were < 5% and < 10%, respectively. Lastly, plasma fibrinogen was quantified using a modified Clauss method and MDA coagulometer (Organon Teknika, Durham, NC).

Analyses—Data analyses were performed using multivariate and univariate techniques. To control for the number of tests, initial test of the hypothesis examined the interaction between gender and sleep variables in multivariate models. Multivariate analysis of covariance (MANCOVA) was performed on inflammatory biomarkers (CRP, IL-6), metabolic indicators (insulin, glucose, IR) and coagulation (fibrinogen) were age, BMI, exercise regularly (Y/N), alcohol use and use of sleep medication as covariates. Use of sleep medication was assessed using a single item on the PSQI (How often have you taken medication (prescribed or “over the counter”) to help you sleep?) with responses ranging from not during the past month, less than once a week, once or twice a week, and three or more times a week. For the study sample, 92% reported no use of medications during the past month, with 6% reporting ‘less than once a week’, 0.5% reporting ‘once or twice a week’ and 1.5% reporting three or more times a week. Given this distribution, this variable was dichotomized and included in the analyses as a yes/no (0/1) coded variable¹.

The multivariate coefficient of the interaction was evaluated using Wilk’s lambda. If the interaction was not significant, multivariate analyses were performed using a main effects only model. As levels of inflammatory biomarkers and HOMA-IR were positively skewed, a logarithmic transformation was applied to these variables prior to analyses.

Analysis was also conducted to test the quadratic effect of sleep duration (number of hours of sleep) and its interaction with gender. This specific quadratic trend was examined in light of preliminary evidence suggesting that the relation of sleep duration to poor health is nonlinear with the greatest risk apparent among individuals with the shortest and longest sleep duration (Gangwisch, et al., 2005). To test this quadratic trend, we squared the sleep duration component of the PSQI and included that effect in the model along with the gender X (sleep duration)² interaction. In the case where neither the two-way nor quadratic

¹Over-the-counter (OTC) sleep medications may have influence on a number of outcome variables. Thus, all analyses were also performed on the 92% (n = 196) of subjects who reported no use of medicines during the past month. Without exception, the results were the same as those reported. Thus, analyses retained the small number of subjects (8%) reporting some use of OTC sleep medications and sleep medication use was entered as a covariate. In addition, the item to assess medication use did not ask for additional details (type/amount). What can be said is that, for the week prior to participating, all subjects reported no use of medications, whether prescribed or over-the-counter.

²Recent evidence has suggested that age may significantly moderate the relation of sleep disturbances to adverse health and putative mechanisms. Although the study sample included a wide age range (18–65 yr), only 5% of the sample was over the age of 50. Thus, it was not possible to examine the moderating effect of age due to lack of power. All analyses, however, used age as a covariate.

interaction is significant, we included only main effects in the multivariate analysis. Analyses controlling for age, exercise status, BMI and use of sleep medication failed to reveal a quadratic trend among males, females or the group as a whole for any of the outcome variables. No statistical results are reported given the lack of a quadratic effect

The primary variable of interest was the total score on the PSQI, which reflects the sum of all components. Analyses of components scores and other sleep variables were considered secondary analyses, and thus are more exploratory. Nevertheless, the consistency of the findings using component scores, and particularly scores on the sleep latency component, argues for reporting of the findings.

3. Results

Additional sample characteristics are presented in Table 1. Of the 210 subjects (age range: 18–65 yr.), 45% were women; 45% were minorities (i.e., African-American, Hispanic, Asian or other); 95% reported some college education or more; 30% were married or living with a significant other; 45% had annual household income of < \$40,000; and 80% reported that they exercised on a regular basis. Men showed significantly higher levels of resting systolic blood pressure (SBP) and fasting glucose and higher hostility scores, whereas women had significantly higher fibrinogen and greater depression and higher levels of perceived social support.

Men and women did not significantly differ in their subjective ratings of over-all sleep quality or PSQI components with the exception of daytime disturbance [$F(1, 208) = 4.64, p = .03$] with more men (19%) reporting greater frequency of daytime disturbance (e.g., 2 days/week or more) than women (6.3%). Age was not associated with either total PSQI score or with any sleep symptoms except daytime disturbance, whereby increasing age was associated with less frequent problems with daytime sleepiness [$r = -0.26, P < .001$]. Self-reported sleep quality and symptoms of sleep problems did not differ by ethnicity.

3. 1. Psychosocial Distress

Results indicated that the relation of PSQI to indicators of psychosocial distress was moderated by gender, Gender by PSQI interaction [Wilk's $\lambda = .94, F(4, 192) = 3.19, p = .015$]. Post-hoc analyses revealed gender-related differences in the relation of PSQI total score to hostility [$F(1, 201) = 4.08, p < .05$], depression [$F(1, 201) = 8.59, p < .01$] and anger [$F(1, 201) = 3.81, p < .05$] but not social support [$F(1, 201) = .04, ns$]. Women with poor sleep quality reported higher levels of hostility [$b = 1.19, p = .003$], anger [$b = .74, p = .002$] and severity of depressive symptoms [$b = 1.20, p < .001$]. In men, self-reported sleep quality was similarly and significantly associated with greater severity of depressive symptoms [$b = .50, p < .001$] but the strength of this association was significantly weaker than that observed in women. Although we failed to detect gender-related differences in the relation of sleep quality to perceived social support, lower levels of perceived social support was significantly associated with poor sleep quality in men [$b = -0.66, P = .009$] and not in women [$b = -0.42, ns$], an observation that has been previously reported in men (Akerstedt, et al., 2002).

To explore whether the above associations were due to specific sleep symptoms, analyses were conducted to examine the interaction of gender with components of the PSQI. Results revealed a significant sleep latency by Gender interaction [Wilk's $\lambda = .88, F(8, 380) = 3.80, p = .002$] with significant gender differences in the relation of sleep latency to anger [$F(2, 199) = 3.80, p = .02$] and depression [$F(2, 199) = 8.44, p = .0002$]. For women, greater frequencies of episodes of difficulty falling asleep were associated with greater levels of

anger and severity of depressive symptoms. For men, sleep latency was not associated with any of the psychosocial factors. No other PSQI components effects were detected.

We also explored whether reported number of hours slept per night (duration) and number of minutes it took to fall asleep (MTFA) predicted psychosocial distress. Neither the main effect for sleep duration nor its interaction with gender predicted psychosocial distress. In contrast, the MTFA by Gender interaction [Wilk's $\lambda = .93$, $F(4, 195) = 3.40$, $p = .01$] and the main effect of time to fall asleep [Wilk's $\lambda = .91$, $F(4, 196) = 5.02$, $p < .001$] were significant. For women, longer MTFA was associated with greater hostility [$b = .12$, $t = 2.17$, $p = .04$], depression [$b = .11$, $t = 3.02$, $p < .01$] and anger [$b = .07$, $t = 2.26$, $p = .03$] but not social support. For men, lower social support was associated with longer MTFA [$b = -.12$, $t = -2.43$, $p = .03$]¹.

Adiposity—Results indicated a significant PSQI by Gender interaction [$F(1, 201) = 4.08$, $p = .03$] with poor sleep quality associated with higher BMI in women [$b = .50$, $t = .215$, $p = .03$] but not men [$b = -0.14$, $t = -0.73$, ns]. Additional analyses showed that gender-related differences in the relation of BMI to daytime dysfunction, with women who reported more frequent episodes of daytime dysfunction being heavier. For men, BMI and daytime dysfunction was not associated.

Inflammatory Biomarkers—A significant PSQI by Gender interaction [Wilk's $\lambda = .95$, $F(2, 184) = 4.40$, $p = .01$] was observed for biomarkers of inflammation with the interaction significantly predicting both CRP [$F(1, 185) = 6.68$, $p = .01$] and IL-6 [$F(1, 185) = 4.32$, $p = .04$]. The PSQI score was significantly and positively associated with CRP [$b = .11$, $t = 2.23$, $p = .03$] and IL-6 [$b = .07$, $t = 2.25$, $p = .03$] in women but not men [CRP: $b = -0.05$, ns; IL-6: $b = -0.16$, ns].

Additional analyses examined whether CRP and IL-6 were more closely associated with specific symptoms of poor sleep. CRP and IL-6 were significantly predicted by the sleep latency component by Gender [Wilk's $\lambda = .94$, $F(4, 364) = 2.52$, $p = .035$] and sleep disturbance component by Gender [Wilk's $\lambda = .95$, $F(4, 364) = 2.56$, $p = .038$] such that more frequent bouts of difficulty falling asleep and greater frequency of sleep disturbances were associated with higher levels of CRP and IL-6 in women, but not men.

Average number of hours slept, either as a main effect or interaction with gender, was not associated with inflammatory biomarkers. The time to fall asleep (TFA) by Gender interaction, however, was significant [Wilk's $\lambda = .97$, $F(2, 187) = 3.12$, $p < .05$] such that among women, longer periods of TFA were associated with IL-6 [$b = .001$, $t = 2.40$, $p = .02$] and CRP [$b = .01$, $t = 1.97$, $p = .05$]. TFA was not associated with inflammatory biomarkers in men.

The total PSQI [$F(1, 193) = 1.17$, ns] or the PSQI by Gender interaction [$F(1, 192) = 2.40$, ns] did not predict fibrinogen levels. Results did indicate a significant sleep latency by Gender interaction [$F(3, 192) = 3.53$, $p = .01$] with women who reported more frequent occurrences of difficulty falling asleep having higher fibrinogen [adjusted mean (SEM) = 231.0 (15) mg/dl] than those reporting no problems falling asleep [adjusted mean (SEM) = 210.8 (15) mg/dl]. For men, frequency of difficulty falling asleep was not related to fibrinogen [211.6 (16) vs. 196.3 (15), adjusted means (SEM) for men with and without problems falling asleep, respectively]. Analyses indicated a significant main effect for estimated hours of sleep, with higher fibrinogen levels associated with longer sleep periods [$b = 6.83$, $t = 2.23$, $p = .02$].

Insulin, Glucose and Insulin Resistance—Results failed to indicate a multivariate main effect for PSQI total [Wilk's $\lambda = .98$, $F(3, 199) = 1.09$, ns] or its interaction with gender [Wilk's $\lambda = .98$, $F(3, 198) = 1.13$, ns]. Analyses using the PSQI components, however, revealed a significant multivariate effect for the interaction between sleep latency and Gender [Wilk's $\lambda = .87$, $F(9, 472) = 3.11$, $p = .001$] with gender moderating the relation of sleep latency to fasting insulin [$F(3, 196) = 6.42$, $p < .001$] but not to glucose or HOMA-IR. Relative to women who reported either no problems during the past month or less than once a week, women with more frequent problems falling asleep had higher fasting insulin. For men, fasting insulin was not associated with frequency of difficulties falling asleep.

There was also a significant multivariate main effect for sleep latency [Wilk's $\lambda = .90$, $F(9, 476) = 2.39$, $p = .01$] with a significant univariate effect for HOMA-IR [$F(3, 199) = 4.79$, $p = .004$]. Individuals reporting problems falling asleep once or more times a week showed greater IR [mean (SEM) = 1.96 (.25)] relative to those with no problems or less frequent (< 1 /week) occurrences of difficulty falling asleep [mean (sem): 1.10 \pm .25 and 1.30 \pm .27, respectively]. No other components of the PSQI were associated with IR measures.

Lastly, the TFA by Gender interaction was also significant [Wilk's $\lambda = .86$, $F(3, 201) = 10.90$, $p < .001$] with women who took 30 min or longer to fall asleep showing significantly higher fasting insulin [$b = .26$, $t = 5.49$, $P < .0001$] and greater IR [$b = .01$, $t = 3.24$, $p < .01$] than those who fell asleep within 30 minutes (see Figure 1). In men, the time it took to fall asleep was not associated with either fasting insulin or IR.

4. Discussion

In a multiethnic sample of adult men and women, poor sleep quality, more frequent occurrences of sleep-related symptoms, and a longer period of time to fall asleep (> 30 min) predicted a mosaic of putative psychosocial and physiological factors associated with increased risk of Type 2 diabetes and CVD. These associations, however, were significantly moderated by gender such that poor sleep quality and prolonged sleep latency incurred a greater psychological and physiological toll on women relative to men. Thus, among male and female subjects classified as poor sleepers by the PSQI *a priori* criteria (Buysse, et al., 1989), 51% of the women and 34% of the men were either overweight (BMI ≥ 25.0 kg/m²) or obese (BMI ≥ 30.0 kg/m²); 31% of the women and 21% of men showed CRP levels at or above 3.0 mg/l, and 27% showed HOMA values above 1.96, a level suggestive of IR in nondiabetic adults (Nakai, et al., 2002). Similarly, among individuals who reported taking 30 minutes or longer to fall asleep, 53% of the women were overweight or obese, 35% exhibiting CRP levels at or above 3.0 mg/l, and 32% had IR values above 1.96. These observations were statistically independent of age¹, BMI, race, severity of depressive symptoms, alcohol use, use of sleep medications during the last month, and exercise participation as well as other potential confounders that were controlled by methodological entry criteria, such as smoking, exogenous hormone use, and menstrual cycle phase (for premenopausal women).

The observed gender disparity has direct relevance to observations from two large epidemiological studies suggesting that symptoms of sleep disturbances incur a greater risk of CVD and hypertension in women than in men (Cappuccio, et al., 2007; Newman, et al., 2000). To date, no study has examined potential mechanisms that could explain these gender specific observations. This is due to the fact that investigators have focused their efforts on examining the relation of sleep disturbances to pathophysiological factors and indicators of psychosocial distress without testing the moderating effects of gender. Therefore, the current findings are the first to suggest that gender significantly moderates the relation of poor sleep to putative mechanisms implicated in a number of chronic diseases. Therefore, an increased

risk of CVD and hypertension associated with disturbed sleep in women could be due to psychosocial distress and pathophysiological mechanisms.

In minimizing the influence of various potential confounders, the current study employed strict methodological procedures. This methodology included inclusion/exclusion criteria that focused on negative history of chronic medical and psychiatric conditions including diagnosis of clinical sleep disorders, lifestyle factors associated with poor health such as smoking, use of medications, hormone therapy/oral contraceptive and holding time of data collection constant. Furthermore, for premenopausal women, data were collected only during the follicular phase of the menstrual cycle. These methodological constraints were coupled with multivariate techniques that were employed to minimize the influence of those factors that were not controlled methodologically, such as adiposity, age, race/ethnicity, exercise or use of sleep medications. Combined, methodological procedures and the statistical approach implemented in this study contribute to a high level of confidence that the observed gender differences were not due to the above mentioned confounding factors. What may explain the current observations, therefore, is opened to speculation.

One possible explanation is that these data reflect gender-related differences in the actions of the amino acid tryptophan (TRP), the neurotransmitter serotonin (5-HT), and the neurohormone melatonin (ML). Evidence suggests both direct and indirect effects of TRP, 5-HT and ML not only on sleep and sleep onset (Voderholzer, et al., 1998) but also on mood regulation (Booij, et al., 2002; Jans, et al., 2006), inflammation (Kubera, et al., 2005; Suarez, et al., 2000), thrombogenesis (Dale, et al., 2002), eating (Waldbillig, et al., 1981), and insulin regulation (Virkkunen & Naervaenen, 1987) with some studies suggesting gender-differences. For example, acute tryptophan depletion, which reduces 5-HT synthesis (Delgado, et al., 1989), has a greater mood altering effects on women than men (Booij, et al., 2002). In this laboratory, we have observed gender-related differences in the relation of TRP to various psychological factors associated with an increased risk of CHD and Type 2 diabetes (Suarez & Krishnan, 2006). Gender differences have also been reported in response to pharmacological treatments for depression with women showing more favorable responses to selective serotonin reuptake inhibitors (SSRI), such as fluoxetine, relative to men (Sloan & Kornstein, 2003). Thus, it may be the case that dysregulation of the serotonergic system, implicated in the regulation of sleep and sleep maintenance (Voderholzer, et al., 1998), is a potential mechanism that underlies the observed gender-specific relationship between sleep symptoms and putative risk factors.

Gender differences in the peroxisome proliferators-activated receptor (PPAR)- α may also explain the current observations (Barbier, et al., 2002; Daynes & Jones, 2002). Growing evidence points to a causative relationship between PPAR activity and the metabolic syndrome, IR, glucose intolerance, Type 2 diabetes, obesity, dyslipidemia, hypertension, atherosclerosis, and albuminuria (Zambon, et al., 2006). Increased PPAR α expression is associated with decreased nuclear factor (NF)- κ B and c-jun, transcription factors implicated in inflammation (Barnes & Karin, 1997). Particularly relevant to these observations, PPAR α is expressed at higher levels in males than in females with higher testosterone associated with greater expression (Dunn, et al., 2007). While PPAR α was not assessed in this study, poor sleep quality in men was associated with higher testosterone (partial $r = .19$, $P = .05$). Thus, in men, testosterone-related increases in the expression of PPAR α leading to a decreased expression of NF- κ B and c-jun may account for the lack of associations between poor sleep quality, inflammatory and metabolic factors.

Perturbations in physiological mechanisms and increases in psychosocial distress may underlie the observed gender differences in the association between poor sleep and BMI. From the current data, we observed that sleep disturbances were more strongly associated

with depression in women than in men. This replicates findings from a recent study showing that depression was associated with higher BMI and this association was stronger in women (Schieman, et al., 2007). Given this, psychosocial distress is one possible pathway that could explain the gender differences in the association of sleep to BMI. Another possibility is that sleep alters regulatory hormones associated with appetite and food intake. Evidence suggests that sleep disturbances are associated with neuroendocrine regulation of appetite with levels of the anorexigenic hormone leptin being decreased and levels of the orexigenic hormone ghrelin increases (Spiegel, et al., 2008). Consistent with this possibility, gender differences in the levels of leptin and brain sensitivity to leptin have been reported (Casabiell, et al., 1998; Clegg, et al., 2003; Licinio, et al., 1998). Insulin may also play an important part in explaining the observed differences in the association of BMI to sleep. As reported, the current study showed that greater sleep disturbances are associated with insulin but only in women. These gender specific sleep related effects, alone or in combination, could explain the stronger association between BMI and poor sleep in women.

For men, higher levels of testosterone provide a biologically plausible explanation for the lack of influence of disturbed sleep on putative mechanisms. Higher testosterone is associated with lower CRP and IL-6, greater insulin sensitivity and lower BMI (Liverman & Blazer, 2004). It is reasonable to assume, therefore, that higher testosterone levels blunt the health damaging consequences of poor sleep in men. Consistent with this hypothesis, one recent study showed that higher testosterone levels reduced the risk of developing Type 2 diabetes associated with sleep duration, and most dramatically among those with short sleep duration (Yaggi, et al., 2006).

The current study has various limitations. The aim of the study was to detect gender-specific differences in the relation of poor sleep to mechanism contributing to cardiovascular and metabolic disease onset and progression. The study was not designed to test directionality. While there is an abundance of data suggesting that psychological and medical conditions promote sleep disturbances, there is emerging evidence to suggest that sleep disturbances can evoke changes in psychological distress and physiological markers of health. In one large population, poor sleep, and particularly those sleep symptoms that are chronic, significantly increased the future risk for the development of anxiety and new episodes of major depression (Ford & Cooper-Patrick, 2001; Neckelmann, et al., 2007) as well as increased risk for hypertension (Cappuccio, et al., 2007). Experimental studies have shown that laboratory sleep restriction leads to greater IR in healthy young adults (Spiegel, et al., 2005). A parallel line of evidence suggests that inflammatory proteins, and specifically some proinflammatory cytokines, can contribute to sleep dysregulation (Opp, et al., 1992). This association has been most clearly illustrated in studies that have employed cytokine therapy, such as interferon (INF)-alpha, in treatment of clinical disease. In those studies sleep disturbances has been frequently noted (Capuron & Miller, 2004). Another limitation is use of a self-report scale in the assessment of sleep problems. Although the PSQI is a well-validated and recognized assessment tool to assess sleep quality, it cannot assess aspects of disturbed sleep that could potentially explain these findings, specifically, sleep disordered breathing (SDB). In a number of clinical studies, SDB has been linked with adverse health outcomes (e.g., Bassetti, et al., 2006; Mooe, et al., 2001; Peppard, et al., 2000; Reichmuth, et al., 2005) as well as potential pathophysiological mechanisms (Vgontzas, et al., 2000). Thus, it will be necessary for future studies to examine whether the observed gender differences emerge when assessment of sleep disturbances include measures of SDB.

Another important caveat is the fact that recruitment was not targeted at individuals with a history of sleep disorders. It is likely, however, that recruitment of individuals with severe sleep pathology would have resulted in even stronger associations given previous reports of

the relationships between clinical sleep disorders and putative mechanisms (Burgos, et al., 2006; Hall, et al., 2000).

There current investigation also has notable strengths one of which is the large sample size, and particularly the sufficient number of women that allowed for the statistical evaluation of the hypothesized gender-specific interaction. As noted, few studies have included sufficient number of women to allow for appropriate statistical evaluation of the moderating effect of gender. Other studies have only included men. Inclusion of women, however, can present interpretational and statistical challenges due to hormonal variations throughout the menstrual cycle (Tworoger, et al., 2005). To reduce the influence of hormonal fluctuations associated with the menstrual cycle, data were collected only during the late follicular phase (days 5–10) in women who were premenopausal. Employing this approach minimized the possibility that differences in levels of ovarian hormones could account for the observed gender differences.

In conclusion, in women but not men, poor sleep and sleep-related symptoms are associated by a mosaic of plasma biomarkers and psychosocial distress associated with increased risk of Type 2 diabetes, CVD and other chronic medical conditions. The rationale underlying for the proposed study stemmed from epidemiological findings of gender-specific associations between sleep and risk of CVD. While limited by the cross-sectional nature of the design, the strength of the current data lies in the extent to which poor sleep quality and prolonged sleep latency were associated with a cluster of risk markers that are inter-related and, in combination, incur a heightened risk of most major chronic diseases. This is particularly true when it comes to the relation of sleep symptoms to both CRP and fibrinogen, a combination that has been shown to identify individuals who are at risk of becoming diabetic due to IR and not poor insulin secretion (Festa, et al., 2003), as well as the combination of hostility-anger-depression, which my laboratory has shown to be the best predictor of incident CHD in a 20-year follow-up of initially healthy adults (Boyle, et al., 2007). That sleep is a modifiable factor suggests its usefulness as a target for clinical intervention programs aimed at reducing primary disease risk. As a result, improvements in sleep as a mean of reducing risk for CVD may prove particularly effective in women. What may pose a greater challenge, however, will be in developing specific interventions particularly effective for women.

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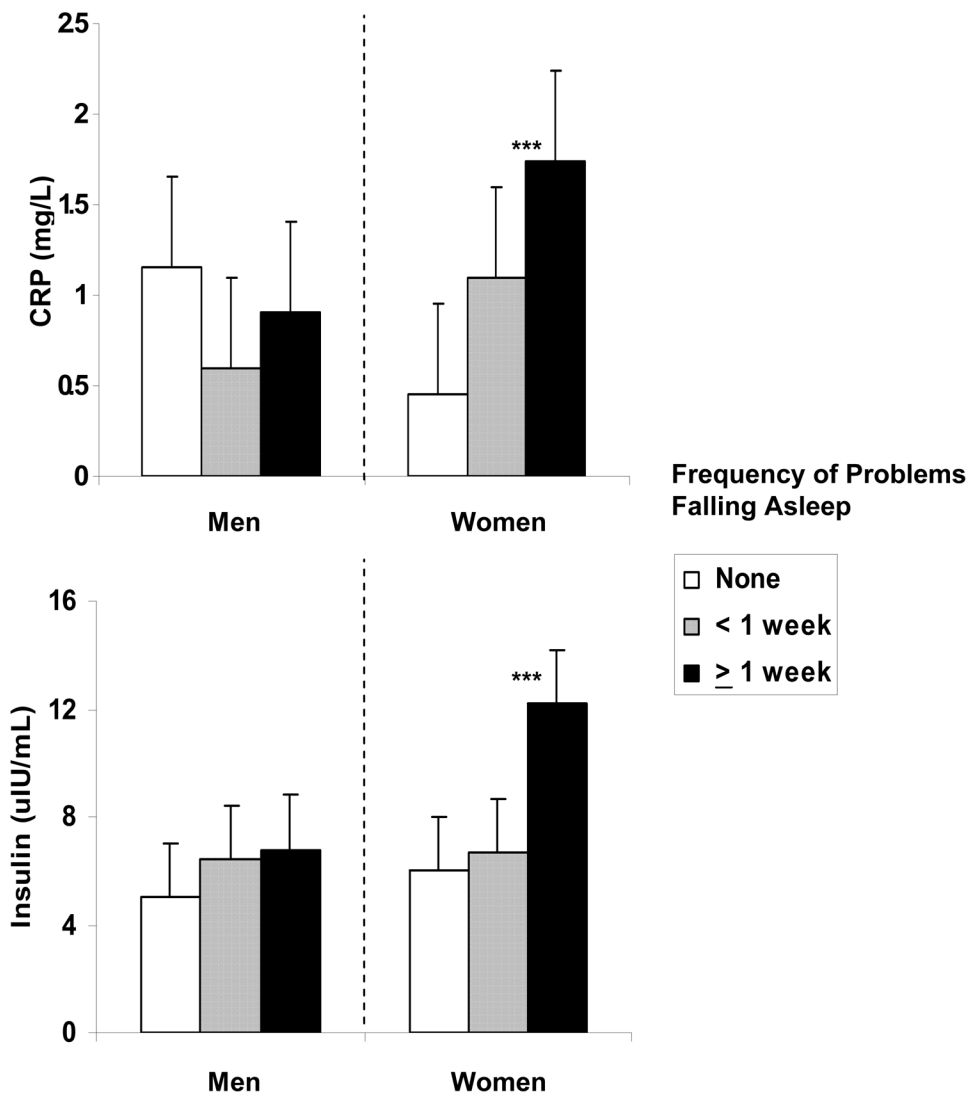


Figure 1. C-reactive protein (CRP), and fasting insulin in men ($n = 110$) and women ($n = 95$) as a function of frequency of problems falling asleep. Means are adjusted for age, body mass index, race, exercise, and use of sleep medication in the prior month.

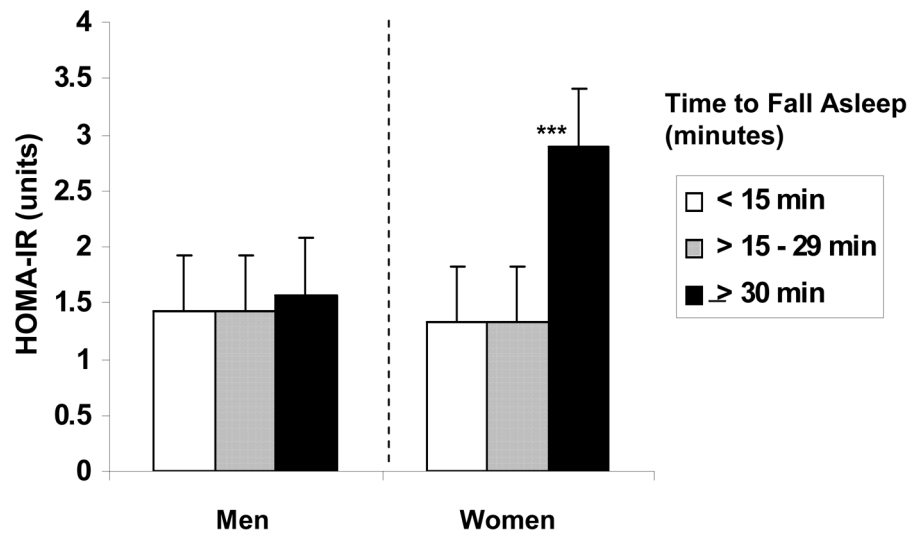


Figure 2. Homeostasis Model Assessment (HOMA) estimated insulin resistance (IR) as a function of length of time to fall asleep. Means are adjusted for age, body mass index, race, exercise, and use of sleep medication in the prior month.

Table 1

Sample characteristics. Means (SD) are presented unless otherwise indicated.

	Men	Women
Age, y	28 (9.7)	30 (9.5)
BMI, kg/m ²	25.3 (4.6)	25.1 (4.9)
Resting SBP, mmHg *	116.6 (15.2)	105.5 (12)
Resting DBP, mmHg	63.4 (8.5)	62.3 (8.1)
Total Cholesterol, mg/dl	168.4 (36)	169 (37)
Insulin, uIU/mL	7.4 (4.4)	8.5 (8.2)
Glucose, mg/dL *	88 (9.2)	85 (8.3)
Fibrinogen, mg/dL *	204.3 (56)	227.2 (51.1)
Interleukin-6, pg/mL ^a	1.34 (.42–6.76)	1.27 (.41–5.56)
C-Reactive Protein, mg/L ^a	1.30 (.16–6.46)	1.35 (.15–6.69)
Insulin Resistance (units) ^a	1.64 (.50–5.53)	1.84 (.47–5.12)
Psychosocial scales		
Pittsburgh Sleep Quality Index	4.5 (2.4)	3.9 (2.3)
Cook Medley Hostility *	20 (7.4)	17.6 (8.3)
Buss-Perry Anger	15 (5.3)	14.1 (4.9)
Beck Depression Inventory *	3.5 (3.5)	5.1 (6.0)
Interpersonal Social Evaluation List *	37.3 (6.4)	39.5 (7.1)

* $p < .05$ for test of gender differences;

^a median with 95% confidence interval