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The association between physical activity, sleep, and quality of life in patients in bio-chemical remission from Cushing's syndrome

Susette A. Moyers[1] · **Jitske Tiemensma**[2]

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Abstract

Purpose Cushing's syndrome can negatively affect patient's quality of life (QoL) after treatment and remission. Exposure to increased cortisol over time can result in visceral obesity, which makes this population vulnerable to cardiovascular risk factors associated with visceral obesity. Sleep disturbances are present in patients in remission from Cushing's syndrome, impacting QoL. Moderate intensity physical activity performed 3 times a week decreases visceral obesity and improves sleep quality, therefore, engaging in physical activity after remission may improve patient's QoL. The current study aims to explore the association between sleep quality, physical activity, and QoL in patients in remission of Cushing's syndrome.

Methods Patients in bio-chemical remission from Cushing's syndrome ($N = 147$) were recruited through the Cushing's Support and Research Foundation. Quality of life was assessed using the Cushing Quality of Life Questionnaire (CushingQoL), sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI), and physical activity levels were assessed with the Godin-Sheppard Leisure-Time Physical Activity Questionnaire (GSLTPAQ).

Results Sleep quality was significantly associated with both subscales of the CushingQoL (both $p < .001$), but physical activity was not significantly associated with either subscale. Sleep was not significantly associated with physical activity engagement in this sample.

Conclusion Results suggest that patients in remission from Cushing's syndrome experience sleep disturbances that are significantly associated with impaired QoL. Future research should focus on ameliorating the persisting clinical features of Cushing's syndrome that are associated with impaired QoL after bio-chemical remission to improve QoL and expedite complete functional remission.

Keywords Cushing's syndrome · Cushing's disease · Quality of life · Sleep · Physical activity · Cortisol

Introduction

Cushing's syndrome is a rare disease, causing excess cortisol secretion. The presenting symptoms of Cushing's syndrome are characteristic of other chronic diseases, such as hypertension, metabolic abnormalities (diabetes, metabolic disease), bone density loss, weight gain, muscle weakness, fatigue, and mood disorders [1, 2]. As such, physicians may misdiagnose presenting symptoms, and Cushing's syndrome may go undetected for long time periods [2]. Exposure to excessive cortisol for long time periods causes lasting impacts on patient's physical and psychological health, which impact their health-related quality of life after treatment and bio-chemical remission [3–8]. While bio-chemical remission refers to the normalized state of cortisol secretion, clinical remission refers to the remission of some of the associated clinical features of Cushing's syndrome, such as weight loss, changes in body composition, bone density improvements, increased muscle strength, memory improvement, and improvement in metabolic disturbances such as hypertension and diabetes [4, 5, 7–9]. Functional remission is defined as the association of clinical remission and recovery of all aspects of daily functioning, including social, professional, and personal domains, which, evidence suggests, rarely occurs in patients [10]. Therefore, there is a need for research on patients who are considered in bio-chemical remission, but may not be in clinical or functional

✉ Jitske Tiemensma
j.tiemensma@erasmusmc.nl

1 Department of Psychological Sciences, University of California, Merced, CA, USA

2 Department of Anesthesiology, Center for Pain Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

remission. Furthermore, studying factors that may directly impact known clinical features may enable patients to expedite clinical remission after bio-chemical remission, impacting QoL outcomes and functional remission [9]. This study will explore two factors that may impact clinical remission; sleep and physical activity, to understand their relationship with each other and with quality of life in patients in bio-chemical remission of Cushing's syndrome.

Health-related quality of life reflects one's subjective state of health and well-being, including physical, psychological, and social aspects of well-being, including feelings, concerns, responses, and daily functioning [11]. After diagnosis and initial treatment, patients may be subject to ongoing medical treatment/s (that may entail hormone replacement medication therapy, surgery, and radiotherapy; or a combination thereof), adrenal insufficiency, frequent check-ups, fatigue, changes in physical appearance, emotional lability, cognitive impairment, sleeping difficulties, anxiety, and depressive symptoms [10]. Due to the impact on QoL, persisting clinical features of Cushing's syndrome should be targeted to improve QoL, as clinical remission is necessary for complete functional remission. One of the most common clinical features in this population is weight gain, specifically, visceral obesity [1, 2]. Visceral obesity is an accumulation of visceral adipose tissue around internal organs in the abdominal area, which significantly changes body composition. Visceral adipose tissue has been associated with cardiometabolic abnormalities in these patients, including metabolic syndrome, diabetes, cardiovascular disease [12, 13], and the development of sleep apnea [14]. Addressing weight gain and visceral adipose tissue levels should be considered a priority after bio-chemical remission to prevent further development of cardiometabolic disease comorbidities and to improve QoL.

Cognitive impairment and mood disorders are also common clinical features that impair QoL after bio-chemical remission. Cortisol overexposure reduces brain derived neurotropic growth factor (BDNF) in the hippocampus, cingulate, and amygdala, causing atrophy in these regions. This atrophy may contribute to disruptions in communication [15, 16], negatively affecting cognition, mood, and sleep [17–19]. Depleted BDNF has been observed in patients in remission from Cushing's syndrome, and is associated with affective abnormalities [20]. Improvements in cognition and mood should also be considered a priority once bio-chemical remission is achieved, to expedite clinical remission, improve QoL, and achieve complete functional remission.

Sleep disturbances have been observed in patients in remission of Cushing's syndrome [15, 16], and quantity of sleep has been associated with improvements of QoL in this population over a 9-month time period [21]. Sleep difficulties persist after bio-chemical remission (including normalized circadian variations in cortisol secretion) in both in validated self-reported measures [21], and qualitative interviews [22, 23]. However, evidence of factors that may impact the relationship between sleep disturbances and QoL in this population remains limited, warranting further examination of factors that may impact this relationship in patients who are considered in bio-chemical remission.

One factor that may impact sleep after remission is engagement in physical activity. There is evidence suggesting a bi-directional relationship between sleep and physical activity, such that engaging in physical activity maintains a healthy sleep pattern, and having a healthy sleep pattern maintains physical activity engagement in adult populations [24, 25]. Physical activity improves sleep quality and QoL in patients who have sleep disturbances [26], and who are obese [27]. While physical activity may improve sleep disturbances in patients after bio-chemical remission, it may also have other benefits. Physical activity is associated with significant improvements in many of the known persisting clinical features of Cushing's syndrome that impact QoL after remission, in non-Cushing's populations. Physical activity is associated with weight loss and decreases in visceral obesity [28], body composition improvements [29], bone density improvements [30], increased muscle strength [31], memory improvements [32], decreased depression and anxiety symptoms [33], and improvement in cardiometabolic disturbances such as hypertension, cardiovascular disease, and diabetes [34]. Furthermore, physical activity has also been found to increase BDNF levels [35, 36], and is associated with decreased hippocampal atrophy, possibly mediated by increased BDNF levels [37].

To our knowledge, one only one study has considered the impact of physical activity on QoL in this population. A study employing a 9-month nursing educational program to Cushing's syndrome patients found that high levels of physical activity are significantly related to improvements in QoL [21]. While the study did not mention any changes in QoL in patients performing moderate or low physical activity levels, this finding suggests that the amount of physical activity engagement may play a vital role in improving QoL. Physical activity performed at certain intensities and durations is required for visceral fat loss, and these factors should be considered in this patient population. A systematic review of the literature suggests that physical activity performed at 10 metabolic equivalents × hours per week (METs h/w) (considered moderate intensity, such as brisk walking or light jogging) is required for visceral fat reduction in obese subjects [28]. There is also a dose–response relationship between physical activity and visceral fat reduction, showing that a minimum of 150 min/week, and preferably more than 200–300 min/week of physical activity is ideal for visceral fat loss [38]. Therefore, aiming to engage in these empirically supported estimates of physical activity to reduce visceral adipose tissue may expedite many aspects of clinical remission, such as decreased cardiovascular risk, weight loss, changes in body composition, and increased muscle strength, which impact daily functioning related to QoL outcomes. Overall, knowledge in this domain is limited to one patient sample, and further evidence is needed to understand the relationship between sleep, physical activity, and QoL in this population to determine if these findings are consistent across different samples of patients to inform further research and possible intervention design.

Study aim

The present study aims to explore the relationship between sleep quality, physical activity engagement levels, and QoL in patients in bio-chemical remission of Cushing's syndrome. First, we will explore the relationship between quality of life and sleep quality. We hypothesize that patients will report sleep disturbances as seen in previous studies [15, 16, 21]. We also predict there will be a significant association between sleep quality and QoL, such that those with a better sleep quality will report better QoL. Second, we will explore the relationship between physical activity and QoL. We predict a significant association between physical activity engagement and QoL, such that those with higher levels of physical activity engagement will have better QoL. Finally, we will explore the relationship between physical activity engagement and sleep quality. We predict that sleep quality will be associated with physical activity engagement, such that those with better sleep will report engaging in higher levels of physical activity than those who do not, due to previous evidence of bi-directionality of these two variables in other populations [24, 25].

Methods

Participants

A health behavior survey was distributed to members of the Cushing's Support and Research Foundation (CSRF), a national U.S. foundation designed to provide information and support to patients in all stages of Cushing's syndrome (active, treatment, and in remission). Patients were eligible for inclusion if they were 18 years or older, a member of the CSRF patient listserv/Facebook page (patients who were not members were welcome to participate; however, it was assumed that the advertisement reached mainly members of the CSRF), if they identified that they were in remission from Cushing's syndrome at the time of completing the survey, and had fully completed the measures of physical activity, sleep, and QoL (incomplete responses on these measures were excluded to avoid issues with missing data). Participants were excluded if they did not indicate that they were 18 years or older, and/or did not indicate being in remission of Cushing's syndrome or Cushing's disease at the time of the survey. Furthermore, Internet Protocol (IP) addresses were analyzed for duplicate survey responses, and only the most completed survey from each IP address was included (to meet independence assumptions for regression analysis). From this survey, 433 total responses were recorded, and 156 patients completed all 3 measures of interest and indicated being in remission of Cushing's syndrome or disease. One patient indicated being under 18, and 8 duplicate IP addresses were identified, which were excluded. A final sample of 147 patients were included in the sample for analysis.

Procedure

Data were collected between January 16, 2018 and March 9, 2018. Participants were invited to participate via a link that was emailed to patients by the CSRF patient coordinator, and through a link posted on the CSRF Facebook page, with reminders to complete the survey sent out by the CSRF patient coordinators on the Facebook page and listserv halfway through data collection. Participants were directed to an online survey via Qualtrics.com, and informed consent was digitally collected from all participants at the beginning of the survey. The survey took approximately 45 min to complete. All study procedures were approved by the Institutional Review Board (IRB) at the University of California, Merced, and individual measures of the survey were presented in a randomized order and questions about demographics were always presented last. Once the patient completed the survey, they were directed to a page with researchers' contact information in case they had any further questions, or required debriefing.

Measures

Cushing quality of life questionnaire (CushingQoL)

The CushingQoL questionnaire [39] is a disease-specific health-related QoL measure consisting of 12 items. Items assess psychological, social and physical aspects of QoL over the past 4 weeks on a 5-point likert scale. The CushingQoL is comprised of two subscales [40]; psychosocial issues and physical problems. Each subscale score is summed and transformed to range from 0 (worst possible QoL) to 100 (best possible QoL). The CushingQoL questionnaire has been widely used to measure disease-related quality of life in patients in remission from Cushing's syndrome, and has demonstrated validity, test–retest reliability, and is more sensitive to change in QoL in Cushing's syndrome patients compared to a non-disease QoL specific measure, such as the EQ-D5, in clinical practice [39, 41]. The physical problems subscale of the CushingQOL contains an item assessing sleep difficulties, which may bias the relationship between this subscale and the sleep measure in this study. Therefore, it has been excluded from the physical problems subscale to address possible colinearity.

Godin–Shephard leisure-time physical activity questionnaire (GSLTPAQ)

The Godin–Shephard leisure-time physical activity questionnaire (GSLTPAQ) is a 4-item scale used to assess self-reported frequency and intensity of physical activity [42]. The first three items assess the number of times one engages in mild, moderate and strenuous leisure-time physical activity (LTPA) bouts of at least 15 min duration in a typical week. Examples of LTPA are provided for each intensity category (for instance, strenuous activities listed include running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long- distance cycling). The last item asks participants how often they engage in LTPA long enough to work up a sweat within a seven-day period. Response options for item 4 include often, sometimes, or rarely/never. Scores derived from the GSLTPAQ include total weekly LTPA, called a Leisure Score Index (LSI), in which the number of activity bouts at each intensity from items 1 through 3 are multiplied by 3, 5, and 9 metabolic equivalents (METs) and summed. An active/insufficiently active classification can be utilized for the LSI. These classification values are based on current American College of Sports Medicine physical activity guidelines [43], that are defined as the following: individuals reporting moderate-to-strenuous (LSI $\geq$ 24) are classified as *active* (estimated energy expenditure > 14 kcal/kg/week), whereas individuals reporting moderate-to-strenuous (LSI $\leq$ 23) are classified as *insufficiently active* (estimated energy expenditure < 14 kcal/kg/week) [29]. This classification coding system was validated to be predictive of activity levels as measured by an accelerometer assessment [44].

Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) was used to examine self-reported sleep patterns. This 19-item measure differentiates "poor" from "good" sleep quality by measuring seven components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. In scoring, each of the seven categories are transformed into scores ranging from 0 to 3, with a higher score representing poorer sleep quality in that category. The sum of these 7 components yields a Global Sleep Quality score ranging from 0 to 21, and a score of 5 or greater indicates poor sleep quality [45]. There is evidence of the good reliability and validity of the PSQI in patients with sleep disturbances [46, 47].

Statistical analyses

Data were analyzed using IBM SPSS software, version 24. There was less than 5% missing data from measures of interest. Outliers that were 2 standard deviations from the mean were removed (this included 7 data points in the Leisure-Time Score Index that were above a LSI score of 180, which were re-coded as missing data points). Independent sample *t* tests could not be utilized to compare the difference of those who scored as having good sleep patterns to those who scored as having poor sleep patterns due to the difference in sample sizes between patients reporting good sleep quality ($N = 3$) and those reporting poor sleep quality ($N = 143$), therefore, independent sample *t* tests were only utilized to compare the difference between those in the sufficient physical activity group to those in the insufficient physical activity group on QoL subscales. Finally, multivariate linear regression was used to explore the association between sleep quality, physical activity, and QoL (all of which were treated as continuous variables).

Previous research has shown that participants who are female, older, less educated, and overweight tend to be less accurate in their recall of physical activity when compared to male, younger, normal weight participants [48, 49]. Furthermore, time in remission has been shown to impact QoL in patients in remission from Cushing's syndrome, suggesting that patients who have been in remission for a shorter amount of time have worse QoL than those who have been in remission for longer time periods [50]. Additionally, patients who receive post-operative radiotherapy have reported worse QoL than those who did not undergo post-operative radiotherapy [4]. Due to these findings, these variables were included as covariates in the final multivariate regression analysis.

Results

Sociodemographic and clinical characteristics

Demographics and clinical characteristics of the patients are detailed in Table 1. This sample seems to reflect disease-wide patient demographics reported in a previous study of 481 patients, such as a higher ratio of females than males, and a large proportion of patients with a high BMI [51]. The mean age of this sample was 51.71, SD = 13.08 years, and 140 patients (95.2%) were female. Disease wide patient demographics report a 4:1 female to male ratio, and mean age at diagnosis being middle age adults; mean age = 44.2, SD = 13.7 [51]. One hundred thirty-five patients indicated

Table 1 Sociodemographic and clinical characteristics

	Total sample $N = 147$
Sex (*N* female; % female)	140; 95.2%
Age: *M;* SD	51.71; 13.08
Ethnicity: *N* (%)	White: 135 (91.8%)
	Hispanic: 3 (2%)
	African-American: 2 (1.4%)
	Asian: 2 (1.4%)
	Other: 5 (3.4%)
Education level: *N* (%)	Highschool or equivalent: 17 (11.6%)
	Associate degree: 33 (22.4%)
	Bachelor's degree: 53 (36.1%)
	Graduate degree: 35 (23.8%)
	Professional degree: 9 (6.1%)
BMI category: *N* (%)	Underweight (BMI below 18.5): 1 (.7%)
	Normal weight (BMI = 18.5–25.0): 42 (28.6%)
	Overweight (BMI = 25–30): 42 (28.6%)
	Obese (BMI = 30+): 55 (37.4%)
Diagnosis: *N* (%)	Cushing's disease: 111 (75%)
	Cushing's syndrome: 37 (25%)
Treatment: *N* (%)	Transsphenoidal surgery: 109 (74.1%)
	Adrenal surgery on one side: 33 (2.4%)
	Bilateral adrenal surgery: 15 (10%)
	Post-operative radiotherapy: 11 (7.5%)
	Other: 9 (6.1%)
Duration of remission: *M;* SD	6.98; 6.91
Indicated hypopituitarism: *N* (%)	56 (38.1%)
Taking hydrocortisone: *N* (%)	46 (31.3%)
Taking fludrocortisone: *N* (%)	18 (12.2%)

that they were white (non-Hispanic) (91.8%). Thirty-seven patients (25.2%) indicated that they were diagnosed with Cushing's Syndrome and 111 patients (75.5%) indicated Cushing's disease. One hundred and nine (74.1%) patients were treated with transsphenoidal surgery, 33 (22.4%) were treated with unilateral adrenalectomy, 15 (10.2%) patients indicated bilateral adrenalectomy, 9 (6.1%) indicated other treatments, and 11 (7.5%) indicated undergoing post-operative radiotherapy. Fifty-six patients (38.1%) indicated hypopituitarism as a result of treatment. Furthermore, 46 patients (31.3%) indicated taking Hydrocortisone and 18 (12.2%) indicated taking Fludrocortisone (Table 1).

Main findings

Overall sleep quality

In assessing the overall sleep quality in this sample, the mean score for the Pittsburgh Sleep Quality Index was 10.69, SD = 3.73, which lies in the poor sleep range. One hundred forty-four patients (98%) in this sample indicated poor sleep quality (Table 2).

The association between sleep and QoL

The psychosocial issues subscale of the CushingQoL was significantly associated with sleep, $\beta_{std} = -0.666$, $p < 0.001$. Sleep quality accounted for 44% of the variability in the psychosocial issues subscale of the CushingQoL in this sample; $R^2 = 0.440$. To control for potential effects of time in remission, sex, age, BMI, education, and post-operative radiotherapy treatment were added to the model as covariates. The psychosocial issues subscale was still significantly associated with sleep quality, $\beta_{std} = -0.567$, $p < 0.001$. In this model, years in remission; $\beta_{std} = 0.165$; $p = 0.011$ and BMI; $\beta_{std} = -0.274$; $p < 0.001$, were also significantly associated with the psychosocial issues subscale. The adjusted $R^2 = 0.536$, suggesting that sleep quality, time in remission, sex, age, BMI, education, and post-operative radiotherapy account for 53.6% of variability in the psychosocial issues subscale of the CushingQoL in this sample (Table 2).

In addition, the physical problems subscale of the CushingQoL was significantly associated with sleep quality, $\beta_{std} = -0.414$, $p < 0.001$. Sleep quality accounts for 16.5% of the variability in the physical problems subscale

Table 2 Regression coefficients of psychosocial issues and physical problems CushingQoL subscales on the Pittsburgh Sleep Quality Index (PSQI)

Variable	Model 1			Model 2			Variable	Model 1			Model 2		
	B	β	SE	B	β	SE		B	β	SE	B	β	SE
Psychosocial issues (QoL)							Physical problems (QoL)						
Constant	88.82**		4.50	97.62**		10.32		87.46**		6.15	93.79**		14.88
PSQI[a]	− 4.27**	− 66	.39	− 3.84**	− .56	.436		− 2.96**	− .41	.54	− 2.67**	− .35	.629
Age[b]				.19	.10	.11					.21	.104	.17
Sex[c]				− .35	6.83	.00					21.92*	.18	9.83
Education[d]				.45	.02	1.38					− .10	.00	1.99
BMI[e]				− .94**	− .27	.21					− .70*	− .18	.31
Time in remission[f]				.59*	.16	.22					.03	.00	.33
Radiotherapy treatment[g]				− 5.75	− .06	5.53					− 20.69*	− .214	7.95
Adj R^2	.44			.53				.16			.22		
ΔR^2				.09							.06		

Index (PSQI) and covariates

$N=147$

We examined the impact of sleep quality (PSQI) on the psychosocial issues and physical problems subscales of the CushingQoL In model 1, we entered PSQI to predict each subscale of the Cushing QoL in separate analyses. In model 2, we added the control variables age, sex, education, BMI, time in remission, and radiotherapy treatment to predict each subscale

*p < .05; **p < .01

[a]Continuous; range = 0–27

[b]Continuous; range = 18–83

[c]Male = 0, female = 1

[d]High School degree or equivalent (GED) = 0, associates degree or occupational degree = 1, college graduate (bachelors degree) = 2, graduate degree (MA, MS, PhD, EdD) = 3, professional degree (MD, DDC, JD) = 4

[e]Continuous; range = 18.65–56.67

[f]Continuous; range = 0–45

[g]No = 0, yes = 1

of the CushingQoL in this sample; $R^2=0.165$. After adding the specified covariates, the physical problems subscale was still significantly associated with sleep quality, $\beta_{std}=-0.356$, $p<0.001$. In this model, sex; $\beta_{std}=0.184$; $p=0.028$ was significantly associated with the physical problems subscale. Females had significantly lower QoL on this subscale than males. However, these results may be biased due to a small sample of male patients ($N=7$). Post-operative radiotherapy was also significantly associated with the physical problems subscale; $\beta_{std}=-0.214$; $p=0.01$, suggesting that those treated with post-operative radiotherapy had significantly poorer quality of life in this domain. BMI was also significantly associated with the physical problems subscale; $\beta_{std}=-0.185$, $p=0.025$. This suggests that as BMI increases, the scores on the physical problems subscale decline significantly. The adjusted R^2 in this relationship suggests that sleep quality, time in remission, sex, age, BMI, education, and post-operative radiotherapy account for 22.3% of variability in the physical problems subscale of the CushingQoL in this sample; $R^2=0.223$.

Overall physical activity

In assessing overall physical activity levels, the mean score on the Godin-Sheppard Leisure-Time Physical Activity Questionnaire was 27.16, SD = 28.24, which lies in the sufficient physical activity range. This indicates that many patients in this sample reported levels of physical activity engagement that meet public health recommendations (estimated energy expenditure > 14 kcal/kg/week), based on current American College of Sports Medicine physical activity guidelines [43].

The association between physical activity and QoL

T-test analyses did not show significant differences between those with sufficient versus those with

Table 3 Regression coefficients of psychosocial issues and physical problems CushingQoL subscales on the Leisure Score Index (LSI) and covariates

Variable	Model 1			Model 2			Variable	Model 1			Model 2		
	B	β	SE	B	β	SE		B	β	SE	B	β	SE
Psychosocial issues (QoL)							Physical problems (QoL)						
Constant	40.07**		2.81	59.16**		12.58		55.48**		3.19	65.78**		15.26
LSI[a]	.10	.12	.07	.03	.04	.06		.02	.02	.08	.01	.01	.08
Age[b]				.30*	.16	.15					.34	.17	.18
Sex[c]				− 6.94	− .06	8.85					16.77	.14	10.73
Education[d]				3.12	.14	1.77					1.31	.05	2.15
BMI[e]				− 1.40*	− .40	.27					− 1.03**	− .26	.33
Time in remission[f]				.57	.15	.30					.08	.02	.36
Radiotherapy treatment[g]				− .87	− .01	7.49					− 19.00*	− .19	9.09
Adj R^2	.00			.23				.00			.10		
Δ R^2				.23							.10		

$N = 147$

We examined the impact of physical activity engagement (LSI) on psychosocial issues and physical problems subscales of the CushingQoL. In model 1, we entered LSI to predict each subscale of the Cushing QoL in separate analyses. In model 2, we added the control variables age, sex, education, BMI, time in remission, and radiotherapy treatment to predict each subscale

*$p < .05$; **$p < .01$

[a]Continuous; range = 0–180

[b]Continuous; range = 18–83

[c]Male = 0, female = 1

[d]High school degree or equivalent (GED) = 0, associates degree or occupational degree = 1, college graduate (bachelors degree) = 2, graduate degree (MA, MS, PhD, EdD) = 3, professional degree (MD, DDC, JD) = 4

[e]Continuous; range = 18.65–56.67

[f]Continuous; range = 0–45

[g]No = 0, yes = 1

*$p < .05$; **$p < .01$

insufficient physical activity levels on the psychosocial subscale (t (139) = − 0.818, $p = 0.415$), or the physical problems subscale (t (138) = − 0.109, $p = 0.914$). This suggests that meeting sufficient levels of physical activity engagement (as defined by American College of Sports Medicine physical activity guidelines [43]) is not related to psychosocial issues or physical problems as measured on the CushingQoL. Furthermore, multivariate regression analyses were conducted on physical activity engagement (as a continuous variable, range = 0–180) to further explore the relationship between physical activity, QoL, and covariates (Table 3). Without covariates added, regression analyses did not support a significant relationship between LSI and the psychosocial issues subscale of the CushingQoL ($\beta_{std} = 0.121$, $p = 0.154$) or the physical problems subscale ($\beta_{std} = 0.025$, $p = 0.774$). After covariates were added, multivariate regression analyses did not support a significant relationship between LSI and the psychosocial issues subscale of the CushingQoL ($\beta_{std} = 0.042$, $p = 0.599$) or the physical problems subscale ($\beta_{std} = 0.011$, $p = 0.856$). This indicates that after accounting for variance of empirically supported covariates, physical activity is not associated with either subscale of QoL in this sample.

The association between sleep and physical activity

A t-test was utilized to examine the difference between sufficient and insufficient physical activity levels in sleep quality (as a continuous variable) in this sample. Physical activity sufficiency was not related to sleep quality in this sample (t (139) = − 0.643, $p = 0.512$). This indicates that there is no significant difference in sleep quality in patients who indicate sufficient physical activity levels, and those

Table 4 Regression coefficients of the Leisure Score Index (LSI) on the Pittsburgh Sleep Quality Index (PSQI) and covariates

Variable	Model 1			Model 2		
	B	β	SE	B	β	SE
Constant	26.79**		7.32	37.43*		17.74
PSQI[a]	.03	.00	.64	.683	.08	.76
Age[b]				− .080	− .03	.19
Sex[c]				− 11.70	− .09	11.34
Education[d]				1.30	.05	2.38
BMI[e]				− .502	− .12	.37
Adj R^2	.00			− .01		
ΔR^2				− .01		

$N=147$

We examined the impact of sleep quality (PSQI) on physical activity engagement (LSI)

In Model 1, we entered PSQI to predict LSI. In Model 2, we added the control variables age, sex, education, and BMI to predict LSI

$*p < .05$; $**p < .01$

[a]Continuous; 0–27

[b]Continuous

[c]Male = 0, Female = 1

[d]High School degree or equivalent (GED) = 0, Associates degree or occupational degree = 1, College graduate (Bachelors degree) = 2, Graduate degree (MA, MS, PhD, EdD) = 3, Professional degree (MD, DDC, JD) = 4

[e]Continuous

$*p<.05$; $**p<.01$

who reported insufficient physical activity levels. Univariate regression analyses were performed on the PSQI and LSI (Table 4; both as continuous variables) in this sample ($\beta_{std}=0.005$, $p=0.957$), also revealing no significant relationship between sleep quality and physical activity engagement. Finally, multivariate regression analysis was performed, and after accounting for the variance in age, sex, education, and BMI, the relationship remained insignificant ($\beta_{std}=0.085$, $p=0.370$).

Discussion

The goal of this study was to explore the relationship between sleep quality, physical activity, and QoL in patients in remission from Cushing's syndrome. This explorative study demonstrates that this sample of patients in remission from Cushing's syndrome are experiencing sleep disturbances that are significantly associated with impaired QoL. Results from this study suggest that only 3 patients (2%) scored in the range of good sleep quality, whereas 144 patients (98%) scored in the poor sleep quality range. This replicates previous findings that sleep quality is significantly impaired in this population [15, 16, 21]. Although speculative and not measured within this study, these sleep disturbances may be related to sleep apnea as observed in patients with visceral obesity [14], and may be explored in future research. Sixty-nine percent of the patients in the present study reported height and weight that is categorized as overweight or obese using national guidelines from the National Center for Chronic Disease Prevention and Health Promotion [52]. BMI was significantly associated with both CushingQoL subscales (psychosocial issues and physical problems), suggesting that BMI significantly contributes to the variance in this model. While a high BMI does not necessarily reflect visceral obesity or one's level of visceral adipose tissue, an obese BMI and visceral adipose tissue levels have been significantly correlated in previous studies of obese individuals [53]. While visceral adipose tissue was not measured in this study, future studies may assess if visceral adipose tissue concentrations are related to sleep disturbances and physical activity engagement, to examine whether self-reported BMI reflects similar results. Furthermore, although BDNF was not measured, speculatively, poor sleep quality may be a result of depletion of BDNF levels [20], as a result of Cushing's syndrome. Both pathways could additively influence the high occurrence of sleep disturbances in patients in remission from Cushing's syndrome which influence QoL [18]. Overall, these findings suggest that sleep quality is a significant factor when looking at QoL after bio-chemical remission of Cushing's syndrome in this patient sample.

Before this study, to our knowledge, physical activity levels have only been investigated in patients in remission from Cushing's syndrome in one prior study [21]. The current study did not find a significant relationship between physical activity and QoL, which contrasts previous findings suggesting a significant relationship [21]. Furthermore, there was not a significant association between physical activity and sleep, contrasting evidence of bi-directionality between these two variables, in this sample. While speculative, there may be a number of factors that contributed to the findings related to physical activity engagement in this study, one being the use of a self-report measure of physical activity engagement. There are certain biases inherent in self-reported physical activity. The findings of the present study suggest that 40.8% of patients in this sample engage in sufficient physical activity levels as outlined by the American College of Sports Medicine physical activity guidelines [28], which is higher than the national average. The center for disease control (CDC) estimates that only 1 in 5 adults (21%) in the United States meet physical activity guidelines [43]. Self-reported physical activity suffers from significant reporting bias attributable to a combination of social desirability bias and the cognitive challenge associated with estimating frequency and duration of physical activity [54]. Social desirability bias was not measured in this study, and should be considered a limitation [55]. Also, cognitive functioning, especially memory, is impaired in patients in remission from Cushing's syndrome [10], which may contribute to an even larger impairment in recalling physical activity engagement accurately. Furthermore, this sample is comprised of a high percentage of older (mean age = 51.71), females (95.2% of the sample), with high BMI (69.3% in the overweight or obese BMI range), which may further impact accuracy of self-reported physical activity [48, 49]. Mean age, sex, and mean BMI in this sample are similar to other Cushing's syndrome samples previously reported [51], and seem to reflect the larger population. However, these sample characteristics may further contribute to reporting bias and may not reflect an accurate estimate of physical activity [48, 49], therefore, these variables were measured and controlled for. However, QoL was not associated with physical activity engagement before or after adding these covariates to the model; suggesting that this study's measure of physical activity engagement was not associated with QoL in this sample, regardless of age, sex, education, and BMI.

Another factor that could be contributing to these findings, although speculative, may reflect an issue with self-selection, such that patients who were physically active may have been more likely to participate in this study because it was advertised as being focused on lifestyle behaviors. There is evidence of participation bias in physical activity intervention studies, such that healthier, fitter participants are more likely to participate [56]. Although this study is cross-sectional and based on self-report, the way it was advertised may have contributed to participation bias, which may explain the high number of participants engaging in sufficient levels of physical activity.

While this is a fairly large sample size for this population, some limitations of this study include solely using self-report measures to assess sleep quality and physical activity levels. Furthermore, there may be selection bias present among this sample because all participants were recruited through the Cushing's Support and Research Foundation. The Cushing's Support and Research Foundation is an informational support group, therefore, includes patients who seek additional support for their experiences with Cushing's syndrome. These members may have distinct characteristics that patients who are not members of this group may not have.

While physical activity was not associated with sleep or quality of life in this study, other evidence has supported a relationship between these variables, and further research is needed to assess contrasting findings. Future research may focus on utilizing objective measures of physical activity, such as accelerometers, in this patient population due to social desirability bias, inherent sample characteristics such as impaired memory, and possible self-selection bias. Using objective physical activity measures would ensure capturing accurate physical activity engagement levels within these patients, because they are not reliant upon memory recall, and circumvent many biases associated with the accuracy of self-reported physical activity, such as age, gender, BMI, education, and social desirability. Also, utilizing objective measures of sleep such as an actigraphy-type device is recommended to assess sleep accurately, due to memory impairments in these patients that may be influencing self-reported recall [10]. Preliminary evidence supporting the occurrence of disturbed sleep with wrist actigraphy has been reported in patients with active Cushing's syndrome, and warrants further exploration [57]. Furthermore, studies that focus on measuring health behaviors should be advertised in a way that limits self-selection bias of those that live a healthier lifestyle (e.g., possibly advertising the study as a general health study). Additionally, since BDNF is depleted in patient's in remission from Cushing's syndrome, examining the effects of sleep quality and physical activity on BDNF levels in patients in remission from Cushing's syndrome may be interesting to explore [23, 24, 39].

While complete functional remission after Cushing's syndrome is rare [10], it is important to address factors that may impede progress in attaining complete functional remission in Cushing's syndrome patients after bio-chemical remission. Persisting clinical features of Cushing's syndrome are associated with impaired QoL [9], therefore, addressing these clinical features may expedite clinical remission to improve QoL and achieve complete functional remission. The findings from this study suggest that sleep quality is significantly associated with QoL after remission of Cushing's syndrome in this sample of patients, but physical activity engagement was not. These preliminary findings support the need for further research aiming to reduce the impact of sleep difficulties on QoL in this population, and to examine the role that physical activity may play in QoL, and achieving clinical and functional remission.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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