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Health-Related Quality of Life, Obesity, Disrupted Sleep, and Psychosocial Problems among Youth with Craniopharyngioma

Kimberly Lauren Klages

HEALTH-RELATED QUALITY OF LIFE, OBESITY, DISRUPTED SLEEP, AND

PSYCHOSOCIAL PROBLEMS AMONG YOUTH WITH CRANIOPHARYNGIOMA

Kimberly Lauren Klages

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Abstract

Patients with craniopharyngioma experience hypothalamic dysfunction, weight gain, disrupted sleep, excessive daytime sleepiness (EDS), fatigue, and psychosocial problems that negatively impact health-related quality of life (HRQoL). The extent of hypothalamic tumor involvement (HI) has been shown to be associated with higher rates of these impairments; however, the direct and indirect effects of these relations have yet to be investigated. The goal of the current study was to examine relations between HI, body mass index (BMI), sleep disruptions, EDS, fatigue, psychosocial problems, and HRQoL among youth with craniopharyngioma. 84 youth with craniopharyngioma (M_{age} =10.27 + 4.3 years, 53.6% female, 64.3% White) were assessed with actigraphy and multiple sleep latency testing prior to proton therapy. Caregivers completed measures of fatigue, psychosocial functioning, and HRQoL. Path analyses revealed direct effects between HI extent and BMI (*Est.* = 2.97, *p* = .003), as well as HI and EDS (*Est.* = 2.53, *p* = .01). Greater fatigue (*Est.* = -.29, *p* < .001) and less disrupted sleep (*Est.* = -.09, *p* = .001) predicted more psychosocial problems. Fatigue positively predicted HRQoL (*Est.* = .23, *p* = .001) and psychosocial problems negatively predicted HRQoL (*Est.* = -.34, *p* = .004). Significant indirect effects of disrupted sleep (*Est.* = .03, *p* = .04) and fatigue (*Est.* = .10, *p* = .02) on HRQoL through psychosocial problems were also found. Results of the current study suggest that youth with craniopharyngioma with greater HI may benefit from weight and EDS reduction interventions. Findings also suggest that youth craniopharyngioma should be prospectively monitored for fatigue and psychosocial problems, as these patients may benefit from interventions focused on enhancing fatigue with a goal of improving overall quality of life and psychosocial health.

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Health-Related Quality of Life, Obesity, Disrupted Sleep, and Psychosocial Problems

among Youth with Craniopharyngioma

Craniopharyngioma is an invasive intracranial tumor of low histologic grade and

represents 1.2 to 4.6% of all childhood central nervous system (CNS) tumors (Garrè & Cama,

2007; Hoffman et al., 1992; Khafaga et al., 1998). Although treatment with various combinations

of surgery and radiation therapy results in excellent survival rates (92%), patients with

craniopharyngioma experience significant neurological, endocrine, somatic, and psychosocial

effects that may be further exacerbated by treatment (De Vile et al., 1996; Fisher et al., 1998;

Merchant et al., 2002; Tomei et al., 1997). Craniopharyngioma arises in the midline of the brain

and is most often located in the suprasellar region, involving or displacing the optic chiasm,

pituitary gland, and/or hypothalamus (Müller, 2008). Gross total resection (GTR) of the tumor

was previously considered the gold-standard treatment for craniopharyngioma; however, it has

since been found to be associated with high rates of recurrence, hypopituitarism, hypothalamic

dysfunction, and neurocognitive impairments (Caldarelli, Massimi, Tamburrini, Cappa, &

Rocco, 2005; De Vile et al., 1996; Hoffman et al., 1992; Poretti, Grotzer, Ribi, Schönle, &

Boltshauser, 2004). Limited surgical resection followed by radiation therapy has resulted in

favorable outcomes in comparison to aggressive surgical resection alone (De Vile et al., 1996;

Kiehna & Merchant, 2010; Merchant et al., 2002); however, radiation therapy has been described

as having significant short- and long-term effects on sleep, resulting in subjective and objective

reports of fatigue, excessive daytime sleepiness (EDS), and insomnia (Davidson, MacLean,

Brundage, & Schulze, 2002; Müller et al., 2006).

Proton therapy is now considered a preferred form of radiation therapy for

craniopharyngioma as it reduces the total volume of normal tissue exposure, and, therefore, may

be associated with greater health-related quality of life (HRQoL), psychosocial, and functional outcomes (Lomax et al., 1999; Müller 2011). Because proton therapy has only been recently established as a treatment modality for craniopharyngioma, the impact on the long-term functioning in areas such as sleep and fatigue of pediatric patients on this treatment remains to be fully elucidated.

Hypothalamic Dysfunction in Youth with Craniopharyngioma

Hypothalamic dysfunction is a devastating consequence of craniopharyngioma that results from displacement of or damage to the hypothalamus and occurs in approximately 52-87% of cases (Müller, 2008). Symptoms of hypothalamic dysfunction, such as fatigue, sleep dysfunction, obesity, and emotional and behavioral changes, persist in 65-80% of patients following treatment and are associated with long-term HRQoL impairments (Caldarelli et al., 2005; De Vile et al., 1996; Elliott & Wisoff, 2010; Jacola et al., 2016; Müller, 2016; Müller et al., 2011; Poretti et al., 2004). The extent of pre- and post-surgical hypothalamic tumor involvement (HI) is an important component of hypothalamic dysfunction, as more severe impairments have been found among patients with extensive HI (De Vile et al., 1996; Jacola et al., 2016; Müller et al., 2011). Specifically, severity of post-operative weight gain and EDS was found to be highest among pediatric patients with greater HI (De Vile et al., 1996; Jacola et al., 2016; Müller et al., 2011). Sterkenburg et al. (2015) demonstrated that adult survivors of childhood craniopharyngioma with greater HI were more likely to be obese and report higher rates of fatigue, psychosocial problems, and HRQoL impairments 20 years following treatment completion (Sterkenburg et al., 2015). Altered diurnal melatonin secretion patterns, including decreased nighttime melatonin secretion, has been detected among youth with craniopharyngioma with severe obesity, resulting in greater reports of EDS and daytime fatigue

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when compared to patients without obesity (Lipton et al., 2009; Müller et al., 2006; Müller, Handwerker, Wollny, Faldum, & Sörensen, 2002; Pickering et al., 2014).

Hormone Deficiencies in Youth with Craniopharyngioma

Pituitary hormone deficiencies are common in youth with craniopharyngioma and occur in approximately 40-87% of patients at diagnosis; the rate dramatically increases to 80-100% following treatment completion (Caldarelli et al., 2005; De Vile et al., 1996; Elliott & Wisoff, 2010; Hoffman et al., 1992; Merchant et al., 2002; Müller et al., 2004; Poretti et al., 2004). Common hormone deficiencies, such as growth hormone (GH), gonadotropin, and adrenocorticotropic (ACTH) deficiencies, have been associated with the development of significant endocrine complications, including poor growth, diabetes insipidus, obesity, and disrupted sleep-wake patterns (Ahmet et al., 2006; Caldarelli et al., 2005; Cohen, Guger, & Hamilton, 2011; Müller et al., 2004; Poretti et al., 2004). The majority of patients with craniopharyngioma require hormone replacement therapy, which effectively promotes growth and decreases associated endocrine complications; however, hypothalamic dysfunction likely interferes with the effectiveness of hormone replacement therapy and may place patients at significant risk for life threatening electrolyte imbalances (Cohen et al., 2011).

Sleep Disturbances in Youth with Craniopharyngioma

Rates of EDS, fatigue, and fragmented sleep patterns are high among survivors of craniopharyngioma (80%) compared to cancer survivors overall (60%) due to the location of the tumor in the hypothalamic-pituitary-adrenal (HPA) region of the brain and damage caused by the tumor itself or surgical resection (Müller, 2008; Rosen & Brand, 2011). Hypothalamic dysfunction likely disrupts the HPA axis among patients with craniopharyngioma, resulting in disordered sleep, such as insomnia, fatigue, and obstructive sleep apnea (OSA; (Buckley &

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Schatzberg, 2005). Actigraph data collected from three survivors of childhood craniopharyngioma demonstrated an altered pattern of circadian rhythm with early morning awakenings, irregular bedtimes, frequent nighttime activity, and periods of inappropriate daytime rest (Lipton et al., 2009). EDS, characterized by daytime napping, difficulty waking and engaging in activities throughout the day, and mean sleep latency of 15 minutes or less on objective measures of daytime sleepiness, and daytime fatigue have been identified in approximately one-third of patients long after treatment completion (Müller et al., 2006; Poretti et al., 2004) and are reportedly the most common complaints among survivors (Müller, 2010; Müller et al., 2002; Rosen, Bendel, Neglia, Moertel, & Mahowald, 2003).

In otherwise healthy children and adolescents, inadequate sleep and EDS have been linked to greater internalizing (i.e., depression, anxiety) and externalizing behaviors, poorer physical health, and HRQoL deficits in children and adolescents (Baum et al., 2014; Beebe, 2008; Crabtree, Varni, & Gozal, 2004; Liu et al., 2007; Mindell & Owens, 2015; Moore et al., 2009; Sadeh, Gruber, & Raviv, 2002). Sleep problems that significantly impact sleep quality, such as OSA and sleep disordered breathing (SDB), both commonly occur in youth with craniopharyngioma (O'Gorman et al., 2010) and have been linked to depressive symptoms and HRQoL impairments (Akashiba et al., 2002; Crabtree et al., 2004; Franco, Rosenfeld, & Rao, 2000). Parent-reported anxiety and depression have also been identified as strong risk factors for EDS among children, with greater likelihood of EDS among youth with more severe ratings of internalizing symptoms (Calhoun et al., 2011). It has been theorized that emotional and sleep disturbances in children occur in a mutually interacting cyclic pattern, such that emotional disturbances lead to sleep difficulties and sleep deprivation, which, in turn, lead to mood disruptions (Dahl, 1996; Ivanenko, Crabtree, & Gozal, 2005).

Excessive Weight Gain and Obesity in Youth with Craniopharyngioma

Endocrine deficits and obesity-related metabolic dysfunctions likely contribute to fragmented sleep, EDS, and poor sleep quality among survivors. Obesity and rapid weight gain affect up to 52% of craniopharyngioma patients, with almost half of these patients reporting the inability to diminish their desire to eat (Müller et al., 2004; Müller et al., 2002). Hypothalamic obesity, or intractable weight gain due to hypothalamic damage or dysfunction, has been documented to occur in 30-77% of craniopharyngioma patients after completion of treatment (Lustig, 2011). Unlike obesity, weight gain in response to hypothalamic damage or dysfunction occurs regardless of calorie restriction, pharmacological treatment, or the implementation of healthy lifestyle interventions (Harz, Müller, Waldeck, Pudel, & Roth, 2003; Lustig, 2011). It develops when the body is unable to transduce signals of adiposity appropriately and results in reduced energy expenditure, increased insulin secretion, and excessive weight gain (Bray & Gallagher, 1975; Harz et al., 2003; Lustig, 2011; Shaikh, Grundy, & Kirk, 2008).

Obesity in patients with craniopharyngioma has been associated with EDS above and beyond that typically described in otherwise healthy patients with obesity (Müller, 2010; Müller et al., 2002; O'Gorman et al., 2010; Rosen et al., 2003), further increasing the likelihood of EDS in this population. EDS has been established to manifest differently in children with obesity when compared to children without obesity. In children without obesity, EDS is associated with attention difficulties and hyperactivity, whereas children with obesity and EDS are more likely to report feeling tired and falling asleep during daily activities in school and at home (Gozal & Kheirandish-Gozal, 2009). Müller and colleagues (2002) surveyed a large group of patients with childhood craniopharyngioma for EDS and found the severity of EDS was high in patients with body mass index (BMI) z-scores > 4. More recently, Brimeyer and colleagues (2016) found that

obesity was highly correlated with parent-report of EDS in survivors of pediatric CNS tumors and concluded that obesity represents a risk factor for EDS in CNS tumor survivors (Brimeyer et al., 2016).

In addition to sleep disruptions, fatigue, and EDS, excessive weight gain and obesity have been identified to have adverse effects on psychosocial functioning and HRQoL. Research in pediatric obesity has consistently revealed that children with obesity are at significant risk for poor self-esteem, body dissatisfaction, peer victimization, depressive symptoms, and decreased HRQoL (Daniels, 2006; Puhl, Luedicke, & Heuer, 2011; Zeller, Roehrig, Modi, Daniels, & Inge, 2006). Among youth with craniopharyngioma, those who developed severe obesity (BMI z-scores > 3 standard deviations [*SD*]) rated greater HRQoL impairments in regard to their physical abilities, body image, and social and emotional functioning compared to patients with lower BMIs (Müller et al., 2001). It has been postulated that HRQoL impairments and psychosocial problems among youth with craniopharyngioma are strongly associated with concerns related to excessive weight gain, such as body dissatisfaction and low self-esteem (Poretti et al., 2004). Findings suggest that the psychosocial and HRQoL difficulties associated with obesity are likely to impact youth with craniopharyngioma similarly; however, it is currently unclear how additional disease sequelae, such as hypothalamic dysfunction, disrupted sleep patterns, fatigue, and EDS, relate to obesity, psychosocial functioning, and HRQoL in youth with craniopharyngioma.

Psychosocial Functioning in Youth with Craniopharyngioma

Behavior changes and impairments in social-emotional functioning have also been reported as a consequence of hypothalamic dysfunction in youth with craniopharyngioma (Mehren et al., 2018; Sterkenburg et al., 2015; Zada, Kintz, Pulido, & Amezcua, 2013). High

rates of apathy, depression, anxiety, and somatic complaints have been found among patients with hypothalamic-pituitary dysfunction (Fox & King, 2016; Mehren et al., 2018; Ondruch, Maryniak, Kropiwnicki, Roszkowski, & Daszkiewicz, 2011; Waber et al., 2006; Zenker, Haverkamp, & Klingmuller, 2002). Using standardized parent-report measures of psychosocial functioning, children with craniopharyngioma were rated to be nervous, sensitive, likely to exhibit unexpected anger outbursts, unkempt, and to be preoccupied with food, all of which were reported to significantly disrupt the child's peer relationships (Ondruch et al., 2011). In comparison to healthy controls, self-reported social and emotional functioning were rated as the most affected psychosocial domains among youth with craniopharyngioma (Poretti et al., 2004; Zada et al., 2013). Although hypothalamic dysfunction likely plays a role in the development of psychosocial problems, it is unclear how the extent of HI, and symptoms related to hypothalamic dysfunction, such as obesity, sleep disruptions, fatigue, and EDS, contribute to the severity of psychosocial problems and HRQoL deficits among youth with craniopharyngioma.

Current Study

To date, the relations between psychosocial functioning, HRQoL, obesity and sleep disruptions among youth with craniopharyngioma have yet to be investigated. Given that disrupted sleep, EDS, fatigue, and hypothalamic obesity are reported as significantly impairing consequences of craniopharyngioma, examination of the interacting relations between these physiological and psychological factors in this vulnerable population is warranted. Furthermore, although previous studies have linked more extensive HI to severe obesity and greater EDS, none have examined the direct impact of HI extent on psychosocial functioning and HRQoL among youth with craniopharyngioma. Examination of existing literature suggests that extensive HI likely results in severe obesity, disrupted sleep, greater EDS and fatigue, more psychosocial

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problems, and significant HRQoL impairments. However, it is currently unclear if HI is directly

associated with psychosocial functioning and HRQoL or indirectly through obesity, sleep

disruptions, EDS, and/or fatigue. Therefore, the current study aims to examine the relations

between HI, BMI, sleep disruptions, EDS, fatigue, psychosocial problems, and disease-specific

HRQoL among youth with craniopharyngioma. It is hypothesized that (1) HI extent will be

positively associated with BMI, sleep disruptions, fatigue, EDS, psychosocial problems, and

HRQoL impairments, (2) BMI, sleep disruptions, fatigue, and EDS will be positively associated

with psychosocial problems and HRQoL impairments, (3) psychosocial problems will be

positively associated with HRQoL impairments, and (4) BMI, sleep disruptions, fatigue, EDS,

and psychosocial problems will mediate the relationship between HI and HRQoL. In the

proposed model, BMI, sleep disruptions, EDS, and fatigue are thought to covary (see Figure 1
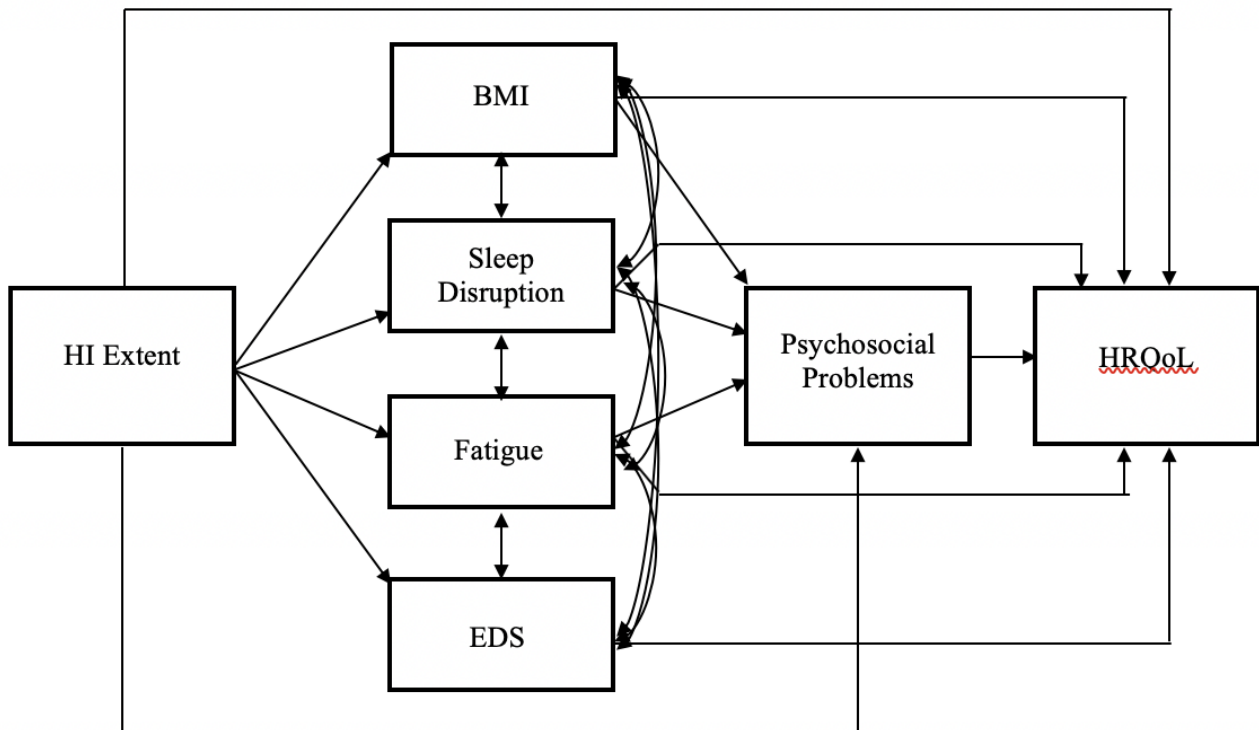
below for conceptual model).

Figure 1. Conceptual Model of Relations Between Hypothalamic Involvement, Obesity, Sleep Disruption, Fatigue, Psychosocial Problems, and Health Related Quality of Life Among Youth with Craniopharyngioma.

Note. BMI = body mass index; sleep disruption = disrupted sleep measured by wake after sleep onset (WASO) from actigraphy; Fatigue = PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) total score; EDS = excessive daytime sleepiness measured by mean sleep latency (MSL) on the multiple sleep latency test (MSLT); psychosocial problems = psychosocial problems measured by Behavioral Symptoms Index (BSI) on BASC-2; HRQoL = health related quality of life measured by PedsQL Brain Tumor Module (PedsQL-BT Module) total score.

Method

Participants and Procedures

Data were collected from 84 youth with craniopharyngioma (M_{age} = 10.27 ± 4.3 years, 56% female, 61.9% White; see Table 1 for demographic and disease characteristics) as part of a larger institutional protocol designed to treat and monitor patients with craniopharyngioma at baseline (defined as within 12 weeks of the initiation of therapy with variances of up to 90 days). Patients were excluded based on a history of prior treatment with fractionated radiation therapy. The group included newly diagnosed patients, those with recurrent tumors after prior radical surgery, patients treated with radical surgery alone, and patients who did not undergo surgery and were diagnosed based on imaging findings alone. Surgery included various combinations of transsphenoidal resection, open craniotomy, and closed stereotactic placement of catheter systems for cyst drainage; patients may have had more than one procedure. Prior to receiving proton therapy, patients completed a comprehensive evaluation that included clinical assessment, neurocognitive testing, actigraphy, and clinical evaluation by a pediatric sleep specialist plus multiple sleep latency testing (MSLT) following overnight polysomnography (PSG). The MSLT and PSG were conducted in an American Academy of Sleep Medicine (AASM)-accredited sleep center, scheduled based upon the patient's typical sleep/wake schedule as determined by a clinical history taken by the sleep specialist, scored by registered polysomnography technologists

trained in scoring pediatric PSG and MSLT, and reviewed and interpreted by a Board-certified sleep specialist with experience in pediatric sleep. Since young children have difficulty cooperating with the MSLT protocol (Mindell & Owens, 2015), patients under the age of 6 years were excluded from the present study. If a patient had significantly poor sleep on the PSG, the MSLT was not conducted; if a patient had significantly delayed sleep onset, the MSLT was delayed to begin at a later time. In the current study, caregivers of patients completed behavior-rating questionnaires to ensure consistency in reporting across domains of psychosocial functioning, fatigue, and HRQoL, and sleep data were collected from each participant nightly for 3-10 nights via actigraphy. Data collection procedures were conducted with approval from the Institutional Review Boards at St. Jude Children's Research Hospital and University of Florida Health Proton Therapy Institute. Additional approval for the current study was obtained from the University of Memphis. Informed consent and assent were obtained for all protocol-based procedures.

Materials and Measures

Demographic and Clinical Variables. Demographic and clinical data, including age, race, Tanner stage, gender, shunt status, date of diagnosis, date of treatment initiation, treatment type, extent of hypothalamic involvement, and extent of resection, were systematically collected through medical record review (see Table 1).

Table 1. Demographic and Disease Characteristics

Variable	$M \pm$SD; RNG (%)
Age	10.27$\pm$4.3 years; RNG = 6-20 years
Gender	47 (56%) female
Tanner Stage ($n = 82$)	
1	62 (73.8%)
>1	20 (23.8%)
Body Mass Index Z-score (zBMI)	1.2$\pm$1
Underweight	0 (0%)

Table 1. (continued)

Variable	$M \pm SD$; RNG (%)
Lean weight	33 (39.3%)
Overweight	20 (23.8%)
Obese	30 (35.7%)
Race	
White	52 (61.9%)
Black	18 (21.4%)
Other	14 (16.7%)
Hypothalamic Tumor Involvement	
Grade 0	13 (15.5%)
Grade 1	22 (26.2%)
Grade 2	49 (58.3%)
# of Surgeries	
0	7 (8.3%)
1	43 (51.2%)
2	20 (23.8%)
≥ 3	14 (16.7%)
Surgical Procedure	
None	7 (8.3%)
Catheter only, craniotomy	6 (7.1%)
Catheter only, burr hole	11 (13.1%)
Resection, craniotomy	42 (50%)
Resection, transphenoidal	15 (17.9%)
Resection, endoscopic	3 (3.6)
MSLT MSL, minutes	8.75 ± 5.6; RNG = .37–20
MSLT SOREM	RNG = 0-4
>2	35 (41.7%)
WASO Actigraphy	64.2±35.8

Multiple Sleep Latency Test. The Multiple Sleep Latency Test (MSLT) is a norm-referenced measure used to evaluate daytime sleepiness and sleep propensity in the absence of alerting factors. Youth were scheduled for overnight PSG followed by MSLT the following day. MSLTs were performed according to guidelines recommended by the AASM (Littner et al., 2005). Following overnight PSG, participants were evaluated with four or five nap opportunities at two-hour intervals throughout the day. With each nap opportunity, patients were instructed to

lie in bed quietly with eyes closed and to try to fall asleep. As per the MSLT protocol, patients were studied in a quiet, darkened room with no television or other electronic devices on. The recording montage used was consistent with that recommended by the AASM, including central and occipital electroencephalogram derivations linked to the contralateral ear or mastoid region, left and right electro-oculograms, mental/submental electromyogram, and electrocardiogram. A registered polysomnography technologist observed patients continuously between naps and encouraged the child not to fall asleep. If sleep onset occurred during a nap opportunity, patients were allowed to sleep for 15 minutes before being awakened. If no sleep occurred after 20 minutes, the nap opportunity ended. The mean sleep latency (MSL) in minutes was calculated as the arithmetic mean of all nap opportunities; the number of naps and the number of sleep-onset REM periods were also recorded. Using EDS cutoff scores for prepubescent versus pubescent children first proposed by Gozal & Kheirandish-Gozal (2009), EDS was defined as a MSL of ≤ 15 minutes in prepubescent children with a Tanner Stage of 1 and of ≤ 10 minutes in pubescent youth with a Tanner Stage of 2 or greater (Gozal & Kheirandish-Gozal, 2009).

Wrist Actigraphy. The Micromini Sleep Watch (Ambulatory Monitoring Inc., Ardsley, NY) was used to collect nightly sleep data. The Micromini Sleep Watch is a wristwatch-style device that contains a biaxial piezoelectric sensor and a microprocessor with programmable epoch length. The system's accompanying software was used to compute the sleep characteristics. Sadeh's algorithm (Sadeh, 1996; Sadeh, Acebo, Seifer, Aytur, & Carskadon, 1995; Sadeh, Hauri, Kripke, & Lavie, 1995; Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991); Sadeh, Sharkey, and Carskadon (1994) was used to compute sleep characteristics including sleep efficiency, total time in bed, and wake after sleep onset (WASO). Sadeh's algorithm has been previously validated against polysomnography in children (Sadeh, 2011; Sadeh et al., 1991). The

wristwatch was worn by participants for 3-10 days depending upon the length of the participant's follow-up visit to the hospital. A minimum of 3 nights of actigraphy data was used to best capture night-to-night variability in sleep.

PedsQL Multidimensional Fatigue Scale. Fatigue was assessed using parent report of The PedsQL Multidimensional Fatigue Scale (PedsQL-MFS; Varni, Burwinkle, & Szer, 2004). PedsQL-MFS is an 18-item scale that is designed to assess the presence and severity of fatigue over the past month along three domains: general fatigue, sleep/rest fatigue, and cognitive fatigue. The parent forms are for three different age groups (5-7 years, 8-12 years, and 13+ years). Responses on the PedsQL-MFS are on a five-point Likert scale (0 = *never* to 4= *almost always*). Items were reverse-scored and linearly transformed to a 0–100 scale, with higher scores indicating less fatigue. A total mean scaled score of the 18 items was computed as the sum of the items divided by the number of items answered in the scales. The PedsQL-MFS has demonstrated good to excellent reliability and validity across a number of pediatric chronic health conditions (Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002; Varni, Burwinkle, Limbers, & Szer, 2007; Varni et al., 2004). The PedsQL-MFS has also been shown to be internally consistent (α = .92-.96) and highly correlated with fatigue and HRQoL measures (Murray, Palermo, & Holmbeck, 2017).

Pediatric Quality of Life Inventory Brain Tumor Module. Disease-specific HRQoL was measured using parent-report of The Pediatric Quality of Life Inventory Brain Tumor Module (PedsQL-BT Module; Palmer, Meeske, Katz, Burwinkle, & Varni, 2007). The PedsQL-BT Module is a 24-item Likert-type scale developed to measure HRQoL in youth who are receiving treatment or survivors of pediatric brain tumors. The module contains six scales and includes cognitive, pain and hurt, movement and balance, procedural anxiety, nausea, and worry.

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Consistent with the PedsQL-MFS, the PedsQL-BT Module has forms for three different age groups (5-7 years, 8-12 years, and 13+ years). Items on the PedsQL-BT Module are reversed scored and transformed to a 0-100 scale (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0) and high scores indicate greater HRQoL. A total mean scaled score of the 24 items was computed as the sum of the items divided by the number of items answered on the scales. The PedsQL-BT Module forms for the research participants and parents have an internal consistency (Cronbach's alpha coefficients of .76-.87 and .78-.92, respectively) with construct validity supported through an analysis of the inter-correlations with the PedsQL-MFS and PedsQL (Palmer et al., 2007).

Body Mass Index. Anthropometric measurements, including height by wall-mounted stadiometer (without shoes) and weight by electronic scale, were obtained from participants by trained clinic staff during their Physical Performance and Movement visit. Smooth BMI z-scores were calculated using Cole's lamda mu sigma (LMS) method (Cole, 1990; Cole & Green, 1992) and Centers for Disease Control and Prevention (CDC) growth charts (Kuczmarski, 2000). Following suggested CDC guidelines, data were screened for biologically implausible values. No biologically implausible values were found.

Behavior Assessment System for Children, Second Edition. The Behavior Assessment System for Children, Second Edition (BASC-2; Reynolds & Kamphaus, 2004) is a questionnaire assessing behavioral, emotional and adaptive functioning of children and individuals between 4-21 years of age. The current study used the parent version only (BASC-2 PRS), which provides a comprehensive measure of the youth's behavior and adaptive skills displayed both within and outside of the home environment. The parent version of the BASC-2 is composed of 10 clinical scales and 6 adaptive indices. The current study utilized the Behavioral Symptoms Index (BSI) as a measure of psychosocial problems. The BSI is a composite score of the Hyperactivity,

Aggression, Depression, Attention Problems, Atypicality, and Withdrawal subtests of the BASC-2 PRS and serves as an overall measure of problem behaviors. Raw subscale scores were converted to T scores ($M = 50$, $SD = 10$) and summed to create the BSI composite score. Scores below 60 indicate normal functioning, scores between 60 and 69 indicate "at risk" behavior (implying mild to moderate impairment), and scores above 70 indicate "significant risk." The BASC-2 has been shown to be internally consistent ($\alpha = .80$-$.90$) and has demonstrated good test-retest reliability (Reynolds & Kamphaus, 2004).

Analytic Plan

Path Analysis was used to test the hypothesized relations between HI, BMI, sleep disruptions (WASO from actigraphy), EDS (MSLT), fatigue (PedsQL-MFS), psychosocial problems (BSI from BASC-2), and disease-specific HRQoL (PedsQL-BT Module; see Figure 1 for conceptual model), with the primary goal of exploring the direct and indirect effects of HI on obesity, sleep disruptions, fatigue, EDS, psychosocial problems, and HRQoL (Kline, 2015). Specifically, path analyses aimed to explore the extent to which obesity, sleep disruptions, fatigue, EDS, and psychosocial problems are potential mediators of the relation between HI and HRQoL. Analyses were conducted in *Mplus* Version 8.2 (Muthén & Muthén, 2018) using two well established methods that address non-normality, (1) maximum likelihood estimation with bootstrapped standard errors and (2) and robust maximum likelihood estimation which adjusts the standard errors and a chi-square test statistics taking into account multivariate kurtosis (Muthén & Muthén, 2018; Nevitt & Hancock, 2001). Monte Carlo simulations were conducted using these results to determine which estimation would be best in terms of low parameter bias, high coverage, and maximal power given these data and the present sample size (Muthén & Muthén, 2002).

Results

When comparing bootstrap and MLR parameter estimation methods, both bootstrap and MLR estimation exhibited similar and acceptable parameter bias (approximately -2 to -4%), and coverage (ranging from .93 to .95); however, MLR uniformly resulted in greater power for every estimated parameter. As such, MLR was chosen over ML estimation with bootstrapping. Since the path model was fully saturated, goodness-of-fit statistics were non-informative (i.e., perfectly reproduced the observed covariance matrix). The percentage of variances accounted for were as follows, 11% BMI (R_2 = .11, p = .12; Cohen's f_2 = .12), 2% disrupted sleep (R_2 = .11, p = .48; f_2 = .02), 1% fatigue (R_2 = .01, p = .57; f_2 = .01), 11% EDS (*Est.* = .11, p = .20; f_2 = .12), 31% psychosocial problems (R_2 = .31, p <.001; f_2 = .45), and 21% HRQoL (R_2 = .21, p = .02; f_2 = .27).

In terms of specific effects, positive (unstandardized) direct effects of HI extent on BMI (*Est.* = 2.97, p = .003) and HI on EDS (*Est.* = 2.53, p = .01) were found. No direct effects of HI extent on disrupted sleep (*Est.* = 6.29, p = .16) and HI extent on fatigue (*Est.* = -3.04, p = .27) were found. There were also no significant direct effects of HI extent on psychosocial problems (*Est.* = -.68, p = .72), BMI on psychosocial problems (*Est.* = -.23, p = .27), or EDS on psychosocial problems (*Est.* = 3.2, p = .28). However, fatigue (*Est.* = -.29, p < .001) was found to predict psychosocial problems. Contrary to our hypotheses, greater disrupted sleep predicted fewer psychosocial problems (*Est.* = -.09, p = .001). Significant direct effects of fatigue on HRQoL and psychosocial problems on HRQoL were also found, such that fatigue positively predicted HRQoL (*Est.* = .23, p = .001) and psychosocial problems negatively predicted HRQoL (*Est.* = -.34, p = .004). No significant direct effects of HI (*Est.* = .82, p = .63), EDS (*Est.* = -5.5, p = .12), BMI (*Est.* = .08, p = .80), or disrupted sleep (*Est.* = .03, p = .54) on HRQoL were found.

No significant residual covariances were found between BMI and disrupted sleep (*Est.* = -6.7, *p* = .72) or BMI and EDS (*Est.* = .24, *p* = .19); however, there was a negative residual association with BMI and fatigue (*Est.* = -26.7, *p* = .04; controlling for HI extent). While no significant residual covariances were found between disrupted sleep and fatigue (*Est.* = -72.7, *p* = .37) and fatigue and EDS (*Est.* = -.21, *p* = .81), there was a positive residual association between disrupted sleep and EDS (*Est.* = 3.6, *p* = .03; controlling for HI extent).

Significant indirect effects of disrupted sleep (unstandardized *Est.* = .03, *p* = .04; standardized *Est.* = .09) and fatigue (unstandardized *Est.* = .10, *p* = .02; standardized *Est.* = .16) on HRQoL through psychosocial problems were found. More specifically, greater disrupted sleep and fatigue were predictive of more psychosocial problems, which, in turn, was predictive of lower HRQoL; however, the indirect effects of HI extent on psychosocial problems and HI extent on HRQoL through all mediators (BMI, disrupted sleep, fatigue, EDS, and psychosocial problems) were not significant (all *p*'s > .05). See Table 2 for all unstandardized direct effects and residual covariances, Table 3 for all unstandardized direct effects and residual covariances, Table 3 for all unstandardized indirect effects, and Table 4 for correlations, means, and standard deviations. The standardized path model with direct effects can be found in Figure 2.

Table 2. Path Analysis Direct Effects and Residual Covariances

Direct Effects	Estimate	*S.E.*	Est./*S.E.*	*p*-value
HI Extent→BMI	2.07**	.69	2.98	.003
HI Extent→Sleep Disruption	6.29	4.45	1.42	.16
HI Extent→Fatigue	-3.04	2.76	-1.10	.27
HI Extent→EDS	0.18*	.07	2.53	.011
HI Extent→Psychosocial Problems	-0.68	1.91	-.36	.72
BMI→Psychosocial Problems	-0.23	.21	-1.11	.27
Sleep Disruption→Psychosocial Problems	-0.09**	.03	-3.21	.001
Fatigue→Psychosocial Problems	-0.29***	.05	-5.5	<.001
EDS→Psychosocial Problems	3.2	2.97	1.08	.28

Table 2. (continued)

Direct Effects	Estimate	*S.E.*	Est./*S.E.*	*p*-value
Fatigue→HRQoL	0.23**	.072	3.23	.001
EDS→HRQoL	-5.5	3.52	-1.57	.12
Psychosocial Problems→HRQoL	-0.34**	.12	-2.87	.004
HI Extent→HRQoL	0.82	1.69	.48	.63
BMI→HRQoL	0.08	.31	.25	.80
Sleep Disruption→HRQoL	0.03	.051	.61	.54
Residual Covariances				
BMI with Sleep Disruption	-6.67	18.68	-.36	.72
BMI with Fatigue	-26.7*	13.33	-2.01	.04
BMI with EDS	0.24	.18	1.30	.19
Sleep Disruption with Fatigue	-72.7	81.3	-.894	.37
Sleep Disruption with EDS	3.6*	1.61	2.23	.03
Fatigue with EDS	-0.21	.88	-.24	.81

Note. $*p < .05$; $**p < .01$; $*** p < .001$. Estimates are unstandardized. BMI = body mass index; sleep disruption = disrupted sleep measured by wake after sleep onset (WASO) from actigraphy; Fatigue = PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) total score; EDS = excessive daytime sleepiness measured by mean sleep latency (MSL) on the multiple sleep latency test (MSLT); psychosocial problems = psychosocial problems measured by Behavioral Symptoms Index (BSI) on BASC-2; HRQoL = health related quality of life measured by PedsQL Brain Tumor Module (PedsQL-BT Module) total score.

Table 3. Path Analysis Unstandardized Indirect Effects

Indirect Effects	Estimate	*S.E.*	Est./*S.E.*	*p*-value
HI Extent→BMI→HRQoL	0.16	.63	.25	.80
HI Extent→Sleep Disruption→HRQoL	0.006	.34	.02	.99
HI Extent→Fatigue→HRQoL	-0.41	.42	-.98	.33
HI Extent→EDS→HRQoL	-0.81	.72	-1.13	.26
HI Extent→Psychosocial Problems→HRQoL	-0.82	1.23	-.67	.51
HI Extent→BMI→Psychosocial Problems→HRQoL	0.16	.17	.94	.35
HI Extent→Sleep→Psychosocial Problems→HRQoL	0.19	.16	1.15	.25
HI Extent→Fatigue→Psychosocial Problems→HRQoL	-0.30	.30	-.99	.32
HI Extent→EDS→Psychosocial Problems→HRQoL	-0.20	.21	-.97	.33
BMI→Psychosocial→HRQoL	0.08	.08	.96	.34
Sleep Disruption→Psychosocial Problems→HRQoL	0.03*	.02	2.03	.04
Fatigue→Psychosocial Problems→HRQoL	0.10*	.04	2.25	.02

Table 3. (continued)

Indirect Effects	Estimate	*S.E.*	Est./*S.E.*	*p*-value
EDS→Psychosocial Problems→HRQoL	-1.10	1.1	-1.00	.32
HI Extent→BMI→Psychosocial Problems	-0.47	.44	-1.08	.28
HI Extent→Sleep Disruption→Psychosocial Problems	-0.55	.42	-1.33	.19
HI Extent→Fatigue→Psychosocial Problems	0.88	.79	1.11	.27
HI Extent→EDS→Psychosocial Problems	0.59	.57	1.04	.30

Note. $*p < .05$; $**p < .01$; $*** p < .001$. Estimates are unstandardized. BMI = body mass index; sleep disruption = disrupted sleep measured by wake after sleep onset (WASO) from actigraphy; Fatigue = PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) total score; EDS = excessive daytime sleepiness measured by mean sleep latency (MSL) on the multiple sleep latency test (MSLT); psychosocial problems = psychosocial problems measured by Behavioral Symptoms Index (BSI) on BASC-2; HRQoL = health related quality of life measured by PedsQL Brain Tumor Module (PedsQL-BT Module) total score.

Table 4. Correlations, Means, and Standard Deviations

Variable	HI Extent	BMI	Sleep Disruption	Fatigue	EDS	Psychosocial Problems	HRQoL
HI Extent	$M = 1.4$ $SD = .75$	$r = .28**$	$r = .13$	$r = -1.3$	$r = .36**$	$r = -.07$	$r = .12$
BMI	$r = .28**$	$M = 22.5$ $SD = 5.5$	$r = .004$	$r = -.28**$	$r = .22$	$r = .03$	$r = -.03$
Sleep Disruption	$r = .13$	$r = .004$	$M = 64.2$ $SD = 35.8$	$r = -.12$	$r = -.29**$	$r = -.19$	$r = .009$
Fatigue	$r = -1.3$	$r = -.28**$	$r = -.12$	$M = 65.8$ $SD = 20.4$	$r = -.08$	$r = -.47**$	$r = .34**$
EDS	$r = .36**$	$r = .22$	$r = -.29**$	$r = -.08$	$M = 8.8_§$ $SD = 5.7$	$r = .02$	$r = -.14$
Psychosocial Problems	$r = -.07$	$r = .03$	$r = -.19$	$r = -.47**$	$r = .02$	$M = 48.7$ $SD = 10.9$	$r = -.40**$
HRQoL	$r = .02$	$r = -.03$	$r = .009$	$r = .34**$	$r = -.14$	$r = -.40**$	$M = 68.9$ $SD = 12.7$

Note. $**p < .01$; $*p < .05$. BMI = body mass index; sleep disruption = disrupted sleep measured by wake after sleep onset (WASO) from actigraphy; Fatigue = PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) total score; EDS = excessive daytime sleepiness measured by mean sleep latency (MSL) on the multiple sleep latency test (MSLT); § = mean sleep latency and standard deviation; psychosocial problems = psychosocial problems measured by Behavioral Symptoms Index (BSI) on BASC-2; HRQoL = health related quality of life measured by PedsQL Brain Tumor Module (PedsQL-BT Module) total score.
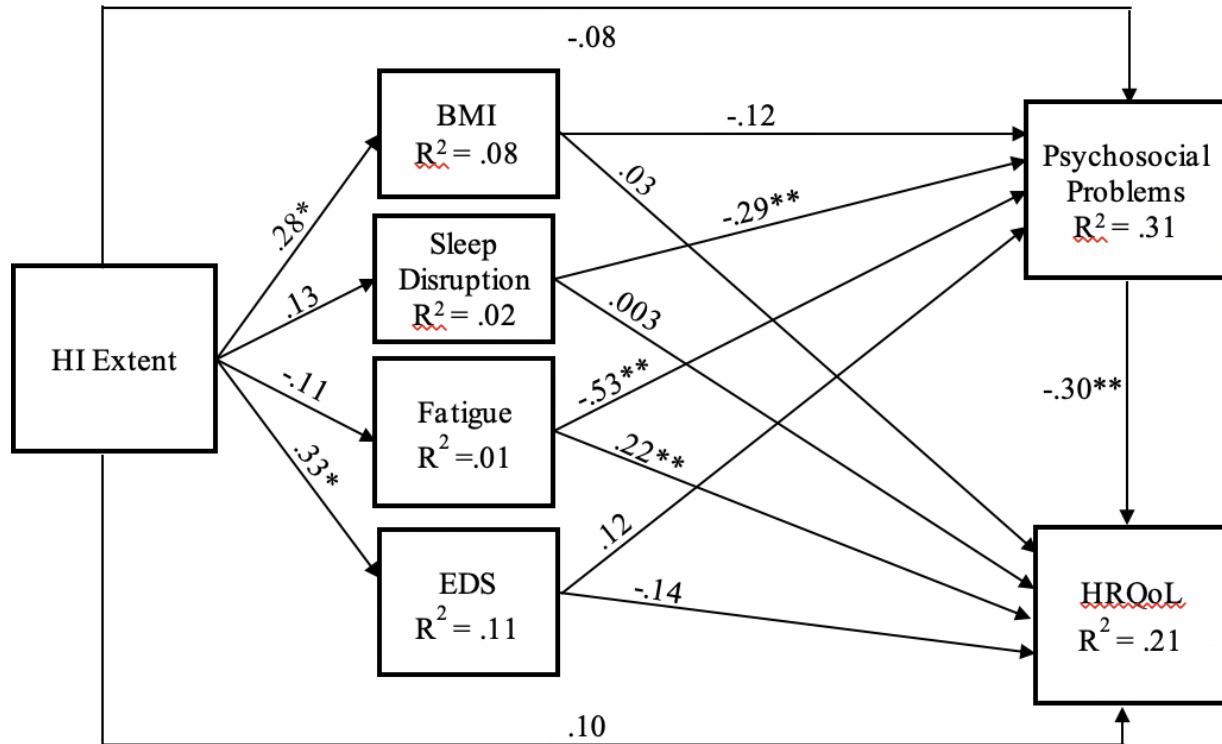
Figure 2. Standardized Path Model with Direct Effects (residual covariances and indirect effects not depicted)

Note. *p < .05; **p < .01; *** p < .001. Estimates are standardized. BMI = body mass index; sleep disruption = disrupted sleep measured by wake after sleep onset (WASO) from actigraphy; Fatigue = PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) total score; EDS = excessive daytime sleepiness measured by mean sleep latency (MSL) on the multiple sleep latency test (MSLT); psychosocial problems = psychosocial problems measured by Behavioral Symptoms Index (BSI) on BASC-2; HRQoL = health related quality of life measured by PedsQL Brain Tumor Module (PedsQL-BT Module) total score.

Discussion

The aim of the current study was to examine the relations between HI, BMI, sleep disruptions, EDS, fatigue, psychosocial problems, and disease-specific HRQoL among youth with craniopharyngioma. Path analysis revealed that greater HI extent predicted higher BMI and more EDS. More psychosocial problems were found among youth with craniopharyngioma experiencing greater fatigue. Contrary to hypotheses, we found fewer psychosocial problems among youth with more disrupted sleep. Regarding HRQoL, less fatigue and fewer psychosocial

problems predicted better HRQoL. Associations were found between BMI and fatigue and disrupted sleep and EDS when controlling for HI extent, psychosocial problems, and HRQoL, such that more EDS was found among youth with higher BMI and those with more disrupted sleep. Finally, indirect effects of disrupted sleep and fatigue on HRQoL through psychosocial problems were found. More specifically, among our sample of youth with craniopharyngioma, greater disrupted sleep and fatigue predicted more psychosocial problems, which in turn, predicted worse HRQoL.

Inconsistent with original hypotheses, HI extent was found to only moderately predict BMI and EDS. Previous research has demonstrated similar findings among pediatric patients and adult survivors of childhood craniopharyngioma (De Vile et al., 1996; Jacola et al., 2016; Müller, Gebhardt, Teske, et al., 2011; Sterkenburg et al., 2015). Specifically, weight gain and EDS were found to be highest among patients with greater HI (De Vile et al., 1996; Jacola et al., 2016; Müller, Gebhardt, Teske, et al., 2011; Sterkenburg et al., 2015). While only small, non-statistically significant associations were found between HI extent and disrupted sleep and fatigue, residual associations were found between BMI and fatigue and between disrupted sleep and EDS. This may be due to our limited sample size ($N = 84$). Of note, Lipton et al. (2009), Müller et al. (2002), Müller et al. (2006), and Pickering et al. (2014) found decreased nighttime melatonin secretion, sleep disruptions, and EDS among youth with craniopharyngioma with obesity following treatment. Furthermore, Manley et al. (2012) reported that most of their sample of long-term survivors of craniopharyngioma experienced significant fatigue and sleep disturbances. Given that the present study utilized baseline data, it may be possible that the associations between obesity, disrupted sleep, fatigue, and EDS may grow in strength over time. Overall, these findings, as well as findings of the current study, suggest HI extent, obesity, EDS,

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fatigue, and disrupted sleep may be associated; however, additional research is needed to determine the magnitude of the direct and indirect relations among these variables within a larger sample of youth with craniopharyngioma over time.

Similar to previous research findings among healthy children and adolescents, we found more psychosocial problems among youth with craniopharyngioma who experience greater fatigue (Clanton et al., 2011; Crabtree et al., 2004; Jones, Cunningham, Kashikar‐Zuck, & Brunner, 2016; Liu et al., 2007; Mindell & Owens, 2015; Moore et al., 2009; Pinquart & Shen, 2010; ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2006). Specifically, we found a medium effect of fatigue on psychosocial problems. Children with chronic medical conditions have been identified to be at risk for poorer psychosocial functioning (Bennett, 1994; Lavigne & Faier-Routman, 1992), and high rates of psychosocial problems (29-70%) have been well documented among youth with craniopharyngioma (Fox & King, 2016; Mehren et al., 2018; Ondruch et al., 2011; Poretti et al., 2004; Sterkenburg et al., 2015; Zada et al., 2013). Poorer psychosocial functioning has been shown to predict fatigue among youth with and without chronic illness (Anderson, Allen, Thornburg, & Bonner, 2015; Meltzer, Logan, & Mindell, 2005; Schanberg et al., 2005; ter Wolbeek et al., 2011), including survivors of childhood cancer (Clanton et al., 2011; Daniel et al., 2016; Meeske, Siegel, Globe, Mack, & Bernstein, 2005; Zeltzer et al., 2009; Zhou & Recklitis, 2014). While fatigue may be a symptom of psychosocial disturbance, it is likely that psychosocial problems and fatigue occur in a mutually interacting cyclic pattern, much like the pattern between sleep and psychosocial disturbances proposed by Dahl (1996).Given that we found positive associations between psychosocial problems and fatigue, pediatric patients with craniopharyngioma should be routinely assessed for fatigue, and psychosocial impairments to determine if targeted psychological interventions are warranted.

Although relations between sleep disturbances and psychosocial functioning have been well supported in the literature, we found a small, yet statistically significant, effect between disrupted sleep and psychosocial problems, such that greater disrupted sleep predicted fewer psychosocial problems ($r = .19$; see Table 4). It is possible that other mediating variables (i.e., obesity, fatigue, EDS) may be confounding this finding; however, we do not have the appropriate sample size to further explore these relations. Despite the contrary finding between disrupted sleep and psychosocial problems, we did find a significant indirect effect of disrupted sleep on HRQoL through psychosocial problems in the expected direction. It may be that HRQoL plays an important role in the relationship between disrupted sleep and psychosocial functioning among youth with craniopharyngioma, though, future research is needed to examine these mechanisms more closely.

It is also somewhat unexpected that we did not find a larger effect of HI extent on psychosocial problems, as psychosocial dysfunction has been linked to hypothalamic dysfunction in youth with craniopharyngioma (Mehren et al., 2018; Sterkenburg et al., 2015; Zada et al., 2013). Though connections between EDS and psychosocial functioning have been previously established in the literature (Calhoun et al., 2011; Zeltzer et al., 2009), we did not find EDS to significantly predict psychosocial problems within our sample. Given that we found a direct effect between HI extent and EDS, as well as residual associations between EDS and disrupted sleep, it is likely that HI extent, EDS, sleep difficulties, and fatigue relate to one another; however, the mechanisms by which are currently unknown. Future research is needed to determine the mechanisms by which HI extent impacts EDS, sleep disturbances, fatigue, and psychosocial functioning among pediatric patients with craniopharyngioma.

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Among our sample of pediatric patients with craniopharyngioma, we found a medium effect of fatigue and psychosocial problems on HRQoL. Specifically, better HRQoL scores were found among youth with less fatigue and fewer psychosocial problems. Fatigue has been reported to be one of the most significant risk factors for poor HRQoL among patients with cancer and survivors (Ferrell, 1996; Meeske et al., 2005; Servaes, Verhagen, & Bleijenberg, 2002; Zebrack & Chesler, 2002), particularly those with brain tumors (Meeske, Katz, Palmer, Burwinkle, & Varni, 2004; Meeske, Patel, Palmer, Nelson, & Parow, 2007). Symptoms of EDS and fatigue are generally higher among those with craniopharyngioma (in comparison to those with other types of brain tumors (Müller, 2008; Rosen & Brand, 2011) and have been shown to negatively predict short- and long-term HRQoL (Lipton et al., 2009; Müller, 2010; Müller, Handwerker, et al., 2006; Müller et al., 2002; Poretti et al., 2004). Despite these previous findings, we did not find the same direct effect of EDS on HRQoL. While EDS and fatigue are thought to be similar constructs, results of the current study reinforce that the underlying pathologies of EDS and fatigue are distinct (Slater & Steier, 2012) and, therefore, likely impact HRQoL differently. Furthermore, current findings suggest that fatigue, not EDS, may be more predictive of HRQoL disruptions; however, additional research is needed to examine the presence and impact of fatigue symptoms on HRQoL in youth with craniopharyngioma.

While the current study has a number of methodological strengths, such as use of objective measures of sleep disturbances and EDS, findings should be interpreted in light of several limitations. First, the sample size was relatively limited ($N = 84$) and, therefore, we were unable to detect small relations between variables or assess further confounding interactions between variables due to limited power (Faber & Fonseca, 2014). Second, caregiver-reports of psychosocial functioning, fatigue, and HRQoL were utilized in the current study. Previous

research has highlighted that caregivers tend to report greater impairments in psychosocial functioning and HRQoL when compared to youth self-report (Levi & Drotar, 1999; Poretti et al., 2004). As such, future studies should include self-report measures of psychosocial functioning, fatigue, and HRQoL to examine response differences in direct and indirect subjective reports. Furthermore, assessment of fatigue may be strengthened by physical examination and/or report by a medical provider (Tham, Holley, Zhou, Clarke, & Palermo, 2013). Third, participants in the current study consisted of youth recently diagnosed with craniopharyngioma. Daniel et al. (2016) suggested that a cancer diagnosis may serve as a precipitating factor to sleep and psychosocial disturbances, thus explaining the relationship between sleep, fatigue, and psychosocial problems. Research is needed to examine sleep and psychosocial functioning over time to account for youths' adjustment to their diagnosis/treatment. Additionally, given that physiological and psychosocial difficulties have been documented to worsen following treatment, it is necessary for providers to continuously assess patients' response to proton therapy and the impact of HI extent over time on sleep and psychosocial functioning. Lastly, the current study sample had a wide age range (range = 6-20), with the majority of youth characterized by a Tanner Stage of 1, which limits our findings to predominantly pre-pubertal children.

To our knowledge, this is the first study to reveal relations between fatigue, sleep disturbances, psychosocial problems, and HRQoL deficits among youth with craniopharyngioma. Consistent with previous research, we found HI extent to predict BMI and EDS among our sample. Although previous research has shown associations between EDS and psychosocial/HRQoL impairments in youth with craniopharyngioma (Calhoun et al., 2011; Müller, 2010; Müller et al., 2002; Rosen et al., 2003), we found a medium to large effect of

fatigue on psychosocial problems and HRQoL. These results indicate that sleep disruptions and fatigue may be most burdensome to youth's overall psychosocial health and wellbeing.

Findings of the current study suggest that youth with craniopharyngioma with more extensive HI are at greater risk for excessive weight gain and EDS. As such, youth with more extensive HI may benefit from weight and EDS reduction interventions. Cohen, Guger, & Hamilton (2011) reported slower rates of BMI increases in youth with craniopharyngioma who attended an interdisciplinary clinic that provided medical, behavioral, dietary, and physical activity family-centered care. Yet, several other studies have found interprofessional behavioral weight management interventions to be ineffective for children with craniopharyngioma due to hypothalamic damage caused by the tumor (Haliloglu & Bereket, 2015; Harz et al., 2003; Lustig, 2011; Müller, 2013, 2017). Several surgical treatments, such as laparoscopic gastric banding and gastric bypass, have been shown to be effective procedures for weight reduction among patients with and survivors of craniopharyngioma; however, these treatment methods remain controversial in pediatric populations due to the invasive and non-reversible nature of these procedures (Müller, Gebhardt, Maroske, & Hanisch, 2011; Rottembourg et al., 2009; Schultes, Ernst, Schmid, & Thurnheer, 2009). Regarding EDS, pharmacological intervention, such as the use of psychostimulant medication (e.g., modafinil), has been established as an effective method for reducing EDS in patients (Crowley et al., 2011; Müller, Müller-Stöver, et al., 2006). It is important to note that pharmacological stimulating agents have been associated with the development of non-alcoholic fatty liver disease in patients with craniopharyngioma (Hoffmann et al., 2015; Müller, 2017). Therefore, it has been recommended that such medications should be prescribed judiciously (Hoffmann et al., 2015; Müller, 2017).

Since we found higher rates of fatigue and HRQoL impairments among youth exhibiting greater psychosocial problems, youth with craniopharyngioma may benefit from specific cognitive-behavioral interventions focused on enhancing fatigue with a goal of improving psychosocial functioning and HRQoL. Preventative interventions may include providing behavioral sleep hygiene/activity recommendations and/or coping ahead strategies to combat potential psychosocial difficulties. Youth with craniopharyngioma who require ongoing psychological support may benefit from cognitive-behavioral based interventions focused on reducing feelings of fatigue (i.e., bolstering youth's involvement in activities/exercise) and ameliorating psychosocial problems (i.e., coping strategies, social skills training, relaxation training, etc.). Additionally, youth with craniopharyngioma should be prospectively monitored for fatigue to ensure that treatments are delivered in a timely fashion with a goal of improving overall quality of life and psychosocial health.

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