Poor sleep correlates with biomarkers of neurodegeneration in mild traumatic brain injury patients: a CENC study

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Abstract

Study Objectives: Sleep disorders affect over half of mild traumatic brain injury (mTBI) patients. Despite evidence linking sleep and neurodegeneration, longitudinal TBI-related dementia studies have not considered sleep. We hypothesized that poor sleepers with mTBI would have elevated markers of neurodegeneration and lower cognitive function compared to mTBI good sleepers and controls. Our objective was to compare biomarkers of neurodegeneration and cognitive function with sleep quality in warfighters with chronic mTBI.

Methods: In an observational warfighters cohort (n = 138 mTBI, 44 controls), the Pittsburgh Sleep Quality Index (PSQI) was compared with plasma biomarkers of neurodegeneration and cognitive scores collected an average of 8 years after injury.

Results: In the mTBI cohort, poor sleepers (PSQI ≥ 10, n = 86) had elevated plasma neurofilament light (NfL, x̄ = 11.86 vs 7.91 pg/mL, p = 0.0007, d = 0.63) and lower executive function scores by the categorical fluency (x̄ = 18.0 vs 21.0, p = 0.0005, d = −0.65) and stop-go tests (x̄ = 30.1 vs 31.1, p = 0.024, d = −0.37). These findings were not observed in controls (n = 44). PSQI predicted NfL (beta = 0.22, p = 0.0002) and tau (beta = 0.14, p = 0.027), but not amyloid β42. Poor sleepers showed higher obstructive sleep apnea (OSA) risk by STOP-BANG scores (x̄ = 3.8 vs 2.7, p = 0.0005), raising the possibility that the PSQI might be partly secondary to OSA.

Conclusions: Poor sleep is linked to neurodegeneration and select measures of executive function in mTBI patients. This supports implementation of validated sleep measures in longitudinal studies investigating pathobiological mechanisms of TBI related neurodegeneration, which could have therapeutic implications.

Statement of Significance

Traumatic brain injury (TBI) and sleep disorders are each independently associated with neurodegeneration. However, longitudinal TBI studies measuring the incidence of dementia or biomarkers of neurodegeneration have not considered potential neurodegenerative effects of sleep. We hypothesized that poor sleep quality would be associated with biomarkers of neurodegeneration and decreased cognitive performance assessed after mild traumatic brain injury (mTBI). Sleep quality scores, plasma biomarkers of neurodegeneration and cognitive scores were collected 2–15 years after TBI and compared. Our data show that sleep quality correlates with plasma levels of neurofilament light and tau as well as two independent measures of cognitive ability. If directionality is established in longitudinal studies with objective sleep data, disrupted sleep physiology may represent a novel, treatable pathomechanism of TBI-associated dementia.

Key words: traumatic brain injury; sleep disorders; military health; dementia; neurofilament; tau; amyloid

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**Introduction**

Large retrospective studies have associated mild traumatic brain injury (mTBI) in early to mid-life with neurodegenerative disease in late life [1–3]. It is also well established that after a TBI, acute elevations in neurofilament light (NFL), tau, and amyloid beta, among others, in the blood and cerebrospinal fluid (CSF) are reliable biomarkers of injury severity [4–7]. Elevated levels may persist for many years and correlate with cognitive outcomes [8–10]. Pathobiological mechanisms of mTBI-related neurodegenerative disease have not yet been fully elucidated. These biomarkers of neurodegeneration have also been shown to correlate with the progression of neurodegenerative disease [11, 12], suggesting their measurement in TBI patients may inform long-term neurodegenerative outcomes.

In studies unrelated to TBI, these same biomarkers of neurodegeneration have been linked to sleep restriction in animals [13, 14] and sleep disorders or sleep deprivation in humans [15–19], implicating a two-way relationship between sleep physiology and Alzheimer’s disease pathogenesis [20]. In the general population, large scale cross-sectional and longitudinal studies have also shown that untreated sleep disorders significantly increase Alzheimer’s risk [21, 22]. Acute sleep deprivation experiments in humans also reveal accumulation of other neurodegenerative biomarkers such as alpha synuclein and tau, which are related to Parkinson’s and other forms of dementia [13], but longitudinal work has not yet demonstrated the link between sleep and these diagnoses. While multiple mechanisms likely underlie the relationship between sleep disorders and neurodegeneration, emerging data implicate disruption of sleep-regulated metabolic waste clearance mechanisms, such as the glymphatic system, resulting in the accumulation of putatively harmful metabolites (e.g. NFL, tau, and Aβ42), markers of neuronal injury and neurodegeneration [23, 24].

Importantly, warfighters with TBI have an elevated incidence of sleep disorders such as insomnia and obstructive sleep apnea (OSA), with reported prevalences of 30 to 75% [25, 26]. Furthermore, sleep disorders such as OSA and subjective poor sleep quality correlate with post-TBI neurobehavioral, cognitive, pain, and posttraumatic stress symptoms [27, 28]. Given their overlap as potential underlying mechanisms for neurodegeneration, it is reasonable to suspect both sleep disorders and TBI could synergistically drive the pathology.

Notably, some authors have questioned whether, in the setting of TBI, sleep might partly contribute to dementia pathogenesis, and they note that sleep has largely been overlooked in studies of TBI-related dementia to date [29]. Indeed, no studies have yet examined whether biomarkers of neurodegeneration are linked to sleep measures in chronic (greater than three months since injury), TBI patients. If TBI-associated dementia is partly caused by sleep disorders or poor sleep quality, then preventative measures could be introduced to reduce the risk of neurodegeneration.

We hypothesize that pathological sleep is associated with elevations in biomarkers of neurodegeneration to include plasma NFL, tau, and Aβ42 and that it may also correlate with decreased cognitive performance on select measures of executive function. We further hypothesize that these correlations will be more robust in TBI patients compared to healthy controls, partly due to the increased metabolic byproducts triggered by an injury, which could theoretically increase the impact of poor sleep [30]. In this study, we explored whether the Pittsburgh Sleep Quality Index (PSQI), a subjective measure of sleep quality often used as an approximation for pathological sleep such as insomnia, sleep apnea, or insufficient sleep syndrome [31, 32], was associated with derangements in plasma NFL, tau, or Aβ42, each a separate outcome, in patients with mTBI as well as in controls. Secondary analyses included a comparison of cognitive score outcomes between good and poor sleepers, which are defined in the methods. Neurobehavioral symptom questionnaires and OSA risk were also compared among groups, and mTBI was evaluated as a potential mediator and modifier of the outcomes.

**Methods**

**Participants, procedures, and study design**

This is a retrospective cross-sectional analysis using available baseline measurements of participants enrolled between 2015 and 2016 in the ongoing Chronic Effects of Neurotrauma Consortium (CENC) longitudinal study. The CENC study is a prospective multisite observational study of “warfighters,” or combat-exposed US military servicemembers and veterans with or without chronic mTBI due to impact and/or blast any time after September 11, 2001 [33]. Because mTBI is the most common injury after combat deployments, CENC was funded to focus exclusively on mTBI. Diagnosis of mTBI during enrollment occurred via an in-depth structured interview process screening for all potential concussive events during military deployments and across the entire lifetime, including childhood, using a modification of the Ohio State University TBI Identification (OSU TBI-ID) instrument [34]. Each potential concussive event identified is then interrogated to determine whether or not it was a true clinical mTBI via a detailed structured interview, the Virginia Commonwealth University retrospective concussion diagnostic interview [35], rendering a preliminary TBI diagnosis of mTBI or not mTBI through an embedded algorithm using the structured interview data and based on the DoD/VA common definition of mTBI [36]. Every preliminary TBI diagnosis is reviewed and vetted against the unstructured free-text portion of the interview and against any found medical documents recorded in proximity to the event (i.e. first responder, emergency department or in-theatre documentation). Using this process, the site principal investigator (PJ) confirms or overrides every preliminary mTBI diagnosis to yield the final diagnosis, mTBI versus not mTBI. If any doubt remains the case is adjudicated by a central diagnosis committee consisting of national experts in TBI. This process is also used to further assess eligibility in terms of whether any event was a TBI of greater severity than mild (moderate or severe). Exclusion criteria included moderate, severe, or penetrating TBI, as described above. Posttraumatic stress disorder (PTSD) and mood disorder were not excluded because of their high prevalence and previously reported correlation with poor sleep quality [27]. All data used in this study, including blood draws (performed between 8 am and 3 pm), questionnaires, and neuropsychological testing, were performed as part of the CENC enrollment protocol at their base-line visit. Procedures and analyses of the CENC protocol were approved by institutional review boards in accordance with federal regulations.

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**References**

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Peripheral blood samples were drawn into polypropylene tubes between, aliquoted for serum, and stored at ~80°C until batch processing using an ultrasensitive, digital immunoassay analyzer capable of single-molecule array (Simoa, Quanterix Corporation, Lexington, MA). 

\[ \text{Aβ42, total tau, and NFL were probed using reagent kits (Quanterix Corporation, Lexington, MA). The Aβ42, NFL, and tau assays have lower limits of detection at 0.045, 0.038, and 0.019 pg/mL, respectively. Groups were randomly distributed across plates, and all assays were tested in duplicate in each run along with calibrators and positive and negative controls provided with the reagent kits. All intra- and interplate coefficient of variation (CV) values were less than 15%.} \]

**Pittsburgh Sleep Quality Index**

Sleep quality was assessed with the PSQI, a standardized self-report scale [0–21] that includes estimates total sleep per night and quality of the sleep that was previously validated in TBI patients [31, 37]. In civilian populations, a cutoff of 5 or 8 has been validated to identify sleep disorders such as insomnia. However, in military populations, where sleep is routinely disrupted, Matsangas et al. demonstrated that a cutoff of 5 in the military population was only 4%–8% specific for detecting clinically significant insomnia, while a cutoff of 10 was 90% sensitive and 69% specific. This elevated cutoff requirement is thought to be secondary to the unpredictable schedules endemic in military lifestyles where the average sleep duration at night was found to be 6 h [32].

**Cognitive tests and other behavioral instruments**

Cognitive domains frequently impacted by mTBI and sleep disorders were selected for analysis from a larger neuropsychological battery, focusing on memory and executive function [38–42]. The three executive function domains reviewed by Diamond: cognitive flexibility, inhibitory control, and working memory were assessed [43]. Cognitive flexibility was assessed with categorical fluency testing from the Delis–Kaplan Executive Function System battery [44]. Inhibitory control was assessed via the Flanker Inhibitory Control Test of the National Institutes of Health Toolbox Cognition Battery, commonly referred to as the “stop-go” test. Working memory was assessed via the Digit Span Backwards subtest of the Wechsler Adult Intelligence Scale 4th version (WAIS-IV). Delayed verbal learning and memory were assessed with the California Verbal Learning Test, second edition (CVLT-II) [45]. A modified version of the STOP-BANG questionnaire was used to assess OSA risk in which items from the PSQI questionnaire were used as proxies for the first two STOP items (“Snoring” and “Tired”), and an item from the Behavioral Risk Factor Surveillance System (BRFSS) questionnaire was used as a proxy for the last STOP item, (“pressure”). For the BANG portion, actual measurements were used for “Body Mass Index” and “Neck” size instead of self-report. Age and gender were captured from the demographics form. The Neurobehavioral Symptom Inventory (NSI) is a 22-item self-report questionnaire designed to assess postconcussive symptom severity in vestibular, somatic, cognitive, and affective domains. Individuals rated the severity of common symptoms in terms of “how much they have disturbed you over the past month” on a scale ranging from 0 (none) to 4 (very severe) [46, 47]. The Medical Symptom Validity Test is a test for identifying poor effort and reliability in neurocognitive assessments, where scores are deemed unreliable if <85% [48]. Analyses were performed both with and without scores that were deemed unreliable.

**Statistical analysis**

For comparisons between control and TBI groups, we used either Student’s t test or Mann–Whitney U test as appropriate. Multiple comparisons were corrected using the Benjamini–Hochberg procedure. Subsequent multiple linear regression models controlled for covariates as described in the results and tested for interaction between mTBI and PSQI resulting in further subgroup analyses on control and TBI groups. Possibility of mediation was assessed following Baron and Kenny’s mediation model, using bivariate tests to evaluate mTBI relationship with the outcomes, as well as verifying the impact of mTBI status in a model with PSQI [49]. Effect sizes were reported as Cohen’s d and standardized beta coefficients. Two-tailed tests were performed using a type I error of \( p < 0.05 \) to determine significance, and all analyses were performed with R (R, v.3.1.1, Foundation for Statistical Computing).

**Results**

From the original dataset 195 CENC participants with available blood sample data, 182 had valid biomarker measurements and had completed baseline enrollment to include blood biomarker measurements and cognitive testing. The chronic mTBI (mean duration since last mTBI = 8.3 years) and non-TBI (control) populations had similar demographics. Overall, mTBI participants had worse sleep quality than controls denoted by PSQI as shown in Table 1 (\( p = 0.015 \)). Compared to controls, mTBI participants had no significant differences in NFL, tau, Aβ42, and cognitive test scores (data not shown).

For our primary analysis, we looked for a link between PSQI and markers of neurodegeneration. We wondered whether those mTBI participants with poor sleep quality may have different outcomes compared to their good sleeper counterparts. An initial linear regression for the biomarkers including mTBI status, PSQI, an interaction of the two, while controlling for age, BMI, ApoE4 status, and gender, revealed a significant interaction in the model for tau (\( p = 0.03 \)), and nonsignificant for NFL (\( p = 0.16 \)) and AB42 (\( p = 0.97 \)). All three models also showed the main effect of mTBI status was not significant at the 0.05 level. The significant interaction suggests that mTBI is a possible effect moderator for the relationship between PSQI and tau. We therefore conducted separate analyses for each mTBI group with the biomarkers. For consistency, this was done for all three biomarkers.

Further, we additionally wondered if the effects of poor sleep combined with mTBI might reveal a difference between mTBI and controls in the neurodegenerative biomarker outcomes. We isolated the poor sleepers (\( n = 99 \)) of both mTBI and control groups using the recommended PSQI cutoff of \( \geq 10 \) for the military [32] (see Methods), creating four subgroups. Among poor sleepers, tau was the only significantly elevated biomarker, with a moderate effect size in the mTBI group compared to controls (pg/mL, \( \bar{x} = 2.60, \) and 1.88 respectively, \( d = 0.57, p = 0.005 \)). As shown in Table 1, demographics remained similar between
these subgroups, and no differences were observed in mTBI subpopulations comparing overall number, timing, or type (blast vs nonblast) of mTBIs. Notably, OSA risk by STOP BANG score and neurobehavioral symptoms by NSI were elevated in the poor sleepers compared to the good sleepers in both mTBI and control groups. In the control group, no differences in levels of plasma NfL, tau, or Aβ elevation of plasma tau (β = –0.65) and a small but significant reduction as did time since mTBI (β = 0.63) and a trend toward the delayed verbal memory subtest of the CVLT-II (mTBI poor sleepers vs. controls, β = –0.65) and a small but significant reduction in the stop-go test (β = 0.63). These findings suggest that poor sleep may contribute to neurodegeneration in both mTBI and control populations.

In our secondary analysis, we compared cognitive scores between good and poor sleepers. In the mTBI population, poor sleepers had lower executive function scores by the categorical fluency test (d = –0.65) and a small but significant reduction in the stop-go test (d = –0.37) but had no differences in measures of working memory by digits backwards (see Figure 2) or the delayed verbal memory subset of the CVLT-II (mTBI poor sleeper x = 10.10 versus mTBI good sleeper x = 10.51, p = 0.51; control poor sleeper x = 7.89 versus control good sleeper x = 9.96, p = 0.07). We constructed linear regression models of cognitive tests controlling for age, sex, BMI, and education, finding that both PSQI (βadj = –0.26, p = 0.009) and plasma NfL (βadj = –0.25, p = 0.009) negatively correlated with categorical fluency (but not other cognitive tests) in the mTBI but not in control group (Figure 2). Number and timing of mTBIs had no correlation with or interaction with cognitive scores. All comparisons remained significant after removing four outliers and/or removal of four potentially unreliable survey results by the medical symptom validity test.
Discussion

We compared sleep quality and markers of neurodegeneration in a population of warfighters with and without mTBI. Although no differences in tau, NFL, or Aβ42 were found between mTBI and controls when examining the whole population, restricting the comparison to the poor sleepers unmasked a significant elevation in plasma tau in mTBI compared to controls. Furthermore, although plasma NFL was not elevated in mTBI poor sleepers compared to control poor sleepers, NFL was significantly elevated in poor sleepers with mTBI compared to good sleepers with mTBI. Together, these findings raise the possibility that comorbid poor sleep with mTBI may have a synergistic effect on neurodegeneration.

Regarding the findings in controls, we saw no significant differences in tau or Aβ42 in poor sleepers compared to good sleepers, although we saw a trend towards elevated plasma NFL and a moderate correlation was observed with NFL and PSQI. This can likely be explained, in part, by the fact that they utilized CSF instead of plasma. Neither tau nor Aβ42, when measured in plasma, have been known to correlate with CSF values, and they are prone to noise coming from plasma [52, 53]. Sample size may also partly explain these differences, and also our population had different demographics (military, predominantly male, younger). It is also possible that inconsistent circadian timing of blood draws in our study lowered sensitivity for detecting relevant differences, as some evidence suggests that some biomarkers of neurodegeneration such as Aβ42 can have a diurnal concentration pattern that may or may not be related to slow-wave activity during sleep [54, 55]. Notably, ApoE4 status also moderately correlated with NFL in controls but not in mTBI, which might simply be related to the overwhelming NFL likely liberated by mTBI and possibly related to subjective sleep quality or diagnosed sleep disorders.

Regarding the findings in mTBI patients, we found that sleep quality correlated moderately with plasma NFL and tau but not Aβ42. Furthermore, poor sleepers had lower executive function scores by the categorical fluency and stop-go tests. Lastly, categorical fluency scores moderately correlated with NFL and mTBI status, suggesting there may be a link between sleep, neurodegeneration, and executive function in the setting of mTBI.

No prior published studies have examined the correlation of sleep quality and biomarkers of neurodegeneration in a TBI population. However, multiple studies have demonstrated that CSF or plasma levels of NFL, tau, and Aβ42 correlate with sleep disorders in healthy adults [18, 56]. This was partly replicated in our study excepting Aβ42—perhaps due to sample size, or limitations of plasma compared to CSF levels.

Our findings could be explained by increased metabolite production and/or impaired glymphatic clearance—both of which may occur after TBI—due to sleep disorders and persistent or new structural damage, causing accumulation of potentially toxic tau, and NFL. This is supported by findings in animal models that glymphatic clearance is reduced after TBI leading to tau accumulation [57, 58]. An additional explanation to consider in future studies includes chronic hypoxia and inflammation secondary to...
OSA. The poor sleepers in our study had significantly increased risk of OSA compared to good sleepers (Table 1), and this has also been independently associated with neurodegeneration [18, 19, 56]. However, we did not have data on OSA diagnoses in our population to corroborate this risk. Alternatively, chronic TBI may be the sole etiology of elevated biomarkers and poor sleep quality, independently. This seems less likely considering the known effects of sleep disorders on biomarker levels and the lack of tau correlation with number or timing of TBIs.

One limitation of this work is the cross-sectional nature of our study, making directionality impossible to assess. Similarly, our snapshot of sleep quality via PSQI assesses only the “last 30 days” of sleep quality and may not be representative of the chronic sleep patterns over the previous years. Another important limitation includes our moderate sample size in the mTBI population and small sample size in the controls. As noted above, the healthy controls data did not completely reflect that of other studies, which were larger in some cases and which utilized CSF instead of plasma. This could limit the generalizability of these results from the controls. We did, however, observe that NfL correlates with PSQI in the controls, and a trend of elevated NfL was observed in poor sleeper controls compared to good sleeper controls. Additionally, the limited selection of cognitive tests, lack of objective sleep measures, lack of formal sleep diagnoses, and unavailable premorbid sleep data are important limitations. We relied on subjective sleep quality to serve as a surrogate for putative sleep disorders—most commonly insomnia, OSA, and insufficient sleep syndrome. Although the increased STOP-BANG scores in the poor sleepers might suggest that OSA played a partial role in our sleep-related observations, diagnostic data will be required to explore such a hypothesis. Should these patients have had sleep disorders prior to injury, they may already have begun to accumulate markers of neurodegeneration prior to their mTBI. However, this seems less likely given the strength of the ApoE4 correlation with neurodegenerative biomarkers observed in the non-TBI control participants. Meanwhile, the contribution of ApoE4 to the model of the mTBI group appears to be masked by the influence of PSQI in the model for this population. One additional limitation in this study is the absence of available diagnostic data for disorders such as PTSD, anxiety, depression, and chronic pain. These conditions were not excluded, and doing so would likely have eliminated a significant number of the

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**Figure 2.** Poor sleepers with mTBI have decreased mental flexibility and inhibitory control but no decreases in working memory or delayed verbal recall. The graphs illustrate cognitive tests in mTBI and control groups when controlling for age, sex, BMI, education, and ApoE4 status. (A) Categorical fluency was significantly lower in mTBI poor sleepers (PSQI ≥ 10) compared to mTBI good sleepers (PSQI < 10). Categorical fluency was also decreased but not significant in poor sleeper controls. (B) PSQI and NfL were not predictors of categorical fluency in the control group, however, they were significantly negatively correlated with categorical fluency in the mTBI group. (C) Stop-Go score was significantly reduced in mTBI poor sleepers. (D) Digits backwards score, evaluating working memory, was not significantly different between groups. BMI, body mass index; mTBI, mild traumatic brain injury; NfL, neurofilament light; PSQI, Pittsburgh Sleep Quality Index.
participants, especially the poor sleepers. The PTSD symptom checklist has been previously shown to have a strong correlation with sleep complaint questionnaires such as the ISI [27]. This highlights a distinct challenge in the field of TBI sleep research given the high prevalence of depression and PTSD after TBI, particularly in the military population [59].

A major strength of this study, regardless of directionality, is the identification of a robust link between sleep quality and neurodegeneration biomarkers in a chronic mTBI population. This is an important advance that justifies resource allocation to monitor sleep outcomes in longitudinal TBI studies and to consider the contribution of chronic sleep disorders to cognitive and neurodegenerative outcomes. This study is unique in that it evaluates neurodegenerative biomarkers in a relatively young population (average age is 37), likely decades before the development of dementia. A population such as this might be ideal for future preventative trials in the field of dementia and neurodegenerative disease. This work also adds potential normative data to the literature for the military population. Other important strengths in this study include relatively robust effect sizes despite the less-invasive use of plasma (rather than CSF) for biomarker measurements.

Future longitudinal studies should include objective sleep measures to investigate mechanistic underpinnings of our findings. If sleep disorders trigger neurodegeneration in these patients, it may be that increased diagnosis and treatment of sleep disorders could reduce, prevent or delay TBI-related dementia. Furthermore, targeted pharmacotherapies for TBI-related sleep disorders are not yet available, and objective biomarkers of sleep pathology in conjunction with biomarkers of neurodegeneration may yield novel insights that better inform the design, stratification, and pharmacodynamic monitoring of novel interventional trials.

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**Author Contributions**

J.K.W., R.N.R., J.G., and K.K. conceived and designed the study; K.K., J.G., C.L., and R.N.R. acquired the data; P.S., J.K.W., S.R., R.D.A., and J.U.P. contributed to the analysis of the data; and J.K.W., S.R., K.K., J.G., C.L., and R.N.R. acquired the data; P.S., J.K.W., S.R., R.D.A., J.U.P. contributed to the analysis of the data; and J.K.W., S.R., R.D.A., J.U.P. drafted a significant portion of the manuscript, tables and figures. All authors have reviewed the manuscript.

**Disclosure Statements**

The authors have no relevant financial interests to declare. The authors have no relevant non-financial interests to declare. The views expressed in this manuscript are those of the authors and do not necessarily represent the official policy or position of the Uniformed Services University, Defense Health Agency, Department of Army/Navy/Air Force, Department of Defense, Veterans Health Administration, U.S. Government, Defense and Veterans Brain Injury Center (DVBiC), or any other U.S. government agency. No official endorsement should be inferred.

**Data availability**

For more information, please contact dha.DVBICInfo@mail.mil. Anonymized data and statistical analysis code will be shared by request from any qualified investigator by determination of the Chronic Effects of Neurotrauma Consortium.

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