Assessment of Hyperphagia in Prader-Willi Syndrome

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Abstract

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Objective: Prader-Willi syndrome (PWS), the leading known genetic cause of obesity, is characterized by intellectual disabilities, maladaptive and compulsive behaviors, and hyperphagia. Although complications of obesity resulting from hyperphagia are the leading cause of death in PWS, quantifying this drive for food has long been an unmet research need. This study provides factor-analytic and within-syndrome analyses of a new measure of hyperphagia in PWS.

Research Methods and Procedure: A 13-item informant measure, the Hyperphagia Questionnaire, was developed and administered to the parents of 153 persons with PWS, 4 to 51 years of age. The intelligence quotients, genetic subtypes of PWS, and BMIs of offspring were obtained, as were measures of their non-food problem behaviors.

Results: Factor analyses with varimax rotation produced three statistically and conceptually robust factors that accounted for 59% of the variance: Hyperphagic Behaviors, Drive, and Severity. Hyperphagic Behavior increased with age, whereas Drive remained stable, and Severity dipped in older adults. Hyperphagic Drive and Severity were positively correlated with non-food behavior problems, and Hyperphagic Drive differentiated the 36% of participants with extreme obesity from those who had overweight/obese (48%) or healthy (16%) BMI classifications.

Discussion: The Hyperphagia Questionnaire is a robust tool for relating breakthroughs in the neurobiology of hyperphagia to in vivo food-seeking behavior and for examining the psychological and developmental correlates of hyperphagia in PWS. The Hyperphagia Questionnaire also offers a nuanced, real-life outcome measure for future clinical trials aimed at curbing the life-threatening drive for food in PWS.

Key words: psychosocial variables, questionnaire design, genetic susceptibility

Introduction

Prader-Willi syndrome (PWS)[1] is the leading known genetic cause of obesity and is marked by a distinctive behavioral phenotype, including hyperphagia. Hyperphagia in PWS is associated with an aberrant satiety response in affected individuals, especially a delay in satiety (1,2). Caused by a paternal deletion or maternal uniparental disomy of chromosome 15q11-q13, PWS affects ~1 in 15,000 births and results in intellectual disabilities and salient maladaptive and compulsive behaviors such as tantrums, skin-picking, hoarding, and concerns with exactness and sameness. Although people with PWS have cognitive and personality strengths (3), their drive for food remains a life-long source of stress for them and their families (4).

Moreover, complications of obesity remain the leading cause of death in PWS. Death rates are six times higher in PWS subjects compared with others with intellectual disabilities (5). Deaths in children often stem from illnesses associated with high fevers and respiratory infections, whereas deaths in adults are typically related to complications of obesity that involve the cardiovascular and respiratory systems (6,7). Hyperphagia is also dangerous in persons who are relatively slim, with increased risks of death caused by choking while sneaking food and gastric perforations after consuming more food than usual (8).

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[1] Nonstandard abbreviations: PWS, Prader-Willi syndrome; FRPQ, Food-Related Problems Questionnaire; IQ, intelligence quotient; K-BIT, Kaufman Brief Intelligence Test; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; CBCL, Child Behavior Checklist.

Although hyperphagia is a highly stressful, life-threatening feature of PWS, accurately measuring this complex behavior has long been a research challenge. Reliable measures are sorely needed, and researchers have tried three different approaches to measuring hyperphagia in PWS.

In the first approach, individuals with PWS are given access to unlimited food in a laboratory setting, and researchers note the amount of food (e.g., sandwich quarters) consumed (1,9). In one such experiment (1), adults with PWS ate three times as many calories as normal controls, and they also showed a delay in satiety. Used predominantly in the U.K., university research review boards in the United States have deemed this approach to be unethical and of high medical risk. Circumventing these restrictions, Young et al. (10) individually placed nine persons with PWS in a room that was baited with limited quantities of foods that varied in their acceptability, concealment, and contamination (11). Only three people engaged in food-seeking behaviors. Similarly, we previously used a task in which persons with PWS were left in a room with the remainder of a low-calorie but desired snack. Finishing the snack or food seeking was virtually non-existent in our sample of 23 persons (unpublished data). These simulated settings do not seem to capture the covert food-seeking that parents reported in these same individuals at home, perhaps because of social desirability effects or to being in a contrived setting.

In light of these difficulties, Dykens (11) used a second approach, a visual analog interview, that identified willingness to eat contaminated foods and appropriate and inappropriate food combinations. Despite their well-developed ideas about the purpose and fate of food, individuals with PWS were more likely than controls with or without mental retardation to endorse eating contaminated foods and odd food combinations (11). These findings suggest novel interventions, such as teaching persons with PWS about germs or the emotion of disgust. However, the hypothetical nature of these tasks makes them less useful as outcome measures in clinical trials.

A third approach uses questionnaires completed by parents or care providers. The Children's Eating Behavior Inventory (12), for example, identifies eating problems such as finickiness in typically developing children, and the Eating Disorders Inventory (13) is designed for patients with anorexia or bulimia. Although occasionally used in PWS research (14), these measures do not capture the range of such unusual food-seeking behaviors in PWS as food sneaking and theft, foraging through the trash for food, getting up at night to food seek, and eating unpalatable items (11).

Recently, however, Russell and Oliver (15) introduced a 16-item Food-Related Problems Questionnaire (FRPQ) that assesses preoccupation with food, impairment of satiety, and related negative behaviors in PWS. Although the FRPQ is a first step, it has three limitations. First, 6 of its 16 items require a verbal response by the individual with PWS. Although it is important to obtain self-report data, people with intellectual disabilities often have difficulty identifying or expressing thoughts or feelings (16) and are prone to inconsistent reporting and acquiescence biases (17), and persons with more limited verbal capacities may end up with artificially lower, or invalid, FRPQ scores. Furthermore, even highly verbal persons with PWS range in their willingness to talk openly about food, they may need reassurance before doing so (e.g., "Will you tell my mother?" "Will I lose my snack?"), and they may stick to "socially acceptable" responses by denying that they like highly caloric foods or that they snitch or hide food. Second, the FRPQ items and domains were derived from focus groups with parents, and items were not subjected to statistical analyses that confirmed these classifications. Third, items on the FRPQ do not directly assess symptom severity. Increased frequency of hyperphagic symptoms certainly implies increased severity, but alternative and well-established ways of determining symptom severity are also derived from psychiatric nosology, specifically the extent to which symptoms are time-consuming, distressful, and cause functional and adaptive impairment.

This study's Hyperphagia Questionnaire addresses these concerns: we used parents or care providers as informants, conducted factor analyses of items, and included several items that assess symptom severity. Because the primary goal of any measure is to find relationships among constructs (18), we related the Hyperphagia Questionnaire to age, sex, and intelligence quotient (IQ), as well as to salient aspects of the PWS behavioral phenotype (genetic subtypes, degree of obesity, and non-food maladaptive and compulsive behavior). Taken together, the factor analytic and within-syndrome analyses in this study address a long-standing need to measure hyperphagia in PWS.

Research Methods and Procedures

Participants

The parents or primary guardians of 153 persons (55% men and 45% women) with PWS were administered the Hyperphagia Questionnaire. Persons with the syndrome ranged in age from 4 to 51 years [mean, 20.23 $\pm$ 11.3 years (standard deviation)]. Participants were recruited from the Vanderbilt Kennedy Center, UCLA-Lili Claire Behavior Genetics Clinic, and an annual conference of the Prader-Willi Syndrome Association (USA). To rule out an ascertainment bias, we compared hyperphagic and other behaviors across these recruitment sources. Because none of these ANOVAs was significant, participants were combined across the three recruitment sources.

Genetic diagnoses of PWS were obtained from parents, and copies of genetic laboratory test results were also avail-

Table 1. Participant characteristics across age groups

	4 to 10 years		11 to 19 years		20 to 29 years		30 years and up	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
N	31		50		43		29	
Age (yrs)	6.75	1.70	14.52	2.69	24.11	2.55	38.53	5.79
IQ	70.27	18.55	64.35	13.62	66.35	15.31	64.57	11.21
BMI (kg/m^2)	24.00	7.01	28.69	8.39	35.07	9.96	33.64	8.27
BMI classifications								
Percent normal-weight	10%		30%		14%		11%	
Percent overweight	21%		32%		26%		30%	
Percent obese (adults)					33%		48%	
Percent extremely obese	69%		38%		27%		11%	

SD, standard deviation; IQ, intelligence quotient. For children and adolescents, BMI ≤85th percentile = normal-weight; 85th to 96th percentile = overweight/obese; and ≥97th percentile = extremely obese. For adults, normal-weight BMI ≤24.9 kg/m^2; overweight = 25 to 29.9 kg/m^2; obese = 30 to 39.9 kg/m^2, and extremely obese ≥40 kg/m^2.

able in ~65% of the sample. Paternal deletions at 15q11–13 were reported in 63% of the sample; 28% had maternal uniparental disomy; 2% had imprinting errors, 2% had microdeletions, and 2% had translocations or other chromosome 15 anomalies; and the remaining 3% had either clinical diagnoses or positive methylation tests.

For some analyses, we divided the sample into four age groups: 4 to 10 (n = 31); 11 to 18 (n = 50); 19 to 29 (n = 43); and ≥30 years (n = 29). We used four age groups because we had ample power to go beyond a dichotomous classification of children vs. adults and because food and non-food behavioral problems in PWS differ across these developmental periods (19,20). Table 1 shows the mean ages within each group.

As measured by the Kaufman Brief Intelligence Test (K-BIT) (21), the average IQ of the sample was 66.08 ± 14.67. IQs were in the range considered typical of those with PWS and did not differ significantly by age (Table 1).

The BMI of participants indicated high rates of obesity in both children and adults. Table 1 shows the mean BMI for each age group and the BMI classifications based on Center for Disease Control and Prevention (22) age and sex criteria. Of note is that 54% of children and youth 4 to 19 years of age were extremely obese, with BMIs that exceeded the 97th percentile; 25% were overweight/obese, and 20% had BMIs in the healthy range. Among adults 20 to 51 years of age, 19% showed extreme obesity based on Center for Disease Control and Prevention guidelines, 41% were classified as obese, 28% were overweight, and 12% had normal BMIs.

Procedure and Measures

Participants were individually administered the K-BIT by trained research assistants, who also obtained each participant's height and weight. Parents reported on basic information about their child (e.g., age, sex, genetic status) and completed the instruments listed below.

The Hyperphagia Questionnaire is a 13-item instrument that was specifically designed to measure food-related preoccupations and problems in PWS, as well as the severity of these concerns. Items reflected parent and offspring reports of hyperphagic symptoms gleaned from our ongoing research and clinic programs for persons with PWS and their families. The severity items were based on the definition of symptom-related impairment as operationalized by the American Psychiatric Association (23). Items on the Hyperphagia Questionnaire were rated on a five-point scale (1 = not a problem to 5 = severe and/or frequent problem) and are listed in Appendix A.

Yale-Brown Obsessive Compulsive Scale. Caregivers completed an informant version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (24) that consisted of 30 symptoms that were rated as occurring ever or in the last week. Obsessions and compulsions were summed for a total score. Additionally, informants rated the degree of distress, time, and adaptive impairment caused by symptoms (1 = none to 5 = extreme); these were summed as a severity score. The Y-BOCS has been used in previous studies of PWS (25,26).

Child Behavior Checklist. The widely used Child Behavior Checklist (CBCL) asks caregivers to rate 112 problems on a three-point scale (0 = not true, 1 = somewhat true, 2 = very true) (27). The CBCL has been used in studies of PWS (20,28) and provides an internalizing domain (comprised of anxious/depressed, somatic complaints, and withdrawn scales), externalizing domain (non-compliant and

Table 2. Factor and item means, SDs, ranges, and factor loadings of the Hyperphagia Questionnaire for 153 persons with PWS

Factors	Mean	SD	Range	Factor loading
Hyperphagic Behavior	13.57	4.52	5 to 25	
How clever or fast in obtaining food	4.05	1.28	1 to 5	0.68
How often bargains, manipulates for more food	3.06	1.32	1 to 5	0.51
How often tries to steal food	2.76	1.46	1 to 5	0.76
How often gets up at night to seek food	1.89	1.20	1 to 5	0.76
How often forages through trash for food	1.80	1.05	1 to 5	0.77
Hyperphagic Drive	12.29	3.32	4 to 20	
How upset when denied food	3.34	1.14	1 to 5	0.85
Once food on mind, how easy to redirect away from food	3.28	1.00	1 to 5	0.82
How persistent in asking or looking for food when told no	3.25	.96	1 to 5	0.76
Level of distress when others stop food talk or behaviors	2.42	.98	1 to 5	0.53
Hyperphagic Severity	4.61	1.63	2 to 10	
Time spent talking about food or engaged in food behavior	2.41	1.18	1 to 5	0.86
Extent that food interferes with functioning, daily routines	2.20	.88	1 to 5	0.62

SD, standard deviation; PWS, Prader-Willi syndrome.

aggressive behavior scales), and total score. Raw scores were used in analyses.

Statistical Approach. Items on the Hyperphagia Questionnaire were subjected to a factor analysis with principal component extraction and varimax rotation. We used the Kaiser criterion, retaining only factors with eigenvalues >1. Factor analyses placed items into groups based on factor loadings; these groupings were labeled. Although we report factor loadings, subsequent analyses examining age, BMI, and other correlates used mean scores of each factor.

Results

Hyperphagia Questionnaire Factor Analyses

Of the 13 items included in the factor analysis, 2 did not load onto any factor—the age of onset of hyperphagia and variability in the drive for food—and these items were deleted from subsequent analyses. Three factors emerged that accounted for 58.93% of the variance. The first factor, labeled Hyperphagic Behavior, accounted for 34.47% of the variance (eigenvalue = 3.79) and had a Cronbach's α (degree to which items are internally consistent) of 0.76. The second factor, labeled Hyperphagic Drive, accounted for 15.28% of the variance (eigenvalue = 1.68) and had a Cronbach's α of 0.80. The third factor, Hyperphagic Severity, accounted for 9.17% of the variance (eigenvalue = 1.01) and had a Cronbach's α of 0.60. All αs showed acceptable internal consistency. Table 2 shows the mean for factors and items, standard deviations, ranges, and factor loadings.

IQ, Genetic Status, and Sex. No significant relationships were found between IQ, sex, or genetic subtypes of PWS (paternal deletion, maternal uniparental disomy) and any of the hyperphagia scores.

Age. Although age was not correlated with Hyperphagic Drive or Severity, it was positively associated with Hyperphagic Behavior [$r(140) = 0.27$, $p < 0.01$]. To further explore this correlation, ANOVAs compared mean hyperphagia scores across the four age groups. An age effect was found for Hyperphagic Behavior [$F(3,147) = 4.72$, $p < 0.01$], with post hoc analysis revealing lower scores in younger children compared with both groups of adults. Hyperphagic Drive was remarkably similar across age groups, whereas Severity scores were lower in older adults compared with either adolescents or young adults

Table 3. Mean Hyperphagic Behavior, Drive, and Severity scores, SDs, and *F* and *p* values across four age groups

Hyperphagic factors	4 to 10 years		11 to 19 years		20 to 29 years		30 years and up			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*, *p*	Post hocs
Behavior	11.21	4.26	13.22	4.55	14.89	4.35	14.83	4.03	4.72*	1 < 3, 4
Drive	12.13	3.31	12.00	3.77	12.24	2.94	12.16	3.19	NS	
Severity	4.56	1.87	4.79	1.58	4.81	1.53	3.96	1.53	4.34†	4 < 2, 3

SD, standard deviation; NS, not significant.
* $p < 0.01$.
† $p < 0.05$.

[$F(3,147) = 4.34$, $p < 0.05$]. Table 3 summarizes mean scores on the hyperphagia factors across age groups.

BMI: Children and Youth. As in the general population, BMI and age were correlated in children with PWS [$r(77) = 0.43$, $p < 0.001$]. As such, age was used as a covariate in subsequent BMI analyses. Analysis of covariance examined hyperphagia scores across the three BMI classifications for children and youth (normal-weight, overweight/obese, extremely obese), with age as the covariate. Because so few children had healthy BMIs, we did not further divide children into age groups. Children who were extremely obese had significantly higher Hyperphagic Drive scores than normal-weight or overweight/obese youngsters [$F(2,70) = 4.82$, $p < 0.01$]. Non-significant trends ($p < 0.10$) emerged for Hyperphagic Behavior and Severity, with extremely obese children and youth having higher scores than their overweight/obese counterparts ($p < 0.06$; Table 4).

BMI: Adults. As expected, age was not correlated with BMI in adults with PWS. ANOVAs compared hyperphagia scores across the four adult BMI classifications (normal-weight, overweight, obese, extremely obese). Few older adults had normal BMIs, so we did not divide adults into age groups. As shown in Table 4, an effect was found for Hyperphagic Drive [$F(3,70) = 6.54$, $p < 0.01$], with post hoc analysis revealing that adults with extreme obesity had

Table 4. Mean Hyperphagic Behavior, Drive, and Severity scores, SDs, and *F* and *p* values across child and adult BMI classifications

Hyperphagic factors	Normal-weight		Overweight/ obese		Extremely obese		*F* and *p*
	Mean	SD	Mean	SD	Mean	SD	
Behavior							
Children and adolescents	12.00	5.57	11.50	3.11	13.62	4.65	2.35*
Adults	14.55	2.17	14.69	4.36	15.54	5.17	0.21; NS
Drive							
Children and adolescents	10.50	3.48	10.06	4.23	13.37	3.51	4.82†; 3 > 1, 2
Adults	12.55	3.21	11.19	2.71	14.23	2.13	6.54†; 3 > 2
Severity							
Children and adolescents	4.92	1.61	4.11	1.81	5.03	1.67	2.09*
Adults	4.22	1.72	4.36	1.51	5.07	1.60	1.20; NS

SD, standard deviation; NS, not significant.
* $p < 0.10$.
† $p < 0.01$.

significantly higher Hyperphagic Drive scores than obese or overweight adults.

Non-food Maladaptive and Compulsive Behavior. Non-food maladaptive and compulsive behaviors were associated primarily with Hyperphagic Drive and Severity. For simplicity, we report correlations for the sample as a whole, because findings were similar within each age group. Hyperphagic Drive and Severity were positively correlated with the CBCL total score [$r(143) = 0.52$ and 0.43, $p < 0.001$, respectively], the CBCL externalizing score [$r(143) = 0.49$ and 0.40, $p < 0.001$, respectively], the CBCL internalizing score [$r(143) = 0.49$ and 0.33, $p < 0.001$ and 0.01, respectively], and the severity of Y-BOCS compulsive symptoms [$r(138) = 0.26$ and 0.29, $p < 0.01$, respectively].

Within the internalizing domain, relationships emerged between Hyperphagic Drive and Severity and the anxious/depressed scale [$r(143) = 0.41$ and 0.20, $p < 0.001$ and 0.01, respectively] and the withdrawal scale [$r(143) = 0.41$ and 0.22, $p < 0.001$ and 0.01, respectively]. In the externalizing domain, Hyperphagic Behavior, Drive, and Severity were correlated with the non-compliant scale [$r(143) = 0.47$, 0.38, and 0.31, $p < 0.001$, respectively], and Hyperphagic Drive and Severity were related to the aggression scale [$r(143) = 0.49$ and 0.39, $p < 0.001$, respectively].

Age of Onset and Variability of Hyperphagia

Exploratory analyses were conducted with the two items that did not load onto factors, because they are relevant to how families and professionals view hyperphagia in PWS. The mean age of onset of hyperphagia was 3.5 ± 1.6 years, with a range from 1.5 to 7 years. Although retrospective, these data are consistent with the range and average age of onset reported in the literature. Contrary to clinical lore, an earlier age of onset was not associated with increased Hyperphagic Behavior, Drive, or Severity, based on correlations and *t* tests comparing earlier vs. later ages of onset. Most persons (68%) showed little variability in their preoccupations with food, 23% showed occasional variability, and 9% showed a lot of variability. No differences in hyperphagia scores were found across persons with a little, some, or high variability in food preoccupation.

Discussion

Although hyperphagia is a salient, life-threatening feature of PWS, measuring this complex trait has long been a research challenge. Our new measure fills this gap, for the first time allowing researchers to examine the correlates and trajectories of this salient feature of PWS. The Hyperphagia Questionnaire also holds considerable promise as an outcome measure for clinical trials aimed at reducing the drive for food and risks of severe obesity that have long characterized this disorder.

Factor analyses of the Hyperphagia Questionnaire produced three robust factors that make conceptual sense and that tap the range and severity of food-related issues in PWS. Hyperphagic Behavior, Drive, and Severity have statistically solid factor loadings, with acceptable Cronbach's α's that justify further psychometric work on this measure, including test-retest reliability.

This study's Hyperphagia Questionnaire has several other strengths. The measure is timely and circumvents previous measurement problems. The study included a large sample size, which is hard to accomplish with a relatively rare genetic disorder, a wide age range of participants, and standardized measures of maladaptive behavior and compulsivity. Furthermore, Hyperphagia Questionnaires were subjected to factor analyses, and subsequent factors were analyzed with respect to salient aspects of the PWS behavioral phenotype.

Even so, the study had several weaknesses. First, in ~35% of the sample, we relied solely on parental reports of genetic subtyping and lacked subtype confirmation through laboratory reports. Second, we did not have data on the living situations of all adult participants. Some adults live outside of their family home, and persons living in specialized PWS group homes often lose and maintain lower weights than people in less structured settings (20). Similarly, some psychotropic medications alter appetite, and we did not have medication data for all participants. Anecdotally, selective-serotonin reuptake inhibitors, often used with variable success to treat compulsivity and problem behaviors in PWS, may also ease the severity of food preoccupations or tantrums, whereas other agents (e.g., atypical antipsychotics) may increase appetite (29). The Hyperphagia Questionnaire may be used to quantify possible side effects of psychotropic medication on appetite in persons with PWS.

A third and major limitation is that we did not have detailed data on the dietary regimens or level of food supervision for all participants. This information could have shed light on relationships between participants' BMIs and the three hyperphagic factors. The Hyperphagia Questionnaire significantly differentiated children or adults with extreme obesity, but did less well differentiating participants with BMIs in the healthy or overweight/obese ranges. Although fat secretes leptin, insulin, and other factors that might lead to increased food seeking in the extremely obese groups, another explanation for BMI findings is that, once persons are diagnosed with PWS, they receive sustained and intensive dietary interventions. Best practices for persons with PWS include life-long, close supervision in settings that involve food; locked refrigerators and kitchen cabinets; regular, daily exercise or activity; and low-calorie diets that take into account the central hypotonia, growth hormone deficiencies, and lower resting metabolic rates seen in most persons with the syndrome (8). Furthermore, many children

with PWS now receive growth hormone therapy, which is associated with lower BMIs (30,31). Some participants with high scores on the Hyperphagia Questionnaire may, thus, have healthy BMIs if they are receiving growth hormone therapy and/or are compliant with environmental interventions. Other persons with high hyperphagia scores, however, may cleverly defy these same environmental safeguards (e.g., sneaking food even when supervised, unscrewing locked cabinets), and these individuals are at risk for higher BMIs. Still others are not adequately supervised or placed on proper diets. To the extent that interventions and compliance with interventions vary, we would expect less of a clear-cut relationship between BMI and the Hyperphagia Questionnaire.

Although further work is needed, the Hyperphagia Questionnaire has promising implications for at least four lines of research. First, the tool can be used to measure changes in hyperphagic symptoms in novel clinical trials. Such trials are likely to increase because of increased advocacy for such trials in the PWS parent and professional community and advances in the neurobiology of appetite regulation in general and in PWS specifically. Various neuropeptides, for example, are implicated in aberrant satiety in PWS, including reduced levels of oxytocin-secreting neurons in the paraventricular nuclei of the hypothalamus (32). Furthermore, compared with controls, persons with PWS also have markedly elevated levels of ghrelin (33,34). Ghrelin, a hormone produced predominantly in the stomach, acts on the hypothalamus to stimulate appetite and food consumption. Short-term clinical trials using somatostatins have led to lower plasma levels of ghrelin (9,35), but they have not reduced appetite in individuals with PWS, at least as measured by sandwich consumption in the laboratory setting (9). As similar trials get underway, the Hyperphagia Questionnaire can provide a more nuanced outcome measure that can extend beyond the laboratory to the real-life settings of persons with the syndrome.

Second, the Hyperphagia Questionnaire extends research on genotype-phenotype correlations in PWS. Although differences have been seen across genetic subtypes of PWS in cognition and maladaptive behavior (28,36,37), hyperphagia has not been included in these studies, as researchers lacked an adequate measure of this symptom. Preliminarily, we found no differences in Hyperphagic Behavior, Drive, or Severity across persons with paternal deletions or maternal uniparental disomy. Recently, however, paternal deletions were further categorized, with type I deletions being ~500 bp larger than type II deletions. Those with type I deletions seem to have lower cognitive skills (38,39), and future work is needed to determine whether hyperphagia differs across type I vs. type II deletions and other subtypes.

Third, the Hyperphagia Questionnaire allows researchers to ask more refined questions about the broader PWS behavioral phenotype, including 1) how hyperphagia relates to non-food problems and 2) how it changes over the course of development. Previous literature has emphasized (and at times sensationalized) more unusual behaviors in PWS: eating odd or unpalatable items and the ingenious, covert, and at times dangerous ways that persons obtain food. In contrast, however, we found that these aberrant food-seeking behaviors were not predictive of non-food behavior problems; instead, behavioral and emotional problems were related to Hyperphagic Drive or Severity. Although correlational, these findings raise important questions on the role that maladaptive or emotional problems play in the manifestation of hyperphagia in PWS. For example, internalizing problems such as anxiety and depression were significantly correlated with Hyperphagic Drive and Severity. It is unclear whether heightened sadness or anxiety leads to increased severity and drive for food or whether, instead, increased severity and drive for food foster sadness or worry, but there is clearly an interplay between hyperphagia and the many non-food behavioral and emotional problems in PWS.

The Hyperphagia Questionnaire also allows for developmental studies that track changes in the drive for food over time. Hyperphagic Behavior increased across age groups, reflecting the capacities of individuals to engage in a wider repertoire of food-seeking behaviors as they get older. In contrast, however, mean scores for Hyperphagic Drive were remarkably similar across all age groups, suggesting that once hyperphagia begins in young children, the drive for food may not fluctuate widely over the course of development. Indeed, when asked directly about such fluctuations, 91% of parents reported little to no variability in their offspring's drive for food. Even so, food management issues may vary and become more challenging for families, as individuals show increased competence in their food-seeking behaviors as they develop. Additionally, we found lower Hyperphagic Severity scores in older adults, which mirror a dampening of non-food maladaptive and compulsive behaviors in older persons (20). Older adults still exhibited hyperphagic drive and behaviors (and 89% were overweight or obese), but they had less food-related impairment than younger groups. Longitudinal studies are needed to identify why some maladaptive and hyperphagic symptoms are turned down a notch in older adults with PWS. Changes in hormones or neuropeptides may be involved, and the selective survival hypothesis would argue that, compared with those who have died, older, surviving adults are healthier, less obese, and presumably have symptom-related impairment (20).

Fourth, although developed for PWS, the Hyperphagia Questionnaire may be useful in more rare genetic syndromes that involve intellectual disabilities and obesity, including Bardet-Biedl syndrome, Cohen syndrome, Albright hereditary osteodystrophy, and Borjeson-Forssman-Lehmann syndrome (40). We have also occasionally used

the Hyperphagia Questionnaire in persons with Down syndrome or undiagnosed intellectual disabilities who show unusual food seeking behaviors and "Prader-Willi–like" preoccupations with food (41). Further work is needed on the use of the Hyperphagia Questionnaire in these rare genetic syndromes or unusual cases.

Although the drive for food varies considerably across people with PWS, to date, researchers have lacked the necessary tools to quantify these individual differences and track them over time. The Hyperphagia Questionnaire allows researchers to examine promising mechanisms associated with this individual variability, including genetic subtypes of PWS, neurobiological factors, emotional functioning, development and aging, and intervention. The Hyperphagia Questionnaire also provides, for the first time, a quantifiable outcome measure for future clinical trials that aim to curb the life-threatening hyperphagic symptoms of PWS.

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Appendix A. Hyperphagia Questionnaire

(1) How upset does your child generally become when denied a desired food?
___ Not particularly upset at all
___ A little upset
___ Somewhat upset
___ Very upset
___ Extremely upset

(2) How often does your child try to bargain or manipulate to get more food at meals?
___ A few times a year
___ A few times a month
___ A few times a week
___ Several times a week
___ Several times a day

(3) Once your child has food on their mind, how easy is it for you or others to re-direct your child away from food to other things?
___ Extremely easy, takes minimal effort to do so
___ Very easy, takes just a little effort to do so
___ Somewhat hard, takes some effort to do so
___ Very hard, takes a lot of work to do so
___ Extremely hard, takes sustained and hard work to do so

(4) How often does your child forage through the trash for food?
___ Never
___ A few times a year
___ 1–2 times a month
___ 1–3 times a week
___ 4 to 7 times a week

(5) How often does your child get up at night to food seek?
___ Never
___ A few nights a year
___ 1–2 nights a month
___ 1–3 nights a week
___ 4 to 7 nights a week

(6) How persistent is your child in asking or looking for food after being told "no" or "no more"?
___ Lets go of food ideas quickly and easily
___ Lets go of food ideas pretty quickly and easily
___ Somewhat persistent with food ideas
___ Very persistent with food ideas
___ Extremely persistent with food ideas

(7) Outside of normal meal times, how much time does your child spend talking about food or engaged in food-related behaviors?
___ Less than 15 minutes a day
___ 15 to 30 minutes a day
___ 30 minutes to an hour
___ 1 to 3 hours a day
___ more than 3 hours a day

(8) How often does your child try to steal food (that you are aware of?)
___ A few times a year
___ A few times a month
___ A few times a week

Appendix A. Continued

___ Several times a week
___ Several times a day

(9) When others try to stop your child from talking about food or engaging in food-related behaviors, it generally leads to:
___ No distress or upset
___ Mild distress or upset
___ Moderate distress or upset
___ Severe distress or upset
___ Extreme distress, behaviors can't usually be stopped

(10) How clever or fast is your child in obtaining food?
___ Not particularly clever or fast
___ A little clever or fast
___ Somewhat clever or fast
___ Very clever or fast
___ Extremely clever of fast

(11) To what extent to food-related thoughts, talk, or behavior interfere with your child's normal daily routines, self-care, school, or work?
___ No interference
___ Mild interference; occasional food-related interference in completing school, work, or hygiene tasks
___ Moderate interference; frequent food-related interference in completing school, work, or hygiene tasks
___ Severe interference; almost daily food-related interference in completing school, work, or hygiene tasks
___ Extreme interference, often unable to participate in hygiene tasks or to get to school or work due to food-related difficulties

Additional items:

(12) How old was your child when they first showed an increased interest in food?

(13) How variable is your child's preoccupation or interest in food?
___ Hardly ever varies
___ Usually stays about the same
___ Goes up and down occasionally
___ Goes up and down quite a lot
___ Goes up and down all the time