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Self-Reported Sleep Disturbance is associated with Lower CD4 Count and 24-Hour Urinary Dopamine Levels in Ethnic Minority Women Living with HIV

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Abstract

Background—Sleep disturbance is associated with dopamine dysregulation, which can negatively impact immune status. Individuals living with HIV experience more sleep difficulties, and poor sleep may compound immune decrements associated with HIV infection. Little research has examined associations between sleep, dopamine, and immune status (CD4 count) in individuals with HIV. As ethnic minority women living with HIV (WLWH) are at heightened risk for HIV disease progression, we related sleep reports to both CD4 count and dopamine levels in a cohort of ethnic minority WLWH.

Methods—Participants were 139 low-income WLWH (ages 20–62; 78.3% African-American or Caribbean) who reported both overall sleep quality and sleep disturbance on the Pittsburgh Sleep Quality Index (PSQI). CD4 count and HIV viral load were measured via morning peripheral venous blood samples, and concentrations of dopamine were measured via 24-hour urine collection. Covariates included HIV viral load, length of time since HIV diagnosis, HAART adherence, perceived stress and depression.

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Conflict of Interest Statement

All authors declare there are no conflicts of interest.

Contributors

Julia S. Seay conducted all data analyses and contributed to literature review and the writing of the manuscript.

Roger McIntosh contributed to the literature review and the writing of the manuscript.

Erin M. Fekete contributed to the writing of the manuscript.

Mary Ann Fletcher was responsible for conducting the laboratory work involved in the measurement of CD4 count and HIV viral load in the study as well as contributed to the editing of the manuscript.

Mahendra Kumar was responsible for conducting the laboratory work involved in the measurement of urinary dopamine in the study as well as contributed to the editing of the manuscript.

Neil Schneiderman designed the original study protocol, secured the funding for the study, and contributed to the editing of the manuscript.

Michael H. Antoni designed the original study protocol and contributed to the writing of the manuscript.

Results—After controlling for all covariates, greater sleep disturbance was associated with significantly lower CD4 count ($r = -.20, p = .03$) and lower levels of dopamine ($r = -.25, p = .04$). Poorer overall sleep quality was marginally associated with lower CD4 count ($r = -.16, p = .08$), and was not associated with dopamine.

Conclusion—Our analyses suggest that sleep disturbance is independently related with immune status and dopamine levels in WLWH. Lower levels of dopamine may indicate neuroendocrine dysregulation and may impact immune and health status. Results highlight sleep disturbance rather than overall sleep quality as potentially salient to neuroendocrine and immune status in ethnic minority WLWH.

Keywords

HIV; Sleep; Dopamine; CD4 Count

Background

Over the past decade, various studies have elucidated sleep as a significant biobehavioral modulator of both neuroendocrine and immune functioning. Following with this work, recent research has revealed disturbed sleep to be significantly associated with lower dopamine levels, which in turn may lead to increased sleepiness and lethargy. Sleep disturbances in particular, such as periodic leg movements, are associated with decreased levels of dopamine (Cohrs et al., 2004). Multiple studies also demonstrate that dopamine agonists improve symptoms of sleep disturbances in patients with conditions such as rapid-eye movement sleep behavior disorder and restless leg syndrome, indicating that dopamine decrements may accompany sleep disruption (Hornyak et al., 2012; Sasai et al., 2012). Sleep disturbances can also significantly impact immune functioning, as sleep deprivation is directly associated with an increase in proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), and decreases in circulating natural killer cells (Irwin et al., 1996; Yehuda et al., 2009; Gomez-Gonzalez et al., 2012).

The relationships between sleep, dopamine, and immune functioning are especially salient within the context of HIV/AIDS, as dysregulation in any of these areas could potentially impact disease progression. Individuals living with HIV experience more sleep difficulties than those who are non-infected including sleep disturbance, daytime sleepiness, fatigue, and overall poorer sleep quality (Norman et al., 1988; Darko et al., 1992; Darko et al., 1995; Low et al., 2011; Lee et al., 2012; Wibbeler et al., 2012). In addition, examination of post-mortem brain tissues indicate HIV-infected individuals often exhibit deficiencies in subcortical dopamine as compared with uninfected controls, which can occur even in those who are adherent to HAART (Kumar et al., 2009; Kumar et al., 2011). Previous research shows that individuals living with HIV can exhibit deficits in fronto-striatal functioning, which may relate to decreased dopamine in subcortical regions (Melrose et al., 2008). Thus, dopamine deficiencies in HIV-positive individuals are associated with neurocognitive dysfunction, and may contribute to the development of HIV-associated neurological disorders (Kumar et al., 2011; Purohit et al., 2013).

Despite this evidence, a paucity of research examines associations between sleep, dopamine, and immune status in individuals living with HIV. Previous work has connected sleep and pro-inflammatory cytokine dysregulation in HIV+ individuals (Darko et al., 1995; Foster et al., 2012) and poor sleep quality and fatigue were found to be associated with lower CD4 count (Darko et al., 1992; Lee et al., 2012). However, to our knowledge, no study examines the influence of sleep disturbance on CD4 count controlling for pertinent confounders such as stress and depression, which are known to relate to immune status in this population (Leserman, 2008). Furthermore, connections between sleep and dopamine have yet to be

elucidated in HIV+ individuals, thus sleep disturbance may relate to immune status via its relationship to reduced dopamine levels.

Current Study

Sleep may be especially salient for ethnic minority women living with HIV (WLWH), as these women experience faster rates of HIV disease progression than white WLWH (Centers for Disease Control, CDC, 2011). Furthermore, healthy African-American women demonstrated poorer sleep quality compared to white women as measured by self-reported sleep quality and NREM electroencephalographic (EEG) power (Hall et al., 2009). Most studies examining sleep in WLWH focus on the associations between sleep and psychosocial outcomes such as fatigue and quality of life (Lee et al., 2001; Phillips et al., 2005; Marion et al., 2009). However, sleep may represent a potentially understudied salient correlate of neuroendocrine and immune processes in WLWH. In addition, while previous research studies examined the impact of neuroendocrine factors such as cortisol and norepinephrine on immune status in individuals living with HIV (Antoni et al., 2005; Ironson et al., 2008); work examining connections between dopamine and immune status in HIV is extremely limited.

The current study seeks to examine both overall sleep quality and sleep disturbance in particular as independent correlates of dopamine and immune status in WLWH, as both overall sleep quality and sleep disturbance were associated with neuroimmune processes in previous studies. While overall sleep quality may play a significant role in both dopamine level and immune status, we aimed to examine sleep disturbance in particular, due to the specific connections previously found between sleep disturbances and abnormalities in dopamine in other conditions such as restless legs syndrome, Parkinson's disease, and schizophrenia (Cohrs et al, 2004; Sarkar et al., 2010). The aims of the current study are first, to compare overall sleep quality and sleep disturbance as independent correlates of urinary dopamine concentration and immune status in women living with HIV (WLWH). Secondly, we aim to examine whether dopamine concentration explains any significant associations between sleep and immune status in WLWH, as dopamine can relate to immune functioning via paradoxical activation of resting CD4 cells and inhibition activated CD4 cells (Sarkar et al., 2010).

Methods

Participants and Procedure

Our study utilized baseline (pre-intervention) data from a larger intervention study conducted from 1998 to 2004, which examined the influence of cognitive behavioral stress management (CBSM) on psychosocial, behavioral, and physiological factors in 139 WLWH on highly active antiretroviral therapy (HAART). To be eligible for the study, the women must have been able to read at a sixth-grade level, have no significant cognitive impairment (measured by the HIV Dementia Scale; Power et al., 1995) and have no current psychosis, alcohol/substance dependence, or panic disorder (assessed through the Structured Clinical Interview for DSM-IV; First et al., 1997). Women were excluded from the study if they were prescribed immunomodulatory medications other than HAART, had previously had chemotherapy or radiation for a non-AIDS related cancer, or had chronic immune illnesses (other than HIV) (Weaver et al., 2005). Women who were interested and eligible for the study signed informed consent, completed psychosocial measures, collected 24-hour urine samples, and provided peripheral venous blood samples between 0800h and 1200h. All study procedures were approved by the university's Human Subjects Research Office.

As shown in Table 1, the 139 participants had a mean age of 38.3 years ($SD = 7.8$ years, range: 20–62 years). They had been diagnosed with HIV for an average of 7.7 years ($SD = 4.54$ years). All participants were taking HAART medications, with 61.5% reporting 95% medication adherence. The majority of participants were African American or Caribbean (78.3%), and about half the participants completed high school (57%). The modal yearly income for the participants was between \$5,000 and \$10,000. In addition, all of the participants were not abusing alcohol or illegal drugs (opiates, cocaine, amphetamines) at the time of the study, as indicated by both a self-report measure asking the frequency of use of particular substances over the past 3 months and a urine screen.

Measures

Sleep Quality and Sleep Disturbance—The 19-item Pittsburgh Sleep Quality Index (PSQI) measured multiple dimensions of sleep quality (Buysse et al. 1989). The PSQI global score is a comprehensive measure of sleep ranging from 0 to 21, with higher scores indicating poorer overall sleep quality. The PSQI global score is comprised of seven component scores which can be analyzed separately to examine subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. For the purposes of our study, we examined the PSQI global score, as well as the sleep disturbance component score, both of which were calculated using the algorithm outlined in Buysse et al. (1989). We also examined the raw score of the sleep disturbance subscale, which consisted of the sum of 9 likert-type items corresponding to the frequency of specific sleep disturbances, such as: “wake up in the middle of the night or early in the morning,” “feel too hot,” and “cannot breathe comfortably.”

Women’s mean global score of sleep quality was 6.9 ($SD = 4.2$; $r = .70$). Prior research suggests that a global score of greater than 5 indicates poor sleep quality (Carpenter & Andrykowski, 1998). In the present sample, 59% of women scored > 5 on the global sleep quality measure. In addition, we calculated both the sleep disturbance raw score and the sleep disturbance component score for each participant. Component scores can range from 0 to 3, with higher scores indicating poorer sleep outcomes for that particular component. Women’s mean sleep disturbance component score was 1.2 ($SD = .70$), and their mean sleep disturbance raw score was 6.5 ($SD = 5.4$).

Immune Measures—Both CD4+ T-cell count and HIV viral load were measured via morning peripheral venous blood samples collected in EDTA tubes. CD4 count was determined by whole blood four-color direct immunofluorescence with a Coulter XL and flow cytometer (Fletcher et al., 2000). Plasma HIV viral load was determined by an in vitro reverse transcriptase polymerase chain reaction (RT-PCR) assay (AMPLICOR, Roche Laboratories, US #83088), which had a lower limit of 50 copies/mL. As the HIV viral load data was heavily skewed and kurtosed, all HIV viral load values were log-transformed (base-10) prior to data analysis. Participants’ CD4 counts ranged from 22–1616 with a mean CD4 count of 484.5 cells/ μ L ($SD = 303.0$ cells/ μ L). In addition, 16% of participants had a CD4 count below 200, indicating that their disease had progressed to AIDS. Participants’ mean $\log_{10}$ HIV viral load was 2.8 ($SD = 1.2$).

Dopamine—Urinary concentrations of dopamine were measured via high performance liquid chromatography (HPLC; Kumar et al., 1991) using disposal columns filled with Biorex-70 resin (a cationic-exchange column). The dopamine from the extract was separated on a HPLC-CoulArray system using reverse-phase C18, 5 μ m column, and determined by a coulometric system. Urinary concentrations of dopamine were expressed as μ G per milliliter

($\mu\text{G/mL}$). Participants' mean urinary dopamine concentration was $1.65 \mu\text{G/mL}$ ($SD = 1.37 \mu\text{G/mL}$).

Covariates—Potential covariates included sociodemographic (i.e., age, education level, income) and health-related (i.e., months post HIV diagnosis, HAART medication adherence, log HIV viral load) characteristics (Table 1). No sociodemographic variables (age, education level, income) were significantly associated with sleep, dopamine or CD4 count, thus we did not control for these factors in our analysis. However, perceived stress, depression, medication adherence, and disease status have been associated with neuroendocrine and immune functioning in prior HIV research (Antoni et al., 2005; Carrico et al., 2005; Antoni et al., 2006; Leserman, 2008). Therefore our study controlled for perceived stress, depression, time post HIV diagnosis, HAART adherence, and disease status (log HIV viral load).

Perceived stress was measured using the Perceived Stress Scale (PSS; Cohen et al., 1983), which measured how often women appraised situations in their lives as being stressful in the past month. Depression was measured using the Beck Depression Inventory II (BDI-II; Beck et al., 1996), which measures cognitive, affective, and somatic aspects of depression. Medication adherence was measured via self-report using the Adult AIDS Clinical Trial Group Adherence to Combination Therapy Guide (ACTG; Chesney et al., 2000), which measures adherence over the past 4 days. Finally disease status was measured by HIV viral load via morning peripheral venous blood draws (see above). Women's mean PSS score was 24.4 ($SD = 7.5$) and their mean BDI-II score was 11.2 ($SD = 9.1$). Women's mean HAART adherence was 89.6% ($SD = 18.3\%$).

Analysis Plan

As all of our variables were normally distributed and our data was missing completely at random (Little's MCAR $\chi^2 = 253.66$, $p > .05$), we used multiple imputation procedures (25 imputations) to estimate all of our missing data, resulting in a sample size of 139 for all variables (Rubin, 1987; Graham et al., 2007). All analyses were conducted on the 25 imputed datasets separately and results were pooled utilizing the methods outlined in Rubin (1987). To examine our study aims we conducted hierarchical multiple regression analyses.

For the first aim we examined the independent influence of both overall sleep quality (PSQI global scores) and sleep disturbance component scores on CD4 count and dopamine. Since the PSQI sleep disturbance component score was limited in range (0–3), we conducted analyses with the continuous sleep disturbance raw score (range: 0–27), which reflects the full variation in sleep disturbances in our sample, in order to more adequately ascertain associations between sleep disturbance, CD4 count, and urinary dopamine. Given that prior research identifies sleep disturbance specifically as a significant correlate of immune status and dopamine we focused on examining sleep disturbance. To be statistically conservative (to minimize Type 1 error), we did not examine the other PSQI subscales as independent variables in our analyses. For these analyses, health-related covariates (log HIV viral load, HAART adherence, time post HIV diagnosis) were entered into the first block, psychological covariates (depression and perceived stress) were entered into the second block, and the independent variable (either PSQI global score or sleep disturbance score) was entered into the final block.

Given that dopamine impacts CD4 cell activity and proliferation (Sarkar et al., 2010) we decided that if an independent variable (either overall sleep quality or sleep disturbance) was significantly associated with both CD4 count and dopamine, we would examine whether dopamine was a significant intermediary variable in the association between the sleep variable and CD4 count (Preacher & Hayes, 2008). For these analyses, health-related

covariates (log HIV viral load, HAART adherence, time post HIV diagnosis) were entered into the first step of the regression model followed by psychological covariates (depression and perceived stress) in the second block, the sleep score (either PSQI global score or sleep disturbance component) in the third block, and the intermediary variable (dopamine) in the final block.

Results

Bivariate Correlations

Bivariate correlation analyses revealed that HAART adherence was positively associated with CD4 count ($r = .23$, $p < .01$), while both log HIV viral load ($r = -.42$, $p < .01$) and time since HIV diagnosis ($r = -.25$, $p < .01$) were negatively associated with CD4 count. No other sociodemographic or health-related covariates were significantly associated with CD4 count. In addition, no sociodemographic or health-related covariates were significantly associated with dopamine concentration. Finally, neither perceived stress (PSS), nor depression (BDI), were significantly associated with CD4 count or dopamine concentration.

Associations Between Overall Sleep Quality, CD4 count, and Dopamine Concentration

Hierarchical regression analyses were first conducted to examine the direct effects of overall sleep quality on CD4 count and dopamine. As shown in Table 2, after controlling for depressive symptoms, stress, medication adherence, and log HIV viral load, higher PSQI global scores (indicating poorer overall sleep quality) were marginally associated with lower CD4 counts ($\beta = -.16$, $SE = 6.7$, $p = .08$). However, PSQI global scores were not significantly associated with dopamine concentration, after controlling for covariates ($\beta = -.17$, $SE = .04$, $p = .15$). Interestingly, higher levels of perceived stress were found to be significantly associated with lower CD4 counts, controlling for all health-related covariates and depression ($\beta = -.20$, $SE = 4.0$, $p = .04$).

Associations Among Sleep Disturbance, CD4 count, and Dopamine

Hierarchical regression analyses were also conducted to examine the association of sleep disturbance with CD4 count and dopamine. As shown in Table 2, after controlling for depressive symptoms, stress, medication adherence, and log HIV viral load, greater sleep disturbances were significantly associated with lower CD4 counts ($\beta = -.19$, $SE = 5.0$, $p = .03$), and were also significantly associated with lower levels of dopamine ($\beta = -.21$, $SE = .03$, $p = .05$).

Next, we examined whether dopamine explained the association between sleep disturbance and CD4 count via multiple regression analyses. Covariates were entered into the first block of the regression, followed by sleep disturbance, and finally dopamine concentration. Dopamine was not significantly associated with CD4 count. Furthermore, the addition of the dopamine to the regression model did not significantly decrease the association between sleep disturbance and CD4 count. Thus, dopamine was not found to be an intermediary variable in the relationship between sleep disturbance and CD4 count (Baron & Kenny, 1986).

Discussion

The current study results indicate a robust association between sleep disturbance and CD4 count in WLWH, which exists independently of mood, stress, HAART adherence and disease status factors. In addition, overall sleep quality may also impact CD4 count; however, our results suggest that compared to overall sleep quality, sleep disturbance may be a more salient and specific correlate of immune status in WLWH. Furthermore, our

results bolster previous findings suggesting that perceived stress is significantly related to immune status in an independent sample of WLWH (Antoni et al., 2008; Ironson et al., 2008).

Our results suggest that chronic sleep disturbance could accompany faster immune decline and progression to AIDS in ethnic minority WLWH. Because the majority of these women were low income, they may have faced more challenges to maintaining a healthy lifestyle within their built environments due to lack of access to exercise facilities and greater exposure to violence/crime (Lovasi et al., 2009), both of which may potentially impact sleep. In addition, Jean-Louis and colleagues (2008) found high prevalence of insomnia symptoms among African-American women (71%) in a multi-ethnic sample, coupled with differences in predictors of insomnia symptoms among ethnic groups. Thus, examining sleep and the detriments associated with poor sleep is integral in ethnic minority WLWH. These women also face higher levels of HIV-related stigma and higher rates of poverty than their white counterparts, both of which can significantly impact disease progression (Johnson et al., 2009; CDC, 2011). Therefore, the alleviation of sleep disturbances may represent a salient and relatively underexplored area of behavioral health intervention in this population.

In addition, while overall sleep quality was not found to be associated with dopamine levels, sleep disturbance was found to be associated with lower levels of dopamine. These results are consistent with previous work associating sleep disturbance with dopamine deficiency in other medical populations (Cohrs et al., 2004; Hornyak et al., 2012; Sasai et al., 2012). Dopamine deficiencies in WLWH could possibly lead to increased lethargy, as well as cognitive impairment (Kumar et al., 2011). Interestingly, dopamine was not found to mediate the association between sleep disturbance and CD4 count. All in all, dopamine may possibly contribute to immune status in ethnic minority WLWH; however, the mechanisms by which it does so in this population have yet to be elucidated.

Limitations and Future Directions

The current study has a number of limitations which should be acknowledged. Firstly, we examined connections among sleep, dopamine, and CD4 count using cross-sectional data; thus, the directionality of the associations we found could not be discerned. Furthermore, given the previous findings (Cohrs et al., 2004; Hornyak et al., 2012; Sasai et al., 2012), it is possible that the connections among sleep, dopamine, and CD4 count in WLWH could be reciprocal.[†] Future work should examine these connections utilizing a longitudinal design. It may also be beneficial to examine more objective measures of sleep architecture, (e.g., EEG, disordered respiration, and limb movement) to compare to subjective reports in future work. Furthermore, because our study was a secondary analysis, we only had access to CD4 count as a primary immune measure, were unable to ascertain whether our sample had clinical sleep disorders, and did not have data on the menopausal status of our sample. Future studies should focus on examining the relationship between sleep and salient immune function markers such as pro-inflammatory cytokines and c-reactive protein (CRP), as well as clinical sleep disorders and menopausal status to increase understanding of the relationship between sleep and immune functioning in WLWH.

Also, while previous work suggested that urinary dopamine excretion is reflective of central nervous system dopamine levels (Chekhonin et al., 2000; Marc et al., 2008), it is important

[†]When examining our analyses in reverse with CD4 count and urinary dopamine as independent variables and overall sleep quality and sleep disturbance as dependent variables, neither CD4 count nor urinary dopamine were significantly related overall sleep quality. However, both lower CD4 count ($r = -.21$, $SE = .02$, $p = .03$) and lower urinary dopamine ($r = -.18$, $SE = .02$, $p = .05$) were associated with greater sleep disturbance.

to acknowledge our use of urinary dopamine as a proxy measure may limit the inferences we can make about the associations between CNS dopamine, sleep, and immune status (Hinz et al., 2011). In addition, we were limited in that we had access to only one immune measure (CD4 count) and one dopamine measure. Future studies should include comprehensive neuroendocrine and immune measures when examining the relationships between sleep, immune status, and dopamine. Finally, our study utilized a sample of WLWH that was mostly African-American or Caribbean, as well as mostly middle-aged. As African-American women are disproportionately affected by HIV we sought to target this group for the current study. However, we acknowledge that our study results may not generalize to other ethnic groups of WLWH, nor to younger and older women. Future work should utilize sociodemographically diverse samples to ascertain whether the connections among sleep, dopamine, and CD4 cell count generalize across various sociodemographic groups.

Conclusion

Our study is the first to establish associations between perceived sleep disturbances and CD4 cell count, as well as perceived sleep disturbances and dopamine levels, independently of disease factors and distress in ethnic minority WLWH. Our results concerning the associations between perceived sleep disturbances, immune status, and dopamine may be relevant for other individuals living with chronic disease, especially if they are bolstered in future study. Behavioral sleep interventions in other medical populations, such as women living with breast cancer, have been found to have salutary effects on immune status (Savard et al., 2005; Smith et al., 2005). Certainly, our results highlight sleep as an extremely salient health behavior and potential target for intervention in WLWH. The associations among perceived sleep disturbances, dopamine levels, and CD4 cell count revealed by the current study suggest that that future studies should examine whether the development of improved sleep skills and patterns in ethnic minority WLWH are associated with salutary effects on both neuroendocrine and immune status in this population.

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Table 1

Socio-Demographic and Health-Related Sample Characteristics (n = 139)

	Mean (SD)/N(%)
Age	38.3 years (7.8 years)
Education Level	
Graduated from High School	79 (57%)
Graduated from College	10 (7%)
Modal Income	\$5,000–\$10,000 per year
Number of Years Post-HIV Diagnosis	7.7 years (4.5 years)
HAART Adherence	89.6% (18.3%)
Log HIV Viral Load	2.8 (1.2)
CD4 Count	484.5 cells/ μ L (303.0 cells/ μ L)
Depressive Symptoms (BDI)	11.2 (9.1)
Perceived Stress (PSS)	24.4 (7.5)
Overall Sleep Quality (PSQI)	6.9 (4.2)
Sleep Disturbance Raw Score (PSQI)	6.5 (5.4)

Table 2

Multiple Regression Demonstrating Sleep Variables as Independent Correlates of Immune Status and Urinary Dopamine Concentrations in Women Living with HIV (n = 139)

	CD4 Count		Dopamine Concentration	
	<u>(SE)</u>	<u>R²</u>	<u>(SE)</u>	<u>R²</u>
<i>Health Related Covariates</i>		.24 **		.03
Log HIV Viral Load	-.37 (21.3) **		-.03 (.12)	
Time Post HIV Diagnosis	-.22 (.47) **		.16 (.00)	
HAART Adherence	.11 (1.4)		-.01 (.01)	
<i>Psychological Covariates</i>		.03		.01
Depression (BDI)	.12 (3.2)		.06 (.02)	
Perceived Stress	-.20 (4.0) *		-.09 (.02)	
<i>Independent Variables[†]</i>				
Overall Sleep Quality	-.16 (6.7) ⁺	.02 ⁺	-.17 (.04)	.03
Sleep Disturbance Raw Score	-.19 (5.0) *	.03 *	-.21 (.03)	.04 *

[†]Independent variables were tested in separate regression models controlling for all covariates

⁺ p < .10

* p < .05

** p < .01