Title Page

Title: The Impact of Sleep Disturbances on Health Related Quality of Life in Children with Acquired Brain Injury after Critical Care

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Abstract

Background/Objective: Each year, more than 60,000 children with acquired brain injury (ABI) in the US require admission to the Pediatric Intensive Care Unit. Over 50% suffer sleep-wake disturbances (SWDs) in the months after hospital discharge. Given the importance of sleep to brain development and repair after injury, we hypothesized SWD would be associated with poorer health related quality of life (HRQOL) outcomes.

Methods: We performed a cross-sectional analysis of prospectively collected data in children with ABI aged 3-18 years evaluated 1 to 3-months after critical care hospitalization (N=151). SWDs were measured by the Sleep Disturbances Scale for Children and defined as any T-score ≥60 signifying moderate or severe risk of clinical sleep disorders. Overall HRQOL was measured by the Pediatric Inventory for Quality of Life, which defines the Minimal Clinically Important Difference (MCID) as 4.5 points in the total score. Secondary outcomes included PedsQL scores for Physical, Emotional, Social, and School Function domains. SWD groups were compared with Mann Whitney tests. Multiple linear regression evaluated association between SWDs and overall HRQOL controlling for patient and ABI characteristics. Significance was defined as p<.05.

Results: SWDs were present in 66% (n=100). HRQOL total score was significantly lower in children with SWDs (median=70; IQR=54, 80) versus without SWDs (median=85; IQR=67, 94; p<.001). Median scores in emotional, social, and school domains were significantly lower in the SWD group (all p<.01). When controlling for age, sex, critical care interventions, pre-admission comorbidities, and decline from pre-admission Functional Status Scale score, presence of SWDs significantly reduced HRQOL total score nearly 3 times the MCID (β-coefficient= -12.1; 95% Confidence Interval= -17.9, -6.2).

Conclusions: We found SWDs following ABI significantly decreased HRQOL overall and across multiple health domains in our sample. Sleep is potentially modifiable, and our data support future studies

targeting sleep to improve outcomes after ABI.

Introduction

Children admitted to the Pediatric Intensive Care Unit (PICU) for acquired brain injury (ABI) require specialized critical care intervention to minimize ongoing injury and optimize outcomes [1]. Operationally defined, ABI includes primary brain injury due to various etiologies including traumatic brain injury, sudden cardiac arrest, stroke, infection, or seizure, as well as ABI secondary to PICU-acquired morbidities like delirium, neuroactive medication exposure, and prolonged immobilization [2-5].

Many PICU survivors with ABI suffer from long-term consequences and impairments that impact their physical, cognitive, emotional, and social health, collectively termed Post-Intensive Care Syndrome (PICS) [6]. Health-related quality of life (HRQOL) is an aspect of PICS and often serves as a comprehensive approach to measuring health outcomes that evaluates an individual's psychosocial, emotional, and physical wellbeing [7]. As such, HRQOL is well-suited for evaluating the multidimensional impact on child and family health of PICU acquired morbidity and ABI [7,8]. While HRQOL outcomes do not measure all possible morbidities encompassed within PICS, it offers a quantifiable, subjective measure of how health following ABI impacts overall wellbeing and global health recovery [9]. Prior studies show reduced HRQOL in children with ABI in the months after hospital discharge with deficits across multiple health domains [8,10-16], akin to other pediatric chronic disease populations [17,18]. Moreover, numerous risk factors have been identified for poor HRQOL after ABI, including worsening from functional baseline, female sex, older age, premorbid chronic conditions, low socioeconomic status, increased length of hospital stay, and the need for critical care interventions while hospitalized [8,15,16,19-22].

Unfortunately, many of the risk factors for poorer HRQOL following ABI are non-modifiable and are often related to severity of illness/injury [8,13,18,20,21]. Sleep, however, is a specific factor integral to health and wellbeing that is potentially modifiable. Research shows that more than 50% of children with ABI experience sleep wake disturbances (SWD) in the months after hospital discharge [23]; however, few studies have evaluated the relationship between SWD and HRQOL after ABI. Sleep disturbances following ABI are prevalent across primary diagnoses and ages, and are even more common in those with pre-hospitalization chronic comorbidities [23]. Impaired sleep can persist for years after ABI, particularly with problems initiating or maintaining sleep [23-25]. Sleep is known to be crucial to childhood brain development and brain healing following injury [26], in that during sleep, the brain re-establishes synaptic and cellular homeostasis [27]. Studies show that the presence of SWD during brain development can impact long-term health of children through effects on consolidation of memories and synaptic plasticity [26,27]. Likewise, sleep disturbances in otherwise healthy children, and a variety of clinical populations, negatively impact multiple health domains including physical, cognitive, emotional, and social wellbeing [28,29].

Considering the above context, the primary aim of our study was to be among the first to evaluate the relationship between sleep and HRQOL in a cohort of pediatric ABI survivors after critical care. Given the importance of sleep to brain development, overall health, and repair after injury, we hypothesized SWDs would be associated with poorer global health outcomes measured by HRQOL.

Methods

Participants and Procedures

We performed a secondary cross-sectional analysis of data collected for a prospective observational study of children aged ≥3 to 18-years admitted to the PICU between November 2017 and January 2021 surviving to hospital discharge and referred for follow-up in the Pediatric Critical Care and Neurotrauma Recovery Program (PCCNRP) for ABI. Eligible patients completed a follow-up visit between 1 and 3-months after hospital discharge. PCCNRP referrals, follow-up patterns and program details were previously described [30-33]. In short, systematic referrals are placed for children with primary neurologic diagnoses (trauma, cardiac arrest, neuro-infectious and inflammatory conditions, stroke) and other patients are referred by clinical providers as needed. Follow-up rates are consistently >70% for PICU survivors. The Institutional Review Board at Oregon Health & Science University approved the study procedures with a waiver of consent.

Demographic and Clinical Variables

Electronic medical records were used to obtain demographic and admission variables. Admission primary diagnosis was categorized as the following: traumatic brain injury, hypoxic ischemic injury from cardiopulmonary arrest, status epilepticus, infectious or inflammatory disease, stroke, or other (toxic ingestion, pulmonary hypertension, heart failure, diabetic ketoacidosis with cerebral edema, acute respiratory distress syndrome). Illness severity was approximated by need for any critical care intervention (e.g., mechanical ventilation, neurosurgical intervention, vasopressor infusion, central venous line placement, arterial line placement, intracranial pressure monitor, dialysis, therapy for refractory status epilepticus, extracorporeal support, in-hospital cardiopulmonary resuscitation [CPR]), admission Glasgow Coma Scale (GCS) and length of stay in hospital and PICU. Medical record review was used to determine whether the patient had premorbid chronic conditions [34], history of psychiatric (e.g., anxiety, depression), or neurodevelopmental disorders (e.g., learning disability, attention-deficit/hyperactivity disorder, autism spectrum disorder). No patients reported premorbid sleep disorder diagnoses. Presence of any chronic condition was dichotomized for analysis consistent with prior work given the wide range of conditions identified [2,22,23]. The presence of any seizure during admission was recorded separate from critical care interventions for refractory status epilepticus as they can occur outside the PICU setting without PICU level intervention. Hospital outcomes were also recorded from medical records including discharge disposition (e.g., home, rehabilitation facility) and change from baseline Functional Status Scale (FSS) score using previously described methodology [2,22].

FSS scores were assigned by a PICU attending physician at admission baseline, discharge, and follow-up visits.

Sleep Disturbance

The primary exposure evaluated in this study was sleep disturbance defined by the Sleep Disturbance Scale for Children (SDSC) [32] measured 1 to 3-months after critical care hospitalization. The sleep disturbance group was defined by any T-score ≥60 on the SDSC. The SDSC is a 26-item standardized parent/caregiver proxy assessment of child and adolescent sleep behaviors for use in children ages 3 to 18 years. Parents report across six domains of sleep disturbances (Disorders of Initiating and Maintaining Sleep, Sleep Breathing Disorders, Disorders of Arousal, Sleep-Wake Transition Disorders, Disorders of Excessive Somnolence, and Sleep Hyperhidrosis) using a 5-point Likert scale with anchors "Never" to "Always (Daily)." Item responses are summed to calculate each factor score and converted to T-scores for ease of interpretation, with higher scores indicating more sleep disturbance. T-scores ≥60 are reported to portend moderate or severe risk of clinically important sleep disorders across six groups of sleep disorders in children and adolescents [35,36]. The SDSC is shown to be reliable and valid in PICU populations [35]. Internal consistency in our sample was excellent (α=0.85).

Health-Related Quality of Life

The primary outcome utilized in this study was overall HRQOL measured 1 to 3-months after hospital discharge in the PCCNRP using the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales total score [37,38]. PedsQL is a standardized 23-item parent/caregiver proxy measure of HRQOL, overall and across domains, in youth ages 2-18 years. Specific HRQOL domains assessed and scored include physical, emotional, social, and school functioning, and were evaluated as secondary outcomes in this study. Individual items are adjusted to be developmentally appropriate across ages, but yield total and domain scores for each age range representing the same HRQOL domains [37,38]. The PedsQL has been validated for use within PICU populations [19]. Internal consistency for PedsQL total and subscales in our sample was excellent (α=0.85-0.94). The PedsQL defines a Minimal Clinically Important Difference (MCID) as 4.5 points in the total score, and impaired HRQOL as a total score ≤65.4 [37].

Data Analyses

Participants with >8 missing items on the SDSC were excluded from analysis for incomplete data. An additional 7 forms had <8 missing items, and we imputed those missing items to a score of 1 ("Never") for SDSC score calculations. Of note, the SDSC was only given in English during clinic visits, and language barriers contributed to missing SDSC data. PedsQL was scored per measure defined guidelines, including exclusion of forms with >50% of overall questions missing from all analyses, invalidating subscale scores with >50% items missing in domain-specific questions, and using mean imputation for <50% items missing within domain-specific questions to calculate subscale scores. The most common reason for invalidating subscale score data was the School Function domain (n=19) marked "not applicable". Physical Function (n=4) and Social Function (n=3) domain scores were invalidated less often for missing data. We used chi-square with Fischer Exact correction for expected cell counts <10 and Mann-Whitney U tests to compare our analysis sample to those excluded with missing or incomplete data to assess for bias in our results. Sixty-seven children had missing or incomplete data for one or both questionnaires, were excluded from analysis (Supplemental Table 1), and were significantly older, had longer length of stay, and lower GCS score than the final analysis cohort.

Descriptive statistics evaluated sociodemographic and illness-related characteristics, as well as primary predictor (sleep disturbances) and outcome (HRQOL) variables. Most continuous variables were not normally distributed and reported as median with interquartile range (IQR). We used chi-square with Fischer Exact correction for expected cell counts <10 and Mann-Whitney U tests as appropriate to compare variables across sleep disturbance groups (Table 1) to assess for confounding variables. We used simple linear regression to evaluate demographic and clinical variables in relation to our primary outcome of overall HRQOL to evaluate covariates for multiple regression models (PedsQL total score; Table 2). The PedsQL total score represents the same construct across developmental modules and has been used as a primary outcome variable in previous HRQOL literature using infant, school-aged, and teen modules [22]. Results were reported as β-coefficients with 95% confidence interval (95% CI). Some continuous predictors were log transformed prior to entering regressions given non-normal distributions. Hierarchical multiple linear regression was used to evaluate the contribution of sleep disturbances to HRQOL at follow-up in our primary analysis. The model included entry of relevant covariates in Step 1 and sleep disturbance group in Step 2. Regression models were evaluated via adjusted R^2 and stepwise R^2 change with addition of sleep disturbance group at the $p<.05$ level. Based on prior HRQOL studies [22], we planned a priori to include age, sex, critical care intervention, pre-admission comorbidity, and worsening in functional status measured by change in FSS in multivariable models. Other potential covariates and confounders were identified from bivariate analyses described above and entered into the model at a significance level of $p<.05$. As the primary analysis for this study was to evaluate variance explained by sleep disturbances, variables were tested individually for collinearity with sleep disturbances and in the multivariable model for multicollinearity. No variables were excluded as the variance inflation factors were all <5. We additionally explored multiple linear regression models for HRQOL domain subscale scores for Physical, Emotional, Social, and School Function. IBM SPSS Version 27 was used for all statistical analyses. Significance defined as $p<.05$.

Table 1. Demographic and Clinical Characteristics by Sleep Disturbance Group

	All patients N=151 (%)	Normal Sleep n=51 (%)	Sleep Disturbance n=100 (%)	P-value
Age in years at admit, Median (IQR)	9.5 (6.5, 13.8)	9.0 (7.0, 13.7)	9.7 (6.2, 13.9)	.75
Primary admission diagnosis				.40
Trauma	117 (78%)	41 (80%)	76 (76%)	
Infectious/Inflammatory	12 (8%)	2 (4%)	10 (10%)	
Cardiac Arrest	6 (4%)	1 (2%)	5 (5%)	
Status epilepticus	5 (3%)	3 (6%)	2 (2%)	
Stroke	6 (4%)	3 (6%)	3 (3%)	
Other	5 (3%)	1 (2%)	4 (4%)	
Male sex assigned at birth	86 (57%)	23 (45%)	63 (63%)	.04
Race				.63
Caucasian	112 (74%)	39 (77%)	73 (73%)	
Asian	7 (5%)	3 (6%)	4 (4%)	
American Indian/Alaskan Native	3 (2%)	0 (0%)	3 (3%)	
Pacific Islander	3 (2%)	2 (4%)	1 (1%)	
African American	2 (1%)	1 (2%)	1 (1%)	
More than one race	16 (11%)	4 (8%)	12 (12%)	
Other	8 (5%)	2 (4%)	6 (6%)	
Hispanic ethnicity	24 (16%)	13 (26%)	11 (11%)	.02
Medicaid insurance	84 (56%)	29 (57%)	55 (55%)	.83
Length of Stay, Median days (IQR)				
Critical care	1.6 (1.0, 3.5)	1.4 (0.9, 2.6)	1.7 (1.0, 3.7)	.20
Hospital	3.5 (1.4, 7.6)	2.2 (1.4, 6.7)	3.9 (1.4, 8.2)	.29
Pre-admission Chronic Comorbidity, Any	47 (31%)	11 (22%)	36 (36%)	.07
Medical	26 (17%)	8 (16%)	18 (18%)	.82
Psychiatric	12 (8%)	3 (6%)	9 (9%)	.75
Neurodevelopmental	22 (15%)	2 (4%)	20 (20%)	<.01
Admit Glasgow Coma Scale, Median (IQR)	15 (14, 15)	15 (12.5, 15)	15 (14, 15)	.29
Pre-admit cardiopulmonary resuscitation	7 (5%)	2 (4%)	5 (5%)	>.99
Critical care intervention, any	85 (56%)	30 (59%)	55 (55%)	.65
Any seizure during admission	10 (7%)	3 (6%)	7 (7%)	>.99
Discharge to inpatient rehabilitation	15 (10%)	5 (10%)	10 (10%)	>.99
Change in Functional Status Scale				.59
No Change	127 (84%)	41 (80%)	86 (86%)	
1-2 point increase	18 (12%)	7 (14%)	11 (11%)	
≥3 point increase	6 (4%)	3 (6%)	3 (3%)	
Time from discharge, Median days (IQR)	55 (40, 81)	52 (37, 75)	57 (42, 85)	.13
PedsQL total score, Median (IQR)	71.7 (56.5, 86.1)	84.8 (65.2, 94.6)	69.6 (53.4, 80.0)	<.01
PedsQL subscale scores, Median (IQR)				
Physical (N=147)	75 (56.3, 93.8)	90 (54.7, 96.9)	75 (56.3, 90.6)	.59
Emotional (N=151)	70 (50.0, 90.0)	90 (75.0, 100)	60 (41.3, 75.0)	<.01
Social (N=148)	85 (65.0, 100)	90 (75.0, 100)	80 (61.9, 95.0)	<.01
School (N=132)	70 (46.3, 90.0)	83.1 (55.0, 100)	67.5 (43.8, 83.7)	<.01

Table 2. Simple linear regression evaluating overall quality of life

	Beta coefficient (95% Confidence Interval)	p-value
Age in years at admission	-.95 (-1.67, -.24)	<.01
Primary admission diagnosis		
Trauma	-6.47 (-23.96, 11.03)	.47
Infectious/Inflammatory	-13.31 (-33.70, 7.08)	.20
Cardiac arrest	-18.61 (-25.81, 22.66)	.90
Stroke	-11.71 (-34.90, 11.49)	.32
Seizure	-1.58 (-41.81, 4.59)	.12
Other (Reference)	--	--
White race	2.51 (-4.63, 9.64)	.49
Hispanic ethnicity	7.78 (-.68, 16.24)	.07
Medicaid insurance	-.60 (-6.90, 5.69)	.85
Male sex assigned at birth	7.78 (1.59, 13.97)	.01
Length of Stay		
Critical care (Log days)	-9.24 (-17.64, -.85)	.03
Hospital (Log days)	-10.18 (-16.28, -4.09)	<.01
Pre-admission chronic comorbidity, any	-12.90 (-19.33, -6.48)	<.01
Medical comorbidity	-8.69 (-16.85, -.53)	.04
Psychiatric comorbidity	-26.47 (-37.21, -15.74)	<.01
Neurodevelopmental comorbidity	-13.03 (-21.64, -4.43)	<.01
Admission Glasgow Coma Scale (Log score)	11.47 (-11.94, 34.88)	.33
Pre-admit cardiopulmonary resuscitation	-7.93 (-22.74, 6.88)	.29
Critical care intervention, any	-6.08 (-12.30, .15)	.06
Seizure during admission	-4.48 (-17.03, 8.07)	.48
Discharge to inpatient rehabilitation	-8.74 (-19.09, 1.62)	.10
Time from discharge to evaluation	-.04 (-.15, .06)	.44
Change in Functional Status Scale:		
No change from pre-admission baseline (reference)	--	--
Any worsening (≥1 point increase)	-9.28 (-17.70, -.86)	.03
Sleep Disturbances Scale for Children T-score		
Total	-.82 (-1.02, -.62)	<.01
Initiation and Maintenance Subscale	-.55 (-.72, -.37)	<.01
Sleep Breathing Subscale	-.44 (-.76, -.11)	<.01
Arousal Subscale	-.31 (-.52, -.10)	<.01
Sleep Wake Transition Subscale	-.53 (-.74, -.32)	<.01
Excessive Somnolence Subscale	-1.36 (-1.67, -1.04)	<.01
Hyperhidrosis Subscale	-.65 (-.99, -.30)	<.01

Results

Among 218 eligible patients completing a follow-up visit, we evaluated 151 (69%) children with complete data a median of 55 days after critical care hospitalization for ABI (Table 1). The most common primary diagnosis was trauma (78%), followed by infectious and inflammatory conditions (8%), cardiac arrest (4%), stroke (4%), seizure (5%), and other (3%). Most of the patient participants were male (57%) and had Medicaid insurance (56%). Forty-seven (31%) patients had one or more prior comorbid medical (17%), psychiatric (8%), or neurodevelopmental (15%) diagnoses. Most patients (n=85, 56%) required at least one critical care intervention, including 33% (n=49) requiring intubation and mechanical ventilation. Fifteen (10%) were discharged to inpatient rehabilitation facilities and 24 (16%) had a decline from pre-admission baseline in functional abilities measured by the FSS at the time of follow-up.

Sleep disturbances were present in 66% (n=100) overall. Disturbances in multiple sleep domains were found in 37% of children. Disturbances were found in all six sleep domains measured by SDSC subscales: Disorders of Initiating and Maintaining Sleep (53%), Sleep Breathing Disorders (12%), Disorders of Arousal (15%), Sleep-Wake Transition Disorders (31%), Disorders of Excessive Somnolence (11%), and Sleep Hyperhidrosis (10%). As seen in Table 1, sleep disturbances were significantly associated with male sex, pre-admission neurodevelopmental comorbidities, and non-Hispanic ethnicity (all $p<0.05$).

Overall, 54 (36%) participants had HRQOL scores below the PedsQL defined cut-off total score for impairment. HRQOL total score was significantly worse in children with sleep disturbances (median=70; IQR=54, 80) versus without (median=85; IQR=67, 94; $p<.001$). Median scores in Emotional, Social, and School Function domains were also significantly worse in the sleep disturbance group (all $p<.01$). As seen in Table 2, poorer HRQOL was significantly associated with older age, female sex, pre-admission comorbidity, longer length of stay, and worsening in functional outcome measured by change from pre-admission FSS (all $p<0.05$). Worse HRQOL was also associated with more sleep disturbance measured by higher SDSC T-scores for total sleep and all SDSC subscales (all $p<0.01$).

As seen in Table 3, when controlling for age, sex, critical care intervention, pre-admission comorbidities, length of stay, and worsening from pre-admission FSS score, presence of sleep disturbance significantly reduced HRQOL total score nearly 3 times the MCID (β-coefficient= -12.1; 95% CI= -17.9, -6.2). Female sex and pre-admission comorbidities remained significant independent predictors of worse overall HRQOL in the multivariable model. The final model was significant (F=8.72, p<.001), and addition of sleep disturbance group to the model significantly increased adjusted r^2 by 8% (p-value for change <.001).

We also explored multivariable models for HRQOL domains using the same covariates described above. Sleep disturbances were independently associated with worsening in Emotional, Social, and School Function, and significantly improved adjusted r^2 in multivariable models (Table 4). Female sex was also associated with worsening Emotional Function scores. Pre-admission comorbidities were associated with worsening Emotional, Social, and School Function scores. Worsening in Physical Function score was associated with female sex and worsening FSS from pre-admission baseline, but sleep disturbances did not contribute significantly to this model.

Table 3. Hierarchical multiple linear regression evaluating overall quality of life

	Step 1 Beta coefficient (95% Confidence Interval)	Step 2 Beta Coefficient (95% Confidence Interval)
Age in years at admission	-.50 (-1.12, .19)	-.52 (-1.17, .14)
Male sex assigned at birth	6.42 (.63, 12.20)	8.39 (2.81, 13.97)
Pre-admission comorbidity	-12.29 (-18.70, -5.87)	-10.64 (-16.79, -4.50)
Hospital length of stay, Log (days)	-5.55 (-12.73, 1.63)	-3.95 (-10.81, 2.92)
Any worsening in Functional Status Scale	-5.04 (-13.27, 3.20)	-5.94 (-13.77, 1.90)
Critical care intervention	-4.14 (-11.21, 2.94)	-5.09 (-11.83, 1.64)
Sleep disturbance	--	-12.06 (-17.90, -6.21)
Step 1 model statistics: F= 6.68, p-value <.01; adjusted R2= .19 Step 2 model statistics: F= 8.72, p-value <.01; adjusted R2 = .27; R2 change = .08; F change= 16.63, p-value change= <.01		

Table 4. Multivariable linear regression models exploring quality of life domains

	Beta coefficient (95% Confidence Interval)	Model Statistics
Physical Function N=147		
Age in years at admission	-.62 (-1.54, .29)	Model F= 4.91
Male sex assigned at birth	10.95 (3.04, 18.85)	Model p= <.01
Pre-admission comorbidity	-7.95 (-16.74, .84)	Model adjusted R2= .16
Hospital length of stay, Log (days)	-4.03 (-13.75, 5.68)	R^2 change sleep disturbance= .02
Any worsening in Functional Status Scale	-13.06 (-24.25, -1.87)	p-value change= .06
Critical care intervention	-5.57 (-15.21, 4.07)	
Sleep disturbance	-7.85 (-16.05, .36)	
Emotional Function N=151		
Age in years at admission	-.36 (-1.14, .42)	Model F= 10.85
Male sex assigned at birth	8.54 (1.90, 15.18)	Model p= <.01
Pre-admission comorbidity	-9.25 (-16.56, -1.93)	Model adjusted R2= .32
Hospital length of stay, Log (days)	-4.30 (-12.47, 3.87)	R^2 change sleep disturbance= .23
Any worsening in Functional Status Scale	2.15 (-7.18, 11.47)	p-value change= <.01
Critical care intervention	-5.46 (-13.48, 2.55)	
Sleep disturbance	-24.79 (-31.75, -17.84)	
Social Function N=148		
Age in years at admission	< -.01 (-.71, .71)	Model F= 6.20
Male sex assigned at birth	5.58 (-.49, 11.65)	Model p= <.01
Pre-admission comorbidity	-13.76 (-20.43, -7.09)	Model adjusted R2= .20
Hospital length of stay, Log (days)	-5.87 (-13.31, 1.58)	R^2 change sleep disturbance= .03
Any worsening in Functional Status Scale	-6.35 (-14.89, 2.20)	p-value change= .02
Critical care intervention	-4.20 (-11.51, 3.10)	
Sleep disturbance	-7.84 (-14.20, -1.47)	
School Function N=132		
Age in years at admission	-.77 (-1.78, .23)	Model F= 4.58
Male sex assigned at birth	6.36 (-1.71, 14.43)	Model p= <.01
Pre-admission comorbidity	-16.06 (-25.00, -7.11)	Model adjusted R2= .16
Hospital length of stay, Log (days)	1.92 (-7.98, 11.81)	R^2 change sleep disturbance= .03
Any worsening in Functional Status Scale	-.20 (-11.83, 11.44)	p-value change= .03
Critical care intervention	-7.91 (-17.59, 1.76)	
Sleep disturbance	-9.59 (-18.07, -1.11)	

Discussion

Sleep disturbances are prevalent among childhood survivors of ABI in the months following hospital discharge and are independently associated with worse overall HRQOL when controlling for demographic and illness characteristics. We found sleep disturbances to be important factors in recovery within multiple health domains relevant to clinical care and research in the ABI population.

Sleep is a potentially modifiable risk factor to target when aiming to improve HRQOL after hospital discharge. Close follow up, or even inpatient evaluation, for sleep disturbance is needed as early interventions could be provided. Overall, our data supports future studies targeting sleep to improve HRQOL after pediatric ABI.

Sleep disturbances impacted two-thirds of the children in our sample using clinically significant cut-offs with a validated sleep measure (SDSC). Our prior work and other studies show similar rates of sleep problems using a variety of methods to measure sleep with both proxy report and direct assessment [11,23,25,39]. Our previous two-center study evaluating SWD after ABI using the SDSC showed that SWD were common and present in 56% of the population [23]. A recent systematic review identified multiple methodologies and showed that at least 20% of pediatric patients post-traumatic brain injury had difficulties with falling or staying asleep and also suffered from fatigue, daytime tiredness, and nightmares [25]. The findings from this current study similarly demonstrate that multiple SWDs, particularly initiating and maintaining sleep, are common in the pediatric ABI population.

We found similar rates of impairment in HRQOL as prior studies of pediatric critical care and brain injury populations, highlighting the multiple morbidities in this population that contribute to overall health and recovery [22,40]. Previous studies have shown that impaired HRQOL occurs in 23-43% of patients following critical care admission and ABI [12,14], and can persist for a year or more [8,21,40]. Patient and clinical risk factors for worse HRQOL in prior works include older age, female sex, low SES, pre-admission comorbidities, increased length of stay, critical care interventions, and worsening in functional status from pre-admission baseline [8,15,16,20-22]. We found similar risk factors for reduced HRQOL, though these prior works have not included evaluation of sleep [8,15,16,20-22], which was strongly associated with HRQOL in the current study. Conversely, one study evaluating sleep and HRQOL in pediatric patients with traumatic brain injury and comorbid attention deficit/hyperactivity disorder, similarly found that those with worse sleep had reduced HRQOL [11].

Most importantly, our study revealed that sleep disturbances were strongly associated with worse overall HRQOL, independent of patient and injury characteristics evaluated in prior studies. We found that total SDSC scores, as well as all sleep domain scores on the SDSC, were associated with worse HRQOL, suggesting multiple aspects of sleep and sleep disturbances impact HRQOL. We also showed that SWD reduced HRQOL scores far beyond the measure-defined MCID, highlighting the importance of sleep in outcomes research and clinical care [37]. The connection between sleep and a global health outcome such as HRQOL is particularly important in children. Sleep is critical for brain maturation and development in that good restorative and regular sleep correlates with grey and white matter volumes, particularly in the dorsolateral, prefrontal, and hippocampal cortex [41]. These brain regions have well-established functional correlates related to executive functioning, emotional and behavioral regulation, memory, and learning likely to affect children across home, school, and community environments [42,43].

In addition to sleep disturbances being strongly associated with worse overall HRQOL, sleep disturbances were significantly associated with domains of Emotional, Social, and School Function evaluated by the PedsQL in this study. While not statistically significant, sleep did impact physical domain scores. Interestingly, the physical domain score includes a question about problems sleeping, but the association with other domains within the HRQOL construct were more strongly associated with sleep disturbances in our study. Our findings highlight the idea that sleep has important implications across multiple health domains in recovery after ABI.

Families of children surviving critical care hospitalizations endorse a high prevalence of psychological sequelae years after hospital discharge [44,45]. A growing body of research shows negative psychological sequelae in critical care survivors, including increased levels of anxiety, depression, post-traumatic stress symptoms (PTSS) or disorder (PTSD), and behavioral symptoms [45,46]. A recent review found that 16-28% of children experienced a deterioration in emotional functioning following PICU hospitalization regardless of injury or illness [44]. Similarly, PICU survivors frequently endorsed moderate or worse anxiety (45.2%) and depressive (32.1%) symptoms [47], and additional work shows significant correlation between child emotional outcomes and physical and cognitive morbidities [35]. Given the increased risk for emotional and psychological morbidity in survivors, there has been a push to develop interventions. The research is still in its infancy, but emerging data suggests interventions can improve child morbidity [30-32,45-48]. The link in other pediatric populations between sleep disturbances and worsened emotional function and mental health disorders is well established [49]. This context is particularly relevant when thinking about the potential for sleep interventions in the ABI population to positively impact outcomes in the emotional domain within HRQOL.

Similarly, families of PICU survivors endorse a high prevalence of social sequelae years after hospital discharge [50-52]. Interviews with parents indicate they perceive the recovery from critical illness to be akin to a chronic disease, with stressors that extend beyond the hospitalization [52]. Parents of PICU survivors report significant social sequelae in their child and themselves including loss of employment, high financial burden, loss of relationships with family and friends, difficulty making new friends, and struggles with social reintegration [50-52]. Prior research in pediatric ABI indicates an association between sleep disturbances and worsening in externalizing and internalizing behaviors [39,53], consistent with findings in healthy pediatric populations [54]. Healthy children with sleep disturbances are prone to risk taking behaviors and poor social participation [49,55]. New mental health problems and symptoms of PTSS or PTSD are also frequently reported in parents after PICU admission, and shown to significantly impact family functioning among survivors [47], as well as access to care for children leading to worse child outcomes [6,30,56,57]. It is likely that child sleep disruption impacts parents' sleep, and potentially the entire family's sleep, and is another possible mechanism behind the association between sleep disruption and poorer Social Function on the PedsQL seen in this study. In fact, a prior study in pediatric ABI showed a link between worse child fatigue and long-term family impact, consistent with this notion [10]. This context is particularly relevant when thinking about potential for sleep interventions to improve HRQOL outcomes.

A recent systematic review of cognitive morbidities in PICU survivors found worse outcomes in comparison to healthy controls or normed population data across cognitive domains of general intelligence, attention, processing speed, executive functioning, memory, visual motor integration, and motor development, and indicated cognitive morbidities may be specifically associated with PICU-related factors and/or critical illness-induced secondary brain injuries, but did not identify studies evaluating sleep as a mediator [58]. Cognitive sequelae are known to persist for years in children after ABI, best evaluated in the trauma population, and can significantly affect school performance and developmental trajectories [3-5,41,59]. Many cognitive sequelae studied in neurologic populations are severity of injury related, but even patients with “mild” brain injury have chronic cognitive deficits, and PICU survivors admitted for other diseases like respiratory failure and sepsis are at risk for cognitive sequelae related to secondary neurologic injury from inflammation, hypoxia, ischemia, and critical care interventions [2,5]. Highlighting this notion, we recently found new neurocognitive or neurodevelopmental concerns in 36.4% of participants in comparison to pre-hospitalization functioning in a cohort of infants and young children who survived the PICU [32] and new neurocognitive disorders in 27% of participants in a cohort of school aged children and adolescents [60]. Prior research in pediatric ABI has shown a significant relationship between sleep disturbances and worsened cognition, particularly in domains of executive function [53,61]. This also aligns with research in other healthy and clinical pediatric populations linking sleep problems to cognitive dysfunction and poorer school performance [54,59,62]. Again, this context is particularly relevant when thinking about potential for sleep interventions to improve HRQOL outcomes.

Overall, more work is needed to evaluate the impact of sleep on multidimensional recovery across the above health domains and overall HRQOL to determine if sleep interventions can improve recovery.

Evidence for effective treatments is lacking for pediatric sleep disturbances in a variety of populations but are particularly understudied in the pediatric ABI population [8,25,26]. In fact, a recent systematic review showed no studies evaluating sleep interventions after hospitalization for pediatric brain injury [25]. Our study supports the need for interventions targeting sleep to improve recovery given the strong association between SWD and HRQOL.

Limitations

There are multiple limitations to consider regarding our study. The PedsQL is a subjective measure of HRQOL, meaning it can be influenced by many factors including those not directly related to ABI, making it challenging to capture all of the variance within multivariable models [22]. The PedsQL and SDSC are parent-reported proxies for HRQOL and sleep disturbances, though both are validated within the pediatric ABI and critical care population. In addition, the PedsQL is not a proxy for PICS. It does not measure all possible morbidity in PICS domains (e.g., specific cognitive functions, adaptive skills, post-traumatic stress, etc.) that are relevant to critical care populations, but no comprehensive measure specific to PICS exists [63,64]. We grouped our sample by primary admission diagnosis, but critical care patients are at risk for secondary brain injuries from infection, hypoxia, ischemia, and seizures regardless of the primary diagnosis that may limit findings with this variable. Our sample is primarily English speaking due to limitations of questionnaire availability in other languages. It is likely that cultural differences could contribute to evaluations of sleep and HRQOL particularly when assessed through questionnaires in medical appointments [65-67]. Our study was a cross-sectional analysis, limiting evaluation of causation between exposures and outcomes and did not include baseline estimates of pre-admission sleep or HRQOL measures. We assessed HRQOL and SWDs data obtained at 1 to 3-months post-discharge, but longitudinal studies are needed to assess how this relationship changes over time. Our study was a single center study that identified a large number of pediatric ABI survivors at our tertiary academic institution with similar demographic and clinical characteristics to other published ABI cohorts in the PICU [1,68,69]. However, population differences were noted in those with complete and missing data that can contribute to bias in our results despite attempts to control for these differences in the analysis. Additionally, being a single center study limits generalizability due to known differences between PICU populations and treatments across centers [1,68]. Specifically, some centers have different PICU admission practices for patients with mild complicated TBI [70], while our center routinely admits these children to the PICU for close monitoring regardless of need for intervention. Overall, recent data suggests primary ABI admissions receive frequent critical care intervention consistent with our results, but vary based on definitions of critical care intervention, and practices vary widely between institutions for the use of some therapies like intracranial pressure monitoring [1,68,69].

Conclusion

In our sample, most pediatric ABI patients surviving critical care hospitalization suffered from sleep disturbances in the months after hospital discharge, particularly falling and staying asleep. Sleep disturbances were associated with significantly reduced HRQOL when controlling for patient and ABI characteristics and may contribute to worse outcomes in multiple health domains. Sleep represents a modifiable factor with potential implications for recovery that is under-evaluated in many outcomes studies within pediatric ABI and critical care populations. Additional research is needed to determine the longitudinal impact of sleep on global health recovery, and to identify effective sleep interventions to improve the trajectory of recovery in this vulnerable patient population.

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Supplemental Table 1. Cohort comparison with missing or incomplete data excluded from analysis

	Excluded patients N= 67 (%)	Analysis cohort N=151 (%)	p-value[a]
Age in years, Median (IQR)	13.3 (7.6, 15.5)	9.5 (6.5, 13.8)	.01
Primary admission diagnosis			.11
Trauma	44 (67%)	117 (78%)	
Infectious/Inflammatory	9 (14%)	12 (8%)	
Stroke	5 (8%)	6 (4%)	
Cardiac arrest	0	5 (3%)	
Status epilepticus	2 (3%)	6 (4%)	
Other	6 (9%)	5 (3%)	
Male sex assigned at birth	40 (60%)	86 (57%)	.71
Race			.22
Caucasian	46 (69%)	112 (74%)	
Asian	0	7 (5%)	
American Indian/Alaskan Native	5 (8%)	3 (2%)	
Pacific Islander	1 (2%)	3 (2%)	
African American	1 (2%)	2 (1%)	
More than one race	8 (12%)	16 (11%)	
Other	6 (9%)	8 (5%)	
Hispanic/Latinx ethnicity	19 (28%)	24 (16%)	.11
Medicaid Insurance	45 (67%)	84 (56%)	.27
Pre-admission comorbidity, any	26 (39%)	47 (31%)	.27
Admission GCS, Median (IQR)	14 (8, 15)	15 (14, 15)	.03
Pre-admission CPR	3 (5%)	7 (5%)	.96
Length of stay days, Median (IQR)			
Intensive care	2.2 (1.3, 7.6)	1.6 (1.0, 3.5)	.04
Hospital	5.5 (2.7, 14.2)	3.5 (1.4, 7.6)	<.01
Critical care intervention	47 (70%)	85 (56%)	.06
Seizure during hospitalization	9 (13%)	10 (7%)	.12
Inpatient rehabilitation discharge	10 (15%)	15 (10%)	.18

a: Chi-square tests with Fischer Exact correction for expected cell counts <10 used to compare categorical variables. Mann-Whitney U tests used to compare continuous variables.

References

1. Williams CN, Piantino J, McEvoy C, Fino N, Eriksson CO. The Burden of Pediatric Neurocritical Care in the United States. Pediatr Neurol 2018;89:31-38. DOI: 10.1016/j.pediatrneurol.2018.07.013.
2. Williams CN, Eriksson CO, Kirby A, et al. Hospital Mortality and Functional Outcomes in Pediatric Neurocritical Care. Hosp Pediatr 2019;9(12):958-966. DOI: 10.1542/hpeds.2019-0173.
3. Babikian T, Asarnow R. Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature. Neuropsychology 2009;23(3):283-96. DOI: 10.1037/a0015268.
4. Babikian T, Merkley T, Savage RC, Giza CC, Levin H. Chronic Aspects of Pediatric Traumatic Brain Injury: Review of the Literature. J Neurotrauma 2015;32(23):1849-60. DOI: 10.1089/neu.2015.3971.

5. Bone MF, Feinglass JM, Goodman DM. Risk factors for acquiring functional and cognitive disabilities during admission to a PICU*. Pediatr Crit Care Med 2014;15(7):640-8. DOI: 10.1097/PCC.0000000000000199.
6. Manning JC, Pinto NP, Rennick JE, Colville G, Curley MAQ. Conceptualizing Post Intensive Care Syndrome in Children-The PICS-p Framework. Pediatr Crit Care Med 2018;19(4):298-300. DOI: 10.1097/PCC.0000000000001476.
7. Fayes PMM, D. Quality of life: The assessment, analysis and interpretation of patient-reported outcomes. 2nd ed. West Sussex, England: John Wiley and Sons Ltd., 2007.
8. Aspesberro F, Mangione-Smith R, Zimmerman JJ. Health-related quality of life following pediatric critical illness. Intensive Care Med 2015;41(7):1235-46. DOI: 10.1007/s00134-015-3780-7.
9. Polinder S, Haagsma JA, van Klaveren D, Steyerberg EW, van Beeck EF. Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. Popul Health Metr 2015;13:4. DOI: 10.1186/s12963-015-0037-1.
10. de Kloet AJ, Lambregts SA, Berger MA, van Markus F, Wolterbeek R, Vliet Vlieland TP. Family impact of acquired brain injury in children and youth. J Dev Behav Pediatr 2015;36(5):342-51. DOI: 10.1097/DBP.0000000000000169.
11. Ekinci O, Okuyaz C, Gunes S, et al. Sleep and quality of life in children with traumatic brain injury and ADHD. Int J Psychiatry Med 2017;52(1):72-87. DOI: 10.1177/0091217417703288.
12. Ambuehl J, Karrer A, Meer A, Riedel T, Schibler A. Quality of life of survivors of paediatric intensive care. Swiss Med Wkly 2007;137(21-22):312-6. DOI: 2007/21/smw-11469.
13. Bisegger C, Cloetta B, von Rueden U, Abel T, Ravens-Sieberer U, European Kidscreen G. Health-related quality of life: gender differences in childhood and adolescence. Soz Praventivmed 2005;50(5):281-91. DOI: 10.1007/s00038-005-4094-2.
14. Conlon NP, Breatnach C, O'Hare BP, Mannion DW, Lyons BJ. Health-related quality of life after prolonged pediatric intensive care unit stay. Pediatr Crit Care Med 2009;10(1):41-4. DOI: 10.1097/PCC.0b013e31819371f6.
15. Ebrahim S, Singh S, Hutchison JS, et al. Adaptive behavior, functional outcomes, and quality of life outcomes of children requiring urgent ICU admission. Pediatr Crit Care Med 2013;14(1):10-8. DOI: 10.1097/PCC.0b013e31825b64b3.
16. Namachivayam P, Taylor A, Montague T, et al. Long-stay children in intensive care: long-term functional outcome and quality of life from a 20-yr institutional study. Pediatr Crit Care Med 2012;13(5):520-8. DOI: 10.1097/PCC.0b013e31824fb989.
17. Perrin JM, Bloom SR, Gortmaker SL. The increase of childhood chronic conditions in the United States. JAMA 2007;297(24):2755-9. DOI: 10.1001/jama.297.24.2755.
18. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:43. DOI: 10.1186/1477-7525-5-43.
19. Aspesberro F, Fesinmeyer MD, Zhou C, Zimmerman JJ, Mangione-Smith R. Construct Validity and Responsiveness of the Pediatric Quality of Life Inventory 4.0 Generic Core Scales and Infant Scales in the PICU. Pediatr Crit Care Med 2016;17(6):e272-9. DOI: 10.1097/PCC.0000000000000727.
20. Cunha F, Mota T, Teixeira-Pinto A, et al. Factors associated with health-related quality of life changes in survivors to pediatric intensive care. Pediatr Crit Care Med 2013;14(1):e8-15. DOI: 10.1097/PCC.0b013e31826012b4.

21. Fineblit S, Selci E, Loewen H, Ellis M, Russell K. Health-Related Quality of Life after Pediatric Mild Traumatic Brain Injury/Concussion: A Systematic Review. J Neurotrauma 2016;33(17):1561-8. DOI: 10.1089/neu.2015.4292.
22. Holding EZ, Turner EM, Hall TA, Leonard S, Bradbury KR, Williams CN. The Association Between Functional Status and Health-Related Quality of Life Following Discharge from the Pediatric Intensive Care Unit. Neurocrit Care 2021. DOI: 10.1007/s12028-021-01271-8.
23. Williams CN, Hartman ME, McEvoy CT, et al. Sleep-Wake Disturbances After Acquired Brain Injury in Children Surviving Critical Care. Pediatr Neurol 2020;103:43-51. DOI: 10.1016/j.pediatrneurol.2019.08.010.
24. Gagner C, Landry-Roy C, Laine F, Beauchamp MH. Sleep-Wake Disturbances and Fatigue after Pediatric Traumatic Brain Injury: A Systematic Review of the Literature. J Neurotrauma 2015;32(20):1539-52. DOI: 10.1089/neu.2014.3753.
25. Luther M, Poppert Cordts KM, Williams CN. Sleep disturbances after pediatric traumatic brain injury: a systematic review of prevalence, risk factors, and association with recovery. Sleep 2020;43(10). DOI: 10.1093/sleep/zsaa083.
26. Williams CN, Lim MM, Shea SA. Sleep disturbance after pediatric traumatic brain injury: critical knowledge gaps remain for the critically injured. Nat Sci Sleep 2018;10:225-228. DOI: 10.2147/NSS.S174608.
27. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 2014;81(1):12-34. DOI: 10.1016/j.neuron.2013.12.025.
28. Owens JA. Neurocognitive and behavioral impact of sleep disordered breathing in children. Pediatr Pulmonol 2009;44(5):417-22. DOI: 10.1002/ppul.20981.
29. Shochat T, Cohen-Zion M, Tzischinsky O. Functional consequences of inadequate sleep in adolescents: a systematic review. Sleep Med Rev 2014;18(1):75-87. DOI: 10.1016/j.smrv.2013.03.005.
30. Bradbury KR, Williams C, Leonard S, et al. Emotional Aspects of Pediatric Post-Intensive Care Syndrome Following Traumatic Brain Injury. J Child Adolesc Trauma 2021;14(2):177-187. DOI: 10.1007/s40653-020-00332-y.
31. Dodd JN, Hall TA, Guilliams K, et al. Optimizing Neurocritical Care Follow-Up Through the Integration of Neuropsychology. Pediatr Neurol 2018;89:58-62. DOI: 10.1016/j.pediatrneurol.2018.09.007.
32. Hall TA, Leonard S, Bradbury K, et al. Post-intensive care syndrome in a cohort of infants & young children receiving integrated care via a pediatric critical care & neurotrauma recovery program: A pilot investigation. Clin Neuropsychol 2020:1-25. DOI: 10.1080/13854046.2020.1797176.
33. Williams CN, Kirby A, Piantino J. If You Build It, They Will Come: Initial Experience with a Multi-Disciplinary Pediatric Neurocritical Care Follow-Up Clinic. Children (Basel) 2017;4(9). DOI: 10.3390/children4090083.
34. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr 2014;14:199. DOI: 10.1186/1471-2431-14-199.
35. Poppert Cordts KM, Hall TA, Hartman ME, et al. Sleep Measure Validation in a Pediatric Neurocritical Care Acquired Brain Injury Population. Neurocrit Care 2020;33(1):196-206. DOI: 10.1007/s12028-019-00883-5.
36. Bruni O, Ottaviano S, Guidetti V, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res 1996;5(4):251-61. DOI: 10.1111/j.1365-2869.1996.00251.x.

37. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3(6):329-41. DOI: 10.1367/1539-4409(2003)003<0329:tpaapp>2.0.co;2.
38. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999;37(2):126-39. DOI: 10.1097/00005650-199902000-00003.
39. Fischer JT, Hannay HJ, Alfano CA, Swank PR, Ewing-Cobbs L. Sleep disturbances and internalizing behavior problems following pediatric traumatic injury. Neuropsychology 2018;32(2):161-175. DOI: 10.1037/neu0000420.
40. Di Battista A, Soo C, Catroppa C, Anderson V. Quality of life in children and adolescents post-TBI: a systematic review and meta-analysis. J Neurotrauma 2012;29(9):1717-27. DOI: 10.1089/neu.2011.2157.
41. Kocevska D, Muetzel RL, Luik AI, et al. The Developmental Course of Sleep Disturbances Across Childhood Relates to Brain Morphology at Age 7: The Generation R Study. Sleep 2017;40(1). DOI: 10.1093/sleep/zsw022.
42. Astill RG, Van der Heijden KB, Van Ijzendoorn MH, Van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychol Bull 2012;138(6):1109-38. DOI: 10.1037/a0028204.
43. Spruyt K. A review of developmental consequences of poor sleep in childhood. Sleep Med 2019;60:3-12. DOI: 10.1016/j.sleep.2018.11.021.
44. Rennick JE, Rashotte J. Psychological outcomes in children following pediatric intensive care unit hospitalization: a systematic review of the research. J Child Health Care 2009;13(2):128-49. DOI: 10.1177/1367493509102472.
45. Baker SC, Gledhill JA. Systematic Review of Interventions to Reduce Psychiatric Morbidity in Parents and Children After PICU Admissions. Pediatr Crit Care Med 2017;18(4):343-348. DOI: 10.1097/PCC.0000000000001096.
46. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. Crit Care Med 2012;40(2):618-24. DOI: 10.1097/CCM.0b013e318236ebf9.
47. Riley AR, Williams CN, Moyer D, et al. Parental Posttraumatic Stress Symptoms in the Context of Pediatric Post Intensive Care Syndrome: Impact on the Family and Opportunities for Intervention. Clin Pract Pediatr Psychol 2021;9(2):156-166. DOI: 10.1037/cpp0000399.
48. Landolt MA, Ystrom E, Sennhauser FH, Gnehm HE, Vollrath ME. The mutual prospective influence of child and parental post-traumatic stress symptoms in pediatric patients. J Child Psychol Psychiatry 2012;53(7):767-74. DOI: 10.1111/j.1469-7610.2011.02520.x.
49. Roberts RE, Roberts CR, Duong HT. Sleepless in adolescence: prospective data on sleep deprivation, health and functioning. J Adolesc 2009;32(5):1045-57. DOI: 10.1016/j.adolescence.2009.03.007.
50. Hooper SR, Alexander J, Moore D, et al. Caregiver reports of common symptoms in children following a traumatic brain injury. NeuroRehabilitation 2004;19(3):175-89. (https://www.ncbi.nlm.nih.gov/pubmed/15502252).
51. Meert K, Slomine BS, Christensen JR, et al. Burden of caregiving after a child's in-hospital cardiac arrest. Resuscitation 2018;127:44-50. DOI: 10.1016/j.resuscitation.2018.03.034.
52. Williams CN, Eriksson C, Piantino J, et al. Long-term Sequelae of Pediatric Neurocritical Care: The Parent Perspective. J Pediatr Intensive Care 2018;7(4):173-181. DOI: 10.1055/s-0038-1637005.
53. Shay N, Yeates KO, Walz NC, et al. Sleep problems and their relationship to cognitive and behavioral outcomes in young children with traumatic brain injury. J Neurotrauma 2014;31(14):1305-12. DOI: 10.1089/neu.2013.3275.
54. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. Child Dev 2002;73(2):405-17. DOI: 10.1111/1467-8624.00414.

55. Catrett CD, Gaultney JF. Possible insomnia predicts some risky behaviors among adolescents when controlling for depressive symptoms. J Genet Psychol 2009;170(4):287-309. DOI: 10.1080/00221320903218331.
56. Yagiela LM, Carlton EF, Meert KL, Odetola FO, Cousino MK. Parent Medical Traumatic Stress and Associated Family Outcomes After Pediatric Critical Illness: A Systematic Review. Pediatr Crit Care Med 2019;20(8):759-768. DOI: 10.1097/PCC.0000000000001985.
57. Banyard VL, Williams LM, Siegel JA. The impact of complex trauma and depression on parenting: an exploration of mediating risk and protective factors. Child Maltreat 2003;8(4):334-49. DOI: 10.1177/1077559503257106.
58. Kachmar AG, Irving SY, Connolly CA, Curley MAQ. A Systematic Review of Risk Factors Associated With Cognitive Impairment After Pediatric Critical Illness. Pediatr Crit Care Med 2018;19(3):e164-e171. DOI: 10.1097/PCC.0000000000001430.
59. Dewald JF, Meijer AM, Oort FJ, Kerkhof GA, Bogels SM. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. Sleep Med Rev 2010;14(3):179-89. DOI: 10.1016/j.smrv.2009.10.004.
60. Hall T, Greene. R., Lee, J., Leonard, S., Bradbury, K., Drury, K., Recht, G., Randall, J., Norr, M., & Williams, C. . Post intensive care syndrome in pediatric ICU survivors: The importance of multidisciplinary follow-up in the acute recovery phase. . Under Review.
61. Osorio MB, Kurowski BG, Beebe D, et al. Association of daytime somnolence with executive functioning in the first 6 months after adolescent traumatic brain injury. PM R 2013;5(7):554-62. DOI: 10.1016/j.pmrj.2012.11.006.
62. Gozal D, Kheirandish-Gozal L. Neurocognitive and behavioral morbidity in children with sleep disorders. Curr Opin Pulm Med 2007;13(6):505-9. DOI: 10.1097/MCP.0b013e3282ef6880.
63. Fink EL, Maddux AB, Pinto N, et al. A Core Outcome Set for Pediatric Critical Care. Crit Care Med 2020;48(12):1819-1828. DOI: 10.1097/CCM.0000000000004660.
64. Williams C. Continuing care for critically ill children beyond hospital discharge: current state of follow up. Hospital Pediatrics 2022(In Press).
65. Chen X, Wang R, Zee P, et al. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). Sleep 2015;38(6):877-88. DOI: 10.5665/sleep.4732.
66. Cheung BY, Takemura K, Ou C, Gale A, Heine SJ. Considering cross-cultural differences in sleep duration between Japanese and Canadian university students. PLoS One 2021;16(4):e0250671. DOI: 10.1371/journal.pone.0250671.
67. Kemmelmeier M. Cultural differences in survey responding: Issues and insights in the study of response biases. Int J Psychol 2016;51(6):439-444. DOI: 10.1002/ijop.12386.
68. Moreau JF, Fink EL, Hartman ME, et al. Hospitalizations of children with neurologic disorders in the United States. Pediatr Crit Care Med 2013;14(8):801-10. DOI: 10.1097/PCC.0b013e31828aa71f.
69. DeSanti RL, Balakrishnan B, Rice TB, Pineda JA, Ferrazzano PA. The Utilization of Critical Care Resources in Pediatric Neurocritical Care Patients. Pediatr Crit Care Med 2022;23(9):676-686. DOI: 10.1097/PCC.0000000000002992.
70. Greenberg JK, Jeffe DB, Carpenter CR, et al. North American survey on the post-neuroimaging management of children with mild head injuries. J Neurosurg Pediatr 2018;23(2):227-235. DOI: 10.3171/2018.7.PEDS18263.