Poor sleep quality is associated with greater circulating pro-inflammatory cytokines and severity and frequency of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) symptoms in women

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ABSTRACT

Objective: Poor sleep quality has been linked to inflammatory processes and worse disease outcomes in the context of many chronic illnesses, but less is known in conditions such as chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). This study examines the relationships between sleep quality, pro-inflammatory cytokines, and CFS/ME symptoms.
Methods: Sixty women diagnosed with CFS/ME were assessed using the Pittsburgh Sleep Quality Index (PSQI), Fatigue Symptom Inventory (FSI) and Center for Disease Control and Prevention (CDC)-based CFS/ME symptom questionnaires. Circulating plasma pro-inflammatory cytokine levels were measured by ELISA. Multiple regression analyses examined associations between sleep, cytokines and symptoms, controlling for age, education, and body mass index.
Results: Poor sleep quality (PSQI global score) was associated with greater pro-inflammatory cytokine levels: interleukin-1β (IL-1β) ($\beta = 0.258$, $p = 0.043$), IL-6 ($\beta = 0.281$, $p = 0.033$), and tumor necrosis factor-alpha (TNF-α) ($\beta = 0.263$, $p = 0.044$). Worse sleep quality related to greater fatigue severity ($\beta = 0.395$, $p = 0.003$) and fatigue-related interference with daily activities ($\beta = 0.464$, $p < 0.001$), and more severe and frequent CDC-defined core CFS/ME symptoms ($\beta = 0.499$, $p < 0.001$, and $\beta = 0.556$, $p < 0.001$, respectively).
Conclusions: Results underscore the importance of managing sleep-related difficulties in this patient population. Further research is needed to identify the etiology of sleep disruptions in CFS/ME and mechanistic factors linking sleep quality to symptom severity and inflammatory processes.

1. Introduction

Poor sleep quality has been implicated in worse health outcomes in various clinical populations and also contributes to diminished physical and psychological well-being in otherwise healthy individuals (Lorton et al., 2006; Okun et al., 2013). In a variety of clinical populations, disrupted sleep has been linked to greater fatigue and poorer health (Lorton et al., 2006). Poor sleep quality can be ascertained objectively by overnight polysomnography and subjectively by questionnaires such as the Pittsburgh Sleep Quality Index (PSQI), which measures sleep quality overall and many of its components (Buysse et al., 1989).

Sleep is commonly disrupted during the course of chronic illnesses (Polo-Kantola et al., 2014) and can also be an important etiological, precipitating, or maintaining factor of disease (Lorton et al., 2006). Sleep deprivation and loss results in an activation of the immune system, which is evident on a cellular and genomic level (Irwin et al., 2006). In the context of inflammatory disorders such as ankylosing spondylitis, sleep quality overall and its composite parts (PSQI subscales) are positively correlated with symptom severity and with circulating C-Reactive Protein (CRP) levels (Aydin et al., 2015).

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a chronic unremitting condition with an estimated worldwide prevalence of 0.8–3.5% (Bhui et al., 2011), and is overrepresented among women (Klimas and Koneru, 2007). The disorder is a poorly misunderstood and debilitating inflammatory illness with no known etiology or cure. CFS/ME symptoms include post-exertional malaise, sore throat, and unrefreshing sleep, among other varied somatic symptoms. Research has revealed physiological manifestations of CFS/ME, such as dysregulated cortisol awakening response (CAR) and cytokine expression imbalance, which are associated with sleep disturbances in other contexts (Klimas and Koneru, 2007; Mariman et al., 2013; Wright et al., 2015). CFS/ME patients' sleep is typically reported as unrefreshing and/or frequently disturbed (Mariman et al., 2013). Recent research has identified subjective and objective accounts of poor sleep quality in CFS/ME—possibly identifying different sleep phenotypes (e.g. hypersomnia, insomnia-like phenotypes) (Gotts et al., 2013; Mariman et al., 2013). Other studies found that CFS/ME patients report poor sleep, even while demonstrating otherwise normal sleep by polysomnography, as compared to healthy age- and gender-matched controls (Maes et al., 2012a; Neu et al., 2007).

In addition to experiencing somatic symptoms and poor sleep, CFS/ME patients reveal increased pro-inflammatory cytokine levels when compared to healthy controls (Fletcher et al., 2009; Klimas and Koneru, 2007; Maes et al., 2012a; Maes et al., 2012b). Elevations in pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and relatively lower levels of anti-inflammatory cytokines (including IL-13) were shown most consistently in CFS/ME patients vs. healthy controls (Fletcher et al., 2009; Gupta et al., 1997; Moss et al., 1999). However, no individual cytokine, set of cytokine expression profiles, or biomarker has been consistently and conclusively found to be a diagnostic marker or known etiological factor in CFS/ME (Broderick et al., 2010). Discrepancies in the CFS/ME cytokine research may be due in part to cytokine measurement issues, including the use of different assays, which change in sensitivity and specificity over time due to methodological and laboratory advances, or the time of day when samples are collected (Fletcher et al., 2009; Klimas et al., 2012; Nakamura et al., 2010; Pandi-Perumal et al., 2007). Inflammatory cytokine levels can also differ by gender, in part because of estrogen's immunomodulatory effects, including in the context of CFS/ME (Klimas and Koneru, 2007; Smylie et al., 2013). The sleep and inflammation literature is not always stratified by gender, which may account for some inconsistencies in the literature.

Poor sleep quality has been shown to contribute to greater inflammation in healthy, and in acutely and chronically ill individuals, though there is evidence for a bi-directional relationship (Irwin, 2002; Irwin et al., 2006; Lorton et al., 2006). In general, pro-inflammatory cytokines promote sleep while anti-inflammatory cytokines prevent sleep (Krueger, 2008; Krueger et al., 2007). IL-1 and TNF-α are consistently found to be directly somnogenic when administered centrally or peripherally (Krueger and Majde, 2003). In rats, IL-6 modulates NREM sleep and is known to contribute to sleepiness, but does not meet full criteria for a sleep regulating substance (Hogan et al., 2003).

Inflammatory control can be disturbed in individuals who suffer from primary sleep disorders, such as insomnia (Vgontzas et al., 2002; Weil et al., 2009). Chronic insomnia can result in a shift and disruption in the circadian release of IL-6 and TNF-α (Vgontzas et al., 2002). Inflammatory cytokines IL-6 and TNF-α are typically elevated in sleep disorders that result in excessive daytime sleepiness, such as sleep apnea and narcolepsy (Vgontzas et al., 1999; Vgontzas et al., 2002). In healthy adults, these cytokines are usually elevated after sleep deprivation and may mediate sleep propensity and fatigue the next day (Vgontzas et al., 1999). It is reasonable that sleep disruptions in CFS/ME patients may therefore promote increased pro-inflammatory signaling and symptomology, yet little is known about the precise relationship between aspects of sleep disruption and specific inflammatory and symptomalogic indicators in this population.

1.1. Present study

Given the association between sleep disruptions and illness severity and also with inflammation, we hypothesized that among women with CFS/ME poor sleep quality (higher PSQI global scores) would be associated with greater circulating pro-inflammatory cytokine levels, and more severe and frequent CFS/ME-related symptoms. Specifically, we hypothesized that poor sleep quality overall and certain subscales (i.e. sleep disturbances, sleep duration, and sleep latency) would predict (a) greater levels of circulating pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, and (b) greater CFS/ME symptom burden including Centers for Disease Control and Prevention (CDC) core CFS/ME symptom severity and frequency, and greater fatigue severity and fatigue-related interference in daily life.

2. Methods

2.1. Participants and procedures

Female participants in this study were recruited from a larger study of stress and coping processes in CFS/ME patients and study findings have been previously published (Hall et al., 2014; Lattie et al., 2012). This is the first report on sleep-related phenomena from this study. All participants received a physician-determined CFS diagnosis, as defined by the CDC criteria (Fukuda et al., 1994). Recruitment methods included physician referral, support groups, CFS/ME conferences, and advertisements in CFS/ME-related websites. Participants were eligible if they were fluent in English, lived within the study area, and were between the ages of 21 and 75 years.

Potential participants were excluded from the study if they met criteria for schizophrenia, bipolar disorder, or substance abuse, or if they were actively suicidal, as assessed by a brief screening measure adapted from the Structured Clinical Interview for the DSM-IV (First et al., 1997). Participants were also excluded if they showed markedly diminished cognitive capabilities, as evidenced by making four or more errors on the Short Portable Mental Status Questionnaire (Pfeiffer, 1975). Presence of another condition (e.g. AIDS, lupus, rheumatoid arthritis) that might influence biological processes associated with CFS/ME symptomatology, or taking medications that would modulate immune or neuroendocrine functioning excluded participants from the study. Potential participants were also excluded from the study if they were suffering from untreated obstructive sleep apnea (OSA).

Participants who met criteria signed an informed consent form and scheduled a home visit between the hours of 11:00 am and 3:00 pm. During this visit, study personnel administered a battery of measures, and a certified phlebotomist drew a blood sample. After completing survey answers and providing blood samples, participants were compensated with $50.

2.2. Measures

2.2.1. Pittsburgh Sleep Quality Index (PSQI)

The 19-item PSQI (Buysse et al., 1989) was used to assess 7 components of sleep difficulties during the past 30 days, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The seven component scores were rated from 0 to 3, with 0 signifying no difficulty and 3 indicating severe difficulty. The composite score added these seven subscale scores to provide a global score ranging from 0 to 21, where higher numbers indicated poorer sleep quality. The PSQI has been validated in many different populations ($\alpha = 0.83$ in healthy individuals), including CFS/ME patients ($\alpha = 0.64$) (Mariman et al., 2012b). The reliability coefficient for the PSQI in our sample was $\alpha = 0.613$ for CFS/ME women ($\alpha = 0.709$, if the "use of sleep medication" item was removed). This is a relatively low alpha, but is comparable to what was shown in the other sample of CFS/ME