Psychometric Evaluation of Two Novel Hyperphagia Questionnaires for Patients with Bardet-Biedl Syndrome (BBS)

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Disclosure Statement

- Usha G. Mallya
- ☒ I have the following potential conflicts of interest to report:

☐ Research Contracts
☐ Consulting
☒ Employment in the Industry
☒ Stockholder of a healthcare company
☐ Owner of a healthcare company

Unmet need in rare melanocortin 4 receptor (MC4R) diseases of obesity

- The MC4R pathway, located in the hypothalamus, is responsible for regulating hunger and energy expenditure, and consequently body weight. Impaired signaling in this pathway, due to rare genetic variants or injury to the hypothalamic region, can lead to hyperphagia and severe obesity [1]
- Hyperphagia is characterized by pathological, insatiable hunger accompanied by abnormal food-seeking behaviors and extreme preoccupation with food
  - Bardet Biedl Syndrome (BBS) is a syndromic MC4R pathway disease with hallmark symptoms of hyperphagia and early-onset severe obesity[2]
    - Available measures of hyperphagia were not developed for and have not been validated in this rare population
- Novel measures: Symptoms of Hyperphagia[3] (SoH) and Impacts of Hyperphagia[3] (IoH)
  - Concepts were identified via semi-structured interviews with clinicians and patients
  - Patient and caregiver versions are available[a]

[a]Patient version developed for patients ≥ 12 years of age who can self-report; caregiver version developed for caregivers of patients <12 years of age or of patients ≥ 12 years of age who cannot self-report

1. Huvenne et al. *Obes Facts*. 2016;9(3):158-173. **2**. Forsythe et al. Eur J Hum Genet. 2013;21(1):8-13.

Objective: Evaluate the performance of caregiver versions of Symptoms of Hyperphagia and Impacts of Hyperphagia in BBS

	Symptoms of Hyperphagia: Caregiver Version (Observer-Reported)	Impacts of Hyperphagia: Caregiver Version (Observer-Reported)	Impacts of Hyperphagia: Caregiver Version (Self-reported)
Items	How often did the person in your care… 1. Try to negotiate or argue for more food than provided 2. Eat extremely quickly 3. Sneak or take food without permission 4. Wake up asking or looking for more food during the night 5. Ask for more food after just finishing a meal or snack	To what extent did the person in your care's hunger negatively affect his/her… 1. Sleep 2. Mood/emotion 3. School 4. Leisure or recreational activities 5. Relationships with family/friends	To what extent did the person in your care's hunger negatively affect your… 1. Sleep 2. Mood/emotion 3. Work 4. Leisure or recreational activities 5. Relationships with family/friends
Recall period	Past 24 hours	Past 7 days	Past 7 days
Response options	0 = Never 1 = One to two times 2 = Three times or more	0 = Not at all 1 = A little 2 = Moderately 3 = A great deal	0 = Not at all 1 = A little 2 = Moderately 3 = A great deal
[a]Scoring	Sum of all items; range: 0 – 10	Sum of all items; range: 0 – 15	Sum of all items; range: 0 – 15

[a]Higher scores indicate greater severity and impact

The Symptoms of Hyperphagia and Impacts of Hyperphagia were evaluated in CARE-BBS, a multi-country caregiver real-world study

- Cross-sectional survey of 242 adult caregivers of patients with BBS in the United States, United Kingdom, Canada, and Germany designed to quantify the burden of hyperphagia and obesity[3,4]
- Data were collected between December 2021 and February 2022
- The survey additionally included:
  - Impact of Weight on Quality of Life (IWQOL)-Kids Parent Proxy
  - Revised Impact on Family Scale (RIOFS)
  - Work Productivity and Activity Impairment (WPAI): BBS-Caregiver
  - PROMIS Scale Global Health of Caregiver
- Mean caregiver age was 41.9 (SD=6.7); 54.1% were male
- Mean patient age was 12 (SD=3.7); 64% were male
  - Mean modified BMI Z score was 4.1 (SD=4.5); hyperphagia contributed to a BBS diagnosis in 95% of cases

3. Forsythe et al. Presented at: Annual Meeting of the European Society of Paediatric Endocrinology (ESPE), September 15–17, 2022, Rome, Italy. **4**. Forsythe et al. Presented at: Annual Meeting of the European Society of Paediatric Endocrinology (ESPE), September 15–17, 2022, Rome, Italy

Validation assessments were performed using data collected in CARE-BBS study

- **Reliability**
  - Internal consistency and item total correlations
- **Validity**
  - **Construct validity**
    - Exploratory factor analysis
  - **Convergent validity**
    - IWQOL-Kids (Parent Proxy), RIOFS and WPAI
  - **Known groups analysis**
    - For SoH: Number of weight management approaches used, RIOFS
    - For IoH: RIOFS, PROMIS Global Health of Caregiver: Mental Health

The IoH demonstrated acceptable internal consistency reliability

- With Cronbach's α < 0.5, Symptoms of Hyperphagia: Caregiver Version showed insufficient interrelatedness among the items

- The IoH (Observer-Reported and Self-Reported) demonstrated acceptable internal consistency reliability with Cronbach's α > 0.6 for the initial exploratory evaluation[5]
- Across the IoH scales, the correlations ranged between 0.558 and 0.798, suggesting the scales are reasonably inter-related

	Item Description	Cronbach's α
Impacts of Hyperphagia: Caregiver Version (Observer-Reported)	Sleep	0.66
	Mood or emotions	
	School	
	Leisure or recreational activities	
	Relationships with family or friends	
Impacts of Hyperphagia: Caregiver Version (Self-Reported)	Sleep	0.72
	Mood or emotions	
	Work	
	Leisure or recreational activities	
	Relationships with family or friends	

5. Hair JF, Black WC, Babin BJ, Anderson RE. *Multivariate data analysis*: Pearson College Division. 2010

Across SoH and IoH, the majority of item-total correlations were considered acceptable

- Majority of the item-total correlations were within 0.30 to 0.70, meeting threshold to test for consistency[6]
- Three items in the IoH (Self-Reported) had item-total correlations > 0.70, suggesting some redundancy in the concepts within the scale

	Item Description	Pearson's Correlation
Symptoms of Hyperphagia: Caregiver Version (Observer-Reported)	Negotiate or argue for more food than provided	0.510*
	Eat extremely quickly	0.514*
	Sneak or take food without permission	0.521*
	Wake up asking or looking for food during the night	0.555*
	Ask for more food after just finishing a meal or snack	0.610*
Impacts of Hyperphagia: Caregiver Version (Observer-Reported)	Sleep	0.647*
	Mood or emotions	0.636*
	School	0.603*
	Leisure or recreational activities	0.671*
	Relationships with family or friends	0.685*
Impacts of Hyperphagia: Caregiver Version (Self-Reported)	Sleep	0.666*
	Mood or emotions	0.630*
	Work	0.717*
	Leisure or recreational activities	0.711*
	Relationships with family or friends	0.719*

6. De Vaus D. *Surveys in Social Research* (5th ed.). London: Routledge. 2004

SoH and IoH showed acceptable convergent validity

- SoH showed moderate correlations with IWQOL-Kids and WPAI- Total Productivity Impairment
- IoH showed moderate correlations with IWQOL-Kids, RIOFS and WPAI scores

Instrument	Domain	Symptoms of Hyperphagia: Caregiver Version (Observer-Reported)	Impacts of Hyperphagia: Caregiver Version (Observer-Reported)	Impacts of Hyperphagia: Caregiver Version (Self-Reported)
IWQOL-Kids (Parent Proxy)[a]	Total Score	-0.363***	-0.492***	-0.447***
	Body Esteem	-0.346***	-0.443***	-0.345***
	Family Relationships	-0.345***	**-0.516*** **	**-0.573*** **
	Physical Comfort	-0.278***	-0.381***	-0.297***
	Social Life	-0.315***	-0.416***	-0.359***
RIOFS	Total Impact	0.279***	0.351***	0.370***
	Personal Strain	0.271***	0.380***	0.385***
	Familial/Social Impact	0.254***	0.274***	0.295***
WPAI: BBS Caregiver	Total Productivity Impairment	0.347***	0.448***	0.435***
	Total Activity Impairment	0.215**	0.417***	0.425***
	Days of school missed in past 7 days	0.438***	0.454***	0.381***

Spearman's rank correlation analysis was conducted. Correlation coefficient: 0.3 to < 0.5 (moderate effect), ≥0.5 (large effect); Abbreviation: IWQOL, Impact of Weight on Quality of Life; RIOFS, Revised Impact on Family Scale [a]: Higher score indicate better quality of life
*P <.05; **P <.01; ***P <.001

Known groups analysis demonstrated SoH severity scores discriminated between weight management approaches and impact on family

- Patients with higher scores on the SoH used significantly greater number of weight management approaches and their caregivers more likely agreed on: “Nobody understands the burden I carry” and “It is hard to find a reliable person to take care of my child”

	Symptoms of Hyperphagia©: Caregiver Version (Observer-Reported)		
	Group Difference (95% CI)	**P-Value**	**Cohen’s D**
# of weight management approaches used			
≤ 5 vs. 6 < x ≤ 10	0.96 (0.29, 1.63)	0.006 **	0.55
6 < x ≤ 10 vs. ≥ 11	0.69 (0.12, 1.27)	0.024 *	0.42
RIOFS: “Nobody understands the burden I carry” (*Yes vs. No*)	1.03 (0.56, 1.49)	<.001 ***	0.86
RIOFS: “It is hard to find a reliable person to take care of my child” (*Yes vs. No*)	0.49 (0.00, 0.98)	0.028 *	0.38

Cohen's d recommended guidelines for small, moderate, or large effects: 0.1 to < 0.3, 0.3 to < 0.5, and ≥ 0.5, respectively
Abbreviation: RIOFS, Revised Impact on Family Scale
*P <.05; **P <.01; ***P <.001

Known groups analysis demonstrated IoH scores discriminated between global mental health of caregiver and impact on family

	Impacts of Hyperphagia: Caregiver Version (Observer-Reported)			Impacts of Hyperphagia: Caregiver Version (Self-Reported)		
	Group Difference (95% CI)	P-Value	Cohen's D	Group Difference (95% CI)	P-Value	Cohen's D
PROMIS Global Health of Caregiver: Mental Health (*Fair/poor vs. excellent/very good/good*)	1.26 (0.26, 2.26)	0.011 *	0.63	1.15 (0.06, 2.24)	0.039 *	0.52
RIOFS: "Nobody understands the burden I carry" (*Yes vs. No*)	1.89 (1.14, 2.63)	<.001 ***	0.89	1.22 (0.38, 2.05)	0.002 **	0.51
RIOFS: "Sometimes I feel like we live on a roller coaster" (*Yes vs. No*)	1.03 (0.23, 1.83)	0.012 *	0.49	1.29 (0.43, 2.16)	0.004 **	0.56
RIOFS: "It is hard to find a reliable person to take care of my child" (*Yes vs. No*)	1.14 (0.35, 1.92)	0.003 **	0.54	1.34 (0.49, 2.19)	0.002 **	0.58
Number of times wake up in the night due to uncontrollable hunger in past 7 days (< 5 vs. ≥ 5)	0.87 (0.08, 1.67)	0.061	0.41	0.90 (0.04, 1.76)	0.040 *	0.40

Cohen's D recommended guidelines for small, moderate, or large effects: 0.1 to < 0.3, 0.3 to < 0.5, and ≥ 0.5, respectively
Abbreviation: RIOFS, Revised Impact on Family Scale
*P <.05; **P <.01; ***P <.001

The caregiver versions of the SoH and IoH demonstrated reasonable reliability and validity

Findings from this study provide preliminary evidence for these questionnaires as suitable instruments to evaluate caregiver-reported hyperphagia impacts on patients with BBS and their caregivers **and allow their use in real world settings**.

Additional research is ongoing across settings and in other MC4R pathway diseases to further confirm the psychometric properties, including responsiveness and sensitivity to change

Please reach out to Usha Mallya at umallya@rhythmtx.com for any questions or additional information