Research Articles

Associations between sleep quality and biomarkers for neurodegeneration - A longitudinal one-year case-control study of patients with bipolar disorder and healthy control individuals

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ABSTRACT

Disturbed sleep during affective episodes may impact levels of cerebrospinal fluid (CSF)-amyloid-beta (Aβ)42 and other biomarkers of neurodegeneration in patients with bipolar disorder (BD). The study aimed to investigate the correlations between sleep and biomarkers for Alzheimer's disease (AD) and neurodegeneration in BD and healthy controls (HC). We present a prospective, longitudinal case-control study of euthymic patients with BD (N = 86) and HC (N = 44). All participants were evaluated with clinical assessments at baseline, and after a year. The patients' affective states were recorded weekly as euthymic, subthreshold level, major depression, or (hypo) mania. Patients were re-assessed during and after an episode if it occurred during follow-up. Total sleep scores based on three Hamilton-17 Depression Scale items were analyzed in relation to concentrations of CSF-Aβ42, CSF-Aβ40, CSF-Aβ38, CSF-Aβ42/40 and 42/38 ratios, CSF-soluble amyloid-precursor proteins α+β, plasma-Aβ42, plasma-Aβ40, CSF-phosphorylated-tau, CSF-total-tau, plasma-total-tau, CSF-neurofilament-light, plasma-neurofilament-light, CSF-neurogranin, serum-S100B, CSF-8-oxo-7,8-dihydro-guanosine, CSF-8-oxo-7,8-dihydro-2′-deoxyguanosine, urine-8-oxo-7,8-dihydro-guanosine, and urine-8-oxo-7,8-dihydro-2′-deoxyguanosine.

The primary outcome was the association between total sleep scores and levels of CSF-Aβ42 at baseline and follow-up estimated by the regression coefficient in a linear mixed model. We found no statistically significant associations between sleep and CSF-Aβ42 (−2.307 pg/ml (95% CI: -9.525–4.911; p = 0.523)) or any other biomarkers. However, higher sleep scores appeared to be associated with higher CSF-Aβ42/40 and CSF-Aβ42/38 ratios, and lower CSF-total-tau concentration, but were not statistically significant after correction for multiple testing. In conclusion attenuated sleep during an affective episode was not associated with changes in biomarkers for AD and neurodegeneration in BD, but larger prospective studies are needed.

1. Introduction

Mounting evidence demonstrates a close relationship between sleep abnormalities and mood disorders (Yan et al., 2021). In bipolar disorder

(BD), an association between sleep disorder residual mood symptoms, and mood episode recurrence is suggested (Schnell et al., 2014). Sleep disturbance is common in patients with mood disorders and sleep disruption is often an early warning symptom of relapse in BD. Non-rapid

eye movement sleep serves as a deep and recovering sleep, and it is a cornerstone in the functioning of the glymphatic system and thereby in the clearance of metabolic waste from the brain (Fultz et al., 2019). The glymphatic system is considered an effective waste-removal system in the brain, which facilitates the exchange between the cerebrospinal fluid (CSF) and interstitial fluid, along with potentially neurotoxic proteins such as amyloid-β (Aβ) (Xie et al., 2013; Rasmussen et al., 2018), and tau proteins (Simon et al., 2018). CSF is the optimal biomaterial to examine molecular status since CSF has been reported to well reflect the state of the central nervous system (Veening and Barendregt, 2010; Knorr et al., 2018). We have recently shown that in patients with BD, levels of CSF-Aβ42 decreased in the patients who had a relapse of a mood episode compared to patients without an episode during a one-year follow-up. This suggests amyloid production/clearance abnormalities during an acute BD episode (Knorr et al., 2022). It is well established that core AD biomarkers are low levels of cerebrospinal fluid (CSF)-Aβ42 and high levels of CSF-total tau (t-tau) and hyperphosphorylated tau (p-tau) (Lleo et al., 2019). The decreasing CSF-Aβ42 mimics the pattern seen in Alzheimer's disease (AD) and may suggest an association with brain amyloidosis. Long-term population-based studies suggest that patients with BD have a higher risk of developing dementia as compared with the background population (da Silva et al., 2013; Fox et al., 2015; Kessing and Andersen, 2017; Velosa et al., 2020). Furthermore, a greater risk of AD is seen in older adults with insomnia (Lim et al., 2013). Accumulating evidence suggests that glymphatic dysfunction is an imperative intermediary factor between sleep disorders, mood disorders, and maybe even AD (Xia et al., 2017). Further, sleep deprivation affects the immunological and redox system resulting in neuroinflammation and oxidative stress. Hence, it is important to understand the molecular and biochemical alterations that are the causative factors leading to these pathophysiological effects on the neuronal system (Bishir et al., 2020). We have previously found that the CSF oxidative stress marker of RNA damage 8-oxoGuo showed both state- and trait dependence in BD and stability in HC (Knorr et al., 2019).

However, the exact neurobiological mechanism of interaction between sleep and mood disorders remains unclear.

1.1. The aims of the study

We aimed at investigating associations between sleep and a line of biomarkers for neurodegeneration including: CSF-Aβ42, CSF-Aβ40, CSF-Aβ38, CSF-Aβ42/40 and 42/38 ratios, CSF-soluble amyloid-precursor proteins α and β, plasma-Aβ42, plasma-Aβ40, CSF-phosphorylated-tau, CSF-total-tau, plasma-total-tau, CSF-neurofilament-light, plasma-neurofilament-light, CSF-neurogranin, serum-S100B, CSF-8-oxo-7,8-dihydro-guanosine, CSF-8-oxo-7,8-dihydro-2′-deoxyguanosine, urine-8-oxo-7,8-dihydro-guanosine, and urine-8-oxo-7,8-dihydro-2′-deoxyguanosine.

We present a prospective, longitudinal study with repeated measures of sleep and CSF, blood, and urine biomarkers of AD and neuro-degeneration during initial euthymia (T0), during an affective episode if it occurred (T1) and in post-episode euthymia (T2), and after a one-year follow-up (T3) in patients with BD and gender and age-matched healthy control individuals (HC).

1.2. Hypotheses

We hypothesized that one mechanism underlying the association between BD and Alzheimer's disease is disrupted sleep that affects the interaction between interstitial and CSF resulting in decreased glymphatic clearance, and increased Aβ in the brain.

Our main hypothesis was that there is a positive association between Hamilton Depression Scale scores for sleep and levels of CSF-Aβ42 corrected for age and gender. In addition, we included explorative endpoints for associations between sleep scores and: a) in CSF Aβ40, Aβ38, sAPPα, sAPPβ, t-tau, p-tau, p-tau /t-tau), NF-L, NG, oxidative stress markers 8-

oxo-Guo and 8-oxo-dG, b) in plasma Aβ42, Aβ40, Aβ42/38, Aβ42/40, t-tau, p-tau, p-tau /t-tau, and NF-L, c) in serum S100B, and e) in urine oxidative stress marker 8-oxo-Guo and 8-oxo-dG.

2. Methods

This prospective, longitudinal case-control study with repeated measurements of biomarkers related to Alzheimer's disease and neuro-degeneration comprised a total of 86 patients with BD in a remitted state, aged 18–60 years and, at the time of inclusion admitted to the outpatient Copenhagen Mood Disorder Clinic, which covers an area of 1.6 million people at all psychiatric centers in the Capital Region of Denmark. Furthermore, the study included healthy, age and gender-matched control individuals recruited via the Danish Donor Register, Frederiksberg Hospital. Participants for the study were investigated from April 1st, 2014 until April 27th, 2017 (Knorr et al., 2019).

The diagnoses of BD were confirmed according to the Schedules for Clinical Assessment in Neuropsychiatry interview (Wing et al., 1990). Remission was defined as scores below 8 on both the Hamilton Depression Rating Scale 17-items (HAMD) and the Young Mania Rating Scale (YMRS) (Bech et al., 1986).

We gave special emphasis to the effect of new affective episodes within follow-up. Thus, a specialist in psychiatry (author Ulla Knorr) evaluated the affective states of patients with BD during a weekly contact (see below). In case of a new affective episode of depression, hypomania, or mania the patients were re-assessed during the episode (T1), and at the time they had regained a euthymic state (T2). Finally, all participants were re-assessed at a one-year follow-up (T3).

2.1. Biological assessments

The participants fasted overnight before the collection of CSF, blood, and urine samples between 0800 and 1000 h in the morning. At each of the points (T0, T1, T2, and T3) the clinical assessments and the urine, blood, and CSF sampling from the participants were done on the same or the following day (Knorr et al., 2022).

Specialists of neurology performed lumbar punctures to collect CSF samples from patients with BD and HC individuals in the lateral decubitus position. The spinal needle was inserted into the L3/L4 or L4/L5 interspace, and a total volume of 10-12 ml of CSF was collected in polypropylene tubes, and gently inverted to avoid gradient effects. Samples were centrifuged on acquisition at 2000 g for 10 min at +4 °C and stored in polypropylene tubes in 250 μL aliquots at −80 °C pending analysis. A general CSF screen was conducted, including albumin, immunoglobulin G (IgG), IgG index, erythrocytes, white blood cells, glucose, and protein.

Board-certified laboratory technicians collected blood samples analyzed at the Clinical Biochemical Laboratory at Rigshospitalet, Denmark, regarding standard biochemical parameters including hematological parameters, blood glucose, C-reactive protein, thyroid hormones, lipid status, ions, metabolites, liver enzymes, and lithium levels.

Patients were followed prospectively for a year. The patients received treatment as usual and were instructed to daily self-monitoring of mood, sleep, alcohol, and medicine intake. Psychiatrist UK maintained weekly contact with the patients by their choice of telephone, Short Message Service, or e-mail. The patients' affective states were recorded weekly as euthymic, subthreshold level, major depression, or (hypo)mania. Patients who experienced a moderate to severe affective episode defined as scores above 13 points on either the HAMD or the YMRS for at least two weeks, had a repeated clinical assessment including urine, blood, and CSF sampling during the episode (T1) and, also following the episode when being in stable remission for at least two weeks (T2). Finally, all participants were assessed at the one-year follow-up in remission, defined as at least eight weeks in a stable remission state (T3), As expected, 50% of the patients experienced a moderate to severe (HAMD or YMRS >13 for two weeks) affective episode during the follow-up period

and these patients have been given repeated CSF, plasma, serum, and urine samples.

The study complies with the Helsinki Declaration and was approved by the local ethics committee (H6-2014-006) and The Danish Data Protection Agency (J.nr: 2014-58-0015). The study is reported according to the STROBE Statement.

2.2. Biochemical analyses

All biochemical analyses, except biomarkers for oxidative stress, were performed at the Clinical Neurochemistry Laboratory in Mölndal, Sweden, by experienced and board-certified laboratory technicians who were blinded concerning the clinical information (Knorr et al., 2022).

CSF-Aβ42, 40, and 38 concentrations were measured using V-plex Peptide Panel 1 Kit Aβ38, Aβ40, Aβ42 (Meso Scale Discovery, Rockville, MD, USA) according to the manufacturer's protocol. sAPPα and sAPPβ were determined using the MSD sAPPα/sAPPβ Multiplex Assay and as described by the manufacturer (Meso Scale Discovery, Gaithersburg, MD, USA).

According to the manufacturer's (INNOTEST, Fujirebio, Japan) protocol, CSF-t-tau was measured by the hTAU Ag ELISA assay and CSF-p-tau by the PHOSPHO-TAU (181p) ELISA assay.

CSF-NF-L concentration was measured using an NF-light ELISA kit (IBL International, Hamburg, Germany) by following the manufacturer's protocol.

CSF-NG concentration was measured using a previously published in-house Meso Scale Discovery assay (De Vos et al., 2015).

Plasma-Aβ42, Aβ40, t-tau, and NF-L concentrations were measured using a commercial Single molecule array (Simoa) assay on an HD-1 Analyzer according to instructions from the kit manufacturer (Quanterix, Billerica, MA).

Serum S100B was measured using a commercial kit with electrochemiluminescence detection on an Elecsys instrument (Roche Diagnostics, Penzberg, Germany).

The inter-assay coefficient of variability was 8% (sAPPα), 20% (sAPPβ), 2% (Aβ38), 15% (Aβ40), and 13% (Aβ42). The intra-assay coefficient of variability was below 10% for all biomarkers.

The cerebrospinal and urinary oxidative stress markers 8-oxoGuo and 8-oxodG were analyzed at the Laboratory of Clinical Pharmacology, Rigshospitalet using ultra-performance liquid chromatography-tandem mass spectrometry, as described in full detail elsewhere (Rasmussen et al., 2016; Weimann et al., 2018).

2.3. Hamilton Depression Scale Scores for sleep at T0, T1, T2, and T3

Sleep scores were obtained by adding the three items from the Hamilton Depression Rating Scale 17-items (HAMD) related to impaired sleep: a) early in the night, b) in the middle of the night, and c) in the early hours of the morning, each rated according to severity by 0-2 points (Beck et al., 1961). Thus, a participant would be rated with total sleep scores between 0 (best sleep) and 6 (worse sleep).

2.4. Statistical analyses

Data were analyzed according to a pre-established statistical analysis plan. All analyses were conducted with SAS software, version 9.4, (Copyright © 2013, SAS Institute Inc., Cary, NC, USA).

2.5. Primary analysis

The association between sleep score and CSF-Aβ42 was evaluated using data from BD and HC at T0 and T3 in a linear mixed model including sleep score, age, and gender as fixed effects and with an unstructured covariance pattern to account for repeated measurements on each study participant.
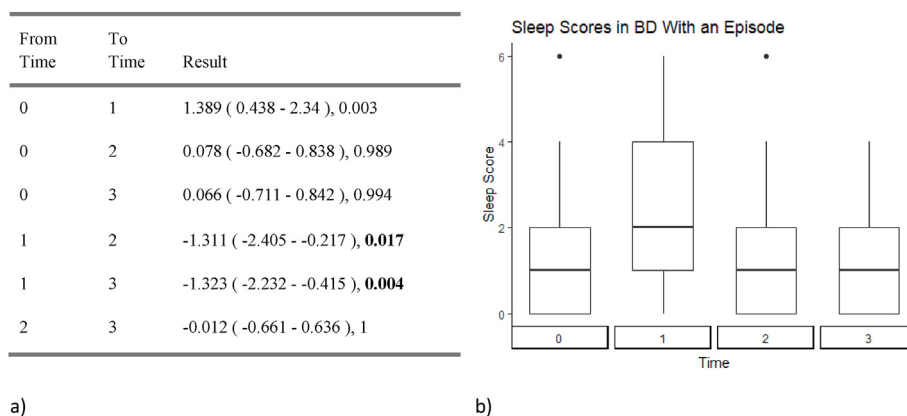
Table 1
Descriptive characterization of study population.

|	BD	HC
Population Size	86	44
Age; median (Q1; Q3)	33 (25.25; 42)	31.5 (24; 41.25)
Women; n (%)	43 (50%)	19 (43.18%)
Smokers; n (%)	30 (35%)	8 (18%)
Alcohol Consumption; median (Q1; Q3)	0.2 (0; 1)	0.5 (0; 1)
Medicine LI; n (%)	43 (50%)	0
Medicine AP; n (%)	36 (41.86%)	0
Medicine AC; n (%)	43 (50%)	0
CSF AB42 (pg/ml)	598.08 (176.96) [26 (30.23%)]	639 (151.18) [6 (13.64%)]
CSF AB40 (pg/ml)	5642.98 (1599.62) [26 (30.23%)]	5954.53 (1306.2) [6 (13.64%)]
CSF AB38 (pg/ml)	2202.25 (676.61) [26 (30.23%)]	2319.32 (572.23) [6 (13.64%)]
CSF AB42AB40ratio	0.11 (0.01) [26 (30.23%)]	0.11 (0.01) [6 (13.64%)]
CSF AB42AB38ratio	0.27 (0.02) [26 (30.23%)]	0.28 (0.02) [6 (13.64%)]
CSF sAPPa (ng/ml)	269.23 (105.73) [26 (30.23%)]	305.32 (114.19) [6 (13.64%)]
CSF sAPPb (ng/ml)	564.95 (186.06) [26 (30.23%)]	613.71 (206.62) [6 (13.64%)]
CSF tTAU (pg/ml)	204.47 (82.17) [26 (30.23%)]	199.47 (70.31) [6 (13.64%)]
CSF pTAU (pg/ml)	34.63 (11.73) [26 (30.23%)]	33.68 (8.69) [6 (13.64%)]
Plasma AB42 (pg/ml)	10.9 (2.35) [5 (5.81%)]	10 (2.36) [1 (2.27%)]
Plasma AB40 (pg/ml)	224.23 (54.81) [4 (4.65%)]	220.93 (57.81) [1 (2.27%)]
Plasma AB42AB40ratio	0.05 (0.01) [5 (5.81%)]	0.05 (0.01) [1 (2.27%)]
Plasma tTAU (pg/ml)	3.02 (0.95) [4 (4.65%)]	2.81 (0.88) [1 (2.27%)]
CSF pTau-tTau ratio	0.17 (0.15; 0.19) [27 (31.4%)]	0.17 (0.15; 0.18) [6 (13.64%)]
CSF NG (pg/ml)	169 (146.75; 194) [26 (30.23%)]	171 (128.75; 216.25) [6 (13.64%)]
CSF NFL (pg/ml)	332 (246; 479.5) [27 (31.4%)]	363.5 (244.75; 583) [6 (13.64%)]
Urine dGuo (nM/(mM Creatinin))	1.38 (1.07; 1.69) [2 (2.33%)]	1.32 (1; 1.42) [0 (0%)]
Urine Guo (nM/(mM Creatinin))	1.76 (1.48; 2.12) [2 (2.33%)]	1.56 (1.31; 1.78) [0 (0%)]
CSF Guo (pM)	55.41 (47.34; 69.07) [25 (29.07%)]	48.09 (39.27; 56.05) [4 (9.09%)]
CSF dGuo (pM)	6.6 (4.55; 9.03) [25 (29.07%)]	5.31 (3.09; 7) [4 (9.09%)]
Plasma NFL (pg/ml)	6.94 (5.02; 9.38) [6 (6.98%)]	5.73 (4.64; 7.84) [1 (2.27%)]
Serum S100 (ug/ml)	0.04 (0.03; 0.05) [5 (5.81%)]	0.04 (0.03; 0.05) [1 (2.27%)]
SleepScoreT0; Median (Q1; Q3)	1 (0; 2)	0 (0; 0)
SleepScoreT1; Median (Q1; Q3)	2 (1; 4)	
SleepScoreT2; Median (Q1; Q3)	1 (0; 2)	
SleepScoreT3; Median (Q1; Q3)	0 (0; 2)	0 (0; 0)

Footnote: Categorical data is described with n (%), normally distributed data with a mean (SD), non-normally distributed quantitative data with median (Q1; Q2), and missing data with [n (%)].

2.6. Secondary analysis

To investigate changes in sleep score before and after the affective episode in patients with bipolar disorder (n with an episode during follow-up = 36), we applied a linear mixed model with follow-up time (T0, T1, T2, and T3) as a fixed effect and with an unstructured covariance pattern to account for repeated measurements on each study participant. Mean differences in sleep score were estimated between all pairs of follow-up times and presented with simultaneous 95% confidence intervals and minP-adjusted p-values which controls the family-wise error rate.

From Time	To Time	Result
0	1	1.389 (0.438 - 2.34), 0.003
0	2	0.078 (-0.682 - 0.838), 0.989
0	3	0.066 (-0.711 - 0.842), 0.994
1	2	-1.311 (-2.405 - -0.217), **0.017**
1	3	-1.323 (-2.232 - -0.415), **0.004**
2	3	-0.012 (-0.661 - 0.636), 1

a)   b)

Fig. 1. Legend: Sleep scores in patients with bipolar disorder (n = 86) before (T0), during (T1), after an episode (T2), and a one-year follow-up (T3)
Footnote: b) Estimated mean differences between follow-up times with simultaneous
95% confidence interval and p-values adjusted for multiple testing using the minP-method.
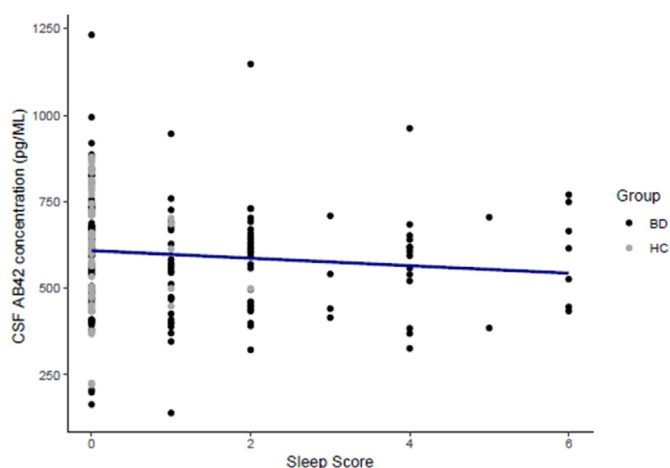
Fig. 2. Legend: Scatterplot of CSF-Aβ42 plotted against sleep scores in patients with bipolar disorder and healthy control individuals (n = 100 study participants, 208 observations)
Footnote: The line represents a rough sightline for the dataset. The rough sightline is an ordinary linear regression. The regression coefficient from the primary analysis has been adjusted for age and gender. The regression line in Fig. 1 is unadjusted (since otherwise, we would have different lines for men and women and all the different ages in the study population).

2.7. Explorative analyses

The associations between sleep scores and various biomarkers were evaluated in a linear mixed model similar to that of the primary analysis and repeated three-fold with and without adjustment for potential confounders:

Model 1. Uncorrected
Model 2. Corrected for age, and gender
Model 3. Corrected for age, gender, smoking (yes/no), alcohol and, medicine (indicators: lithium (yes/no), antipsychotics (yes/no), and anticonvulsants (yes/no).

Furthermore, the analysis was repeated using data from both BD and HC and data from BD only. Regression coefficients were standardized by the SD of the HC group at T0 and plotted in forest plots to visualize the results. Substantially skewed biomarkers were log-transformed before analysis. P-values from the explorative analysis were adjusted for multiple testing using the method of Benjamini and Hochberg which controls the false discovery rate.

3. Results

Descriptive characteristics of the study population are displayed in Table 1. Patients with BD and HC individuals were well matched for age and gender and there were no statistically significant differences between the groups regarding years of education. Alcohol consumption was lower and smoking more frequent among patients with BD compared to HC. Standard biochemical parameters were within reference intervals. At baseline 62 participants with BD and 40 HC accepted lumbar puncture.

3.1. Change in sleep scores before, under, and after an affective episode

Initially, we investigated changes in sleep scores in patients with bipolar disorder who experienced an affective episode during follow-up (n = 36). During the affective episode, the sleep scores at T1 were statistically significantly higher (= worse sleep) than sleep scores at T0, T2, and T3. The analyses point to patients with bipolar disorder experience worsen sleep during an episode and that the differences disappear after the episode at T2 (Fig. 1).

3.2. Association between CSF biomarkers of Alzheimer's disease and sleep

CSF-Aβ42 plotted against sleep scores are displayed in Fig. 2. We found no statistically significant associations between sleep and CSF-Aβ42. Thus, after adjusting for age and gender, CSF-Aβ42 decreased non-significantly by −2.307 pg/ml (95% CI: -9.525 – 4.911, p = 0.523) for every point increase in sleep score.

3.3. Explorative analyses

Increased sleep scores seemed to be associated with a) increasing CSF-Aβ42/40 ratio and CSF-Aβ40/38 ratio, and b) decreasing levels of CSF-t-tau in all levels of adjustments (Fig. 3). However, none of these findings remained statistically significant after adjustment for multiple testing (Table 2). Furthermore, as can be seen from Table 2 we found no statistically significant associations between sleep scores and in CSF Aβ40, Aβ38, sAPPα, sAPPβ, p-tau, p-tau /t-tau, NF-L, NG, oxidative stress markers 8-oxo-Guo and 8-oxo-dG, b) in plasma Aβ42, Aβ40, Aβ42/38, Aβ42/40, t-tau, p-tau, p-tau /t-tau, and NF-L, c) in serum S100B, and e) in urine oxidative stress marker 8-oxo-Guo and 8-oxo-dG.

4. Discussion

This study was designed to investigate whether abnormalities in sleep are associated with levels of biomarkers for AD and neurodegeneration. Firstly, we identified disruption of sleep in patients with BD during an
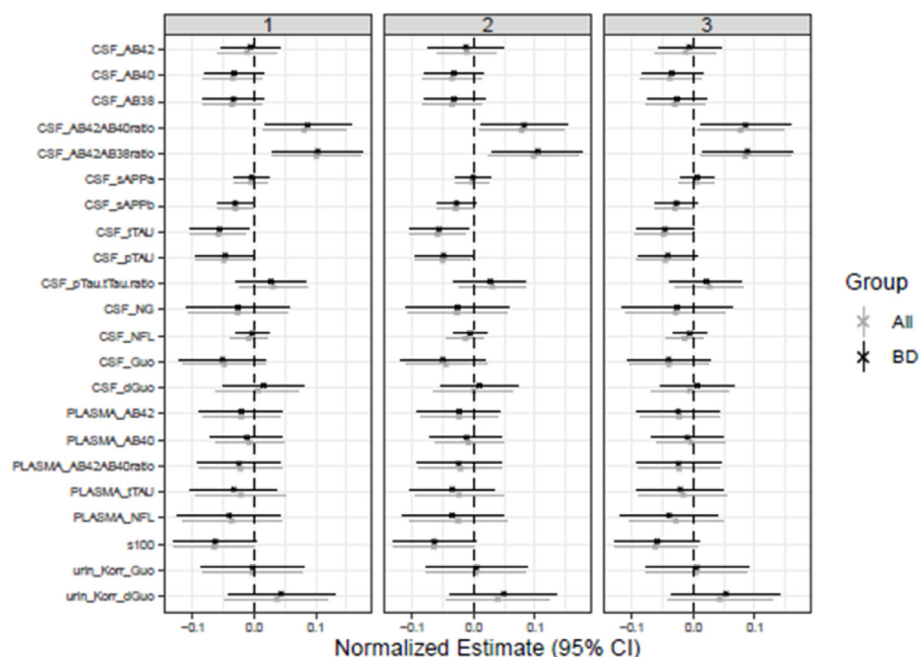
Fig. 3. Legend: Forest Plot of Estimates Based on All Participants and Patients with Bipolar Disorder Footnote: The figure shows normalized estimates of 95% intervals of confidence visualized in a forest plot. The estimates and intervals of confidence are normalized with the standard deviation for the outcomes of HC at baseline. The estimates are changes in the number of standard deviations when the sleep score increases by one point. 1,2, and 3 refer to models 1, 2, and 3.

affective relapse. Secondly, we found no statistically significant associations between sleep and CSF-Aβ42 or any of the related biomarkers for AD, neurodegeneration and oxidative stress when corrected for multiple testing. Thirdly, we identified positive associations between sleep scores and CSF-Aβ42/40 ratio and CSF-Aβ42/38 ratio (worse sleep was associated with higher Aβ42/40 and Aβ42/38 ratios), and negative associations between sleep and levels of CSF-t-tau (worse sleep was associated with lower CSF-t-tau) in all levels of adjustments, however not when corrected for multiple testing since the association between sleep and CSF-Aβ42 was defined as the primary outcome.

We have previously found that both decreasing global cognition and verbal memory were significantly associated with decreasing CSF-Aβ42 (unpublished data). Furthermore, we previously found that decreasing CSF-Aβ42/40 ratio, CSF-Aβ42/38 ratio, and decreasing concentrations of CST-t-tau were associated with decreasing global cognitive function in the same study sample as in the present. Thus, these findings are not in line with Rolstad et al., who found that higher ratios of CSF-Aβ42/40 were associated with decreased cognitive performance in 82 euthymic patients with BD (Rolstad et al., 2015). Rolstad et al. found their finding puzzling, but we find similar increases in CSF amyloid ratios associated with poorer sleep.

In a study of cognitively healthy adults at risk for AD (N = 101, age 62.9 ± 6.2 years) self-report of poor sleep was associated with low Aβ42/40 ratio (Sprecher et al., 2017). Studies of polysomnography data have interestingly found that in a sample of healthy participants (N = 13) five to eight consecutive nights of partial sleep-deprivation, with preserved slow-wave sleep, had no effect on CSF concentrations of Aβ42, Aβ40, Aβ38, p-tau, p-tau, and NF-L (Olsson et al., 2018).

However, in a study of healthy participants (N = 17) an intervention <u>with</u> slow wave activity disruption increased amyloid-β levels acutely, and poorer sleep quality over several days increased tau (Ju et al., 2017). It was hypothesized that since these effects were specific to neuronally-derived proteins, they are likely driven by changes in neuronal activity during disrupted sleep (Ju et al., 2017).

Interestingly, associations between slow wave activity and mood states have been suggested (Eidelman et al., 2010; Soehner et al., 2018). As we did not perform detailed sleep analysis (polysomnography data), it is not possible to establish whether the normal diurnal amyloid fluctuations in CSF, slow wave sleep patterns and sleep-related clearance of amyloid species into CSF are disturbed in the participants in our study.

The findings of this present study suggest that changes in the dynamics of amyloid and tau are linked to sleep but changes during sleep do not resemble patterns seen in the AD syndrome. However, changes in the dynamics of amyloid and tau during an affective episode may contribute to neurotoxicity along the trajectory to AD. This present finding strengthens the evidence regarding changes in the dynamics of amyloidosis as a contributing etiological factor for cognitive impairment in BD. Notably, the revealed associations between abnormalities in sleep and changes in CSF-Aβ42/40 ratio, CSF-Aβ42/38 ratio, and CSF-total tau do not clarify which comes first. Changes in amyloid in the brain may lead to sleep disruption or sleep disruption may lead to amyloid deposits in the brain or both in a vicious cycle (Wang and Holtzman, 2020). Interestingly, a prior study on short-term sleep deprivation in young individuals with normal sleep patterns showed no effect on CSF biomarkers for amyloid deposition and, neuronal injury including NF-L.

Regarding oxidative stress Cudney suggested that circadian disturbance was independently associated with increased lipid peroxidation in 52 patients with BD (p < 0.005) (Cudney et al., 2014). Our data did not confirm an association between abnormalities in sleep and oxidative stress. Previously, we found no association between perceived stress and neither systemic nor central oxidative stress in patients with BD (Knorr et al., 2021).

Clinical characteristics showed no significant differences between patients who had a relapse or not (See Table 1 in (Knorr et al., 2019)). Within the subset of BD patients that had a relapse, we previously found no statistically significant effect of the polarity of a relapse, clinical subtypes BD I/II, prior history of psychoses or mood fluctuations during a one-year follow-up regarding global cognitive function (Knorr et al., 2020). Furthermore, there were no statistically significant differences between global cognitive scores or any of the cognitive subdomains between patients with BD with (BD-E) and without (BD-NE) an affective relapse during follow-up at neither T0 nor T3 (Knorr et al., 2020).

Associations between sleep quality and biomarkers for neurodegeneration have been investigated in other major diseases in which sleep is affected e.g., obstructive sleep apnoea syndrome (OSAS), narcolepsy, and REM Sleep Behavior Disorder (RBD). Thus, no statistically significant associations were found between NFL and increasing severity of OSAS (Arslan et al., 2021), and the measurements of CSF total-tau, phosphorylated-tau, amyloid-beta 1–40 and 1–42, and NFL proteins were not informative in narcolepsy (Baiardi et al., 2020). Further, in the

Table 2

Associations between Hamilton Depression Scales Scores for sleep and concentrations of a line of biomarkers for Alzheimer's disease and neurodegeneration.

Biomarker	Group	n	analysis 1	analysis 2	analysis 3
CSF AB42	All	100	−1.776(-9.046 - 5.495), 0.625 / 0.818	−1.692(-8.975 - 5.591), 0.642 / 0.818	−1.908(-9.463 - 5.647), 0.613 / 0.817
CSF AB40	All	100	−0.046(-0.108 - 0.016), 0.144 / 0.441	−0.045(-0.107 - 0.017), 0.147 / 0.441	−0.049(-0.114 - 0.015), 0.129 / 0.441
CSF AB38	All	100	−0.021(-0.048 - 0.007), 0.134 / 0.441	−0.02(-0.047 - 0.007), 0.147 / 0.441	−0.017(-0.045 - 0.01), 0.204 / 0.528
CSF AB42AB40ratio	All	100	0.001(0−0.001), 0.02 / 0.219	0.001(0−0.001), 0.025 / 0.219	0.001(0−0.001), **0.034** / 0.239
CSF AB42AB38ratio	All	100	0.002(0.001−0.004), 0.006 / 0.219	0.002(0.001−0.004), 0.009 / 0.219	0.002(0−0.004), **0.024** / 0.219
CSF sAPPa	All	100	−0.571(-3.696 - 2.554), 0.714 / 0.857	−0.306(-3.429 - 2.817), 0.844 / 0.915	0.538(-2.641 - 3.717), 0.733 / 0.871
CSF sAPPb	All	100	−6.435(-12.401 to −0.469), 0.035 / 0.239	−6.008(-12.04 - 0.023), 0.051 / 0.261	−6.195(-12.65 - 0.26), 0.059 / 0.261
CSF tTAU	All	100	−4.111(-7.278 to −0.943), 0.012 / 0.219	−4.131(-7.302 to −0.96), 0.012 / 0.219	−3.394(-6.582 to −0.207), **0.037** / 0.239
CSF pTAU	All	100	−0.427(-0.816 to −0.038), 0.033 / 0.239	−0.443(-0.831 to −0.054), 0.027 / 0.222	−0.391(-0.795 - 0.013), 0.057 / 0.261
CSF pTau.tTau.ratio	All	100	0.008(-0.006 - 0.023), 0.259 / 0.619	0.008(-0.007 - 0.023), 0.267 / 0.619	0.007(-0.008 - 0.022), 0.337 / 0.683
CSF NG	All	100	−0.012(-0.048 - 0.024), 0.497 / 0.743	−0.012(-0.048 - 0.023), 0.489 / 0.743	−0.013(-0.049 - 0.023), 0.483 / 0.743
CSF NFL	All	100	−0.008(-0.035 - 0.019), 0.564 / 0.759	−0.013(-0.04 - 0.014), 0.352 / 0.683	−0.013(-0.041 - 0.015), 0.357 / 0.683
CSF Guo	All	102	−0.018(-0.042 - 0.006), 0.144 / 0.441	−0.016(-0.04 - 0.007), 0.167 / 0.47	−0.014(-0.037 - 0.009), 0.219 / 0.555
CSF dGuo	All	102	0.004(-0.046 - 0.055), 0.864 / 0.927	0(-0.048 - 0.048), 0.998 / 0.998	−0.005(-0.052 - 0.043), 0.846 / 0.915
Plasma AB42	All	129	−0.05(-0.2 - 0.1), 0.513 / 0.743	−0.056(-0.206 - 0.094), 0.459 / 0.743	−0.054(-0.205 - 0.098), 0.482 / 0.743
Plasma AB40	All	130	−0.432(-3.651 - 2.786), 0.791 / 0.892	−0.468(-3.677 - 2.741), 0.773 / 0.892	−0.184(-3.341 - 2.974), 0.908 / 0.953
Plasma AB42AB40ratio	All	129	0(-0.001 - 0), 0.502 / 0.743	0(-0.001 - 0), 0.517 / 0.743	0(-0.001 - 0), 0.492 / 0.743
Plasma tTAU	All	130	−0.019(-0.084 - 0.045), 0.548 / 0.752	−0.021(-0.085 - 0.043), 0.513 / 0.743	−0.015(-0.078 - 0.049), 0.648 / 0.818
Plasma NFL	All	129	−0.021(-0.069 - 0.026), 0.37 / 0.688	−0.015(-0.061 - 0.032), 0.528 / 0.743	−0.017(-0.061 - 0.028), 0.455 / 0.743
s100	All	130	−0.034(-0.068 - 0), 0.053 / 0.261	−0.034(-0.068 - 0.001), 0.054 / 0.261	−0.032(-0.067 - 0.003), 0.071 / 0.286
urin Korr Guo	All	130	−0.001(-0.028 - 0.027), 0.956 / 0.963	0.001(-0.027 - 0.029), 0.941 / 0.962	0.001(-0.027 - 0.029), 0.927 / 0.962
urin Korr dGuo	All	130	0.015(-0.019 - 0.049), 0.382 / 0.7	0.016(-0.018 - 0.05), 0.357 / 0.683	0.018(-0.016 - 0.052), 0.308 / 0.683
CSF AB42	BD	62	−0.914(-8.3 - 6.473), 0.804 / 0.892	−1.954(-11.188 - 7.279), 0.667 / 0.822	−0.974(-8.629 - 6.68), 0.798 / 0.892
CSF AB40	BD	62	−0.044(-0.106 - 0.019), 0.166 / 0.47	−0.042(-0.105 - 0.021), 0.188 / 0.507	−0.046(-0.11 - 0.019), 0.16 / 0.47
CSF AB38	BD	62	−0.019(-0.047 - 0.009), 0.173 / 0.477	−0.018(-0.046 - 0.01), 0.197 / 0.519	−0.015(-0.043 - 0.012), 0.273 / 0.621
CSF AB42AB40ratio	BD	62	0.001(0−0.001), **0.016** / 0.219	0.001(0−0.001), **0.023** / 0.219	0.001(0−0.001), **0.023** / 0.219
CSF AB42AB38ratio	BD	62	0.002(0.001−0.004), **0.006** / 0.219	0.002(0.001−0.004), **0.006** / 0.219	0.002(0−0.004), **0.02** / 0.219
CSF sAPPa	BD	62	−0.446(-3.626 - 2.735), 0.779 / 0.892	−0.133(-3.308 - 3.042), 0.933 / 0.962	0.705(-2.376 - 3.786), 0.643 / 0.818
CSF sAPPb	BD	62	−6.442(-12.565 to −0.318), 0.04 / 0.239	−5.788(-12.035 - 0.458), 0.068 / 0.281	−5.699(-12.542 - 1.143), 0.099 / 0.364
CSF tTAU	BD	62	−3.973(-7.263 to −0.684), **0.019** / 0.219	−3.995(-7.279 to −0.711), **0.018** / 0.219	−3.221(-6.513 - 0.071), **0.055** / 0.261
CSF pTAU	BD	62	−0.41(-0.816 to −0.003), 0.048 / 0.261	−0.429(-0.833 to −0.024), 0.039 / 0.239	−0.358(-0.776 - 0.059), 0.089 / 0.344
CSF pTau.tTau.ratio	BD	62	0.007(-0.008 - 0.023), 0.346 / 0.683	0.007(-0.009 - 0.023), 0.363 / 0.685	0.006(-0.01 - 0.022), 0.469 / 0.743
CSF NG	BD	62	−0.012(-0.048 - 0.025), 0.518 / 0.743	−0.012(-0.049 - 0.025), 0.523 / 0.743	−0.012(-0.051 - 0.028), 0.552 / 0.752
CSF NFL	BD	62	−0.003(-0.028 - 0.021), 0.793 / 0.892	−0.005(-0.03 - 0.019), 0.651 / 0.818	−0.005(-0.03 - 0.02), 0.674 / 0.822
CSF Guo	BD	62	−0.019(-0.044 - 0.007), 0.145 / 0.441	−0.018(-0.043 - 0.006), 0.145 / 0.441	−0.015(-0.039 - 0.009), 0.229 / 0.56
CSF dGuo	BD	62	0.011(-0.037 - 0.06), 0.644 / 0.818	0.007(-0.041 - 0.054), 0.778 / 0.892	0.005(-0.041 - 0.05), 0.84 / 0.915
Plasma AB42	BD	85	−0.05(-0.207 - 0.107), 0.529 / 0.743	−0.056(-0.213 - 0.101), 0.482 / 0.743	−0.058(-0.218 - 0.101), 0.468 / 0.743
Plasma AB40	BD	86	−0.707(-4.068 - 2.655), 0.677 / 0.822	−0.702(-4.06 - 2.656), 0.679 / 0.822	−0.547(-3.861 - 2.768), 0.744 / 0.877
Plasma AB42AB40ratio	BD	85	0(-0.001 - 0), 0.468 / 0.743	0(-0.001 - 0), 0.478 / 0.743	0(-0.001 - 0), 0.486 / 0.743
Plasma tTAU	BD	86	−0.03(-0.091 - 0.032), 0.341 / 0.683	−0.031(-0.092 - 0.03), 0.318 / 0.683	−0.019(-0.08 - 0.043), 0.546 / 0.752
Plasma NFL	BD	85	−0.024(-0.073 - 0.025), 0.332 / 0.683	−0.021(-0.069 - 0.028), 0.4 / 0.723	−0.023(-0.069 - 0.024), 0.329 / 0.683
s100	BD	86	−0.033(-0.068 - 0.002), 0.061 / 0.261	−0.033(-0.068 - 0.002), 0.061 / 0.261	−0.031(-0.066 - 0.005), 0.092 / 0.347
urin Korr Guo	BD	86	−0.001(-0.029 - 0.027), 0.952 / 0.963	0.002(-0.027 - 0.03), 0.91 / 0.953	0.002(-0.026 - 0.03), 0.891 / 0.949
urin Korr dGuo	BD	86	0.018(-0.017 - 0.053), 0.318 / 0.683	0.02(-0.015 - 0.055), 0.267 / 0.619	0.022(-0.014 - 0.057), 0.228 / 0.56

Footnote: Results of exploratory analyses are presented as regression coefficient (0.95% CI), p-value/adjusted p-value. Analysis 1 refers to the unadjusted analysis, analysis 2 refers to the adjustment for age and gender. Analysis 3 refers to the correction for gender, age, smoking, alcohol, and medication.

Parkinson Progression Marker Initiative cohort, early Parkinson's disease patients with RBD showed lower CSF Aβ42 levels, which predicted faster cognitive decline (Liguori et al., 2019).

The limitations of the study were the modest sample size. Furthermore, with a longer follow-up period, the effect of multiple relapses could have been estimated. The patients were appointed to a specialty mood disorder clinic for treatment of bipolar disorders and the close follow-up may have prevented more relapses. However, it probably facilitated the high adherence to the study protocol.

In conclusion, we cannot exclude that attenuated sleep during an affective episode may impact the dynamics of amyloid and tau concentrations in CSF in patients with BD and HC individuals. This highly important area of research needs more investigations. Future prospective case-control studies may investigate the possible sleep-related clearance of amyloid species into CSF by assessing amyloid concentrations in CSF during euthymia and affective relapses, and slow wave sleep patterns in patients with BD across a wide age range.

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Declaration of competing interest

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