Fachbereich Erziehungswissenschaft und Psychologie
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# Disorders of Sex Development

## Psychosocial Aspects

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# Table of Content

# Theoretical Background

## Introduction

The typical prenatal male or female development of the somatic sex is a complex differentiation process affected by multiple genes, enzymes and hormones. Conditions in which the development of the somatic sex is atypical are medically summarised under the umbrella term “Disorders of Sex Development“ (DSD) that was invented in 2005 by the „Chicago Consensus Group on management of intersex conditions“ - an international congress of experts. The Chicago Consensus Group defined DSD as congenital conditions with incongruence between chromosomal, gonadal and phenotypic sex (Lee, Houk, Ahmed, & Hughes, 2006). Along with the new terminology and classification the Chicago Consensus Group stated new clinical guidelines that emphasize the importance of psychosocial care: Because of the complexity of the conditions, counselling and treatment should be provided by multidisciplinary teams that include psychological expertise.

In Germany the need for psychological support of persons with DSD and their families was confirmed by the German Ethical Committee in 2012, a statement of the German Medical Association in 2015 and new guidelines of the German Association of the Scientific Medical Societies (AWMF) published in 2016 (Deutscher Ethikrat, 2012; Stellungnahme der Bundesärztekammer, 2015).

Yet knowledge about DSD is not adequately addressed in university studies ans postgraduate training in psychotherapy. Most research studies focus on medical aspects rather than on psychological or social aspects (Cohen-Kettenis, 2010; Schweizer, Brunner, Schützmann, Schonbucher, & Richter-Appelt, 2009). The two interdisciplinary multicentre studies network DSD and dsd-LIFE were initiated to close these research gap with a quantitative study design based on patient reported outcome and medical diagnoses. With the present cumulative thesis the request for psychosocial research will be addressed, a basis for implementing DSD care in education programme as it was required by the German Ethical Committee and others (Birnbaum et al., 2013; Cohen-Kettenis, 2010; Deutscher Ethikrat, 2012; Richter-Appelt & Schweizer, 2010).

In the following, first the typical prenatal sex development and DSD, then changes in clinical guidelines will be described. Subsequently the current research status, resulting in the research questions, will be presented. The methodical approach will be introduced followed by the three studies of the cumulative thesis. Finally, there is the general discussion which includes a review of the main findings, considerations on training of mental health professionals and the general conclusion of the thesis.

## Prenatal somatic sex development

Although the following description of the typical development of the somatic sex is simplified, it represents a basis to understand a variety of different DSD conditions.[1] This medical background is important for psychosocial research, as DSD is a somatic condition and not a mental health problem.

In the beginning there is no anatomical or gonadal sex in the embryo. Like all organs the reproductive system, the anatomical sex (internal and external sex characteristics) and the gonads (testis and ovaries) develop prenatally during pregnancy. The reproductive organs differentiate sex-dichotomous into male or female when different factors such as genetical information and hormones take effect. The foetal gonads, glands[2] that are able to produces sex characteristic hormones, are able to differentiate into testis or ovaries (a so called bipotential gonad). They produce sex characteristic hormones such as androgens and oestrogens. These hormones exist in both sexes but differ in level. Within the typical prenatal sex development, the undifferentiated gonads develop into testes or ovaries depending on the karyotype of the foetus. The karyotype is usually either XY or XX, as prior to fertilisation the ovule contains a X sex chromosome and the spermatozoon and X or an Y sex chromosome.

Consequently, three sexes can be distinguished: gonadal sex, anatomic sex and chromosomal sex.

The chromosomal sex determines the sex development. The Y chromosome contains the sex determining region (SRY gen)[3], which provides genetic information necessary for the development of the gonads into testes. If this information is missing, which usually is the case if there is an XX karyotype, the undifferentiated gonads will develop into ovaries.[4] Similar to the gonadal sex the anatomic sex (internal and external sex organs) is undifferentiated in the foetus at first. All foetuses have Mullerian and Wolffian ducts - that can develop into female or male internal organs - and undifferentiated external organs. During typical sex development, the genital tubercle for instance will develop in phallus or clitoris. In typical male development with XY karyotype the gonads will develop into testes with Leydig cells which increasingly produce androgens effecting the development of the anatomic sex. The synthesis and action of androgens like testosterone and dihydrotestosterone (DHT) is complex, for different enzymes and receptors cells are needed. Androgens initiate a characteristic male development of the

[1] Parts of the description of the somatic basis have been published in German (Bennecke & Köhler, 2015)

[2] Other glands: thyroid gland, parathyroid, pancreas, pituitary gland, hypothalamus and adrenal glands. Along with the gonads the adrenal glands can produce androgens which can lead to a condition labelled as DSD (Congenital adrenal hyperplasia, CAH)

[3] SRY is known since the late 1980s. SRY directs the production of the protein responsible for the initiation of the testes development: testis determining factor (TDF). TDF stimulates cells to develop into Leydig cells. These testicular cells are able to produce androgens when stimulated.

[4] In addition to SRY numerous other genes are significant for gonadal development e.g. SOX9, DHH, TSPYL1 or DAX1, WNT4, WT1, SF1 that influence SRY and WNT4, RSPO1 and FOXL2 that influence the development of ovaries (Rey & Grinspon, 2011).

external sex organs (androgenisation). Without androgenisation the external sex organs develop female phenotype. At the same time the internal sex organs differentiate into female or male characteristics. The development of the internal sex organs mainly depends on the influence of anti-Mullerian hormone (AMH). AMH is produced by Sertoli cells in the testes. In typical male development, there are high levels of AMH that supress the development of the Mullerian ducts so the Wolffian ducts can differentiate into male internal sex organs. If there is little AMH, the Mullerian ducts will develop into female internal sex organs and the Wolffian ducts do not differentiate (MacLaughlin & Donahoe, 2004).

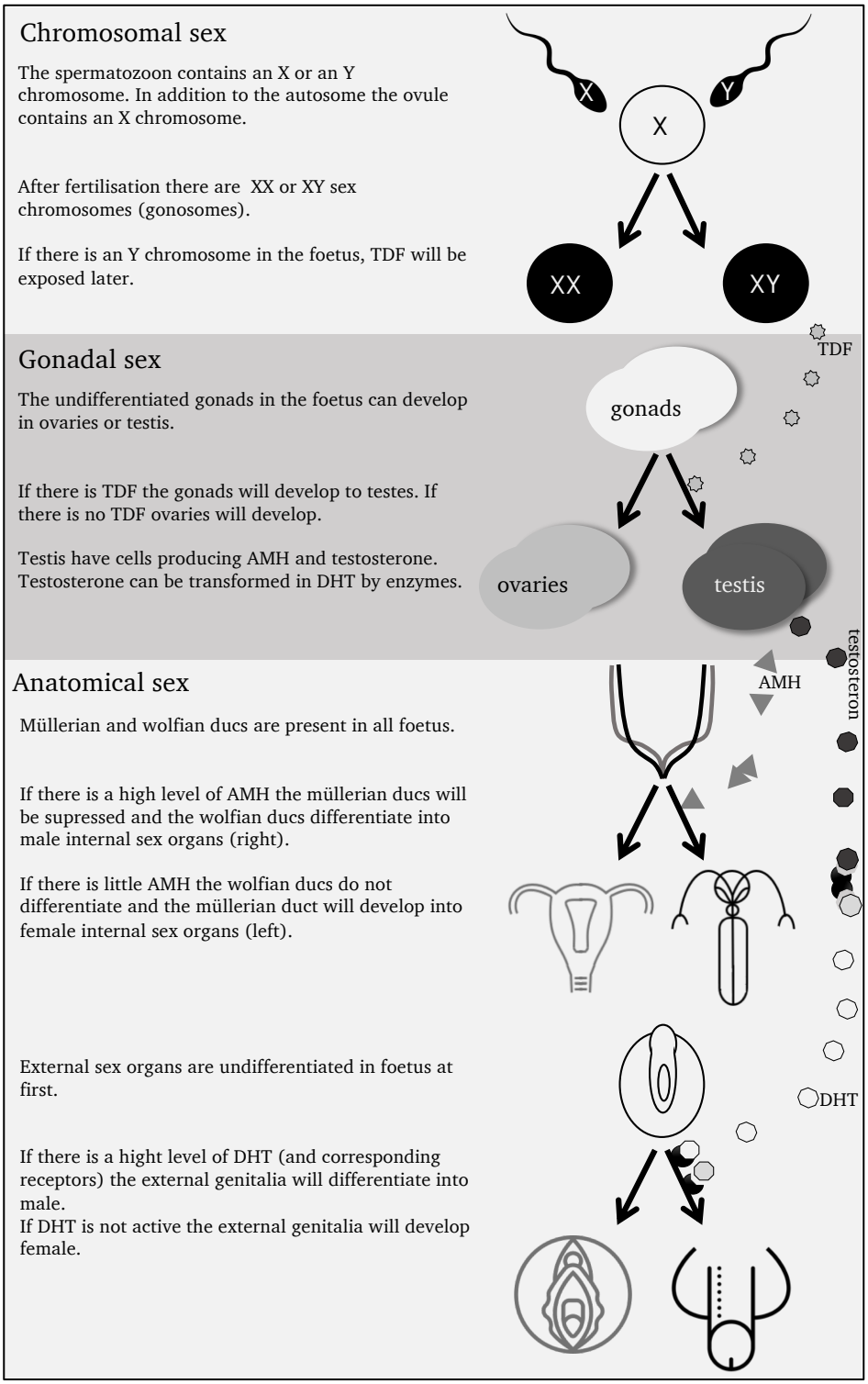
The development of the somatic sex therefore consists of three stages:

a. the undifferentiated stage, when bipotential primitive structures develop independently of the chromosomal sex,
b. gonadal differentiation into ovaries or testes that is initiated by sex characteristic genes,
c. the differentiation of the anatomic sex (internal and external genitalia), which depends on the action of testicular hormones (Figure 1).

If testicular hormones are absent the embryo will develop a female anatomic sex (Rey & Grinspon, 2011). As the foetal sex development is complex, variations of the typical two differentiation pathways occur naturally. In biology, there is no distinct cut-off between male and female; and neither the chromosomal sex, the gonadal sex nor the anatomic sex develop constantly as expected.

Variations in sex development can be related to sex chromosomes, when e.g. ovule or sperm contain more than just one sex chromosome (XXY karyotype in Klinefelter syndrome) or one sex chromosome is missing partly or completely (X0 karyotype in Turner syndrome). In spite of a common set of sex chromosomes, other factors, e.g. a gene variation on SRY, can affect the development of the gonads, which then do not develop into fully functional testis or ovaries (gonadal dysgenesis). Gonadal variation influences their hormonal output, which can affect the development of the anatomic sex. Even though there is a typical XY karyotype, the adrenal steroidogenesis can be variegated due to absence of different enzymes. This can lead to low levels of testicular hormones such as testosterone and dihydrotestosterone (DHT) (in 5a-reductase deficiency and 17βHSD-3 enzyme deficiency). This can lead to little or no androgen effect on the anatomic sex. Even with high levels of androgens there can be little or no androgen effect, if there is a partial or complete absence of receptors for androgens (androgen insensitivity syndrome, AIS). Also, enzyme variations can lead to high levels of androgens produced in the adrenal gland, even when the chromosomal sex and gonadal development was typical for female development. This leads to a prenatal effect of androgens on the anatomic sex (congenital adrenal hyperplasia, CAH).

**Figure 1: Prenatal sex development**




TDF: testis determining factor (TDF), DHT: dihydrotestosterone, AMH: Anti-Müllerian Hormone

There are many different atypical pathways for prenatal sex developments and not all genetic reasons have been found, yet. Genetic variations can be found on manifold genes that determine proteins, enzymes or receptors and most of these genes are not located on the sex chromosomes. E.g. the gene for the enzyme 5α-reductases (SRD5A2) that converts testosterone in DHT is located on chromosome 2. In foetal development DHT is essential for androgenisation of the anatomic sex. Over 100 variations of this gene are known resulting in atypical sex development and still new variations are discovered constantly (Ittiwut et al., 2017).[5]

The DSD classification proposed by the Chicago Consensus Group is summarising divers atypical sex developments (Lee et al., 2006). The new nomenclature was supposed to be a simple and logical classification of the causes of DSD (Hughes, 2008). Conditions were classified depending on the karyotype: Sex chromosome DSD, 46,XY DSD and 46,XX DSD. Table 1 lists the DSD conditions.

**Table 1: DSD classification proposed by the Chicago Consensus Group**

| Sex Chromosome DSD | 46,XY DSD | 46,XX DSD |
|---|---|---|
| 45,X (Turner syndrome and variants) | Disorders of gonadal (testicular) development: (1) complete gonadal dysgenesis (Swyer syndrome); (2) partial gonadal dysgenesis; (3) gonadal regression; and (4) ovotesticular DSD | Disorders of gonadal (ovarian) development: (1) ovotesticular DSD; (2) testicular DSD (e.g., SRY, duplicate SOX9); and (3) gonadal dysgenesis |
| 47,XXY (Klinefelter syndrome and variants) | Disorders in androgen synthesis or action: (1) androgen biosynthesis defect (e.g., 17-hydroxysteroid dehydrogenase deficiency, 5_RD2 deficiency, StAR mutations); (2) defect in androgen action (e.g., CAIS, PAIS); (3) luteinizing hormone receptor defects (e.g., Leydig cell hypoplasia, aplasia); and (4) disorders of anti-Müllerian hormone and anti-Müllerian hormone receptor (persistent Müllerian duct syndrome) | Androgen excess: (1) foetal (e.g., 21-hydroxylase deficiency, 11-hydroxylase deficiency); (2) fetoplacental (aromatase deficiency, POR [P450 oxidoreductase]); and (3) maternal (luteoma, exogenous, etc) |
| 45,X/46,XY (MGD, ovotesticular DSD) | | Other (e.g., cloacal exstrophy, vaginal atresia, MURCS [Müllerian, renal, cervicothoracic somite abnormalities], other syndromes) |
| 46,XX/46,XY (chimeric, ovotesticular DSD) | | |

Sex chromosome DSD has an incidence of 1:426, the most common conditions are Turner syndrome and Klinefelter syndrome (Nielsen & Wohlert, 1991). Even if only occurring in 1:2000-5000 individuals CAH is one of the most frequent DSD conditions (46, XX DSD) (Marumudi et al., 2013). Most other specific conditions, most of them classified as 46, XY DSD, have an incidence of 1:100.000 birth and less (Lux et al., 2009).

[5] As DHT is not necessary in female development, a variation of SRD5A2 in individuals with XX karyotype has no effect on the sex development.

All in all, approximately up to 1 of 200 individuals has an atypical prenatal sex development (Arboleda et al., 2013; Lee et al., 2016).

The effects of an atypical sex development are very diverse, as are their causes. Particularly individuals, after whose birth the question "Is it a boy or a girl?" cannot be answered easily, are in the public discourse. Usually the anatomic sex is the basis for this first gender determination. In DSD the anatomic sex may have developed neither typically female nor typically male. These “ambiguous” genitals[6] can cause a lot of confusion among parents as well as obstetricians. In this context often the term “intersexuality” is used. Other DSD conditions are associated with a typical female appearance of the external genitalia. Later in life for instance due to the absence of puberty, surprising androgenisation or other medical examinations (e.g. after a hernia) a DSD condition is discovered.

## Medical guidelines

The change in medical care over the last decades is particularly significant in terms of variants of sex development, where there is both, "male" and "female" characteristics. Such developments have previously been labelled with the term "intersexuality" or "hermaphroditism". In these cases, the so-called "Optimal Gender Policy" had been the medical treatment guideline since the 1950s (Money, 1994; Money, Hampson, & Hampson, 1955). The fundament of the "Optimal Gender Policy" was the assumption that the development of a stable gender identity as a man or woman is of great importance for mental health. It was assumed that the (genital) appearance as a boy or girl was crucial for the development of a stable gender identity in childhood. It was also assumed that gender-based education promotes the development of a stable gender identity. Prenatal biological factors were viewed as less important for the development of gender identity.[7] The "Optimal Gender Policy" therefore assumed, in accordance with the social perceptions of its time, that children are born neutral with regard to their gender and that a gender identity as a boy or girl is built up as a result of socialisation. In order to ensure the development of stable gender identity in children with "ambiguous" genitalia, it was recommended that the child’s anatomy should be surgically adjusted to one of the two sexes at an early stage. This usually led to feminisation of the external and internal genitalia. It was then recommended to the parents to raise the children according to the chosen gender. In the process, the children were not told about

[6] The term “ambiguous” is used in order to describe that the genital appearance cannot be classified in one of the two sex categories male or female. Nevertheless, these genitals are unambiguously genitals. The term “ambiguous” is therefore not accurate.

[7] The case study of David Reimer gained tragic fame. Born in 1965 the toddler "Bruce" lost his penis through an accident and was then assigned female and sex assignment surgery was performed at an early age (Money, 1975). In his childhood “Brenda” was not told about the natal sex (Bradley, Oliver, Chernick, & Zucker, 1998). In adolescents “Brenda” found out about the condition and thereupon he choose to live as a male, but unfortunately was not able to cope with his experiences and committed suicide in 2004.

their condition, since it was to be feared that this could destabilise the children (Bradley et al., 1998).

The "Optimal Gender Policy" has been increasingly criticised within the last decades, especially by support groups and those affected. Treatment guidelines as well as patient rights have changed gradually. Since the early 1990s, the clinical care of individuals with DSD has developed into a holistic and patient-oriented approach in specialised teams (Roen & Pasterski, 2013). Changes of treatment recommendations were described by the Chicago Consensus Group, which met in 2005 (Lee et al., 2006). The Chicago Consensus statement also confirmed the importance of specialized interdisciplinary teams that include psychosocial care (Lee et al., 2006; Liao & Simmonds, 2013). In contrast to the traditional role of mental health specialists, psychological care in DSD is supposed to be an integral part of the care right from the start (Moran & Karkazis, 2012; Sandberg & Mazur, 2014). In Germany, the German Ethics Committee began to engage to the topic in 2010, followed by the new AWMF guidelines for "variants of sex development" and an statement of the German Medical Association (Deutscher Ethikrat, 2012; Stellungnahme der Bundesärztekammer, 2015). In addition to the specialised interdisciplinary care, current treatment recommendations focus on informed consent. Informed consent means that children must be informed about their medical condition at an early stage and should participate in decisions about medical treatment. Current statements and guidelines have in common that they do not give a general treatment recommendation and refer to the heterogeneity of medical conditions. Surgical procedures, which are not a medical necessity, are discussed with regard to ethical and legal aspects. Current recommendations renounce from early surgical interventions in children with "ambiguous" genitalia, to which the "optimal gender policy" primarily referred.[8] But still especially surgical interventions in individuals with CAH and XX karyotype and a high level of androgenisation are discussed controversially.

## Content of psychosocial research

Psychosocial research in DSD is both, broad - as many different topics are taken into consideration – and limited, especially as most studies include only small sample sizes and medical condition of the study participants are diverse.

### Terminology

The first issue when approaching DSD is its terminology. Even if the DSD terminology is widely accepted especially in medical research, it is not accepted by all clinicians and researchers. The new terminology of the Consensus Group resulted in criticism and was largely discussed right after its proposal (Clune-Taylor, 2010; Diamond & Beh, 2006; Feder, 2009; Feder & Karkazis, 2008; Guntram, 2013; Hughes, 2015; Hughes, Nihoul-

[8] The topic “gender identity” has lost importance in current guidelines. Although “gender identity” is based on a bio-psycho-social explanatory model, nowadays the opinion that biological, mostly prenatal factors determine gender identity seems to spread.

Fékété, Thomas, & Cohen-Kettenis, 2007; Liao & Roen, 2013; Lin-Su, Lekarev, Poppas, & Vogiatzi, 2015; Pasterski, Prentice, & Hughes, 2010a; Simmonds, 2007). On the one hand the classification of some of the conditions under the umbrella term has been criticised. Some authors stated that CAH should not be included in the DSD classification (Gonzalez & Ludwikowski, 2016). Others proposed to exclude Klinefelter syndrome and Turner syndrome from the DSD classification, contrary to the inclusive approach of the consensus (Pasterski, Prentice, & Hughes, 2010b; Wit, Ranke, & Kelnar, 2007). Consequently, research about these three conditions rarely includes the DSD nomenclature. On the other hand, the nomenclature "Disorders of Sex Development" resulted in criticism. The term *disorder* was regarded as too pathologizing, failing to recognise that DSD could be considered as variants of normal and implying that all individuals with DSD are in need of fixing (Diamond & Beh, 2006; Reis, 2007). Consequently, alternative terms like *Variations of Reproductive Development* or *Variations of Sex Development* were proposed (Diamond & Beh, 2006; Simmonds, 2007). Some authors avoid the term *disorder* by using DSD as an acronym for *Differences of Sex Development*, *Divergences of Sex Development* or *Diverse Sex Development* (Arbeitsgruppe Ethik, 2008; Brunner et al., 2016; D'Alberton et al., 2015; Liao & Simmonds, 2013; Reis, 2007; Schweizer, Brunner, Handford, & Richter-Appelt, 2013; Streuli, Köhler, Werner-Rosen, & Mitchell, 2012; Streuli, Vayena, Cavicchia-Balmer, & Huber, 2013; Tamar-Mattis, Baratz, Baratz Dalke, & Karkazis, 2013; Wiesemann, Ude-Koeller, Sinnecker, & Thyen, 2010). Moreover some authors decided to use the term "intersex", some linked this term with the DSD acronym "intersex/DSD" and others refer to the phenotype of the anatomic sex by using „ambiguous genitalia"(Kraus, 2015; Lathrop, Cheney, & Hayman, 2014; Michala, Liao, Wood, Conway, & Creighton, 2014; Roen & Pasterski, 2013). Despite the extensive discussions, which are held by support groups, empirical studies on the opinion of those affected are rare. There are four studies addressing this issue (Davies, Knight, Savage, Brown, & Malone, 2011; Davis, 2013; Guntram, 2013; Lin-Su et al., 2015). These studies include only small samples sizes with recruitment bias, as they were recruited mainly via support groups. Partly these studies refer to caregivers and not to individuals with DSD themselves. In one study the DSD condition of the participants remained unclear and in another individuals with conditions not classified as DSD were included. Furthermore, these studies show that there is equivocal opinion on the DSD terminology. So far there is no systematic evaluation of the opinion on the term DSD from a large sample of adults with different conditions classified as DSD.

**Quality of Life and psychological wellbeing**

Despite the controversy of the DSD classification, all DSD conditions have in common, that they are long-term physical conditions. Depending on the impact of androgens, the functional impairment of the gonads and the reproductive system, DSD can have different effects on the individual's body and health. In general long-term physical health conditions are associated with higher levels of psychological problems compared to the general population (Liao & Simmonds, 2013). Often in psychosocial research Quality of

Life and psychological wellbeing are addressed, two indicators of successful adaptation to the condition. Until 1999, no studies adequately addressed Quality of Life for individuals with DSD (Meyer-Bahlburg, 1999; Schober, 1999b). Recently, an increasing number of psychologically oriented outcome studies assessing a wider range of psychosocial topics have been performed (Roen & Pasterski, 2013). Reviews on Quality of Life and psychological outcomes for adults with DSD cited nine original articles from 1995 to 2004 and fifteen from 2005 to 2014 (Nordenstrom, 2015; Schützmann et al., 2009; Wisniewski & Mazur, 2009; Zainuddin, Grover, Shamsuddin, & Mahdy, 2013). Although these studies address Quality of Life and psychological wellbeing of individuals with DSD, the results varied greatly. The studies are hardly comparable due to different diagnostic groups, heterogeneous samples, marked variations in overall quality, age groups and recruitment strategies. Often sample sizes are small. Additionally, it is difficult to compare the results directly due to many differences in the methodologies, but even in studies using the same method, the findings varied (Zainuddin et al., 2013). Consequently, the results are inconsistent and many findings cannot be generalised as almost all studies were limited by selection bias (Schützmann et al., 2009). It can be concluded that research about Quality of life and psychosocial outcomes in individuals with DSD are both scarce and inconsistent (Nordenstrom, 2015). All current reviews highlight the poor research status and conclude that all conditions are understudied (Wisniewski & Mazur, 2009).

**Psychological support for parents of children with DSD**

On one hand parents influence the wellbeing of their child, on the other they are most often addressees of the interdisciplinary DSD team when diagnosis is given in early childhood. Parents of children with other chronic conditions reported massive changes in daily life – a broken life world (Seiffge-Krenke, 2013). In addition to coping with the chronic condition of a child, the uncertainty, if a decision on the gender of rearing is needed, is especially likely to increase parental stress (Jürgensen, Hampel, Hiort, & Thyen, 2006). Gough, Weyman, Alderson, Butler, and Stoner (2008) highlighted the fundamental shock caused by the uncertain sex status of a child and documented parental struggles to negotiate a coherent gender identity for their children. There is a basic belief in a dichotomous sex in society and therefore in most parents; a profound conviction that a child is a boy or a girl (Lathrop et al., 2014; Sanders, Carter, & Goodacre, 2011). Atypical gender role behaviour and gender dysphoria in childhood and adolescence may foster confusion and stress in parents. It is likely that parents who experience caring, accepting and encouraging support are more prone to be able to develop these attitudes towards their child (Richter-Appelt, 2012). An atmosphere of uncertainty, fear and denial hampers positive development as described above (Richter-Appelt, 2013). Psychological support could be a successful approach to help parents to cope with their child's condition and foster positive family relationships. Therefore it has been recommended that interdisciplinary care of DSD should include a psychologist (Deutscher Ethikrat, 2012; Lee et al., 2006). It is assumed that appropriate counselling of parents and family starting at diagnosis is needed in order to achieve the best possible

development and quality of life for children and adolescents with DSD (Hiort, 2012; Moran & Karkazis, 2012). But yet it is unknown to what extent parents of children with DSD express their need for psychological support and if uncertainty of the sex, atypical gender behaviour or other factors influence this need.

**Other areas of psychosocial research**

Next to these fields of psychosocial research that will be addressed within the following research questions, psychosexual development and ethical considerations are often focussed in current research about DSD. In this thesis, it was chosen not to focus on these particular topics, as research about psychosexual development is frequent and does not primarily refer to clinical care. At the same time articles about ethical considerations most often make early sex assignment the subject of research, a topic only relevant for a minority of the DSD conditions. The acceptance of the DSD nomenclature, mental wellbeing and the need for psychological support of parents of children with DSD on the other hand, are closely linked to clinical care and relevant for most individuals with DSD. Nevertheless, research about psychosexual development and ethics is significant and was addressed within other sub studies of the two multicentre research studies that will be described after the specification of the research questions of this thesis.

## Research Questions

Considering the gap in psychosocial research three research questions that are relevant for clinical DSD care were identified:

1. Does the opinion of individuals with conditions classified as DSD about the DSD terminology conform with the dissatisfaction expressed by researchers, clinicians and support groups and should it be therefore avoided?
2. How do individuals with different DSD conditions rate their Quality of Life and their psychological wellbeing, and how do diagnostic groups differ?
3. Do parents of children with DSD express a need for psychological support and does gender and treatment related factors influence this need, so that psychological care for parents may focus on specific issues?

## Methodical approach

The research questions were approached with two quantitative multicentre research studies. Details of the methods will be described within each of the sub studies addressing the research questions. Yet the two multicentre research studies network DSD and dsd-LIFE will be introduced shortly in the following.

**Network DSD**

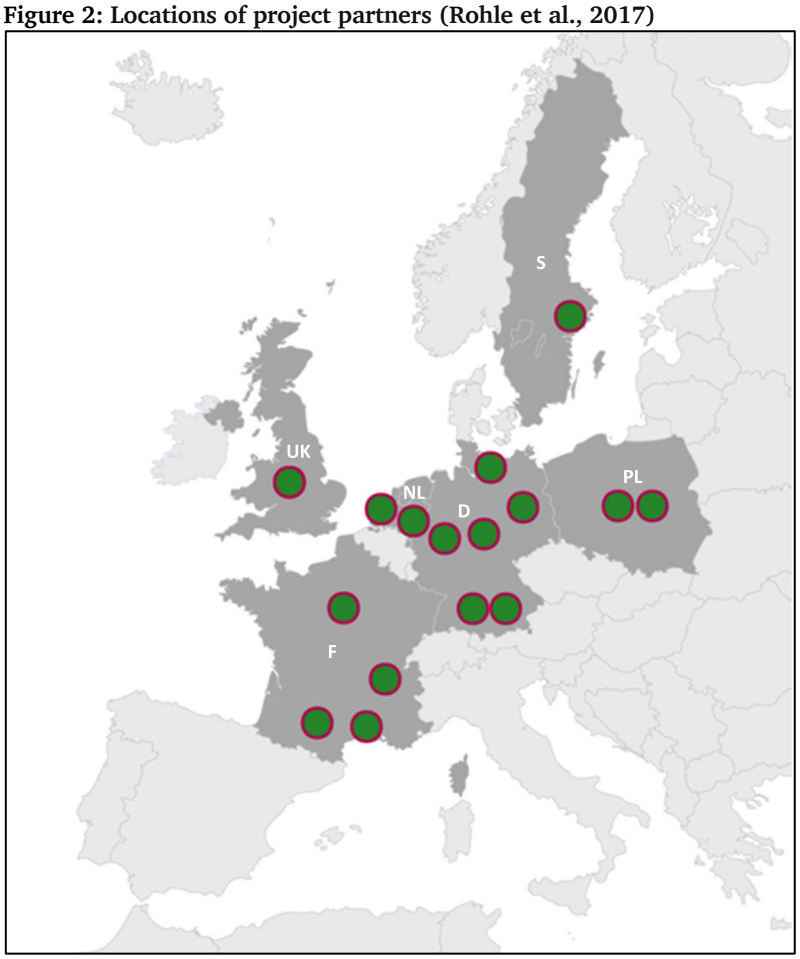
The clinical evaluation study of the German network DSD funded by the German Federal Ministry of Education and Research (BMBF) investigated the clinical outcomes and health care situation of children, adolescents, and adults with DSD. It was the first multicentre outcome study in this field including individuals with DSD conditions

following the generic definition of a discrepancy of chromosomal, gonadal and phenotypical sex (excluding Klinefelter and Turner Syndromes) in German speaking countries. Network DSD was a large-scale clinical evaluation study on quality of life, gender identity, treatment satisfaction, coping, and problems associated with diagnoses and therapies in individuals with disorders of sex development (DSD). Recruitment took place at four study centres in Germany and at five sites in Austria and Switzerland between January 2005 and December 2007. A psychosocial inquiry of children, adolescents and adults with DSD and their parents was performed. All participants and/or their parents gave written informed consent for participation and release of medical data to the interviewer and the principal investigator. A total of 439 children and adolescents, their parents and adults with DSD participated. The study was described in detail by Lux et al. (2009).

**dsd-LIFE**

The European research group dsd-LIFE initiated a multicentre clinical evaluation study funded by the European Union Seventh Framework Programme (FP7/ 2007-2013). The study aimed to assess quality of life (QoL) as a measure of psychosocial adaptation, psychosexual and mental health aspects as major outcomes. Health status and functioning, medical and surgical therapies, participants' views on health care, psychological and social support as well as sociodemographic factors were investigated. In addition, ethical considerations in the field of DSD were addressed and previous experiences with health care were gathered. Recruitment between 2014 and 2015 took place in 14 different medical centres in six countries: Poland, Sweden, Germany, France, United Kingdom and the Netherlands (Figure 2). Inclusion criteria of the study followed a generic definition of DSD as incongruence of the chromosomal, gonadal, and phenotypic sex with a laboratory-confirmed diagnosis or clinical diagnosis by a physician. The dsd-LIFE study comprised two parts: a) A medical interview, with blood tests, bone scans and a physical examinations and b) a patient reported outcome questionnaire consisting of standard questionnaires and questionnaires specifically developed for the purpose of this study. All participants gave written informed consent for the study. In total 1040 individuals with DSD participated in dsd-Life, making it the largest study with individuals with DSD worldwide to date. For details of the study design see Rohle et al. (2017).

**Figure 2: Locations of project partners (Rohle et al., 2017)**




The following centres participated in the study: France: Université Claude Bernard Lyon; Le Centre Hospitalier Universitaire Montpellier; Université Paris-Sud, Paris; Le Centre Hospitalier Universitaire de Toulouse. Germany: Charité Universitätsmedizin Berlin; Ludwig-Maximilians-Universität, München; University of Lübeck; Universitätsmedizin Göttingen; Westfälische Wilhelms-Universität Münster. Poland: Medical University of Lodz; Children's Memorial Health Institute, Warszawa. Sweden: Karolinska Institutet, Stockholm. United Kingdom: University of Birmingham. The Netherlands: VU University Medical Center, Amsterdam; Radboud University Nijmegen Medical Center, Nijmegen

# Study I

## „Disorders or Differences of Sex Development? View of Affected Individuals on DSD Terminology“

A slightly changed version of this chapter has been published as:

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Bennecke, E., & De Vries, A. (2016). *The DSD-LIFE study: First results on terminology, mental health and gender*. Presentation at the EuroPSI, Surrey.

## Abstract

Over a decade ago, the "Consensus Group on management of intersex condition" proposed *Disorders of Sex Development* (DSD) as umbrella term for "congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical". The Group recommended the terminology be sensitive to concerns of individuals having these conditions. Yet, controversy rages over the term DSD. This multicentre clinical evaluation study was initiated as part of the European research group dsd-LIFE to evaluate patient-reported outcome. In total, 1040 individuals with conditions labelled as *Disorders of Sex Development* were recruited in Poland, Sweden, Germany, France, United Kingdom and the Netherlands. All participants were asked to rate the terms describing their conditions. Overall, a large majority of participants (69%) reported that the term *Disorders of Sex Development* applies to their condition or that they feel neutral about it. Most participants preferred terms that were specific to their somatic condition. Overall, our data do not support the view that, in general, the term *Disorders of Sex Development* is insensitive to concerns of affected persons and that it should therefore be abandoned. However, in the clinical encounter, we recommend that clinicians evaluate each patient's preferences.


## Introduction

Over a decade ago the "International Consensus Conference on Intersex" in Chicago proposed *Disorders of Sex Development* and its acronym *DSD* as a new umbrella term for "congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical" (Lee et al., 2006). One goal of the Chicago Consensus issued in 2006 was to replace "particularly controversial terms" such as "intersex, pseudohermaphroditism, hermaphroditism, sex reversal, and gender-based diagnostic labels", which had been criticized as imprecise and stigmatizing (Dreger, Chase, Sousa, Gruppuso, & Frader, 2006; Dreger, Chase, Sousa, Gruppuso, & Frader, 2005; Houk, Lee, & Rapaport, 2005). A more appropriate terminology, the Chicago consensus argued, should be:

(1) Precise when applying definitions and diagnostic labels,
(2) Flexible to incorporate new information, yet robust enough to maintain a consistent framework,
(3) Descriptive and reflecting genetic aetiology when available and accommodate the spectrum of phenotypic variation,
(4) Valued by clinicians and scientists,
(5) Understandable to individuals and their families,
(6) Sensitive to the concerns of individuals with these conditions (Lee et al., 2006).

According to the Chicago consensus, conditions can be classified into three groups depending on karyotype and pathogenesis: sex chromosome DSD, XY DSD and XX DSD. Sex chromosome DSD includes mixed gonadal dysgenesis (46,XY/45,XO), 46,XY/46,XX conditions as well as Turner syndrome and Klinefelter syndrome. XY DSD incorporates XY gonadal dysgenesis, androgen insensitivity syndrome (AIS), disorders of androgen synthesis, disorders of AMH synthesis and action, and severe hypospadias. The XX DSD category includes congenital adrenal hyperplasia (CAH), XX gonadal dysgenesis, and uterine and

vaginal anomalies. Thus, the umbrella term *Disorders of Sex Development* includes conditions with diverse genetic aetiology, varying levels of prenatal androgen effects, and varying phenotypes of genitalia (Jürgensen et al., 2010). It is recognized that this is not an ideal classification as, for example, ovotesticular DSD karyotypes vary to a large degree and may be listed within any of the three categories.

Today, the new nomenclature is widely accepted, although not by all clinicians and researchers (Pasterski et al., 2010a). Some authors argue that the diagnosis CAH should not be included in *Disorders of Sex Development,* since in most cases gender identity and gender assignment is not problematic. Also, males with CAH do not present with developmental problems of the reproductive system (Gonzalez & Ludwikowski, 2016). The ESPE Diagnosis Classification published in 2007 stated that "disorders of gonadal differentiation, that do not result in sex reversal/virilised female infant/under virilised male such as: Klinefelter syndrome and Turner syndrome" should be excluded from the section sex chromosome DSD (Wit et al., 2007), contrary to the inclusive approach of the Chicago consensus (Pasterski et al., 2010b). A search in PubMed over the last decade shows that in publications on "Turner syndrome" only 2.6%, and on "Klinefelter syndrome" only 4.4%, mention the term *Disorders of Sex Development*. Rather than using *Disorders of Sex Development*, some authors prefer umbrella terms like *ambiguous genitalia* (Michala et al., 2014), *intersex* (Kraus, 2015; Lathrop et al., 2014) or *intersex/DSD* (Roen & Pasterski, 2013) for conditions which could be labelled as *Disorders of Sex Development*.

Although the Chicago consensus aimed at replacing potentially stigmatizing vocabulary by less controversial terms, the new terminology nevertheless resulted in criticism (Clune-Taylor, 2010; Diamond & Beh, 2006; Feder, 2009; Feder & Karkazis, 2008; Guntram, 2013; Hughes, 2015; Hughes et al., 2007; Liao & Roen, 2013; Lin-Su et al., 2015; Simmonds, 2007). Some critics complained that international peer support groups had not sufficiently been consulted when creating the new term. The term *disorder* was seen as unnecessarily pathologizing, falsely implying that all persons with *Disorders of Sex Development* are in need of surgical or hormonal intervention, whereas that some or all conditions labelled as *Disorders of Sex Development* could be considered variants of the normal (Diamond & Beh, 2006; Reis, 2007). Consequently, alternative terms like *Variations of Reproductive Development* or *Variations of Sex Development* have been proposed (Diamond & Beh, 2006; Simmonds, 2007). Some authors avoid the term *disorder* by using *DSD* as an acronym for *Differences of Sex Development*, *Divergences of Sex Development* or *Diverse Sex Development* (Brunner et al., 2016; D'Alberton et al., 2015; Liao & Simmonds, 2013; Reis, 2007; Roen, 2019; Schweizer et al., 2013; Streuli et al., 2012; Streuli et al., 2013; Tamar-Mattis et al., 2013; Wiesemann et al., 2010). There is an ongoing controversy between some health professionals and some support groups over the use and understanding of the term *Disorders of Sex Development*. This may also explain why some clinicians apparently do not value its use.

Yet, in spite of the ongoing controversy among experts, there is insufficient empirical evidence on how individuals having conditions that might be classified as *Disorders of Sex Development* think about the terminology themselves. In a UK study with a rather small

sample of parents of children having *Disorders of Sex Development*, 18 out of 19 preferred the term *Disorders of Sex Development* over the term *intersex*, yet, only 7 agreed that *Disorders of Sex Development* was an acceptable term to describe an individual's overall condition when it has not been possible to assign them male or female at birth (Davies et al., 2011). In-depth interviews with 37 participants from the USA who were all familiar with the term *Disorders of Sex Development* also indicated that the term was not uniformly accepted by those it purports to describe (Davis, 2013). Interviews with individuals with Turner syndrome and Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome from Sweden showed that none of the interviewed persons (N = 23) used the term *Disorders of Sex Development* (Guntram, 2013). Another study in the US examining via e-mail survey the views of 128 women with CAH and 408 parents or other family members showed that only 1.0% of the total cohort had a favourable opinion of the term *Disorders of Sex Development*, whereas over 71.0% disliked or strongly disliked it (19.1% neutral, 8.9% don't mind it) (Lin-Su et al., 2015). In a study evaluating the opinions of 202 members of an AIS support-group, only 17% liked the term. The majority preferred *intersex*, *Variation in Sex Development*, and *Difference of Sex Development* over *Disorders of Sex Development* (Johnson et al., 2017). A qualitative interview study with 33 parents and 22 young people with personal experience of *intersex/DSD* showed that the vast majority of participants across samples agreed that *DSD* understood as *Disorders of Sex Development* was a negative term, even though some thought it was accurate (Lundberg, Hegarty, & Roen, 2018).

These studies show that there are equivocal opinions on the term *Disorders of Sex Development*, although many participants seem to dislike the term. However, the empirical evidence, so far, does not justify generalized conclusions. Most studies include only small samples sizes (Davies et al., 2011; Davis, 2013; Guntram, 2013; Lundberg et al., 2018), two studies only recruited parents (Davies et al., 2011; Tiryaki et al., 2018), and in one study the majority of participants were parents or other family members (Lin-Su et al., 2015). In one study, the medical condition of the participants was unclear (Guntram, 2013). In one study individuals with CAH and XY karyotype were included, although this condition is not covered by the DSD classification (Lin-Su et al., 2015). Finally, in many studies participants were recruited through support groups and therefore samples might not represent the views of individuals who are not organized in such groups.

To date, the views of individuals representing the full range of conditions that could be classified as *Disorders of Sex Development* (*DSD*) have not been systematically evaluated. There is no conclusive evidence whether these individuals feel that the term *Disorders of Sex Development* applies to their condition, whether they prefer other terms and whether their views are related to their respective medical condition. Moreover, the reluctance of some clinicians to adopt the DSD classification scheme may be because of uncertainty regarding their patients' concerns and objections. Thus, it is unclear whether the use of this terminology in clinical contacts should be recommended or not.

The current study addressed these questions using a large dataset from a quantitative cross-sectional outcome study carried out by the dsd-LIFE research network.

# Method

## Participants

In total, 1,040 individuals with congenital atypical development of chromosomal, gonadal or anatomical sex were recruited. Recruitment took place in Poland (Pl), Sweden (S), Germany (D), France (F), United Kingdom (UK) and the Netherlands (NL) between 2014 and 2015. Inclusion criteria of the study followed a generic definition of DSD as incongruence of the chromosomal, gonadal, and phenotypic sex with a laboratory-confirmed diagnosis or clinical diagnosis by a physician. Participants were classified into five diagnosis groups: CAH, Turner syndrome, Klinefelter syndrome, conditions with XY karyotype, and participants with conditions that do not fit into the other groups ("other conditions") (Table I.1). This was deemed necessary to clarify if the medical condition and related experiences were associated with participants' view on the terminology. The most frequent conditions were CAH, Turner syndrome, and Klinefelter syndrome. Given the varying incidences of conditions labelled as *Disorders of Sex Development*, and in order to build comparable group sizes, different rare conditions with XY karyotype were summarized in one separate group, in accordance with the proposed DSD classification "XY DSD". Participants with some extremely rare conditions were grouped separately. If sample sizes of subgroups with different rare conditions in the heterogeneous groups XY karyotype and other conditions were large enough, data were analysed quantitatively. This was possible for complete AIS, partial AIS, complete and partial gonadal dysgenesis, XX gonadal dysgenesis, hypospadias, 17-beta HSD, 45,X/46,XY and others with Y material. Overall, 173 (17.8 %) participants had contact with a support group within the last 12 months (by country: Pl 6.7%, S 15.4%, D 19.2%, F 4.4%, UK 28.6%, NL 35.3%). Other sample characteristics were described in detail previously (Rohle et al., 2017).

**Table I.1. Description of the cohort and group classification**

| Group | CAH | | Turner | | Klinefelter | | conditions with XY Karyotype | | Other conditions | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n = 226* | | *n = 301* | | *n = 218* | | *n = 222* | | *n = 73* | |
| Medical condition | Salt-wasting (*n*=111), Simple virilizing (*n*=66), Non-classical (*n*=34), STAR (*n*=1), 3b-hydroxylase deficiency (*n*=2), 11b-hydroxylase deficiency (*n*=6), POR (*n*=2), Unknown (*n*=4) | | Monosomy [*45,X*] (*n*=150), Mosaics [*45,X/46,XX*] (n=31), Isochromosomes (*n*=59), Deletions (*n*=19), Polyploidy (*n*=16), Ring material [*45,X/46,X,r(X)*] (*n*=12), Not to classify and unknown (Turner) (*n*=14) | | 47,XXY (*n*=204), 47,XXY/46,XY (*n*=6), 47,XXY/46,XX (*n*=3), Not to classify and unknown (Klinefelter) (*n*=5) | | Complete gonadal dysgenesis (*n*=21), Partial gonadal dysgenesis (*n*=37), XY ovotestis (*n*=5), cAIS (*n*=71), pAIS (n=35), 3b-hydroxylase deficiency (*n*=2), 17-beta HSD (*n*=11), 5-alpha RD (*n*=4), 17-Hydroxylase/ 17,20 lyase defect (*n*=1), Hypospadias (*n*=25), Not to classify and unknown (with XY Karyotype) (*n*=10) | | 45,X/46,XY and others with Y material (*n*=45), 47,XYY (*n*=1), XX gonadal dysgenesis (*n*=20), XX ovotestis (*n*=1), 46,XX testicular males (*n*=6) | |
| | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* |
| Germany | 91 | 40.3 | 43 | 14.3 | 38 | 17.4 | 57 | 25.7 | 15 | 20.5 |
| France | 62 | 27.4 | 116 | 38.5 | 26 | 11.9 | 42 | 18.9 | 28 | 38.4 |
| The Netherlands | 27 | 11.9 | 82 | 27.2 | 88 | 40.4 | 46 | 20.7 | 7 | 9.6 |
| Poland | 15 | 6.6 | 3 | 1 | 23 | 10.6 | 54 | 24.3 | 12 | 16.4 |
| Sweden | 12 | 5.3 | 46 | 15.3 | 35 | 16.1 | 18 | 8.1 | 11 | 15.1 |
| United Kingdom | 19 | 8.4 | 11 | 3.7 | 8 | 3.7 | 5 | 2.3 | 0 | 0 |
| Age | | | | | | | | | | |
| mean (*sd*) | 30.44 | (11.38) | 32.23 | (13.28) | 39.56 | (15.25) | 28.79 | (12.24) | 28.19 | (11.5) |
| <19 years | 40 | 17.7 | 54 | 17.9 | 28 | 12.8 | 51 | 23.0 | 20 | 27.4 |
| 20-24 | 46 | 20.4 | 59 | 19.6 | 17 | 7.8 | 51 | 23.0 | 12 | 16.4 |
| 25 - 44 | 112 | 49.6 | 130 | 43.2 | 89 | 40.8 | 93 | 41.9 | 34 | 46.6 |
| ≥45 | 28 | 12.4 | 58 | 19.3 | 84 | 38.6 | 27 | 12.2 | 7 | 9.6 |
| Contacted support group in the past 12 month | | | | | | | | | | |
| No | 189 | 87.5 | 217 | 77.2 | 163 | 81.1 | 172 | 82.3 | 60 | 89.6 |
| Yes | 27 | 12.5 | 64 | 22.8 | 38 | 18.9 | 37 | 17.7 | 7 | 10.4 |

CAH= congenital adrenal hyperplasia, AIS= androgen insensitivity syndrome: cAIS= complete androgen insensitivity syndrome, pAIS= partial androgen insensitivity

Syndrome Isochromosomes: *45,X/46,X,i(Xq)* | *46X,i(Xq)* | *45,X/46,X,i(Xq)/47,X,i(Xq)*; Deletions: *45,X/46,X,del(X)* | *46,X,del(X)*; Polyploidy: *45,X/46,XX/47,XXX* | *45,X/47,XXX* | *45,X/46,XX/47,XXX/48,XXXX*;

### Study design

A multicentre clinical evaluation study was initiated as part of the European research group dsd-LIFE, funded by the European Union Seventh Framework Programme (FP7/ 2007-2013). Details of the study design were described previously (Rohle et al., 2017). All participants gave written informed consent for the study.

### Measures

All participants were asked whether the term *Disorders of Sex Development* applied to their medical condition: "The term *Disorders of Sex Development* applies to my medical condition". Response options were: strongly agree, partly agree, neither agree nor disagree, partly disagree, strongly disagree.[9]

Additionally, participants were asked to rate a number of alternative terms. They were derived from a literature survey and feedback from advocacy and support groups. Since the study was performed in six European countries, terms were translated in compliance with the linguistic validation process of the international translation guidelines (Rohle et al., 2017). Participants answered the questions (a) "Which of the following terms should be used by doctors to describe your condition in medical terms?", (b) "Which term do you prefer to use for your condition in everyday life e.g. with friends, family, colleagues?". They could choose up to ten term from various terms from a list (Table I.3) and, if deemed necessary, also insert new ones. Rating was on a Likert scale from 10 = very good to 0 = very bad. Alternative terms were later classified into four groups: (i) potential umbrella terms for all conditions, (ii) umbrella terms including a potentially pathologizing messages such as *disorder*, *dysgenesis* or *defect*, (iii) umbrella terms without pathologizing messages, and (iv) terms applying only to specific conditions (see Table I.3). Because of its prominence in the literature, the term *intersex* was analysed separately. Rating of alternative terms was optional, in order not to burden participants with too many obligatory questions.

### Statistical analysis

In order to analyse the influence of (1) age, an ordered logistic regression model with age as the only parameter was applied. Moreover, we analysed the association between the views on *Disorders of Sex Development* and 2) being a member of a support group, (3) recruitment country, and (4) diagnosis group using $\chi 2$ tests and (5) small diagnosis subgroups using Fisher's exact test. Post-hoc comparisons were done with the $\chi 2$ test (diagnosis group) and Fisher's exact test (country).

Regarding alternative terms that could be used by (a) doctors and (b) in everyday life, no detailed statistical analysis was possible, since rating was optional and not all individuals rated all terms. The groups rating specific terms cannot be regarded as independent from each other and, therefore, no inter-individual and no intra-individual testing was done. Terms are presented using the mean values of their ratings (integers from 0 – very bad to 10

[9] Since we wanted to assess the participants' understanding of the term, we did not provide an explanation of the DSD terminology.

– very good; regarded as continuous) and standard deviations. In order to compare ratings of two terms or two groups of terms, differences in ratings were calculated and expressed in relation to their pooled standard deviation. If terms were to be grouped (i-iv), their weighted mean values and pooled standard deviations were used.

The term "intersex" was assessed separately using simple, linear regression to identify associations of ratings to (1) age, (2) being a member of a support group, (3) country, and (4) diagnosis group.

Due to the exploratory nature of the analysis, *p* values were considered non-confirmatory and no adjustment for multiple testing was done. R (version 3.2.2) was used for all analyses (R_Core_Team, 2016).

## Results

### Disorders of Sex Development

Results for the question "The term *Disorders of Sex Development* applies to my medical condition" are presented in Table I.2 and Figure I.1. No association with (1) age and (2) being a member of a support group could be identified (data not shown). There was an association between ratings of the term *Disorders of Sex Development* (3) and recruitment country ($p < 0.001$) (Figure I.2). The post hoc tests showed that participants from Poland and Sweden rated the terminology more positive than participants from the other countries (post hoc test with $p<0.05$: Pl vs. D, F, NL, S; S vs. F, NL; D vs. NL). An association between ratings of the term *Disorders of Sex Development* and (4) diagnostic group was identified ($p < 0.001$) (Figure I.2). Post hoc tests showed that participants with XY karyotype in particular rated the terminology more positive than the Turner, Klinefelter, and CAH groups (post hoc with $p < 0.01$: XY karyotype vs. Turner, Klinefelter and CAH). There was an association between the ratings of *Disorders of Sex Development* and (5) small diagnosis subgroups ($p < 0.001$). Participants with conditions with no androgen effect on phenotype (complete AIS, complete gonadal dysgenesis, XX gonadal dysgenesis), and participants with hypospadias rated *Disorders of Sex Development* less positively than participants having conditions with androgen effect (partial AIS, partial gonadal dysgenesis, 45,X/46,XY and others with Y material, 17-beta HSD).

**Figure I.1. Participants' responses to the statement "The term *Disorders of Sex Development* applies to my medical condition" (*n*=941)**

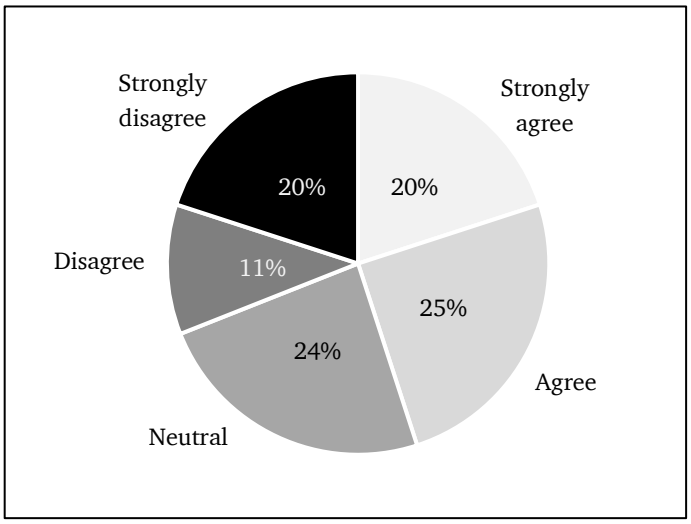



**Figure I.2. Participants' responses to the statement "The term *Disorders of Sex Development* applies to my medical condition"; Country and group comparison**

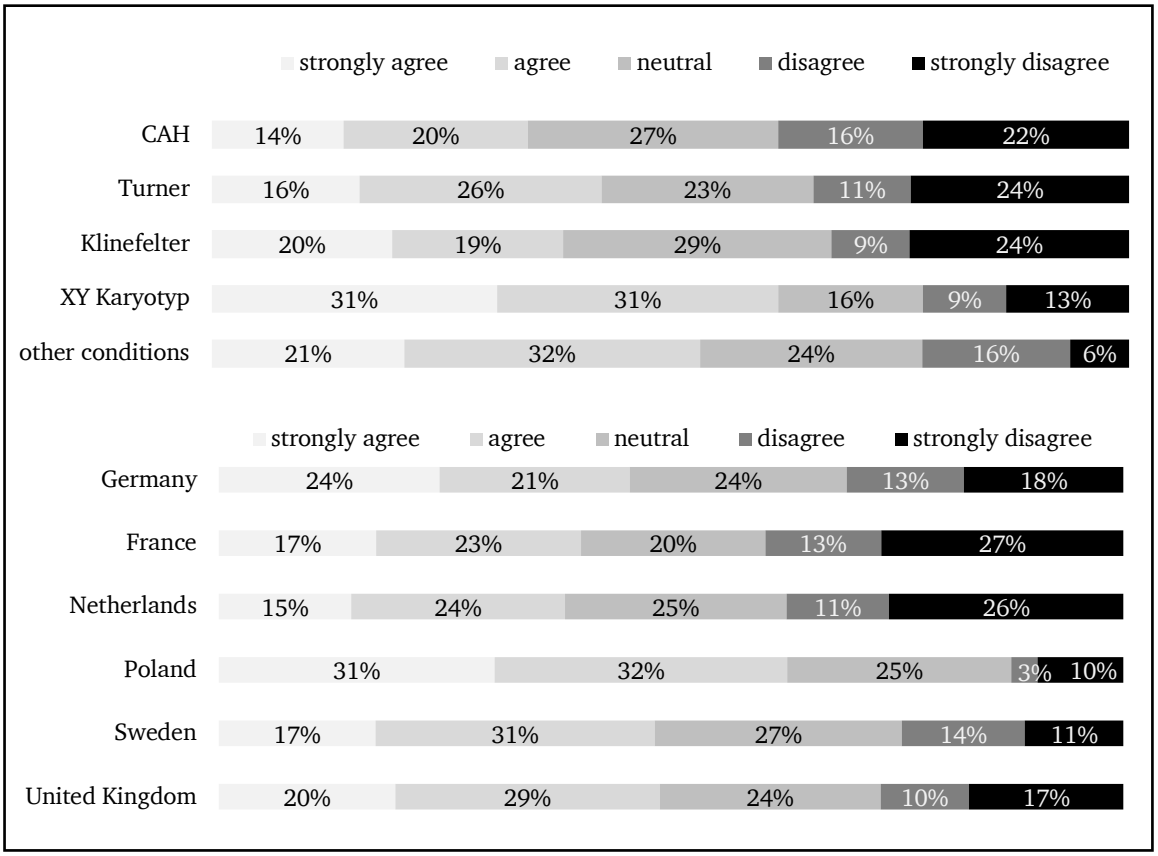


**Table I.2. Participants' responses to the statement "The term *Disorders of Sex Development* applies to my medical condition"**

| | | Strongly agree | Agree | Neutral | Disagree | Strongly disagree | Total |
|---|---|---|---|---|---|---|---|
| | | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) |
| Total | | 189 (20.1) | 233 (24.8) | 223 (23.7) | 107 (11.4) | 189 (20.1) | 941 (100) |
| Country comparison: | Germany | 58 (24.4) | 50 (21.0) | 57 (23.9) | 31 (13.0) | 42 (17.6) | 238 |
| | France | 41 (17.4) | 53 (22.6) | 48 (20.4) | 30 (12.8) | 63 (26.8) | 235 |
| | The Netherlands | 31 (14.6) | 50 (23.6) | 52 (24.5) | 24 (11.3) | 55 (25.9) | 212 |
| | Poland | 32 (30.5) | 34 (32.4) | 26 (24.8) | 3 (2.9) | 10 (9.5) | 105 |
| | Sweden | 19 (17.3) | 34 (30.9) | 30 (27.3) | 15 (13.6) | 12 (10.9) | 110 |
| | United Kingdom | 8 (19.5) | 12 (29.3) | 10 (24.4) | 4 (9.8) | 7 (17.1) | 41 |
| Group comparison: | CAH | 30 (14.4) | 42 (20.1) | 57 (27.3) | 33 (15.8) | 47 (22.7) | 209 |
| | Turner | 44 (16.1) | 72 (26.4) | 63 (23.1) | 29 (10.6) | 65 (23.8) | 273 |
| | Klinefelter | 37 (19.7) | 35 (18.6) | 55 (29.3) | 16 (8.5) | 45 (23.9) | 188 |
| | XY Karyotype | 65 (31.1) | 64 (30.6) | 33 (15.8) | 19 (9.1) | 28 (13.4) | 209 |
| | others | 13 (21.0) | 20 (32.3) | 15 (24.2) | 10 (16.1) | 4 (6.5) | 62 |
| Rare conditions*: | cAIS | 21 (30.4) | 21 (30.4) | 10 (14.5) | 7 (10.1) | 10 (14.5) | 69 |
| | Complete gonadal dysgenesis | 7 (33.3) | 4 (19.0) | 3 (14.3) | 1 (4.8) | 6 (28.6) | 21 |
| | XX gonadal dysgenesis | 5 (35.7) | 3 (21.4) | 0 | 5 (35.7) | 1 (7.1) | 14 |
| | pAIS | 12 (37.5) | 15 (46.9) | 3 (9.4) | 1 (3.1) | 1 (3.1) | 32 |
| | Partial gonadal dysgenesis | 9 (27.3) | 9 (27.3) | 10 (30.3) | 2 (6.1) | 3 (9.1) | 33 |
| | 45,X/46,XY and others with Y material | 6 (15.0) | 14 (35.0) | 15 (37.5) | 2 (5.0) | 3 (7.5) | 40 |
| | 17-beta HSD | 7 (63.6) | 2 (18.2) | 0 | 0 | 2 (18.2) | 11 |
| | Hypospadias | 2 (9.5) | 8 (38.1) | 5 (23.8) | 5 (23.8) | 1 (4.8) | 21 |

*with $n \geq 10$ participants in dsd-LIFE; cAIS= complete androgen insensitivity syndrome, pAIS= partial androgen insensitivity syndrome

**Alternative terms**

A minority of the cohort chose to rate alternative terms (Table I.3). Participants who rated *Differences of Sex Development* had a slightly better opinion about this term than participants who rated *Disorder of Sex Development* (see Table I.3). On average, (i) potential umbrella terms were rated positively (m = 5.49, pooled sd = 3.37). The weighted mean of (ii) potentially pathologizing and of (iii) non-pathologizing terms differed in 0.01 pooled standard deviations only (m = 6.24, pooled sd = 3.13 to m = 6.26, pooled sd = 3.05). (iv) Specific terms (m = 7.86, pooled sd = 2.98) were rated 0.75 pooled standard deviations better than umbrella terms.

Participants were asked to rate terms with regard to usage in (a) medical context as compared to (b) everyday life. In most cases ratings of the terms in (a) medical context and (b) everyday life differed less than 0.25 pooled standard deviations (data are not presented). With respect to five terms the ratings of (a) and (b) differed more than 0.25 (but less than 0.5) pooled standard deviations. Participants rated four specific terms (*hormonal disorder of the gonads*, *XXY*, *complete AIS* and *21-hydroxylase deficiency)* slightly better, if used by (a) doctors (m = 6.25, sd = 3.1/ m = 7.55, sd = 3.07/ m = 8.14, sd = 2.88/ m = 7.54, sd = 2.78) as compared to in (b) everyday life (m = 5.27, sd = 3.17/ m = 6.62, sd = 3.56/ m = 7.29, sd = 3.25/ m = 6.16, sd = 3.2). In contrast, the term *intersex* was rated slightly more positively if used in (b) everyday life (m = 5.75, sd = 3.72) as compared to by (a) doctors (m = 4.6, sd = 3.6).

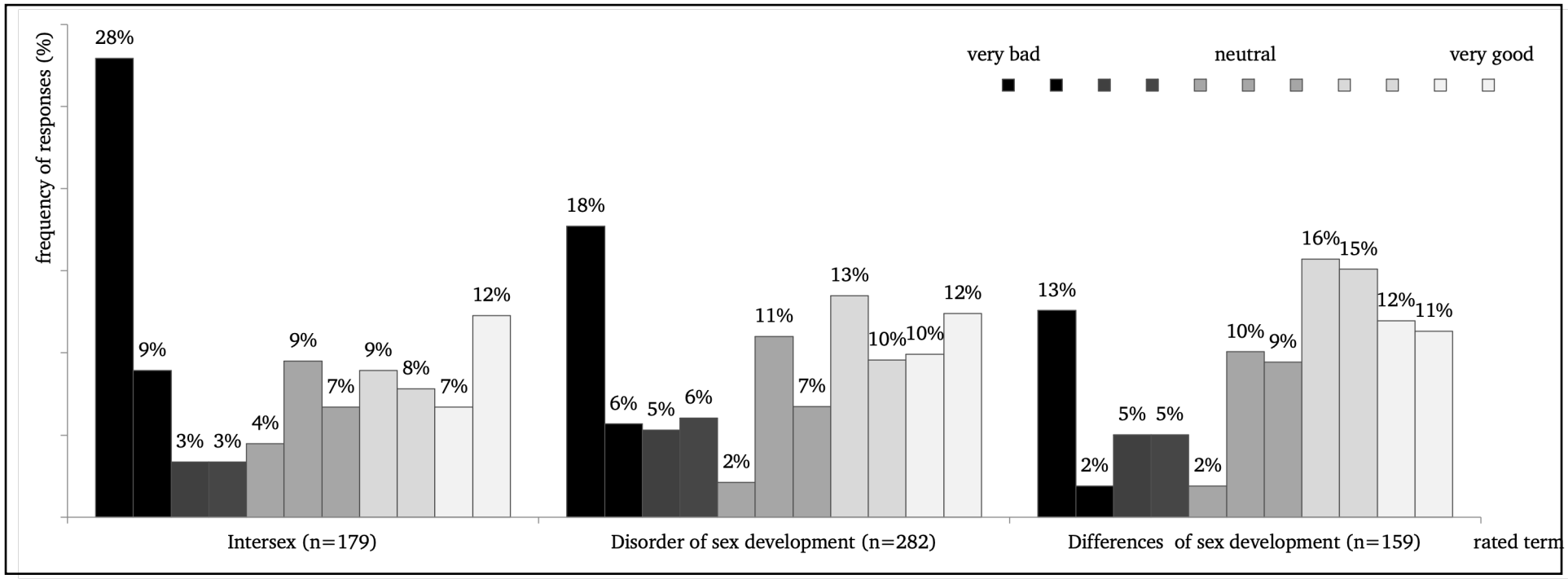
Figure I.3 shows the distribution of the ratings of the terms *intersex*, *Disorders of sex Development* and *Differences of Sex Development*. There was no association between participants' views of the term *intersex* and (1) age, (3) country, or (4) diagnosis group (data are not presented). Participants who had engaged in (2) support groups in the last 12 months rated *intersex* better than other participants (no support group membership: m = 3.94; support group membership: m = 5.51; p = 0.011 for linear regression).

**Table I.3. Participants' responses to the question "Which of the following terms should be used by doctors to describe your condition in medical terms?"**

| | *n* | mean | *sd* |
|---|---|---|---|
| (i) Potential umbrella terms: | | | |
| DSD as 'Disorder of Sex Development' | 282 | 5.23 | 3.5 |
| DSD as 'Difference of Sex Development' | 159 | 5.93 | 3.18 |
| DSD as 'Diverse Sex Development' | 98 | 5.05 | 3.32 |
| VSD as 'Variation of Sex Development' | 139 | 5.82 | 3.38 |
| (ii) Umbrella terms with a potential pathological message: | | | |
| Hormonal disorder of the gonads | 81 | 6.25 | 3.1 |
| Hormonal disorder of the adrenals | 79 | 6.96 | 2.89 |
| Hormonal disorder | 248 | 6.05 | 3.1 |
| Metabolic disorder | 127 | 6.5 | 3.31 |
| Genetic condition | 260 | 6.68 | 2.86 |
| Genetic mutation | 148 | 5.27 | 3.46 |
| Gonadal dysgenesis | 79 | 5.92 | 3.53 |
| Adrenal enzyme defect | 57 | 6.35 | 2.98 |
| (iii) Umbrella terms without a potential a pathological message: | | | |
| Hormonal imbalance of the gonads | 73 | 5.71 | 3.12 |
| Hormonal imbalance of the adrenals | 59 | 7.14 | 2.85 |
| Hormonal variation of the gonads | 46 | 5.85 | 3.1 |
| Hormonal variation of the adrenals | 42 | 6.36 | 2.99 |
| Hormonal variation | 139 | 6.07 | 3.17 |
| Genetic variation | 157 | 6.09 | 3.07 |
| Differences of sex chromosomes | 220 | 6.36 | 2.99 |
| (iv) Specific terms: | | | |
| Turner syndrome | 290 | 8.21 | 2.97 |
| Klinefelter syndrome | 160 | 7.93 | 3.07 |
| XXY | 120 | 7.55 | 2.92 |
| Congenital adrenal hyperplasia (CAH) | 170 | 7.49 | 3.12 |
| Complete Androgen Insensitivity Syndrome (cAIS) | 56 | 8.14 | 2.88 |
| Partial Androgen Insensitivity Syndrome (pAIS) | 17 | 7.82 | 2.38 |
| 21-hydroxylase deficiency | 85 | 7,54 | 2,78 |

Scale: 10=very good to 0= very bad; 5 = neutral; Answers to specific terms were only evaluated if the medical term applied to the medical condition of the participant.

**Figure I.3. Participants' responses to the question "Which of the following terms should be usedby doctors to describe your condition in medical terms?"; Distribution of the answers to *Intersex*, *Disorders of Sex Development* and *Differences of Sex Development*.**



# Discussion

## Disorders of Sex Development

Overall, a minority of 296 out of 941 participants (31%) reported that the term *Disorder of Sex Development* did not apply to their condition. This result is surprising given the rather critical appraisal of the term in other patient surveys (Clune-Taylor, 2010; Davis, 2013; Diamond & Beh, 2006; Feder, 2009; Feder & Karkazis, 2008; Guntram, 2013; Hughes, 2015; Hughes et al., 2007; Johnson et al., 2017; Liao & Roen, 2013; Lin-Su et al., 2015; Simmonds, 2007). Rates varied according to country of origin and diagnosis group.

Within the XY karyotype and "other conditions" groups, only 61 out of 271 (23%) objected to the use of *Disorder of Sex Development*. A detailed analysis showed that participants with partial prenatal androgen effect had the least negative view of the term *Disorders of Sex Development*.

Thirty-eight percent of participants with CAH, 35% of those with Turner syndrome, and 32% of those with Klinefelter syndrome stated that the term *Disorders of Sex Development* does not apply to their condition. Hence, these responses differ from those of persons with CAH reported by Lin-Su et al. (2015).

Overall, only a minority objected to the term *Disorders of Sex Development*. It may be advantageous for individuals with these rare conditions if their condition is classified as *Disorders of Sex Development*. Umbrella terms and classifications facilitate communication about different conditions; a consistent use, for example, between researchers and clinicians can render communication more precise and therefore improve clinical care and research. It can increase visibility and, thus, help to provide support for persons concerned. This might explain our observation that persons with rarer conditions tend to evaluate *Disorders of Sex Development* more positively. For individuals, there may also be a positive sense of belonging to a larger group with similar concerns. *Disorders of Sex Development* as an umbrella term may come as a relief because it implies that individuals have a condition "like many others" have - not a condition like "no one else" has (Feder, 2009). Also, participants with conditions with partial prenatal androgen effects might favour the term *Disorders of Sex Development* since it replaced even more controversial terms such as pseudohermaphroditism or hermaphroditism.

## Alternative terms

When asked about other umbrella terms, no clear alternative preferences could be identified. Participants had the opportunity to rate an individual choice of terms. A total of 179 participants chose to rate the term *intersex*, and 50 (28%) of these strongly disapproved of doctors using this term to describe their condition. In contrast, only 18% (50 out of 282) strongly disapproved of *Disorders of Sex Development* and only 13% (20 out of 159) of *Differences of Sex Development*. Persons disapproving of the term *intersex* were more likely not to be in contact with a support group. Support groups, thus, seem to promote a more positive view of *intersex*. Another explanation might be that individuals with a negative perception of the term *intersex* tend to avoid participating in support groups, especially since

some of them have the term *intersex* in their name. Since a number of previous studies recruited their samples from support groups (Davis, 2013; Johnson et al., 2017; Lundberg et al., 2018), this might explain why in our study the term intersex was rated less positively. In a medical as well as in a social sense, *intersex* can be interpreted in many different ways and there is no agreement on what *intersex* means or on what kind of conditions it comprises (Reis, 2007). This ambivalence is reflected in our study results.

Other umbrella terms proposed in the literature like *Variation of Sex Development*, *Differences of Sex Development*, and *Diverse Sex Development* (D'Alberton et al., 2015; Diamond & Beh, 2006; Liao & Simmonds, 2013; Streuli et al., 2012; Streuli et al., 2013; Tamar-Mattis et al., 2013; Wiesemann et al., 2010) were rated more positively than *intersex*, despite the semantic issues sometimes associated with this terms. Moreover, we found no major differences regarding pathologizing and non-pathologizing terms. Ratings of *Disorders of Sex Development* were similar to those of *Difference of Sex Development*, *Diverse Sex Development* and *Variations of Sex Development*. Considering the intense debates about the potentially pathologizing message of the term *disorder,* this is a surprising result. Some persons may actually consider the term helpful because it helps them to understand their condition and opens up opportunities for medical care. Another explanation is that the majority of participants in our study were recruited at medical centres and therefore were used to medical terms such as *disorder*, *mutation* or *defect*.

On average, terms were rated slightly better if they did not include the term *Sex Development*. This was true for both potentially pathologizing and non-pathologizing terminology. Moreover, participants favoured a nomenclature that described their somatic condition more precisely in terms such as gonads, adrenals, genetic or chromosomal as compared to a nomenclature which included the term *sex*, which may be interpreted as relating to sexuality, rather than anatomy (Lin-Su et al., 2015). They rated their respective individual diagnostic terms the highest. Thus, they favoured specific names over general ones, confirming results of previous studies (Lundberg et al., 2018; Tiryaki et al., 2018).

**Strengths and Limitations**

This study was part of a large European quantitative cross-sectional outcome study. Nine hundred forty-one individuals with conditions which are medically labelled as *Disorders of Sex Development* were included, so far, the largest cohort ever consulted regarding terminology. All somatic conditions were medically confirmed, thus securing that only participants affected by the DSD classification participated. We could therefore evaluate the views of individuals by diagnostic group and add more differentiated empirical data to the ongoing ethical debate. Nevertheless, quantitative data have limitations in explaining why individuals prefer specific terminology. Furthermore, a selection bias cannot be ruled out, as the study carried *DSD* in its acronym. Individuals who dislike the term *Disorders of Sex Development* might not have accepted the invitation to participate in this study. Though generalization is limited, it can be assumed that our results are applicable to individuals treated at clinical centres similar to the ones in this study. We did not ask whether participants were acquainted with the term *Disorders of Sex Development* and classification. Furthermore, one must be particularly careful with interpretations of the results regarding

alternative terms. Because of the option of multiple responses to each question, results may be biased by those agreeing to more than one response. Moreover, many participants chose not to rate all terms, this might be because they were indifferent regarding the terminology concerning their condition. Because participants with a distinctive opinion were more likely to rate the terms there was a bimodal distribution therefore, interpretability of the mean values is limited.

**General Discussion**

When in 2006 the Chicago consensus introduced the term *Disorders of Sex Development* (DSD), one goal was to render the new terminology more understandable to patients and their families and be sensitive to their concerns. Four years after the initial publication, 100% of the paediatric endocrinologists in Europe reported using the new terminology (Pasterski et al., 2010a) and between 2010 and 2014 there was an exponential increase in the use of the term *Disorders of Sex Development* across a range of journals (Hughes, 2015). Such a profound and rapid change in terminology is without parallel in recent medical practice (Pasterski et al., 2010a). *Disorders of Sex Development* can be considered as being a paradigm shift, not only in the use of a new nomenclature but also in the underlying classification (Khadilkar & Phanse-Gupte, 2014). However, since its introduction, the new term has attracted criticism by members of support groups, as well as ethicists, sociologists, clinicians, and researchers. The term *disorder* is said to pathologize atypical sex development and, thus, nurture the widespread, yet false, attitude that a medical, instead of a social or political, approach is appropriate. Empirical studies – quantitative as well as qualitative – conducted since 2006 appear to support the view that the term *Disorders of Sex Development* is not sensitive to patient concerns, but the evidence is still inconclusive. Some authors underline that the change of the nomenclature can also be understood as normalizing conditions labelled as *Disorders of Sex Development* in a positive sense (Feder, 2009).

The purpose of this study was to ascertain the views of affected individuals on the term *Disorders of Sex Development* as a medical concept. From our results, it appears that the majority of participants in the dsd-LIFE cohort had a neutral or positive opinion about the term *Disorders of Sex Development*. The high acceptance rate applied to participants from all diagnosis groups, although participants with CAH, Turner, and Klinefelter syndrome were slightly less accepting. Participants did not show a tendency to prefer alternative terms with no pathologizing potential, and, in general, they appeared to prefer terms that were specific to their somatic condition over the general *Disorders of Sex Development* designation. Most interestingly, the term *intersex* which is often used by support groups was rated the lowest. Our data suggest that the aim of the Chicago consensus to eliminate stigmatizing terminology and to replace it by terms more sensitive to individuals with *Disorders of Sex Development* concerns was, at least partially, achieved, especially since acceptance rates were the highest in the group of participants with conditions that prior to 2006 had been labelled hermaphroditism and pseudohermaphroditism. However, objection rates of 32-38% in CAH, Turner, and Klinefelter syndromes and, particularly, of 37-40% in the Netherlands and France should caution clinicians and researchers against an uncritical use of the new

terminology. Depending on the condition, up to one out of four participants strongly objected to the term *Disorders of Sex Development*.

In the clinical situation, we therefore recommend clinicians evaluate and be sensitive to their patients' preferences. Specific terminology related to the individual's somatic condition or diagnosis should be preferably used. In the context of healthcare research, a combination of the two most acceptable terms *difference* and *disorder*, as in *Difference/Disorder of Sex Development*, can be considered appropriate. However, since individuals in our cohort rated *Differences* the highest and given the fact that some critics strongly denounce the term *disorder*, *Differences of Sex Development* may be considered as the recommended alternative umbrella term. This would imply only a slight change in communicating with the patient about DSD: while one has a disease, one's sex development is different, e.g. with regard to sex-typical characteristics. Overall, our data do not support the view that, in general, the term *Disorders of Sex Development* is insensitive to patients needs and should therefore be abandoned.

# Study II

## "Health-related Quality of Life and Psychological Wellbeing in Adults with Differences of Sex Development"

A slightly changed version of this chapter has been published as:

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## Abstract

*Objective:* Rare congenital conditions with incongruence of chromosomal, gonadal, and phenotypic sex have been classified as Differences/ Disorders of Sex Development (DSD). Included in DSD are conditions with diverse genetic aetiology, varying levels of prenatal androgen effects, phenotypes, and subsequently, different medical treatments. Quality of life (QoL) and psychological wellbeing are indicators of successful psychosocial adaptation to the conditions. We sought to investigate the HRQOL and psychological wellbeing in this population.

*Design:* This multicentre clinical evaluation study was part of a German network related to DSD funded by the German Ministry of Science and Education (BMBF 2003 to 2007).

*Methods:* To assess health-related quality of life (HRQoL), we used the Short Form Health Survey (SF-36) and for psychological wellbeing, the Brief Symptom Inventory (BSI). Participants were classified into five groups: females with CAH, females with XY DSD conditions where there is a partial androgen effect (partial androgen insensitivity, mixed/ partial gonadal dysgenesis, disorders of androgen biosynthesis), females with XY DSD without androgen effect (complete androgen insensitivity, complete gonadal dysgenesis), males with XY DSD, and individuals with DSD conditions and a other gender.

*Results:* Participants included 110 adults with DSD (age range 17-62). We found a trend of lowered mental HRQoL and significant higher physical HRQoL for participants as compared to a norm. The high physical HRQoL especially applied to females with androgen effect and XY karyotype. Participants reported significant higher psychological distress compared to the norm. Forty-seven participants (42.7%) reported distress in a clinically relevant range on the BSI.

*Conclusions:* Although we did not find significant impairments in overall HRQoL, participants reported significant impaired psychological wellbeing. Specialized interdisciplinary care should focus in particular on psychological issues to ensure overall good health and wellbeing.


## Introduction

Rare congenital conditions with incongruence of chromosomal, gonadal, and phenotypic sex characteristics are medically classified as Differences/ Disorders of Sex Development (DSD) (Lee et al., 2006). DSD include conditions with diverse genetic aetiology, varying levels of prenatal androgen effects, as well as varying phenotypes of genitalia. Subsequently, medical treatments differ for the conditions (Jürgensen et al., 2010). In 2005, the Chicago DSD Consensus Group on Management of Intersex Conditions introduced the umbrella term Disorders of Sex Development (DSD). The term was chosen to replace nomenclature such as intersexuality, hermaphroditism, or testicular feminization (Lee et al., 2006). According to the Chicago DSD Consensus Group, conditions included in DSD are classified into three groups according to the karyotype and pathogenesis: 1. Sex chromosome DSD that includes 46,XY/45,XO and 46,XY/46,XX conditions, as well as Turner syndrome and Klinefelter syndrome.; 2. XY DSD that encompasses XY gonadal dysgenesis, androgen insensitivity

syndrome (AIS), impaired androgen or anti-Müllerian hormone synthesis or action, and unclassified severe hypospadias; and 3. XX DSD which comprises congenital adrenal hyperplasia (CAH), XX gonadal dysgenesis and uterine and vaginal anomalies (Lee et al., 2006).

The term “Disorders of Sex Development” is controversial within interdisciplinary teams and affected individuals as it is perceived as pathologizing and might be confused with aberrant sexuality or gender identity (Lin-Su et al., 2015). The authors therefore prefer “Differences in Sex Development”, which was introduced by other researchers (Brunner et al., 2016; D'Alberton et al., 2015; Roen & Pasterski, 2013). Depending on the impact of androgens, the functional impairment of the gonads and the reproductive system DSD can have different effects on the individuals’ body and health. Medical treatments, such as hormonal therapy or surgical interventions, are often necessary. Two indicators of successful adaptation to the condition are quality of life (QoL) and psychological wellbeing. The World Health Organization (WHO) defines QoL as, “the individual’s perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concerns”. Although there is overlap in the two concepts, psychological wellbeing refers to distress and symptoms of psychiatric disorders.

Until 1999, no studies adequately addressed QoL for individuals with DSD (Meyer-Bahlburg, 1999; Schober, 1999b). Recently, an increasing number of psychologically oriented outcome studies assessing a wider range of psychosocial and psychosexual outcomes have been performed (Roen & Pasterski, 2013). Reviews on QoL and psychological outcomes for adults with DSD cited nine original articles from 1995 to 2004 and fifteen from 2005 to 2014 (Nordenstrom, 2015; Schützmann et al., 2009; Wisniewski & Mazur, 2009; Zainuddin et al., 2013). In 2015, five novel studies were published (D'Alberton et al., 2015; Ediati et al., 2015; Ediati et al., 2015; Engberg et al., 2015; Wang & Tian, 2015). Although these studies address QoL and/or psychological wellbeing of individuals with DSD, the results varied greatly. Reviews highlighted the poor research status and concluded that all conditions are understudied (Wisniewski & Mazur, 2009). In addition, the studies are hardly comparable due to different diagnostic groups, heterogeneous samples, marked variations in overall quality, age groups, small sample sizes, and recruitment strategies. Consequently, the results are inconsistent and many findings cannot be generalized as almost all studies were limited by a selection bias (Schützmann et al., 2009). Additionally, it is difficult to compare the results directly due to many differences in the methodologies (Zainuddin et al., 2013). A wide spectrum in QoL is expressed by individuals with DSD ranging from very poor to similar to better than the norm population (Amaral, Inacio, Brito, Bachega, Domenice, et al., 2015; D'Alberton et al., 2015). Better QoL ratings were found for individuals with DSD from tertiary care centres (Amaral, Inacio, Brito, Bachega, Oliveira, et al., 2015; Wang & Tian, 2015). Even in studies using the same method the findings varied (Zainuddin et al., 2013). It can be concluded that the results concerning QoL and psychosocial outcomes in individuals with DSD are both scarce and inconsistent (Nordenstrom, 2015).

This study is a part of the clinical evaluation study of the German DSD network investigating the clinical outcomes and health care situation of children, adolescents, and adults with DSD

from 2005 to 2007 (Lux et al., 2009). It was the first multicentre outcome study in this field including individuals with DSD conditions following the generic definition of a discrepancy of chromosomal, gonadal and phenotypical sex (excluding Klinefelter and Turner Syndromes) in German speaking countries. In this sub-study, we analysed the HRQoL and psychological wellbeing in a sample of 110 adults with rare DSD conditions using standardized instruments with normative data for the general population available.

## Methods

### Study design

This multicentre clinical evaluation study was part of the larger German network of individuals with DSD, funded by the German Federal Ministry of Education and Research (BMBF). The details of the study design were described previously (Lux et al., 2009). Recruitment took place at four study centres in Germany and at five sites in Austria and Switzerland between January 2005 and December 2007. Most adult participants were recruited via doctors from the study centres or cooperation partners, support groups recruited 16 participants. There were no differences between non-participants (23.6% of those approached) and participants regarding sociodemographic data or type of diagnosis (Lux et al., 2009). Inclusion criteria of the study followed a generic definition of DSD as incongruence of the chromosomal, gonadal, and phenotypic sex with a laboratory-confirmed diagnosis or clinical diagnosis by a physician. Individuals with Klinefelter and Ullrich-Turner syndrome were excluded[10]. None of the adult participants had to be excluded due to their inability to respond to the interview due to mental illness or intellectual disability. Trained psychologists conducted personal interviews and assessments of the participants at the study centres or at participant's home, depending on preferences of the participants. The psychologists had been recruited by the study and were not involved in routine care and not been known to the participants prior to the study. All participants gave written informed consent for the study.

This study aimed to describe the health related QoL (HRQoL) and psychological wellbeing of adults with DSD. In order to construct groups with similar conditions, participants were classified into five groups reflecting gender at the time of the interview, diagnosis and exposure to prenatal androgen effects affecting sex development: females with congenital adrenal hyperplasia (CAH), participants with female (f) or male (m) gender, XY DSD with partial (pa) or no (na) androgen effects, participants with various conditions and a different gender from male or female (f-CAH-pa, f-XY-pa, f-XY-na, m-XY-pa, other gender). The subgroups of this analysis differ slightly from previous subgroup analysis of the cohort using the classification: DSD-XX-P-F, DSD-XY-P-F, DSD-XY-C-F, and DSD-XY-P-M (Köhler et al., 2012; Lux et al., 2009; Thyen, Lux, Jurgensen, Hiort, & Kohler, 2014). The group f-CAH-pa includes only females with CAH from the previous group DSD-XX-P-F. Participants with other gender were separated from the previous groups DSD-XY-P-F, DSD-XY-C-F, and DSD-XY-P-M (Table II.1). The evaluation was performed on the total cohort and between groups.

[10] Nevertheless one individual with 47,XXY participated

Participants with gender changes and conditions not fitting the five groups are described within the total cohort but are excluded from group comparison. These single case descriptions are not shown, as they are anecdotic and there is risk to confidentiality due to ease of recognition of these individuals.

**Health-related quality of life**

To assess HRQoL, the German version of the Short Form Health Survey (SF-36) was used. The SF-36 is a well-evaluated standardized instrument including eight subscales and two summary measures: a physical component summary (PCS) and a mental component summary (MCS). The PCS includes physical function, physical role, bodily pain, and general health. The MCS includes vitality, social function, emotional role, and mental health with varying response categories (Cronbach's alpha >.85). Higher scores indicated better HRQoL (Bullinger & Kirchberger, 1998). Our z-scores were calculated with reference data from the German norm population of the 1998 German National Health Survey (N = 6967), taking into consideration age and gender. For participants with other gender only age was considered.

**Psychological wellbeing**

Psychological wellbeing was assessed with the German version of the Brief Symptom Inventory (BSI), which is a short version of the Symptom-Checklist-90 (SCL-90) (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974). This instrument includes 53 items on nine subscales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and three global characteristic values: global severity index (GSI), positive symptom total (PST), and positive symptom distress (PSD). Participants rated the extent to which they have been bothered (0=not at all to 4=extremely) in the past week by various symptoms. Higher scores indicated a higher level of psychological distress (Franke, 2000). The absolute BSI values were transformed into T-scores (considering gender) in respect to a German norm population (N=600)(Franke, 2000). Participants that had T-scores≥63 indicated significant distress on the BSI. Criteria for being classified as a clinical case were either a Global Severity Index of T≥63 or two single subscale scores of T≥63 (Schützmann et al., 2009).

**Statistical analysis**

SPSS Version 22 was used for all analyses. The nonparametric Wilcoxon test was used to evaluate group median differences from the norm population. The *p* values were calculated with the nonparametric Wilcoxon signed rank test against test value z=0.00 or T=50.00. The Kruskal-Wallis test followed by Dunn-Bonferroni test as pairwise post hoc test was used to evaluate group differences. All *p* values <.05 were considered statistically significant.

**Table II.1: Definitions and conditions of the groups**

| Group | Definition | Condition |
|---|---|---|
| f-CAH-pa<br>*n=44* | Participants indicating having a female gender, 46,XX DSD due to CAH | 12 simple virilising<br>32 salt-wasting |
| f-XY-pa<br>*n=26* | Participants indicating having a female gender, 46,XY DSD or sex chromosome mosaicism and partial androgen effects | 13 partial/ mixed gonadal dysgenesis<br>6 pAIS<br>3 17beta-hydroxysteroid- dehydrogenase III deficiency<br>2 5alpha-reductase II deficiency<br>1 LH-receptor defect<br>1 unclassified |
| f-XY-na<br>*n=13* | Participants indicating having a female gender, 46,XY DSD and no androgen effects | 5 complete gonadal dysgeneses<br>8 cAIS |
| m-XY-pa<br>*n=10* | Participants with male gender, 46,XY DSD or sex chromosome mosaicism and partial androgen effects | 3 partial/mixed gonadal dysgenesis<br>1 pAIS<br>3 severe hypospadias<br>1 ovotestis<br>1 epispadias<br>1 penile hypospadias and micropenis |
| other gender<br>*n=9* | Participants indicating having a different gender from female or male with 46,XY DSD or mosaicism | 2 partial/mixed gonadal dysgenesis<br>1 complete gonadal dysgenesis<br>3 cAIS<br>1 pAIS<br>1 5alpha-reductase II deficiency<br>1 17beta-hydroxysteroid- dehydrogenase III deficiency |
| others<br>*n=8* | Participants included in the total cohort but excluded from group comparison | Females:<br>1 pAIS with gender change at 30 years (46,XY)<br>1 penile agenesis and gender change the age of 1month (46,XY)<br>1 Klinefelter syndrome with gender change at the age of 20 years (46,XXY)<br>1 aromatase deficiency (46,XX)<br>1 ovarian insufficiency (46,XX)<br>1 complete gonadal dysgenesis (46,XX)<br>Males:<br>2 CAH (46,XX); one had a gender change at the age of 20 years |

CAH= congenital adrenal hyperplasia, cAIS= complete androgen insensitivity syndrome, pAIS= partial androgen insensitivity syndrome

# Results

## Sample

In total 110 adults with DSD participated (age range 17-62; Table II.2). 101 participants reported to have a female (n=89, 80.9%) or male (n=12, 10.9%) gender. Nine individuals (8.2%) reported a gender different from male or female (Table II.3). Participants, whose conditions did not fit into the classified groups were excluded from group comparison (n=8) but were included in the description of the total sample (Table II.1).

**Table II.2: Sociodemographic data**

| | total[1] | | f-CAH-pa | | f-XY-pa | | f-XY-na | | m-XY-pa | | other gender | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 110[1] | | 44 | | 26 | | 13 | | 10 | | 9 | |
| mean age in years | 28.38 | | 28.25 | | 28.44 | | 27.06 | | 23.81 | | 33.18 | |
| (sd) | (9.74) | | (7.67) | | (11.13) | | (7.03) | | (9.98) | | (8.11) | |
| Age range in years | 17-62 | | 17-48 | | 17-62 | | 17-40 | | 17-50 | | 22-49 | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Migration background | 12 | 10.9 | 3 | 6.8 | 6 | 23.1 | - | | 2 | 20.0 | - | |
| Education level[2] | | | | | | | | | | | | |
| Low | 22 | 21.6 | 10 | 23.8 | 3 | 12.5 | 1 | 8.3 | 1 | 14.3 | 1 | 11.1 |
| Medium | 34 | 33.3 | 20 | 47.6 | 7 | 29.2 | 3 | 25.0 | 3 | 42.9 | - | |
| High | 29 | 28.4 | 8 | 19.1 | 7 | 29.2 | 5 | 41.7 | 3 | 42.9 | 5 | 55.6 |
| Very high | 17 | 16.7 | 4 | 9.5 | 7 | 29.2 | 3 | 25.0 | - | | 3 | 33.3 |
| Living in current partnership | 44 | 43.6 | 14 | 31.8 | 13 | 50.0 | 9 | 69.2 | 1 | 10.0 | 6 | 66.7 |
| Member of a DSD association or support group | 21 | 19.1 | 1 | 2.3 | 6 | 23.1 | 5 | 38.5 | - | | 8 | 88.9 |

[1]Including single case descriptions; [2]missing data n=8

**Table II.3: Description of the group "other gender"**

| Current gender[1] | Grew up as | condition |
|---|---|---|
| third gender | female | complete gonadal dysgenesis |
| „female hermaphrodite“ | female | cAIS |
| third gender | female | cAIS |
| "official as female, but I cannot identify with this" | female | cAIS |
| "intersexual female" | female | 17beta-hydroxysteroid-dehydrogenase III deficiency |
| Undecided | female | partial gonadal dysgenesis |
| Undecided | female | 5alpha-reductase II deficiency |
| third gender | female | mixed gonadal dysgenesis |
| "in private human, work-related male" | female (gender change from male to female as a toddler)[2] | pAIS |

[1]categories of answer: female, male, third gender, undecided, other: ___; [2]second gender change at the age of 30 years from female to male. cAIS= complete androgen insensitivity syndrome. pAIS= partial androgen insensitivity syndrome

### Health-related quality of life

The total sample reported higher physical HRQoL (PCS) as compared to the population reference data (Table II.4). In the total cohort, we found higher scores in the subscale bodily pain (indicating lower levels of pain) and lower scores in physical function and physical role. The effects were explained by significantly better HRQoL in the subscale bodily pain in f-CAH-pa and better HRQoL in all subscales of the physical summary score (PCS) in f-XY-pa. Nevertheless, there was no significant group difference in overall physical HRQoL (PCS), but significant group differences in the subscales physical function ($p$=.025; post-hoc: m-XY-pa<f-XY-pa; $p$=.044 & f-CAH-pa<f-XY-pa; $p$=.093), bodily pain ($p$=.009; post-hoc: m-XY-pa<f-CAH-pa; $p$=.030), and general health ($p$=.023; post-hoc: m-XY-pa<f-XY-pa; $p$=.036). There were no significant differences between females with simple virilising or salt wasting CAH (data not shown). Regarding mental HRQoL, we found a trend of lower mental HRQoL (MCS) that failed to reach significance in comparison to norm data. In comparisons between groups we found significant group differences in the subscale emotional role ($p$=.006; post-hoc: f-XY-pa>other gender; $p$=.069 & f-CAH-pa>other gender; $p$=.013).

### Psychological wellbeing

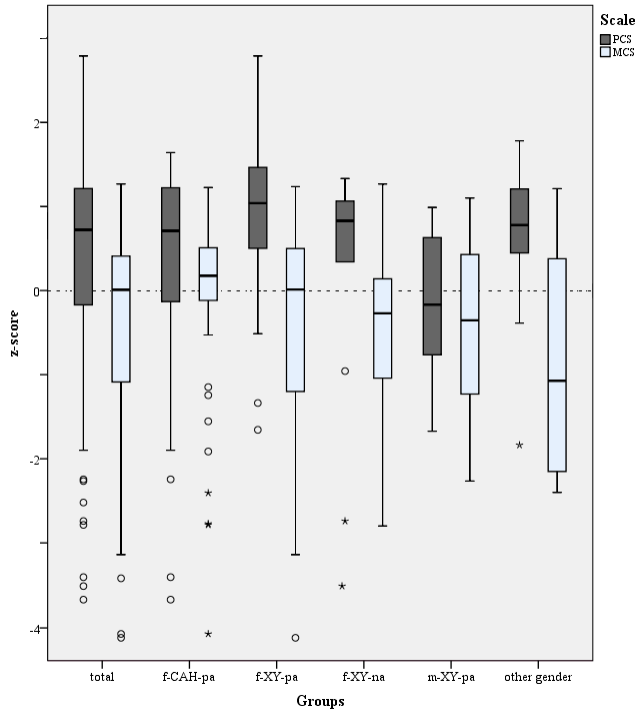
Participants reported significantly higher distress compared to the norm on most subscales of the BSI such as obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, paranoid ideation, psychoticism (Table II.4). Only the subscales somatization and phobic anxiety participants reported distress similar to the norm. Within the subgroups, most of this difference failed to be significant. There were significant group differences on the subscales phobic anxiety ($p$=.006; post-hoc: f-CAH-pa<other gender; $p$=.021 & f-CAH-pa<m-XY-pa; $p$=.055) and psychoticism ($p$=.005; post-hoc: f-CAH-pa<other gender; $p$=.0391 & f-CAH-pa<m-XY-pa; $p$=.069). No significant differences were found between females with simple virilising or salt wasting CAH (data not shown). Forty-seven participants (42.7%) reported in a clinically relevant range on the BSI (clinical case). There was a significant correlation between mental HRQoL (MCS) and psychological wellbeing (GSI) (r=-.640; $p$<0.001).

**Table II.4: Comparison of the total sample and the subgroups to population based reference data.**

| | total[1] | | f-CAH-pa | | f-XY-pa | | f-XY-na | | m-XY-pa | | other gender | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 110[1] | | 44 | | 26 | | 13 | | 10 | | 9 | | |
| SF-36 | *z* | *sd* | *z* | *sd* | *z* | *sd* | *z* | *sd* | *z* | *sd* | *z* | *sd* | group differences |
| physical function | ***-.04*** | ***1.04**** | -.23 | 1.23 | **.35** | **0.41**** | -.04 | 1.27 | -.02 | 0.70 | -.12 | 1.17 | * |
| physical role | ***-.23*** | ***1.49***** | -.17 | 1.31 | **.05** | **1.37**** | -.71 | 1.79 | -.14 | 1.52 | .24 | 0.56 | |
| bodily pain | **.51** | **1.05**** | **.66** | **0.95**** | **.63** | **1.13**** | .63 | 1.10 | -.14 | 1.10 | .28 | 0.97 | ** |
| general health | .00 | 1.38 | .01 | 1.27 | **.59** | **1.30**** | -.40 | 1.41 | -.94 | 1.68 | .30 | 1.10 | * |
| PCS | **.33** | **1.30**** | .22 | 1.36 | **.84** | **0.98**** | .14 | 1.57 | -.24 | 1.15 | .56 | 1.09 | |
| vitality | -.16 | 1.23 | .12 | 1.25 | -.25 | 1.15 | -.33 | 1.00 | -.56 | 1.44 | -.29 | 1.07 | |
| social function | -.21 | 1.22 | -.01 | 1.05 | -.05 | 1.09 | -.14 | 1.06 | -.24 | 1.25 | -.51 | 0.90 | |
| emotional role | -.52 | 1.52 | -.08 | 1.10 | -.63 | 1.63 | -.83 | 1.82 | -.22 | 1.22 | -1.21 | 1.71 | ** |
| mental health | -.28 | 1.12 | -.09 | 0.98 | -.29 | 1.04 | -.35 | 1.22 | -.43 | 1.13 | -.24 | 1.13 | |
| MCS | -.42 | 1.22 | -.07 | 1.07 | -.58 | 1.37 | -.56 | 1.23 | -.43 | .92 | -.80 | 1.36 | |
| BSI | T | sd | T | sd | T | sd | T | sd | T | sd | T | sd | |
| somatization | 50.68 | 10.76 | 49.68 | 10.44 | 48.54 | 8.39 | 49.92 | 10.83 | 54.60 | 11.67 | 52.89 | 11.46 | |
| obsessive-compulsive | ***52.98*** | ***12.35**** | 49.91 | 11.49 | 53.15 | 11.60 | 54.54 | 12.26 | 53.10 | 12.60 | 57.11 | 10.13 | |
| interpersonal sensitivity | ***53.99*** | ***11.72***** | 50.98 | 9.92 | ***57.31*** | ***12.36**** | 51.23 | 9.36 | 53.90 | 10.40 | 55.33 | 12.42 | |
| depression | ***54.79*** | ***11.84***** | 52.54 | 11.26 | 54.61 | 11.31 | 53.69 | 8.16 | ***60.00*** | ***11.24**** | 53.22 | 13.40 | |
| anxiety | ***52.81*** | ***10.84**** | 50.31 | 11.55 | 54.27 | 10.73 | 52.31 | 6.54 | 54.60 | 9.52 | 53.89 | 9.85 | |
| hostility | ***56.10*** | ***11.52***** | ***53.90*** | ***9.91**** | ***56.88*** | ***13.82**** | 57.15 | 11.82 | 54.80 | 9.60 | ***60.11*** | ***6.33***** | |
| phobic anxiety | 50.56 | 9.05 | 48.75 | 8.70 | 51.46 | 9.88 | 50.31 | 7.98 | 50.40 | 7.17 | 52.56 | 7.54 | ** |
| paranoid ideation | ***54.75*** | ***11.37***** | ***54.30*** | ***11.54**** | 53.84 | 12.09 | 51.46 | 6.38 | 54.80 | 9.47 | 54.44 | 9.77 | |
| psychoticism | ***54.06*** | ***11.63**** | 49.72 | 9.67 | ***55.38*** | ***10.89**** | 52.69 | 9.49 | 57.60 | 12.43 | ***58.22*** | ***12.37**** | ** |
| GSI | ***54.39*** | ***13.54***** | 51.48 | 12.40 | 54.61 | 14.35 | 53.77 | 9.18 | 57.20 | 11.78 | 58.22 | 10.53 | |
| PST | ***54.79*** | ***12.04***** | 51.37 | 10.74 | 55.92 | 13.38 | 53.38 | 8.13 | 56.60 | 10.17 | 57.67 | 10.48 | |
| PSD | ***53.45*** | ***12.46***** | 51.93 | 12.39 | 53.00 | 12.08 | 52.00 | 9.35 | 54.40 | 11.75 | ***57.56*** | ***9.30**** | |
| Clinical cases | 47 (42.7%) | | 14 (31.8%) | | 12 (46.2%) | | 7 (53.8%) | | 4 (40. 0%) | | 5 (55.6%) | | |

[1]Including single case descriptions; p values are calculated with the nonparametric Wilcoxon signed rank test z equals 0.00 and T equals 50.00; p≤ .05* and p≤.01**; SF-36: Higher scores indicate a higher HRQOL z=0 is the mean of the norm; (sd=1); BSI: higher scores indicate a higher level of psychological distress T=50 mean of the norm (sd=10); significant better outcome then the norm are marked bold; significant impaired outcome then the norm are marked italic and bold. Abbreviations: PCS: physical component summary, MCS: mental component summary, GSI: global severity index, PST: positive symptom total, PSD: positive symptom distress

**Figure II.1 Comparison of physical and mental HRQoL**




PCS: physical component summary, MCS: mental component summary; Higher scores indicate a higher HRQoL; z=0 is the mean of the norm; (sd=1)

# Discussion

In this study, a considerable difference between psychological and physical wellbeing was identified in a cohort of 110 adults with various DSD conditions. Participants reported overall higher physical HRQoL, normal mental HRQoL but high psychological distress (42.7%) measured by SF-36 and BSI accordingly.

## Health-related quality of life

Within HRQoL a difference between physical HRQoL and mental HRQoL was identified (Figure II.1). Participants rated their physical HRQoL higher than the norm and their mental HRQoL similar to the norm. However, most participants showed rather low mental HRQOL, which failed to reach significance. This might be due to the inhomogeneous group distribution, larger variation and non-normal distribution of the data. Using a different questionnaire (WHOQOL-BREF, WHOQOL), other studies described the same effect (D'Alberton et al., 2015; Wang & Tian, 2015). Likewise, previous analysis of the German DSD network study of adolescents with DSD reared as girls showed higher HRQoL scores than girls of the reference group regarding physical wellbeing. The authors suggested two possible explanations of this finding: On one hand exposure to high prenatal androgens has a long-lasting positive effect on the girls' physical wellbeing lasting until adolescence. On the other, unlike girls who experience typical female puberty changes, girls with DSD are not exposed to hormonal fluctuations of the sex hormones (Kleinemeier, Jurgensen, et al., 2010). Both explanations may apply to adult females as well and could explain why participants within the group f-XY-pa reported higher physical HRQoL as compared to the other groups.

In contrast, a previous study of adults with DSD conditions in Brazil found that males reported a significantly better QoL when compared to females. In group comparisons, males of our study with XY DSD (m-XY-pa) reported the lowest HRQoL (Amaral, Inacio, Brito, Bachega, Oliveira, et al., 2015). Cultural differences might be the cause of these varying results but overall data on QoL of males with XY DSD conditions are still scarce. When compared to previous studies also using the SF-36 in adults with CAH, the group f-CAH-pa in this study showed a better HRQoL (Table II.5a).

Another study from Germany showed similar results as our study, in that they did not differ from the controls. The authors concluded that good HRQoL can be achieved when individuals with CAH are under tight endocrine specialist observation starting in early childhood (Reisch et al., 2011). This applies to participants of our study as well, as they were recruited mainly from tertiary centres. Other than CAH, the SF-36 has not been used in previous studies analysing HRQoL for individuals with DSD conditions. Currently, there are several studies indicating normal QoL in individuals with DSD (Table II.5b). These studies show that individuals with DSD are able to cope well with their conditions. However, methodological problems like different samples, various measurements and selection bias prevent generalizability (Amaral, Inacio, Brito, Bachega, Domenice, et al., 2015; Nordenstrom, 2015; Schützmann et al., 2009; Wisniewski & Mazur, 2009; Zainuddin et al., 2013). Especially selection bias might affect results, as individuals are recruited via multiple strategies and not all individuals invited chose to participate. There are studies in which 39-47% of the invited participants chose not to participate (D'Alberton et al., 2015; Fagerholm et al., 2012). These individuals may have refused to participate due to impaired wellbeing. Authors of studies in which the cohort indicated normal QoL suggest that this outcome may be attributable to proper treatment, including regular follow-ups and psychological support (Wang & Tian, 2015). The authors of one study highlight that the participants were followed in the same tertiary referral centre by a multidisciplinary team including psychological support. In this study the mean period of psychological support was approximately 7 years (Amaral, Inacio, Brito, Bachega, Oliveira, et al., 2015). It seems likely that this extensive support has resulted in good QoL. In our study, HRQoL was associated with satisfaction with care as described in our previous analysis of the health care situation of this cohort (Thyen et al., 2014).

**Table II.5: Literature Review**

**Table II.5a: HRQoL in CAH with SF-36**

| Study | Country | N | Condition | Questionnaire | Result |
|---|---|---|---|---|---|
| Nermoen, Husebye, Svartberg, and Lovas (2010) | Norway | N=104 | CAH (39 males; 65 females) | SF-36 | HRQoL was significantly impaired across all eight domains.<br>No difference between the salt wasting and simple virizing form of CAH. Working disability was reported by 19% of the patients. |
| Arlt et al. (2010) *respectively** | UK | N= 203 *respectively* | CAH (65 males; 138 females) | SF-36 | HRQoL was impaired across all eight domains. |
| Han, Walker, Arlt, and Ross (2014) | | N=151 | CAH (50 males; 101 females) | | QoL scores were associated with type of glucocorticoid treatment. QoL was not related to PreDEq (prednisolone dose equivalent) or mutation severity. Increased adiposity, insulin resistance and use of prednisolone or dexamethasone are associated with impaired QoL. |
| Reisch et al. (2011) | Germany | N=81 | CAH (36 males; 45 females) | SF-36 | HRQoL scores did not differ from controls. |
| This study | Germany | n= 44 | CAH (females) | SF-36 | Participants had impaired HRQoL in three of five GBB-24 scores whereas SF-36 and HADS scores did not differ from controls.<br>Overall HRQoL scores did not differ from controls. HRQoL in the subscale bodily pain was better than the norm.<br>No difference between the salt wasting and simple virilising form of CAH. |

**Table II.5b: Latest quantitative studies evaluating QoL in adults with various DSD conditions**

| Study | Country | N | Condition | Questionnaire | Result |
|---|---|---|---|---|---|
| Fagerholm, Mattila, Roine, Sintonen, and Taskinen (2012) | Finland | N=24 | 16 CAH<br>3 cAIS<br>5 pAIS<br>(all female) | QoL: Life Situation Survey questionnaire<br>HRQoL: 15D questionnaire | QoL and HRQoL scores appeared normal in most of the participants. |
| Amaral, Inacio, Brito, Bachega, Oliveira, et al. (2015) | Brazil | N= 144 | 56 CAH (49 females, 7 male)<br>26 AIS (19 female, 7 male)<br>25 GD (13 female, 12 male)<br>16 5a-RD 2 deficiency (6 female, 10 male)<br>10 17b- HSD3 deficiency (6 female, 4 male)<br>11 other conditions (10 female, 1 male) | WHOQOL-Bref | QoL was comparable to the general population.<br>The chronological age at the start of treatment was significantly associated with general QoL score.<br>Among the 46,XY DSD group, the male social sex patients had better QoL compared with the female social sex participants. |
| Wang and Tian (2015) | China | N=87 | 16 CAH,<br>22 AIS<br>22 GD<br>23 Turner syndrome,<br>4 other conditions<br>(all female) | WHOQOL-Bref | No significant difference between DSD patients and general population.<br>The scores of psychological and environmental domains were lower than that of the physical and social relationship domains, but the difference was not significant. |
| D'Alberton et al. (2015) | Italy | N=43 | 34 AIS<br>1 GD<br>4 5α-reductase deficiency,<br>4 other conditions<br>(all female) | WHOQOL | Normal QoL, even though participants showed higher degree of psychological distress than the comparison group. Less satisfied in psychological and social areas.<br>Younger persons living with a 46,XY DSD showed better psychosocial adjustment than older ones. |
| de Neve-Enthoven et al. (2016) | Netherlands | N=120 | 42 CAH (41 female, 1 male)<br>29 AIS (27 female, 2 male)<br>25 GD (22 female, 3 male)<br>24 other conditions (15 female, 9 male) | TNO-AZL Quality of Life questionnaire (TAAQOL) | Individuals across all diagnostic groups generally reported a good psychosocial well-being. |
| This study | Germany | N=110 | 46 CAH (44 female, 2 male)<br>20 AIS (15 female, 1 male, 4 other gender)<br>25 GD (19 female, 3 male, 3 other gender)<br>19 other conditions (11 female, 6 male, 2 other gender) | SF-36 | Higher physical HRQoL and normal mental HRQoL compared to the population reference data.<br>Higher scores in the subscale bodily pain and lower scores in physical function and role physical. |

**Table II.5c: Previous studies evaluation psychological wellbeing in persons with various DSD condition using similar Questionnaire**

| Study | Country | N | Condition | Questionnaire | Result |
|---|---|---|---|---|---|
| Schützmann, Brinkmann, Schacht, and Richter-Appelt (2009) | Germany | N=37 | 11 CAH (female)<br>26 other conditions (23 females, 3 males) | BSI | Overall higher psychological distress compared to the norm population. 59% can be classified as clinical case according to predefined BSI criteria. |
| Johannsen, Ripa, Mortensen, and Main (2006) | Denmark | N=70 | 40 CAH<br>11 cAIS<br>3 GD<br>16 other conditions (all female) | SCL-90 | The total SCL-90 score was higher in participants with DSD than in controls, reaching significance for anxiety with highest score in females with CAH. |
| Fagerholm et al. (2012) | Finland | N=24 | 16 CAH<br>8 AIS<br>(all female) | SCL-90 | Similar psychological distress compared to a community sample. |
| This study | Germany | N=110 | 46 CAH (46,XX, 44 females, 2 males)<br>20 AIS (15 females, 1 male, 4 other gender)<br>25 GD (19 females, 3 male, 3 other gender)<br>19 other conditions (11 females, 6 males, 2 other gender) | BSI | High psychological distress compared to the norm population. 42.7% of the participants can be described as a clinical case due to BSI criteria. |

*Both studies use data form the Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE); Abbreviations: CAH: congenital adrenal hyperplasia, AIS - androgen insensitivity syndrome, GD: gonadal dysgenesis SCL-90: Symptom-Checklist-90 (long version of the BSI)

**Psychological wellbeing – BSI**

The high psychological distress of participants in this study is in line with previous studies (D'Alberton et al., 2015; Engberg et al., 2015; Johannsen et al., 2006; Schützmann et al., 2009). An overview of findings from our and other studies using the BSI or the SCL-90 to describe psychological wellbeing is presented in Table II.5c. In contrast to the only study using the BSI the number of clinical cases of our study was lower (59% versus 42.7%) (Schützmann et al., 2009). Psychological wellbeing differs in the two studies, although both were performed in the same period in Germany using the same instruments. The authors of the other German study described a potential selection bias as the study was conducted by an institute of Institute for Sex Research and Forensic Psychiatry and may have attracted persons with DSD who were more psychologically distressed (Schützmann et al., 2009). On the other hand, also a selection bias of our study could explain the different results as participants were predominately invited through their hospital and physicians (Thyen et al., 2014). Moreover, physicians could have avoided informing severely distressed patients. The cases criteria on the BSI can be used as a selection criterion for those individuals who would require further formal mental health assessment; therefore, the definition does not indicate mental disease but the presence of subjective impairment (Kellett, Beail, Newman, & Frankish, 2003). Our results demonstrate that adults with DSD are markedly psychologically distressed and care should focus more on psychological wellbeing in addition to physical aspects. It was recommended only in 2005 that psychological support should be part of multidisciplinary care of individuals with DSD (Lee et al., 2006). As the participants of this study were recruited from 2005 to 2007, they mostly could not benefit from professional psychological support as it was only offered to 31 % of the cohort (Thyen et al., 2014). However, it seems that psychological support is still not sufficient in patients with DSD conditions, as also recent studies of younger individuals with DSD showed significant impaired psychological outcome (D'Alberton et al., 2015; de Neve-Enthoven et al., 2016).

**Other gender**

In this study, nine participants (8.2%) describe themselves as a gender other than male or female. They rated their HRQoL and psychological distress as similar to the rest of the cohort. This observation indicated that identification with a gender outside or overriding male or female dichotomy is not associated with impaired QoL or psychological distress. It could be a way of coping with the feelings of gender ambiguity.

Schweizer et al. (2013) described that 7% of their cohort reported gender roles other than male or female, and 3% reported a neither female nor male gender identity. Three of the participants with other gender in our cohort have the condition cAIS. Our result is concordant to the findings of Brunner et al. (2016), in which 5 out of 11 participants with cAIS chose the gender/sex category of other. However, an overlap of participants might be possible as they are both German studies. These results are different to previous studies, in which female gender identity and role was established and maintained in all individuals diagnosed with cAIS (Mazur, 2005). An explanation might be that out of the 9 individuals, 8 declaring other gender were member of a DSD association or support group. In the other groups, such as the f-CAH-pa and m-XY-pa group, only a minority are members of a DSD

association or support group. Being a member of a support group might explain the declaration of another gender as these participants had more information and broader understanding of sex and gender. Otherwise, it could also be, that individuals not identifying as male or female might be more prone to participate in DSD associations. The results of this subgroup serve to show that feeling neither clearly male nor female does not necessary inhibit good HRQoL and psychological wellbeing, even though some challenging experiences in a dichotomous society might appear.

**Limitations**

A potential for selection bias and social desirability bias limits the generalizability of our results. Comparisons to the norm are limited as available German norm data for the SF-36 are from 1998 and from 2000 for the BSI, while the cohort was recruited from 2005 to 2007. Potential difference within and between these groups and the norm may not be significant due to small sample size of the different groups. Quality criteria and factor structure of the BSI have been criticized (Franke, 2000; Skeem et al., 2006). Beside general scepticism on the concept of QoL there is specific doubt on the reliability of the SF-36 (Pukrop, 2003). Additionally, the SF-36 measures limitations in QoL but it fails to identify the subjective importance of these limitations for the individual (Bullinger, 2000). Moreover, it should be noted that although it seems to be a positive outcome, if QoL of individuals with DSD does not differ from the norm, one must take into account that the goal of treatment should be to provide the best possible health status, not a health status similar to the norm population.

## Conclusion

We found a trend of lowered mental HRQoL and significant higher physical HRQoL for participants as compared to a norm. Group comparison leads to the hypothesis that females with XY DSD might profit from an early effect of androgens, thus contributing to positive physical HRQoL. Although there is a high physical HRQoL participants reported significant impaired psychological wellbeing, 42.7% can be described as a clinical case. Impaired psychological wellbeing is an unfortunate outcome in many persons with DSD conditions and we conclude that specialized interdisciplinary care with a focus in particular on psychological care is needed to improve wellbeing.

# Study III

## "Subjective need for psychological support (PsySupp) in parents of children and adolescents with Differences of Sex Development"

A slightly changed version of this chapter has been published as:

Bennecke, E., Werner-Rosen, K., Thyen, U., Kleinemeier, E., Lux, A., Jurgensen, M., A. Gruters & Köhler, B. (2015). Subjective need for psychological support (PsySupp) in parents of children and adolescents with disorders of sex development (dsd). *Eur J Pediatr*. doi:10.1007/s00431-015-2530-8

https://doi.org/10.1007/s00431-015-2530-8

Publications based on the original article:

Bennecke, E., Werner-Rosen, K., Krude, H., Thyen, U., Lux, A., Kleinemeier, E., Lux, A., Jurgensen, M., A. Gruters & Köhler, B. (2014). *Subjektive need for psychological support in partens of children dsd - results from the German Clinical Evaluation Study*. Poster presented at the ESPE, Dublin.

## Abstract

Differences/ disorders of sex development (DSD) is an umbrella term for congenital conditions often diagnosed within childhood. As most parents are unprepared for this situation psychological support (PsySupp) is recommended. The aim of this study was to analyse the extent to which parents express a need for PsySupp. 329 parents of children with DSD were included. 40.4% of the parents indicated to have a need for PsySupp, only 50% of this group received it adequately. The diagnoses partial gonadal dysgenesis, partial androgen insensitivity syndrome (pAIS) and disorders of androgen synthesis are associated with a high need for PsySupp in parents (54%, 65%, 50%). Sex assignment surgery neither reduced nor increased the need for PsySupp. Taking a picture, radiography, laparoscopy, gonadal biopsy, gonadectomy and hormonal puberty induction are associated with a high need for PsySupp. There was no association between the need for PsySupp and the parents' perception of the appearance of the genitalia. *Conclusion*: Having a child with DSD is associated with a high need for PsySupp in parents. In particular, parents of children with XY-DSD with androgen effects other than hypospadias expressed a high need of PsySupp. PsySupp for parents should be an obligatory part of interdisciplinary care to reduce fears and concerns.


## Introduction

"Differences/ disorders of sex development" (DSD) is an umbrella term for rare congenital conditions with incongruence between chromosomal, gonadal and phenotypic sex. DSD include conditions with diverse genetic aetiology, varying levels of prenatal androgen effects and phenotypes of genitalia and subsequent different medical treatments (Jürgensen et al., 2010). The term "DSD" was introduced 2005 by the Chicago DSD Consensus Group on management of intersex condition to replace nomenclature such as "intersexuality" "hermaphroditism" or "testicular feminization" (Lee et al., 2006). According to the Chicago DSD Consensus Group, DSD conditions are classified depending on the karyotype and pathogenesis in 3 groups: sex chromosome DSD, XY DSD and XX DSD. Sex chromosome DSD include mixed gonadal dysgenesis (46, XY/45, XO), 46XY/46 XX conditions, Turner and Klinefelter syndrome. 46,XY DSD encompass XY gonadal dysgenesis, androgen insensitivity syndrome (AIS), disorders of androgen synthesis and severe hypospadias. 46,XX DSD comprises congenital adrenal hyperplasia (CAH), XX gonadal dysgenesis and uterine and vaginal anomalies. Most parents are unprepared for this complex and challenging situation which can cause confusion, emotional stress, anxiety and perhaps feelings of guilt and shame (Lev, 2006; Medeiros Rocha Santos & Cavalcanti Ferreira de Araujo, 2008; Sandberg, Gardner, & Cohen-Kettenis, 2012). Gough et al. (2008) highlighted the fundamental shock engendered by the uncertain sex status of children and document parental struggles to negotiate a coherent sex identity for their children. Two recent studies revealed that parents reported overall levels of post-traumatic stress (PTSS) that was comparable to those reported by parents of children diagnosed with cancer (Hullmann, Fedele, Wolfe-Christensen, Mullins, & Wisniewski, 2011; Pasterski, Mastroyannopoulou, Wright, Zucker, & Hughes, 2014). Moreover another study showed that parents of children with CAH demonstrated

symptoms of depression that did not abate with the passage of time (de Silva, de Zoysa, Dilanka, & Dissanayake, 2014).

The reaction of parents to the birth of a child with DSD has crucial effects on the atmosphere in which the parent-child relationship will develop. Parents who also experience caring, accepting and encouraging support from the medical and psychological staff are more likely to be able to develop these attitudes towards their child (Richter-Appelt, 2012). An atmosphere of uncertainty, fear and denial hampers this development (Richter-Appelt, 2013). Subsequently, DSD of a child can have an impact on the dynamic of the parent-child relationships, the parental and family relationships (Hullmann et al., 2011; Richter-Appelt, Brinkmann, & Schützmann, 2006; Schober et al., 2012). The uncertainty, if a decision on the gender of rearing is needed, is especially likely to increase parental stress (Jürgensen et al., 2006). Atypical gender role behaviour and gender dysphoria in childhood and adolescence may foster the need for PsySupp in parents.

It has been recommended by the Chicago DSD Consensus Group and the German Ethical Committee (Deutscher Ethikrat, 2012; Lee et al., 2006) that interdisciplinary care of DSD should include a psychologist. On the one hand, the psychologists act as educators and counsellors regarding the psychological aspects of DSD. On the other, they have a unique position among all team members facilitating the group process within the team and between the team and family (Sandberg et al., 2012). The appropriate counselling of parents and family starting at diagnosis is needed in order to achieve the best possible development and quality of life of children and adolescents with DSD (Hiort, 2012; Moran & Karkazis, 2012). This study is a part of the German clinical evaluation study investigating the clinical outcomes and health care situation of individuals with DSD from 2005-2007 (Lux et al., 2009). The aim of this study is to analyse the extent to which parents of children with DSD express a need for PsySupp. To further improve clinical care, factors which are associated with a greater need for PsySupp in parents should be identified.

## Methods

### Study design

The multicentre clinical evaluation study was part of the German network of DSD, funded by the German Ministry of Education and Science (BMBF) (Lux et al., 2009). The aim of the study was to describe the clinical outcomes and health-care situation in individuals with DSD. Recruitment took place at four study centres in Germany and at five sites in Austria and Switzerland between January 2005 and December 2007. A psychosocial inquiry of children, adolescents and adults with DSD and their parents was performed. Inclusion criteria of the study followed a generic definition of DSD with laboratory-confirmed diagnosis or clinical diagnosis by a physician. Individuals with Klinefelter or Ullrich-Turner syndrome, severe psychiatric comorbidity and mental disabilities were excluded. Only diagnoses which were formerly known as “intersexuality” and CAH were included. The assessment of the participants and their parents was conducted by trained psychologists during personal encounters. All participants and their parents gave written informed consent for participation and release of medical data to the interviewer and the principal investigator.

A total of 439 children and adolescents, their parents and adults with DSD participated (Lux et al., 2009).

**Instruments**

The study design of the multicentre clinical evaluation study has been described previously (Lux et al., 2009). For the substudy the "DSD-questionnaire" was used: a questionnaire for parents of children with DSD which was developed after consulting experts in the field and reviewing the literature. The DSD-questionnaires included socio-demographic variables, questions about medical history, child development, peer relations, and questions concerning DSD (e.g. gender change, knowledge about diagnosis) (Jürgensen et al., 2010). Beside the DSD-questionnaire parents were asked to fill out the Child Behaviour and Attitudes Questionnaire (CBAQ) (Meyer-Bahlburg, Sandberg, Yager, Dolezal, & Ehrhardt, 1994). The questionnaire allows for calculating on two scales. The Femininity Scale measuring the extent of typical feminine behaviour (bipolar; high scores = feminine) and the Cross-Gender-Scale measuring the extent of cross-gender behaviour (unipolar; high scores = more cross-gender behaviour) (Jürgensen et al., 2010).

The need for PsySupp in parents was assessed within the DSD-questionnaire: "*Please indicate if you have received psychological counselling/ psychotherapy*". The three categories of response which are related to need for PsySupp in parents were: "*We have received psychological counselling/ psychotherapy*", "*We have received psychological counselling/ psychotherapy partly*", "*We have not received, but we would needed psychological counselling/ psychotherapy*". The answer category "*We have not received, and we do not need psychological counselling/ psychotherapy*" is associated with no need for PsySupp in parents.

Variables that could be related to the need of the parents were selected based on the content from the remaining pool of items and exploratory data analysis was undertaken.

Diagnoses of children and adolescents were classified into DSD-XX or XY without (c) or with partial (p) androgen effects, and female (f) or male (m) sex of rearing: DSD-XX-p-f, DSD-XY-p-f, DSD-XY-p-m, DSD-XY-c-f. The evaluation was performed on basis of the total cohort and between the diagnostic groups.

**Statistical analysis**

For all analyses, SPSS version 22 statistical software was used. The $\chi^2$ test (2-sided) or, if necessary, the Fisher's Exact Test and t-test for independent samples were used to measure associations. P values$<$0.05 were considered statistically significant.

# Results

## Sample

Caregivers of 329 children and adolescents with DSD (mean age 7.25 years; SD 4.96) participated (Table III.1). In 125 cases both parents together, in 185 the mothers, in 14 the fathers and in 4 cases other caregivers answered the questionnaire. In one case no data as to which caregiver completed the questionnaire was available. Diagnoses of children and adolescents were classified in four diagnostic groups (DSD-XX-p-f, DSD-XY-p-f, DSD-XY-p-m, DSD-XY-c-f) (Table III.2) (Lux et al., 2009).

**Table III.1: Age, nationality, education level of the parents**

| | Mothers | Fathers |
|---|---|---|
| Total (n) | 315 | 278 |
| Mean age (SD; range) | 37.3 (6.3; 22-57) | 40.0 (6.9; 20-62) |
| Nationality | | |
| German | 253 | 249 |
| Austrian | 17 | 18 |
| Swiss | 19 | 19 |
| Two nationalities | 2 | 2 |
| other | 36 | 31 |
| Total (n) | 327 | 319 |
| Education level | | |
| Secondary school qualification (*without higher education entrance qualification)* | 169 | 150 |
| Secondary school qualification (*with higher education entrance qualification)* | 57 | 46 |
| University degree | 82 | 94 |
| *Total (n) | 308 | 290 |

*Total numbers are unequal due to missing answers.

## Need for PsySupp

128 parents (40.4%) parents indicated to have a need for PsySupp. 189 parents (59.6%) reported having no need for PsySupp (Table III.3). The need for PsySupp could not be assessed in 12 parents.

## Diagnoses

There was a significant association between the need for PsySupp and the diagnostic groups ($p=0.010$). The need for PsySupp was highest in the group of parents with the child's diagnosis of DSD-XY-p-f (58.7%). There was a significant association ($p=0.025$) between the need of PsySupp and the most common diagnoses such as partial/mixed gonadal dysgenesis (54.2%), pAIS (65%) and disorders of androgen synthesis (50%) included in DSD-XY-p-f. The need for PsySupp was lowest in parents of children with CAH (33.9%) or severe hypospadias (26.5%) (Table III.4).

**Table III.2: Description of the cohort: diagnostic groups, diagnoses and age of the children and adolescents with DSD**

| Group | DSD-XX-p-f<br>*n = 132* | DSD-XY-p-f<br>*n = 66* | DSD-XY-p-m<br>*n = 108* | DSD-XY-c-f<br>*n =22* |
|---|---|---|---|---|
| Definition | female gender of rearing with 46,XX DSD and androgen effects | female gender of rearing with 46,XY DSD or mocaicism and partial androgen effects | male gender of rearing with 46,XY DSD or mocaicism and partial androgen effects | female gender of rearing with 46,XY DSD without androgen effects |
| Karyotype | XX | XY+ | XY+ | XY |
| Gender of rearing | female | female | male | female |
| Androgen effects | present | present | present | none |
| Condition | | | | |
| AIS | - | 12 pAIS | 9 pAIS | 12 cAIS |
| Gonadal dysgenesis | 1 partial/mixed gonadal dysgenesis | 29 partial/mixed gonadal dysgenesis | 21 partial/mixed gonadal dysgenesis | 9 complete gonadal dysgenesis |
| Disorders of androgen synthesis | - | 17beta-hydroxysteroid-dehydrogenase III deficiency (7), 5 alpha-reductase II deficiency (4), LH-receptor defect (1), 17/20-Lyase deficiency (1) | 5alpha-reductase II deficiency (3), LH-receptor defect (3), 17beta hydroxysteroid-dehydrogenase III deficiency (2), not precisely classified (2) | - |
| CAH | CAH (128) | - | - | - |
| Severe hypospadias | - | severe hypospadias (1) | severe hypospadias (50) | - |
| Other conditions | complex malformation (1), aromatase deficiency (2), | complex malformation (5), penile agenesis (1), cloacal exstrophy (1), unclassified clinical diagnoses of DSD (4) | disorder of anti-mullerian hormone (1), Complex malformation (3), 46, XX-male*(3), micropenis (2), unclassified clinical diagnoses of DSD (9) | clinically most likely SF1 mutation, but defect was not found (1) |
| Age | | | | |
| Newborns | 8 | 4 | 10 | 1 |
| 6 months – 3 years | 29 | 7 | 36 | 1 |
| 4 – 7 years | 29 | 12 | 34 | 5 |
| 8 – 12 years | 33 | 24 | 21 | 8 |
| 13 – 16 years | 33 | 19 | 7 | 7 |

AIS= androgen insensitivity syndrome: CAH= congenital adrenal hyperplasia, cAIS= complete androgen insensitivity syndrome, DSD= disorders/diversity of sex development, pAIS= partial androgen insensitivity syndrome.+ incl. mosaics with parts of „Y chromosome" (in some cases chromosome status has not been investigated, in these cases classification results according to the clinical status), *Included in XY-DSD-p-m despite karyptype 46,XX; Excluded from diagnosis group comparisons: one child with 46, XX & without androgen effects (6month-3 years)

**Table III.3: Need for PsySupp in parents (N=317)**

| | | n | % |
|---|---|---|---|
| Need for PsySupp | | 128 | 40.4 |
| *Divided in:* | *"We have received psychological counselling/ psychotherapy"* | 29 | (22.7) |
| | *"We have received psychological counselling/ psychotherapy partly"* | 32 | (25.0) |
| | *"We have not received but we needed psychological counselling/ psychotherapy"* | 67 | (52.3) |
| No need for PsySupp | | 189 | 59.6 |
| *"We have not received, and we do not need psychological counselling/ psychotherapy"* | | | |

**Table III.4: Significant results of the study**

| | | Need for PsySupp | | No need for PsySupp | | |
|---|---|---|---|---|---|---|
| | | n | % | n | % | n |
| Total | | 128 | 40.4 | 189 | 59.6 | 317 |
| Diagnostic groups** | DSD-XX-p-f | 43 | 33.6 | 85 | 66.4 | 128 |
| | DSD-XY-p-f | 37 | 58.7 | 26 | 41.3 | 63 |
| | DSD-XY-p-m | 40 | 38.5 | 64 | 61.5 | 104 |
| | DSD-XY-c-f | 8 | 38.1 | 13 | 61.9 | 21 |
| Main conditions* | pAIS | 13 | 65.0 | 7 | 35.0 | 20 |
| | cAIS | 5 | 41.7 | 7 | 58.3 | 12 |
| | Partial/mixed gonadal dysgenesis | 26 | 54.2 | 22 | 45.8 | 48 |
| | complete gonadal dysgenesis | 3 | 37.5 | 5 | 62.5 | 8 |
| | Disorders of androgen synthesis | 11 | 50.0 | 11 | 50.0 | 22 |
| | CAH | 42 | 33.9 | 82 | 66.1 | 124 |
| | Severe hypospadias | 13 | 26.5 | 36 | 73.5 | 49 |
| | other | 15 | 44.1 | 19 | 55.9 | 24 |
| Surgeries | Gonadectomy* | 36 | 52.2 | 33 | 47.8 | 69 |
| Investigations in context of the diagnosis | | | | | | |
| | Taking a picture** | 70 | 49.0 | 73 | 51.0 | 143 |
| | Radiography* | 63 | 47.7 | 69 | 52.3 | 132 |
| | Laparoscopy** | 16 | 66.7 | 8 | 33.3 | 24 |
| | Gonadal biopsy** | 38 | 56.7 | 29 | 43.3 | 67 |
| | Induction of puberty** | | | | | |
| | Hormonal induction of puberty - received | 15 | 50.0 | 15 | 50.0 | 30 |
| | Hormonal induction of puberty - planned | 28 | 58.3 | 20 | 41.7 | 48 |
| | No hormonal introduction of puberty | 63 | 35.0 | 117 | 65.0 | 180 |
| Nationality of the father** | | | | | | |
| | German. Austrian. Swiss. two nationalities | 105 | 37.6 | 174 | 62.4 | 279 |
| | other | 19 | 65.5 | 10 | 34.5 | 29 |
| Education level of the mother* | | | | | | |
| | Secondary school qualification (without higher education entrance qualification) | 69 | 61.7 | 93 | 57.4 | 162 |
| | Secondary school qualification (with higher education entrance qualification) | 14 | 25.0 | 42 | 75.0 | 56 |
| | University degree | 37 | 47.4 | 41 | 52.6 | 78 |
| Occupation of the father*** | | | | | | |
| | Full-time work | 89 | 35.6 | 161 | 64.4 | 250 |
| | Part-time work | 8 | 53.3 | 7 | 46.7 | 15 |
| | Unemployed | 10 | 71.4 | 4 | 28.6 | 14 |
| | Retired | 6 | 85.7 | 1 | 14.3 | 7 |

only significant results are stated: *p≤0.05; **p≤0.01; ***p≤0.001 with respect to corresponding crosstab

### Parents' perception of the appearance of the genitalia, gender of rearing and gender role behaviour

No significant association could be found between the need for PsySupp of parents and their perception of the genitalia of the child at birth and gender of rearing (Table III.5). A change of the gender of rearing was performed in 32 children of the diagnostic groups DSD-XX-p-f (male to female n=15; diagnosis CAH; mean age of change of gender of rearing 0.30 years), DSD-XY-p-f (male to female n=9; diagnoses: partial gonadal dysgenesis n=6; PAIS n=2; other n=1; mean age of change of gender of rearing 0.72 years) and DSD-XY-p-m (female to male n=8; diagnoses: partial gonadal dysgenesis n=2; severe hypospadias n=2; other n=4; mean age of change of gender of rearing 0.84 years). The gender change was initiated by doctors in 19 cases (mean age 0.37 years) and by parents in 9 cases (mean age 1.01 years). There was no second change of the gender of rearing in the sample. 16 parents (53.3%) reported a need for PsySupp if there was a change of the gender of rearing (p=0.171). There was an association of need for PsySupp in parents and preferred gender of playmates of the child in the diagnostic group DSD-XX-p-f (p=0.038). There was a high need for PsySupp if the children preferred to play with boys (81.8%) or girls (64.0%). There was a low need for PsySupp in parents if the children preferred to play with both genders (37.5%) (Table III.6). This was not the case in the other diagnostic groups. Although not significant due to small sample size, a difference may also apply to the diagnostic group DSD-XY-p-m.

Gender role behaviour measured with the CBAQ (Jürgensen et al., 2010; Jürgensen et al., 2014) was also associated with need for PsySupp in parents of children within the diagnostic group DSD-XY-p-f. There was a higher need for PsySupp when the parents indicated that their child showed more cross gender behaviour (Table III.7). This was not case in the other diagnostic groups.

**Table III.5: Parents' perception of the genitalia and need for PsySupp**

| "How did you assess your child's genitalia immediately after birth?" | male | | ambiguous | | female | |
|---|---|---|---|---|---|---|
| | n | Need for PsySupp n (%) | n | Need for PsySupp n (%) | n | Need for PsySupp n (%) |
| DSD-XX-p-f | 30 | 13 (43.3) | 34 | 9 (26.5) | 57 | 16 (28.0) |
| DSD-XY-p-f | 8 | 5 (62.5) | 14 | 8 (57.1) | 40 | 24 (60.0) |
| DSD-XY-p-m | 72 | 24 (33.3) | 19 | 8 (42.1) | 6 | 9 (66,7) |
| DSD-XY-c-f | 0 | | 0 | | 21 | 8 (38.1) |
| Total | 110 | 42 (38.2) | 67 | 25 (37.3) | 127 | 54 (42.5) |

Not significant

**Table III.6: Preferred gender in friendships and need for PsySupp in parents**

| "Who are currently your child's friends?" | girls | | boys | | both | | unknown | |
|---|---|---|---|---|---|---|---|---|
| | n | Need for PsySupp (%) | n | Need for PsySupp (%) | n | Need for PsySupp (%) | n | Need for PsySupp |
| DSD-XX-p-f | 37 | 15 (40.5) | 25 | 8 (32.0) | 42 | 13 (31.0) | 4 | 2 |
| DSD-XY-p-f* | 25 | 16 (64.0) | 11 | 9 (81.8) | 16 | 6 (37.5) | 2 | - |
| DSD-XY-p-m | 7 | 5 (71.4) | 35 | 13 (37.1) | 37 | 13 (35.1) | 3 | - |
| DSD-XY-c-f | 13 | 4 (30.8) | 1 | - | 6 | 3 (50.0) | - | - |
| Total | 82 | 40 (48.8) | 72 | 30 (41.7) | 102 | 35 (34.3) | 9 | 3 |

*significant p≤0.05

**Table III.7: CBAQ and need for PsySupp in parents; diagnostic group DSD-xy-p-f**

| | Need for PsySupp | No need for PsySupp |
|---|---|---|
| N (%) | 21 (65.6) | 11 (34.4) |
| Femininity scale** Mean (SD) | 63.3 (8.8) | 72.6 (7.5) |
| Cross-gender scale*** Mean (SD) | 26.6 (7.6) | 18.4 (4.1) |

Femininity Scale measuring the extent of typical feminine behaviour (bipolar; high scores = feminine); Cross-Gender-Scale measuring the extent of cross-gender behaviour (unipolar; high scores = more cross-gender behaviour); only significant results are stated: **p≤0.01; ***p≤0.001

### Surgery, medical investigations and hormonal treatment

No association between the need for PsySupp in parents and genital reconstructive surgery could be found. Genital reconstructive surgeries were: female urethral correction (n=27, scheduled in n=7), male urethral correction (n=67, scheduled in n=18), vaginoplasty (n=84 scheduled in n=41), feminizing surgery of the clitoris (n=102, scheduled in n=12), vaginal dilation (n=11, scheduled in n=13), testicular relocation (n=38 scheduled in n=10) and masculinisation surgery of the penis (n=59 scheduled in n=16). 270 (82%) parents (117 DSD-XX-p-f; 49 DSD-XY-p-f; 98 DSD-XY-p-m; 6 DSD-XY-c-f) indicated that genital surgery of the child was recommended. No association between the need for PsySupp in parents and recommended genital surgery could be found. In our sample, parents reported different previous medical procedures. An association (p=0.027) between gonadectomy (n=72, scheduled in n=9) and need for PsySupp in parents could be found (Table III.4). Parents reported various medical investigations in the context of their child's diagnosis. There was a significant association between need for PsySupp in parents and medical investigations such as taking a photo (p=0.006), radiography (p=0.028), laparoscopy (p=0.009), gonadal biopsy (p=0.003) (Table III.4). No association to need for PsySupp was found for blood sampling (n=285), magnetic resonance imaging (MRI; n=23), computerised tomography (CT; n=18), endoscopy (n=43) or ultrasound (n=249). An association between need for PsySupp in parents and previous or planned hormonal induction of puberty could be found (p=0.01) (Table III.4).

### Understanding of the diagnosis

119 (40.9%) parents reported that they did not completely understand the information about the final diagnosis. 172 (59.1%) parents reported that they did understand the information. No association between the need for PsySupp and understanding the diagnosis could be found.

### Age at diagnosis, duration of making the diagnosis and sources of information

No significant association with the need for PsySupp of parents could be found for: the age at first diagnosis (in 26 cases the diagnosis was confirmed before birth, in 240 cases in the first 5 days after birth, in 39 cases in the first year and in 24 cases after one year), the duration of making the diagnosis (in 74 cases making the diagnosis took 1-7 days, in 80 cases 1-4 weeks, in 90 cases 1-12 months and in 20 cases longer than one year); for presence of previous case of familial DSD (n=39) and for sources of information. In addition to

information about the condition from medical staff, parents used the internet (n=177) books (n=107) and/or information from self-help groups (n=104).

**Sociodemographics**

Significant associations between need for PsySupp in parents and nationality of the father (p=0.005), level of education of the mothers (p=0.024) and unemployment of the father (p=0.001) could be found (Table III.4). No significant association could be found between the need of PsySupp and who responded the questionnaire, age of the parents, age of the child, importance of religion, persuasion, size of the hometown and number of siblings.

**Free comments of the parents**

In addition to the quantitative questions, the parents could express their views and opinions as free comments. Some qualitative impressions of desires and needs of the parents with need for PsySupp were: *"I needed somebody giving me confidence and information", "in the first years I strongly desired psychological care", "Open conversation with hospital staff", "Psychological guidance for the development of my child", "psychological support at diagnosis immediately after birth", „contact and exchange with other parents", "That I was perceived", "someone who encourages me and stands by me during the period of uncertainty immediately after birth and in the first weeks", "I would like to have a contact person to get some advice for upcoming problems and fears in the future", "Support within the family", "Counselling about the future, puberty; e.g. medical examinations, advice on possible hormonal treatments, possible problems and how to be prepared for them", "to be able to talk about concerns and fears before surgery", "a better comprehension of the physicians", "during the first surgery I should have had help, but I was much too focused on my child to ask"*

## Discussion

The study shows that parents of children with DSD have a high subjective need for PsySupp (40.4%). However, only about half of the parents with need for PsySupp received it adequately or partly and half needed it but did not receive any PsySupp. We assume that, in the 21st century, the services offering professional PsySupp in children's' hospitals were not well developed in Germany. Leidolf, Curran, Scout, and Bradford (2008) reported that 69% of 29 paediatric endocrinology fellowship training offered PsySupp and 58% had a mental health specialist on staff, but only 19% of individuals with DSD or families received emotional support at diagnosis and only 15% of individuals with DSD or families after diagnosis. Pasterski et al. (2010a) found that 95% of centres in Europe treating children with DSD in 2010 offered primary psychological support services such as a child psychiatrist or psychologist. Moreover, they found that the average uptake of PsySupp services by parents of a child with DSD was only 54%, which is higher than the need of for PsySupp in parents in this study (40%) (Pasterski et al., 2010a). However, no data are available how often PsySupp was offered in this study. Subsequently, potential average uptake cannot be evaluated. Although only 40% of the parents indicated a subjective need for PsySupp, a higher real need for PsySupp in parents might exist from a psychotherapeutic perspective. We assume that fears of stigmatisation by psychotherapy and psychological counselling or

ignorance about the benefit, content or aims of the different forms of PsySupp are still factors for parents not accepting PsySupp or for physicians not offering it. Additionally, parents without offered PsySupp might not be aware of their needs. These studies show that the recommendations of the Chicago consensus 2005, to involve a psychologist in the care of a child with DSD, have been mostly implemented now in Europe. Thus, parents with need for PsySupp have better access to it than before 2005.

**Diagnoses**

The highest need for PsySupp (58.7%) was reported by parents of children with conditions included in the diagnostic group DSD-XY-p-f. The diagnoses of partial gonadal dysgenesis, partial androgen insensitivity syndrome (pAIS) and disorders of androgen synthesis, which are included in the diagnostic group DSD-XY-p-f and DSD-XY-p-m, are particularly associated with a high need for PsySupp in parents (54.2%, 65.0%, 50.0%). This high need of PsySupp in parents of children with these conditions can be explained by the uncertainties about the sex of the child where a decision about the gender of rearing is needed. In contrast, parents having a child with severe hypospadias or CAH (46,XX) had much less need for PsySupp (33.9%, 26.5%). This difference can be explained by the more consistent assignment to male or female gender of rearing. Individuals with CAH (46,XX) are primarily seen as girls and individuals with severe hypospadias (46,XY) as boys. This association is not only related to the appearance of the external genitalia but also to the internal genitalia and possible future fertility. The unambiguity of the gender of rearing reduces uncertainties and confusion and apparently simplifies dealing with DSD for parents and for the medical staff because the question, “Is it a boy or a girl?” can be answered (Gough et al., 2008).

**Surgery, medical investigations and hormonal treatments**

Our data show that sex-assignment surgery neither reduces nor increases the need for PsySupp in parents. Schober (1999a) argues that surgery makes parents and doctors more comfortable, but counselling makes people comfortable too, and it is not irreversible (Lev, 2006). Crissman et al. (2011) point out that immediate surgery reduces early parental concerns regarding genital appearance but does not eliminate worries about the child’s future gender development or sexual functioning. As surgery does not reduce the need for PsySupp in parents, the fears and concerns of parents should not be the reasons for sex assignment surgery. It is therefore important to keep in mind that parents want to do the “right thing” (Nelson, Caress, Glenny, & Kirk, 2012). Moreover, parental decisions concerning early sex assignment surgery depend highly on the medical advice. But neither physicians nor parents are fully aware of the magnitude of this medically induced influence (Streuli et al., 2013) and may later be burdened with decision regret.

Investigations in context of the diagnosis such as taking a photo, radiography, laparoscopy and gonadal biopsy are associated with a great need for PsySupp in parents (49.0%, 47.7%, 66.7%, 56.7%). Consequently, only those interventions specifically indicated for further treatment planning should be performed. To reduce their stress and concerns, parents should always be informed in an adequate and understandable manner about the aims and procedures of the different medical investigations. Taking a picture might be associated with

need for PsySupp in parents because of stress to them from pointing out the unusual nature of the child's genitalia. Taking a picture should therefore not be undertaken unless absolutely necessary for treatment planning. In the medical context, a drawn sketch is often sufficient.

There was a greater need of PsySupp in parents when gonadectomy of the child was performed (52.2%) and if puberty was induced or was planned to be induced hormonally (50.0%, 58.3%). Gonadectomy is an irreversible intervention with far-reaching consequences for affected individuals as it results in deficiency of own sex hormone production and necessitates subsequent lifelong hormone substitution. Therefore, it is important that the interdisciplinary team respond to fears and concerns of parents if a gonadectomy is planned. Hormonal induction of puberty should be raised and discussed, if needed, in the period from childhood to adolescence as, even in early childhood, it can cause insecurity in parents.

**Parents' perception of the appearance of the genitalia, gender of rearing and gender role behaviour**

There was no association between parents' perception of the appearance of the child's external genitalia and need of PsySupp in parents. Duguid et al. (2007) and Pasterski et al. (2014) also did not find an association between parental post-traumatic stress, self-esteem, psychological stability and genital ambiguity of the child. Therefore, it can be assumed that, in the context of the need for PsySupp in parents, the isolated issue of ambiguous genitalia plays a minor role. It is more likely that the whole complex situation of having a child of uncertain sex and future, without a definite option of "cure", causes distress for parents.

Gender-role behaviour and gender specifics in the preferred gender of playmates of the child play a role only in the diagnostic group DSD-xy-p-f. In the other groups atypical gender behaviour is not associated with need for PsySupp in parents. We assume that this association is connected to the uncertainty of gender in this diagnostic group as already discussed under *diagnoses*. As the assignment to a male or female gender of rearing of the children is more consistent in the other diagnostic groups, atypical gender behaviour may not confuse parents. If children behave atypically, in cases where there was a difficult decision on gender of rearing, parents could be insecure with respect to this previous decision. This may foster the need for PsySupp in parents.

**Understanding of the diagnoses**

Unexpectedly, there was no association between understanding the diagnoses and the need for PsySupp. It can be concluded that, with respect to the need for PsySupp, a precise understanding of the DSD condition is not crucial. However, it appears alarming that 41% of the parents did not understood the diagnosis completely. This is probably due to the complexity of the individual condition, which even for professionals is often difficult to understand. Nevertheless, parents and patients should be informed adequately and understandably about the DSD-condition.

**Sociodemographic factors**

We found no association between the age of the children and need for PsySupp in parents. Thus, it can be concluded that PsySupp for parents is relevant from childhood to adulthood. Hullmann et al. (2011) confirm that caregivers of children with DSD may have different psychosocial needs depending upon their child's development stage and based upon the disorder-related challenges that are salient at that developmental stage. Despite our sample not including parents directly at the first suspicion of a DSD condition, it is possible that the need for PsySupp in parents is greater at diagnosis than at a later point of time when the parents have adapted to the situation (Sandberg et al., 2012). No distinction between the maternal and paternal need of PsySupp could be performed as parents answered the questionnaire together. Nevertheless, we found associations between maternal and paternal sociodemographic data and the parental need for PsySupp. The need for PsySupp was greater (>65%) if fathers had non-German citizenship, being part-time employed, unemployed or retired. It is likely that fathers of non-German citizenship might have problems with understanding the DSD-condition and treatment. Moreover, different cultural views of DSD and stigmatisation might be factors inducing increased need of PsySupp in these families. In contrast, impaired paternal employment by itself can be a factor for increased need of PsySupp for families. Moreover, differences in the need for PsySupp related to the maternal education level were found. There was a higher need for parental PsySupp when the mother held a university degree. This finding could be explained by a higher uptake of PsySupp due to less stigmatisation of psychological counselling in academics. In contrast, parents with low maternal education level also had a higher need for PsySupp which might be caused by less understanding of DSD and fears of stigmatisation. Studies differentiating between maternal and paternal need of PsySupp in DSD are needed to verify these differences. Some authors particularly highlighted the need for information and education by parents, as DSD is a rare condition and mostly unknown in society (Dayner, Lee, & Houk, 2004; Duguid et al., 2007).

**Limitations of the study**

The study was part of a large quantitative cross-sectional outcome study. Consequently, neither quantitative data explaining why such a high proportion of parents did not receive PsySupp nor on the specific needs for PsySupp of DSD families could be collected. However, some qualitative comments of parents were available. Parents expressed the following needs: *openness, confidence and information, encouragement, advice how to be prepared for possible problems in the future, contact and exchange with other parents, possibility of talking about fears and concerns before surgery, family support* (see results: free comments of the parents).

## Conclusion

Parents of a child with DSD have a high subjective need for PsySupp, but half of them did not receive it as needed. In particular, a high need for PsySupp is indicated for parents of children and adolescents with partial or mixed gonadal dysgenesis, pAIS and disorder of androgen synthesis (children with XY-DSD with androgen effects). In the last decade, the

possibility of receiving PsySupp for families of a child with DSD have improved in Europe but the uptake of PsySupp seems not to be adequate.

PsySupp for parents of children with DSD should be an obligatory part in the interdisciplinary care of children and adolescents to reduce fears of stigmatisation by psychological counselling and to enable parents to provide their children with good parental support. So far, the method, extent and content of PsySupp is be based on the individual situation and needs of the parents as yet no special concepts for PsySupp in DSD are available. Interdisciplinary teams with psychologically trained medical staff and medically trained psychologists are needed to reduce fears and concerns regarding gender issues, hormonal treatment and surgery. However, the structure, scope and content of PsySupp for DSD have to be improved and programmes for PsySupp for DSD developed.

# General Discussion

## Review of the main findings

The three studies of this cumulative thesis gave evidence-based answers to the research questions arising from the research status.

1. Does the opinion of individuals with conditions classified as DSD about the DSD terminology conform with the dissatisfaction expressed by researchers, clinicians and support groups and should it be therefore avoided?

The results of the first study showed, that the majority of participants in the dsd-LIFE cohort had a neutral or positive opinion about the term *Disorders of Sex Development*. The high acceptance rate applied to participants from all diagnosis groups. Participants did not show a tendency to prefer alternative terms with no pathologizing potential, and, in general, they appeared to prefer terms that were specific to their somatic condition over the general *Disorders of Sex Development* designation. Most interestingly, the term *intersex* which is often used by support groups was rated the lowest. The Chicago consensus aimed at eliminating stigmatising terminology and to replace it by terms more sensitive to individuals with *Disorders of Sex Development*. The data suggest that this aim was, at least partially, achieved. Especially since acceptance rates were the highest in the group of participants with conditions that prior to 2006 had been labelled hermaphroditism and pseudo-hermaphroditism. However, objection rates of 32-38% in CAH, Turner, and Klinefelter syndromes and, particularly, of 37-40% in the Netherlands and France should caution clinicians and researchers against an uncritical use of the new terminology. Overall, the data does not support the view that, in general, the term *Disorders of Sex Development* is insensitive to patients needs and should therefore be abandoned. Nevertheless, in the clinical situation it is recommended to evaluate and to be sensitive to patients' preferences.

2. How do individuals with different DSD conditions rate their Quality of Life and their psychological wellbeing, and how do diagnostic groups differ?

Study II identified a trend of lowered mental health related Quality of life (HRQoL) and significantly higher physical HRQoL for participants as compared to a normative population. Group comparison leads to the hypothesis that females with XY DSD might profit from an early effect of androgens, thus contributing to positive physical HRQoL. Although there was a high physical HRQoL, participants reported significantly impaired psychological well-being; 42.7% could be described as clinical cases. Impaired psychological well-being is an unfortunate outcome in many people with DSD, and it can be concluded, that specialised interdisciplinary care with a focus in particular on psychological care is needed to improve well-being.

3. Do parents of children with DSD express a need for psychological support and does gender and treatment related factors influence this need, so that psychological care for parents may focus on specific issues?

Study III showed that parents of a child with DSD have a high subjective need for psychological support, but half of them did not receive it as needed. In particular, a high need for psychological support is indicated for parents of children and adolescents with partial or mixed gonadal dysgenesis, pAIS and disorder of androgen synthesis (children with XY-DSD with androgen effects). In the last decade, the possibility of receiving psychological support for families of a child with DSD have improved in Europe but the uptake of psychological support seems not to be adequate. For parents of children with DSD getting to know the mental health provider should be an obligatory part of the interdisciplinary DSD care. This can avoid fears and reservations towards psychological counselling. A low threshold psychological support is likely to increase the uptake of the service, which can enable parents to provide their children with good parental support. So far, the method, extent and content of psychological support is based on the individual situation and the parents needs as no special concepts for psychological support in DSD are yet available. Interdisciplinary teams with psychologically trained medical staff and medically trained mental health professionals are needed to reduce fears and concerns regarding gender issues, hormonal treatment and surgery. However, the structure, scope and content of psychological support for DSD have to be improved and programmes developed.

**Strength and limitations**

The three presented studies were part of two large quantitative cross-sectional outcome studies, network DSD and dsd-LIFE. In network DSD 110 adults and 329 caregivers, in dsd-LIFE 1040 adults with conditions which are medically labelled as *Disorders of Sex Development* were included. So far, the largest cohort in DSD research. It was therefore possible to evaluate the views of individuals by diagnostic group and add more detailed empirical data to the current scientific knowledge. In addition to the great size of the cohort (given the rareness of DSD), all somatic conditions were medically confirmed, thus securing that only participants affected by DSD participated. Therefore, both studies did not need to rely solely on information from the participants themselves.[11] Furthermore network DSD and dsd-LIFE included a diversity of psycho-social patient reported outcomes which was rare in DSD research when the studies were designed. Both studies added empiric information in DSD research to a high extent.

Network DSD published 13 original articles: Jürgensen, Hiort, Holterhus, and Thyen (2007); Jürgensen et al. (2010); Jürgensen et al. (2013); Jürgensen et al. (2014); Kleinemeier, Jürgensen, et al. (2010); Kleinemeier, Jürgensen, et al. (2010); Kleinemeier, Werner-Rosen, Jürgensen, and Thyen (2007); Köhler et al. (2012); Lux et al. (2009); Thyen, Lanz,

[11] Which, in my experience in dsd-LIFE were unreliable; e.g. in Berlin three participants managed to participate in the study after showing medical certificate and were excluded after the medical examination as they did not have any DSD condition (two of them had gender dysphoria, one had a disorder of the adrenal gland).

Holterhus, and Hiort (2006); Thyen et al. (2014) as well as Bennecke, Thyen, Grüter, Lux, and Köhler (2016) and Bennecke et al. (2015)

So far dsd-LIFE has published 17 original research paper: de Vries et al. (2019); Engels et al. (2018); Falhammar et al. (2018); Gehrmann et al. (2019); Kreukels et al. (2019); Kreukels et al. (2018); Noordman et al. (2019); Nordenstrom et al. (2018); Nygren, Sodersten, Thyen, Kohler, and Nordenskjold (2019); Rapp et al. (2018); Riehl et al. (2019); Rohle et al. (2017); Sowikowska-Hilczer et al. (2017); Thyen et al. (2018); van de Grift, Cohen-Kettenis, de Vries, Kreukels, and dsd-Life group (2018); van de Grift and Kreukels (2019) as well as Bennecke et al. (2020). Further manuscripts are submitted or in preparation.

Although network DSD and dsd-LIFE helped to objectify various discourses in DSD care there were significant methodical problems. Both studies emphasised on including almost all areas of interests in DSD research satisfying multiple stakeholders' interests. This plurality of questionnaires and single item questions resulted in multiple testing and repeated utilisation of outcomes, while other questions could not be included in any evaluation.[12] Therefore, analyses have an exploratory character and interpretation of statistical characteristics is limited. As known, quantitative data of observational studies has limitations in explaining, why individuals preferred specific terminology, reported limited or higher quality of life or desired psychological support. Various confounding variables could influence associations between condition and patient reports. Moreover, selective memories of participants socially desirable response behaviour could lead to an information bias. Furthermore, generalisation of the results is limited. Although both studies emphasise on including many participants from different backgrounds, a selection bias can be assumed. Reasons are diverse:

- Most participants were (former) patients of the centres (often paediatric)
- Recruitment was more successful if there was a good doctor-patient-relationship
- Not all individuals with DSD are aware of their condition (and its classification as DSD, a term introduced 2005).
- Negative experiences and fears of medicine could have prevented participating.
- The term DSD and its controversy hindered participation
- The study required participants to have a conscious look on what was for some unpleasant or even traumatising experiences.
- Questionnaires about sexuality might not have been appropriate for culture or religious reasons.
- Study participation took several hours (with no financial compensation), sometimes traveling to the centre and overnight stay was needed.

Although some of the methodical difficulties might be solved with improved study design, most of them are more profound and deal with the subject of the research. The rarity of the conditions, especially of some conditions labelled as XY DSD makes enables reliable quantitative research extremely difficult. Even though the cohorts of network DSD and dsd-

[12] Especially parts of the self-constructed questionnaires could not be analysed statically.

LIFE are impressive, the DSD classification includes an extreme heterogeneous group of conditions, which differ substantially among each other. This results e.g. in different timing of diagnoses, different needs for hormonal treatment or surgical procedures. When grouping individuals with these different conditions in one group, or subgroup, interindividual differences are underestimated and too much emphasis is given on differences to comparative groups.

But even if some participants have the same condition, they are likely to have made very different experiences. DSD care, clinical guidelines, medical procedures e.g. surgical techniques, thus the experiences of the individuals with DSD, have changed significantly within the last decades. Therefore, older individuals received a highly different clinical care than families and adolescents nowadays, this also implies changes in decision making and education. Moreover, the medical perspective on surgical procedures on genitalia in infancy changed considerably and will keep changing furthermore, as changes in children's rights, self-determination and views on sex and gender in society are proceeding. Moreover, DSD care is influenced by religious and cultural norms, therefore transferring results from one country or subculture to another is problematic. Consequently, identifying condition related factors influencing psychological wellbeing and need for psychological support due to quantitative research is hardly possible.

In conclusion, generalisation of the results of the presented studies is limited. Together with DSD research in all psychosocial areas the three studies of this thesis showed, that there is a great diversity in the needs of individuals with DSD. Empiric research on its own fails to identify an evidence-based gold standard for DSD care, therefore guidelines depend on clinical expertise and up-to-date ethical considerations. All key documents about DSD care agree on the importance of psychological support which was underpinned by the present studies. Mental health professionals working with individuals with DSD need to be experts of rare medical conditions in order to be able to support affected individuals and their families the best possible way.

## Training for mental health professionals

It becomes evidential, that when offering psychological support in DSD care a profound training in DSD is essential. Unfortunately, there are rarely mental health professionals with sufficient expertise (Birnbaum et al., 2013). Atypical sex development is complex, even for health professionals difficult to understand. A curriculum for psychologists and psychotherapists is required (Birnbaum et al., 2013; Richter-Appelt & Schweizer, 2010; Schweizer et al., 2009).

**What is DSD?**

Working on the thesis as a psychotherapist I was often confronted with manifold questions from colleagues about DSD. On the one hand this confirmed the lack of DSD education in mental health professionals, on the other it gave me the opportunity to identify how one may explain DSD with a non-stigmatising inclusive approach. I now use this approach in psychological counselling for individuals with DSD and their families, in education for

students and in the theoretical background of this thesis. This education starts by not using terms, that categorizes individuals with DSD as "other" than the addressee of my education. Therefore, the term "intersex" is used at a later point. The education includes an explanation of typical sex development. By explaining its complexity (that all embryos can develop in a typically male or typically female way no matter of the sex chromosomes, that multiple genes are needed and that different hormones and enzymes influence the development of the anatomic sex, which is the same in all embryos) the addressee might feel a bit overwhelmed at first. But the knowledge about the complexity gives the opportunity to come to the conclusion, that variations of dichotomous differentiation pathways, thus DSD exist naturally. With the biological background given, most DSD conditions can be understood. After the typical development, the DSD classification can be introduced and specific DSD conditions and their genesis can be presented. In doing so, the focus lies on the frequency of all DSD conditions together, rather than on the rarity of specific conditions. The DSD classification proposed by the Chicago Consensus Group is helpful, as the classification under one umbrella term is an inclusive approach which helps individuals with these rare conditions not be exposed as curiosities[13, 14]. Rather than gender identity, psychological wellbeing and quality of life should be in the focus of trainings about DSD care. Conditions were there is atypical genitalia most often gain most interests of addressees. When focusing on these conditions, other conditions will be outshined, even though they are more frequent and do need a similar clinical approach. Reasons for surgeries and other medical treatments are diverse and most often in need for complex ethical and medical considerations. A simple solution usually does not do justice to the situation. Most often only mental health professionals working in interdisciplinary DSD teams take part in such decision making. For other mental health professionals discussing medical treatments in DSD, especially surgeries in childhood, is most often not of clinical, but of political interest. Even if these political considerations are important, they often simplify the situation families and individuals with DSD are facing. Therefore, training in DSD includes an education about the limited knowledge of the addressee.

**Psychological support**

During the period of time when individuals receive their diagnose and when medical interventions are needed, optimal psychological support for individuals with DSD, requires an understanding of treatment choices. This is only possible in interdisciplinary teams with a close collaboration between mental health professional and medical professionals. Only with profound knowledge mental health professionals will be able to fulfil the expectations

[13] It can be assumed that excluding conditions such as Turner syndrome, Klinefelter syndrome and CAH is motivated by the desire not to link these conditions to other rare conditions that are stigmatised.

[14] Although the DSD classification as an umbrella term is helpful for education, in clinical context terminology should be individualised. By contrasting that it is not a "disease" one female with CAIS insisted on having a „disorder". Another female with the medical diagnose Turner syndrome demanded that her condition should not be named Turner syndrome as she had a chromosomal mosaic and she didn't want to be associated with representations and images of individuals with Turner syndrome in textbooks and the internet.

of psychological support that was included in the statements of the Chicago Consensus Group and the German Ethical Committee;

- Monitoring of the diagnoses and the mediation of treatment proposals
- Education on the most frequent consequences of the DSD, e.g. reproductive capacity, intimate contacts, behavioural problems, adaptation problems;
- Supporting all stakeholders in stress situations and anticipating feelings such as shame, guilt, stigma;
- Support for coping strategies and communication with third parties about the condition;
- Strengthening family resources;
- Evaluation of gender identity, in order to help in the case of decision-making processes;
- Transition: transfer of young adults into adult medicine (gynaecology, internal medicine, psychology);
- Structured documentation of long-term monitoring;
- Mediation of contacts with psychotherapists and sexologists living near the place of residence, with other persons concerned (with their written consent) and self-help groups (Birnbaum et al., 2013).

This integrative mental health approach differs from the traditional role of a mental health provider – who would be consulted only when psychiatric problems are suspected (Sandberg & Mazur, 2014).

In addition to the interdisciplinary DSD team mental health professionals can be involved in the care of individuals with DSD in different situations. Apart from psychological issues such as coping, shame, communication and compliance, which might be relevant in other chronicle somatic conditions as well, individuals with DSD have some special psychological topics. In the following the main areas of concerns of adolescents and adults with DSD will be described. On the one hand these are contexts when mental health professionals not working in an interdisciplinary DSD team get in touch with individuals with DSD, on the other these are areas where there is need for special training of mental health professionals. These topics are mentioned in most research and recommendations about DSD care and were - next to general topics - the most frequent issues I was confronted with in my clinical experience with over a hundred individuals with DSD. To outline areas of training for mental health professionals, these topics will be hinted below.

**Traumatisation due to medical treatment**

In most DSD conditions hormonal treatment is needed, therefore the majority of individuals with DSD had or have some kind of medical treatment. Especially individuals with CAH or XY DSD conditions may have had multiple contacts to different medical experts and often genitalia surgery or gonadal removal were performed. Particularly if treated according to former guidelines these individuals were often not well informed about the procedures and sometime were told lies about their condition. Some were asked to show their private parts frequently, not just for medical reason, but for education of medical students. Such experiences can be traumatising and discriminating. Under these circumstances, individuals with DSD may have lost their trust in medical and psychological care and might be sceptical

or anxious and have difficulties in utilisation of medical and psychosocial services. Therefore, mental health professionals should be trained in recognising symptoms of traumatisation, even though there is high psychological functioning in most individuals with DSD. In order to be prepared for potentially shocking case reports, mental health professionals should also be aware of former treatments. They should also keep in mind, that experiences are subjective and that dealing with negative experiences does not always mean to clarify the past.

**Infertility**

In most DSD conditions, other that CAH, there is infertility and some DSD conditions (like Klinefelter Syndrome) are often diagnosed in a fertility clinic. In some conditions, there might be the opportunity for fertility treatment such as sperm donation or in vitro fertilisation, but most often individuals with DSD are not able to have their own biological children. Infertility is relevant for parents of children with DSD and the affected individual in different stages of life, not only at the age of a realistic desire to have children. Individuals with DSD may hope that they will get their own children in the future, when treatment options improve.[15] Adoption could be an alternative for some individuals with DSD but is not necessarily realistic for all. Infertility might also impact (desired) partnership and could isolate individuals with DSD from their peers. Mental health professionals counselling individuals with DSD should be aware of the somatic condition and the chances for fertility in order to help individuals with DSD to cope with their infertility.

**Gender**

In their identity development, some individuals with DSD are questioning their gender identity. Given the incongruence of the somatic sex, it can be a challenge to discover their own gender identity for some individuals with DSD, which may not be male or female. If this affects children, not only the child but also the family and the environment are affected. Sometimes a gender change is needed. This is especially complex if individuals had genital surgery and feel gender incongruence later in life. Mental health professionals in DSD care should be aware of different non-normative pathways of gender development; therefore, reflection of the own gender and of gender in society is needed. Experiences with individuals having gender dysphoria may be helpful in order to counsel and support individuals with DSD appropriately. Most often individuals with DSD do not suffer from gender dysphoria, but often the condition has an impact on ones gender identity in a more holistic sense: “What kind of men am I, if I need testosterone injections/ …when I can’t use the urinal”, “What kind of a women am I, if I cannot have children/ …if I have an enlarged clitoris/…if I have XY chromosomes”. Such questions of life can be very significant for the affected individuals, but as well for their caregivers.

[15] E.g. Uterus transplantation

**Partnership and sexuality**

The conglomerate of condition related factors, concealment in communication, bad experiences in medical treatment, infertility and gender problems can affect partnership and sexuality in many ways. Sexual dysfunction may arise from former surgery or is related to the condition, e.g. when the vaginal entrance is very narrow. Also, insufficient hormonal treatment can result in a lack of sexual desire, erectile dysfunction or lack of lubrication. An interdisciplinary approach including endocrinology, gynaecology/ urology and surgery may be necessary. However, these issues can as well be psychosomatic. Mental health professionals therefore should be able to talk openly about sexuality, at best they have training in sex and couple therapy. Similar to the approach in dealing with gender, mental health professionals should reflect non-normative ways of sexuality and sexual orientation. This is especially relevant in counselling adolescents, as sexuality, attraction to others and partnership are new and exciting, but also challenging areas in this age group.

**Education**

Especially in psychological counselling in the time of diagnosis, education about the condition is crucial. If mental health professionals counsel parents with children with DSD or affected individuals, they have to have a sufficient expertise about the condition, in order to be able to inform without confusing individuals seeking for help. Also, individuals with DSD may need education about their condition later in life, because they either may have forgotten information or might not have been educated appropriately in the past. If compliance to important medical treatments is missing, education about the consequences is important. Mental health professionals should be aware of sex hormonal influencing psychosocial wellbeing, health risks such as osteoporosis if sex hormones are missing or mortal danger if cortisol treatment is suspended. They then should refer to a medical practitioner or should talk about potential fears hindering patients to consult medical practitioner. Beside the education of individuals with DSD, health professionals with expertise could be contact person for other people caring for the individuals with DSD – e.g. the general practitioner, the psychotherapist, teachers, social workers, partners or family members.

## General Conclusion

Network DSD and dsd-LIFE were two extraordinary research studies adding needed empiric information to existing DSD research. This thesis compromises three sub studies about psychosocial aspects; The view of individuals with DSD on the term *Disorders of Sex Development*, health-related quality of Life and psychological wellbeing of adults with DSD and the subjective need for psychological support in parents of children and adolescents with DSD. Next to the empirical results, strength and limitations of the studies were discussed. It was concluded, that empiric research on its own fails to identify an evidence-based gold standard for DSD care. Therefore, DSD guidelines depend on clinical expertise and ethical considerations. As problem areas of individuals with DSD vary, mental health professionals need a training when offering the best psychological support. The extent of specialised training in DSD for mental health professionals depends on the part they have in clinical

DSD care; supporting families at the time of diagnosis and in times of decision making requires the most comprehensive knowledge. These mental health professionals should work in an interdisciplinary DSD team, which includes experts in endocrinology, ethics, genetics, surgery, paediatrics, urology and gynaecology[16]. Training for mental health professionals should be broad, as needs and problem areas of individuals are diverse. It should include biological basics, information about chronic health conditions and medical treatments. It should incorporate education about mental disorders, gender, ethics and sexuality. Moreover, mental health professionals should be trained in working with children, adolescents and adults and additionally ought to be able to work in individual setting, but as well feel comfortable in working with parents, families and couples.

Members of the two research teams from network DSD and dsd-LIFE presented their work over the years countless times in different national and international conferences, gave lectures and poster presentations. That way they not only added empirical data but communicated up to date knowledge to a wide public and taught their audience about DSD. In addition, all members of the studies got educated in DSD themselves while researching, in conferences and at meeting with support groups. In addition, all team members who were involved in the data collection were able to learn from experts and their own experience. Since the studies emphasised on involving mental health professionals, over thousand participating individuals with DSD received psychological support or were at least enabled to get in touch with a mental health professional with expertise in DSD.

I therefore conclude that network DSD, dsd-LIFE and this thesis addressed the request for research studies focusing on psychological and social aspects and contributed to a better psychological support of persons with DSD and their families. Moreover, the presented cumulative thesis outlined the basis for implementing DSD care in education programmes for mental health professionals as it was required inter alia by the German Ethical Committee.

[16] This teams should work together with support groups and implement peer to peer counseling.

# Summary

The typical prenatal male or female development of the somatic sex is a complex differentiation process affected by multiple genes, enzymes and hormones. Conditions in which the development of the somatic sex is atypical are medically summarised under the umbrella term “Disorders of Sex Development“ (DSD). Although new clinical guidelines emphasize the importance of psychosocial care, there is a research gap, since most research studies focus on medical aspects rather than on psychological or social aspects. The aim of the present cumulative thesis is to close this research gap with a quantitative study design based on patient reported outcomes.

The three studies in this thesis were part of two large quantitative cross-sectional outcome studies, network DSD and dsd-LIFE. So far, these two studies have the largest cohorts in DSD research. Furthermore, network DSD and dsd-LIFE included a diversity of psycho-social outcomes, which was rare in DSD research when the studies were designed. It was therefore possible to evaluate the views of individuals by diagnostic group and add more detailed empirical data to the current scientific knowledge.

The first evaluation focused on the term *Disorders of Sex Development* (DSD) invented in 2005 by the „Chicago Consensus Group on management of intersex conditions“ - an international congress of experts. The DSD terminology is controversial, as dissatisfaction about it was expressed by researchers, clinicians and support groups. It is stated that it should therefore be avoided. The European research group dsd-LIFE evaluated opinions on the terminology from 1040 individuals with conditions labelled as *Disorders of Sex Development*. Overall, a large majority of participants (69%) reported that the term *Disorders of Sex Development* applies to their condition or that they feel neutral about it. Overall, the data does not support the view that, in general, the term *Disorders of Sex Development* is insensitive to concerns of affected persons and that it should therefore be abandoned.

In the second study, health related Quality of life (HRQoL) and psychological wellbeing of individuals with DSD were evaluated as indicators of successful psychosocial adaptation to the conditions. 110 adults with DSD from the multicentre clinical evaluation study of the German network DSD were included. A trend towards a lower mental HRQoL and a significantly higher physical HRQoL of the participants compared to a norm was found. Participants reported significant higher psychological distress compared to the norm. Forty-seven participants (43%) reported distress in a clinically relevant range. This outcome supports the demand for psychological support in DSD care.

In the third study the subjective need for psychological support in parents of children and adolescents with DSD was analysed. 329 parents of children with DSD who took part in the multicentre clinical evaluation study of the German network DSD were included. 40% of the parents indicated to have a need for psychological support, only 50% of this group received

it adequately. In particular, parents of children with XY-DSD with androgen effects other than hypospadias expressed a high need for psychological support. Psychological support therefore should be improved and should be an integral part of DSD care with families with children and adolescents with DSD.

Although network DSD and dsd-LIFE helped to objectify the discourse about the DSD terminology and support the demand of psychosocial support in DSD care there were significant methodical problems. In summary, the results of the studies presented can only be generalised to a limited extent. Together with DSD research in all psychosocial areas, the three studies of this thesis showed, that there is a great diversity in the needs of individuals with DSD. Empirical research alone cannot establish an evidence-based gold standard for DSD care, therefore guidelines depend on clinical expertise and current ethical considerations. In summary, training of mental health professionals is needed and training should cover clinically relevant topics such as traumatisation, infertility, gender, partnership, sexuality and education on DSD.

# Zusammenfassung

Die pränatale Entwicklung des somatischen Geschlechts ist ein komplexer Differenzierungsprozess verschiedener Organe, der von unterschiedlichen Genen, Enzymen und Hormonen beeinflusst wird. Körperliche Entwicklungen, bei denen diese Differenzierung untypisch verläuft, werden in der Medizin unter dem Überbegriff „Varianzen/ Störungen der Geschlechtsentwicklung“ (engl. Disorders of Sex Development, kurz DSD) zusammengefasst. Die meisten Menschen mit DSD benötigen irgendwann in ihrem Leben medizinische Versorgung. Aktuelle klinische Leitlinien betonen aber zunehmend auch die Notwendigkeit psychologischer Unterstützung für diese Menschen und ihre Familien. Der Fokus wissenschaftlicher Forschung liegt hingegen auf medizinischen und nicht auf psycho-sozialen Aspekten, wodurch eine Forschungslücke entstanden ist und wenig empirisch belastbare Untersuchungen zu psychosozialen Aspekten bei Menschen mit DSD vorliegen. Diese Forschungslücke soll mit der vorliegenden kumulativen Arbeit geschlossen werden.

Die drei Studien der kumulativen Arbeit sind Teilstudien zweier großer quantitativer Querschnittsstudien, dem Netzwerk DSD und der europäischen Studie dsd-LIFE. Zwei der bisher größten DSD Studien, die durch ihre großen Stichproben (angesichts der Seltenheit von DSD) Analysen zwischen Untergruppen erlaubten und detailliertere empirische Daten zu dem aktuellen Wissensstand ergänzen konnten.

Die erste Teilstudie fokussiert auf den Begriff *Störung der Geschlechtsentwicklung* (DSD), der 2005 von der „Chicago Consensus Group on management of intersex conditions“ einem internationalen Komitee mit Expertise vorgestellt wurde. Dieser Begriff wird kontrovers diskutiert und teilweise stark abgelehnt. Die Forschungsfrage war, ob dies auch die Meinung von Menschen mit körperlichen Entwicklungen, die als DSD klassifiziert werden, ist und daraus folgend, der Begriff daher vermieden werden sollte. Die Meinungen von 1040 Teilnehmenden der europäischen dsd-LIFE Studie wurden analysiert. Die Mehrheit (69%) gab an, dass sie den Begriff für sich als passend empfindet oder ihm neutral gegenüber steht. Zusammenfassend zeigen die empirischen Daten nicht, dass die Mehrheit der Menschen mit DSD sich von dem DSD Begriff angegriffen fühlt und die Verwendung daher grundsätzlich eingestellt werden sollte.

In der zweiten Studie wurden gesundheitsbezogene Lebensqualität und psychisches Wohlbefinden von 110 Menschen mit DSD, die an der Studie des Netzwerk DSD teilnahmen, analysiert. Die Teilnehmenden berichteten von einer besseren körperlichen Lebensqualität als die Norm, während die psychische Belastung höher war. Insgesamt erreichten 43% der Teilnehmenden psychische Belastungswerte innerhalb eines klinisch relevanten Bereichs. Diese Ergebnisse untermauern die Forderung nach psychologischer Unterstützung bei der Versorgung von Menschen mit DSD.

Die dritte Studie geht der Frage nach, inwieweit Eltern von Kindern oder Jugendlichen mit DSD einen Bedarf nach psychologischer Unterstützung äußern. Antworten von 329 Eltern, die an der Studie des Netzwerk DSD teilnahmen wurden analysiert. 40% der Eltern äußerten einen Wunsch nach psychologischer Unterstützung, wobei nur 50% dieser Eltern angaben, diese Versorgung hinreichend erhalten zu haben. Besonders Eltern von Kindern mit XY-DSD mit partiellem Androgeneffekt äußerten einen hohen Bedarf an psychologischer Unterstützung.

Das Netzwerk DSD und dsd-Life waren in der Lage, die Diskurse in der DSD Versorgung zu objektivieren und untermauern die Forderung nach psychologischer Unterstützung. Dennoch gibt es methodische Schwierigkeiten, die die Generalisierbarkeit der Ergebnisse eingeschränken. Die drei Studien dieser Arbeit zeigten, dass es eine große Diversität in den Bedürfnissen von Menschen mit DSD gibt. Um die bestmöglichen Leitlinien für DSD Versorgung zu definieren, reicht wissenschaftliche Forschung allein daher nicht aus. Auch klinische Expertise und aktuelle ethische Überlegungen müssen berücksichtigt werden. Um eine hinreichende psychologische Versorgung zu gewährleisten, erscheinen Schulungen von psychologischem Personal unerlässlich. Eine solche Schulung sollte Themen wie Traumatisierungen, Unfruchtbarkeit, Geschlecht, Partnerschaft, Sexualität und Aufklärung beinhalten, da diese für Menschen mit DSD von besonderer Relevanz sind.

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# List of Figures

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# List of Abbreviations

AIS - androgen insensitivity syndrome
AMH - anti-Mullerian hormone
BSI - Brief Symptom Inventory
CAH - congenital adrenal hyperplasia
cAIS - complete androgen insensitivity syndrome
CBAQ - Child Behaviour and Attitudes Questionnaire
DHT - dihydrotestosterone
DSD - Differences/ disorders of sex development
GSI - global severity index
HRQoL - health-related quality of life
MCS - mental component summary
pAIS - partial androgen insensitivity syndrome
PCS - physical component summary
PSD - positive symptom distress
PST - positive symptom total
PsySupp - Psychological Support
QoL - quality of life
SF-36 - health survey
SRY - sex determining region on the Y chromosome
TDF - testis determining factor

# Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektrischen Version meiner Arbeit nicht veröffentlicht.

# List of Publications


Bennecke, E., Werner-Rosen, K., Thyen, U., Kleinemeier, E., Lux, A., Jurgensen, M., Gruters, A., & Köhler, B. (2015). Subjective need for psychological support (PsySupp) in parents of children and adolescents with disorders of sex development (dsd). *European Journal of Pediatriatrics*. doi:10.1007/s00431-015-2530-8

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Streuli, J., Bennecke, E., Thyen, U. & Wiesemann, C. (2020) *Stigma¸ openness¸ shame and dignity in individuals with disorders/differences of sex development (DSD) - a comprehensive cross-sectional clinical outcome study*. Manuscript in preparation

Bennecke, E., Kohler, B., Kreukels, B., Strandqvist, A., Marchall, L. & De Vries, A. (2020) *Psychological Support for Individuals with Differences of Sex Development (DSD)*. Manuscript in preparation

# Contribution Statement

In dsd-LIFE I took active part in the development of the questionnaires, coordinated the translation process (Polish, German, Swedish, France) and reviewed the German version of all questionnaires and study material. I mediated between clinicians and data management and supported the coordinator of the study Birgit Köhler in multiple ways. Together with her I was responsible for dissemination of the study during recruitment for the Berlin study centre. During the data collection I looked after all participants in Berlin over the course of the hole survey. Most importantly I was the mental health professional of the Berlin centre and offered psychological support for all participants, during the survey and at a later time when needed. If necessary, I coordinated further psychosocial support. Of course, I was available not only for participants of dsd-LIFE, but for all individuals with DSD approaching our centres at that time.

Study I: Together with the second author Birgit Köhler I was in charge for concept and design of the sub study. I preformed the data analysis and was responsible for interpreting the data, drafting the article and final approval of the version to be published. Robert Röhle, Ute Thyen, Katharina Gehrmann, Peter Lee, Anna Nordenström, Peggy Cohen-Kettenis and Claire Bouvattier revised the paper critically and approved the final version to be published. The last author Claudia Wiesemann was involved in all stages of the manuscript.

Study II: I was responsible for concept, design, analysis and interpretation of the data, drafting the article and final approval of the version to be published. Ute Thyen contributed her interpretations of the data and revised it critically. Anke Lux helped analysing the data. Annette Grüters approved the final version to be published. The last author Birgit Köhler was involved in all stages of the manuscript.

Study III: My responsibility was the conception and design, analysis and interpretation of data, drafting the article and final approval of the version to be published. Knut Werner-Rosen was involved in conception and design of the article. Ute Thyen supported me with her interpretation of the data, and, together with Eva Kleinemeier, Martina Jürgensen, revised it critically. Anke Lux helped in analysis of data. Annette Grüters approved the final version to be published. The last author Birgit Köhler was involved in all stages of the manuscript.

# Selbstständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne die (unzulässige) Hilfe Dritter verfasst und nur die angegebenen Quellen und Hilfsmittel benutzt habe. Weiterhin erkläre ich, dass die Dissertation keiner anderen wissenschaftlichen Hochschule zur Begutachtung in einem Promotionsverfahren vorliegt oder vorgelegen hat.

Berlin, den 20.09.2020

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Unterschrift

„Der Glaube, es gebe nur eine Wirklichkeit,
ist die gefährlichste Selbsttäuschung.“

Paul Watzlawick