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Sex-Based Differences in Plasma Cytokine Concentrations and Sleep Disturbance Relationships Among People Living With HIV

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Understanding the biological underpinnings of symptoms and identifying potential biomarkers is an important part of symptom research. Genomic and hormonal activities 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-1β, IL-1R2, IL-2, IL-6, IL-13, NF-κB1, tumor necrosis factor (TNF)-A; 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-based differences in relationships between plasma levels of 10 key inflammation makers and self-reported sleep disturbance in PLWH.

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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 before 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

Patient-Reported Outcomes Measurement Information System (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 of 0.85.

Detection and quantification of plasma inflammatory cytokines. Cytokine concentrations in the plasma samples were measured in a non–Clinical Laboratory Improvement Amendments-certified research laboratory environment using a multiplex electrochemiluminscent 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-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and 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 *SD*s 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 indifferentiable from general background noise and were entered in the data set 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, and those with skewed data based on skewness (<-3 or >3) were reported with median and interquartile range values. Because our pilot study consisted of a small sample, sex-based differences in demographics and plasma cytokine concentrations were evaluated using Mann–Whitney *U* test with a p of $<.05$, 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 were 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 *SD* of the general population standard set for the subscale. Neither the *t*-score nor individual item scores significantly differed by sex (Table 1).

Sex-Based Differences in Measured Inflammatory Biomarkers

Four of the 10 measured inflammatory biomarkers, IL-13, IL-4, IL-2, and IL-1β, 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 ($p > .05$).

Table 1. Sample Characteristics and PROMIS-29 Sleep Disturbance Scale Scores

Characteristic	Total	Female	Male	*p*-Value
N (%)	20	11 (55%)	9 (45%)	
Age, years	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/μL)	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/μL)	269.5 (184.0)	201.9 (126.2)	382.2 (220.2)	.792
No. 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 (*SD*) unless noted; *p*-values from Mann–Whitney *U* by sex; ART = antiretroviral therapy; PROMIS = Patient-Reported Outcomes Measurement Information System.
[a] Median (interquartile range) used for skewed data.

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 (Table 3). Among men, sleep disturbance scores did not significantly correlate with any of the inflammatory protein concentrations. Among women, sleep disturbance correlated significantly with plasma concentrations of IFN-γ ($r_s = -.697$; 95% BCa CI, −.970 to −.120; $p = .017$) and TNF-α ($r_s = -.697$; 95% BCa CI, −.981 to −.070; $p = .017$).

Discussion

We demonstrated that within our pilot sample, no significant differences was found by sex in demographic or HIV-related characteristics nor on the PROMIS-29

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 (*SD*) unless otherwise noted. *p*-values from Mann–Whitney *U* tests 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.
[a] Median (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. Significant values are indicated by boldface. *$p < .05$. 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.

Sleep Disturbance subscale ($p > .05$). There were, however, significant differences in plasma levels of IL-10 between the men and women in the study sample. Also, significant negative correlations were found between sleep disturbance and both IFN-γ and TNF-α in women, whereas none of the cytokine–sleep disturbance correlations were significant among men.

When we put these findings into context with previous findings of sex-based differences in markers of inflammation with and without sleep disturbances, some interesting consistencies and unique findings were observed. 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 with 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) is 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). Furthermore, the functional implications for the polymorphism are not known, and although it may alter the function of TNF-α, they 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 of 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; 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 because 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 although 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, Rodriguez-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 postmenopausal women living with HIV and what forms might those changes take. Furthermore, some of our female participants were on postmenopausal period, 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). Although 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.

Disclosures

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

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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

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

Castilho, J. L., Melekhin, V. V., & Sterling, T. R. (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

Cuesta, M., Boudreau, P., Dubeau-Laramée, G., Cermakian, N., & Boivin, D. B. (2016). Simulated night shift disrupts circadian rhythms of immune functions in humans. *Journal of Immunology*, 1502422. doi.10.4049/jimmunol.1502422

Davis, C. J., & Krueger, J. M. (2012). Sleep and Cytokines. *Sleep Medicine Clinics*, *7*(3), 517-527.

Enns, D. L., & Tiidus, P. M. (2010). The influence of estrogen on skeletal muscle: sex matters. *Sports Medicine*, *40*(1), 41-58. doi.10.2165/11319760-000000000-00000

Gay, C. L., Zak, R. S., Lerdal, A., Pullinger, C. R., Aouizerat, B. E., & Lee, K. A. (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, J. D., Dunn, L., West, C., … Aouizerat, B. E. (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

Irwin, M. R., & Opp, M. R. (2017). Sleep health: Reciprocal regulation of sleep and innate immunity. *Neuropsychopharmacology*, *42*(1), 129-155. doi.10.1038/npp.2016.148

Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. *Nature Reviews. Immunology*, *16*(10), 626-638. doi.10.1038/nri.2016.90

Krebs, S. J., Slike, B. M., Sithinamsuwan, P., Allen, I. E., Chalermchai, T., Tipsuk, S., … Valcour, V. G. (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

Kwak, Y., Lundkvist, G. B., Brask, J., Davidson, A., Menaker, M., Kristensson, K., & Block, G. D. (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

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.org/10.1684/ecn.2011.0285

Opp, M. R. (2005). Cytokines and sleep. *Sleep Medicine Reviews*, *9*(5), 355-364. doi.10.1016/j.smrv.2005.01.002

Phillips, K. D., Moneyham, L., Murdaugh, C., Boyd, M. R., 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

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

Rockstrom, M. D., Chen, L., Taishi, P., Nguyen, J. T., Gibbons, C. M., Veasey, S. C., & Krueger, J. M. (2018). Tumor necrosis factor alpha in sleep regulation. *Sleep Medicine Reviews*, *40*, 69-78. doi.10.1016/j.smrv.2017.10.005

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 STDS*, *31*(2), 43-48. doi.10.1089/apc.2016.0252

Störk, S., van der Schouw, Y. T., Grobbee, D. E., & Bots, M. L. (2004). Estrogen, inflammation and cardiovascular risk in women: a critical appraisal. *Trends in Endocrinology and Metabolism: TEM*, *15*(2), 66-72. doi.10.1016/j.tem.2004.01.005

Straub, R. H. (2007). The complex role of estrogens in inflammation. *Endocrine Reviews*, *28*(5), 521-574. doi.10.1210/er.2007-0001

Taibi, D. M. (2013). Sleep disturbances in persons living with HIV. *The Journal of the Association of Nurses in AIDS Care: JANAC*, *24*(Suppl 1), S72–S85. doi.10.1016/j.jana.2012.10.006

Viña, J., Gambini, J., García-García, F. J., Rodriguez-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

vom Steeg, L. G., & Klein, S. L. (2016). SeXX matters in infectious disease pathogenesis. *PLoS Pathogens*, *12*(2), e1005374. doi.10.1371/journal.ppat.1005374

Webel, A. R., Moore, S. M., Longenecker, C. T., Currie, J., Davey, C. H., Perazzo, J., … Josephson, R. A. (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

Wirth, M. D., Jaggers, J. R., Dudgeon, W. D., Hébert, J. R., Youngstedt, S. D., Blair, S. N., & Hand, G. A. (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

Yu, L., Buysse, D. J., Germain, A., Moul, D. E., Stover, A., Dodds, N. E., … Pilkonis, P. A. (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

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