

# Substantial Burden Associated With Hyperphagia and Obesity in Children With Bardet-Biedl Syndrome

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## Summary

- An analysis of data from the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS), an international registry of patients with Bardet-Biedl syndrome (BBS), showed a significant positive correlation between degree of hyperphagia and body mass index (BMI) in children aged 3-17 years

- Hyperphagia may be a useful target of obesity management strategies in individuals with BBS

## Introduction

- BBS is a rare genetic disease characterized by multiorgan pathology, hyperphagia (ie, pathologic, insatiable hunger), and early-onset, severe obesity associated with primary cilia dysfunction and impaired signaling in the hypothalamic melanocortin-4 receptor (MC4R) pathway<sup>1-5</sup>
- Hyperphagia is associated with high disease burden and substantially impaired quality of life for patients and caregivers<sup>1,6,7</sup>
- The relationship between BMI and hyperphagia has not been well studied<sup>2</sup>

## Objective

- To examine the correlation between the degree of hyperphagia and BMI in patients with BBS

## Methods

- Data were collected from patients with BBS aged 3-17 years who were enrolled in CRIBBS, an international registry of patients with BBS established in June 2014 by the Marshfield Clinic Research Institute in Wisconsin (NCT02329210)
  - Children treated with investigational drugs (eg, setmelanotide) were censored at the last assessment before the start of the investigational drug
- BMI was collected annually
  - Patients with BMI <85th percentile, ≥85th to <95th percentile, or ≥95th percentile were categorized as having under/normal weight, overweight, or obesity, respectively
- The Hyperphagia Questionnaire<sup>8</sup> was completed by the caregiver at the 4th annual CRIBBS assessment
  - The Hyperphagia Questionnaire is a 13-item questionnaire initially designed to measure food-related preoccupation in patients with Prader-Willi syndrome, another rare MC4R pathway disease<sup>3,8</sup>
  - The questionnaire consists of a total score and behavior, drive, and severity of hyperphagia subscales; each item is rated on a 5-point scale, where 1 = not a problem and 5 = severe and/or frequent problem<sup>8</sup>
  - Scores range from 11 to 55, with higher scores indicating more substantial hyperphagia<sup>8</sup>
- Hyperphagia Questionnaire scores were assessed by weight category
- Pearson's correlations were used to examine the relationship between Hyperphagia Questionnaire score and BMI percentile at the 4th annual assessment
  - Given that small percentile changes on standard BMI growth charts correspond to large BMI changes for children with severely high BMIs and therefore do not capture clinically meaningful weight changes, we also report Pearson's correlations between Hyperphagia Questionnaire score and percent of the 95th BMI percentile (%BMI<sub>95</sub>), which captures variation of weight among children with severe obesity<sup>9</sup>

## Results

### Population

- The Hyperphagia Questionnaire was completed by caregivers of 39 patients with BBS (61.5% male; mean [median] age 10.9 [11.0] years) (Table 1)

Table 1. Demographics

	Pediatric patients with BBS (N=39)
Age at hyperphagia assessment, mean (median; min-max), y	10.9 (11.0; 4.0-17.0) <sup>a</sup>
Sex, n (%)	
Male	24 (61.5)
Female	15 (38.5)
Race, n (%)	
White	30 (76.9)
Black	1 (2.6)
Asian	2 (5.1)
Other <sup>b</sup>	6 (15.4)
Region, n (%)	
North America (United States)	29 (74.4)
Europe (Denmark, Germany, UK, unknown)	5 (12.8)
Australia	4 (10.3)
Asia (unknown)	1 (2.6)
Type of healthcare insurance, n (% among 29 children in the United States)	
Public	9 (31.0)
Private	13 (44.8)
Both public and private	7 (24.1)

<sup>a</sup>Although the minimum age at the 4th annual assessment, during which hyperphagia was measured, was 4 years, eligibility for all analyses herein was age 3-17 years. <sup>b</sup>Middle Eastern, American Indian or Alaska Native, Pacific Islander. BBS, Bardet-Biedl syndrome.

- Across all patients, the degree of hyperphagia was moderate, with mean (median; interquartile range [IQR]) Hyperphagia Questionnaire score of 23.9 (25.0; 16.0-30.0) (Table 2)
- Mean (median; IQR) BMI was 27.3 (27.7; 22.3-31.8) kg/m<sup>2</sup> (Table 2)
  - Five patients had under/normal weight, 5 patients had overweight, and 29 patients had obesity at the 4th annual assessment

Table 2. Clinical Measurements

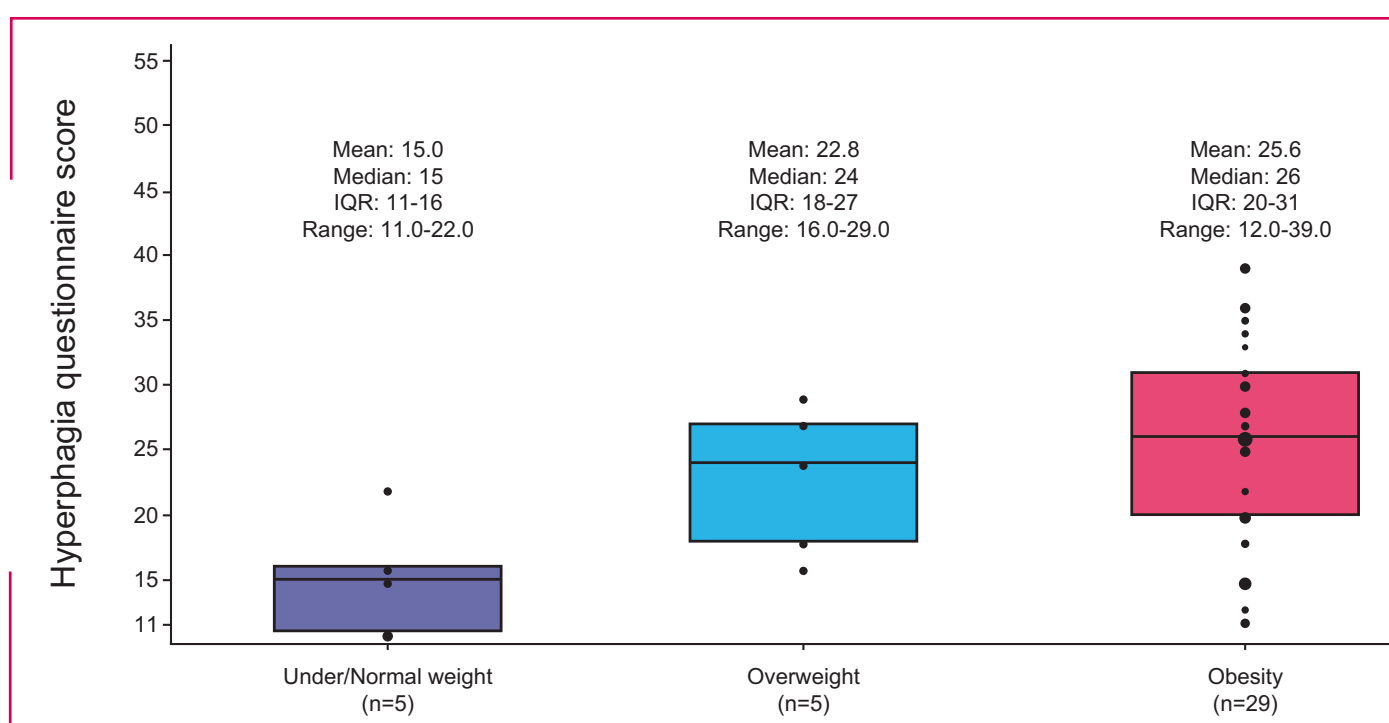
	Pediatric patients with BBS (N=39)
Hyperphagia Questionnaire score, mean (median)	23.9 (25.0)
IQR	16-30
Range	11-39
BMI, mean (median), kg/m <sup>2</sup>	27.3 (27.7)
IQR	22.3-31.8
Range	13.0-38.2
BMI percentile, mean (median)	93.6 (98.5)
IQR	94.5-99.6
Range	0.2-100.0
Underweight or normal weight, n (%)	5 (12.8)
Overweight, n (%)	5 (12.8)
Obesity, n (%)	29 (74.4)

BBS, Bardet-Biedl syndrome; BMI, body mass index; IQR, interquartile range (ie, first to third quartile).

## Relationship between hyperphagia and obesity

- The Hyperphagia Questionnaire score increased by weight category, with mean (median) scores of 15.0 (15), 22.8 (24), and 25.6 (26) in patients with under/normal weight, overweight, and obesity, respectively (Figure 1)

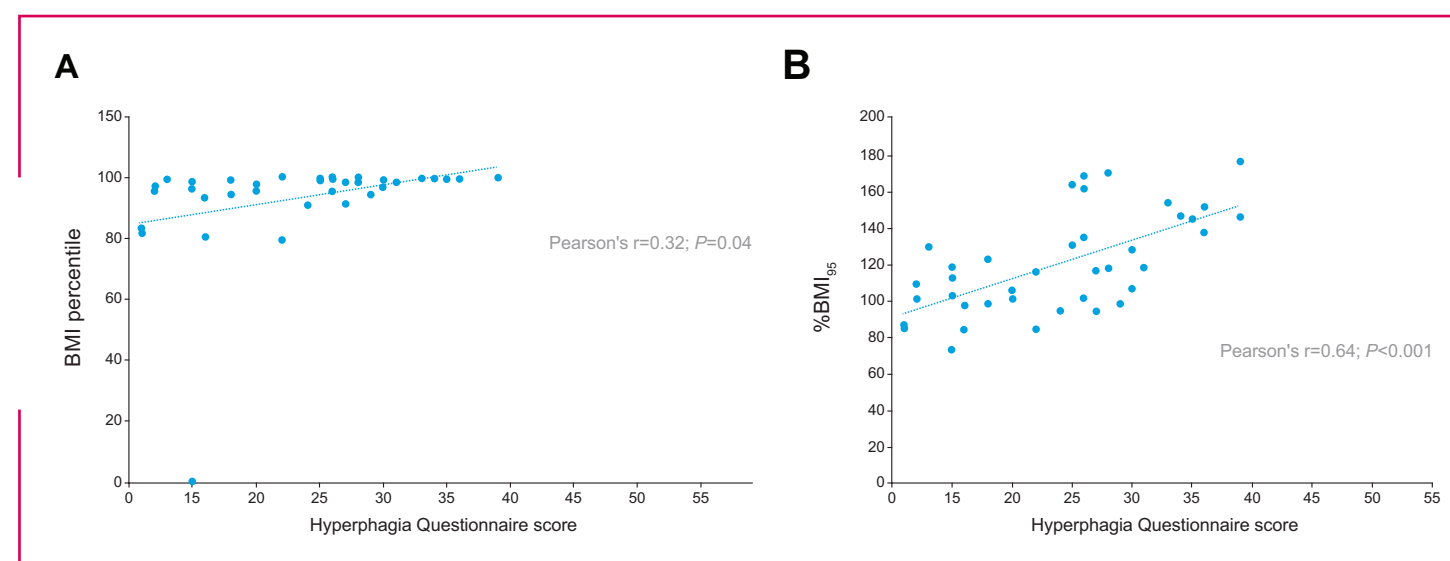
Figure 1. Mean, median, IQR, and individual hyperphagia scores by weight category.



Horizontal lines inside boxes are the median, boxes are Q1-Q3, and black circles are the individual data, with increasing circle size representing increasing number of patients with the same value. IQR, interquartile range; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile.

- The Hyperphagia Questionnaire score was significantly positively correlated with BMI percentile (Pearson's  $r=0.32$ ;  $P=0.04$ ) (Figure 2A) and with %BMI<sub>95</sub> (Pearson's  $r=0.64$ ;  $P<0.001$ ) (Figure 2B), which enables the discrimination between different levels of severe obesity<sup>9</sup>

Figure 2. Relationship between hyperphagia and obesity. (A) Correlation between BMI percentile and Hyperphagia Questionnaire score. (B) Correlation between %BMI<sub>95</sub> and Hyperphagia Questionnaire score.



Each data point indicates 1 patient in the sample of 39 children with Bardet-Biedl syndrome. Lines are trend lines illustrating the average increase in BMI (panel A) and %BMI<sub>95</sub> (panel B) per point increase in hyperphagia score. The trend lines were estimated from ordinary least squares regression models, with BMI and %BMI<sub>95</sub> as dependent variables and hyperphagia score as independent variable. BMI, body mass index; %BMI<sub>95</sub>, percent of the 95th BMI percentile.

## Strengths and limitations

- A strength of this study is that the CRIBBS registry includes the largest sample to date of children with BBS across a range of countries and socioeconomic environments
- Limitations are that hyperphagia was caregiver reported, some weight-related measures were self-reported and thus less precise than those obtained in prospective studies, and hyperphagia and obesity were assessed cross-sectionally at the 4th annual assessment

## Conclusions

- In pediatric patients with BBS, there was a significant positive correlation between Hyperphagia Questionnaire score and obesity; these results indicate that hyperphagia can contribute to obesity in these patients
- Hyperphagia may be a result of impaired MC4R pathway signaling in patients with BBS<sup>3</sup>
- Weight management treatments that target underlying hyperphagia may prove effective for patients with obesity due to rare MC4R pathway diseases, including BBS
- Future work should assess whether a causal relationship exists between hyperphagia and obesity

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