

Title: Stigma and Differences of Sex Development: A Scoping Review Protocol

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Introduction:

Differences of Sex Development (DSD; also known by other labels, including Intersex) is an umbrella term describing a heterogeneous group of congenital conditions that impact the course of sex determination and differentiation (Cools et al., 2018; Lee, Houk, Ahmed, & Hughes, 2006; see Table 1 for examples). DSD are estimated to affect 1/4,500 births (Lee, et al., 2006) and can have a range of complex medical, psychological and social impacts (Sandberg, Gardner, & Cohen-Kettenis, 2012; Wisniewski et al., 2019; Wisniewski & Sandberg, 2015). For example, DSD may be associated with: atypical and/or ambiguous genitalia; sex discordant features (e.g., sex chromosomes that do not match the gender in which the person is reared; gynecomastia; excess facial and body hair in females); complex proxy decision making regarding gender of rearing and whether or when to pursue genital and/or gonadal surgery; infertility or impaired fertility; and sexual dysfunction.

Table 1. Example of a DSD Classification System.

Sex Chromosome DSD	46,XY DSD	46,XX DSD
A: 47,XXY (Klinefelter syndrome) and variants	A: Disorders of gonadal (testis) development Complete or partial gonadal dysgenesis (e.g., <i>SF1/NR5A1</i> , <i>WT1</i> , <i>GATA4</i> , <i>FOG2/ZFPM2</i> , <i>CBX2</i> , <i>SRY</i> , <i>SOX9</i> , <i>SOX8</i> , <i>MAP3K1</i> , <i>ESR2/NR3A2</i> , <i>DMRT1</i> , <i>TSPYL1</i> , <i>DHH</i> , <i>SAMD9</i> , <i>ARX</i> , <i>MAMLD1/CXorf6</i>)	A: Disorders of gonadal (ovary) development Gonadal dysgenesis Ovotesticular DSD (e.g. <i>NR5A1</i> , <i>NR2F2</i> , <i>RSP01</i>) Testicular DSD (e.g., <i>SRY</i> ⁺ , dup <i>SOX9</i> , dup <i>SOX3</i> , <i>NR5A1</i> , <i>NR2F2</i> , <i>RSP01</i> , <i>WNT4</i>)
B: 45,X (Turner syndrome) and variants	Ovotesticular DSD Testis regression	
C: 45,X/46,XY (mosaicism) and variants	B: Disorders in androgen synthesis or action Disorders of androgen synthesis Luteinizing hormone (LH) receptor mutations Smith-Lemli-Opitz syndrome StAR protein mutations Cholesterol side-chain cleavage (<i>CYP11A1</i>) 3 β -hydroxysteroid dehydrogenase 2 (<i>HSD3B2</i>) 17 α -hydroxylase/17,20-lyase (<i>CYP17</i>) P450 oxidoreductase (<i>POR</i>) Cytochrome b ₅ (<i>CYB5A</i>) Aldo-keto reductase 1C2 (<i>AKR1C2</i>) 17 β -hydroxysteroid dehydrogenase (<i>HSD17B3</i>) 5 α -reductase 2 (<i>SRD5A2</i>)	B: Androgen excess Fetal 3 β -hydroxysteroid dehydrogenase 2 (<i>HSD3B2</i>) 21-hydroxylase (<i>CYP21A2</i>) P450 oxidoreductase (<i>POR</i>) 11 β -hydroxylase (<i>CYP11B1</i>) Glucocorticoid receptor mutations Fetoplacental Aromatase (<i>CYP19</i>) deficiency Oxidoreductase (<i>POR</i>) deficiency
D: 46,XX/46,XY (chimerism)	Disorders of androgen action Androgen insensitivity syndrome Drugs and environmental modulators	Maternal Maternal virilizing tumors (e.g., luteomas) Androgenic drugs
	C: Other Syndromic associations of male genital development (e.g., cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium) Persistent müllerian duct syndrome Vanishing testis syndrome Isolated hypospadias Cryptorchidism (<i>INSL3</i> , <i>GREAT</i>) Environmental influences	C: Other Syndromic associations (e.g., cloacal anomalies) Müllerian agenesis/hypoplasia (e.g., MKRH) Uterine abnormalities (e.g., MODY5) Vaginal atresias (e.g., McKusick-Kaufman) Labial adhesions

CYP, Cytochrome P450 isoenzyme; *DSD*, disorders of sex development; *MODY5*, maturity-onset diabetes of the young type 5; *MFRH*, Mayer-Rokitansky-Küster-Hauser; *StAR*, steroidogenic acute regulatory (protein).

Note. Table from Chan, Y.-M., Hannema, S. E., Achermann, J. C., & Hughes, I. A. (2020). Disorders of Sex Development. In S. Melmed, R. J. Auchus, A. Goldfine, B., R. J. Koenig, & C. J. Rosen (Eds.), *Williams Textbook of Endocrinology* (Fourteenth ed., pp. 867-936.e814). Elsevier

Historically, as in many areas of medicine, DSD management, was paternalistic (Karkazis, Tamar-Mattis, & Kon, 2010; Siminoff & Sandberg, 2015). In accordance with the optimal gender policy (Money, Hampson, & Hampson, 1955a, 1955b), medical treatment centered on normalizing the child's genitalia through gender-validating surgery performed during infancy in order to protect the child and family from stigma and psychological distress (Nordenström & Thyen, 2014; Roen & Pasterski, 2014). Although secrecy was not an explicit tenet of the optimal gender policy (Money, 1968, 1994), it was common for physicians (and caregivers) to withhold information about DSD diagnoses and related medical treatment from affected individuals. Unfortunately, this secretive approach engendered shame, stigma, and distrust in healthcare providers and had other negative physical and psychosocial impacts for individuals treated during this era (Chase, 1998; Frader et al., 2004).

Advances in genetics, diagnostics, and treatment approaches, combined with continued reports of dissatisfaction with care practices from advocacy groups, patients and families, led to a consensus meeting of patients and healthcare professionals and subsequent creation of the 2006 Consensus Statement (Hughes, Nihoul-Fékété, Thomas, & Cohen-Kettenis, 2007; Lee et al., 2006). Care practices have changed significantly in accordance with the 2006 Consensus statement, including recommendations for early, ongoing information sharing with affected individuals (Lee et al., 2006; Roen & Pasterski, 2014) to reduce the likelihood of shame and stigma potentially associated with the DSD diagnosis and related detrimental effects on the individual's psychosocial adjustment and well-being.

DSD and related treatments can impact psychosocial functioning for both affected individuals and their caregivers (de Vries et al., 2019; Kleinemeier, Jürgensen, Lux, Widenka, & Thyen, 2010). Stigma is often cited as a contributing factor to poor psychosocial outcomes in persons with DSD and their caregivers. For example, Rolston et al. (2015) found that stigma is associated with increased risk for emotional distress and social isolation among individuals with DSD (Rolston et al., 2015). According to Goffman (1963), stigma is "an attribute that is deeply discrediting" and that diminishes a person in the eyes of others "from a whole and usual person to a tainted, discounted one" (p. 3). More recently, stigma has been further categorized into two types, "enacted" and "felt stigma". Enacted stigma refers to instances of negative or unfair treatment such as discrimination (e.g., not hiring a person with a physical difference) and/or other types of unwanted attention/treatment because of the devalued characteristic (e.g., avoiding or staring at a person with physical differences, teasing/bullying; Scambler, 2009). Felt stigma refers to the affected individual's fear of enacted stigma or anticipation of social rejection. In other words, felt stigma reflects the belief that negative treatment will occur if the difference is exposed (Quinn & Earnshaw, 2013).

At the time of their child's birth and during childhood, parents/caregivers of children with DSD may fear or experience stigma related to the child's DSD condition. Stigma in turn can be detrimental to parents' coping and use of social support, particularly if they are fearful to disclose the child's condition to others. Parental concerns about experienced or anticipated stigma may persist throughout childhood and adolescence as parents may worry that their child's participation in daily (e.g., using a public restroom) or specific activities (e.g., extracurricular activities like swimming) will inadvertently reveal the child's DSD-related

differences. Parents may also worry about whether their child will experience teasing and/or bullying if their differences are revealed. Furthermore, parents' perceived/experienced stigma can impact how they communicate to their child about the DSD, inadvertently instilling shame and secrecy.

As they grow older, individuals with DSD-related physical differences may experience feelings of self-consciousness and/or shame, particularly in situations where their difference could be exposed. They may also experience and/or fear teasing, bullying, or rejection because of their differences. These concerns may intensify during adolescence and adulthood when interest in forming romantic partnerships and when having children may take on greater salience and focus. Although, there is little longitudinal, prospective data about adjustment in persons with DSD over time and across developmental stages.

While stigma is often cited as a factor that negatively affects well-being and adjustment, it is unknown how many studies have assessed stigma (enacted or felt) among parents/caregivers or individuals with DSD, nor how these studies were conducted. The goal of this scoping review is to examine evidence for stigma experiences/perceptions (felt or enacted) in parents/caregivers of children with DSD as well as youth/adults with DSD. A preliminary search for scoping and systematic reviews on stigma across DSD was conducted in 2020 and again in 2021 with no scoping or systematic reviews identified. The objective of this scoping review is to investigate stigma experiences as reported by individuals with DSD (children, adolescents, adults) their parents/caregivers, and non-affected individuals (e.g., healthcare providers).

Inclusion Criteria:

- Qualitative or quantitative studies that evaluated stigma in DSD populations or stigma-related attitudes towards individuals with DSD
- Studies published in peer-reviewed journals
- Studies published in the English language
- Studies published after publication of the optimal gender policy (Money et al., 1955a, 1955b) in 1955
- Exclusion criteria: any article not written in English; articles written before 1955

Types of participants

- Parents, legal guardians or family members of children [of any age] with DSD defined in accordance with the 2006 Consensus Statement (Lee et al., 2006) as congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical
- Children, adolescents, adults with DSD (as defined above)
- Non-affected adults or children (any age), as long as they are reporting on the stigma related to DSD (e.g., healthcare providers, policy-makers).

Concept

The concept of interest for this scoping review is understanding stigma in DSD.

Context

No particular context will be applied to this project. However, sources will be limited to those written in English. As such, this scoping review will include studies published from any cultural or regional setting that is written in the English language.

Types of evidence sources

We will include the following study designs:

Quantitative and qualitative primary research studies will be included in the scoping review. This will include randomized controlled trials, time series analyses, non-randomized studies, and observational studies, including controlled before-after studies, and pre-post studies.

The following will be excluded: literature reviews, commentaries, book chapters, unpublished dissertations, and editorials.

Methods:

The methods used in this scoping review will follow the frameworks proposed by Arksey and O'Malley (2005) and Levac and colleagues (Peters et al., 2020), using the methods outlined in the JBI Manual for Evidence Synthesis. The review team followed a multi-step, iterative process for developing and refining the search strategy.

Search Strategy:

Description of strategy:

The review team met with two informationists (LJ, KS) in early 2020. Using a short list of sentinel articles provided by the review team, the informationists were able to craft an initial search strategy that was used to inform the selection of potential databases, concepts, and search terms. The search strategies were developed to identify published primary studies. The databases that were selected for this project include Cochrane Library, PubMed, Ovid MEDLINE (Ovid MEDLINE(R) and Epub Ahead of Print, In-process & Other Non-INDEXED Citations, Daily and Versions(R)), (ELSEVIER) Embase, (EBSCO) CINAHL Complete, (EBSCO) PsycInfo, (EBSCO) LGBT Life, and (ELSEVIER) Scopus.

As a group, the team reviewed preliminary searches for scoping and systematic reviews on stigma across DSD in Cochrane Library and PubMed. This initial search was also used to identify relevant concepts, controlled vocabulary, and keywords.

After initial search strategies were analyzed and refined, it was later determined that Ovid MEDLINE would be the preferred database for searching MEDLINE. As the searches were translated across the remaining databases, the entire team reviewed search terms and results for each database and provided feedback on controlled vocabulary and keywords. The final search strategy was built around three main concepts: disorders of sex development and stigma. The review team was also unable to provide translation for articles in languages other than English, so an English language limit was also applied to the searches. When available, publication limits were applied to exclude reviews, commentaries, and book chapters. The final searches were run on 12/8/2020, and EndNote X9 was used to manage citations, and to identify and remove duplicates.

A complete search strategy for Ovid MEDLINE has been included in Appendix A.

Supplemental strategies:

A hand-search for non-indexed and difficult to locate studies will be conducted, including examining key journals. We will also scan the reference lists of all included articles.

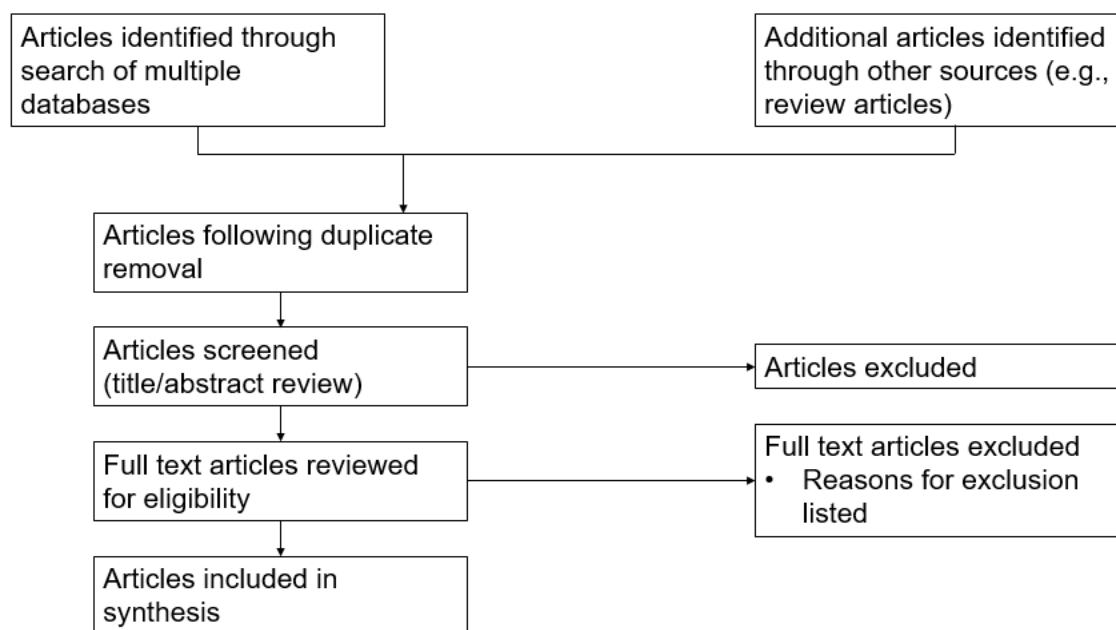
Source of evidence selection:

The review of sources will utilize the program DistillerSR. Article selection will be based on the inclusion/exclusion criteria described above and will include a review of title and abstract, followed by a full-article review.

All reviewers will undergo a training process including reading relevant articles and reviewing the codebook developed for this project. Pilot testing will take place, including the entire review team completing a title/abstract and full-text review of 25 randomly selected articles, with the use of the inclusion/exclusion criteria and the codebook. Throughout pilot testing, the review team will meet to review and update inclusion/exclusion criteria and codebook. Screening will commence once all 25 articles have been reviewed and discussed and when there is at least 75% agreement among reviewers. When completing the screening, at least 2 reviewers will review each source at each level (title abstract and full-article review) and disagreements will be reconciled by consensus or by a third reviewer. See Figure 1 for flowchart of review process.

In accordance with the PRISMA-ScR statement (Tricco et al., 2018), a flowchart and narrative description of the evidence selection process will be created [from the search, source selection, duplicates, full-text retrieval, and any additions from third search, data extraction and presentation of the evidence].

Figure 1. Review process



Details will be provided in a table for all articles identified for inclusion in the final synthesis for this scoping review. Reasons for exclusion will also be provided about excluded articles.

Data extraction/charting:

The data extraction form will extract the following key information from each article:

1. Author(s)

2. Year of publication
3. Origin/country of origin (where the source was published or conducted)
4. Aims/purpose
5. Population and sample size within the source of evidence including sampling strategy (procedure followed to select sample)
 - a. DSD diagnosis/identity, race, ethnicity, sex, gender, sexual orientation
6. Methodology / methods (see Table 2 below)
7. Stigma outcomes and details of these (e.g. how measured)

The data extraction form will be utilized during the pilot phase of the project and further refined, as needed. If additional data is determined to be needed during the screening and data extraction process, the data extraction form will also be updated.

Analysis of the evidence:

Simple frequency counts of stigma concepts, populations, characteristics or other fields of data will be calculated.

Presentation of the results:

Results of the scoping review will be presented in a table (see Table 2 below for example).

Table 2: Example tabular presentation of data for a scoping review

Parameter	Results
Numbers of publications	Total number of sources of evidence Total numbers between 1955 until January 2021 Number of publications every year
Types of studies	Randomized controlled trials Non-randomized controlled trials Quasi-experimental studies Before-and-after studies Prospective cohort studies Retrospective cohort studies Case-control studies Cross-sectional studies Other quantitative studies Qualitative studies Mixed methods studies
Population/s identified	Population (e.g., parent, patient, healthcare provider, policy-maker, sibling, other), age, race, sex, gender, ethnicity, DSD diagnosis/identity (when applicable)
Stigma domains	Enacted [refers to instances of negative or unfair treatment such as discrimination (e.g., not hiring a person with a physical difference) and/or other types of unwanted attention/treatment

	<p>because of the devalued characteristic (e.g., avoiding or staring at a person with physical differences, teasing/bullying]</p> <p>Felt [Felt stigma refers to the affected individual's fear of enacted stigma or anticipation of social rejection. In other words, felt stigma reflects the belief that negative treatment will occur if the difference is exposed]</p> <p>Other (not classified in any of the above) (e.g., institutionalized)</p>
Assessment type	<p>Standardized questionnaire</p> <p>Non-standardized items/questionnaire</p> <p>Qualitative interviews</p> <p>Other methodology</p>
Assessment measure	<p>Measure(s)/assessment battery utilized</p>

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Appendix A

Ovid MEDLINE

Ovid MEDLINE(R) and Epub Ahead of Print, In-process & Other Non-INDEXED Citations, Daily and Versions(R)

1.

(17-Hydroxysteroid Dehydrogenase Deficiency OR Anorchia).rs. OR exp Cloaca/ OR exp Disorders of Sex Development/ OR exp Hypospadias/ OR exp Intersex Persons/ OR exp Kallmann Syndrome/ OR exp Klinefelter Syndrome/ OR exp Ovotesticular Disorders of Sex Development/ OR exp Turner Syndrome/ OR exp WAGR Syndrome/ OR Mullerian [aplasia.rs.](#) OR Mullerian Ducts/ab OR Penis [agenesis.rs.](#) OR (17 beta hydroxysteroid dehydrogenase OR 21-hydroxylase deficiency OR 5 alpha reductase deficiency OR 5-alpha-reductase-2 OR 5alpha-rd2 deficiency OR 5rd2 deficiency OR adrenal hyperplasia OR adrenogenital syndrome OR androgen insensitivity syndrome OR anorchia OR aphallia OR clitoromegaly OR cloaca OR cloacal exstrophy OR disorders in androgen synthesis OR empty scrotum OR gonadal regression OR hermaphrodite OR hermaphrodites OR hermaphroditism OR hermaphroditismus OR hypospadias OR hypospadias OR intersex OR intersexualities OR intersexuality OR kallmann's syndrome OR kallmanns syndrome OR luteinizing hormone receptor mutation OR mayer rokitansky kuster hauser syndrome OR macroclitoris OR micro-penis OR micropenis OR microphallus OR ovotestes OR ovotesticular OR pseudohermaphrodite OR pseudohermaphrodites OR pseudohermaphroditism OR sex chromosome mosaicism OR sex reversal OR swyer syndrome OR testicular feminization syndrome OR turner's syndrome OR turners syndrome OR vanishing testes OR wagr OR wagro).mp. OR ((sex OR sexual) adj3 (difference OR differences OR differentiation) adj3 (development OR developments)).mp. OR ((sex OR sexual) adj3 (difference OR differences OR differentiation) adj3 (disorder OR disorders)).mp. OR ((sex OR sexual) adj3 (development OR developments) adj3 (disorder OR disorders)).mp. OR ((atypical OR atypia OR ambiguous OR ambiguity OR ambiguities) adj3 (genitalia OR genital OR genitals)).mp. OR (((penis OR penile OR clitoris OR mullerian OR gonadal OR uteri OR uterus OR uteruses OR uterovaginal OR vagina OR vaginal OR testis OR testes OR testicular) adj3 (dysgenesis OR agenesis OR atresia OR aplasia OR hypoplasia OR regression OR absence OR absent OR vanishing)) OR ((uteri OR uterus OR uteruses) adj3 (didelphys OR bicornus OR absent))).mp.

2.

exp social stigma/ OR exp Homophobia/ OR Prejudice/ OR exp Social Discrimination/ OR exp Stereotyping/ OR exp Scapegoating/ OR exp Dehumanization/ OR exp Non-Sexual Harassment/ OR exp Social Desirability/ OR exp Social Distance/ OR exp Social Isolation/ OR exp Social Marginalization/ OR exp Sexual Harassment/ OR exp Incivility/ OR exp Crime Victims/ OR exp Violence/ OR exp Workplace Violence/ OR exp Rejection, Psychology/ OR exp sexism/ OR exp Human Rights Abuses/ OR exp Attitude to Health/ OR ("gender bias" OR "human rights" OR "sex bias" OR "social desirability" OR "social distance" OR "verbal abuse" OR alienation OR attitude OR attitudes OR bullied OR bully OR bullying OR dehumanization OR dehumanize OR dehumanizing OR discriminate OR discriminated OR discrimination OR disparities OR disparity OR harass OR harassed OR harassment OR heteronormative OR heteronormativity OR heterosexism OR homonegativity OR homophobia OR homophobic OR incivility OR "social

inclusion" OR "social exclusion" OR isolation OR marginalization OR marginalize OR marginalized OR marginalise OR marginalised OR marginalisation OR prejudice OR rejection OR scapegoat OR scapegoating OR scapegoats OR sexism OR stereotype OR stereotyped OR stereotypes OR stereotyping OR stigma OR stigmas OR stigmatize OR stigmatized OR stigmatization OR tease OR teased OR teasing OR transphobia OR transphobic OR victim OR victimization OR victims OR violence).mp

3.

(animals.sh. NOT humans.sh.)

(1 AND 2) NOT 3

Limits: English

1685 results 12/8/20