Illness Uncertainty Longitudinally Predicts Distress Among Caregivers of Children Born With DSD

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Abstract

Objective A subset of parents of children with disorders/differences of sex development (DSD) including ambiguous genitalia experience clinically elevated levels of anxious and depressive symptoms. Research indicates that uncertainty about their child's DSD is associated with parent psychosocial distress; however, previous studies have been cross-sectional or correlational in nature. The current study is the first to examine the longitudinal trajectory of the relationship between caregiver-perceived uncertainty about their child's DSD and caregiver anxious and depressive symptoms across the first 12 months following genital surgery in young children, or if surgery was

not performed, the first 12 months following study entry. **Methods** One hundred and thirteen caregivers ($M_{\text{age}} = 32.12$; 57.5% mothers; 72.6% Caucasian) of children ($N=70$; $M_{\text{age}} = 9.81$ months; 65.7% female) with DSD were recruited from 12 DSD specialty clinics in the United States. Caregivers completed psychosocial measures at baseline, 6 and 12 months following genitoplasty, or study entry if parents elected not to have surgery for their child. **Results** Caregiver illness uncertainty and both anxious and depressive symptoms were highest at baseline and decreased over time ($ps < .05$). Caregiver illness uncertainty predicted symptoms of anxious and depressive symptoms across all time points ($ps < .05$). **Conclusions** Caregivers' perceptions of uncertainty about their child's DSD are highest soon after diagnosis, and uncertainty continues to predict both anxious and depressive symptoms across time. Thus, the initial diagnostic period is a critical time for psychological assessment and intervention, with parent illness uncertainty being an important clinical target.

Key words: anxiety; depression; disorders of sex development; endocrinology; parents.

Introduction

Disorders/differences of sex development (DSD) are rare congenital conditions that affect sex differentiation and may result in ambiguous genitalia (Hughes et al., 2006; Lee et al., 2016; Szymanski et al., 2018a; Szymanski et al., 2018b; Thyen et al., 2006). DSD is typified by a discordance in genetic chromosomal sex, gonadal sex, and/or the appearance of internal/external reproductive organs (Hughes et al., 2006; Wisniewski et al., 2012). Certain types of DSD are diagnosed prenatally or soon after birth, leaving caregivers with an array of challenging and stressful medical or surgical decisions, which may be exacerbated by the limited information about the long-term outcomes of DSD and potential interventions (Wisniewski et al., 2012). Although some caregivers appear to cope well with their child's condition and medical management, a subset experience clinical levels of anxious and depressive symptoms (Ellens et al., 2017; Kim et al., 2018; Perez et al., 2019; Suorsa et al., 2015; Wolfe-Christensen et al., 2012) and concern for their child's future (Ali et al., 2020; Crissman et al., 2011). Approximately a quarter of caregivers report clinically significant anxious symptoms and depressive symptoms during the immediate period following an affected child's birth (Perez et al., 2019). Furthermore, anxious and depressive symptoms are highest following their child's DSD diagnosis and significantly decrease over time (Ellens et al., 2017; Sharkey et al., 2018). Although, these studies have begun to detail parental experiences, relatively little is still known about the nature of psychosocial functioning of caregivers (Sandberg et al., 2017), and even less is known about predictors of such functioning.

Caregivers of children with DSD can experience uncertainty and distress related to the lack of formal diagnosis, unknown long-term outcomes of surgery or timing of surgery, lack of predictability about future gender identity, the need for life-long pharmacological

treatments, unpredictable responses of friends and families, and potential difficulties with sexual functioning and fertility (Crissman et al., 2011; Hughes et al., 2006; Lampalzer et al., in press; McCauley, 2017). Recent research indicates that caregiver perceptions of *illness uncertainty* are important for understanding early parent psychosocial adjustment to their child's DSD (Delozier et al., 2019; Ellens et al., 2017; Perez et al., 2019; Suorsa et al., 2015). Specifically, cross-sectional or correlational studies utilizing portions of the current dataset demonstrate that caregiver-perceived illness uncertainty is associated with increased parent post-traumatic stress, anxious symptoms, and depressive symptoms following a child's DSD diagnosis (Delozier et al., 2019; Ellens et al., 2017; Perez et al., 2019; Suorsa et al., 2015). Furthermore, caregiver perceptions of illness uncertainty within the first 2 years of their child's DSD diagnosis is associated with greater parent decisional regret 12 months later (Ellens et al., 2017).

Importantly, caregiver uncertainty and a range of distress outcomes in both parents and youth have also been linked in the context of other pediatric populations, including families affected by pediatric inflammatory bowel disease, juvenile rheumatic diseases, cancer, and diabetes (Baudino et al., 2019; Chaney et al., 2016; Mullins et al., 2016; Page et al., 2012; Roberts et al., 2019; Szulczewski et al., 2017). Previous research also indicates that caregiver-perceived illness uncertainty is an important predictor of caregiver psychosocial adjustment across a range of pediatric chronic illnesses when evaluating both short-term (e.g., Franck et al., 2015) and long-term follow-up (e.g., Carpentier et al., 2006). Specifically, Carpentier et al. (2006) found that among families affected by type 1 diabetes, caregiver perception of illness uncertainty at baseline was associated with caregiver distress more than 5 years later. However, this study did not examine the trajectory of illness uncertainty and its relationship to caregiver distress,

leaving a gap in the current understanding of the temporal relationship between illness uncertainty and caregiver outcomes.

To date, there remains limited knowledge about the relationship between uncertainty and distress outcomes across time, especially among parents of children with DSD. Therefore, further examination of parental appraisals are needed to better understand familial adjustment processes following a DSD diagnosis. Given the ongoing complexities associated with managing a child's DSD, post-surgical care, and social needs, evaluating the role of uncertainty may be particularly valuable from a longitudinal perspective (Sharkey et al., 2018). Furthermore, it appears that parent uncertainty and psychological distress are highest soon after diagnosis and decrease over time (Ellens et al., 2017; Katz et al., 2018; Sharkey et al., 2018), but the longitudinal trajectory of the relationship of uncertainty to anxious and depressive symptoms has not been examined in parents of children with DSD. A longitudinal study design allows for a more nuanced picture of the psychosocial risk experienced by caregivers during the early course of their child's DSD diagnosis and treatment process, and for identification of when and for whom psychological intervention may be necessary.

The present study aimed to examine caregiver illness uncertainty and both anxious and depressive symptoms across the first 12 months after early genitoplasty (or after study entry for parents who opted to forgo surgery for their child). Utilizing a longitudinal study design with multi-level modeling (MLM), the current study sought to better understand the nature of psychological adjustment among caregivers in the early course of their child's diagnosis with a DSD. First, we hypothesized that higher caregiver illness uncertainty would predict greater anxious and depressive symptoms over time. Second, we hypothesized that caregiver illness uncertainty, anxious and depressive symptoms would decrease over time as parents began to adjust to their child's diagnosis and surgery, if surgery was conducted. Finally, because little is known about those parents who opt for no surgery for their child with a DSD, we provide descriptives of illness uncertainty, anxious and depressive symptoms at each time point in this understudied subgroup of caregivers as an exploratory aim.

Methods

Participants and Procedures

Caregivers were recruited from 12 DSD specialty clinics in the United States. Caregivers were consented during regularly scheduled clinic visits and completed demographic, medical, and psychosocial questionnaires as part of a larger prospective 10-year study.

Portions of this dataset have been previously reported, with different aims and hypotheses (Delozier et al., 2019; Ellens et al., 2017; Perez et al., 2019; Sharkey et al., 2018; Suorsa et al., 2015; Wolfe-Christensen et al., 2017). These previous studies included earlier data collection points, while the current study utilized a larger sample accrued over time and uniquely examined the longitudinal trajectory of the relations of parent illness uncertainty, anxious and depressive symptoms using MLM analyses.

Participants were considered eligible if they were the caregiver of a child who: (a) was <2 years old and was diagnosed with a DSD with moderate to severe genital atypia, as defined by a Prader score of 3–5 for 46, XX DSD and a Quigley score of 3–6 for 46, XY DSD or sex chromosome DSD, (b) had not undergone genitoplasty, and (c) had no organ malformations other than those that affect the reproductive system. Caregivers had to be at least 18 years old, speak English or Spanish as a primary language, and have no severe psychiatric disorders at study enrollment. Caregivers completed measures in-person or via mail at baseline (prior to surgical intervention, if surgery was elected), 6 months after baseline or after genitoplasty when conducted, and at a 12-month follow-up. When two caregivers of the same child each completed the questionnaires, they were asked to respond to items independently. The enrollment rate was 86.4% at the initial report with an attrition rate of 19.0% (Suorsa et al., 2015). Compensation was given to caregivers for cost of travel for study visits. The current study procedure was approved by the Institutional Review Boards at each of the study sites.

Measures

Demographics Form and Chart Review

Caregivers completed a demographics questionnaire assessing child sex of rearing, child age, caregiver relation to child, and race/ethnicity, among other demographic characteristics. Medical chart review provided disease information, such as karyotype and DSD diagnosis, if known.

Parent Perception of Uncertainty Scale

The Parent Perception of Uncertainty Scale (PPUS; Mishel, 1983) is a 31-item questionnaire designed to measure caregiver self-reported uncertainty about their child's illness, its course, and treatment (e.g., "Because of the unpredictability of my child's illness, I cannot plan for the future"). Caregivers respond to items on a 5-point Likert-scale from "strongly disagree" to "strongly agree". The PPUS examines four components of illness uncertainty: ambiguity, lack of information, lack of clarity, and unpredictability. Higher scores indicate greater perceived illness uncertainty. The measure showed good internal consistency

in previous studies of parents with a child with a chronic illness (e.g., [Baudino et al., 2019](#)) and in the current sample ($\alpha = .80$).

Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI; Beck et al., 1988) is a 21-item questionnaire used to assess caregiver self-reported anxious symptoms, with higher scores demonstrating greater levels of anxiety. The BAI is a commonly used measure of adult anxious symptoms examining both physiological and cognitive symptoms experienced during the past month. Symptoms are deemed minimal if they fall in the range from 0 to 7, mild 8 to 14, moderate 15 to 25, and severe 26 to 63. Scores of 14 or greater are considered clinically significant ([Bardhoshi et al., 2016](#)). The measure has previously exhibited good internal consistency in adult samples (e.g., [Fydrich et al., 1992](#)) and in the current sample ($\alpha = .92$).

Beck Depression Inventory-II Edition

The Beck Depression Inventory-II (BDI-II; [Beck et al., 1996](#)) is a 21-item measure used to assess caregiver self-reported depressive symptoms. The BDI-II is one of the most widely used self-report questionnaires to assess adult depressive symptoms. Higher scores demonstrate greater symptoms of depression. Scores that range from 0 to 13 are considered minimal, mild 14 to 19, moderate 20 to 28, and severe 29 to 63. Clinically significant symptoms are considered scores of 14 or greater ([Viinamäki et al., 2004](#)). The measure has demonstrated good internal consistency in adult samples (Beck et al., 1988) and in the current sample ($\alpha = .93$).

Data Analytic Plan

Descriptive statistics and bivariate correlations were conducted as preliminary analyses. Primary analyses controlled for demographic and medical variables, including child sex of rearing, child age, parent sex and age, race/ethnicity, family income, and DSD diagnosis.

Stata version 14.2 was used to conduct MLM, which accounts for clustering of ratings from the same parent (Level 1), or from parents within the same family (Level 2; [Rabe-Hesketh & Skrondal, 2012](#)). Thus, MLM adjusts for the expected similarities in ratings between caregivers of the same child, or between a parent's own ratings at each time point. Intraclass Correlation Coefficients (ICC) examined the proportion of variance due to each level of clustering. All models used maximum likelihood estimation to account for missing data (missing at random), and likelihood-ratio tests after estimation were examined to assess if more complex models (e.g., models that included more predictors) improved fit over simpler models ([Enders, 2010](#)). The variance explained by

fixed and random effects of predictors were also evaluated.

Separate unconditional models first tested the variance of PPUS, BAI, and BDI-II scores without any predictor variables or controls. Conditional models including control variables, followed by BAI and BDI-II models with fixed and random effects of PPUS were then tested. Finally, models testing interactions between PPUS and predictors were examined. The final and most parsimonious models are presented in the results below. Due to the limited power afforded by the small sample size of caregivers who opted for no genitoplasty, analyses were not conducted to assess differences in caregiver uncertainty, anxious and depressive symptoms between those parents whose child had surgery and those who did not. However, exploratory descriptive statistics are included in [Table II](#).

Results

Sample Descriptives

Participants included 113 caregivers ($M_{\text{age}} = 32.12$, $SD = 6.45$; 57.5% mothers) of 70 children ($M_{\text{age}} = 9.81$ months, $SD = 7.31$ months; 65.7% raised female) at baseline. Caregivers were primarily Caucasian (72.6%) and a majority reported an income over \$70,000 (51.3%). The child sample included 45 children with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency and 25 children with another type of DSD, such as 46, XY DSD ([Table I](#)). The majority of the sample (90%) underwent surgery. Additional demographic and disease information can be found in [Table I](#). See [Finlayson et al. \(2019\)](#) and [Perez et al. \(2019\)](#) for further description of clinical and demographic information.

Preliminary Analyses

Caregivers reported an average uncertainty rating of 64.99 ($SD = 15.83$), anxious symptoms rating of 8.42 ($SD = 8.94$), and depressive symptoms rating of 8.81 ($SD = 9.34$) at baseline. Based on clinical cutoff scores ([Bardhoshi et al., 2016](#); [Viinamäki et al., 2004](#)), at baseline 25.9% of caregivers reported clinically significant levels of anxious symptoms and 23.9% caregivers reported clinically significant levels of depressive symptoms (see [Table II](#)). Caregiver uncertainty, anxious and depressive symptoms were highest at baseline, prior to surgery if surgery was conducted. Mother and father reports of anxious and depressive symptoms significantly differed ($ps < .05$), with mothers reporting higher levels of anxious and depressive symptoms. Bivariate correlations identified that several demographic variables were related to the primary variables of interest at baseline. Of note, family income was associated with missingness on outcomes ($p < .05$), with families of lower income having more

Table I. Demographic and Disease Information

	Child (N = 70), N (%)	Caregiver (N = 113), N (%)
Age, mean (SD)	9.81 (7.31)*	32.12 (6.45)
Race/ethnicity		
Caucasian	—	82 (72.6%)
Black/African American	—	4 (3.5%)
Asian/Pacific Islander	—	9 (8.0%)
Multi-racial	—	8 (7.1%)
Other	—	10 (8.8%)
Hispanic	—	37 (32.7%)
Sex of rearing		
Female	46 (65.7%)	65 (57.5%)
Male	23 (32.9%)	48 (42.5%)
Unsure	1 (1.4%)	—
Karyotype		
46, XY	21 (30.0%)	—
46, XX	42 (60.0%)	—
45, X/46, XY	3 (4.3%)	—
Other	4 (5.7%)	—
DSD diagnosis		
CAH	45 (64.3%)	—
Other (e.g., 5-alpha reductase deficiency, androgen insensitivity syndrome)	25 (35.7%)	—
Received genitoplasty	63 (90.0%)	—
Family income		
0–14,999	—	8 (8.9%)
15,000–29,999	—	22 (19.5%)
30,000–49,999	—	15 (13.3%)
50,000–69,999	—	10 (8.9%)
70,000–89,999	—	11 (9.7%)
90,000–99,999	—	9 (8.0%)
100,000+	—	38 (33.6%)

Note. *Age for child is in months. Information collected at baseline. CAH = congenital adrenal hyperplasia; DSD = disorders/differences of sex development.

Table II. Descriptives for Anxious Symptoms, Depressive Symptoms, and Illness Uncertainty

	Overall sample			CS	Surgery			Non-surgery		
	N	M	SD		N	M	SD	N	M	SD
Illness uncertainty										
Baseline	113	64.99	15.83	—	103	64.98	15.91	10	65.10	15.75
6 months	87	61.52	17.47	—	82	61.73	17.92	4	60.75	2.06
12 months	73	54.88	13.25	—	66	54.35	13.40	4	62.25	7.54
Anxious symptoms										
Baseline	112	8.42	8.94	25.9%	102	8.45	8.73	10	8.10	11.48
6 months	86	6.83	8.90	16.3%	81	7.06	9.12	4	3.50	2.38
12 months	71	4.44	6.27	9.9%	66	4.55	6.46	2	2.00	2.83
Depressive symptoms										
Baseline	113	8.81	9.34	23.9%	103	8.81	9.50	10	8.80	7.96
6 months	87	7.05	8.21	14.9%	82	7.01	8.37	4	5.75	4.37
12 months	73	5.86	7.21	11.0%	66	6.08	7.53	4	3.25	0.96

Note. Clinical cutoff scores for the BAI, assessing anxious symptoms, and the BDI-II, assessing depressive symptoms, is a score of 14 or greater. The sample size of non-surgery parents was underpowered for statistical analysis. BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II Edition; CS = percentage of parents with clinically significant scores.

missing data at follow-up. The baseline correlation matrix is included in Table III.

A comparison between parents of those who did or did not have surgery could not be conducted, as only a few families in the current sample elected not to have genitoplasty. This subset of parents ($n = 10$) reported an average uncertainty rating of 65.10 ($SD = 15.75$),

anxious symptoms rating of 8.10 ($SD = 11.48$), and depressive symptoms rating of 8.80 ($SD = 7.96$) at baseline. Anxious and depressive symptoms appear to decrease across the 12 months of the study for this subgroup. Illness uncertainty appeared to decrease from baseline to 6 months, but remained consistent from 6 to 12 months. Further descriptive statistics of

Table III. Bivariate Correlations

Variables	Illness uncertainty	Anxious symptoms	Depressive symptoms
1. Illness uncertainty	–	–	–
2. Anxious symptoms	0.27**	–	–
3. Depressive symptoms	0.30**	0.62***	–
4. Family income	–0.01	–0.32**	–0.22*
5. Caregiver sex	–0.03	–0.28**	–0.32**
6. Caregiver Age	0.08	–0.32**	–0.15
7. Child age	–0.15	0.12	–0.03
8. Child sex of rearing	–0.13	–0.06	–0.07
9. Child DSD diagnosis	–0.08	–0.01	–0.04

Note. * $p < .05$, ** $p < .01$, *** $p < .001$. Time point of report, clustering effects, and suppression effects are not accounted for in this matrix. Variable coding includes: Child Sex, Female = 0, Caregiver Sex, Mother = 0, Child DSD Diagnosis, CAH = 1, Other Diagnoses = 0. Correlation analyses are at baseline. CAH = congenital adrenal hyperplasia; DSD = disorders/differences of sex development.

the non-surgery subset of the sample are provided in [Table II](#).

Illness Uncertainty

In the unconditional model, the proportion of variance explained by differences between families ($ICC = 0.37$) was smaller than that explained by differences between caregivers ($ICC = 0.42$). Thus, greater uncertainty is accounted for by individual caregiver factors (e.g., individual parent illness appraisals), rather than commonalities due to being a part of the same family (e.g., family home environment). Uncertainty decreased over time ($b = -3.10$, $SE = 1.31$, $p < .05$), with no other covariates significantly predicting uncertainty when accounting for time ($p > .05$). Family income trended toward significance ($b = -0.75$, $SE = 0.39$, $p = .05$), with parents in families with greater income reporting less uncertainty. Multi-level model results, excluding interactions and random slopes, are presented in [Table IV](#).

Anxious Symptoms

In the unconditional model, the proportion of variance explained by differences between families ($ICC = 0.22$) was smaller than the proportion of variance explained by differences between caregivers ($ICC = 0.53$). The final model included covariates, uncertainty, and an interaction between uncertainty and time, as predictors of anxious symptoms ($\chi^2(1) = 3.87$, $p < .05$). Anxious symptoms decreased over time, although when accounting for illness uncertainty, time was no longer a significant predictor of anxious symptoms ($p = .17$), due to the presence of a significant interaction. Caregivers with greater uncertainty experienced greater anxious symptoms ($b = 0.18$, $SE = 0.04$, $p < .001$), and this effect weakened over time ($b = -0.06$, $SE = 0.03$, $p < .05$). There was also a random slope of uncertainty at the caregiver level ($b = 0.06$, $SE = 0.01$, 95% CI [0.04–0.09]), meaning that, although the relationship between uncertainty and anxious symptoms weakens overall, it

remains stronger for some parents over time, while weakening more quickly for others.

Caregiver sex ($b = -2.42$, $SE = 1.07$, $p < .05$) and age ($b = -0.22$, $SE = 0.11$, $p < .05$) also predicted anxious symptoms, with fathers and older caregivers having lower anxious symptoms scores than mothers and younger caregivers. No other demographic or medical variables, including child sex of rearing and DSD diagnosis ($p > .05$), significantly predicted anxious symptoms.

Depressive Symptoms

In the unconditional model, the proportion of variance explained by differences between families ($ICC = 0.11$) was smaller than the proportion of variance explained by differences between parents ($ICC = 0.61$). Thus, depressive symptoms are more dependent on individual parental factors, rather than factors related to parenting the same child. The final model included uncertainty, covariates, a random slope of uncertainty at the caregiver level, and an interaction between caregiver sex and uncertainty, as predictors of depressive symptoms ($\chi^2(2) = 9.05$, $p < .05$). Depressive symptoms decreased across time, although when accounting for other covariates, time only trended toward significance ($p = .05$) as a predictor of caregiver depressive symptoms. Caregivers who reported greater uncertainty experienced higher levels of depressive symptoms ($b = 0.23$, $SE = 0.36$, $p < .001$). There was also a random slope of uncertainty at the caregiver level ($b = 0.63$, $SE = 0.01$, 95% CI [0.04–0.10]), meaning that the strength of the relationship between uncertainty and depressive symptoms varied between caregivers. Of note, caregivers of the same child (e.g., mother compared to father of the same child) had more similar patterns of relation between uncertainty and depressive symptoms than caregivers from other families (e.g., mother of one child compared to the mother of another child).

The relationship between uncertainty and depressive symptoms was moderated by caregiver sex ($b = -0.16$, $SE = 0.05$, $p < .01$), with a weaker

Table IV. Multi-Level Model Fixed Effects Results

Outcome	Illness uncertainty	Time	Family income	Caregiver sex	Caregiver age	Caregiver race	Caregiver ethnicity	Child age	Child sex of rearing	Child DSD diagnosis
Illness uncertainty	–	–3.10*	–0.75^	–0.82	0.40	0.10	–2.42	–0.13	–6.78	3.76
Anxious symptoms	0.18***	2.59	2.59	–2.42*	–0.22	–0.50	0.08	–0.00	–0.49	0.79
Depressive symptoms	0.23***	–0.82^	–0.32	5.36	0.022	–0.57	–0.37	0.03	–0.59	0.53

Note. ^ p = .05, * p < .05, *** p < .001. DSD = disorders/differences of sex development.

relationship for fathers. No other demographic or medical variables, including child sex of rearing and type of DSD diagnosis ($p > .05$) significantly predicted depressive symptoms in the final model.

Discussion

Although illness uncertainty is a well-established predictor of caregiver psychological distress in parents of youth with chronic health conditions (e.g., Szulczewski et al., 2017), this study is the first to directly assess the longitudinal trajectory of illness uncertainty among parents of children with DSD and the relation to parental anxious and depressive symptoms. Our findings indicate that illness uncertainty does indeed predict anxious and depressive symptomology across time, with parents of children with DSD who report greater uncertainty also reporting greater distress. These findings are consistent with the literature demonstrating that illness uncertainty is associated with greater worry about the future, negative illness expectations, and ultimately distress (e.g., Chaney et al., 1999; Grupe & Nitschke, 2011). Findings also align with our earlier cross-sectional or correlational studies that used portions of the current dataset with unique aims and hypotheses (Delozier et al., 2019; Ellens et al., 2017; Perez et al., 2019; Suorsa et al., 2015). Thus, parent psychological adjustment may be negatively impacted over time by the added strain associated with uncertain perceptions of the treatment and prognostic ambiguities, which may lead to greater worry about the future impact of the illness, and subsequently heightened distress.

Importantly, in the current study caregivers reported the greatest levels of illness uncertainty, anxious and depressive symptoms at baseline, which was within the first 2 years of having a child born with a DSD ($M_{\text{age}} = 9.81$ months). Similar to the adjustment trajectories identified among families affected by other pediatric chronic medical conditions (Katz et al., 2018) and caregivers of children with DSD (Ellens et al., 2017; Sharkey et al., 2018), it may be that the lack of information about DSD may contribute to greater caregiver distress in this early stage. DSD is a group of rare congenital conditions with great variability that bears unique implications for health and/or treatment. Therefore, parents often have to learn a

considerable amount of new information about their child's specific condition, its etiology, and its management. This initial lack of knowledge may then lead to increased perceptions of uncertainty in their child's condition (Wisniewski et al., 2012). It is promising that levels of uncertainty, anxious and depressive symptoms all decreased over time, yet it may be that the initial diagnostic period is a critical point of intervention for some families.

Indeed, we found that caregivers who reported greater uncertainty at baseline continued to experience greater anxious and depressive symptoms over time. This relationship between uncertainty and greater anxious and depressive symptoms was strongest for mothers and younger caregivers. However, these findings were also observed across the sample, controlling for demographic and disease variables, including child sex of rearing, child age, parent sex and age, parent race/ethnicity, family income, and DSD diagnosis, demonstrating that the impact of illness uncertainty exists regardless of disease and demographic variables. Contrary to previous findings (Wolfe-Christensen et al., 2017), differences in parent psychosocial variables based on child sex of rearing were not observed, which may be attributed to a larger sample size, additional time points, and differences in analytic approach, which presently accounted for clustering by family. In addition, the trending relationship between income and parental perceptions of uncertainty may be explained by the heightened risk for difficulties accessing medical care and resources associated with lower family income. Notably, the current sample included a predominantly wealthy sample, thus an evaluation of a sample of families with greater financial diversity is needed to further explore this trend.

Although, analyses comparing experiences between families of children who did or did not undergo surgery were not possible due to limited sample size, it also appeared that parents who declined surgery experienced similar patterns of decreasing illness uncertainty, anxious symptoms, and depressive symptoms across the time points. However, it appears that in this small subset of the sample, illness uncertainty was consistent from 6 to 12 months. Overall, these findings suggest that many caregivers may learn to cope with or manage their uncertainty over time, as resources are garnered, information is obtained, or families

learn to adjust. However, the initial elevations in distress warrant future assessment of how uncertainty and adjustment may change at other critical periods in child development, such as during puberty.

Notably, the present study illustrates the important role of subjective illness appraisals in relationship to important parent adjustment outcomes. As illness uncertainty is an identifiable and potentially modifiable risk factor, it would likely be a beneficial target for screening and intervention in parents of youth with DSD. To date, no specific evidence-based psychosocial interventions targeting the distress of children with DSD or their parents have been evaluated (Gardner & Sandberg, 2018). However, research does suggest that interventions targeting parent perceived uncertainty benefit parents and youth with other pediatric medical conditions, such as diabetes and cancer (Fedele et al., 2013; Hoff et al., 2005). Consistent with the present findings, interventions that include components of psychoeducation about DSD and its inherent uncertainty, enhancing problem-solving skills to navigate the healthcare system and address family needs, improving communication skills to increase understanding of their child's DSD, and cognitive coping skills to identify and modify uncertain perceptions of DSD may be valuable for caregivers of children with DSD. This may be particularly true for mothers and younger parents, as these demographic factors were related to heightened levels of illness uncertainty and distress. Given that illness uncertainty was greatest for parents at baseline, it may be most beneficial to target illness uncertainty close to the time of diagnosis in an effort to promote adaptive coping strategies early on in the adjustment process.

Although the longitudinal design and novel analytic approach of the present study contribute significantly to our understanding of parental adjustment following their child's diagnosis of a DSD, there are limitations that should be considered. First, it is important to note that our participants were recruited from specialized DSD clinics, and were comprised of mainly Caucasian and relatively affluent families. Income was also related to missingness on our primary outcomes, suggesting a greater loss to follow-up of lower-income families. Replication of these findings with more diverse samples, including families without access to specialized care and those with less severe genital ambiguity, along with recruitment efforts aimed at retaining a diverse sample, are necessary. Although the current sample is relatively large for a group of rare conditions, our power may be limited and replication of our findings in additional samples is imperative. Furthermore, as the current sample did not include a sufficient number of parents who elected for their child to not have surgery, analyses specifically examining the subjective experiences and patterns as to why

these parents choose non-surgery options should be conducted in future studies. The current study relied on parent self-report and future studies should include clinical interviews or multi-modal assessments of parental distress. In the present study, illness uncertainty was assessed broadly, which limits our understanding of which specific aspects of parenting a child with DSD might contribute to caregivers' endorsement of heightened uncertainty. Multi-modal assessments including qualitative interviews may provide additional validity to our clinical assessment and greater understanding of what events or specific patterns of events (e.g., genitoplasty, gender identity, puberty) this population may perceive as most uncertain. The study also was limited to a focus on the first 3 years after diagnosis; future studies should examine even later time points in order to better understand the potential fluctuations in illness uncertainty and parent distress throughout the child's development.

Despite these limitations, our data present novel findings regarding the trajectory of parental distress shortly after their child receives a DSD diagnosis, and how this distress may be impacted by illness uncertainty. Collectively, the results extend previous findings that highlight the role of illness uncertainty in parents of youth of DSD by providing a greater understanding of its longitudinal trajectory in relation to parent anxious and depressive symptoms. This study confirms that illness uncertainty is an important risk factor for later parent anxious and depressive symptoms in a subset of the sample and may be a potential target of interventions aimed at addressing early psychological adjustment for parents of children diagnosed with DSD.

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