TRAJECTORIES OF PSYCHOLOGICAL DISTRESS FOR PARENTS OF CHILDREN WITH ATYPICAL GENITALIA DUE TO DISORDERS OF SEX DEVELOPMENT (DSD): A LATENT CLASS GROWTH ANALYSIS

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Abstract: Objective: The current study sought to identify individual trajectories of parent depressive symptoms after having a child born with genital atypia due to a disorder of sex development (DSD) and across the first year post-genitoplasty (for parents who opted for surgery) or post-baseline (for parents who elected against surgery for their child). Hypotheses for four trajectory classes were guided by parent distress patterns previously identified among other medical conditions. Methods: Participants included 70 mothers and 50 fathers of 71 children diagnosed with a DSD with moderate to severe genital atypia. Parents were recruited from 11 US DSD specialty clinics within two years of the child's birth and prior to genitoplasty, and were followed up at one-year post-genitoplasty/post-baseline. A growth mixture model (GMM) was conducted to identify classes of parent depressive symptoms over time. Results: The best fitting model was a five-class linear GMM with freely estimated intercept variance, in which the classes identified were termed: "Resilient", "Recovery", "Chronic", "Escalating", and "Elevated Partial Recovery". The first four classes are consistent with the previous literature. However, a fifth class of "elevated distress" was additionally identified. The "Resilient" class was the largest (67.6%) and the one in which the majority of fathers (86%) were placed. Conclusions: The current study provides insight into individual parental distress trajectories. Future studies are needed to identify developmental, medical, or familial predictors of these trajectories. Moreover, evidence-based interventions specifically tailored to parents of children with DSD are needed to assist families who experience clinically significant and ongoing distress.

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CHAPTER I

INTRODUCTION

The majority of parents of children with chronic medical conditions appear to cope well over time with the stressors that arise from their child's illness and subsequent treatments (Katz et al., 2018; Price et al., 2016). However, the literature on whether this statement holds true for parents of a child diagnosed with a disorder/difference of sex development remains limited compared to other types of child health challenges (Sandberg, Gardner, et al., 2017). Disorder/Difference of sex development (DSD) is an umbrella term used to describe a heterogenous set of congenital conditions in which there is discordance between a person's chromosomal, gonadal, or anatomical sex (Hughes et al., 2006). Combined prevalence rates for DSDs range from 1:100 to 1:5000 (Sandberg, Gardner, et al., 2017; Sandberg, Pasterski, et al., 2017; Thyen et al., 2006), with rates of DSD with secondary atypical genital development being closer to 1:5000 (Lee et al., 2016; Sax, 2002). Only recently has research begun to systematically explore the impact of a DSD diagnosis on families' psychological adjustment using reliable and valid measures, and prospective analyses of parental adjustment remain understudied for these rare diagnoses (Sandberg, Gardner, et al., 2017).

After receiving a diagnosis of DSD for their child, parents must navigate complex interactions with a variety of medical professionals (Cools et al., 2018; Lee et al., 2016; Rothkopf & John, 2014; Woodward & Roberts, 2016). Notably, parents endorse interference with bonding with their child after birth due to frequent medical interventions (Crissman et al., 2011; Sanders et al., 2008). Furthermore, parents' unfamiliarity with the nature of DSD can generate considerable uncertainty and numerous complex questions (Chivers et al., 2017; Gough et al., 2008). During this time of heightened uncertainty, many parents have to make decisions concerning sex of rearing, genital surgery, and with whom to disclose information about the child's diagnosis (Crissman et al., 2011). The child's birth, surgical interventions, and designation of sex of rearing are events that may result in stress and be perceived as traumatic for parents (Delozier et al., 2019; Duguid et al., 2007; Pasterski et al., 2014).

Although a diagnosis of DSD does not appear to result in ubiquitous distress in all parents, a subset of parents are indeed at risk for increased levels of clinical distress (Sandberg, Pasterski, et al., 2017). Factors such as lack of a specific diagnosis, increased parenting stress, greater perceptions of child vulnerability, greater illness uncertainty, and perceived severity of illness have all been associated with greater parental distress (Delozier et al., 2019; Sharkey et al., 2018; Wolfe-Christensen et al., 2013). Only recently have researchers attempted to quantify these levels of parent distress after having a child born with a DSD, and to examine specific distress symptoms such as depression, anxiety, and posttraumatic stress (Ellens et al., 2017; Pasterski et al., 2014; Perez et al., 2019; Suorsa et al., 2015; Wolfe-Christensen et al., 2017). These studies have identified mean levels of depressive symptoms early in the child's life as comparable to population norms, with mean levels of anxious symptoms below population norms, and PTSS mean levels equivalent to parents of children with cancer (Perez et al., 2019; Suorsa et al., 2015). Further, approximately a quarter of parents endorse clinical levels of depressive and anxious symptoms, and rates of clinical levels of PTSS range from 14-28% (Delozier et al., 2019; Perez et al., 2019). Findings indicate depressive

symptoms are higher than anxious symptoms in this population, and a quarter of parents endorse clinically significant depressive symptoms prior to the child's genitoplastly. Importantly, this suggests depressive symptoms are particularly relevant for these parents and warrant further investigation.

To date, our preliminary findings suggest that parents' level of depressive symptoms are maintained six-months post-surgery (Wolfe-Christensen et al., 2017); however, these symptoms significantly decrease by 12-months post-surgery compared to pre-surgery levels (Ellens et al., 2017). Although mean rates of distress for parents appear to reduce across time, a subset of parents do continue to endorse moderate to severe symptoms (Ellens et al., 2017; Wolfe-Christensen et al., 2017). These initial findings demonstrate a potential trend in parental distress, yet the results only address mean levels of depressive symptoms, and fail to elucidate distinct variability of parent experiences. Moreover, mean scores limit insight into potential parent gender differences in distress over time. Current findings of parent gender differences in distress are mixed in the context of DSD (Pasterski et al., 2014; Wolfe-Christensen et al., 2014). Some studies demonstrate that mothers endorse greater distress than fathers (Delozier et al., 2019; Perez et al., 2019; Suorsa et al., 2015); whereas other studies report no differences (Pasterski et al., 2014). Time of assessment may be a factor in explaining these varying results as parent gender differences reportedly decrease across time (Ellens et al., 2017; Wolfe-Christensen et al., 2017). Further research is certainly needed to ascertain such gender differences in parent psychological adjustment to their child's DSD, including whether such differences change over time.

Although relatively little is still known about distress patterns in parents of youth with a DSD, substantial research has examined pediatric cancer and other illnesses, such that a theoretical model has been developed (Price et al., 2016). The Integrative Trajectory Model of Pediatric Medical Traumatic Stress is a framework that conceptualizes child and family trauma experienced from medical illnesses and injuruies (Kazak et al., 2006; Price et al., 2016). Notably, this model has been

supported in the context of several pediatric illnesses, suggesting similarities across illnesses and injuries (Price et al., 2016). Empirical studies have established four trajectory patterns or classes of pediatric medical traumatic stress (PMTS), inclduing Resilient, Recovery, Chronic, and Escalating trajectory patterns (Price et al., 2016). The Resilient trajectory characterizes the majority of families and is characterized by a potential slight increase in distress, which quickly reduces and remains at minimal levels. Recovery is a pathway in which an increase in distress occurs, but it reduces to low levels across time. Lastly, the Chronic and Escalating pathways reflect the maintenance of high levels across time, with some individuals reporting an actual increase in distress (Price et al., 2016).

The trajectories of traumatic stress in this model may provide insight into the experiences of parents of children with DSD. Although this model focuses on PMTS, a recent analysis of parents of children with cancer found that similar trajectories held for depressive and anxious symptoms in addition to PTSS (Katz et al., 2018). These findings suggest that the model may be a useful heurestic for understanding a range of parent psychological distress symptoms in DSD.

In summary, little empirical literature exists on the experience of distress in parents of a child with a DSD, including changes in distress from early in the child's life to post-surgery. The current literature reports an average decrease in parent distress symptoms associated with time and the completion of surgical interventions, suggesting that parents find ways in which to cope with the child's illness, or that perhaps parent distress is alleviated after moving past difficult decisions and surgical interventions. However, a subset of parents continue to endorse clinical levels of distress beyond surgery. Assessing mean scores across time and among both mothers and fathers fails to capture nuances within individual trajectories of distress. Identification of individual patterns of distress from pre-surgical interventions to post-surgery would provide insight into the extent to which parents are adjusting to their child's diagnosis and subsequent decisions about treatments. Moreover, creation of these profiles will additionally help to discern potential gender differences in parent

trajectories. Lastly, establishment of classes of distress patterns would allow for a more in depth analysis of predictors of risk and resilience within these subgroups of parents.

Therefore, the primary aim of the current study was to evaluate individual distress trajectories for parent depressive symptoms starting prior to surgical interventions through one-year post-surgery. The Integrative Trajectory Model of Pediatric Medical Traumatic Stress (Price et al., 2016) was utilized to guide the hypotheses for DSD parent distress trajectories. It was hypothesized that four patterns or classes would emerge, with the majority of parents falling in the Resilient class, with low levels of distress. It was hypothesized that a second pattern would include a Recovery class, in which parents have an increase in distress early in the child's life around diagnostic procedures and decision making, yet distress would decrease by 12-months post-surgery. Additionally, a Chronic class was hypothesized to emerge, in which parents would have continued elevated symptoms of distress from baseline to 12-months. Although the original model includes a fourth class of Escalating distress, it was anticipated that the small sample size may preclude identification of this pathway, and as such escalating parents may be captured within the Chronic path. Because the literature is mixed with regard to gender differences in distress, a secondary aim was to evaluate gender differences in trajectories; however, no specific hypotheses were made concerning gender given the past discrepant findings.

CHAPTER II

REVIEW OF LITERATURE

Disorders of Sex Development

Disorders of sex development (DSD) is an umbrella term used to describe a heterogenous set of congenital conditions in which there is discordance between a person's chromosomal, gonadal, or anatomical sex (Hughes et al., 2006). Diagnoses categorized under the overarching term include three overlapping classifications, including: 1) sex chromosome DSD, which includes abnormality in the number of sex chromosomes, 2) 46,XY DSD, which include defects in synthesis and metabolism of androgens, resistance to androgens, or other malformations, and 3) 46,XX DSD, of which most are due to excess androgens (Hughes et al., 2006; Murphy et al., 2011; Rothkopf & John, 2014). Combined prevalence rates for these disorders range from 1:100 to 1:5000, (Sandberg et al., 2017; Sandberg, Pasterski, & Callens, 2017; Thyen, Lanz, Holterhus, & Hiort, 2006), with rates of DSD with secondary atypical genitalia being closer to 1:5000 (Lee et al., 2016; Sax, 2002). The extent of atypicality in external genitalia can vary from slight discordance with genotype to complete virilization in 46,XX or complete feminization in 46,XY. Additionally, internal sex structures can vary in the degree of female and male development (Murphy et al., 2011; Wisniewski et al., 2012).

Although several diagnoses are included under the DSD umbrella, the focus of the current study is on diagnoses that lead to atypical genital development, which excludes most sex chromosome DSDs and some 46,XY diagnoses. Atypical genital development is often identified at birth and parents are required to make various decisions, including decisions concerning medical and surgical procedures. The nature of DSD diagnoses, their complexity, and the potential for parental distress will be explored below.

Sex Determination and Differentiation

Typical human sex development includes two sex chromosomes: an X chromosome received from the mother and either an X or a Y chromosome from the father. Genotypical females have two X chromosomes (46,XX) and males have an X and Y chromosome (46,XY; Murphy et al., 2011; Sinisi, Pasquali, Notaro, & Bellastella, 2003). All embryos begin with sex neutral bipotential gonads and Mullerian and Wolffian ducts capable of becoming female or male internal sex structures (Sinisi et al., 2003; Wisniewski et al., 2012). Typically, the presence of XX chromosomes differentiates primordial gonadal tissue into ovaries and Mullerian Ducts into fallopian tubes, uterus, cervix, and vagina, while the Wolffian ducts regress (Murphy et al., 2011; Wisniewski et al., 2012). The presence of XY chromosomes typically includes an SRY gene (i.e., sex determining region of the Y chromosome) on the Y chromosome (Murphy et al., 2011). This gene stimulates gonadal development into testes. The testes then produce testosterone, which stimulates the Wolffian ducts to develop into internal male structures (i.e., vas deferens, seminal vesicles, epididymis, and prostate), and Mullerian inhibiting substance (MIS), which regresses the Mullerian ducts (Sinisi et al., 2003; Wisniewski et al., 2012). Enzymes change testosterone into dihydrotestosterone (DHT), a potent androgen that will virilize external structures into a penis and scrotum (Bao & Swaab, 2011; Wisniewski et al., 2012). Without the presence of androgens, such as the case with 46,XX, external sex structures will develop female (Bao & Swaab, 2011).

However, sex differentiation can be altered in numerous other ways, resulting in atypical genital development and a DSD diagnosis.

46,XX DSD

Over 50% of children born with atypical genitalia DSDs are diagnosed with 46,XX congenital adrenal hyperplasia (CAH; Kim & Kim, 2012), specifically, 21-hydroxylase deficiency CAH (Trapp et al., 2011). The adrenal cortex produces cortisol, aldosterone, and testosterone. Individuals with CAH, 21-hydroxylase deficiency and 11□-hydroxylase deficiency are unable to produce cortisol (and potentially aldosterone), yet they can sufficiently produce testosterone (Wisniewski et al., 2012). Typically, the body controls cortisol levels by regulating the release of adrenocorticotropic hormone (ACTH), which converts into cortisol with the 21-hydroxylase enzyme (Trapp et al., 2011). Without the enzyme necessary to convert ACTH into cortisol, individuals with CAH cannot regulate ACTH levels; therefore, the developing fetus continues hormone production, leading to increased levels of testosterone (Murphy et al., 2011). As DHT is responsible for development of the penis and scrotum, a 46,XX fetus exposed to high levels of DHT will begin to develop enlarged clitoris and fusing of the labia (Murphy et al., 2011; Wisniewski et al., 2012). The greater the deficiency of 21-hydroxylase enzyme or 11□-hydroxylase, the more masculinized the genitalia. While the external genitalia masculinizes from DHT, the fetus lacks testes, and thus lacks MIS; therefore, all female internal structures will develop (Wisniewski et al., 2012).

46,XY DSD

While 46,XX DSDs are primarily caused by CAH, 46,XY DSD can have multiple causes. Moreover, approximately half of 46,XY DSD individuals will not be given an exact diagnosis (Woodward & Roberts, 2016). Insufficient levels of testosterone, DHT, or MIS will create varied differentiation of internal and/or external sex structures (Sinisi et al., 2003; Wisniewski et al.,

2012). Diagnoses within three categories of 46,XY DSDs will be addressed below and include resistance to androgens, gonadal development, and insufficient synthesis of androgens.

The hormones MIS and testosterone develop from the testes. However, damaged androgen receptors minimize the binding of androgens, thus impacting the degree of sex differentiation (Murphy et al., 2011; Wisniewski et al., 2012). Androgen Insensitivity Syndrome (AIS), or the inability to respond to androgens, can be both complete or partial. Complete androgen insensitivity syndrome (CAIS) has no response to androgens; therefore, CAIS individuals lack internal sex structures (yet testes remain in the abdomen) and are phenotypically female (Wisniewski et al., 2012). If the receptors are only partially damaged (PAIS), MIS will still inhibit Mullerian duct development, but only partial internal and external male structures will develop, leading to atypical external genitalia (Hewitt & Warne, 2012; Wisniewski et al., 2012).

The SRY gene on the Y chromosome stimulates gonadal development into testes. Lack of an SRY gene or a malfunctioning gene may lead to failure to develop gonadal tissue (complete gonadal dysgenesis) or may only partially develop (partial gonadal dysgenesis; Wisniewski et al., 2012). Complete gonadal dysgenesis will fail to develop testes and the hormones MIS and testosterone, leading to complete female internal and external development. Partial gonadal dysgenesis, and the subsequent partial development of testes, leads to insufficient amounts of MIS and testosterone (Wisniewski et al., 2012). Insufficient MIS cannot completely inhibit female internal structure development, leading to partial internal male and female structures. Insufficient testosterone can lead to atypical external genital development (Wisniewski et al., 2012).

Lastly, some 46,XY DSD diagnoses occur from insufficient enzymes that convert testosterone into DHT, such as 5□ reductase type-2 (Sinisi et al., 2003; Wisniewski et al., 2012; Woodward & Roberts, 2016). DHT binds to androgen receptors 5-10 times stronger than

testosterone (Hewitt & Warne, 2012). Therefore, testosterone may be present in the developing fetus's body, but without sufficient function of 5□ reductase type-2 and the conversion of testosterone into DHT, testosterone alone lacks sufficient strength to fully create male genital development in utero (Hewitt & Warne, 2012). These individuals will, however, masculinize later with increased testosterone during puberty (Bao & Swaab, 2011).

Medical Procedures and Surgical Interventions

To determine an accurate DSD diagnosis, several tests are conducted early in the child's life, which include a karyotype, hormone levels (e.g., 17-hydroxyprogesterone, DHT, testosterone, androstenedione, gonadotropins, DHEA, and anti-Mullerian-inhibiting factor), serum electrolytes, urinalysis (due to potential renal anomaly), and imaging (e.g., ultrasound, MRI; Brain et al., 2010; Rothkopf & John, 2014). Furthermore, reconstructive surgery may be performed to improve obstruction of urination, to allow for future sexual intercourse, and to improve cosmetic appearance (Creighton et al., 2012). Surgical interventions can include gonadectomy (due to potential malignancy and endogenous hormone production that conflicts with sex of rearing) and feminizing or masculinizing genitoplasty (S. Kim et al., 2018).

Timing of surgery, and surgery in general, is controversial. Historically, elective surgical interventions (i.e., those not needed urgently for life-threatening or disabling reasons; Gardner & Sandberg, 2018) were performed as standard of care on babies born with atypical genitalia to align genitalia with sex of rearing (Johnston, 2012; S. Kim et al., 2018). It was previously believed that gender identity would be shaped by sex of rearing (Gardner & Sandberg, 2018), yet research now challenges this assumption (Gardner & Sandberg, 2018). Recently, the timing, efficacy, and purpose of early surgery has been questioned (Johnston, 2012). Following early surgical interventions, parents and physicians have reported increased satisfaction with cosmetic appearance of the child's genitalia as compared to pre-surgical ratings (Bernabe et al., 2018).

However, some reports of adults with DSD who had undergone genital surgery in childhood have identified lower satisfaction with urinary function, sexual function, and genital appearance compared to controls (Tourchi & Hoebeke, 2013). Furthermore, minor to major complications from surgical interventions have been reported, such as urinary tract infections or urinary retention to urethrocutaneous fistula and vaginal stenosis (Bernabe et al., 2018). Surgical complications as well as dissatisfaction with surgical results for people who have undergone early genitoplasty has generated questions to the necessity of performing surgery early in the child's life (Gardner & Sandberg, 2018).

Some advocacy groups support deferment of surgical interventions until the child is old enough to consent (Ernst et al., 2018; Rothkopf & John, 2014). Moreover, organizations (e.g., The World Health Organization, United Nations, and Human Rights Watch) have recently called for a ban on any non-medically necessary surgical interventions until the child is of an age to consent (S. Kim et al., 2018). However, medical societies are concerned about a preemptive cease to early surgical procedures due to lack of sufficient empirical support for the benefits of surgical deferral compared to early intervention (S. Kim et al., 2018). It is, however, recommended that early surgical intervention focus on issues of function over that of cosmetic appearance (Hughes et al., 2006). Moreover, it is recommended to combine surgical interventions in order to minimize surgeries (Hughes et al., 2006).

In addition to surgical interventions, some diagnoses may require long-term hormone replacement therapy (Rothkopf & John, 2014). This therapy can assist with penile growth and induce puberty in children who are unable to produce sufficient pubertal hormone levels (Rothkopf & John, 2014). Importantly, CAH can include a deficiency in aldosterone levels in addition to cortisol. Without early identification of CAH, infants can go into salt-wasting crisis, which can lead to reduced sodium, excess potassium, and shock (Trapp et al., 2011). A person with CAH will require life-long steroid supplementation in order to maintain healthy living and

survival (Trapp et al., 2011; Wisniewski et al., 2012). Lastly, due to the nature of prenatal urogenital development, other organ development may also be impacted, causing gastrointestinal, cardiovascular, or kidney complications, which may also be life-threatening (Wisniewski et al., 2012).

Parental Experiences and Decisions Following the Birth of a Child with DSD

The complexity of DSD underscores the importance of understanding parents' experiences when their child is born with a DSD. The delivery of children with a DSD may occur at hospitals where personnel are lacking in experience and extensive knowledge of atypical genitalia and DSD diagnoses. Providers may delay announcement of the child's sex at birth, which can be perceived by parents as there being something wrong with the child (Crissman et al., 2011). Moreover, families may encounter unprofessional and careless treatment by medical professionals (Brain et al., 2010; Gough et al., 2008). The birth experience can, therefore, be traumatic for parents (Brain et al., 2010). Once informed about the child's atypical genitalia, parents' unfamiliarity with DSDs can produce further uncertainty and questions (Chivers et al., 2017; Gough et al., 2008). Importantly, parents have endorsed difficulty bonding with their child after birth due to interference from medical interventions and various medical professionals looking at the child's genitalia, using the child as a teaching case (Crissman et al., 2011; Sanders et al., 2008).

A diagnosis of atypical genitalia results in parents navigating complex interactions with a variety of medical professionals, which can include endocrinologists, urologists, gynecologists, geneticists, social workers, psychologists, nurses, and fetal specialists (Cools et al., 2018; Lee et al., 2016; Rothkopf & John, 2014; Woodward & Roberts, 2016). Parents are then faced with making decisions concerning genital surgery and sex of rearing, and disclosing information to friends and/or family (Crissman et al., 2011).

Decision Making

Decision making for parents of a child with DSD is complex. Mothers have reported desiring additional support, particularly soon after diagnosis and during times of surgery (Chivers et al., 2017). These are key times in which parents are making critical decisions for the child's future. Notably, parents have identified experiencing a sense of grief and loss for the child they envisioned having, and feelings of being rushed or not included in decision making compounds these feelings by not allowing time to grieve (Sanders et al., 2008). Therefore, it has been argued that parents should be allowed considerable time and support as they navigate these important decisions.

Sex of Rearing

Parents have identified concerns about their child's future gender identity, and whether it will align with the one they have elected to raise the child. This is particularly true if the child has undergone surgical interventions to align genitalia with sex of rearing (Crissman et al., 2011). Greater concern for gender identity has been expressed by parents if their child's sex of rearing is discordant with genotype (Crissman et al., 2011). Multiple factors are to be considered for sex of rearing decisions, including genotype, diagnosis, external genital development, fertility potential, surgical options or interventions, need for hormonal replacement therapy, and cultural and family practices (Hughes et al., 2006). Gender identity in 46,XX CAH children has been reported at rates of 95% identifying as female (Lee et al., 2016). Whereas, individuals born with 46,XY DSD diagnosed with PAIS and partial gonadal dysgenesis have rates of gender dysphoria at of about 25% despite sex of rearing (Hughes et al., 2006). In utero exposure to testosterone has been linked to later male gender identity, for example, children diagnosed with CAIS and reared female will identify as male 60% of the time (Bao & Swaab, 2011). Recommendations to delay sex of rearing decisions are typical until information is available concerning the genotype and

diagnosis, and considerations for fertility potential, surgical options or interventions, and need for hormonal replacement therapy have been addressed (Hughes et al., 2006). However, this can delay disclosure of the child's gender to friends and family, or lead to disclosing a change in gender, which can be distressing (Sanders et al., 2008).

Surgery

As identified above, considerable controversy exists concerning the choice of early surgical interventions for children with atypical genitalia. Concerns for delaying surgical interventions include the possibility of interference with parent-child bonding, potential for malignancy, impact on sexual function, body-image, psychological well-being, and social acceptance (Cools et al., 2018). Parents have identified concerns for their child's future social interactions and potential stigma as reasons for electing early surgery (Crissman et al., 2011; Sanders et al., 2008). Moreover, the option to delay surgical interventions has not always been presented to parents, nor have parents been aware of the controversy surrounding genital surgery in children with DSD (Gardner & Sandberg, 2018; Sanders et al., 2008). Although, the decision to proceed with surgical interventions ultimately lies with the parent or legal guardian (Gardner & Sandberg, 2018), many parents have reportedly followed physician guidance, placing trust in their expertise (Crissman et al., 2011). Such communications by physicians have often conveyed that they can "fix" the child's genitalia (Crissman et al., 2011).

Disclosure

Disclosing information about a child's DSD, and subsequent atypical genitalia to friends and family can be difficult for families, for fear of stigma for one's child or oneself (Crissman et al., 2011; Duguid et al., 2007; Rolston et al., 2015). Disclosure can be further complicated when family and friends have previously been notified of the baby's sex (Brain et al., 2010). Parents also fear that disclosing partial information may lead to even more specific questions about their

child's anatomy, which can be challenging due to their personal nature (Crissman et al., 2011). Some parents have reported allowing the child to decide with whom to disclose the information (Crissman et al., 2011), thus electing to not disclose themselves. Importantly, lack of disclosure may lead to families isolating themselves, and thereby minimizing potentially positive interactions with social support systems (Rothkopf & John, 2014).

Importantly, at a time in which parents are making important and complex decisions for their child's future, particularly decisions with great uncertainty, parents may encounter negative interactions and possible isolation from friends and family. These negative experiences may be in turn lead to distress in parents.

Parent Psychological Distress

Currently, relatively little is known about distress in parents of youth born with a DSD compared to parents of children with other chronic illnesses (Sandberg, Gardner, et al., 2017). Much of the literature has been anecdotal in nature, and only recently have researchers begun to more clearly document the nature of distress in parents. Nevertheless, it has been established that early life experiences/stressors (e.g., diagnosis, uncertainty about gender) and the prospect of surgical interventions reportedly result in significant distress for parents of a child with a DSD (Alpern et al., 2017). Moreover, parents often express guilt and blame, feeling responsible for genetically passing the diagnosis on to their child, or for causing the DSD during pregnancy (Sanders et al., 2008). Although a diagnosis of DSD does not result in ubiquitous distress in all parents, a subset of parents are indeed at risk for increased distress (e.g., Sandberg, Pasterski, et al., 2017). Factors such as increased parenting stress, greater perceptions of child vulnerability, lack of a specific diagnosis, greater illness uncertainty, and perceived severity of illness have all been associated with greater parental distress (Delozier et al., 2019; Sharkey et al., 2018; Wolfe-Christensen et al., 2013).

As noted earlier, much of what is currently known about parental experiences following the diagnosis of a DSD comes from qualitative studies. It has been only recently that research has started to quantify parent distress after having a child born with a DSD, and to examine specific distress symptoms using standardized measures, such as those used to assess posttraumatic stress, anxiety, and depression (Ellens et al., 2017; Pasterski et al., 2014; Suorsa et al., 2015; Wolfe-Christensen et al., 2017). In the section to follow, the literature on parental posttraumatic stress, depressive, and anxious symptoms will be discussed in more detail.

Posttraumatic Stress Symptoms

Recent literature has identified that parents do indeed endorse posttraumatic stress symptoms (PTSS) shortly after their child's diagnosis of a DSD and several years later, with means comparable to parents of children with cancer (Delozier et al., 2019; Pasterski et al., 2014; Perez et al., 2019; Suorsa et al., 2015). Comparatively, parents of children with DSD endorse clinically significant PTSS at rates ranging from 14% to 28% (Delozier et al., 2019; Pasterski et al., 2014; Perez et al., 2019), whereas rates of clinical PTSS for parents of children with other chronic illnesses averages around 19% (Pinquart, 2019). The child's birth, surgical interventions, and designating sex of rearing are events that promote stress responses and can be perceived as traumatic for parents (Delozier et al., 2019; Duguid et al., 2007; Pasterski et al., 2014). Importantly, it has been noted in the pediatric cancer literature, and supported in recent DSD literature, that it is the interpretation or appraisal of these events that is most predictive of experiencing trauma during the child's illness (Delozier et al., 2019; Kazak et al., 2006; Pasterski et al., 2014). As an example, increased levels of parental PTSS have not differed between parents of girls or boys (Perez et al., 2019; Suorsa et al., 2015). This is important as children with 46,XX CAH have a potentially life-threatening diagnosis that requires life-long treatments, whereas 46,XY diagnoses may not have the same threat to life (Wisniewski et al., 2012). Although a CAH diagnosis may be objectively more severe, parents report traumatic experiences similar to parents

of children with other DSD diagnoses. This again suggests that traumatic experiences occur from the perceptions of the diagnosis and subsequent events, rather than just from the direct threat to the child's life.

PTSS in mothers and fathers have been found to be at equivalent levels by some researchers (Pasterski et al., 2014), whereas other studies identify mothers experiencing greater distress than fathers (Delozier et al., 2019; Suorsa et al., 2015). Discrepancies in distress based on parent gender have also been noted in pediatric cancer literature (Phares et al., 2005). It is important to note, however, that studies with samples of fathers is limited, and samples of fathers are quite low. Historically, fathers have been underrepresented in pediatric health research (Phares et al., 2005), potentially due to a single primary caregiver being included in research studies. This lack of inclusion of fathers limits comparison of parents' trauma experiences in DSD to that experienced in other chronic illnesses. Further evaluation is needed to better understand parent PTSS, and if mothers and fathers equally perceive the DSD diagnosis as traumatic.

Anxious Sympotoms

Overall, studies suggest that mean levels of parent-reported anxious symptoms prior to genitoplasty appear to be below established population norms (Perez et al., 2019; Suorsa et al., 2015). Although as a group these mean scores fall below norms, up to 26% of parents have been found to endorse symptoms in the clinical range for anxiety (Perez et al., 2019; Suorsa et al., 2015). One potential explanation for relatively lower group means may be the inclusion of fathers in the calculation of mean scores, as fathers reported lower anxious symptoms than mothers in these studies (Perez et al., 2019; Suorsa et al., 2015). The literature on parent gender differences on anxiety levels is mixed, however. One study found no differences on anxiety between mothers and fathers, unless the child had atypical genitalia and a life-threatening illness (Wolfe-

Christensen et al., 2014). However, this study included families at various time periods since diagnosis (i.e., child ages 0.5 to 15). Other research noted that mothers endorsed greater anxious symptoms than fathers early in the child's life, but that these differences diminished across time (Sharkey et al., 2018). Thus, it may be that differences in these findings is due to different time points in which the parents are assessed. It may also be the case that mothers and fathers may have different experiences of anxious symptoms across their child's treatment and early health events. Again, further research is needed to assess parent anxious symptoms both across time and between mothers and fathers.

Depressive Symptoms

Lastly, parents have endorsed mean levels of depressive symptoms equivalent to what would be expected based on population norms. Again, a subset of parents (24%) have reported depressive symptoms at the clinical level early on in their child's life (Perez et al., 2019). As with anxious symptoms, comparison of depressive symptoms between mothers and fathers have been mixed, with one study identifying equivalent levels for mothers and fathers (Wolfe-Christensen et al., 2014); whereas, a study of parental distress early in the child's life identified greater symptom levels in mothers than fathers (Perez et al., 2019). As with above, discrepancies in findings based on parent gender may be due to limited inclusion of fathers. Further research is clearly indicated to ascertain differences in parent adjustment and responses to their child's DSD.

Parent Psychological Distress Over Time

Preliminary studies evaluating changes in parental distress over time have identified that parents' anxious and depressive symptoms were maintained six-months post-surgery, and then significantly decreased by 12-months post-surgery (Ellens et al., 2017; Sharkey et al., 2018; Wolfe-Christensen et al., 2017). These studies also noted that PTSS were significantly reduced by six-months, earlier than reductions in anxious and depressive symptoms, and this reduction was

maintained at 12-months post-surgery as compared to pre-surgery levels (Ellens et al., 2017; Wolfe-Christensen et al., 2017). Parent gender differences in distress have also been demonstrated to diminish across time, such that mothers reported only greater depressive symptoms than fathers at 12-months post-surgery, but no longer reported greater anxious or posttraumatic stress symptoms than fathers (Ellens et al., 2017; Wolfe-Christensen et al., 2017).

Although, mean rates of distress for parents have been reported to lessen across time, a subset of parents continue to endorse moderate to severe symptoms (Ellens et al., 2017; Wolfe-Christensen et al., 2017). Specifically, one study found that at a 12-month post-surgery follow up, approximately 10% of parents still reported moderate to severe anxious and depressive symptoms, and 2.4% identified clinically significant levels of PTSS (Ellens et al., 2017). As one parent of children with 46,XX CAH noted, "[s]urgery in childhood to cosmetically reduce the obvious physical effects of differences in genitalia may help parents to feel that their child is more 'normalised' and therefore help alleviate some of the anxiety and stress. However, this alone does not help parents to come to terms with, deal with the challenges and fully accept a complex and private condition and to know how best to support their child." (Magritte, 2012; p. 573).

In summary, relatively little empirical literature exists on parental distress in DSD, including changes of distress from early in the child's life to post-surgery and differences between mothers and fathers. The current literature indicates that parent distress decreases with time, suggesting that parents find ways in which to manage the child's illness. Although mean scores have been reported to decrease across time, a subset of parents continue to endorse clinical levels of distress.

Integrative Model of Pediatric Medical Traumatic Stress

Various theoretical models have been set forth to understand processes of coping and adaptation. One such model specifically evaluates parental adjustment to a medical diagnosis has been selected to guide potential hypotheses for the current study due to its relevance to medical conditions. The Integrative Trajectory Model of Pediatric Medical Traumatic Stress is a framework that conceptualizes how children and their families cope with the trauma associated with medical illnesses, injuries, and their treatments (Kazak et al., 2006; Price et al., 2016). Pediatric medical traumatic stress (PMTS) is considered separate from other traumatic stress disorders in the Diagnostic and Statistical Manual, as the diagnostic criteria for traumatic stress disorders may not be entirely appropriate for families dealing with medical trauma (Kazak et al., 2006). Rather, the focus of PMTS is on the experience of posttraumatic stress symptoms, without concern for whether the symptoms meet diagnostic criteria. This integrative model describes three phases for experiencing trauma and its' effects, and importantly offers assessment and intervention guidance for each phase (Price et al., 2016).

The first phase of the model includes Peri-Trauma, or the phase in which the traumatic medical experiences occur (e.g., communication of the diagnosis, treatments, surgical interventions; Kazak et al., 2006; Price et al., 2016). The second phase is referred to as the Acute Medical Care phase, which includes active medical treatment. The last phase is referred to as Ongoing Care or Discharge of Care, which could be months or years beyond the traumatic medical experiences (Kazak et al., 2006; Price et al., 2016). Empirical studies have established patterns of PMTS across the three phases, which concluded with the identification of four trajectory patterns, including Resilient, Recovery, Chronic, and Escalating patterns (Price et al., 2016). The Resilient trajectory encompasses the experience of the majority of families, and is characterized by a potential initial slight increase in distress, which quickly reduces after the Peri-Trauma phase to low levels (Price et al., 2016). Recovery is a pathway in which distress

increases, but reduces to lower levels after the acute medical phase (Price et al., 2016). Lastly, the Chronic and Escalating pathways maintain high levels of distress after the acute medical phase, and individuals in the Escalating path report an additional increase in distress beyond the acute phase (Price et al., 2016). Notably, this model has been supported in the context of several pediatric illnesses, suggesting similarities across illnesses and injuries (Price et al., 2016), and although the model was created for PMTS, a recent examination of parents of children with cancer found that the model also held for anxious and depressive symptoms (Katz et al., 2018).

As this model held for multiple illness populations and various forms of distress, this suggests that the model may be useful for understanding parent psychological distress in DSD. Specifically, phase 1 (Peri-Trauma) may include the timeframe including initial diagnosis, early decisions parents are required to make, and the surgical interventions children may undergo. Parent distress post-surgery and into follow-up care may follow similar patterns of PMTS as described in phases 2 and 3 of the original model.

Summary

A diagnosis of a disorder of sex development with subsequent ambiguous genitalia can be confusing and stressful for parents. Parents often have no knowledge whatsoever of DSD as a diagnostic entity at the time their child is born. Diagnoses of ambiguous genitalia are mostly identified at birth, and a series of tests are needed to establish genotype and the extent of internal and external sex development to ascertain a diagnosis. Diagnostic procedures can be complex and may not lead to a confirmed etiology for about 50% of children born with a 46,XY DSD. Furthermore, children with 46,XX salt-wasting CAH have a potentially life-threatening chronic illness, requiring parents to manage medical treatments beyond the child's ambiguous genitalia.

After the child's birth and identification of ambiguous genitalia, parents are tasked with navigating appointments with multiple medical and psychological professionals, and they are

faced with a number of critical decisions for their child's future, including sex of rearing, whether or not to have the child undergo surgical interventions, and with whom to disclose the diagnosis. Parents have reported unprofessional and distressing experiences, and not always feeling fully informed prior to making decisions (Brain et al., 2010; Gough et al., 2008). Moreover, parents have endorsed feeling guilt, shame, and stigma (Crissman et al., 2011; Rolston et al., 2015; Sanders et al., 2008). Although efforts have been made to improve parent and child experiences through consensus statements and guidelines for care (Hughes et al., 2006; Lathrop & Cheney, 2015; Speiser et al., 2018), a need continues to exist for medical professionals to be aware and sensitve to the complex decisions parents will encounter and the potential for distress.

Very little literature exists on the nature of parental distress in the context of DSD, including how distress changes from early in the child's life to post-surgery. The current literature suggests that parent distress decreases with time and the completion of surgical interventions, suggesting that parents find ways in which to cope with the child's illness. It may also be that perhaps parents' distress diminishes after moving past difficult decisions and surgical interventions. Although mean scores on measures of adjustment have been reported to decrease across time, a subset of parents continue to endorse clinical levels of distress. Assessing average scores across time and among both mothers and fathers collectively fails to capture nuances that occur within individual trajectories of distress.

Analysis of individual patterns of distress from pre-surgical interventions to post-surgery would provide insight into the extent to which parents are adjusting to their child's diagnosis and the subsequent decisions and treatments. Moreover, examining individual paths of distress will help to elucidate gender differences, if they exist, in trajectories of distress. Further, establishment of classes of distress patterns would allow for more in depth analysis of predictors of risk and resilience within these parents. Therefore, the aim of the current study is to evaluate classes of distress trajectories for parental psychological distress (i.e., depressive symptoms) beginning

prior to any surgical interventions and following one year post-surgery. Although little is known about how parents of youth with a DSD adjust over time, substantial research has been performed on parents of children with cancer and other illnesses. As such, the theoretical model of traumatic stress Integrative Trajectory Model of Pediatric Medical Traumatic Stress (Price et al., 2016), which has been developed and tested with parents of children with cancer, will be used to guide the specific hypotheses for possible DSD parent distress trajectories.

CHAPTER III

METHODOLOGY

Participants and Procedures

Participants included parents (70 mothers and 50 fathers) of a child (n = 71) diagnosed with a Disorder/Difference of Sex Development (DSD) with secondary moderate to severe genital atypia. Demographic information on the child can be found in Table 1 and parent demographic information in Table 2. Participants were recruited from 11 sites across the United States between September 2013 and November 2017 as part of a larger prospective longitudinal study evaluating parental psychosocial adjustment to their child's DSD diagnosis. Approval was obtained from institutional review boards at each site prior to participant consent. Participants were eligible if they: 1) were a caregiver (e.g., parent) of a child diagnosed with DSD with genital atypia as defined by a Prader rating of 3-5 in children with 46,XX DSD or a Quigley rating 3-6 in children with 46,XY DSD or 45,XO/46,XY sex chromosome DSD, 2) were English-speaking, 3) were at least 18-years-old, and 4) had a child within two years of birth who had not yet undergone genitoplasty. Children with other co-morbid medical conditions not related to their DSD were deemed ineligible. Families were consented and recruited at regularly scheduled clinic visits. All parent dyads included a mother and father pair (i.e., biological, step, or adoptive). One secondary

caregiver identified as a grandmother; however, the primary caregiver, who was the child's mother, also completed measures. Therefore, the current analyses removed the grandmother in order to focus on mother and father trajectories. Parents completed baseline measures prior to the child undergoing genitoplasty, and then at approximately 6-months (M = 5.70, SD = 1.73) and 12-months (M = 12.90, SD = 2.43) post-surgery, or post-baseline for parents who opted against surgery for their children. Participants were compensated $50 for participation.

Materials

Demographic Questionnaire

A demographic questionnaire gathered child and parent information including, but not limited to, child age, sex of rearing, type of DSD, and diagnosis (if one had been determined), as well as the parent age, sex, marital status, race/ethnicity, education, employment status, and household income.

Beck Depression Inventory-II

The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report measure of depressive symptoms. Participants respond to multiple-choice items with scores ranging from 0 to 3. Higher total scores represent greater levels of depressive symptoms. Total scores from 0 to 13 indicate minimal depression, 14 to 19 indicate mild depression, 20 to 28 indicate moderate depression, and 29 to 63 indicate severe depression. Total scores of 14 or greater are considered clinically significant (Viinamäki et al., 2004). Internal consistency in the current sample was excellent ($\alpha_{Baseline}$ = .93; $\alpha_{6\text{-}Month}$ = .94; $\alpha_{12\text{-}Month}$= .93).

Statistical Analysis

The sample for the current study was previously established and post-hoc power analyses may provide unwarranted confidence in the results (Wolf et al., 2013). Moreover, determination

of sample size is complex for a growth mixture model (Berlin et al., 2014b), which was the planned analyses. Rule of thumb guidelines suggest 5–10 participants per estimated parameter, yet this could lead to under or overestimation of the sample needed (Berlin et al., 2014a). In consideration of this, a power analysis was not conducted.

Over the three timepoints for each of the 120 parents, 54 parents had data at all three timepoints, 39 had two timepoints, and 27 had data at one timepoint. Missing timepoints were due to missing measure items, such that a total score could not be calculated, or due to the measure missing completely. Analyses of missing data examined associations between demographic variables and parent missing data as well as parent depressive symptoms. No timepoint was identified in which demographic variables were related to both missing data and to depressive symptoms. Full-information maximum likelihood estimation was used to address missing data. This method is preferable as it estimates parameters using all available information and is a better method for smaller sample sizes (Berlin et al., 2014b; Preacher et al., 2008).

A growth mixture model (GMM) was conducted to evaluate parent depressive symptoms across the three timepoints. GMM is a type of latent growth modeling that assesses changes in individual outcomes across time, and identifies unobserved, latent, classes of individuals who have similar trajectories (Berlin et al., 2014b).

Current recommendations suggest a four stepped approach to latent variable mixture modeling: 1) problem definition, 2) model specification, 3) model estimation, and 4) model selection and interpretation (Berlin et al., 2014b; Ram & Grimm, 2009).

Problem Definition

Theory, previous literature, and analysis of descriptives were used to create hypotheses about growth patterns. To account for the non-independence in observations due to mothers and fathers parenting the same child with shared experiences, standard errors were adjusted by using

complex analyses in the model (TYPE=COMPLEX syntax in M*plus*, which accounts for clustering; Muthén & Muthén, 2017) in which the child variable was identified for clustering. Next, a latent growth curve model was conducted to identify the best fitting growth curve, in which both an intercept only and linear growth curve model were tested. Goodness of fit for the nonmixture model was assessed utilizing recommended fit statistics, with excellent models demonstrating CFI $\geq$ .95, RMSEA <.05, and SRMR <.05 (comparative fit index, root mean square error approximation, and standardized root mean residual respectively; Berlin et al., 2014b; Hu & Bentler, 1999). Further, models with lower Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), and the Sample Size Adjusted BIC (SSA-BIC) are indicative of a better model fit (Berlin et al., 2014a; Geiser, 2013; Jung & Wickrama, 2008). Between class differences based on parent gender was assessed using R3STEP, which assesses for covariates without changing class structure (Asparouhov & Muthén, 2014).

Model Specification

A model building approach was utilized to identify the optimal number of latent classes. Theory and research were used to create hypotheses about expected number of classes and differences between classes. Initial hypotheses were based off of previous literature on parent distress in the context of pediatric chronic illness (e.g., Katz et al., 2018; Price et al., 2016). Guided by the Integrative Trajectory Model of Pediatric Medical Traumatic Stress, it was hypothesized that the data would be best described as linear with a negative slope, and that four classes would emerge. Further, it was hypothesized that most parents would start with low distress and remain low, which would be classified as the Resilient class. The other hypothesized classes would be Recovery (i.e., higher means than Resilient, with a negative slope), Chronic (i.e., higher means than Resilient, and steady across time), and Escalating (i.e., a positive slope over time). To start, a Latent Class Growth Analysis (LCGA; a type of GMM) was conducted in which the intercept and slope variances are fixed to zero within classes, and only between class

variance is allowed (Berlin et al., 2014b; Jung & Wickrama, 2008). Fixing the within class variance reduces the number of estimated parameters, which can assist with convergence for smaller samples (Berlin et al., 2014b). Therefore, this approach was utilized first due to the small sample size of this rare illness population. Models were then run to evaluate if models with freed variances were a better fit to the data. Analyses were conducted to at least one class greater than the four expected classes. Next, variances were systematically allowed to be freely estimated (i.e., intercepts for each class, then intercept and slope for each class).

Model Estimation

All models were estimated using M*plus* (version 8.3; Muthén & Muthén, 2017), utilizing maximum likelihood estimation with robust standard errors and chi-square test statistic (MLR) to account for skewness and non-independence in the data (Muthén & Muthén, 2017). Starting values were initially set at default and systematically increased to optimize replication and ensure global maxima rather than local maxima.

Model Selection and Interpretation

The optimal number of latent classes was assessed using several information criteria indices. Lower AIC, BIC, and SSA-BIC are indicative of a better model fit (Berlin et al., 2014a; Geiser, 2013; Jung & Wickrama, 2008). The Lo, Mendell, and Rubin test (LMR) was utilized to evaluate the model fit by comparing a model with *G* classes to a model with *G*-1 classes (Geiser, 2013). A significant LMR suggests model *G* is the best model (Geiser, 2013). The bootstrap likelihood ratio test (BLRT) is considered a better indicator of model fit compared to LMR; however, the BLRT is not provided when TYPE=COMPLEX syntax is used in model specification. Therefore, BIC is recommended for model comparison (Berlin et al., 2014b). Entropy was also used to determine the accuracy of classification of participants into a class, with numbers closer to 1 representing better accuracy of individual placement (Berlin et al., 2014a;

Geiser, 2013; Jung & Wickrama, 2008). The final model included no less than 1% in each class (Jung & Wickrama, 2008). In addition, theory and prior research were utilized in conjunction with model fit information to deem the best fitting model(Berlin et al., 2014b).

CHAPTER IV

FINDINGS

Overall, observed means of parent depressive symptoms were below clinical cutoff at each timepoint ($M_{Baseline}$ = 9.04, $Var_{Baseline}$ = 89.55; $M_{6\text{-}Month}$ = 7.09, $Var_{6\text{-}Month}$ = 68.21; $M_{12\text{-}Month}$ = 5.78, $Var_{12\text{-}Month}$ = 49.65).

Growth Modeling

Problem Definition

Latent Growth Curve Modeling was conducted evaluating both an intercept only model and a linear model to determine the best single-group representation of change (Ram & Grimm, 2009). These analyses adjusted for clustering of parent data. Model fit statistics were evaluated for the best fit, and a linear model was selected as it had excellent fit of the CFI, TLI, RMSEA, and SRMR, and had lower BIC and SSA-BIC than an intercept only model (see Table 3). See Figure 2 for plot of raw scores.

Model Specification

As the hypotheses included a four-class model, initial analyses evaluated a LCGA (with intercept and slope within class variances fixed to zero), estimating two to five classes (one class

greater than hypothesized as recommended) adjusting for clustered data. A review of model information criteria demonstrated a five-class model was similar to a four-class, so a sixth class was evaluated. To assess whether models with estimating growth factor variances fit the data better, GMMs were executed using a stepwise approach in which models first freed intercept variances and then models with freed intercept and slope variances were estimated.

Model Estimation

Growth mixture analyses were conducted constraining intercept and slope variance to zero. Models for classes one to six successfully terminated, without warnings or negative residual variances. Evaluation of plots of observed data demonstrated high variability within classes, and suggested that within class variance constrained to zero is likely not the most appropriate model. Analyses were conducted in which intercept variance was allowed to be estimated for models of classes one to six. Starting values were increased to optimize opportunity for loglikelihood to replicate. Next, models with the intercept and slope variances were estimated; however, problems with parameter estimates occurred (i.e., negative residual variance error messages), despite increased iterations and starting values. Negative residual variance suggests the slope variance cannot be freely estimated and should be set at zero, as it had been in the previous models.

Model Selection and Interpretation

For the LCGA estimation, increase in classes resulted in lower AICs, BICs, and SSA-BIC up to six classes. Due to in class variability, LCGA is likely not the best fit for the current data. GMMs were estimated for classes one to five, with a freely estimated intercept, slope set to zero, and increased starts and iterations; however, the six-class model produced errors of negative residual variance. The GMMs with freely estimated intercept and slope variances produced error messages. Loglikelihood was replicated for all models.

Comparison of fit statistics between the LCGAs and GMMs indicated the GMMs with estimated intercept variances produced better model fit. Fit statistics are presented in Table 4. Analysis of fit indices across all classes demonstrated similarity between the 4-class and 5-class GMMs with intercept variances estimated. The 5-class model had a lower Loglikelihood, AIC, and SSA-BIC, with a slightly higher BIC compared to the 4-class model. Review of the estimated means and observed data within each class demonstrated the 5-class model allowed for individuals with increasing levels of depressive symptoms to be placed within their own class and removed from the low mean across time class, therefore, the addition of that class made theoretical and meaningful sense. As such, a 5-class GMM with an estimated intercept variance was selected as the final model. Plots of each tested GMM are in Figures 3-7.

Identified Latent Classes

Individual class estimated means per timepoint can be seen in Table 5. The cutoff score of 14 for clinically significant depressive symptoms from the BDI-II was used descriptively to help gauge severity of symptoms within classes. The intercept variance was the same across all classes, so it is only provided in the first described class below.

Resilient Class. The largest class (# 3) presented with low initial depressive symptoms ($M_{Intercept}$ = 4.11, p < .001; $Var_{Intercept}$ = 6.24, p = .003; slope = -0.78, p = .132), with no significant change in symptoms over time ($M_{12\text{-}month}$ = 3.33). This class included 67.6% of parents (n = 81.09). Given the low levels of symptoms reported across time and using class names already described in the literature (e.g., Price et al., 2016), this class was named the "Resilient" class.

Recovery Class. The next largest class (#1; 18.1%; n = 21.78) presented with mean levels of depressive symptoms above the clinically significant cutoff at baseline ($M_{Intercept}$ = 17.92, p < .001; slope = -11.95, p < .001). As can be seen in Figure 7, this class had a significant

decrease in distress resulting in non-clinical levels at the last time point ($M_{12\text{-}month}$ = 5.97). This pattern is consistent with the "Recovery" class in the literature (see Price et al., 2016).

Chronic Class. The third class (#2) included 7.4% of parents (n = 8.91) and represents parents who report higher levels of depressive symptoms that do not reduce over time. This class has initial levels reaching clinical significance ($M_{Intercept}$ = 24.40, p < .001; slope = -0.54, p = .831), followed by non-significant changes in symptoms across time ($M_{12\text{-}month}$ = 23.86), suggesting chronic and ongoing clinically significant distress. Given this pattern of symptoms and its congruence with prior literature (see Price et al., 2016), this class was named the "Chronic" class.

Escalating Class. The second to smallest group (#4, 5.2%; n = 6.19) included parents who reported low, but statistically different from zero, levels of distress at baseline ($M_{Intercept}$ = 5.22, p = .033; slope = 13.34, p < .001); however, their depressive symptoms significantly increased over time to clinically significant mean levels by the 12-month assessment ($M_{12\text{-}month}$ = 18.55). This pattern was named the "Escalating" class due to its increasing symptoms over time, as described in previous literature (see Price et al., 2016).

Elevated Partial Recovery Class. Lastly, the smallest class (#5, 1.7%; n = 2.04) included parents who reported the highest baseline symptoms ($M_{Intercept}$ = 45.12, p < .001), who also had the largest negative slope over time (slope = -27.08, p < .001). As can be seen in Figure 7, despite this decline, these parents continued to endorse clinically significant levels over time ($M_{12\text{-}month}$ = 18.04). As this class had significant reduction in symptoms, yet was distinguishable from the Recovery class, and this class was not previously portrayed in the literature, it was named the "Elevated Partial Recovery" class.

Parent Gender Differences

Based on multinomial logistic regressions from R3STEP, fathers were more likely than mothers to be in any class other than the Elevated Partial Recovery class (see Table 6). Further, fathers were more likely than mothers to be in the Resilient class relative to the Recovery class (see Table 6).

Based off of most likely class membership for mothers and fathers, the following gender differences were descriptively assessed. The majority of fathers (86%) were within the Resilient class, with 10% in the Recovery class, 2% in Chronic class, and 2% in the Escalating class. For mothers, the majority (58.6%) fell within the Resilient class, with 22.6% in the Recovery class, 10% in Chronic class, 5.7% in the Escalating class, and 2.8% in Elevated Partial Recovery class.

CHAPTER V

CONCLUSION

DSD diagnoses are rare medical conditions, and DSDs with secondary genital atypia occur even less commonly. Research on parental psychological adjustment to their child's DSD diagnosis is quite limited, even in comparison to other rare medical conditions. Although research has begun to analyze parent distress early in the child's diagnosis and treatment phases, studies have primarily examined mean levels of distress in comparison to established norms. These studies have importantly characterized average parent experiences; however, discussion of mean distress levels limits our understanding of the nuanced individual experiences of parents over time. Moreover, previously reported large standard deviations suggest considerable variability in parent symptoms. Therefore, examination of parent distress patterns across these key early stages is essential for identification of subgroups of parents who might be at particular risk. As such, the current study sought to fill this gap in the literature by determining trajectories of parental depressive symptoms across time. Parent distress trajectories have previously been identified for parents of children with other chronic or life-threatening illnesses, and therefore, the Integrative Trajectory Model of Pediatric Medical Traumatic Stress (Price et al., 2016) was used to guide hypotheses for patterns of parental depressive symptoms.

The current study identified the four classes consistent with the Integrative Trajectory Model of Pediatric Medical Traumatic (i.e., Resilient, Escalating, Recovery, and Chronic classes; Price et al., 2016) among parents of a child with a DSD. In addition, a fifth but very small class emerged as well (i.e., Elevated Partial Recovery). Consistent with previous literature (Price et al., 2016), the majority of parents fell within the Resilient class, with consistent symptom levels below clinical significance. This demonstrates that the majority of parents adjust well to their child's diagnosis, and it suggests that parents who endorse relatively low levels of distress early in the course of their child's diagnosis and treatment, will remain low across time. However, the emergence of the Escalating class highlights the importance of routine ongoing screening to identify the subset of parents who, although initially adjust well, experience clinically increased distress over time (see Ernst et al., 2019; Sandberg, Gardner, et al., 2017). Future studies are needed to identify stressors or developmental challenges that may trigger late onset of distress for these parents.

Although the majority of parents initially endorse low nonclinical levels depressive symptoms, the Recovery class represents a subset of parents who reported early clinical levels of distress. Notably, this class demonstrated a lowering of symptom levels over time to below clinical significance by one-year. These findings suggest that these parents are distressed early on, yet begin to adjust and adapt over time to their child's diagnosis. Thus, it may be that parents experience less stress as they move past the difficult decisions of sex of rearing or choosing surgery for their child. Specifically, parents who had a child undergo genitoplasty may feel reduced distress once early medical interventions are complete. Although speculative, parents' symptoms may reduce when their child's external genitalia more closely aligns with sex of rearing (Wisniewski, 2017). Moreover, these parents may have received increased support and/or resources from their medical team, including support from behavioral health services, or additional family support. This additional support may, therefore, alleviate stress and enhance

psychological adjustment to the child's diagnosis over time. It is not known, however, to what extent behavioral health services were received, either as part of the multidisciplinary DSD clinic or through additional resources, that could account for the reduction in their symptoms.

Conversely, a Chronic class was identified in which parents experience clinically significant levels of depressive symptoms across time. This underscores the importance of early psychosocial screening and ongoing access to mental health services. Perhaps these parents encounter challenges across their child's treatment, such as medical complications, complexity of treatment, or increased financial burden from medical treatments (Ellens et al., 2017; Perez et al., 2019). Moreover, perhaps these parents have negative cognitive appraisals about their child's diagnosis and treatment, such as perceived stigma towards their child or themselves concerning their child's DSD (Rolston et al., 2015), or perceived intrusiveness of the child's illness into their work, family, or personal life. These parents may also experience greater illness uncertainty, or appraisals of ambiguity or lack of information concerning their child's diagnosis and treatment (Roberts et al., n.d.).

Finally, a very small class referred to as the Elevated Partial Recovery class was identified. This class represented parents who had very high levels of depressive symptoms at baseline; however, importantly these parents also had a significant reduction in symptoms across time. This class is distinguishable from the Recovery class due to the significantly higher baseline levels, and although follow-up symptoms remain above clinical significance at one-year, the diminishing symptoms represents a form of recovery for these parents. Additional information is needed to discern factors related to such high early distress, such as familial or medical factors. Further, as described above within the Recovery class, research on the aspects related to this significant decrease in symptoms is needed. Lastly, as these parents continue to endorse clinically significant depressive symptoms, ongoing screening and support are warranted.

The current results also identified that fathers are more likely than mothers to fall within the Resilient class as compared to Recovery or Elevated Partial Recovery classes. Although more than half of mothers fall in the Resilient class as well, 41% also evidence distress trajectories in one of the other four classes, suggesting greater variability in mothers' distress than fathers. The current finding of gender differences in parent distress in the context of DSD is consistent with other reports (Ellens et al., 2017; Perez et al., 2019). Moreover, the current findings demonstrate a narrowing of the gender difference with 82% of mothers being below the clinical cutoff at one-year, as were 96% of fathers. In contrast, at baseline 64% of mothers were below the clinically significant cutoff and 88% of fathers had scores below clinical cutoffs. Although gender differences appear to diminish over time, mothers still represent the majority of parents who endorse clinically significant symptoms at one-year.

Strengths and Limitations

There are several strengths to the current study. First, the prospective, longitudinal design offers an insight into the changing aspects of parental psychological adjustment that had previously not been captured for these families. Second, the current study conducted sophisticated person-centered statistical analyses to distinguish individual parent experiences over time. Further, the current sample included a large sample of fathers, who have previously not been well represented in the DSD literature. Moreover, data collected from multiple sites across the country offered analyses of parents from a large geographic area.

Although the novel analyses of parental trajectories adds significant insight into parental adjustment in DSD, certain limitations should be considered. First, the current study included an ethnically homogenous sample, who also had relatively higher incomes and levels of education. Therefore, these results may not generalize to parents of other races and socioeconomic backgrounds. Participants were also recruited exclusively from DSD specialty clinics. Future

studies are needed to understand parent adjustment among families who receive services at other types of medical clinics, such as smaller clinics without access to a multidisciplinary team or expertise in DSD. Further the sample predominantly included parents who elected surgery for their child; thus, future studies are needed to evaluate potential differences between those who elect surgery and those who do not. Due to the rarity of genital atypia with DSD, the sample size of the current study was relatively small for the statistical analyses conducted. Further studies are recommended to confirm the current findings and address generalizability of these results (Grimm & Ram, 2009). Lastly, as the current study utilized parent self-report of depressive symptoms, future studies would benefit from including clinical interviews or multi-modal assessments to better understand parent experiences of depressive symptoms.

Clinical Implications and Future Directions

The current findings evidenced that the majority of parents demonstrate resiliency or recover to below clinically significant depressive symptoms by one-year post-genitoplasty/post-baseline. However, the challenge for clinicians will be to identify parents who fall within the Chronic, Escalating, and Elevated Partial Recovery classes, as these parents are experiencing clinically significant levels of depressive symptoms over time. Early and ongoing screening (e.g., Ernst et al., 2019; Sandberg, Gardner, et al., 2017), will be needed to identify families across time as the findings indicate variability in patterns of symptoms. Additionally, studies are needed to identify specific predictors of parents who experience ongoing, non-remitting distress. Previous literature has identified some risk factors for distress, such as financial burden (Perez et al., 2019). Importantly, recent findings have also identified that early levels of parent illness uncertainty, a cognitive appraisal of uncertainty concerning the child's illness and treatment (Mishel, 1990), are predictive of later parent depressive symptoms (Roberts et al., under review). Although currently there are no evidence-based interventions targeting distress in parents of children with DSD (Gardner & Sandberg, 2018), an illness uncertainty targeted intervention has

demonstrated reductions in both illness uncertainty and distress for parents of children with other illnesses (Fedele et al., 2013; Hoff et al., 2005; Mullins et al., 2012). Moreover, cognitive behavioral and problem solving interventions evaluated with parents of children with cancer have shown positive results (e.g., Kazak et al., 1999, 2005; Sahler et al., 2005, 2013). Therefore, these interventions have the potential to benefit parents of children with DSD as well.

With the establishment of distress patterns for parents of children with DSD, future studies are needed to identify additional predictors of class membership for parents, particularly predictors that can be assessed with screening. Future studies should evaluate for medical risk factors including those associated with specific diagnoses, medical procedures, and complications (e.g., Ellens et al., 2017; Wolfe-Christensen et al., 2017). Furthermore, as the current study evaluated parents early in the child's life and soon after genitoplasty, future studies should evaluate trajectories of distress as the child ages through different developmental stages, such as gender expression (e.g., Crissman et al., 2011), starting school, and puberty. Moreover, risk factors for mothers and fathers may differ, including during developmental stages and with medical treatment outcomes. Lastly, research is needed to discern the effects of early interventions and resources for parents to create better guidance for clinicians working with families during these early years.

Conclusion

The current study fills a significant gap in the DSD literature and provides insight into unique patterns of parental distress symptoms across time. Notably, the current study demonstrates that although reporting mean levels of parent distress symptoms may characterize the experience for some parents, it fails to address specific distress trajectories of other parents over time, specifically those parents who experience varying levels of distress and those who have an increase in distress. Future studies are needed to identify developmental, medical, or

familial factors that lead to increased parent distress over time. Moreover, evidence-based interventions specifically for parents of children with DSD are needed to assist families who experience clinically significant and ongoing distress.

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APPENDICES

Table 1.

Child Demographics

N	71
Age in Months *M* (*SD*)	9.03 (6.90)
Sex of Rearing *N* (%)	
Girl	44 (62.0)
Boy	25 (35.2)
Unsure/Non-designated	2 (2.8)
Sex of Rearing Aligns with Karyotype *N* (%)	62 (88.6)
Diagnosis *N* (%)	
46,XX	42 (59.2)
21-Hydroxylase Deficiency	35 (49.3
11-Hydroxylase Deficiency	1 (1.4
Ovotesticular DSD	1 (1.4)
Unknown/Unclassified	1 (1.4)
Other	2 (2.8)
46,XY or 45,XO/46,XY	27 (38)
5-Alpha Reductase Deficiency	1 (1.4)
Androgen Insensitivity Syndrome	2 (2.8)
Gonadal Dysgenesis	6 (8.5)
Ovotesticular DSD	1 (1.4)
Unknown/Unclassified	15 (21.1)
Other	1 (1.4)
Received Genitoplasty *N* (%)	65 (91.5)

Table 2.

Parent Demographics

	Mothers	Fathers
N	70	50
Age *M* (*SD*)	31.92 (5.34)	34.36 (7.07)
Parent Status		
Biological	69 (98.6)	49 (98.0)
Adoptive	1 (1.4)	1 (2.0)
Child had Genitoplasty *N* (%)	64 (91.4)	48 (96.0)
Race/Ethnicity *N* (%)		
Hispanic	16 (22.9)	7 (14.0)
Black/African American	3 (4.3)	3 (6.0)
White/Caucasian	46 (65.7)	34 (68.0)
Asian/Pacific Islander	4 (5.7)	4 (8.0)
Multiracial	3 (4.3)	1 (2.0)
Other	5 (7.1)	5 (10.0)
Marital Status *N* (%)		
Single, Never Married	10 (14.3)	2 (4.0)
Divorced	2 (2.9)	0 (0.0)
Married to Parent of Child with DSD	53 (75.7)	43 (86.0)
Living with Parent of Child with DSD	7 (10.0)	5 (10.0)
Not Living with, but Partnered with Parent of Child with DSD	1 (1.4)	0 (0.0)
Highest Education Attained *N* (%)		
Some High School or Less	2 (2.9)	1 (2.0)
Finished High School/GED	8 (11.4)	7 (14.0)
Some College or Associates Degree	19 (27.14)	15 (30.0)
Bachelor's Degree	24 (34.3)	17 (34.0)
Graduate Degree	12 (17.1)	9 (18.0)
Household Income *N* (%)		
$0 – 19,999[†]	12 (17.1)	3 (6.0)
$20,000 – 39,999	12 (17.1)	9 (18.0
$40,000 – 59,999	6 (8.6)	5 (10.0)
$60,000 – 79,999	7 (10.0)	5 (10.0)
$80,000 – 99,999	7 (10.0)	6 (12.0)
$100,000 +	22 (31.4)	21 (42.0)

Note. The sum for participant race is greater than the sample due to participants being able to select Hispanic as ethnicity as well as a race. The sum of participant marital status is greater than the sample due to participants being able to select more than one option.

[†]Below the federal poverty line for a family of 3.

Table 3.

BDI Fit Statistics for Single-Group (Nonmixture) Models Model of Change

Model of Change	CFI	TLI	RMSEA	SRMR	χ^2	df	χ^2/df	AIC	BIC	Adjusted BIC
Intercept	0.892	0.919	0.102	0.114	9.012	4	2.253	1822.525	1836.463	1820.655
Linear	1.0	1.031	0.0	0.019	0.515	1	0.515	1812.447	1834.747	1809.454

Note. AIC = Akaike Information Criteria; BIC = Bayesian information criteria.

Table 4.

Loglikelihood, Information Criteria, and Entropy Tests for LCGA and GMM

Measure	1 Class	2 Classes	3 Classes	4 Classes	5 Classes	6 Classes
LCGA						
Loglikelihood	-945.493	-885.947	-878.436	-859.572	-855.344	-855.344
AIC	1900.987	1787.893	1778.871	1747.143	1744.688	1750.688
BIC	1914.924	1810.193	1809.533	1786.168	1792.075	1806.437
SSA-BIC	1899.117	1784.901	1774.757	1741.907	1738.329	1743.207
Entropy	-	0.907	0.795	0.881	0.818	0.830
LMR *test*	-	111.342	14.044	19.724	7.905	-0.660
LMR, *p*-value	-	0.1085	0.4625	0.1336	0.8339	0.7708
GMM						
Loglikelihood	-901.784	-881.00	-867.252	-856.575	-849.920	-
AIC	1815.568	1780.00	1758.504	1743.150	1735.854	-
BIC	1832.293	1805.088	1791.954	1784.963	1786.029	-
SSA-BIC	1813.324	1776.634	1754.016	1737.540	1729.122	-
Entropy	-	0.896	0.933	0.888	0.871	-
LMR *test*	-	38.862	25.706	19.964	12.43	-
LMR, *p*-value	-	0.2784	0.2893	0.1146	0.3772	-

Table 5.

Individual Class Estimated Means at each Timepoint

	Baseline *M*	6-Months *M*	12-Months *M*
Resilient Class (#3)	4.11	3.72	3.33
Recovery Class (#1)	17.92	11.94	5.97
Chronic Class (#2)	24.40	24.12	23.86
Escalating Class (#4)	5.22	11.88	18.55
Elevated Partial Recovery Class (#5)	45.12	31.58	18.04

Table 6.

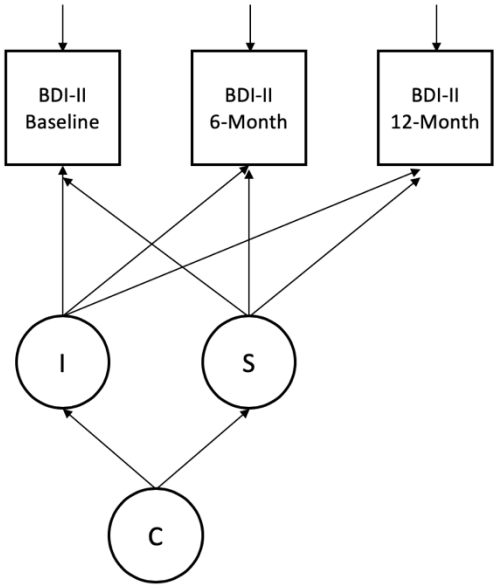
Categorical Latent Variable Multinomial Logistic Regressions Using 3-STEP Procedure

Reference Class Comparison Class	*B*	SE	*p*	OR	95% CI
Elevated Partial Recovery (Class 5)					
Resilient (Class 3)	20.84	1.61	< .001	999.000	-
Recovery (Class 1)	19.50	1.69	< .001	-	-
Chronic (Class 2)	18.66	2.07	< .001	-	-
Escalating (Class 4)	18.86	0.00	< .001	999.000	-
Resilient (Class 3)					
Recovery (Class 1)	-1.34	0.67	0.045	0.26	.071, .969
Chronic (Class 2)	-2.18	1.35	0.107	0.11	.008, 1.598
Escalating (Class 4)	-1.98	1.61	0.218	0.14	.006, 3.217
Elevated Partial Recovery (Class 5)	-20.84	1.61	< .001	0.00	.000, .000

Note. Mothers = 0, Fathers = 1. Positive coefficients represent fathers were more likely than mothers to fall within the comparison class than the reference class.

Figure 1.

Linear Growth Mixture Model



Note. C = class; I = intercept; S = Slope

Figure 2.

Plot of Participant Raw Scores

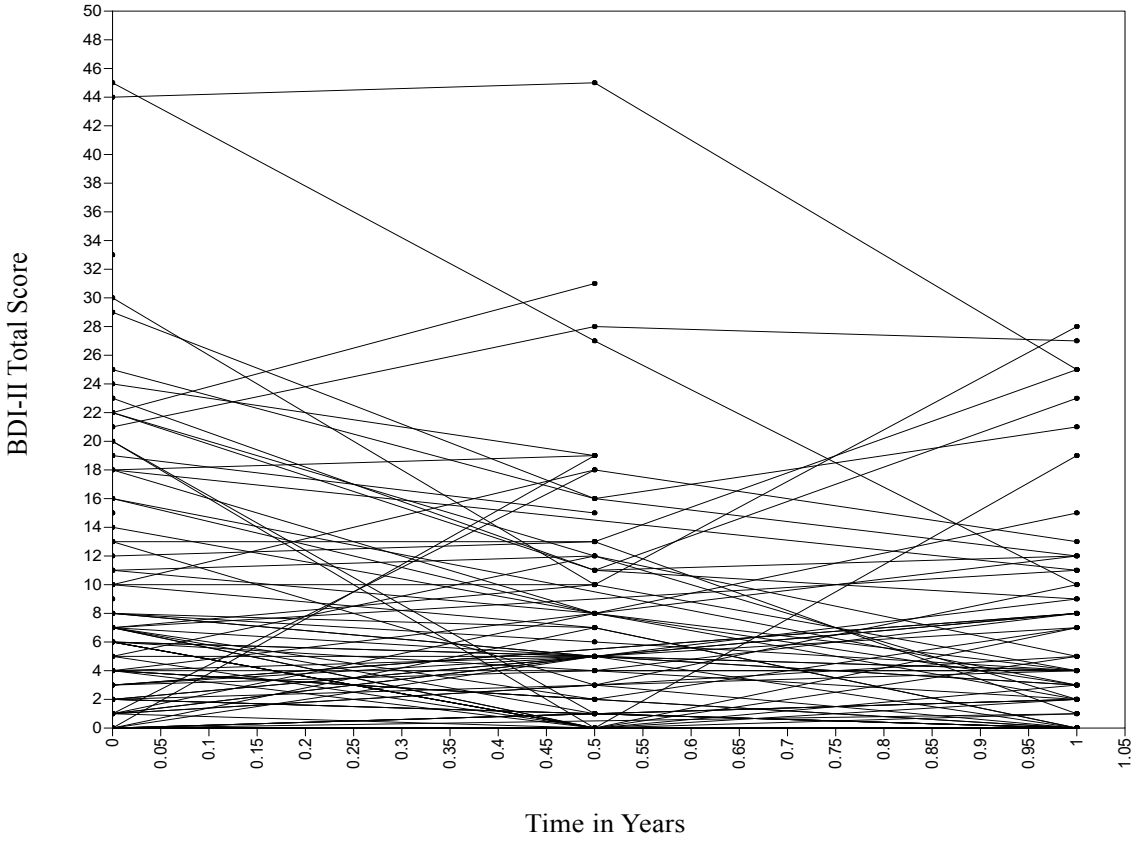


Figure 3.

One-Class Growth Mixture Model

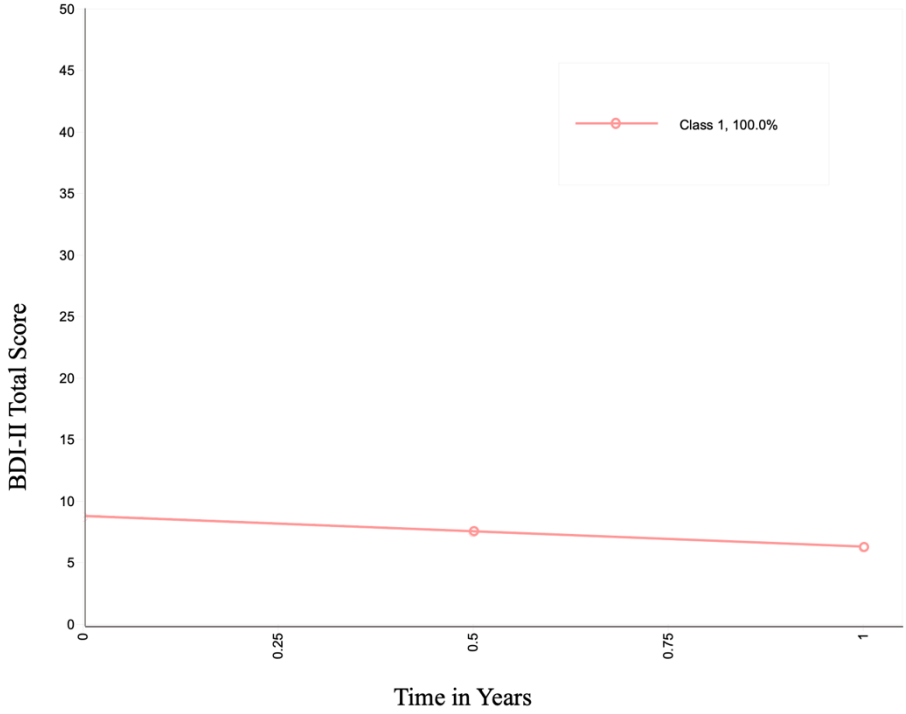


Figure 4.

Two-Class Growth Mixture Model

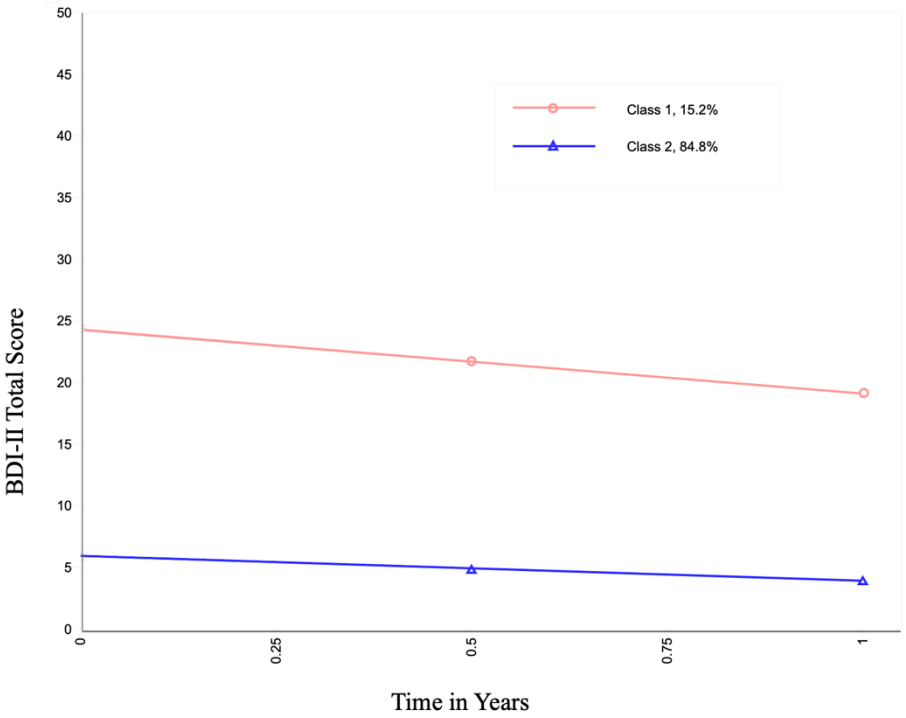


Figure 5.

Three-Class Growth Mixture Model

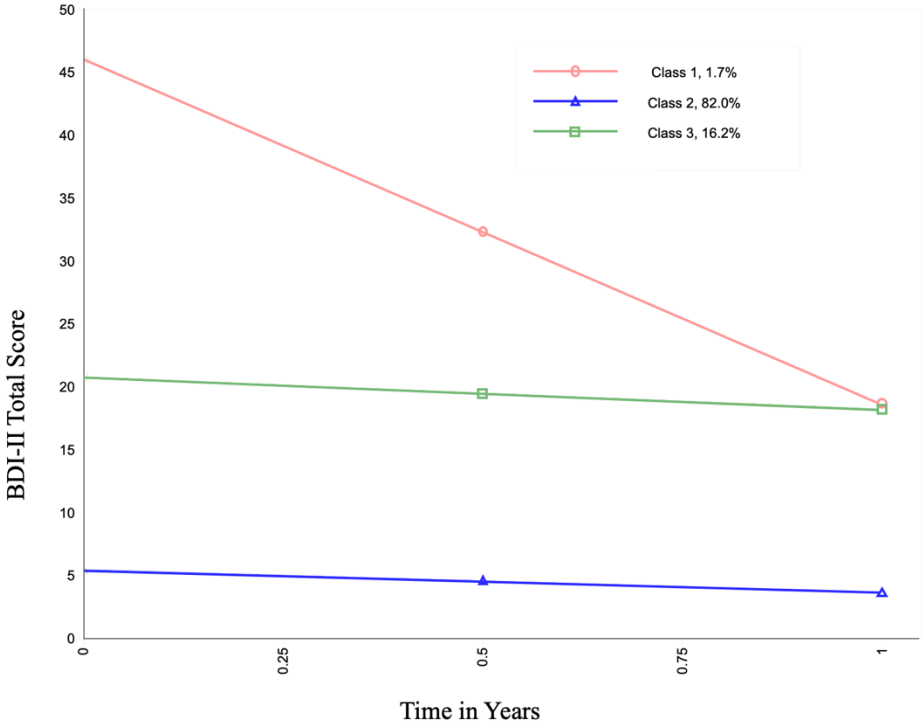


Figure 6.

Four-Class Growth Mixture Model

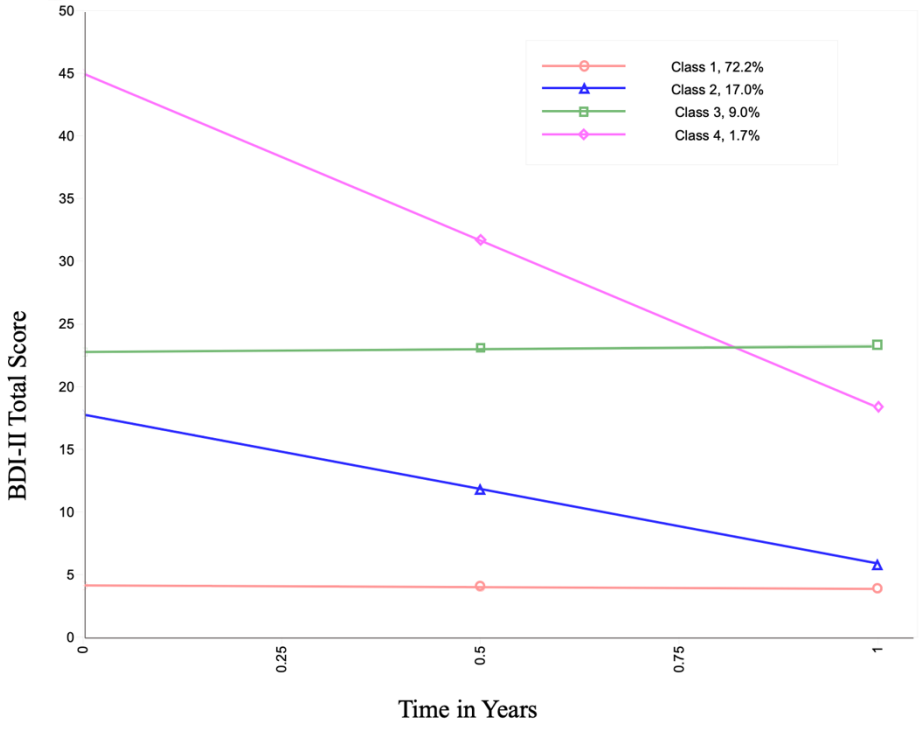
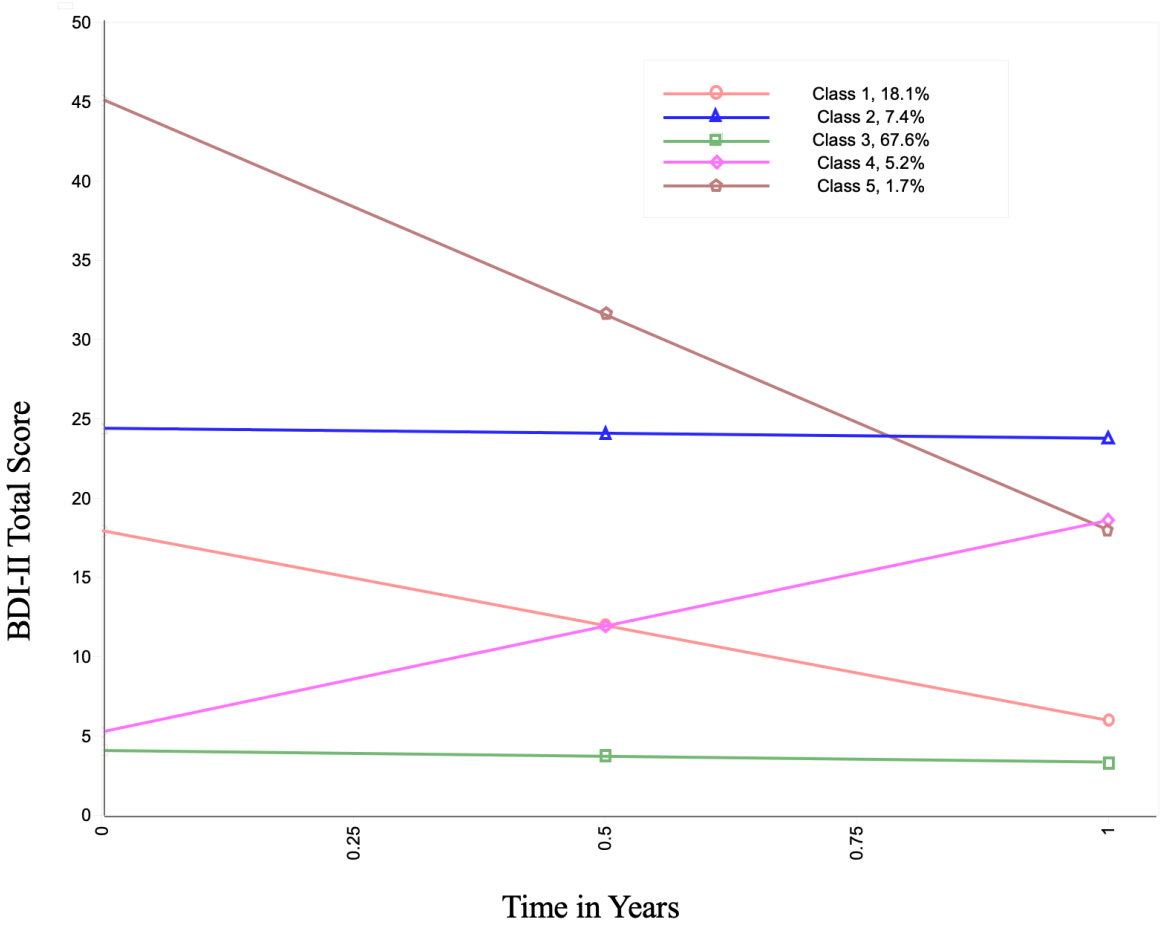


Figure 7.

Five-Class Growth Mixture Model



VITA

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