SOCIAL ISOLATION AND LONELINESS IN PRADER-WILLI SYNDROME

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

PSYCHOLOGY

August 9, 2024

Nashville, Tennessee

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Introduction

Isolation and Loneliness in the General Population

Social isolation is a potent threat to survival for inherently social creatures. In mice, rats, pigs, and even fruit flies, social isolation is associated with a host of harmful effects that impact the development, health, or lifespan of the animal (Cacioppo & Hawkley, 2009). In humans, isolation both objective (i.e., having little or no contact with others) and subjective (i.e., loneliness) has been linked to depression, psychosis, substance abuse, obesity, earlier death and other negative health outcomes (Cacioppo & Cacioppo, 2014; Holt-Lunstad, Smith, Baker, Harris & Stephenson, 2015). Loneliness itself may be felt separate from objective isolation. For example, a person may have a large social network and still feel lonely, another may value objective isolation and have little contact with others without experiencing loneliness. Yet loneliness does appear to be part of a universal human experience shared across cultures and age groups (Barreto et al., 2021).

In the research literature, loneliness has been conceptualized as comprising two interrelated components related to threats to social bonds. On one hand, there is a cognitive component that comprises the discrepancy (in either quality or quantity) between one's desired social relationships and the actual social relationships one may have. On the other hand, there is also an affective component comprising the negative emotional experiences we typically associate with sadness and label as lonely (Rotenberg & Hymel, 1999). Different theorists weight these components differently according to their own viewpoint, but it is generally assumed that both components are

present. As previously mentioned, the subjective state of loneliness is separate from the objective degree of social isolation an individual experiences. While it may seem apparent that objective isolation would logically increase the chances that one would feel lonely, it is important to note that this is an assumption. Instead, isolation and loneliness should be considered separate constructs until shown otherwise for any given person or population.

As loneliness is a subjective construct, research has primarily relied on self-report questionnaires that tap key dimensions of loneliness. An example of such is the UCLA Loneliness Scale (Russell, 1996) which has been widely used to measure loneliness in adult populations. Loneliness in children, which at a time was thought nonexistent, has been successfully measured through targeted questionnaires such as the Children's Loneliness and Social Dissatisfaction Questionnaire (Asher, Hymel, & Renshaw, 1984). Studies using these quantitative measures helped disprove initial theoretical beliefs that children, supposedly reliant upon their parental attachment relationships, did not experience loneliness until adolescence when they struggle to manage and develop peer relationships. The quantitative measurement of loneliness in children helped advance theories of loneliness across the life course.

Loneliness may affect some populations more than others, depending on the amount of risk factors present in that population. For example, older individuals may be at particularly high risk because of the lack of structured social supports provided by employment, the absence of accessible family members, and losses of current relationships in their peer group. The impact of isolation and loneliness has been widely studied in older individuals, a vulnerable population where isolation corresponds to an average 29% increased risk for mortality (Holt-Lunstad et al., 2015). Metanalyses involving 35 separate studies and over 77,000 participants have found loneliness to be a risk factor for mortality in older citizens even after accounting for the effect of

comorbid depression (Rico-Uribe et al., 2018). There are, however, other populations that are also at increased risk for both isolation and loneliness.

Isolation and Loneliness in People with Intellectual Disabilities

Compared to research on older, aging individuals, there are considerably fewer studies of social isolation or loneliness in those with intellectual or developmental disabilities (IDD). Even so, this population is at high risk for both isolation and loneliness (Gilmore & Cuskelly, 2014). Intellectual disability affects about 1-2% of the population and is defined by three criteria. The first is the presence of significant deficits in intellectual functioning, which is assessed by cognitive testing scores that are more than two standard deviations below the normative mean. The second is the presence of significant deficits in adaptive functioning, or the ability to perform tasks required for personal and social self-sufficiency. The final criterion is that the onset of disability must occur during childhood, i.e. before age 18 (5th ed.; DSM-5; American Psychiatric Association, 2013). There are many possible etiologies for IDD, including prenatal, perinatal and post-natal causes, as well as variability in the degree of disability (i.e. mild, moderate, severe, profound) across the IDD population, with 85% of those with IDD falling into the mild range of impairment.

Regardless of severity, people with IDD are at risk for isolation and loneliness. Social networks are one way of objectively measuring social isolation. In research concerning IDD, social networks have been measured through detailed interviews such as the Social Network Map (Tracy & Abell, 1994; Robertson et al., 2001) that taps both the number and types of people in one's social network. The Social Network Map consists of two sections. In the first, the researcher measures the number of network members across a variety of life roles. In the second, each network member listed, up to fifteen, is rated on a Likert scale across a variety of criteria, such as the level of emotional support provided or how often they might see that person. As a quantitative analysis of the Social

Network Map shows, each subject may generate between 16 and 128 data points (Beckers, Koekkoek, Tiemens, & Hutschemaekers, 2020). The large amount of information that the Social Network Map provides per individual makes it cumbersome for quantitative studies. Additionally, statistical comparisons on the different qualities of social networks may be underpowered if networks are small in size.

More commonly used measures of social network size include the Social Support Self Report (Lunsky & Benson, 1997) or the Circle of Communication Partners (Blackstone & Hunt-Berg, 2003); both utilize briefer questionnaires to elicit data on an individual's social network. These questionnaires measure the number of people within a social network, mirroring the first step of the Social Network Map. The Circle of Communication Partners (CCP) is a clinical tool originally designed for use in augmentative and alternative communication practices that quantify the number of communication partners an individual has across five different areas of life. By assessing communication partners, the CCP is also in effect assessing social network members in a similar manner as the first part of the Social Network Map. In fact, the CCP has been used to measure and compare social network characteristics in school age children (Thirumanickam, Raghavendra, & Olsson, 2011). Common among any of the methods used to study social networks is a focus on network size as a primary outcome.

Isolation is marked by small and unstable social networks. Studies in IDD populations consistently report smaller network sizes than those found in typically developing individuals. Furthermore, the social networks of those with IDD are primarily made up of family, others with IDD, or service providers (Lippold & Burns, 2009; Robertson et al., 2001). In a comprehensive review of 23 studies on community participation in IDD, the average social network size was found to be 3.1, with at least one network member being a service provider (Verdonschot et al., 2009).

This review also found that leisure activities for those with IDD tend to be solitary or passive. Further, when engaged in community activities people with IDD are typically accompanied by a family member or service provider.

Prader-Willi Syndrome and Risk Factors for Isolation and Loneliness

Specific etiologies of IDD may also carry variable and unique risks for social isolation and loneliness. Prader-Willi Syndrome (PWS) is one such example. PWS is a neurodevelopmental disorder resulting from loss of function of paternally derived genes on chromosome 15q11-13. It typically results in mild to moderate intellectual disability, irritability, compulsivity, rigidity, social impairments, growth hormone deficiency, and excessive hunger or hyperphagia, which is a risk factor for 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. Finally, paternally inherited imprinting errors can also cause PWS and account for 1-3% of all cases (Cassidy, Schwartz, Miller, & Driscoll, 2012).

Individuals with PWS share the same risks for isolation and/or loneliness as the general IDD population. Yet they also have additional risks due to the nature of the syndrome and the additional stigma carried by common comorbid disorders. PWS carries increased risk for comorbidities with both autism spectrum disorder (ASD) and psychosis, both of which are independently associated with social isolation. Research using direct observation and gold standard assessment measures reveals that rates of ASD in PWS may be between 12-14% (Dykens et al., 2017; Fine et al., 2005),

a lower rate than previously thought based upon parent screener measures yet still elevated with respect to the general population. The majority of those meeting ASD criteria were of the mUPD genetic subtype. In addition to ASD, individuals with PWS (especially those with the mUPD subtype) have an increased likelihood of developing psychosis in young adulthood (Holland et al., 2003; Whittington & Holland, 2004).

Briefly, and as detailed below, hyperphagia (i.e. an increased hunger drive) creates intense preoccupations with food that make social interactions difficult for many. Obesity associated with hyperphagia also introduces an additional layer of stigma and there is a known bias for negative attitudes towards those who are overweight or obese (Puhl & Heuer, 2010). PWS is also associated with challenging behaviors as well as executive functioning impairments, each of which may also contribute risk for isolation and loneliness.

Hyperphagia is a chronic condition associated with PWS that creates lifelong stress for individuals with PWS and their families. Infants with PWS may have eating issues due to hypotonia (low muscle mass) but typically do not display signs of hyperphagia. Hyperphagia onsets in early childhood, typically between 4-8 years of age (Goldstone, Holland, Butler, & Whittington, 2012). Hyperphagia is associated with a lack of a normal satiety response leading to intense hunger, though the exact causal mechanisms are unknown. Families often must take behavioral precautions to secure food, including locking all sources of food such as refrigerators, pantries, and trash receptacles. Additionally, close and constant supervision is required around food. Hyperphagic individuals will often obsess over food, understandably so as they feel as if they are starving, yet this may lead to problematic behaviors such as repetitive questioning about food, manipulation to access food, theft of food, or food-seeking at night. While obesity related to the intense hunger has its own significant physical and mental health risks, hyperphagia is also a

risk factor for those with normal weight as there is increased risk of death from choking or gastric tearing from overeating (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007). As such, people with PWS are hyperphagic regardless of their weight, and while measurement of obesity through Body Mass Index (BMI) is certainly an important health indicator in this population, BMI is not a direct indicator of hyperphagia.

Hyperphagia may impact social functioning through several possible means. An increased desire for food, alongside a lack of a normal satiety response, may reduce one's ability to focus on social cues or behaviors from others. This notion is supported by a qualitative study of how people with PWS view themselves where hunger is described as overpowering and immensely distracting (Dykens, Roof, & Hunt-Hawkins, 2022). The desire for food may simply outweigh any desire to socialize or follow the complex social norms and rituals of social interaction. In typically developing individuals, hunger has been shown to have similar detrimental effects on maintaining attention to non-food related stimuli (Al-Shawaf, 2016). In this way hyperphagia may impact social skills by narrowing a person's ability to attend to pertinent cues in social interactions. In other words, it may be possible that hyperphagia is associated with impaired executive functioning skills important to social interaction. Hyperphagia is thus an important variable to consider when evaluating the relationship between loneliness and other constructs as well.

A common stressor for those with PWS and their families are social gatherings with food, which are most social gatherings as food is a common cultural means of bringing people together. For those with PWS however, the presence of food at, for example, a birthday party may be very distracting. The knowledge that there is food that may be accessible may be much more important to someone with PWS than talking with other people at the party. Families of those with PWS often must plan ahead of time how to approach such situations, or avoid them entirely, as these

situations may easily lead to emotional or behavioral dysregulation. It can be easy to see why such dysregulation may occur, it is a common occurrence for many to be more irritable or have less focus when hungry. Research in typically developing individuals shows that even mild-to-moderate hunger is associated with irritability, aggression, and anxiety (Al-Shawaf, 2016). Additionally, there is also evidence that hunger impairs processing of emotional stimuli, specifically the ability to discriminate between neutral and emotionally intense stimuli (Montagrin, Martins-Klein, Sander, & Mather, 2019). In this way even mild hunger can lead to hyperarousal in response to even neutral stimuli. Now instead imagine that it is not just the hunger from missing a meal or eating late, but instead a constant and intense hunger that may feel overwhelming. When denied the opportunity to feed that hunger, meltdowns can happen as is common in PWS. Thus, hyperphagia may also be important to understanding a potential relationship between executive functioning and behavioral dysregulation in PWS as well.

Behavioral issues in IDD are often studied under the umbrella term of challenging behavior, including issues such as aggression, self-injury, or destructive behavior (Emerson et al., 2001). Challenging behaviors have been conceptualized in IDD as independent behaviors but also as manifestations of comorbid psychopathology and emotional problems such as anxiety or depression (Emerson et al., 2001). Specific behaviors have been associated with the PWS behavioral phenotype, including behavioral rigidity, compulsivity, and insistence on sameness (Dykens, 1995). Children with PWS were found to have more internalizing behavioral problems than age and IQ-matched controls as measured by the Child Behavioral Checklist (CBCL), particularly for somatic, thought, and social problems (Skokauskas, Sweeny, Meehan, & Gallagher, 2012). Researchers using a separate measure, the Developmental Behavior Checklist, found that children with PWS were also much more likely to have severe temper tantrums,

stubbornness, and become distressed over small changes in their environment than matched controls as well (Einfeld, Smith, Durvasula, Florio, & Tonge, 1999). Behavioral and emotional dysfunction in PWS has been found to be more frequent and severe than behavioral issues in other developmental disorders such as Down syndrome or unspecified IDD (Dykens & Kasari, 1997). While much of the PWS behavioral research has focused on children, there is evidence to suggest that behavioral issues may increase with age, being highest in early adulthood (Dykens, Hodapp, Walsh, & Nash, 1992). This increase may possibly be linked with the transition period out of the formal education system (Dykens, 2004). Interestingly, the increase in maladaptive behavior over time may not occur as frequently in those with a Type 1 deletion (Dykens & Roof, 2008) suggesting potential subtype differences in the development of maladaptive behaviors.

To this point behavioral problems have been discussed as risk factors for isolation and loneliness. The relationship between these variables is likely bidirectional however as isolation and loneliness are themselves known risks for behavioral problems in IDD (Griffiths & Gardner, 2002). The exact mechanisms connecting isolation or loneliness to behavioral problems in IDD are unclear. One study found that early externalizing problems, alongside negative family environments, did predict later reported loneliness in children with disabilities (Howell, Hauser-Cram, Kersh, & Floyd, 2007). This finding would suggest that those children with the most prevalent behavioral issues may be more likely to experience loneliness as they grow older and have difficulties forming interpersonal relationships. Interpersonal stress is often reported to be among the most distressing problems reported by individuals with IDD (Lunsky & Bramston, 2006). When interpersonal stressors arise, challenging behavior itself may be a maladaptive response to stress including dangerous adaptations such as suicidality (Lunksy, 2004). Isolation and loneliness may serve to increase the likelihood of interpersonal stress and subsequent

dysregulation in PWS and other IDDs by creating negative social experiences that then increase the risk for further isolation or loneliness.

Executive functioning includes the set of abilities related to planning, self-monitoring, and purposive action and involves multiple cognitive processes such as attention, working memory, shifting, and response inhibition, among others (Willner, Bailey, Parry, & Dymond, 2010). Executive functioning is also related to the ability to control behavior and emotion. In a social setting, executive functioning is necessary to attend to social cues, retain social information, and respond to a complex and dynamic social environment that may include emotional or physical stressors. Deficits in executive functioning therefore may relate to challenging behavior in PWS and in turn to the experience of loneliness. For example, behavioral rigidity and an insistence on sameness is a common observation for PWS. These traits represent an impairment in a key component of executive functioning known as shifting, or the ability to move from one situation or perspective to another as the circumstances demand. If a person with PWS cannot shift their attention and insist interactions occur in a certain way, they are likely to create social tension in their environment. Additionally, these situations can often lead to anxiety and distress associated with challenging behaviors in response the distress. The negativity of these interactions may make others less likely to interact with the person with PWS, increasing possible social isolation and increasing their chances of loneliness.

In PWS, executive functioning abilities have been studied using multiple neuropsychological tests and measures specific to executive functioning. The majority of these studies suggest impaired executive functioning abilities in PWS (Woodcock, Oliver, & Humphreys, 2009a; Juaregi et al., 2007; Chevalère, Postal, Jauregui, Copet, Laurier, & Thuilleaux, 2013; Hutchison et al., 2015; Walley & Donaldson, 2005). It is difficult to determine the exact nature of executive

functioning impairment in PWS as different studies use different instruments and comparison samples, and are often too underpowered to differentiate between the genetic subtypes of PWS. That said, several studies have found task-shifting impairments in PWS. Task shifting, or task switching, refers to changing from responding to stimuli based on one set of criteria to responding to the same set of stimuli based on another set of criteria. For example, in a research study participants may be asked to select a word from a set of words based first on word length, and then be tasked to select a word from a set of words based on part of speech. In vivo, shifting occurs all the time as we must cognitively adapt to changing environmental demands.

Woodcock, Oliver, & Humphreys (2009a) compared executive functioning abilities including task shifting across PWS, fragile X syndrome, and typically developing children. Both the PWS and fragile X groups showed broad executive functioning impairments compared to typically developing children; however, when controlled for cognitive ability task shifting impairment was unique to the PWS children. In a separate study, Chevalère et al. (2015) also found shifting impairments in adults with PWS in comparison to healthy controls. In this study, the shifting impairment was the only executive function impairment that persisted when controlled for cognitive ability. Taken together, these findings suggest a deficit in task shifting in PWS.

Additional support for this theory was found in single-case experiments of individuals with PWS that also provided preliminary evidence of a connection between shifting impairments, environmental change, and behavioral outbursts. Woodcock, Oliver and Humphrey (2009b) proposed a model to demonstrate how a task shifting impairment may connect the PWS genotype to the dysregulated behavior characteristic of the PWS phenotype. In essence, an environmental change (such as a change in routine) would force those with PWS to switch to a different way of thinking about the stimuli around them, taxing their task shifting ability. If there is a shifting

impairment present, as research would suggest, then overly demanding tasks or changes may cause distress resulting in anxiety or temper outbursts, i.e., behavioral and emotional dysregulation. While the exact relationship between isolation or loneliness and executive functioning is untested in PWS, dysregulation that manifests as tantrums, aggression, and an insistence on sameness may lead to eventual feelings of loneliness or social isolation.

Although there is compelling evidence for a task shifting impairment in PWS, it is important to note that other executive functioning impairments have been found as well. Chevalère et al. (2013) found broad executive functioning impairments in their sample, with those of the mUPD subtype demonstrating worse shifting and planning abilities. Juaregi et al. (2007) also found impairment across all measured executive functions, while Hutchison et al. (2015) found clinical impairment across all executive functions except initiation and organization of materials. While Woodcock and colleagues (2011) provide a rationale connecting executive functioning impairment to dysregulation, none of the existing research into executive functioning in PWS has tried to connect executive functioning with loneliness or isolation. Thus, at this time examination of a broader scope of global executive functioning is warranted in PWS. If a global executive functioning impairment is noted, then the role of task shifting individually may be of particular interest.

Environmental Risk Factors for Isolation and Loneliness

Those with PWS and IDD as a whole face additional risk factors for isolation and loneliness that go beyond the phenotypes associated with their disability. The social networks for some with IDD are often related to their residential status. Adults with IDD typically require some level of sustained care, often provided by family or through residential settings such as group homes. In a study of 500 adults with IDD in varying levels of residential care, Robertson et al. (2001) found

that the median social network size, excluding staff, was just two. Only a third of the sample reported to know someone who was not a staff member, family member, or another adult with IDD. A separate study reported similar social network characteristics, with staff members and service providers being the main sources of emotional support. This study also importantly found that these relationships were more likely to be non-reciprocal in nature (Forrester-Jones et al., 2006).

Those who leave residential settings or are deinstitutionalized into the community may not fare much better. In a longitudinal study of middle-aged adults who moved out of institutionalized care Bigby (2008) found that in the following five years new relationships were infrequent, that family contact decreased over time, and that over half of adults lost regular social contact with anyone outside of the service system. Most adults with IDD, however, do not live in residential settings and instead reside at home with their families. While over time some individuals adopt members from their parents' or siblings' social networks, it takes significant effort to prevent network loss. In summary, regardless of where they live, people with IDD tend to have smaller and less diverse social networks, placing them at increased risk for isolation.

People with IDD are uniquely challenged to form strong social networks, more so than other disability types. Lippold & Burns (2009) contrasted the networks of those with IDDs versus physical disabilities (PD). Despite having participated in fewer activities than the IDD group , the PD group had broader networks and greater levels of social support. Additionally, the PD group was more likely to have networks that included both disabled and non-disabled people. Those with IDD were more likely to have social networks that consisted primarily of others with disability. While any expansion of social network size may be positive, educational research has strongly

suggested that more inclusive environments that do not segregate those with disabilities into their own social groups have the best outcomes (Idol, 2006).

Aside from reduced network size, social isolation in IDD is related to risk factors including school transition and unemployment. Employment of any kind is a struggle for many with IDD to achieve (Taylor & Hodapp, 2012) leading to a loss of opportunity to create social connections and practice various social skills in a workplace. Competitive employment, or employment similar to typically developing peers, is uncommon and found in only 18% of those with IDD in the United States (Siperstein, Parker, & Drascher, 2013). Globally, rates of unemployment are significantly higher in the IDD population than average, typically being approximately fifty percent higher than the general unemployment rate. In some developing countries however, unemployment is an overwhelming problem with up to 80% of individuals with IDD being unemployed (Groce, 2004).

The lack of competitive or other employment opportunities is a serious risk factor for the IDD population as the workplace is often a source of opportunities to expand one's social network, both on and off the job. Jobs may bring about feelings of efficacy and agency in the world along with improved self-esteem that might protect from mental health concerns (Evans & Repper, 2000). Outside of paid employment volunteerism is also an option available to some which may also provide these positive benefits. While some research has been done regarding volunteerism in IDD further studies are needed to determine if volunteerism may lead to later employment, and to identify specific benefits of volunteerism (Trembath, Balandin, Stancliffe, & Togher, 2010).

A period of risk for isolation in IDD occurs during the transition out of the educational system. At this time systematic supports that were once relied upon may be withdrawn leaving families to support their adult children's social networks alone. Families must navigate new adult services that, unlike schools, do not have a singular central location where services are provided. With few

outside resources to help provide structure or support, youth are left at risk of being at home doing nothing (Taylor & Hodapp, 2012). This transition period has been associated with increased feelings of loneliness in IDD (Beresford, 2004). Several factors may underlie this association. The focus of transition services provided to young adults with disability may be one issue. Special education law in the United States requires that students aged 14-16 have an official transition plan created for them. These plans tend to focus on employment goals or job training programs. Transition services have been found to play little to no attention to the social needs of disabled young adults, despite these needs often being regarded as important by the individuals themselves (Beresford, 2004). Additionally, low expectations from the young adults as well as the family and staff working with them also limit the possible impact of transition services. In a longitudinal study of children with disabilities (Carter, Austin, & Trainor, 2012), the expectations of family members were found to be strong predictors of employment after high school. The transition to adult services is often difficult for individuals and their families, making older adolescents and young adults an important demographic to consider when measuring isolation and loneliness.

A Model for Understanding Loneliness in PWS

Previous loneliness research has identified models based on the typically developing population to better understand the causes of loneliness, yet these models may not fit the PWS or IDD populations. For example, isolation and loneliness have been theorized to reinforce further isolation and loneliness in a positive feedback loop (Cacioppo & Cacioppo, 2014). In the typically developing population, the social pain of loneliness is thought to induce hypervigilance for social threats. This hypervigilance produces cognitive biases to perceive the environment as more threatening than it might be in reality. These cognitions in turn increase the chance for unpleasant behavior that confirms the existence of social threats, resulting in negative social experiences and

further feelings of isolation and loneliness. While the self-reinforcing nature of isolation may also be observed in IDD, the underlying processes may be different for those with IDD and PWS. There is little evidence for hypervigilance for social threat in PWS or in others with IDD. Emotion recognition studies typically do not find a bias to attribute negative affect to neutral social stimuli, such as faces. Instead, emotion recognition research often finds that the ability to differentiate negative affects is impaired in PWS and other forms of IDD (Dykens et al., 2019; Moore, 2001).

Given the lack of existing frameworks for understanding loneliness in IDD or PWS, I am presenting a model to understand loneliness specifically within PWS. The proposed theoretical model (Figure 1) illustrates how symptoms of PWS may be related to experiences of loneliness and isolation. In addition to the genetic abnormalities that define PWS, there is a behavioral phenotype unique to the syndrome. While phenotypes refer to the observable expression of a genotype, behavioral phenotypes refer to the increased likelihood that people with a genetic syndrome will display certain behavioral or developmental features relative to those without the syndrome. Behavioral phenotypes can include characteristic patterns of behavior, personality, cognition, development, psychiatric disorders, and personality traits that help define a syndrome beyond the specific genetic differences that, alongside environmental factors, may cause them (Dykens, 1995; Cassidy & Morris, 2002). As mentioned, PWS is associated with behavioral traits such as aggression and personality traits like rigidity and compulsivity seen in 70-90% of individuals (Cassidy & Driscoll, 2009). In addition to intellectual disability PWS is also associated with cognitive deficits in areas of executive functioning, emotion regulation, and social cognition (Dykens et al., 2019; Whittington & Holland, 2017). These patterns of impairment all contribute to poor social development and poor execution of social skills that are necessary for successful social functioning.

Poor social skill development in PWS may lead to behavioral and emotional dysregulation when interacting with others. Many of the phenotypic features of PWS, hyperphagia especially, likely increase the risk for emotional and behavioral dysregulation leading to a heightened risk for negative social experiences. To put these concepts together, take for example the scenario of a parent taking their child with PWS to a grocery store to do routine shopping. Hyperphagia leads to a preoccupation with food that especially in a grocery store can be overwhelming. When the parent places demands on the child for how to behave, this may lead to anger or frustration from the child. This anger can be outwardly expressed through a tantrum that is noticed by others in the store creating a negative social experience. These negative experiences can in turn lead to increased risk for isolation and experiences of rejection for the individual that may manifest into loneliness. Furthermore, feelings of loneliness may in turn promote more loneliness by leading to a maladaptive withdrawal from social settings to distance oneself from the pain of loneliness. Such withdrawal reduces opportunities for social interaction, possibly limiting social networks, and thereby further impairs social skills leading to a repetition of the cycle.

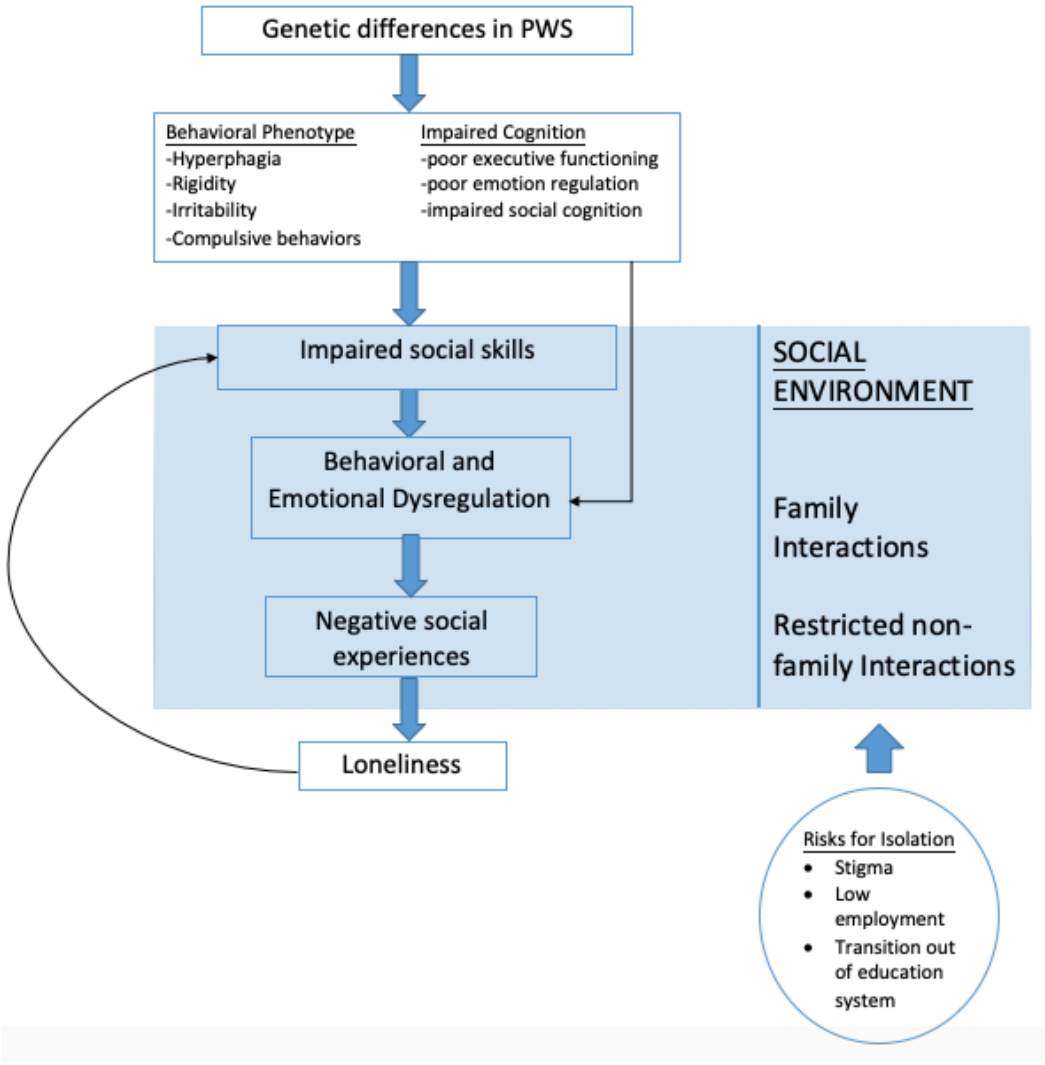

Figure 1**:** A proposed model of loneliness in PWS. The genetic differences inherent to PWS result in a behavioral and cognitive phenotype that prime individuals for dysregulation and impaired social skills development. When in interaction with the social environment, impaired social skills in turn result in increased risk for dysregulation which is associated with negative social experiences. These negative experiences increase the likelihood of loneliness, which may perpetuate itself by either leading to social withdrawal or a repetition of a negative social experience. Additionally, the social environment for those with PWS is weighted towards more family than non-family interactions due to variant risks for social isolation in PWS.

The following study will explore features within Figure 1. There are several promising factors to study in PWS within this model. If this model is accurate, we would expect many of these factors to be related to loneliness and one another. The proposed study aims to test and evaluate those relationships specifically highlighting the roles of hyperphagia, executive functioning, and behavioral and emotional dysregulation. These variables were chosen due to their previous study in PWS as well as due to their theoretical relationship with loneliness. Many previous studies have described the behavioral phenotype of PWS, yet this study would be the first to relate phenotypic features such as hyperphagia to isolation and loneliness.

There is virtually no loneliness research specific to PWS. Current research does support the notion that those with IDD experience both significant isolation and loneliness (Alexandra, Angela, & Ali, 2018; McVilly, Stancliffe, Parmenter, & Burton-Smith, 2006) and, therefore, there is reason to believe both may be present in PWS as well. The present study aims to characterize the degree of isolation and loneliness in PWS as well as possible predictors of loneliness in this population as proposed through the aforementioned model. The PWS phenotype has been well described in the literature yet features of the syndrome have not yet been well studied in relation to social characteristics like isolation and loneliness.

This study examines key features of the phenotype, including levels of emotional and behavioral problems, hyperphagia, and executive functioning in relation to isolation and loneliness. In this study social isolation is measured from a caregiver perspective while loneliness is measured from self-report. Self-report measurement of loneliness is important as it provides information on the subjective social reality of those with PWS. Previous research supports the notion that these subjective feelings are more closely related to negative health outcomes than objective isolation itself, making it is essential to provide accurate information on this feeling state

within PWS and to compare it with measures of objective social isolation. Given that transition out of the formal education system is a possible risk factor for social isolation and loneliness, and that the negative effects of loneliness have been most studied in older adults, a broad range of ages will be studied. Both adolescents who have not yet transitioned out of the education system and adults of all ages with PWS will be studied.

Hypotheses

In the study, the following hypotheses will be evaluated:

Hypothesis 1: Measures of social isolation and loneliness will be significantly correlated, where greater levels of isolation relate to greater levels of loneliness. Due to additional syndrome specific risk factors, loneliness in the present PWS sample will be reported at a greater level than in a literature-based comparison sample of individuals with IDD.

Hypothesis 2: Given the lack of gender differences in previous PWS research, isolation and loneliness will not be related to gender. As people with the mUPD versus paternal deletion genetic subtypes are more susceptible to ASD and psychosis, they are likely to have higher levels of social isolation and loneliness than their genetic subtype counterparts. Reported levels of loneliness will positively correlate with reported levels of hyperphagia and problem behaviors while negatively correlating with executive functioning scores.

Hypothesis 3: As reported by parents, the largest social network circle within the CCP will consist of family members as individuals with PWS carry significant risk factors for isolation and may struggle to form larger and more diverse social networks. Those still attending school will report larger social network sizes than those who do not attend school. Adults with PWS will have greater

levels of isolation and loneliness than younger participants as they no longer have the social network support from school systems. Those who are unemployed or inactive are likely to have higher levels of social isolation and loneliness than those who are employed or otherwise active in settings which may provide additional social support.

Hypothesis 4: Pending upon the correlations purported in Hypothesis 2, the following relationships may be further explored. Executive functioning, emotional and behavioral problems, and levels of hyperphagia will each predict the degree of social isolation present as they contribute additional risk for social withdrawal for people with PWS. Executive functioning, emotional and behavioral problems, and levels of hyperphagia will also each predict reported loneliness scores.

Chapter II

Methods

Participants

This study utilized an online questionnaire that was completed by caregivers (n = 46) of those with PWS and by those with PWS themselves (n = 34). Participants were included in the study if they spoke English and if the individual with PWS was age 12 or older. No other specific exclusion criteria were used. Participants were recruited through online advertising from national PWS research organizations including the Prader-Willi Syndrome Association USA (PWSA-USA) and the Foundation for Prader-Willi Research (FPWR), as well as direct recruitment from local families with PWS who have previously participated in research at Vanderbilt University Medical Center (VUMC).

As summarized in Table 1, participants with PWS (37% females, 54% males) ranged in age from 12 to 43 years (M = 19.74, SD = 8.39). Genetic subtypes were available for all participants, and consistent with the literature, most had paternal deletions. Most of the sample was White (78%) with 67.4% of the sample still enrolled in an educational system.

This study was approved by the VUMC Institutional Review Board, Integrated Science Committee. All caregivers provided informed consent using the e-consent function of the secure, online platform, REDCap (Harris et al., 2019). After consenting, participants were invited to complete the surveys. All individuals with PWS provided electronic informed assent through the same means.

Measures

Demographics

A demographics questionnaire gathered information regarding the age, gender, race, genetic subtype, employment/volunteering status, current height, and current weight of the individual with PWS. Height and weight were used to calculate body mass index (BMI), which is commonly used as a descriptor of participants in PWS studies. Employment/volunteering status were selected as either: full employment (≥30 hours per week), part-time employment (<30 hours per week), participation in a day program, volunteering, member of a job-training program, other, or none. Additionally, parents/caregivers were asked if their child is currently in a formal education system and if not, how many years they have been out of school, and if they lived at home with them.

Table 1: Demographic Information

Gender (%)	Number, %
Male	25 (54)
Female	17 (37)
Prefer not to say	4 (8.7)
Race (%)	
American Indian	1 (2.2)
Asian	2 (4.3)
Black/AA	3 (6.5)
Hispanic	3 (6.5)
Hawaiian/Pacific Islander	1 (2.2)
Southeast Asian	1 (2.2)
White/Caucasian	36 (78.3)
Genetic Subtype (%)	
UPD	16 (34.8)
Type 1 Deletion	19 (41.3)
Type 2 Deletion	8 (17.4)
Other	3 (6.5)
Employment Status (%)	
Full Employment	2 (4.3)
Part time Employment	4 (8.7)
Participation in a day program	4 (8.7)
Volunteering	3 (6.5)
Job-training program	7 (15.2)
Other	7 (15.2)

None	22 (47.8)
Attends School (%)	29 (67.4)
Mean Years out of School (± SD)	5.52 ± 6.35
Living At Home (%)	45 (97.8)
Mean Age (± SD)	19.74 ± 8.39
Mean BMI (± SD)	30.32 ± 16.15

Social Support Measures: Circle of Communication Partners

The Circle of Communication Partners (CCP) task is a measure that has been used in disability populations (Blackstone & Hunt-berg, 2003) to acquire a contemporary snapshot of an individual's social network. It uses a visual aid to guide informants to list the members of their children's social network. Parents or caregivers were asked to list individuals across a set of different roles that exist within five circles (Figure 2), specifically: 1) lifelong partners, such as family and close relatives living with the individual 2) good friends and other close family not living with the individual 3) acquaintances such as classmates or neighbors, 4) paid workers or staff, and finally 5) groups of unfamiliar partners they may interact with such as store clerks.

The primary outcome measure of the CCP was the total number of individuals listed across these five groups. Caregivers were not limited to a specific time frame for who their child may interact with, and instead were encouraged to list all individuals within each category who may be a part of their social network. This method mirrored how the CCP and other measures of social network size have been used in research. Caregivers were asked to specify if interactions take place primarily in-person, online, or both. For the persons listed, parents/caregivers were asked to identify how many of these individuals also have a disability.

Benefits of the CCP include its accessibility and history of use in disability populations. Several studies have made use of the CCP to gather information on social network size and characteristics. The CCP has been used across a variety of populations including those with

complex communication needs and those with profound IDD or multiple disabilities (Thirumanikam, Raghavendra, & Olsson, 2011; Wilder & Granlund, 2015). Vickers (2009) utilized the CCP to measure social network characteristics in a group of adults with aphasia. One drawback to the CCP is that, beyond size, it does not provide additional social network metrics such as network density or measurement of the quality of relationships listed beyond circle category. It is important to note, however, that the quality of interactions is not typically measured in social network research in the IDD field, and that many studies instead rely on network size.

In addition to descriptive analyses, the CCP has been used in comparative analyses to determine differences in the number of partners between the different circles, between different groups, or between different raters. For example, the CCP has been used to assess social network differences between children with complex communication needs, children with physical disabilities, and typically developing children (Raghavendra, Olsson, Sampson, Mcinerney, & Connell, 2012). The CCP has also been used to assess the effects of interventions aiming to increase social network size (Raghavendra, Grace, Newman, Wood, & Connell, 2013).

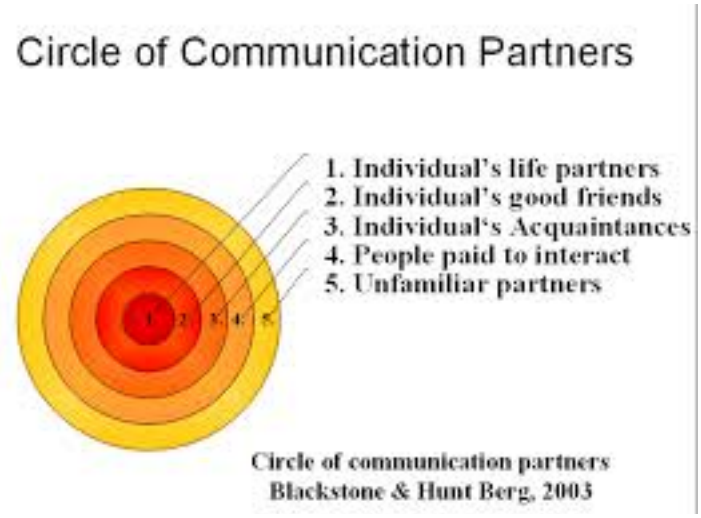

Figure 2: An illustration of the CCP measure that describes the five levels of communication partners that may be found within a social network.

The CCP provides a snapshot of the objective social lives of those with PWS and contrasts with the subjective feelings of social isolation, i.e. loneliness, that will be measured separately. It is important to measure isolation and loneliness separately, as the two constructs do not necessarily or inherently co-occur. Further, as the first study to examine social isolation and loneliness in PWS, separate measurements of these constructs are needed to determine if they are associated with one another or are separately related to such other variables of interest such as hyperphagia or problem behaviors.

Modified Children's Loneliness and Social Dissatisfaction Questionnaire

The study utilized a modified form of Asher, Hymel, & Renshaw's (1984) Children's Loneliness and Social Dissatisfaction Scale. McVilly, Stancliffe, Parmenter, & Burton-Smith (2006) successfully administered an adapted version of the Children's Loneliness and Social Dissatisfaction Scale to 51 adults with IDD. The original scale consists of 24 items and is validated for children ages 8-12 years. Sixteen items focus on primary aspects of loneliness while the remaining eight items act as filler items about hobbies and activities to incentivize more honest responses to the core 16 items and to detect for response biases. The adaptation for IDD involved restating items into the first-person (e.g., 'I have friends' instead of "Do you have friends?") and adapting the three-point rating scale (i.e., Yes, No, Sometimes) into a five-point rating scale (i.e., Never, Rarely, Sometimes, Usually, and Always) to increase possible variability. Finally, adults with IDD responded using a visual analog represented by ticks instead of providing verbal or written responses. The adapted scale is scored by adding the values of all responses (with some items requiring reverse scoring before addition) to create a total loneliness score that ranges from 0 to 64. Higher scores indicate higher levels of loneliness.

In the current study, individuals with PWS completed the adapted questionnaire stated in the first-person. Each question was given one at a time and was presented both visually and with REDCap's audio functionality. After viewing and listening to the prompt, participants were asked "How often does this sound like you?" and responded by clicking upon the best option.

Child Behavior Checklist

The Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) is a well validated parent/caregiver measure that assesses specific behavioral and emotional problems across 113 items rated on a 3-point Likert scale (0= absent, 1= occurs sometimes, 2= occurs often). It has been widely used to study both PWS and other IDD populations. The CBCL calculates broad Internalizing and Externalizing domains, derived from 5 psychometrically robust subdomains: Internalizing (consisting of Anxious/Depressed, Withdrawn, Somatic Complaints subdomains) ; Externalizing (Delinquent/Rule-Breaking Behavior, and Aggressive Behavior subdomains). The CBCL also contains three additional subdomains Social Problems, Thought Problems, Attention Problems. To reduce administrative time burden for participants, however, only items pertinent to the Internalizing or Externalizing Domain scores were administered. As well, three items were slightly modified to be inclusive of both children and adults (e.g. Fears going to school *or work*). One CBCL item checks for "Loneliness" as a problem and is counted within the Anxious/Depressed subscale.

Consistent with previous studies involving adults with IDD (and with previous permission from Achenbach), raw scores were used in analyses. Raw scores are preferred to scaled scores because of the potential floor effects that come with making comparisons to chronological age matched groups.

Hyperphagia Questionnaire for Clinical Trials

The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is a 9-item caregiver report questionnaire developed to assess and quantify the drive for food in Prader-Willi Syndrome (Dykens et al., 2007; Fehnel et al., 2015). The measure was developed and evaluated in over 270 families affected by PWS and included a wide variety of ages. The HQ-CT has been used as a primary outcome measure in multiple clinical trials aimed at attenuating hyperphagia. Factor analyses show that two robust factors comprised the measure: Hyperphagic Drive/Severity, and Self-Directed Hyperphagic Behaviors. The HQ-CT also produces a total score which was used as in analyses.

Executive Functioning Measures

Two versions of the Behavior Rating Inventory of Executive Functioning (BRIEF) were used: the Behavior Rating Inventory of Executive Functioning, Second Edition (BRIEF-2) and the Behavior Rating Inventory of Executive Functioning, Adult Version (BRIEF-A). Two measures were chosen to reflect the broad age range of the desired sample which spans multiple developmental periods. Both questionnaires are designed to generate comprehensive profiles on executive functioning and have been used in a variety of developmental disorders, including Down syndrome, fragile X syndrome, and PWS.

The BRIEF-2 and BRIEF-A questionnaires provide a profile for executive functioning can serve as a measure of possible impairment within the syndrome. Table 2 illustrates the conceptual overlap between the BRIEF-2 and BRIEF-A. Importantly, both measures contain the same clinical scales, and both include a summary score.

Table 2: Comparison of BRIEF-2 and BRIEF-A Measures

Measure	BRIEF-2	BRIEF-A

Index Scores • Clinical Scales	Behavioral Regulation Index (BRI) • Inhibition • Self-monitor Emotion Regulation Index (ERI) • Shift • Emotional Control Cognitive Regulation Index (CRI) • Initiate • Working Memory • Plan and Organize • Organization of Materials • Task Monitor	Behavioral Regulation Index (BRI-A) • Inhibit • Shift • Emotional Control • Self-monitor Metacognition Index (MI) • Initiate • Working Memory • Plan and Organize • Task Monitor • Organization of Materials
Summary Score	Global Executive Composite (GEC)	Global Executive Composite (GEC)

Table 2: A comparison of the BRIEF-2 and BRIEF-A scoring scales. Both tests share the same nine clinical scales and utilize an overall composite score (GEC). The BRIEF-A generates a Behavioral Regulation Index (BRI-A) that is a composite of the BRI and ERI of the BRIEF-2. The CRI of the BRIEF-2 and MI of the BRIEF-A are comprised of the same scales.

Behavior Rating Inventory of Executive Functioning, Second Edition (BRIEF-2)

The BRIEF-2 is a rating scale designed for individuals between the ages of 5 and 18. The parent version consists of 63 items across nine clinical scales (Gioia, Isquith, Guy, & Kenworthy, 2015). Two scales comprise the behavioral regulation index (BRI): inhibition (ability to not act on

an impulse), and self-monitor (keeping track of the effect of behavior on others). Two scales comprise the emotion regulation index (ERI): shift (ability to change freely from one situation, activity, or thought to another as the situation requires), and emotional control (ability to regulate emotions). Five scales comprise the cognitive regulation index (CRI): initiate (ability to self-start tasks or problem solve on one's own), working memory (hold information in mind to complete a task), plan and organize (plan and manage current and future task demands), organization of materials (ability to organize work, play space, etc.), and task monitor (ability to monitor own work). The BRI, ERI, and CRI combine to form the global executive composite (GEC), a composite measure of all subscales. As caregivers completed this measure, the parent rating from was used. As with the CBCL, total raw scores were used as the primary outcome for the BRIEF-2.

Behavior Rating Inventory of Executive Functioning—Adult Version (BRIEF-A)

The BRIEF-A is a rating scale developed for individuals between the ages of 18 and 90. Both the informant and self-report measures include 75 items across nine clinical scales that comprise two index scores (Roth et al., 2013). The BRI is comprised of the inhibit, shift, emotional control, and self-monitor scales. In this way the BRIEF-A BRI is similar to a combination of the BRIEF-2's BRI and ERI index scales and may be referred to as Behavioral Regulation Index-Adult (BRI-A). The BRIEF-A also has a Metacognition Index score (MI) made of the initiate, working memory, plan and organize, task monitor, and organization of materials subscales. In this way the MI is comparable to the CRI of the BRIEF-2 as they are made of the exact same subscales. Also, similarly to the BRIEF-2, the BRIEF-A generates a GEC that is a summary score of all clinical scales. As caretakers completed the measure for this study the informant report version was used. Total raw scores were used as the primary outcome for the BRIEF-A.

Statistical Approach, Analyses

Descriptive analyses were run on all variables assessing for completeness, outliers, and normality. Missing data were scant and replaced via mean imputation. Outliers were identified on the CCP and loneliness measures and removed from analyses as needed. Skewed data were transformed via logarithmic transformation to reduce skewness.

Hypothesis 1: I have previously hypothesized that measures of social network size and loneliness would significantly correlate with one another. Pearson's correlation was calculated between scores on the CCP and Loneliness Scale. I have also hypothesized that loneliness would be higher in the present sample than in a literature-based control. An independent samples t-test was conducted comparing mean scores on the Loneliness Scale between the present sample and those scores reported in McVilly et al. (2006).

Hypothesis 2: As previously noted, I hypothesized that there will be no gender differences in scores on either the CCP or Loneliness Scale. I also hypothesized that those with mUPD (versus deletion) subtypes will have higher levels of isolation and loneliness. Furthermore I hypothesized that measures of loneliness and isolation will relate to measures of hyperphagia, problematic behavior, and executive functioning. Independent samples t-tests were conducted to assess differences in loneliness or social isolation across gender and genetic subtype. Pearson's correlations were conducted among the scores on the CCP, Loneliness Scale, CBCL, BRIEF-A, BRIEF-2, and HQ-CT.

Hypothesis 3: As described above, I predicted that the largest social network circle within the CCP will consist of family members. Frequencies of social network size within each circle were reported and compared with one another via within subjects repeated measures ANOVA. I also hypothesized that adults (versus younger participants) will have higher levels of isolation and loneliness, as will adults who are unenrolled in school or without employment or involvement in structured activities. Pearson's correlations were conducted to examine the relationship between age and the total loneliness and CCP scores. Independent samples t-tests assessed differences across education status in the number of people listed within each circle of the CCP, total CCP, and in reported loneliness scores. ANOVA assessed differences among categories of employment status.

Hypothesis 4: I have hypothesized that the CBCL, BRIEF, and HQ-CT scores would each predict levels of social isolation and loneliness. Variables that were significantly associated with CCP or Loneliness scores were entered into separate linear regression analyses to assess their unique contributions to variance in the respective dependent variables. Linear regressions were conducted to predict unique contributions of independent variables to either the isolation or loneliness outcomes. For all regression analyses, residuals were normally distributed, such that parametric linear regressions were considered appropriate.

Chapter III

Results

Hypothesis 1

CCP total scores and loneliness scores were significantly correlated with one another (r = 0.-649, p = <0.001). Raw scores on the Modified Children's Loneliness and Social Dissatisfaction Questionnaire (n=34) ranged from 2 to 60, with a mean score of 30.91 (SD = 13.37). The range of possible scores on the scale is from 0 to 64, with higher scores indicating more loneliness. The McVilly et al. (2006) study, which consisted of 51 participants aged 16-52 with IDD, utilized a similarly adapted version of the Modified Children's Loneliness and Social Dissatisfaction Questionnaire with scores ranging from 0 to 60 with higher scores also indicating more loneliness. A comparison of the mean loneliness scores reported in the McVilly et al. (2006) sample (M = 18.04, SD = 10.41) with the PWS sample showed that the PWS sample reported significantly more loneliness (t = 4.98; p = <0.001).

Hypothesis 2

There were no significant differences in either total CCP scores or loneliness scores across gender. There were no significant differences in reported loneliness or CCP scores between PWS genetic subtypes. Neither CCP total scores or loneliness scores were significantly correlated with the HQ-CT or executive functioning measures. Both loneliness scores and CCP total scores were significantly correlated with various domains of the CBCL. Specifically, loneliness scores were significantly correlated with both the Internalizing (r = 0.690, p = <0.001) and Externalizing (r = 0.633, p = <0.001) domains. As higher scores on the loneliness scale indicated greater levels of

loneliness, these correlations are indicative that more loneliness was associated with higher reported problems on the CBCL. Within the Internalizing domain, loneliness was correlated with both the Withdrawn ($r = 0.754$, $p = <0.001$) and Anxious/Depressed ($r = 0.705$, $p = <0.001$) subdomains. Within the Externalizing domain, loneliness was correlated with each of the Aggressive ($r = 0.659$, $p = <0.001$) and Delinquent ($r = 0.523$, $p = 0.002$) subdomains.

CCP total scores were significantly correlated with all CBCL domains and subdomains. CCP total scores were correlated with both the CBCL Internalizing domain ($r = -0.615$, $p = <0.001$) and CBCL Externalizing domain ($r = -0.506$, $p = 0.001$). Within the Internalizing domain CCP total scores were related to the Withdrawn ($r = -0.665$, $p = <0.001$), Somatic ($r = -0.472$, $p = 0.003$), and Anxious/Depressed ($r = -0.529$, $p = <0.001$) subdomains. Within the Externalizing domain, CCP total scores were correlated with each of the Aggressive ($r = -0.505$, $p = 0.001$) and Delinquent ($r = -0.458$, $p = 0.004$) subdomains.

CBCL scores were also significantly correlated with the HQ-CT and executive functioning measures. The CBCL Externalizing domain was correlated with the HQ-CT ($r = 0.507$, $p = 0.002$) and with the BRIEF-2 ($r = 0.517$, $p = 0.01$). The Aggressive subdomain was correlated with the BRIEF-A ($r = 0.747$, $p = 0.021$). Additionally, the HQ-CT was correlated with both the BRIEF-2 ($r = 0.485$, $p = 0.012$) and BRIEF-A ($r = 0.695$, $p = 0.026$).

Regarding the relationship between the CCP, loneliness scores, and CBCL, group comparisons were made between those with the lowest (first quartile) and highest (fourth quartile) scores on each of the CCP and loneliness scales and then compared to the CBCL. Those who scored as most lonely had significantly higher CBCL scores across both the Internalizing ($p = 0.007$) and Externalizing ($p = 0.039$) domains. Those with the smallest networks as reported by the CCP also had significantly higher scores across both the CBCL Internalizing ($p = 0.009$) and

Externalizing ($p = 0.025$) domains.

Hypothesis 3

Results of the CCP ($N = 43$) were positively skewed, and thus a logarithmic transformation was done upon the CCP dataset to ensure normality and compatibility with regression analyses. A value of one was added to all datapoints so that a logarithmic transformation could occur for reported social networks with zero individuals. The CCP was the only outcome variable with this degree of skewness. Average social network sizes as reported by the CCP in transformed data are presented in Table 3. Figure 3 shows the positive skew of total social network size within the sample, with the majority of the sample reporting network sizes of 15 or less.

Within subjects repeated measures ANOVA show that Circle 1 (in-home family) and Circle 5 (unfamiliar partners) were significantly smaller than the other three categories measured by the CCP. Circles 2 (Good friends and other family), 3 (Acquaintances), and 4 (Paid workers) did not statistically vary in size from one another. Across all respondents an average of 16% of social networks were comprised of others with a disability.

Table 3: Circle of Communication Partners Findings

	Transformed Mean (SD)
CCP Total	1.22 (0.32)
Circle 1: In-home family	0.51 (0.14)
Circle 2: Good friends and other family	0.64 (0.35)
Circle 3: Acquaintances	0.62 (0.36)
Circle 4: Paid workers	0.65 (0.36)
Circle 5: Unfamiliar partners (e.g. store clerks)	0.44 (0.38)
Proportion disability across all circles	16% (19)

Figure 3

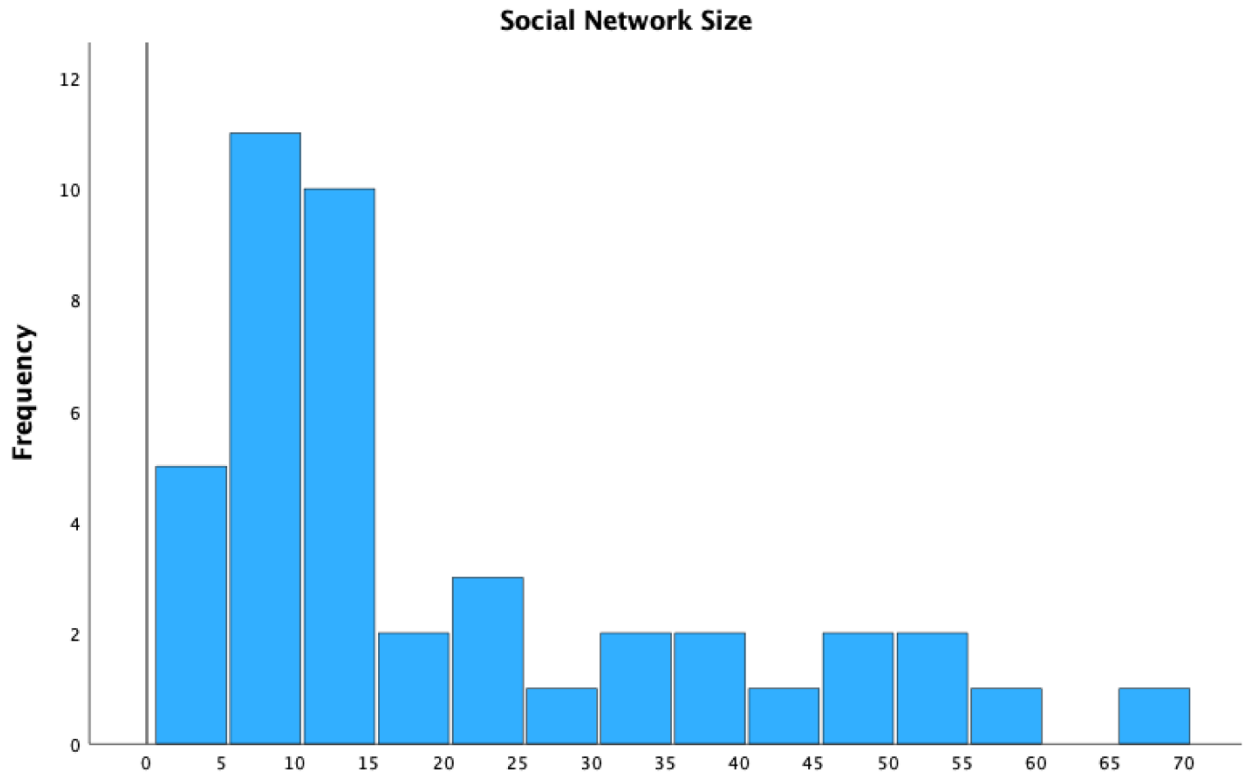

Figure 3: A histogram showing the spread of social network sizes across the total sample.

There were no significant differences in CCP or loneliness scores when comparing those who were employed, engaged in other activity, or were engaged in no activity. Highest social network sizes were reported by those who engaged in volunteering. Neither CCP nor loneliness scores were significantly correlated with age. Neither loneliness scores nor social network size significantly varied by education status.

Hypothesis 4

A regression analysis including CBCL domains significantly associated with CCP total scores (i.e. the Internalizing and Externalizing domains) accounted for 38.4% of the variance in CCP total scores ($F_{2, 35} = 10.896$, $p = <0.001$, see Table 4). Only the Internalizing domain ($\beta = -0.530$, $t = -2.692$, $p = 0.011$, $sr^2 = -0.414$) was a significant predictor after controlling for other significant bivariate correlates of CCP total scores.

Table 4: Regression model predicting CCP Total scores

Predictor	**β**	t	p	Semipartial r
(Constant)		16.581	<0.001	
CBCL Internalizing	-0.530	-2.692	0.011	-0.414
CBCL Externalizing	-0.115	-0.583	0.563	-0.077

An exploratory regression analysis was performed including the Withdrawn, Somatic, and Anxious/Depressed subdomain scores within the Internalizing domain which were themselves significantly associated with total CCP scores. These variables accounted for 49.3% of the variance in social network sizes ($F_{3, 34} = 11.03$, $p = <0.001$, see Table 5). Only the Withdrawn subdomain ($\beta = -0.929$, $t = -3.358$, $p = 0.002$, $sr^2 = -0.499$) was a significant predictor after controlling for other significant bivariate correlates of CCP scores.

Table 5: Exploratory regression model predicting CCP Total scores

Predictor	**β**	t	p	Semipartial r
(Constant)		17.908	<0.001	
CBCL Withdrawn	-0.929	-3.358	0.002	-0.499
CBCL Somatic	-0.205	-1.381	0.176	-0.231
CBCL Anxious/Depressed	0.418	1.487	0.146	0.247

A regression analysis including variables significantly associated with loneliness scores (i.e. CBCL Internalizing and Externalizing domain scores) accounted for 52% of the variance in

loneliness scores ($F_{2, 29}$ = 15.701, p = <0.001, see Table 6). Only the Internalizing domain (β = 0.484, t = 2.68, p = 0.012, sr^2 = 0.446) was a significant predictor after controlling for other significant bivariate correlates of loneliness scores.

Table 6: Regression model predicting loneliness scores

Predictor	**β**	T	p	Semipartial r
(Constant)		2.464	0.020	
CBCL Internalizing	0.484	2.680	0.012	0.446
CBCL Externalizing	0.293	1.623	0.115	0.289

An exploratory regression analysis was performed including the Withdrawn and Anxious/Depressed subdomain scores within the Internalizing domain which were themselves significantly associated with loneliness scores. These variables accounted for 57.4% of the variance in loneliness scores ($F_{2, 29}$ = 19.528, p = <0.001, see Table 7). Only the Withdrawn subdomain (β = 0.613, t = 2.277, p = 0.030, sr^2 = 0.389) was a significant predictor after controlling for other significant bivariate correlates of loneliness scores.

Table 7: Exploratory regression model predicting loneliness scores

Predictor	**β**	T	p	Semipartial r
(Constant)		2.236	0.033	
CBCL Withdrawn	0.613	2.277	0.030	0.389
CBCL Anxious/Depressed	0.158	0.586	0.562	0.108

Chapter IV

Discussion

This study is the first to examine the degrees of isolation and loneliness in PWS and to explore possible connections between these variables and other key aspects of the syndrome. The results have implications for both the theoretical model in Figure 1, which inspired the study, as well as broader beliefs concerning loneliness. Finally, this study may have important implications for policies that may impact the lives of those with PWS and their families.

The raw CCP data show social network sizes in this study that are larger than the average networks found from other IDD populations (Verdonschot et al., 2009). There was significant positive skew however in the reported results from the CCP. Small numbers of high reporters give the impression that the PWS sample has large social networks as a whole, when in fact the sample is more suggestive of a highly skewed population where some individuals may have robust social networks while the majority are much smaller and more in line with what can be expected when compared to other IDD populations. The skewness of the present sample may be indicative of a more broadly skewed population, yet the variance in reported network size across each circle may also be a product of the subjective nature of the CCP.

The study's finding that current school attendance was unrelated to feelings of loneliness or social network size is surprising and does not mirror previous literature focusing on the social importance of school in other IDD populations (van Asselt-Goverts, Embregts & Hendriks, 2013). The educational system can provide a structure for social supports that families of individuals who are not a part of the education system must replace on their own. The current findings do not

support the hypothesis that transitioning out of the education system is a highly sensitive time for those with PWS in this sample. Nevertheless, school transition should be a focus of policies aimed at improving the social health of those with PWS and broader IDD and is a common topic among broader IDD research (Beresford, 2004; Davies & Beamish, 2009). The discordant findings of this study with broader IDD research, which supports the significance of school transition, signals the need for further research in this area.

Respondents did not report significant differences in social network size or loneliness across gender or genetic subtype. There are mixed results in evaluating gender differences in loneliness in the broader typically developing population. A recent meta-analysis found no differences in reported loneliness by gender (Maes et al., 2019) though other studies have found men to be more lonely while also facing a social stigma that may lead them to underreport loneliness when compared to women (Barreto et al., 2021). Loneliness research focusing on the broader IDD population has found females to be more likely to report feelings of loneliness than males (Lunsky, 2003; Pagan, 2020; Papoutsaki, Gena, & Kalyva, 2013). It is possible in the IDD population too that males may be influenced by social stigma to underreport loneliness or other depressive symptoms. As this is the first study on loneliness specific to PWS, there were no expected differences across gender and future studies should continue to monitor possible gender differences in their samples.

It is somewhat surprising that there were no differences across PWS genetic subtypes. While no previous literature exists to suggest the UPD subtype would be more encumbered by loneliness or isolation specifically, there is evidence that the UPD subtype is more susceptible to comorbid diagnoses that may impair social and emotional health (Dykens et al., 2017; Holland et

al., 2003; Whittington & Holland, 2004). The current study may not have had enough participants with the mUPD subtype to show genetic subtype differences.

It is surprising to not find differences in reported loneliness across different levels of employment. Whether across type of employment or the presence of any job or volunteering activity at all, no significant differences were found across the modified loneliness questionnaire. More information about the social contributions of employment, such as number of coworkers or if individuals spent meaningful time with coworkers, may have been useful in explaining the perceived lack of benefit to employment in this population. The modal response to employment type was none (n = 22) which was expected from the literature, though the sample of the present study showed higher levels of full or part time employment than typically reported in PWS or IDD samples (Siperstein, Parker, & Drascher, 2013). Improving meaningful employment rates has long been a goal for those with PWS and broader IDD (Lysaght, Ouellette-Kuntz, & Lin, 2012) and this study's failure to capture social and emotional benefits of employment should not change that focus. With respect to the CCP however, those who volunteered did report the largest social network sizes. This finding supports the possible benefits of volunteering, particularly as it relates to social engagement.

The present study found a moderately strong significant relationship between loneliness, as measured by the Modified Children's Loneliness and Social Dissatisfaction Questionnaire, and isolation, as measured by the total score of the CCP. A relationship between the two variables was anticipated through the theoretical model, which surmised that loneliness may lead to withdrawal from further social interaction, which may in turn lead to greater loneliness. In this way isolation and loneliness pair together as they are theorized to in the general population. The strength of the relationship between the two was stronger than has been found in other population-based research

in typically developing older adults, which has found only mild (r = 0.2) correlations (Cornwell & Waite, 2009; Donovan et al., 2017). As the CCP was measured via caregiver report and loneliness measured via self-report, there is the possibility that if isolation and loneliness were both measured from self-report that the relationship between the two would be even stronger. Additionally, the present sample reported significantly more loneliness than the IDD sample in the McVilly et al. (2006) study. While both studies utilized the same modified loneliness measure, the current study utilized online questionnaires while McVilly et al. gathered results in person. Further research comparing two samples in the same study with the exact same methodology is warranted to explore if PWS may have a greater preponderance for loneliness than the general IDD population.

Aspects of the theoretical model in Figure 1 were supported by the study. Perhaps most strongly supported was evidence for the role of behavioral and emotional dysregulation. In the proposed theory, aspects of the PWS phenotype such as hyperphagia or impaired executive functioning were purported to prime individuals with PWS for emotional and behavioral dysregulation. This dysregulation in turn would contribute towards negative social experiences that may facilitate feelings of loneliness. As measured by the CBCL, dysregulation in this study significantly correlated to both aspects of the cognitive and behavioral PWS phenotype as well as loneliness and isolation. More specifically, the HQ-CT, BRIEF-2, and BRIEF-A scores each moderately correlated with the CBCL Externalizing domain. Examining the CBCL subdomains within the Externalizing domain, the HQ-CT shared significant correlations of similar strength with both the Aggressive and Delinquent subdomains, whereas the two executive functioning measures only significantly correlated with the Aggressive subdomain. Both loneliness and CCP scores were significantly and moderately related to both the Internalizing and Externalizing domains of the CBCL. Regression analyses suggest that the Internalizing domain may carry more

predictive weight than the Externalizing domain, and that the Withdrawn subdomain may be even more important in evaluating the underlying relationships between the CBCL and loneliness or CCP scores.

The significance of the Withdrawn domain coincides with current theoretical considerations of loneliness. Lippke & Warner (2022) expertly summarize the many different theoretical approaches taken towards combatting a global issue such as loneliness. Common to many theories is the idea of approach and avoidance and the role loneliness plays in modulating approach behaviors. The discrepancy model of loneliness describes loneliness as stemming from a disconnect between social needs and desires, leading to emotional distress (Iyer et al., 2023). Evolutionary approaches towards loneliness view it as an adaptive mechanism to facilitate social drive and motivation necessary for survival (Cacioppo & Hawkley, 2009). Furthermore, loneliness is theorized to self-propagate through maladaptive cognitive processes such as hypervigilance or negative cognitive reappraisal. In a comparison of emotion regulation strategies for loneliness versus general distress, researchers found that social withdrawal was a common maladaptive response unique to loneliness (Tan et al., 2022). Much like how avoidance of fears is known to promote greater long-term anxiety, further withdrawal from social connection may shield oneself from social threats while perpetuating isolative behaviors and cognitions. A longitudinal study of the PWS population would help establish support for this theoretical mechanism of loneliness in PWS as well.

It is important to highlight that while the proposed theoretical model suggests a direction for how the broader PWS phenotype may lead to dysregulation which may lead to loneliness (which may in turn recursively lead to more dysregulation) the correlational results of the study are insufficient to conclude a direction for these relationships. The current study is the first

evaluation of the proposed theoretical model and the presence of these significant correlations do indicate that these variables may be related to one another in a potentially meaningful way and do in fact belong within the model. With respect to loneliness itself, the presence of dysregulation within the model appears to be supported by the study results. The lack of direct significant relationships between either loneliness or CCP scores and the HQ-CT and BRIEF measures does cast doubt on whether these variables themselves may be useful indicators or predictors of loneliness in future studies, though each were related to domains of the CBCL. The CBCL however, and in particular the Withdrawn subdomain, may be a useful proxy for measuring loneliness or isolation if the relationships found in this study could be replicated across other samples. While the modified loneliness questionnaire and CCP used in this study have face validity for measuring these concepts within this study, the CBCL has been used in far more publications and with a diverse range of populations making it a useful and accessible research tool that could be used for future study of loneliness in the PWS population.

Future studies into this topic in PWS may aim to replicate these findings and further test the theoretical model proposed in Figure 1. Alternate methods for measuring social network size, such as the Social Network Map (Tracy & Abell, 1994) may be useful as well as other means of measuring loneliness such as direct interview as opposed to the online measures utilized in the present study. The present study's findings suggest that caregiver report may be a valuable source of information regarding the social health of those with PWS and future studies may also wish to incorporate a combined caregiver and self-report study design.

One area unexplored in the present study is the degree to which isolation and loneliness in PWS may relate to depression or other comorbid metal health disorders. As such relationships have been robust in typically developing populations (Cacioppo & Cacioppo, 2014), it may be

expected that loneliness will also relate to significant health concerns in PWS though direct data is not available. Additionally, comparisons between PWS and other IDD groups or typically developing groups were beyond the scope of the present study and may be of interest for future research in order to identify if there are unique characteristics to loneliness felt in PWS.

Future research may utilize theoretical approaches to loneliness as presented in this study to focus instead at the intervention level. Masi et al. (2011) compared multiple types of interventions including social cognitive approaches, social skills training, improved social supports, and increased opportunity for interaction in their respective impacts on reducing loneliness. They found that social cognitive training was significantly more effective at reducing loneliness than all other approaches. Recently our lab completed an online based social skills training program for individuals with PWS (Dykens et al., 2022). The intervention consisted of 10 weekly online group sessions aimed towards improving social skill deficits. The study utilized the CBCL as well as the Social Responsiveness Scale (SRS) in addition to coded semi-structured interviews as outcomes. Part of the participant interview involved questions related to loneliness and the study also used a single item from the CBCL concerning loneliness to track parent reported changes from the intervention. The proof of concept study was a success, as participants showed significant and sizable benefit as measured by the SRS during and after intervention as well as fewer reports of loneliness following the intervention. In this study both parent and self-reported loneliness was correlated to the CBCL, in this case primarily the Anxious/Depressed subdomain. These findings support the role of the CBCL Internalizing domain in predicting loneliness in PWS that was found in the present study. They also support the assumptions of the theoretical model in Figure 1 that social skill deficits contribute to loneliness in this population. Future intervention studies should focus on the abilities of those with PWS as compared to control groups (either other

IDD populations or typically developing populations) to benefit from evidence-based approaches towards reducing loneliness.

The present study explored both caregiver and self-report perspectives. As many with PWS live with their family or caregivers, the role of parent loneliness and the interaction between parent and child loneliness is another area of future research in PWS. Bernhold & Giles (2021) utilized attachment theory to conceptualize the dyadic relationships between parents and their adult children in explaining loneliness, finding that attachment anxiety and avoidance are important predictors.

There were several limitations to the present study. While the sample size was adequate for a study of a rare disease population and it is common for publications focused on PWS to have sample sizes of this range (Chevalère et al., 2013; Einfeld et al., 1999; Hutchison et al., 2015; Juaregi et al., 2007), nevertheless a larger sample would have allowed for more sophisticated statistical analyses and comparisons. The online nature of the questionnaire has tradeoffs where the benefit of easy access and geographical spread must be weighed against the risk of false reports. Efforts were made in the present study to limit distribution of the study link to private groups through trusted national research organizations, yet it cannot be guaranteed that all respondents chose to answer the questions honestly. The method of distribution for the study link also leaves room for a potential selection bias, as those who could see the link were a part of online groups that could theoretically provide more social support for those individuals with PWS than families who could not access these online groups. As these groups were primarily used by caregivers and not those with PWS themselves, it is unknown to what degree involvement with these groups would impact the social networks of those with PWS.

Another limitation of the study was the inability to completely explore the proposed theoretical model. Variables such as cognitive ability or social skills were beyond the scope of the present study yet were important aspects of the theoretical model. Future research is needed that directly measures these constructs in relation to loneliness and social network size in order to determine their theoretical relevance.

Similarly, the present study utilized cross sectional data that is unable to provide information on sequential or directional relationships as purported in the theoretical model. Further testing of the model would eventually require a longitudinal study evaluating changes in social networks and loneliness over time and the potential mediating impact of phenotypic variables such as the dysregulation measured in this study.

Loneliness and isolation are both phenomena known to carry significant health risk in the broader population, yet as with many areas of study they are little researched in a rare disease population such as PWS. Whether or not loneliness functions similarly in those with PWS or carries the same risks as it does in the general population are important considerations for those who live with or care for people with this syndrome. This study is the first to focus and theorize upon these issues in the PWS population and takes a first step in answering these questions. The study has established the salience of behavioral withdrawal in predicting and understanding loneliness in this population which may or may not function similarly to loneliness in the typically developing population. Additionally, the study characterizes a sample that is largely relatively isolated, though some individuals carry robust social networks. Further study is critical in advancing our understanding of the social and emotional lives of those with PWS and their caregivers.

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