Diagnoses and Characteristics of Autism Spectrum Disorder in Adults with Prader-Willi Syndrome

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CHAPTER 1

BACKGROUND

Currently adults with autism spectrum disorders (ASD) are a growing population whose cognitive, adaptive, and behavioral outcomes have been difficult for researchers to measure due to evolving concepts of what a successful adulthood involves (Henninger & Taylor, 2013). What has been consistently found, however, is that low IQ is associated with poorer outcomes for adults (Howlin, Goode, Hutton, & Rutter, 2004) and that intellectual or developmental disability (IDD) is commonly comorbid with ASD (Matson & Shoemaker, 2009). ASD is behaviorally defined by social and communication deficits and the presence of restricted and repetitive behaviors, and is linked to many genetic mutations and disorders. One of the strongest reported genetic associations with ASD has been with Prader-Willi Syndrome (PWS) (Miles, 2011). PWS is a neurodevelopmental disorder resulting from loss of function of paternally derived genes on chromosome 15q11-13 and typically results in mild to moderate intellectual disability, irritability, compulsivity, rigidity, social impairments, growth hormone deficiency, and excessive hunger or hyperphagia which often leads to obesity (Dykens & Roof, 2008).

There are several genetic mechanisms which cause PWS, the most common being paternal deletions which are classified by their size; Type I deletions are around 500mb larger than Type II deletions. There are cases of atypical deletions which do not share the breakpoints of Type I or II deletions but these are less commonly seen. Another mechanism is maternal uniparental disomy (mUPD), which accounts for 20-30% of PWS cases and results when the child receives both copies of chromosome 15 from the mother. The mUPD subtype of PWS in particular carries a heightened risk for ASD and psychotic disorders, presumably accounted for by the overexpression of maternal genes in the PWS critical region (Holland et al, 2003; Whittington & Holland, 2004). Finally,

paternally inherited imprinting errors can also cause PWS and account for 1-3% of all cases (Cassidy, Schwartz, Miller, & Driscoll, 2012).

Most of the research concerning comorbidity between PWS and ASD has utilized parent completed autism screeners, such as the Social Communication Questionnaire (SCQ), instead of utilizing direct observation. While screeners are not intended to be diagnostic tools alone and instead are signals for more detailed measures to be used, they have been widely used to associate ASD with PWS. Two different literature reviews, conducted a decade apart, found elevated rates of autism in PWS at a rate of 25.3% (Veltman, Craig, & Bolton, 2005) and 26.7% (Bennett, Germani, Haqq, & Zwaigenbaum, 2015) with even higher rates in mUPD specifically (37.7% and 35.3% respectively). None of the studies covered by these reviews used direct observation and assessment of individuals with PWS for diagnosis of autism, with most relying upon parent-completed screeners. Rates may in fact be lower, as has been found in the case of 22q11.2 deletion syndrome. In this genetic disorder, screeners indicated a 31-35% rate of ASD, whereas more stringent measurement using the Autism Diagnostic Interview-Revised (ADI-R) revealed lower rates at 14% (Fine et al., 2005).

Although it is clear that autism has some genetic component, no causal biological pathways have been found (Rutter & Thapar, 2014). Accurate estimates of ASD in PWS, or other genetic syndromes, can facilitate study of potential genetic mechanisms for ASD. Genetic disorders that are associated with ASD may be used as biological models for animal research specifically focused upon studying ASD. The 15q11-13 region implicated in PWS has been studied in mice specifically to answer research questions about ASD including the study of repetitive behavior, social learning, and anxiety (Meziane et al., 2015; Lewis, Tanimura, Lee & Bodfish, 2007; Nakatani et al., 2009). If the actual association between ASD and PWS is weaker or more complicated than what has

been reported, then models using the genes implicated in PWS may not be appropriate for use in ASD research. Alternatively, studies focusing on these genetic regions may require more specific research questions to study ASD.

There are several methodological issues with measuring an association between PWS and ASD, particularly so for adults. As ASD is inherently a developmental disorder, retrospective reporting can be a significant bias in parent completed measures where many questions ask about early developmental behaviors (Hardt & Ruttter, 2004). Additionally, many studies cover a wide age range of participants. Ranges including very young children up to adults may complicate findings concerning PWS as a whole if retrospective reporting adversely affects reporting of adults more so than children.

Researching the profile and phenomenology of ASD in genetic syndromes can be potentially useful for the development of appropriate interventions. However, assessing autism within genetic syndromes can be challenging due to the difficulty of differentiating syndrome specific behaviors from those of idiopathic (i.e. of unknown cause) autism. PWS is just one of several genetic syndromes that have an association with ASD. In fact, over a dozen different syndromes have been studied for their possible linkage to autism as researchers seek to understand the role different genetic pathways can play in the etiology of ASD. Additionally, the vast majority of studies in this field focus upon children, leaving assessment in adults largely understudied. In their comprehensive review, Moss and Howlin (2009) emphasize the need for detailed assessment of ASD in syndromic populations due to the subtle differences in social impairment possible in different conditions that may be separate from those impairments found in idiopathic ASD.

The use of single measures to categorize ASD has been shown to be misleading for several genetic syndromes. Two syndromes that exemplify the complexities of making ASD diagnoses are

Fragile X Syndrome (FXS) and Down Syndrome (DS). Recent research using standardized methods estimate a prevalence range of ASD in Fragile X syndrome between 21-50% (Moss and Howlin, 2009). While it has been shown that individuals with FXS and ASD display similar ADOS profiles as those with ASD alone (Dissanayake, Bui, Bulhak-Paterson, Huggins, & Loesch., 2009) closer inspection of behavior has revealed several key differences between the groups. The levels of reciprocal social interaction and communication in individuals with FXS may be substantively different from those with idiopathic autism (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010). People with FXS are also known to have clinically higher levels of social anxiety, shyness, and gaze avoidance along with emotional sensitivity (Cornish, Turk, & Levitas, 2007; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007) which all may appear symptomatic of ASD.

Down Syndrome (DS), the most common chromosomal cause of ID, is another genetic disorder whose relation to ASD is significant. Down syndrome had been thought to be protective against ASD with rates of comorbid autism being low (Turk, 1992). The stereotypical positive personality of those with DS and their perceived lack of additional psychiatric disorders led to this reasoning. Recent research, however, shows that ASD may be more common with 8-10% of those with DS meeting diagnostic criteria (DiGuiseppi et al., 2010). DS research shows that even genetic syndromes previously thought to have relatively low rates of comorbidity with ASD may instead have comorbid but complex relations with autism.

Other genetic syndromes have been studied with association with ASD, including Angelman syndrome, Rett syndrome, CHARGE, and neurofibromatosis. Though much more research is needed, individuals with neurofibromatosis show elevated scores on the Social Responsiveness Scale (SRS) and there have been rates of ASD reported as high as 25% using the Autism Diagnostic Observation Schedule (ADOS) in this population (Garg et al., 2013). As ASD has been

implicated in such a variety of genetic disorders, it is important to carefully assess each for social impairments that may be unique to these disorders as well as those in idiopathic ASD.

PWS is a challenging condition to diagnose ASD within because of the presence and nature of repetitive behaviors in PWS. Repetitive behaviors such as ordering and arranging, repeated questioning, and insistence on sameness are commonly found in PWS (Clarke et al., 2002; Dykens, Leckman, & Cassidy, 1996; Moss, Oliver, Arron, Burbidge, & Berg, 2009). While these behaviors may resemble the restricted and repetitive behaviors (RRBs) characteristic of ASD, they alone are not enough to justify a diagnosis. Understanding the comorbidity between PWS and ASD may not only help guide future ASD research, but also may help differentiate any behaviors unique to PWS that are separate from ASD.

Recently Dykens et al (2017) have found that with a full diagnostic assessment rates of ASD in children with PWS may be 12.7%, which is lower than what has been typically reported. While ASD is considered a stable diagnosis unlikely to change over time, adults with PWS have not been studied in this way and there are few studies that have used direct observation methods with this population. The current study assesses rates of ASD in adults with PWS using valid, reliable, and direct observation measures in combination with clinicians with expertise in both ASD and PWS. Additionally, the current study compares phenotypic differences in PWS adults with and without ASD in relation to their adaptive and cognitive outcomes. It is predicted that the use of direct observation and clinical judgment, as compared to parent screener measures used in previous literature, will indicate a more accurate rate of ASD as is comparable to those rates found in children with PWS using similar measures (Dykens et al., 2017). It is also expected that adults with both a PWS and ASD diagnosis may have more impaired cognitive and adaptive profiles when compared to those with PWS only. The current study aims to provide a more accurate

understanding of comorbidity in a sizable cohort of well-characterized adults with this rare genetic disorder.

CHAPTER 2

METHODS

Participants

The study included 60 adults aged 17 to 55 with genetically confirmed PWS. Participants were recruited for a national longitudinal study on behavior and development in PWS and were oversampled for the mUPD subtype. Families provided written documentation affirming genetic status of participants, with genetic testing provided for those families who were unable to provide such documentation. As shown in Table 1, adults averaged 26.1 years of age, and the majority were female (55% female), 68.3% of the sample had paternal deletions (30% Type I deletions, 33.3% Type II deletions), and 23.3% had mUPD. 3 adults (5.0%) had atypical deletions.

Table 1: Sample Demographics and PWS Genetic Subtypes

	Sample M (SD)
Age (years)	26.1 (8.98)
% Male	45%
BMI	34.0 (9.4)
% Obese	51.7
Genetic Subtypes	
Deletions	68.3
mUPD	23.3
Other	8.3

Procedures

Consistent with University IRB regulations, parents of offspring with PWS provided written, informed consent for the study, and adults with PWS provided written, informed assent. Following consent and assent, a test battery was administered by trained research assistants who were experienced in working with individuals with PWS and their families.

Autism Assessments. Two tools were used to assess autism symptomatology. The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al., 2012) is a widely used, clinician-administered standardized observational assessment for establishing autism classifications. The ADOS-2 involves multiple activities aimed at eliciting social interactions and the repetitive behaviors associated with autism. Diagnostic algorithms and severity scores (based on raw scores) were created for the ADOS-2 which create an overall Calibrated Severity Score (CSS; Gotham, Risi, Pickles, & Lord, 2007), as well as separate Calibrated Severity Scores for two behavioral domains; Social Affect (SA) and Restricted and Repetitive Behaviors (RRB) (Hus, Gotham & Lord, 2014). The revised severity scores are less influenced by characteristics such as IQ, have established reliability and validated cut-offs for ASD classification, and allow for a standard metric across three of the four age and language based modules of the ADOS-2 (Gotham et al. 2007). The majority of participants in this study were administered Module 3, intended for use with verbally fluent children and adolescents. A clinician with research reliable ADOS-2 training and experience working with adults with PWS completed these assessments.

ADOS-2 calibrated severity scores are pertinent for Modules 1 to 3 in children up to age 16 years; however, Module 3 was also administered to adults aged 18 to 55 years (n = 59). Module 3 was used instead of Module 4 in certain cases due to the delays typical of PWS and of the successful use of other ADOS-2 modules in severely delayed adults with intellectual disability (Sappok et al,

2013). ADOS-2 test guidelines suggest using modules that are well within examinee's abilities in order to minimize language as a confounding factor in social tasks. Importantly, ADOS-2 instructions allow clinicians to determine module fit based not only on age or language abilities, but also on the relevance of tasks to the examinee's interests and abilities. We found that young adults with PWS were compliant, interested in and responsive to the tasks involved in Module 3. Module 4 was used for one adult due to this individual's level of language use and comprehension.

Best estimate autism diagnoses were made with the research team and a clinical psychologist, all of whom had both clinical and research expertise in ASD and IDD, and were based upon videotapes and scores from the ADOS-2 as well as all other pertinent clinical data (Leckman, Sholokskas, Thompson, Belanger, & Weissman, 1982). These data included developmental, medical and family histories, and tests of current cognitive, adaptive and behavioral functioning. Disagreements concerning diagnoses were discussed until consensus was achieved.

The Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) is a 40-item parent report questionnaire that asks about multiple behaviours symptomatic of autism. Items are scored 0 or 1, with 1 indicating the presence of the symptom. The first item screens for language functioning and is not scored resulting in a total score ranging from 0 to 39. Nineteen items ask about current behaviour, while 20 items apply to when the adult was a child 4-5 years old. The SCQ is based upon the Autism Diagnostic Interview – Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), and has discriminated between ASD and non-ASD cases with a sensitivity index of 0.85 and a specificity of 0.75 (Berument, Rutter, Lord, Pickles, & Bailey, 1999). The recommended cut off score of $\geq$ 15 was used to maintain comparisons with existing literature.

Other Assessments: Demographic and other information, examined as possible correlates of ASD status, included: age, gender, PWS genetic subtype, and current employment status.

Measures of IQ and adaptive behavior were also used in order to better inform ASD diagnoses. Standard medical histories were obtained, with some modification of items pertinent to those with IDD.

The Kaufman Brief Intelligence Test-2 (KBIT-2; Kaufman & Kaufman 2004) was administered to each participant. The KBIT-2 is designed for research and screening purposes and has often been used for neurodevelopmental disability populations. The KBIT-2 provides standard scores (M = 100, SD = 15) for a Verbal, Nonverbal and overall IQ Composite score. The KBIT-2 has excellent test-retest reliability of the Composite (r = .90), Verbal (r =. 91) and Nonverbal IQ scores (r = .83).

The Vineland Adaptive Behavior Scales-II: (Sparrow, Cicchetti, & Balla., 2005) is a widely used, semi-structured interview that assesses adaptive functioning in an overall Adaptive Behavior Composite score and in three domains: Communication, Daily Living Skills and Socialization. The Vineland-II yields domain and composite standard scores (M = 100; SD = 15) that were used in analyses.

The Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) is a well validated parent report form assessing a variety of behavioral and emotional problems. The CBCL's questions are associated with problems on eight scales referred to as syndrome scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention problems, Rule-Breaking Behavior, and Aggressive Behavior. The CBCL calculates broad Internalizing and Externalizing and Total problem scores drawn from the syndrome scales. Consistent with previous studies in adults with IDD, raw scores were used in analyses. Additionally, select items were modified for adult use (e.g. Fears going to school *or work*).

The CBCL also provides Social, Activity, and School Competence scale scores. Due to the age range of participants in the study the School domain was not assessed. Information about the social activity of individuals was assessed at the item level instead of standard scores as comparison with the CBCL's normalization sample was not a goal of the study.

CHAPTER 3

Results

Autism Diagnoses

ADOS-2 and SCQ Classifications and Best-Estimate Diagnoses. Based on the SCQ cutoff point of ≥ 15, 8 (13.6%) adults in the sample were classified as having a possible ASD. Based on the ADOS-2 scoring criteria alone, 17 adults (28.4%) were classified as having ASD. After the clinical team reviewed ADOS-2 data and videotapes alongside developmental and medical histories, only 7 adults were diagnosed with ASD (11.7%) in the sample. Adults with clinician diagnoses of ASD are referred in future analyses as the PWS+ASD group. The majority of these adults were male (5 of 7) and of the mUPD genetic subtype (5 of 7).

As shown in Table 2, only three of the seventeen adults classified as having ASD on the ADOS-2 met cutoff criteria on the SCQ. Similarly, only three of the eight adults that met SCQ criteria were identified by the ADOS-2. None of the adults who met SCQ criteria were given a clinician diagnosis. Six of the seventeen adults that met diagnostic criteria on the ADOS-2 were given a clinician diagnosis. One adult did not meet either SCQ or ADOS-2 criteria and was given a clinician diagnosis of ASD.

Table 2: ASD Classification and Agreement Across Measures

Measures and ASD Classification (+/-)	N
SCQ (+) ADOS-2 (+) Clinician (+)	0
SCQ (+) ADOS-2 (+) Clinician (-)	3
SCQ (+) ADOS-2 (-) Clinician (+)	0
SCQ (+) ADOS-2 (-) Clinician (-)	5
SCQ (-) ADOS-2 (+) Clinician (+)	6

SCQ (-) ADOS-2 (+) Clinician (-)	11
SCQ (-) ADOS-2 (-) Clinician (+)	1
SCQ (-) ADOS-2 (-) Clinician (-)	34
Total	60

Between-Group Comparisons of PWS+ASD versus PWS Only

Power analysis for between-groups testing was done, indicating power to detect large effect sizes and as such results should be interpreted as exploratory in nature. Group comparisons revealed no significant differences between PWS and PWS+ASD groups in their adaptive functioning as measured by the Vineland Adaptive Behavior Scales or cognitive functioning measured by the KBIT-2. A follow-up MANCOVA controlling for age was done and was also nonsignificant. As shown in Table 3, the PWS+ASD group was lower in all domains (except Vineland Socialization domain) though not reaching significance. There were additionally no significant differences in either the externalizing or internalizing domains on the CBCL between those with or without ASD.

Table 3: Cognitive, Adaptive, and Behavioral Comparisons Between Diagnostic Groups

	PWS Only M (SD)	PWS + ASD M (SD)	t
Verbal IQ	68.4 (15.0)	67.1 (24.6)	.194
Nonverbal IQ	68.0 (19.4)	57.1 (24.1)	1.36
IQ Composite	64.6 (16.7)	61.1 (24.5)	.491
Communication	62.6 (23.6)	57.4 (25.6)	.541

Daily Living	57.6 (15.2)	52.8 (17.8)	.754
Socialization	59.5 (17.3)	65.0 (7.8)	-.760
Adaptive Behavior Composite	57.8 (16.7)	56.8 (14.0)	.137
Internalizing Problems	9.9 (6.8)	11.7 (3.3)	-.687
Externalizing Problems	13.8 (9.9)	20.0 (5.9)	-1.623
Total Problems	50.4 (18.0)	50.0 (17.0)	.027

Social Activities

As shown in Table 4, there were no significant differences between groups regarding school enrollment, employment, having close friends, and amount of social interaction with friends. The majority of the sample were no longer in school (62.5%). Fourteen adults (23% of total sample) were reported to be employed in some way or to volunteer work for an organization.

Table 4: Social Activities Across Diagnostic Groups

	PWS Only (Total N = 53) N (group%)	PWS + ASD (Total N = 7) N (group%)	Chi-Square
Attends school	15 (34.8)	3 (42.9)	0.844
Employed/Volunteers	14 (32.5)	0 (0)	2.294
Interacts with friends outside of school at least once a week	19 (44.2)	4 (57)	2.152
Has at least one close friend	36 (83.7)	3 (42.9)	0.773
Participates in at least one organization/club/group	38 (88.4)	4 (57)	0.369

Health Outcomes

There were no significant differences between groups in reported health outcomes. As a whole, adults in the sample reported problems in all domains assessed. As shown in Table 5, problems were most common concerning nutritional concerns (e.g. overweight), oral problems (e.g. restricted diet, cavities), musculoskeletal problems (e.g. muscle weakness, chronic lower back pain), psychiatric problems (e.g. depression, anxiety), infectious diseases (e.g. skin infection), and eye problems (e.g. stigmatism). Additionally, 70% of the sample reported healthcare visits for acute illness in the past two years (with 33.3% of the sample having over 3), and 36.7% reported visiting the emergency room at least once in that same time frame.

Table 5: Percentage of Participants showing Specific Health Concerns

Health Category	% Total Sample	% PWS Only	% PWS+ASD
Nutritional Concerns	81.7	79.2	100
Oral Problems	78.3	79.2	71.4
Musculoskeletal Problems	75.0	73.6	85.7
Infectious Disease	73.3	69.8	100
Eye Problems	70.0	67.9	85.7
Psychiatric Problems	50.0	47.2	71.4
Skin Problems	45.0	43.4	57.1
Endocrine Problems	41.7	37.7	71.4
Gastrointestinal Problems	40.0	37.7	57.1
Gynecological Problems (of females)	36.4	35.5	50

Neurologic Problems	15.0	15.1	14.3
Urinary/Kidney Problems	13.3	11.3	28.6
Audiologic Problems	8.3	9.4	0
Heart Problems	8.3	7.5	14.3
Blood Disease	5.0	3.8	14.3

CHAPTER 4

DISCUSSION

This study identifies the rate of ASD in a large number of adults with PWS using best-estimate diagnoses based upon standardized assessments and thorough clinical review. The study provides data on the cognitive and adaptive functioning of the PWS+ASD phenotype in adults across both gender and genetic subtypes. Beyond the presence of ASD diagnoses, the study also characterizes the understudied nature of adulthood in PWS.

Our best-estimate diagnoses revealed a 11.7% rate of ASD in the sample, a rate far below the 25-41% rates that have been reported in the literature. These findings are similar to the 12.3% rate found in children using a similar methodology (Dykens et al., 2017) and provide additional evidence to suggest the actual rate of PWS in ASD is within this range. There are several possible explanations for this lower rate. Past estimates of ASD in PWS that utilized screeners may have inflated the diagnostic rate in this population. These screeners may suffer from the impact of memory biases particularly so for adults whose early developmental histories are more difficult for caregivers to immediately recall (Hardt & Ruttter, 2004). What is not commonly reported in the literature is further follow up with direct observation from those adults who do screen positive to test whether an ASD diagnosis is truly appropriate. It is also possible in the current study that the clinical team were overly conservative in assigning ASD diagnoses to the sample. The eleven adults who reached diagnostic criteria on the ADOS-2 but did not receive clinical diagnoses reflects this possibility. However, it must be noted that it is inappropriate to assign an ASD diagnosis based upon an ADOS-2 score alone. While the ADOS-2 is a highly valuable clinical instrument it is meant to elicit observational experiences for trained clinicians to use with their judgment and expertise in assigning a diagnosis along with other pertinent medical or

developmental history (Gotham et al., 2007). Careful use of ADOS-2 data along with knowledge of PWS is essential when making diagnostic decisions for this population.

Closer inspection of the eleven adults who met ADOS-2 criteria but did not receive a diagnosis was done to better understand the similarities between PWS specific behaviors and those of ASD. These adults did not significantly differ from the clinician diagnosed group in their Social Affect Totals, Restricted and Repetitive Behavior Totals, or Severity Scores on the ADOS-2. However, the clinical team noted that four of these adults had clear social rigidity. Rigidity is known to be a common behavioral characteristic of PWS (Dykens & Roof, 2008) which may lead to poorer social interactions but is not equivalent to the social communication deficits in ASD. Additionally, four of the eleven adults were noted to have marked social interest despite having repetitive interests or questioning. Social motivation may also be an important difference in distinguishing PWS specific behavior from that of ASD. One individual's poor social interaction was better accounted for by another psychological disorder. Additionally, the one adult who received an ASD diagnosis but did not meet ADOS-2 criteria was noted to have significant difficulty understanding social cues. Additional research is needed to distinguish PWS from idiopathic ASD at both a behavioral and biological level as the current sample implies there are individuals who behaviorally may appear to have both conditions yet their behaviors are truly accounted for by PWS alone.

In our sample males were more likely to receive an ASD diagnosis than females, which is consistent with rates found in the general population. There is little research upon gender differences in ASD within PWS, as most research utilizing screeners have not reported results by gender. The results of the current study are consistent with those found in children with PWS (Dykens et al. 2017), indicating that gender may be an important factor for those with PWS, though

future research is needed to clarify gender influences. The majority of the ASD+PWS group also shared the mUPD genetic subtyping (5 out of 7; 71%). 35% of the whole mUPD sample were given an ASD diagnosis. Further study of this subtype and its relation to the autism spectrum is required and may provide insights into possible biological pathways for ASD. It may be possible, for example, that the mUPD subtype primarily drives the association of PWS with ASD and that genetic models of ASD using the 15q11-13 region should focus upon replicating the mechanisms behind mUPD. Conversely, it may also be possible that mUPD and ASD operate on separate biological pathways and that individuals with mUPD may be more likely to appear to behaviorally present with ASD due to intensification of PWS-specific behaviors that impair social functioning.

Compared to those with PWS alone, the PWS+ASD group did not significantly differ in terms of their cognitive or adaptive functioning. It was initially expected that the PWS+ASD group would have lower adaptive functioning levels, particularly so for the Socialization domain but this test was non-significant. This lack of a significant difference between the groups may be due to the small number of adults with ASD in the sample or potential floor effects as all group means were in the Low adaptive level. Additionally, the two groups did not differ in terms of externalizing or internalizing problem behaviors. In contrast, children with PWS+ASD were observed to have lower Verbal IQ scores and poorer daily living and socialization skills (Dykens et al., 2017). These findings may indicate that discrepancies between the two groups are reduced over time, or may reflect a lack of statistical power in the current study given the small number of adults in the combined PWS and ASD group. The between-group analyses in this study are exploratory in nature, however, to test for any large differences that may have been present. Therefore, interpretation of these results should be made cautiously. Future studies with greater PWS+ASD

samples are likely required to better compare the PWS and PWS+ASD phenotypes, though acquiring large samples of this type may be difficult in a rare disorder population.

The present data show that adults with PWS, with or without comorbid ASD, face significant health adversities, and is consistent with prior research (Butler et al., 2002). The weight gain that is commonly seen in PWS puts many adults at risk for a number of health related issues and in the current sample a variety of health problems were endorsed in the majority of the sample. In a population based study of 66 individuals with PWS, Butler et al (2002) reported high rates of diabetes, recurrent respiratory infections, fractures, sleep disorders, and scoliosis, among other health-related issues. The current sample displays health concerns in a broader array of categories and suggests that adults with PWS are likely to face a multitude of concerns across several different domains. The weight gain associated with hyperphagia increases risk for many chronic conditions and diseases and the hypotonia characteristic of PWS also increases risk for musculoskeletal and respiratory problems.

Additionally concerning is the high use of emergency rooms by the sample. Adults with IDD are known to use the emergency department more often than those without IDD (Lunsky et al., 2011). In a qualitative study of caregiver perspectives, several primary reasons for high emergency department (ED) use in IDD were offered. First, the presence of aggressive or severely challenging behavior pushed many families to utilize the ED for safety concerns. Such behavior is commonly associated with PWS. Secondly, many families utilized the emergency department as a last resort due to not being able to access other options in their community (Weiss, Lunksy, Gracey, Canrinus & Morris, 2009). Significant health and mental health disparities continue to exist for those with IDD as they experience high numbers of adverse conditions, as shown by the

current sample, and inadequate access and attention to their care (Dykens, 2016; Krahn, Hammond & Turner, 2006).

An additional challenge that adults with PWS face is a lack of social supports or activities in which they can engage. Inactivity has been shown to be a predictor of maladaptive behavioral and emotional outcomes (Dykens, 2007; Taylor & Hodapp, 2012). The majority of our sample (60%) were no longer in school, and a similar percentage of the sample were reported to do activities with friends less than one time a week. Adulthood should continue to be studied in PWS as it is possible that over time adults with less social support may have worsening social functioning that could appear symptomatic of an ASD even if they did not present so earlier in life. A minority of the sample were employed or otherwise engaged in volunteer work and none were able to live independently. Approximately a quarter of all adults with intellectual disabilities are able to achieve employment in some capacity (Yamaki & Fujiura, 2002; Taylor & Hodapp, 2012), a figure similar to the employment rate found in the current study. Studies of employment specific to PWS are rare and dated, but also suggest high unemployment rates for this population. For example, Greenswag (1987) surveyed 208 adults with PWS and found that only 3.9% of adults were employed by the government or private business, while 35.3% were unemployed. 45.7% adults in his sample received their vocational services in a sheltered workshop, while the remainder of the sample volunteered (2.6%) or worked only in the home (2.2%).

There are several factors beyond intellectual disability that make employment difficult for adults with PWS and may account for the low employment found in the current sample. Hyperphagia prevents most adults from being able to work in areas with unrestricted food access and necessitates constant supervision regarding food, a challenge for most employment settings. Additionally, the behavioral challenges common with PWS, such as irritability or

argumentativeness, make it difficult for some adults to work with others. When these issues are coupled, managing adults with PWS can be very challenging relative to people with other IDDs.

Our findings suggest several directions for adult PWS research. First, to reach precise estimates of ASD in this population, full diagnostic assessments should be utilized over any single measure. The eleven adults who met ADOS-2 specific criteria but did not receive a clinician diagnosis as well as the poor agreement between the individual ASD measures in this study exemplify the need for stringent assessment in this population. These assessments should involve direct observation from a trained clinical team and should be done in context of the adults' cognitive and functional ability and developmental history. This recommendation coincides with the recommendations of Moss and Howlin (2009) to consider ASD in genetic syndromes within the developmental context of those syndromes specifically.

The study has several strengths, which include a well-characterized sample of adults as well as multi-modal assessments done by trained clinicians who were experts in both PWS and ASD. However, there were notable limitations to the study as well. A greater number of adults are needed in further studies in order to detect potential age related effects on development and social functioning. Additionally, while assessments in adults were performed with both Module 3 and Module 4 of the ADOS-2, the current lack of severity algorithms for Module 4 limit the ability to compare subjects along ADOS-2 domains. When these algorithms are available, such data will allow for more detailed analysis of specific social deficits adults with PWS+ASD may display more than their PWS only counterparts. The use of Module 3 in adults may also be atypical, but does have precedent in previous research (Sappok et al., 2013). While originally intended for verbally fluent young children and adolescents, the presence of physical materials in Module 3

helped maintain adult attention in the sample during testing and results using the Module 3 were considered valid by the clinical team.

Additionally, we would recommend additional research upon interventions aimed at increasing social skills and activity for adults with PWS, both with and without comorbid ASD. Adults with IDD, especially those no longer socially connected to a school system, are at greater risk for isolation than children or adolescents. The current evidence base for adult intervention across either PWS, ASD, or IDD in general pales compared to child intervention efforts, and much work is needed in this area. The current study shows that employment is still a challenge for adults with PWS, indicating the increased need for effective job training programs for this population. Wadsworth, McBrien, & Harper (2003) outline several guidelines for rehabilitation professionals working with adults with PWS highlighting the need to maximize autonomy while balancing the inherent boundaries and supports needed to prevent harm. Use of basic social skills that are necessary for work environments can be a foundation of such vocational training. Volunteerism also allows for opportunities for social skills modeling and practice and should be encouraged for adults. The majority of adults (74%) in this sample endorsed participating in at least one organization, such as Best Buddies or Special Olympics. Finally, there are sizable health concerns for adults with PWS. Increased focus and attention to the healthcare needs and access of those with PWS and other forms of IDD are essential to establishing adequate healthcare in this vulnerable population.

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