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Cho, Hyong Jin
Savitz, Jonathan
Dantzer, Robert
et al.

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Sleep Disturbance and Kynurenine Metabolism in Depression

Hyong Jin Cho^a, Jonathan Savitz^{b,c}, Robert Dantzer^d, T. Kent Teague^e, Wayne C. Drevets^f, and Michael R. Irwin^a

^aCousins Center for Psychoneuroimmunology, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

^bLaureate Institute for Brain Research, Tulsa, OK

^cOxley College of Health Sciences, The University of Tulsa, Tulsa, OK

^dDepartment of Symptom Research, Division of Internal Medicine, University of Texas MD Anderson Cancer Center, Houston, TX

^eDepartment of Surgery, University of Oklahoma College of Medicine, Tulsa OK

^fJanssen Pharmaceuticals of Johnson & Johnson, Titusville, NJ

Abstract

Objective—Although the interrelationships between sleep disturbance, inflammation, and depression have been found, molecular mechanisms that link these conditions are largely unknown. Kynurenine metabolism is hypothesized to be a key mechanism that links inflammation and depression. Inflammation activates the kynurenine pathway, leading to increases in 3-hydroxykynurenine (3HK) and quinolinic acid (QA), potentially neurotoxic metabolites, and decreases in kynurenic acid (KynA), a potentially neuroprotective compound. This relative neurotoxic shift in the balance of kynurenine metabolites has been associated with depression, but never been examined regarding sleep disturbance. We tested the association between sleep disturbance and this relative neurotoxic shift in 68 currently depressed, 26 previously depressed, and 66 never depressed subjects.

Methods—Sleep disturbance was assessed using the Pittsburgh Sleep Quality Index. Serum concentrations of kynurenine metabolites were measured using high performance liquid chromatography. Putative neuroprotective indices reflecting the relative activity of neuroprotective and neurotoxic kynurenine metabolites were calculated as KynA/QA and KynA/3HK (primary outcomes).

Results—Sleep disturbance was associated with reduced KynA/QA in the currently depressed group only (unadjusted beta -0.43 , $p < 0.001$). This association remained significant even after

Corresponding author: Dr. Cho, 300 UCLA Medical Plaza, Suite 3200A, Los Angeles, CA 90095, hjcho@mednet.ucla.edu.

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CONFLICT OF INTEREST

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controlling for age, sex, analysis batch, body-mass index, and depressive symptoms in currently depressed subjects (adjusted beta -0.30 , $p=0.02$). There was no significant association between sleep disturbance and KynA/3HK in any of the groups. Sleep disturbance was associated with increased C-reactive protein in currently depressed subjects only (unadjusted beta 0.38 , $p=0.007$; adjusted beta 0.33 , $p=0.02$).

Conclusion—These data support the hypothesis that altered kynurenine metabolism may molecularly link sleep disturbance and depression.

Keywords

sleep disturbance; inflammation; depression; kynurenine pathway; kynurenine acid; quinolinic acid

1. INTRODUCTION

Sleep disturbance, characterized as insomnia complaints and extremes of sleep duration, has a major public health impact because approximately 25% of the US population report insomnia symptoms [1] and almost 10% fulfill diagnostic criteria for chronic insomnia [2–4]. Furthermore, sleep disturbance increases the risk of several major medical and mental illnesses including infectious disease, cardiovascular disease, cancer, and depression, ultimately contributing to all-cause mortality [5–10]. Depression by itself is also a major public health burden because it is highly prevalent—the lifetime prevalence of major depression is almost 20% in the US general population [11]—and it represents a leading cause of disability worldwide [12].

Although sleep disturbance is an important risk factor for depression [7, 13, 14] and thus a prime target for depression prevention [15, 16], the mechanisms underlying this association remain poorly understood. Inflammation is one potential mechanism underlying the relationship between sleep and depression; sleep disturbance increases inflammation [17–23], which in turn causally contributes to or is intimately associated with certain forms of depression occurring in the context of immune-activating treatments (e.g., interferon- α) or chronic diseases (e.g., cardiovascular, infectious, and autoimmune) [24–26]. Poor sleep quality strongly predicts risk for developing major depressive disorder during interferon- α treatment [27]. We have shown that preexisting mild sleep disturbance increases vulnerability to inflammation-induced depression in a human experimental model using endotoxin [28]. However, the downstream molecular mechanisms underlying the link between sleep disturbance, inflammation, and depression are not yet clear.

Inflammatory mediators activate indoleamine 2,3 dioxygenase (IDO), an enzyme that metabolizes tryptophan (TRP) to kynurenine (KYN); hence the ratio of kynurenine/tryptophan (KYN/TRP) represents a measure of IDO activity. In turn, KYN is metabolized into 3-hydroxykynurenine (3HK) by the enzyme kynurenine monooxygenase (KMO), which is also upregulated under inflammatory conditions [29, 30], leading to an increase in quinolinic acid (QA) on the putatively neurotoxic branch of the kynurenine pathway (Figure 1). Concurrently, these inflammation-induced metabolic steps lead to a relative decrease in kynurenine acid (KynA) on the putatively neuroprotective branch of the kynurenine pathway. While 3HK is a free radical generator and QA is an N-methyl-D-aspartate (NMDA) receptor

agonist that has been associated with a plethora of neurotoxic effects, KynA is an antagonist of NMDA receptors [31, 32] and is protective against the excitotoxic action of QA [33, 34]. Neuroprotective indices of kynurenine metabolites calculated as KynA/QA and KynA/3HK reflect the relative activity of the two distinct branches of the kynurenine pathway [35]. Activation of glutamate receptors—specifically NMDA receptors—by excessive QA could conceivably cause neuronal damage through the process of excitotoxicity, ultimately leading to the development of depression [36].

Kynurenine metabolism is increasingly recognized as a potential mechanistic pathway in the link between inflammation and depression. For example, when activation of the kynurenine pathway is genetically or pharmacologically blocked, systemic immune stimulation (i.e., lipopolysaccharide administration) fails to induce depression-like behavior in rodents, which would otherwise occur following increases in levels of pro-inflammatory cytokines [37, 38]. Similarly, in studies of patients with inflammatory diseases or patients treated with interferon- α , there is a robust association between depressive symptoms and the production of neurotoxic kynurenine metabolites, implicating the kynurenine pathway as a potential mechanism [39–41]. Additionally, several cross-sectional studies have reported that patients with depressive spectrum disorders, including major depression [42, 43], bipolar depression [44], and suicidality [45, 46], display a decrease in KynA and/or an increase in 3HK or QA in blood [42–44] and CSF [45, 46]. Further, electroconvulsive therapy was demonstrated to significantly reduce QA [43] and increase KynA as well as KynA/3HK [47] in patients with depression. However, it should be noted that there have also been more nuanced or negative findings regarding the role of the kynurenine pathway in depression pathophysiology. For example, in one study, somatization but not depression was characterized by disorders in the kynurenine pathway [48]; and in another study, kynurenine pathway markers were not significantly different between patients with major depressive disorder and healthy controls [49].

In sum, sleep disturbance is associated with higher levels of inflammation [17], and kynurenine metabolism is increasingly recognized as a potential pathway linking inflammation to depression [50]. However, the relationship between sleep disturbance and kynurenine metabolism has never been examined in depressed subjects. This study aimed to examine the associations between sleep disturbance and kynurenine metabolism in currently depressed, previously depressed, and never depressed subjects. We hypothesized that sleep disturbance would be associated with reduced neuroprotective indices of circulating kynurenine metabolites (i.e., reductions in the ratio of neuroprotective KynA relative to neurotoxic 3HK and QA). We tested this hypothesis in currently depressed, previously depressed, and never depressed subjects using a cross-sectional study design. Furthermore, consistent with prior findings, we hypothesized that sleep disturbance would be associated with increased systemic inflammation as assessed by circulating high-sensitivity C-reactive protein (hs-CRP). Lastly, the associations between sleep disturbance and biomarkers of inflammation and kynurenine metabolism would be stronger among currently depressed subjects compared to previously depressed and never depressed subjects, given the increased severity of sleep disturbance in those who are currently depressed.

2. METHODS

2.1. Participants

One hundred sixty participants completed this study, composed of 68 currently depressed, 26 previously depressed, and 66 never depressed subjects. Participants were recruited through a variety of sources including: the clinical services of the Laureate Psychiatric Clinic and Hospital (LPCH), newspaper, flyer, radio, Facebook or other media advertisements in the Tulsa metropolitan area. Subjects provided written informed consent after receiving a full explanation of the study procedures and risks, as approved by the IRB overseeing the study. All subjects were interviewed with the Structured Clinical Interview for the DSM-IV-TR (SCID). Additionally, in order to confirm the SCID diagnosis, unstructured psychiatric interviews with board-certified psychiatrists were obtained on all currently and previously depressed subjects, who met the criteria for current and prior major depressive disorder (MDD) respectively. The majority of the currently depressed subjects had Montgomery-Asberg Depression Rating Scale (MADRS) scores in the moderately-to-severely depressed range. Previously depressed subjects were not only required to meet DSM-IV-TR criteria for full remission but were also asymptomatic at the time of the study with a MADRS score of <10 (corresponding to the non-depressed range). Currently and previously depressed subjects had not received any psychotropic medication for at least 4 weeks (8 weeks for fluoxetine) prior to the blood draw. Exclusion criteria were as follows: suicidal ideation or behavior; medical conditions or concomitant medications likely to influence central nervous system or immunological function including cardiovascular, respiratory, endocrine and neurological diseases, and a history of drug or alcohol abuse within 6 months or a history of drug or alcohol dependence within 1 year. Never depressed subjects met the same exclusion criteria except that they had no personal or family (first-degree relatives) history of psychiatric illness assessed using the Structured Clinical Interview for the DSM- IV-TR and the Family Interview for Genetic Studies. We have previously reported between-group differences in serum concentrations of kynurenine metabolites in 49 of the currently depressed, 21 of the previously depressed, and 58 of the never depressed subjects [51], as well as associations between kynurenine metabolites and hippocampal and amygdalar volumes in 29 of the currently depressed and 20 of the never depressed subjects [52]. However, the previous analyses did not consider sleep disturbance; furthermore, the present study included more participants (32 more than the former and 111 more than the latter).

2.2. Procedures

Sleep disturbance, the primary exposure variable, was assessed using the Pittsburgh Sleep Quality Index (PSQI), which interrogates subjects about sleep behaviors and sleep complaints during the last month. For biomarker assessment, the subjects fasted overnight and blood was sampled between 8 am and 11 am. Serum samples were collected with BD Vacutainer serum tubes, processed according to the standard BD Vacutainer protocol, and stored at -80°C . Concentrations of TRP, KYN, KynA, 3HK, and QA were measured blind to diagnosis by Brains Online, LLC in 2 separate batches. The metabolite concentrations were determined by high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection using their standard protocols. The intra-assay and inter-

assay coefficients of variation have been previously reported [51]. KYN/TRP was used as a surrogate marker of IDO activity. KynA/QA and KynA/3HK were used as *neuroprotective indices of kynurenine metabolites*; these were considered *the primary outcome variables* because the main hypothesis was that sleep disturbance would be associated with reduced neuroprotective indices of circulating kynurenine metabolites. High sensitivity CRP was measured in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory with an immunoturbidimetric assay (the Kamiya Biomedical K-Assay, Abbott c8000 System). The analytical measurement range for the assay is 0.2 mg/L to 480.0 mg/L.

2.3. Statistical Analysis

Deviations from normality were assessed using the Skewness and Kurtosis test, and non-normally distributed variables were natural log transformed. Sample characteristics were compared across the diagnostic groups using χ^2 -test or ANOVA. Associations between sleep disturbance (PSQI total score as a continuous variable) and the outcome variables (i.e., primary and secondary outcome variables) were examined using linear regression analysis, first in the entire sample and then in each diagnostic group separately. Given the differences in the group characteristics, in particular regarding the severity of sleep disturbance and depression, we focused on the findings in the individual diagnostic groups. Primary outcome variables were KynA/QA and KynA/3HK. Secondary outcome variables were hs-CRP, TRP, KYN, KYN/TRP, KynA, 3HK, and QA. Multivariable analyses were conducted for the primary outcome variables and hs-CRP. Covariates for multivariable linear regression included sex, age, analysis batch, body-mass index (BMI), diagnosis (currently, previously, or never depressed), and depressive symptoms. Because sleep disturbance was the primary exposure variable, MADRS score calculated without the single sleep item was used as a covariate for the purpose of statistical analysis, representing depressive symptoms. Additionally, the associations between sleep disturbance as a binary variable, defined using the PSQI cutoff (≤ 5 vs. >5), and the primary outcome variables were examined using linear regression. For the primary outcomes, a statistical threshold of $p < 0.05$ was used for determining statistical significance, whereas for the secondary outcomes, a Bonferroni correction for multiple testing was used ($p < 0.008$).

3. RESULTS

3.1. Sample Characteristics

Sample characteristics according to each diagnostic group are shown in Table 1. As expected, currently depressed subjects were more sleep-disturbed ($df=2$, $F=127$, $p < 0.0001$) and more depressed ($df=2$, $F=495$, $p < 0.0001$) compared to never depressed and previously depressed subjects. No other characteristic significantly differed across the diagnostic groups. The KynA/QA and KynA/3HK ratios were normally distributed. In contrast, hs-CRP, KYN/TRP, and all the individual kynurenine metabolites were non-normally distributed and therefore natural log transformed.

3.2. Sleep Disturbance and Kynurenine Metabolism

3.2.1. Entire Sample—In the entire sample, sleep disturbance was significantly associated with reduced TRP (unadjusted beta -0.23 , $p=0.003$) and reduced KynA levels (unadjusted

beta -0.22 , $p=0.005$) (Table 2). There was a trend toward significance—given the adoption of a Bonferroni correction—in the association between sleep disturbance and increased KYN/TRP (unadjusted beta 0.16 , $p=0.04$). Sleep disturbance was also significantly associated with reduced KynA/QA (unadjusted beta -0.22 , $p=0.005$) and KynA/3HK (unadjusted beta -0.24 , $p=0.002$), indicating a relative neurotoxic shift in the balance of kynurenine metabolites. In multivariable linear regression analyses that adjusted for sex, age, analysis batch, BMI, diagnosis, and depressive symptoms, the association remained significant for KynA/QA (adjusted beta -0.31 , $p=0.02$) but not for KynA/3HK (adjusted beta -0.20 , $p=0.13$).

When the analyses were repeated using sleep disturbance as a binary variable, the results were similar. For example, for the entire sample, both putative neuroprotective indices were significantly lower in sleep-disturbed subjects (unadjusted beta for KynA/QA -0.19 , $p=0.02$; unadjusted beta for KynA/3HK -0.16 , $p=0.04$). After adjusting for all the covariates, the association remained significant for KynA/QA (adjusted beta -0.23 , $p<0.05$) but not for KynA/3HK (adjusted beta -0.06 , $p=0.60$).

3.2.2. Each Diagnostic Group—As shown in Table 2 and Figure 2, when analyzed in each diagnostic group separately, the only variable significantly associated with sleep disturbance was KynA/QA in currently depressed subjects (unadjusted beta -0.43 , $p<0.001$). Again only in the currently depressed group, there was a trend toward significance—given the adoption of a Bonferroni correction—in the associations between sleep disturbance and increased QA (unadjusted beta 0.16 , $p=0.04$) and between sleep disturbance and reduced KynA/3HK (unadjusted beta -0.22 , $p=0.07$). In multivariable linear regression analyses that adjusted for sex, age, analysis batch, BMI, and depressive symptoms, the association between sleep disturbance and KynA/QA was significant in currently depressed subjects (adjusted beta -0.30 , $p=0.02$) but not in previously depressed (adjusted beta 0.07 , $p=0.70$) or never depressed subjects (adjusted beta -0.09 , $p=0.50$). The association between sleep disturbance and KynA/3HK was not significant in any of the currently-, previously-, and never-depressed groups (adjusted betas respectively -0.21 , -0.04 , -0.03 , p 's 0.10).

3.3. Sleep Disturbance and Systemic Inflammation

In the entire sample, sleep disturbance was not associated with hs-CRP either when unadjusted (unadjusted beta 0.11 , $p=0.21$) or when adjusted for sex, age, analysis batch, BMI, diagnosis, and depressive symptoms (adjusted beta 0.24 , $p=0.10$). However, as shown in Table 2 and Figure 3, when analyzed *in each diagnostic group separately*, sleep disturbance was significantly associated with increased hs-CRP among currently depressed subjects (unadjusted beta 0.38 , $p=0.007$; adjusted beta 0.33 , $p=0.02$). This association was not significant either in the previously depressed group (unadjusted beta 0.17 , $p=0.49$; adjusted beta -0.23 , $p=0.23$) or in the never depressed group (unadjusted beta 0.14 , $p=0.30$; adjusted beta -0.01 , $p=0.95$).

4. DISCUSSION

This study demonstrated a significant association between sleep disturbance and a reduction in the ratio of serum KynA to QA, a putatively neuroprotective index of kynurenine

metabolites, in currently depressed subjects. Importantly, this association remained significant after covarying for the effects of sex, age, analysis batch, BMI, and depressive symptoms. However, this association was not significant in either previously depressed or never depressed subjects. Likewise, the association between sleep disturbance and hs-CRP was significant in currently depressed subjects but not in previously depressed or never depressed subjects.

To our knowledge, this is the first study to demonstrate an association between sleep disturbance and kynurenine metabolism in depressed subjects. A recent study has shown statistically non-significant correlations between some kynurenine measures and polysomnography-measured sleep efficiency in healthy controls [53]. In general agreement with this previous study, here the associations between sleep disturbance and most kynurenine metabolites (including the primary outcome variables, KynA/3HK and KynA/QA) were not significant in never depressed subjects. Nonetheless, for the primary outcome variable KynA/QA, there was a significant relationship with sleep disturbance in the currently depressed subjects. The relationship between sleep disturbance and kynurenine metabolites may be enhanced in currently depressed subjects as they experience more severe sleep disturbance as observed in the present study. The relationship between sleep disturbance and CRP concentration was significant also only in currently depressed subjects. Furthermore, the associations between sleep disturbance and two outcomes, KynA/QA and hs-CRP, were stronger in the currently depressed group compared to the entire sample, which again may be because sleep disturbance is primarily present in the currently depressed group. This is notable when viewed in the context of a higher statistical power of the entire sample compared to each individual group, which expectedly produced significant associations between sleep disturbance and the other variables in the entire sample but not in any individual groups.

Previous studies have shown that associations between the imbalance of kynurenine metabolism and depression are driven either by an increase in neurotoxic QA [39, 54, 55] or by a reduction in neuroprotective KynA [42, 43, 45]. In the present study, the association between sleep disturbance and the individual metabolite QA appears to be driving the association between sleep disturbance and the reduction in KynA/QA observed in currently depressed subjects. However, as the latter association was twice as strong as the former association, both QA and KynA might have contributed to the association between sleep disturbance and KynA/QA in different degrees.

In our previous study [51], the neuroprotective index KynA/QA was reduced in both currently depressed and previously depressed subjects compared to never depressed subjects. However, the present study focused on the association between sleep disturbance and KynA/QA rather than KynA/QA itself, and found that the association between sleep disturbance and KynA/QA was significant only in the currently depressed group but not in the previously depressed group. The lack of a significant association in the previously depressed group may be due to the small magnitude and range of sleep disturbance scores in this group whereas the neuroprotective index KynA/QA remained reduced in this group as shown by our previous study [51]. Indeed, in the previously depressed group, there was a positive correlation between the number of months in remission and KynA/QA [51],

suggesting that kynurenine dysregulation might persist beyond the resolution of depressive symptoms including sleep disturbance and might normalize as the remission period extends. Hence, in the previously depressed group, it is likely that neurotoxic profile of kynurenine metabolism did not improve while sleep disturbance did, making their association non-significant.

In this study, KYN/TRP, a measure of IDO activity, was not significantly different across the never depressed, previously depressed, and currently depressed groups. The absence of a significant difference across groups in KYN/TRP is consistent with the fact that there was no significant difference in hs-CRP concentrations across groups, since inflammatory mediators are known to activate IDO [41]. Furthermore, neither KynA/3HK nor KynA/QA levels were significantly different across groups. Although inflammation and kynurenine metabolism have been implicated in the pathophysiology of depression, there have been negative studies [47, 48, 55], and these biological processes are believed to contribute to depression in a subset rather than the entirety of patients [56]. Notwithstanding, sleep disturbance was significantly associated with hs-CRP and KynA/QA in this study, which suggests that kynurenine metabolism might be more robustly associated with a subtype of depression characterized by prominent sleep disturbances.

The following mechanisms can be proposed to explain the current findings. Depression is increasingly conceptualized as a neuropathological condition characterized by regional abnormalities such as hippocampal volume reduction and glial cell loss [56]. Dysregulation of the kynurenine pathway has been reported in neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's disease [31]. Consistent with the possible neurotoxic effects of kynurenine metabolites in depression, our previous study found a positive correlation between KynA/QA and hippocampal volume in depressed patients [52]. Sleep disturbance is a well-known risk factor for depression [7, 13, 14], and emerging evidence indicates that sleep disturbance contributes to the development and progression of neurodegenerative diseases [57]. Based on these previous research findings and the results of the present study, it can be posited that sleep disturbance might contribute to the pathophysiology of depression through the potential neurotoxic effects of kynurenine metabolites. Alternatively, given the correlational nature of the present study, it is also possible that depression could increase systemic inflammation, which in turn could activate the kynurenine pathway and lead to sleep disturbance. Depression and inflammation have been shown to bidirectionally influence each other [58, 59]; and both depression and inflammation can homeostatically regulate sleep, suggesting that sleep disturbance might be a product of these countervailing homeostatic processes [60, 61].

The following limitations should be considered. First, the cross-sectional design of this study did not allow any inference on the directionality of the associations between sleep disturbance and kynurenine metabolism. Second, the assessment of sleep disturbance relied on a self-report questionnaire, whereas polysomnography is arguably the objective standard to assess insomnia. However, the PSQI shows a high sensitivity (98.7%) and specificity (84.4%) in identifying insomnia in addition to significant correlations with other sleep measures including sleep diaries and polysomnography [62]. Additionally, assessment of sleep problems in clinical practice primarily relies on patients' subjective evaluation. Third,

kynurenine metabolites were assessed in peripheral blood rather than cerebrospinal fluid (CSF). However, the existing evidence shows high correlations between peripheral and central kynurenine metabolites [39]. Fourth, there was no comparison group with sleep disturbance but without depression, which could be included in future studies to provide information on the specific role of sleep disturbance in kynurenine metabolism. Fifth, it is not currently known whether kynurenine metabolites show diurnal variation. To mitigate the potential confounds of diurnal variation, all blood samples were obtained in the morning (8am–11am). Nevertheless, it is theoretically possible that sleep disturbance could affect waking time, such that differences in kynurenine metabolite concentrations could reflect blood sampling at a different point in the circadian cycle among those with sleep disturbance.

In conclusion, the present study demonstrated a cross-sectional association between sleep disturbance and a neurotoxic profile of kynurenine metabolism in currently depressed subjects. Our results raise the possibility that alterations of kynurenine metabolism may be one mechanism through which sleep disturbance predisposes to both the development and the recurrence of depression. Alternatively, given the existing evidence on the reciprocal influences between depression, inflammation, and sleep disturbance, it is also possible that depression could contribute to kynurenine dysregulation and sleep disturbance. Further investigation into this relationship using prospective and experimental approaches may elucidate the biological mechanisms underlying the link between sleep and depression, which may ultimately translate to novel therapeutic and preventive interventions for depression.

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References

1. LeBlanc M, Merette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. *Sleep*. 2009; 32(8):1027–37. [PubMed: 19725254]
2. Morin CM, LeBlanc M, Daley M, Gregoire JP, Merette C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med*. 2006; 7(2):123–30. [PubMed: 16459140]
3. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002; 6(2):97–111. [PubMed: 12531146]
4. Ohayon M. Epidemiological study on insomnia in the general population. *Sleep*. 1996; 19(3 Suppl):S7–15. [PubMed: 8723370]
5. Mallon L, Broman JE, Hetta J. Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population. *J Intern Med*. 2002; 251(3):207–16. [PubMed: 11886479]

6. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev.* 2013; 17(4):241–54. [PubMed: 23419741]
7. Cho HJ, Lavretsky H, Olmstead R, Levin MJ, Oxman MN, Irwin MR. Sleep disturbance and depression recurrence in community-dwelling older adults: a prospective study. *Am J Psychiatry.* 2008; 165(12):1543–50. [PubMed: 18765482]
8. Dew MA, Hoch CC, Buysse DJ, Monk TH, Begley AE, Houck PR, Hall M, Kupfer DJ, Reynolds CF 3rd. Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosom Med.* 2003; 65(1):63–73. [PubMed: 12554816]
9. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry.* 2002; 59(2):131–6. [PubMed: 11825133]
10. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. *Annu Rev Psychol.* 2015; 66:143–72. [PubMed: 25061767]
11. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lepine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 2011; 9:90. [PubMed: 21791035]
12. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet.* 2007; 370(9590):851–858.
13. Baglioni C, Battagliese G, Feige B, Spiegelhalter K, Nissen C, Voderholzer U, Lombardo C, Riemann D. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord.* 2011; 135(1–3):10–9. [PubMed: 21300408]
14. Lee E, Cho HJ, Olmstead R, Levin MJ, Oxman MN, Irwin MR. Persistent sleep disturbance: a risk factor for recurrent depression in community-dwelling older adults. *Sleep.* 2013; 36(11):1685–91. [PubMed: 24179302]
15. Leibenluft E. The rhythm of the blues. *Am J Psychiatry.* 2008; 165(12):1501–4. [PubMed: 19047326]
16. Gosling JA, Glozier N, Griffiths K, Ritterband L, Thorndike F, Mackinnon A, Hehir KK, Bennett A, Bennett K, Christensen H. The GoodNight study—online CBT for insomnia for the indicated prevention of depression: study protocol for a randomised controlled trial. *Trials.* 2014; 15:56. [PubMed: 24524214]
17. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry.* 2015
18. Irwin MR, Carrillo C, Olmstead R. Sleep loss activates cellular markers of inflammation: sex differences. *Brain Behav Immun.* 2010; 24(1):54–7. [PubMed: 19520155]
19. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med.* 2006; 166(16):1756–62. [PubMed: 16983055]
20. Irwin MR, Witarama T, Caudill M, Olmstead R, Breen EC. Sleep loss activates cellular inflammation and signal transducer and activator of transcription (STAT) family proteins in humans. *Brain Behav Immun.* 2015; 47:86–92. [PubMed: 25451613]
21. Irwin MR, Olmstead R, Breen EC, Witarama T, Carrillo C, Sadeghi N, Arevalo JM, Ma J, Nicassio P, Bootzin R, Cole S. Cognitive behavioral therapy and tai chi reverse cellular and genomic markers of inflammation in late-life insomnia: a randomized controlled trial. *Biol Psychiatry.* 2015; 78(10):721–9. [PubMed: 25748580]
22. Irwin MR, Olmstead R, Breen EC, Witarama T, Carrillo C, Sadeghi N, Arevalo JM, Ma J, Nicassio P, Bootzin R, Cole S. Cognitive Behavioral Therapy and Tai Chi Reverse Cellular and Genomic Markers of Inflammation in Late Life Insomnia: A Randomized Controlled Trial. *Biol Psychiatry.* 2015

23. Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, Martinez-Maza O, Cole S. Sleep Loss Activates Cellular Inflammatory Signaling. *Biol Psychiatry*. 2008; 64(6):538–540. [PubMed: 18561896]
24. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews*. 2008; 9(1):46–56.
25. Lotrich FE. Inflammatory cytokine-associated depression. *Brain research*. 2015; 1617:113–25. [PubMed: 25003554]
26. Kunugi H, Hori H, Ogawa S. Biochemical markers subtyping major depressive disorder. *Psychiatry Clin Neurosci*. 2015; 69(10):597–608. [PubMed: 25825158]
27. Franzen PL, Buysse DJ, Rabinovitz M, Pollock BG, Lotrich FE. Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment. *Psychiatry Res*. 2010; 177(1–2):240–5. [PubMed: 20381876]
28. Cho HJ, Eisenberger NI, Olmstead R, Breen EC, Irwin MR. Preexisting mild sleep disturbance as a vulnerability factor for inflammation-induced depressed mood: a human experimental study. *Transl Psychiatry*. 2016; 6(3):e750. [PubMed: 26954978]
29. Saito K, Markey SP, Heyes MP. Effects of immune activation on quinolinic acid and neuroactive kynurenines in the mouse. *Neuroscience*. 1992; 51(1):25–39. [PubMed: 1465184]
30. Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, Kelley KW, Dantzer R. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology*. 2013; 38(9):1609–16. [PubMed: 23511700]
31. Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in the mammalian brain: when physiology meets pathology. *Nat Rev Neurosci*. 2012; 13(7):465–77. [PubMed: 22678511]
32. Guillemin GJ. Quinolinic acid, the inescapable neurotoxin. *FEBS J*. 2012; 279(8):1356–1365. [PubMed: 22248144]
33. Stone TW, Darlington LG. Endogenous kynurenines as targets for drug discovery and development. *Nat Rev Drug Discov*. 2002; 1(8):609–620. [PubMed: 12402501]
34. Kim JP, Choi DW. Quinolinic neurotoxicity in cortical cell culture. *Neuroscience*. 1987; 23(2):423–32. [PubMed: 2963969]
35. Kocki T, Wnuk S, Kloc R, Kocki J, Owe-Larsson B, Urbanska EM. New insight into the antidepressants action: modulation of kynurenine pathway by increasing the kynurenine acid/3-hydroxykynurenine ratio. *J Neural Transm (Vienna)*. 2012; 119(2):235–43. [PubMed: 21660485]
36. Haroon E, Miller AH, Sanacora G. Inflammation, Glutamate, and Glia: A Trio of Trouble in Mood Disorders. *Neuropsychopharmacology*. 2016
37. O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol Psychiatry*. 2009; 14(5):511–22. [PubMed: 18195714]
38. Lawson MA, Parrott JM, McCusker RH, Dantzer R, Kelley KW, O'Connor JC. Intracerebroventricular administration of lipopolysaccharide induces indoleamine-2,3-dioxygenase-dependent depression-like behaviors. *Journal of neuroinflammation*. 2013; 10:87. [PubMed: 23866724]
39. Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, Spivey JR, Saito K, Miller AH. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. *Mol Psychiatry*. 2010; 15(4):393–403. [PubMed: 19918244]
40. Geogin-Lavialle S, Moura DS, Salvador A, Chauvet-Gelinier JC, Launay JM, Damaj G, Cote F, Soucie E, Chandesris MO, Barete S, Grandpeix-Guyodo C, Bachmeyer C, Alyanakian MA, Aouba A, Lortholary O, Dubreuil P, Teyssier JR, Trojak B, Haffen E, Vandel P, Bonin B, Hermine O, Gaillard R. Mast cells' involvement in inflammation pathways linked to depression: evidence in mastocytosis. *Mol Psychiatry*. 2016
41. Wichers MC, Koek GH, Robaey G, Verkerk R, Scharpe S, Maes M. IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Mol Psychiatry*. 2005; 10(6):538–44. [PubMed: 15494706]

42. Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: Evidence of impaired neuroprotection. *J Affect Disord.* 2007; 98(1–2):143–151. [PubMed: 16952400]
43. Schwieler L, Samuelsson M, Frye MA, Bhat M, Schuppe-Koistinen I, Jungholm O, Johansson AG, Landen M, Sellgren CM, Erhardt S. Electroconvulsive therapy suppresses the neurotoxic branch of the kynurenine pathway in treatment-resistant depressed patients. *Journal of neuroinflammation.* 2016; 13(1):51. [PubMed: 26925576]
44. Savitz J, Dantzer R, Wurfel BE, Victor TA, Ford BN, Bodurka J, Bellgowan PS, Teague TK, Drevets WC. Neuroprotective kynurenine metabolite indices are abnormally reduced and positively associated with hippocampal and amygdalar volume in bipolar disorder. *Psychoneuroendocrinology.* 2015; 52:200–11. [PubMed: 25486577]
45. Bay-Richter C, Linderholm KR, Lim CK, Samuelsson M, Traskman-Bendz L, Guillemin GJ, Erhardt S, Brundin L. A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. *Brain Behav Immun.* 2015; 43:110–7. [PubMed: 25124710]
46. Erhardt S, Lim CK, Linderholm KR, Janelidze S, Lindqvist D, Samuelsson M, Lundberg K, Postolache TT, Traskman-Bendz L, Guillemin GJ, Brundin L. Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology.* 2013; 38(5):743–52. [PubMed: 23299933]
47. Guloksuz S, Arts B, Walter S, Drukker M, Rodriguez L, Myint AM, Schwarz MJ, Ponds R, van Os J, Kenis G, Rutten BP. The impact of electroconvulsive therapy on the tryptophan-kynurenine metabolic pathway. *Brain Behav Immun.* 2015; 48:48–52. [PubMed: 25765557]
48. Maes M, Galecki P, Verkerk R, Rief W. Somatization, but not depression, is characterized by disorders in the tryptophan catabolite (TRYCAT) pathway, indicating increased indoleamine 2,3-dioxygenase and lowered kynurenine aminotransferase activity. *Neuro Endocrinol Lett.* 2011; 32(3):264–73. [PubMed: 21712776]
49. Dahl J, Andreassen OA, Verkerk R, Malt UF, Sandvik L, Brundin L, Ormstad H. Ongoing episode of major depressive disorder is not associated with elevated plasma levels of kynurenine pathway markers. *Psychoneuroendocrinology.* 2015; 56:12–22. [PubMed: 25770856]
50. Dantzer R, Walker AK. Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? *J Neural Transm (Vienna).* 2014; 121(8):925–32. [PubMed: 24633997]
51. Savitz J, Drevets WC, Wurfel BE, Ford BN, Bellgowan PS, Victor TA, Bodurka J, Teague TK, Dantzer R. Reduction of kynurenic acid to quinolinic acid ratio in both the depressed and remitted phases of major depressive disorder. *Brain Behav Immun.* 2015
52. Savitz J, Drevets WC, Smith CM, Victor TA, Wurfel BE, Bellgowan PS, Bodurka J, Teague TK, Dantzer R. Putative neuroprotective and neurotoxic kynurenine pathway metabolites are associated with hippocampal and amygdalar volumes in subjects with major depressive disorder. *Neuropsychopharmacology.* 2015; 40(2):463–71. [PubMed: 25074636]
53. Heitkemper MM, Han CJ, Jarrett ME, Gu H, Djukovic D, Shulman RJ, Raftery D, Henderson WA, Cain KC. Serum Tryptophan Metabolite Levels During Sleep in Patients With and Without Irritable Bowel Syndrome (IBS). *Biol Res Nurs.* 2016; 18(2):193–8. [PubMed: 26156003]
54. Baranyi A, Meinitzer A, Breitenacker RJ, Amouzadeh-Ghadikolai O, Stauber R, Rothenhausler HB. Quinolinic Acid Responses during Interferon-alpha-Induced Depressive Symptomatology in Patients with Chronic Hepatitis C Infection - A Novel Aspect for Depression and Inflammatory Hypothesis. *PLoS One.* 2015; 10(9):e0137022. [PubMed: 26368809]
55. Steiner J, Walter M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, Mawrin C, Brisch R, Bielau H, Meyer zu Schwabedissen L, Bogerts B, Myint AM. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? *Journal of neuroinflammation.* 2011; 8:94. [PubMed: 21831269]
56. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. *Nat Med.* 2001; 7(5):541–7. [PubMed: 11329053]
57. Abbott SM, Videnovic A. Chronic sleep disturbance and neural injury: links to neurodegenerative disease. *Nat Sci Sleep.* 2016; 8:55–61. [PubMed: 26869817]

58. Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers M. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? *Brain Behav Immun.* 2010; 24(1):96–101. [PubMed: 19683568]
59. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain Behav Immun.* 2009; 23(7):936–944. [PubMed: 19416750]
60. Thase ME. Depression and sleep: pathophysiology and treatment. *Dialogues in clinical neuroscience.* 2006; 8(2):217–26. [PubMed: 16889107]
61. Irwin MR, Opp MR. *Sleep Health: Reciprocal Regulation of Sleep and Innate Immunity.* Neuropsychopharmacology. 2016
62. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res.* 2002; 53(3):737–40. [PubMed: 12217446]

HIGHLIGHTS

- Sleep disturbance is associated with a relative neurotoxic shift in the balance of kynurenine metabolites in depressed subjects.
- Sleep disturbance is associated with increased systemic inflammation in depressed subjects.
- Altered kynurenine metabolism may molecularly link sleep disturbance and depression.

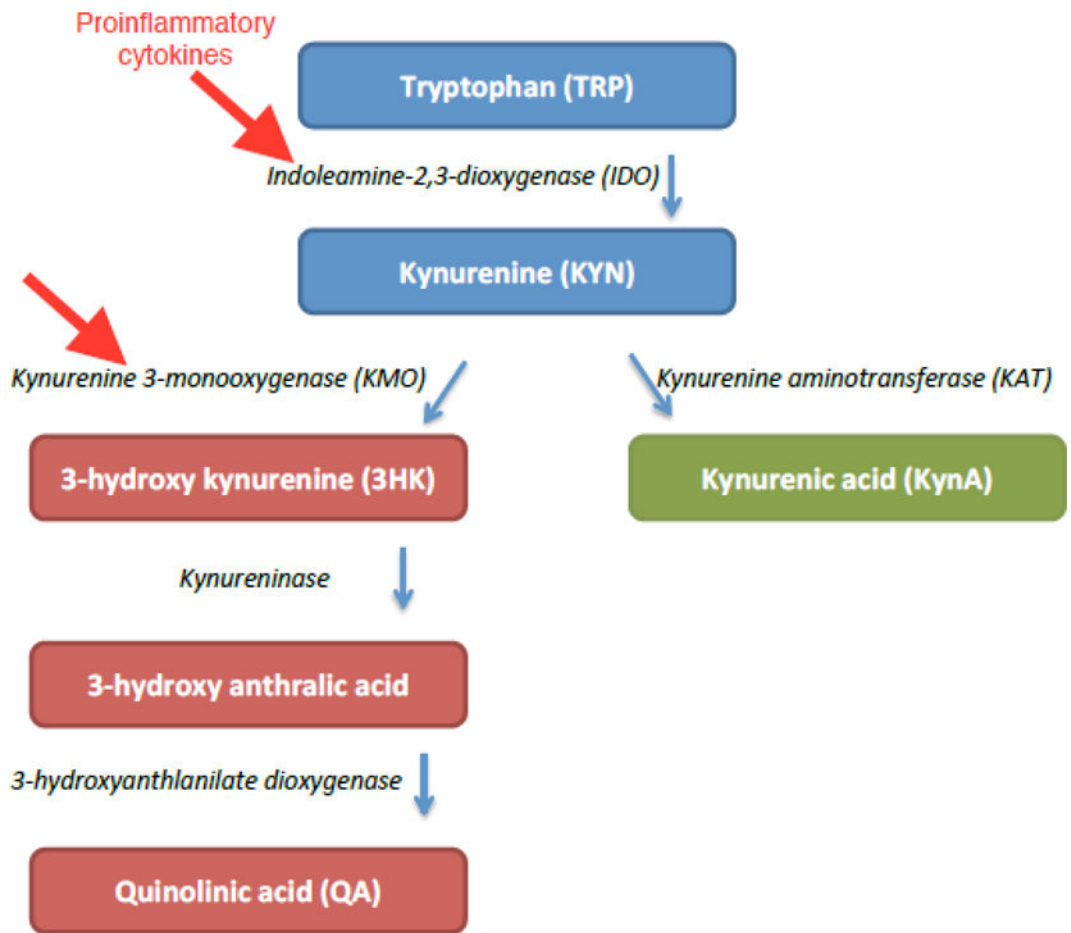


Figure 1. Main branches of the kynurenine pathway

Each box represents a metabolite resulting from the oxidation of tryptophan. Putative neurotoxic metabolites are colored red whereas KynA, which is putatively neuroprotective, is colored green. The black italicized text shows the enzymes that catalyze each step in the metabolic pathway.

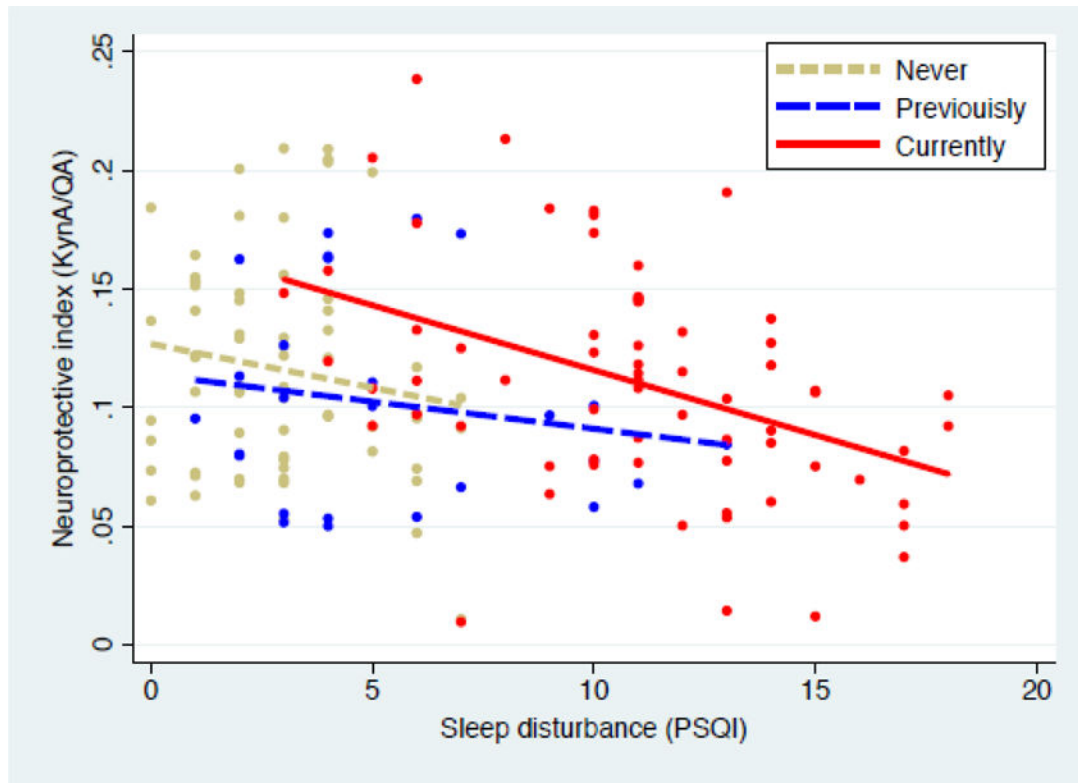


Figure 2. Associations between sleep disturbance and neuroprotective index (KynA/QA) in never depressed, previously depressed, and currently depressed subjects

Scatter plots and linear prediction lines are shown here according to diagnostic groups.

Abbreviations: PSQI = Pittsburgh Sleep Quality Index; KynA = kynurenic acid; QA = quinolinic acid

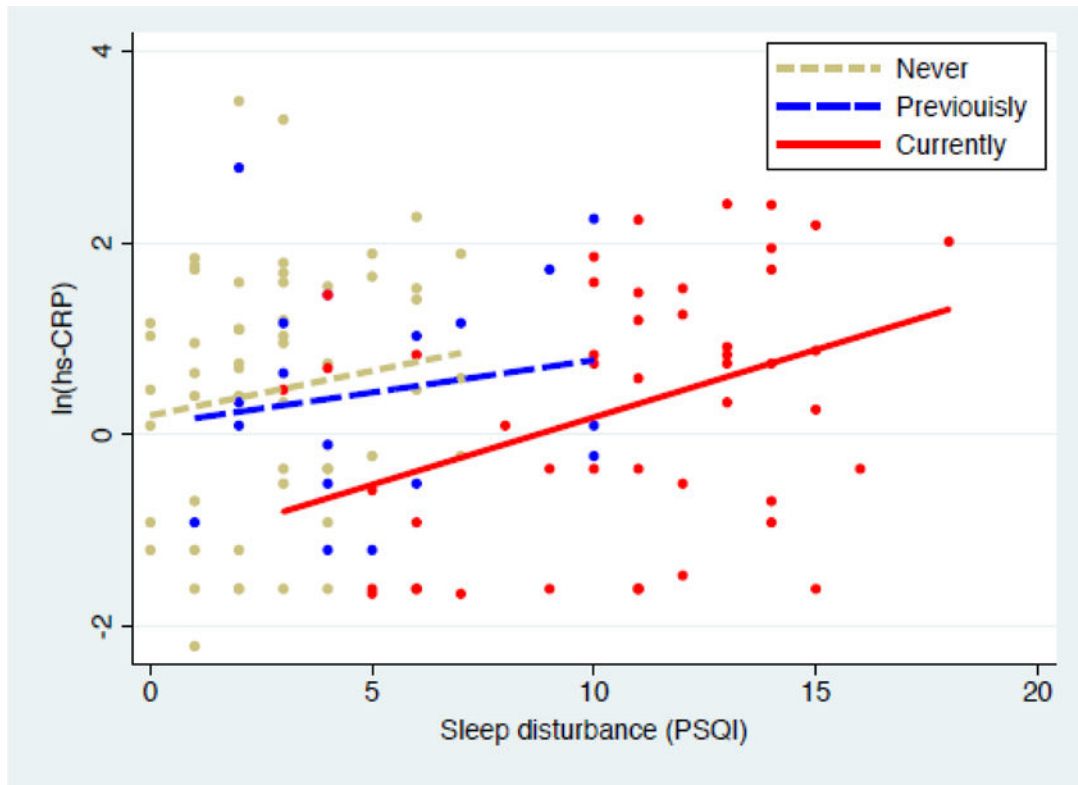


Figure 3. Associations between sleep disturbance and systemic inflammation (hsCRP) in never depressed, previously depressed, and currently depressed subjects
 Scatter plots and linear prediction lines are shown here according to diagnostic groups.
 Abbreviations: PSQI = Pittsburgh Sleep Quality Index; hsCRP = high sensitivity C-reactive protein

Table 1

Demographic, clinical and biomarker data according to diagnostic groups (N=160)

Variable	Never Depressed	Previously Depressed	Currently Depressed	p
N	66	26	68	NA
Sex (% female)	64%	65%	81%	0.07
Age (mean \pm SD)	32.3 \pm 10.2	33.3 \pm 11.1	36.2 \pm 9.9	0.08
BMI (mean \pm SD)	27.2 \pm 5.7	26.5 \pm 5.2	28.5 \pm 6.8	0.26
Sleep disturbance (PSQI; mean \pm SD)	2.9 \pm 1.9	5.4 \pm 3.3	11.0 \pm 3.7	<0.0001
Depressive symptoms (MADRS; mean \pm SD)	1.0 \pm 1.8	4.4 \pm 4.5	27.4 \pm 7.0	<0.0001
hs-CRP (pg/mL; median [IQR])	1.95 (0.65–4.65)	1.25 (0.60–3.20)	1.80 (0.40–4.30)	0.79
TRP (μ M; median [IQR])	61.0 (53.3–68.3)	58.7 (47.5–66.2)	56.0 (49.1–61.2)	0.09
KYN (nM; median [IQR])	1.89 (1.60–2.30)	1.82 (1.36–2.20)	1.94 (1.61–2.22)	0.82
KYN/TRP (median [IQR])	0.032 (0.026–0.037)	0.033 (0.027–0.037)	0.034 (0.027–0.040)	0.21
KynA (nM; median [IQR])	39.0 (29.3–49.8)	36.1 (23.7–46.1)	36.3 (28.6–43.5)	0.28
3HK (nM; median [IQR])	29.7 (24.0–38.0)	29.3 (23.7–37.3)	31.8 (26.6–41.3)	0.62
QA (nM; median [IQR])	356 (281–422)	365 (283–460)	344 (262–401)	0.55
KynA/3HK (mean \pm SD)	1.33 \pm 0.45	1.24 \pm 0.48	1.14 \pm 0.44	0.07
KynA/QA (mean \pm SD)	0.12 \pm 0.04	0.10 \pm 0.04	0.11 \pm 0.05	0.37

Note:

There were missing values for MADRS and CRP, which were available for 156 and 123 subjects respectively. Non-normally distributed variables were described using median and IQR. The variables were compared across the diagnostic groups using X^2 -test or ANOVA. The data from an overlapping sample with the current one have been previously published [51].

Abbreviations: BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; MADRS = Montgomery Asberg Depression Rating Scale; hs-CRP = high sensitivity C-reactive protein; IQR = interquartile range; TRP = tryptophan; KYN = Kynurenine; 3HK = 3-hydroxykynurenine; KynA = kynurenic acid; QA = quinolinic acid

Table 2

Associations between sleep disturbance and circulating biomarkers (N=160)

Variable	Entire sample (N=160)		Never Depressed (N=66)		Previously Depressed (N=26)		Currently Depressed (N=68)	
	Beta*	P	Beta*	P	Beta*	P	Beta*	P
hs-CRP (pg/mL)	0.11	0.21	0.14	0.30	0.17	0.49	0.38	0.007
TRP (uM)	-0.23	0.003	-0.20	0.11	-0.16	0.43	-0.17	0.17
KYN (nM)	-0.04	0.64	-0.15	0.22	-0.17	0.40	0.02	0.86
KYN/TRP	0.16	0.04	0.03	0.79	-0.04	0.84	0.15	0.23
KynA (nM)	-0.22	0.005	-0.23	0.07	-0.22	0.29	-0.20	0.11
3HK (nM)	0.03	0.75	-0.03	0.80	-0.19	0.36	-0.02	0.90
QA (nM)	0.02	0.80	0.01	0.91	-0.12	0.55	0.26	0.03
KynA/3HK	-0.24	0.002	-0.09	0.50	-0.15	0.46	-0.22	0.07
KynA/QA	-0.22	0.005	-0.16	0.21	-0.17	0.40	-0.43	<0.001

* Unadjusted standardized regression coefficient

Abbreviations: hs-CRP = high sensitivity C-reactive protein; TRP = tryptophan; KYN = Kynurenine; 3HK = 3-hydroxykynurenine; KynA = kynurenic acid; QA = quinolinic acid