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PSYCHOLOGICAL AND PSYCHIATRIC ASPECTS IN WOMEN WITH DISORDERS OF SEX DEVELOPMENT

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Illustration by Sara Rutberg

The eye is the mirror of the soul. A boarder land where our inner world is reflected to our outer world and, at the same time, the outside world can reflect in us. The eye is the boarder land where recognition between people can take place.

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Psychological and psychiatric aspects in women with disorders of sex development

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To my family

*Not everything that can be counted counts.
Not everything that counts can be counted.*

- William Bruce Cameron

ABSTRACT

Disorders of sex development (DSD) are an umbrella term for conditions where biological development of sex is affected. Included in this thesis are women with different DSD; women with congenital adrenal hyperplasia (CAH), a disorder causing androgen excess, women with complete androgen insensitivity (CAIS), a disorder of androgen action, and women with complete gonadal dysgenesis (CGD), a complete absence of testicular or ovarian development. Although the etiologies are different, living with a chronic condition is interlaced with continuous learning and new challenges. During the last decades research has focused on elucidating the genetic background in DSD and, the effect of androgens on psychosexual development. Thus, mental health issues and psychological outcomes need to be explored. Therefore, the overall aim of this thesis was to investigate psychological and psychiatric aspects regarding women with DSD. The methods used to achieve this aim were interview studies analyzed by qualitative content analysis (**Studies I and II**), matched case cohort study using the Swedish nationwide registries and 1:100 age-matched male and female controls (**Study III**), and a cross-sectional study using structured clinical interviews (MINI+) with women with CAIS and GD compared to women with premature ovarian insufficiency (POI) and age-matched controls (1:1). The findings from 13 interviews with women with CAH (**Studies I and II**), revealed that knowledge about CAH facilitates disclosure of information. Similarly, knowledge about one's body facilitates the initiation of sexual activities. On the other hand, repeated genital examinations can threaten autonomy and lead to traumatic experiences. Participation in research was considered to be important to improve future caretaking, however, much research was not considered important for the individual patient. Participants identified as women, however, some participants did not feel feminine enough. Subsequent, motherhood was described as a confirmation of being a woman. Participants had shifting opinions as to what role CAH has played in their lives, and how it affected their experiences and views. Moreover, shame was fueled by experiences of exposure in interaction with health professionals, as well as parental shame, and a recurrent focus on evaluation and normality. In conclusion, all participants described their struggle to be seen as individuals. The specific objective of **Study III** and **Study IV** was to increase knowledge of psychiatric disorders among women with DSD. Linkage of Swedish registries with the National CAH Registry (**Study III**) showed an increased risk of psychiatric disorders among girls and women with CAH, and in particular substance use disorders, compared to population controls. Lastly, in **Study IV**, screening for psychiatric disorders with MINI+ revealed significantly increased frequencies of psychiatric disorders in women with CAIS and CGD compared to women with POI and population-derived controls. Thus, the increased frequencies reported in both **Study III** and **Study IV**, call for clinical attention to psychiatric symptoms in women with DSD. In conclusion, women with DSD are a diverse group of individuals with different needs and experiences. They have a higher risk for psychiatric disorders. By acknowledging this fact, health professionals can aid with age-appropriate information, information disclosure strategies, attention to psychiatric symptoms, and support, to help women with DSD reach the fullest possible physical and mental health. Furthermore, involvement of persons with a DSD in care and research may help to understand the variability in outcome. Moreover, increased awareness of DSD among health professionals, and the general public could eventually make life easier for persons with a DSD.

SAMMANFATTNING

Disorders of sex development (DSD) är en övergripande term för tillstånd som påverkar biologisk könsutveckling. Den här avhandlingen inkluderar kvinnor med medfödd binjurebarkssvikt (CAH) som leder till överskott av androgener (t.ex. testosteron) och kvinnor med komplett androgen okänslighet (CAIS) som pga. dysfunktion i androgenreceptorer inte har någon effekt av androgener, samt kvinnor med komplett gonaddysgenesi (CGD) som har en medfödd påverkad utveckling av testiklar eller ovarier. Således är orsakerna till DSD olika men att leva med en kronisk sjukdom innebär ständigt lärande och nya utmaningar. De senaste decennierna har forskning kring DSD fokuserat på att förstå den bakomliggande genetiken samt att utforska androgeners påverkan på psykosexuell utveckling. Men för att förbättra omhändertagande behövs studier kring mental hälsa och vad som påverkar psykologiskt välbefinnande. Målet med avhandlingen var därför att fördjupa kunskaperna kring vilka psykiatriska och psykologiska aspekter som är viktiga för kvinnor med DSD. Metoderna som användes var intervjustudier med kvinnor med CAH (**studie I** och **II**) som analyserades med kvalitativ innehållsanalys, registerstudie där psykiatriska diagnoser i en kohort av kvinnor med CAH jämfördes med 1:100 åldersmatchade kontroller (**studie III**) och till sist, en tvärsnittsstudie där en kortfattad standardiserad diagnostisk intervju (MINI+) användes för att studera förekomsten av psykiatriska symtom hos kvinnor med CAIS och CGD i jämförelse med kvinnor med prematur ovariell insufficiens (POI) och åldersmatchade kontroller (**studie IV**). Resultaten från intervjuer med kvinnor med CAH (**I,II**) visade att adekvat kunskap om CAH underlättade när informanterna skulle berätta om sitt tillstånd för andra. Kunskap kring den egna kroppen underlättade också initierandet av sexuella aktiviteter. Upprepade underlivsundersökningar upplevdes hota informanternas autonomi och beskrevs som traumatiska. Forskning kring CAH, och forskningsdeltagande, beskrevs som viktigt för att förbättra framtida vård men mycket forskning ansågs inte vara viktig för den individuella patienten. Informanterna identifierade sig som kvinnor men beskrev att de inte kände sig tillräckligt kvinnliga. De hade olika syn på barnönskan och graviditet samt vilken roll CAH spelade i deras liv och hur detta påverkade deras upplevelser och perspektiv. Skam var ett återkommande underliggande tema och understöddes av utsatthet i relation till sjukvårdspersonal, föräldrars skam över sjukdomen och återkommande utvärderingar och fokus på normalitet. Sammanfattningsvis så beskrev alla informanter att de kämpade för att bli sedda som individer. Målet för **studie III** och **IV** var att öka kunskapen kring psykiatriska tillstånd bland kvinnor med DSD. **Studie III** var en registerstudie där CAH-registret länkades med patientregister och visade ökad risk för psykiatrisk sjuklighet i allmänhet och beroendesjukdomar i synnerhet hos kvinnor med CAH. Den sista studien (**IV**) visade att kvinnor med CAIS och kvinnor med GD har större risk för psykiatrisk sjukdom i jämförelse med kvinnor med POI och friska kvinnor i befolkningen. Den ökade risken för psykiatrisk sjuklighet bör föranleda ökad uppmärksamhet på psykiatriska symtom hos kvinnor med DSD. Sammanfattningsvis så är kvinnor med DSD en heterogen grupp individer med olika behov och erfarenheter. Genom att vara uppmärksamma på psykiatriska symptom, bistå med åldersadekvat information och strategier för att berätta om CAH för andra, kan vårdpersonal hjälpa dessa kvinnor att må så bra som möjligt, både fysiskt och psykiskt. Avslutningsvis, genom att involvera personer med DSD i vård och forskning kan vi kanske förstå variationen i utfall mellan patienter. På sikt kan vi kanske också underlätta för de här personerna genom ökad medvetenheten om DSD.

LIST OF SCIENTIFIC PAPERS

The following papers will be referred to by their roman numerals.

- I. **Engberg H**, Möller A, Hagenfeldt K, Nordenskjöld A, Frisén L.
The experience of women living with Congenital Adrenal Hyperplasia: impact of the condition and care given.
Clinical Endocrinology 2016 Jul;85(1):21-8
- II. **Engberg H**, Möller A, Hagenfeldt K, Nordenskjöld A, Frisén L.
Identity, sexuality, and parenthood among women with congenital adrenal hyperplasia.
Submitted
- III. **Engberg H**, Butwicka A, Nordenström A, Hirschberg AL, Falhammar H, Lichtenstein P, Nordenskjöld A, Frisén L, Landén M.
Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: A total population study.
Psychoneuroendocrinology 2015;60:195-205
- IV. **Engberg H**, Strandqvist A, Nordenström A, Butwicka A, Nordenskjöld A, Hirschberg AL, Frisén L.
Psychiatric morbidity in women with disorders of sex development.
Submitted

LIST OF RELATED PAPERS

Örtqvist L, **Engberg H**, Strandqvist A, Nordenström A, Holmdahl G, Nordenskjöld A, Frisén L.

No increase in psychiatric symptoms in men with hypospadias –
A case-control study

Submitted

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LIST OF ABBREVIATIONS

21-OH	The enzyme 21-Hydroxylase
ACTH	Adrenocorticotrophic hormone
AMH	Anti-Müllerian duct hormone
AR	Androgen receptor
AIS	Androgen insensitivity syndrome
CAH	Congenital adrenal hyperplasia
CAIS	Complete androgen insensitivity syndrome
CGD	Complete gonadal dysgenesis
CI	Confidence interval
<i>CYP21A2</i>	Gene for the enzyme 21-hydroxylase
DHT	5 α -dihydrotestosterone
DSD	Disorders of sex development
GD	Gonadal dysgenesis
HPA	Hypothalamic–pituitary–adrenal axis
HRQoL	Health related quality of life
MAIS	Mild androgen insensitivity syndrome
MINI	M.I.N.I. International Neuropsychiatric Interview
NC-CAH	Non-classic congenital adrenal hyperplasia
OR	Odds ratio
PAIS	Partial androgen insensitivity syndrome
POI	Premature ovarian insufficiency
QoL	Quality of life
SV-CAH	Simple virilizing congenital adrenal hyperplasia
SW-CAH	Salt wasting congenital adrenal hyperplasia

LIST OF DEFINITIONS

Androgens: Any steroid hormone that activates or controls the development and maintenance of male sex characteristics, for example testosterone.

Androgen insensitivity syndrome: Conditions that cause partial or complete inability of cells to respond to androgens.

Chromosomal sex: Most humans are born with 46 chromosomes in 23 pairs. The X and Y-chromosomes usually determine a person's biological sex. Most women have 46,XX chromosomes and most men have 46,XY chromosomes. Chromosomal sex can also be called **genetic sex**.

Confidence interval: The probability that a population parameter will fall between two set values.

Congenital adrenal hyperplasia: CAH is an inherited disorder of the steroid synthesis of the adrenal glands.

Disorders of sex development: Congenital conditions where development of chromosomal, gonadal or anatomical sex is atypical.

Gender: Gender is commonly understood as the social construction, typically described in terms of masculinity and femininity and that differs across cultures and over time. Psychosexual development involves three main components. Gender identity is the feeling of being a boy or a girl. Gender role refers to gender-typical behavior such as preferences in toys. Sexual orientation refers to the direction of a person's sexual interest.

Genotype: The genotype of an organism is the inherited map it carries within its genetic code.

Gonad: The gonads in males are the testes and the gonads in females are the ovaries.

Gonadal sex: The sex determined by which kind of gonadal tissue is present (ovaries or testes).

Intersex: A term that was used in medical practice for a person born with a DSD, however since the 1990s it also carries a political identity.

Karyotype: The description of sorted chromosomes in an organism visualized during cell division. The most common human karyotype is 44 chromosomes plus two specific sex chromosomes (46,XX or 46,XY).

Odds ratio: The ratio of the likelihood of an event occurring in one group compared to the likelihood of the event occurring in another group. Odds ratios are used as a measure of the association between an exposure and an outcome.

Phenotype: Defined as an organism's expressed physical traits.

Premature ovarian insufficiency: Loss of ovarian function before age 40, premature menopause.

Quality of Life: A concept that usually includes multiple dimensions of subjective assessments of both positive and negative aspects of life.

Sex: Is commonly known as the state of being male or female.

In this thesis 'sex' will be used in relation to somatic and physiological characteristics and 'gender' in relation to psychosocial aspects. However, sex will also be used as a term with reference to sexual activity.

Sex hormones: In most genetic females the primary sex hormones are estrogen and progesterone produced by the ovaries. In most genetic males the principal sex hormone is testosterone produced by the testes.

Phenotypic sex: Sex determined by the internal and external genitalia and expression of secondary sex characteristics e.g., beard and breast.

Secondary sexual differentiation: Secondary sexual differentiation comprises features that appear at puberty in humans and distinguishes the sexes, but are not directly part of the reproductive system. Visible sex characteristics include pubic hair, enlarged breasts in female and facial hair and darker voice in males.

Virilization: The induction or development of male-typical secondary sex characteristics in a female or a prepubertal male.

1 INTRODUCTION

In 1948 the World Health Organization described health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (1). At that time many chronic diseases led to an early death and several of the diseases we treat today were not diagnosed because they were unknown to the medical community.

Thus, ageing with chronic illnesses has become more frequent, largely thanks to the introduction of new pharmaceutical preparations and surgical interventions. Because of this, new questions arise that need to be addressed in the care of patients.

The introduction of glucocorticoids in the 1950s constitutes a paradigm shift in the medical treatment of many diseases, such as congenital adrenal hyperplasia (CAH). CAH is a hereditary disease involving insufficient production of cortisol and aldosterone from the adrenal glands and, at the same time, increased production of androgens. Without cortisol, the body cannot regulate salt and glucose balance, leading to an early death. However, with glucocorticoid treatment, the majority of children with CAH can now reach adulthood. This means that there are now grown-up women and men who have lived with this disease for more than 60 years.

In the beginning of the 1950s an American gynecologist John Morris reported on a group of 80 patients that appeared to be female but did not menstruate, had sparse pubic hair and had testes instead of a uterus (2). It would take several years before chromosomes could be analyzed and these women turned out to have the XY chromosomes. After an additional 30 years, it was concluded that this condition was due to dysfunction of the androgen receptor, and the Androgen Insensitivity Syndrome (AIS) was given its present name.

AIS and CAH are included in Disorders of Sex Development (DSD), an umbrella term used when a person is born with a condition which in some way, affects the development of sex.

Given the medical and surgical advances, and the opportunity for accurate diagnosis during the last few decades, questions about how to care for patients with DSD in a broader perspective needed to be addressed. Thus, in 2005 a consensus meeting was held in Chicago, Illinois, USA. Fifty medical experts and two patient representatives discussed a number of aspects of disorders affecting sex development. Among other things, the meeting focused on aspects on how to live with chronic conditions in the best possible way, they concluded that: "Quality of life encompasses falling in love, dating, attraction, ability to develop intimate relationships, sexual functioning, and the opportunity to marry and raise children, regardless of biologic indicators of sex" (3).

In addition, DSD has been surrounded by questions regarding gender, normativity, and social norms. Surgical interventions in the childhood years to correct an atypical sex have been debated, as well as what role the health care services play in applying social principles to disease or gender, by labeling conditions as sick or healthy, and normal or abnormal (4).

In the summer of 2009 the subject of DSD was brought into public consciousness when Caster Mokgadi Semenya, a then 18-year-old woman from South Africa, won the women's 800 meters at the 2009 World Championships in Berlin, Germany. Following her victory questions were raised about her sex, thereby initiating an international debate on sex, gender, and normality (5).

2 THESIS AT A GLANCE

Study	Research question	Method	Results	Conclusions
I	How do women with CAH describe their experiences of having CAH, and the care given?	Thirteen semi-structured interviews with women with CAH analyzed by inductive content analysis.	Information sharing is difficult because of lack of CAH-specific knowledge. Genital examinations can be experienced as traumatic. Research is considered important but it reproduce normative gender roles. Fighting shame is a recurrent theme.	Information disclosure can be facilitated by increased knowledge. Genital examinations should be kept to a minimum. New research perspectives are needed. Shame can be counteracted by increased support to parents and patients.
II	How do women with CAH describe their experiences of identity formation, sexuality, and parenthood?	Thirteen semi-structured interviews with women with CAH analyzed by inductive content analysis.	Feeling like a woman is threatened by normative expectations of femininity. Intimate relationships are hindered by sexual difficulties, and insufficient knowledge. Fertility is not taken for granted and the wish for children varies among participants.	Increased sexual education for patients and raised awareness of DSD in society can facilitate psychosexual adjustment and sexual relationships. Increased information on fertility and at transitions, can aid in the adjustment and support women with CAH.
III	What is the frequency of psychiatric disorders in a Swedish cohort of girls and women with CAH compared to controls?	By using the Swedish registries the risk of psychiatric diagnosis among 355 women with CAH was compared to 1:100 age-matched male and female controls.	Girls and women with CAH have a higher risk than both male and female controls, to have received a psychiatric diagnosis. In particular they have a higher risk of alcohol misuse disorders.	Increased attention to psychiatric symptoms among women with CAH is warranted, in particular symptoms of addiction, depression and, anxiety.
IV	Is the frequency of psychiatric disorders in women with DSD (CAIS and 46,XX CGD and 46,XY CGD) different from women with POI and age-matched controls?	20 women with CAIS, 7 women with 46,XX CGD, 6 women with 46,XY CGD, 21 women with POI and 61 population-derived female controls were assessed using MINI+ screening for psychiatric morbidity	Women with DSD have an increased lifetime risk of any psychiatric disorder. Mood disorders and anxiety disorders in particular. There were no significant differences in risk between women with DSD and women with POI.	Women with different DSD have higher risks of developing mood and anxiety disorders. More attention to mental health issues in women with DSD is needed.

3 BACKGROUND

“Disorders of sex development (DSD)” is an umbrella term for conditions in which the reproductive organs and genitals do not develop as expected (6). Since these are rare conditions, this Background section is aimed at giving a brief overview of sex differentiation in humans, and the etiology, symptoms, and treatment of the DSD conditions included in this thesis. In addition, this chapter will summarize the hypotheses of hormone-driven sex differences, the focus of much of the research on DSD during the last few decades, and it also presents a background to the posed research questions in the four consecutive research studies.

3.1 SEX DEVELOPMENT

In brief, one might say that nature’s recipe is by default, that all human fetuses will be born as baby girls if they are not showered with the right hormones at different periods of the pregnancy. Before seven weeks of gestation, all fetuses have an identical reproductive anatomy. After this, the fetuses with two X chromosomes start to develop ovaries, and a little later, those with a Y chromosome start to develop testes (Figure 1). There are several steps during gestation and later, after birth, that affects our perception of sex. The binary division between male and female might seem clear and easy, but sex is more complex than what it looks like on the outside (7). In the following section, the usual sex development is explained in more detail.

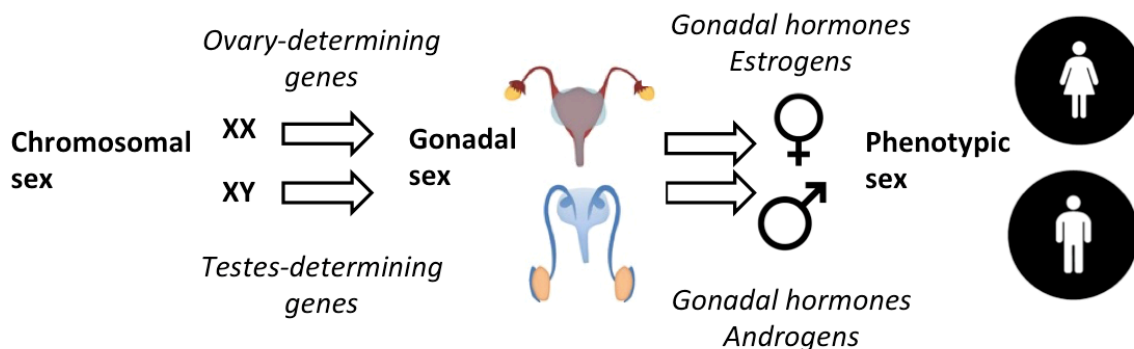


Figure 1. Simplified sex differentiation in humans. Sex differentiation begins with sex determination, depending on the chromosomal sex. Sex determination involves the specification of the gonads into testes or ovaries. Sex hormones are needed for development of external genitalia and secondary sex characteristics.

Chromosomal and gonadal sex

In humans the successful sex-defining strategy is chromosomal because this allows for early and exact programmed sex differentiation. Since all fetuses are sexually undifferentiated until seven weeks of gestation, the gonads can be either testes or ovaries, and are therefore called bipotential (8). The Y-chromosome has the testes determining genes and they determine

which developmental path the gonads will follow, the typical male or female path. For example, in persons with two X chromosomes and one Y-chromosome (Klinefelter syndrome, 47,XXY), the sex is male. In persons with only one X chromosome (Turner syndrome 45,X), the sex is female, but the ovaries do not develop normally, for that, two X chromosomes are needed (9).

This bipotential stage of the gonads occurs from week four until week seven of fetal development (9). The major genes for testes determination is proposed to be the *SRY* gene (Sex-determining Region of the Y chromosome), together with an autosomal gene, *SOX-9* (a gene that is not located on a sex chromosome), and a transcription factor *SF1* (a protein that binds to specific parts of DNA). The formation of the ovaries is also an active gene-directed process that involves *DAX1*, a gene on the X chromosome. *DAX1* has been proposed to suppress the *SF1* gene and to be involved in the initiation of the ovary through *WNT-4* (Figure 2). However, there are persons with no Y chromosome and no *SRY* gene that develops testes, which suggests theories that the X-chromosome has factors that are testis-suppressive and ovary-supporting, but these factors are yet to be fully understood (9).

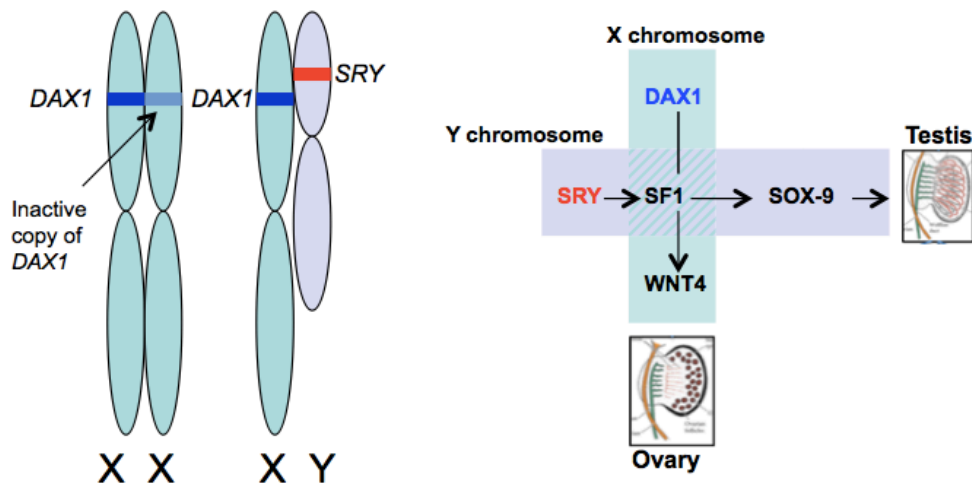


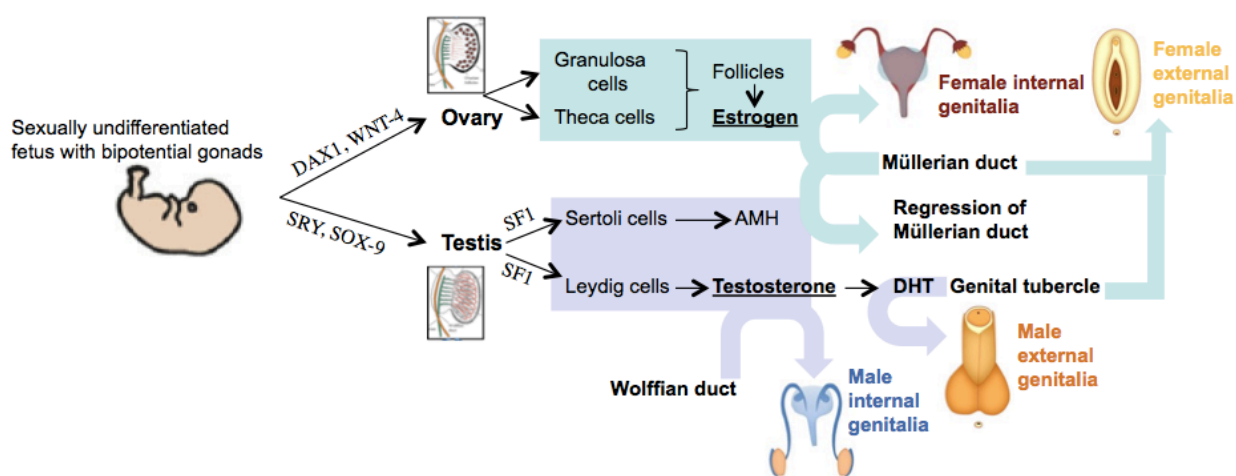
Figure 2. Proposed mechanism for sex determination, where *SRY* blocks the inhibition by *DAX1* on *SF1*. Together with *SOX-9*, *SF1* directs the bipotential gonad into a testis. If two copies of *DAX1* are present (XX or no Y chromosome), the *SF1* will be suppressed. Via *WNT-4* *DAX1* then stimulates development of the ovaries. After inspiration from Gilbert, 2013.

Phenotypic sex

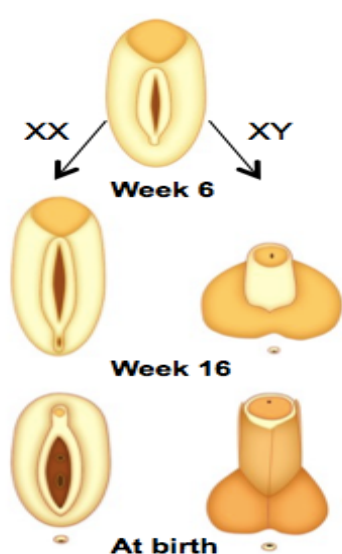
During week six, the germ cells (cells that create reproductive cells) will migrate into the bipotential gonad. If the fetus is 46,XX, the germ cell will be enclosed in follicles formed by theca cells and granulosa cells. Together, these cells will be able to synthesize estrogen, which will be secreted by the follicles. Estrogen, first from the mother and then from the gonad, enables the development of the Müllerian duct into an uterus, fallopian tubes and the cervix, the upper end of the vagina (8), shown in figure 3. In XY fetuses, the germ cells will

form sperms, and Sertoli cells will aid proliferation of the gonad towards the testis. Sertoli cells nurture sperm, and produce anti-Müllerian duct hormone (AMH) which suppresses the formation of female genitals (10). Meanwhile, Leydig cells in the testes produce testosterone, and enable the formation of typical internal male genitals from the Wolffian duct (Figure 3). Testosterone is also converted to 5 α -dihydrotestosterone (DHT) by binding to the androgen receptor. DHT is responsible for the development of the genital tubercle (urogenital sinus and swellings) into the typical external male genitalia, the penis.

Figure 3. Proposed formation of the sexual phenotypes in humans. *DAX1* and *WNT-4* moves the bipotential gonad into ovary development, this leads to formation of follicles and production of



estrogen, which enables the Müllerian duct to differentiate to typical female genitals. The SRY gene moves the development towards testis formation via *SFI* and *SOX-9*. The testis produce AMH that causes regression of the Müllerian duct, and testosterone that differentiates the Wolffian duct into internal male typical genitalia. Testosterone is converted into DHT that drives the development of the penis and the prostate gland. After inspiration from Gilbert, 2013.



The external genitalia look the same until about nine weeks of gestation, and are then directed by sex hormones (estrogen, testosterone, and DHT) as shown in figure 4. A genital tubercle is formed that first develops into a phallus which, in females, forms the clitoris, and in males, the phallus forms the glans of the penis. The urogenital fold forms the shaft of the penis in males, and the inner labia in females. The labioscrotal swelling forms the outer labia in females, and the scrotum in males (8).

Figure 4. The development of the external genitalia in week 6, week 16, and at birth. Published with the kind permission of “Föräldrainsformation om DSD”, Karolinska University Hospital.

3.2 DISORDERS OF SEX DEVELOPMENT

Even though the differentiation into typical male and female sex most often follows the same paths, sometimes the development of chromosomal, gonadal, or phenotypic sex is different (3). These differences in development result in several conditions that are included under the umbrella term: Disorders, or differences, of sex development (DSD). DSD refers to a heterogeneous group of conditions with a range of symptoms and physical differences from being born with one extra chromosome, 47,XXY (Klinefelter syndrome), no development or underdevelopment of gonads (gonadal dysgenesis), or unclear sex at birth (e.g., 46,XX CAH). Individuals included in the DSD classification have different medical problems and needs due to distinct underlying causes, but many share the same difficulties concerning social, emotional, and psychical sequelae when growing up (11). In addition, some persons with a DSD share hormonal imbalances with known long-term effects and a need for multidisciplinary lifelong care (12). The DSD classification is based on subcategorization according to sex chromosomes (13), namely, sex chromosome DSD, DSD 46,XY, and DSD 46,XX, shown in Table 1.

Table 1. Classification of disorders of sex development based on sex chromosomes, sex chromosomes being the starting point for medical investigations.

The DSD conditions investigated in this thesis are written in bold.

SEX CHROMOSOME DSD	DSD 46,XY	DSD 46,XX
45,X For example: Turner Syndrome.	Disorders of testicular development For example: Complete gonadal dysgenesis (Swyer syndrome)	Disorders of ovarian development For example: Gonadal dysgenesis
47,XXY For example: Klinefelter Syndrome	Disorders of androgen synthesis or action: For example, defects in androgen action: Complete androgen insensitivity syndrome	Disorders of androgen excess: For example: Congenital adrenal hyperplasia
45,X/46XY For example: Mixed gonadal dysgenesis	Other: For example: Severe hypospadias	Other: For example: Vaginal atresia
46,XX/46,XY For example: Ovotesticular DSD		

The overall incidence of DSD has been estimated to be 1,7%, however, this includes all conditions independently of whether they present with ambiguous genitalia or not (3,14–16). In Sweden, one in 5000 children (15-20 children each year) is born with a genital anomaly that results in unclear sex at birth. Hypospadias is more common, affecting 1 in 125 boys, which is an increase from 1 in 223 in the 1990s (17). The most common condition involving a DSD in girls is congenital adrenal hyperplasia (CAH), which affects one child in 10,000-20,000 live births (18).

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition: this means that, in order for the condition to appear, a mutated gene from the mother and a mutated gene from the father must be inherited (19). One person out of 50 in the general population is a carrier of a mutated gene and one out of 70 are carriers of more severe mutations (20). In 95% of cases of CAH, the condition is caused by a mutation in the *CYP21A2* gene that provides instructions for production of the enzyme 21-hydroxylase (21-OH) which, is involved in the synthesis of cortisol, mineralocorticoids (e.g., aldosterone), and androgens (18).

Cortisol, together with aldosterone, is vital for maintaining electrolyte and fluid balance in the body, managing stress response, and mobilizing energy (21). The secretion of cortisol is controlled by the stress hormone system in the body, also known as the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus produces corticotrophin-releasing hormone (CRH), which stimulates both the synthesis and secretion of adrenocorticotrophic hormone (ACTH) in the anterior pituitary, as a response to physical stress (e.g., fever, exercise) and emotional stress (e.g., stressful experiences). In healthy individuals, ACTH is secreted in a circadian rhythm, and follows the blood stream to the adrenal glands, just above the kidneys, where it causes secretion of cortisol and aldosterone, as shown in Figure 5. Cortisol is highest in the morning, and lowest overnight since cortisol, for example, mobilizes energy sources to help us through the day. In stressful situations, cortisol levels will decrease, thereby sending messages to the hypothalamus, through an intricate feedback, to increase production of ACTH.

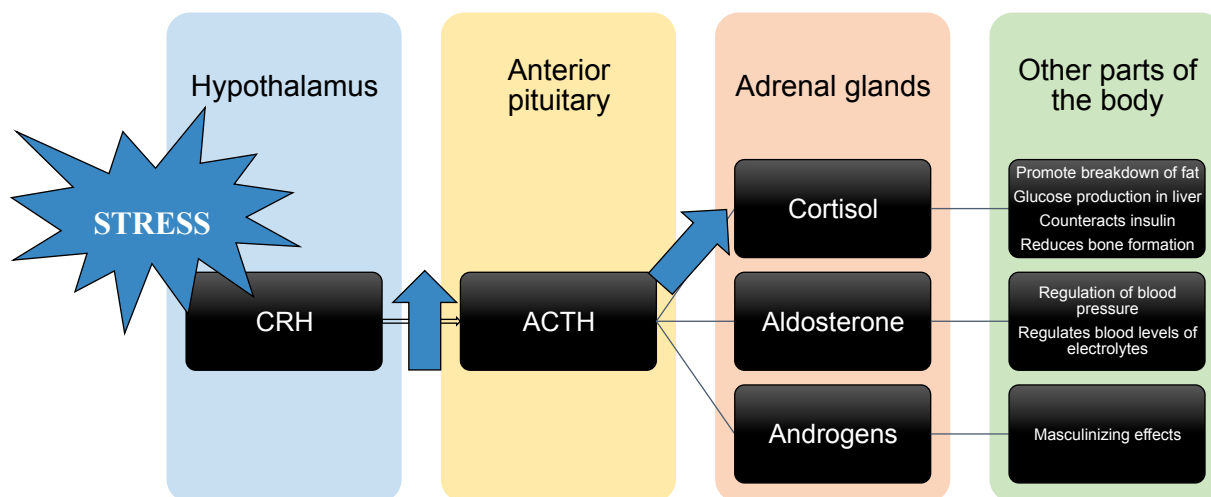


Figure 5. The secretion of cortisol is controlled by the stress hormone system in the body (the HPA axis). In healthy individuals ACTH is secreted in a circadian rhythm.

The 21-OH mutation in CAH interrupts the biosynthesis of cortisol, resulting in low levels of cortisol (19). Because of the intrinsic feedback system, production of ACTH will then increase and this will lead to increased synthesis of steroid precursors before the enzyme block in the adrenal glands. In lack of the 21-OH enzyme, the precursors will be converted

into androgens instead of cortisol, as shown in Figure 6. During pregnancy, the affected fetus will produce excess androgens, but will be provided with maternal cortisol.

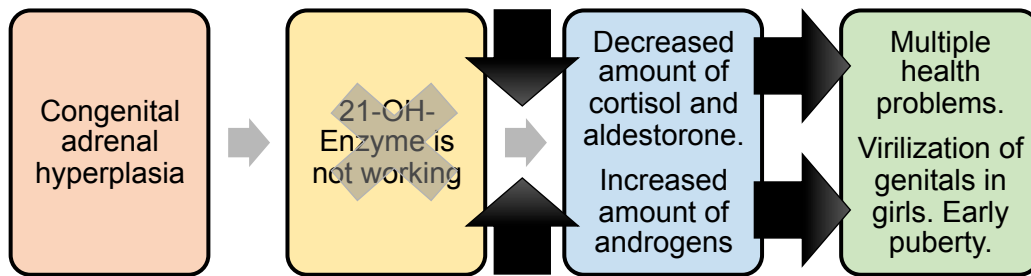


Figure 6. A defect in the CYP21A gene will affect the development of 21-OH enzyme in the adrenal glands. This will lead to production of excess androgens in the adrenal glands.

Persons with CAH are often classified into genotype groups according to the severity of the milder of their two variants of the gene (alleles) since this determines the phenotypic severity, with few exceptions. When children are born with the most severe mutation, they will spontaneously develop a hypotensive salt crisis in the neonatal period (the first months after birth), which untreated, will lead to death. This type of CAH is referred to as “salt wasting” CAH (SW-CAH), and is associated with the null mutation, or the I2splice mutation (22). Children who do not spontaneously present with salt crisis in the neonatal period, but have a cortisol deficiency, and overproduction of androgens, are classified as “simple virilizers” (SV-CAH). SV-CAH is correlated with a I172N mutation. The SW and SV forms of CAH are called classic CAH, and have their onset before five years of age.

Persons with non-classic CAH (NC-CAH) have sufficient cortisol levels, but excessive production of precursors due to a partial enzymatic block that results in increased androgen levels. The NC-CAH is usually due to V281L and P453S mutations. Despite a vast clinical difference between SW-CAH and NC-CAH, there is, in reality, a continuum based on the severity of the underlying mutation (23), as shown in Figure 7 .

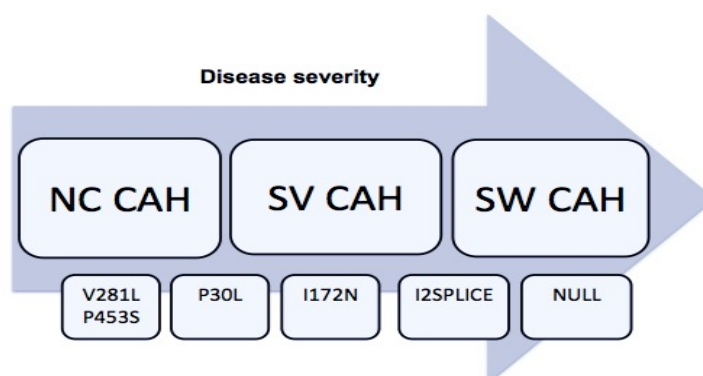


Figure 7. A continuum of disease severity (clinical phenotype) based on the underlying mutation (genotype). The clinical phenotype is based on the mildest mutation in the affected CYP21A2 gene.

To prevent neonatal death from salt crisis, CAH was included in the Swedish newborn screening program in 1986 (24). As the aim of the neonatal screening program is to detect severe forms of CAH that can cause salt crisis, milder forms of the disorder are not detected. Therefore, some children with non-classic CAH are diagnosed later in life, because of e.g., early pseudo puberty due to high androgen levels (19): for example, an increased growth rate, or teenage girls who present with increased body and facial hair (hirsutism), or menstrual disturbances.

In classic CAH, replacement therapy with glucocorticoid and mineralocorticoid, as well as sodium, is administered to adjust the fluid and electrolyte balance. This will also reduce ACTH production, and consequently the excess androgen production (19). Treatment is life-long and needs to be monitored since the need for cortisol varies over the day, and increases with stress, and infections. Classic CAH is the most common cause of unknown sex at birth in 46,XX individuals (19). The increased prenatal androgen levels result in varying degrees of virilization of the external genitalia, in newborn baby girls (Figure 8). CAH in girls and women is therefore characterized as a 46,XX DSD, as described in Table 1. Boys with CAH are not virilized, but they also have a life-threatening chronic condition.

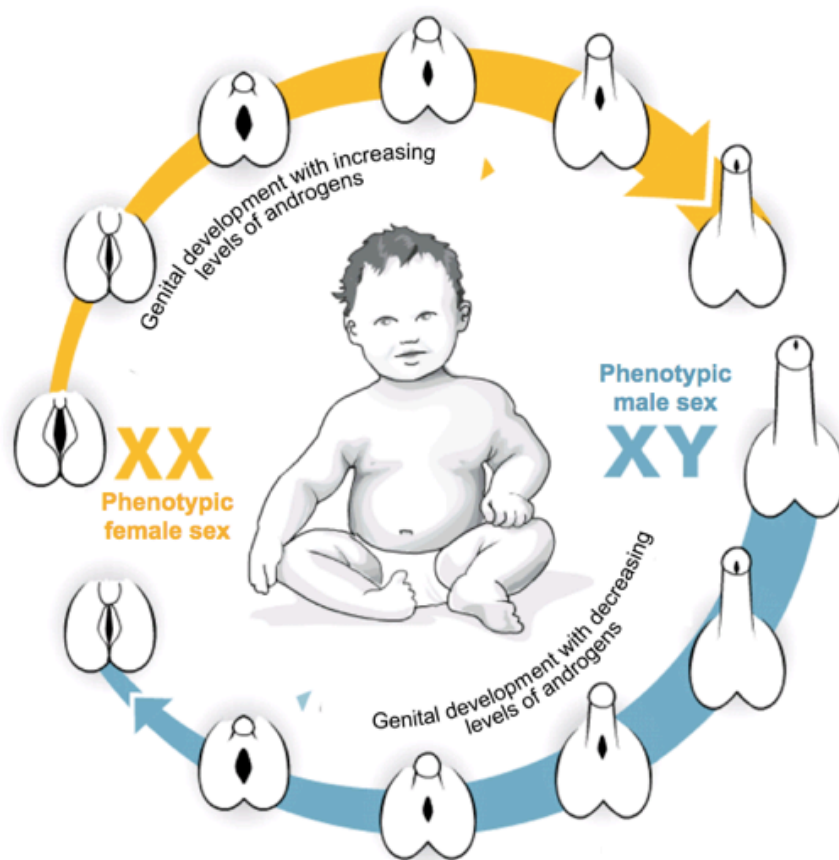


Figure 8. Development of external genitalia depending on androgen levels. Increasing levels results in virilization of the genitals, independently of sex chromosomes. *Graphics: Johan Andersson, DN. Published with kind permission from Dagens Nyheter.*

In the past, genital reconstruction for girls with virilized genitalia was usually performed early after birth (25), since the prevailing notion was that psychosexual development was dependent on the genitals looking like they were in conformity with the assigned gender (26,27). However in 1997, evidence was presented that overturned this type of management (28). Nowadays, psychosexual development is known not to be dependent on genital appearance, however, functional and reconstructive genital surgery is still being performed, but is debated mostly regarding timing, and to what extent the reconstruction should be performed (29). The strongest argument for postponing surgery after the neonatal period, is to wait until the child can express his or her own preferences and, preferably, can give his or her informed consent; however, in any case, the child's well-being should always be prioritized (30).

Gender assignment in persons with CAH, and 46,XX karyotypes, are predominantly female since they have female internal genitalia, and can reproduce. Rearing of male gender in 46,XX individuals is very rare, but there are cases where the degree of virilization is very severe and the parents are reluctant to raise their child as a female (31). Male rearing of persons with 46,XX CAH might be more common in countries where there is a lack of newborn screening programs, and where the genital virilization is not directly understood to be because of CAH, and in addition, the prevailing culture has a preference for male gender (32). A review of a case series of 46,XX individuals with CAH reared as males showed that they have a relatively good psychosocial situation (33).

During childhood the focus of treatment is optimization of growth, and pubertal progression and, in adults, the focus shifts to quality of life and long-term health (34). Despite medical advances, and more adequate treatment, short stature remains a problem for many persons with CAH, as well as the development of overweight, which can be a consequence of overtreatment with glucocorticoids (35). There are also reports on an increased risk of the metabolic syndrome and cardiovascular disease (36). The level of compliance may shift during different periods of life (e.g., the teenage years), with the result of raised androgen levels. This can lead to reversible androgenic effects, such as hirsutism, and irreversible effects, such as a deeper voice, because of enlargement of the laryngeal prominence, the Adam's apple (37,38).

Women with classic CAH have children to a lesser extent than their healthy peers (39). However, the causes of the low fertility are unclear, but they have been explained in terms of insufficient hormonal control, leading to secondary polycystic ovaries and high progesterone levels. Same-sex relationships, and unsatisfactory surgical outcomes, have also been proposed as plausible causes (40). On the other hand, there are reports that only 25% of women with CAH attempt to get pregnant, and that they have less of a wish for children of their own (34,41). Among women with CAH who get pregnant the fecundity rates, i.e., the possibility to reproduce, are normal with proper treatment (34,42).

Androgen insensitivity syndrome

As mentioned before, androgen stimulates development, and maintains typical male sex characteristics, by binding to the androgen receptor (AR). Therefore, a dysfunction in the androgen receptor, as in androgen insensitivity syndrome (AIS), will lead to no development or underdevelopment of typical male genitals, and sex characteristics (43), as shown in Figure 8. The clinical presentation depend on the severity of the dysfunction of the AR, resulting in different degrees of insensitivity to androgens resulting in a continuum of phenotypes (44). Besides complete AIS (CAIS), there are also partial androgen insensitivity (PAIS), and a mild form (MAIS). AIS is an X-bound condition, which means that individuals with an XX karyotype are usually only carriers, because the X with mutation will be inactivated. Thus, only XY individuals are born with AIS. The estimated incidence of AIS ranges from 1 to 5 in 100,000 live births (45).

In CAIS, a baby with a chromosomal sex of 46,XY, and a severe dysfunction of the androgen receptor, will present with a female phenotype (Figure 9). However, the baby will have age-appropriate testicular androgen levels, but they cannot bind to the AR. There is a lack of sex-determining genes for the female pathway will result in a shallow vagina without a uterus (46). This is because the testes are functioning, and produce AMH, which leads to normal regression of the Müllerian ducts, that otherwise would have formed the uterus.

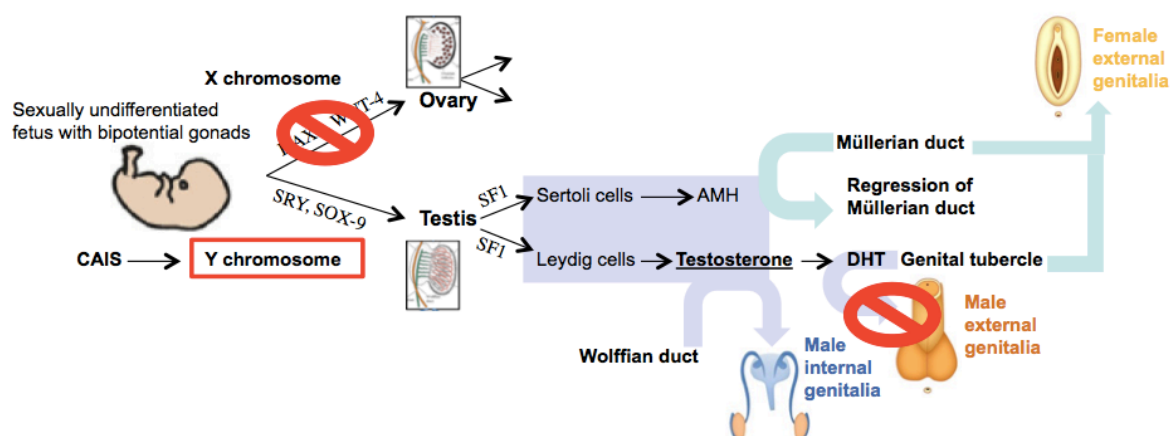


Figure 9. In CAIS the chromosomal sex is XY, and testes determining genes are present, thus internal male genitals will develop. However, a dysfunction in the androgen receptor will lead to no action of circulating androgens, and the phenotype will therefore be female.

In the case of CAIS, the majority of patients identify as females (47). The girls with CAIS usually presents with primary amenorrhea in adolescence; however, a suspicion can be raised sometimes if a baby girl presents with inguinal hernia where testes are found (48). If there is a family history (X-linked recessive), or with new forms prenatal testing, such as noninvasive prenatal testing (NIPT), a mismatch can be found between a fetal 46,XY karyotype, and a baby girl being born.

In women with gonads, there will be plentiful androgens circulating in the body. Androgens will, through an aromatization (a chemical reaction) form estrogens, which will lead to a typical female phenotypic pubertal development with breast and female adiposity. Since there is no androgenic action, these women will have none, or sparse pubic and axillary hair. Women with CAIS will also be taller than the average woman, but not as tall as the average man (46). In general, the vagina is underdeveloped (hypoplastic) and the first line treatment option is self-dilatation therapy and second-line treatment is surgery (vaginoplasty) (49). Since women with CAIS have no uterus, and thus no menstruation, there is no possibility of conceiving, or bearing children.

There is a tumor risk in gonads that have not developed as expected, however, the general recommendation in CAIS is to perform biopsies of the gonads after puberty, and then do regular clinical controls, if the biopsy specimens show no sign of malignancy (50). The treatment is then substitution with estrogens, e.g., combined oral contraceptive pills (51). Hormonal supplementation is also important for bone health and prevention of osteoporosis. Some women with CAIS prefer treatment with supplementary testosterone after gonadectomy because this improves their well-being (51).

Gonadal dysgenesis

In CAH there is an excess of androgens from the adrenals causing a virilization, and in CAIS there is a dysfunction of the androgen receptor, that results in a lack of androgen action. In gonadal dysgenesis (GD), the ovaries or testes do not develop as expected, resulting in lack of estrogens and androgens (52,53).

Ovarian dysgenesis results from genetic defects in ovarian development in the bipotential gonad, or later in sex differentiation. The exact underlying cause is unknown in most cases, and several genes, including *DAX-1* and *SF-1*, as well as *SRY*, have been implicated in the causation of the defects (54,55). In persons with 46,XX CGD, hormone stimulation from the gonads is totally absent and, instead of ovaries, they have undeveloped lumps of tissue called streak gonads. However, they present with a typical female phenotype, and develop a uterus (Figure 10). This is also the case in persons with 46,XY CGD, also known as Swyer syndrome (52). In 46,XY CGD, a uterus is formed together with Fallopian tubes, because the testes are non-functional, and does not produce testosterone, or anti-Müllerian hormones. The underlying cause of the Swyer syndrome has not been fully established; however, in approximately 15% of cases there is a mutation in the *SRY* gene (52). It is also known that two X chromosomes are needed for fully develop ovaries (9).

Persons with CGD are typically raised as girls and have a female gender identity. Swyer syndrome occurs in approximately 1 in 80,000 persons (56). The prevalence for 46,XX CGD is unknown, but it is thought to be less than 1 in 10,000 live births (57).

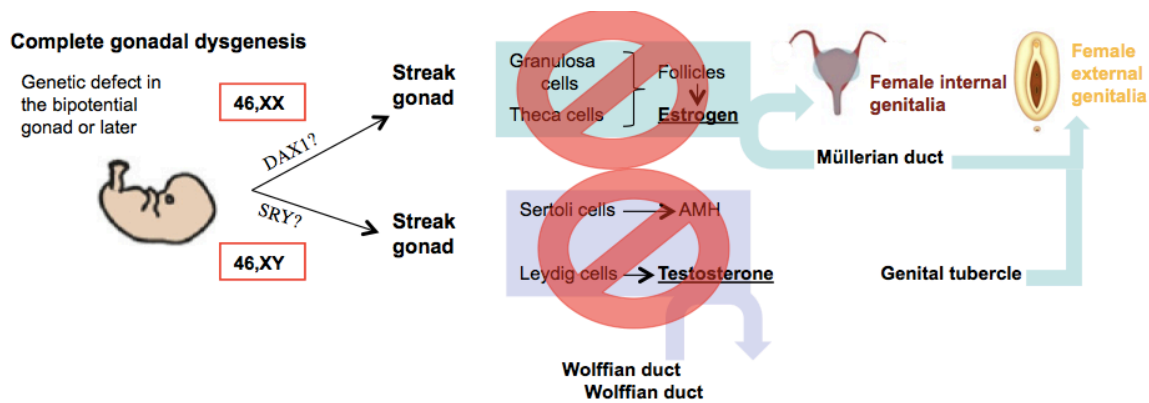


Figure 10. Genetic defects of ovarian or testicular development, or other causes of non-development, will result in absence of hormone production (estrogens or androgens) and the phenotype will be female.

Medical management includes hormone replacement therapy, and protection of bone health with supplements of calcium, and vitamin D (51,58). As in the case of CAIS, there is an increased risk of gonadal tumors in women with 46,XY CGD (54). Thus, surgical removal of gonads are recommended (50,53). Since women with CGD do not have oocytes (because they have no ovaries), or hormone production, no fertility is expected. However, pregnancy may be feasible through zygote donation, i.e., a fusion between an egg and sperm (51,59).

3.3 HORMONE-DRIVEN SEX DIFFERENCES

Given that different DSD result from chromosomal, gonadal, or hormonal differences during development, DSD has served as an "experiment of nature" for elucidating sex hormones' effect on gender development, gender behavior, and sexual orientation (12). The two following sections of this background will therefore address the theories pertaining to hormone-driven sex differences in behavior, in relation to persons with DSD.

It all started in 1959, when a paper was published on sexual behavior in male and female guinea pigs, whose mothers had received synthetic testosterone during most of the pregnancy. In addition, after birth the guinea pigs received high doses of testosterone until adulthood (60). The experiment showed that high doses of testosterone changed external genitalia in newborn female guinea pigs, to external genitalia identical to those of newborn male guinea pigs. The adult female guinea pigs also showed a mating behavior that differed from unaffected females, and were more like adult male guinea pigs, suggesting that androgens administered during pregnancy (prenatally), had an organizing effect on the brain, and an activating effect on the brain in adulthood, leading to more male-like mating behavior (60). The paper was first considered to be radical, but the hypothesis first posed by the authors is now referred to as the "organizational hypothesis", and it is the predominant explanation for the origin of sex differences in behavior (61).

Much research has followed in the footsteps of this first article, and several studies on non-human mammals have repeatedly shown results in line with those of Phoenix and his colleagues (62,63). Today, with the increased level of knowledge that is available, the organizational theory can be summarized as the notion that the nervous system differs between males and females, and that, during sensitive periods hormones produce permanent changes in brain structures, as well as the rest of the body, thereby generating masculine or feminine behavior (61,64,65).

Behavioral sex differences between humans are, for example, gender identity and sexual orientation, with more than 90% of adults reporting sexual attraction to persons of the opposite sex (64). Other differences include childhood play and personality traits, such as aggression and empathy. In addition, behavioral sex differences in the brain have also been suggested to be involved in psychiatric disorders. For example, the extreme male brain theory of autism suggests that prenatal androgens contribute to such autistic traits as impairment in empathy and an extreme drive to systemize (66). Differences are of course, measured on a group level and cannot be applied to a specific individual. In addition, gender differences are also dependent on other things, such as cultural expectations, and cannot be explained solely by hormones.

Women with DSD and the organizational hypothesis

In 1968, Ehrhardt, Epstein, and Money noted that girls with CAH had a more boy-like behavior than girls without CAH (67). Since then, much of the focus on the management of children with a DSD has been on gender identity, gender role behavior, and sexual orientation (68).

In several research studies, girls and women with CAH, show an increase in masculinized behavior, such as gender-typical toy preferences (69–71), and more interest in male-typical activities, than unaffected girls and women (71,72). In addition, they also show increased rates of same-sex attraction compared to unaffected women (65,73,74). The Swedish group was able to show that gender-atypical behavior in girls with CAH is correlated with the severity of the *CYP21A2* mutation, suggesting that prenatal androgens have dose-dependent effects on the development of gender-specific brain functions (69,75). To summarize, prenatal exposure to higher levels of androgen is correlated with more male-typical behavior (64). The majority of women with CAH who are reared as female, have a female gender identity, suggesting that prenatal androgens do not alter gender identity (76). Nonetheless, there are higher rates of gender dysphoria among women with CAH compared to population controls, as well as not feeling content, or satisfied with female gender (74,77–79).

The organizational hypothesis has also been applied to women with an XY karyotype (e.g., CAIS) who, unlike women with CAH, are suggested to have insufficient levels of active

androgens. The strength of CAIS as a model disorder for studying the effect of androgens on gender development is the separation of prenatal androgens and sex chromosomes (80). Studies have shown significantly more feminine gender-related behaviors in girls with CAIS than in children with PAIS and unaffected children (81). In addition, several studies on women with CAIS show that they have a female gender identity from childhood, that persists through adulthood, and almost always, a sexual orientation toward the opposite sex (47,82–84). This implies that the Y chromosome may be unrelated to sexual orientation and gender identity.

There are, of course, alternative explanations concerning the hypothesis of prenatal androgen excess, such as the indirect effect of masculinized genitalia on psychosexual development (85). In addition, it is still unclear as to what extent biological factors, such as genes or sex hormones, or psychosocial factors, such as parental attitude, or the cultural context, influence gender identity development, and the stability of that identity.

3.4 PSYCHIATRIC AND PSYCHOLOGICAL ASPECTS

The focus on androgen effects has influenced research in CAH. A review of psychological outcome studies on CAH presented in 2010, showed that the majority, 68% of studies, investigated endpoints related to psychosexual development, and even more studies (76%) examined whether psychological outcomes were associated with prenatal androgen exposure (76). The evaluation of clinical management has also been heavily focused on gender assignment outcomes, and the timing and need of surgery (86–89).

As mentioned before, in the 1950s, the standard care given, including reconstructive genital surgery, emerged from the prevailing notion that if a child's body was gender-typical, it would make the child's adjustment easier (27). It was also advocated that withholding information could help the child not to question the gender of rearing (4). However, in 1997 evidence was reported that gender identity was not dependent on gender-congruent bodies (28). In the 1990s, criticisms of various aspects of clinical practice related to DSD were raised by affected adults who were not satisfied with their treatment, or the focus on gender: *"Intersexuality is primarily a problem of stigma and trauma, not gender"* (90). The criticism also included assertions that psychosocial problems could not be handled medically or surgically (4). Voices were raised questioning what "normalizing" surgery is, to what extent genitals are considered abnormal, or untypical of a certain sex and if a DSD is a disease or if the individual just fails to fit the definition of normality (4). Furthermore, the term "disorders of sex development", has been debated, and patient advocacy groups argue that a disorder is something that needs to be corrected (91).

According to the Consensus Statement on Management of Intersex Disorders from 2005 (3), evaluation of long-term outcomes in DSD should consider the phenotype of the internal and external genitalia, somatic health, fertility, sexual function and psychosexual adjustment,

mental health, quality of life, and social adjustment and participation. Multidisciplinary teams including a mental health professional were recommended to take care of persons with a DSD, at the time of diagnosis, and during their lives, in order to improve the education of the affected persons and their parents on their specific DSD (11).

Parents

Since many individuals with a DSD are diagnosed at an early age, decisions pertaining to surgery and treatment are handled by treating clinicians and parents until the child can give his or her own informed consent to such interventions as reconstructive genital surgery (3). Evidently, most parents will find it highly traumatic if their child is born with unknown sex, and parents of children with a DSD have showed high rates of posttraumatic stress (92). Even after the diagnosis is made, the parents will have to handle both treatment, decision-making regarding surgery (together with a multidisciplinary team) and cope with uncertainties about the child's development. Parents show the highest levels of stress when thinking about past, or future events, regarding their child's condition, but, regarding gender expression, they have low levels of stress (93). The parents' ability to cope with the condition, may affect the child (11). A Brazilian study showed that parents' main concerns were related to having a child with unclear sex at birth, was that physicians did not talk openly with them about their child's condition. This led parents not to inform their children, and subsequently, to patients protecting their parents from additional suffering by also withholding information (94). Good communication between parents and caregivers is looked upon as being extremely important and can decrease stress and improve outcomes for children with a DSD (95).

Psychosocial adjustment

For a long time, it was common praxis that physicians and parents withheld information about a DSD diagnosis, or sex characteristics (e.g., XY chromosomes in a girl) because it was believed that this could make the patient confused or upset. However, this has been shown to do more harm than good, because the individuals' limited knowledge about their bodies leads to a lack of compliance with treatment, and contributes to silence and shame (96). Women with CAH have described their experiences of information sharing as resulting in a sense of isolation and embarrassment (97). Although the consensus statements on the management of DSD assert that all medical information should be age-appropriate when shared with the person affected (3,98), information management has still proven to be difficult, both between persons with a DSD, and parents, and caregivers, as well as between persons with a DSD, and their peers (99,100).

Adult persons with CAIS also show major distress related to questions of infertility, identity, secrecy, stigma, and shame (101). However, there were no significant differences regarding psychological wellbeing in adult women with CAIS, compared to data on norms (82). A long-term medical follow-up of women with CAIS, concluded that they did not differ in

medical, surgical, and psychosocial outcomes, although 80% had had psychological counseling (47). The presence of a psychologist in the outpatient routine has shown to be particularly important for the medical consultation (94).

Two studies found no significant differences between adult women with CAH and controls regarding psychological wellbeing (102,103). However, Swedish registry research shows that women with CAH have increased rates of disability pensions and sick leave compared to sex- and age-matched controls (39). They were also less often married, and had fewer children. However, epidemiological studies cannot answer the question of “Why”, which prompts further studies using other methods.

Quality of life (QoL) is the general well-being of individuals, including both positive, and negative parts of life. The health related quality of life (HRQoL) also encompasses such health related issues as lack of energy. Measurements of QoL and HRQoL are used in persons with DSD to determine the impact of medical interventions on psychosocial well-being, and adjustment. Now, specific QoL instruments for children with DSD and their parents are under development, and preliminary results show the need for increased psychosocial support (93). However, specific QoL measurements for adult persons with a DSD are lacking (76). Previous studies have shown both compromised and equal, as well as better, QoL for women with CAH than for a reference group (75,89,102,104). Persons with 46,XX and 46,XY DSD have been reported to have a good QoL (105,106), but late treatment impaired the QoL (106). Persons with CAH seem to have a QoL equal to that of persons with CAIS and GD (107,108). To summarize, the results are inconsistent and it is not fully understood what predicts QoL among adult women with DSD.

Psychosexual adjustment

The consensus statement on the management of DSD (3), asserts that the focus should not be solely on sexual function and activity, but also on interpersonal relationships. Studies looking at psychosexual endpoints have been criticized for drawing too far-reaching conclusions about DSD as the sole factor or the mediator for impaired psychosexual adjustment, and for neglecting alternative conclusions, such as living with a chronic illness, or such psychological factors as just knowing that you could have sexual difficulties because of early surgery or a notion that you deviate from the norm (76,109).

It has been reported previously that women with CAH have varying experiences of the perception of their gender roles and gender identity (97). Furthermore, in women with CAH, reduced genital sensitivity, impaired body image, as well as lack of female identification, have been suggested to be reasons for psychosexual impairment, and difficulties in relating to a sexual partner (102,110). Compared to age-matched women with diabetes, women with CAH were less sexually experienced in all areas and reported higher levels of problems with lubrication, pain, and penetration (111). In addition, there are difficulties in dealing with

questions involving sexuality among persons with CAH (112). In contrast, when in a relationship, women with CAH seem to have more stable and satisfying partnerships than healthy controls (110).

A small study investigating adult women with CAIS (n=12), concluded that they seem to have stable gender identity throughout their lives (84). However, it has been reported that women with CAIS who know about their XY karyotype, can start questioning their gender identity, and that this affects their self-esteem, and results in a lack of sexual confidence and sexual satisfaction (113). There are also reports on women with XY chromosomes who are not content with a female identity, because of the lack of menstruation and infertility (101). As well as fear of "devaluation", because they do not feel like "normal" women, and deviate from the norm (96,109). The sexual impairments reported in a study of older women with CAIS (median age 45), were found to not be due to CAIS per se, but to obesity or experiences of previous sexual violence (47). In addition, some studies show an overall satisfaction with sexual development and sex life, among women with XY chromosomes (47,82,114).

Mental health

Studies on long-term mental health outcome in women with DSD are scarce and there are such limitations as small sample sizes, a lack of control groups or use of standardized measures. However, the consensus statement calls for a multidisciplinary team that includes mental health providers specialized in DSD (6).

The results of studies evaluating mental health among persons with DSD are contradictory, e.g., not showing a higher prevalence of psychiatric disorders (103), or significant psychopathology in several studies (115–117). On the other hand, results for children and adolescents with CAH show increased rates of psychiatric manifestations (79,118,119). Adult women with SW-CAH have been found to have increased rates of depression, anxiety, and substance misuse, compared to controls (120). In line with these circumstances, persons with CAH report high rates of distress, with the highest rates occurring among persons with SW-CAH (121). A Swedish epidemiological study on men with CAH (n = 253) showed increased rates of psychiatric disorders, particularly suicides, attempted suicides, and substance misuse (122). In persons with XY DSD increased rates of distress have been reported (105), as well as critical levels of depression (113), suicidal thoughts, and previous suicide attempts (101,121). Persons with a XY DSD also report concerns regarding poor surgical outcome, and distressful memories (108).

3.5 RATIONALE FOR THIS THESIS

During the last decade, the field of DSD research has been dominated by the sequencing of new genes in order to understand the genetic causes of DSD and studies elucidating the organizational hypothesis regarding women exposed to an excess or lack of androgens. However, what the factors are that may account for the variability of outcomes in women with DSD is still unclear. Moreover, there have been few studies about how women with a DSD cope with their condition or experience the care that they have received.

Furthermore, previous research evaluating mental health in cases of DSD has shown increased self-rated mental symptoms, which warrants the use of structured clinical interviews and large cohorts. This may ascertain whether or not DSD diagnoses are linked to common psychiatric morbidities, such as depression or anxiety. It is challenging, however, to perform large studies on such rare conditions as DSD and, therefore, studies evaluating mental health among persons with DSD are scarce. Sweden provides unique investigational possibilities since all Swedish residents have a unique personal identification number that can be linked to nationwide registries. Thus, the Swedish registries can provide data enabling total population studies.

Some diagnoses included in the umbrella term DSD might force individuals to have life-long medical treatment, e.g., because of a deficiency of stress hormones, leading to situations where simple infections can be life-threatening. In addition, women with DSD also have to handle lifestyle and intellectual challenges, and they also have to process the emotional consequences of a chronic condition. They may also have the added burden of being born with XY chromosomes, or differently developed external genitalia. In addition to this, not much is known about how women with DSD understand the elusive research on androgens' effect on behavior.

Increased knowledge about psychological and psychiatric aspects can help in the improvement of caretaking and mental health outcomes. In particular, patient perspectives can reduce the knowledge gap comprising the discrepancies between clinical outcomes, research results, and the patients' experiences. In addition, the perspective of the patients is vital in patient-centered care since their experiences may enable new solutions to problems, and to improving management in health care.

Taken together, the findings in this thesis may deepen our understanding of personal experiences of living with a DSD, and the mental health status of individuals with DSD with the potential goal of both improved caretaking and improved well-being of individuals with DSD.

4 AIM

The overarching aim of this thesis was to investigate psychological and psychiatric aspects in women with disorders of sex development.

The specific objectives, and research questions addressing the overarching aim were:

- To explore women's personal experiences of living with CAH.
 - i. How do women with CAH describe their experiences of having CAH, and the care given? **(Study I)**
 - ii. How do women with CAH describe their experiences of identity formation, sexuality, and parenthood? **(Study II)**
- To increase the knowledge of psychiatric disorders among women with DSD.
 - i. What is the frequency of psychiatric disorders in a Swedish cohort of girls and women with CAH, compared to matched controls? **(Study III)**
 - ii. Is the frequency of psychiatric disorders in women with DSD (CAIS and 46,XX CGD and 46,XY CGD) different from that of women with POI, and age matched controls? **(Study IV)**

5 METHODS

The choice of method should be guided by the scientific problem and the particular research question, and the method should enable the researchers to collect the data that is needed to answer the research question (123). However, there is always a question of such practical issues as knowledge of the subject under study, available data, and time, which, over the trajectory of the research project, will influence decisions and choices of paths.

5.1 METHODOLOGICAL ASSUMPTIONS

When conducting research, the researcher always has his or her own research approach, a paradigm that affects perceptions, beliefs, and understanding of the research (124). A paradigm can be understood as being the lens we use to look through, when we observe what is around us. In addition, a paradigm can also be understood as an aid to deciding what questions are asked, what answer are given, and how the research experiments should be performed (125).

Quantitative health research is often positioned in a post-positivistic tradition, searching for an objective truth, but taking potential confounders and biases are taken into account. Thus, the post-positivistic research paradigm assumes that it is possible to approximate, but never fully know the truth (124,126). In contrast, many social scientists have an interpretative approach in research that does not strive towards a single truth, but rather implies that humans make sense of their world, and give it meaning. The interpretative approach seeks to understand the individual's everyday experience (127). Moreover, with a pragmatic approach, quantitative and qualitative approaches can be seen as different methods of research, to be used in relation to the particular research question (128). The research approach guides and frames which question should be asked (e.g., why, how many), and what methods should be used to answer it (e.g., interview studies, surveys).

Given my background as a medical doctor, I had a post-positivist approach at the beginning of this project. However, after starting to understand qualitative methods and employing approaches to analyzing interview data, I realized that I had adopted more of an interpretive approach concerning how to look upon knowledge. Thus, I look at knowledge as something that we create through interactions, and that reality is a product of interactions between people: for example, between participants and researchers (124). However, since this thesis uses both qualitative and quantitative methods, parts of this project are positioned within the post-positivistic tradition (**Studies III-IV**), whereas other parts are conducted with interpretative influences (**Studies I-II**). Therefore, I find myself endorsing a pragmatic stance and approach to my research, using the lens most appropriate for the research questions I intend to answer.

5.2 OVERVIEW OF METHODS

Given the pragmatic approach taken in this thesis, both qualitative and quantitative research strategies were used, guided by the specific research questions shown in table 2. In **Studies I** and **II**, a qualitative approach was used to answer the research questions concerning how women with CAH describe their experiences of living with the condition. In **Studies III** and **IV**, quantitative methods were used to answer the research questions concerning the frequencies of psychiatric morbidity in women with DSD. By linking the Swedish registries frequencies of psychiatric disorders in women with CAH were estimated, and structured clinical screening instrument were used to evaluate psychiatric disorders in women with DSD, and those with POI. The results in **Studies I** and **II** answers the questions of “How?” and “Why?” and the results in **Studies III** and **IV** answer the question of “How much?”, thereby complementing the results of the qualitative studies.

Table 2. Schematic overview of methods in Studies I-IV

	Research question	Approach	Design	Study population	Study sample	Data	Analysis
I	How do women with CAH describe their experiences of having CAH, and the care given?	Qualitative	Interview study	Women with CAH	13 women with CAH	In-depth semi-structured interviews	Inductive qualitative content analysis
II	How do women with CAH describe their experiences of identity formation, sexuality, and parenthood?	Qualitative	Interview study	Women with CAH	13 women with CAH	In-depth semi-structured interviews	Inductive qualitative content analysis
III	What is the frequency of psychiatric disorders in a Swedish cohort of girls and women with CAH compared to controls?	Quantitative	Matched case cohort study	Women with CAH	335 women with CAH	Linked data from Swedish registries.	Conditional logistic regression.
IV	Is the frequency of psychiatric disorders in women with DSD different from that of women with POI and controls?	Quantitative	Cross sectional study	Women with DSD and women with POI	32 women with DSD and 21 women with POI	MINI+ screening	χ^2 Test or Fisher's exact test. Logistic regression

5.3 QUALITATIVE STUDIES

The following section will address the methods in the first two studies. They were designed as interview studies, given that the aim of the studies was to explore women's personal experiences of living with CAH.

Study population and sample

Women with CAH were chosen as a study population since previous research prompted studies on women's own experiences of having CAH. As described earlier, much of what is known about the psychological aspect of having CAH is derived from research focused on demonstrating the influence of androgen exposure in 46,XX individuals (76); thus the individual patient perspective is lacking.

The treating gynecological endocrinologist asked women with CAH if they would like to participate in an interview study, as part of a larger follow-up study at Karolinska University Hospital in Stockholm, Sweden (129). Women with known intellectual disabilities, women who did not speak Swedish, or women younger than 18 years of age were excluded from recruitment.

Purposeful sampling comprises different non-probability sampling techniques, which can also be called purposive, judgmental, or selective sampling (130). Since one aim of qualitative methods is to collect rich information related to the phenomenon under study, purposeful sampling can identify persons who can contribute with rich, phenomenon-specific information, and thus 'information power' (131). Consequently, purposeful sampling increases the probability of the participants providing rich and varied information (130). Moreover, a prerequisite for participation in interview studies is willingness to share thoughts and experiences (132).

Guided by purposeful sampling (130), the participants were recruited to achieve richness and variation in the data: thus, they varied in age (19-51 years, mean age 33), and had different disease severities (SW, SV, and NC CAH), with corresponding genotypes (Null, I2splice, I172N and P453). However, during interviews and the analysis, the information regarding each participant was blinded to the research group. Eleven of the 13 women had experienced genital surgery, and all participants had substitution therapy. All participants identified themselves as females. At the time of the interviews, four women had children, and ten had a current romantic partner.

In total, 32 women were asked to participate, 16 declined due to a lack of time, geographical limitations, or being tired of research studies. Three persons were never interviewed due to time and geographical limitations. The women who did not want to participate were comparable to the interviewees concerning children, phenotypes, genotypes, and the number of surgeries.

Data collection

The DSD research group in Stockholm has published a substantial number of studies on fertility, sexual function, surgical and metabolic outcomes, and gender role behavior. However, the impact of CAH on childhood and relationships was not correlated with the severity of CAH (75), thus prompting studies on individual experiences of the care given, the experience and views of living with CAH, and to what extent this has influenced relationships, gender identity, and sexuality.

The interview guide was developed to cover the areas identified by clinicians and researchers at the Karolinska University Hospital and Karolinska Institutet (Table 3). All interviews ended with questions regarding “How can we do things differently (regarding care)?” and “What can we learn from your experiences?” The interviews were conducted in a semi-structured way, which means that the interviewer follows the interview guide, but has the opportunity to ask individual follow-up questions regarding interesting subjects that might arise (133).

Table 3. Semi-structured interview guide questions for Studies I and II with example supplementary questions.

	Fixed questions	Example supplementary questions
Having CAH	Could you tell me about your condition and your experiences of having CAH? Your knowledge of your condition? What are your experiences of health care? What are your experiences of research?	<i>When did you first learn about your condition?</i> <i>How, when, and who informed you about your condition?</i> <i>What are your experiences of treatment regimes?</i> <i>Why do you agree to participate in research studies?</i>
Gender identity & gender behavior	What were your interest as a child? What are your interests today? Do you have any thoughts about gender identity?	<i>What do you think about the term “tomboy”?</i> <i>How has having CAH affected your childhood?</i> <i>How has CAH affected your teenage years?</i>
Relationships & sex	Have you had any romantic relationships? Have you had any sexual experiences?	<i>Are there any difficulties you would like to share?</i> <i>Were you worried before hand?</i>
Children & family	What are your thoughts about having children?	<i>Do you have children of your own?</i> <i>Was it hard to get pregnant?</i>
For the future	What we can learn from your experiences?	<i>What can we, as caregivers, change in the future for girls and women with CAH?</i>

All interviews were individual, face-to-face interviews, and were organized at a time and place most convenient for the participant: most participants preferred to be at home and some at the hospital. The interviewer (main supervisor) was, at that time, not involved in the care of persons with DSD, and had had no prior contact with the participants, thus, she introduced herself as a medical doctor with a PhD who had written a thesis about hypospadias. The interviews lasted between 60 and 90 minutes and were recorded and transcribed verbatim. In the transcripts, such observations as laughter, crying, or sighing, were also noted. In total, 424 pages of data were transcribed.

Data analysis

The data analysis was performed using inductive content analysis. Given that all interviews were completed when the analysis started, the method was well suited to condense extensive raw data text, into a shorter comprehensive format (134–136). The primary purpose of using an inductive method, was to allow an interpretative approach with subjective interpretations of the research findings to emerge from the raw data, and to give rich descriptions of the experiences of women with CAH, without a pre-determined theory or pre-existing coding framework (135). The analyses for **Studies I** and **II** were, however, also inspired by directed content analysis since prior research on the phenomenon guided the research questions, comprising deductive assumptions (137). The use of an inductive approach was intended to facilitate understanding of complex data, by developing categories from the raw data.

The stepwise process of qualitative content analysis includes the following steps (135): 1). Reading the transcribed interviews several times, 2). Identifying meaning units related to the aim of the study, and questions in the study guide, 3). Condensing meaning units and assigning codes describing the investigated phenomenon, 4). Group codes into subcategories, and categories 5). Analyzing the data on an interpretational (latent) level (Figure 11).

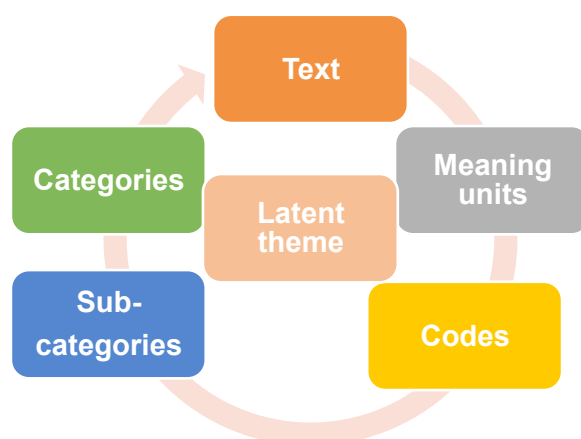


Figure 11. Qualitative content analysis is stepwise process with a back and forth movement between emerging categories and the raw data, i.e., the transcribed text from the interviews. The latent theme is the interpretation of the underlying meaning of the text.

Following these steps, the analysis started with becoming familiar with the text by thoroughly re-reading the transcribed interviews, and highlighting important parts of the text that was judged to be important, or that corresponded to the research questions, related to the care given and having CAH (**Study I**), or experiences of identity formation, sexuality, and parenthood (**Study II**). The highlighting was done separately by the PhD student and the main supervisor and then compared to look for similar or different judgments of what was expressed in the text. Data were discussed iteratively during the analysis and the second author, an experienced qualitative researcher, supervised the analytical process and facilitated research group discussions throughout the analytical process.

To facilitate the sorting of the data, the free software Open Code was used (138). First, the highlighted parts of the text related to **Study I** (content areas), were analyzed. The highlighted text, the meaning units, were imported into Open Code, and then shortened into condensed meaning units, shorter segments of text that preserves the core content. The condensed meaning units were then assigned codes and then classified and reclassified into different mutually exclusive subcategories and then categories. Examples of the manifest analysis, including meaning units, condensed meaning units, codes, subcategories, and categories are shown in Table 4.

Table 4. Examples of the analytical process for the manifest content in Studies I and II.

Meaning unit (Participant's quote)	Condensed meaning unit	Code	Subcategory	Category
<i>There was a lot of "hush hush" around it (CAH). Why I was in the hospital, well it was made up that it was because I had asthma. I almost believed I had asthma when I grew up because it (CAH) was something that you absolutely could not talk about.</i>	"Hush hush" around CAH. It was made up that it was because I had asthma. Something you absolutely not could talk about.	Information from parents. Information to peers. Shameful condition.	Parents and peers	Information (Study I)
<i>It is important that children who are born with my disease will have better conditions than I have had /.../ in order to develop knowledge it is important that I am a part of this (study).</i>	Better conditions for children. In order to develop knowledge, it is important to be part of the study.	Improve health care Important to be part of research.	Being the subject of research	Research (Study I)
<i>It is really hard to understand, I can imagine, but during my childhood, the question if I am a boy or a girl, I got it so many times. It happens even today, but now I don't care because men can't have children.</i>	Questions if boy or girl - I got it so many times. I don't care because men can't have children.	Questions of gender Men can't have children	As a girl As a woman	Forming identity (Study II)

The first and the last author then classified and reclassified the codes of the first two transcribed interviews until a consensus was reached, and the first author then coded the subsequent 11 interviews, using the evolving code manual that was initiated during the first two interviews. When all data were coded, the coding consistency was rechecked to see that new codes had not emerged or that the understanding of the codes was consistent in all the data.

Subsequently, the codes were sorted into different mutually exclusive subcategories, and the emerging subcategories were discussed in the research team, consisting of specialists in gynecological endocrinology, pediatric surgery, and psychology, who were well suited to judge the credibility of the findings. Comparisons between the subcategories and the original parts of the data were made in order to provide trustworthiness, and a broad understanding of the data. Subcategories were then sorted in to exclusive categories, and the discussions in the research team occurred regularly during the analysis period to avoid analytical preconceptions, and to attain a consensus in the emerging categories. There are two specific criteria to distinguish categories, internal homogeneity and external heterogeneity. Internal homogeneity refers to the requirement that data within each category should belong together in a meaningful way. The external criteria are met when there are obvious differences between individual categories (130).

When the manifest analysis was finished, the codes, subcategories, and categories were re-read, reflected upon, and discussed, as a latent content analysis to extract the latent theme (135). The aim of the latent content analysis was to communicate the underlying meaning of the text, i.e., what was not explicitly said but ran as a red thread throughout the text. Quotations were translated from Swedish into English after the analysis was finished. The same procedure was then repeated in **Study II**.

Trustworthiness

As qualitative content analysis can be regarded as an interpretive method (137). The conventional criteria of judging research results (e.g., validity, objectivity) are unsuitable for judging the results of the qualitative content analysis. In the qualitative research methods, trustworthiness is used as the notion that the interpretation of the research is the most probable interpretation of the data (139). Trustworthiness will, however, increase if it also allows the reader to look for other interpretations of the findings. There are four criteria that are used to evaluate trustworthiness of qualitative methods, credibility, transferability, dependability, and confirmability. In the following section, the measures taken for achieving trustworthiness in **Studies I** and **II** are presented.

Credibility

Credibility is the extent to which the study's results are trustworthy, and believable to others (123,135). The sampling of the participants was not random, but rather purposeful, so as to interview participants who would like to talk about their experiences. The variation in experiences because of the participants' various ages and a research team with various perspectives contributed to a richer understanding of the phenomenon under study. On comparing the participants with the non-participants, they were found to be comparable regarding age, severity of disease, medical history, and treatments.

Semi-structured interviews were chosen as the method for data gathering since the aim was to describe variability in experiences of living with CAH. The amount of data generated can give the reader a notion of whether the data gathering method used can answer the research question in the most credible way. Inductive content analysis as a method of analysis method was considered to be the closest conformity with the data since the intention was not to derive new hypotheses, but to give a rich description of the real-life experiences of women with CAH.

In addition, credibility was also improved by analyst triangulation made in the beginning of the analysis for **Studies I** and **II** to ensure coding consistency, and by checking interpretations against the text. Since credibility also encompasses how well the data, categories, and themes match, the entire process is described in detail and quotes are added to the description of the findings. Investigator triangulation was also used, to help to ensure the integrity of the findings. Thus, the research team consisted of a varied group of individuals, representing the medical and research communities, and everyone was involved in discussions, scrutiny, and debriefing, surrounding the coding and interpretation of the data, thus

Transferability

Transferability is an important aspect of trustworthiness because it refers to the question of how applicable the results may be to other contexts. The researcher can facilitate and suggest

transferability, but it is for the reader to judge, whether the results are transferable or not (135). By describing the setting, sample, approach, and analysis in rich descriptions, as well as the findings, and by inserting quotes where it is appropriate, the reader is given the opportunity to evaluate the extent to which the conclusions drawn are transferable to other women with CAH. The transferability of the findings can also be judged by contrasting the findings with previous research from similar contexts.

Dependability

Dependability can be understood as to the extent to which the results are consistent, in relation to the contexts in which they were generated. Dependability is determined by the consistency of the study process and thus takes into account the degree to which data change over time, and what changes have been made surrounding the analysis during the analytical process. Recruiting women from different age groups with different severities of disease, and thus different experiences, promoted dependability. Discussions were ongoing in the research team with open dialogues about how to judge similarities, and differences in the data, and also to avoid preconceptions (140).

Confirmability

Confirmability is the extent to which the findings are the results obtained from the study's participants and settings instead of being research-biased. Confirmability has been addressed by means of strategies the described above, such as analyst and investigator triangulation to reduce the effect of researcher bias (135). Thus, an open dialogue was established between the researchers, who also discussed the interpretation of the data until a consensus was reached. The confirmability can be understood as the internal consistency in the final manuscript, i.e., if the data, the findings, the interpretations, and the recommendations are coherent.

Reflexivity

Reflexivity refers to the process of examining the researcher's perspective, and pre-understandings of the field of study. All research is influenced by the researchers background, feelings, or opinions, and the relationships between participants and researchers (141). The researcher's background will affect the angle, from which and how the investigation is performed, and what findings are considered most probable (142). In this section, I will try to present my background, and my approach to this research.

When I entered this project, the interviews had already been performed. At first I was hesitant to analyze qualitative data collected by someone else, but since I have a close relationships, and open dialogue with the interviewer (main supervisor), I thought, why not? The participants' narratives concerning their experiences are important contributions to both the clinical and the research communities.

In health research, clinical researchers have often been socialized into professional ways of thinking (143). As a medical doctor I have, of course, been socialized into the thinking like a physician. However, I also have a background in sexual education and norm critical contexts. Therefore, I am not unfamiliar with the idea of the interpretative approach, believing that we make our experiences in relation to others. Thus, in these studies, I have tried to understand the meaning other people give to their surrounding world. You cannot walk in other people's shoes, but you can try to think what it would be like.

CAH is a disorder that can affect phenotypic traits of a person given excess androgen. Before reading the narratives in the interview transcripts, I had never met a woman with CAH. I believe this enabled me not to dismiss their described feelings of not looking like a woman, or being too masculine, because I did not know what they looked like. In addition, I have no personal experience as a physician of caring for patients with DSD. As such, I think that I have contributed to the analytical process by not having a caregiver perspective. Thus, I did not have any preconceptions about the care given, and I did not have any need to defend or argue for pros, or cons of the care process. In contrast, three out of five researches on our team are, or have been, in a caregiver position, which of course was an important perspective in the analysis which increased the trustworthiness of the findings.

5.4 QUANTITATIVE STUDIES

The following section will address the methods used in **Studies III** and **IV**.

Matched-case cohort study

Study III was designed as a matched-case cohort study to compare the frequency of psychiatric disorders in girls and women with CAH with that of age-matched male and female controls.

Study population and sample

All Swedish residents are assigned a personal registration numbers (PNR) that is used in all official records and registries (144). The PNR makes it possible to follow every individual over time and can be used to derive data by linking the population-based registers in Sweden. A de-identified version of this personal number was used to link the data from the registries.

The National Registry of CAH (20,39) was used to identify 306 girls and women with CAH with a clinically, and in most cases, genetically proven 21-hydroxylase deficiency. In addition, 180 patients had received the CAH diagnosis (ICD-8 codes 255.01, 255.08, ICD-9 codes 2552, 255C, ICD-10 code E25.0) at least twice in the National Patient Registry (NPR, National Board of Health and Welfare); however, on excluding patients who had also received a diagnosis of primary adrenal insufficiency (Addison's disease), acromegaly, or malignancy, a total of 43 patients remained and out of them, 29 were female (Figure 12).

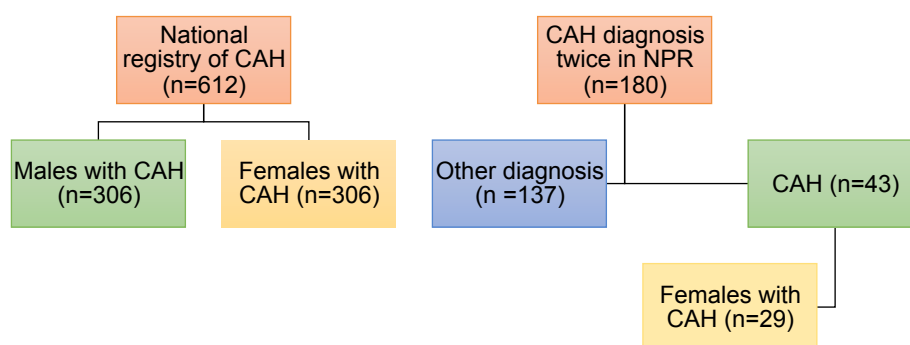


Figure 12. The procedure for identifying girls and women with CAH from the National CAH Registry and the NPR, in total 335 girls and women with CAH were identified.

In total, 335 girls and women with CAH born between April 1915, and January 2010, were identified (Table 5). The participants' age in January 2010 was calculated for descriptive purposes. Large differences in the survival rate can explain the low median age since a low number of individuals survived during the earlier years (20). The girls and women with CAH were grouped after clinical presentation and/or known *CYP21A2* mutations. Individuals with unknown *CYP21A2* mutations were given a clinical classification of SW, SV, or NC, if clinical data were available, and if they clearly contained information that could be used for classification (20).

Table 5. Characteristics of the girls and women included in the study
Median age calculated from January 2010

Median age	25,3 years (IQR, 15.8-37.8)			
Born in Sweden	n = 302 (90.1%)			
Clinical phenotypes n = 282	SW n = 135	SV n = 91	NC n = 56	
Most common CYP21A2 genotypes, n = 237	Null n = 59	12splice n = 67	P30L n = 12	V281L n = 42

For each case with CAH one hundred female controls (1:100) and one hundred male controls (1:100) were randomly selected from the general population (Total population registry, Swedish Tax Agency). Controls were matched on year, county of birth, and migration status. Controls did not have a diagnosis of CAH. Migration status was defined as being born in or outside Sweden. Girls and women with CAH who had immigrated to Sweden were matched with female and male controls that had also immigrated, via the Migration Records (Statistics Sweden), containing all documented migrations since 1901. Matched controls had to be living currently in Sweden at the time of the study.

The rationale for only including girls and women with CAH in the study population was that 46,XX individuals with CAH are known to have high prenatal androgen levels, but it is unclear whether prenatal androgen levels are elevated in males with CAH (145). Male controls were used to test the organizational hypothesis of androgens concerning psychiatric morbidity because it stipulates that prenatal androgens would organize the brain in a more masculine way, and thus, the girls and women with CAH would show a pattern of psychiatric morbidity comparable to that of male controls rather than of female controls.

Data collection

The individual PNR of all girls and women with CAH and their controls were used to derive data through linkage of population-based registers in Sweden. In order to insure anonymity for girls and women with CAH and matched controls, the PNR was replaced with an unidentifiable number by Statistics Sweden before linkage of the registers. Only Statistics Sweden had access to the code key and thereby the possibility to identify specific patients. In other words, it was impossible to go back and forth between the registries and the medical records to identify any given individual.

Information on the included psychiatric diagnoses was drawn from NPR, which contains the discharge diagnoses of inpatient care since 1964 and outpatient care since 2001. Since 1987, it includes all inpatient care, and since 2001, also outpatient visits including psychiatric care. Diagnoses in NPR are coded according to the International Classification of Diseases (ICD), a statistical classification system used to group diseases and causes of death. The ICD is a standard diagnostic tool used for clinical purposes as well as epidemiology and health management (146). The ICD-8, ICD-9 and ICD-10 were used which cover diagnoses from

1968 onward according to Statistics Sweden. In addition, to access psychiatric co-morbidity in detail, outcomes were subdivided into secondary endpoints (see **Paper III**)

The Cause of Death Register (CDR, National Board of Health and Welfare) was used to obtain data on completed suicides. The register provides data on all registered deaths since 1952. Thus, suicidal attempts and completed suicides were analyzed separately when looking at psychiatric comorbidity.

Socio economic status is known to negatively correlate with mental illness (147). To be able to adjust the results for socio-economic status, participants' parents' highest level of education was used as a proxy. The Multi-Generation Register (Statistics Sweden) was used to identify parents since it contains connections between index persons (born in 1932 or later, or registered in Sweden since 1961) and their biological or adoptive parents. To obtain data on the parents' highest level of education, the Swedish Register of Education (Statistics Sweden) was used.

Data analysis

The association between diagnosis of CAH and psychiatric outcomes was evaluated by conditional logistic regression since it is most suitable for studies in which cases and controls are matched individually. SAS version 9.3 was used for all statistical analyses and matching procedures.

Conditional logistic regression is a special type of logistic regression and is used when the case subjects with a specific condition (e.g., females with CAH) are matched with controls without the condition (e.g., Those without CAH). Conditional logistic regression is used to investigate the relationship between outcomes while potential confounders are being controlled for. The results were presented as odds ratios (OR) and 95% confidence intervals (CI). When it comes to rare disorders odds ratios are said to be equal to risk ratios. The results were adjusted for parents' highest education, a proxy for socioeconomic status.

Data were stratified based on different aspects, known and unknown genotype, known and unknown phenotype. The group with a known genotype was stratified with regard to mutation (null, I2splice, I172N, and, P30L), and the known phenotype group was stratified according to clinical severity (SW, SV and NC). In addition, data were stratified to see if subjects had received their psychiatric diagnoses before or after 18 years of age, which, in a Swedish setting, can correlate with pediatric or adult care. Data were also stratified into before and after the introduction of nationwide neonatal screening in Sweden in 1986, to see if the frequency of psychiatric diagnosis was associated with earlier diagnosis, and thus treatment. Lastly, the data were stratified according to if subjects had received their psychiatric diagnosis <12.0 years of age, between 12.0 - 17.9 years of age, or ≥18.0 years of age, since this would give clinicians a better overview as to when the psychiatric conditions were diagnosed.

Cross-sectional study

Study IV was designed as a cross-sectional study to answer the questions of whether the psychiatric disorders in women with DSD and women with POI differ from those of population-derived female controls. It was also hypothesized that congenital hormonal imbalance (e.g., CAIS and CGD) or acquired hormonal imbalance (POI) could affect the frequencies of psychiatric disorders differently.

Study population and sample

Women with CAIS, 46,XX CGD, 46,XY CGD, and POI were recruited via their treating gynecologist as part of a Swedish multidisciplinary study focusing on women with congenital and acquired hormonal imbalances. If they agreed to participate, a research nurse or midwife would call them and book an appointment for the research reception at the Karolinska University Hospital. Inclusion criteria were being Swedish-speaking and ≥ 18 years of age.

The Total Population Registry was used to find suitable controls to the participants with either DSD or POI. The personal registration number (PNR) of included women was used to select population controls. An invitation letter was sent to the women living in the greater Stockholm area with the consecutive PNR in the Total Population Registry. The purpose of this procedure was to recruit population-derived controls born on the same year and date as the included women with DSD, or POI. If women who were invited declined participation or did not answer, the next woman with a consecutive PNR in the Total Population Registry living in Stockholm was invited and so on. If they were willing to attend a research nurse or midwife would call them and make an appointment for the research reciprocity at Kvinnohälsan, Karolinska University Hospital. In the end seven women had two population-derived controls, and 47 had one population-derived control, which explains the slightly younger age among controls. In total 33 women with DSD, 21 women with POI and 61 population-derived controls were recruited (Table 6).

Table 6. Characteristics of the study sample

	Sample size, n	Age (standard deviation, range)	In a relationship	Highest completed level of education	
				Secondary education	University
Women with DSD	33	32.8 (9.4, 21-57)	21 (64%)	15 (45%)	18 (55%)
Women with POI	21	32.3 (6.6, 21-44)	15 (71%)	9 (43%)	12 (57%)
Controls	61	31.8 (8.2, 21-57)	46 (75%)	22 (36%)	38 (62%)
Subgroups of DSD:					
Women with CAIS	20	34.1 (10.1, 21-57)	10 (50%)	11 (55%)	8 (40%)
Women with 46,XX CGD	7	28.0 (4.6, (23-36)	5 (71 %)	2 (29%)	5 (71%)
Women with 46,XY CGD	6	34.2 (10.9, 24-47)	3 (50%)	2 (33%)	4 (67%)

Data collection

Study IV was designed as a cross-sectional follow-up study using The MINI+, International Neuropsychiatric Interview plus (MINI+), a brief structured diagnostic psychiatric interview for generating DSM-IV diagnoses convertible to ICD-10 criteria of psychiatric disorders (146,148,149). Validity and reliability studies have compared MINI with more extensive systematic interviews (e.g., SCID-P and CIDI) and, in comparison, MINI shows a high inter-rater validity for anxiety and affective disorders. It can also be administered in a shorter period of time, and has good acceptance among patients (148,150–153). The MINI+ is an extended version of the MINI that includes specific phobias and an expanded module for psychosis. The MINI+ consists of 15 modules corresponding to diagnoses and collects information regarding past and current symptoms in 23 axis-I problem areas. It is a widely used instrument in both clinical and research settings, including patients with somatic conditions (154,155). The PhD student conducted the MINI+ evaluation in the majority of cases and the duration of the interviews were between 15 minutes and one hour. If any questions arose regarding the diagnosis the case was discussed in the research team.

In addition to the MINI+ evaluation, the women were also asked to fill out a web-based survey questionnaire containing questions concerning the level of education, occupational status, relationship status, and medical history regarding psychiatric morbidity. Data collection was ongoing from 2011 to 2016. The MINI+ evaluation was an integral part of the multidisciplinary study in which women with CAIS, 46,XX CGD, 46,XY CGD, and POI underwent one day of medical and psychological examinations at the Karolinska University Hospital, Stockholm, Sweden.

Data analysis

The statistical analysis was carried out using IBM SPSS Statistics 22 and descriptive statistics were used. For categorical data, Pearson's χ^2 Test was used for cross-tabulation tables to assess differences in the frequency of psychiatric disorders across groups. For groups equal to or smaller than five cases Fisher's exact test was used. In addition, significant findings ($p < 0.05$) were included in a logistic regression to calculate odds ratios (OR) for the significant differences. An OR with a 95% confidence interval not including 1 was considered significant.

Subgroup analyses were performed for women with CAIS, using the same method as in the primary analysis. However, women with 46,XX CGD and 46,XY CGD were excluded from subgroup analyses because of small groups and thus low power.

5.5 ETHICAL CONSIDERATIONS

Persons with DSD carry a significant psychological burden. Thus, it can be considered unethical not to learn more about what can be done to improve their care. For **Studies I, II** and **IV** all persons have signed a written consent form before participation in the study. The participants were also informed that they could withdraw from the study at any time and that all data would be anonymized and kept safely. All women were granted confidentiality and travel expenses were reimbursed. Moreover, all studies had been granted ethical approval by the Regional Ethics Committee at Karolinska Institutet.

Representatives from the Swedish patient organization, as well as DSD patient organizations in other countries, have expressed a wish for more follow-up studies. One may fear that it would be intrusive to ask these individuals intimate questions about personality, cognitive function, and sexual matters, and, not least to bring up the subject of atypical sex development. However, some of the participants expressed the opinion that they are constantly aware of this anyway, and it may even be a relief to talk openly about it and to learn more about their diagnosis. The studies are also facilitated by the fact that clinicians caring for these patients are themselves involved in the project and thus can recruit patients and take the individual patient's best interest into account. The interviews for **Studies I-II** were all carried out at a time and place that was most convenient for the interviewee to make her feel safe and comfortable.

For **Study III**, a prerequisite to obtain approval by the Ethics Committee was that all included individuals were anonymized to protect the integrity of the included individuals and thus, all analyses were made on anonymized data and the code key was kept by Statistics Sweden.

Participants in **Study IV** were included as a part of a larger study. All participants and controls received remuneration (1000 SEK) for participating, which was intended to cover travel expenses and lost income. The women could choose to participate in some or all parts of the project. They were offered follow-up and referral for further investigation if they met the diagnostic criteria for a psychiatric disorder or if they desired counseling.

Many women expressed a wish to partake of the results and appreciate the increased information and knowledge they gained by participation in clinical studies. We have presented the results for both adult women and for parents to children with a DSD, and we plan to invite interested participants, other patients, relatives, and patient support groups to a seminar when more results from the large follow-up study (**Study IV**) are published.

6 FINDINGS

The findings in this thesis will be presented according to the specific objectives for each study, as shown in table 7.

Table 7. Schematic overview of main findings in Studies I-IV

	Specific objectives	Research question	Approach	Findings
I	To explore women's personal experiences of living with CAH	How do women with CAH describe their experiences of having CAH, and the care given?	Qualitative	Participants experience information sharing as being facilitated by CAH-specific knowledge. Genital demonstrations are experienced as traumatic. The idea of being healthy varies between the participants. Some never feel healthy because of CAH and some feel healthy because of correct medication. Research is considered to be important, but it reinforces normative gender roles. The participants describe different types of struggles against shame and stigma.
II	To explore women's personal experiences of living with CAH	How do women with CAH describe their experiences of identity formation, sexuality, and parenthood?	Qualitative	Participants describe feeling different because of CAH. Feeling like a woman is threatened by normative expectations of femininity. Intimate relationships are hindered by sexual difficulties, and insufficient knowledge. Fertility is not taken for granted and the wish for children varies. Participants have shifting perspectives on their condition depending on their experiences and different situations in life.
III	To increase knowledge of psychiatric disorders among women with DSD	What is the frequency of psychiatric disorders in a Swedish cohort of girls and women with CAH compared with matched controls?	Quantitative	Girls and women with CAH have a higher risk to having received any psychiatric diagnosis. In particular they have a higher risk of alcohol misuse disorders, with girls and women with the null mutation having the highest risk. In addition, they also have an increased risk of stress and adjustment disorders.
IV	To increase knowledge of psychiatric disorders among women with DSD	Is the frequency of psychiatric disorders in women with DSD different from that of women with POI and matched controls?	Quantitative	Women with different DSD have a higher lifetime risk of any psychiatric disorder, and in particular mood disorders and anxiety disorders, compared to unaffected women. Women with POI did not have a significantly higher risk than women with a DSD or controls.

6.1 PERSONAL EXPERIENCES OF LIVING WITH CAH

Studies I and II

The qualitative content analysis of data in **Studies I** and **II** yielded both manifest and latent findings, the variations of findings are shown in Table 8.

In both studies, a latent analysis was performed and the emerged latent themes were identified as striving for dignity, individuality, and self-agency, but also a struggle against shame (**Study I**) and shifting perspectives on the impact of CAH on the individual experience of living with CAH (**Study II**). The latent themes comprise underlying assumptions of wanting to be seen as a human being and not as a condition. The struggle against shame was more pronounced for different participants and in different periods of their lives, which was also the case for the shifting of perspectives. CAH could be regarded as just something that they had to take medication for and, as long as they did, they were healthy. On the other hand, CAH was sometimes regarded as being the explanation for all obstacles they have met in their lives. It was interpreted from the analysis that the perspectives shifted, depending on what happened and in what period of life the women found themselves.

Parental secrecy was described as something that was shame-inducing: *“It felt like she (my mother) did not want anyone to know, and that feeling is still with me today.”* The first years of having CAH were understood through the parents’ experiences of loss of control, frustration surrounding decision (e.g., surgery), and uncertainty of how to tell friends and family. The participants stated that the feelings conveyed by their parents had affected their own ability to cope with the condition.

Parental support was described as being important to help with information disclosure and the understanding of CAH, *“They (my parents) told me that I have a fault in my adrenal glands and that I can’t make cortisol and that makes me loose salt and I can die without treatment.”* Information sharing with peers was negotiated between disclosure and the potential risk of stigma: *“This disorder is so tough because you can’t tell anyone about it because it is so strange and difficult and unpleasant.”* However, disclosure could also be considered as potentially life saving, since their peers could come to understand acute treatment, and by disclosing, the participants’ experienced inclusion and understanding by their peers.

When asked about peer support groups, the participants explained that they often refrained from joining support groups because they did not identify with other persons with CAH, or did not want to be identified as someone with CAH. However, some participants were involved in support groups and described them as important for adjustment and a feeling of belonging.

The positive interactions with medical professionals included gaining knowledge and being an active part of the discussions surrounding treatment regimens and management. In addition, the doctor-patient relationships was also looked upon as salient if the clinician

understood that CAH is not just an endocrine condition, but also a condition that affects emotions, cognitions, identity, and relationships: *“We are also humans, we who are sick.”* However, several participants explained that they refrained from acquiring knowledge about CAH because they did not want to feel sick or deviant: *“You want to be a normal human being”*. Thus, the participants explained that they had no knowledge of previous surgery and that they had learned such things as adults, e.g., that their clitoris had been amputated by reconstructive surgery when they were born, *“I actually believed that I had a clitoris, but obviously I don’t.”*

Being exposed in the doctor- patient meeting was experienced both as children and as adult women. Firstly, the participants had experienced that they did not understand why they were frequently admitted to hospital as children. Secondly, the absence of CAH-specific knowledge among medical professionals was considered stressful, for example, participants felt that they had to take responsibility for the right acute treatment, and also to explain that being born with ambiguous genitalia does not equal sex reassignment. Thirdly, genital examinations during childhood were perceived as the main focus of physicians and that these examinations were experienced as a threat to personal integrity and that the parents were unable to provide adequate protection, *“I always had to wash ‘down there’ before going to the doctor.”* Lastly, both as children and as adults, the participants had been subjected to situations where they were expected to show their genitalia to medical professionals and students, or to be photographed naked. The overall impression among the participants that this was expected since they have a rare disorder and thus, a responsibility to increase knowledge among medical professionals and students: *“So that there can be an improvement compared to when I was a child.”* However, the demonstrations and photography were experienced as safe, but also as traumatic and since the medical incentives were not always clearly communicated, some participants believed that it was mostly done out of the physician’s curiosity. In addition, this resulted in avoidance of, e.g., regular gynecological exams and fortified feelings of being deviant: *“It confirms that it is not normal, that you need to take a photo of it.”*

Similarly, participation in research studies was considered a way to enhance care for other patients: *“I think that it is okay if you can give something to others in some way.”* In addition, it was important to participate in order to share different experiences and to show that women with CAH are different individuals: *“We who are not tomboys have only taken up a small space.”* When reading research results it was considered informative if you could recognize yourself in the findings. However, research was thought of as being biased and reinforcing the gender prejudice that surrounds CAH, e.g., interpretations of gender behavior, such as: *“If you like cars it is only because of the disorder /.../.”* In addition, research was regarded as only pointing out what was wrong or abnormal, instead of focusing on how to improve management and treatment.

Medication and surgery were described with shifting perspectives. Medication could be experienced as something that facilitated living a normal life and in contrast, something that made you never feel healthy. In conformity with medication, early genital reconstructive surgery could be considered to facilitate feeling 'normal' but could also fortify the notion of having to be corrected. Some participants wished that they could have decided on surgery for themselves. Following surgery, some participants used dilators to preserve vaginal size, which was experienced as time-consuming, stressful, and painful, but also important to facilitate having 'normal' (i.e., penetrating) sex. Vaginal size and disclosure of being born with a DSD could be regarded as a hinder to starting a romantic relationship: *"I do not dare living my life to the fullest and starting a relationship because my vagina is too tight."* However, women who were in a current relationship experienced that vaginal size was not a problem, and neither was disclosure about CAH or surgery. Experiences surrounding sexual activities were varied among the participants, ranging from being totally uncomplicated to something experienced as painful and never feeling lust, but also that sexual activities were unachievable. Same-sex relationships were considered easier since this did not imply penetrating sex.

Feeling different was a common experience during childhood, mostly because of frequent hospital visits but also because of early puberty: *"It was not that I was taller than everyone else, it was that I went through puberty, got hair on different places."* Some participants had experienced bullying, which made them question whether CAH was visible on the outside: *"I thought that it is visible on the outside even though I know that it wasn't."*

The focus on gender-related issues and gender atypical behavior in CAH research, and also in clinical management, made the participants reflect upon their female identity. Women with CAH have carelessly been called tomboys, given the findings of male-typical play behavior and male typical interests (69,71). This could be considered to be positive, and some participants described themselves as tomboys since they identified as a woman who prefers socializing with men and has typically traditional masculine hobbies. However, they did not associate this with CAH: *"I know many women who love cars just like me, and they do not have CAH."* In contrast, "tomboy" was experienced as a limiting term and that giving women with CAH the label of tomboys excluded women who do not identify as tomboys from the group of individuals with CAH.

Supplementing the above, some did not experience problems with their gender identity while others described feelings of not being a real woman and not being feminine enough. Not being interested in make-up or feminine clothing was experienced as problematic since these accessories could help them fit into the normative picture of "a real woman". Some participants had always been questioned about their female gender and had experienced being mistaken for a man, which led to questions about what their true gender identity is: *"Maybe I am not a woman, but I feel like a woman."*

Parenthood could be regarded as a confirmation of being a real woman and, for others, it did not change anything regarding their self-perceived gender identity. In addition, the lack of female self-identification was considered to be troublesome when raising children: “*I don’t feel like a female role model for my daughter because I never wear feminine clothes or make-up.*” Thinking of parenthood and children could also involve fear of infertility or that the child would be born with CAH or not be healthy: “*If I have children, they probably won’t be completely healthy; no one ever said anything about that, but I think so.*”

In addition, biological parenthood was not regarded as obligatory, and some participants had no longing for becoming pregnant or having biological children; however, they enjoyed living with children. Some interpreted the absence of a wish for children as being because of CAH: “*I do not have any desire to have children; maybe I have unconsciously put it away because of my disease – but I have always preferred cars to dolls.*”

Table 8. Examples of the variation of experiences in the categories of Studies I and II

Manifest analysis						
	Categories	Subcategories		Variation		
Study I	<i>Information</i>	Health professionals	Inclusion	↔	Exclusion	
		Parents and peers	Secret	↔	Public	
		<i>Exposure</i>	Focus on genitalia	Safe	↔	Exposed
	Photography		Autonomy	↔	Dependent	
	<i>Health</i>	Medication Surgery	Healthy	↔	Never healthy	
			Facilitating	↔	Complicating	
	<i>Research</i>	Research subjects	Important for future care	↔	Focus on deviation	
		Interpretation of research	Represented	↔	Not generalizable	
		Study II	<i>Forming identity</i>	As a girl	Unaffected	↔
	As a tomboy			Recognition	↔	Limiting
As a woman	Good enough			↔	Not enough	
<i>Establishing relationships</i>	Intimate relationships		Safe	↔	Exposed	
	Parenthood	Autonomy	↔	Dependence		
Latent analysis						
	Themes					
Study I	<i>Struggle against shame</i>	Dignity Self-agency Individuality	↔	Shame Stigma-conscious		
Study II	<i>Shifting Perspectives</i>	CAH in the background	↔	CAH in the foreground		

6.2 PSYCHIATRIC MORBIDITY IN WOMEN WITH DSD

In summary, the results showed that the frequencies of psychiatric disorders are increased among women with different DSD, compared to population controls.

Study III

In **Study III**, girls and women with CAH had a doubled risk of having received a diagnosis of any psychiatric disorders in the National Patient Registry compared to both male and female population controls (Table 9). Girls and women with CAH also had an increased risk of mental and behavioral disorders due to psychoactive substance use, particularly alcohol misuse, compared with both female and male population controls. In the sub-analysis of anxiety disorders, there were also high risks of stress-related and adjustment disorders compared to female controls [OR 2.1, (95% CI 1.3-3.6)].

Table 9. Psychiatric disorders in girls and women with CAH compared with controls (1:100). Presented as odds ratio, OR, (95% CI). OR=1 means no difference.

	CAH girls and women, n=335	
	Female controls	Male controls
Any psychiatric disorder	1.9 (1.4-2.5)*	2.2 (1.7-2.9)*
Mood disorders	1.5 (0.9-2.4)	2.9 (1.8-4.6)*
Anxiety disorders	1.5 (1.0-2.3)	2.7 (1.8-4.2)*
Alcohol misuse	2.8 (1.7-4.7)*	2.1 (1.2-3.5)*

* p < 0.05

When stratifying by age, only women 18 years or older had a significant increase of any psychiatric morbidity, compared to female controls. Stratification before or after the introduction of neonatal screening in 1986 or known and unknown genotypes or phenotypes did not change the risk estimates. On controlling for parents' highest level of education, the increased risk for any psychiatric disorder, anxiety disorders, and alcohol misuse was still significant in comparison with female controls, but not compared to male controls (Table 10).

Table 10. Psychiatric disorders in girls and women with CAH compared with female controls (1:100), presented by strata and adjusted for the parents' highest level of education. Presented as the odds ratio, OR, (95% CI). OR=1 means no difference.

	Stratified by			Adjusted for
	≥ 18 years	Born before 1986	Born 1986 or after	Parents' highest level of education
	Female controls	Female controls	Female controls	Female controls
Any psychiatric disorder	1.9 (1.4-2.7)*	1.7 (1.2-2.5)*	2.1 (1.2-3.3)*	1.9 (1.4-2.5)*
Mood disorders	1.7 (1.1-2.8)*	1.7 (1.0-2.8)*	1.0 (0.3-3.1)*	1.5 (1.0-2.4)*
Anxiety disorders	1.7 (1.1-2.7)*	1.6 (1.0-2.6)*	1.2 (0.4-3.0)*	1.5 (1.0-2.3)*
Alcohol misuse	3.0 (1.6-5.8)*	2.5 (1.2-5.2)*	3.2 (1.4-6.9)*	2.2 (1.3-3.7)*

* p < 0.05

In-depth analyses of the data regarding phenotype groups showed that the subjects with SW-CAH had twice the risk of any psychiatric disorder, compared to female controls. Individuals with SW-CAH were also associated with three times the risk for alcohol and drug misuse disorders, compared with unexposed female controls. Girls and women with SV-CAH had a higher risk of alcohol misuse. The subjects with NC-CAH had a ten times increased risk for specific phobias. On analyzing data regarding genotype groups, the girls and women with the most severe genotype, including the null mutation, had more than a five times higher risk for substance misuse disorders [OR 6.7, (95% CI (2.6-17.8)], and an almost ten times higher risk for drug misuse [OR 9.8 (95% CI 2.9-33.7)] compared with female controls. Subjects with the null genotype were also associated with a higher risk for ADHD, but the higher risk was only true for subjects born before 1986 when data were stratified in accordance with the introduction of screening that year. (See **Paper III**).

Study IV

In **Study IV**, 85% of women with DSD fulfilled criteria for a psychiatric condition, compared with 76% of the women with POI and 54% of population-derived controls. They also had a significant increase in the risk for any psychiatric morbidity [OR 5.1, (95% CI 1.7-14.9)] and in mood disorders [OR 2.7, (95% CI 1.1-6.5)] and anxiety disorders in particular [OR 4.2, (95% CI 1.69-10.3)] compared to population-derived controls. In addition, there was a 20-fold increase in the risk for an obsessive-compulsive disorder (OCD) in women with DSD, compared to controls [OR 21.1, (95% CI 2.5-175.3)]. However, co-morbidity involving DSD and OCD encompasses few individuals (n = 7 women with DSD). For women with POI, there were no significant findings on comparing women with DSD, or on comparing with controls (Table 11).

Table 11. P-values for differences in frequencies of psychiatric disorders among women with DSD compared with women with POI and age-matched controls. Odds ratios are presented for significant differences between DSD and controls. OR=1 means no difference. *= p <0.05

	DSD (n = 33)		OR (95% CI)	POI (n=21)
	POI	Controls		Controls
At least one psychiatric disorder	0.476	0.003*	5.1 (1.7, 14.9)	0.07
At least two psychiatric disorder	0.451	0.008*	3.2 (1.3, 7.8)	0.29
Major depressive episode	0.775	0.030*	2.7 (1.1, 6.5)	0.14
At least one anxiety disorder	0.403	0.003*	4.2 (1.7, 10.3)	0.16
Obsessive compulsive disorder	0.131	<0.000*	21.1 (2.5, 175.3)	0.26

Previous contacts with healthcare because of psychiatric symptoms were reported by 64% of the women with DSD, and all 64% met the criteria for at least one current or lifetime psychiatric disorder in the MINI+. This was numerically higher than in women with POI and controls (43% and 40%, respectively), but not statistically significant. This was also true for current psychopharmacological treatment.

Subgroup analyses showed a higher risk among women with CAIS (n=20) for any psychiatric disorder [OR 3.5, (95% CI 1.1-11.7)] compared with population-derived controls. Women with CAIS also showed a higher risk to fulfill criteria for depression [OR 3.1, (95% CI 1.1,9.3)], and for an OCD diagnosis [OR 15.3, (95% CI 1.6-146.1)] in comparison with population controls.

7 DISCUSSION

This thesis set out to investigate psychological and psychiatric aspects concerning women with disorders of sex development. The specific objectives were to explore the women's own experiences of having CAH and to increase knowledge regarding psychiatric morbidity in women with different forms of DSD. By interviewing women with CAH, several important factors could be identified that had an impact on these women's psychosocial adjustment. Psychosocial adjustment among these women is dependent on several factors, such as interactions with healthcare providers, support from family and peers, information sharing, and attitudes in society. In addition, by linking individuals from the nationwide CAH Registry to Swedish nationwide registries and performing structured clinical assessments in women with DSD, the different DSD can be linked to psychiatric disorders. The discussion around the findings is presented according to the specific objectives.

7.1 PERSONAL EXPERIENCES OF LIVING WITH CAH

During the past decade, more attention has been paid to psychological outcomes in individuals with CAH. There is also a wider interest in trying to understand what comprises different outcomes in psychological and psychosocial adjustment in persons with CAH and other DSD (76,156,157).

When this thesis project started there were few studies that had explored the experiences of the care given (97,158). Even though many of the aspects that women brought up in the interviews for **Studies I** and **II** are not entirely new, but they are important because they add valuable details that are useful for information purposes and for understanding the variability in CAH and other DSD, regarding psychological outcomes, and can potentially improve clinical management strategies.

The importance of knowledge

The results of a Swedish study of nine young women with CAIS and gonadal dysgenesis, exploring the experience of receiving a DSD diagnosis, implied that all women had different unanswered questions after consultation, and that clinicians need to explore individual circumstances surrounding each person (159). Given that CAH and other DSD are rare and complex disorders, age-appropriate information and a proper language to describe the conditions are important for conveying correct knowledge and thus avoiding negative judgments. Similarly, it has been reported that, with differentiated medical knowledge, women with DSD can describe themselves as "differently normal" or "normally different". Where the first referring to presenting oneself as another kind of normal and the second to the fact that we are all different (160).

The previously prevailing notion that a knowledge of different genitalia and previous reconstructive genital surgery could make adjustment difficult led to a culture of secrecy

between medical professionals, parents, and patients (161). This is, for example, in line with the participants' descriptions of learning first as adults, that they did not have a clitoris. This nondisclosure of diagnosis-related information is also described by the participants as a result of experienced parental secrecy. In line with the findings in **Study I**, parents have been described as important sources of information for patients with CAH (97,162), and it is now known that the ability of the parents to cope with CAH affect the child's adjustment (163,164). In addition, knowledge of the condition is important for facilitating adjustment (163,165).

Disclosure of a DSD diagnosis has been described as a conflict between accessing social support and protect privacy among both parents and the affected individuals (95,97,99,166). For example, young women with DSD perceived risks of sharing aspects of their conditions with others and they tried to learn how to keep themselves safe until they understood how their information would be received (167). Providing parents and individuals with DSD with information-sharing strategies is important since information-sharing and disclosure can facilitate social support (168). Experiences of social support and treatment experiences have been associated with psychological outcome during all stages of life (169). Previous research have shown that peer support groups are linked to positive adjustment in chronic conditions, for both the affected persons and the parents (170). However, some participants in **Study I** were hesitant to engage in support groups since they did not want to be recognized as someone with CAH.

Similar experiences in persons with diabetes type 1

The experiences of information disclosure described by women with CAH are similar to the experiences of individuals with diabetes mellitus type 1. Similarly, this is another potentially life-threatening condition that requires life-long medication, with the difference that diabetes is a well-known disease in society (171,172). In a previous interview study, individuals with diabetes mellitus type 1 reported that they did not feel shame but that they were angry because of the stigma that they had experienced when disclosing their condition (172).

In contrast to DSD, a Google search for diabetes does not reveal pictures of virilized genitalia or naked female bodies. This substantial difference from diabetes is what might make disclosure of having a DSD shameful and stigmatizing. To overcome the internal shame related to the disclosure of having a DSD that can involve different genitalia, norms and beliefs about "normal" bodies needs to be recognized (160,173). These norms and beliefs needs be discussed among researchers and health professionals as these norms underpin society and in extension, research and practice, and thus affect parents and patients (173).

Lack of knowledge among health professionals

In addition to critically questioning norms and beliefs, the lack of DSD-specific knowledge among health professionals was described as being stressful among participants. It has been

previously reported that it is important that clinicians do not assume that all individuals with CAH present with the same concerns (158). Previously, satisfaction with the care has been correlated with psychological well-being in persons with CAH (174). A lack of knowledge among health care professionals have also been described by women with other DSD (166). Continuous education of both health professionals and parents, as well as patients, has been suggested to further facilitate adjustment (156,175).

Genital examinations and surgery

Given that CAH affects the development of external genitalia, genital examinations have been used both as treatment controls and for the purpose of educating health professionals on rare disorders (176). Genital examinations are described as being traumatic and as fortifying the feeling of being abnormal. In line with these findings, a new study has shown that genital examinations during childhood and adolescence were experienced as being strongly stigmatizing, especially when combined with the teaching of medical staff (177). This implies that genital examinations should be minimized, which is in line with current management in Sweden (178)

In addition, the experience of genital surgery was varied: it could be considered to either help or impair adjustment among the participants, depending on whether genital surgery was regarded as something that facilitates the feeling of being normal or that it reinforces feelings of abnormality. In the same way, among women with DSD, the psychological consequences of gonadectomy (surgically removal of the gonads) depend on the social perception of the surgery (96,109). Some individuals perceive that they have been “corrected” and others that they have had a malfunctioning organ at risk of malignancy removed.

In **Studies I and II**, the participants had had surgery at an early age without consent and are now living as adults. Today, the discourse determining the clinical practice involving DSD is changing toward a demand for informed consent for all irreversible interventions (161), which might help decrease the psychosocial burden after surgery. Nonetheless, psychological support and discussions around the dual perspective of surgery are needed before and after surgical interventions to aid psychological adjustment.

Psychosexual adjustment

To supplement the above, sexual behavior may be influenced by emotions and cognitions related to having a condition that affects the external genitalia, and that this affects sexual responses by increasing anxiety about sexual performance (111). It is, however, unclear whether this relates to the initial malformation, the outcome of the surgical procedure or the genital surgery itself (97). Medical controls during childhood and adolescence have also been focused on the genital status, thereby fortifying feelings of not being normal, as described before. Sexual difficulties reported by the participants were related to having a tight vagina and a need to dilate. However, concerns about pain and difficulty of penetration and about

normality in relation to the genitalia are also common among women in the general population (179).

Such concerns may have an added impact on women with CAH because their condition necessitates regular hospital visits, lifelong medication, and sometimes surgery. As has been asked elsewhere (97), could hearing that one is too tight and knowing that something is, or was, wrong “down there” affect the sexual adjustment? Could the notion “I know that I do not have a clitoris” be enough not to be able to have an orgasm? In other words, is there a psychological component of dissatisfaction with sexual activities among women with CAH? If so, would psychological support, increased knowledge, and refined coping strategies improve their sexual satisfaction?

In addition, a more differentiated sexual education, challenging assumptions about female bodies and, including a norm critical discourse, may help women with DSD to make sense of their bodies (160,180). Raised public knowledge about physical variations of the body, and different ways of sex development can also help to make DSD less difficult to talk about and facilitate peer support. Likewise, raised awareness about what it means not to fit into a binary model of biological sex is needed (181).

To be a woman with CAH

To become a woman, or the concept of female embodiment, was described by Simone de Beauvoir as “one is not born, but, rather, becomes a woman” in *The Second Sex*, first published in 1949 (182). Female embodiment is used in critical feminist theory in discussion differentiating between gender and sex, and what makes a woman (183,184). Women with CAH describe that motherhood is a confirmation of being a woman, contrasting with men who can’t give birth. In doing so, they describe the notion that a woman is someone who can reproduce. Likewise, women with the XY karyotype describe how learning about the condition, and that it might involve internal male reproductive organs, can challenge gender identity and the notion of being female (96). In addition, female embodiment is also described “Maybe I am not a woman, but I feel like a woman” which can be understood in relation to the theory of multifactorial gender identity (185–187). According to the conceptualization of the theory of multifactorial gender identity, gender identity comprises a person’s self-perceptions of gender typicality, gender satisfaction, and perceived pressure to comply with gender stereotypes (185–187). The participant described experienced gender atypicality, but, at the same time, content with her gender as a woman. It can also be speculated that some women with CAH experience significant social pressure to behave “femininely”. However, it is not only the women’s own self-perception of gender that is questioned, there are also experiences of being mistaken for a man. This is also described by other women with CAH (188) resulting in internalizing stigma and shame.

Similarly, the label “tomboy” in relation to CAH referring to girls or women who behave like boys or men and thus challenge some theories of sex-typing (189), were experienced differently among the participants. It was considered to be a correct label, but also as a limiting term that excluded more gender-typical women from the CAH patient community. However, in a study on tomboys the “gender identity scores” of CAH girls were more gender-typical than those in a sample of girls without CAH, who were considered tomboys and recruited through newspapers (189).

Some participants described that children could be a confirmation of their being a woman, but some participants also stated that they did not have a wish for biological children or to become pregnant. However, a lack of knowledge was also described, such as whether or not their children would be healthy or whether they would also have CAH. These are misunderstandings, children to women with CAH have a normal development (190). In order to develop CAH one mutated gene is needed from each parent, and therefore, genetic counseling should be offered to patients planning for children (18).

Psychosocial factors, such as less of a wish for children, have previously been suggested to partly explain the low pregnancy rates among women with CAH (40,41). If the low rates are also caused by a lack of knowledge, health professionals have another task to deal with since it is known that well-treated women with CAH have equal fecundity rates, i.e., the possibility to reproduce, equal to those of women without CAH (34,42).

A potential CAH-paradigm

Some participants base their knowledge on inaccurate facts (e.g., my children will not be healthy), and this leads them to interpret the world through a CAH-paradigm, in the sense that CAH is overrepresented as the most possible cause or explanation for different experiences. By applying labeling theory additional insights can be obtained. It states that individuals are socially “tagged” with a label when they deviate from the norm, and the more attention that is paid to the label, the more individuals will identify with this label (191). Consequently, one could argue that CAH is used as an explanation by some participants since women with CAH have been exposed to research studies looking at CAH as a cause of e.g., gender identity, gender role behavior, choice of occupation, and choice of hobbies (69,70,75,192). It has also been suggested that much research uses CAH as the most plausible explanation even though the results might not be caused by the condition itself but mediated by experiences and consequences of living with CAH (76). In that sense researchers in the field of CAH are also affected by a CAH-paradigm. To counteract this phenomenon, men with CAH can be used as controls since CAH give rise to the same somatic challenges such as lack of adrenaline (epinephrine), life-long treatment and the risk of salt-crisis due to simple infections. Patient involvement in setting the research agenda might also contribute to changes in what type of research questions are asked, how the results are understood and what the future caretaking of all DSD patients may include (173,193).

Moreover, as researchers it is important that we give individuals with CAH and other DSD a way to “make sense” of their condition, and to help them find fair explanations of what makes them e.g., “normally different” or “differently normal” (160), and to help them navigate the research around DSD and what is applicable to the individual person and what is of interest for the understanding of biological concepts (e.g., sex hormones and gender behavior).

In conclusion, the analysis of individual experiences of women with CAH shows that they are a diverse group of individuals and that their different needs should be prioritized when providing care. Health professionals can help them to navigate through the trajectory of their condition, support them at transitions and help them make sense of their condition and prevent mental ill-health related to the DSD diagnosis.

7.2 PSYCHIATRIC MORBIDITY IN WOMEN WITH DSD

This thesis presents two unique studies on psychiatric morbidity in women with different forms of DSD. **Study III** is to date the largest population study on psychiatric morbidity in girls and women with CAH. **Study IV** is the first study to survey psychiatric disorders in women with DSD and women with POI and, in an age-matched population-derived control group by means of structured clinical interviews.

The main findings from **Study III** were that girls and women with CAH had a higher lifetime incidence of any psychiatric disorder, including a doubled risk of alcohol misuse disorder, and twice the risk of stress related adjustment disorders when comparing with both male and female population controls. Similarly, the main findings in **Study IV**, were that women with DSD had a five times higher lifetime risk of satisfying the criteria for any psychiatric disorder, including past or recurrent mood disorders, anxiety disorders, and particularly obsessive-compulsive disorder (OCD), than population-derived controls.

Previous research

Psychiatric disorders among girls and women with DSD have been scarcely studied previously. Nonetheless, women with CAH, women with CAIS and women with GD have all been found to have increased rates of psychiatric symptoms (105,107,118,119,194). The findings of an increased risk for anxiety disorders and substance misuse among girls and women with CAH have been demonstrated before, as well as higher risks among individuals with SW CAH, the most severe phenotype (120). In contrast, studies evaluating psychiatric disorders in women with CAIS show both impaired psychological functioning, e.g., psychological distress and suicidal tendencies (82,96,101,121), as well as equal, or even better, psychological functioning than in a reference group (47,107,195). The increased risk of mood disorder among women with CAIS and GD has been reported before (105,107,121,194). Given that CAIS and GD are more rare than CAH studies evaluating

mental health among women with DSD often have small samples, based on self-assessed instruments and with a lack control groups (196).

Sex and gender differences

What accounts for suboptimal psychological functioning in girls and women with DSD is most probably an interaction between different psychosocial and biological factors. There are well-documented gender differences in the incidence of mood and anxiety disorders with a doubled risk for women (197). This has been hypothesized to be related to the natural fluctuations in women's sex hormones puberty, pregnancy, and menopause (198). However, there are similar trends regarding anxiety and depression when studying both women and men with CAH (199) which suggests that hormones might not be the full answer.

There were no significant differences between women with POI and women with DSD or controls. Nonetheless, 76% of the women in **Study IV** fulfilled criteria for a lifetime psychiatric diagnosis. A POI diagnosis has previously been linked to an increase risk of depression, and that the POI diagnosis has a significant negative impact on quality of life, perceived stress, and psychological well-being (200,201).

Anxiety disorders and exposure to stress

Regarding anxiety, a doubled risk of a reaction to severe stress and adjustment disorders was shown to account for the increased risk in girls and women with CAH; however, no increased risk of OCD could be found in girls and women with CAH, contrary to women with CAIS and CGD.

In addition, CAH is a complex metabolic condition and anxiety symptoms might be explained by dysregulation of the HPA-axis or adrenaline production that can lead to inabilities to regulate stress response (202). It is known that CRH secretion increases if CAH is not treated optimally (203) and dysregulation of the HPA axis can be associated with anxiety, as well as depression and posttraumatic stress disorders (204). However, parents to children with CAH have showed high levels of posttraumatic stress symptoms and even though they are known carriers of one affected gene, a previous population study showed that *CYP21A2* carriers are less vulnerable to psychological stress and had a reduced risk of having a psychiatric diagnosis (92,205). These findings suggest that genetic factors or social factors are not likely to mediate increased psychiatric morbidity in persons with CAH, suggesting that the diagnosis of CAH and the disease situation in itself is a mediator for stress symptoms.

Similarly, stressful life events have been linked to the onset of OCD, and have also been suggested to predict the onset of depressive symptoms (206,207), Women with the XY karyotype report receiving the diagnosis in relation to impaired mental health (96). It is not farfetched to believe, that being diagnosed with a condition, such as a DSD and POI, which

overturns expectations concerning identity, fertility, and future health, can constitute a stressful life event. In line with this reasoning, women with an XY DSD have reported higher distress than individuals with other chronic disease (121). Women with DSD also describe possible traumatic events, such as bullying and repeated genital examinations (176,177), which may add to the increased vulnerability to psychiatric disorders. Social support and individual coping factors are known protective factors against developing psychiatric symptoms after a potentially traumatizing event (208), which further strengthens the incentives for giving psychological support to all parents and persons with a DSD, as well as broadening DSD knowledge in order to facilitate peer support.

Potential mediators of psychiatric disorders

Women with CAH have fecundity rates that are comparable to those of unaffected individuals and women with GD who have a uterus can become pregnant by means of an assisted zygote donation, but women with CAIS are infertile. Given that infertility is, irrespective of its cause, is associated with higher rates of depression, compared with the reported rates in fertile women (209), it is not unlikely that infertility can explain part of the high rates of psychological distress and depressive symptoms in women with POI (200). Infertility might also contribute to the psychological distress in women with DSD, but this has yet to be evaluated.

CAH treatment consists of glucocorticoids in doses that attempt to mimic the physiological levels. It is known that higher doses of glucocorticoids are associated with depression and anxiety as well as mania and psychotic disorders (210). Since the Swedish Prescribed Drug Register has been in place since 2005 and does not cover drugs prescribed on license, aspects of treatment can not be assessed using this the study design in **Study III**, however, different glucocorticoid treatments have been shown to impair the quality of life in adult persons with CAH (211,212).

Women with CAIS have reported feelings of decreased vitality after gonadectomy and, in addition, women with DSD report increased symptoms of fatigue which are suggested to be caused by a premature loss of gonadal functioning and a shift from testosterone driven hormonal balance to estrogen (51,195).

In contrast to women with CAH, the primary treatment for women with CAIS, CGD, and POI is hormone replacement, often with combined contraceptives or hormone replacement therapy with e.g., ethinylestradiol (51,58). A recently published nationwide prospective Danish cohort study suggest that depression is an adverse effect of hormonal contraception therapy (213). This might be a contributor to the increased risk of depression in women with CAIS and the high numerical rates in POI.

Substance use disorders

The high rates of substance use disorders among women with CAH were a striking find. Androgens are hypothesized to mediate alcohol addiction by sensitizing the brain's reward system for alcohol (214). Moreover, reward processing in CAH is suggested to be impaired due to androgen excess and cortisol impairment (215). Similarly, cortisol impairment because of a disturbed HPA-axis might lead to an overly sensitive stress system which, together with low levels of ACTH might increase the risk of developing alcoholism (216). Elevated ACTH levels can be found in women with CAH, particularly before the morning dose of glucocorticoids. On the other hand, replacement of glucocorticoids might result in decreased levels of ACTH (36). Moreover, alcohol might also be self-medication for coping with anxiety disorders or for living with a DSD condition. Women with the highest risk of alcohol misuse were women with the most severe null mutation, who have previously been reported to be most impaired with regard to the quality of life and psychosexual outcomes (87). However, increased risks of alcohol misuse disorders are also prevalent in men with CAH (199), which implies that addiction might be related to the physiology of CAH, or to psychosocial factors surrounding the condition. For example, men with CAH have also been exposed to repeated genital examinations pertaining to CAH since it is important to recognize the on-set of puberty, in order to evaluate whether signs of virilization are due to puberty or undertreatment of CAH, and there is also a non-negligible risk of testicular adrenal rest tumors in men with CAH.

Psychiatric morbidity and the organizational hypothesis

According to the organizational hypothesis, girls and women with CAH would display a panorama of psychiatric disorders comparable to that in male controls. However, the results from **Study IV** do not show results that can be explained by prenatal androgen effects.

Androgens have been suggested to explain psychiatric disorders that are more usual in men, e.g., ADHD, autism, and substance misuse. The higher rates of substance misuse in **Study III** could have been suggested to be an androgenic effect, had it not been that the risk was also higher in male controls, as well as, in men with CAH (199). The theory of the extreme male brain stipulates that excessive androgens contribute to autism disorder could not be reproduced in this total population cohort, nor did the findings show an increased risk of ADHD. Moreover, girls and women with CAH also have an increased risk of conditions that are typically increased in women such as anxiety.

In line with this reasoning and given that hormonal imbalance and XY chromosomes have been claimed to contribute to psychiatric symptoms, women with DSD would have a higher risk for psychiatric conditions, compared to women with POI and female controls. However, no conclusions can be drawn from **study IV** regarding the different hormonal milieus, neither

how congenital nor acquired hormonal imbalance affects the onset or trajectory of psychiatric disorders.

This reflects the limitations of using such conditions as CAH as a form of natural experimentation because in medical conditions, such as CAH as in other examples of DSD (e.g., CAIS), other factors contribute to behavior, and it is reasonable to believe that the pathogenesis of mental health is multifactorial, involving both genetic and hormonal, as well as psychosocial factors (80).

7.3 METHODOLOGICAL CONSIDERATIONS

Qualitative studies

Studies I and II

The major strength of the qualitative design is that it elucidates individual experiences, thoughts and perceptions concerning what it is like to have and live with CAH. This can contribute to a refined and deepened understanding in relation to women with CAH. However, qualitative methods cannot explain why there is variability in the patients' experiences e.g., if it is due to a specific phenotype or genotype.

Moreover, it is not possible to determine what is specific to CAH and what is specific to girls and women with CAH and which of these themes would also emerge if, for instance, men with CAH were interviewed or adults with very different chronic illnesses were interviewed. Certainly, some of the categories and themes that emerged from the content analysis might apply or be transferable to males, as well as to females: for example, affected boys undergo many genital exams because of concerns about precocious sexual development. However, this does not diminish the importance of these 13 women's individual experience and what insight we can get from them. Nevertheless, conducting more qualitative research would be interesting since the patient perspective is important and might help us to understand what accounts for the variability in outcomes between individuals.

Even though the sample size is considered to be adequate for qualitative studies it limits the transferability of the results (217). Thus, the results are not representative of all women with CAH, but that was never our intention when we started this project. Nevertheless, by recruiting women with different medical histories, with different birth years, and who have various experiences, we achieved rich data and this makes the findings transferable in the sense that they speak for more women than the 13 participants interviewed (132).

Thirteen of 32 eligible women (41%) participated and the likelihood that the non-participants would be systematically different from those of the participants can be debated. Of course, there will be various experiences in a population but the non-participants and the participants were comparable regarding age, disease severity, medication and the number of surgeries, which might generate similar experiences, at least regarding interaction with health professionals.

Nonetheless, an obvious limitation of the studies is the self-selected nature of the sample. The women who agreed to take part in this research are individuals who believe in the value of research. They were also coping with their condition well enough at the time of the interviews to have agreed to discuss experiences with a researcher. However, in qualitative research it is also important to recruit informants who are willing to share their experiences, to generate rich data (130,131).

When translating quotations from Swedish to English there is a risk that important nuances will go missing, since it is hard to find words that have the same cultural connotation in a different language. To counter this, we have made use of a native English speaker to confirm the appropriateness of our translations.

As researchers with an interpretative approach wishes to find the individuals' own definition of reality, these records are considered valid. Given that the answers and narratives in the interviews are their own explanations of events or their own understanding of their experiences. Moreover, researchers cannot always trust the participants' accounts, but they can take the participants' narratives as reflections of the underlying meanings.

Quantitative studies

Studies III and IV

The primary strength of **Study III** was the use of a nationwide cohort, a population-based cohort of girls and women with CAH, with almost no loss to follow-up (20,39,199,218) and it is at present, also the largest published study on psychiatric morbidity in girls and women with CAH. Nevertheless, even though the inclusion in the National CAH Registry was based on all neonatal screening and CYP21A2 investigations, the accuracy of the diagnoses and the likelihood of missed diagnoses are currently unknown (20). In addition, since Sweden is a country with a small population and CAH is an uncommon condition, there is limited power because of a limited number of subjects who have received a psychiatric diagnosis in the registries.

In **Study IV**, the strengths are the recruitment of a comparatively large number of patients and the use of the validated MINI+ semi-structured interview. However, CAIS and GD are very rare disorders and older individuals might not even have been diagnosed. Thus, we have recruited a relatively large sample, given the population of Sweden and the incidences of the disorders (1-9/100,000). Successful collaboration with clinicians and research midwives and nurses, resulted in the participation of almost all of the known patients. The high participation rate ensures that even the most vulnerable patients, e.g., those with a current psychiatric morbidity participated in the study, thereby increasing the reliability of the results.

Internal validity

In epidemiological studies, the internal validity is classified as random errors or systematic errors. Random errors are related to problems with precision and are statistical fluctuations caused by chance or random variation in a study. Since we have only used a sample of the reference population, we cannot completely eliminate random errors. Thus, the best way to reduce random errors would be to increase the size of the study sample or to decrease variability in the measurements. Moreover, since random errors causes inaccurate measures of association we use statistical methods in assessing risk estimates in combination with the

calculation of 95% confidence intervals (CI) with the aim of showing the degree of precision and the risk of random error. In both **Studies III** and **IV**, the results were considered to have occurred by chance if the 95% CI included 1, or p-values were above 0.05.

Because of the numerically small subgroups in both **Studies III** and **IV** the analysis of the subgroups must be interpreted with caution. The failure to reach statistical significance for an association might well be due to low power rather than to a lack of association (type II error). This means that the association exists, although, given the small sample the testing will not be significant. Furthermore, given that we performed many different subgroup analyses, this might bring about a few significant results just by chance (type I error).

Generally speaking, the power is good in the entire cohort of females with CAH, compared to their controls; therefore, the results regarding the most frequent psychiatric disorders can be considered to be informative in **Study III**. Even though the subgroups are small, we believe it is interesting to report on the different subgroups since they differ quite a lot clinically. Moreover, the results are similar to those for the boys and men with CAH, which we think strengthens our results despite the low number of individuals and a small number of subjects with a psychiatric diagnosis (122). This may also give rise to new hypothesis, which can be investigated further in future studies.

A register-based methodology cannot resolve the issue concerning what accounts for the differences between genotypes with respect to the risk of psychiatric disorders. If we were to compare the genotype groups with each other, we would have to adjust for age, where they live in Sweden, and migration since this give different opportunities for specialist care, and we cannot adjust for these things with low number of individuals. Thus, a clinical study where individuals with CAH with different genotypes are prospectively interviewed by standardized diagnostic interviews (e.g., MINI+) would be a more appropriate approach.

External validity

Given the young cohort of patients in **Study IV** with a median age of 25 years in January 2010, the results describe psychiatric diagnosis with onset from childhood up to young adulthood. The young median age is explained by increased survival rates after the introduction of glucocorticoids in the 1950s and the implementation of the neonatal screening program in 1986 (20). Thus, with a longer follow-up period the results may change

Reliability of the data

In **Study III** misclassification of psychiatric disorders in the registries might lead to affected individuals being classified as not affected (false negative) and not affected individuals being classified as affected (false positive). In addition, the diagnostic criteria for the psychiatric disorders are based on specified clinical symptoms and the diagnoses rely on the ascertainment of the treating physicians. Since there are no biomarkers for most psychiatric

disorders, the risk of misclassification is high and the accuracy of the diagnoses have been examined in validation studies. No study has yet validated all psychiatric DSM codes in the inpatient registry: however, the validity for bipolar disorders has been found to be sufficiently sensitive and specific to be used in an epidemiological study (219).

The use of MINI+ in **Study IV** provided an objective survey of psychiatric disorders in comparison to self reported measures. However, the interviewers were not blinded to the purpose of the study, but the use of a structured diagnostic interview performed by clinically trained physicians decreases the potential self-reported bias. The credibility of the results is strengthened by the fact that every one who stated a previous contact with the healthcare services due to psychiatric symptoms also fulfilled the diagnostic criteria according to the MINI-screening.

In **Study III** there is also a risk of an ascertainment bias since girls and women with CAH might have more healthcare contacts because of their condition they might be more likely to receive a psychiatric diagnosis than persons without CAH. Moreover, in **Study IV** there is a risk of a recall bias since the data on psychiatric symptoms were collected retrospectively (lifetime psychiatric disorders), in addition to current symptoms of a psychiatric disorder. Thus, the quality of the data is determined according to the ability of the individual to recall past symptoms. This may result in an under- or overestimation of the association between exposure (having a DSD) and outcome (psychiatric morbidity).

Selection bias consists of systematic differences in including patients and controls. This type of bias may be present in **Study IV** since we do not have data on the patients who did not participate. By virtue of the study design, i.e., using face-to-face interviews, persons who are socially well adjusted will be more prone to volunteer. Regarding controls, it is known that individuals who volunteer are not likely to be representative of the general population; however, we have attempted to limit the bias by recruiting from the Total Population Registry and matching by date and year of birth. A selection bias among those who volunteered is possible, e.g., 31% of the population-derived controls have had treatment for psychiatric symptoms, which was almost twice as high as in a Swedish epidemiological study from 2013 (220).

A confounder is an external variable in a statistical model that directly or inversely correlates with both the dependent and the independent variable. In **Study III** we adjusted for the parents' highest level of education as a proxy for socioeconomic status, since socioeconomic status could affect treatment of CAH and could also contribute to psychiatric morbidity. In addition, mediators explain the relationships between the dependent and the independent variable. In **Study III**, stress could be suggested to be a mediator.

8 IMPLICATIONS AND FUTURE DIRECTIONS

The studies in this thesis imply that there are some things that can be done by clinicians, researchers, individuals with DSD, and society. They also point toward future research areas to pursue.

Clinical implications

The most important clinical implication of the studies in this thesis is that clinicians who meet women with DSD should appreciate that these women are a diverse group of individuals, with different experiences, wishes, and outlooks on life, and that they all have shifting perspectives on what role their DSD plays in their lives. Experiences are hard to understand and therefore it is important to include the patients in management and decisions. Secondly, women with different DSD are at high-risk for developing psychiatric disorders, especially affective disorders, anxiety disorders and addiction. This warrants attention to psychiatric symptoms in clinical follow-up.

Parents are an important source of information. Parental support and, later, peer support, are important for children and adults coping with DSD conditions. Thus, psychosocial and psychiatric outcomes for women with CAH women may be improved by psychological support given to parents. In addition, support to facilitate disclosure to peers including age-appropriate knowledge and specific information at transitions in order to counteract such myths as “My children will not be healthy”.

To counteract feelings of exposure and limit potential traumatic experiences, both these and other studies highlights that only medically indicated genital examinations should be performed, after consent, and with as few persons as possible involved.

Challenging preconceptions

As clinicians and researchers, it is very important to be aware of the predominant medical discourse with a positivistic stance implying that there is one truth and one ultimate way to do the right thing. In this discourse, normal is seen as being most typical or within the standard deviation. By being of aware of this, we can help individuals with DSD to navigate through the medical discourse and broaden the concept of normality. It is also important to question our own normative preconceptions before we meet the patients and before we analyze our research results. Results might not always be best explained by a DSD; however, they might be mediated through experiences and consequences of living with a DSD.

Findings in this thesis and other studies support the notion that individuals with DSD would be helped by raised public awareness concerning DSD and a knowledge of the variations in bodies and differences in sex development. This may help persons with DSD to challenge assumptions concerning ‘normal’ bodies and also add DSD to people’s general knowledge.

Future directions

There is a need to evaluate the impact of clinical management on DSD and to assess the long-term outcomes in large unbiased cohorts, both for the sake of persons with DSD and their parents. Furthermore, it would be interesting to know what it is that may account for the variability in individuals' experiences since this might lead us to the development of interventions to optimize health-related quality of life outcomes. In the same way, it would be interesting to assess the impact of peer support and patient support groups on psychological adjustment and the QoL with a life-long chronic condition. In addition, studying the prevalence of stressful or traumatic life events and their impact on adjustment and the QoL could provide us with further implications for future care. Lastly, in order to guide future research, it is important to include the parents' and the affected individuals' opinions about what outcomes are important from their perspective. Moreover, persons with DSD and their parents can aid in the design of studies by evaluating the choice of words and improving the language related to research on DSD.

9 CONCLUSIONS

The aim of this thesis was to investigate psychological and psychiatric aspects in women with DSD, which ultimately give insights into how the care for children and adults can be optimized. These findings give support to the notion that psychological and psychiatric aspects in individuals with DSD are important and need to be prioritized in clinical management. In particular, this thesis shows that women with DSD are individuals with different experiences and needs. Further, women with DSD have increased risk of psychiatric disorders. This highlights the need for clinical attention to psychiatric symptoms among these persons. Clinical treatment and management strategies of women with DSD need continual evaluation to possibly mitigate psychiatric morbidity and psychological challenges. The perspective of women with DSD shed light on how clinical management of these patients have been developed, mainly from a medical perspective, however, to more successfully address the challenges these women experience, their perspective needs to be further investigated in future research.

10 PERSONAL REFLECTIONS

Doctoral education comprises four years filled with new knowledge, insight, frustration, challenges, laughter, and coffee, which will hopefully result in a doctoral degree (PhD). Given that it is an education, I thought that I would take this opportunity to reflect upon what I have learnt.

The studies that make up this thesis were conducted to achieve the overarching research aims. In addition, they were also chosen to make the doctoral education as rewarding as possible. Three out of the four studies apply to different methods and given that they are all complex, I cannot claim to be an expert in any of them. However, I do know the possibilities and the limitations of these methods, and I have learned that the most important thing is to ask for help. We also chose to include studies that would not only have a variation of methods, but also different sampling methods in order to give me the opportunity to learn how to recruit research subjects and controls. For **Study IV** we had our research reception on Fridays at Kvinnohälsan at the Karolinska University Hospital. Since the DSD conditions are rare and patients are, just like everyone else, busy, the data collection was, to say the least, time-consuming. Some Fridays all the research personnel were there, in total 5-6 individuals, but no research subjects showed up.

The fact that these conditions are rare makes it hard to recruit subjects but also to use statistics if you also want significance in your findings. It is known that with larger groups, it is easier to find significance. Regarding **Study IV** we could, of course, have included patients for several years to come to in order to reach statistical significance in all groups, since it always feels good, personally, when the p is smaller than 0.05. However the importance of the findings are not always determined by statistical significance. Because, during this project, I have, learned that not everything that can be counted counts, and everything that counts cannot always be counted!

Moreover, one of the biggest challenges during this project was to publish the first qualitative manuscript (**Study I**). It turned out that it was hard being in a medical context trying to publish a qualitative study on psychological aspects. It was either too psychological or not psychological enough. After seven subsequent rejects, we decided that the most important thing was that clinicians read our findings, so I rewrote the manuscript for a medical journal aimed at endocrinologist, and in this case, the eighth time was the charm.

In conclusion, I have learned that research is fun, frustrating and, there is no such thing as the perfect study. However, I hope that the findings in this thesis can contribute in some way to improved caretaking of individuals with DSD. It will probably never be unproblematic to have a chronic condition that also affects the appearance of the body, but I hope that the confidence interval for normality will become broader and thus make it easier for everyone to feel “normal”.

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