



Published in final edited form as:

J Assoc Nurses AIDS Care. 2020 ; 31(2): 249–254. doi:10.1097/JNC.000000000000125.

Sex-based differences in plasma cytokine concentrations and sleep disturbance relationships among people living with HIV

Scott Emory Moore, PhD, APRN, AGPCNP-BC [Assistant Professor],

Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio, USA.

Joachim G. Voss, PhD, RN, ACRN, FAAN [Professor and Director],

Sarah Cole Hirsh Institute, Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio, USA.

Allison R. Webel, PhD, RN, FAAN* [Associate Professor]

Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio, USA.

Keywords

Interferon- γ (IFN- γ); Interleukin-10 (IL-10); Tumor Necrosis Factor- α (TNF- α)

Understanding the biological underpinnings of symptoms and identifying potential biomarkers is an important part of symptom research. Genomic and hormonal activity differ by biological sex and are important biomolecular components of the complex phenomena associated with chronic disease, symptoms, and aging (vom Steeg & Klein, 2016). Sex-based differences have been identified in the immune system including differences in levels of immune and inflammatory proteins (vom Steeg & Klein, 2016). Additionally, sex-based differences in people living with HIV (PLWH) include differences in symptom profiles, severity of HIV, clinical/laboratory outcomes, antiretroviral therapy (ART) side effects, adherence, and complications (Castilho, Melekhin, & Sterling, 2014).

Sleep alterations have been linked to immune function changes in both healthy and chronically ill populations (Besedovsky, Lange, & Born, 2012; Davis & Krueger, 2012; Wirth et al., 2015). Sleep disturbance is an important symptom in PLWH and has a wide range of effects including associations with adherence and depression (Phillips et al., 2005; Taibi, 2013). Studies have linked sleep disturbance to biomarkers in PLWH, including urine dopamine, CD4+ T cell count, interleukin (IL)-13, and single nucleotide variants in inflammatory marker genes (IL-1 β , IL1R2, IL2, IL6, IL13, NF κ B1, TNFA; Gay et al., 2015). Sex-based differences in the relationship between sleep disturbance and inflammation in PLWH have not been examined. Thus, the purpose of our pilot study was to examine sex-

*Corresponding Author: Allison R. Webel, Phone: 216.368.3939, arw72@case.edu.

Conflict of Interest: The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

based differences in relationships between plasma levels of 10 key inflammation makers and self-reported sleep disturbance in PLWH.

Methods

Ethical Oversight and Protection of Study Participants

The pilot and parent studies were approved by the University Hospitals, Cleveland Medical Center Institutional Review Board, and all participants provided written informed consent prior to enrollment in the study, which included permission to store biological samples in a biorepository for future studies.

Study Design

Our cross-sectional pilot study used baseline data and accompanying plasma samples from 20 participants enrolled in a larger intervention trial that was conducted between Fall 2014 and Spring 2016 in an urban city in the Midwest United States. The parent study evaluated the influence of a behavioral intervention on cardiovascular health in PLWH; results are reported elsewhere (Webel et al., 2018). Inclusion criteria included: (a) older than 18 years of age, (b) confirmed diagnosis of HIV, (c) currently prescribed ART and at least one HIV viral load less than 400 copies/mL in the past 3 months, and (d) high lifetime risk for developing cardiovascular disease. Exclusion criteria were: (a) a contraindication for exercise per American Heart Association criteria; (b) meeting the U.S. Department of Health and Human Services recommendations for exercise; (c) having uncontrolled diabetes; (d) unable to understand spoken English; (e) pregnant or planning on becoming pregnant; (f) expect to move out of the area within 12 months; or (g) enrolled in a formal exercise, diet, or weight loss program.

The pilot study sample was selected via purposive sampling from parent study participants based on age (> 40 years); selections were made to balance biologic sex, race, and age. Additionally, participants had to have had an adequate amount of plasma stored from a baseline blood draw in the parent study. To minimize the risk of interventional influence, only baseline data were used.

Measures

PROMIS-29 Sleep Disturbance Subscale.—The PROMIS-29 Sleep Disturbance Subscale is a self-reported measure that assesses sleep quality. The subscale consists of four, 5-option (scored 1–5), Likert-type items assessing concerns with falling asleep, staying asleep, quality of sleep, and satisfaction with sleep (Yu et al., 2012). Validated in PLWH, it was found to have high internal consistency (Cronbach's α coefficient = 0.87; Schnall et al., 2017). In our pilot sample the Sleep Disturbance Subscale had a Cronbach's α coefficient = 0.85.

Detection and quantification of plasma inflammatory cytokines.—Cytokine concentrations in the plasma samples were measured in a non-CLIA-certified research lab environment using a multiplex electrochemiluminescent detection system (Meso Scale Discovery V-PLEX® Proinflammatory Panel 1 Human Kit, Meso Scale Discovery,

Rockville, Maryland). The kit simultaneously measures concentrations of 10 analytes including interferon (IFN)- γ , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and tumor necrosis factor (TNF)- α . Per manufacturer protocol, samples from participants were thawed and prepared for analysis, and then run in duplicate on the same plate. Cytokine concentrations were calculated using the MSD DISCOVERY WORKBENCH® analysis platform per manufacturer protocols.

Cytokine concentrations were evaluated for viability and detectability on an analyte-by-analyte basis. To meet the threshold of viability, reported signals from the duplicate samples from each participant had to exceed 2.5 standard deviations of the blank (null) wells. Detectability was evaluated by comparing the average of the duplicate sample concentrations with the manufacturer's reported lower limit of quantification (LLOQ) for each analyte. Average measured cytokine concentrations below the LLOQ were considered to be indistinguishable from general background noise and were entered in the dataset as 0 pg/mL. All cytokine plasma levels were described; however, only cytokines with at least 50% of values above LLOQ were included in comparative statistical analyses.

Statistical Analysis

We completed the statistical analysis using IBM SPSS Statistics Version 25 software (2017, Armonk, NY). Demographic and health characteristics of the sample were analyzed in total and by biologic sex. The measures of central tendency and frequency were reported for these measures, those with skewed data based on skewness (< -3 or > 3) were reported with median and interquartile range values. As our pilot study consisted of a small sample, sex-based differences in demographics and plasma cytokine concentrations were evaluated using Mann-Whitney U with a $p < 0.05$, considered the threshold for statistical significance. Next, relationships between detectable cytokine concentrations and sleep disturbance were evaluated by sex using Spearman's Rho correlations with bootstrapped bias corrected accelerated (BCa) confidence intervals.

Results

Sample Characteristics

In our pilot study sample ($n = 20$), 11 were women and 9 were men; 19 identified as Black. Among demographic, socioeconomic, HIV-related, metabolic, and cardiovascular measures, no significantly different characteristics were found between men and women. Selected demographic information and HIV-related measures are shown in Table 1.

PROMIS-29 Sleep Disturbance Subscale

Average t -scores for the PROMIS-29 Sleep Disturbance Subscale fell within one standard deviation of the general population standard set for the subscale. Neither the t -score nor individual item scores significantly differed by sex (See Table 1).

Sex-Based Differences in Measured Inflammatory Biomarkers

Four of the 10 measured inflammatory biomarkers, IL-13, IL-4, IL-2, and IL-1 β , did not have concentrations that met the threshold of viability and, thus, were not included in sex-

based differences calculations. Data for the remaining six markers are reported in Table 2. Only one marker differed significantly between men ($Mdn = .113$) and women ($Mdn = .292$), with women more likely to have higher IL-10 levels ($U = 77.00$, $z = 2.089$, $p = .038$, $r = .47$). The IFN- γ , IL-12p70, IL-6, IL-8, and TNF- α levels did not differ significantly between men and women ($p > 0.05$).

Correlations of Cytokines and Sleep Disturbance by Sex

We calculated Spearman's Rho correlations between sleep disturbance scores and plasma levels of IFN- γ , IL-10, IL-12p70, IL-6, IL-8, and TNF- α by sex (see Table 3). Among men, sleep disturbance scores were not significantly correlated with any of the inflammatory protein concentrations. Among women, sleep disturbance was significantly correlated to plasma concentrations of IFN- γ ($r_s = -.697$, 95% BCa CI $[-.970, -.120]$, $p = .017$) and TNF- α ($r_s = -.697$, 95% BCa CI $[-.981, -.070]$, $p = .017$).

Discussion

We demonstrated that, within our pilot sample, there were no significant differences by sex in demographic or HIV-related characteristics, nor on the PROMIS-29 Sleep Disturbance subscale ($p > 0.05$). There were, however, significant differences in plasma levels of IL-10 between the men and women in the study sample. There were also significant negative correlations between sleep disturbance and both IFN- γ and TNF- α in females, while none of the cytokine-sleep disturbance correlations were significant among males.

When we put these findings into context with previous findings of sex-based differences in markers of inflammation with and without sleep disturbances, there were some interesting consistencies and unique findings. Regardless of sleep disturbance, IL-10 was the only marker of inflammation with significant sex-based differences in our sample, and this finding was similar to sex-based differences noted in a study of PLWH by Krebs et al. (2016), who found higher plasma IL-10 levels in women compared to men, and those differences continued after 48 weeks of ART. Continued elevation of IL-10 among women living with HIV was not clearly attributed to a source; however, other studies have reported IL-10 concentrations associated with progesterone and estrogen (Klein & Flanagan, 2016; vom Steeg & Klein, 2016).

Relationships between plasma inflammatory marker levels and sleep disturbance severity differed between men and women; only two markers, TNF- α and IFN- γ , had significant correlations with sleep disturbance, and both of those significant relationships were found in women but not in men. Associations between sleep loss and TNF- α have been found (Davis & Krueger, 2012). Some animal studies described a relationship between TNF- α inhibition and disturbed or less restful sleep, those findings have not been replicated in human studies (Opp, 2005; Rockstrom et al., 2018), but the negative correlation between plasma TNF- α and sleep disturbance in the women in our pilot study sample implied a similar relationship as that identified in animal models.

One possible underlying reason for the negative correlation between plasma TNF- α and sleep disturbance could be the presence of TNF- α production and activity inhibitory

substances including glucocorticoids, estrogens, IL-4, IL-10, and IL-13 (Rockstrom et al., 2018). Sleep disturbance and TNF- α have been linked together related to a gene polymorphism, specifically TNF- α -308G>A (rs1800629), found to be associated with less severe sleep disturbance in oncology patients and their family caregivers (Illi et al., 2012). One meta-analysis found that in healthy individuals the 308G>A polymorphism did not influence mRNA or protein levels of TNF- α (Mekinian et al., 2011). Further, the functional implications for the polymorphism are not known and, while it may alter the function of TNF- α , have not been described with regard to sleep.

The study of the relationship between the immune system and sleep has uncovered some sleep-related functions for IFN- γ across varied animal models and populations (Irwin & Opp, 2017; Kwak et al., 2008; Redwine, Dang, Hall, & Irwin, 2003). We found that IFN- γ had a negative relationship with sleep disturbance for women, and this finding was similar to that of animal studies showing that IFN- γ enhanced non-rapid eye movement sleep (Opp, 2005). Another possible consideration is an alteration of the rhythmic secretions of cytokines by immune cells as a result of disturbed sleep, thus resulting in a lower than expected IFN- γ value. Cuesta, Boudreau, Dubeau-Laramée, Cermakian, and Boivin (2016) found distinct release patterns for IFN- γ (night-time) and TNF- α (night-time and day-time pattern) and both cytokine release patterns shifted by 4.5 to 6 hours following the simulation of night shift sleep patterns, although their study had a small sample ($n = 9$) with only one woman, so these patterns may not fully represent both sexes.

Limitations

These results provide an initial look at possible sex-based differences among PLWH and relationships between inflammatory biomarkers and sleep disturbance, but some study limitations exist. Most importantly, our study had a small sample and was not sufficiently powered to do more complex analyses or control for potential confounders. This does not mean that our results do not offer some support for future investigation of sex-based differences in sleep and inflammation markers in PLWH. Additionally, sleep disturbance and plasma inflammatory marker concentrations may change over time, so the use of a single time point was a limitation. Single time point studies are not the gold standard for sleep biomarkers, and some have suggested multiple collections through the day and night (Besedovsky et al., 2012; Davis & Krueger, 2012). Outside of polysomnography or actigraphy while sleeping, we relied on subjective, self-report measures for sleep disturbance. The PROMIS-29 Sleep Disturbance Subscale offered a general understanding of sleep, but other tools might probe aspects of sleep beyond the subscale's scope. Additionally, some studies have examined other sources to quantify inflammatory markers (e.g., cerebrospinal fluid, cellular cytokine production potentials, neural tissue) and so, as plasma is not as central to the nervous system and depicts the extracellular concentrations of analytes, the results, while still comparable, may not be the same.

Conclusion

We provide a first look at sex-based differences in sleep-inflammation biomarker relationships in PLWH, and the findings warrant further exploration because of similarities

to findings in other studies. Nurses and clinicians should be aware of possible sex-based differences when evaluating symptoms (even common ones) and considering possible relationships to other biological processes (e.g., inflammatory and immune responses). As nursing science continues to work toward better understanding of patient symptom experiences, finding objective biomarkers to support the design, targeting, and monitoring of interventions is an important next step. In the pursuit of symptom biomarkers, as in the care of patients, we must consider the person-specific differences that may change the biologic context in which we observe relationships between symptoms and biomarkers. In general, the connections between sleep, inflammation, and immunity are much more complex than a single time point and single marker, and the complexity of these relationships warrants approaches that can fully appreciate the contributions of the many interdependent factors. The relationships between estrogen and some inflammatory markers have been a topic of much study and while these studies have varied findings, estrogen's dual-nature, having the capability of being both pro- and anti-inflammatory, leaves many questions open for further study (Au et al., 2016; Enns & Tiidus, 2010; Störk, van der Schouw, Grobbee, & Bots, 2004; Straub, 2007; Viña, Gambini, García-García, Rodríguez-Mañas, & Borrás, 2013). Subsequently, it must be asked if we should anticipate changes in the course and nature of symptoms and/or inflammatory markers in post-menopausal women living with HIV, and what forms might those changes take. Further, some of our female participants were post-menopausal so we may also need to ask what could be keeping the estrogen-linked inflammatory markers (e.g., IL-10) elevated in the plasma of those women. Even if we could remove the influence of estrogen on the physiological processes related to immune and inflammatory responses, the chronic immune activation that has been well documented in HIV makes aging and age-related alterations another key consideration (Hearps, Schafer, High, & Landay, 2016). While our pilot study was not complex, we believe that the results offer new directions that may be of importance in increasing clinical considerations and biopsychosocial understandings of the symptom experiences of patients, especially how biologic sex must be considered in symptom science.

Acknowledgements:

The authors acknowledge the substantial and invaluable contributions of the participants who made this research possible. This work was supported by the American Heart Association (grant number 14CRP20380259, PI: Webel), a developmental grant from the National Institutes of Health funded University Hospitals/Case Western Reserve University Center for AIDS Research (grant number P30 AI036219, PI: Karn), and also by National Institutes of Health (grant numbers UL1 RR024989, PI: Davis; T32 NR015433, PI: Moore; R01 NR018391, PI: Webel). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

References

- Au A, Feher A, McPhee L, Jessa A, Oh S, & Einstein G (2016). Estrogens, inflammation and cognition. *Frontiers in Neuroendocrinology*, 40, 87–100. doi.10.1016/j.yfrne.2016.01.002 [PubMed: 26774208]
- Besedovsky L, Lange T, & Born J (2012). Sleep and immune function. *Pflügers Archiv - European Journal of Physiology*, 463(1), 121–137. doi.10.1007/s00424-011-1044-0 [PubMed: 22071480]
- Castilho JL, Melekhin VV, & Sterling TR (2014). Sex differences in HIV outcomes in the highly active antiretroviral therapy era: A systematic review. *AIDS Research and Human Retroviruses*, 30(5), 446–456. doi.10.1089/aid.2013.0208 [PubMed: 24401107]

- Cuesta M, Boudreau P, Dubeau-Laramée G, Cermakian N, & Boivin DB (2016). Simulated night shift disrupts circadian rhythms of immune functions in humans. *Journal of Immunology*, 10.4049/jimmunol.1502422
- Davis CJ, & Krueger JM (2012). Sleep and cytokines. *Sleep Medicine Clinics*, 7(3), 517–527. [PubMed: 25177229]
- Enns DL, & Tiidus PM (2010). The influence of estrogen on skeletal muscle: Sex matters. *Sports Medicine*, 40(1), 41–58. doi.10.2165/11319760-000000000-00000 [PubMed: 20020786]
- Gay CL, Zak RS, Lerdal A, Pullinger CR, Aouizerat BE, & Lee KA (2015). Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS. *Brain, Behavior, and Immunity*, 47, 58–65. doi.10.1016/j.bbi.2014.11.018
- Hearps A, Schafer K, High K, & Landay A (2016). HIV and aging: Parallels and synergistic mechanisms leading to premature disease and functional decline In Sierra F & Kohanski R (Eds.), *Advances in geroscience* (pp. 509–550). New York City, NY: Springer International Publishing.
- Illi J, Miaskowski C, Cooper B, Levine JD, Dunn L, West C, ... Aouizerat BE (2012). Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. *Cytokine*, 58(3), 437–447. doi.10.1016/j.cyto.2012.02.015 [PubMed: 22450224]
- Irwin MR, & Opp MR (2017). Sleep health: Reciprocal regulation of sleep and innate immunity. *Neuropsychopharmacology*, 42(1), 129–155. doi.10.1038/npp.2016.148 [PubMed: 27510422]
- Klein SL, & Flanagan KL (2016). Sex differences in immune responses. *Nature Reviews Immunology*, 16(10), 626–638. doi.10.1038/nri.2016.90
- Krebs SJ, Slike BM, Sithinamsuwan P, Allen IE, Chalermchai T, Tipsuk S, ... Valcour VG (2016). Sex differences in soluble markers vary before and after the initiation of antiretroviral therapy in chronically HIV infected individuals. *AIDS*, 30(10), 1533–1542. doi.10.1097/QAD.0000000000001096 [PubMed: 26990631]
- Kwak Y, Lundkvist GB, Brask J, Davidson A, Menaker M, Kristensson K, & Block GD (2008). Interferon- γ alters electrical activity and clock gene expression in suprachiasmatic nucleus neurons. *Journal of Biological Rhythms*, 23(2), 150–159. doi.10.1177/0748730407313355 [PubMed: 18375864]
- Mekinian A, Tamouza R, Pavy S, Gestermann N, Ittah M, Mariette X, & Miceli-Richard C (2011). Functional study of TNF- α promoter polymorphisms: Literature review and meta-analysis. *European Cytokine Network*, 22(2), 88–102. doi.10.1684/ecn.2011.0285 [PubMed: 21768061]
- Opp MR (2005). Cytokines and sleep. *Sleep Medicine Reviews*, 9(5), 355–364. doi.10.1016/j.smrv.2005.01.002 [PubMed: 16102986]
- Phillips KD, Moneyham L, Murdaugh C, Boyd MR, Tavakoli A, Jackson K, & Vyavaharkar M (2005). Sleep disturbance and depression as barriers to adherence. *Clinical Nursing Research*, 14(3), 273–293. doi.10.1177/1054773805275122 [PubMed: 15995155]
- Redwine L, Dang J, Hall M, & Irwin M (2003). Disordered sleep, nocturnal cytokines, and immunity in alcoholics. *Psychosomatic Medicine*, 65(1), 75–85. doi.10.1097/01.PSY.0000038943.33335.D2 [PubMed: 12554818]
- Rockstrom MD, Chen L, Taishi P, Nguyen JT, Gibbons CM, Veasey SC, & Krueger JM (2018). Tumor necrosis factor alpha in sleep regulation. *Sleep Medicine Reviews*, 40, 69–78. doi.10.1016/j.smrv.2017.10.005 [PubMed: 29153862]
- Schnall R, Liu J, Cho H, Hirshfield S, Siegel K, & Olender S (2017). A health-related quality-of-life measure for use in patients with HIV: A validation study. *AIDS Patient Care and STDs*, 31(2), 43–48. doi.10.1089/apc.2016.0252 [PubMed: 28051875]
- Störk S, van der Schouw YT, Grobbee DE, & Bots ML (2004). Estrogen, inflammation and cardiovascular risk in women: A critical appraisal. *Trends in Endocrinology & Metabolism*, 15(2), 66–72. doi.10.1016/j.tem.2004.01.005 [PubMed: 15036252]
- Straub RH (2007). The complex role of estrogens in inflammation. *Endocrine Reviews*, 28(5), 521–574. doi.10.1210/er.2007-0001 [PubMed: 17640948]
- Taibi DM (2013). Sleep disturbances in persons living with HIV. *Journal of the Association of Nurses in AIDS Care*, 24(Suppl. 1), S72–S85. doi.10.1016/j.jana.2012.10.006 [PubMed: 23290379]

- Viña J, Gambini J, García-García FJ, Rodríguez-Mañas L, & Borrás C (2013). Role of oestrogens on oxidative stress and inflammation in ageing. *Hormone Molecular Biology and Clinical Investigation*, 16(2), 65–72. doi:10.1515/hmbci-2013-0039 [PubMed: 25436748]
- vom Steeg LG, & Klein SL (2016). SeXX matters in infectious disease pathogenesis. *PLOS Pathogens*, 12(2), e1005374. doi:10.1371/journal.ppat.1005374 [PubMed: 26891052]
- Webel AR, Moore SM, Longenecker CT, Currie J, Davey CH, Perazzo J, ... Josephson RA (2018). Randomized controlled trial of the SystemCHANGE intervention on behaviors related to cardiovascular risk in HIV+ adults: *Journal of Acquired Immune Deficiency Syndromes*, 78(1), 23–33. doi:10.1097/QAI.0000000000001635 [PubMed: 29373392]
- Wirth MD, Jagers JR, Dudgeon WD, Hébert JR, Youngstedt SD, Blair SN, & Hand GA (2015). Association of markers of inflammation with sleep and physical activity among people living with HIV or AIDS. *AIDS and Behavior*, 19(6), 1098–1107. doi:10.1007/s10461-014-0949-y [PubMed: 25399034]
- Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, ... Pilkonis PA (2012). Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. *Behavioral Sleep Medicine*, 10(1), 6–24. doi:10.1080/15402002.2012.636266

Table 1

Sample Characteristics and PROMIS-29 Sleep Disturbance Scale Scores

Characteristic	Total	Female	Male	<i>p</i> -value
<i>N</i> (%)	20	11 (55%)	9 (45%)	
Age	52.6 (5.96)	52.0 (5.12)	53.3 (7.09)	.456
Years with HIV	14.5 (1.34)	15.5 (4.58)	12.8 (6.52)	.428
Years on ART	11.9 (1.75)	13.8 (6.18)	9.2 (7.25)	.181
CD4+ T Cell Count (cells/ μ L)	812.9 (427.2)	817.7 (503.7)	805.0 (301.1)	.792
Viral Load ^a (copies/mL)	20 (0)	20 (0)	20 (12.75)	.313
CD4+ T cell Nadir (cells/ μ L)	269.5 (184.0)	201.9 (126.2)	382.2 (220.2)	.792
Number of Co-morbidities	5.90 (6.67)	7.91 (8.04)	3.44 (3.54)	.175
Sleep Disturbance Scale	52.17 (9.22)	53.65 (10.54)	50.36 (7.50)	.230
Sleep Quality	2.80 (1.06)	3.09 (1.14)	2.44 (0.88)	.201
Sleep was Refreshing	2.85 (1.09)	3.09 (1.22)	2.56 (0.88)	.230
Problem with Sleep	2.90 (1.41)	3.27 (1.49)	2.44 (1.24)	.201
Difficulty Falling Asleep	2.75 (1.37)	2.73 (1.49)	2.78 (1.30)	.941

Note. mean (standard deviation) unless noted; *p*-values from Mann-Whitney U by sex; ART = antiretroviral therapy.

^aMedian (interquartile range) used for skewed data

Table 2

Inflammatory Cytokine Plasma Concentrations (pg/mL)

	Total	Female	Male	P-value
IFN- γ^a	2.755 (2.464)	3.799 (7.616)	2.269 (0.999)	.152
IL-10 ^a	0.185 (0.281)	0.292 (0.256)	0.113 (0.206)	.038*
IL-12p70	0.106 (0.139)	0.073 (0.107)	0.1461 (0.170)	.261
IL-6	0.892 (0.548)	0.878 (0.619)	0.910 (0.484)	.941
IL-8 ^a	4.493 (3.832)	4.409 (4.722)	4.576 (3.581)	.824
TNF- α	2.876 (1.275)	3.279 (1.520)	2.384 (0.690)	.131

Note: Entries represent mean (standard deviation) unless otherwise noted; *p*-values from Mann-Whitney U tests by sex;

* $p < 0.05$;

IFN- γ = interferon gamma; IL-10 = interleukin 10; IL-12p70 = interleukin 12 active heterodimer; IL-6 = interleukin 6; IL-8 = interleukin 8; TNF- α = tumor necrosis factor- α .

^aMedian (interquartile range) used for skewed data

Table 3

Cytokine Plasma Correlations with Sleep Disturbance

	Total	Female	Male
IFN- γ	-.140	-.697*	.542
IL-10	-.089	-.164	-.542
IL-12p70	-.078	.022	-.069
IL-6	.086	-.405	.661
IL-8	.267	.383	.102
TNF- α	-.357	-.697*	-.220

Note. Spearman Rho Correlations displayed by sex;

*
 $p < .05$;

IFN- γ = interferon gamma; IL-10 = interleukin 10; IL-12p70 = interleukin 12 active heterodimer; IL-6 = interleukin 6; IL-8 = interleukin 8; TNF- α = tumor necrosis factor- α .

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript